Individualized cardiovascular disease prevention

Clinical implementation of risk prediction

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Individualized cardiovascular disease prevention

Clinical implementation of risk prediction

Klinische implementatie van risicopredictie in de individuele preventie van cardiovasculaire ziekte

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H. Kummeling, ingevolge het besluit van het college door promoties in het openbaar te verdedigen op
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Steven Henricus Johannes Hageman

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Promotores: Prof. dr. F.L.J. Visseren
Prof. dr. E. di Angelantonio

Copromotor: Dr. J.A.N. Dorresteijn

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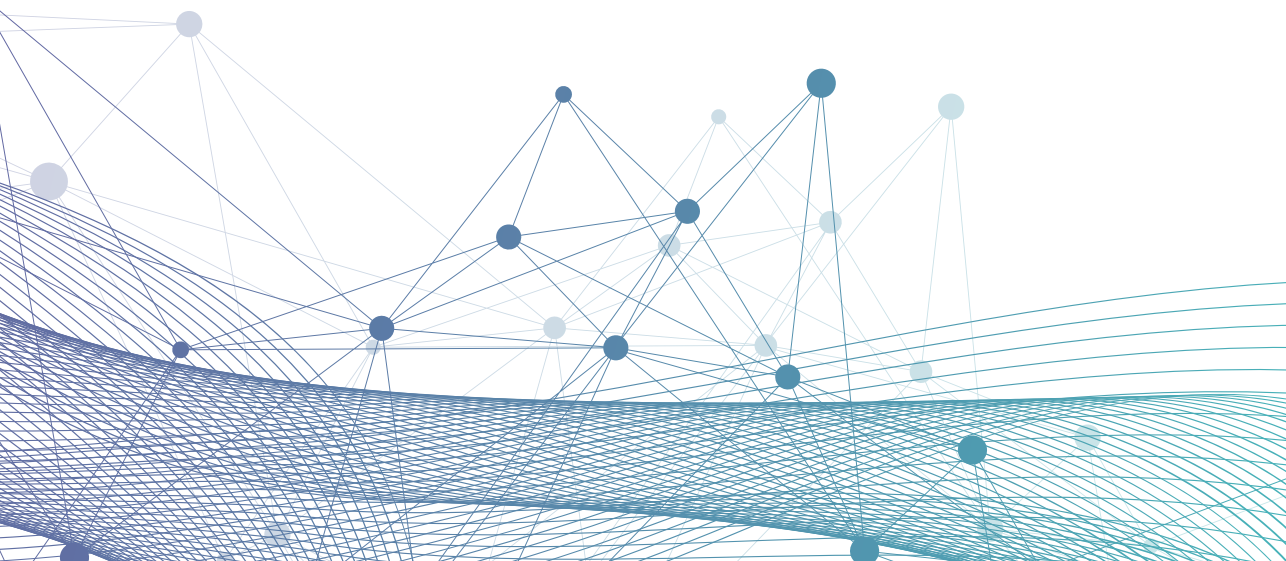
CHAPTER 1

General introduction



General introduction

Cardiovascular disease (CVD), including coronary heart disease and cerebrovascular disease, are the most common non-communicable diseases globally, and were responsible for an estimated 17.8 million deaths worldwide in 2017.[1] In the prevention of CVD events, effective strategies have been developed by reduction of the most important modifiable risk factors: smoking, systolic blood pressure and cholesterol. Interventions in risk factor levels have all been proven to effectively reduce these CVD events,[2–4] similar to treatment with antithrombotic medication.[5,6] Whereas all these treatment options are effective in reducing CVD risk on a population level, most of these therapies also have disadvantages like the risk of adverse events, increased medicalization or substantial costs in the case of some novel lipid lowering options like PCSK9 inhibitors.[7] Even intensive lifestyle interventions may not be beneficial for all.[8] Therefore, risk factor interventions are not recommended to all individuals but only to those who are expected to benefit most from preventive therapy.[9]

To identify those who benefit most, the potential risk reduction from preventive therapy should be weighed against disadvantages like the risk of adverse events, treatment costs, and the preferences of both patient and physician, taking the expected treatment duration into account. All these elements may be used in the shared decision process between health care provider and patient to decide upon treatment initiation.

Individualized prevention

Clinical trials investigating the preventive effect of risk factor interventions, such as cholesterol lowering, blood pressure lowering or antithrombotic treatment, report an average result for the whole study population.[10,11] In clinical practice, however, treatment decisions need to be taken for a single individual rather than for the whole population. The relative effect measures of risk factor interventions are generally representative to the individual, but the absolute effect of such interventions also depends on an individual's risk factor levels and risk of CVD events.[10,11] As those at the highest predicted CVD risk generally benefit most from preventive therapy, the prediction of CVD event risk to decide upon treatment initiation has already been recommended for quite some time for apparently healthy individuals.[12,13] The use of such a risk-based approach to initiate statin therapy or blood pressure reduction have been shown to be effective and cost-effective strategies.[14,15]

Prediction reliability

To reliably use such predictions in the shared decision process to decide upon treatment initiation, it is important that the predictions for individual patients are accurate and the prediction model is applicable to the specific clinical situation. Of all currently available models for the prediction of CVD, the vast majority shows

important methodological shortcomings or is not externally validated, thereby hampering clinical usefulness.[16] To prevent systematic under- or overoptimistic expectations from the benefit of preventive treatment, the predicted risks should match the actual disease incidence for the individual of interest, i.e. the model should be well-calibrated. Ideally, this should be proven in independent data, which is as representative to the clinical target population as possible.

Since the incidence of CVD greatly varies over geographical regions and over periods of time, more than can be explained by risk factors in the model alone, regional recalibration with contemporary data is usually a necessary step to ensure reliable individual predicted risks.[17] Moreover, the used prediction model should be up to the latest methodological standards, and should include correction for competing risks in those cases where this is necessary to prevent systematic overestimation of predicted CVD risks.[18]

Apart from the accuracy of the prediction models, the clinical applicability should be as high as possible, meaning that the model should be well suited for the clinical practice is intended for and should be as easy to use as possible. This is affected by model-specific factors, like the use of routinely available or easy-to-measure risk predictors and the prediction of an outcome that captures the actual burden of disease. In addition, the prediction measure used is in the shared decision process is only useful if this is understandable to both patient and physician.

In addition, clinical applicability is also related to factors not directly in the model. These include how well a model is implemented for use in clinical practice, the way the model is distributed (for example, easy scoring charts is a lot easier than an excel calculator) and guideline adaption. A model is only really applicable if both patient and physician feel confident that predictions from a certain CVD prediction model present a reliable prediction for this individual.

Apparently healthy individuals

The best-known model for the European clinical practice is the SCORE model, published in 2003 to predict the 10-year risk of CVD mortality for apparently healthy individuals using age, sex, systolic blood pressure, total cholesterol and current smoking status.[13] This model has been widely used throughout Europe. In those with predicted risks higher than 5% 10-year risk of CVD mortality ('very high risk'), risk factor reduction was recommended.[19] Even though this model has been the recommended model for some time, the model's predictions may be improved on in several ways. First, the SCORE model to predict the risk of 10-year CVD mortality in the apparently healthy was already published in 2003, based on relatively old data, often from before 1980.[13] The model, nor the treatment thresholds associated with the SCORE model have been updated since then. The SCORE model was only derived and validated

in Western European data, using no data from the regions classified as high or very high risk in the 2021 ESC CVD prevention guidelines.[9] In addition, SCORE includes only fatal CVD outcomes, meaning it underestimates total CVD burden, which in recent decades has shifted toward non-fatal outcomes, especially for younger people.[1]

Secondary prevention

With higher survival rates from acute CVD events, as well as due to the aging society, the number of individuals with established atherosclerotic cardiovascular disease (ASCVD) is increasing.[20] As these individuals have a high risk of recurrent CVD events, this is an increasingly relevant group for prevention strategies. Clinical guidelines advise classification of all patients with established ASCVD as being at 'very high risk' for future (recurrent) CVD events.[9,21,22] After treatment to risk factor targets recommended for all these individuals at very high risk of CVD events, large variation in CVD risk remains between these patients.[23] More intensive treatment options, such as lower treatment targets for blood pressure and low-density lipoprotein cholesterol, or additional antithrombotic strategies have been proven to further reduce the risk of CVD events, including novel treatment options like PCSK9 inhibitors and dual platelet inhibition.[5,7] However, their implementation has been generally modest, in part reflecting uncertainties about cost benefits from implementing these at scale or uncertainties about individual risk-benefits such as the risk of major bleeding. This makes identification of patients who may benefit most from more intensive therapy is a key issue in clinical practice today.[5,7] Therefore, more recent guidelines have begun to recommend risk stratification to guide treatment decisions for secondary prevention,[9,24] for example using the SMART risk score or the EUROASPIRE risk calculator.[25,26]

The SMART risk score to predict residual CVD event risk was developed in a single center in the Netherlands[27], and whereas it was externally validated in several trial and routine care populations[23,28,29], it has currently no parameter to reflect regional incidence differences. The EUROASPIRE model was developed using contemporary data from the EUROASPIRE registry, using different centers from many European countries in order to assess and implement regional incidence differences.[26] However, the EUROASPIRE risk calculator only predicts two-year risk of CVD-events and includes predictors not routinely available in clinical practice. None of these guideline recommended models for those with established ASCVD have been adjusted for competing risks.[9]

Thesis objective

The general objectives of this thesis are to improve upon the accuracy and clinical applicability of prediction-based treatment by developing or updating CVD risk prediction algorithms in apparently healthy individuals and individuals with

established ASCVD, and to evaluate the effectiveness of prediction-based treatment strategies.

Thesis outline

In **chapter 2**, the SCORE2 model to estimate 10-year fatal and non-fatal CVD risk in individuals without previous CVD or diabetes aged 40-69 years in Europe is developed, validated, and illustrated. In **chapter 3**, the SCORE2-OP model was developed and validated, which can be used to estimate 10-year fatal and non-fatal CVD risk in older persons without previous CVD or diabetes. In **chapter 4**, the reclassification potential of possible risk modifying characteristics in addition to the SCORE2 algorithm for apparently healthy individuals was evaluated and as well as the accuracy and reclassification potential of adding a variable number of additional risk factors for these predictions. In **chapter 5**, the goal was to illustrate the clinical impact of competing risk adjustment with real-world data. In **chapter 6**, the pragmatic method for real time and geographic calibration was adapted to the lifetime setting and applied to recalibrate the LIFE-CVD model to facilitate accurate predictions of 10-year CVD risk of apparently healthy individuals. In **chapter 7**, the clinical endpoint of major adverse limb events is evaluated, assessing incidence in different patient populations and to explaining to which extent these are attributable to non-HDL cholesterol, systolic blood pressure and smoking. **Chapter 8** shows the providing derivation, geographic recalibration, and external validation of SMART2 risk algorithm to estimate 10-year residual ASCVD event risk in patients with established ASCVD aged 40-80 years. The aim of the **chapter 9** was to evaluate the effectiveness and cost-effectiveness of blood pressure lowering, lipid lowering and antithrombotic therapy guided by predicted lifetime benefit compared to treatment based on risk factor threshold levels in terms of total gain in CVD-free lifetime and CV events avoided in patients with symptomatic atherosclerotic disease. **Chapter 10** illustrates the potential benefit on a lifetime perspective of reaching guideline-recommended risk factor targets for stroke patients. **Chapter 11** assesses current prescription patterns of lipid lowering therapy in stroke patients in order to evaluate patient groups with most potential for further CVD risk reduction.

References

1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7
2. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338(may19 1):b1665-b1665. doi:10.1136/bmj.b1665
3. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326(7404):1423-0. doi:10.1136/bmj.326.7404.1423
4. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-Century Hazards of Smoking and Benefits of Cessation in the United States. N Engl J Med. 2013;368(4):341-350. doi:10.1056/NEJMsa1211128
5. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377(14):1319-1330. doi:10.1056/NEJMoa1709118
6. Collins R, Peto R, Hennekens C, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849-1860. doi:10.1016/S0140-6736(09)60503-1
7. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664
8. de Vries TI, Dorresteijn JAN, van der Graaf Y, Visseren FLJ, Westerink J. Heterogeneity of Treatment Effects From an Intensive Lifestyle Weight Loss Intervention on Cardiovascular Events in Patients With Type 2 Diabetes: Data From the Look AHEAD Trial. Diabetes Care. 2019;42(10):1988-1994. doi:10.2337/dc19-0776
9. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
10. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FLJ. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J. 2014;35(13):837-843. doi:10.1093/eurheartj/ehu004
11. Dorresteijn JAN, Visseren FLJ, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ. 2011;343(7828):1-13. doi:10.1136/bmj.d5888
12. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106
13. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. Eur Heart J. 2003;24(11):987-1003. doi:10.1016/S0195-668X(03)00114-3
14. Herrett E, Gadd S, Jackson R, et al. Eligibility and subsequent burden of cardiovascular disease of four strategies for blood pressure-lowering treatment: a retrospective cohort study. Lancet. 2019;394(10199):663-671. doi:10.1016/S0140-6736(19)31359-5
15. de Vries FM, Denig P, Visser ST, Hak E, Postma MJ. Cost-Effectiveness of Statins for Primary Prevention in Patients Newly Diagnosed with Type 2 Diabetes in The Netherlands. Value Heal. 2014;17(2):223-230. doi:10.1016/j.jval.2013.12.010

16. Damen JAAG, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: Systematic review. BMJ. 2016;353. doi:10.1136/bmj.i2416

17. Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. Eur Heart J. 2019;40(7):621-631. doi:10.1093/eurheartj/ehy653

18. Moons KGM, Wolff RF, Riley RD, et al. PROBAST: A tool to assess risk of bias and applicability of prediction model studies: Explanation and elaboration. Ann Intern Med. 2019;170(1):W1-W33. doi:10.7326/M18-1377

19. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106

20. Dégano IR, Salomaa V, Veronesi G, et al. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. Heart. 2015;101(17):1413-1421. doi:10.1136/heartjnl-2014-307310

21. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-3104. doi:10.1093/eurheartj/ehy339

22. Goff DCJ, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25):S49-73. doi:10.1161/01.cir.0000437741.48606.98

23. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016;134(19):1419-1429. doi:10.1161/CIRCULATIONAHA.116.021314

24. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455

25. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: The SMART risk score. Heart. 2013;99(12):866-872. doi:10.1136/heartjnl-2013-303640

26. De Bacquer D, Ueda P, Reiner Ž, et al. Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE Risk Model. Eur J Prev Cardiol. 2020;32(0). doi:10.1093/eurjpc/zwaa128

27. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013;99(12):866-872. doi:10.1136/heartjnl-2013-303640

28. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. J Am Heart Assoc. 2018;7(16). doi:10.1161/JAHA.118.009217

29. McKay AJ, Gunn LH, Ference BA, et al. Is the SMART risk prediction model ready for real-world implementation? A validation study in a routine care setting of approximately 380 000 individuals. Eur J Prev Cardiol. Published online June 23, 2021:1-10. doi:10.1093/eurjpc/zwab093

CHAPTER 2

SCORE2 risk prediction algorithms: revised models to estimate 10-year risk of cardiovascular disease in Europe

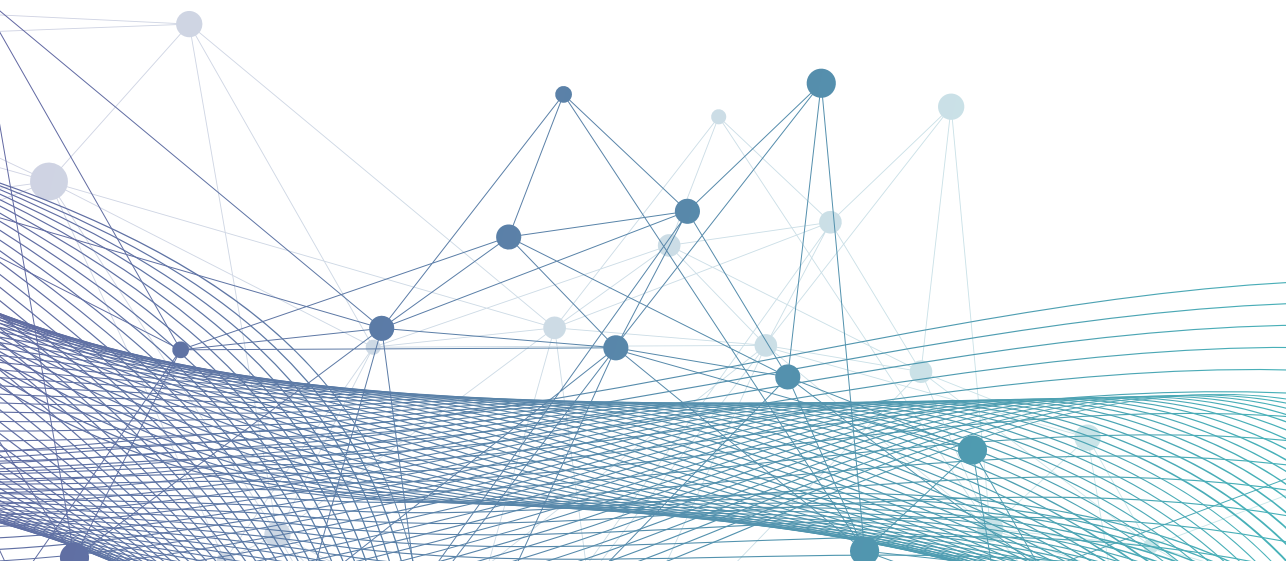
SCORE2 working group and ESC Cardiovascular risk collaboration

Steven Hageman*, Lisa Pennells*, Francisco Ojeda*, Stephen Kaptoge*, Kari Kuulasmaa*, Tamar de Vries, Zhe Xu, Frank Kee, Ryan Chung, Angela Wood, John William McEvoy, Giovanni Veronesi, Thomas Bolton, Paul Dendale, Brian A. Ference, Martin Halle, Adam Timmis, Panos Vardas, Ian Graham†, Veikko Salomaa†, Frank Visseren†, Dirk De Bacquer†, Stefan Blankenberg†, Jannick Dorresteijn†, Emanuele Di Angelantonio†,

On behalf of all other authors of the SCORE2 prediction algorithm, who are listed online

Eur Heart J. 2021;42(25):2439-2454

*Contributed equally
†Contributed equally



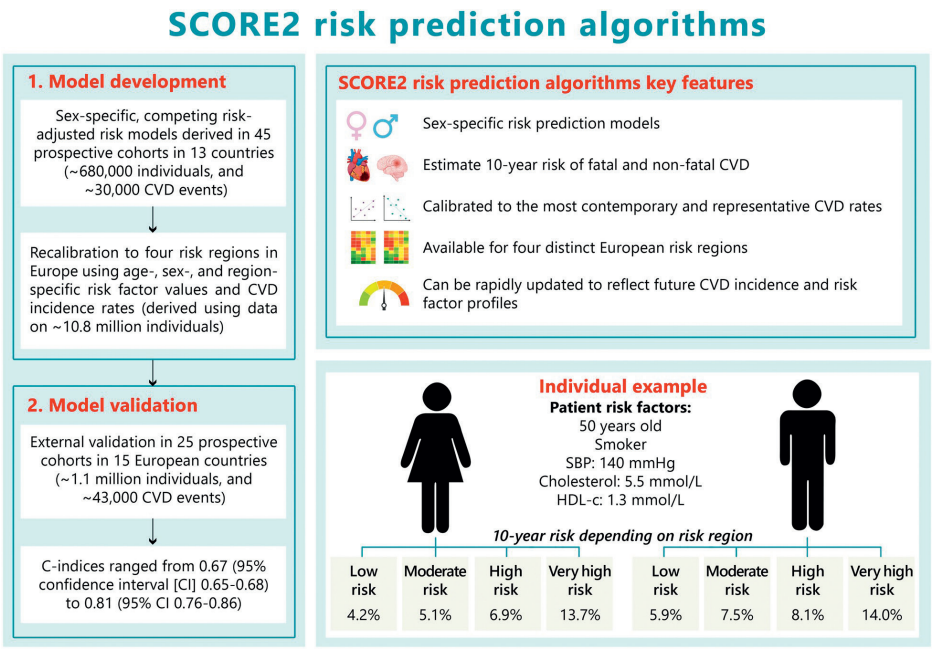
Abstract

Aims To develop, validate, and illustrate an updated prediction model (SCORE2) to estimate 10-year fatal and non-fatal cardiovascular disease (CVD) risk in individuals without previous CVD or diabetes aged 40-69 years in Europe.

Methods and Results We derived risk prediction models using individual-participant data from 45 cohorts in 13 countries (677,684 individuals, 30,121 CVD events). We used sex-specific and competing risk-adjusted models, including age, smoking status, systolic blood pressure, total- and HDL-cholesterol. We defined four risk regions in Europe according to country-specific CVD mortality, recalibrating models to each region using expected incidences and risk factor distributions. Region-specific incidence was estimated using CVD mortality and incidence data on 10,776,466 individuals. For external validation, we analysed data from 25 additional cohorts in 15 European countries (1,133,181 individuals, 43,492 CVD events). After applying the derived risk prediction models to external validation cohorts, C-indices ranged from 0.67 (0.65-0.68) to 0.81 (0.76-0.86). Predicted CVD risk varied several-fold across European regions. For example, our results suggested that the estimated 10-year CVD risk for a 50-year-old smoker, with a systolic blood pressure of 140mmHg, total cholesterol of 5.5mmol/L, and HDL-cholesterol of 1.3mmol/L, ranged from 5.9% for men in low-risk countries to 14.0% for men in very-high-risk countries, and from 4.2% for women in low-risk countries to 13.7% for women in very-high-risk countries.

Conclusion SCORE2 - a new algorithm derived, calibrated, and validated to predict 10-year risk of first-onset CVD in European populations - enhances the identification of individuals at higher risk of developing CVD across Europe.

Graphical abstract



Introduction

Cardiovascular diseases (CVD), which include coronary heart disease and stroke, are the most common fatal non-communicable diseases globally, responsible for an estimated 18.6 million deaths in 2019.[1,2] CVD remains a major cause of morbidity and mortality in Europe. The European Society of Cardiology (ESC) provides guidelines and advocates the use of risk prediction models to enhance healthcare and population-wide prevention.[3,4] Risk models, which integrate information on several conventional risk factors, typically estimate individual risk over a 10-year period. The goal is to identify people at higher risk of CVD who should benefit most from preventive action.

The ESC has convened an effort to revise its recommended risk prediction algorithm, known as the Systematic COronary Risk Evaluation (SCORE) model,[5] to address inter-related needs. SCORE includes only fatal CVD outcomes, meaning it underestimates total CVD burden, which in recent decades has shifted toward non-fatal outcomes, especially for younger people.[1] SCORE does not allow for substantial variations of risk across countries from the same risk region, meaning it may mis-estimate risk in these circumstances. SCORE was developed from cohorts recruited before 1986 and has not been systematically "recalibrated" (i.e., statistically adapted) to contemporary CVD rates, meaning it is not ideal for use in contemporary European populations. Finally, risk prediction models recommended for other global regions,[6,7] may not be readily applicable to European populations because they typically include risk factors not available in routine European data sources needed for risk model recalibration.[6,8-10]

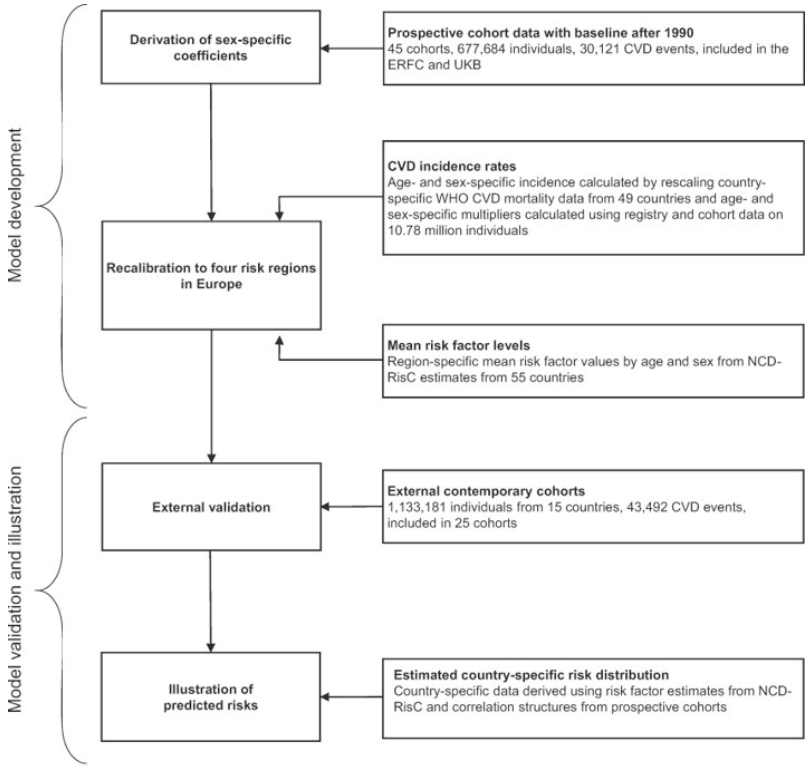
To address these limitations we provide development, validation, and illustration of SCORE2 to estimate 10-year fatal and non-fatal CVD risk in individuals in Europe without previous CVD or diabetes aged 40-69 years.

Methods

Study design

The SCORE2 project involved multiple data sources (**Figure 1**). First, to enable reliable estimation of age- and sex-specific relative risks, we derived prediction models for fatal and non-fatal CVD outcomes using individual-participant data from 45 prospective cohorts involving 677,684 participants in 13 countries. Second, to adapt risk prediction models to the circumstances of each European regions, we recalibrated the derived risk models using estimated contemporary age- and sex-specific incidences and risk factor distributions. Third, to enhance validity and generalisability, we completed external validation using individual-participant data from a further 25 prospective cohorts (i.e., studies not in the model derivation) involving 1,133,181 participants in 15 European countries. Fourth, to illustrate the variation of CVD risk across European regions, we applied the model to contemporary populations.

Figure 1: Study design



CVD, cardiovascular disease; ERFC, Emerging Risk Factors Collaboration; UKB, UK Biobank; WHO, World Health Organization; NCD-RisC, Non-Communicable Disease Risk Factor Collaboration

Data sources and procedures

For model derivation, we used individual-participant data from the 44 cohorts included in the Emerging Risk Factor Collaboration (ERFC) and the UK Biobank (UKB).[11,12] The ERFC has collated and harmonised individual-participant data from many long-term prospective cohort studies of CVD risk factors and outcomes. Prospective studies in the ERFC were included in this analysis if they met all the following criteria: had recorded baseline information on risk factors necessary to derive risk prediction models (age, sex, smoking status, history of diabetes mellitus, systolic blood pressure, and total- and HDL-cholesterol); were approximately population-based (i.e., did not select participants on the basis of having previous disease [e.g., case-control studies] and were not active treatment arms of intervention studies); had a median year of baseline survey after 1990; and had recorded cause-specific deaths and/or non-fatal CVD events (i.e., non-fatal myocardial infarction or stroke) for at least 1-year of follow-up. The UKB is a single large prospective cohort study with individual-participant data on approximately 500,000 participants aged >40 years recruited across 23 UK based assessment centres during 2006-2010, and followed-up for cause-specific morbidity and mortality through linkages to routinely available national datasets and disease-specific registers. Data selection for model derivation is shown in **Supplementary Figure 1**. Details of contributing cohorts are provided in **Supplementary Appendix 1** and **Supplementary Table 1**.

For recalibration of models, we obtained country-specific CVD mortality rates reported by the World Health Organization (WHO),[13] and estimated fatal and non-fatal CVD incidences by using age- and sex-specific multipliers. Multipliers were derived in the Clinical Practice Research Datalink (CPRD),[14] the Finnish CVD register,[15] the Swedish population data (linked to the Swedish National Inpatient and cause of death registries),[16] the Estonian Biobank,[17] and the Health, Alcohol and Psychosocial factors In Eastern Europe (HAPPIEE) study.[18] Details of these data sources are provided in **Supplementary Table 2.** Age-specific and sex-specific risk factor values were obtained from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC).[19,20] The incidence rates predicted by the recalibrated models for low and moderate risk regions were then compared to 2018 incidence rates as reported in national registry data from the Netherlands, Denmark, UK, Germany and Spain (**Supplementary Table 3**).

For external validation of models, we included prospective cohort studies if they met the following criteria: did not contribute to the model derivation; met the same criteria as for the cohorts selected from the ERFC for the model derivation stage; and made individual-participant data available to our working group. The following consortia and individual studies were used for external validation: the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) project,[21] the Biomarker for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium,[22] the European Prospective

Investigation into Cancer and Nutrition - cardiovascular disease (EPIC-CVD),[23] CPRD,[14] Heinz-Nixdorf Recall study (HNR),[24] Estonian Biobank,[17] HAPIEE study,[18] HUNT study,[25] DETECT study,[26] and Gutenberg Health Study (GHS).[27] Details of these cohorts are provided in the **Supplementary Appendix 1** and **Supplementary Table 4**.

The primary outcome was CVD, defined as a composite of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. The CVD mortality component of the primary outcomes resembles the endpoint definition of the original SCORE model and includes death due to coronary heart disease, heart failure, stroke and sudden death.[5] Follow-up was until the first non-fatal myocardial infarction, non-fatal stroke, death or end of the registration period. Deaths from non-CVD were treated as competing events. Details of the different ICD-10 codes included in both the fatal and non-fatal components of the endpoint are provided in **Supplementary Table 5.**

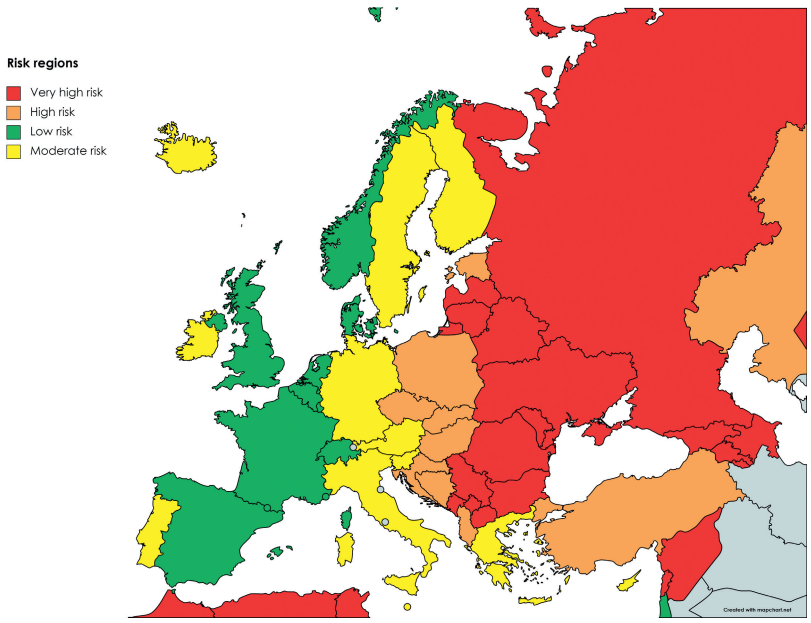
Statistical analysis

Details of statistical analysis are provided in **Supplementary Methods**. For model derivation, sex-specific coefficients (i.e. subdistribution hazard ratios [SHRs]) were estimated using Fine and Gray competing risk-adjusted models stratified by cohort. The sex-specific models included the following predictors: age, current smoking, history of diabetes mellitus, systolic blood pressure, and total- and HDL-cholesterol. The risk factors were selected due to their predictive ability as well as their availability in: derivation cohorts, target populations for screening, and population statistics needed for model recalibration. Since previous research showed that associations of these risk factors with CVD decline with increasing age, age-interactions were added for all predictors.[28] To maximise statistical power when estimating age-interactions, risk models were derived in participants aged 40–79 years at baseline without previous CVD. However, SCORE2 risk models are intended for use in people aged 40-69 years. Similarly, while the SCORE2 risk models are not intended for use in individuals with diabetes, participants with a history of diabetes were included at the model derivation stage (with appropriate adjustment for diabetes status), since people with diabetes cannot be excluded from population-level mortality statistics and risk factor data used in re-calibration efforts. There were no (or only very minimal) violations of the proportional hazards assumptions. Meta-regression was used to determine temporal and geographical heterogeneity.

Risk models were recalibrated to risk regions using age- and sex-specific mean risk factor levels and CVD incidence rates.[29] All European countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD 10 chapters IX, I00-I99).[13] The four groupings were: low risk (<100 CVD deaths per 100,000), moderate risk (100 to <150 CVD deaths per 100,000), high risk (150 to <300 CVD deaths per 100,000), and very high risk (≥300 CVD deaths per 100,000). Incidence rates were

estimated by rescaling region-specific CVD mortality rates, by derived age-, sex- and region-specific multipliers, estimated in contemporary representative cohorts from each region (**Figure 2** and **Supplementary Table 6**). We assessed discrimination using external validation cohorts by calculating Harrell's C-index, adjusted for competing risks,[30] and in the case of EPIC-CVD weighting according to the case-cohort structure of the data.[31] Comparison of SCORE2 and SCORE in relation to discrimination and calibration was performed in CRPD, as the only nationally representative data source with both risk factor and outcome information available at the individual-participant level. To compare the proportion of the population at different levels of CVD event risk according to the SCORE2 models, predicted risk distributions were simulated using age- and sex-specific risk factor value means and prevalences from NCD-RisC and correlation structures observed in ERFC cohorts.

Figure 2: Risk regions based on standardised CVD mortality rates



Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD chapter 9, 100-199). The four groupings were: low risk (<100 CVD deaths per 100,000), moderate rist (100 to<150 CVD deaths per 100,000), high risk (150 to <300 CVD deaths per 100,000), and very high risk (≥300 CVD deaths per 100,000).

Approaches used to handle missing data are described in the **Supplementary Methods**. We adopted analytical approaches and reporting standards recommended by the PROBAST guidelines[32] and TRIPOD[33]. Analyses were performed with R-statistic programming (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 15.1, StataCorp, College Station, Texas). The study was designed

and completed by the SCORE2 Working Group in collaboration with the ESC Cardiovascular Risk Collaboration, the ERFC academic coordinating centre, and the MORGAM and BiomarCaRE coordinating centres.

Results

Model derivation involved 677,684 participants from 45 cohorts without previous CVD recruited between 1990 and 2009. Mean age at recruitment was 57 (SD 9) years, 300,735 (44%) were male (**Table 1**). During median follow-up of 10.7 (5^{th}, 95^{th} percentile; 5.0, 18.6) years, a total of 30,121 CVD events and 33,809 non-CVD deaths were recorded. SHRs are shown in **Supplementary Table 7**. The strength of associations of model predictors decreased with older age of participants (**Supplementary Figure 2**). Associations of smoking and diabetes mellitus with CVD were stronger in women than men. Calibration and "goodness of fit" for the prediction models were reasonable within the derivation dataset, both overall and in region-specific and in time period-specific analyses. The C-index in the derivation dataset was 0.739 (95% CI 0.736-0.741). Results were similar in sensitivity analyses that omitted UK Biobank, or excluded studies with information only on fatal events (**Supplementary Table 8**). Similar SHRs were also found in analyses of the MORGAM/BiomarCaRE consortium (**Supplementary Table 9**).

Table 1: Summary of available data used in SCORE2 risk model derivation

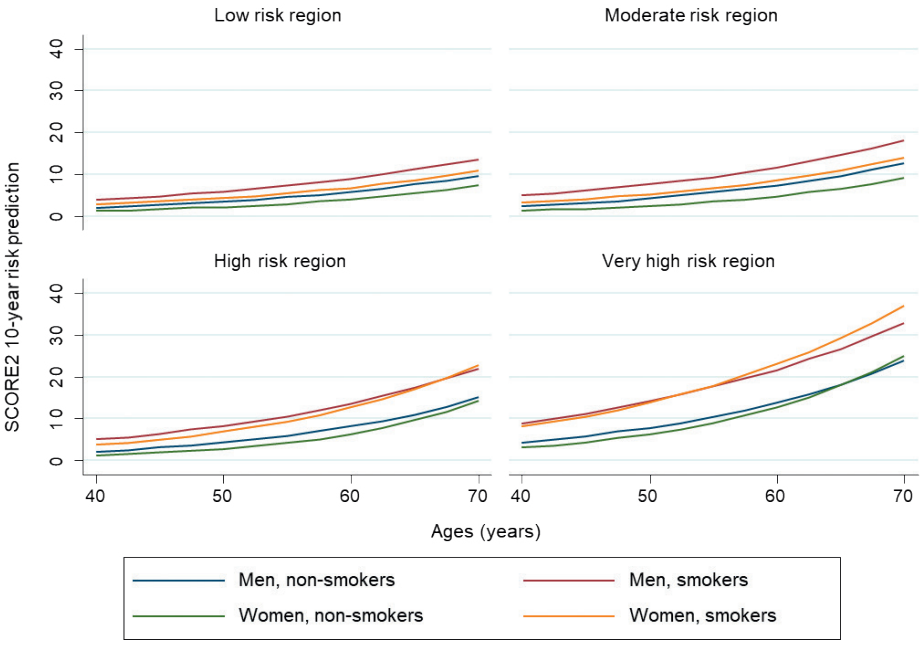
	N (%) or mean (SD)
Total participants	677,684
Male sex	300,735 (44%)
Age (years)	57 ± 9
Current smoker	101,211 (15%)
Systolic blood pressure (mmHg)	136 (19)
Diabetes mellitus	31413 (5%)
Total cholesterol (mmol/l)	5.8 (1.1)
HDL-cholesterol (mmol/l)	1.4 (0.4)
Follow-up (years, 5^{th}/95^{th} percentile)	10.7 (5.0-18.6)
Cardiovascular events	30,121
Non-cardiovascular deaths	33,809

Regional sex- and age-specific multipliers for conversion of CVD mortality rates to incidence rates involved 5,256,013 men and 5,520,453 women, with 731,265 CVD events recorded during follow up (**Supplementary Table 2**)**.** Multipliers were similar over calendar time, and across different data sources within each risk region, but

decreased with age, were somewhat greater in women than men, and were lower in the high/very high-risk regions compared to low/moderate risk regions (**Supplementary Table 10**, and **Supplementary Figures 3-5**). Age- and sex-specific mean risk factor levels used for recalibration are presented by region in **Supplementary Figure 6**. Age and sex-specific 10-year mortality CVD rates and derived incidence rates are shown for each region in **Supplementary Figures 7-8**. After recalibration, the SCORE2 predicted risks based on mean risk factor levels showed good agreement with the estimated CVD event incidence (**Supplementary Figure 9**) and with incidence rates obtained from external national registries **(Supplementary Figure 10)**.

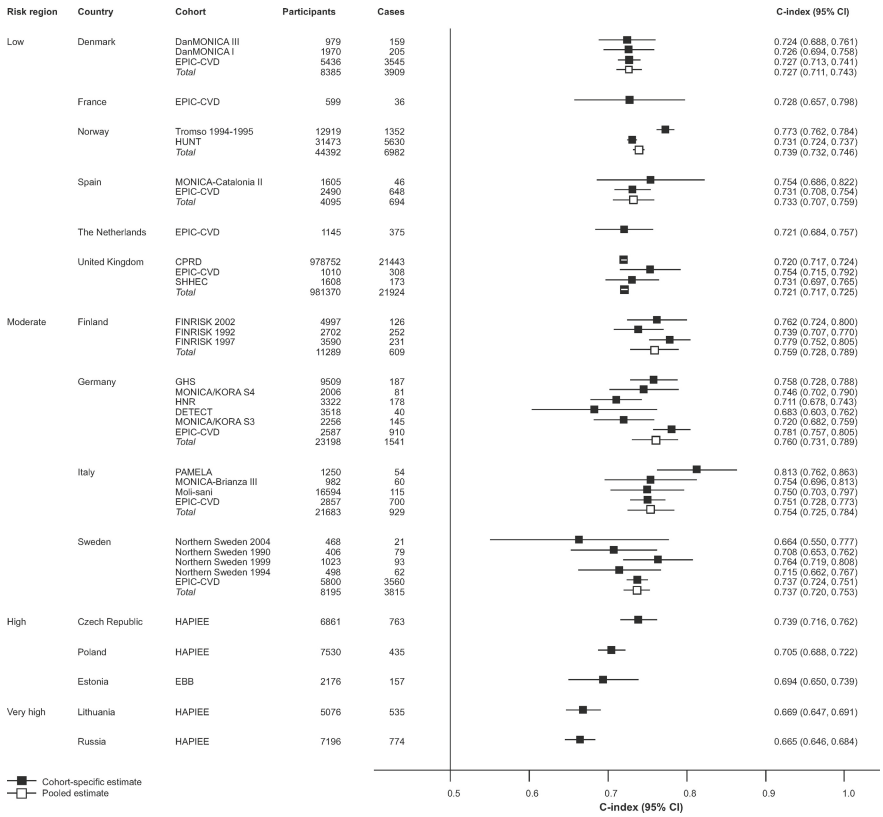
The SCORE2 charts for CVD risk estimation in four European risk regions are shown in the **Supplementary Appendix**. For practical and presentational purposes, the charts are displayed according to non-HDL cholesterol rather than total cholesterol and HDL-cholesterol. The estimated absolute risk for a given age and combination of risk factors seemed to differ substantially across regions. For example, the estimated 10-year CVD risk for a 50-year-old male smoker and with a systolic blood pressure of 140mmHg, total cholesterol of 5.5mmol/L and HDL cholesterol of 1.3mmol/L, ranged from 5.9% in low risk countries to 14.0% in very high-risk countries. Similarly, the 10-year risk for a 50-year-old woman with the same risk factor profile ranged from 4.2% in low risk countries to 13.7% in very high-risk countries (**Figure 3**).

Figure 3: Predicted 10-year cardiovascular disease risks for an individual with total cholesterol concentrations of 5.5 mmol/L, HDL cholesterol of 1.3 mmol/L, and systolic blood pressure of 140 mm Hg, for each region



External validation of risk models involved calculation of C-indices using data from 1,133,181 individuals without previous CVD or diabetes in 25 prospective studies from 15 European countries (43,492 CVD events were observed). C-indices showed moderate-to-good discrimination in all regions (**Figure 4**), with country-specific values ranging from 0.67 (0.65-0.68) to 0.81 (0.76-0.86). In comparison to SCORE, SCORE2 improved overall risk discrimination (difference in C-index: 0.0100, 95% CI 0.0085, 0.0115; P<0.001), particularly at younger ages (difference in C-index at ages 40-50 years: 0.0216, 95% CI 0.0164, 0.0269; P<0.001), and for non-fatal CVD outcomes (difference in C-index: 0.013, 95% CI 0.0097, 0.0130; P<0.001; **Supplementary Tables 11-12,** and **Supplementary Figure 11**).

Figure 4: C-index upon assessing ability of the SCORE2 model to discriminate CVD in external validation cohorts



Removing the contribution of total and HDL-cholesterol from SCORE2 model reduced C-index by 0.0078 (95% CI 0.0091, 0.0064), providing context for the C-index improvement of 0.01 observed in using SCORE2 rather than SCORE. To directly compare SCORE and SCORE2, we converted fatal CVD risk estimated using SCORE

to fatal and non-fatal CVD risk using the approach recommended by the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias (i.e., to multiply estimates by 3 in men and by 4 in women), showing SCORE2 outperformed SCORE by avoiding overestimation of risk (**Supplementary Figure 12**) and by appropriately classifying as high-risk individuals with higher observed lifetime CVD risk (**Supplementary Figure 13**).

When we applied recalibrated SCORE2 models to simulated data representing populations from each risk region, the proportion of individuals aged 40–69 years with an estimated risk greater than 10% varied by region, from 3.4% in the low-risk region to 51% in the very-high risk region in men and from 0.1% to 32% respectively in women, with these proportions increasing with age, as would be expected (**Figure 5** and **Supplementary Figure 14**).

Discussion

We have developed SCORE2, an updated algorithm tailored to European populations to predict 10-year risk of first-onset CVD. The 2021 European Guidelines on CVD Prevention in Clinical Practice, and its associated ESC CVD risk prediction application, have adopted SCORE2 and its risk charts as the ESC's recommended risk prediction algorithm. By updating SCORE in several aspects, the use of SCORE2 will enhance the identification of individuals at higher risk of developing CVD across Europe.

First, SCORE2 provides risk estimates for the combined outcome of fatal and non-fatal CVD events, in contrast with SCORE's use of CVD mortality only. Furthermore, SCORE2 has been systematically recalibrated, using the most contemporary and representative CVD rates available, whereas the original SCORE model was based on data collected before 1986. Although it would have been possible to recalibrate SCORE to contemporary CVD mortality rates, CVD mortality-only risk models underestimate total risk, particularly when the case-fatality rates are lower (as in younger individuals). Our results suggest that SCORE2 better estimates the total burden of CVD, particularly among younger individuals, as well as showing better risk discrimination, than SCORE.

of CVD risk and over-estimation of the benefit of treatment in populations where the risk of competing non-CVD deaths is high. For example, this adjustment should predominantly benefit treatment decisions in older individuals, and those from high or very-high risk regions.

Figure 5: Distribution of 10-year CVD risk according to recalibrated SCORE2 models across European countries

The proportion of individuals expected in each risk category was estimated to reflect the age-group and sex- specific risk factor values and specific population structure of each country (Supplementary Methods 1.3).

Second, SCORE2 accounts for the impact of competing risks by non-CVD outcomes whereas SCORE did not do so. This statistical adjustment prevents overestimation

Third, the recalibration of SCORE2 to four distinct European regions defined by varying CVD risk levels improves on the two-level regional stratification provided by SCORE.[5] Furthermore, as the recalibration used for SCORE2 avoids reliance on sparse cohort or country-level data, it provides recalibrated calculators tailored to sex-specific CVD rates and risk factor levels of each region. Because the recalibration approach we used is based on registry data, the model can be readily updated to reflect future disease CVD incidence and risk factor profiles of any target population of apparently healthy individuals to be screened.[28,29] This means that if descriptive age- and sex-specific epidemiological data are available from individual European countries (or within-country regions), they can be readily incorporated to revise models at a country-level.[4]

Fourth, the derivation, calibration, validation, and illustration of SCORE2 have been underpinned by exceptionally powerful, extensive and complementary datasets of contemporary relevance to European populations. These features enhance the accuracy, generalisability and validity of the approach. In particular, SCORE2 was developed using data on a total of more than 12.5 million individuals from dozens of countries.

Fifth, our project illustrated the performance of SCORE2 with data estimated from all European countries, showing that the proportions of individuals in specific risk categories seem to differ across countries. This diversity highlights why policy makers and practitioners need tailored tools like SCORE2 to help make more appropriate and locally informed decisions about the allocation of prevention resources.

The potential limitations of this effort merit consideration. We derived risk prediction models from 45 cohorts, mostly in European regions and populations at low- or moderate-risk CVD risk. Ideally, however, the derivation of risk models for use in high and very high-risk countries would have involved large nationally representative, prospective cohorts in these countries, coupled with prolonged follow-up and validation of fatal and non-fatal CVD endpoints. Unfortunately, such data do not yet generally exist. Indeed, even in low- and moderate-risk regions, the cohorts involved may not be nationally representative, reflecting past periods of time or self-selected participants such as healthy volunteers.[34] While healthy volunteer bias can lead to low estimates of absolute risk, relative risks are generally unaffected.[35] Furthermore, our approach makes the assumption that the relative risks obtained in the derivation dataset are transferable across different populations, as evidenced by broadly similar relative risk and good discrimination in external validation populations in all regions. We then recalibrated models using nationally representative incidence rates from all regions, an important step not commonly considered by other CVD risk scores, avoiding the limitations of mis-calibration provided by potentially non-representative incidence rates in cohort studies.[6,8,9]

Data on medication use, family history, socio-economic status, nutrition, physical activity, renal function, or ethnicity, were not available in cohorts and registries used for model derivation and recalibration. Hence, interpretation of SCORE2 estimates may require clinical judgement, especially for individuals in whom these factors may be relevant (e.g., those taking lipid or blood pressure lowering treatments, [36] with a family history of CVD,[37] with chronic kidney disease,[38] or in at-risk socio-economic and ethnic groups[37]). In addition, some individuals in our model derivation cohorts may have initiated preventative treatment (e.g., statin) during follow-up and accounting for this could improve model calibration and discrimination. However previous analyses have suggested that inclusion of information on statin-initiation during follow-up provides only limited clinical and public health benefit.[39] We did not compare the performance of SCORE2 models with other risk equations already developed for use in specific high-income countries because these equations contain variables often not available in European datasets used for derivation and recalibration. However, previous analyses have suggested that only minor differences exist in risk discrimination among guideline-recommended risk prediction models. By contrast, the clinical performance of risk prediction models depends importantly on differing ability to predict the correct level risk in the target population (i.e., extent of "calibration").[29] We, therefore, ensured SCORE2 was well-calibrated to current absolute risk levels for each European region by adapting the model to contemporary CVD incidence rates. We did not assess calibration of SCORE2 in our external validation cohorts other than the large nationally representative dataset from the CPRD, because these cohorts do not necessarily reflect contemporary absolute risk levels across European regions. We did not include diabetes as a risk predictor in SCORE2 as individuals with diabetes are generally considered at high risk of CVD (and, therefore, automatically eligible for statin medications and other preventive interventions), and specific risk scores already exist for this population.[40,41]

To recalibrate SCORE2 to the target European populations, we used CVD mortality rates provided by the WHO, rescaled to estimate CVD event incidence rates, based on multipliers derived from representative cohort studies or national registries from three of the four risk regions we defined in Europe. For the very high-risk region we did not have suitable data for deriving the multipliers, and therefore applied the same multipliers as for the high-risk region. Our approach assumes that CVD mortality rates provided by WHO are representative of each country, and that multipliers are valid across countries within the same region, an assumption that is difficult to test due to the lack of available incidence data in particular in the high and very high-risk regions. However, we observed that multipliers were similar across available studies from the same region and over calendar time, suggesting that they are stable despite differences in CVD event rates. Furthermore, estimated CVD rates agreed well with national incidence rates from available independent external registries. Our risk models might have underestimated CVD risk because

data used to estimate multipliers were likely to include some people already on CVD prevention therapies (eg, statins or anti-hypertensive medication), but available data were insufficient to evaluate this possibility. As we have not evaluated SCORE2 in non-European populations, its value in such settings is not entirely known. Finally, further studies should assess the value of longer-term risk prediction (especially in younger individuals),[39] understand barriers to implementations,[42] and define the role of using CVD risk prediction models in primary CVD prevention.[43,44]

In summary, the 2021 European Guidelines on CVD Prevention in Clinical Practice, and its associated ESC CVD risk prediction application, have adopted SCORE2 and its risk charts as the ESC's recommended risk prediction algorithm, which we have derived, recalibrated, validated and illustrated in this report.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. Journal of the American College of Cardiology 2020; 76(25): 2982-3021.
2. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 2020; 396(10258): 1204-22.
3. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal 2019; 41(1): 111-88.
4. Rossello X, Dorresteijn JA, Janssen A, et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). European Journal of Preventive Cardiology 2019; 26(14): 1534-44.
5. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European Heart Journal 2003; 24(11): 987-1003.
6. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014; 63(25, Part B): 2935-59.
7. Pylypchuk R, Wells S, Kerr A, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. The Lancet 2018; 391(10133): 1897-907.
8. Ridker PM, Buring JE, Rifai N, Cook NR. Development and Validation of Improved Algorithms for the Assessment of Global Cardiovascular Risk in WomenThe Reynolds Risk Score. JAMA 2007; 297(6): 611-9.
9. Assmann G, Cullen P, Schulte H. Simple Scoring Scheme for Calculating the Risk of Acute Coronary Events Based on the 10-Year Follow-Up of the Prospective Cardiovascular Münster (PROCAM) Study. Circulation 2002; 105(3): 310-5.
10. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017; 357: j2099.
11. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLOS Medicine 2015; 12(3): e1001779.
12. The Emerging Risk Factors Collaboration. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. European Journal of Epidemiology 2007; 22(12): 839-69.
13. World Health Organization. WHO Mortality Database. Accessed March 6, 2021. https://www.who.int/data/data-collection-tools/who-mortality-database.
14. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International Journal of Epidemiology 2015; 44(3): 827-36.
15. Salomaa V, Havulinna AS, Koukkunen H, et al. Aging of the population may not lead to an increase in the numbers of acute coronary events: a community surveillance study and modelled forecast of the future. Heart 2013; 99(13): 954.

16. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11(1): 450.

17. Leitsalu L, Haller T, Esko T, et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. International Journal of Epidemiology 2014; 44(4): 1137-47.

18. Peasey A, Bobak M, Kubinova R, et al. Determinants of cardiovascular disease and other non-communicable diseases in Central and Eastern Europe: Rationale and design of the HAPIEE study. BMC Public Health 2006; 6(1): 255.

19. Zhou B, Bentham J, Di Cesare M, et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. The Lancet 2017; 389(10064): 37-55.

20. Zhou B, Lu Y, Hajifathalian K, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. The Lancet 2016; 387(10027): 1513-30.

21. Evans A, Salomaa V, Kulathinal S, et al. MORGAM (an international pooling of cardiovascular cohorts). Int J Epidemiol 2005; 34(1): 21-7.

22. Zeller T, Hughes M, Tuovinen T, et al. BiomarCaRE: rationale and design of the European BiomarCaRE project including 300,000 participants from 13 European countries. European Journal of Epidemiology 2014; 29(10): 777-90.

23. Danesh J, Saracci R, Berglund G, et al. EPIC-Heart: The cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. European Journal of Epidemiology 2007; 22(2): 129.

24. Schmermund A, Möhlenkamp S, Stang A, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL Study. American Heart Journal 2002; 144(2): 212-8.

25. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol 2013; 42(4): 968-77.

26. Wittchen HU, Glaesmer H, März W, et al. Cardiovascular risk factors in primary care: methods and baseline prevalence rates--the DETECT program. Curr Med Res Opin 2005; 21(4): 619-30.

27. Wild PS, Zeller T, Beutel M, et al. [The Gutenberg Health Study]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012; 55(6-7): 824-9.

28. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. The Lancet Global Health 2019; 7(10): e1332-e45.

29. Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. European Heart Journal 2018; 40(7): 621-31.

30. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic Models With Competing Risks: Methods and Application to Coronary Risk Prediction. Epidemiology 2009; 20(4): 555-61.

31. Sanderson J, Thompson SG, White IR, Aspelund T, Pennells L. Derivation and assessment of risk prediction models using case-cohort data. BMC Medical Research Methodology 2013; 13(1): 113.

32. Wolff RF, Moons KGM, Riley RD, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Annals of Internal Medicine 2019; 170(1): 51-8.

33. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement. Annals of Internal Medicine 2015; 162(1): 55-63.

34. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. American Journal of Epidemiology 2017; 186(9): 1026-34.

35. Huang JY. Representativeness Is Not Representative: Addressing Major Inferential Threats in the UK Biobank and Other Big Data Repositories. Epidemiology 2021; 32(2): 189-93.

36. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117(6): 743-53.

37. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007; 93(2): 172-6.

38. Matsushita K, Jassal SK, Sang Y, et al. Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. EClinicalMedicine 2020; 27: 100552.

39. Xu Z, Arnold M, Stevens D, et al. Prediction of Cardiovascular Disease Risk Accounting for Future Initiation of Statin Treatment. American Journal of Epidemiology 2021.

40. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, et al. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. Eur Heart J 2019; 40(34): 2899-906.

41. Read SH, van Diepen M, Colhoun HM, et al. Performance of Cardiovascular Disease Risk Scores in People Diagnosed With Type 2 Diabetes: External Validation Using Data From the National Scottish Diabetes Register. Diabetes Care 2018; 41(9): 2010-8.

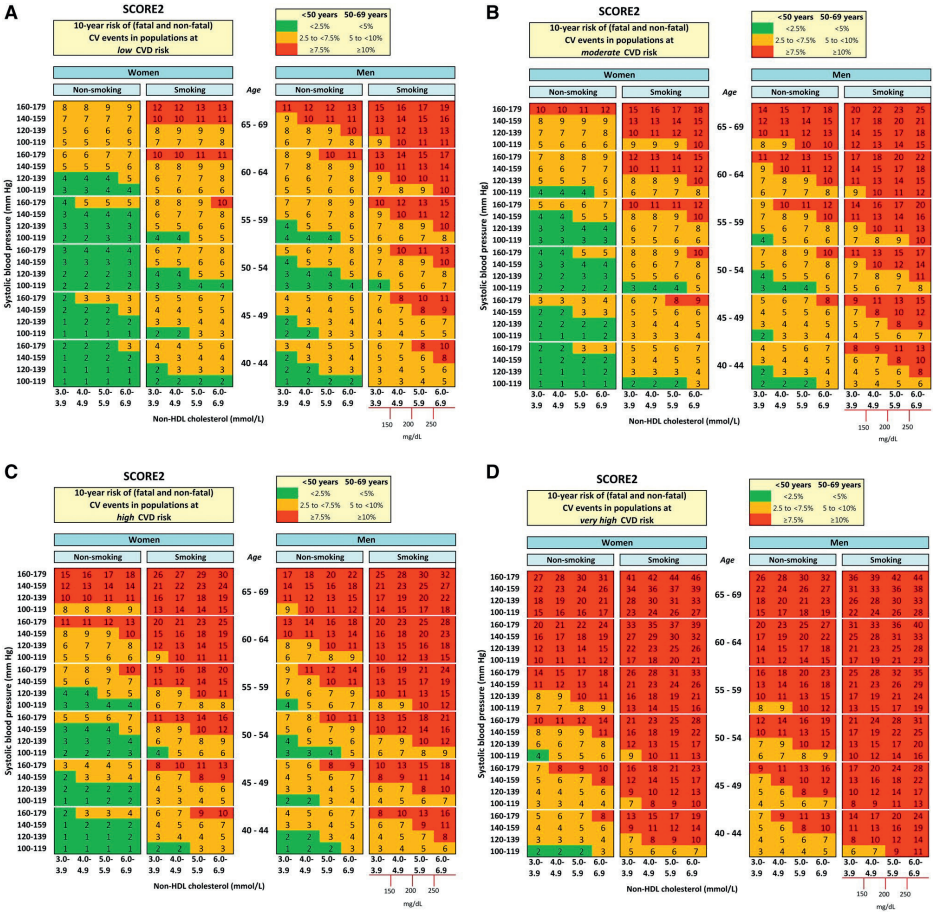
42. Muthee TB, Kimathi D, Richards GC, et al. Factors influencing the implementation of cardiovascular risk scoring in primary care: a mixed-method systematic review. Implementation Science 2020; 15(1): 57.

43. Jaspers NEM, Blaha MJ, Matsushita K, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Eur Heart J 2020; 41(11): 1190-9.

44. Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2017; 3(3): Cd006887.

Supplementary Materials

Supplementary Appendix: SCORE2 charts for estimation of CVD risk in four European risk regions.



Supplementary Methods

1.1 Model Development

The interlinked stages of model development, including model derivation and recalibration are summarised in Figure 1. An overview of the process is as follows: Fine and Gray models were derived using data from the UK Biobank (UKB) and 43 cohorts included in the Emerging Risk Factor Collaboration (ERFC) (Box 1); Four risk regions in Europe were defined according to the age-standardised country-specific cardiovascular mortality rates. For each region, annual age and sex-specific mortality rates were then translated to 10-year mortality risk estimates, allowing for competing risk of non-CVD death (Box 2); In order to translate 10-year mortality to 10-year risk of fatal and non-fatal CVD, region- age- and sex-specific multiplication factors were estimated using representative registry data and cohorts from each risk region. Multiplication factors were defined as the ratio between the cumulative incidence of fatal and non-fatal CVD events and the cumulative incidence of fatal CVD (Box 3); Multipliers were then used to translate region, sex and age specific 10-year mortality incidence to expected 10-year risk of fatal and non-fatal CVD events (Box 4); Region, sex and age-specific predicted 10-year risks were then estimated using the core, un-calibrated 10-year risk models (derived in Box 1) with region, sex and age-specific risk factors from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) (Box 5). The region and sex and age-specific predicted risks (from Box 5) were compared to expected risks (from Box 4) and rescaling factors were estimated to recalibrate the models for each region and sex (Box 6). Finally, the rescaling factors are applied with the original un-calibrated model to give new, recalibrated risk predictions in new individuals (Box 7).

The methods applied in Boxes 1, 2, 3 and 6 warrant further explanation and are detailed as follows:

Box 1: For model derivation, sex-specific coefficients were estimated using Fine and Gray competing risk-adjusted models stratified by cohort. Risk predictors were age, sex, current smoking, history of diabetes mellitus, systolic blood pressure, and total and HDL cholesterol and age-interactions were added for all predictors. Continuous risk predictors were centred before analysis. The SCORE2 risk models are not intended for use in individuals with diabetes since CVD risk among people with diabetes may depend on additional risk factors not considered in SCORE2 (e.g. age of diagnosis, duration, current treatment, and others). However, participants with a history if diabetes were included at the model derivation stage, since they cannot be excluded from population-level mortality statistics and risk factor data used in the re-calibration process. Appropriate adjustment using a dummy-indicator for presence of diabetes mellitus was applied, and this indicator was removed (i.e. set to zero) for individual predictions with the final risk algorithm. There were no or minimal violations of the proportional hazards assumptions as assessed visually based on

plotted Schoenfeld residuals. Meta-regression was used to determine temporal or geographical heterogeneity, which was found to be minimal.

Box 2: Estimation of 10-year competing risk adjusted mortality for each risk region

WHO cause-specific mortality rates were supplied by country and coded in ICD-9 or ICD-10. Rates included all mortality which was included in the original SCORE endpoint. Non-CVD mortality was defined as all mortality not included in the SCORE endpoint. Region-level estimates were obtained by taking the age- and sex- specific median of all country-specific estimates of CVD mortality rates from the relevant region.

For every age-group, WHO rates representative of the midpoint of the 10-year interval ahead were used - i.e. for the 40 to 44 year age-group the rates for 45 to 49 years was used. WHO rates of both the fatal cardiovascular outcome and the competing outcome non-CVD mortality were converted to 1–year mortality risks (r) using the following formula:

$$r = 1 - e^{(-fatal\ rate)}$$

The 1-year risks of fatal CVD were corrected for the competing risk of non-CVD death and extrapolated to 10-year risks. This was done using life-tables with 1-year intervals, using follow-up time as a timescale. For every interval, CVD-free survival was calculated using the following formula:

$$S_{t+1} = S_t \times (1 - r_{cvd,t} - r_{comp,t}).$$

In which S_t=probability of being alive at start of interval *t*; S_{t+1}=probability of being alive at end of interval *t*; and $r_{cvd,t}$ and $r_{comp,t}$ are the probabilities of experiencing a fatal CVD event or competing event respectively during interval *t,* given disease-free survival up to start of interval *t*; For every 1-year interval of the 10-year time frame of interest, the cause-specific cardiovascular mortality risk was calculated using:

$$\mathrm{CVrisk}_t = \frac{r_{cvd,t}}{r_{cvd,t} + r_{comp,t}} * (S_t - S_{t+1})$$

The fatal 10-year cumulative cause-specific risk was then calculated as the sum of the 1-year cause-specific risks:

$$\mathrm{CVrisk}_{t1-10} = \sum_{1-10} CVrisk_t$$

A worked example of this process is shown in the bottom panel of **Table 1,** for the 40-45 age group**.**

Box 3: Estimation of Multipliers to convert mortality to incidence estimates in each risk region

To convert 10-year mortality estimates to incidence estimates, age- and sex-specific multiplication factors were defined as:

$$\frac{Cumulative\ 10\ year\ incidence\ total\ CV\ events_{without\ prior\ CVD}}{Cumulative\ 10\ year\ incidence\ fatal\ CV\ events_{entire\ population}}$$

These allowed the population level mortality statistics, which are calculated among the whole population, regardless of prior disease status, to be converted into first event incidence estimates, representative of the target primary prevention population (those without prior CVD). Multiplication factors were derived in the CPRD cohort, the Swedish Population linked to National Patient Registry and cause of death register, and the Finnish CVD regster data for the low/moderate risk region, the Estonian biobank and the HAPIEE study of Czech Republic for the high and very high risk region. In each cohort and sex, two Fine and Gray models, adjusted for baseline age and age-squared were fit: one modelling 1st CVD event as the outcome and using only individuals without prior CVD, and one with fatal CVD as the outcome and including all participants (regardless of prior disease). In the Finnish register, which provided mortality and incidence rates for three years, 10-year risks were calculated using life-table methods, as described in Box 2 above. The relevant cumulative 10-year incidence was then predicted using each model, for each age group, and age group-specific 10-year CVD event risk was then estimated as follows:

$$\mathrm{CVDrisk}_{total,10} = \frac{Cumulative\ incindence\ fatal + nonfatal\ CV\ events_{without\ prior\ CVD}}{Cumulative\ incindence\ fatal\ CV\ events_{General\ population}} * \mathrm{CVrisk}_{t1-10}$$

Multiplication factors were assumed to be stable within each region and over time (supplementary figure 3-5). To aggregate the multipliers from the different cohorts to a single set of multipliers for the low/moderate risk region, the mean was used of the different sets of nationally representative multipliers. For the high/very high risk regions, the mean was calculated of all relevant multipliers, weighted by the size of the multiplier-derivation cohort.

Box 6 Relate expected to predicted risks to calculate rescaling factors for model recalibration

Recalibration of the core SCORE2 models was completed separately for each target region and sex using the previously published general process described in **Figure 2**. This involved the use of country-sex-specific mean risk factor levels (from NCDRisc) and region-sex-specific estimates of expected cumulative 10-year risk, estimated

as described above and in **Boxes 2** and **3**. We used the core SCORE2 risk models to estimate 10-year predicted risk of each endpoint for each of the age groups (40-80) using the mean risk factor values as described in **Box 5**. **Table 1** shows a worked example for the single age group 40-45, using the model parameters as shown in **Table 2**. Having completed this process for each age group, as shown in **Figure 2** we then regressed transformed expected 10-year risk across age groups on that predicted by the core SCORE2 models to derive recalibration factors (the intercept and slope of the resulting regression line, **Table 3**). The SCORE2 risk models, rescaled using the recalibration factors were then used to estimate appropriate risks for each potential risk factor combination, for a new individual or for formation of the example risk charts. An example calculation for a new individual is shown in **Table 4**.

1.2 Missing data

Because complete case analysis may lead to loss of statistical power and possible bias[24], values of predictors were imputed by single regression imputation with predictive mean matching for all cohort data.

As the CPRD consists of care-as-usual data, missing data was much more frequent and missingness was more likely to correlate with cardiovascular disease risk. Therefore, multiple imputation was performed for the external validation in CPRD with fully conditional specification using 5 imputed datasets.

1.3 Estimation of nationally representative predicted risk distributions

To compare the proportion of the population at different levels of CVD event risk according to the SCORE2 algorithms, predicted risk distributions were simulated using age- and sex-specific risk factors values means and prevalences from NCD-RisC and correlation structures observed in ERFC cohorts. This involved the following steps for men and women separately:

Within four subgroups of the population defined according to smoking and diabetes status, and for 5 year age groups (agegrp) between 40 and 70 years a multivariate normal was assumed:

pdf(sbp, tchol, hdl, bmi | agegrp) ~ MVN([mean_sbp, mean_tchol, mean_hdl, mean_bmi], [sd_sbp, sd_tchol, sd_hdl, sd_bmi] & corr_matrix])

where

mean_* = agegrp-specific risk factor means from NCD-RisC

sd_* = global standard deviation calculated using ERFC data

corr_matrix = assumed correlation matrix based on ERFC data

Under the above assumptions, the probability of belonging to each cell of the risk chart was estimated by integrating the multivariate normal probability density function defined by the parameters and the lower and upper bounds of the risk factor classification.

The age-specific prevalence of smoking and diabetes from NCD-RisC was used to subdivide the age-specific total population numbers (npop, according to the Global Burden of Disease study 2017) into the four following population subgroups, under the assumption that smoking and diabetes are approximately independent:

a) Non-diabetic, non-smoker = npop*(1 - prev_smoking)*(1 - prev_diabetes)

b) Non-diabetic, smoker = npop*(prev_smoking)*(1 - prev_diabetes)

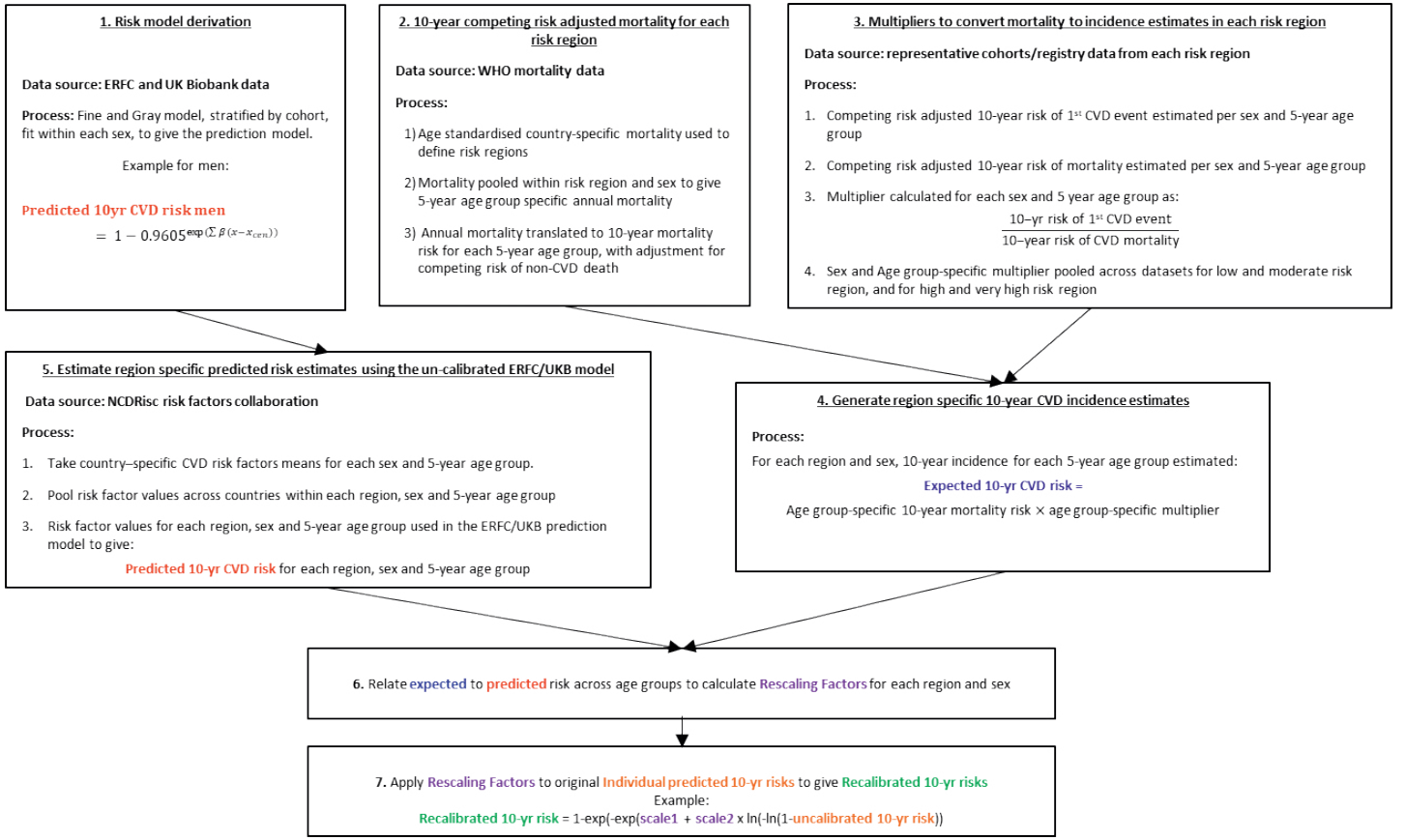
c) Diabetic, non-smoker = npop*(1 - prev_smoking)*(prev_diabetes)

d) Diabetic, smoker = npop*(prev_smoking)*(prev_diabetes)

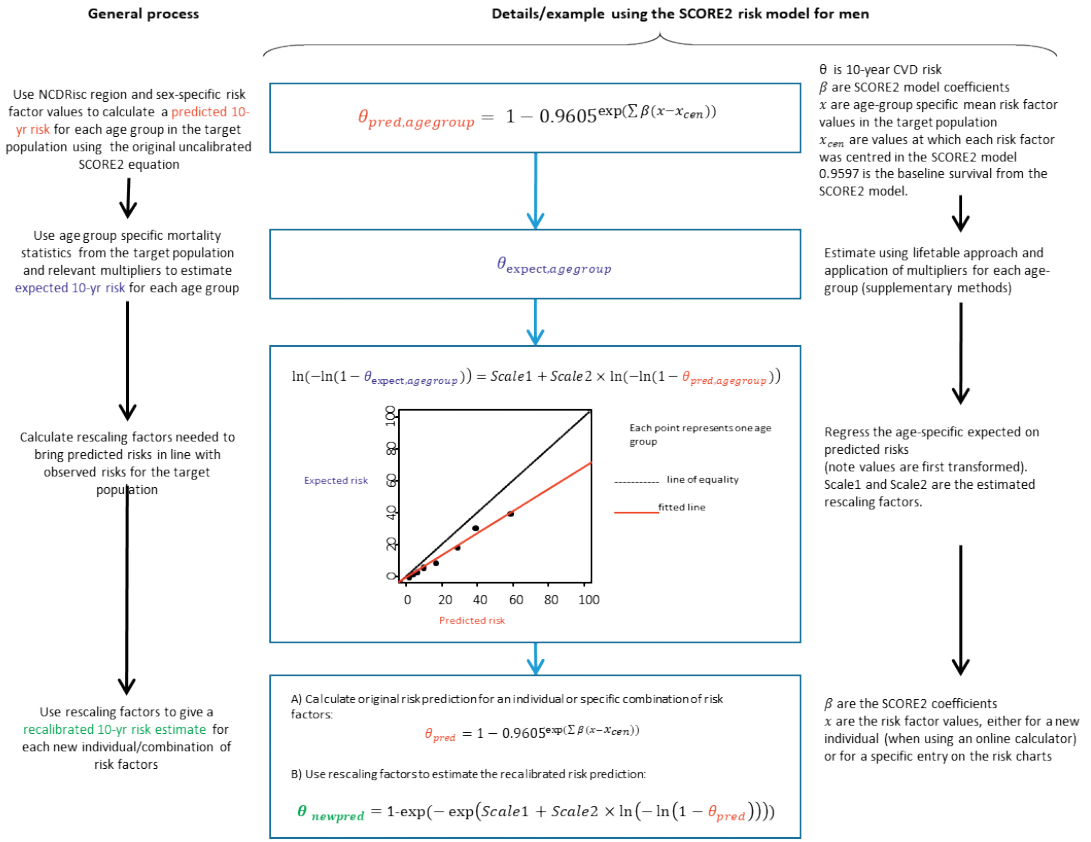
Expected population numbers for each cell of the risk chart were obtained by multiplying the cell probabilities estimated in 2) by the expected population denominators for the 4 population subgroups estimated in 3).

Estimated expected population numbers from 4) were used as weights when assessing risk distributions based on averaging or classifying the predicted probabilities for each cell of the risk chart (**Figure 5** of the main paper and **Supplementary Figure 14,** which represent those without diabetes only)

Supplementary methods figure 1: SCORE2 Model development process



Supplementary methods figure 2: Methods used for recalibration of risk scores



Supplementary methods table 1: Example calculation of predicted and observed 10-year cumulative incidence of CVD for a the male 40-45 year age group based on aggregate level data

Calculation of predicted risk using core ERFC/UKB models – example high risk region men			
Mean or prevalence of risk factor values for age group 40-45	**Log SHRs from ERFC/UKB fitted model**		**Calculation of 10-year cumulative incidence using ERFC/UKB model**
Age = 42.5 Total cholesterol = 5.2 mmol/l HDL cholesterol =1.3 SBP = 132 mmHg Diabetes=0.07 Smoking=0.45	Age	0.3742	$\sum \beta (x - x_{cen})$ = 0.3742x (42.5-60)/5 + 0.1458 x (5.2-6) -0.2698x (1.3-1.3)/0.5 + 0.2777x (132-120)/20 + 0.6457x 0.07 + 0.6012x 0.45 -0.0281x (42.5-60)/5 x (5.2-6) +0.0426x (42.5-60)/5 x (1.3-1.3)/0.5 -0.0255x (42.5-60)/5 x (132-120)/20 -0.0983x (42.5-60)/5 x 0.07 -0.0755x (42.5-60)/5 x 0.45 = -0.82612 10-yr risk = 1-0.9605^exp($\sum \beta (x - x_{cen})$) = 1-0.9605^exp(-0.82612) Predicted risk = 0.01748= 1.7%
	Total cholesterol	0.1458	
	HDL cholesterol	-0.2698	
	SBP	0.2777	
	Diabetes	0.6457	
	Smoking	0.6012	
	T. cholesterol interaction with age	-0.0281	
	HDL interaction with age	0.0426	
	SBP interaction with age	-0.0255	
	Diabetes interaction with age	-0.0983	
	Smoking interaction with age	-0.0755	

Supplementary methods table 1 (continued)

Calculation of observed risk				
Annual CVD and non-CVD mortality at the midpoint of the relevant 10-year range (incidence for age group 45-50 used)	**Annual cumulative mortality**	**Annual cumulative incidence of CVD mortality**	**Expected 10-year cumulative incidence of CVD mortality for the 40-45 year age group**	**Application of multipliers to give Expected 10-yr cumulative incidence of CVD events**
Midpoint of FU range for group with baseline age 40-45 is observed incidence in 45-55 year old Annual CVD mortality incidence per 100.000 person years=92.7 Incidence per 1 person year: 0.000927 Annual non-CVD mortality incidence per 100000 person years=313 Incidence per 1 person year: 0.0031	$r_{cvd,t} = 1 - e^{(-0.000927)}$ = 0.00093 $r_{comp,t} = 1 - e^{(-0.0031)}$ = 0.0031 Repeat from t=1 to 10: $S_{t1} = 1 \times (1 - 0.00093 - 0.0031) = 0.996$ $S_{t2} = 0.996 \times (1 - 0.00093 - 0.0031) = 0.992$ (..) $S_{t10} = 0.964 \times (1 - 0.00093 - 0.0031) = 0.960$ S_{t10} = probability of being healthy and alive at the end of t_{10}	$CVrisk_t = \frac{r_{cvd,t}}{r_{cvd,t}+r_{comp,t}} * (S_t - S_{t+1})$ Repeat from t=1 to 10: $CVrisk_{t1}$ =0.00093/(0.004) x (1-0.996) = 0.00094 $CVrisk_{t2}$ =0.00093/(0.004) x (0.996-0.992) = 0.00093 (..) $CVrisk_{t10}$ =0.00093/(0.004) x (0.964-0.960) = 0.00090	$CVrisk_{t1-10} = \sum_{1-10} CVrisk_t$ = 0.0091 = 0.9%	Region- sex- and age group-specific multiplier = 3.1 10-yr cumulative incidence of CVD events = 0.0091 x 3.1 = 0.0280 =2.8%

Supplementary methods table 2: Model coefficients and baseline survival of the SCORE2 algorithm

Risk factor (units)	Transformation equation	Log SHR		SHR	
		Male	Female	Male	Female
Age (yrs)	cage = (age - 60)/5	0.3742	0.4648	1.45	1.59
Smoking (current vs. other)	Current = 1, other = 0	0.6012	0.7744	1.82	2.17
Systolic blood pressure (SBP, mm Hg)	csbp = (sbp - 120)/20	0.2777	0.3131	1.32	1.37
Diabetes* (yes vs. no)	Yes = 1, no = 0	0.6457	0.8096	1.91	2.25
Total cholesterol (mmol/L)	ctchol = (tchol - 6)/1	0.1458	0.1002	1.16	1.11
HDL cholesterol (mmol/L)	chdl = (hdl - 1.3)/0.5	-0.2698	-0.2606	0.76	0.77
Smoking x age interaction	cage x smoking	-0.0755	-0.1088	0.93	0.90
SBP x age interaction	cage x csbp	-0.0255	-0.0277	0.98	0.97
Total cholesterol x age interaction	cage x ctchol	-0.0281	-0.0226	0.97	0.98
HDL cholesterol x age interaction	cage x chdl	0.0426	0.0613	1.04	1.06
Diabetes* x age interaction	cage x diabetes	-0.0983	-0.1272	0.91	0.88
Baseline survival		0.9605	0.9776		

*Diabetes mellitus was included in the modelling since this was necessary for the recalibration approach, which relies data from the whole population, including those with diabetes. However, SCORE2 is not intended for use in individuals with diabetes and has not been validated in this population. For risk prediction in the target population of individuals without diabetes this risk factor will always be 0, meaning the coefficient can effectively be ignored.

Supplementary methods table 3: Region and sex-specific recalibration scales of the SCORE2 algorithm

	Male		Female	
Risk region	Scale1	Scale2	Scale1	Scale2
Low risk region	-0.5699	0.7476	-0.7380	0.7019
Moderate risk region	-0.1565	0.8009	-0.3143	0.7701
High risk region	0.3207	0.9360	0.5710	0.9369
Very high risk region	0.5836	0.8294	0.9412	0.8329

Rescaling factors for the SCORE2 model to scale individual predicted risks to the target population, based recent nationally representative estimates of incident cardiovascular disease and risk factor levels.

Supplementary methods Table 4: Illustration of risk estimation for a non-diabetic man or woman with given risk factor values

1) Calculation of Linear Predictor

Risk factor (units)	Risk Factor Value	Transformed value	Log HRx transformed value	
			Male	Female
Age (yrs)	50	(50-60)/5 = -2	0.3742 x -2 = -0.7484	0.4648 x -2 = -0.9296
Smoking (current vs. other)	yes+	1	0.6012 x 1 = 0.6012	0.7744 x 1 = 0.7744
Systolic blood pressure (SBP, mm Hg)	140	(140 - 120)/20 = 1	0.2777 x 1 = 0.2777	0.3131 x 1 = 0.3131
Total cholesterol (mmol/L)	6.3	(6.3 - 6)/1 = 0.3	0.1458 x 0.3 = 0.04374	0.1002 x 0.3 = 0.03006
HDL cholesterol (mmol/L)	1.4	(1.4- 1.3)/0.5 = 0.2	-0.2698 x 0.2 = -0.05396	-0.2606 x 0.2 = -0.05212
Smoking x age interaction		-2 x 1 = -2	-0.0755 x -2 = 0.151	-0.1088 x -2 = 0.2176
SBP x age interaction		-2 x 1 = -2	-0.0255 x -2 = 0.051	-0.0277 x -2 = 0.0554
Total cholesterol x age interaction		-2 x 0.3 = -0.6	-0.0281 x -0.6 = 0.01686	-0.0226 x -0.6 = 0.01356
HDL cholesterol x age interaction		-2 x 0.2 = -0.4	0.0426 x -0.4 = -0.01704	0.0613 x -0.4 = -0.02452
		Linear predictor:	Σ = 0.3221	Σ = 0.39788

2) 10-year risk estimation (un-calibrated) = $1\text{-basesurv}^{\exp(\text{linear predictor})}$

Male	Female
$1\text{-}0.9605^{\exp(0.3221)}=0.0541$	$1\text{-}0.9776^{\exp(0.39788)}=0.0332$

3) Calibration of risk estimate according to region specific scaling factors

Calibrated 10-year risk = 1-exp(-exp(scale1 + scale2 x ln(-ln(1-un-calibrated 10-yr risk))

Risk region	Male	Female
Low	1-exp(-exp(-0.5699+0.7476 x ln(-ln(1-0.0541)))) = 0.0631	1-exp(-exp(-0.7380+0.7019 x ln(-ln(1-0.0332)))) = 0.0434
Moderate	1-exp(-exp(-0.1565+0.8009 x ln(-ln(1-0.0541)))) = 0.0811	1-exp(-exp(-0.3143+0.7701 x ln(-ln(1-0.0332)))) = 0.0523
High	1-exp(-exp(0.3207+0.9360 x ln(-ln(1-0.0541)))) = 0.0881	1-exp(-exp(0.5710+0.9369 x ln(-ln(1-0.0332)))) = 0.0713
Very high	1-exp(-exp(0.5836+0.8294 x ln(-ln(1-0.0541)))) = 0.1506	1-exp(-exp(0.9412+0.8329 x ln(-ln(1-0.0332)))) = 0.1414

Note: final estimate should be multiplied by 100 in order to express as a percentage rather than a probability

Supplementary Table 1: Summary of available data in cohorts used for model derivation

Country	Cohort	No of partici-pants	Ages Mean (SD)	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean(SD)	Total cholesterol (mmol/L) Mean (SD)	HDL cholesterol (mmol/L) Mean (SD)	Diabetes n (%)	Median follow up (5th and 95th percentile)	CVD	CVD before 10-years	other death	Other death before 10 years	Median year of study recruitment
Europe															
Denmark	COPEN	6780	61 (10)	2854 (42)	3426 (51)	141 (22)	6.3 (1.2)	1.60 (0.51)	224 (3.3)	16.4 (2.3 to 18.4)	1554	941	1684	860	1993
France	DESIR	3328	52 (7)	1636 (49)	543 (16)	133 (16)	5.9 (1.0)	1.65 (0.44)	225 (6.8)	9.0 (3.0 to 9.3)	50	50	1	1	1995
France / NI	PRIME	9583	55 (3)	9583 (100)	2544 (27)	134 (19)	5.7 (1.0)	1.26 (0.33)	312 (3.3)	5.2 (5.0 to 26.0)	580	298	710	236	1992
Germany	ESTHER	7823	61 (7)	3316 (42)	1341 (17)	139 (20)	5.7 (1.3)	1.40 (0.40)	928 (11.9)	5.0 (2.0 to 5.9)	223	223	74	74	2001
Germany	SHIP	2575	58 (11)	1255 (49)	651 (25)	141 (21)	6.1 (1.2)	1.45 (0.45)	360 (14.0)	10.3 (0.0 to 11.9)	54	46	0	0	1999
Greek	ATTICA	1960	53 (10)	993 (51)	808 (41)	128 (19)	5.3 (1.0)	1.25 (0.39)	192 (9.8)	5.0 (5.0 to 10.0)	25*	25*	15	15	2001
Italy	ATENA	4408	51 (7)	0 (0)	1738 (39)	135 (21)	6.2 (1.2)	1.62 (0.42)	115 (2.6)	6.8 (5.2 to 8.1)	30	30	29	29	1995
Italy	BRUN	800	57 (11)	391 (49)	195 (24)	145 (22)	5.7 (1.0)	1.47 (0.37)	29 (3.6)	20.2 (4.5 to 20.5)	143	52	150	70	1990
Italy	EMOFRI	360	55 (6)	176 (49)	92 (26)	146 (18)	5.9 (1.1)	1.54 (0.42)	17 (4.7)	6.8 (6.5 to 7.2)	8	8	5	5	1996
Italy	MATISS93	989	52 (8)	492 (50)	248 (25)	142 (23)	5.7 (1.1)	1.30 (0.36)	55 (5.6)	8.3 (7.0 to 9.3)	28	28	16	16	1994
Italy	MONFRI94	1091	51 (7)	522 (48)	275 (25)	140 (20)	5.9 (1.1)	1.50 (0.39)	55 (5.0)	8.5 (6.9 to 8.8)	39	39	26	26	1994
Netherlands	HOORN	2285	61 (7)	1009 (44)	725 (32)	135 (20)	6.7 (1.2)	1.34 (0.37)	219 (9.6)	8.8 (3.5 to 9.9)	177	177	149	149	1991
Netherlands	MORGEN	13214	50 (6)	6064 (46)	4779 (36)	125 (17)	5.6 (1.0)	1.37 (0.39)	220 (1.7)	10.7 (4.3 to 13.0)	139*	104*	418	317	1995
Netherlands	PREVEND	4934	54 (10)	2380 (48)	1619 (33)	132 (21)	5.9 (1.1)	1.33 (0.40)	223 (4.5)	10.6 (3.6 to 11.2)	253	233	290	258	1998
Netherlands	ProspectEPIC	15819	57 (6)	0 (0)	3589 (23)	133 (20)	6.1 (1.1)	1.49 (0.41)	321 (2.0)	14.3 (7.6 to 17.2)	740	516	935	571	1995
Netherlands	RS_I	4448	66 (7)	1745 (39)	1086 (24)	138 (22)	6.7 (1.2)	1.38 (0.38)	281 (6.3)	12.0 (3.5 to 14.2)	611	431	752	521	1992
Netherlands	RS_II	2104	63 (6)	930 (44)	519 (25)	142 (21)	5.9 (0.9)	1.39 (0.37)	212 (10.1)	10.1 (4.2 to 10.9)	141	134	167	164	2000
Norway	FINNMARK	5266	59 (9)	2352 (45)	1933 (37)	140 (23)	6.1 (1.1)	1.50 (0.42)	213 (4.0)	7.5 (5.0 to 7.5)	116*	116*	267	267	2002
Norway	HUBRO	14141	54 (13)	6132 (43)	4037 (29)	135 (19)	5.8 (1.1)	1.52 (0.43)	411 (2.9)	8.5 (6.0 to 9.5)	240*	238*	748	744	2001
Norway	OPPHED	9484	52 (12)	4282 (45)	2969 (31)	135 (22)	5.8 (1.1)	1.38 (0.37)	233 (2.5)	8.5 (7.0 to 9.5)	162*	162*	424	424	2001
Norway	OSLO2	5108	69 (7)	5108 (100)	1116 (22)	147 (21)	6.1 (1.0)	1.44 (0.40)	267 (5.2)	9.5 (3.0 to 9.5)	270*	270*	828	828	2000
Norway	TROMS	1977	51 (12)	853 (43)	679 (34)	135 (21)	5.8 (1.1)	1.41 (0.37)	57 (2.9)	7.5 (7.5 to 7.5)	26*	26*	52	52	2002
Scotland/ Ireland/ Netherlands	PROSPER	1511	74 (3)	647 (43)	542 (36)	156 (21)	5.7 (0.9)	1.31 (0.35)	181 (12.0)	3.2 (1.1 to 3.9)	184	184	66	66	1998
Spain	DRECE	1477	50 (6)	699 (47)	390 (26)	127 (19)	5.6 (1.1)	1.42 (0.38)	153 (10.4)	19.3 (11.9 to 19.6)	38*	15*	130	43	1991
Spain	ZARAGOZA	4176	58 (11)	1849 (44)	801 (19)	133 (16)	5.9 (1.0)	1.42 (0.36)	532 (12.7)	5.1 (4.7 to 5.1)	114	114	2	2	1994
Sweden	GOTO43	775	50 (0)	775 (100)	239 (31)	130 (16)	5.9 (1.0)	1.31 (0.34)	16 (2.1)	11.0 (7.9 to 11.7)	47	41	21	20	1993
Sweden	MOSWEGOT	2915	52 (7)	1358 (47)	837 (29)	132 (19)	6.1 (1.2)	1.45 (0.42)	85 (2.9)	13.8 (6.0 to 19.6)	284	170	158	104	1990
UK	BWHHS	3263	68 (5)	0 (0)	391 (12)	148 (25)	6.7 (1.2)	1.67 (0.45)	141 (4.3)	12.2 (3.3 to 13.3)	347	264	494	372	2000
UK	EPICNOR1	20833	59 (9)	9236 (44)	2415 (12)	135 (18)	6.2 (1.2)	1.43 (0.43)	597 (2.9)	9.7 (5.9 to 12.0)	960	872	0	0	1996

Supplementary Table 1 (continued)

Country	Cohort	No of partici-pants	Ages Mean (SD)	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean(SD)	Total cholesterol (mmol/L) Mean (SD)	HDL cholesterol (mmol/L) Mean (SD)	Diabetes n (%)	Median follow up (5th and 95th percentile)	CVD	CVD before 10-years	other death	Other death before 10 years	Median year of study recruitment
UK	HCS	2707	66 (3)	1356 (50)	369 (14)	133 (19)	6.3 (1.1)	1.54 (0.42)	350 (12.9)	8.9 (5.6 to 11.6)	62*	57*	205	198	2001
UK	LEADER	427	67 (8)	427 (100)	168 (39)	149 (22)	5.7 (0.9)	1.22 (0.39)	64 (15.0)	4.3 (1.0 to 6.8)	76	76	36	36	1997
UK	MIDFAM	1826	47 (5)	801 (44)	453 (25)	128 (16)	5.4 (1.0)	1.42 (0.37)	25 (1.4)	17.4 (9.6 to 17.8)	97	46	98	46	1996
UK	UKB	431965	56 (8)	192334 (45)	45305 (10)	138 (19)	5.8 (1.1)	1.46 (0.38)	18452 (4.3)	10.8 (7.8 to 12.4)	13778	11939	15947	13637	2009
UK	WHITEI	3137	75 (3)	3137 (100)	427 (14)	145 (20)	5.6 (1.0)	1.11 (0.38)	142 (4.5)	12.9 (2.5 to 13.3)	529*	368*	930	660	1997
UK	WHITEII	8621	50 (6)	5907 (69)	1636 (19)	121 (14)	6.5 (1.2)	1.44 (0.41)	148 (1.7)	12.2 (3.9 to 13.0)	323	323	280	280	1992
UK	WOSCOPS	3293	55 (6)	3293 (100)	1460 (44)	136 (17)	7.0 (0.6)	1.14 (0.25)	35 (1.1)	4.8 (2.5 to 6.0)	300	300	59	59	1990
Subtotal (Europe)		**605403**	**57 (9)**	**273892 (45)**	**90345 (15)**	**137 (19)**	**5.8 (1.1)**	**1.45 (0.39)**	**26090 (4.3)**	**10.6 (5.0 to 13.0)**	**22748**	**18916**	**26166**	**21150**	
Americas															
Canada	NSHS	1146	57 (11)	552 (48)	295 (26)	129 (17)	5.6 (1.0)	1.29 (0.37)	70 (6.1)	9.7 (4.3 to 10.0)	51	51	96	96	1995
USA	ARIC	12006	57 (6)	5365 (45)	2927 (24)	121 (19)	5.4 (1.0)	1.29 (0.43)	1771 (14.8)	25.3 (4.3 to 27.6)	2798	2798	3126	3126	1991
USA	CHS1	3380	71 (4)	1250 (37)	433 (13)	135 (21)	5.5 (1.0)	1.44 (0.41)	434 (12.8)	12.2 (2.4 to 12.9)	893	674	619	449	1989
USA	CHS2	414	71 (4)	155 (37)	70 (17)	142 (24)	5.4 (1.0)	1.49 (0.40)	96 (23.2)	9.1 (1.9 to 9.5)	83	83	49	49	1993
USA	HONOL	1877	76 (2)	1877 (100)	152 (8)	148 (22)	5.0 (0.8)	1.33 (0.34)	485 (25.8)	6.3 (1.5 to 7.6)	204	204	255	255	1992
USA	MESA	6515	61 (10)	3082 (47)	1008 (15)	126 (21)	5.0 (0.9)	1.32 (0.38)	814 (12.5)	15.7 (2.8 to 17.1)	504	310	467	251	2001
USA	NHANESIII	8242	58 (12)	3838 (47)	2208 (27)	132 (20)	5.6 (1.1)	1.33 (0.41)	860 (10.4)	18.4 (3.8 to 22.4)	1143*	519*	2248	843	1990
USA	USPHS2	10724	64 (8)	10724 (100)	507 (5)	128 (12)	5.3 (0.9)	1.15 (0.38)	25 (0.2)	10.9 (4.9 to 11.5)	645	634	690	626	1997
USA	WHS	27977	55 (7)	0 (0)	3266 (12)	127 (12)	5.5 (1.1)	1.39 (0.39)	768 (2.7)	19.1 (8.9 to 20.0)	1052	560	93	36	1994
Subtotal (Americas)		**72281**	**59 (9)**	**26843 (37)**	**10866 (15)**	**128 (17)**	**5.4 (1.0)**	**1.32 (0.41)**	**5323 (7.4)**	**17.1 (4.6 to 26.2)**	**7373**	**5833**	**7643**	**5731**	
TOTAL		**677684**	**57 (9)**	**300735 (44)**	**101211 (15)**	**136 (19)**	**5.8 (1.1)**	**1.44 (0.40)**	**31413 (4.6)**	**10.7 (5.0 to 18.6)**	**30121**	**24749**	**33809**	**26881**	

*CVD events include only fatal events

Supplementary Table 2: Summary of data sources for derivation of the multiplication factors

Risk region	Country	Data source	Number of participants	Ages Mean (SD)	Men n (%)	Median follow-up years (IQR)	CV events	Median year of study recruitment
Low	United Kingdom	CPRD	2,589,074	53.2 (13.8)	1,293,091 (49%)	7.5 (3.4-11.0)	119,656	2004
Moderate	Sweden	Swedish Population data*	5,344,076	57.9 (14.7)	2,598,559 (48%)	10.0 (10.0-10.0)	588,148	2009
Moderate	Finland	Finnish CVD Register	2,766,988	59.5 (11.7)	1,338,807 (48%)	N/A**	16,511	2015**
High	Estonia	Estonian Biobank	67,471	55.16 (10.8)	21433 (31.8%)	0.76 (0.21-8.87)	5780	2018
High	Czech Republic	HAPIEE	8,857	57.7 (8.9)	4123 (47%)	15.1 (14.2-15.8)	1170	2003

*endpoints were obtained through linkage to the Swedish National Inpatient Register and Swedish cause of death registry
**Annual rates were averaged over a three year period (2014-2016) and extrapolated to estimates 10-year risks (see Supplementary methods)

Supplementary Table 3: Summary of registry data used to check derived incidence
Registry data sources (all from year 2018):

	Country	Source	Reference	ICD codes included in endpoint
Mortality data	The Netherlands	CBS statistics Netherlands	https://www.volksgezondheidenzorg.info/	I0-99
	Denmark	Hjerteforeningen	https://hjerteforeningen.dk/	I0-99
	United Kingdom	Office of National Statistics	https://www.nomisweb.co.uk/	I0-99
	Germany	Destatis	https://www-genesis.destatis.de/	I0-99
	Spain	National Institute of Statistics	https://www.ine.es	I10:16, 20:25 46:52, 60:69; 70:73; R96
Incidence data	The Netherlands	Dutch Hospital Data	https://www.dhd.nl/	I21; I60-69
	Denmark	Hjerteforeningen	https://hjerteforeningen.dk/	I21-22; I60-69
	United Kingdom	British Heart Foundation	https://www.bhf.org.uk/	I21; I60-69
	Germany	Destatis	https://www-genesis.destatis.de/	I21-23; I60-69
	Spain	National Institute of Statistics	https://www.ine.es	I21-23; I6-69

Supplementary Table 4: Summary of available data in cohorts used for external validation

Data sources	Country	Cohort	Risk region	No of participants	Ages Mean (SD)	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean (SD)	Total cholesterol (mmol/L) Mean (SD)	HDL cholesterol (mmol/L) Mean (SD)	Median follow-up years (IQR)	CVD events*	Median year of study recruitment
MORGAM/ BIOMARCARE	Denmark	DanMONICA I	Low	1970	51.1 (8.1)	959 (49)	1027 (52)	126 (18)	6.1 (1.1)	1.4 (0.4)	16.6 (16.1-17.1)	205	1994
MORGAM/ BIOMARCARE	Denmark	DanMONICA III	Low	979	53.4 (8.5)	484 (49)	496 (51)	127 (18)	6.1 (1.1)	1.5 (0.4)	19.3 (16.1-19.6)	159	1991
EPIC-CVD	Denmark	EPIC-CVD	Low	5436	58 (4)	3287 (60)	2415 (44)	145 (22)	6.2 (1.2)	1.36 (0.45)	10.4 (5.9 to 13)	3545	1996
EPIC-CVD	France	EPIC-CVD	Low	599	56 (6)	0 (0)	56 (9)	125 (18)	6.0 (1.0)	1.84 (0.41)	10.5 (9.7 to 11)	36	1997
HUNT	Norway	HUNT	Low	31473	53.1 (8.5)	14793 (47)	10270 (33)	138 (20)	6.2 (1.2)	1.4 (0.4)	22.1 (19.1-22.8)	5630	1996
MORGAM/ BIOMARCARE	Norway	Tromso 1994-1995	Low	12919	51.6 (8.1)	6162 (48)	4985 (39)	138 (19)	6.3 (1.2)	1.5 (0.4)	15.8 (14.2-16.1)	1352	1995
MORGAM/ BIOMARCARE	Spain	MONICA-Catalonia II	Low	1605	52.2 (7.1)	1030 (64)	591 (37)	123 (19)	5.7 (1.0)	1.3 (0.4)	7.6 (7.2-8.0)	60	1991
EPIC-CVD	Spain	EPIC-CVD	Low	2490	52 (7)	1171 (47)	712 (29)	131 (20)	6.0 (1.1)	1.44 (0.38)	14.5 (13.5 to 16)	648	1994
EPIC-CVD	The Netherlands	EPIC-CVD	Low	1145	52 (6)	680 (59)	474 (41)	130 (19)	6.5 (1.2)	1.33 (0.39)	11.6 (9.1 to 13)	375	1995
MORGAM/ BIOMARCARE	United Kingdom	SHHEC	Low	1608	53.5 (8.1)	754 (47)	717 (45)	134 (22)	6.2 (1.1)	1.4 (0.4)	14.6 (14.3-17.5)	173	1995
CPRD	United Kingdom	CPRD	Low	978,752	53.0 (8.3)	483350 (49)	462842 (47)	132 (16)	5.5 (1.1)	1.5 (0.4)	7.5 (3.4-11.0)	21,443	2006
EPIC-CVD	United Kingdom	EPIC-CVD	Low	1010	57 (8)	370 (37)	158 (16)	135 (20)	6.2 (1.2)	1.48 (0.44)	12.5 (10.9 to 13)	308	1996
MORGAM/ BIOMARCARE	Finland	FINRISK 1992	Moderate	2702	51.0 (7.1)	1241 (46)	725 (27)	137 (19)	5.8 (1.1)	1.4 (0.4)	18.8 (18.8-18.9)	252	1992
MORGAM/ BIOMARCARE	Finland	FINRISK 1997	Moderate	3590	52.7 (8.4)	1742 (49)	961 (27)	136 (19)	5.7 (1.0)	1.4 (0.4)	13.8 (13.8-13.9)	231	1997
MORGAM/ BIOMARCARE	Finland	FINRISK 2002	Moderate	4997	53.1 (7.8)	2313 (46)	1347 (27)	138 (20)	5.8 (1.0)	1.5 (0.4)	8.8 (8.8-8.9)	126	2002
DETECT	Germany	DETECT	Moderate	3518	54.7 (8.7)	1355 (39)	819 (23)	130 (17)	5.9 (1.1)	1.5 (0.5)	3.8 (1.0-4.0)	40	2003
GHS	Germany	GHS	Moderate	9509	53.7 (8.5)	4565 (48)	1954 (21)	130 (17)	5.8 (1.0)	1.5 (0.4)	5.0 (5.0-5.0)	187	2009

Supplementary Table 4 (continued)

Data sources	Country	Cohort	Risk region	No of participants	Ages Mean (SD)	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean (SD)	Total cholesterol (mmol/L) Mean (SD)	HDL cholesterol (mmol/L) Mean (SD)	Median follow-up years (IQR)	CVD events*	Median year of study recruitment
MORGAM/ BIOMARCARE	Germany	MONICA/KORA S3	Moderate	2256	54.3 (8.3)	1119 (50)	584 (26)	136 (20)	6.1 (1.1)	1.4 (0.4)	14.0 (10.5-14.3)	145	1995
MORGAM/ BIOMARCARE	Germany	MONICA/KORA S4	Moderate	2006	54.0 (8.4)	959 (48)	449 (22)	131 (19)	6.1 (1.1)	1.5 (0.4)	8.7 (8.3-9.2)	81	2000
EPIC-CVD	Germany	EPIC-CVD	Moderate	2587	53 (7)	1420 (55)	669 (26)	134 (19)	6.1 (1.1)	1.42 (0.43)	8.6 (6.9 to 10)	910	1996
Heinz-Nixdorf Recall	Germany	Heinz-Nixdorf Recall	Moderate	3322	56.2 (6.6)	1525 (46)	817 (25)	130 (19)	6.0 (1.1)	1.5 (0.5)	13.6 (10.1-15.5)	178	2001
MORGAM/ BIOMARCARE	Italy	Moli-sani	Moderate	16594	53.2 (8.2)	7671 (46)	4198 (25)	139 (19)	5.6 (1.1)	1.5 (0.4)	4.2 (3.4-5.3)	115	2007
MORGAM/ BIOMARCARE	Italy	MONICA-Brianza III	Moderate	982	52.9 (7.4)	484 (49)	252 (26)	132 (20)	6.0 (1.1)	1.5 (0.4)	14.6 (14.2-14.9)	60	1994
MORGAM/ BIOMARCARE	Italy	PAMELA	Moderate	1250	54.5 (8.9)	612 (49)	362 (29)	135 (20)	6.0 (1.1)	1.5 (0.4)	11.3 (10.9-11.7)	54	1991
EPIC-CVD	Italy	EPIC-CVD	Moderate	2857	53 (7)	1180 (41)	859 (30)	134 (19)	6.1 (1.1)	1.42 (0.41)	11.1 (9.5 to 12)	700	1995
MORGAM/ BIOMARCARE	Sweden	N. Sweden 1990	Moderate	406	52.0 (6.9)	191 (47)	123 (30)	134 (19)	6.7 (1.2)	1.4 (0.4)	21.8 (19.0-21.9)	79	1990
MORGAM/ BIOMARCARE	Sweden	N. Sweden 1994	Moderate	498	53.8 (8.2)	237 (48)	159 (32)	134 (22)	6.5 (1.3)	1.4 (0.4)	17.8 (17.7-17.9)	62	1994
MORGAM/ BIOMARCARE	Sweden	N. Sweden 1999	Moderate	1023	54.1 (8.6)	504 (49)	260 (25)	135 (21)	6.1 (1.2)	1.5 (0.4)	12.8 (12.7-12.9)	93	1999
MORGAM/ BIOMARCARE	Sweden	N.Sweden 2004	Moderate	468	54.2 (8.4)	220 (47)	110 (24)	132 (19)	6.2 (1.2)	1.1 (0.3)	7.9 (7.8-7.9)	21	2004
EPIC-CVD	Sweden	EPIC-CVD	Moderate	5800	57 (7)	3086 (53)	1899 (33)	142 (20)	6.1 (1.2)	1.34 (0.41)	12.1 (7.2 to 14)	3560	1994
HAPIEE	Czech Republic	HAPIEE	High	6861	57.7 (8.9)	3093 (47)	1700 (27)	139 (20)	5.1 (1.0)	1.4 (0.4)	15.1 (14.2-15.8)	763	2003
Estonian Biobank	Estonia	Estonian Biobank	High	2167	50.0 (7.4)	736 (32)	758 (33)	123 (13)	6.1 (1.1)	1.7 (0.5)	10.8 (9.8-11.1)	157	2008
HAPIEE	Poland	HAPIEE	High	7530	57.2 (7.0)	3581 (48)	2539 (34)	138 (22)	5.8 (1.1)	1.4 (0.4)	13.7 (13.5-14.4)	435	2003
HAPIEE	Lithuania	HAPIEE	Very high	5076	60.4 (7.6)	2309 (45)	1127 (22)	140 (22)	6.0 (1.1)	1.5 (0.4)	9.5 (8.9-10.1)	535	2006
HAPIEE	Russia	HAPIEE	Very high	7196	57.7 (7.1)	3182 (44)	2109 (29)	143 (25)	6.3 (1.3)	1.5 (0.5)	9.4 (6.7-13.3)	774	2003

* Also includes cases outside the sub-cohort; relevant for EPIC-CVD only which follows a case-cohort design

*Individuals with diabetes were excluded from the validation dataset since SCORE2 is not proposed for use in individuals with diabetes

Suppementary Table 5: Endpoint definitions

Fatal cardiovascular disease– cause specific mortality due to any of the following:		
Endpoints included	*ICD10-codes*	*ICD9-codes*
Hypertensive disease	I10-16	401 – 405
Ischemic heart disease	I20-25	410 - 414
Arrhythmias, heart failure	I46-52	426 - 429
Cerebrovascular disease	I60-69	430 - 438
Atherosclerosis/AAA	I70-73	440 - 443
Sudden death and death within 24h of symptom onset	R96.0-96.1	798.1 , 798.2
Endpoints excluded from the above endpoint:		
Myocarditis, unspecified	I51.4	426.7
Subarachnoid haemorrhage	I60	429
Subdural haemorrhage	I62	430
Cerebral aneurysm	I67.1	432.1
Cerebral arteritis	I68.2	437.3
Moyamoya	I67.5	437.4
Non-fatal cardiovascular disease		
Non-fatal myocardial infarction	I21-I23	*410*
Non-fatal stroke	I60-69	*430-438*
Excluded from the non-fatal stroke endpoint:		
Subarachnoid hemorrhage	I60	429
Subdural hemorrhage	I62	430
Cerebral aneurysm	I67.1	432.1
Cerebral arteritis	I68.2	437.3
Moyamoya	I67.5	437.4

Supplementary Table 6: Age- and sex- standardized WHO CVD mortality rates per country

Country	Age and sex standardised CVD mortality per 100 000 person years, ICD chapter 9	Year collected
Low risk region		
France	70.9	2014
Israel	76.7	2015
Spain	89.4	2015
Netherlands	89.9	2016
Switzerland	90.2	2015
Denmark	90.4	2015
Norway	90.8	2015
Luxembourg	92.9	2015
Belgium	99.2	2015
United Kingdom	99.7	2015
Moderate risk region		
Iceland	101.0	2016
Portugal	107.9	2014
Sweden	109.0	2016
Italy	110.1	2015
San Marino	-	
Ireland	111.5	2014
Cyprus	111.5	2016
Finland	128.5	2015
Austria	130.9	2016
Malta	133.3	2015
Greece	138.8	2015
Germany	139.0	2015
Slovenia	143.3	2015
High risk region		
Albania	184.5	2010
Czech Republic	195.0	2016
Turkey	199.5	2015
Kazakhstan	214.0	2015
Croatia	214.6	2016
Poland	223.8	2015
Estonia	234.8	2015
Slovakia	239.2	2014
Hungary	274.1	2016
Bosnia and Herzegovina	279.2	2014
Very high risk region		
Armenia	306.3	2016
Lithuania	309.0	2016
Georgia	309.6	2015
Latvia	327.2	2015
Serbia	329.1	2015
Romania	330.5	2016
Montenegro	348.4	2009
Russian Federation	368.8	2015
TFYR Macedonia	387.8	2013
Belarus	395.4	2014
Azerbaijan	416.5	2007
Bulgaria	421.2	2014
Republic of Moldova	442.2	2016
Ukraine	476.7	2015
Kyrgyzstan	476.9	2015
Uzbekistan	478.6	2014
Egypt	543.7	2015
Morocco	-	
Syria	-	
Tunisia	-	
Lebanon	-	
Algeria	-	
Libya	-	

Countries without available population or incidence data in the WHO database (indicated by -) were grouped using rates available from neighbouring countries.

Supplementary Table 7: Summary of subdistribution hazard ratios for predictor variables in the SCORE2 risk models

	Men (292710 participants, 16339 CVD cases)		Women (370957 participants, 11072 CVD cases)	
	Main effect	**Age interaction term**	**Main effect**	**Age interaction term**
Age (per 5 years)	1.45 (1.43, 1.48)	-	1.59 (1.56, 1.62)	-
Current smoking	1.82 (1.76, 1.89)	0.93 (0.91, 0.95)	2.17 (2.07, 2.27)	0.90 (0.87, 0.92)
SBP (per 20mmHg)	1.32 (1.30, 1.34)	0.98 (0.97, 0.98)	1.37 (1.34, 1.39)	0.97 (0.96, 0.98)
Total cholesterol (per 1 mmol/L)	1.16 (1.14, 1.17)	0.97 (0.96, 0.98)	1.11 (1.09, 1.12)	0.98 (0.97, 0.99)
HDL cholesterol (per 0.5 mmol/L)	0.76 (0.74, 0.78)	1.04 (1.03, 1.06)	0.77 (0.75, 0.79)	1.06 (1.05, 1.08)
History of diabetes mellitus*	1.91 (1.81, 2.01)	0.91 (0.88, 0.93)	2.25 (2.11, 2.40)	0.88 (0.85, 0.91)

Sex-specific subdistribution hazard ratios (SHR) from Fine and Gray models predicting the risk of fatal and non-fatal CVD events as derived in the ERFC and UK Biobank. Age was centered at 60 years, systolic blood pressure at 120 mmHg, total cholesterol at 6 mmol/L, and HDL cholesterol at 1.3 mmol/L. The median baseline survival at 10 years in the derivation cohorts was 0.9605 for men and 0.9776 for women.

These SHRs are relevant for risk estimation only and have not real eatiological interpretation. Log(SHRs) are shown in supplementary methods Table 2 with sufficient precision for risk estimation.

*Diabetes mellitus was included in the modelling since this was necessary for the recalibration approach, which relies data from the whole population, including those with diabetes. However, SCORE2 is not intended for use in individuals with diabetes and has not been validated in this population. For risk prediction in the target population of individuals without diabetes this risk factor will always be 0, meaning the coefficient can effectively be ignored.

Supplementary Table 8: Model derivation sensitivity analyses

	Complete population		Excluding UK Biobank		Exlcuding cohorts that reported only fatal CVD events	
	Main effect	Age interaction term	Main effect	Age interaction term	Main effect	Age interaction term
Female coefficients						
Age (per 5 years)	1.59 (1.56, 1.62)	-	1.64 (1.60, 1.68)	-	1.57 (1.54, 1.60)	-
Current smoking	2.17 (2.07, 2.27)	0.90 (0.87, 0.92)	2.09 (1.98, 2.22)	0.89 (0.86, 0.92)	2.18 (2.08, 2.29)	0.89 (0.87, 0.92)
Systolic blood pressure (per 20mmHg)	1.37 (1.34, 1.39)	0.97 (0.96, 0.98)	1.39 (1.36, 1.43)	0.97 (0.96, 0.98)	1.37 (1.34, 1.39)	0.97 (0.96, 0.98)
Total cholesterol (per 1 mmol/L)	1.11 (1.09, 1.12)	0.98 (0.97, 0.99)	1.11 (1.09, 1.14)	0.98 (0.97, 0.99)	1.11 (1.09, 1.13)	0.98 (0.97, 0.99)
HDL cholesterol (per 0.5 mmol/L)	0.77 (0.75, 0.79)	1.06 (1.05, 1.08)	0.81 (0.78, 0.84)	1.06 (1.04, 1.07)	0.76 (0.74, 0.78)	1.06 (1.04, 1.07)
History of diabetes	2.25 (2.11, 2.40)	0.88 (0.85, 0.91)	2.21 (2.05, 2.40)	0.89 (0.85, 0.92)	2.26 (2.12, 2.42)	0.87 (0.83, 0.90)
Male coefficients						
Age (per 5 years)	1.45 (1.43, 1.48)	-	1.50 (1.47, 1.53)	-	1.43 (1.40, 1.45)	-
Current smoking	1.82 (1.76, 1.89)	0.93 (0.91, 0.95)	1.77 (1.69, 1.86)	0.92 (0.90, 0.94)	1.81 (1.74, 1.88)	0.92 (0.90, 0.94)
Systolic blood pressure (per 20mmHg)	1.32 (1.30, 1.34)	0.98 (0.97, 0.98)	1.33 (1.30, 1.37)	0.98 (0.97, 0.99)	1.31 (1.29, 1.34)	0.98 (0.97, 0.98)
Total cholesterol (per 1 mmol/L)	1.16 (1.14, 1.17)	0.97 (0.96, 0.98)	1.13 (1.11, 1.15)	0.98 (0.97, 0.99)	1.18 (1.17, 1.20)	0.97 (0.97, 0.98)
HDL cholesterol (per 0.5 mmol/L)	0.76 (0.74, 0.78)	1.04 (1.03, 1.06)	0.80 (0.78, 0.83)	1.04 (1.02, 1.06)	0.75 (0.73, 0.77)	1.04 (1.02, 1.06)
History of diabetes	1.91 (1.81, 2.01)	0.91 (0.88, 0.93)	1.87 (1.74, 2.02)	0.90 (0.87, 0.94)	1.92 (1.82, 2.02)	0.89 (0.87, 0.92)

Supplementary Table 9: Subdistribution hazard ratios in MORGAM/BiomarCaRE consortium

	SCORE derivation population		MORGAM/BiomarCaRE	
	Main effect	Age interaction term	Main effect	Age interaction term
Female coefficients				
Age (per 5 years)	1.59 (1.56, 1.62)	-	1.61 (1.51, 1.71)	-
Current smoking	2.17 (2.07, 2.27)	0.90 (0.87, 0.92)	1.93 (1.69, 2.21)	0.85 (0.80, 0.91)
Systolic blood pressure (per 20mmHg)	1.37 (1.34, 1.39)	0.97 (0.96, 0.98)	1.40 (1.33, 1.48)	0.94 (0.91, 0.96)
Total cholesterol (per 1 mmol/L)	1.11 (1.09, 1.12)	0.98 (0.97, 0.99)	1.16 (1.10, 1.22)	0.95 (0.92, 0.97)
HDL cholesterol (per 0.5 mmol/L)	0.77 (0.75, 0.79)	1.06 (1.05, 1.08)	0.77 (0.71, 0.83)	1.04 (1.00, 1.08)
History of diabetes	2.25 (2.11, 2.40)	0.88 (0.85, 0.91)	2.03 (1.60, 2.57)	0.87 (0.78, 0.98)
Male coefficients				
Age (per 5 years)	1.45 (1.43, 1.48)	-	1.40 (1.34, 1.46)	-
Current smoking	1.82 (1.76, 1.89)	0.93 (0.91, 0.95)	1.45 (1.32, 1.59)	0.89 (0.85, 0.93)
Systolic blood pressure (per 20mmHg)	1.32 (1.30, 1.34)	0.98 (0.97, 0.98)	1.36 (1.30, 1.41)	0.95 (0.93, 0.97)
Total cholesterol (per 1 mmol/L)	1.16 (1.14, 1.17)	0.97 (0.96, 0.98)	1.25 (1.21, 1.30)	0.99 (0.98, 1.01)
HDL cholesterol (per 0.5 mmol/L)	0.76 (0.74, 0.78)	1.04 (1.03, 1.06)	0.68 (0.64, 0.73)	1.03 (1.00, 1.07)
History of diabetes	1.91 (1.81, 2.01)	0.91 (0.88, 0.93)	1.88 (1.60, 2.21)	0.87 (0.80, 0.95)

Supplementary Table 10: Multiplication factors by age and sex

Age-group	Low/moderate risk region		High/very high risk region	
	Men	Women	Men	Women
45-50	7.5	11.3	3.1	5.0
50-55	5.7	8.0	2.5	4.3
55-60	4.3	5.9	2.2	3.7
60-65	3.3	4.2	1.9	3.1
65-70	2.6	3.2	1.6	2.5
70-75	2.1	2.5	1.4	1.9
75-80	1.6	1.9	1.3	1.5
80-85	1.3	1.5	1.1	1.4
85+	1.1	1.1	0.9	1.0

Multiplication factors for the SCORE2 model specific for each agegroup, sex and region. Multiplication factors were defined as the ratio between the cumulative incidence of fatal CVD and the cumulative incidence of CVD events. Multipliers were used to multiply observed CVD mortality rates in the agegroup stated in this table and are therefore used to recalibrate 10-year risks in one agegroup below.

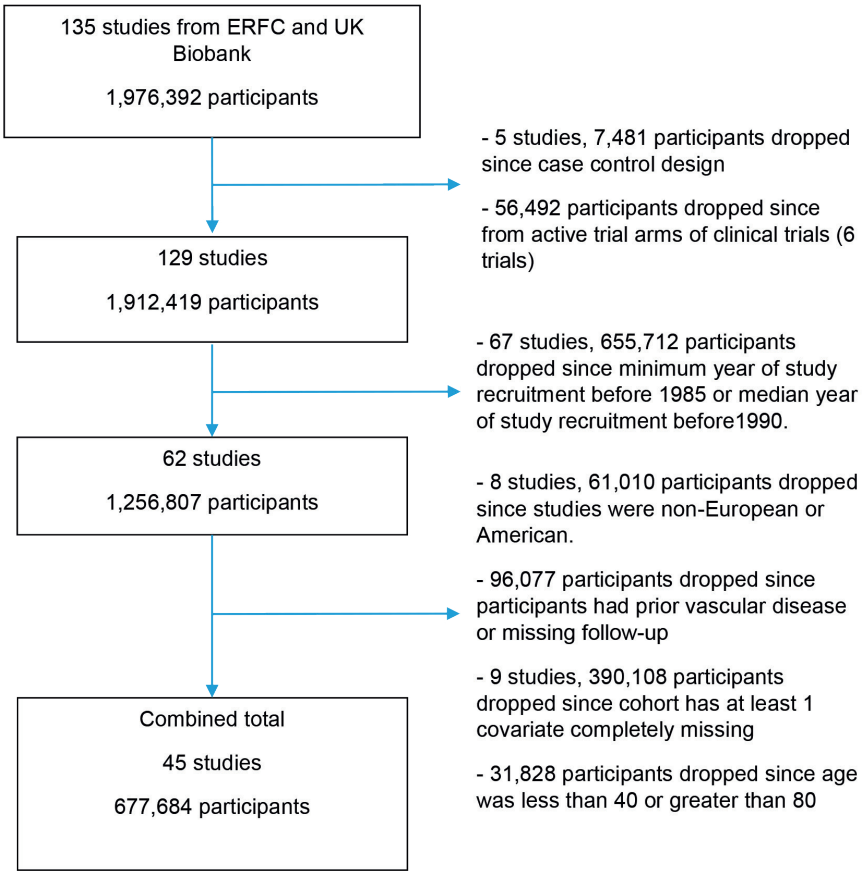
Supplementary Table 11: Comparison of the discrimination of SCORE and SCORE2 in CPRD dataset

Population size: n = 927,079	Algorithm		
	SCORE	SCORE2	Difference: SCORE2-SCORE
All ages			
C-statistic fatal+nonfatal CVD events (SCORE2 endpoint)	0.7103 (0.7069, 0.7138)	0.7203 (0.7170, 0.7237)	0.0100 (0.0085, 0.0115)
C-statistic first CVD events: fatal	0.7853 (0.7771, 0.7934)	0.7850 (0.7767, 0.7933)	-0.0003 (-0.0040, 0.0035)
C-statistic first CVD events: non-fatal	0.7005 (0.6968, 0.7042)	0.7118 (0.7083, 0.7154)	0.0113 (0.0097, 0.0130)
Ages 40-50			
C-statistic fatal+nonfatal CVD events (SCORE2 endpoint)	0.6761 (0.6676, 0.6846)	0.6975 (0.6892, 0.7058)	0.0213 (0.0162, 0.0265)
C-statistic first CVD events: fatal	0.7113 (0.6757, 0.7470)	0.7274 (0.6911, 0.7638)	0.0161 (-0.0083, 0.0406)
C-statistic first CVD events: non-fatal	0.6742 (0.6655, 0.6830)	0.6959 (0.6874, 0.7044)	0.0216 (0.0164, 0.0269)
Ages 50-59			
C-statistic fatal+nonfatal CVD events (SCORE2 endpoint)	0.6359 (0.6293, 0.6424)	0.6529 (0.6465, 0.6594)	0.0170 (0.0138, 0.0203)
C-statistic first CVD events: fatal	0.6547 (0.6343, 0.6751)	0.6671 (0.6470, 0.6871)	0.0124 (0.0022, 0.0225)
C-statistic first CVD events: non-fatal	0.6338 (0.6269, 0.6408)	0.6514 (0.6446, 0.6582)	0.0176 (0.0141, 0.0210)
Ages 60-69			
C-statistic fatal+nonfatal CVD events (SCORE2 endpoint)	0.6094 (0.6036, 0.6152)	0.6196 (0.6139, 0.6254)	0.0102 (0.0078, 0.0126)
C-statistic first CVD events: fatal	0.6259 (0.6115, 0.6404)	0.6436 (0.6296, 0.6576)	0.0177 (0.0114, 0.0239)
C-statistic first CVD events: non-fatal	0.6064 (0.6001, 0.6127)	0.6153 (0.6090, 0.6215)	0.0089 (0.0063, 0.0115)

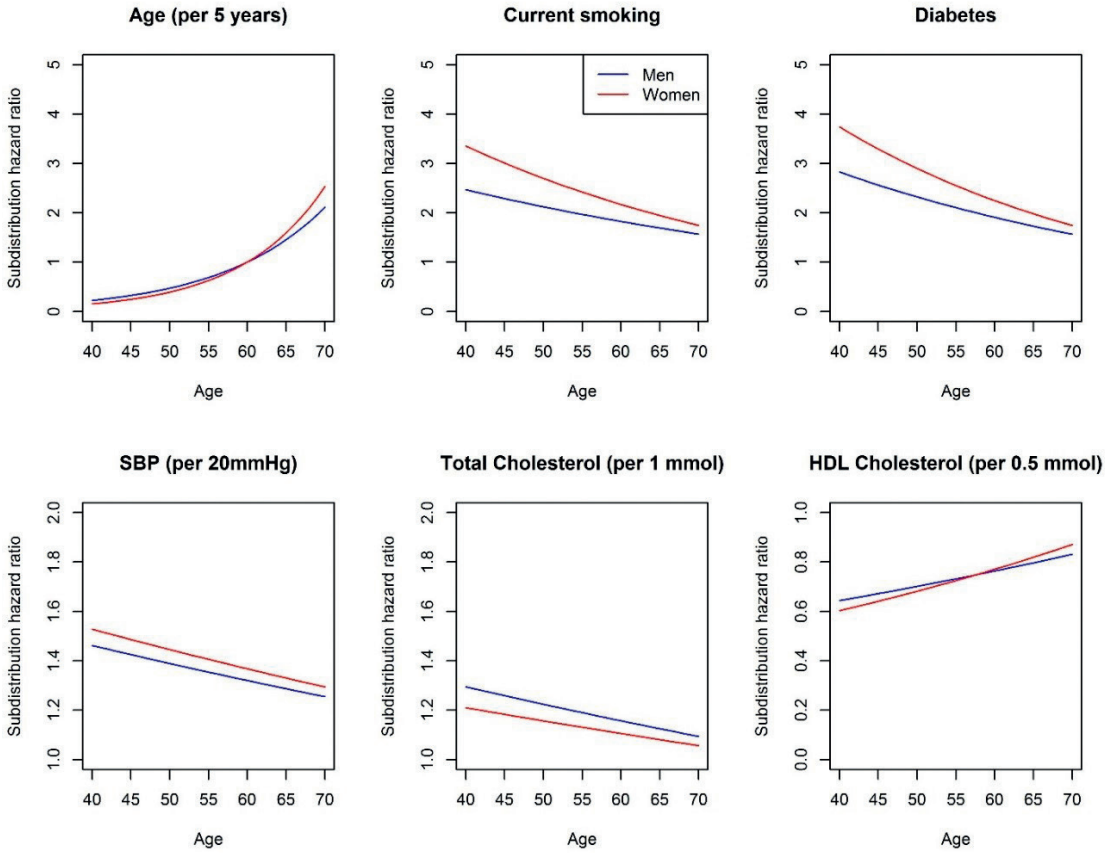
Supplementary Table 12: Comparison of the discrimination of SCORE and SCORE2 in CPRD dataset; sensitivity analysis using the AUROC at 10-years

Population size: n = 927,079	Algorithm		
	SCORE	SCORE2	Difference: SCORE2-SCORE
All ages			
AUROC fatal+nonfatal CVD events (SCORE2 endpoint)	0.7058 (0.7022, 0.7094)	0.7173 (0.7138, 0.7208)	0.0115 (0.0099, 0.0130)
AUROC first CVD events: fatal	0.7809 (0.7725, 0.7893)	0.7819 (0.7735, 0.7904)	0.0010 (-0.0028, 0.0048)
AUROC first CVD events: non-fatal	0.6957 (0.6918, 0.6995)	0.7085 (0.7048, 0.7123)	0.0129 (0.0112, 0.0145)
Ages 40-50			
AUROC fatal+nonfatal CVD events (SCORE2 endpoint)	0.6772 (0.6686, 0.6858)	0.6986 (0.6902, 0.7069)	0.0214 (0.0161, 0.0266)
AUROC first CVD events: fatal	0.7077 (0.6727, 0.7426)	0.7212 (0.6848, 0.7575)	0.0135 (-0.0121, 0.0391)
AUROC first CVD events: non-fatal	0.6755 (0.6666, 0.6843)	0.6973 (0.6887, 0.7059)	0.0218 (0.0164, 0.0272)
Ages 50-59			
AUROC fatal+nonfatal CVD events (SCORE2 endpoint)	0.6374 (0.6306, 0.6442)	0.6558 (0.6492, 0.6625)	0.0184 (0.0150, 0.0218)
AUROC first CVD events: fatal	0.6578 (0.6375, 0.6781)	0.6713 (0.6514, 0.6912)	0.0135 (0.0032, 0.0238)
AUROC first CVD events: non-fatal	0.6351 (0.6280, 0.6423)	0.6541 (0.6471, 0.6611)	0.0189 (0.0154, 0.0225)
Ages 60-69			
AUROC fatal+nonfatal CVD events (SCORE2 endpoint)	0.6112 (0.6051, 0.6173)	0.6208 (0.6148, 0.6269)	0.0097 (0.0071, 0.0122)
AUROC first CVD events: fatal	0.6305 (0.6160, 0.6451)	0.6471 (0.6329, 0.6612)	0.0165 (0.0102, 0.0228)
AUROC first CVD events: non-fatal	0.6076 (0.6010, 0.6142)	0.6160 (0.6094, 0.6225)	0.0084 (0.0057, 0.0111)

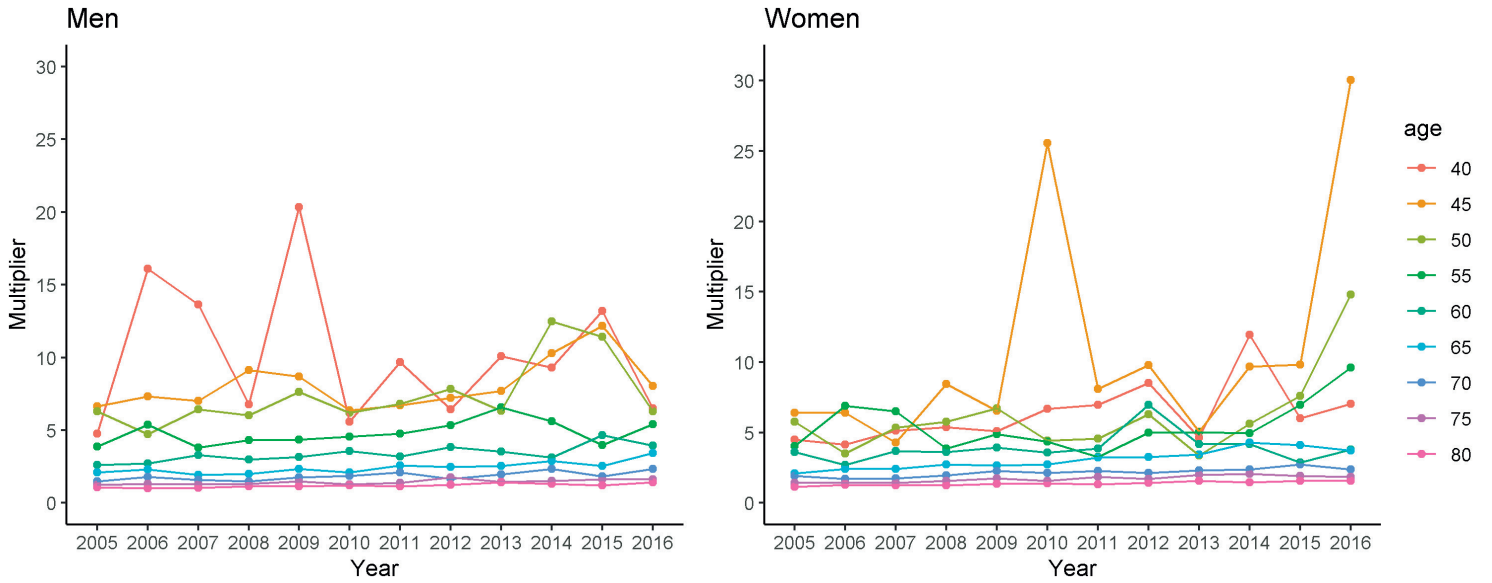
Supplementary Figure 1: Data selection for model derivation



Supplementary Figure 2: The relative effect of risk factors at different ages

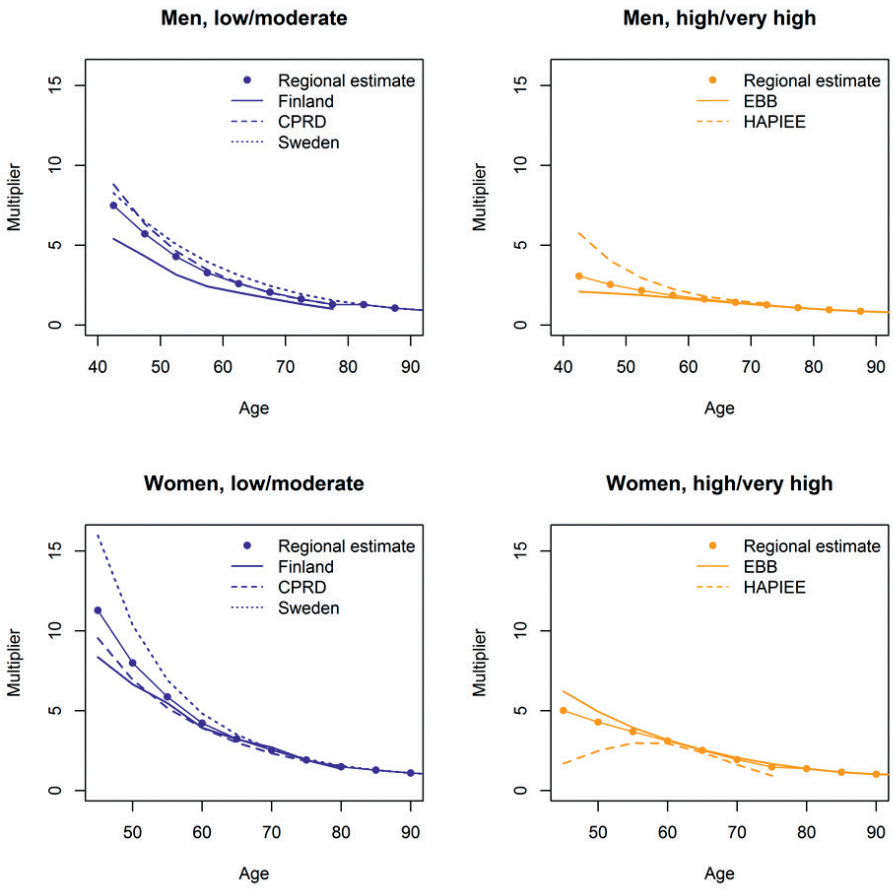


Supplementary Figure 3: Temporal differences in multiplication factors from CPRD



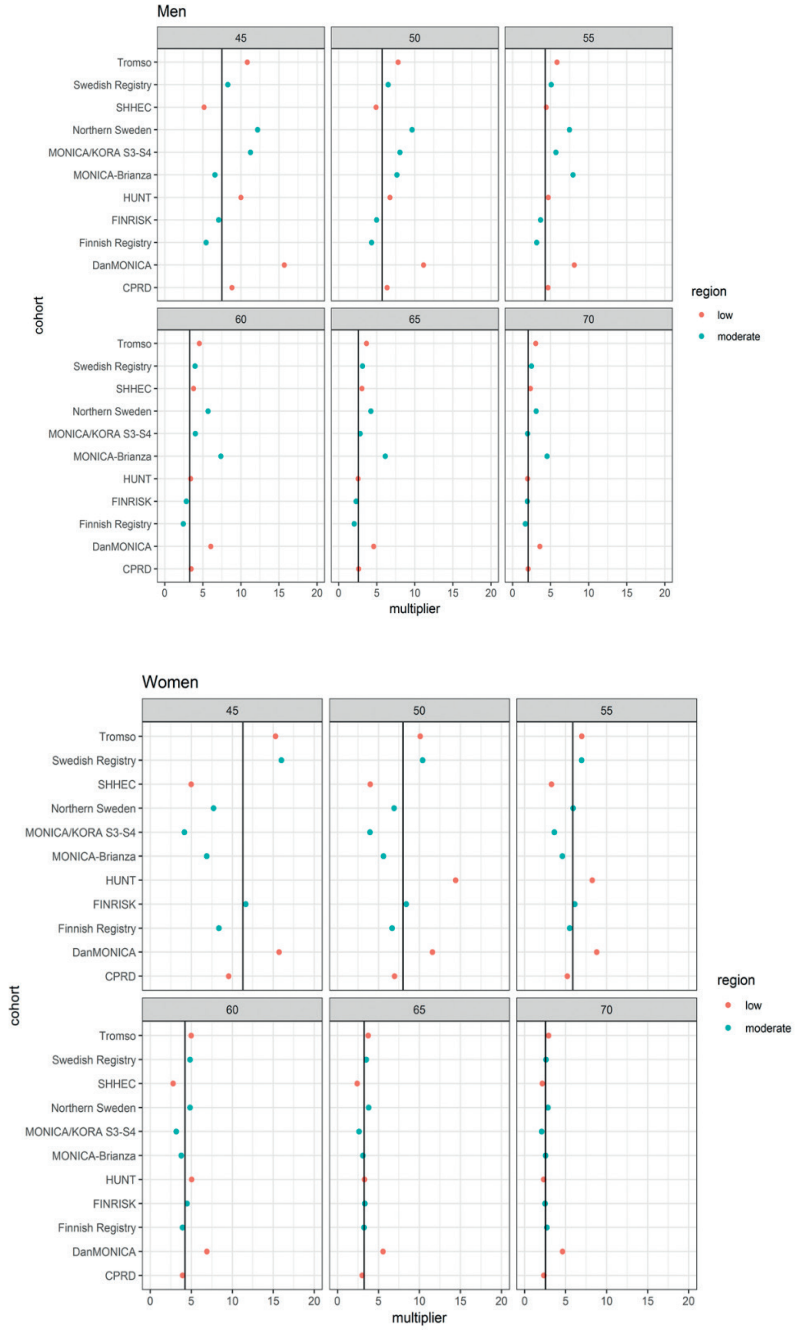
Multiplication factors in the low risk region, as calculated over single year intervals in CPRD, UK. Multiplication factors were defined as the ratio between the cumulative incidence of fatal CVD in the complete population and the cumulative incidence of CVD events in the population without prior CVD events.

Supplementary Figure 4: Aggregated and cohort-specific multiplication factors



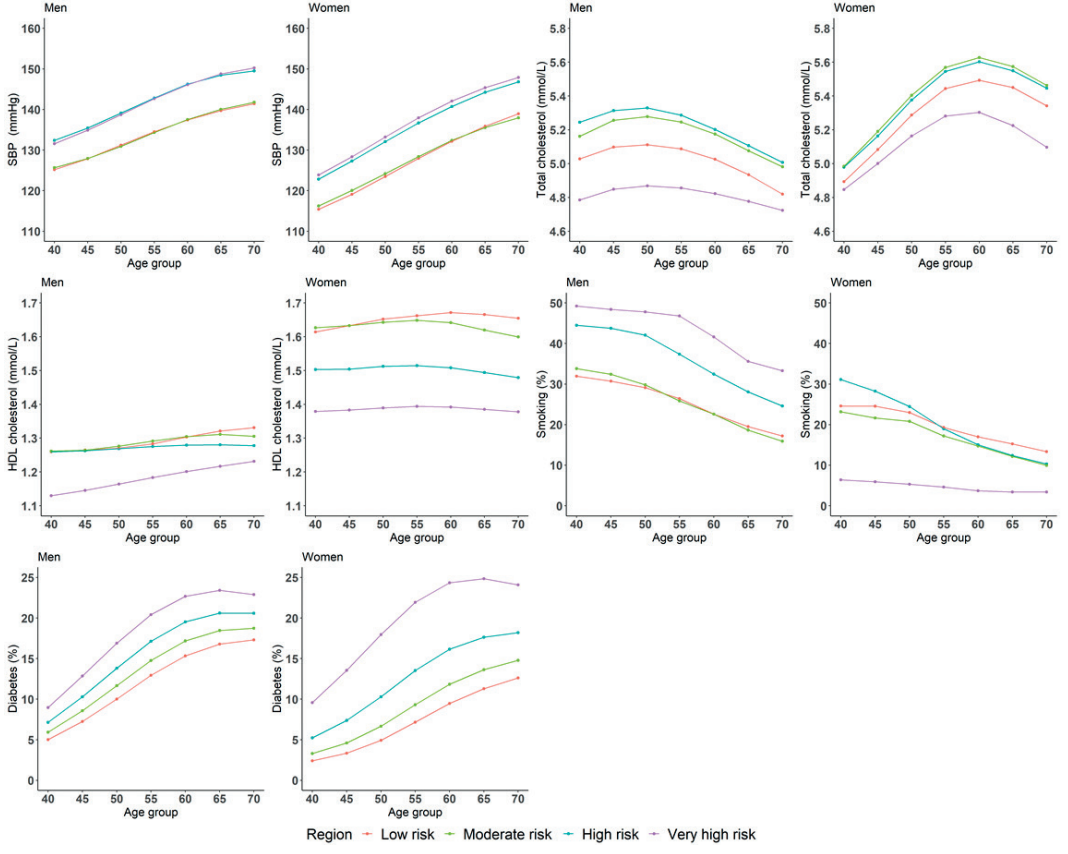
Multiplication factors as derived in all relevant cohorts. The regional estimate lines shows the final multiplication factors as used for the recalibration, a weighted mean of the regional cohort-specific estimates.

Supplementary Figure 5: Comparison of SCORE2 age and sex specific-multipliers with those estimated in several validation cohorts

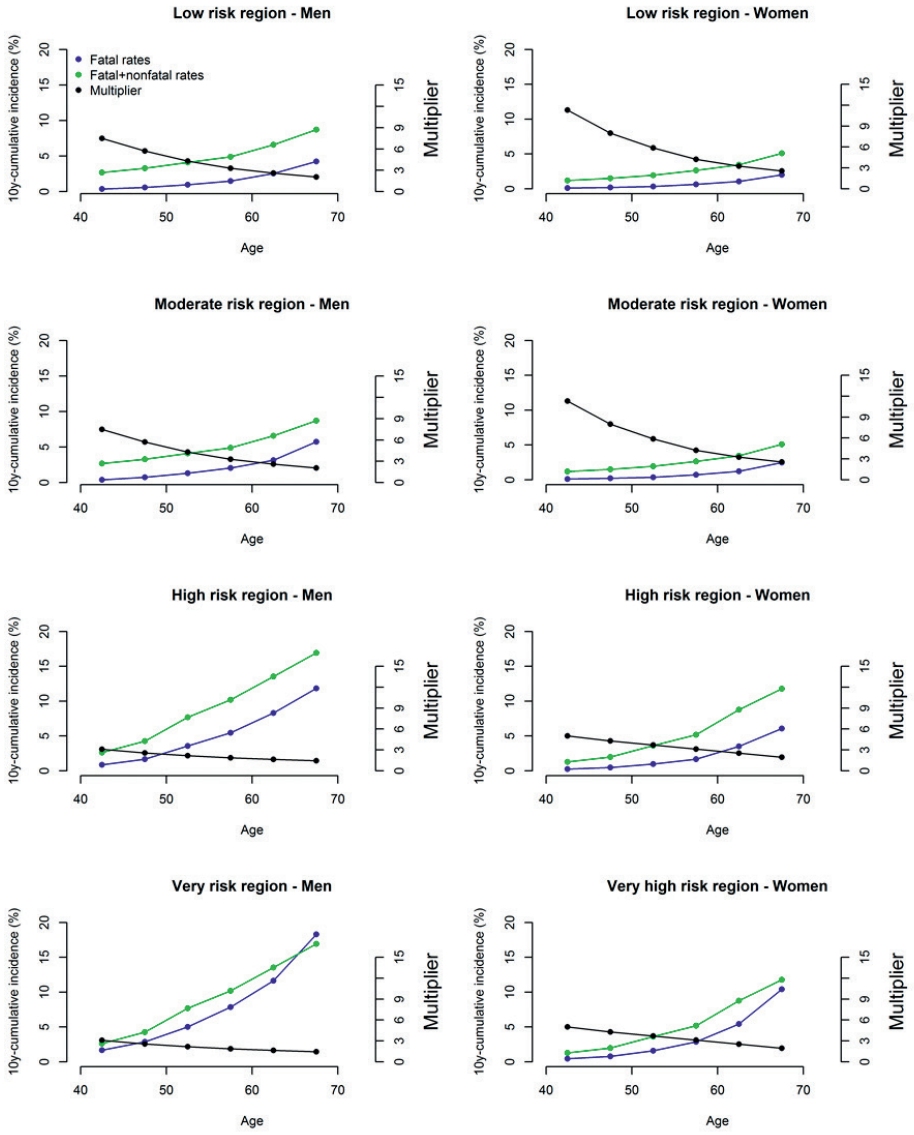


Verticle line indicates the pooled SCORE2 multiplier, as shown in Supplementary Figure 4 and Supplementary Table 9

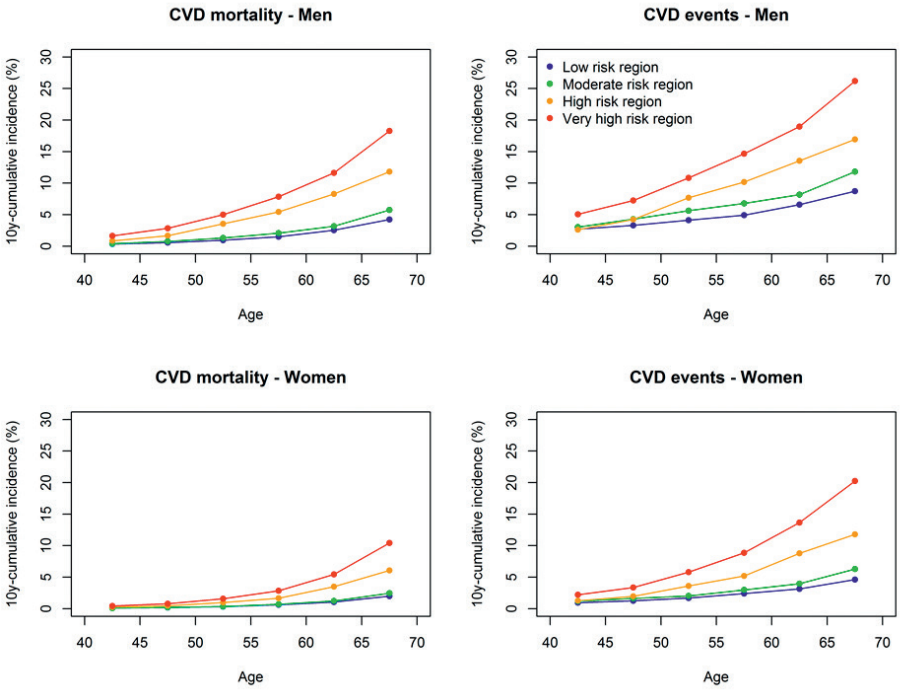
Supplementary Figure 6: Regional risk factor levels used for recalibration



Supplementary Figure 7: Cardiovascular mortality, derived incidence, and multipliers by risk region

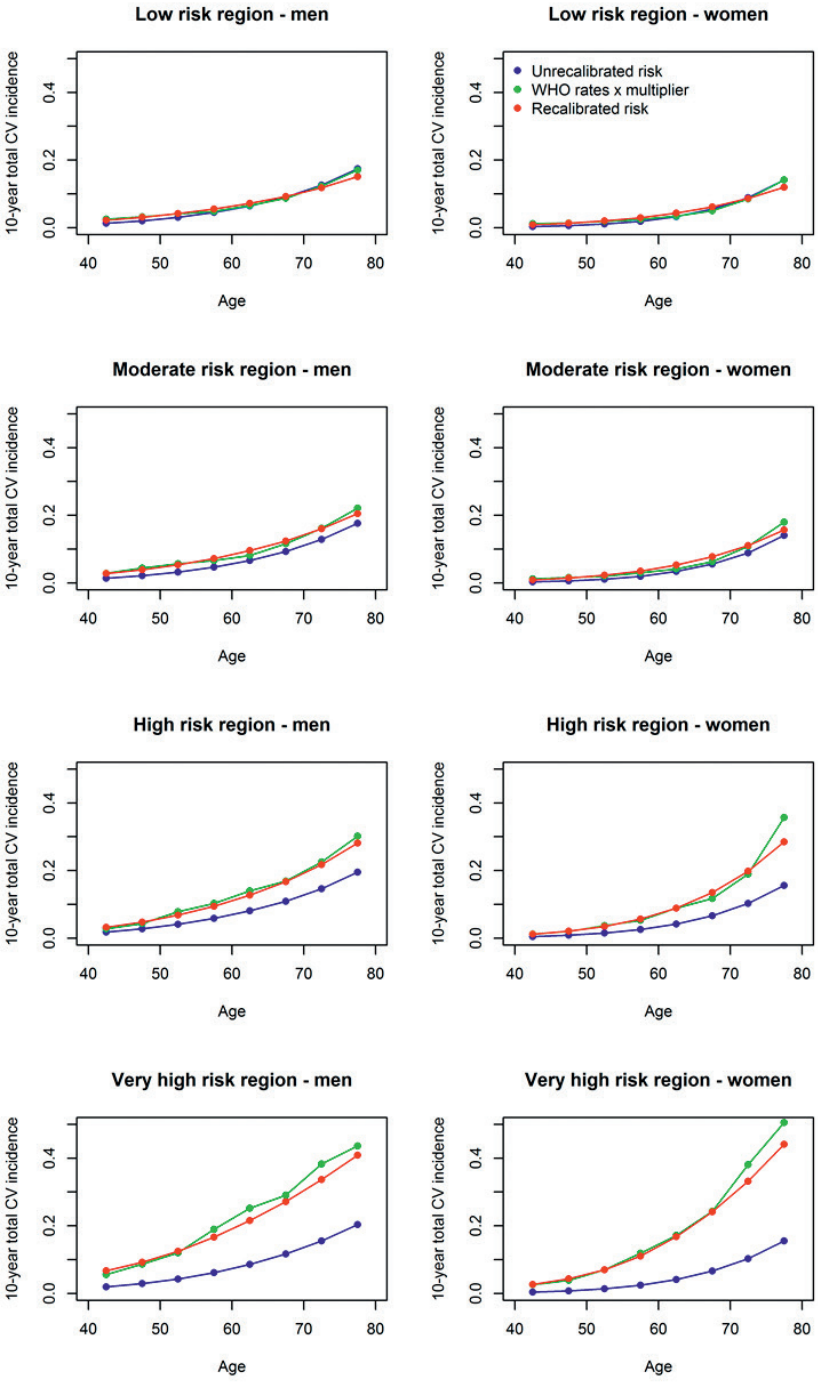


Supplementary Figure 8: Cardiovascular mortality and derived incidence in all risk regions

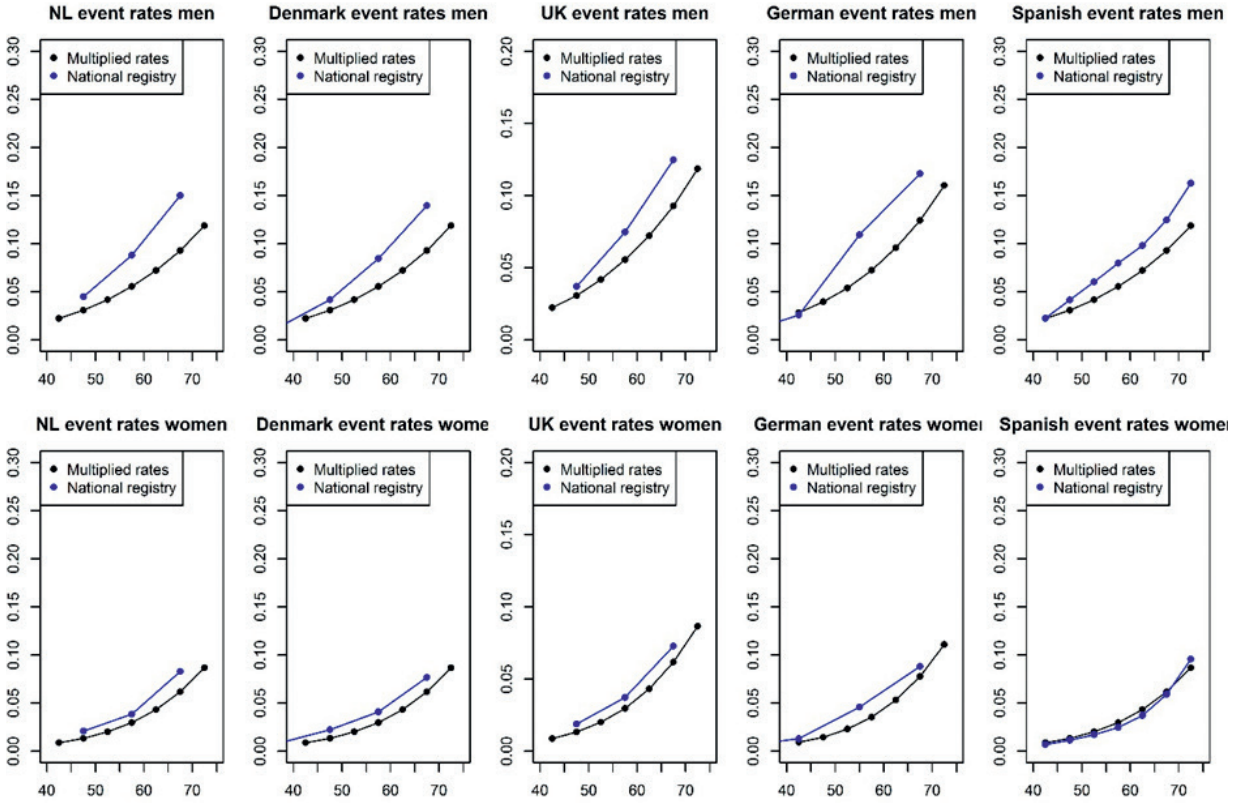


10-year cumulative incidences of cardiovascular mortality (left) and fatal or non-fatal cardiovascular events (right) in every region for every age-group.

Supplementary Figure 9: Estimated CVD incidence rates and predicted risks

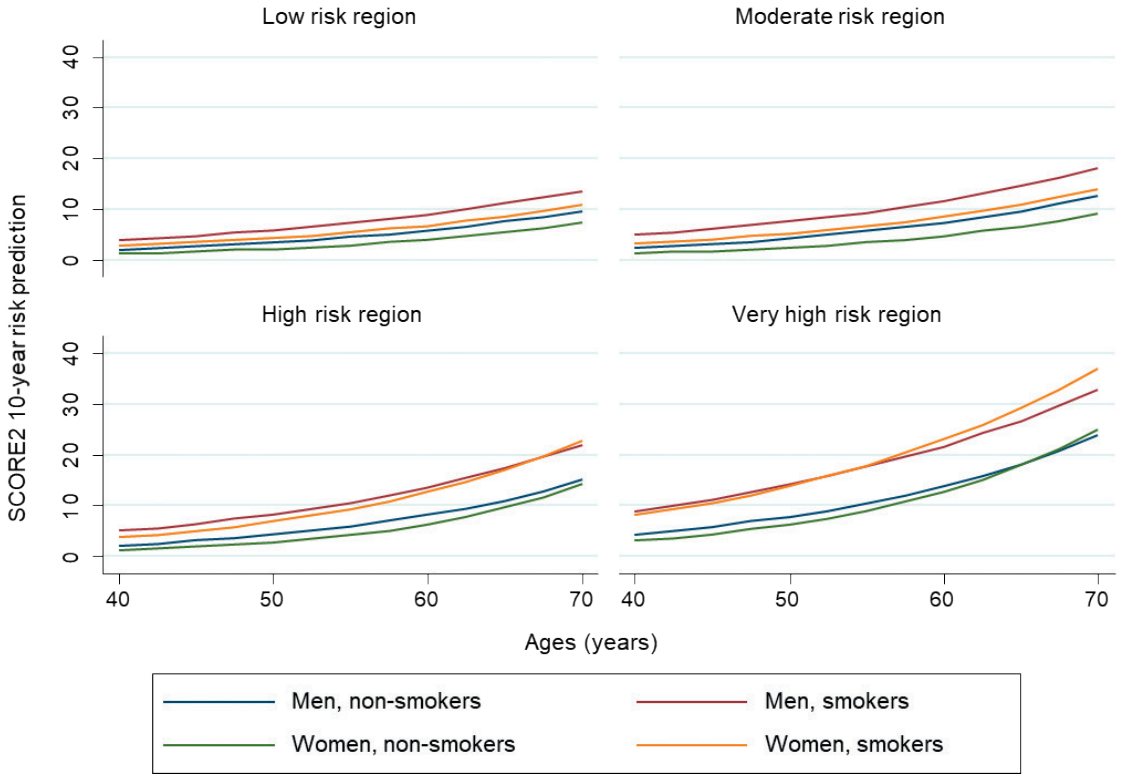


Supplementary Figure 10: Validation of estimated CVD incidence against independent registry data

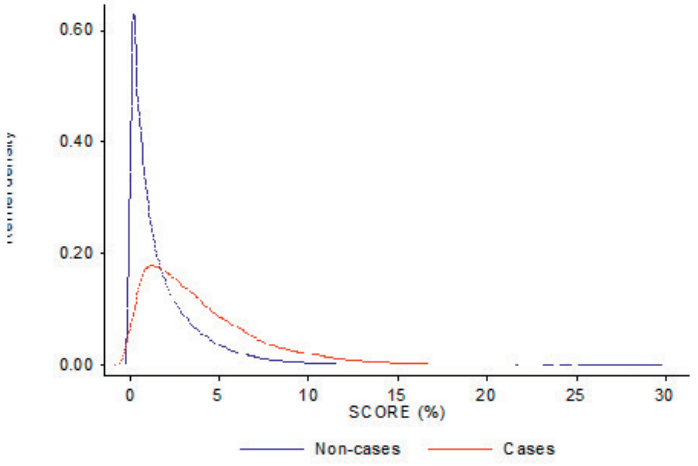


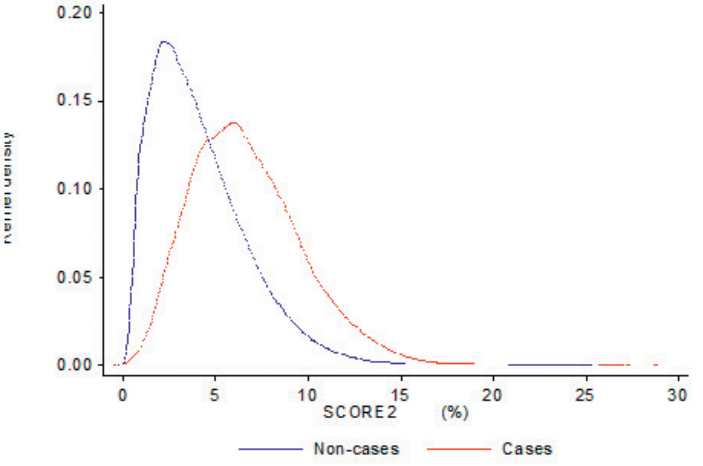
Comparison of registry-based incidence rates of total and fatal cardiovascular disease, with those used in the recalibrated SCORE2. The SCORE2 predicted risks were obtained by combining regional NCD risk factor levels to the risk algorithms. Registry incidences were extrapolated to a 10-year cumulative incidence. Note that Netherlands, German and Spanish registry-based incidences include also CVD events in patients with prior vascular disease. Only the Spanish registry rates have been corrected for competing risks.

Supplementary Figure 11: Predicted 10-year cardiovascular disease risks for an individual with total cholesterol concentration of 5.5 mmol/L, HDL cholesterol of 1.3 mmol/L, and systolic blood pressure of 140 mm Hg, for each region

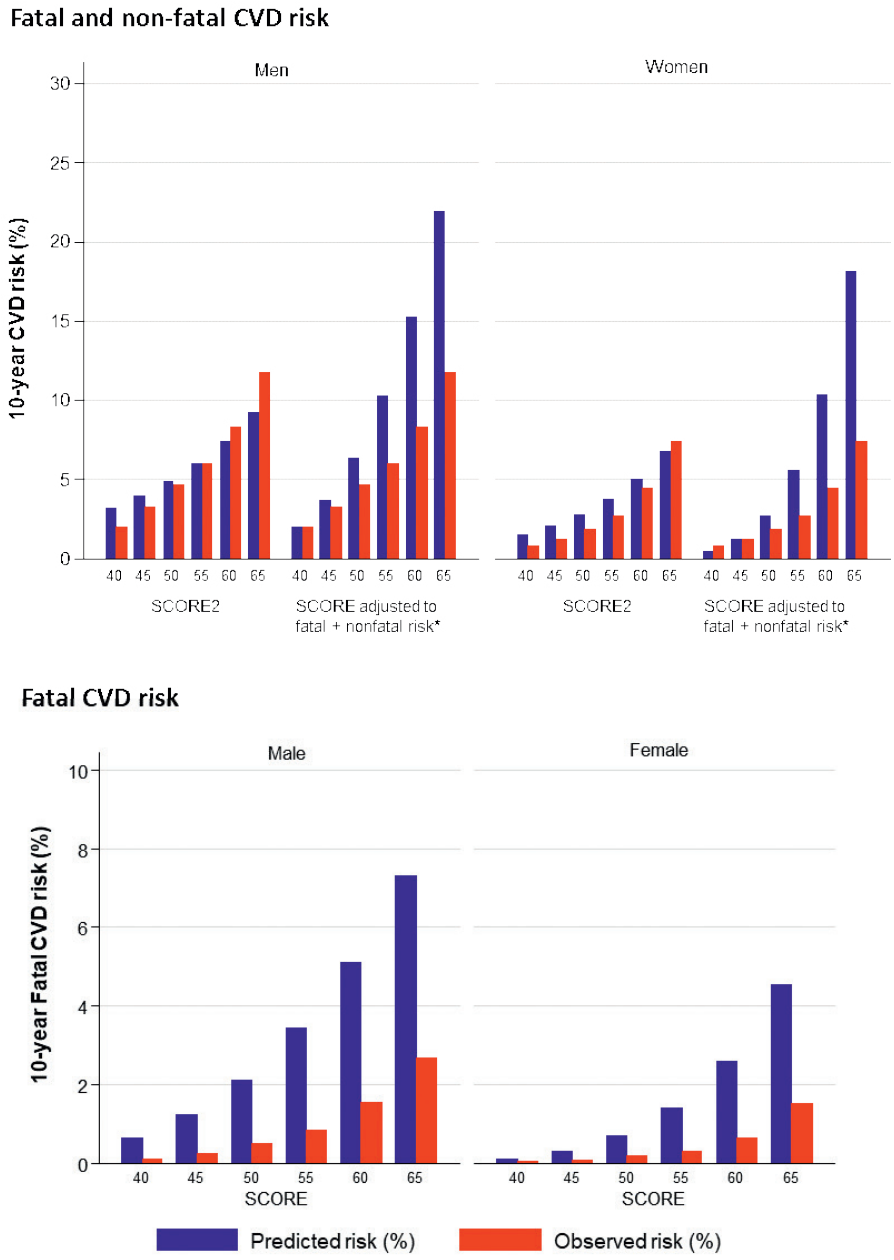


Supplementary Figure 12: Distributions of predicted risks for cases and non-cases



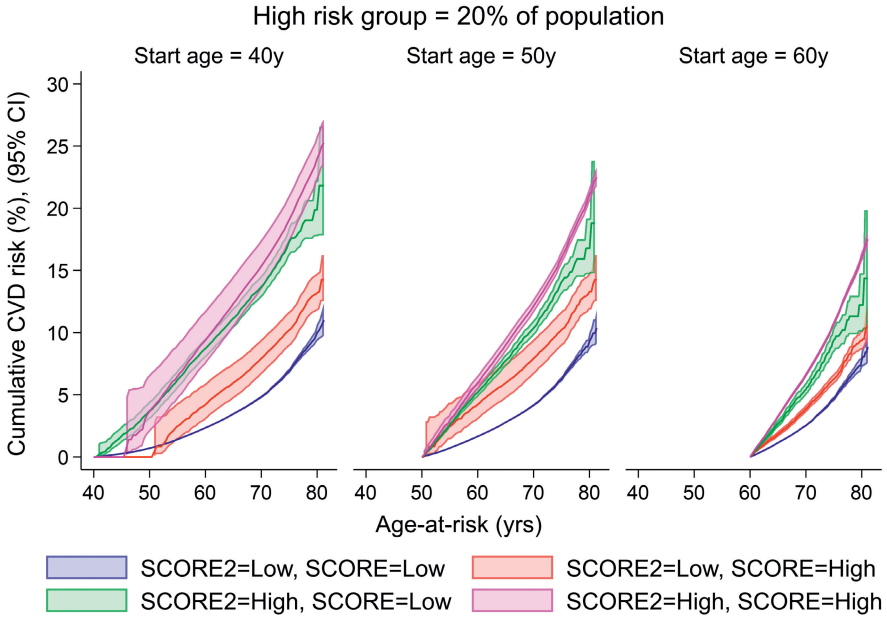


Supplementary Figure 13: Calibration of SCORE and SCORE2 in CPRD data



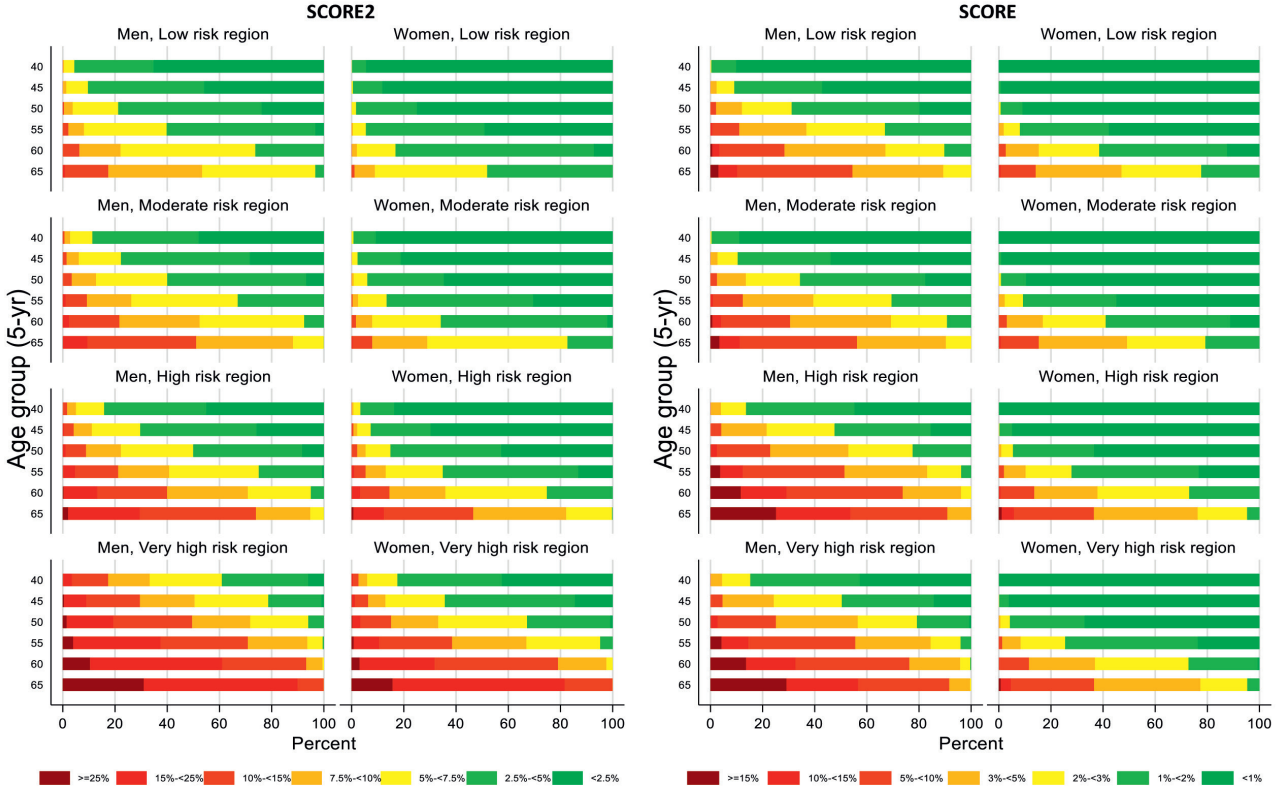
Conversion of fatal CVD risk estimated using SCORE to fatal and non-fatal CVD risk, was completed using the approach recommended by the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias (i.e., to multiply estimates by 3 in men and by 4 in women).

Supplementary Figure 14: Risk stratification using SCORE2 and SCORE and observed lifetime risk of CVD



Comparison of appropriateness of risk stratification using SCORE2 and SCORE in CPRD assuming that both were used to independently select 20% of the population at "high-risk". Observed CVD risk over the lifetime were devided into four groups according to "high-risk" status using SCORE and SCORE2.

Supplementary Figure 15: SCORE2 and SCORE risk distributions by age and risk region



The proportion of individuals expected in each risk category was estimated to reflect the age-group and sex- specific risk factor values and specific population structure of each country (Supplementary Methods 1.3

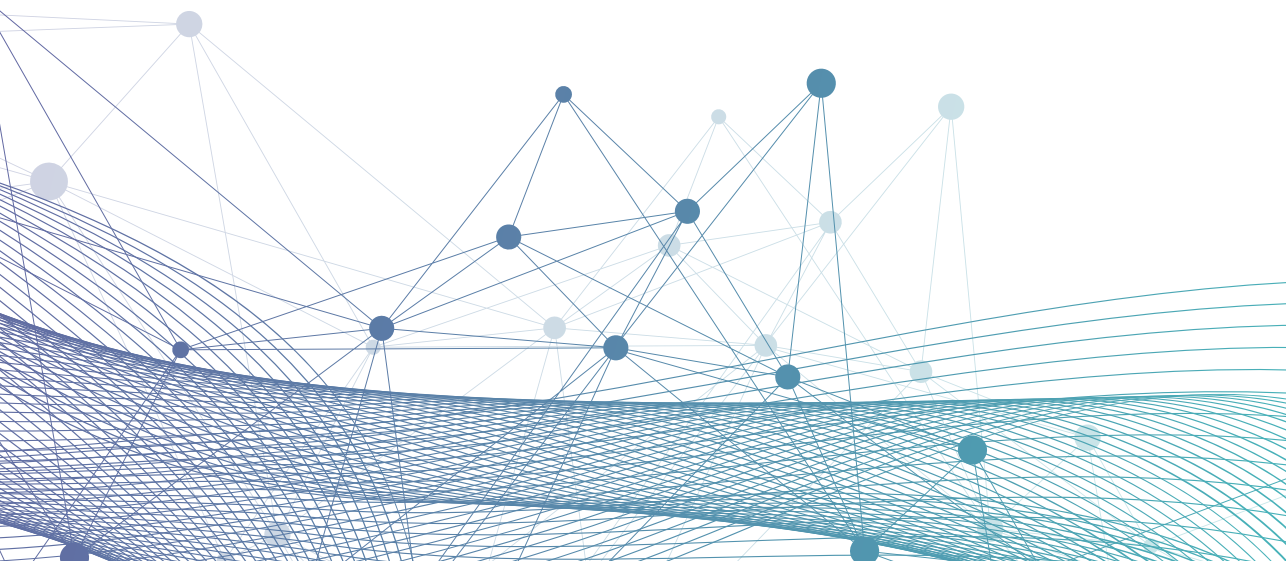
CHAPTER 2

SCORE2 models allow consideration of sex-specific CVD risks by region

Steven Hageman, Lisa Pennells, Francisco Ojeda, Stephen Kaptoge, Jannick Dorresteijn, Emanuele Di Angelantonio

on behalf of the SCORE2 working group and ESC Cardiovascular Risk Collaboration

Eur Heart J. 2022;43(3):241-242



This commentary refers to 'SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe', by the SCORE2 working group and European Society of Cardiology (ESC) Cardiovascular Risk Collaboration, https://doi.org/10.1093/eurheartj/ehab309 and the discussion piece 'A sex-specific prediction model is not enough to achieve equality for women in preventative cardiovascular medicine', by D.M. Kimenai *et al.*, https://doi.org/10.1093/eurheartj/759.

SCORE2 is a risk algorithm developed to estimate 10-year cardiovascular disease (CVD) risk in men and women from four different risk regions of Europe,[1] which is now recommended for use by the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice.[2] We agree with Kimenai *et al.*[3] on the need for consideration of sex differences in cardiovascular disease risk in both basic, clinical and translational research and prevention guidelines. Indeed, our development of the SCORE2 algorithm recognized this, with all steps of model development performed separately for each sex. This has resulted in accurate and externally validated prediction algorithms for both men and women, with further research validation and clinical application facilitated by different translational tools already provided (or in progress), including: easy-to-use risk charts (main paper Figure 3), and the statistical software program—score2risk—(https://www.phpc.cam.ac.uk/ceu/erfc/programs/).

Furthermore, all relevant sex-specific model parameters were included in the Supplementary materials, in particular: Supplementary Table 7 (for beta coefficients and baseline hazards) and Supplementary Methods Table 3 (for recalibration scales).[1] We do, however, recognize the relevance of making all model parameters available to a greater precision in order to facilitate appropriate usage. Therefore, we have included with this comment an additional table of sex-specific model coefficients and recalibration scales (**Table 1**) rounded to four decimal places. To make these parameters as easily accessible as possible, these tables have been included in the updated version of the article supplement.

Table 1: Model coefficients, baseline survival and recalibration scales of the SCORE2 algorithm

Model coefficients:					
Risk factor (units)	**Transformation**	**Log HR**		**HR**	
	equation	**Male**	**Female**	**Male**	**Female**
Age (yrs)	cage = (age - 60)/5	0.3742	0.4648	1.45	1.59
Smoking (current vs. other)	current=1, other=0	0.6012	0.7744	1.82	2.17
Systolic blood pressure (SBP, mm Hg)	csbp = (sbp - 120)/20	0.2777	0.3131	1.32	1.37
Diabetes* (yes vs. no)	yes=1, no=0	0.6457	0.8096	1.91	2.25
Total cholesterol (mmol/L)	ctchol = (tchol - 6)/1	0.1458	0.1002	1.16	1.11
HDL cholesterol (mmol/L)	chdl = (hdl - 1.3)/0.5	-0.2698	-0.2606	0.76	0.77
Smoking x age interaction	cage x smoking	-0.0755	-0.1088	0.93	0.90
SBP x age interaction	cage x csbp	-0.0255	-0.0277	0.98	0.97
Total cholesterol x age interaction	cage x ctchol	-0.0281	-0.0226	0.97	0.98
HDL cholesterol x age interaction	cage x chdl	0.0426	0.0613	1.04	1.06
Diabetes* x age interaction	cage x diabetes	-0.0983	-0.1272	0.91	0.88
Baseline survival		0.9605	0.9776		
10-year risk estimate (un-calibrated) =	1-baseline survival $^{\exp(\text{linear predictor}^{**})}$				
Recalibration scales		**Male**		**Female**	
	Risk region	Scale1	Scale2	Scale1	Scale2
	Low risk region	-0.5699	0.7476	-0.7380	0.7019
	Moderate risk region	-0.1565	0.8009	-0.3143	0.7701
	High risk region	0.3207	0.9360	0.5710	0.9369
	Very high risk region	0.5836	0.8294	0.9412	0.8329
Calibrated 10-year risk = 1-exp(-exp(scale1 + scale2 x ln(-ln(1-un-calibrated 10-yr risk))					

*Diabetes mellitus was included in the modelling since this was necessary for the recalibration approach, which relies on data from the whole population, including those with diabetes. However, SCORE2 is not intended for use in individuals with diabetes and has not been validated in this population. For risk prediction in the target population of individuals without diabetes this risk factor will always be 0, meaning the coefficient can effectively be ignored.
** linear predictor= Σ(transformed risk factor value x log HR)
Final estimate should be multiplied by 100 in order to express as a percentage rather than a probability

References

1. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J.* 2021;42(25):2439-2454.
2. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42(34):3227-3337.

CHAPTER 3

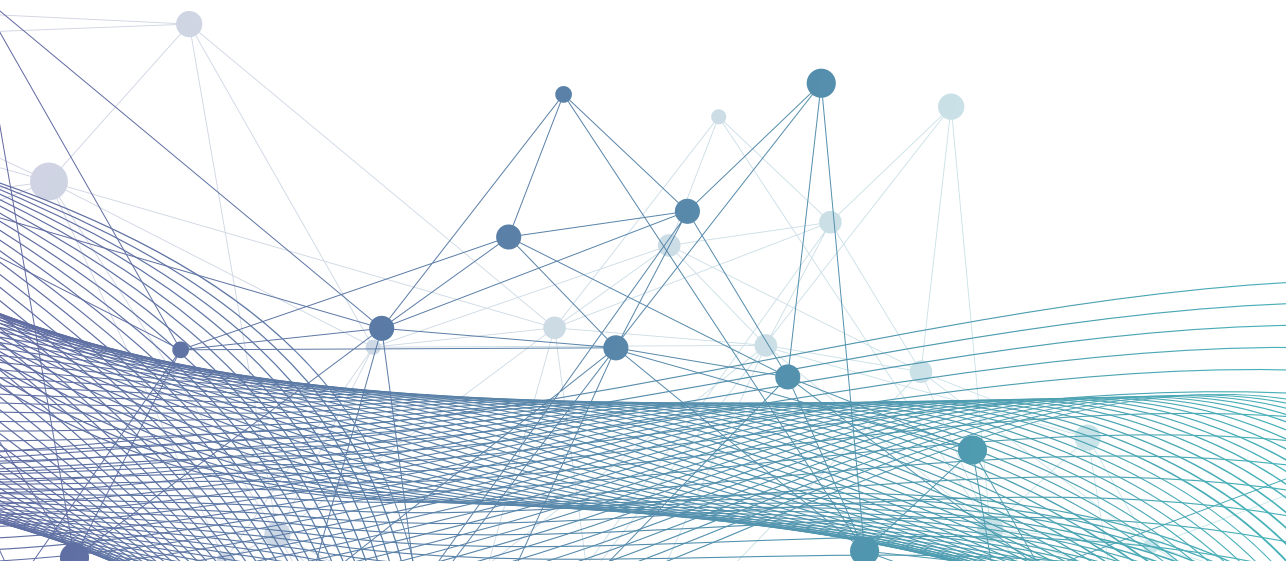
SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions

SCORE2-OP working group and ESC Cardiovascular risk collaboration

Tamar I. de Vries*, Marie Therese Cooney*, Randi M. Selmer*, Steven H.J. Hageman*, Lisa A. Pennells, Angela Wood, Stephen Kaptoge, Zhe Xu, Jan Westerink, Kjersti S. Rabanal, Grethe S. Tell, Haakon E. Meyer, Jannicke Igland, Inger Ariansen, Kunihiro Matsushita, Michael J. Blaha, Vijay Nambi, Ruth Peters, Nigel Beckett, Riitta Antikainen, Christopher J. Bulpitt, Majon Muller, Marielle H. Emmelot-Vonk, Stella Trompet, Wouter Jukema, Brian A. Ference, Martin Halle, Adam D. Timmis, Panos E. Vardas, Jannick A.N. Dorresteijn, Dirk De Bacquer†, Emanuele Di Angelantonio†, Frank L.J. Visseren†, and Ian M. Graham†

Eur Heart J. 2021;42(25):2455-2467

*Contributed equally.
†Contributed equally.



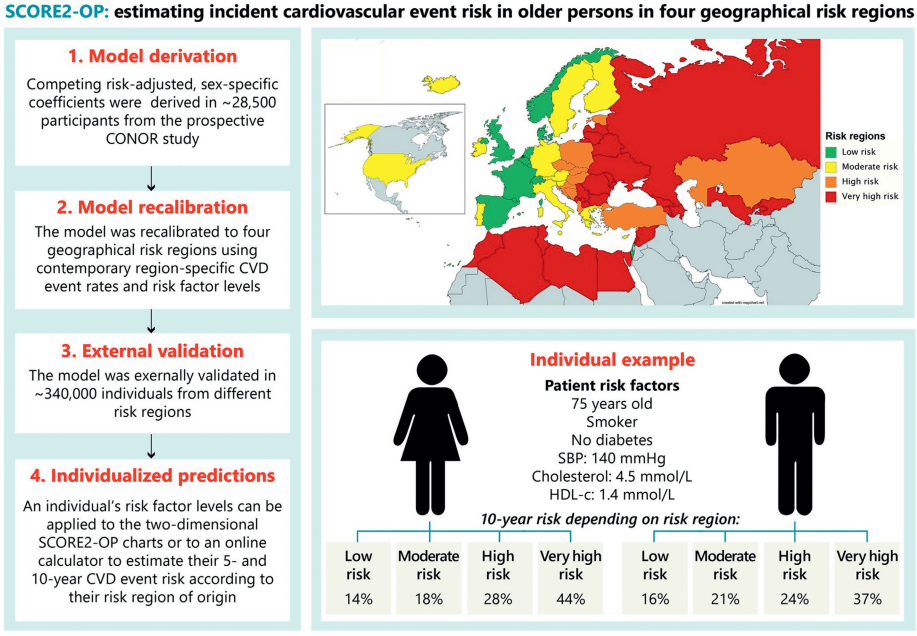
Abstract

Aims: To derive and validate the SCORE2-Older Persons (SCORE2-OP) risk model to estimate 5- and 10-year risk of cardiovascular disease (CVD) in individuals aged over 65 years in four geographical risk regions.

Methods and results: Sex-specific competing risk-adjusted models for estimating CVD risk (CVD mortality, myocardial infarction, or stroke) were derived in individuals aged over 65 without pre-existing atherosclerotic CVD from the Cohort of Norway (28,503 individuals, 10,089 CVD events). Models included age, smoking status, diabetes, systolic blood pressure, total- and HDL-cholesterol. Four geographical risk regions were defined based on country-specific CVD mortality rates. Models were recalibrated to each region using region-specific estimated CVD incidence rates and risk factor distributions. For external validation, we analyzed data from 6 additional study populations (338,615 individuals, 33,219 CVD validation cohorts, C-indices ranged between 0.63 (95%CI 0.61-0.65) and 0.67 (0.64-0.69). Regional calibration of expected-versus-observed risks was satisfactory. For given risk factor profiles, there was substantial variation across the four risk regions in the estimated 10-year CVD event risk.

Conclusions: The competing risk adjusted SCORE2-OP model was derived, recalibrated and externally validated to estimate 5- and 10-year CVD risk in older adults (aged 65 or older) in four geographical risk regions. These models can be used for communicating the risk of CVD and potential benefit from risk factor treatment, and may facilitate shared decision making between clinicians and patients in CVD risk management in older persons.

Graphical abstract



Introduction

Risk of cardiovascular disease (CVD) increases with age.[1] The risk of non-CVD mortality generally *also* rises with age so that remaining life expectancy inevitably decreases with age. Hence, the treatment of important CVD risk factors needs to be carefully considered to balance the benefits and risks in this population. Meaningful treatment benefit is different in this population where life expectancy is limited,[2,3] while older persons are generally at high risk of developing adverse drug events and side effects.[4,5] It is thus important to identify those individuals who might benefit from preventive treatment.

For this purpose, CVD risk prediction models can be used to identify those at higher risk of CVD and those potentially benefiting the most from risk factor treatment.[6] These prediction models may also aid in patient-centred clinical decision making, taking into account other patient characteristics such as frailty, biological age and patient preferences.[7]

Most 10-year CVD risk prediction models generally have a poor performance in older individuals for several reasons.[8–11] First, the relationship between traditional risk factors and CVD attenuates with age,[12] and traditional risk prediction models do not take into account competing risk of non-CVD mortality, leading to overestimation of CVD risk and consequently overestimation of potential benefit from risk factor treatment in older persons.[3,13,14] This overestimation may lead to unnecessary treatment in older persons, polypharmacy, increased risk of drug interactions, adverse events, reduced quality of life and unnecessary costs.[15] To deal with short-comings of traditional risk models, an older person-specific risk score should be used. However, previously developed risk models for older persons only estimate risk of cardiovascular mortality while non-fatal events are also of importance (e.g. stroke and heart failure). Finally, previous models have not been extensively externally validated and shown to be applicable in different geographical risk regions where risk levels vary.[2,16,17]

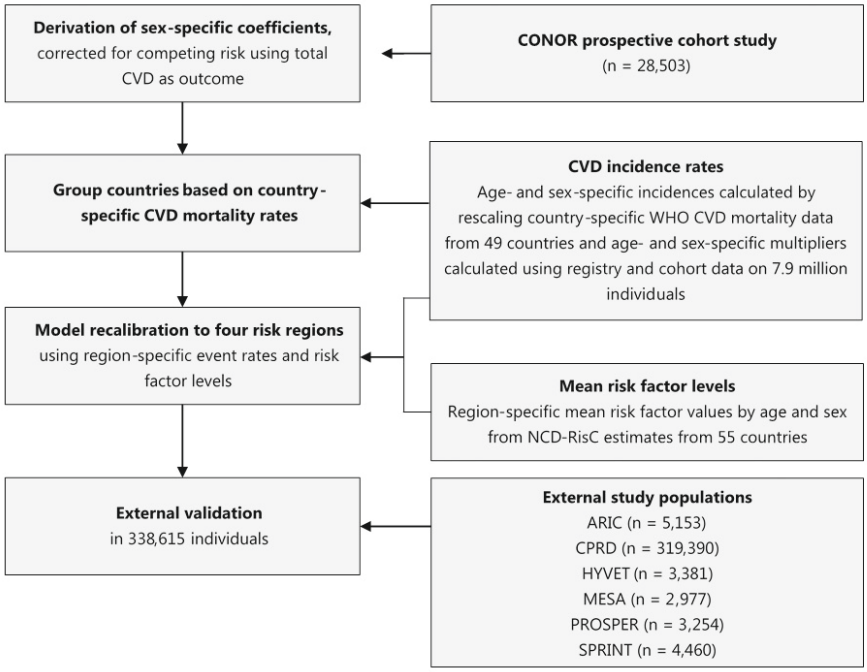
We aimed to develop and validate a competing risk-adjusted model for individuals aged over 65 years without pre-existing CVD to estimate 5- and 10-year risk of incident CVD – the new SCORE2-Older Persons (SCORE2-OP). This risk model is calibrated to four different geographical risk regions using an approach based on aggregate level data that can be easily applied to further update the accuracy of risk predictions with changing CVD epidemiology in the future.

Methods

Study design

The SCORE2-OP project involved several interrelated components and data sources (**Figure 1**). The study design is closely related to the new SCORE2 model that estimates 10-year fatal and non-fatal CVD risk in individuals without previous CVD or diabetes aged 40-69 years.[18] First, model coefficients were derived in the Cohort of Norway (CONOR) study (**Supplementary Methods**).[19] This study population was selected because it is a large, representative population-based cohort and has previously been used for model derivation.[16,17,20] Second, the model was recalibrated to four geographical risk regions across Europe and beyond using estimated contemporary age- and sex-specific incidences and risk factor distributions. Third, external validation was performed in prospective cohorts from different risk regions. Finally, the model was applied to estimate individualized treatment benefit from blood pressure and cholesterol lowering to illustrate how SCORE2-OP can be used for treatment decision making in clinical practice.

Figure 1: Study design



Abbreviations: ARIC = Atherosclerosis Risk in Communities; CONOR = Cohort of Norway; CPRD = Clinical Practice Research Datalink; CVD = cardiovascular disease; MESA = Multi-Ethnic Study of Atherosclerosis; NCD-RisC = non-Communicable Disease Risk Factor Collaboration; PROSPER = PROspective Study of Pravastatin in Elderly at Risk; SPRINT = Systolic Blood Pressure Intervention Trial; WHO = World Health Organisation

Sources of data

This study derived the risk model coefficients from the prospective CONOR study,[19] and used combined data from several cohort studies and clinical trials for external validation and testing: the Atherosclerosis Risk in Communities (ARIC) study,[21] from which we used baseline data from visit 5 to include more individuals aged over 65 years; the Clinical Practice Research Datalink (CPRD);[22] the Hypertension in the Very Elderly Trial (HYVET);[23] the Multi-Ethnic Study of Atherosclerosis (MESA);[24] the "PROspective Study of Pravastatin in Elderly at Risk" (PROSPER) trial;[25] and the Systolic Blood Pressure Intervention Trial (SPRINT).[26,27] Details of the included studies can be found elsewhere and have been summarized in the **Supplementary Methods.** The current study was conducted using data from the target population of individuals aged 65 years or over. Individuals with a history of CVD (i.e. coronary heart disease, stroke, or peripheral artery disease) were excluded from analysis. All included studies comply with the Declaration of Helsinki, were approved by local institutional review boards and all participants provided written informed consent.

Endpoint definitions

The primary endpoint was a composite of the first fatal or non-fatal CVD events in each study participant, defined as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality. Secondary endpoint included also hospitalization from heart failure (HF), as this is an important source of morbidity and loss in quality of life in older persons.

The CVD mortality component of the primary and secondary outcomes resembles the endpoint definition of the original SCORE project, including e.g. death from coronary heart disease, HF, stroke, and sudden death. An overview of the ICD-10 codes included in both the fatal and non-fatal component of the composite endpoint can be found in **Supplementary Table 1**. Deaths from non-CVD were treated as competing events. Follow-up time was defined as years until the first event, death, or end of the registration period.

Risk regions

The four risk regions (low, moderate, high, and very-high risk) were chosen based on the definition used in the newly developed SCORE2 risk model, according to the most recent overall age- and sex-standardized CVD mortality rates in all included countries (ICD 10 chapter IX, I00-I99). The following age-standardized rates were used for categorization: <100 CVD deaths per 100,000 (low risk), 100-149 CVD deaths per 100,000 (moderate risk), 150-299 CVD deaths per 100,000 (high risk), and ≥300 CVD deaths per 100,000 (very-high risk). The four geographical risk regions can be found in **Supplementary Figure 1** and **Supplementary Table 2**.

Statistical analysis

Details of statistical analysis are provided in **Supplementary Methods**. For model derivation, sex-specific coefficients were estimated in the CONOR study using competing risk-adjusted Fine and Gray proportional subdistribution hazards models. The models included the following pre-specified baseline predictors: age, current smoking, diabetes mellitus, systolic blood pressure (SBP), total cholesterol (TC), and high density lipoprotein cholesterol (HDL-c). The risk factors were selected based on their predictive ability as well as availability in the derivation dataset and population statistics needed for model recalibration. Variable selection was not applied in order to prevent overfitting of the model to the derivation data (over-optimism). Age interaction terms were added as the effect of these risk factors may change with age.[28] Continuous predictors were truncated at the 1st and 99th percentile to minimize the influence of outliers in the model.[29] Whether the association of continuous predictors with the outcome variable was adequately explained with a log-linear relationship was assessed using the Akaike information criterion. Internal model performance was assessed with Harrell's C-index for discrimination, and visually with calibration plots of estimated versus observed risk in a random sample with replacement of the CONOR study population to account for overfitting. The model was then recalibrated internally for the risk of the secondary CVD endpoint including heart failure using age- and sex-specific multiplication factors, using the same model coefficients.

Risk models were recalibrated to risk regions using age- and sex-specific mean risk factor levels and CVD incidence rates.[30] Age-specific and sex-specific risk factor values were obtained from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC).[31,32] We obtained country-specific, age- and sex-specific CVD mortality rates reported by the World Health Organisation (WHO),[33] and estimated fatal and non-fatal CVD incidences by using age- and sex-specific multipliers derived in the SCORE2 project in multiple cohorts from the different risk regions with a total of 4,056,218 men and 3,869,443 women, with 732,471 CVD events.[18] The multipliers for fatal CVD to total CVD events per region are listed in **Supplementary Table 3**.

External validation was performed in 6 studies, including the ARIC, MESA, and CPRD cohorts, and the combined study populations of the HYVET, PROSPER and SPRINT trials (adding the trial treatment effect to account for differences in observed risk between the active treatment and control arm of the trials) as the separate trial populations have limited number of events in a short follow-up time. External model performance was assessed in terms of discrimination using Harrell's C-index, and in terms of model calibration using plots of observed versus estimated risks recalibrated using cohort-specific observed-versus-expected (O/E) ratios reflecting differences in baseline risk. SCORE2-OP was compared in terms of discrimination with the ASCVD (Atherosclerotic Cardiovascular Disease) risk calculator from AHA/ACC, an

internationally widely used risk model for the general population also including older persons.[34]

All analyses were conducted with R-statistic programming (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria). Our approach to model development and validation complies with PROBAST guidelines,[35] and TRIPOD.[36] The approaches used to handle missing data are described in the **Supplementary Methods**.

Absolute CV event risk reduction from risk factor treatment in older people
SCORE2-OP can be used to estimate individualized treatment effect estimations from cardiovascular risk factor treatment,[6] as described in detail in the **Supplementary Methods**. To estimate the effect of blood pressure lowering on CVD, average relative treatment effects from large meta-analyses were added to SCORE2-OP. We estimated absolute treatment effect from blood pressure lowering to the target of <140mmHg in older persons with hypertension from the HYVET and SPRINT trials,[26,37] using a hazard ratio (HR) of 0.80 per 10 mmHg SBP reduction from a large meta-analysis.[38] For the effect of lipid lowering, a HR 0.78 per 1 mmol/L LDL-cholesterol lowering was used,[39] and the absolute risk reduction (ARR) of lowering LDL-cholesterol to <2.6 mmol/L was estimated in participants with hypercholesterolemia from the PROSPER trial.[25] The ARR is defined as the baseline ("untreated") CVD risk minus the CVD risk with added risk factor management.

Table 1: Study and baseline patient characteristics of the included study populations

	Derivation population	External validation and testing populations					
	CONOR	**ARIC**	**CPRD**	**HYVET**	**MESA**	**PROSPER**	**SPRINT**
	N = 28,503	N=5,153	N=319,390	N =3,381	N =2,977	N =3,254	N =4460
Recruitment period	1994-2003	2011-2013	2006*	2001-2007	2000-2002	1997-1999	2010-2013
Country	Norway	USA	UK	Eastern Europe (n=1895), Western Europe (n=84), other (n=1402)	USA	UK (n=1288), Ireland (n=1339), Netherlands (n=627)	USA
Baseline characteristics:							
Male sex	50%	39%	42%	38%	48%	42%	59%
Age (years)	73 ± 5	75 ± 5	74 ± 6	83 ± 3	72 ± 5	75 ± 3	74 ± 6
Current smoking	20%	7%	25%	7%	8%	33%	5%
SBP (mmHg)2	152 ± 23	130 ± 18	141 ± 16	173 ± 9	134 ± 22	157 ± 21	141 ± 15
Total cholesterol (mmol/L)	6.4 ± 1.2	4.8 ± 1.1	5.5 ± 1.2	5.3 ± 1.1	5.0 ± 0.9	5.7 ± 0.9	4.9 ± 1.0
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	1.6 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4
Type 2 diabetes mellitus	6%	31%	10%	9%	15%	12%	0%
Lipid-lowering drugs use	9%	49%	21%	0.3%	22%	49%	44%
Median follow-up (IQI)	13 (8-15)	6 (5-6)	7 (4-10)	2 (1-3)	13 (9-14)	3 (3-4)	3 (3-tab4)
Primary endpoint	10,089 (35%)	427 (8%)	31,484 (10%)	225 (7%)	501 (17%)	396 (12%)	186 (4%)
Total mortality	16,642 (58%)	683 (13%)	60,077 (19%)	356 (11%)	981 (33%)	274 (8%)	194 (4%)

All data in n (%) or mean ± standard deviation unless stated otherwise

* Baseline for measurement of exposure was set at 1/1/2006

SBP = systolic blood pressure; HDL = high-density lipoprotein; IQR = interquartile interval; UK = United Kingdom; USA = United States of America

Results

A total of 211,184 women and 155,934 men aged 65 years or over from seven studies were included in the analysis for model derivation and validation. Study and baseline characteristics of all study populations are presented in **Table 1**.

Model derivation and recalibration

A total of 10,089 non-fatal and fatal CVD events occurred in 305,640 person years of follow-up in the 28,503 participants included from the CONOR study, the derivation data. SCORE2-OP model coefficients and subdistribution hazard ratios for CVD events are shown in **Table 2**. **Supplementary Figure 2** shows the change in the effect of model predictors with increasing age.

Table 2: Sex-specific coefficients and subdistribution hazard ratios for CVD events of SCORE2-OP

	Men		Women	
	Coefficients (95% CI)	Subdistribution hazard ratios	Coefficients (95% CI)	Subdistribution hazard ratios
Age (per year)	0.063 (0.055-0.071)	1.07	0.079 (0.070-0.087)	1.08
History of diabetes	0.425 (0.305-0.544)	1.50	0.601 (0.465-0.737)	1.80
History of diabetes * age (per year)	-0.017 (-0.040-0.005)		-0.011 (-0.032-0.011)	
Current smoking	0.352 (0.279-0.426)	1.39	0.492 (0.398-0.587)	1.59
Current smoking * age (per year)	-0.025 (-0.040- -0.009)		-0.026 (-0.043- -0.008)	
SBP (per 10 mmHg)	0.094 (0.079-0.109)	1.09	0.102 (0.085-0.119)	1.10
SBP (per 10 mmHg) * age (per year)	-0.005 (-0.008- -0.002)		-0.004 (-0.007- -0.002)	
Total cholesterol (per 1 mmol/L)	0.085 (0.054-0.116)	1.10	0.060 (0.027-0.094)	1.06
Total cholesterol (per 1mmol/L) * age (per year)	0.007 (0.002-0.013)		-0.001 (-0.056-0.004)	
HDL cholesterol (per 1 mmol/L)	-0.356 (-0.445- -0.268)	0.71	-0.304 (-0.403- -0.205)	0.75
HDL cholesterol (per 1 mmol/L) * age (per year)	0.009 (-0.009-0.027)		0.015 (0.0002-0.031)	

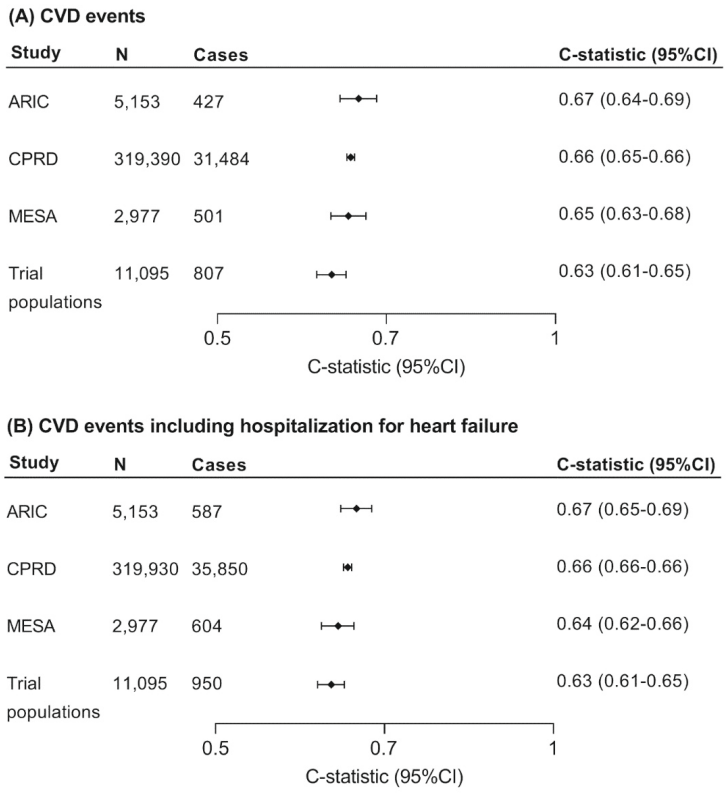
95% CI = 95% confidence interval
Sex-specific coefficients and subdistribution hazard ratios (SHRs) from Fine and Gray models predicted the risk of fatal and non-fatal CVD events as derived in the CONOR study. The SHRs are shown for age centred at 73 years, systolic blood pressure at 150 mmHg, total cholesterol at 6 mmol/L, and HDL cholesterol at 1.4 mmol/L.
These SHRs are relevant for risk estimation only and have no etiological interpretation.

In the internal validation set of the CONOR study, the 10-year estimated risk showed good agreement with the 10-year observed risk over all deciles for all outcomes of interest (**Supplementary Figure 3**). C-index were 0.66 (95% confidence interval [95% CI] 0.65-0.66) for CVD events, and 0.65 (95% C 0.65-0.66) for CVD events including heart failure. The age- and sex-specific multiplication factors for estimating the risk of CVD events including heart failure can be found in **Supplementary Table 4**.

Age and sex-specific 10-year mortality CVD rates and derived incidence rates are shown for each region in **Supplementary Figure 4**. The age-specific and sex-specific mean risk factor levels and estimated CVD event rates used for recalibration are presented by region in **Supplementary Table 5**. After regional recalibration, SCORE2-OP estimated risks based on mean risk factor levels agreed well with the regional estimated CVD event incidence in the four risk regions across age-groups (**Supplementary Figure 5**).

In the external validation study populations, a total of 33,219 primary outcome events were observed in 338,615 individuals in 2,259,933 person-years of follow-up. The external validation showed C-index for discrimination (**Figure 2**) ranging between 0.63 (95% CI 0.61-0.65) and 0.67 (95% CI 0.64-0.69). Calibration plots per study population after accounting for differences in baseline risk are shown in **Supplementary Figure 6**. For the secondary CVD endpoint including heart failure, the external C-index ranged between 0.63 (95% CI 0.61-0.65) and 0.67 (95% CI 0.65-0.69). When we applied the recalibrated SCORE2-OP models from each risk region to individual risk factor data from participants from ARIC and MESA, the risk distribution varied greatly between risk regions (**Figure 3**). Comparison of SCORE2-OP and the ASCVD risk engine can be found in **Supplementary Table 6**. C-index for SCORE2-OP were comparable to or higher than for ASCVD in the other study populations. In the external validation cohorts, the time-dependent ROC were comparable to or higher than Harrell's C-index (**Supplementary Table 7**).

Figure 2: External validation of SCORE2-OP for (A) the estimation of risk for myocardial infarction (MI), stroke, or CVD mortality (primary endpoint); (B) the estimation of risk for MI , stroke, hospitalization for heart failure, or CVD mortality (CVD events including heart failure)

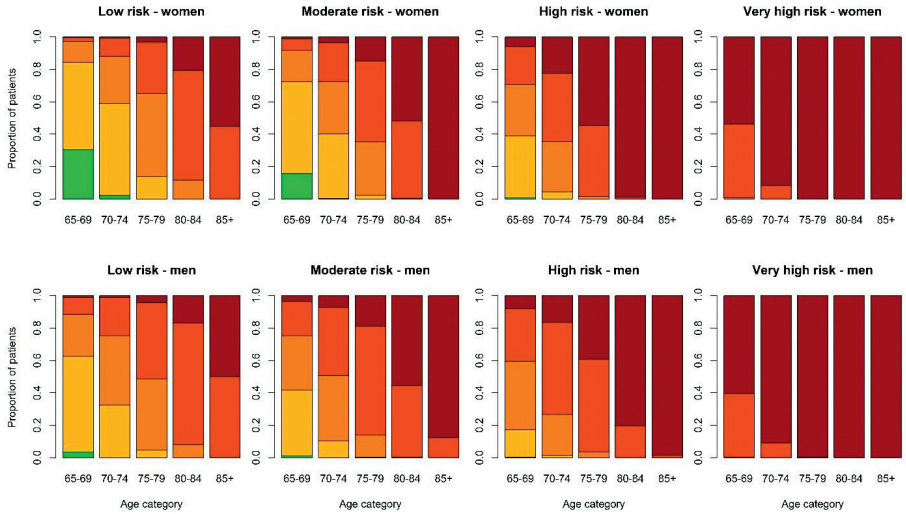


Trial populations: HYVET, PROSPER and SPRINT

Two-dimensional risk charts of SCORE2-OP for all four risk regions are shown in the **Supplementary Appendix**, for practical purposes displayed according to non-HDL rather than total cholesterol and HDL-cholesterol. We have also added risk charts for the estimated 5-year risk, as this may fulfil a clinical need especially in the very old. The estimated absolute risk for a given age and combination of risk factors differed substantially across regions. For example, the estimated 10-year CVD risk for a 75-year-old male smoker with a systolic blood pressure of 150 mmHg, and a non-HDL cholesterol of 4.5, ranged from 16% in a low risk country to 37% in a very high-risk country (**Supplementary Figure 7**). Similarly, the 10-year risk for a 75-year-old woman with the same risk factor profile ranged from 14% in a low risk country to 44% in a very high-risk country. A sensitivity analysis taking into account uncertainty

around individual predictions is described in the **Supplementary Methods** and shown in **Supplementary Figures 8.**

Figure 3: Age- and sex-specific distributions of fatal and non-fatal CVD risk in the four risk regions according to SCORE2-OP.

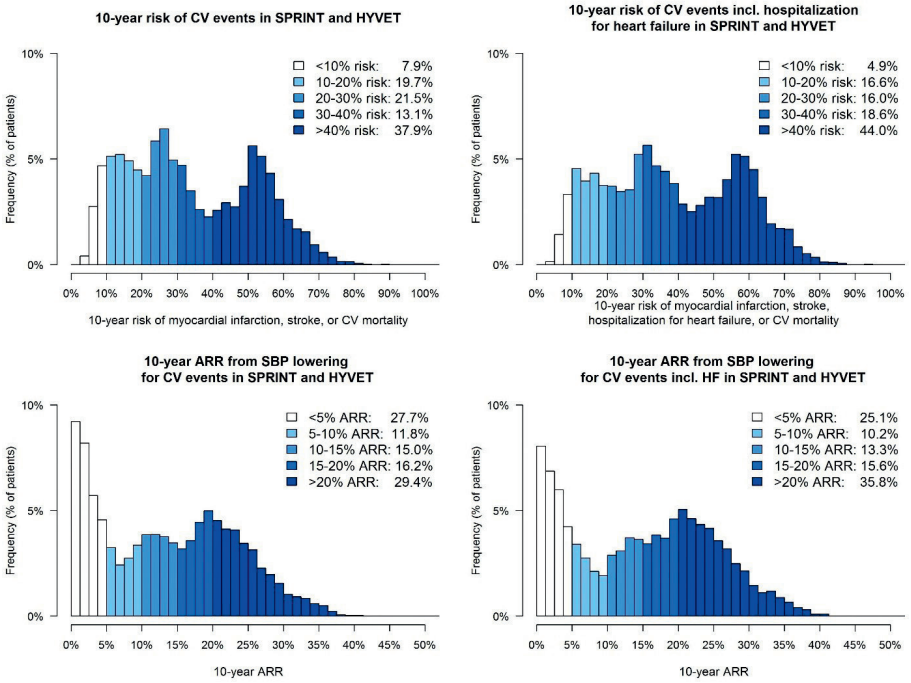


Age- and sex-specific risk distribution in the different risk regions, based on risk factor data in ARIC and MESA cohorts (n = 8,130).

Absolute 10-year CVD event risk reduction from risk factor treatment in older people

The distribution of individual estimated 10-year CVD risk and associated ARR for blood pressure lowering therapy when targeting an SBP of <140 mmHg in 5,579 older persons with hypertension (SBP at baseline >140) in the SPRINT and HYVET blood pressure lowering trials is shown in **Figure 4**. The overall median estimated 10-year risk for CVD events was 30% (IQR 19-50%); for CVD events including heart failure, this was 36% (22-55%). The overall median estimated individual 10-year ARR from blood pressure lowering for the primary endpoint CVD events was 13% (IQR 4-21%); for CVD events including heart failure, this was 16% (IQR 5-23%). The distribution of the individual estimated 10-year CV event risk and associated ARR for lipid lowering therapy targeting an LDL-cholesterol <2.6 mmol/L in the PROSPER trial is shown in **Figure 5**. In these 3,051 older persons, the overall median estimated 10-year risk for CVD events was 18% (IQR 13-24%), for CVD events including heart failure this was 21% (16-28%); the overall median estimated individual 10-year ARR from lipid lowering for the primary CVD endpoint was 4% (IQR 3-6%); for the secondary CVD endpoint including heart failure this was 5% (IQR 3-7%).

Figure 4: Distribution of estimated 10-year fatal and non-fatal CVD events and estimated 10-year absolute risk reduction (ARR) from blood-pressure lowering in older persons with hypertension (SBP >140 mmHg) in the HYVET and SPRINT trials (n = 5,579).



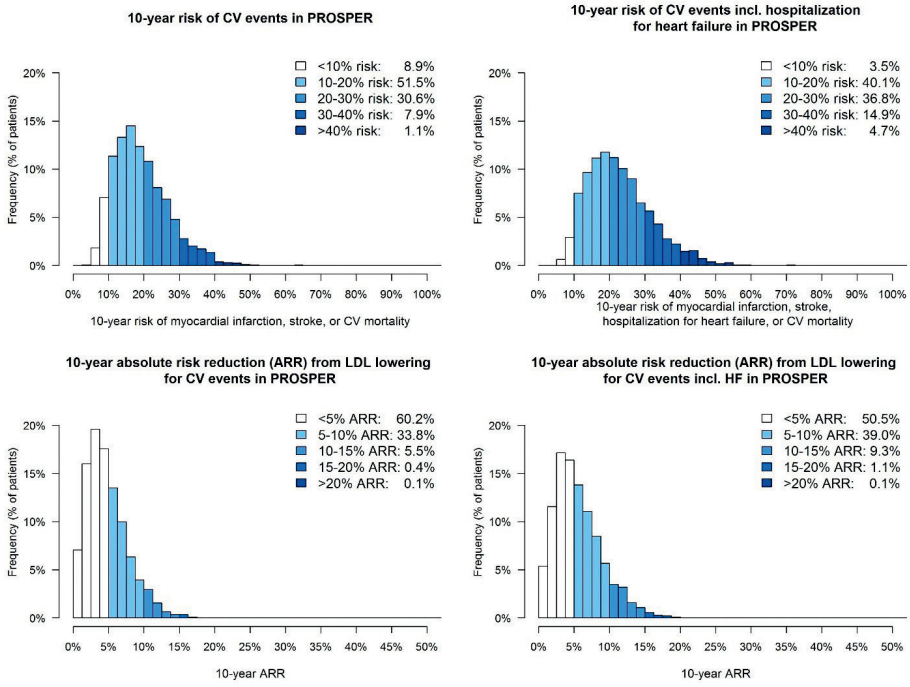
Discussion

The current report describes the development, recalibration, and external validation of a new competing-risk adjusted model for older individuals aged over 65 years without pre-existing CVD – SCORE2-OP to estimate 5- and 10-year risk of incident CVD. There is a wide range in estimated individual CVD event risk in older persons. Using SCORE2-OP, individualized effects of CVD risk factor treatment can be estimated, e.g. from blood pressure lowering or lipid lowering, which can be used for treatment decision making in clinical practice. The full clinical tool for individualized estimations will be made available to use in online calculators.

In the SCORE2-OP project investigators from 3 previously published older person CV risk algorithms joined forces by combining datasets and using advanced methodology for data analyses. The original SCORE O.P. model,[16] derived in more than 40,000 European older individuals (including participants from the CONOR study) estimated risk of fatal CVD. However, it did not take into account non-fatal CVD events, (such as non-fatal stroke), that are clinically relevant in older persons, and was not adjusted for competing non-CVD mortality risk. Another risk model derived in CONOR is the

NORRISK2 model for CVD risk estimation in elderly men and women up to age 79 years.[17] This risk score is competing risk adjusted, includes interaction terms with age, and was externally validated within Norway, but it was not recalibrated or externally validated outside Norway. Additionally, it was not derived specifically in older persons, including persons aged <65 years.[17,20] The older person-specific risk score derived in the PROSPER trial is competing-risk adjusted, and estimates the risk of fatal *and* non-fatal CVD events.[2] However, this risk model was derived in a relatively small study population from a randomized clinical trial, and did not include age interactions.

Figure 5: Distribution of estimated 10-year non-fatal and fatal CVD events and estimated 10-year absolute risk reduction from lipid lowering in older persons with cholesterol >2.6 mmol/L in the PROSPER trial (n = 3,051).



The SCORE2-OP model has combined these previous efforts and as such has several important strengths and advantages. First, the coefficients been derived in a large population-based cohort study, specifically in older persons. The model has been externally validated in populations with different baseline risks including both cohorts and trials from several countries. It was shown that SCORE2-OP recalibrated to the different risk regions corresponds well to the regional estimated WHO incidence rates, suggesting that calibration between estimated and observed risk is good for all risk regions. Although the discrimination in the external study populations is only moderate, the excellent calibration shows that the risk model can be used for clinical

decision making and risk communication. For this purpose, calibration is arguably the more important metric than discrimination.[40] Use of the risk model in regions outside of the included countries should be done with caution, as no validation has (yet) been performed outside of these regions.

Second, SCORE2-OP can be used to estimate the risk for the combined outcome of both fatal and non-fatal CVD events. Especially in older persons, non-fatal CVD events may be of clinical importance, as they may severely impact quality of life. The model also gives the option to include hospitalization for heart failure in the composite endpoint, which is an important source of morbidity in the older population.[41] In clinical practice, this may therefore be a very relevant endpoint for older persons especially when considering the consequences of heart failure for quality of life.

Third, the model is competing risk adjusted and includes age-interactions for all risk factors to account for differences in the relationship between risk factors and outcomes across different ages. This allows for estimations of 5- and 10-year prognosis truly tailored to the individual person.

Fourth, the model has been recalibrated using contemporary CVD rates currently available for the different risk regions using WHO data. The method used for systematic recalibration has previously been shown to give reliable estimations with good agreement between estimated and observed risks.[30] The recalibration methods avoid reliance on sparse or unreliable cohort or country-level data, providing stable recalibrations using age- and sex-specific CVD rates and risk factor levels of each risk region. Due to the flexible recalibration approach based on the most recent registry data, the model can easily be updated in the future to accommodate changes in CVD risk and risk factor levels in populations over time. If individual countries or even regions within a country have reliable data sources available, the model may even be recalibrated for even more precise risk estimations in that country or region. Because the same risk regions and data sources were used for systematic recalibration of SCORE2-OP as used in the SCORE2 project,[18] these two models can be used next to each other with persons naturally progressing from the SCORE2 model to SCORE2-OP as they get older.

Finally, the model can be used to estimate the absolute CVD risk reduction from blood pressure and cholesterol-lowering to blood pressure and LDL-cholesterol treatment goals, by applying the HRs from meta-analyses or clinical trials in older persons to the SCORE2-OP risk estimations. Higher levels of non-HDL-c confer a smaller increase in CV risk in older persons compared to young and middle-aged people. It should be noted that lowering cholesterol produces significant reductions in major vascular events irrespective of age, although there is still less direct evidence of benefit among people older than 75 years without a history of previous vascular

disease.[42] In general older persons are at high 10-year CVD risk as age is a major driver of risk. For older persons there are currently no CVD risk threshold for initiating risk factor lowering treatment in international guidelines. Should those thresholds appear, these may differ according to age as both the potential harms and the gain in CVD-free life expectancy from preventive therapy heavily depend on age. National and international guidelines need to consider (different) treatment thresholds for young, middle-aged and older persons. For example, the Norwegian guideline for primary prevention of CVD has a graded recommendation for consideration of intervention with pharmacological risk factor management (10-year CV risk over 5% in ages 45 - 54 years, over 10% in ages 55 - 64 years and over 15% in ages 65 - 74 years).[43] Using the SCORE2-OP model, no uncertainty regarding individual predictions was estimated. 10-year risk of CVD events can already be hard to interpret in clinical practice and having to interpret confidence intervals as well might make risk communication even more difficult, rather than more informed. Clinicians who want to incorporate the uncertainty of treatment decisions could consider adding the confidence intervals from meta-analyses or trials in the calculation of the ARR.

Estimation of absolute benefit may therefore guide treatment decisions in a shared decision making process taking frailty, biological age and patient preferences into account. Although on average the CVD risk is high in older persons, the current study shows that there is a wide distribution in 10-year CVD event risk in older persons, and that risk factor treatment does not necessarily yield a clinically significant benefit in all older persons. Therefore, in the future it might be interest to focus more on lifetime benefit from risk factor treatment based on lifetime CVD risk calculators.[44–46]

Several potential limitations of the current study should also be considered. First, the model was developed in a cohort study from the low-risk region alone. As such, the assumption is made that the model coefficients are transferrable to other risk regions. Previous studies have indeed shown homogeneity of model coefficients across different geographical regions and also across time for a CVD risk model, indicating transferability of model coefficients across different populations.[18,28] Results from the current study have shown that discrimination was adequate in all countries where external validation was performed, indicating transferability of model coefficients was valid, although this validation could not be performed in all risk regions due to lack of adequate data. Ideally, the SCORE2-OP algorithm should be validated in those regions as soon as reliable data are available in these regions.

Second, for the systematic recalibration approach estimated total CVD event incidence rates rather than observed CVD event incidence rates were used within the four risk regions by using a multiplier-based approach. This approach is based on the assumption that the multipliers are valid across all countries within the same risk region. Previous studies have shown that the multipliers showed good consistency

across both different cohorts from the same region and across time.[18] As such, we believe that this assumption is sufficiently met to give reliable estimations of total CVD event risk after systematic recalibration.

Third, part of the European validation data consisted of trial populations rather than unselected cohort data. Whereas the discrimination in our cohort populations was acceptable, especially compared to discrimination of a general risk model (namely ASCVD) in the same populations, slightly lower C-indices were reported in the external validation in the trial populations. Trial populations often make up a much more selected proportion of the population at large in comparison to cohort data (e.g. HYVET only contains patients aged 80 or older, with SBP ranging from 156 to 200 mmHg) and the maximum C-index is strongly associated to the distribution of risk within a study population.[40] Therefore, it is likely that the discrimination in these trials is an underestimation of the discrimination in real-life populations. As regional calibration (i.e. goodness of fit of the model) is satisfactory for all risk regions, the model can be used reliably for risk communication and treatment decisions in older persons.

Fourth, during model derivation in CONOR, no adjustment was made for treatment of risk factors at baseline. The assumption is made that, for example for cholesterol or blood pressure levels, the *current* risk factor level is predictive of the 10-year risk, regardless of whether this is treated or untreated. SCORE2-OP can thus be used for estimating 10-year risk in both untreated and treated individuals. However, caution should be given when risk factor treatment has been recently initiated. However, SCORE2-OP can be used for making treatment decisions in persons on a stable treatment regimen. Together with the fact that only one baseline risk factor measurement was used, which means that there may be underestimation of risk associations due to "regression dilution",[47,48] this may contribute to the relatively low discrimination. Additionally, no adjustment was made for the potential initiation of risk factor treatment during study follow-up, which may also influence discrimination. However, it has been shown that accounting for statin drop-in during follow-up in model development had only a limited impact on model performance.[49]

Fifth, predictors related to co-morbidity or frailty (e.g. kidney function, height and body weight, co-morbidity at baseline) may be important determinants for CVD risk in older persons, but were not included in SCORE2-OP due to the availability in the data sources. Including the number of drugs used as a measure of co-morbidity added to the predictive accuracy in the PROSPER older person score,[25] but this variable was not available in all relevant data sources.

Finally, an inherent limitation of absolute risk estimations, is that older individuals are invariably at higher risk for CVD than younger individuals with the same risk

factors. As higher CVD risk translates to higher absolute risk reductions, this may give the impression that risk factors such as blood pressure and LDL-cholesterol should always be treated in the very old. It should be noted that 5- or 10-year CVD risk estimation should be combined with some assessment of treatment benefit, as life expectancy could be limited, together with patient preferences to make individual treatment decisions. For this purpose, lifetime treatment benefit approaches could be used, such as the LIFE-CVD model for primary prevention.[44]

In conclusion, the competing risk adjusted SCORE2-OP model to estimate 5- and 10-year CVD event risk in persons aged over 65 years was derived, recalibrated, and externally validated in four risk regions. These models can be used for communicating the risk of CVD events and potential benefits from risk factor treatment, and may facilitate shared decision making in CVD risk management in older persons.

References

1. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res 2012;110:1097–1108.
2. Stam-Slob MC, Visseren FLJ, Jukema J, Graaf Y van der, Poulter NR, Gupta A, Sattar N, Macfarlane PW, Kearney PM, Craen AJM de, Trompet S. Personalized absolute benefit of statin treatment for primary or secondary prevention of vascular disease in individual elderly patients. Clin Res Cardiol 2017;106:58–68.
3. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology 2009;20:555–561.
4. Hohl CM, Dankoff J, Colacone A, Afilalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med 2001;38:666–671.
5. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. Pharmacoepidemiol Drug Saf 2010;19:901–910.
6. Dorresteijn JAN, Visseren FLJ, Ridker PM, Wassink AMJ, Paynter NP, Steyerberg EW, Graaf Y van der, Cook NR. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ 2011;343:d5888.
7. Kent DM, Steyerberg E, Klaveren D van. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. BMJ 2018;363:k4245.
8. Sabayan B, Gussekloo J, Ruijter W de, Westendorp RGJ, Craen AJM de. Framingham stroke risk score and cognitive impairment for predicting first-time stroke in the oldest old. Stroke 2013;44:1866–1871.
9. Ruijter W de, Westendorp RGJ, Assendelft WJJ, Elzen WPJ den, Craen AJM de, Cessie S le, Gussekloo J. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ 2009;338:a3083.
10. Rodondi N, Locatelli I, Aujesky D, Butler J, Vittinghoff E, Simonsick E, Satterfield S, Newman AB, Wilson PWF, Pletcher MJ, Bauer DC. Framingham risk score and alternatives for prediction of coronary heart disease in older adults. PLoS One 2012;7:e34287.
11. Nanna MG, Peterson ED, Wojdyla D, Navar AM. The Accuracy of Cardiovascular Pooled Cohort Risk Estimates in U.S. Older Adults. J Gen Intern Med 2020;35:1701–1708.
12. Kannel WB, D'Agostino RB. The Importance of Cardiovascular Risk Factors in the Elderly. Am J Geriatr Cardiol 1995;4:10–23.
13. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation 2016;133:601–609.
14. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. J Am Geriatr Soc 2010;58:783–787.
15. Field TS, Gurwitz JH, Harrold LR, Rothschild J, DeBellis KR, Seger AC, Auger JC, Garber LA, Cadoret C, Fish LS, Garber LD, Kelleher M, Bates DW. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc 2004;52:1349–1354.
16. Cooney MT, Selmer R, Lindman A, Tverdal A, Menotti A, Thomsen T, DeBacker G, Bacquer D De, Tell GS, Njolstad I, Graham IM. Cardiovascular risk estimation in older persons: SCORE O.P. Eur J Prev Cardiol 2016;23:1093–1103.
17. Selmer R, Igland J, Ariansen I, Tverdal A, Njølstad I, Furu K, Tell GS, Klemsdal TO. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. Eur J Prev Cardiol 2017;24:773–782.
18. SCORE2 Working Group. European Society of Cardiology SCORE2 risk prediction algorithms: revised models to estimate 10-year risk of cardiovascular disease in Europe. Under review.

19. Naess O, Søgaard AJ, Arnesen E, Beckstrøm AC, Bjertness E, Engeland A, Hjort PF, Holmen J, Magnus P, Njølstad I, Tell GS, Vatten L, Vollset SE, Aamodt G. Cohort profile: cohort of Norway (CONOR). Int J Epidemiol 2008;37:481–485.

20. Rabanal KS, Igland J, Tell GS, Jenum AK, Klemsdal TO, Ariansen I, Meyer HE, Selmer RM. Validation of the cardiovascular risk model NORRISK 2 in South Asians and people with diabetes. Scand Cardiovasc J 2020;1–7.

21. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 1989;129:687–702.

22. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, Staa T van, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–836.

23. Bulpitt C, Fletcher A, Beckett N, Coope J, Gil-Extremera B, Forette F, Nachev C, Potter J, Sever P, Staessen J, Swift C, Tuomilehto J. Hypertension in the Very Elderly Trial (HYVET): protocol for the main trial. Drugs Aging 2001;18:151–164.

24. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux A V, Folsom AR, Greenland P, Jacob DRJ, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881.

25. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RGJ. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–1630.

26. SPRINT Research Group, Wright J, Williamson J, Whelton P, Snyger J, Sink K, Rocco M, Reboussin D, Rahman M, Oparil S, Lewis C, Kimmel P, Johnson K, Goff DJ, Fine L, Cutler J, Cushman W, Cheung A, Ambrosius W. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103–2116.

27. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JTJ, Pajewski NM. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. JAMA 2016;315:2673–2682.

28. Kaptoge S, Pennells L, Bacquer D De, Cooney MT, Kavousi M, Stevens G, Riley LM, Savin S, Khan T, Altay S, Amouyel P, Assmann G, Bell S, Ben-Shlomo Y, Berkman L, Beulens JW, Björkelund C, Blaha M, Blazer DG, Bolton T, Bonita Beaglehole R, Brenner H, Brunner EJ, Casiglia E, Chamnan P, Choi Y-H, Chowdry R, Coady S, Crespo CJ, Cushman M, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Heal 2019;7:e1332–e1345.

29. Steyerberg EW. Clinical prediction models: a practical approach to development, validation and updating. New York, USA: Springer; 2009.

30. Pennells L, Kaptoge S, Wood A, Sweeting M, Zhao X, White I, Burgess S, Willeit P, Bolton T, Moons KGM, Schouw YT van der, Selmer R, Khaw K-T, Gudnason V, Assmann G, Amouyel P, Salomaa V, Kivimaki M, Nordestgaard BG, Blaha MJ, Kuller LH, Brenner H, Gillum RF, Meisinger C, Ford I, Knuiman MW, Rosengren A, Lawlor DA, Volzke H, Cooper C, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. Eur Heart J 2019;40:621–631.

31. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet 2017;389:37–55.

32. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet 2016;387:1513–1530.

33. World Health Organization. WHO Mortality Database. https://apps.who.int/healthinfo/statistics/mortality/whodpms/ (7 December 2020)

34. Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelser C, Gulati M, Masoudi FA, Goff DC. Estimating Longitudinal Risks and Benefits From Cardiovascular Preventive Therapies Among Medicare Patients. J Am Coll Cardiol 2017;69:1617–1636.

35. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med 2019;170:51.

36. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. BMC Med 2015;13:1–10.

37. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–1898.

38. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967.

39. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–590.

40. Cook NR. Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction. Circulation 2007;115:928–935.

41. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, Ferranti S de, Despres J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, et al. Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. Circulation 2016;133:447–454.

42. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 2019;393:407–415.

43. Klemsdal TO, Gjelsvik B, Elling I, Johansen S, Kjeldsen SE, Kristensen Ø, Madsen S, Njølstad I, Selmer R, Tonstad S, Voie H. New guidelines for the prevention of cardiovascular disease. Tidsskr Nor Laegeforen 2017;137.

44. Jaspers NEM, Blaha MJ, Matsushita K, Schouw YT van der, Wareham NJ, Khaw K-T, Geisel MH, Lehmann N, Erbel R, Jöckel K-H, Graaf Y van der, Verschuren WMM, Boer JMA, Nambi V, Visseren FLJ, Dorresteijn JAN. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Eur Heart J 2019;31:1–10.

45. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB, Massaro JM, Graaf Y van der, Cramer MJM, Kappelle LJ, Borst GJ de, Steg PG, Visseren FLJ. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: The SMART-REACH model. J Am Heart Assoc 2018;7.

46. Dorresteijn JAN, Kaasenbrood L, Cook NR, Kruijsdijk RCM van, Graaf Y van der, Visseren FLJ, Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. BMJ 2016;352:i1548.

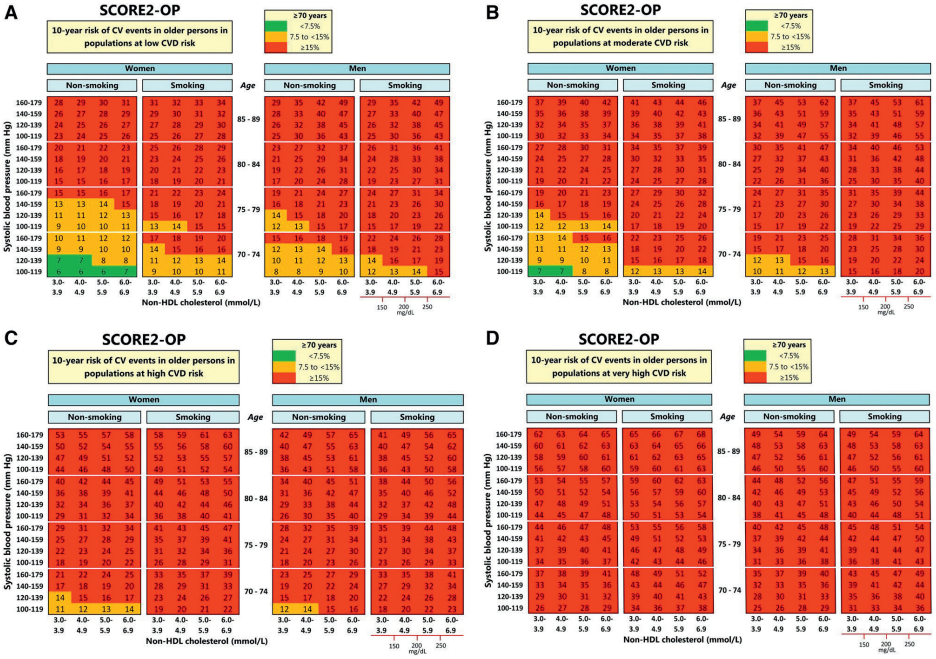
47. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. BMJ 2010;340:c2289.

48. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. Am J Epidemiol 1999;150:341–353.

49. Xu Z, Arnold M, Stevens D, Kaptoge S, Pennells L, Sweeting MJ, Barrett J, Angelantonio E Di, Wood AM. Prediction of Cardiovascular Disease Risk Accounting for Future Initiation of Statin Treatment. Am J Epidemiol 2021;

Supplementary Materials

Supplementary Appendix: Regional risk charts of predicted 10-year cardiovascular disease risks.



Supplementary Methods

1.1 Model derivation study population

Cohort of Norway (CONOR) is a collaboration between several population based regional health surveys in Norway carried out between 1994 and 2003. The data collection followed a standard procedure. Participants underwent a simple physical examination and a non-fasting blood sample was drawn at the screening site. Participants filled in one or more questionnaires about their health and disease, family history of disease, use of medication and lifestyle [1].

Cardiovascular endpoints were obtained through the CVDNOR project (CVDNOR) project (https://cvdnor.b.uib.no) [2,3]. The CVDNOR project is a collaboration between the University of Bergen and the previous Norwegian Knowledge Centre for the Health Services, now part of the Norwegian Institute of Public Health. CVDNOR includes information from cardiovascular-related discharge diagnosis [International Classification of Disease (ICD)-9 codes 390-459 or ICD-10 codes I00-I99)] retrieved from the electronic patient administrative systems (PAS) of all Norwegian hospitals from 1994 through 2009. The project obtained date and cause of death from the Cause of Death Registry and information about hospital stays 2008-2014 from the Norwegian Patient Registry. CONOR was linked to the endpoint registries by means of the personal identification number unique for each resident in Norway and this leads to high level of complete outcome registration of both fatal and non-fatal events [4,5].

The Regional Ethics Committee approved the baseline health surveys and follow-up record linkages. The participants have signed a written informed consent for research and linkage of health registries.

Selmer *et al.* have previously used the linked CONOR data in the development of a Norwegian cardiovascular risk model (NORRISK2) which is included in the Norwegian guidelines for prevention of cardiovascular disease [6]. Furthermore, the CONOR study has previously been used for model derivation for SCORE O.P., using only the fatal CVD endpoint [7].

1.2 External validation study populations

ARIC

This study is a cross-sectional analysis, using data from visit 6 (2016–2017) of the ARIC study, which was originally designed to investigate the natural history of atherosclerotic disease from mid- to late-life. 15,792 participants were recruited during 1987–1989 from four communities in the United States (Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD) and completed the first study visit (visit 1). The participants subsequently completed six study visits (visit 2 in

1990–1992, visit 3 in 1993–1995, visit 4 in 1996–1998, visit 5 in 2011–2013, visit 6 in 2016–2017, and visit 7 in 2018–19). Additionally, they were contacted annually (semiannually, beginning in 2012) to obtain updated information on medical history and lifestyle. For the current study, baseline data collected at visit 5 were used, including assessment for cardiovascular disease and risk factors including laboratory testing. The ARIC study was approved by the institutional review board of each participating center, and written informed consent was obtained from participants at each study visit. Further details on ARIC study design have been described elsewhere [8].

CPRD

We used data from the UK Clinical Practice Research Datalink (CPRD) that were linked to Hospital Episode Statistics (HES) inpatient data, and Office for National Statistics (ONS) mortality data. The CPRD database prospectively collects primary care records from consenting general practitioners across the UK. Approximately 7% of the UK population are represented in the database. CPRD obtained approval from a national research ethics committee for researchers to use deidentified data for observational research subject to the approval of a study protocol from the Independent Scientific Advisory Committee. Approximately 80% of CPRD practices registered in England have consented to their patients' primary care records being linked to other data sources. HES records include all National Health Service–funded inpatient hospitalizations in England since 1997, including diagnoses and procedures. ONS-linked mortality data contain the underlying cause of death, recorded on the death certificate, along with up to 15 other recorded causes of death. The data requested for this study covers the period 2006 to 2017 and participants could be enrolled in the study at any time between these years. Further details on CPRD study design have been described elsewhere [9].

HYVET

HYVET was a double blind placebo controlled trial of an antihypertensive regimen (thiazide-like diuretic, indapamide 1.5 sustained release, with the optional addition of an angiotensin converting enzyme inhibitor, perindopril 2–4 mg) in those aged 80 and over. Participants with hypertension (mean systolic BP 160–199 mm Hg and a standing systolic BP ≥140 mm Hg) were recruited between February 2001 and October 2007 from over 90 primary and secondary care centres in 13 countries and randomised to receive trial treatment or matching placebo. All required ethical approvals were obtained. Participants were seen during a 2-month placebo run-in phase, at baseline, every 3 months during the first year and every 6 months thereafter. Trial endpoints were reported as they occurred and included death, stroke, myocardial infarction, and incident or worsening heart failure. Validation of trial endpoints was carried out by a trial endpoint committee of international experts blinded to trial treatment allocation and with full access to supporting documentation, for example, death certificates, hospitalization reports etc. Median follow-up was 1.8 years, after the study was

stopped preliminary at second interim analysis due to a significant reduction in all-cause mortality in the active treatment arm. Full details of the HYVET protocol have been published elsewhere [10].

MESA

MESA is a multi-ethnic, community-based, multiethnic prospective cohort study of 6,814 men and women of 4 self-identified racial/ethnic groups (non-Hispanic whites, African American, Hispanic, or Chinese American). MESA participants were recruited between 2000 and 2002 in 6 field centers: Wake Forest University in Winston-Salem, NC; Columbia University in New York, NY; The Johns Hopkins University in Baltimore, MD; University of Minnesota in Minneapolis; Northwestern University in Chicago, IL; and University of California in Los Angeles. The age range at baseline was 45 to 84 years, and participants had to be free of clinically overt atherosclerotic cardiovascular conditions to be eligible for inclusion. All study participants provided written informed consent at each examination, and study protocols were approved by site-specific Institutional Review Boards at respective MESA-participating institutions. Further details on the MESA study design have been described elsewhere [11].

PROSPER

The PROSPER trial is a large, prospective multicenter randomized clinical trial that assessed whether treatment with pravastatin diminishes the risk of major vascular events in older individuals from three countries (the Netherlands, Scotland, Ireland). Between December 1997 and May 1999, 5804 men and women aged 70–82 years were enrolled if they had pre-existing vascular disease or increased risk due to smoking, hypertension, or diabetes. Participants with the following conditions were not recruited in the PROSPER study: congestive heart failure; significant arrhythmia; cognitive impairment (Mini-Mental Score Examination score <24). Included participants were randomly assigned to either pravastatin or placebo for an average 3.5-year intervention period. The full methodology of PROSPER has been described in more detail elsewhere [12].

SPRINT

The design, eligibility, and baseline characteristics of SPRINT have been described elsewhere [13,14]. SPRINT was a randomized, controlled, open-label trial that was conducted at 102 clinical sites (organized into 5 clinical center networks) in the United States. The trial protocol was approved by the institutional review board at each participating site. Study participants were required to be at increased risk for cardiovascular disease. A person was excluded if he or she had type 2 diabetes, a history of stroke, symptomatic heart failure within the past 6 months or reduced left ventricular ejection fraction (<35%), a clinical diagnosis of or treatment for dementia, an expected survival of less than 3 years, unintentional weight loss (>10% of body weight) during the preceding 6 months, an SBP of less than 110 mm Hg following 1 minute of standing, or resided in a nursing home. Sociodemographic data were collected at baseline, whereas both clinical and laboratory data were obtained at baseline and every 3 months. Eligible participants were assigned to a systolic blood-pressure target of either less than 140 mm Hg (the standard-treatment group) or less than 120 mm Hg (the intensive-treatment group). For the current study, patients aged 65 years or older were included between November 2010 and March 2013. To investigate the effect of blood pressure lowering therapy in older persons, a subgroup of elderly aged 75 years or older was pre-specified in the study design and, as such, well-represented within the study population [14].

A committee unaware of treatment assignment adjudicated the protocol-specified clinical outcomes. The primary cardiovascular disease outcome was a composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. Secondary outcomes included all-cause mortality and the composite of the SPRINT primary outcome and all-cause mortality. In August 2015, the trial was ended preliminarily after interim analysis, after a median follow-up of 3.3 years.

1.3 Model development (adapted from Hageman et al. 15)

The interlinked stages of model development, including model derivation and recalibration are summarised in **Supplementary Methods Figure 1**. An overview of the process as follows: Fine and Gray models were derived using data from CONOR (**Box 1**). Four geographical risk regions were defined according to the age-standardized country-specific cardiovascular mortality rates. For each region, annual age- and sex-specific mortality rates were then translated to 10-year mortality risk estimates, allowing for competing risk of non-CVD death (**Box 2**). In order to translate 10-year mortality to 10-year risk of fatal and non-fatal CVD, region- age- and sex-specific multiplication factors were estimated using representative registry data and cohorts from each risk region. Multiplication factors were defined as the ratio between the cumulative incidence of fatal and non-fatal CVD events and the cumulative

incidence of fatal CVD (**Box 3**). Multipliers were then used to translate region, sex and age specific 10-year mortality incidence to expected 10-year risk of fatal and non-fatal CVD events (**Box 4**). Region, sex and age-specific predicted 10-year risks were then estimated using the core, un-calibrated 10-year risk models (derived in **Box 1**) with region, sex and age-specific risk factors from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) (**Box 5**). The region and sex and age-specific predicted risks (from **Box 5**) were compared to expected risks (from **Box 4**) and rescaling factors were estimated to recalibrate the models for each region and sex (**Box 6**). Finally, the rescaling factors are applied with the original un-calibrated model to give new, recalibrated risk predictions in new individuals (**Box 7**).

The methods applied in **Boxes 1, 2, 3** and **6** warrant further explanation and are detailed as follows:

Box 1: Model derivation
For model derivation, sex-specific coefficients were estimated using Fine and Gray competing risk-adjusted models. Risk predictors were age, sex, current smoking, history of diabetes mellitus, systolic blood pressure, and total and HDL cholesterol and age-interactions were added for all predictors. Continuous risk predictors were centred before analysis. There were no or minimal violations of the proportional hazards assumptions as assessed visually based on plotted Schoenfeld residuals.

Box 2: Estimation of 10-year competing risk adjusted mortality for each risk region
Estimates of CVD event incidence were based on the most recent WHO cardiovascular mortality rates, which were transformed to estimates of CVD event incidence using a multiplier approach. WHO cause-specific mortality rates are supplied by every country and coded in ICD-9 or ICD-10. Rates included mortality from all causes included in the original SCORE endpoint [16] (Supplementary Table 1). Non-CVD mortality was defined as all mortality from causes not included in the SCORE endpoint.

For every age-group, CVD mortality rates were used which were observed at the midpoint of the projected 10-year follow-up period, so the CVD mortality rates of one 5-year age-group ahead (i.e. for prediction in the 40 to 44 year age-group the rates for 45 to 49 years were used as these are at the midpoint of the 10-year interval). WHO rates of both the fatal cardiovascular outcome and the competing outcome non-CVD mortality were converted to 1–year mortality risks (r) using the following formula:

$$r = 1 - e^{(-fatal\ rate)}$$

The 1-year risks of fatal CVD were corrected for the competing risk of non-CVD death and extrapolated to 10-year risks. This was done using life-tables with 1-year intervals,

using follow-up time as a timescale [17,18]. For every interval, CVD-free survival was calculated using the following formula:

$$S_{t+1} = S_t \times (1 - r_{cvd,t} - r_{comp,t}).$$

In which S_t=probability of being alive at start of interval *t*; S_{t+1}=probability of being healthy and alive at end of interval *t*; and $r_{cvd,t}$ and $r_{comp,t}$ are the probabilities of experiencing a fatal CVD event or competing events respectively during interval *t*, given disease-free survival up to start of interval *t*; For each 1-year interval of the 10-year timeframe of interest, the cause-specific CV mortality risk was calculated using:

$$\text{CVrisk}_t = \frac{r_{cvd,t}}{r_{cvd,t} + r_{comp,t}} * (S_t - S_{t+1})$$

The 10-year cumulative cause-specific risk was calculated as the sum of the 1-year cause-specific risks:

$$\text{CVrisk}_{t1-10} = \sum_{1-10} CVrisk_t$$

Box 3: Estimation of Multipliers to convert mortality to incidence estimates in each risk region

To convert 10-year mortality estimates to incidence estimates, age- and sex-specific multiplication factors were defined as:

$$\frac{Cumulative\ 10\ year\ incindence\ total\ CV\ events_{without\ prior\ CVD}}{Cumulative\ 10\ year\ incindence\ fatal\ CV\ events_{entire\ population}}$$

These allowed the population level mortality statistics, which are calculated among the whole population, regardless of prior disease status, to be converted into first event incidence estimates, representative of the target primary prevention population (those without prior CVD). Multiplication factors were derived in Clinical Practice Research Datalink [9] (CPRD; n = 2,589,074) for the low risk region, the Swedish Patient Registry [19] for the moderate risk region (n = 5,252,592), the Estonian biobank [20] (n = 67,474) for the high risk region, and the HAPIEE study [21] (Lithuania + Russia, n = 16,521) for the very high risk region. In each cohort and sex, two Fine and Gray models, adjusted for baseline age and age-squared were fit: one modelling 1st CVD event as the outcome and using only individuals without prior CVD, and one with fatal CVD as the outcome and including all participants (regardless of prior disease). The relevant cumulative 10-year incidence was then estimated using each model, for each age group, and age group-specific 10-year CVD event risk was then estimated as follows:

$$\mathrm{CVDrisk}_{total,10} = \frac{Cumulative\ incindence\ fatal + nonfatal\ CV\ events_{without\ prior\ CVD}}{Cumulative\ incindence\ fatal\ CV\ events_{General\ population}} * \mathrm{CVrisk}_{t1-10}$$

Multiplication factors were assumed to be stable within each region and over time [15]. To aggregate the multipliers from the different cohorts to a single set of multipliers for the low/moderate and for the high/very high risk regions, the mean was calculated of all relevant multipliers, weighted by the size of the multiplier-derivation cohort. The region-, age- and sex-specific multipliers can be found in Supplementary Table 4. Age and sex-specific 10-year mortality CVD rates and derived incidence rates are shown for each region in Supplementary Figure 4. The age-specific and sex-specific estimated CVD event rates used for recalibration are presented by region in Supplementary Table 5.

Box 6: Relate expected to predicted risks to calculate rescaling factors for model recalibration

Recalibration of the core SCORE2-OP model was performed separately for each geographical risk region, using a previously described methodology, which is summarized in Supplementary Methods Figure 2 [15,22]. This involved the use of regional age- and sex-specific mean risk factor levels (from NCD-RisC) and age- and sex-specific estimates of expected cumulative 10-year risk, estimated as described above. We used the core SCORE2-OP risk models to estimate 10-year predicted risk of the endpoint for each of the age groups using the mean risk factor values. Having completed this process for each age group, as shown in Figure 2 we then regressed transformed expected 10-year risk across age groups on that predicted by the core SCORE2-OP models to derive recalibration factors (the intercept and slope of the resulting regression line, Supplementary Methods Table 1). The SCORE2-OP risk models, rescaled using the recalibration factors were then used to estimate appropriate risks for each potential risk factor combination, for a new individual or for formation of the example risk charts.

A stepwise approach for how to estimate individualized 10-year CVD event risk estimations can be found in Supplementary Methods Table 2, with individual example calculations shown in Supplementary Methods Table 3.

1.4 Missing data

Because complete case analysis may lead to loss of statistical power and possible bias, values of predictors were imputed by single regression imputation with predictive mean matching for all cohort data. As the CPRD consists of care-as-usual data, missing data was much more frequent and missingness was more likely to correlate with cardiovascular disease risk. Therefore, multiple imputation was performed for the external validation in CPRD with fully conditional specification using 5 imputed datasets.

1.5 Uncertainty of risk predictions

In clinical practice, clinical decision are made based on the best available evidence. In risk prediction, this is the point estimate as estimated with the risk model. However, it is good to realize that there is uncertainty around these point estimates. To calculate confidence intervals surrounding individual predicted risks based on the uncertainty of all model coefficients, risk predictions were repeated with the lower or upper bounds of the confidence intervals of all beta coefficients **(Table 2)**. In **Supplementary Figure 8** the uncertainty around the point estimates is presented in risk charts.

1.6 Predicting treatment effects from risk factor treatment using SCORE2-OP

It has previously been shown that risk estimations can be combined with relative treatment effects from trials to calculate absolute individualized treatment effects [18].

To show the potential use of using SCORE2-OP in daily practice, we included analyses on the individual absolute benefit of blood pressure lowering and lipid lowering in older persons. To estimate the effect of blood pressure lowering on CVD, average relative treatment effects were added to SCORE2-OP, using a hazard ratio (HR) of 0.80 per 10 mmHg SBP reduction taken from a large meta-analysis for blood pressure lowering [23], and estimating the benefit from the reduction of office SBP to the target of <140mmHg for persons with hypertension at baseline (SBP >140 mmHg) from the HYVET and SPRINT trials (both blood pressure lowering trials [13,24]). For lipid lowering, an HR of 0.78 per 1 mmol/L LDL reduction was used [25], and the treatment benefit of lowering LDL cholesterol to < 2.6 mmol/L was estimated for all patients with an LDL cholesterol >2.6 mmol/L from the PROSPER trial (a lipid lowering trial [12]). For both treatment effects, it was assumed that the HR can be applied across the entire age range. Indeed, no evidence for heterogeneity of these treatment effects across different age ranges has been found [23,26,27].

First, we tested the assumption that the same relative treatment effect can be used in all individuals by making a Cox model in respectively the HYVET, SPRINT, and PROSPER study populations including a *"model linear predictor * trial allocation"* interaction term [28].

Then treatment benefit was calculated for the respective risk factor treatment by combining the hazard ratio with the individualized estimated 10-year CVD event risk (here shown for SBP reduction):

$$Risk_{with\ treatment} = 1 - (1 - risk_{original}^{\exp\left(\log(HR)\times\left(\frac{SBP\ reduction}{10}\right)\right)})$$

Treatment benefit for individual patients is defined as the absolute risk reduction (ARR) from treatment:

$$ARR = \left(risk_{original} - risk_{with\ treatment}\right) * 100$$

Histograms were constructed showing the distribution of treatment effects from blood pressure lowering in the combined study population from the HYVET and SPRINT trials (Figure 4), and from lipid lowering in the PROSPER trial (Figure 5), respectively.

Supplementary Methods Table 1: Region-specific rescaling factors

	Men		**Female**	
	Scale 1	*Scale 2*	*Scale 1*	*Scale 2*
Low risk region	-0.34	1.19	-0.52	1.01
Moderate risk region	0.01	1.25	-0.1	1.1
High risk region	0.08	1.15	0.38	1.09
Very high risk region	0.05	0.7	0.38	0.69

Rescaling factors for the SCORE2-OP model to scale predicted risks to the target population in very risk region, based recent nationally representative estimates of incident cardiovascular disease and risk factor levels.

Supplementary Methods Table 2: A stepwise approach to estimating 10-year CVD risk for an individual patient

Calculate 10-year CVD event risk	
1. Calculate individual model linear predictor (LP)	**$LP = \Sigma\beta_{sex\text{-}specific} * (x - x_{cen})$** Where: $\beta_{sex\text{-}specific}$ are the sex-specific coefficients (Table 2), x is the individual person value of the predictor x_{cen} is the value at which each predictor was centered: age = 73, SBP = 150; total cholesterol = 6; HDL cholesterol =1.4.
2. Calculate the original (or unrecalibrated) 10-year risk ($\theta_{original}$)	**$\theta_{original} = 1 - basesurv_{sex\text{-}specific}$^exp(LP – $meanLP_{sex\text{-}specific}$)** Where: $Basesurv_{sex\text{-}specific}$ is the sex-specific 10-year baseline survival for an average patient: for men, 0.758; for women, 0.808 meanLP is the sex-specific mean linear predictor: for men, 0.093; for women, 0.229
3. Use the age-, sex-, and region-specific rescaling factors from Supplementary Methods Table 1 to calculate the recalibrated 10-year risk for your individual patient (θ)	**$\theta = 1 - \exp(-\exp(Scale1 + Scale2 \times \ln(-\ln(1- \theta_{original}))))$** Multiply by 100 to get your individual 10-year risk as a percentage.
Calculate 10-year risk of CVD events incl. heart failure	
Include the multiplication factor from Supplementary Table 4 in step 2, the rest of the procedure is identical	**$\theta_{original} = 1 - basesurv_{sex\text{-}specific}$^exp(LP – $meanLP_{sex\text{-}specific}$ - $\ln(multiplier_{age,sex})$)** Where: $Multiplier_{age,sex}$ is the age- and sex-specific multiplier

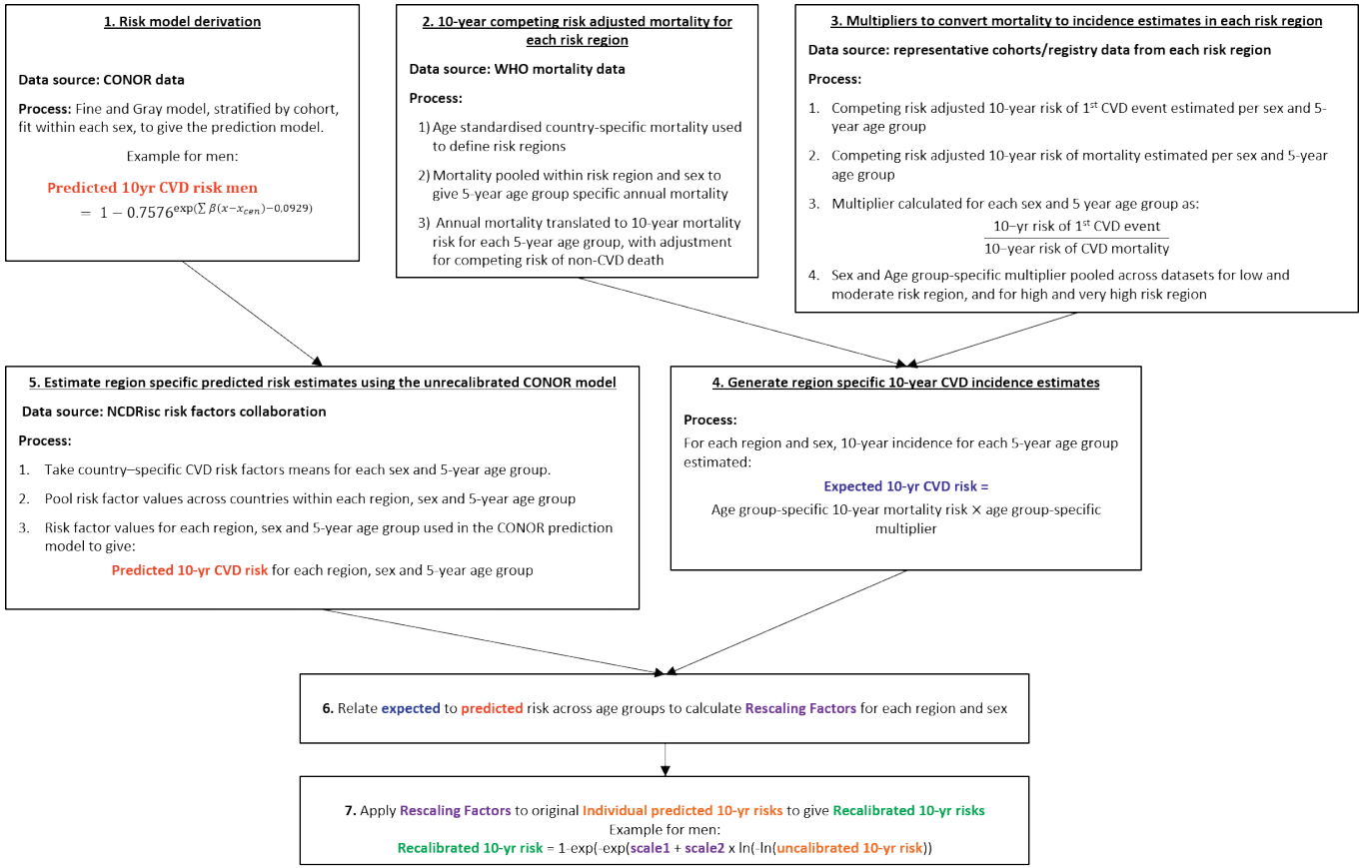
Supplementary Methods Table 3: Example calculations for the estimated CVD event risk for an individual patient using SCORE2-OP

Calculation of estimated 10-year CVD event risk using SCORE2-OP			
Individual risk factor levels	**Model coefficients (women)**		**Calculation of 10-year CVD event risk using SCORE2-OP**
Sex = female Age = 75 Total cholesterol = 5.5 HDL cholesterol =1.3 SBP = 140mmHg Diabetes = No Smoking = Yes	Age (per year)	0.0789	$\sum \beta(x - x_{cen})$ = 0.0789 x (75-73) + 0.6010 x 0 + 0.4921 x 1 + 0.0102 x (140-150) + 0.0605 x (5.5-6) - 0.3040 x (1.3-1.4) - 0.0107 x (75-73) x 0 - 0.0255 x (75-73) x 1 - 0.0004 x (75-73) x (140-150) - 0.0009 x (75-73) x (5.5-6) + 0.0154 x (75-73) x (1.3-1.4) = -0.5029 Unrecalibrated (original) risk: 10-yr risk = 1-0.8082^exp($\sum \beta (x - x_{cen}) - 0.229$) = 1-0.8082^exp(0.5029 – 0.229) = 0.2442 = 24.4% Recalibrate to low risk region: 10-yr risk = 1-exp(-exp(-0.85+0.82 x ln(-ln(1- original risk)))) = 1-exp(-exp(-0.85+0.82 x ln(-ln(1- 0.2442)))) = 0.1397 = 14%
	Diabetes	0.6010	
	Smoking	0.4921	
	SBP (per mmHg)	0.0102	
	Total cholesterol (per mmol/L)	0.0605	
	HDL cholesterol (per mmol/L)	-0.3040	
	Diabetes interaction with age	-0.0107	
	Smoking interaction with age	-0.0255	
	SBP interaction with age	-0.0004	
	Total cholesterol interaction with age	-0.0009	
	HDL cholesterol interaction with age	0.0154	

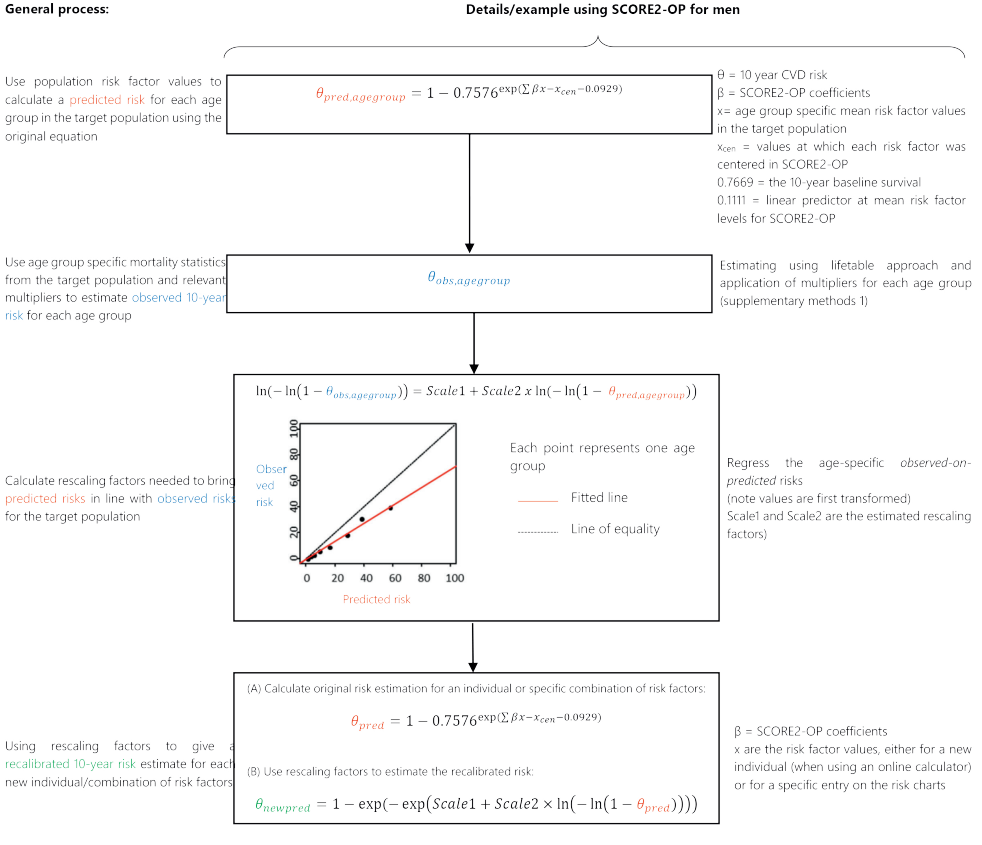
Supplementary Methods Table 3 (continued)

Individual risk factor levels	Model coefficients (men)		Calculation of 10-year CVD event risk using SCORE2-OP
Sex = male Age = 75 Total cholesterol = 5.5 HDL cholesterol =1.3 SBP = 140mmHg Diabetes = No Smoking = Yes	Age (per year)	0.0634	$\sum \beta(x - x_{cen})$ = 0.0634 x (75-73) + 0.4245 x 0 + 0.3524 x 1 + 0.0094 x (140-150) + 0.0850 x (5.5-6) - 0.3564 x (1.3-1.4) - 0.0174 x (75-73) x 0 - 0.0247 x (75-73) x 1 - 0.0005 x (75-73) x (140-150) + 0.0073 x (75-73) x (5.5-6) + 0.0091 x (75-73) x (1.3-1.4) = -0.3298 Unrecalibrated (original) risk: 10-yr risk = 1-0.7576^exp($\sum \beta (x - x_{cen}) - 0.0929$) = 1-0.7576^exp(0.3298 – 0.0929) = 0.2966 = 29.7% Recalibrate to low risk region: 10-yr risk = 1-exp(-exp(-0.61+0.89 x ln(-ln(1- original risk)))) = 1-exp(-exp(-0.61+0.89 x ln(-ln(1- 0.2966)))) = 0.1930 = 19.3%
	Diabetes	0.4245	
	Smoking	0.3524	
	SBP (per mmHg)	0.0094	
	Total cholesterol (per mmol/L)	0.0850	
	HDL cholesterol (per mmol/L)	-0.3564	
	Diabetes interaction with age	-0.0174	
	Smoking interaction with age	-0.0247	
	SBP interaction with age	-0.0005	
	Total cholesterol interaction with age	0.0073	
	HDL cholesterol interaction with age	0.0091	

Supplementary Methods Figure 1: SCORE2-OP model development process



Supplementary Methods Figure 2: Methods used for recalibration of risk scores



Supplementary Table 1: Endpoint definitions

1. Fatal cardiovascular disease– cause specific mortality due to any of the following:	
Endpoints included	**ICD10-codes**
Hypertensive disease	I10-16
ischemic heart disease	I20-25
Arrhythmias, heart failure	I46-52
Cerebrovascular disease	I60-69
Atherosclerosis/AAA	I70-73
instantaneous death and death within 24h of symptom onset	R96.0-96.1
The following ICD codes are to be excluded from the above endpoint:	
Myocarditis, unspecified	I51.4
subarachnoid hemorrhage	I60
Subdural hemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I68.2
Moyamoya	I67.5

2. Hospitalization from cardiovascular disease	
Endpoints included	**ICD10-codes**
Non-fatal myocardial infarction	I21-23
Non-fatal stroke	I60-69
Excluded from the non-fatal stroke endpoint:	
Subarachnoid hemorrhage	I60
Subdural hemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I682
Moyamoya	I675

Supplementary Table 2: Age- and sex- standardized CVD mortality rates per country

Countries	Age- and sex-standardized CVD mortality rates (per 100,000 persons)	Year collected
Low risk region		
France	70.9	2014
Israel	76.7	2015
Spain	89.4	2015
Netherlands	89.9	2016
Switzerland	90.2	2015
Denmark	90.4	2015
Norway	90.8	2015
Luxembourg	92.9	2015
Belgium	99.2	2015
United Kingdom	99.7	2015
Moderate risk region		
Iceland	101.0	2016
Portugal	107.9	2014
Sweden	109.0	2016
Italy	110.1	2015
San Marino	-	
Ireland	111.5	2014
Cyprus	111.5	2016
Finland	128.5	2015
Austria	130.9	2016
Malta	133.3	2015
USA	131.8	2016
Greece	138.8	2015
Germany	139.0	2015
Slovenia	143.3	2015

Countries	Age- and sex-standardized CVD mortality rates (per 100,000 persons)	Year collected
High risk region		
Albania	184.5	2010
Czech Republic	195.0	2016
Turkey	199.5	2015
Kazakhstan	214.0	2015
Croatia	214.6	2016
Poland	223.8	2015
Estonia	234.8	2015
Slovakia	239.2	2014
Hungary	274.1	2016
Bosnia and Herzegovina	279.2	2014
Very high risk region		
Armenia	306.3	2016
Lithuania	309.0	2016
Georgia	309.6	2015
Latvia	327.2	2015
Serbia	329.1	2015
Romania	330.5	2016
Montenegro	348.4	2009
Russian Federation	368.8	2015
TFYR Macedonia	387.8	2013
Belarus	395.4	2014
Azerbaijan	416.5	2007
Bulgaria	421.2	2014
Republic of Moldova	442.2	2016
Ukraine	476.7	2015
Kyrgyzstan	476.9	2015
Uzbekistan	478.6	2014
Egypt	543.7	2015
Morocco	-	
Syria	-	
Tunisia	-	
Lebanon	-	
Algeria	-	
Libya	-	

Supplementary Table 3: Age- and sex-specific multiplication factors for fatal CVD events to total events in the different risk regions

	Low/moderate risk region		High/very high risk region	
Age group	*Men*	*Women*	*Men*	*Women*
65-70	2.6	3.2	1.6	2.5
70-75	2.1	2.5	1.4	1.9
75-80	1.6	1.9	1.3	1.5
80-85	1.3	1.5	1.1	1.4
85+	1.1	1.1	0.9	1.0

Multiplication factors for the SCORE2-OP model specific for each age group, sex and region. Multiplication factors were defined as the ratio between the cumulative incidence of fatal CVD and the cumulative incidence of CVD events. Multipliers were used to multiply observed CVD mortality rates in the agegroup stated in this table and are therefore used to recalibrate 10-year risks in one age group below.

Supplementary Table 4: Age- and sex-specific multiplication factors in CONOR for the primary endpoint to secondary endpoint CVD events plus HF

Age group	**65**	**70**	**75**	**80**	**85+**
Men	1.10	1.15	1.19	1.20	1.17
Women	1.14	1.20	1.22	1.22	1.20

Supplementary Table 5: Regional risk factor levels and incidence rates used for recalibration

Agegroup	Region	Sex	Systolic blood pressure (mmHg)	Smoking (%)	Total cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	Diabetes mellitus (%)	Expected 10-year cumulative incidence (%)
65	Low	Men	140	19.5	4.9	1.3	16.8	8.7
70	Low	Men	141	17.2	4.8	1.3	17.3	12.3
75	Low	Men	143	16.5	4.7	1.3	17.1	17.1
85	Low	Men	144	15.8	4.4	1.3	15.3	24.8
65	Low	Women	136	15.2	5.4	1.7	11.3	5
70	Low	Women	139	13.4	5.3	1.7	12.6	8.6
75	Low	Women	141	12.3	5.2	1.6	13.6	14.1
85	Low	Women	145	10.9	5.3	1.6	15.6	25.8
65	Moderate	Men	140	18.6	5.1	1.3	18.5	11.6
70	Moderate	Men	142	15.9	5	1.3	18.7	16.2
75	Moderate	Men	143	14	4.9	1.3	18.3	22.1
85	Moderate	Men	142	11.5	4.7	1.3	16.3	34.2
60	Moderate	Women	136	12.2	5.6	1.6	13.6	6.3
65	Moderate	Women	138	10	5.5	1.6	14.8	10.8
70	Moderate	Women	141	8.8	5.4	1.6	15.6	18
75	Moderate	Women	141	7.6	5.4	1.6	17.7	35.3
85	Moderate	Women	148	28	5.1	1.3	20.6	16.9
65	High	Men	150	24.6	5	1.3	20.6	22.5
70	High	Men	150	22.3	4.9	1.3	19.7	30.1
75	High	Men	149	20.1	4.7	1.3	17.3	38.7

Supplementary Table 5 (continued)

Agegroup	Region	Sex	Systolic blood pressure (mmHg)	Smoking (%)	Total cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	Diabetes mellitus (%)	Expected 10-year cumulative incidence (%)
85	High	Men	144	12.4	5.5	1.5	17.6	11.8
65	High	Women	147	10.3	5.4	1.5	18.2	19
70	High	Women	149	9.1	5.3	1.5	18.2	35.7
75	High	Women	150	7.8	5.5	1.5	19.4	49.8
85	High	Women	149	39.9	5.2	1.3	19.8	29.1
65	Very high	Men	151	36.2	5.1	1.3	19.9	38.3
70	Very high	Men	152	32.7	5	1.3	19.2	43.6
75	Very high	Men	151	30.5	4.8	1.3	16.7	46.3
85	Very high	Men	147	4.2	5.5	1.5	19	24.3
65	Very high	Women	148	3.6	5.4	1.4	19.2	38.1
70	Very high	Women	150	3.4	5.3	1.4	19	50.6
75	Very high	Women	151	2.9	5.4	1.4	19.9	58.2
85	Very high	Women	140	19.5	4.9	1.3	16.8	8.7

Supplementary Table 6: Comparison between SCORE2-OP and ASCVD risk engine in terms of discrimination (Harrell's C-statistic [95% confidence interval])

	ASCVD	SCORE2-OP
ARIC	0.644 (0.618-0.669)	0.668 (0.643-0.693)
CPRD	0.663 (0.659-0.666)	0.657 (0.655-0.662)
MESA	0.645 (0.621-0.668)	0.654 (0.631-0.678)
Pooled trial populations	0.612 (0.593-0.630)	0.632 (0.613-0.651)

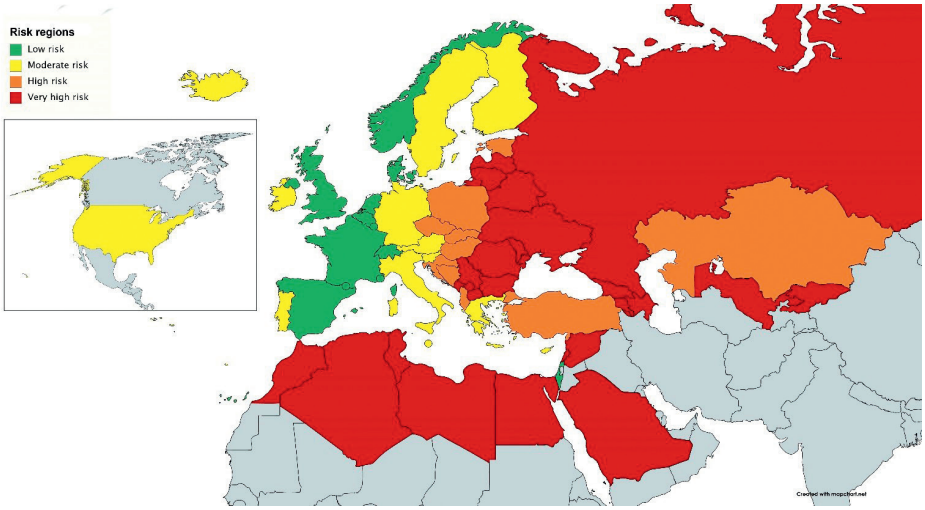
Supplementary Table 7: Comparison of the area under the curve of the Model Harrell's C-statistic, the 1-year time-dependent ROC and the time-dependent ROC at longer follow-up in the external validation cohorts

	Harrell's C-statistic	1-year time-dependent ROC	Time-dependent ROC**
ARIC	0.668 (0.643-0.693)	0.711 (0.646-0.777)	0.683 (0.655-0.710) at 5 years follow-up
CPRD*	0.657 (0.655-0.662)	0.679 (0.669, 0.688)	0.646 (0.642-0.650) at 10 years follow-up
MESA	0.654 (0.631-0.678)	0.701 (0.626-0.794)	0.692 (0.663-0.721) at 10 years follow-up
Pooled trial populations	0.632 (0.613-0.651)	0.639 (0.657-0.670)	0.677 (0.657-0.698) at 3 years follow-up

* Due to computational reasons, the time-dependent ROC was calculated using an unweighted rather than the weighted approach used in the other study populations. In this approach, patients censored without an event *before* 10 years follow-up were not included. This can lead to an underestimation of the actual area under the curve of the time-dependent ROC.

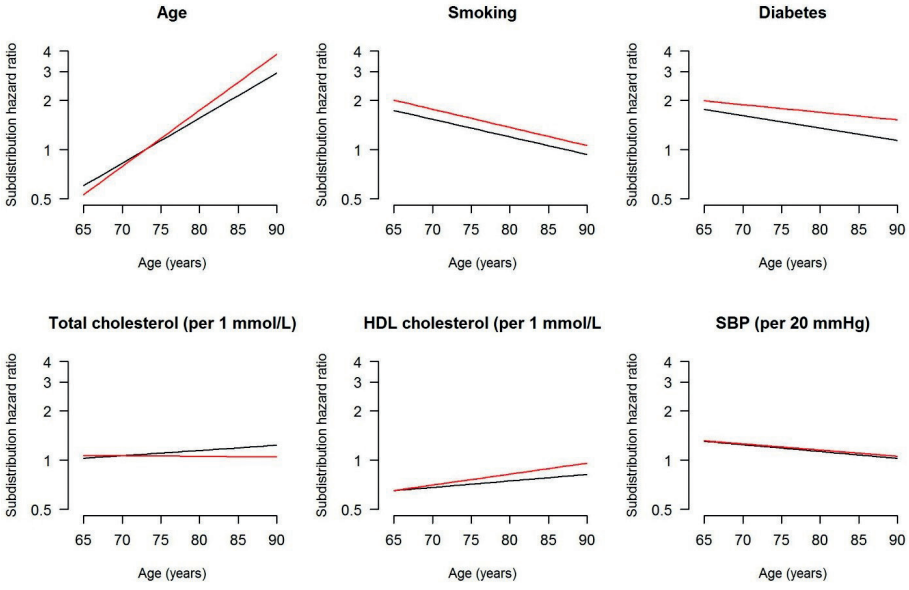
** Years of follow-up depending on the maximum number of years of follow-up available per study population that could give a reliable estimate of model performance, with a maximum of 10 years

Supplementary Figure 1: The distribution of countries in risk regions based on the age-standardized CVD mortality rates

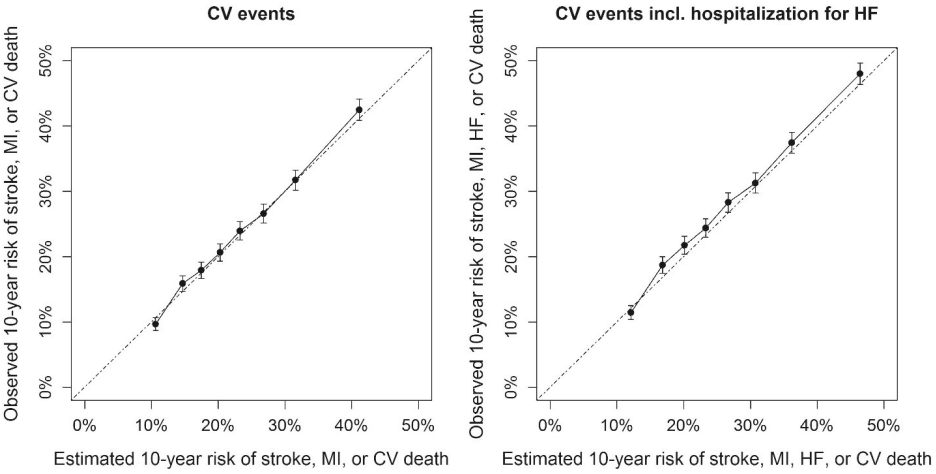


Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD chapters 9, I00-I99). The four groupings were: low risk (<100 CVD deaths per 100,000), moderate risk (100 to <150 CVD deaths per 100,000), high risk (150 to <300 CVD deaths per 100,000), and very high risk (≥300 CVD deaths per 100,000).

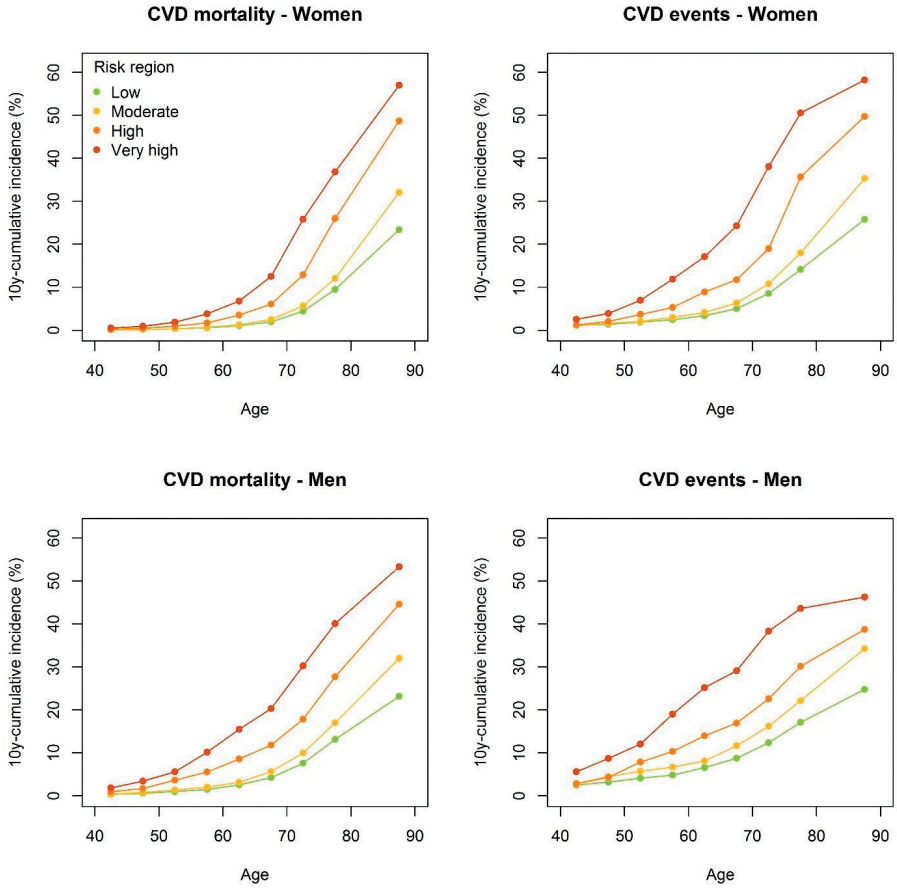
Supplementary Figure 2: The relative effect of risk factors at different ages (black=male; red=female)



Supplementary Figure 3: Calibration plots of observed versus estimated risks in deciles of risk in the CONOR study population (internal validation) for (left) CVD event risk, and (right) CVD event risk including hospitalization for heart failure

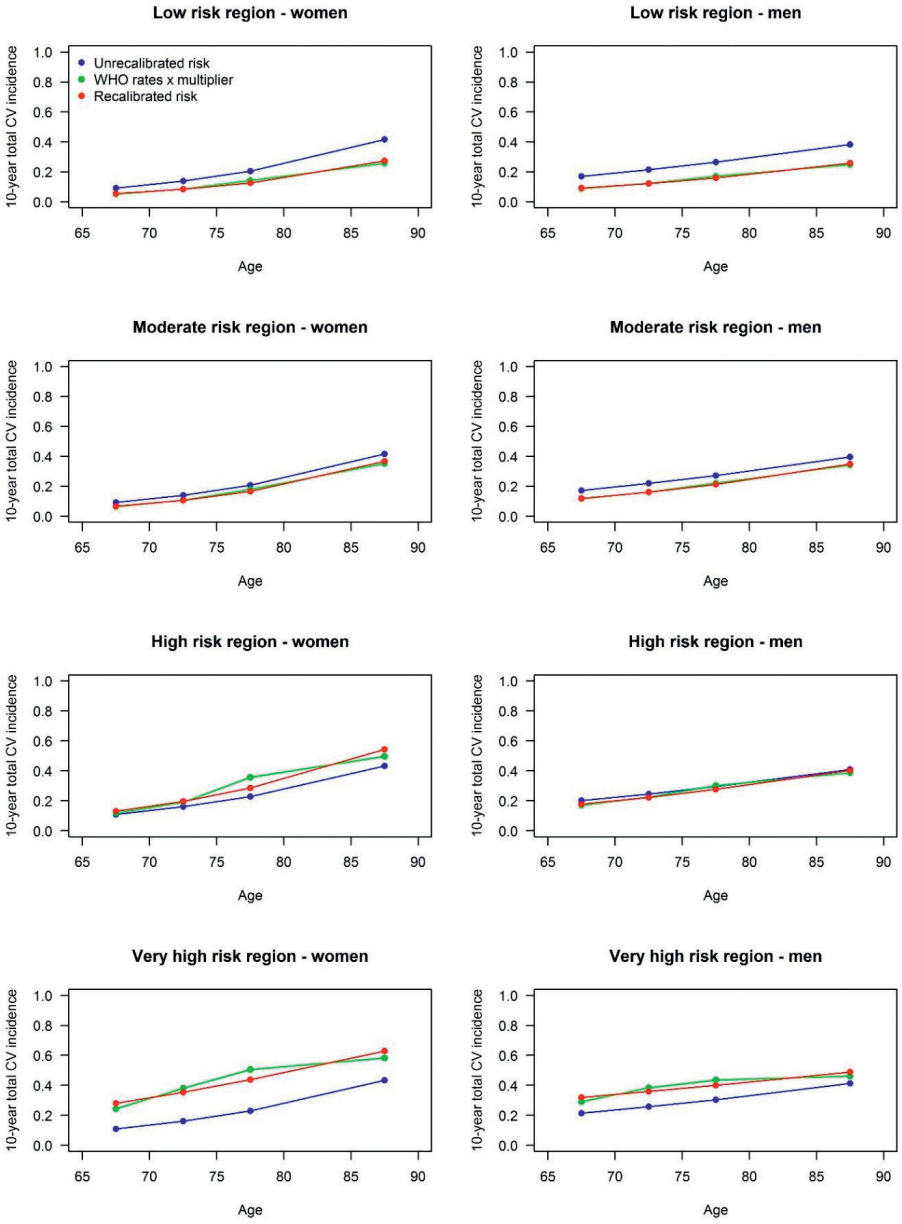


Supplementary Figure 4: Cardiovascular mortality and incidence in all risk regions in the entire middle-aged and older population.

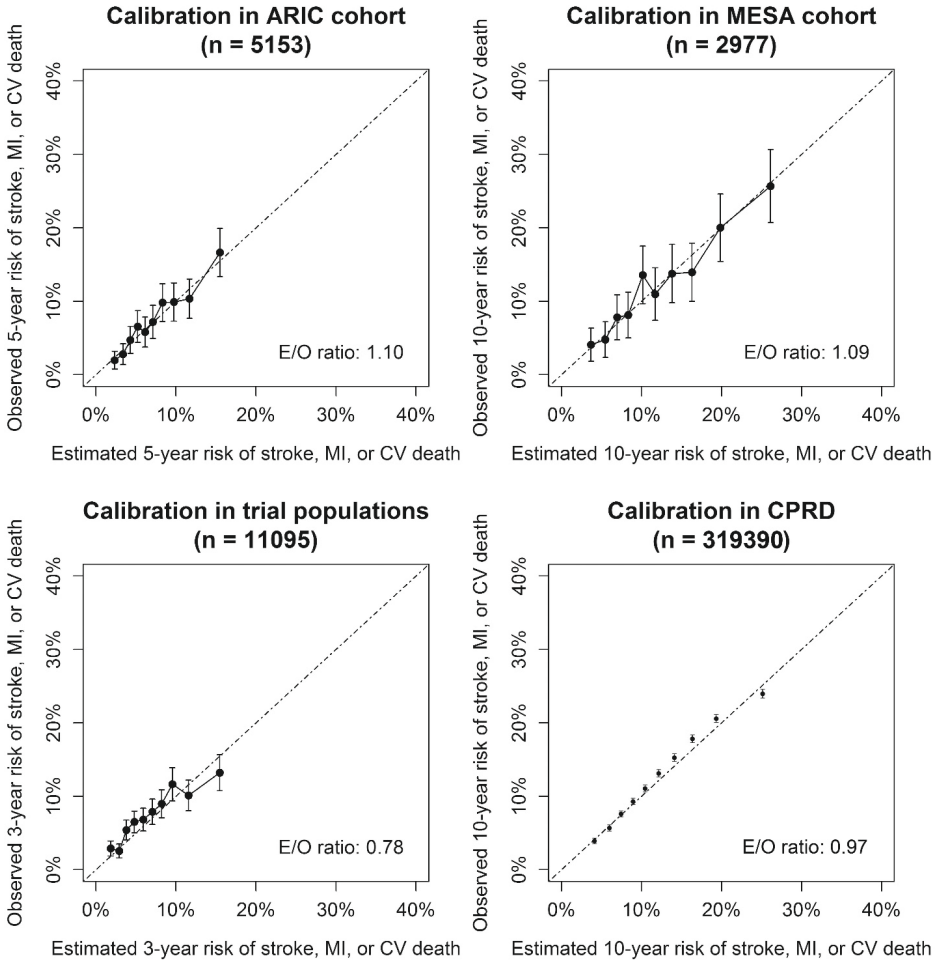


Regional age- and sex-specific CVD mortality rates (left) in the general population; regional age- and sex-specific CVD event rates in the primary prevention setting.

Supplementary Figure 5: Estimated CVD incidence rates and predicted risks

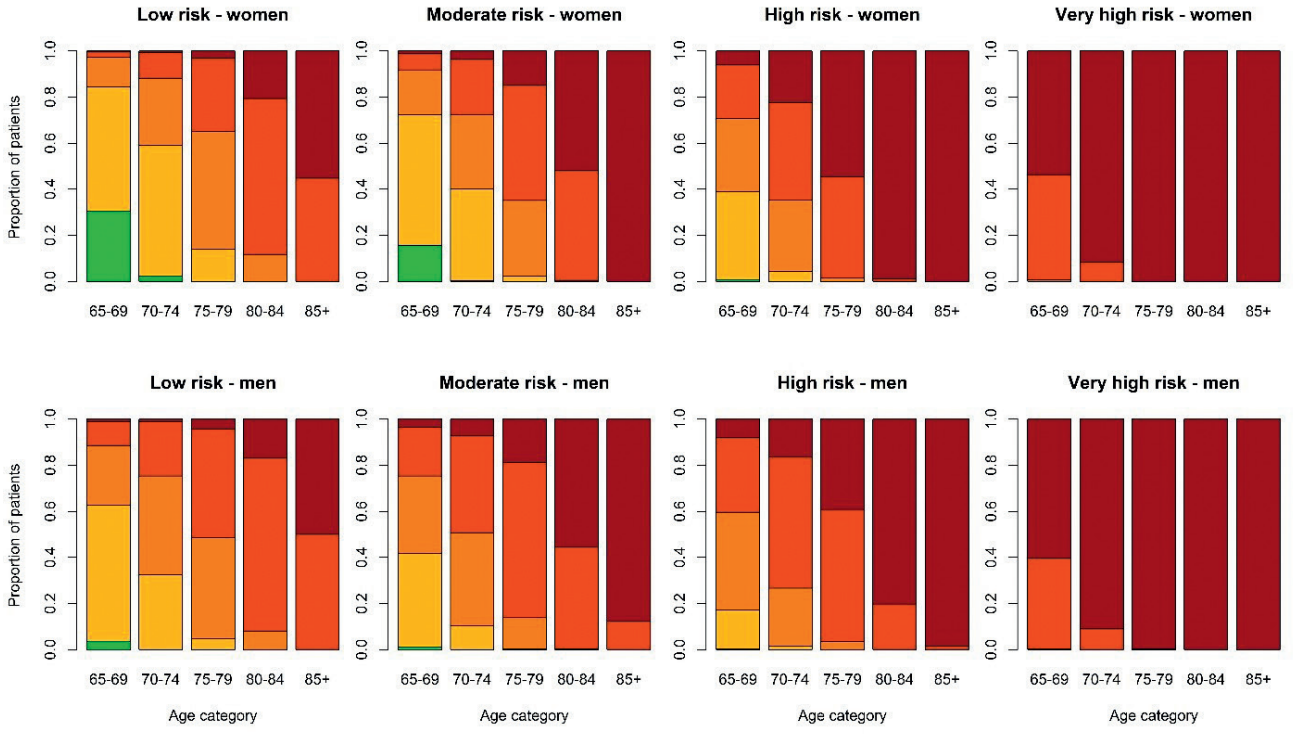


Supplementary Figure 6: Calibration plots of observed versus estimated (O/E) risks with O/E ratios within deciles of the external validation study populations. Risks were estimated for 3, 5, or 10 year time periods depending on available follow-up per study.



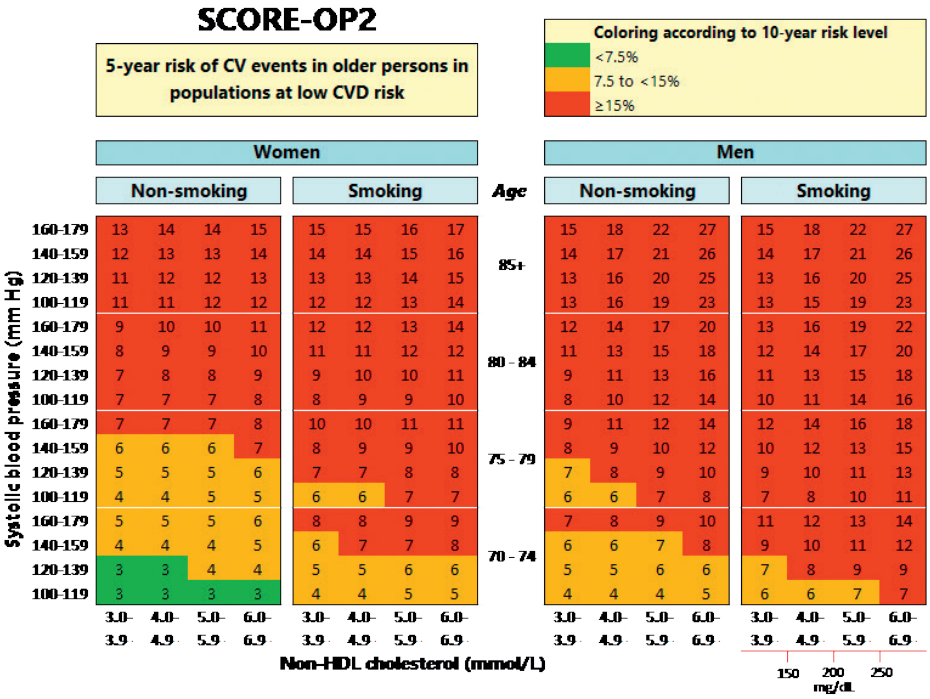
The estimated risks were recalibrated per study using the study-specific O/E ratio. The O/E ratio reflects the difference in baseline risk between the study population and risk region from which the study population comes, which may be affected due to participant selection and timeliness of the data.

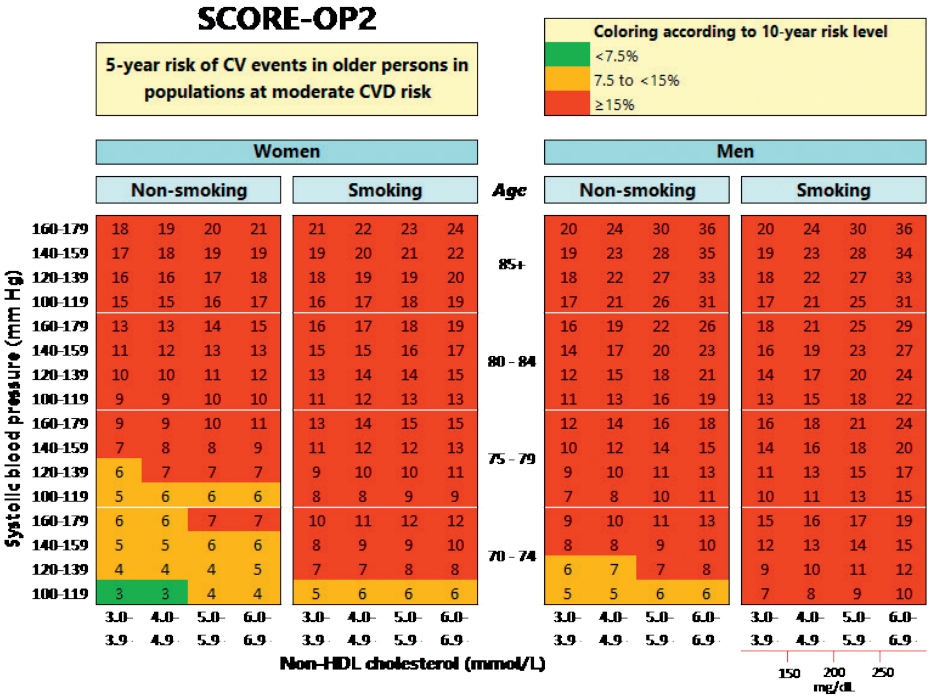
Supplementary Figure 7: Age- and sex-specific distributions of fatal and non-fatal CVD risk in the four risk regions according to SCORE2-OP.



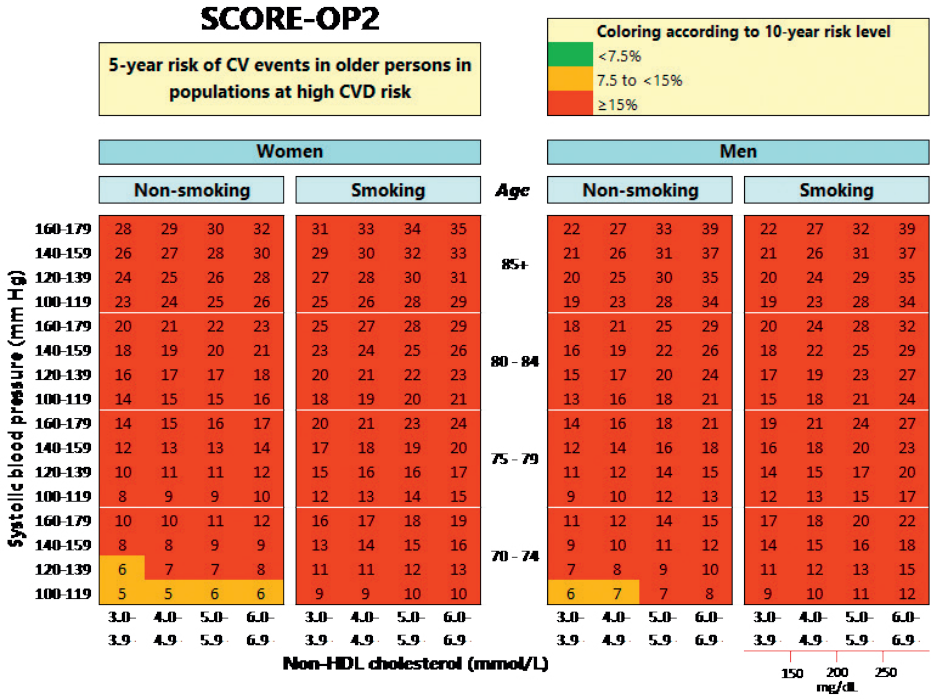
Age- and sex-specific risk distribution in the different risk regions, based on risk factor data in ARIC and MESA cohorts (n = 8,130).

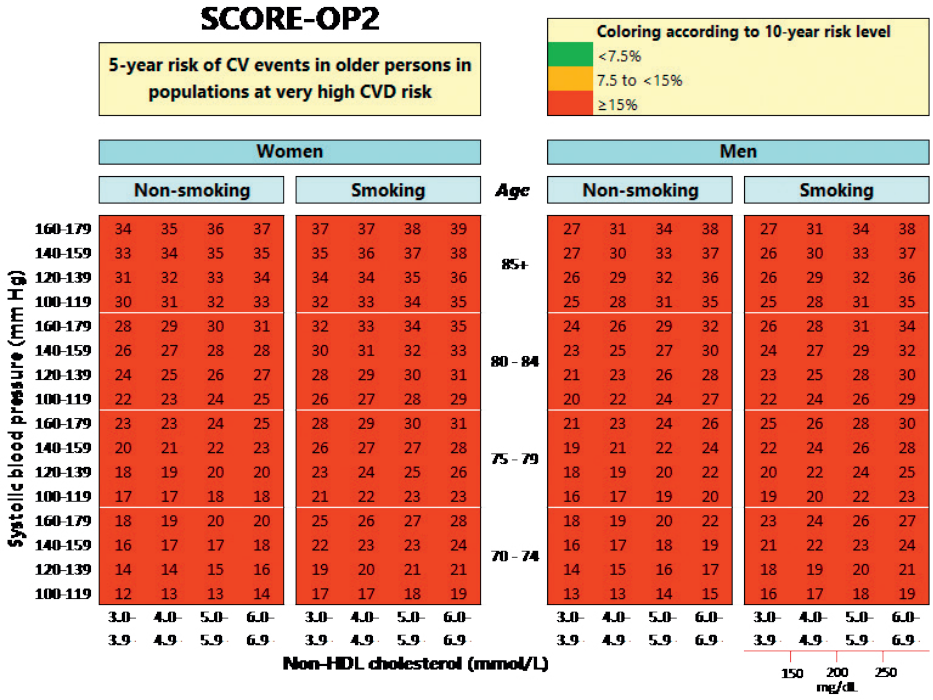
Supplementary Figure 8: Risk charts of 5-year risk in all four risk regions



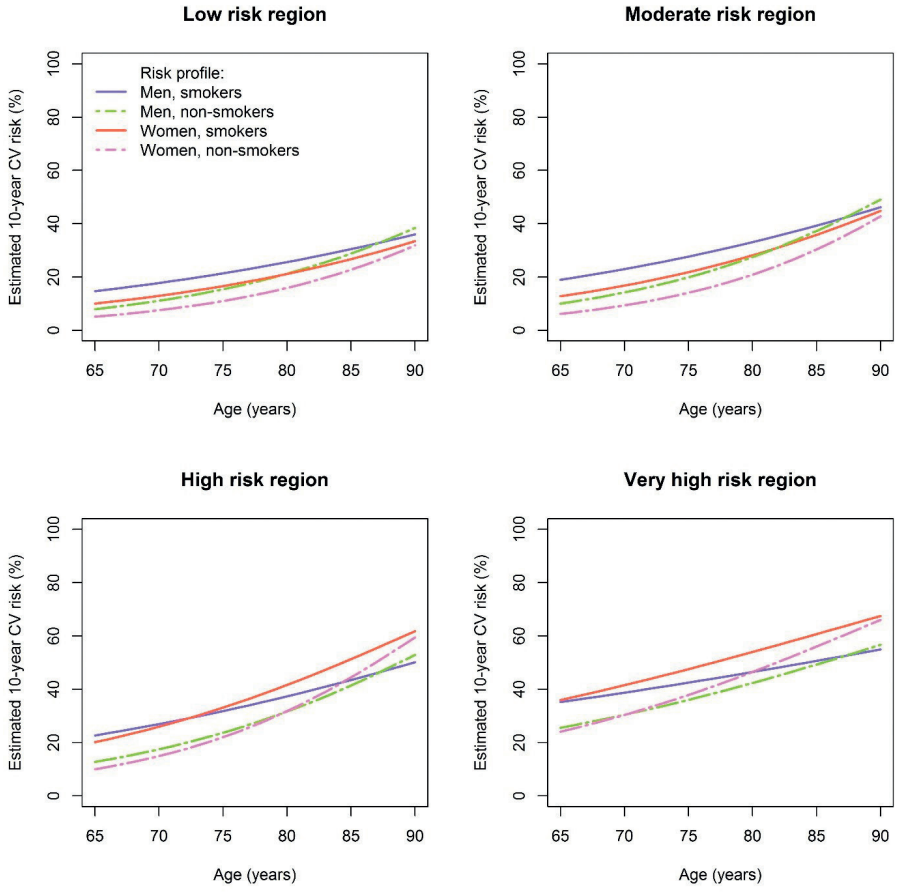


Supplementary Figure 8 (continued)



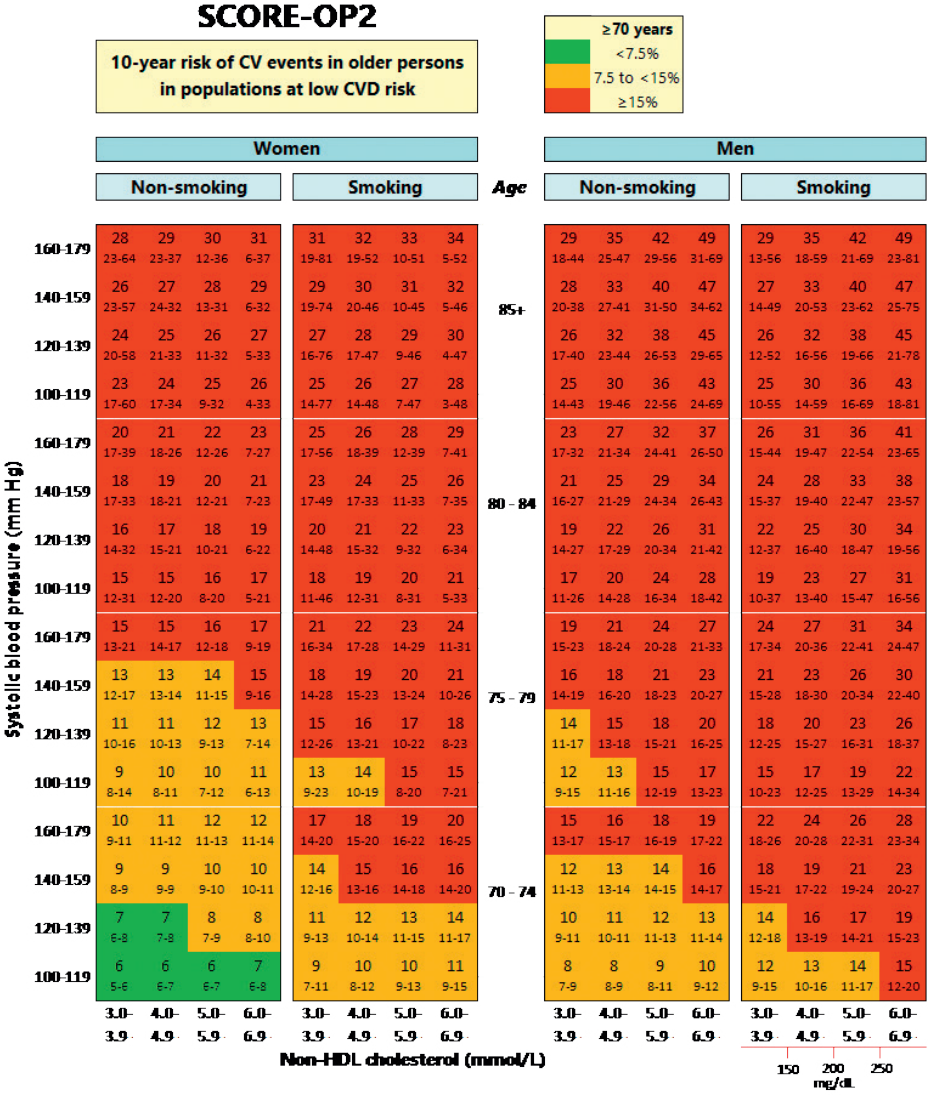


Supplementary Figure 9: SCORE2-OP predicted risks for given risk factors in all European regions

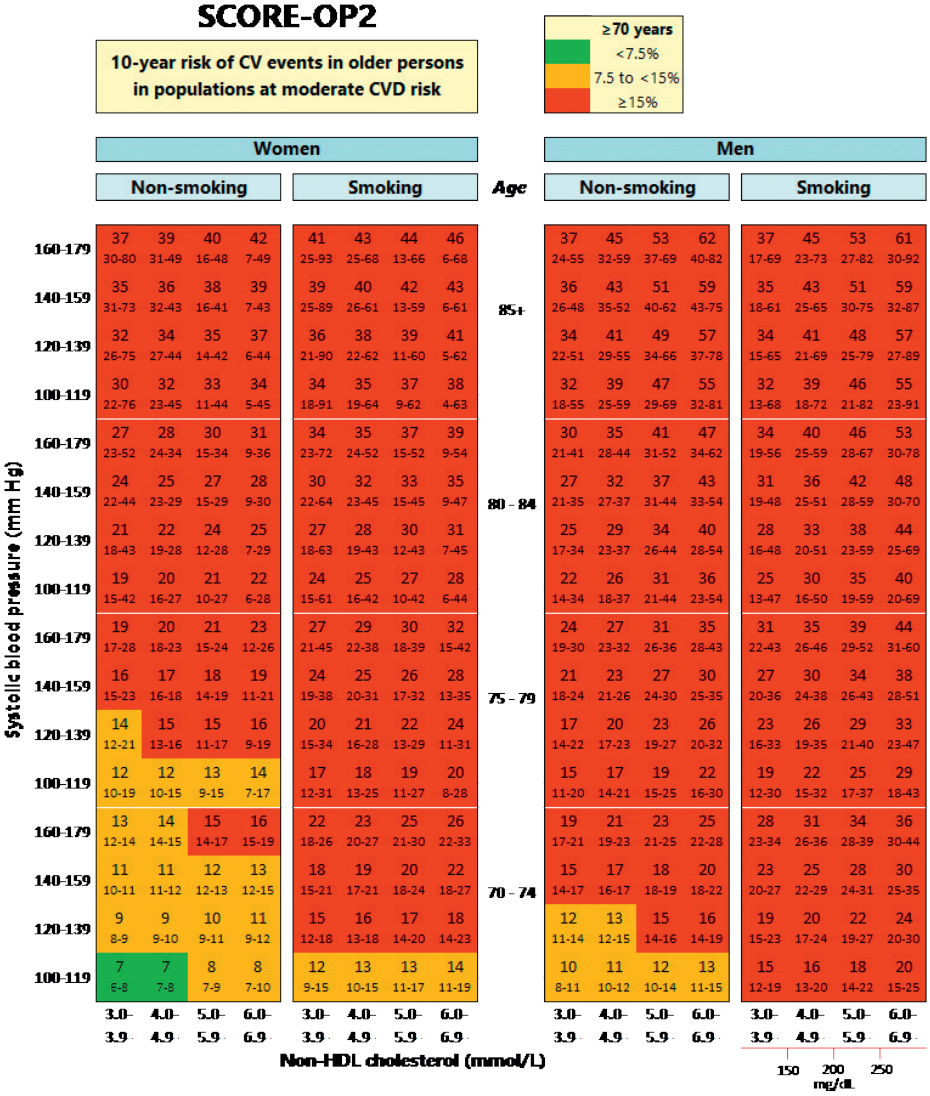


Predicted risks in all European regions for different risk profiles. Predictions for individuals with a non-HDL cholesterol of 4.5 mmol/l, and systolic blood pressure of 150mmHg, assuming no diabetes mellitus.

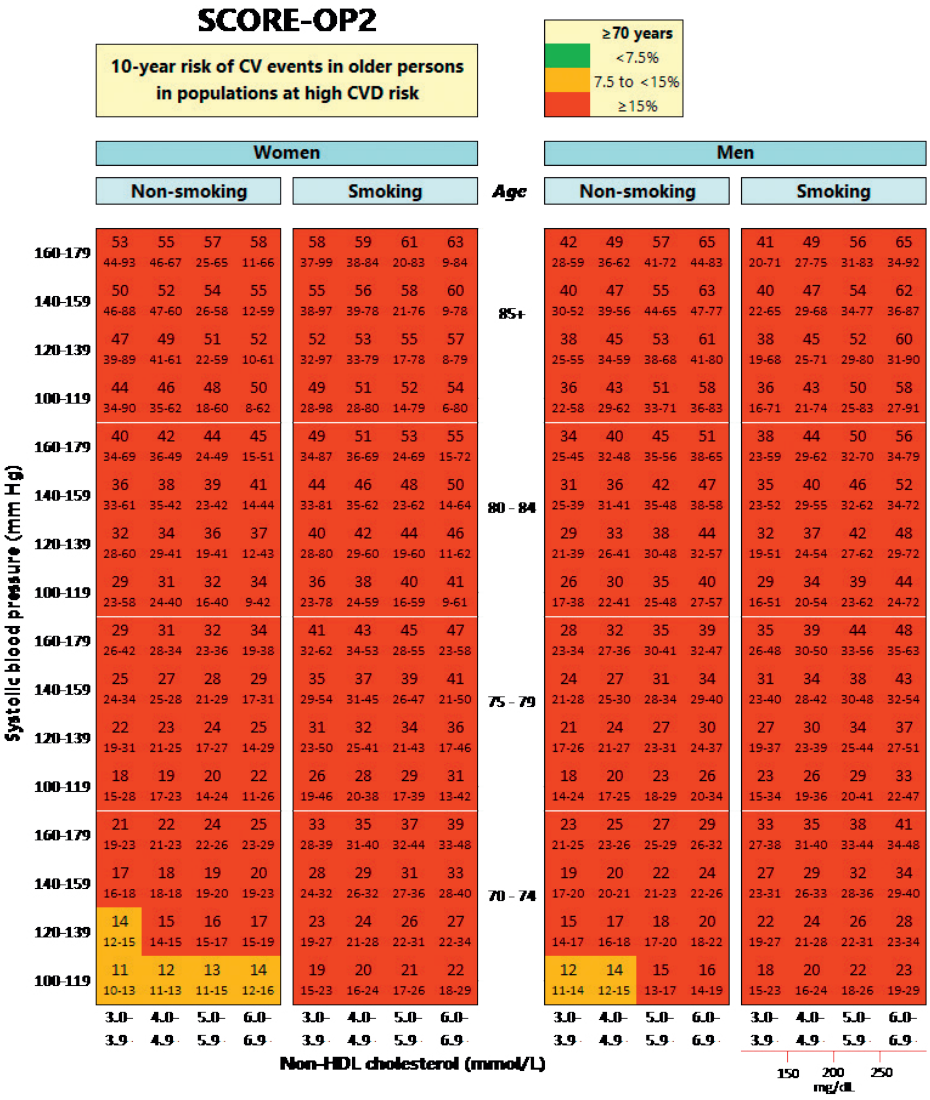
Supplementary Figure 10: Risk charts of 10-year risk in all four risk regions with uncertainty bounds based on the 95% CI of the risk model parameters



Supplementary Figure 10 (continued)



Supplementary Figure 10 (continued)



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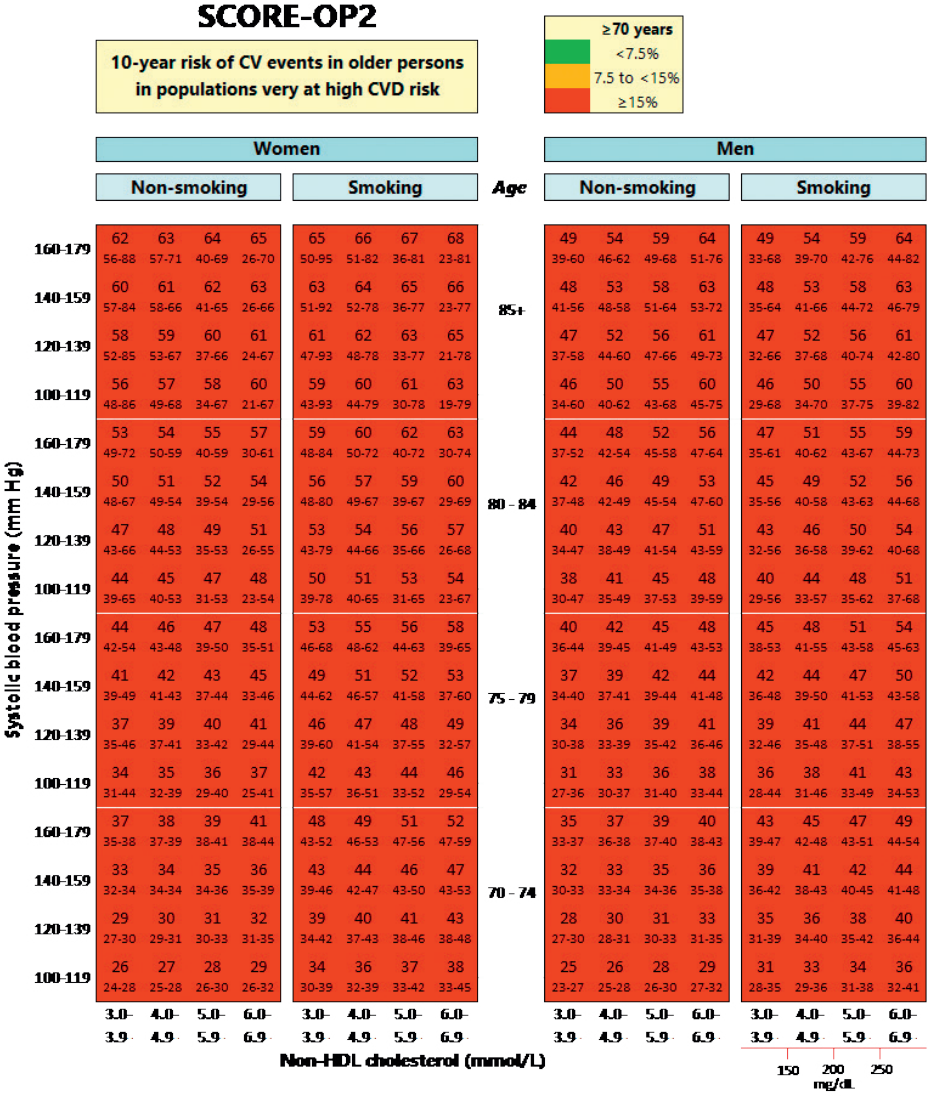

CHAPTER 4

The value of additional risk factors for improving 10-year cardiovascular risk prediction in apparently healthy people

Steven HJ Hageman, Lisa Pennells, Stephen Kaptoge, Romin Pajouheshnia, Taavi Tillman, Michael J Blaha, Robyn L McClelland, Kunihiro Matsushita, Vijay Nambi, Olaf H Klungel, Patrick C Souverein, Yvonne T van der Schouw, WM Monique Verschuren, Nils Lehmann, Raimund Erbel, Karl-Heinz Jöckel, Emanuele Di Angelantonio, Frank LJ Visseren, Jannick AN Dorresteijn

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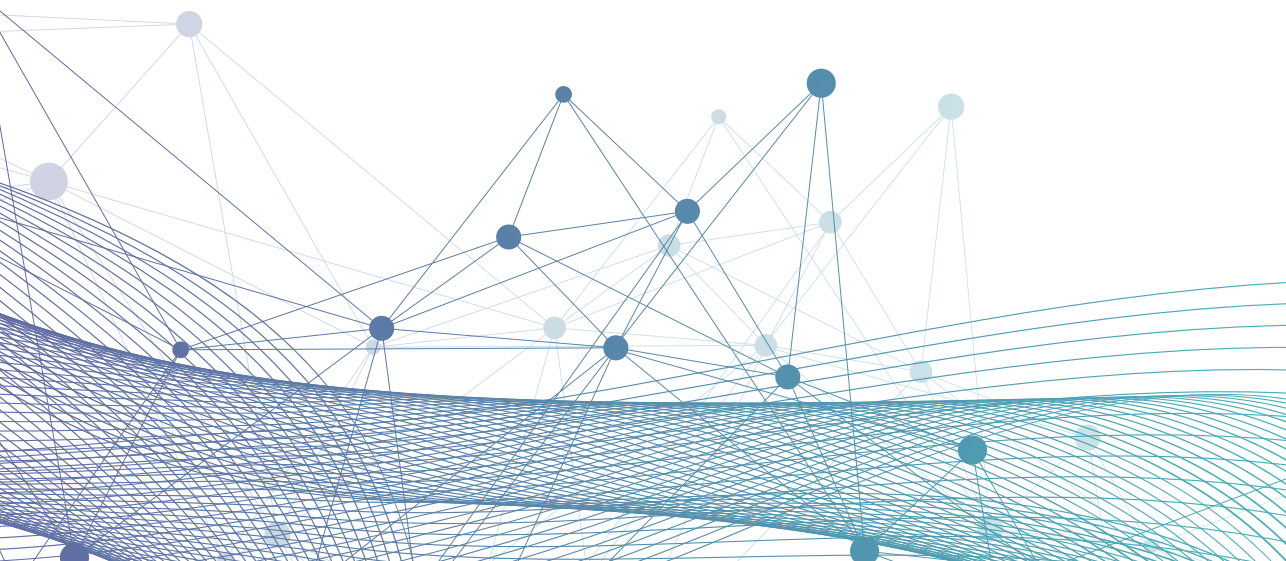


Abstract

Background: In clinical practice, additional risk modifying characteristics are often known which are not directly incorporated in cardiovascular risk prediction models, like albuminuria, education level, or coronary calcium score. The aim of the current study was to quantify the added value of potential risk modifying characteristics when added to the SCORE2 algorithm for individuals without diabetes mellitus (DM) or prior cardiovascular disease (CVD).

Methods and results: Individuals without previous CVD or DM were included from the ARIC, MESA, EPIC-NL and HNR studies (n=46,285) in whom 2,177 CVD events and 2,062 non-cardiovascular deaths were observed over exactly 10.0 years of follow-up. The effect of each possible risk modifying characteristic was derived using Fine and Gray models that included an offset term for the SCORE2 linear predictor. Subdistribution hazard ratios were derived in each cohort separately and then pooled. External validation was performed in the CPRD cohort (UK, n = 518,015, 12,675 CVD events). Adjustment of SCORE2 predicted risks with both single and multiple risk modifiers did not negatively affect calibration and led to a modest increase in discrimination (C-index 0.742 [95%CI 0.737-0.746] versus unimproved SCORE2 risk C-index 0.737 [95%CI 0.732-0.741]). The net reclassification index for adding all these predictors was +0.032 (95%CI 0.025; 0.028) for future events and -0.008 (95%CI -0.009; -0.007) for future non-events. The coronary calcium score was found to the single strongest added predictor.

Interpretation: The current paper presents a method on how to integrate possible risk modifying characteristics that are not included in existing CVD risk models for the prediction of CVD event risk in apparently healthy people. This flexible methodology improves the accuracy of predicted risks and increases applicability of prediction models for individuals with additional risk known modifiers

Introduction

Atherosclerotic cardiovascular disease (CVD) remains a major cause of both morbidity and mortality, despite declines in its incidence and mortality rates in several countries. Current guidelines advocate the use of risk prediction models to enhance healthcare and population-wide prevention.[1–3] Risk models like the SCORE2-model[4] and the atherosclerotic cardiovascular disease pooled cohort equations (PCE)[5] integrate information on several conventional prognostic factors to estimate individual 10-year CVD event risks for apparently healthy people, those without prior CVD, diabetes mellitus, or severe comorbidity. The goal is to identify people at higher risk of CVD, as those benefit most from preventive action.[6–8] These models are widely-used and practical because they use easy to measure and generally available prognostic factors to calculate CVD risk. In clinical practice, however, there are often other prognostic factors known apart from those in the prediction model, for example parental history for premature myocardial infarction, body mass index (BMI), estimated glomerular filtration rate (eGFR), albuminuria, social-economic status, coronary calcium score (CAC), or ankle-brachial-index (ABI).

The 2021 ESC CVD prevention guidelines state that some of these prognostic factors may modify predicted risk, but no clear quantitative solution is given as to how to deal with additional information for more accurate risk prediction in individual patients.[3] In practice, healthcare providers and patients may decide to ignore a risk model's prediction, because they feel the patient profile is not fully captured by the algorithm. A clear strategy on how to deal with any such possible risk modifying characteristics help providers and patients to further personalize clinical practice. Therefore, the aims of the current study were to quantify the added value of possible risk modifying characteristics in addition to the SCORE2 algorithm for apparently healthy individuals and to evaluate the accuracy and added value of adding a variable number of these additional risk modifying characteristics.

Methods

Study design

The effect of pre-specified list of possible risk modifying characteristics was derived and internally validated in several contemporary European and North-American research cohorts: the Atherosclerosis Risk in Communities Study (ARIC, 4th visit as a baseline, United States, n = 8,796),[9] Multi-Ethnic Study of Atherosclerosis (MESA)-study (United States, n = 5,670),[10] European Prospective Investigation into Cancer, The Netherlands (EPIC-NL, n = 28,099), and Heinz Nixdorf Recall (HNR, Germany, n = 3,679).[11] Finally, all results were externally validated in real-world general practitioners data from the Clinical Practice Research Datalink (CPRD, United Kingdom, n = 518,015).[12] In all data sources, participants aged 40-80 year without prior CVD or diabetes mellitus were included. Prior CVD was defined as history of any clinical diagnosis of atherosclerotic CVD, including angina pectoris, myocardial infarction, stroke or peripheral artery disease. Detailed descriptions of all data sources can be found in the Supplementary Methods.

Predictors

Possible risk modifying characteristics were pre-specified based on existing literature and availability in the cohorts. The following characteristics were investigated in the current study: albuminuria, ABI, atrial fibrillation, Chronic inflammatory disease, BMI, carotid plaque, carotid intima media thickness (cIMT), coronary calcium score (MESA percentile[13], direct Agatston score as a sensitivity analysis), parental history of premature myocardial infarction, lower education level, eGFR, high-sensitivity C-reactive protein (hsCRP), high-sensitivity troponin, lipoprotein(a) [Lp(a)]. N-terminal pro-B-type natriuretic peptide (NT-proBNP), number of medications, history of cancer (excluding non-melanoma skin cancer), gestational hypertension or pre-eclampsia. The availability of each of the predictors in all the cohorts and all definitions and cut-offs are described in detail in the **Supplementary Methods**.

The primary outcome was CVD events, defined as a composite of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke (**Supplementary Table 1**), similar to the endpoint of the SCORE2 algorithm.[4] Follow-up was until the first non-fatal myocardial infarction, non-fatal stroke, or death or end of the event registration period. Follow-up was truncated at 10 years as the effect of predictors on the risk of CVD events because this period is of most interest. Deaths from non-cardiovascular causes were treated as competing events.

Statistical analysis

First, the effect of all risk modifying characteristics on top of the SCORE2 predictions was estimated using Fine and Gray competing risk models. This was performed separately for each characteristic. As not all individual patient data was in the same

geographical location, analyses were performed separately for every cohort and subsequently pooled using inverse variance weighting. In the derivation models, single additional predictors were used together with the SCORE2 coefficients, which were added as 'fixed predictors' (offset term). The use of fixed predictors ensured that the adjustment was made to the exact coefficients as published. The SCORE2 model was stratified upon sex and included the prognostic factors: age, systolic blood pressure, non-HDL cholesterol, and current smoking. For all continuous predictors, Akaike information criterion was used to check the linearity of the association with the outcome variable by comparing model fit of models with linear fit to squared or log-transformed variables.

The risk modifying characteristics can be applied to individual predictions of the SCORE2 model using the "*naïve approach*",[14–16] which modifies individual predicted risks based on the population prevalence and the subdistribution hazard ratio (SHR) of the relevant predictor. This method is described in more detail in the Supplementary Methods, including a worked out example (**Supplementary Table 2**). The naïve method is a flexible method as it can be used on top of the recalibrated SCORE2 risks for every region for which the prevalence or population mean of the risk factor is known, and may be used to improve upon predictions using different combinations of risk modifying characteristics without the need to derive different prognostic models.

Internal validation was performed for addition of each characteristic separately, in all cohorts where the characteristic was available. Performance of risk reclassification based on each characteristic was assessed in terms of discrimination, net reclassification index (NRI) and goodness-of-fit. Discrimination was assessed using Harrell's C-index, corrected for competing risks.[17] All relevant discrimination measures were calculated in every cohort separately and subsequently pooled using a random effects model. The NRI was calculated based on the 2021 ESC prevention guideline cut-offs for individuals 50-69 years old: 5% and 10% 10-year CVD risk.[3] NRI was presented separately for events and non-events and confidence intervals were obtained using bootstrapping (r-package *nricens)*.[18,19] To assess whether model goodness-of-fit was negatively affected by the risk modification, visual assessment was conducted using predicted versus observed risk plots – showing deciles of predicted risks plotted against CVD cumulative incidences. The intercept of the SCORE2 model was recalibrated to every cohort prior to these analyses. In addition, analyses were performed to evaluate the effect of adding multiple risk modifying characteristics at once with the naïve method. Analyses evaluating a varying number of risk modifying characteristics were performed in the MESA cohort, as this had the largest number of additional predictors available. For this analysis, first the recalibrated risk was predicted for all participants. This risk was then modified with the required number of random predictors for every individual. Handling of missing data is described in the Supplementary Methods. All analyses were performed with

R-statistical programming (*version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria*).

External validation in real-world clinical data
In clinical practice, most additional risk modifying characteristics as evaluated in the current study are not randomly measured. The fact that these predictors were measured itself may carry predictive information, and thus the current approach was validated in care-as-usual primary care data from CPRD GOLD. For this analyses, only the individuals were used to which the SCORE2 model currently applies (no individuals with diabetes mellitus, only aged 40-69 years). External validation was performed assessing the effect of modification with all available risk factors to modify SCORE2 risks on model calibration, discrimination and NRI. This way, the real-world availability of these risk factors in the primary care setting was implemented in the validation. CAC-score was not available in the CPRD GOLD data. In addition, a sensitivity analysis was performed in CPRD to evaluate the applicability of the methods and derived SHRs in combination with predicted risks from SCORE2-OP and PCE. The same SHRs were used as in the main analyses. For the analyses with SCORE2-OP, only individuals of 70 years or older were included. For the analyses with PCE risks the respective target population was included (age 45-80 years, no prior DM or CVD).

Results

For the derivation of all predictor effects, 46,285 individuals were included from 4 cohorts. Median age at baseline was 57±8 years old, and 71% were female. Detailed participant characteristics are presented in **Table 1**. In a median of 10.0 years of follow-up (IQR 10.0-10.0), 2,177 CVD events and 2,062 non-cardiovascular deaths were observed. The SHRs of all additional predictors are presented in **Table 2** and **Supplementary Table 3-4**.

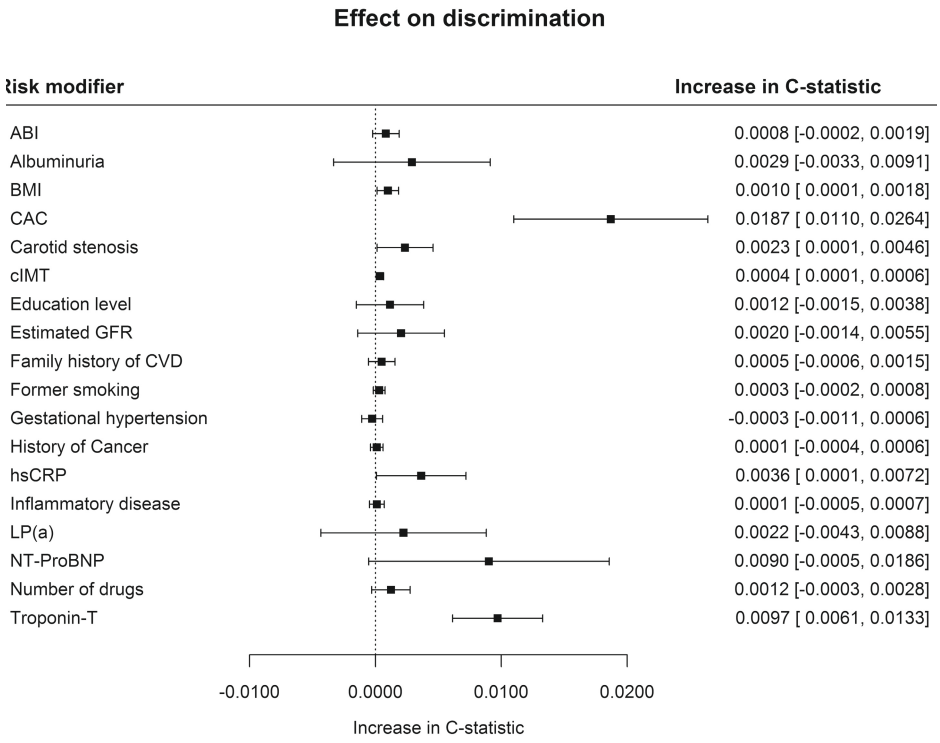
Without addition of any of the risk modifying characteristics, the C-index of the SCORE2 model was 0.716 (95% CI 0.695-0.736) in the derivation cohorts. Addition of most risk modifying characteristics led to a modest increase in discrimination. Risk modifying characteristics most effectively increasing discrimination were coronary calcium score (+0.0187), NT-proBNP (+0.0085) and hs-Troponin-T (+0.0094) (Figure 1). Addition of single risk modifying characteristics led to a modest increase in NRI for events for most risk factors, and a small reduction in NRI for non-events (**Table 3**). The highest increase in NRI was seen for CAC-score (+0.122 [95%CI 0.072-0.171] for events, -0.024 [95%CI -0.033 - -0.015] for non-events). CAC-score led to a higher increase in discrimination and a similar NRI when added as a percentile, in comparison to when an Agatston score was used (**Supplementary Table 5**)

Table 1: Characteristics of the included individuals at baseline

	ARIC	EPIC-NL	HNR	MESA	CPRD
	n = 8,796	n = 28,099	n = 3,679	n = 5,670	n = 518,015
Male sex	3,633 (41%)	5,569 (20%)	1,674 (46%)	2,646 (47%)	260,424 (50%)
Age (years)	63 ± 6	54 ± 7	59 ± 8	61 ± 10	49 ± 9
Former smoker	3,684 (42%)	9,709 (35%)	1,193 (32%)	2,066 (36%)	126,207 (26%)
Current smoker	1,310 (15%)	7,908 (28%)	850 (23%)	764 (13%)	119,246 (24%)
Body mass index (kg/m2)	28.1 ± 5.0	26.0 ± 3.9	27.4 ± 4.3	28.0 ± 5.1	25.9 ± 5.0
Systolic blood pressure (mmHg)	126 ± 18	129 ± 19	131 ± 20	125 ± 20	130 ± 17
Total cholesterol (mmol/L)	5.2 (4.6-5.8)	5.7 (5.1-6.4)	6.0 (5.3-6.6)	5.0 (4.4-5.6)	5.3 (4.7-6.1)
HDL-cholesterol (mmol/L)	1.3 (1.0-1.6)	1.5 (1.2-1.8)	1.5 (1.2-1.8)	1.3 (1.1-1.6)	1.4 (1.1-1.7)
LDL-cholesterol (mmol/L)	3.2 (2.6-3.7)	2.9 (2.4-3.5)*	3.8 (3.2-4.4)	3.0 (2.5-3.5)	-
Triglycerides (mmol/L)	-	1.2 (0.9-1.8)*	1.4 (1.0-1.9)	1.2 (0.9-1.8)	-
Estimated GFR (ml/min/1.73m2)	87 ± 15	101 ± 12*	80 ± 14	78 ± 15	77 ± 13
Ankle brachial index <0.9	511 (6%)	-	-	156 (3%)	23 (12%)
CAC Agatston-score ≥100	-	-	848 (23%)	1,160 (20%)	-
Carotid stenosis >25%	-	-	53 (1%)	646 (11%)	-
cIMT (mm)	-	-	0.7 (0.6-0.8)	0.8 (0.7-1.0)	-
hsCRP (mg/L)	2.1 (1.0-4.6)	1.2 (0.6-2.4)*	1.3 (0.7-2.8)	1.8 (0.8-3.9)	3.0 (1.2-5.0)
Gestational hypertension		5,252 (19%)			1635 (0%)
Parental history of myocardial infarction	903 (10%)	4,088 (15%)	345 (9%)	603 (11%)	-
History of cancer	-	1,448 (5%)	257 (7%)	316 (6%)	26,465 (5%)
Lp(a) (30mg/dL)			5 (5-23)		-
Lower education	1,454 (17%)	12,443 (44%)	38 (1%)	899 (16%)	-
Albuminuria >30mg/g	435 (5%)	-	-	356 (6%)	1,538 (24%)
Number of drugs (n)	4.0 (2.0-7.0)	-	1.0 (0.0-3.0)	2.0 (1.0-4.0)	0.0 (0.0-1.0)
NT-ProBNP (pg/mL)	66 (33-123)	-	67 (38-120)	51 (23-101)	-
Troponin-T (pg/mL)	4.0 (3.0-7.0)	-	-	4.1 (3.0-6.7)	-

n (%), mean ± SD, or median (interquartile range; IQR). Additional risk modifiers in CPRD were not imputed and shown here as percentage of available cases only. GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] 2009 formula), CAC= coronary calcium score, cIMT = carotid intima-media thickness, hsCRP = high sensitivity C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein, Lp(a) = lipoprotein(a), NT-proBNP = N-terminal pro-B-type natriuretic peptide.
* = only measured in 6% random sample.

Figure 1: Effect of individual risk factors on the discrimination of the SCORE2 model



GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula), CAC= coronary calcium score, cIMT = carotid intima-media thickness, hsCRP = high sensitivity C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein, Lp(a) = lipoprotein(a), NT-proBNP = N-terminal pro-B-type natriuretic peptide

Table 2: Subdistribution hazard ratios of the additional predictors

Predictor	Subdistribution hazard ratio (95% CI)
Ankle brachial index (<0.9)	1.28 (1.03-1.59)
Body mass index (kg/m²)ǂ	1.02 (0.96-1.09)
Coronary calcium Agatston-percentileǂ	1.91 (1.60-2.21)
History of cancer	1.17 (0.94-1.44)
Carotid stenosis (>25%)	1.59 (1.26-2.01)
Carotid intima media thickness (mm)ǂ	1.01 (0.91-1.12)
Estimated GFR (ml/min/1.73m2)ǂ	1.03 (0.93-1.18)
hsCRP (mg/L)ǂ	1.32 (1.05-1.67)
History of chronic inflammatory disease	0.95 (0.54-1.67)
Lower education level	1.28 (1.16-1.41)
Parental history of myocardial infarction	1.34 (1.19-1.51)
Former smoking (versus never)	1.12 (1.01-1.25)
Gestational hypertension	1.17 (0.98-1.39)
Lp(a) (mg/dL)ǂ	1.13 (0.93-1.36)
Albuminuria (>30mg/g)	1.91 (1.60-2.28)
Number of drugs (n)ǂ	1.18 (1.10-1.26)
NT-ProBNP (pg/ml)*	1.48 (1.38-1.58)
Troponin-T (pg/ml)*	1.53 (1.42-1.66)

Predictors marked with (*) are log-transformed, predictors marked with (ǂ) are squared, and predictors marked (ǂ) are linear. For all these continuous predictors, the subdistribution hazard ratios are presented as 3rd versus 1st quartile. To aid clinical interpretation, squared and log coefficients are additionally displayed in Supplementary Table 3. GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula), CAC= coronary calcium score, cIMT = carotid intima-media thickness, hsCRP = high sensitivity C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein, Lp(a) = lipoprotein(a), NT-proBNP = N-terminal pro-B-type natriuretic peptide.

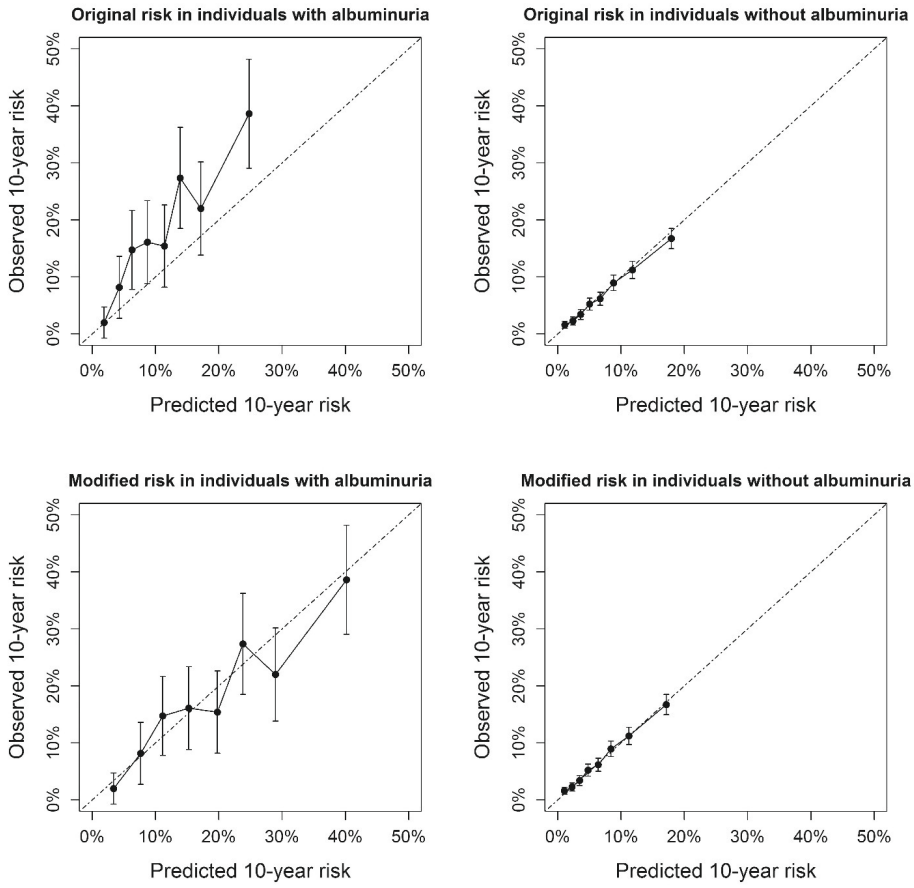
The effect on calibration of using a single predictor to modify predicted risks was illustrated in **Figure 2**. In individuals with albuminuria, SCORE2 risks were under-predicted before modification of the predicted risks. After modification, calibration was adequate. In individuals without albuminuria, calibration was adequate before and after modification of predicted risks. A clinical example was shown in **Supplementary Table 2**, illustrating the application of the methodology for a 50-year-old smoking woman from Europe's low risk region. Her SCORE2 predicted risk was 5.3%. Her medical history shows a MESA CAC percentile of p95. Implementing this in her risk prediction would almost double her risk to 10.2%. Another woman with exactly the same risk factor levels had no CAC-score, but a negative parental history of CVD before the age of 65. Implementing this information would slightly lower her 10-year risk (4.9%).

Table 3: Effect of the different risk modifiers on NRI

Risk modifier	Event (95%CI)	Non-event (95%CI)	Combined (95%)
Coronary calcium score	0.122 (0.072;0.171)	-0.024 (-0.033;-0.015)	0.098 (0.049;0.146)
Troponin-T	0.051 (0.027;0.076)	0.001 (-0.006;0.007)	0.052 (0.026;0.078)
NT-ProBNP	0.040 (0.016;0.066)	-0.006 (-0.012;0.000)	0.034 (0.008;0.059)
Albuminuria (>30mg/g)	0.001 (-0.014;0.018)	0.023 (0.019;0.027)	0.024 (0.009;0.040)
Education level (lower vs other)	0.021 (0.009;0.033)	-0.003 (-0.006;-0.002)	0.018 (0.006;0.030)
History of inflammatory disease	0.010 (-0.010;0.034)	0.002 (-0.001;0.004)	0.012 (-0.008;0.035)
Estimated GFR	0.004 (-0.009;0.016)	0.008 (0.004;0.011)	0.011 (-0.001;0.024)
Body mass index	0.011 (0.002;0.020)	-0.002 (-0.004;-0.001)	0.009 (0.000;0.018)
History of cancer	-0.007 (-0.015;0.001)	0.000 (-0.001;0.000)	-0.007 (-0.015;0.000)
Parental history of MI	0.000 (-0.012;0.011)	0.004 (0.003;0.006)	0.004 (-0.007;0.015)
hsCRP	0.007 (-0.015;0.026)	-0.004 (-0.009;0.001)	0.003 (-0.018;0.025)
Former smoking (versus never)	0.002 (-0.011;0.013)	0.001 (-0.001;0.003)	0.003 (-0.008;0.014)
Carotid stenosis (>25%)	-0.002 (-0.024;0.023)	0.004 (0.000;0.008)	0.002 (-0.021;0.026)
Number of drugs (n)	0.003 (-0.011;0.019)	-0.006 (-0.010;-0.001)	-0.002 (-0.020;0.013)
Carotid intima media thickness (mm)	0.002 (-0.006;0.012)	0.000 (-0.002;0.001)	0.002 (-0.007;0.011)
Lp (a)	0.004 (-0.011;0.018)	0.001 (-0.003;0.005)	0.001 (-0.016;0.017)
Ankle brachial index (<0.9)	-0.005 (-0.020;0.012)	0.006 (0.002;0.011)	0.001 (-0.009;0.010)
Gestational hypertension	0.001 (-0.018;0.021)	-0.001 (-0.004;0.001)	0.000 (-0.019;0.019)

GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula), CAC= coronary calcium score, cIMT = carotid intima-media thickness, hsCRP = high sensitivity C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein, Lp(a) = lipoprotein(a), MI = myocardial infarction, NT-proBNP = N-terminal pro-B-type natriuretic peptide

Figure 2: Calibration example showing the effect of additional stratification on microalbuminuria

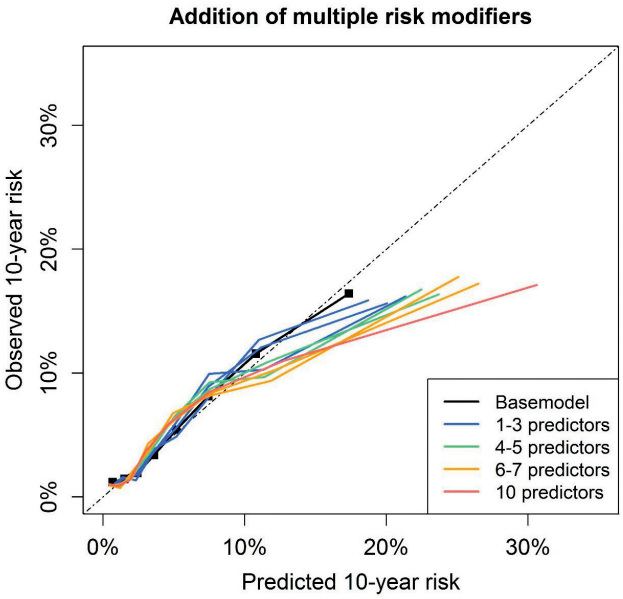


Calibration of SCORE2 predicted risks in all combined cohort data before and after modification of 10-year CVD risk. Before modification, the SCORE2 intercept of the SCORE2 model was recalibrated to the cohorts.

Addition of multiple predictors

In the lower risk deciles, no major over- or underestimation was observed regardless of the number of additional risk modifying characteristics added (**Figure 3**). For the highest risk decile, a minimal overestimation of predicted risks was observed even without adding risk factors. This overestimation increased gradually with adding more risk factors.

Figure 3: Effect of adding multiple random predictors on model calibration



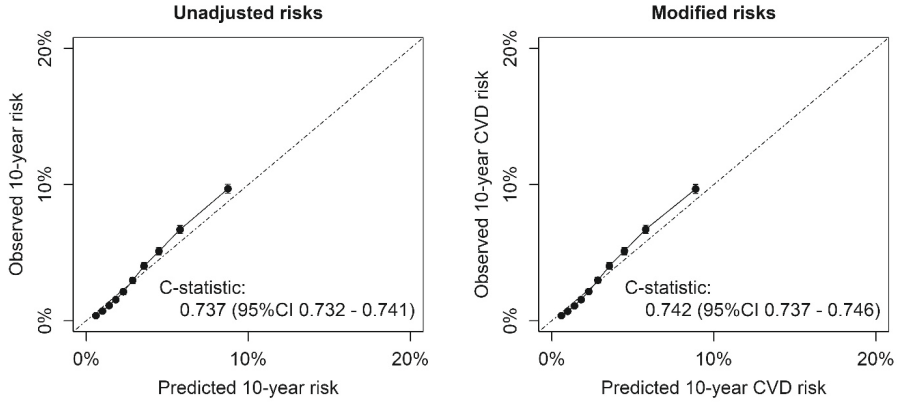
Effect of adding multiple random risk modifiers at once for individuals of the MESA study, shown in deciles of predicted risk. Risk modifiers were randomly selected for every individual. Base model predictions were made with the SCORE2 model after recalibration of the model intercept to the MESA cohort.

External validation in real-world data

For external validation in real-world data, 518,015 individuals were included, detailed participant characteristics are presented in **Table 1**. In 5.9 years of follow-up (IQR 2.5-9.4) 12,675 CVD events and 28,998 fatal non-CVD events were observed. Disease history (cancer, gestational hypertension) and number of medications were available in all individuals (**Supplementary Table 6**). Other risk modifying characteristics commonly available were former smoking status (77%), BMI (85%) and eGFR (29%). Information on a median of 4 (IQR 3-5) risk modifying characteristics was available per person. Unadjusted, the C-index of the SCORE2 model in the CPRD data was 0.737 [95%CI 0.732-0.741], **Figure 4**). Risk modification with all available risk modifying characteristics did not lead to miscalibration of SCORE2 risks. After reclassification using all available information on risk modifying characteristics in this real-world dataset, the C-index increased to 0.742 (95%CI 0.737-0.747) (**Figure 4**). The NRI for adding all these predictors was +0.032 (95%CI 0.025; 0.028) for events and -0.008 (95%CI -0.009; -0.007) for non-events. A gain in discrimination and positive NRI was observed in both men and women (**Supplementary Table 7**). Within those with predicted 10-year CVD risks between 7.5 and 12.5%, the C-index was 0.014 (95%CI 0.004-0.023) higher when using all available risk modifying characteristics, and the

NRI was 0.079 (95%CI 0.061; 0.099) for events and -0.060 (95%CI -0.066; -0.055) for non-events.

Figure 4: External validation in the real-world data of CPRD using all available risk modifiers (n=517,595)



Calibration in the CPRD data of the original low risk region SCORE2 model (left) and after reclassification using all available information on risk modifying characteristics in this real-world dataset (right).

Sensitivity analyses

Using the methodology on top of PCE predicted risks showed an increase in discrimination as well. The C-index increased from 0.750 [95%CI 0.747-0.754] when using the original PCE to 0.754 [95%CI 0.751-0.758] after reclassification using all available information on risk modifying characteristics in CPRD. The NRI on top of PCE predictions was 0.028 (95%CI 0.024; 0.032) for events and -0.015 (-0.015; -0.014) for non-events. Using SCORE2-OP risks in the persons aged 70 years or older showed an increase in discrimination as well. The C-index increased from 0.738 (95%CI 0.734-0.741) when using the original SCORE2-OP risk score to 0.741 [95%CI 0.737-0.745] after reclassification using all available information on risk modifying characteristics in CPRD). The NRI on top of SCORE2-OP predictions was +0.036 (95%CI 0.032; 0.040) for events and -0.018 (95%CI -0.018; -0.017) for non-events.

Discussion

The current report describes flexible methods for handling additional risk modifying characteristics on top of basic prediction models for the prediction of CVD risk in apparently healthy people. The effect of several common additional risk modifying characteristics was quantified for use in clinical practice, increasing clinical utility in terms of improved applicability as well as increased discrimination and NRI, while not negatively affecting calibration. External validation in real-world routine care data

showed similar improvements in model performance as were observed in cohort data.

The methodology presented in the current study improves the clinical utility of CVD prediction models for apparently healthy individuals in several ways. First, the applicability of prediction models is improved upon in the presence of potential risk modifying characteristics. Current and previous guidelines acknowledged some of these factors may alter predicted 10-year CVD risks, but offer no clear solutions on how to mathematically deal with the presence of certain factors.[3] If such factors are available but not incorporated in the prediction, both physicians and patients may intuitively feel the predicted risks are over- or underestimated and be reluctant to rely upon predicted risks. As the degree of this potential inaccuracy is unknown, risk communication and treatment decisions based on predicted risk become more difficult. Using the methodology presented in the current study. however, these risk modifying characteristics can be incorporated in the risk prediction algorithm, thereby improving confidence in predicted risks. For individuals with certain risk modifiers present, this will also result in more relevant predicted risks. Second, results from the current study show that these risk modifications improve upon discrimination on top of the SCORE2 model, in cohort data as well as in real-world data. Categorization of events was especially improved with most risk modifiers, thereby slightly reducing accuracy of the categorization for non-events. Most importantly, calibration was not affected by adding the risk factors available in clinical practice.

The methodology as described in the current paper can be applied to add a single modifying characteristic, but also with a few risk modifying characteristics at once. Using too many risk modifying characteristics at once may lead to overestimation of CVD risk in the higher risk deciles, which gradually increases with a higher number of risk modifying characteristics. As this group is generally well above treatment thresholds, the effect of this overestimation is likely limited in clinical practice. The reason for this overestimation is the fact that the different risk modifiers as used in the current study are not corrected for each other, but may carry overlapping predictive information. The maximum of risk modifying characteristics that can be added, while ensuring accurate risks, likely depends on an individual's predicted risk, as well as the effect size and collinearity of the risk modifiers, making a maximum number of modifying characteristics to be added hard to define. In the CPRD cohort a median of four risk modifiers could be added without visible effect on the calibration, suggesting at least up until this number of risk modifiers could be added.

There are several other strategies available to handle additional available risk modifiers. One possibility is to use prediction models developed with more prognostic factors, including the one of interest, like the MESA CHD risk score.[20] A disadvantage of using more extensive risk models is the decreased clinical applicability because

it requires more variables to be known in clinical practice, or a separate algorithm to be derived for individuals with and without the predictor present. In addition, it would require well-validated models for each relevant combination of predictor availability. More extensive models using have not yet been well calibrated to European clinical practice using representative registry data. An alternative approach has been proposed by the CKD Prognosis Consortium, consisting of a 'patch' to enhance predicted risks according to kidney disease measures eGFR and albuminuria.[21] This method uses the difference between the individual expected eGFR and actual eGFR to modify predicted risks, rather than the absolute value as used in the current study. An advantage of this method could be that the effects of eGFR and albuminuria are adjusted for each other – potentially benefitting those with moderate to severe chronic kidney disease. The method described in the current study may best benefit apparently healthy individuals due to the flexibility of the method and broad range of potential risk modifiers.

In the current study, CAC-score was used to update individual risk predictions after transformation to MESA percentiles, which was also shown to most effectively increase model discrimination. Previous studies have found that the predictive value of the direct Agatston value may be higher in comparison to the MESA percentiles.[22] An important difference with the current study is the fact that in the current analyses, the predictive value *on top of* an existing model was evaluated, rather than the predictive value of solely Agatston or MESA percentile. In addition, the current methodology did not allow for changes in the original SCORE2 baseline hazard or coefficients. The MESA percentiles, which are already adjusted for age, sex, and race, may be most suitable in this situation.

An important strength of the proposed methodology is the flexibility of the method. The method can be easily implemented in online calculators such as on www.U-prevent.com to accommodate additional risk stratification based on whichever predictors are available. In those cases, in which one of the many evaluated predictors is available, this can be incorporated in the risk prediction, improving model applicability and prediction accuracy. In those cases where no additional risk modifiers are available, no additional information is required and risks can be predicted with the regular SCORE2 algorithm. Another strength is use of large and contemporary datasets with long follow-up duration for both derivation and validation in the current study. The validation in the real-world data in CPRD GOLD showed that the methodology can be used with routinely measured medical data. Moreover, the methodology as described in the current study accounts for the impact of competing risks by non-CVD outcomes, similar to the SCORE2 model itself. This statistical adjustment prevents overestimation of CVD risk, which is especially of importance for individuals with higher risks of non-CVD mortality, such as older persons.

There are also some limitations which have to be considered. First, an assumption of the methodology is knowledge of the population prevalence of the risk modifier of interest. These prevalence estimates for North America and Western Europe were obtained from powerful, contemporary cohorts. In cohort data there is often a certain degree of healthy participant bias, possibly affecting the derived risk factor prevalence estimates and with that, to systematic over- or underestimation of predicted risks. In the current study however, no evidence was observed of systematic miscalibration in the external validation in the relatively unselected population of CPRD.[12] For regions outside of Western Europe and North America, reliable local risk factor prevalence would be preferred to ensure reliable implementation of this methodology in clinical practice.

Second, the effect of some relevant risk modifying characteristics was not evaluated in the current study. Potentially relevant predictors which were not available in the current study, but potentially could improve risk prediction include race/ethnicity, frailty, and social deprivation.[3,23,24] In addition, some of the variables, including CAC score, were not available in the real-world data, which may have underestimated the total gain in discriminative power from adding all risk modifiers. Future studies could apply the methodology presented in the current study to those risk modifiers as well, and results could be combined with those of the current study.

In conclusion, a solution was presented on how to implement additional risk modifying characteristics on top of existing models for the prediction of CVD event risk in apparently healthy people. The methods were shown to be accurate using a broad range of potential risk modifying characteristics and was accurate even when using multiple risk modifying characteristics. Allowing for incorporation of these factors in clinical practice will increase confidence in predicted risks in those cases where a risk modifier is present, thereby improving upon clinical applicability of existing prediction models.

References

1. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation*. 2014;129(25 SUPPL. 1):49-73. doi:10.1161/01.cir.0000437741.48606.98
2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106
3. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
4. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. 2021;42(25):2439-2454. doi:10.1093/eurheartj/ehab309
5. Preiss D, Kristensen SL. The new pooled cohort equations risk calculator. *Can J Cardiol*. 2015;31(5):613-619. doi:10.1016/j.cjca.2015.02.001
6. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106
7. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FLJ. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. *Eur Heart J*. 2014;35(13):837-843. doi:10.1093/eurheartj/ehu004
8. Dorresteijn JAN, Visseren FLJ, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. *BMJ*. 2011;343(oct03 1):d5888-d5888. doi:10.1136/bmj.d5888
9. Fretz A, Schneider ALC, McEvoy JW, et al. The Association of Socioeconomic Status With Subclinical Myocardial Damage, Incident Cardiovascular Events, and Mortality in the ARIC Study. *Am J Epidemiol*. 2016;183(5):452-461. doi:10.1093/aje/kwv253
10. Qureshi WT, Michos ED, Flueckiger P, et al. Impact of Replacing the Pooled Cohort Equation With Other Cardiovascular Disease Risk Scores on Atherosclerotic Cardiovascular Disease Risk Assessment (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*. 2016;118(5):691-696. doi:10.1016/j.amjcard.2016.06.015
11. Schmermund A, Möhlenkamp S, Stang A, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL study. *Am Heart J*. 2002;144(2):212-218. doi:10.1067/mhj.2002.123579
12. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836. doi:10.1093/ije/dyv098
13. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: Results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2006;113(1):30-37. doi:10.1161/CIRCULATIONAHA.105.580696
14. Berkelmans GFN, Read SH, Gudbjörnsaottir S, et al. Dealing with Missing Patient Characteristics When Using Cardiovascular Prediction Models in Clinical Practice.; 2018.
15. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. In: *Statistics in Medicine*. Vol 23. ; 2004:1111-1130. doi:10.1002/sim.1668
16. Kooter AJ, Kostense PJ, Groenewold J, Thijs A, Sattar N, Smulders YM. Integrating Information From Novel Risk Factors With Calculated Risks. *Circulation*. 2011;124(6):741-745. doi:10.1161/CIRCULATIONAHA.111.035725

17. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic Models With Competing Risks. *Epidemiology*. 2009;20(4):555-561. doi:10.1097/EDE.0b013e3181a39056

18. Kerr KF, Wang Z, Janes H, McClelland RL, Psaty BM, Pepe MS. Net Reclassification Indices for Evaluating Risk Prediction Instruments. *Epidemiology*. 2014;25(1):114-121. doi:10.1097/EDE.0000000000000018

19. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30(1):11-21. doi:10.1002/sim.4085

20. McClelland RL, Jorgensen NW, Budoff M, et al. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors. *J Am Coll Cardiol*. 2015;66(15):1643-1653. doi:10.1016/j.jacc.2015.08.035

21. Matsushita K, Jassal SK, Sang Y, et al. Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. *EClinicalMedicine*. 2020;27:100552. doi:10.1016/j.eclinm.2020.100552

22. Budoff MJ, Nasir K, McClelland RL, et al. Coronary Calcium Predicts Events Better With Absolute Calcium Scores Than Age-Sex-Race/Ethnicity Percentiles. *J Am Coll Cardiol*. 2009;53(4):345-352. doi:10.1016/j.jacc.2008.07.072

23. Kivimäki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol*. 2018;15(4):215-229. doi:10.1038/nrcardio.2017.189

24. Afilalo J, Alexander KP, Mack MJ, et al. Frailty Assessment in the Cardiovascular Care of Older Adults. *J Am Coll Cardiol*. 2014;63(8):747-762. doi:10.1016/j.jacc.2013.09.070

25. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087-1091. doi:10.1016/j.jclinepi.2006.01.014

Supplementary Methods

Data sources

MESA	*Method of recruitment:* Participants were recruited from six communities (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago and the village of Maywood, Illinois; and Los Angeles County, California) proceeded according to the discretion of the Field center according to the characteristics of its community, past experience, available resources, and site-specific logistics. Inclusion proceeded via pre-defined sex, age, and race/ethnicity proportions. Enrollment period: 2000-2002 *Cohort participation criteria:* 45-84 years of age, free of known (self-reported) clinical cardiovascular disease, active cancer treatment, pregnancy, any serious medical condition which would prevent long-term participation.
ARIC	*Method of recruitment:* Probability sampling within four communities (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland) was used to randomly select households. All individuals aged 45-64 years were asked to participate. Participants were re-examined every three years. *Enrollment period:* Initial recruitment: 1987-1989. For this study, variables collected at the fourth follow-up visit were used (1996-98). Cohort participation criteria: Willing and able to participate.
HNR	*Method of recruitment:* Random samples of men and women aged 45-74 were drawn from mandatory residency lists of three cities in the Ruhr area of Northwestern Germany (Essen, Mülheim and Bochum). Participants were invited via letter, and a maximum of two reminder letters and phone calls were made to the initial non-responders. *Enrollment period:* December 2000 – August 2003 *Cohort participation criteria:* All subjects without cardiovascular disease willing to participate, without any conditions precluding follow-up over 5 years, pregnancy, or severe psychiatric illness.
EPIC-NL	*Method of recruitment:* The Monitoring Project on Chronic Risk Factors (MORGEN project) recruited a random sample of participants from the general Dutch population, and included those aged 20-65 years. Prospect-EPIC cohort is based on volunteers recruited among women participating in a regional breast cancer screening program for whom all women, aged 50-69 receive biannual invitations. Enrollment period: 1993 – 1997 *Cohort participation criteria:* Willing and able to participate and allow for linkage with the national hospital registries and mortality registries.
CPRD	*Method of recruitment:* The Clinical Practice Research Datalink (CPRD) is an ongoing primary care database of anonymized medical records from general practitioners. For this study we used data from CPRD GOLD with coverage of over 11.3 million patients from 674 practices in the UK. With 4.4 million active (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included and patients are broadly representative of the UK general population in terms of age, sex and ethnicity. The data used for this study was restricted to the region of England and to patients that could be linked to Hospital Episodes Statistics (HES) and Mortality data from the Office for National Statistics(ONS). For endpoints, the CPRD was linked to HES for hospital outcomes and ONS for fatal outcomes. Use of CPRD data was granted by the Independent Scientific Advisory Committee: protocol 09-110 (protocol 20_155R) *Enrollment period:* All individuals registered and alive at 01/01/2006 were included in the current study. For the current study, entry date was defined as the first moment after 01/01/2006 at which an individual was both registered and was at least 40 years old. *Participation criteria:* Age 40-80 and no cardiovascular disease prior to baseline.

Legend: MESA = Multi-Ethnic Study of Atherosclerosis; ARIC = Atherosclerosis Risk in Communities Study; HNR = Heinz Nixdorf Recall Study; EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands;

Predictor definitions

In the derivation of all SHRs, predictors were defined the following (if no cohorts specified, definitions were similar in all cohorts where the predictor was available): Albuminuria (urine albumin/creatinine ratio >30mg/g versus none); Ankle-brachial index (ABI): measured in supine participants with systolic blood pressures measured in both arms and legs with appropriately sized cuffs. For both legs (when possible), the systolic blood pressure was measured in each posterior tibial and dorsalis pedis artery. The ABI was calculated as the higher systolic blood pressure in the posterior tibial or dorsalis pedis artery divided by the higher of the arm systolic blood pressures values. At least one leg with ABI <0.9 was used versus both legs ≥0.9. Chronic inflammatory disease: self-reported history of chronic inflammatory disease, including rheumatoid arthritis. BMI was calculated as weight in kilograms divided by height in meters squared. History of cancer: self-reported history of any cancer excluding non-melanoma skin cancer; Carotid media thickness (cIMT): obtained using B-mode sonography at the right and left common carotid artery and measured 1 cm starting from the bulb. Carotid stenosis: any carotid stenosis measured of any of both carotid arteries, stenosis of at least 25%, (MESA cohort) or at least 40% (HNR cohort); CT-coronary calcium (CAC) score: measured on coronary CT, mean phantom adjusted Agatston calcium score. Education level: lower education versus middle or higher education; in the separate cohorts, lower was defined as primary education (EPIC-NL), pre-primary or lower-secondary (HNR), less than 12th grade education (ARIC, MESA). Estimated glomerular filtration rate calculated using CKD-EPI formula. Parental history of myocardial infarction: self-reported history of premature (prior to age 60) myocardial infarction in either parent. Former smoking: self-reported history of tobacco smoking, analyzed in comparison to never smokers. High-sensitivity C-reactive protein (hsCRP), measured in non-inflammatory state. Values higher than 15 were excluded from analyses as those are likely associated with an acute inflammatory response rather than signaling a chronic inflammatory state. Lp(a): Serum concentration of Lp(a) in mg/dL quantified using a particle-enhanced immunonephelometric method. Troponin-T: High-sensitivity cardiac troponin T, not measured during acute clinical event. N-terminal pro-B-type natriuretic peptide (NT-proBNP): not measured during acute clinical event. Number of medications: sum of all different medications used at baseline (defined as 3rd level ATC codes, not taking into account nasal sprays and topical medicines). For CPRD, this included only medication as prescribed by GPs. Gestational hypertension: self-reported history of gestational hypertension including pre-eclampsia. Reference group consisted of women without self-reported history of gestational hypertension, men were excluded from these analyses.

Naïve method

The additional predictors can be applied to individual predictions of the SCORE2 model using the "naïve approach",[14,15] which modifies individual predicted risks in the

following way for categorical variables: *1-(1-individual predicted risk)^(SHR/population relative risk)* for those having the predictor of interest, and *1-(1-individual predicted risk)^(1/population relative risk)* for those who do not have the predictor. In this formula, the population relative risk is equal to *(prevalence of a factor)*SHR of the factor + (1-prevalence). C*ontinuous predictors were added to individual predictions using the following formula: *1-(1-individual predicted risk)^(SHR*[individual continuous value - mean value of population]).* An important advantage of this method as this can be used on top of the recalibrated SCORE2 risks in any region as long as the prevalence or mean of the risk factor is known. A worked out example of the application to individual predictions is presented in **Supplementary Table 2**.

Missing data

Because complete case analysis may lead to loss of statistical power and possible bias,[25] predictor values in the derivation data were imputed by single regression imputation using predictive mean matching (*Aregimpute* function in, R). In EPIC-NL some additional predictors were measured in a completely random subset of 6% of the population (hsCRP, eGFR). As these missings are completely at random, the predictive effect of these variables was analyzed in only those with available data.

In the real-world data of CPRD, the SCORE2 predictors (HDL and total cholesterol, smoking status, SBP) were multiply imputed with 5 imputed datasets, using the R-package *mice*. As the predictive effect of the availability of the additional predictors was of interest for the current study, these were not imputed. The availability of all predictors in CPRD is shown in **Supplementary Table 5**.

Supplementary Table 1: Endpoint definitions

Fatal cardiovascular disease	
Endpoints included	ICD10-codes
Hypertensive disease	I10-16
Ischemic heart disease	I20-25
Arrhythmias, heart failure	I46-52
Cerebrovascular disease	I60-69
Atherosclerosis/AAA	I70-73
Sudden death and death within 24h of symptom onset	R96.0-96.1
Excluding the following	
Myocarditis, unspecified	I51.4
Subarachnoid haemorrhage	I60
Subdural haemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I68.2
Moyamoya	I67.5
Non-fatal events	
Non-fatal myocardial infarction	I21-I23
Non-fatal stroke	I60-69
Excluding the following	
Subarachnoid hemorrhage	I60
Subdural hemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I68.2
Moyamoya	I67.5

Endpoint definitions depend on cohort availability but where ideally defined as stated above

Supplementary Table 2: Example of risk modification with the naïve method

1) Calculation of SCORE2 10-year risk based on SCORE2 predictors, ignoring additional risk factors			
Region	Europe, region	Moderate risk	Transformed
Sex	Female		
Age (yrs)	50		
Smoking (current vs. other)	yes		
SBP (mm Hg)	140		
Total cholesterol (mmol/L)	6.3		
HDL cholesterol (mmol/L)	1.4		
CAC-score (MESA percentile from 0 to 1))	0.95		0.95^2= 0.9025
Parental history of MI	negative		
SCORE2 10-year risk = 0.0523			
2) Overview of all required parameters population RR = (prevalence of a factor)*SHR of the factor + (1-prevalence)			
	SHR	Prevalence (Parental history) or mean (CAC)	Population RR
CAC-score	0.4997	0.5690	
CAC-score (squared term)	6.4268	0.3888	
Parental history of MI	1.3420	0.1393	1.0476
3) Modify predicted risks			
1-(1-individual predicted risk)^(1/population relative risk), *if categorical, factor absent* 1-(1-individual predicted risk)^(SHR/population relative risk), *if categorical, factor present* 1-(1-individual predicted risk)^(SHR*[individual continuous value - mean value of population]), *if continuous variable*			
Modify predicted risk with CAC percentile:			
1-(1-0.0523)^(*0.4997*(0.95– 0.5690)+ 6.4268*(0.9025-0.3888)*) = 0.1017; 10% 10-year risk Modify predicted risk with negative parental history of MI 1-(1-0.0523)^(1/1.0476) = 0.0499; 5% 10-year risk Modify predicted risk with both 1-(1-0.0523)^(0.4997*(0.95– 0.5690)+ 6.4268*(0.9025-0.3888)+ (1/1.0476)) = 0.09713; 10% 10-year risk			

Calculation example showing the effect of parental history of MI or CAC-score.

Supplementary Table 3: Subdistribution hazard ratios of non-linear predictors in comparison to clinically relevant reference groups

Predictor	Value	Subdistribution hazard ratio
CAC-score (MESA percentile)	10	0.84
	50	1.00 (ref)
	90	2.16
	99	2.77
Troponin-T (pg/mL)	3	0.86
	4	1.00 (ref)
	7	1.33
	10	1.60
NT-ProBNP (pg/mL)	20	0.72
	60	1.00 (ref)
	90	1.13
	120	1.23
Body mass index (kg/m2)	15	1.06
	25	1.00 (ref)
	30	1.04
	35	1.14
Estimated GFR (mL/min/1.73m2)	90	1.00 (ref)
	60	1.23
	30	2.79
	15	5.32
Lp(a) (mg/dL)	30	1.00 (ref)
	60	1.09
	90	1.14
	120	1.13
hsCRP (mg/L)	1	1.00 (ref)
	3	1.21
	5	1.41
	10	1.81

Subdistribution hazard ratios of the squared predictors at certain values versus the reference values. Subdistribution hazard ratios shown were obtained by combining the shown predictors with the model coefficients and are for illustrative purposes.

Supplementary Table 4: Unrounded prediction parameters

Risk modifier	SHR	Prevalence		Mean	
		NA	EU	NA	EU
Ankle brachial index, <0.9	1.2761	0.0483	-		
Body mass index	0.9581			28.1624	26.2015
Body mass index, squared	1.0009			822.1063	702.7641
Coronary calcium score	0.4997			0.498	0.569
Coronary calcium score, squared	6.4268			0.3109	0.3888
History of cancer	1.1651	0.0317	0.0536		
Carotid stenosis (>25%)	1.5907	0.1142	0.0141		
Carotid intima media thickness	1.0393			0.8535	0.7004
Estimated GFR	0.9434			83.3487	90.7666
Estimated GFR, squared	1.0003			7193.603	8524.095
hsCRP	1.1161			3.0489	2.1476
hsCRP, squared	0.9960			17.9213	10.0934
Lower education level	1.2824	0.1627	0.1815		
Parental history of myocardial infarction	1.3420	0.1041	0.1393		
Former smoking (versus never)	1.1238	0.4645	0.4735		
Gestational hypertension	1.1671	-	0.2331		
History of inflammatory disease	0.9478	-	0.0787		
LP(a)	1.0051			25.536	19.954
LP(a), squared	0.9999			1534.0	1056.8
Albuminuria >30 mg/g	1.9089	0.0560	-		
Number of drugs (n)	1.0417			4.0881	1.8570
NT-proBNP (pg/ml), log	1.3452			4.0130	4.2210
Troponin-T (pg/ml), log	1.6747			1.6143	-

Supplementary Table 5: Comparison between adding coronary calcium score as MESA percentile versus Agatston score

	Gain in C-index (95%CI)	Net Reclassification index (95%CI)
Percentile (squared)	0.0187 (0.0110-0.0264)	0.098 (0.049-0.146)
Agatston score	0.0148 (0.0091-0.0204)	0.096 (0.045-0.146)
Illustration of individual effect	**Value**	**Subdistribution hazard ratio**
CAC percentile	10	0.84
	50	1.00 (ref)
	90	2.16
	99	2.77
Agatson CAC-score	0	1.00 (ref)
	100	1.85
	300	2.06

Supplementary Table 6: Availability of the additional predictors in clinical practice of CPRD GOLD

	Baseline values	Available (n, %)
	n = 518,015	
Male sex	260,424 (50%)	518,015 (100%)
Age (years)	49 ± 9	518,015 (100%)
Former smoker	126,207 (26%)	491,928 (95%)
Current smoker	119,246 (24%)	491,928 (95%)
Body mass index (kg/m2)	25.9 ± 5.0	438,857 (85%)
Systolic blood pressure (mmHg)	130 ± 17	469,917 (91%)
Total cholesterol (mmol/L)	5.3 (4.7-6.1)	249,207 (48%)
HDL-cholesterol (mmol/L)	1.4 (1.1-1.7)	207,781 (40%)
Estimated GFR (ml/min/1.73m2)	77 ± 13	146,023 (28%)
Ankle brachial index <0.9	12 (12%)	98 (0%)
hsCRP (mg/L)*	3.0 (1.2-5.0)	94,579 (18%)
Gestational hypertension	1645 (0%)	518,015 (100%)
History of cancer	26,465 (5%)	518,015 (100%)
Albuminuria >30 mg/g	1,538 (24%)	6,377 (1%)
Number of drugs (n)	0.0 (0.0-1.0)	518,015 (100%)

Availability of baseline variables in CPRD before imputation. Only variables necessary for the SCORE2 predictions were imputed (smoking status, systolic blood pressure, total and HDL-cholesterol). hsCRP is coded as missing for values higher than 10 mg/L as this may signal acute inflammation.

Supplementary Table 7: Discrimination and NRI stratified on sex

	Original C-index (95%CI)	C-index using all risk modifiers(95%CI)	NRI event (95%CI)	NRI non-event (95%CI)	NRI combined (95%CI)
Men	0.687 (0.681-0.693)	0.693 (0.688-0.699)	0.013 (0.006; 0.021)	0.003 (0.001;0.004)	0.017 (0.001;0.024)
Women	0.746 (0.737-0.754)	0.756 (0.747-0.764)	0.078 (0.065; 0.092)	-0.019 (-0.020;-0.018)	0.059 (0.046;0.721)

CHAPTER 5

The relevance of competing risk adjustment in cardiovascular risk prediction models for clinical practice

Steven HJ Hageman, Jannick AN Dorresteijn, Lisa Pennells. Stephen Kaptoge. Maarten van Smeden. Michiel L Bots. Emanuele Di Angelantonio. Frank LJ Visseren

on behalf of the UCC-SMART Study Group

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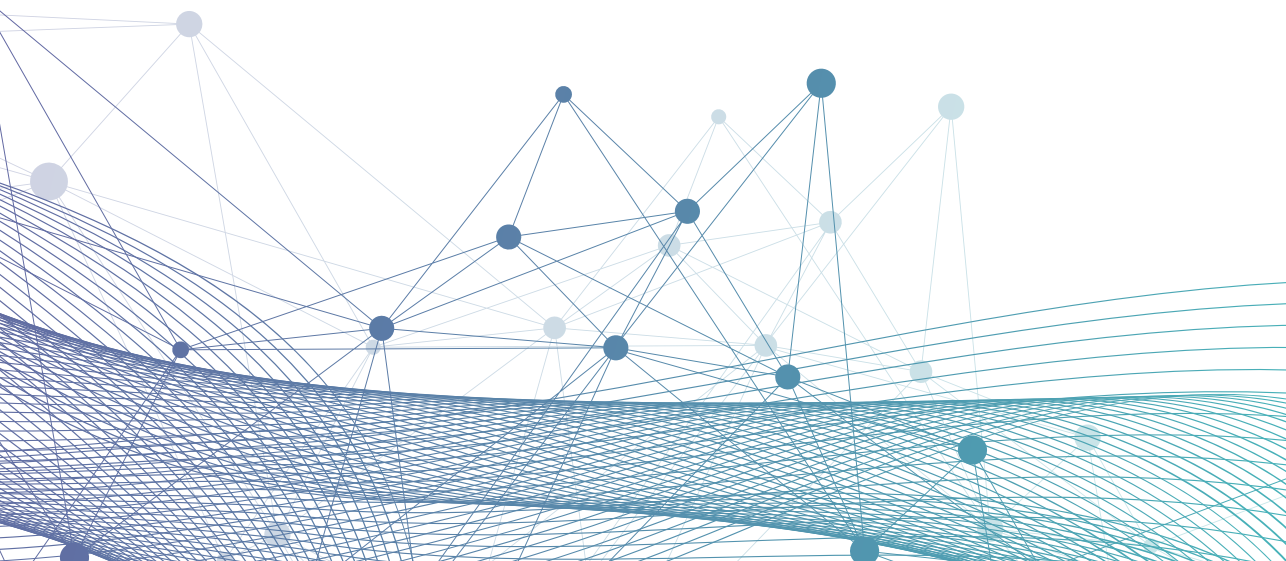


Abstract

Background: Many models developed for predicting the risk of cardiovascular disease (CVD), are adjusted for the competing risk of non-CVD mortality, which has been suggested to reduce potential overestimation of cumulative incidence in populations where the risk of competing events is high. The objective was to evaluate and illustrate the clinical impact of competing risk adjustment when deriving a CVD prediction model in a high-risk population.

Methods and Results: Individuals with established atherosclerotic CVD were included from the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART). In 8,355 individuals, followed for median of 8.2 years (IQR 4.2-12.5), two similar prediction models for the estimation of 10-year residual CVD risk were derived: once with competing risk adjustment using a Fine and Gray model and once without using a Cox proportional hazards model. On average, predictions were higher from the Cox model. The Cox model predictions overestimated the cumulative incidence ((predicted-observed ratio 1.14 [95%CI 1.09-1.20), which was most apparent in the highest risk quartiles and in older persons. Discrimination of both models was similar. When determining treatment eligibility on thresholds of predicted risks, more individuals would be treated based on the Cox model predictions. If, for example, individuals with a predicted risk >30% were considered eligible for treatment, 13% of the population would be treated according to the Fine and Gray model predictions and 21% according to the Cox model predictions.

Interpretation: With increasing interest in risk-based treatment in populations where competing risks may be present, competing risk adjustment should be considered to prevent overestimation of cumulative incidence.

Introduction

In the prevention of cardiovascular disease (CVD), current guidelines advise an individual approach to preventive treatment based on an individual's absolute 10-year CVD risk.[1] There are many prediction models available to estimate the 10-year risk of CVD events, targeted at different populations and using different methodologies. Examples include the SCORE2 model[2], the WHO CVD risk charts[3], and the Pooled Cohort Equations[4]. Some of the risk models have been adjusted for the impact of competing risks, which involves taking into account the possibility of non-cardiovascular mortality after which cardiovascular events can no longer occur. Not accounting for competing events in time-to-event analyses may lead to overestimation of cumulative CVD incidence, especially in populations in which the risk of non-CVD mortality is the highest, like older persons.[5]

In addition, the meaning of individual predicted risks based on a competing risk adjusted model are different from those based on unadjusted models. For a competing risk adjusted model, the risk can be interpreted as the probability of developing disease in a certain period of time given everything else that may happen ("*Your risk of a cardiovascular event in the next 10 years is 5%*"). Conversely, traditional time-to-event models not taking into account the possibility of competing risks are based on the assumption that people will stay alive during the predicted timeframe as long as a cardiovascular event does not occur. This should be interpreted as the probability of developing disease in the theoretical situation in which dying from non-cardiovascular causes is impossible ("*Assuming you will not die due to any non-cardiovascular cause, your risk of a cardiovascular event is the next 10 years is 5%*").[6] In diagnostic models, there is no time-to-event analysis, making competing risks irrelevant.[7] In prognostic models predicting the risk of all-cause mortality, competing risks are also irrelevant as there are no competing events which may prevent the outcome of interest.

The use of competing risk adjustment in the development and validation of medical prediction models is not common practice, even in situations where competing risks are likely present.[8] The fact that many of these models have not been adjusted for competing risks could reflect unfamiliarity of clinicians with the necessity of competing risk-adjustment.[8] However, other potential disadvantages of competing risks adjustment may also affect these decisions, like the presumed increased complexity of the modelling and validation. These practical disadvantages of competing risk adjustment may be evident to the researcher, whereas the clinical impact of possible ignoring competing risks may be unclear. In this study, we set out to illustrate the clinical impact of competing risk adjustment for CVD prediction models using an example with data from the high risk population included in the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART).

Methods for competing risk-adjustment

To correct for competing risks, commonly used methodology for model derivation are Fine and Gray (FGR) models and cause-specific hazard models. In the FGR model direct regression on the cumulative incidence function is performed.[9] With FGR models, the predicted risks in individual patients can be relatively easily calculated from the baseline hazard, individual patient characteristics, and model coefficients. Alternatively, cause-specific hazard models can be used, an approach involving two fitted Cox proportional hazard models: a model for the outcome of interest and a similar model for the competing outcome. Additional, complicated calculations are then needed, combing the output from the two Cox models to estimate individual risks, making the process somewhat more complex than the FGR approach.[10]

Clinical illustration of competing risk adjustment

To illustrate the clinical impact of competing risk adjustment with real-world data, two new models were derived with the same predictors as the previously published SMART risk score[11,12],one with and one without competing risk adjustment. All individuals with established ASCVD aged 40-80 years were included from Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART). UCC-SMART is a single-center ongoing prospective cohort study at the University Medical Center Utrecht, the Netherlands.[13] Patients newly referred to the University Medical Centre Utrecht with established ASCVD were included in the period 1996 to 2019. Detailed information about the study population is shown in the Supplementary Methods. The outcome of interest was the combination of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

The model not adjusted for competing risks was a Cox proportional hazards model, the competing risk adjusted model was a FGR model, including the competing outcome of non-cardiovascular mortality. Both models use the same predictors as the original SMART risk score to predict the risk of recurrent CVD events in patients with established atherosclerotic CVD (ASCVD): age; sex; current smoking; diabetes mellitus; systolic blood pressure (in mmHg); non-High Density Lipoprotein-cholesterol (in mmol/L); presence of coronary artery disease, cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysm; estimated glomular filtration rate (eGFR) (mL/min/1.73m2); high sensitivity C-reactive protein (hsCRP; mg/L); and years since first clinical manifestation of ASCVD.

The predictive performance of the 2 models was compared with evaluating discrimination with Harrell's C-index, adjusted for competing risks. Calibration was evaluated in tenths of predicted risk by comparing the mean predicted risk in this group with the observed cumulative incidence. The cumulative incidence is the appropriate comparator for competing risk adjusted risk estimates, in contrast to the

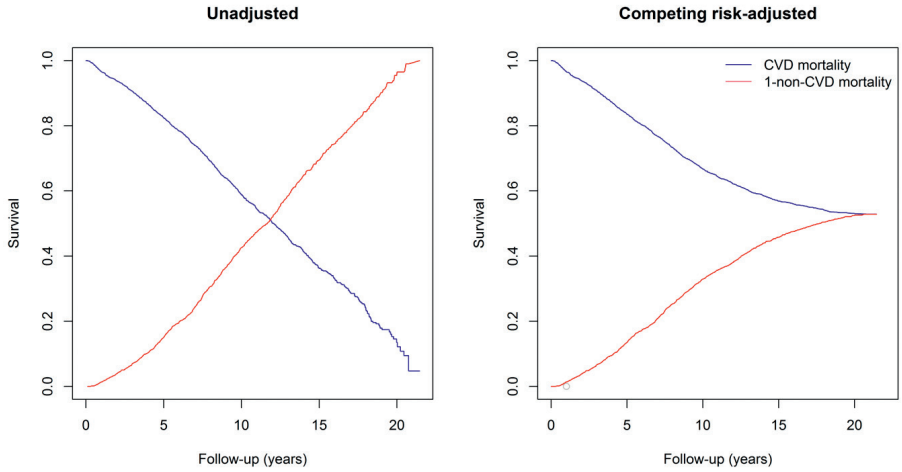
Kaplan-Meier estimator which, like the Cox model, estimates the observed probability of survival in a world where occurrence of a competing event is not possible.[10,14] Clinical outcomes of interest were the proportion of individuals which would be treated under certain treatment thresholds and the effectivity of treatment initiation based on predicted risks (**Supplementary Methods**).

Results

In total 8,355 patients with established ASCVD were included from UCC-SMART. Mean age at baseline was 61±9 years old, and 74% were male. Detailed patient characteristics are presented in **Supplementary Table 1**. During a median of 8.2 years of follow-up (IQR 4.2-12.5; 72,057 person years), 1,706 ASCVD events and 978 non-cardiovascular deaths were observed.

In the individuals who died during follow-up (n=2,111), the Kaplan-Meier and cumulative incidence plots of CVD mortality and non-CVD mortality are shown in **Figure 1**. As all of these individuals have died once, either due to a cardiovascular cause or to a non-cardiovascular cause, the incidences should sum to 100% at the end of the follow-up.

Figure 1: Survival free of CVD mortality and non-CVD mortality in individuals dying during follow-up (n=2,111)



In all individuals dying during follow-up, it is expected that the incidence of CVD mortality and the incidence from non-CVD mortality sum to 100% (everyone will die once, either from a cardiovascular or a non-cardiovascular cause). The unadjusted (Kaplan-Meier) curve will eventually estimate an incidence of 100% for both causes of death separately, whereas the FGR model eventually estimates an incidence of 100% for both endpoints combined.

The unadjusted (Kaplan-Meier) curve, which uses the same underlying methods as the Cox proportional hazards model, eventually estimates an incidence of 100% for both causes of death individually – reflecting the interpretation as the probability of a CVD death occurring in a world where death from any other cause is not possible. For the cumulative incidence curves, working like the Fine and Gray model, the incidences exactly add up to 100% at the end of the follow-up.

In the complete population of 8,355 individuals with established ASCVD both the Cox model and the FGR model were derived. Model parameters of both the FGR and Cox model are presented in **Table 1**. For most predictors, the hazard ratios from the Cox model were similar to the subdistribution hazard ratios from the FGR model. The largest difference was in the effect of smoking, with an unadjusted hazard ratio of 1.58 (95%CI 1.42-1.76) versus the competing risk adjusted subdistribution hazard ratio of 1.49 (95%CI 1.34-1.66). The baseline survival of the Cox model was slightly lower than the survival of the FGR model (0.81 for the Cox model versus 0.83 for the FGR model). For all individuals in the UCC-SMART data, risks can be predicted from these model parameters using the same, easy to use, formula for both the Cox model and the FGR model (**Supplementary Table 2**).

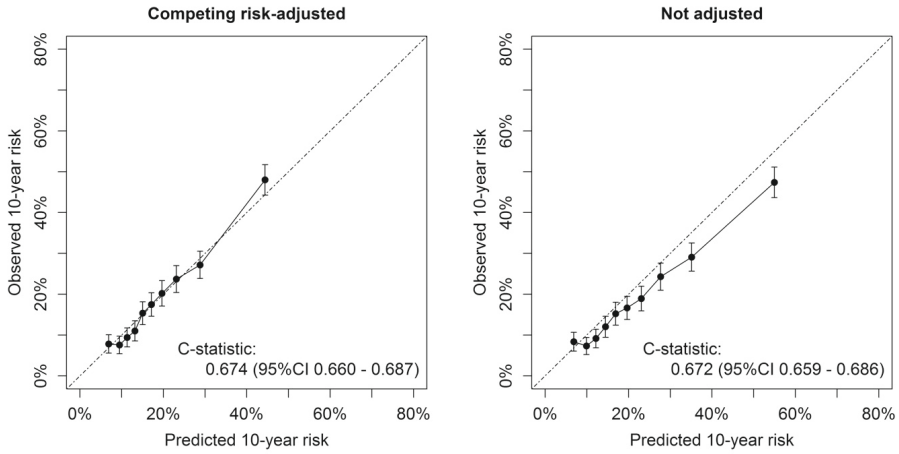
Table 1: Model coefficients with and without competing risk adjustment

Predictor	(Subdistribution) hazard ratio (95%CI)	
	Cox model	FGR model
Age	1.04 (1.03-1.05)	1.03 (1.02-1.04)
Male sex	1.41 (1.25-1.59)	1.36 (1.21-1.53)
Diabetes mellitus	1.47 (1.31-1.65)	1.45 (1.29-1.62)
Current smoking	1.58 (1.42-1.76)	1.49 (1.34-1.66)
Systolic blood pressure (per 10mmHg)	1.03 (1.00-1.05)	1.02 (1.00-1.05)
Non-HDL cholesterol (mmol/L)	1.13 (1.08-1.17)	1.15 (1.10-1.19)
hsCRP	1.01 (1.01-1.01)	1.01 (1.00-1.01)
Estimated glomular filtration ratio	0.99 (0.98-0.99)	0.99 (0.98-0.99)
Years since first ASCVD diagnosis	1.01 (1.00-1.02)	1.01 (1.00-1.01)
Prevalent coronary artery disease	1.45 (1.27-1.65)	1.46 (1.28-1.68)
Prevalent cerebrovascular disease	1.54 (1.36-1.75)	1.51 (1.33-1.72)
Prevalent peripheral artery disease	1.43 (1.25-1.63)	1.37 (1.20-1.57)
Prevalent abdominal aortic aneurysm	1.61 (1.39-1.87)	1.55 (1.33-1.80)
Baseline survival	0.81	0.83

Subdistribution hazard ratios from Cox and Fine and Gray models predicting the risk of fatal+non-fatal ASCVD. ASCVD = Atherosclerotic cardiovascular disease. hsCRP = High-sensitivity C-reactive protein, HDL = high density lipoprotein, FGR = Fine and Gray.

The internal validation C-indexes were 0.674 (95% CI 0.660 – 0.687) for the FGR model and 0.672 (95% CI 0.659 – 0.686) for the Cox model. In the Cox model, an overestimation of cumulative CVD incidence was observed (predicted-observed ratio 1.14 [95%CI 1.09-1.20]). In the predictions from the FGR model, no systematic over- or underestimation was observed (predicted-observed ratio 0.98 [95%CI 0.93-1.03], **Figure 2**). The unadjusted model's predicted risks agreed well with the Kaplan-Meier estimates (**Supplementary Figure 1**).

Figure 2: Calibration and discrimination in the UCC-SMART cohort, with and without competing risk adjustment



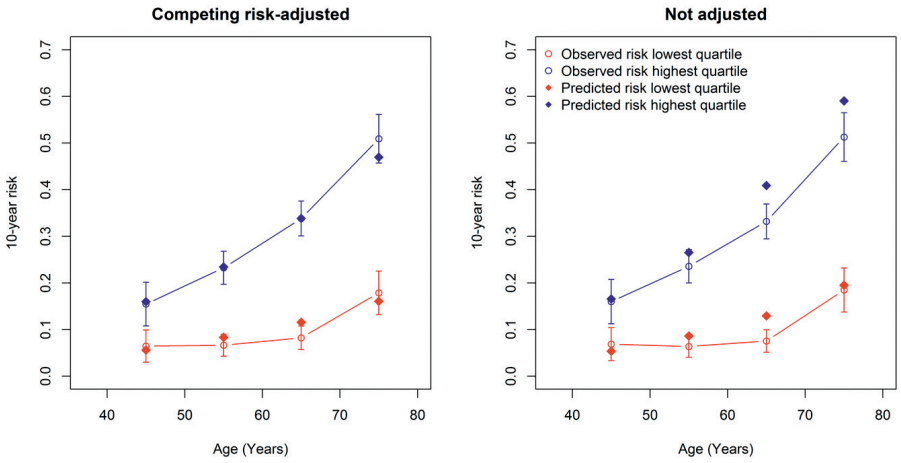
Calibration and discrimination of the competing risk adjusted model (Fine and Gray) and the model not adjusted for competing risks (Cox proportional hazards). Observed incidence is determined using the cumulative incidence.

The agreement between predicted and observed risks within 10-year age groups is shown in **Figure 3**. Overestimation in the Cox proportional hazards predictions is most visible in the highest risk quartile within those aged 60-69 years (predicted-observed ratio 1.21 [95%CI 1.09-1.36]) and those aged 70-79 years (predicted-observed ratio 1.16 [95%CI 1.05-1.29])

Clinical utility

For patients with established ASCVD no specific treatment thresholds for residual CVD risk have been recommended in the latest ESC prevention guidelines.[1] To further illustrate the impact of prediction models with and without competing risk adjustment on treatment decisions a range of relevant treatment thresholds were used as an example for two clinically relevant therapeutic options for residual risk reduction, namely adding low-dose direct oral anticoagulant (DOAC) to antiplatelet therapy based on the COMPASS trial[15] and with Proprotein convertase subtilisin/kexin type 9 (PCSK9)-monoclonal antibodies.[16] For each of those thresholds, it was evaluated how many individuals would be eligible for treatment based on either of the models.

Figure 3: Agreement between predicted and observed risk in the highest and lowest quarter of predicted risk within each 10-year age group



The theoretical effectiveness of treatment in all individuals above certain thresholds was projected by combining the observed cumulative incidence in the UCC-SMART cohort with the relevant treatment effects from trials and meta-analyses (**Supplementary Methods**). When simulating treatment of all individuals in UCC-SMART based on certain treatment thresholds, more individuals would be treated based on the Cox model, in comparison to the predictions from the FGR model (**Table 2**). For example, using a treatment threshold of 30% residual 10-year risk leads to 1,105 individuals (13% of the population) being eligible for treatment using FGR models, whereas this would be 1,759 individuals (21% of the population) based on the Cox model. Of the individuals who had an event in the first 10 years after follow-up, 420 (33%) would be eligible for treatment according to the FGR model and 566 (44%) to the Cox model. On the other side, of those not having an event in the first 10 years after follow-up, 6380 (90%) would be below the treatment threshold for the FGR model and 5872 (83%) for the Cox model (**Supplementary Table 3**).

Table 2: Projected clinical impact of competing risk adjustment on treatment with low-dose DOACs in combination with aspirin versus aspirin alone.

Threshold (10-year risk %)	Treated n(%)	CVD events avoided, (ARR%)	10-year NNT
Competing risk adjusted (FGR model)			
10	6880 (82%)	324 (5%)	21
20	2818 (34%)	186 (7%)	15
30	1105 (13%)	92 (8%)	12
40	456 (5%)	43 (9%)	11
50	195 (2%)	19 (10%)	10
60	75 (1%)	7 (10%)	10
Unadjusted (Cox model)			
10	7069 (85%)	328 (5%)	22
20	3660 (44%)	223 (6%)	16
30	1759 (21%)	132 (7%)	13
40	880 (11%)	77 (9%)	11
50	455 (5%)	43 (9%)	10
60	232 (3%)	23 (10%)	10
Treated with Cox model, not with FGR model			
10	217 (3%)	3 (1%)	70
20	844 (10%)	35 (4%)	24
30	654 (8%)	37 (6%)	17
40	424 (5%)	33 (8%)	13
50	261 (3%)	23 (9%)	11
60	157 (2%)	16 (10%)	10

The clinical impact of using either a competing risk adjusted (FGR) or unadjusted (Cox) model to treat all individuals in the UCC-SMART cohort with risks higher than several treatment targets with a low-dose DOAC. All individuals were assumed to currently be on aspirin monotherapy. ARR = absolute risk reduction, defined as number of avoided events divided by number of treated individuals. NNT = Number needed to treat. NNH = Number needed to harm. FGR = Fine and Gray.

Using the same 30% residual 10-year risk threshold for the initiation of the combination of aspirin and a low-dose DOAC (i.e. dual pathway inhibition) would lead to projected reduction of approximately 116 CVD events in 1,105 individuals treated based on the FGR model – equal to a projected absolute risk reduction (ARR) of 8% and a number needed to treat (NNT) of 12. For the Cox model predictions this would be a reduction of 132 events in 1,759 individuals (ARR of 7% and NNT of 13). In the group of individuals only eligible for treatment according to the Cox model but not to the FGR model (n=654, 8% of the population), a smaller treatment benefit is expected (37 avoided CVD events, ARR 6%, NNT 17). In the example of PCSK9 inhibition a similar pattern is observed (**Supplementary Table 4**). Treating all individuals with both a predicted CVD risk of 40% or greater and a low-density lipoprotein cholesterol (LDL-c) of >1.8 mmol/L leads to 5% of the population being treated based on the FGR model and 9% of the population based on the Cox model. A slightly lower treatment effectiveness is observed when determining PCSK9 inhibitor treatment eligibility on the Cox proportional hazard model (ARR 15% and NNT of 7) versus the FGR model (ARR 17% and NNT of 6).

Discussion

In the current report, an example including high risk individuals is presented to illustrate the potential clinical relevance of competing risk adjustment for prediction models of cardiovascular disease in such populations. Two similar prediction models were derived, with and without competing risk adjustment. On average, predictions were higher from the unadjusted model, reflecting the different interpretations of both models. When compared to the observed cumulative incidence, the unadjusted model predictions were overestimated, especially in older persons.

The use of individual predicted risks unadjusted for competing risks could lead to different treatment decisions as would have been taken in the case of an adjusted model. In the 2021 ESC guidelines, a two-step approach was introduced with a second step allowing for further intensification of treatment based for apparently healthy people, patients with diabetes mellitus and patients with established ASCVD.[1] One of the factors to consider in this individual approach, is predicted 10-year CVD risk. If overestimated predictions would be used in this situation, then both patient and physician could expect too optimistic benefit from risk factor treatment and may be more inclined to intensify preventive therapy.

To determine which exact populations require competing risk adjustment for accurate prediction of absolute CVD risks cannot exactly be defined. In several populations, like older persons or patients with significant comorbidity such as cancer patients, the relevance seems clear. For the young and apparently healthy individuals the probability of competing mortality preceding a CVD event in the next 10-years is likely to be small, and with that the difference between the models adjusted and unadjusted for competing risks are also small. In many cases the relevance of competing risk adjustment will not be as clear as in these examples. As the competing risk adjusted model performs similar to the unadjusted model in those cases competing risks would be absent, the use of a competing risk model should be encouraged if this is potentially relevant for (part of) the target population. In this study illustrations are given for cardiovascular risk prediction, but the same reasoning might hold for prediction algorithms in other fields of medicine.

The differences in interpretation may make the competing risk adjusted or unadjusted approach more suitable, depending on the specific clinical situation and target population. Results from the current study have demonstrated a slight overestimation of the cumulative incidence as estimated by the model unadjusted for competing risks. This cumulative incidence can in interpreted as the absolute probability of disease during the time horizon of interest. Therefore, in those cases in which an individual's absolute disease risk is of interest, and competing risks are likely present, adjustment for competing risk should be considered. Relevant examples of this are

treatment decisions in the prevention of CVD, for which risk prediction is performed under the assumption that a high CVD risk signals a high benefit of preventive therapy.[1] This assumption may be violated in those populations with a high impact of competing risks, such as older persons: individuals may die due to alternate causes before profiting from CVD prevention.

Alternatively, the estimates from the Cox model may give a more accurate picture of an individual's underlying disease-specific health. For example, should the person's CVD-specific health be of key isolated interest, regardless of their risk of other diseases, then the estimates from a Cox model could be considered most relevant. . However, this comes with the cost of having a more complex interpretation: the risk of a CVD event in a world where dying of anything else is not possible. The relative harms of treatment should also be carefully considered when taking such an approach.

The added complexity to the statistical analyses due to competing risk adjustment is usually limited. Especially in the case of a FGR model, any additional complexity is almost exclusively in the mathematics underlying these models. The data preparation, model derivation and external validation are actually very similar and individual predictions can be made with the same function using a baseline hazard, model coefficients and individual predictor values. As concerns of increased complexity likely often reflect unfamiliarity with the methodology, this should generally not be a reason to use a model unadjusted for competing risks to predict absolute CVD risks. The computational time of the analyses required for both models is equal, except for the model derivation time which is increased for the Fine and Gray model. However, even the model derivation of the SCORE2 model (n=677 684) could be performed on a regular computer.

A potential disadvantage of competing risk adjustment, specifically Fine and Gray models, is the fact that the SHRs from the model are not causally interpretable.[17] Whereas SHRs indeed have no causal interpretation, if the aim of the model is to predict an individual's absolute risk for the occurrence of a disease in the future as accurately as possible, rather than to determine a causal relationship, the lack of interpretable coefficients is of limited concern.

With increasing interest in risk-based treatment in CVD prevention guidelines, including in high-risk populations such as the elderly and those with established ASCVD, where high levels of competing risks may be evident, prognostic predictions not estimating the risk of all-cause mortality should consider allowance for this. If competing risks are ignored in such populations, overestimation of cumulative incidence is a potential consequence which may result in less effective and less cost-effective treatment decisions.

References

1. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
2. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-2454. doi:10.1093/eurheartj/ehab309
3. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Heal. 2019;7(10):e1332-e1345. doi:10.1016/S2214-109X(19)30318-3
4. Preiss D, Kristensen SL. The new pooled cohort equations risk calculator. Can J Cardiol. 2015;31(5):613-619. doi:10.1016/j.cjca.2015.02.001
5. Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond). 2001;101(6):671-679. doi:10.1042/CS20000335
6. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic Models With Competing Risks. Epidemiology. 2009;20(4):555-561. doi:10.1097/EDE.0b013e3181a39056
7. van Smeden M, Reitsma JB, Riley RD, Collins GS, Moons KG. Clinical prediction models: diagnosis versus prognosis. J Clin Epidemiol. 2021;132:142-145. doi:10.1016/j.jclinepi.2021.01.009
8. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? Stat Med. 2012;31(11-12):1089-1097. doi:10.1002/sim.4384
9. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144
10. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic Models With Competing Risks. Epidemiology. 2009;20(4):555-561. doi:10.1097/EDE.0b013e3181a39056
11. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013;99(12):866-872. doi:10.1136/heartjnl-2013-303640
12. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016;134(19):1419-1429. doi:10.1161/CIRCULATIONAHA.116.021314
13. Simons PCG, Algra A, Van De Laak MF, Grobbee DE, Van Der Graaf Y. Second manifestations of ARTerial disease (SMART) study: Rationale and design. Eur J Epidemiol. 1999;15(9):773-781. doi:10.1023/A:1007621514757
14. Grunkemeier GL, Jin R, Eijkemans MJC, Takkenberg JJM. Actual and Actuarial Probabilities of Competing Risks: Apples and Lemons. Ann Thorac Surg. 2007;83(5):1586-1592. doi:10.1016/j.athoracsur.2006.11.044
15. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377(14):1319-1330. doi:10.1056/NEJMoa1709118
16. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664
17. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017;36(27):4391-4400. doi:10.1002/sim.7501

18. Zhang X-L, Zhu Q-Q, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med. 2015;13(1):123. doi:10.1186/s12916-015-0358-8

19. Bonaca MP, Nault P, Giugliano RP, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease. Circulation. 2018;137(4):338-350. doi:10.1161/CIRCULATIONAHA.117.032235

20. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5

21. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59(10):1087-1091. doi:10.1016/j.jclinepi.2006.01.014

Supplementary Methods

Population

In the current study, individuals with established ASCVD were included from the UCC-SMART cohort. UCC-SMART is a single-center ongoing prospective cohort study at the University Medical Center Utrecht, the Netherlands.[13] Patients newly referred to the University Medical Centre Utrecht with established ASCVD, or an increased risk hereof, were included in the period 1996 to 2019. Among those, the patients with a history of any type of established ASCVD were included for the current study, including coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral artery disease (PAD), and/or abdominal aortic aneurysm (AAA). CAD was defined as angina pectoris with documented stenosis, myocardial infarction, or coronary revascularization (coronary bypass surgery or coronary angioplasty); CeVD as a transient ischemic attack, cerebral infarction, amaurosis fugax or retinal infarction, or a history of carotid surgery; PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg or a history of vascular surgery of the leg (percutaneous transluminal angioplasty, bypass, or amputation); and patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured at baseline examination with ultrasonography) or a history of AAA surgery. From these patients, everyone aged 60 years and above was included for the current analyses as for those individuals the adjustment for competing risks is likely most relevant.

Treatment effect estimation

Treatment effects were estimated by combining the observed cumulative incidence with hazard ratios known from trials and meta-analyses. For PCSK9 inhibitors, the treatment effect was projected through LDL-c reduction. The expected decrease in baseline LDL-c of PCSK9 inhibitors was assumed to be 59%,[18,19] which lowered the risk of CVD with HR of 0.78 (95%CI 0.76 - 0.80) per 1 mmol/L reduction of LDL-c.[16,20] The effect of initiating a low-dose DOAC was assumed to be HR 0.76 (95%CI 0.66-0.86) compared to aspirin alone.[15] It was assumed that all individuals were using aspirin monotherapy at baseline.

The expected number of events was calculated by multiplying the observed cumulative incidence with the number of treated individuals and for the treated scenario, which was used rather than the observed number of events to account for censoring of individuals with less than 10 years of follow-up. The expected number of events for treated individuals was calculated the same, but in this calculation the hazard ratio was combined with the cumulative incidence in the following formula:

$$\text{Cumulative incidence}_{\text{treated}} = 1 - (1 - \text{cumulative incidence}_{\text{observed}})^{\wedge \text{HR}}$$

Event reductions were calculated by subtracting the number of events expected with therapy from the number of events expected without therapy. To calculate the expected event reduction from starting a low-dose DOAC (HR 0.76) in 1000 individuals (cumulative CVD incidence at 10 years 20%) currently treated with aspirin, it would be done the following:

(1000 * 0.2) - (1000 * (1 -(1-0.2)^0.76)) = 44 avoided events

The number needed to treat was calculated by dividing the number of treated individuals by the number of avoided events, in this case *1000/44 = 23*.

Statistical analyses

All analyses were performed with R-statistical programming (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria). Cox regression analyses were performed with the *coxph* function from the *survival* package, version 3.2). FGR analyses were performed with the *FGR* function from the *riskRegression* package version *2020.12.08*. Cumulative incidence of CVD at 10 years for the model calibration was assessed by using the *cuminc* function from the *cmprsk* package, version 2.2. The predicted-observed ratio was calculated by dividing the mean predicted risk by the observed cumulative incidence at 10 years.

Because complete case analysis may lead to loss of statistical power and possible bias,[21] values of the following variables in the derivation data were imputed by single regression imputation using predictive mean matching: smoking status (n=32, 0.4%), creatinine (n=31, 0.3%), hsCRP (n=250, 3.2%), SBP (n=18, 0.2%), HDL-c (n=80, 1.0%), and total cholesterol (n=34, 0.4%). Single imputation was performed due to the illustrative nature of the current study, but could have slightly underestimated the presented confidence intervals.

Supplementary Table 1: Patient characteristics at baseline

	UCC-SMART
	n = 8,355
Male sex	6,198 (74%)
Age (years)	61 ± 9
Current smoker	2,504 (30%)
Body mass index (kg/m²)	27 ± 4
Systolic blood pressure (mmHg)	139 ± 20
Diabetes mellitus	1,467 (18%)
Established coronary artery disease	5,215 (62%)
Established peripheral artery disease	1,459 (17%)
Established cerebrovascular disease	2,424 (29%)
Established abdominal aortic aneurysm	706 (8%)
Total cholesterol (mmol/L)	4.6 (3.9-5.5)
HDL-cholesterol (mmol/L)	1.2 (1.0-1.4)
LDL-cholesterol (mmol/L)	2.7 (2.1-3.5)
Triglycerides (mmol/L)	1.4 (1.0-2.0)
Estimated GFR (mL/min/1.73m²)	77 ± 18
hsCRP (mg/dL)	2.0 (1.0-4.4)
Statin	5,764 (69%)
Antiplatelet therapy or anticoagulants	6,494 (78%)

n (%), mean ± SD, or median (interquartile range; IQR). eGFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula). ASCVD = cardiovascular disease, hsCRP = C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein

Supplementary Table 2: Formulae for individual risk prediction using Cox or Fine and Gray models

General formula for prediction of individual risks $CVDrisk_t = 1 - basesurvival_t \text{^} (e^{\sum \beta_{age} * age + \beta_{sex} * sex + \beta_x * x \ldots})$
Formula to predict individual risks from Cox model $CVDrisk_{10}$ = 1-0.81^(e^(0.038*age + 0.343 if sex is male + 0.384 if diabetes mellitus + 0.457 if current smoker + 0.025*SBP + 0.119*non-HDL-c + 0.011*hsCRP + -0.014*eGFR + 0.011*years since first vascular diagnosis + 0.369 if coronary artery disease + 0.434 if cerebrovascular disease + 0.355 if peripheral artery disease + 0.479 if abdominal aortic aneurysm))
Formula to predict individual risks from Fine and Gray model $CVDrisk_{10}$ = 1-0.83^(e^(0.029*age + 0.307 if sex is male + 0.370 if diabetes mellitus + 0.400 if current smoker + 0.024*SBP + 0.138*non-HDL-c + 0.008*hsCRP + -0.013*eGFR + 0.007*years since first vascular diagnosis + 0.381 if coronary artery disease + 0.412 if cerebrovascular disease + 0.315 if peripheral artery disease + 0.435 if abdominal aortic aneurysm))

Supplementary Table 3: Proportion of future cases and future non-cases treated based on predictions from competing risk-adjusted or unadjusted models

Treatment threshold (10-year risk %)	Treated, n(%)	Cases treated (% of total cases)	Non-cases untreated (% of total non-cases)
Competing risk adjusted (FGR model)			
10	6880 (82%)	1209 (94%)	1394 (20%)
20	2818 (34%)	761 (59%)	5008 (71%)
30	1105 (13%)	420 (33%)	6380 (90%)
40	456 (5%)	221 (17%)	6830 (97%)
50	195 (2%)	112 (9%)	6982 (99%)
60	75 (1%)	43 (3%)	7033 (100%)
Unadjusted (Cox model)			
10	7069 (85%)	1218 (94%)	1214 (17%)
20	3660 (44%)	885 (69%)	4209 (61%)
30	1759 (21%)	566 (44%)	5872 (83%)
40	880 (11%)	359 (28%)	6544 (93%)
50	455 (5%)	221 (17%)	6831 (97%)
60	232 (3%)	129 (10%)	6962 (99%)

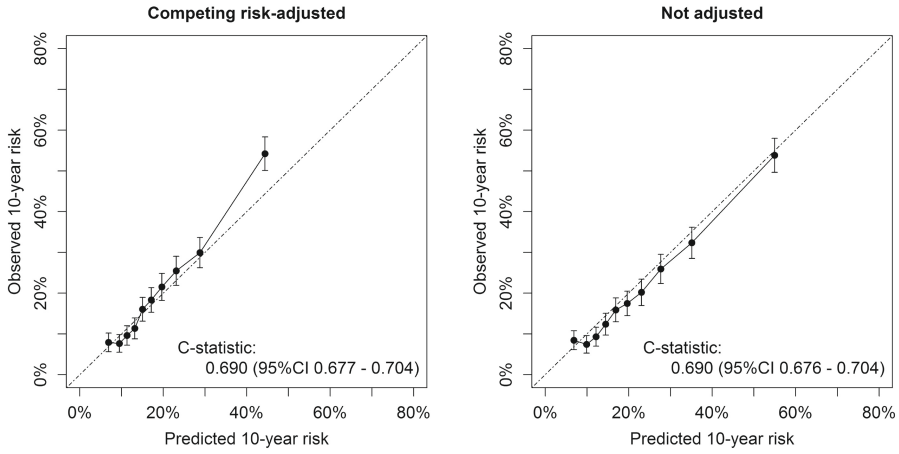
The proportion of the total population (column treated) and cases (column cases treated) with predicted risks higher than a risk threshold. For the non-cases, the proportion that is correctly identified as non-case. Cases were defined as those with a CVD event in the first 10 years of follow-up.

Supplementary Table 4: Clinical impact of competing risk adjustment on treatment with PCSK9i when treating all individuals with a LDL-c of >1.8 mmol/L and a risk greater than several risk thresholds

Threshold (10-year risk %)	Treated n(%)	CVD events avoided, (ARR%)	10-year NNT
Competing risk adjusted (FGR model)			
10	5934 (71%)	435 (7%)	14
20	2494 (30%)	266 (11%)	9
30	994 (12%)	140 (14%)	7
40	406 (5%)	68 (17%)	6
50	176 (2%)	32 (18%)	6
60	69 (1%)	13 (19%)	5
Unadjusted (Cox model)			
10	6063 (73%)	436 (7%)	14
20	3181 (38%)	308 (10%)	10
30	1555 (19%)	191 (12%)	8
40	779 (9%)	115 (15%)	7
50	399 (5%)	66 (16%)	6
60	208 (2%)	36 (17%)	6
Treated with Cox model, not with FGR model			
10	157 (2%)	3 (2%)	52
20	689 (8%)	42 (6%)	16
30	561 (7%)	49 (9%)	11
40	373 (4%)	45 (12%)	8
50	224 (3%)	33 (15%)	7
60	139 (2%)	23 (17%)	6

The clinical impact of using either a competing risk adjusted (FGR) or unadjusted (Cox) model to treat all individuals in the UCC-SMART cohort who have both a LDL-c level of >1.8 mmol/L as well as a risk higher than several treatment targets with a PCSK9 inhibitor. ARR = absolute risk reduction, defined as number of avoided events divided by number of treated individuals. NNT = Number needed to treat. NNH = Number needed to harm. FGR = Fine and Gray.

Supplementary Figure 1: Calibration and discrimination unadjusted for competing risks for both models



Calibration and discrimination of the competing risk adjusted model (Fine and Gray) and the model not adjusted for competing risks (Cox proportional hazards). Observed incidence is determined using the Kaplan-Meier estimate.

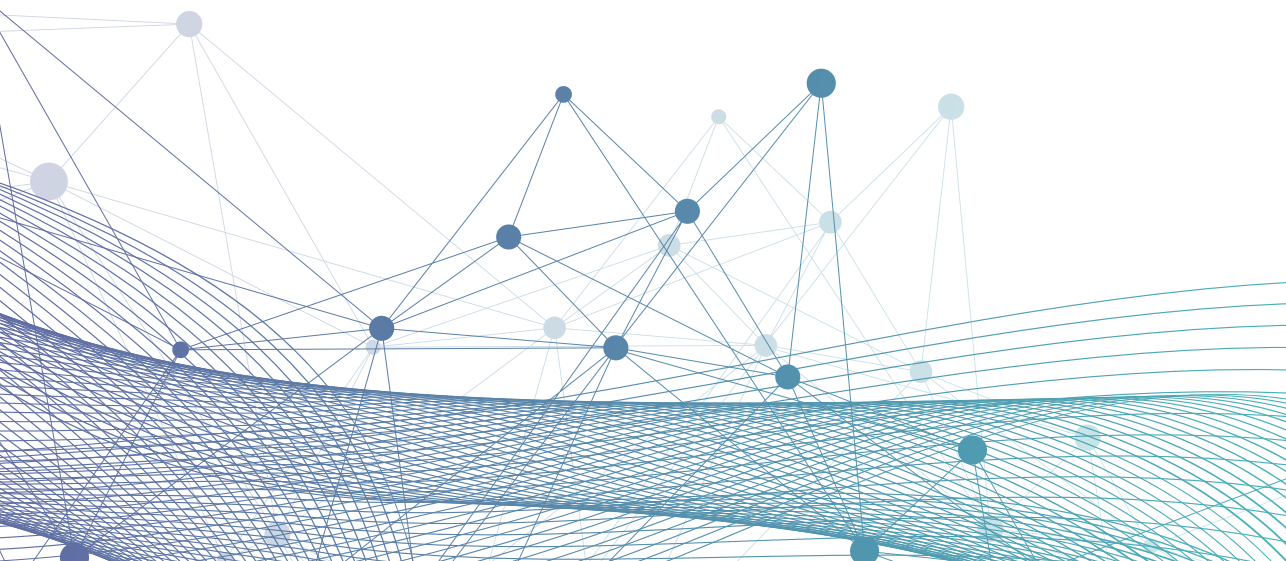
CHAPTER 6

Prediction of lifetime cardiovascular risk and individual lifetime treatment benefit in four European risk regions: geographic recalibration of the LIFE-CVD model

Steven HJ Hageman, Wentian Lu, Steven Kaptoge, Kristi Läll, Lisa Pennells, Tamar I de Vries, Martin Bobak, Hynek Pikhart, Ruzena Kubinova, Sofia Malyutina, Andrzej Pająk, Abdonas Tamosiunas, Raimund Erbel, Andreas Stang, Börge Schmidt, Sara Schramm, Emanuele Di Angelantonio, Frank LJ Visseren*, Jannick AN Dorresteijn*

Manuscript draft

*: Contributed equally



Abstract

Background: The life expectancy free of cardiovascular disease (CVD) in individuals without previous CVD can be estimated with the LIFEtime-perspective CardioVascular Disease (LIFE-CVD) model, as recommended by the 2021 ESC CVD prevention guidelines. Our aim was to systematically recalibrate the LIFE-CVD model to four European risk regions using contemporary and representative registry data.

Methods and Results: The LIFE-CVD model was systematically recalibrated to four distinct risk regions within Europe, using representative aggregate data on age- and sex-specific expected CVD and non-CVD mortality incidences and risk factor distributions. For external validation, 1,451,077 individuals without previous CVD were included from seven European cohorts, with 53,721 CVD events and 62,902 non-CVD deaths during follow up. After applying the recalibrated risk prediction models to external validation cohorts, C-indices ranged from 0.670 (95%CI 0.650-0.690) to 0.787 (95%CI 0.785-0.789). Predicted risks matched the observed risks in the CPRD data. With the recalibrated LIFE-CVD model, the estimated gain in CVD-free life expectancy from preventive therapy differed per region, for example a 50-year-old smoking women with a systolic blood pressure of 140mm Hg was estimated to gain 0.4 years of CVD-free life from 10 mm Hg SBP reduction in the low risk region, whereas this would be 1.5 years in the very high risk region.

Interpretation: By taking into account geographical differences in CVD incidence, the recalibrated LIFE-CVD model provides a more accurate tool for the prediction of lifetime risk and CVD-free life expectancy for individuals without previous CVD, facilitating shared decision-making in cardiovascular prevention options as recommended by the 2021 European Prevention Guidelines.

Introduction

A key strategy in the prevention of cardiovascular disease (CVD) is the use of risk prediction algorithms to target preventive interventions on people who benefit from them most.[1,2] In the 2021 European Society of Cardiology (ESC) prevention guidelines, a 2-Step approach was introduced as an individualized prevention strategy.[3] In Step 2, intensified prevention goals should be considered for each individual, taking into account personal preferences, expected side effects, predicted 10-year CVD risk, and/or lifetime prediction measures.[3] Lifetime prediction measures can be informative for supporting patient-doctor communication and can also be used to project the lifetime effect of preventive therapies. As age is the primary driver of 10-year CVD risk, lifetime estimates may be especially interesting for young individuals with high risk factor levels and for older persons. Even though the 10-year risks of younger persons are generally well below treatment thresholds due to their age, their benefit from preventive treatment in terms of gain in CVD-free life expectancy may be substantial.[4] Therefore, the 2021 ESC CVD prevention guidelines specifically recommend the lifetime benefit perspective in the communication with younger people.[3] Older individuals, on the other hand often have very high 10-year CVD risks, but can have limited treatment benefit due to their limited remaining life expectancy. Lifetime measures, like CVD-free life expectancy, are directly related to the life expectancy and have been corrected for competing risks. This makes those measures suitable for use in this population. For individuals without previous CVD, CVD-free life expectancy can be estimated with the LIFEtime-perspective CardioVascular Disease (LIFE-CVD) model.[4]

Often, algorithms developed in one population may not accurately predict risk in another population (i.e. they may not be well 'calibrated'). This is almost exclusively due to the fact that CVD event rates and average risk factor levels vary over time and per geographic region. After adjustment for such variances in CVD event rates and risk factor levels, the performance of most risk prediction algorithms is usually good.[5] The classical solution for this problem of inadequate calibration is to refit a model using a more recent or more local dataset than the dataset that was used for original model development.[3] A limitation of this approach, however, is that model recalibration is always based on historical data, because sufficient follow-up years and clinical events are required. Additionally, cohort data always has a certain degree of selection. Recently, a more pragmatic method for recalibration of risk prediction algorithms was introduced.[6–8] This method does not require the availability of a local and temporary dataset, but rather uses aggregated data of age-and-sex-specific average risk factor levels and CVD incidence, obtained from nationally representative registry data. This new method has already been validated for updating 10-year risk CVD risk algorithms.[6–8]

The aims of the current study were to adapt the pragmatic method for real-time and geographic calibration to the lifetime cardiovascular risk setting and to apply this to recalibrate the LIFE-CVD model to facilitate accurate predictions of CVD-free life-expectancy and lifetime risk for individuals without previous CVD in four European risk regions.

Methods

LIFE-CVD model

For the current study, coefficients of the original LIFE-CVD model were used for recalibration and external validation, thus no new models were derived. Details about the LIFE-CVD model development are published elsewhere. [4] In summary, the LIFE-CVD model was derived in the Multi-Ethnic Study of Atherosclerosis (MESA) study (n = 6,715), an ethnically and geographically diverse American cohort with recruitment starting in 2000.[4-9] From this cohort, all individuals aged <45 years, with a history of CVD, heart failure, estimated glomerular filtration rate (CKD-EPI eGFR) <30 mL/min/1.73 m2, and terminal malignancy at baseline were excluded.[4] The LIFE-CVD model consists of two complementary Fine and Gray proportional hazards functions for cardiovascular events and mortality respectively.[10] These functions use age as the time axis (i.e. left truncation). Lifetime predictions are generated by calculating cumulative survival for both outcomes combined based on repetitive one-year predictions for all future life years of an individual patient using life table methods. The LIFE-CVD model includes the following predictors: sex, systolic blood-pressure, non-high-density lipoprotein cholesterol, body-mass index, smoking status (current, former, never), diabetes mellitus, and positive history of premature (prior to age 60) MI in either parent. As the prevalence of a positive history of premature (prior to age 60) MI in either parent was unavailable in the recalibration data, this predictor was omitted from the recalibrated model to prevent systematic over- or underestimation of model predictions. The original LIFE-CVD model predicts the risk of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and resuscitated cardiac arrest. For this study, however, we omitted resuscitated cardiac arrest from this composite endpoint as this was not available in the recalibration data and was a minor component of the outcome in the derivation data (<5% of CVD included events). The competing endpoint of the LIFE-CVD model is death from any non-cardiovascular cause.

Recalibration

In order to systematically recalibrate the LIFE-CVD model using aggregate data on CVD incidence and risk factor levels, an adaption was made to the previous methods as used for the SCORE2 and SCORE2-OP models.[7,8] The same data sources were used for recalibration, and the model was recalibrated to the same risk regions as were defined in the SCORE2 paper (**Supplementary Figure 1**).[7,8] To estimate age-,

sex- and region-specific incidence of fatal and non-fatal disease, CVD mortality rates as reported by the WHO[11] were combined with the SCORE2 multipliers.[7,8] Age-specific and sex-specific risk factor values were obtained from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC).[12,13] The recalibration of SCORE2 was performed by regressing the expected 10-year CVD risk (by mean risk factor levels with SCORE2 model coefficients) versus the observed 10-year CVD risk (regional incidence estimated by rescaled WHO CVD mortality rates). To systematically recalibrate the LIFE-CVD model, a similar regression strategy was performed, but now on these 1-year CVD risks in the lifetable (expected: mean risk factor levels combined with life CVD predictors for CVD event, observed: WHO mortality rates combined with SCORE2 multipliers). In addition, a similar recalibration was performed on the non-CVD mortality predictions (expected: mean risk factor levels combined with life CVD predictors for competing outcome, observed: WHO mortality rates). The recalibration methodology is explained in more detail in the **Supplementary Methods**. To check the assumption that the SCORE2 multipliers for 10-year risk could also be used with the 1-year risk estimates from the LIFE-CVD model, the ratio between the cumulative incidence of CVD mortality rates and CVD events at 1-year and at 10-year were compared. If 10-year data was not available for these analyses, the latest year with 80% follow-up duration was used. Prior to the recalibration, extrapolation of the baseline hazard to ages 35 to 100 years was performed to allow for predictions below and beyond original age range, which was 45 to 90 years (for details see **Supplementary Methods** and **Supplementary Methods Table 2 and 3**).

Population

The recalibrated LIFE-CVD model was externally validated in several independent study populations in every European risk region. Individual patient data was used from the Clinical Practice Research Datalink (CPRD, United Kingdom, low risk region), Heinz Nixdorf Recall study (HNR, Germany, moderate risk region)[14], the Estonian Biobank (high risk region)[15] and the Health, Alcohol and Psychosocial factors In Eastern Europe study (HAPIEE, Poland and Czech Republic [high risk region], Russia and Lithuania [very high risk region]).[16] The CPRD database is a United Kingdom repository containing longitudinal individual primary care patient data collected from 1987 onwards. The primary care data are collected during routine general practice activities, which are linked to Hospital Episode Statistics admissions data from English hospitals and Office for National Statistics mortality data for endpoint registration. HNR is a population-based study in the large, heavily industrialized Ruhr area, Germany. From December 2000 to August 2003 random samples of men and women aged 45-75 were drawn from mandatory residency lists of three cities in the Ruhr area of North-West Germany. The Estonian Biobank is a population-based biobank of the Estonian Genome Center of the University of Tartu. Follow-up of incident fatal and non-fatal coronary heart disease and stroke events of a subset of the cohort is on-going as our database is being linked with the national healthcare

registries and regional and central hospital databases. The HAPIEE study comprises four prospective urban population based cohorts from Eastern Europe, located in Novosibirsk (Russia), Krakow (Poland), Kaunas (Lithuania), and six cities of the Czech Republic. Each cohort recruited a random sample of men and women aged 45-69 years at baseline conducted in 2002–2005 (2005–2008 in Lithuania), stratified by sex and 5-year age group. From these cohorts, all individuals aged 35 and older without prior CVD were included.

Statistical analyses

Discrimination was assessed using Harrell's C-statistic corrected for competing risks.[17] Calibration was assessed in the CPRD data, as this was the only cohort deemed approximately nationally representative. Calibration was evaluated visually using predicted versus observed risk plots – showing deciles of predicted risks plotted against CVD cumulative incidences.[17] The handling of missing data is further described in the Supplementary Methods. All analyses were performed with R-statistical programming (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria) or Stata (version 15.1, StataCorp, College Station, Texas).

Estimation of treatment effects

Similar to the original LIFE-CVD model, lifetime treatment effects can be estimated with the updated model. For this, hazard ratios (HR) from trials and meta-analyses are combined with yearly event rates for CVD events or non-CVD mortality. For LDL reduction an HR of 0.78 reduction of CVD events per 1 mmol/L was modelled.[18,19] The effect of 10mm Hg SBP reduction was modelled with an HR of 0.80.[20] The benefit of smoking cessation was modelled though both CVD events and non-CVD mortality, using an HR of 0.60 for CVD events and 0.73 for non-CVD mortality.[21,22]

Results

Using the age-, sex-, and region-specific mean risk factor levels and incidence data, the LIFE-CVD model was recalibrated to four European risk regions (**Supplementary Figure 2**). After recalibration, predicted risks based on mean risk factor levels showed good agreement with the estimated CVD event incidence (**Supplementary Figure 3**) and adequate with incidence rates obtained from external national registries (**Supplementary Figure 4**). The ratio between the 1-year cumulative incidence of fatal and non-fatal CVD was similar to the ratio at 10-years (**Supplementary Figure 5**).

Table 1: Baseline characteristics of the external validation populations

Cohort	CPRD*	HNR	HAPIEE	HAPIEE	HAPIEE	HAPIEE	Estonian Biobank
	n =1,416,257	n = 4,162	n = 6,925	n = 7,607	n = 5,762	n = 7,263	n = 3,101
Country	United Kingdom	Germany	Czech republic	Poland	Lithuania	Russia	Estonia
Male sex	683,476 (48%)	1,965 (47%)	3,139 (45%)	3,627 (48%)	2,612 (45%)	3,214 (44%)	1,017 (33%)
Age (years)	53 ± 8	59 ± 8	56 ± 7	56 ± 7	59 ± 8	56 ± 7	48 ± 10
Former smoker		1,370 (33%)	1,883 (27%)	2,005 (26%)	997 (17%)	899 (12%)	2,066 (36%)
Current smoker	613,819 (43%)	954 (23%)	1,911 (28%)	2,558 (34%)	1,170 (20%)	2,120 (29%)	764 (13%)
Diabetes mellitus	66,524 (5%)	475 (11%)	678 (10%)	704 (9%)	353 (6%)	270 (4%)	80 (3%)
Body mass index (kg/m2)	27.7 ± 5.4	27.8 ± 4.6	27.9 ± 4.6	27.9 ± 4.5	29 ± 5.2	28.3 ± 5.4	25.6 ± 4.6
Systolic blood pressure (mm Hg)	133 ± 17	132 ± 21	138 ± 20	137 ± 21	139 ± 22	141 ± 24	122 ± 14
Total cholesterol (mmol/L)	5.4 (4.7-6.1)	5.9 (5.3-6.6)	5.0 (4.5-5.6)	5.8 (5.1-6.5)	5.9 (5.2-6.6)	6.2 (5.4-7.0)	5.0 (4.4-5.6)
HDL-cholesterol (mmol/L)	1.4 (1.2-1.7)	1.5 (1.2-1.8)	1.4 (1.1-1.6)	1.2 (1.4-1.7)	1.5 (1.2-1.7)	1.5 (1.3-1.7)	1.3 (1.1-1.6)
Follow-up (years)	8.2 (4.9-10.3)	13.9 (10.3-15.6)	15.0 (13.8-15.8)	6.3 (6.0-6.9)	8.3 (7.8-9.0)	9.2 (6.7-10.4)	10.3 (9.8-11.1)
CVD events	50,318	299 (7%)	980 (14%)	450 (6%)	686 (12%)	783 (11%)	205

n (%), mean ± SD, or median (interquartile range; IQR). GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula), CVD = Cardiovascular, HDL = high density lipoprotein. *Baseline characteristics from CPRD are based on a previous version with a smaller age range and will be updated.

External validation

For external validation, 1,451,077 individuals without previous CVD were recruited from 7 European cohorts. Of these individuals, 699,050 were female (52%) and the mean ages per cohort ranged from 48 years in the Estonian Biobank to 59 years in HNR (**Table 1**). The median follow-up times per cohort ranged from 6.3 years (IQR 6.0-6.9) in HAPIEE Poland to 15.0 years (IQR 13.8-15.8) in HAPIEE Czech Republic. During this follow-up, total of 53,721 CVD events and 62,902 non-CVD deaths were recorded. C-indices for the prediction of CVD events ranged from 0.670 (95%CI 0.650-0.690) in HAPIEE Lithuania to 0.787 (95%CI 0.785-0.789) in CPRD (**Figure 1**). C-indices for the competing endpoint of non-CVD mortality ranged from 0.712 (95%CI 0.692- 0.731) in HAPIEE Lithuania to 0.834 (95%CI 0.832-0.836) (**Supplementary Figure 6**). In the CPRD data, predicted 10-year CVD event and non-CVD mortality risks agreed well with the observed events (**Figure 2**).

Figure 1: C-index of the recalibrated LIFE-CVD model to discriminate in external validation cohorts upon assessing CVD events

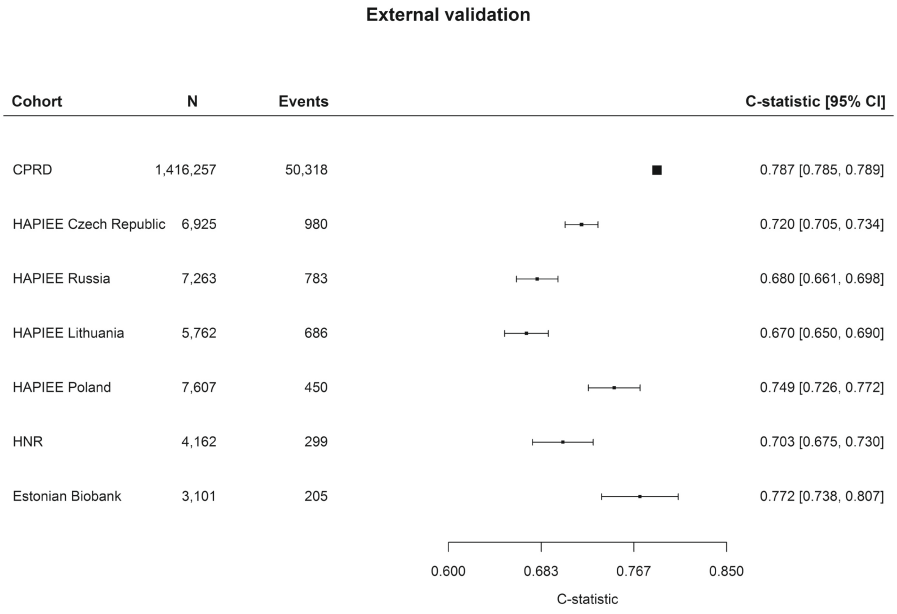
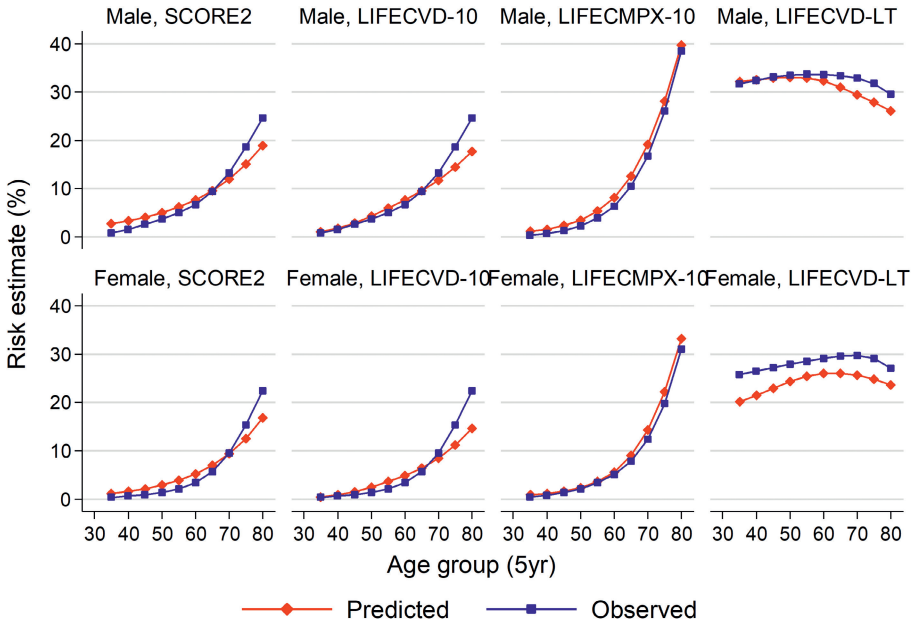


Figure 2: Calibration of the recalibrated LIFE-CVD model in CPRD (n=1,146,257)

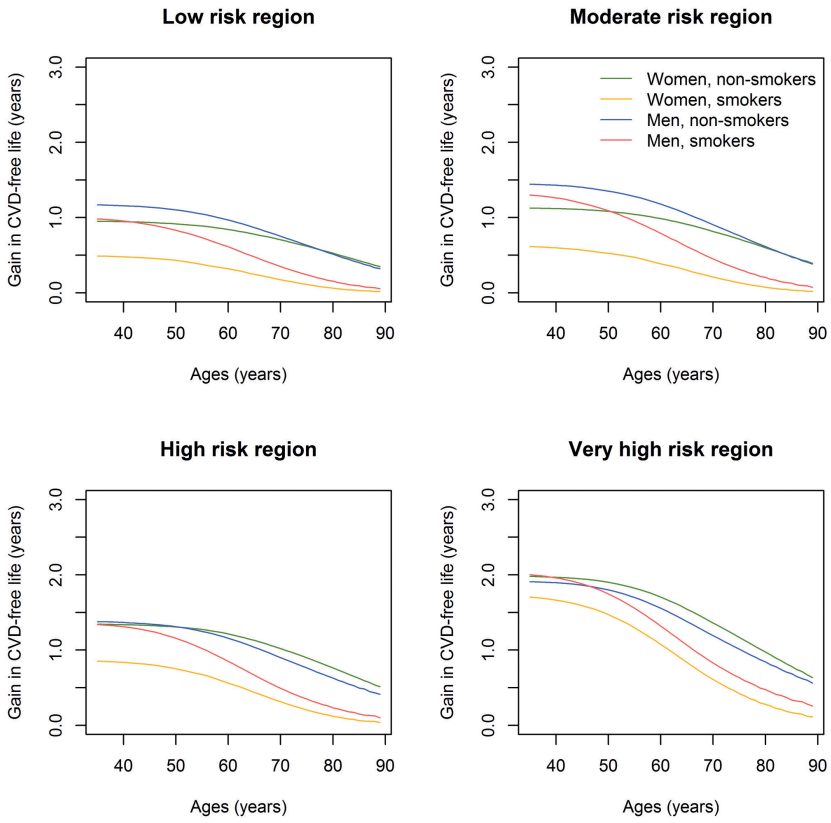


Predicted versus observed risks in every age group for the SCORE2 model, as well as the recalibrated LIFE-CVD model. LIFECVD10 = predicted 10-year CVD risk, LIFECMPX-10 = predicted 10-year risk of non-CVD mortality

Estimation of treatment effects

Figure 3 shows how the estimated gain in CVD-free life expectancy from lifelong 10 mm Hg blood pressure reduction estimated by the recalibrated LIFE-CVD model differs across regions for an individual person with a systolic blood pressure of 140mm Hg, total cholesterol of 5.5mmol/L and HDL cholesterol of 1.3mmol/L. For example, the gain in CVD-free life expectancy from 10 mm Hg blood pressure reduction for a 50-year-old male smoker ranges from 0.8 years in low risk countries to 1.7 years in very high-risk countries. Similarly, for a 50-year-old woman this ranges from 0.4 years in low risk countries to 1.5 years in very high-risk countries (**Figure 3**). In comparison, the individual gain in CVD-free life expectancy from smoking cessation in the same individuals ranged from 2.9 years from women in the low risk region up to 5.8 years to men in the very high risk region (**Supplementary Figure 7**). The estimated individual gain in CVD-free life expectancy for each combination of risk factor levels is displayed in in two-dimensional risk charts in **Appendix 1** for lipid lowering smoking cessation, and blood pressure reduction for each of the four European risk regions.

Figure 3: Predicted gain in CVD-free life expectancy from 10 mm Hg blood pressure reduction for an individual with total cholesterol concentrations of 5.5 mmol/L, HDL cholesterol of 1.3 mmol/L, body-mass index of 27 kg/m², and systolic blood pressure of 140 mm Hg, for each region



Discussion

The current report describes the adaption of the real-time and geographic calibration method to the lifetime setting, which was applied to the LIFE-CVD model to predict CVD-free life expectancy and lifetime risk in individuals without previous CVD. After recalibration of the LIFE-CVD model to four European risk regions, external validation was performed in all these regions and estimations of lifetime treatment benefits were illustrated for several risk factor profiles.

The updated LIFE-CVD model confers several advantages over the originally published version of the model. First, the age range of the model has been extended by extrapolation of the model baseline hazards to the age of 100 years. This allows

the model to be applied to individuals with a current age between 35 and 90 years. In addition, this improves the stability of estimates in people of all ages with a very high life-expectancy. As the worldwide life expectancy keeps increasing,[23] this will be increasingly important. Another important advantage is the extensive recalibration using contemporary and representative data on CVD incidence and risk factor data, which further broadens the generalizability of the LIFE-CVD model across European risk regions. Because the recalibration approach was based on registry data, the model can be readily updated to reflect future disease CVD incidences and risk factor profiles as soon as new updated data become available.[6,7]

Several prediction measures can be obtained by using the LIFE-CVD model, either on a 10-year or on a lifetime perspective. To effectively use these measures in clinical practice, a good understanding of the communicated prediction measure is vital. A predicted risk for example, though commonly used, can be very hard to really understand.[24] A lifetime risk is even more difficult to explain as it also relies on the life expectancy: living longer means having a larger period at risk of CVD events, resulting in a higher lifetime risk. The lifetime treatment benefit, defined as the gain in CVD-free life expectancy from preventive therapy, can be estimated with the LIFE-CVD model. This has been shown to be an intuitive measure that lowers the decisional conflict among individuals considering preventive treatment.[25] When using lifetime treatment benefit measures in the shared decision process, these should be weighed against the intended treatment duration. All these measures to take into account when considering treatment initiation, should be used in conjunction with potential risk modifiers and patient preferences.

There are a few other tools to estimate lifetime risk for individuals without previous CVD, the QRISK-lifetime score and the Pooled Cohort Equations (PCE), both of which are available through online calculators.[26,27] The PCE works slightly different, by estimating 30-year cumulative incidence rather than modelling the life expectancy, and is not adjusted for competing risks. The QRISK-lifetime model has been corrected for competing risks but was derived and validated only in the United Kingdom. Neither of these models have been adequately calibrated to all European risk regions.[26,27]

In the current study, calibration of the LIFE-CVD model was not assessed in our external validation cohorts other than the large nationally representative dataset from the CPRD, because these cohorts do not necessarily reflect contemporary absolute risk levels across European regions. In the CPRD data however, good agreement was observed between 10-year predicted and observed CVD incidences. Furthermore, estimated CVD rates agreed well with national incidence rates from available independent external registries from several countries. Results from the current study show that the expected gain in CVD-free life expectancy was differed across geographical locations. It was shown that interventions are expected to lead to

a higher absolute treatment benefit in Eastern European countries, reflecting higher disease incidences in this region.

The potential limitations of this effort merit consideration. For the derivation of the LIFE-CVD model, only American data from the MESA study was used, whereas this would have ideally involved data from all relevant regions the model is to be used. However, previous studies have shown that the relative effects of model coefficients are stable over geographical areas,[6] which was further supported by the satisfactory discriminatory results in high and very high risk region validation cohorts as observed in the current study.

Another potential limitation is the fact that validation was only performed with 10-year risks, as it is not feasible to perform validation of life expectancy measures within the scope of cohort follow-up durations. Previous studies have shown the validity of lifetime predictions for up to 17 years.[28] Should long-term data become available, the model could profit from validations at even longer timescales to further validate the underlying methodology.

A limitation specific to the current update is the unavailability of reliable, nationally representative data on the prevalence of CVD family history. To prevent systematic over- or underestimation of model predictions by misspecification of this predictor in the recalibration phase, the predictor was left out of the recalibrated LIFE-CVD model. This approach may have slightly reduced model discrimination, but increases the applicability of the recalibrated LIFE-CVD model.

The original LIFE-CVD model was not recalibrated separately for both sexes, possibly ignoring differences in the relative effects of certain predictors between men and women. The sex-specific derivation of the SCORE2 algorithm resulted in small sex-differences of the smoking and diabetes mellitus coefficients, indicating that these risk factors may have been modelled even more accurately.[7] The recalibration efforts as described in the current study were performed separately for both sexes. This allowed for adjustment on much more detailed sex differences in CVD incidence or risk factor values for every European risk region, ensuring the recalibrated LIFE-CVD model is well-adapted to the contemporary clinical practice for both sexes in all throughout Europe.

In conclusion, by taking into account geographical differences in CVD incidence, the recalibrated LIFE-CVD model provides a more accurate tool for the prediction of lifetime risk and CVD-free life expectancy for individuals without previous CVD, facilitating shared decision-making on Step 2 cardiovascular prevention options as recommended by the 2021 European Prevention Guidelines.

References

1. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FLJ. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J. 2014;35(13):837-843. doi:10.1093/eurheartj/ehu004
2. Dorresteijn JAN, Visseren FLJ, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ. 2011;343(oct03 1):d5888-d5888. doi:10.1136/bmj.d5888
3. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
4. Jaspers NEM, Blaha MJ, Matsushita K, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Eur Heart J. 2019;31:1-10. doi:10.1093/eurheartj/ehz239
5. Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. Eur Heart J. 2019;40(7):621-631. doi:10.1093/eurheartj/ehy653
6. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Heal. 2019;7(10):e1332-e1345. doi:10.1016/S2214-109X(19)30318-3
7. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-2454. doi:10.1093/eurheartj/ehab309
8. de Vries TI, Cooney MT, Selmer RM, et al. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455-2467. doi:10.1093/eurheartj/ehab312
9. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol. 2002;156(9):871-881.
10. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144
11. World Health Organization. WHO Mortality Database. Accessed May 7, 2020. https://apps.who.int/healthinfo/statistics/mortality/whodpms/
12. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017;389(10064):37-55. doi:10.1016/S0140-6736(16)31919-5
13. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet. 2016;387(10027):1513-1530. doi:10.1016/S0140-6736(16)00618-8
14. Schmermund A, Möhlenkamp S, Stang A, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL study. Am Heart J. 2002;144(2):212-218. doi:10.1067/mhj.2002.123579
15. Leitsalu L, Haller T, Esko T, et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. Int J Epidemiol. 2015;44(4):1137-1147. doi:10.1093/ije/dyt268
16. Peasey A, Bobak M, Kubinova R, et al. Determinants of cardiovascular disease and other non-communicable diseases in Central and Eastern Europe: Rationale and design of the HAPIEE study. BMC Public Health. 2006;6(1):255. doi:10.1186/1471-2458-6-255
17. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic Models With Competing Risks. Epidemiology. 2009;20(4):555-561. doi:10.1097/EDE.0b013e3181a39056

18. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664

19. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5

20. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. Lancet. 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8

21. Mons U, Muezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ. 2015;350(apr20 2):h1551-h1551. doi:10.1136/bmj.h1551

22. Gellert C, Schöttker B, Brenner H. Smoking and All-Cause Mortality in Older People. Arch Intern Med. 2012;172(11):837-844. doi:10.1001/archinternmed.2012.1397

23. World Health Organization. Life expectancy and Healthy life expectancy: Data by WHO region. Accessed December 3, 2021. https://www.who.int/data/gho/data/themes/topics/indicator-groups/indicator-group-details/GHO/life-expectancy-and-healthy-life-expectancy

24. Dickinson R, Raynor DK, Knapp P, MacDonald J. Providing additional information about the benefits of statins in a leaflet for patients with coronary heart disease: a qualitative study of the impact on attitudes and beliefs. BMJ Open. 2016;6(12):e012000. doi:10.1136/bmjopen-2016-012000

25. Jaspers NEM, Visseren FLJ, van der Graaf Y, et al. Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial. BMJ Open. 2021;11(7):e041673. doi:10.1136/bmjopen-2020-041673

26. Lloyd-Jones DM, Huffman MD, Karmali KN, et al. Estimating Longitudinal Risks and Benefits From Cardiovascular Preventive Therapies Among Medicare Patients. J Am Coll Cardiol. 2017;69(12):1617-1636. doi:10.1016/j.jacc.2016.10.018

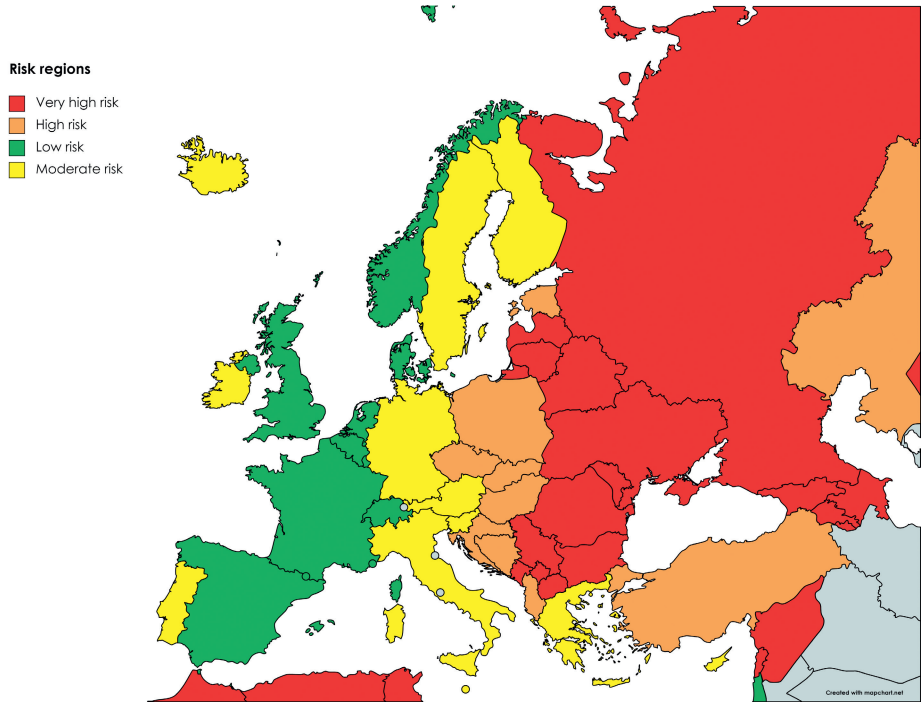
27. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ. 2010;341(dec09 1):c6624-c6624. doi:10.1136/bmj.c6624

28. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. BMJ. 2016;352:i1548. doi:10.1136/bmj.i1548

29. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59(10):1087-1091. doi:10.1016/j.jclinepi.2006.01.014

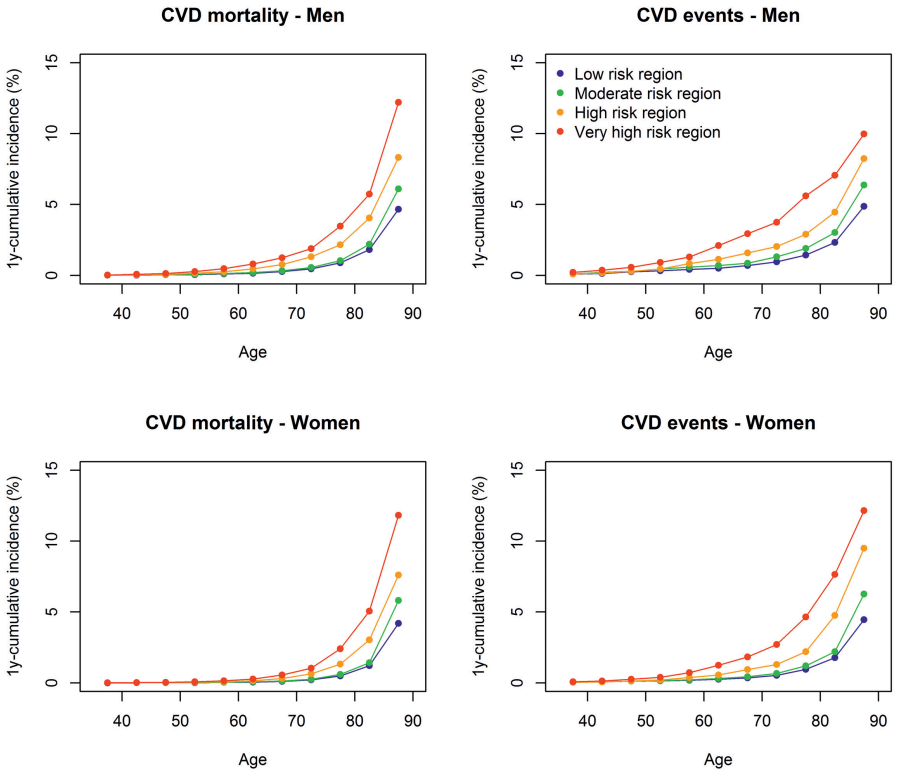
Supplementary Materials

Supplementary Figure 1. Risk regions based on standardised CVD mortality rates (From SCORE2, Hageman et al 2021)



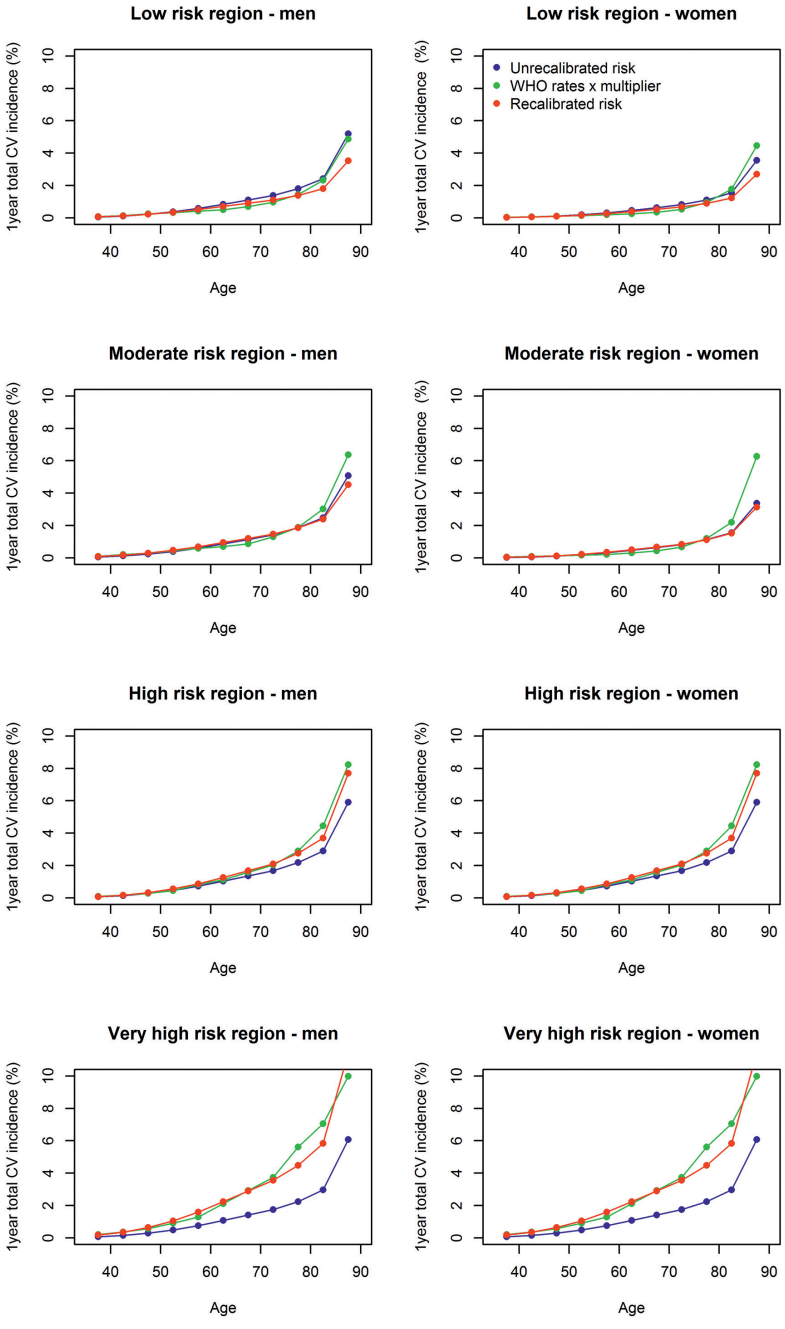
Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD chapter 9, 100-199). The four groupings were: low risk (<100 CVD deaths per 100,000), moderate rist (100 to<150 CVD deaths per 100,000), high risk (150 to <300 CVD deaths per 100,000), and very high risk (≥300 CVD deaths per 100,000).

Supplementary Figure 2: Cardiovascular mortality and derived incidence in all risk regions

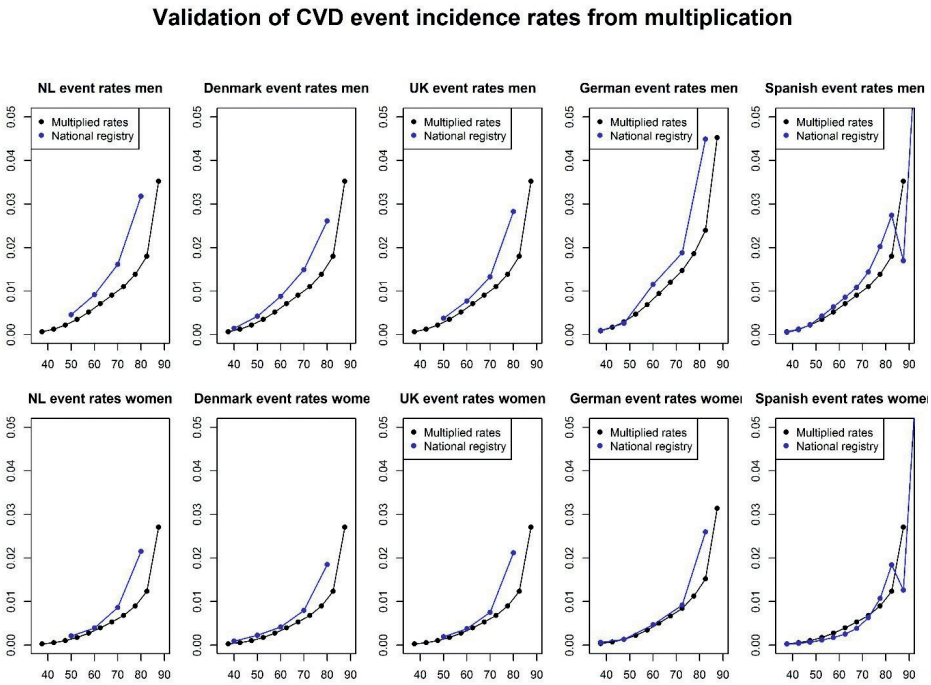


1-year cumulative incidences of cardiovascular mortality (left) and fatal or non-fatal cardiovascular events (right) in every region for every age-group.

Supplementary Figure 3: Estimated CVD incidence rates and predicted risks

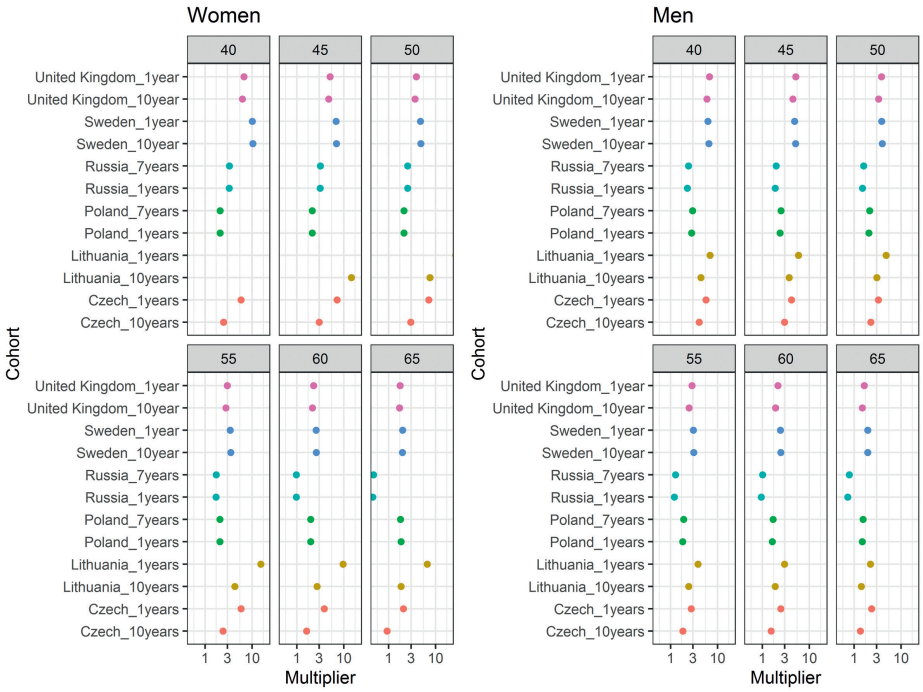


Supplementary Figure 4: Validation of estimated CVD incidence against independent registry data

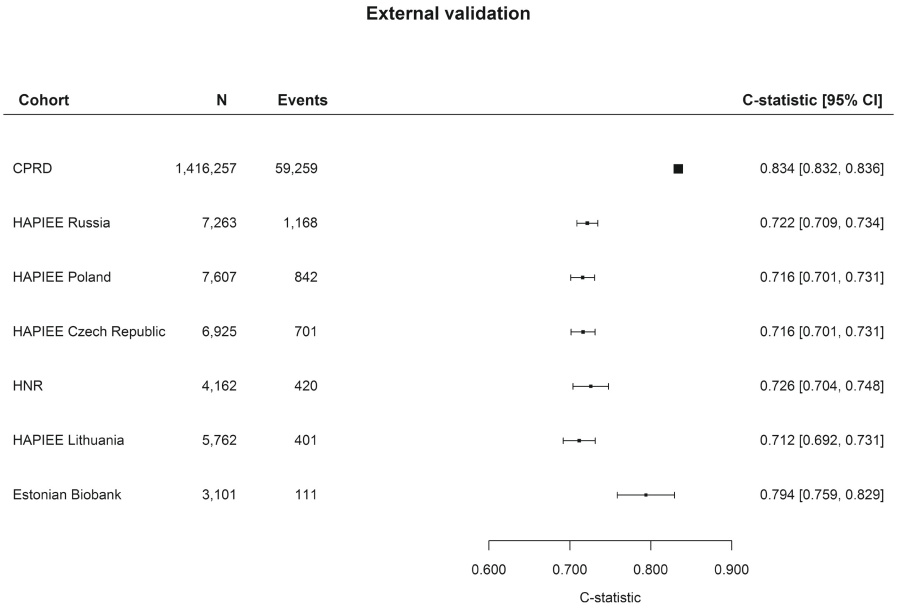


Comparison of registry-based incidence rates of total and fatal cardiovascular disease, with those used in the recalibrated LIFE-CVD. The LIFE-CVD predicted risks were obtained by combining regional NCD risk factor levels to the risk algorithms. Note that Netherlands, German and Spanish registry-based incidences include also CVD events in patients with prior vascular disease. Only the Spanish registry rates have been corrected for competing risks.

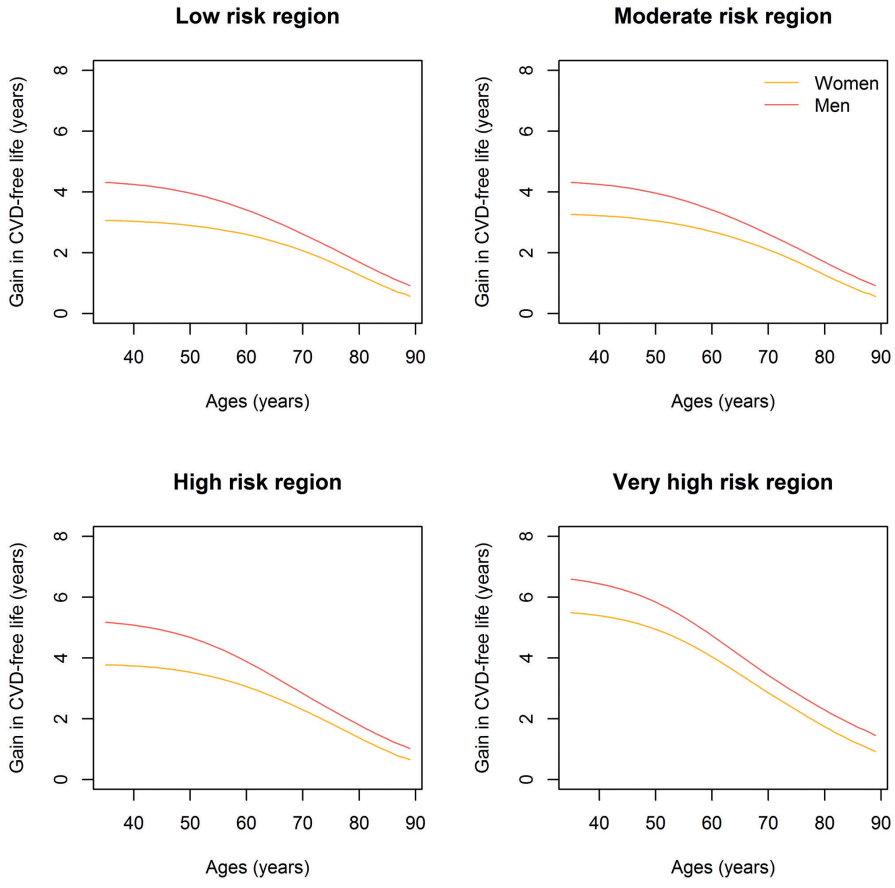
Supplementary Figure 5: Comparison of 10-year versus 1-year multipliers



Supplementary Figure 6: C-index upon assessing ability of the LIFE-CVD model to discriminate non-CVD mortality in external validation cohorts



Supplementary Figure 7: Predicted gain in CVD-free life expectancy from smoking cessation for an individual with total cholesterol concentrations of 5.5 mmol/L, HDL cholesterol of 1.3 mmol/L, body-mass index of 27 kg/m², and systolic blood pressure of 140 mm Hg, for each region



Supplementary Table 1: Region-specific recalibration scales for calculation of the 1-year CVD event and non-CVD mortality risks

	Male		Female	
	Scale 1	**Scale 2**	**Scale 1**	**Scale 2**
CVD events				
Low risk region	-0.757	0.877	-0.464	0.944
Moderate risk region	-0.463	0.884	-0.278	0.939
High risk region	0.386	1.040	1.159	1.167
Very high risk region	0.540	0.956	1.344	1.078
Non-CVD mortality				
Low risk region	-0.272	0.875	3.146	1.571
Moderate risk region	-0.388	0.848	3.183	1.581
High risk region	-0.562	0.755	2.723	1.463
Very high risk region	-1.336	0.591	1.659	1.244

Rescaling factors for the LIFE-CVD model to scale individual predicted risks within the life table to the target population, based recent nationally representative estimates of incident cardiovascular disease and risk factor levels.

Supplementary Methods

Missing data

Because complete case analysis may lead to loss of statistical power and possible bias[29], values of predictors were imputed by single regression imputation with predictive mean matching for all cohort data.

As the CPRD consists of care-as-usual data, missing data was much more frequent and missingness was more likely to correlate with cardiovascular disease risk. Therefore, multiple imputation was performed for the external validation in CPRD with fully conditional specification using 5 imputed datasets.

Recalibration

The interlinked stages of recalibration are summarised in **Supplementary Methods Figure 1**. The LIFE-CVD coefficients were obtained from the original paper, the baseline hazards were extrapolated to allow for predictions beyond the original age range (**Box 1**); Four risk regions in Europe were similar to those defined by SCORE2.[7] The SCORE2 investigators have defined these risk regions according to the age-standardised country-specific cardiovascular mortality rates. For each region, annual age and sex-specific mortality rates were obtained from the WHO and converted to risk estimates, for both CVD mortality and the risk of non-CVD death (**Box 2**); In order to translate 1-year mortality to 1-year risk of fatal and non-fatal CVD, the SCORE2

region- age- and sex-specific multiplication factors were applied to the 1-year CVD mortality risks. For the non-CVD mortality rates, multiplication is not necessary, since predicted risk can be recalibrated using age and sex-specific non-CVD mortality rates only (**Box 3+4**); Region, sex and age-specific predicted 1-year risks were then estimated using the un-calibrated LIFE-CVD model with region, sex and age-specific risk factors from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) (**Box 5**). The region and sex and age-specific predicted risks (from **Box 5**) were compared to expected risks (from **Box 4**) and rescaling factors were estimated to recalibrate the models for each region and sex (**Box 6**). Finally, the rescaling factors are applied with the original un-calibrated model to give new, recalibrated risk predictions in new individuals (**Box 7**).

Box 1: Model coefficients
The original LIFE-CVD coefficients were used: no additional model derivation was performed. The original coefficients are based on two complimentary Fine and Gray models and are shown in **Supplementary Methods Table 1**. The baseline hazards of the original models were extrapolated to allow for predictions beyond the original age range (**Supplementary Methods Table 2+3**).

Box 2: Estimation of 10-year competing risk adjusted mortality for each risk region
WHO cause-specific mortality rates were supplied by country and coded in ICD-9 or ICD-10. Rates included all mortality which was included in the original SCORE endpoint. Non-CVD mortality was defined as all mortality not included in the SCORE endpoint. Region-level estimates were obtained by taking the age- and sex- specific median of all country-specific estimates of CVD mortality rates from the relevant region.

In the SCORE2 project, for every age-group, WHO rates representative of the midpoint of the 10-year interval ahead were used - i.e. for the 40 to 44 year age-group the rates for 45 to 49 years was used. **As currently 1-year rather than 10-year intervals are used for recalibration, this is done differently in comparison to the SCORE2 project. Instead, the 40-44 year age-group is recalibrated based on rates observed in the 40-44 year age group**. WHO rates of both the fatal cardiovascular outcome and the competing outcome non-CVD mortality were converted to 1–year mortality risks (r) using the following formula:

$$r = 1 - e^{(-fatal\ rate)}$$

As the WHO rates cover 1-year intervals already, no extrapolation is required to 10-year risks as is done in the SCORE2 recalibration procedure.

Box 3: Estimation of Multipliers to convert mortality to incidence estimates in each risk region

To convert 1-year mortality estimates to incidence estimates, age- and sex-specific multiplication factors were defined as:

$$\frac{Cumulative\ 1\ year\ incidence\ total\ CV\ events_{without\ prior\ CVD}}{Cumulative\ 1\ year\ incidence\ fatal\ CV\ events_{entire\ population}}$$

These allowed the population level mortality statistics, which are calculated among the whole population, regardless of prior disease status, to be converted into first event incidence estimates, representative of the target primary prevention population (those without prior CVD). To be as consistent as possible to the SCORE2 methodology, no new multipliers were derived. Instead, SCORE2 multipliers were applied to these 1-year mortality rates. The validity of this methodology was further assessed in additional analyses (**Supplementary Figure 5**).

Multiplication factors were assumed to be stable within each region and over time which was additionally verified in several analyses in the SCORE2 project (SCORE2 Supplementary Figure 3-5).[7]

Box 6: Relate expected to predicted risks to calculate rescaling factors for model recalibration

Recalibration of the core LIFE-CVD models was completed separately for each target region and sex using the previously published general process described in **Supplementary Methods Figure 2**. This involved the use of country-sex-specific mean risk factor levels (from NCDRisc) and region-sex-specific estimates of expected cumulative 1-year risk, estimated as described above and in **Boxes 2** and **3**. We used the recalibrated 1-year risk models to estimate 1-year predicted risk of each endpoint for each of the age groups using the mean risk factor values as described in **Box 5**. Having completed this process for each age group, as shown in **Supplementary Methods Figure 2** we then regressed transformed expected 1-year risk across age groups on that predicted by the core LIFE-CVD models to derive recalibration factors (the intercept and slope of the resulting regression line, **Supplementary Table 1**). The LIFE-CVD risk models, rescaled using the recalibration factors were then used to estimate appropriate risks for each potential risk factor combination, for a new individual or for formation of the example risk charts.

Extrapolation of the baseline hazard

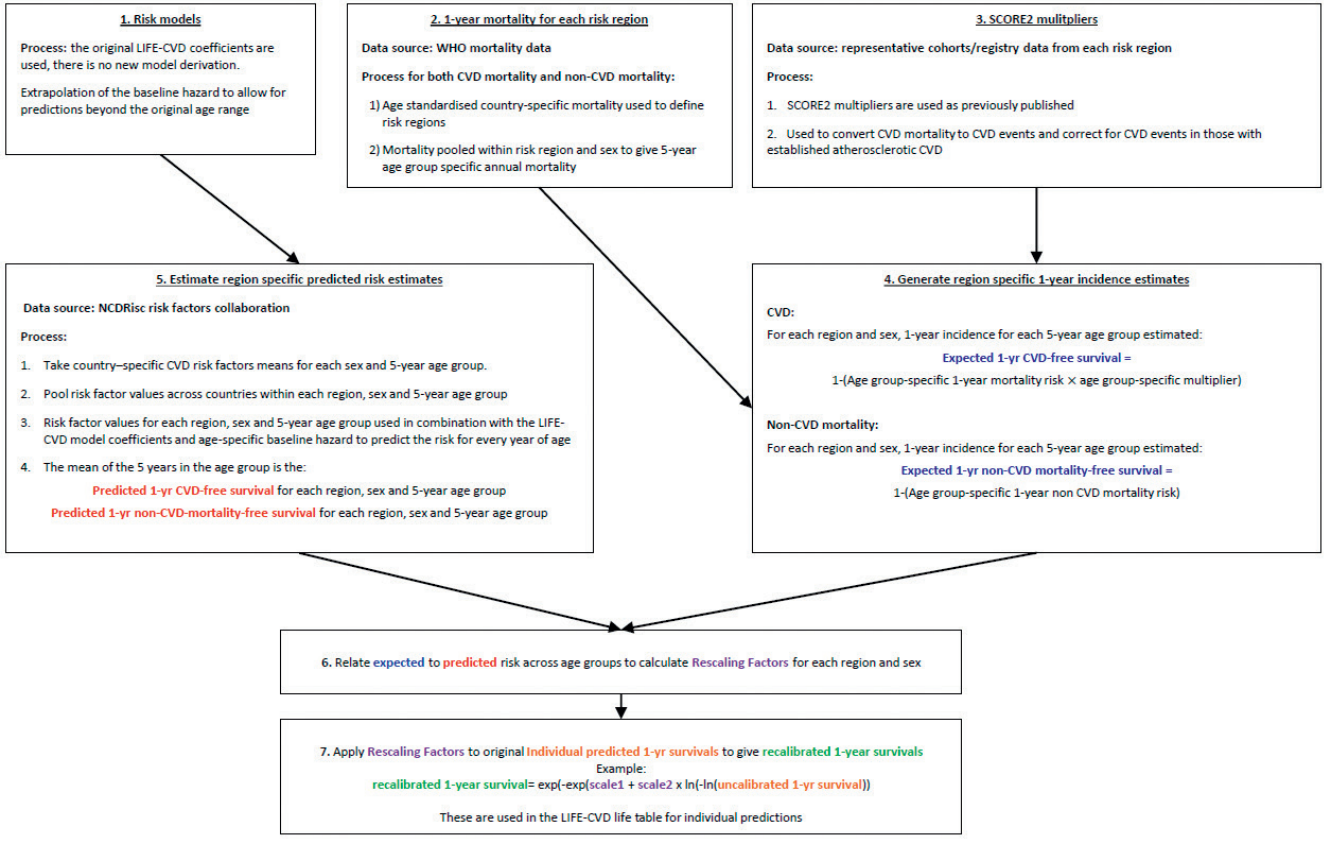
The age-specific baseline survivals for the original LIFE-CVD prediction algorithm (presented in Supplemental Table 3 of the 2019 paper[4], and **Supplementary Methods Table 2** of this report) 1 were based on the observed risk in the MESA study for each life year (i.e. at which age the observed events occurred). Due to chance,

there is some variation between life years that cannot be explained by the natural progression of the 1-year risk for CVD or non-CVD mortality with increasing age. By modelling the progression of baseline survivals with age, the corresponding individual survival plots are smoothed and therefore more intuitive than when using the directly observed baseline survivals. Additionally, by modelling the progression of baseline survivals with age, rather than using the observed age-specific baseline survivals, it becomes possible to extrapolate the baseline survivals for ages outside of this original age range according to the formula predicting the baseline survivals (**Supplementary methods Figure 3**). The updated baseline survivals were predicted according to functions weighted for the number of individual participants contributing data to each life-year. The CVD baseline survivals were predicted and smoothed using local polynomial regression (function loess, package stats in R studio) using a smoothing parameter α of 1.05. The non-CVD mortality baseline survivals followed an exponential function according to the form $E(Y) = a * \exp(bx) + c$ and were predicted using a non-linear regression function (Figure 1). The baseline survivals were then extrapolated to the age range of 35 to 100 years, allowing predictions over a wider age range (**Supplementary Methods Table 3**).

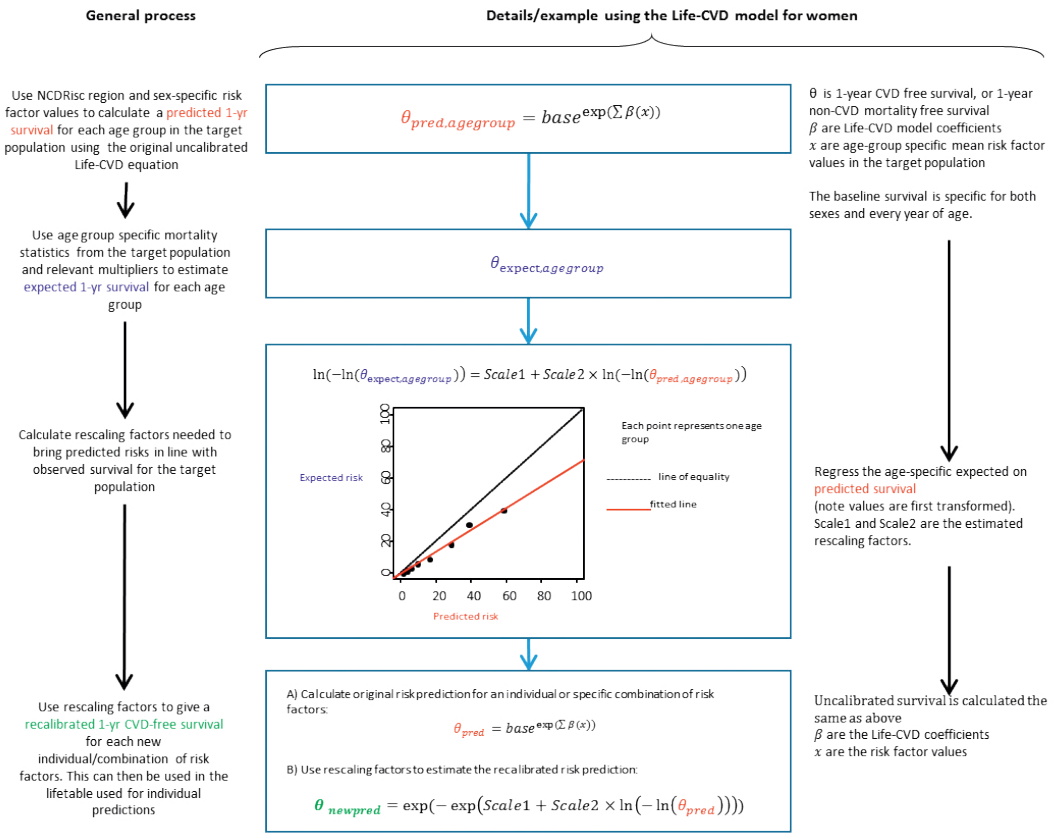
Calculating treatment effects when the life expectancy exceeds 100 years

Treatment benefit for each risk factor treatment is estimated as the difference between on- and off-treatment median CVD-free life expectancy. In people whose life expectancy exceeds the model's maximum age, this approach cannot be used as the cumulative survival curve does not drop below 50%. Previously, we proposed using the difference in area under the curve (AUC) in such cases as a possible solution. However, the AUC-method gives underestimation of true lifetime treatment benefit. As a better alternative, we here propose a new method of using the last observed cumulative survival. This means that in the case the on-treatment CVD-free cumulative survival exceeds 50% at the maximum age (i.e. 100 years), lifetime treatment benefit is defined as the difference between the maximum age and the age with the corresponding predicted percentage off-treatment cumulative survival. For example, should the predicted survival at the end of the lifetable be 54%, then the median survival can't be read from the lifetable. Instead, the age at which the survival of 54% rather than 50% is compared on- and off- treatment. With the extended age range due to the extrapolation of the baseline hazard though, this is seldom required, but more accurate in those theoretical cases in which it is necessary.

Supplementary Methods Figure 1: Model recalibration process

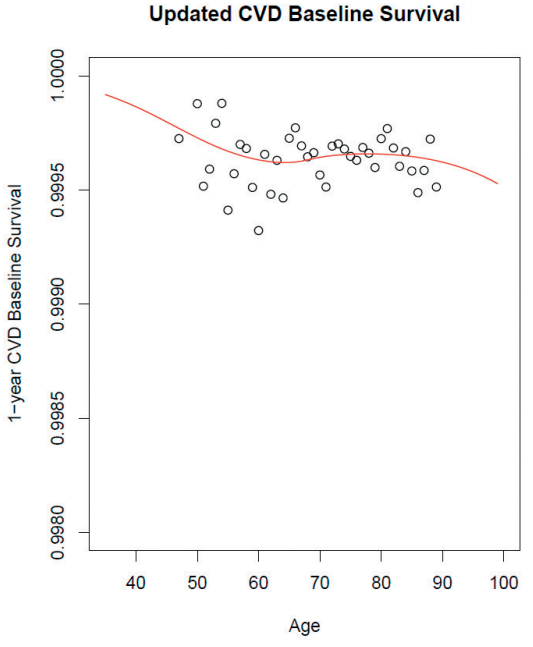


Supplementary Methods Figure 2: Methods used for recalibration of risk scores

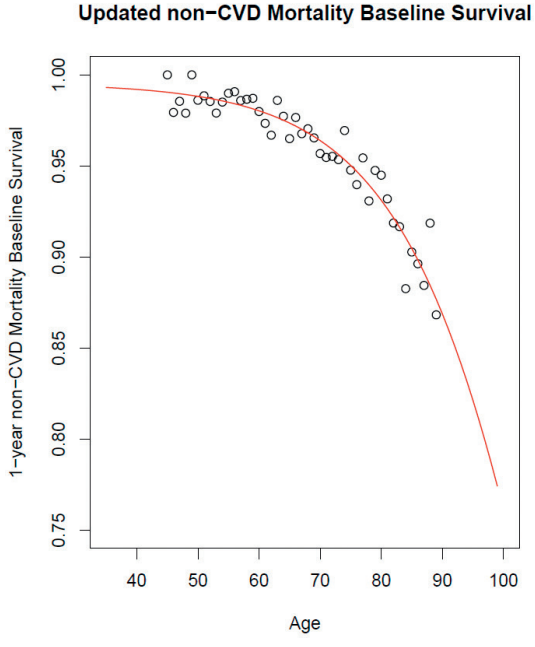


Supplementary Methods, Figure 3: Smoothing and extrapolation of baseline survivals for (A) 1-year CVD baseline survival (using local polynomial regression), and (B) 1-year non-CVD mortality baseline survival (using non-linear regression). Black dots indicate the original baseline survivals based on the observed events per life-year, the red lines show the predicted progression of baseline survivals from the age of 35 years to 100 years (the updated baseline survivals).

A



B



Supplementary Methods, Table 1: Unrounded, original LIFE-CVD model coefficients for individual predictions

	CVD events	Non-CVD mortality
Gender (male)	0.4847	-2.6221
Gender (male) * age (per year)		0.0420
Systolic blood pressure (per 1 mmHg)	-0.0166	0.0033
Systolic blood pressure * age (per 1 mmHg per year)	0.0005	
Non-HDL cholesterol (mmol/L)	0.1235	-0.5967[a]
Body mass index (kg/m2)	0.0115	-0.1121
Body mass index, squared (kg/m2)		0.0020
Former smoker	0.0278	0.2285
Current smoker	2.1116	-0.7902
Current smoker*age (per 1 year)	-0.0266	0.0243
Diabetes mellitus	1.7320	0.6876
Diabetes mellitus *age (per 1 year)	-0.0188	-0.0068
Parental history of premature MI[b]	*0.3787*	*-0.0723*

a: log-transformed; b: omitted in recalibrated LIFE-CVD model due to the lack of reliable population-level data for recalibration

Supplementary Methods, Table 2: Original age-specific baseline survival for CVD-events and non-CVD mortality based on the observed events per life-year

Age	1-year CVD baseline survival	1-year non-CVD mortality baseline survival	Age	1-year CVD baseline survival	1-year non-CVD mortality baseline survival
45	1	1	68	0.999645771	0.970398098
46	1	0.979380684	69	0.999663492	0.965410198
47	0.999725398	0.985480904	70	0.999566041	0.956805621
48	1	0.978988162	71	0.999513256	0.954653450
49	1	1	72	0.999692656	0.955233741
50	0.999878410	0.98607217	73	0.999702516	0.953443559
51	0.999516952	0.988522333	74	0.999679667	0.969421315
52	0.999591619	0.985415629	75	0.999647779	0.947674229
53	0.999792279	0.979056609	76	0.999630632	0.939724478
54	0.999879900	0.985072499	77	0.999686488	0.954401682
55	0.999412090	0.989896930	78	0.999661579	0.930794801
56	0.999571482	0.990764307	79	0.999598915	0.947523700
57	0.999699809	0.985900751	80	0.999725086	0.944907534
58	0.999682114	0.986623736	81	0.999769337	0.931903316
59	0.999511434	0.987138590	82	0.999684311	0.918651265
60	0.999322636	0.979874870	83	0.999603926	0.916640537
61	0.999656409	0.973393148	84	0.999668146	0.882636308
62	0.999481427	0.966878497	85	0.999583733	0.902748240
63	0.999630190	0.985990456	86	0.999488751	0.896307118
64	0.999465298	0.977289395	87	0.999585936	0.884407038
65	0.999726810	0.964981886	88	0.999723251	0.918574710
66	0.999772552	0.976599292	89	0.999513316	0.868249158
67	0.999693501	0.967697361			

Original age-specific baseline survival for CVD-events and non-CVD mortality based on the observed events per life-year as published in the original LIFE-CVD model. For the current, recalibrated model, these have been replaced by the extrapolated and smoothed variant (**Supplementary Methods Table 3**)

Supplementary Methods, Table 3: Updated age-specific baseline survival for CVD-events and non-CVD mortality

Age	1-year CVD baseline survival	1-year non-CVD mortality baseline survival
35	0.99991823	0.99307706
36	0.99990882	0.99289348
37	0.99989875	0.99269573
38	0.99988803	0.99248272
39	0.99987669	0.99225328
40	0.99986477	0.99200614
41	0.99985230	0.99173997
42	0.99983936	0.99145329
43	0.99982601	0.99114455
44	0.99981233	0.99081206
45	0.99979842	0.99045401
46	0.99978436	0.99006846
47	0.99977027	0.98965332
48	0.99975627	0.98920634
49	0.99974247	0.98872513
50	0.99972899	0.98820709
51	0.99971594	0.98764944
52	0.99970343	0.98704922
53	0.99969156	0.98640322
54	0.99968043	0.98570803
55	0.99967011	0.98495998
56	0.99966066	0.98415513
57	0.99965211	0.98328928
58	0.99964450	0.98235793
59	0.99963787	0.98135627
60	0.99963223	0.98027914
61	0.99962760	0.97912105
62	0.99962404	0.97787613
63	0.99962160	0.97653813
64	0.99962042	0.97510036
65	0.99962066	0.97355572
66	0.99962260	0.97189666
67	0.99962652	0.97011515
68	0.99963267	0.96820266
69	0.99963845	0.96615015
70	0.99964348	0.96394804
71	0.99964759	0.96158622
72	0.99965088	0.95905400
73	0.99965348	0.95634012
74	0.99965548	0.95343274
75	0.99965695	0.95031941
76	0.99965794	0.94698712
77	0.99965847	0.94342224
78	0.99965857	0.93961058
79	0.99965824	0.93553740
80	0.99965748	0.93118742
81	0.99965629	0.92654486
82	0.99965466	0.92159349
83	0.99965258	0.91631671
84	0.99965001	0.91069758
85	0.99964692	0.90471895
86	0.99964327	0.89836352
87	0.99963904	0.89161400
88	0.99963418	0.88445322
89	0.99962867	0.87686428
90	0.99962247	0.86883075
91	0.99961554	0.86033685
92	0.99960784	0.85136764
93	0.99959933	0.84190928
94	0.99958995	0.83194926
95	0.99957966	0.82147664
96	0.99956838	0.81048235
97	0.99955607	0.79895946
98	0.99954263	0.78690343
99	0.99952800	0.77431242

CHAPTER 7

Cardiovascular risk factors and the risk of major adverse limb events in patients with symptomatic cardiovascular disease

Steven HJ Hageman, Gert J de Borst, Jannick AN Dorresteijn, Michiel L Bots, Jan Westerink, Folkert W Asselbergs, Frank LJ Visseren

on behalf of the UCC-SMART studygroup

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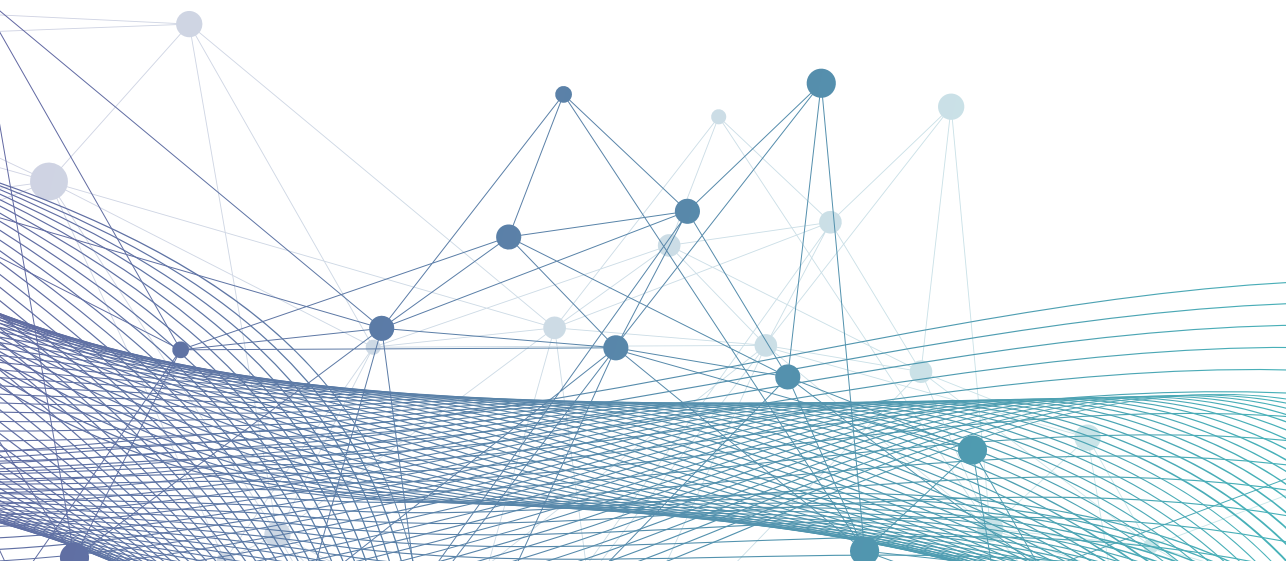


Abstract

Aims: To determine the relationship between non-high-density lipoprotein cholesterol (non-HDL-c), systolic blood pressure (SBP) and smoking and the risk of major adverse limb events (MALE) and the combination with major adverse cardiovascular events (MALE/MACE) in patients with symptomatic vascular disease.

Methods: Patients with symptomatic vascular disease were included from the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART) (1996–2017). The effects of non-HDL-c, SBP and smoking on the risk for MALE were analyzed with Cox proportional hazard models stratified for presence of peripheral artery disease (PAD). MALE was defined as major amputation, peripheral revascularization or thrombolysis in the lower limb.

Results: In 8139 patients (median follow-up 7.8 years, IQR 4.0-11.8) 577 MALE (8.7/1000 person-years) and 1933 MALE/MACE were observed (29.1/1000 person-years). In PAD patients there was no relation between non-HDL-c and MALE, in patients with coronary artery disease (CAD), cerebrovascular disease (CVD) or abdominal aortic aneurysm (AAA) the risk of MALE was higher per 1 mmol/L non-HDL-c (HR 1.14, 95%CI 1.01 -1.29). Per 10 mmHg SBP the risk of MALE was higher in PAD patients (HR 1.06, 95%CI 1.01-1.12) and CVD/CAD/AAA patients (HR 1.15, 95%CI 1.08-1.22). The risk of MALE was higher in smokers with PAD (HR 1.45, 95%CI 0.97-2.14) and CAD/CVD/AAA (HR 7.08, 95%CI 3.99-12.57).

Conclusions: The risk of MALE and MALE/MACE in patients with symptomatic vascular disease differs according to vascular disease location and is associated with non-HDL-c, SBP and smoking. These findings confirm the importance of MALE as an outcome and underline the importance of risk factor management in patients with vascular disease.

Introduction

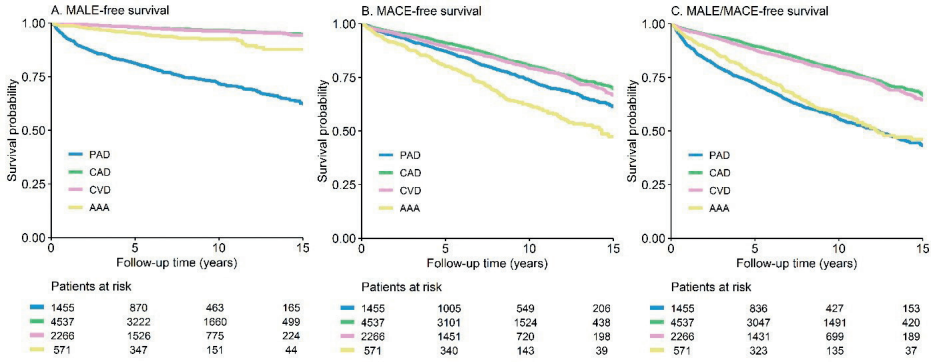
Patients with symptomatic cardiovascular disease are at high risk for recurrent major adverse cardiovascular events (MACE). Major adverse limb events (MALE), including amputations and peripheral revascularizations, lead to significant morbidity[1–3] but are rarely reported as a (primary) outcome in trials and cohorts. Patients with peripheral artery disease (PAD) are at especially high risk of these events, having a 3-fold increase in incident MACE[4] and over 10-fold increase in MALE incidence.[5] Hypercholesterolemia is associated with a 20% higher risk of PAD in the general population[6] and 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL-c) leads to a 22% decrease in MACE incidence.[7] Lipid lowering with a statin in PAD patients is associated with a 18% reduction of adverse limb outcomes.[8] The FOURIER trial showed that by lowering LDL-c with PCSK9-monoclonal antibody, the risk of MALE is lowered by 42% in comparison to placebo.[5] Non-high-density lipoprotein cholesterol (non-HDL-c) includes both LDL-c and remnant cholesterol and has a stronger association with cardiovascular outcomes in comparison to LDL-c.[9] Hypertension is associated with an increased risk of PAD and MALE in the general population.[10,11] In PAD patients however, it has been suggested that lowering blood pressure below a critical level may worsen PAD symptoms and progression by decreasing peripheral perfusion.[12] Smoking is one of the most important risk factors for PAD and is attributable to more than half of the prevalence of PAD.[13,14] Also, smoking cessation increases the amputation free survival in patients with PAD (Hazard ratio [HR] of 0.43, 95%CI 0.22-0.86).[15]

The aims of the current study were to determine the incidence of MALE and MALE/MACE in patients with symptomatic vascular disease, to assess to what extent non-HDL-c, SBP and smoking increase the risk of MALE and MALE/MACE and to quantify the population attributable fractions (PAF) of these risk factors.

Methods

Patients originate from the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART), a single-center ongoing prospective cohort study in Utrecht, the Netherlands. A detailed description of the study protocol has been described previously.[16] Study patients are newly referred patients to the University Medical Center Utrecht with atherosclerotic disease or increased risk for atherosclerotic disease and were included between January 1996 and March 2017 (supplementary figure 1). From this cohort, we included all patients with symptomatic PAD, coronary artery disease (CAD), cerebrovascular disease (CVD) and/or abdominal arterial aneurysm (AAA). PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg (ankle brachial index ≤0.90), a revascularization procedure of the leg (percutaneous transluminal angioplasty or bypass surgery) or a prior amputation. CAD was defined as a clinical diagnosis of angina pectoris, myocardial infarction, cardiac arrest, or coronary revascularization, CVD as a clinical diagnosis of a transient ischemic attack or ischemic or hemorrhagic stroke and AAA was defined as a history of abdominal aortic surgery or an abdominal aortic anteroposterior diameter of ≥3 cm at baseline. The study was approved by the local Medical Ethics Committee and written informed consent was obtained from all patients. Patients and public were not involved in the design, conduct or reporting of this study.

Figure 1: MALE-free, MACE-free and MALE/MACE-free survival according to vascular disease location at baseline



Kaplan-Meier curves according to atherosclerotic disease location. Patients in CAD, CVD and AAA groups do not have PAD at baseline. MALE, Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events; PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm.

Data collection

After inclusion, all baseline characteristics were determined using a standardized screening protocol consisting of questionnaires, physical examination, laboratory

testing, ankle-brachial index (ABI), and abdominal aortic and carotid ultrasound. Non-HDL-c was defined as total cholesterol minus HDL-cholesterol and was measured from fasting venous blood samples, LDL-c was calculated using the Friedewald formula. Office SBP was measured in sitting position twice in the both arms, the highest mean of the measurements on one arm was used. Smoking and the amount of pack-years were self-reported. Diabetes mellitus (DM) at baseline was either self-reported DM type 1 or 2 or a fasting glucose of >7.0 mmol/L at baseline. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Medication use was self-reported.

The primary outcome of this study was the incidence of MALE, a composite outcome consisting of a lower limb revascularization (vascular intervention or thrombolysis), and major amputation (at the level of the ankle or more proximal). Minor amputations were not regarded as a MALE in accordance to prior studies.[2,17] The incidence of MACE was assessed to serve as a comparison to MALE. MACE was a composite outcome consisting of non-fatal myocardial infarction, non-fatal stroke or vascular death. MALE/MACE was a composite outcome consisting of either MALE or MACE Patients received biannual questionnaires to evaluate possible endpoints. Whenever a possible event was reported, hospital discharge letters, GP letters, and results of relevant laboratory and radiology examinations were collected and the endpoint was verified by three independent experienced physicians from the UCC-SMART endpoint committee. Interventions already planned at inclusion in the UCC-SMART cohort were not regarded endpoints.

Data analyses

Because complete case analysis may lead to loss of statistical power and possible bias,[18] values of determinants or possible confounders were imputed by single regression imputation. Missing data was <1.0% except for C-reactive protein (CRP) (n=224, 2.8%). Follow-up was defined as time from inclusion until MALE-event, death, loss to follow-up (n=543, 6.7%) or until march 2017. Cox proportional hazards models were fitted to determine the effect of the risk factors on the risk of MALE, MACE or MALE/MACE. Presence of PAD at baseline was an effect modifier in the relation between the risk of MALE and non-HDL-c (p for interaction <0.01), SBP (p for interaction 0.01), and smoking (p for interaction <0.01). All models were stratified on presence of PAD at baseline. Using restricted cubic splines, there was no evidence for a non-linear relation between SBP and the incidence of MALE (p for nonlinearity 0.28), MACE (p for nonlinearity 0.06), and MALE/MACE (p for nonlinearity 0.16). There was no evidence for violations of the proportional hazard assumption, assessed visually on plotted Schoenfeld residuals.

Potential confounders were selected prior to the analysis based on causal diagrams. To adjust for potential confounding factors the model investigating the relation

between non-HDL-c and MALE and MACE occurrence was adjusted for age, sex, DM, SBP, smoking, statin use and eGFR. The presence of DM was no effect modifier for the relation between non-HDL-c and the occurrence of MALE (p for interaction 0.63). In the relation between SBP and the risk of MALE and MACE, the following possible confounders were added to the models: age, sex, non-HDL-c, smoking, DM, BMI and CRP. The relation between smoking and the risk MALE and MACE was adjusted for the possible confounders: age, sex, SBP, DM, BMI, non-HDL-c and eGFR. A dose-response relationship was assessed for the relation between smoking and the incidence of MALE and MACE for the categories 0-20 pack-years, 21-40 pack-years or >40 pack-years.

The PAF was quantified for all three relationships and was defined as the proportion of cases that could be prevented if the risk factor would be completely removed from the population. The PAF was based on Cox models adjusted for confounding factors using the R-package 'AF' (version 0.1.4).[19] In order to calculate the PAF, non-HDL-c was dichotomized at below or above 2.6 mmol/L, for SBP a cut-off at 140mmHg was used and smoking was analyzed as current smoking versus never or former smoking.

All analyses were performed with R-statistic programming (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

A sensitivity analysis was performed in which minor amputations were included in the definition of MALE. Because previous studies found a non-linear relation between SBP and the risk of MACE with a nadir around 140mmHg,[20,21] a separate analysis was done in which only people with a blood pressure of more than 140mmHg were included. Also, further exploratory Cox models were fitted for all relations in which atherosclerotic disease location, number of atherosclerotic disease locations, HbA1C, aspirin, alcohol, eGFR, and different classes of antihypertensive drugs were added to the models. In order to assess the impact of competing risks, the analyses were repeated with Fine and Gray competing risk models.

Results

Baseline characteristics

A total of 8,139 patients were included with a total follow-up of 66,359 person-years (median follow up 7.8 years, IQR 4.0-11.8 years). The baseline characteristics of the included patients are presented in Table 1. The mean age was 60.0 ± 10.3 years, 74% percent of the patients were male, 61% had a history of CAD, 30% of CVD, 18% of PAD and 9% of AAA. Baseline characteristics across quartiles of non-HDL-c, SBP and smoking status are presented in supplementary Table 1-3.

Table 1: Patient characteristics according to vascular disease location

	PAD	Patients without PAD (n = 6,684)		
		CAD	CVD	AAA
	n = 1,455	n = 4,537	n = 2,266	n = 571
Male sex	983 (68%)	3,695 (81%)	1,410 (62%)	489 (86%)
Age (years)	59.6 ± 10.5	60.7 ± 9.6	59.0 ± 11.3	65.0 ± 9.5
Former smoker	558 (38%)	2,388 (53%)	992 (44%)	308 (54%)
Current smoker	755 (52%)	1,062 (23%)	714 (32%)	186 (33%)
Packyears (years)	27.2 ± 19.8	18.4 ± 19.3	18.6 ± 20.0	26.7 ± 22.5
Body mass index (kg/m^2)	26.3 ± 4.2	27.3 ± 3.8	26.6 ± 4.3	26.5 ± 3.9
Diastolic blood pressure (mmHg)	81 ± 12	80 ± 11	82 ± 12	84 ± 12
Systolic blood pressure (mmHg)	145 ± 21	137 ± 20	141 ± 22	143 ± 20
Ankle brachial index	0.9 ± 0.2	1.2 ± 0.1	1.1 ± 0.2	1.1 ± 0.2
Diabetes mellitus	296 (20%)	848 (19%)	345 (15%)	79 (14%)
Coronary artery disease	402 (28%)	4,537 (100%)	401 (18%)	238 (42%)
Peripheral artery disease	1,455 (100%)	0 (0%)	0 (0%)	0 (0%)
Cerebrovascular disease	196 (13%)	401 (9%)	2,266 (100%)	87 (15%)
Abdominal aortic aneurysm	122 (8%)	238 (5%)	87 (4%)	571 (100%)
No. of vascular disease locations				
1	867 (60%)	3,934 (87%)	1,814 (80%)	282 (49%)
2	463 (32%)	567 (12%)	416 (18%)	253 (44%)
3	125 (9%)	36 (1%)	36 (2%)	36 (6%)
Laboratory values				
Total cholesterol (mmol/l)	5.3 ± 1.2	4.6 ± 1.1	4.9 ± 1.2	5.1 ± 1.3
LDL-cholesterol (mmol/l)	3.2 ± 1.1	2.6 ± 0.9	2.9 ± 1.1	3.1 ± 1.1
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.4
Non-HDL cholesterol (mmol/l)	4.1 ± 1.3	3.4 ± 1.1	3.6 ± 1.2	3.9 ± 1.3
Triglycerides (mmol/l)	1.9 ± 1.4	1.7 ± 1.4	1.6 ± 1.2	1.7 ± 1.1
Estimated GFR (ml/min/1.73m^2)	76 ± 20	77 ± 17	77 ± 18	70 ± 20
Medication use				
Statin	708 (49%)	3,695 (81%)	1,325 (58%)	290 (51%)
Diuretics	277 (19%)	968 (21%)	527 (23%)	158 (28%)
ACE inhibitors	347 (24%)	1,694 (37%)	638 (28%)	168 (29%)
Beta-blockers	421 (29%)	3,407 (75%)	694 (31%)	232 (41%)
Calcium channel blockers	287 (20%)	1,127 (25%)	358 (16%)	132 (23%)
Platelet inhibitor	797 (55%)	3,815 (84%)	1,525 (67%)	306 (54%)
Oral anticoagulants	202 (14%)	550 (12%)	213 (9%)	74 (13%)

PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; HDL, high-density lipoprotein cholesterol; GFR, glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula). All data in n (%) or mean ± standard deviation

Prescription frequencies of guideline medications increased over the years in the UCC-SMART cohort. In the first 10 years of inclusion (1996-2006), 54% of the patients was prescribed a statin and 24% an ACE-inhibitor, which increased to 80% statin use and 37% statin use after 2006. Patients with CAD were more often prescribed statins (82%) than patients with PAD (49%), CVD (58%) or AAA (51%).

Incidence rates of MALE and MACE

A total of 577 first MALE were observed, of which 48 were major amputations, 311 surgical interventions and 218 revascularizations (incidence rate 8.7/1000 person-years, Figure 1A). In patients with PAD at baseline 376 first MALE occurred (incidence rate 29.9/1000 person-years). In patients with a history of CAD but without PAD, the MALE incidence rate was 3.8 per 1000 person-years. For CVD, the MALE incidence rate was 4.1/1000 person-years and for AAA this incidence rate was 9.3/1000 person-years. The incidence rates were highest in patients with PAD + DM (44.6/1000 person-years) and PAD + polyvascular disease (36.1/1000 person-years).

A total of 1568 MACE were observed (incidence rate 24.0/1000 person-years, figure 1B). The incidence rate of MACE was 31.3/1000 in PAD patients. In the patients without PAD, the incidence rates were 21.8/1000 in CAD patients, 24.3/1000 in CVD patients and 47.4/1000 person-years in AAA patients. The combined endpoint MALE/MACE was observed 1933 times (incidence rate 29.1/1000 person-years, figure 1C), incidence rates per 1000 person-years were 57.3/1000 for PAD, 23.1/1000 for CAD, 25.4/1000 for CVD and 50.6/1000 for AAA.

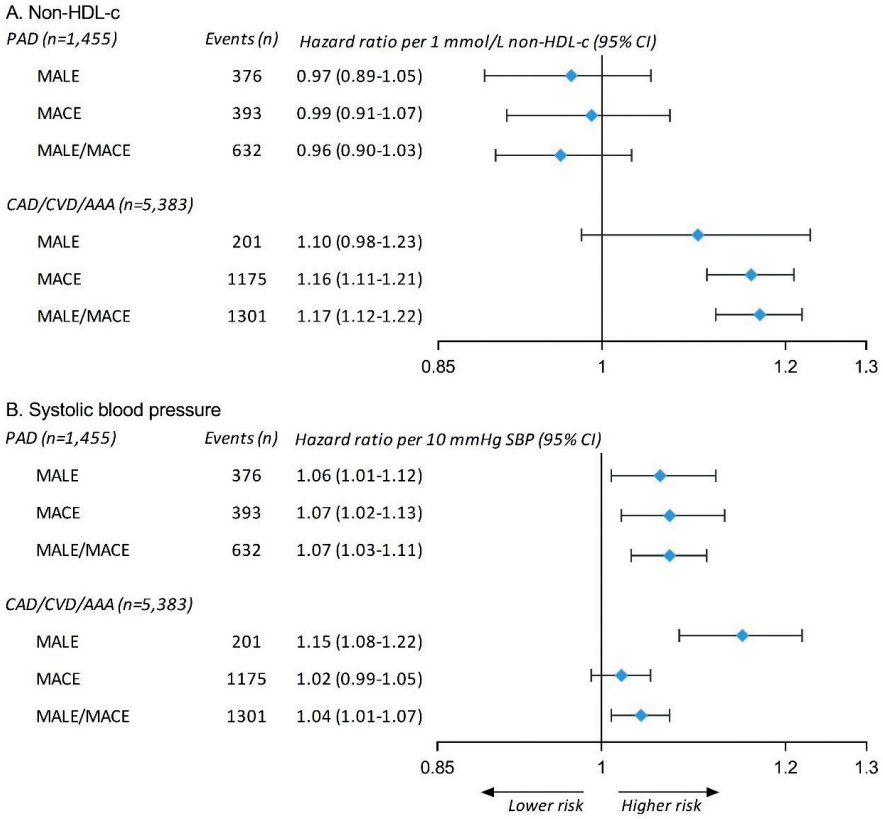
Relation between non-HDL-c, SBP and smoking and occurrence of MALE, MACE and MALE/MACE

There was no significant relation between non-HDL-c and the occurrence of MALE, MACE or MALE/MACE in patients with PAD (Figure 2A). In patients with CAD/CVD/AAA but without PAD, the risk of all outcomes was higher with higher non-HDL-c.

There was a positive relation between SBP and the occurrence of MALE, MACE and MALE/MACE in patients with PAD (Figure 2B). In patients with CAD/CVD/AAA but without PAD, the occurrence of MALE and MALE/MACE was positively related to SBP, there was no significant effect of SBP on MACE.

In patients with PAD, former and current smoking increased the risk of MALE insignificantly (figure 3). In these patients, both former and current smoking were associated with an increased risk of MACE and MALE/MACE. In patients with CAD/CVD/AAA but without PAD, former and current smoking increased the risk of MALE, MACE and MALE/MACE.

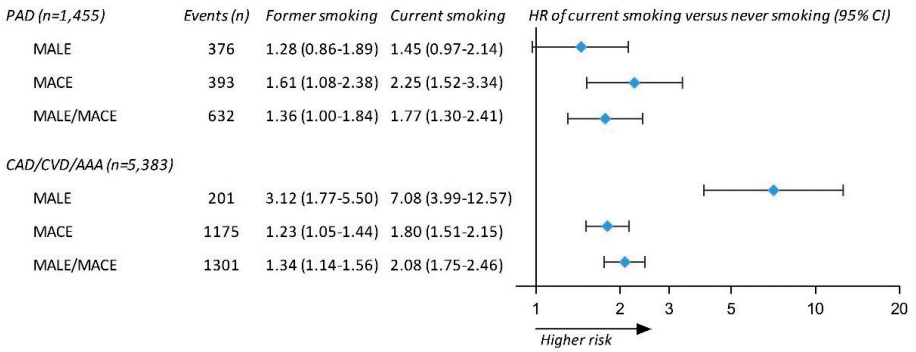
Figure 2: Relation between non-HDL-c and SBP and the risk of MALE, MACE and MALE/MACE according to vascular disease location



This figure shows the hazard rates for the risk of MALE, MACE and MALE/MACE per mmol increase of non-HDL-c (A) and per 10mmHg increase of SBP (B). A was adjusted for: age, sex, SBP, DM, smoking and eGFR, B for age, sex, non-HDL-c, smoking, DM, BMI and CRP. PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; MALE Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events.

A dose response effect was observed in the relation between smoking and MALE. In comparison to smokers with <20 pack-years, the risk was increased for 21-40 pack-years (HR 1.45, 95%CI 1.18-1.78) and >40 pack-years (HR 2.18, 95%CI 1.54-2.38). A similar effect was observed for MACE (HR 1.10, 95%CI 9.97-1.10 for 21-40 pack-years and HR 1.25, 95%CI 1.09-1.45 for >40 pack-years) and MALE/MACE (HR 1.19, 95%CI 1.07-1.34 for 21-40 pack-years and HR 1.41, 95%CI 1.25-1.61 for >40 pack-years).

Figure 3: Relation between smoking and the risk of MALE, MACE and MALE/MACE according to vascular disease location

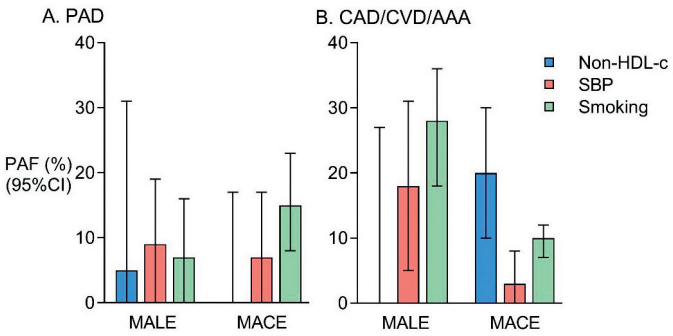


The figure shows the hazard ratios of current smoking versus never smoking for MALE, MACE and MALE/MACE. Hazard ratios for former smoking are displayed in supplementary figure 1.Models were adjusted for: age, sex, SBP, non-HDL-c, DM, BMI and eGFR. PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; MALE. Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events.

Population attributable fraction

The PAF of incident MALE in PAD patients was 5% (95%CI 0-31) for non-HDL-c, 9% (95%CI 0-19) for SBP and 7% (95%CI 0–16) for smoking. In patients with CAD/CVD/AAA this was 0% (95%CI 0-27) for non-HDL-c, 18% (95%CI 5-31) for SBP and 28% (95%CI 18-36) for smoking (figure 4).

Figure 4: The population attributable fractions of MALE and MACE for elevated non-HDL-c, elevated SBP and smoking



This figure shows the population attributable fractions of incident MALE and MACE attributable to non-HDL-c (>2.6 mmol/L), SBP (>140mmHg) and current smoking ±95% confidence intervals for patients with (A) PAD and (B) CAD/CVD/AAA. The PAF is the proportion of cases that could be prevented if the risk factor would be completely removed from the population. PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; AAA, abdominal aortic aneurysm; MALE, Major Adverse Limb Events; MACE, Major Adverse Cardiovascular Events; non-HDL-C, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure.

Sensitivity analyses
Including minor amputations in the MALE endpoint resulted in 15 additional MALE events, repeating the analyses with this definition of MALE did not meaningfully change the relations between risk factors and risk of MALE. The effect of non-HDL-c, SBP and smoking on the risk of MALE was similar in the highest risk groups, PAD + DM or PAD + polyvascular disease (supplementary table 4), except for current smoking in patients with PAD + DM. In this group current smoking led to a non-significant lower risk of MALE. Inclusion of only patients with a SBP of ≥140 mmHg SBP led to a stronger relation between SBP and risk of MACE in the patients with PAD (HR 1.16, 95%CI 1.07-1.25) but did no change the estimate in patients with CAD/CVD/AAA. There was no effect on the risk of MALE in both groups. Further adjustment for additional possible confounders did not change the estimates meaningfully. The competing-risk adjusted analysis showed similar results as the main analysis (supplementary table 5).

Discussion

In the present study it is shown that the incidence of MALE and MALE/MACE differs according to vascular disease location. The highest incidence of MALE was observed in patients with PAD, in these patients the incidence of MALE was higher than of MACE. In patients with CAD/CVD/AAA, higher non-HDL-c, higher SBP and smoking were associated with an increased risk of MALE, the effect of smoking and SBP on the incidence of MALE was much stronger than on the incidence of MACE.

In previously published studies it is shown that lipid-lowering therapy resulted in a reduction in amputations or limb events in patients with PAD.[8,22,23] In the FOURIER trial, a 42% reduction in MALE incidence was shown after treatment with a PCSK9-inhibitor in comparison to placebo.[5] In contrast to the current study, non-urgent revascularizations were not included in the MALE-endpoint of the FOURIER trial. In FOURIER's secondary endpoint consisting of all peripheral revascularizations, no difference was observed, indicating non-HDL-c may not be associated with non-urgent revascularizations. Therefore, inclusion of non-urgent revascularizations in the current study may have weakened the observed relation between non-HDL-c and the incidence of MALE.

The positive relation between SBP and risk of MALE as observed in this study is consistent with earlier studies in patients in the general population or with PAD.[10,11,24,25] Results from the current study show that SBP also increases the risk of MALE in patients with vascular disease at other locations and that this effect is stronger than on the incidence of MACE. These estimates did not change when only patients with a SBP of ≥140 mmHg were analyzed to account for a potential J-shaped relationship.

Current smoking is a strong risk factor for incident MALE and PAD, which is consistent with previously published results.[15,26] Results from the current study show that this effect is very strong in patients with CAD/CVD/AAA and that the effect of smoking on the incidence of MALE is stronger than on the incidence of MACE. Previous studies reported a dose-dependent relation between smoking and the incidence and prevalence of PAD,[13,26,27] results from the current study show that a similar effect also applies to incident MALE.

The effects of non-HDL-c, SBP and smoking on the incidence of MALE were smaller in patients with PAD in comparison to in patients with CAD/CVD/AAA. These differences could be partially explained by a difference in pathophysiology. In patients without PAD, MALE may primarily be a result generalized progression of atherosclerosis, whereas a recurrent MALE might also occur due to restenosis or thrombosis of a peripheral artery stent or bypass in patients with PAD. However, it is also possible that these differences are due to selection on the index event. This can be understood by viewing the onset of PAD as the sum of the effect of multiple causal factors. If one very strong causal factor, for example smoking, is already present, less effect of the other factors is required for the onset of disease. Subsequently comparing the smokers and non-smokers that have already developed PAD leads to the smokers having a relatively healthy risk profile in comparison to the non-smokers in both measured and non-measured factors, which cannot be completely corrected for.[28]

Because the FOURIER study found similar relative effect sizes on the incidence of MALE in patients with PAD as in patients with vascular disease at other locations from lipid-lowering,[5] it is likely that the actual effect is closer towards the estimate of the CAD/CVD/AAA group.

Results from the current study contribute to the evidence that the modifiable risk factors for MACE also increase the risk of MALE in patients with symptomatic vascular disease, including patients with preexisting PAD. In comparison to MACE, the fraction of MALE that can be attributed to the modifiable risk factors SBP and smoking is even larger. This implies that improved risk factor management in patients with symptomatic atherosclerotic disease could prevent many cases of incident MALE, apart from the benefit on reduction of MACE risk. In light of the high incidence the numbers needed to treat are expected to be low. The morbidity associated with MALE can be very high and a large fraction is attributable due to treatable risk factors, inclusion of those events in (primary) composite outcomes of intervention studies as MALE/MACE could therefore better reflect the effect of an intervention on the total disease burden due to atherosclerotic disease.

Strengths of this prospective cohort study include the large number of patients with symptomatic atherosclerotic disease with long and complete follow-up, resulting in a

high number of MALE and MACE. Also, the generalizability of the results is high as the UCC-SMART cohort resembles a referred patient population with vascular disease. A possible limitation is the fact that baseline characteristics were only recorded at the start of the study but may have changed in the duration of the follow-up. Furthermore, the results in patients with PAD may have been affected by selection on the index event and are therefore expected to be closer to the results in the CAD/CVD/AAA group.

In conclusion, the incidence of MALE in patients with clinical manifest vascular disease differs according to vascular disease location and is associated with non-HDL-c, SBP and smoking. A large fraction of incident MALE is attributable to modifiable risk factors. These findings confirm the importance of MALE as an outcome and underline the importance of classic risk factor management in patients with vascular disease, not only to prevent MACE, but also to prevent disabling MALE.

References

1. Mahoney EM, Wang K, Keo HH, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes* 2010; 3: 642–651.
2. Anand SS, Caron F, Eikelboom JW, et al. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease. *J Am Coll Cardiol* 2018; 71: 2306–2315.
3. Duval S, Keo HH, Oldenburg NC, et al. The impact of prolonged lower limb ischemia on amputation, mortality, and functional status: The FRIENDS registry. *Am Heart J* 2014; 168: 577–587.
4. Aboyans V, Desormais I, Lacroix P, et al. The General Prognosis of Patients With Peripheral Arterial Disease Differs According to the Disease Localization. *J Am Coll Cardiol* 2010; 55: 898–903.
5. Bonaca MP, Nault P, Giugliano RP, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease. *Circulation* 2018; 137: 338–350.
6. Fowkes FGR, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013; 382: 1329–1340.
7. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010; 376: 1670–1681.
8. Kumbhani DJ, Steg PG, Cannon CP, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014; 35: 2864–2872.
9. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012; 307: 1302–9.
10. Emdin CA, Anderson SG, Callender T, et al. Usual blood pressure, peripheral arterial disease, and vascular risk: cohort study of 4.2 million adults. *BMJ* 2015; 351: h4865.
11. Itoga NK, Tawfik DS, Lee CK, et al. Association of Blood Pressure Measurements With Peripheral Artery Disease Events. *Circulation* 2018; 138: 1805–1814.
12. Lane DA, Lip GY. Treatment of hypertension in peripheral arterial disease. *Cochrane Database Syst Rev* 2013; 10–13.
13. Willigendael EM, Teijink JAW, Bartelink M, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg* 2004; 40: 1158–1165.
14. Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. *Rev Cardiovasc Med* 2004; 5: 189–93.
15. Armstrong EJ, Wu J, Singh GD, et al. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg* 2014; 60: 1565–1571.
16. Simons PCG, Algra A, Van De Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: Rationale and design. *Eur J Epidemiol* 1999; 15: 773–781.
17. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; 376: 1713–1722.
18. Donders ART, van der Heijden GJMG, Stijnen T, et al. Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; 59: 1087–1091.
19. Sjölander A, Vansteelandt S. Doubly robust estimation of attributable fractions in survival analysis. *Stat Methods Med Res* 2017; 26: 948–969.

20. Dorresteijn JAN, van der Graaf Y, Spiering W, et al. Relation Between Blood Pressure and Vascular Events and Mortality in Patients With Manifest Vascular Disease. *Hypertension* 2012; 59: 14–21.

21. Bangalore S, Messerli FH, Wun C-C, et al. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J* 2010; 31: 2897–2908.

22. Arya S, Khakharia A, Binney ZO, et al. Association of Statin Dose With Amputation and Survival in Patients With Peripheral Artery Disease. *Circulation* 2018; 137: 1435–1446.

23. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg* 2007; 45: 645–655.

24. Joosten MM, Pai JK, Bertoia ML, et al. Associations Between Conventional Cardiovascular Risk Factors and Risk of Peripheral Artery Disease in Men. *JAMA* 2012; 308: 1660.

25. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet* 2014; 383: 1899–1911.

26. Conen D, Everett BM, Kurth T, et al. Smoking, smoking cessation and risk for symptomatic peripheral artery disease in women: a cohort study. *Ann Intern Med* 2011; 154: 719–26.

27. Lee Y-H, Shin M-H, Kweon S-S, et al. Cumulative smoking exposure, duration of smoking cessation, and peripheral arterial disease in middle-aged and older Korean men. *BMC Public Health* 2011; 11: 94.

28. Dahabreh IJ, Kent DM. Index Event Bias as an Explanation for the Paradoxes of Recurrence Risk Research. *JAMA* 2011; 305: 822.

Supplementary Materials

Supplementary table 1: Baseline characteristics per quartile of non-HDL-c

	Q1	**Q2**	**Q3**	**Q4**
	n = 2,037	n = 2,048	n = 2,025	n = 2,029
Non-HDL cholesterol - range (mmol/l)	0.7 - 2.7	2.7 - 3.4	3.4 - 4.3	4.3 - 20.6
Male sex	1,519 (75%)	1,531 (75%)	1,511 (75%)	1,441 (71%)
Age (years)	60.9 ± 10.4	60.3 ± 10.3	59.6 ± 10.4	59.4 ± 10.2
Current smoker	454 (22%)	564 (28%)	689 (34%)	819 (40%)
Former smoker	1,065 (52%)	997 (49%)	928 (46%)	860 (42%)
Packyears	17.6 ± 19.6	18.8 ± 19.7	21.0 ± 20.0	23.2 ± 20.1
Body mass index (kg/m^2)	26.5 ± 3.9	26.9 ± 4.1	27.1 ± 4.1	27.0 ± 4.0
Diastolic blood pressure (mmHg)	79.9 ± 10.9	80.3 ± 11.4	81.5 ± 11.5	82.3 ± 11.6
Systolic blood pressure (mmHg)	137.0 ± 20.0	137.5 ± 19.5	140.1 ± 21.0	143.3 ± 21.5
Ankle brachial index	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
Diabetes mellitus	390 (19%)	392 (19%)	336 (17%)	297 (15%)
Coronary artery disease	1,411 (69%)	1,384 (68%)	1,212 (60%)	932 (46%)
Peripheral artery disease	194 (10%)	265 (13%)	399 (20%)	597 (29%)
Cerebrovascular disease	608 (30%)	581 (28%)	612 (30%)	661 (33%)
Abdominal aortic aneurysm	114 (6%)	141 (7%)	189 (9%)	249 (12%)
No. of vascular disease locations				
1	1,780 (87%)	1,758 (86%)	1,682 (83%)	1,677 (83%)
2	224 (11%)	259 (13%)	301 (15%)	297 (15%)
3	33 (2%)	31 (2%)	42 (2%)	55 (3%)
Laboratory values				
Total cholesterol (mmol/l)	3.5 ± 0.5	4.3 ± 0.4	5.1 ± 0.4	6.4 ± 0.9
LDL-cholesterol (mmol/l)	1.8 ± 0.4	2.4 ± 0.4	3.0 ± 0.5	4.2 ± 0.9
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.3
Trigylerides (mmol/l)	1.1 ± 0.5	1.5 ± 0.7	1.8 ± 1.0	2.4 ± 2.1
Estimated GFR (ml/min/1.73m^2)	77 ± 18	77 ± 18	77 ± 18	76 ± 19
Medication use				
Statin	1,821 (89%)	1,673 (82%)	1,280 (63%)	727 (36%)
Diuretics	428 (21%)	460 (22%)	435 (21%)	396 (20%)
ACE inhibitors	768 (38%)	702 (34%)	601 (30%)	482 (24%)
Beta-blockers	1,233 (61%)	1,209 (59%)	1,056 (52%)	846 (42%)
Calcium channel blockers	412 (20%)	428 (21%)	450 (22%)	421 (21%)
Platelet inhibitor	1,676 (82%)	1,585 (77%)	1,421 (70%)	1,240 (61%)
Oral anticoagulants	217 (11%)	231 (11%)	216 (11%)	231 (11%)

HDL, high-density lipoprotein cholesterol; non-HDL, non-high-density lipoprotein cholesterol; GFR, glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula). All data in n (%) or mean ± standard deviation

Supplementary table 2: Baseline characteristics per quartile of SBP

	Q1	**Q2**	**Q3**	**Q4**
	n = 2,139	n = 2,004	n = 1,981	n = 2,015
Systolic blood pressure - range (mmHg)	79 - 125	126 - 137	138 - 151	152 - 244
Male sex	1,530 (72%)	1,517 (76%)	1,490 (75%)	1,465 (73%)
Age (years)	56.5 ± 10.5	58.8 ± 10.2	61.2 ± 9.9	63.9 ± 9.1
Current smoker	744 (35%)	631 (31%)	587 (30%)	564 (28%)
Former smoker	910 (43%)	940 (47%)	977 (49%)	1,023 (51%)
Packyears	18.5 ± 18.7	19.5 ± 19.7	21.0 ± 20.2	21.8 ± 21.1
Body mass index (kg/m^2)	26.3 ± 4.0	27.0 ± 4.0	27.2 ± 4.0	27.0 ± 4.0
Diastolic blood pressure (mmHg)	72.1 ± 7.5	78.7 ± 7.9	83.0 ± 8.7	90.8 ± 11.7
Ankle brachial index	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
Diabetes mellitus	245 (11%)	313 (16%)	412 (21%)	445 (22%)
Coronary artery disease	1,445 (68%)	1,243 (62%)	1,202 (61%)	1,049 (52%)
Peripheral artery disease	266 (12%)	312 (16%)	372 (19%)	505 (25%)
Cerebrovascular disease	584 (27%)	577 (29%)	606 (31%)	695 (34%)
Abdominal aortic aneurysm	137 (6%)	156 (8%)	197 (10%)	203 (10%)
No. of vascular disease locations				
1	1,882 (88%)	1,747 (87%)	1,637 (83%)	1,631 (81%)
2	222 (10%)	230 (11%)	293 (15%)	336 (17%)
3	35 (2%)	27 (1%)	51 (3%)	48 (2%)
Laboratory values				
Total cholesterol (mmol/l)	4.7 ± 1.1	4.7 ± 1.2	4.9 ± 1.2	5.0 ± 1.3
LDL-cholesterol (mmol/l)	2.7 ± 1.0	2.8 ± 1.0	2.8 ± 1.0	3.0 ± 1.1
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.4	1.3 ± 0.4
Non-HDL cholesterol (mmol/l)	3.5 ± 1.1	3.5 ± 1.2	3.6 ± 1.2	3.8 ± 1.3
Triglycerides (mmol/l)	1.6 ± 1.3	1.6 ± 1.1	1.7 ± 1.2	1.8 ± 1.7
Estimated GFR (ml/min/1.73m^2)	80 ± 17	79 ± 17	77 ± 18	72 ± 19
Medication use				
Statin	1,535 (72%)	1,397 (70%)	1,333 (67%)	1,236 (61%)
Diuretics	397 (19%)	386 (19%)	426 (22%)	510 (25%)
ACE inhibitors	685 (32%)	585 (29%)	586 (30%)	697 (35%)
Beta-blockers	1,278 (60%)	1,056 (53%)	1,020 (51%)	990 (49%)
Calcium channel blockers	355 (17%)	390 (19%)	454 (23%)	512 (25%)
Platelet inhibitor	1,624 (76%)	1,474 (74%)	1,441 (73%)	1,383 (69%)
Oral anticoagulants	246 (12%)	200 (10%)	213 (11%)	236 (12%)

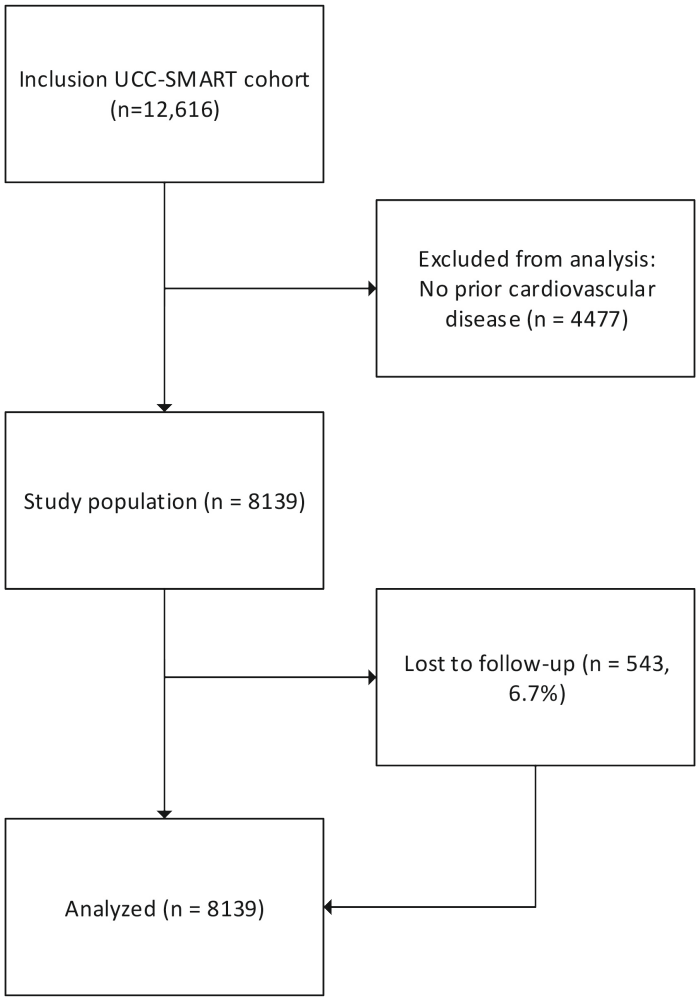
HDL, high-density lipoprotein cholesterol; non-HDL, non-high-density lipoprotein cholesterol; GFR, glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula). All data in n (%) or mean ± standard deviation

Supplementary table 3: Baseline characteristics per smoking status

	Never smoker	Former smoker	Current smoker
	n = 1,763	n = 3,850	n = 2,526
Male sex	1,113 (63%)	3,095 (80%)	1,794 (71%)
Age (years)	60.6 ± 11.1	62.3 ± 9.4	56.1 ± 10.1
Packyears	0.0 ± 0.0	22.5 ± 18.3	30.7 ± 19.1
Body mass index (kg/m^2)	26.8 ± 4.0	27.2 ± 3.8	26.5 ± 4.4
Diastolic blood pressure (mmHg)	81.3 ± 11.8	81.2 ± 11.0	80.4 ± 11.5
Systolic blood pressure (mmHg)	139.0 ± 20.9	140.8 ± 20.6	137.8 ± 20.4
Ankle brachial index	1.2 ± 0.1	1.1 ± 0.2	1.0 ± 0.2
Diabetes mellitus	302 (17%)	747 (19%)	366 (14%)
Coronary artery disease	1,120 (64%)	2,601 (68%)	1,218 (48%)
Peripheral artery disease	142 (8%)	558 (14%)	755 (30%)
Cerebrovascular disease	580 (33%)	1,097 (28%)	785 (31%)
Abdominal aortic aneurysm	85 (5%)	365 (9%)	243 (10%)
No. of vascular disease locations			
1	1,610 (91%)	3,175 (82%)	2,112 (84%)
2	143 (8%)	583 (15%)	355 (14%)
3	10 (1%)	92 (2%)	59 (2%)
Laboratory values			
Total cholesterol (mmol/l)	4.7 ± 1.2	4.7 ± 1.2	5.1 ± 1.2
LDL-cholesterol (mmol/l)	2.7 ± 1.0	2.8 ± 1.0	3.0 ± 1.1
HDL-cholesterol (mmol/l)	1.3 ± 0.3	1.2 ± 0.4	1.2 ± 0.4
Non-HDL cholesterol (mmol/l)	3.4 ± 1.1	3.5 ± 1.2	3.9 ± 1.3
Triglycerides (mmol/l)	1.6 ± 1.0	1.6 ± 1.1	1.9 ± 1.8
Estimated GFR (ml/min/1.73m^2)	75 ± 18	75 ± 17	81 ± 18
Medication use			
Statin	1,215 (69%)	2,758 (72%)	1,528 (60%)
Diuretics	401 (23%)	905 (24%)	413 (16%)
ACE inhibitors	586 (33%)	1,291 (34%)	676 (27%)
Beta-blockers	1,021 (58%)	2,184 (57%)	1,139 (45%)
Calcium channel blockers	348 (20%)	942 (24%)	421 (17%)
Platelet inhibitor	1,300 (74%)	2,892 (75%)	1,730 (68%)
Oral anticoagulants	193 (11%)	495 (13%)	207 (8%)

HDL, high-density lipoprotein cholesterol; non-HDL, non-high-density lipoprotein cholesterol; GFR, glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula). All data in n (%) or mean ± standard deviation

Supplementary figure S1: Flowchart of patients in the UCC-SMART cohort for the current analysis



Supplementary table 4: Risk factors and the risk of MALE in high-risk PAD patients

	Hazard ratio (95% CI) for the risk of MALE		
	Non-HDL-c (per 1 mmol/L)	**SBP (per 10 mmHg)**	**Current smoking**
Overall PAD patients (n = 1455)	0.98 (0.89-1.07)	1.06 (1.01-1.12)	1.45 (0.97-2.14)
PAD + DM (n=296)	1.01 (0.84-1.23)	1.04 (0.95-1.15)	0.67 (0.34-1.31)
PAD + polyvascular disease (n = 588)	1.03 (0.89-1.19)	1.08 (1.00-1.16)	1.63 (0.86-3.09)

Non-HDL, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure; PAD, peripheral artery disease; DM, diabetes mellitus. Polyvascular disease is defined as PAD + coronary artery disease, cerebrovascular disease or abdominal aortic aneurysm.

Supplementary table 5: The effect of non-HDL-c, SBP and smoking on the risk of MALE with and without competing-risk adjustement

	Main analysis	Competing-risk adjusted analysis
Patients with PAD	**HR (95%CI)**	**Subdistribution HRs (95% CI)**
Non-HDL-c (per mmol/L)	0.98 (0.89-1.02)	1.01 (0.92-1.10)
SBP (per 10 mmHg)	1.06 (1.01-1.12)	1.05 (1.00-1.10)
Former smoking	1.28 (0.86-1.89)	1.21 (0.82-1.78)
Current smoking	1.45 (0.97-2.14)	1.26 (0.86-1.86)
Patients without PAD		
Non-HDL-c (per mmol/L)	1.14 (1.01-1.29)	1.13 (1.00-1.27)
SBP (per 10 mmHg)	1.15 (1.08-1.22)	1.14 (1.07-1.22)
Former smoking	3.12 (1.77-5.50)	3.02 (1.71-5.32)
Current smoking	7.08 (3.99-12.57)	6.32 (3.56-11.20)

The effect on the risk of major adverse limb events per mmol increase of non-HDL-c, per 10mmHg increase of SBP and for former and current smoking. Competing risk-adjusted results were obtained from Fine and Gray analyses with all-cause mortality as competing risk, adjusted for the same confounders as the main analysis. PAD, peripheral artery disease; Non-HDL, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure;

CHAPTER 8

Estimation of recurrent atherosclerotic cardiovascular event risk in patients with established cardiovascular disease: the updated and geographically recalibrated SMART2 algorithm

Steven HJ Hageman, Ailsa J McKay, Peter Ueda, Laura H Gunn, Tomas Jernberg, Emil Hagström, Deepak L Bhatt, Ph. Gabriel Steg, Kristi Läll, Reedik Mägi, Mari Nordbø Gynnild, Hanne Ellekjær, Ingvild Saltvedt, José Tuñón, Ignacio Mahíllo, Álvaro Aceña, Karol Kaminski, Malgorzata Chlabicz, Emilia Sawicka, Taavi Tillman, John W McEvoy, Emanuele Di Angelantonio, Ian Graham, Dirk De Bacquer, Kausik K Ray, Jannick AN Dorresteijn*, Frank LJ Visseren*

on behalf of the UCC-SMART Study Group.

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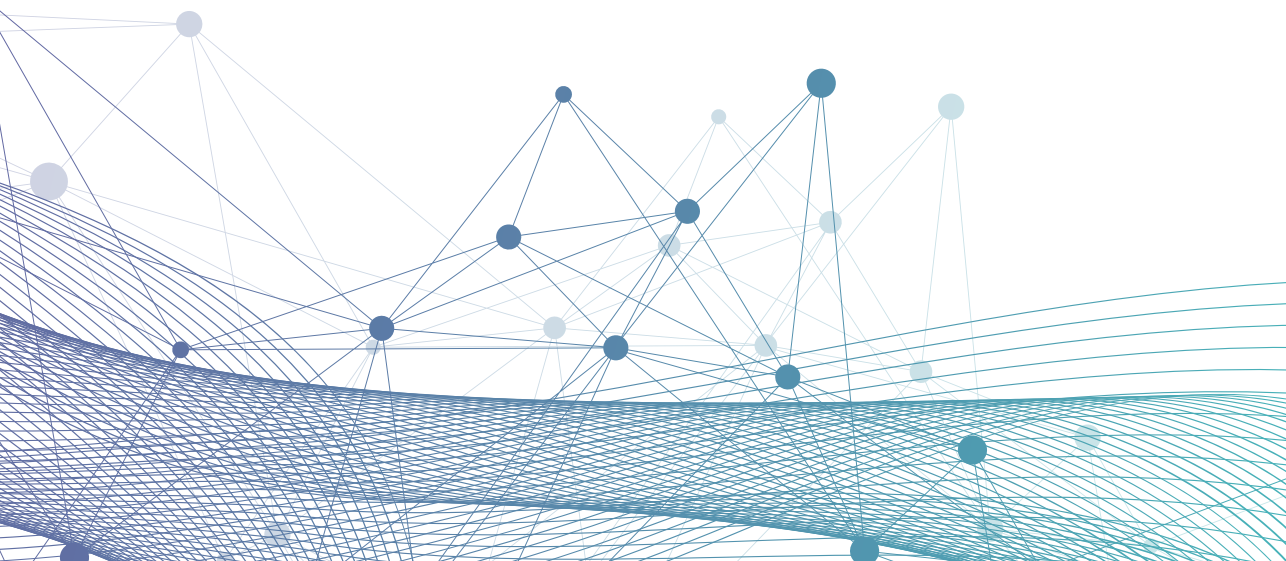
*Contributed equally



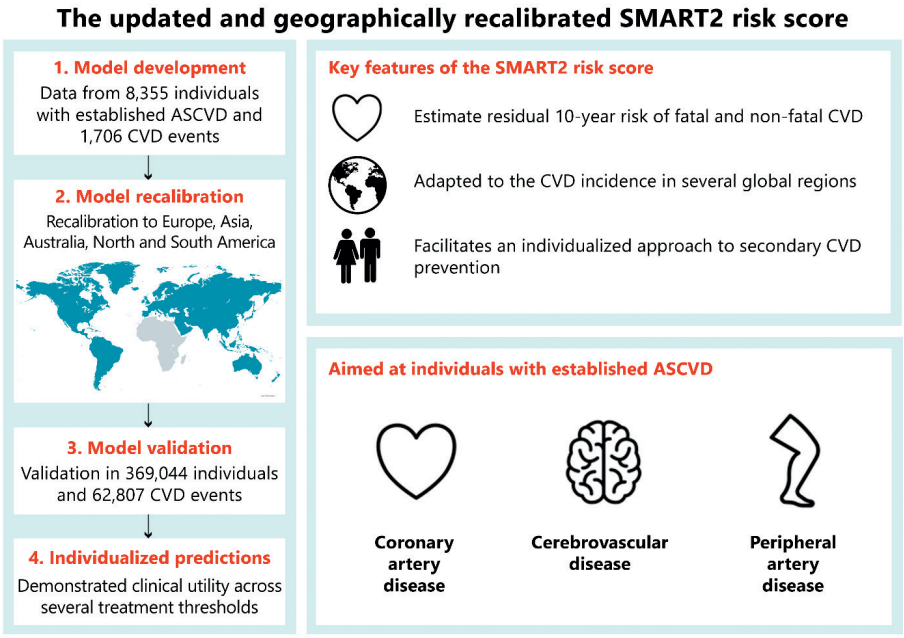
Abstract

Background: The 10-year risk of recurrent atherosclerotic cardiovascular disease (ASCVD) events in patients with established ASCVD can be estimated with the SMART risk score, and may help refine clinical management. To broaden generalizability across regions, we updated the existing tool (SMART2 risk score) and recalibrated it with regional incidence rates and assessed its performance in external populations.

Methods and Results: Individuals with coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysms were included from the UCC-SMART cohort (n=8,355; 1,706 ASCVD events during a median follow-up of 8.2 years [IQR 4.2-12.5]) to derive a 10-year risk prediction model for recurrent ASCVD events (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular mortality) using a Fine and Gray competing risk-adjusted model. The model was recalibrated to 4 regions across Europe, and to Asia (excluding Japan), Japan, Australia, North America, and Latin America using contemporary cohort data from each target region. External validation used data from 7 cohorts (CPRD, SWEDEHEART, REACH Registry, Estonian Biobank, BACS/BAMI, Nor-COAST, and Bialystok PLUS/Polaspire) and included 369,044 individuals with established ASCVD of whom 62,807 experienced an ASCVD event. C-statistics ranged from 0.605 (95%CI 0.547-0.664) in BACS/BAMI to 0.772 (95%CI 0.659-0.886) in REACH Europe high risk region. The clinical utility of the model was demonstrated across a range of clinically relevant treatment thresholds.

Interpretation: The SMART2 risk score provides an updated, validated tool for prediction of recurrent ASCVD events in patients with established ASCVD across European and non-European populations. Use of this tool could allow for a more personalized approach to secondary prevention based upon quantitative rather than qualitative estimates of residual risk.

Graphical abstract



Introduction

Atherosclerotic cardiovascular diseases (ASCVD), such as coronary heart disease and cerebrovascular disease, are the most common non-communicable diseases globally, and were responsible for an estimated 17.8 million deaths worldwide in 2017.[1] Clinical guidelines advocate the use of risk prediction models in patients without vascular disease or diabetes, since those at high risk of ASCVD are more likely to benefit from preventive startegies.[2–4] Clinical guidelines have traditionally advised classification of all patients with established vascular disease as being at 'very high risk' for future (recurrent) ASCVD events.[5–7] This universal approach to allocating risk among secondary prevention patients ignores that fact that the individual level of CVD risk can vary in these patients[8] and precludes the option for a more personalized approach to risk factor management in secondary prevention. More intensive treatment options, such as lower treatment targets for blood pressure and low-density lipoprotein cholesterol (LDL-C), or additional antithrombotic strategies have been proven to further reduce the risk of ASCVD events. However, their implementation has been generally modest, in part reflecting uncertainties about cost benefits from implementing these at scale or uncertainties about individual risk-benefits such as the risk of major bleeding. This makes identification of patients who may benefit most from more intensive therapy a key issue in clinical practice today.[9,10] For this reason, more recent European Society of Cardiology (ESC) guidelines now recommend that clinicians consider including information on risk to help inform clinician-patient joint decision-making for secondary prevention treatments.[7,11]

For patients with established ASCVD, the 10-year risk of recurrent ASCVD can be estimated with the previously published Secondary Manifestations of ARTerial disease (SMART) risk score.[12] The SMART risk score was developed using the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART)[13] and externally validated in several trial and routine care populations.[8,14,15] It was made available via online calculators on the European Society of Cardiology (ESC) website, the ESC CVD risk prediction app, and U-prevent.com. However, the SMART risk score has several limitations. First, the model was derived using data from participants recruited before 2010 and followed for a median of 4.7 years, and hence may not be directly applicable to predicting 10-year risk in contemporary populations. Second, the model has no parameter to reflect regional differences in CVD incidence, possibly limiting the applicability of the prediction model to the low risk region where it was developed. Third, the SMART risk score does not take competing risk for non-CVD death into account, which might lead to an overestimation of ASCVD risk in patients at higher risk of competing 'non-CVD' death, such as older individuals.[16] Therefore, we set out to update the SMART risk score by providing derivation (taking competing risk into account), geographic recalibration, and external validation of the new risk score

(SMART2) to estimate 10-year residual ASCVD event risk in patients with established ASCVD aged 40-80 years.

Methods

Population

Following the previous version of the SMART risk score, the target population for the SMART2 risk score consists of individuals with stable, established ASCVD. The SMART2 risk score was developed using patients with established ASCVD from the UCC-SMART cohort aged 40-80 years. UCC-SMART is a single-center ongoing prospective cohort study at the University Medical Center Utrecht, the Netherlands.[13] Patients newly referred to the University Medical Centre Utrecht with established ASCVD, or an increased risk thereof, were included in the period 1996 to 2019. For the current analysis, we included patients with a history of any type of established ASCVD; which comprised of coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral artery disease (PAD), and/or abdominal aortic aneurysm (AAA). CAD was defined as angina pectoris with documented stenosis, myocardial infarction, or coronary revascularization (coronary bypass surgery or coronary angioplasty); CeVD as a transient ischemic attack, cerebral infarction, amaurosis fugax or retinal infarction, or a history of carotid surgery; PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg or a history of vascular surgery of the leg (percutaneous transluminal angioplasty, bypass, or amputation); and patients with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured at baseline examination with ultrasonography) or a history of AAA surgery. All baseline characteristics were determined at baseline using a standardized screening protocol consisting of questionnaires, physical examination and laboratory testing.

For external validation, patients were included from the Clinical Practice Research Datalink (CPRD) in the United Kingdom,[17] the international REduction of Atherothrombosis for Continued Health (REACH) Registry,[18–20] the Bialystok PLUS/Polaspire cohort from Poland,[21] the Estonian Biobank,[22] Spanish Biomarkers in Acute Coronary Syndrome and Biomarkers in Acute Myocardial Infarction (BACS/BAMI),[23] the Norwegian COgnitive Impairment After STroke (Nor-COAST) study,[24] and the SWEDEHEART registry.[25] Detailed descriptions of the external validation cohorts can be found in the Supplementary Methods. Where possible, predictor definitions were the same as in the derivation data. Disease history variables were based on questionnaires (REACH registry, Bialystok PLUS/Polaspire, BACS/BAMI) or linkage to hospital records or primary care (CPRD, Estonian Biobank, Nor-COAST, SWEDEHEART). Endpoints were followed-up by linkage to primary care records, hospital records or disease/mortality registries (CPRD, Estonian Biobank, Nor-COAST,

SWEDEHEART, BACS/BAMI, Bialystok PLUS/Polaspire), or by annual questionnaires (REACH registry).

Statistical analyses

The SMART2 coefficients were estimated using Fine and Gray competing risk-adjusted subdistribution hazard model.[26] This model was chosen as it requires no assumptions regarding the shape of the baseline survival function, whereas it can reliably correct for competing risks.[26] The primary outcome was the occurrence of new ASCVD events, defined as the composite of non-fatal myocardial infarction, non-fatal stroke, and vascular death (**Supplementary Table 1**). The SMART2 risk score used the same predictors as the original SMART model: baseline age; sex; current smoking; diabetes mellitus; systolic blood pressure (in mmHg); non-high density lipoprotein (non-HDL) cholesterol (in mmol/L); presence of CAD, CeVD, PAD, or AAA; estimated glomular filtration rate (eGFR) (mL/min/1.73m^2); high sensitivity C-reactive protein (hsCRP; mg/L); and years since first clinical manifestation of ASCVD (CAD, CeVD, PAD, or AAA). To account for the use of aspirin or equivalent antithrombotic drugs at baseline (including other antiplatelet drugs and oral anticoagulant drugs), the effect of the drugs was added to the model as a fixed predictor[27,28] (offset term) with a hazard ratio of 0.81.[29,30] Antithrombotic therapy use was treated as a fixed predictor because treatment it is intended that decisions guided by the risk score may involve use of these drugs (especially the initiation of dual pathway inhibition); as such they could not be included in the model as a regular predictor. Using the same predictors as the original SMART score would require 34 events per parameter with a total of 544 CVD events. The baseline survival was obtained by predicting the cumulative survival from the SMART2 model based on derivation data mean risk factor levels with the predictEventProb function (*pec* package) in R. To check whether the association of continuous predictors with the outcome variable was adequately explained with a log-linear relationship, Akaike information criterions were used to compare log-linear model fits to a log-transformations, squared transformations or restricted cubic splines. Based on this, log transformations were used for non-HDL cholesterol and hsCRP, and squared transformations for years since first ASCVD diagnosis and eGFR, no predictors showed best model fit by using restricted cubic splines. Internal validation discrimination and calibration slope were evaluated by 10-fold cross-validation. Handling of missing data is described in the Supplementary Methods.

Regional recalibration

The SMART2 risk score was recalibrated to 4 risk regions within Europe, which were grouped based on age- and sex-standardized ASCVD mortality rates identical to the grouping used for SCORE2 (**Supplementary Figure 1**).[31,32] Details about the risk regions within Europe are shown in the Supplementary Methods. The model was recalibrated to 4 risk regions within Europe by recalibrating the baseline hazard

(shifting with a single multiplicative constant per region) of the SMART2 risk score to the data source in the region deemed most representative. First, the expected-observed ratio was calculated in the recalibration data, by dividing the mean predicted risk by the observed cumulative incidence of ASCVD. Then, the baseline hazard was recalibrated by implementing this expected-observed ratio from the target region in the formula for individual risk predictions (**Supplementary Table 1+2**). For the low risk region (CPRD, n=240,443) and the moderate risk region (SWEDEHEART n=67,428), large, contemporary data sources were available with minimal selection. In the other regions, the model was recalibrated to local clinical practice by averaging the recalibration factors of the different cohorts in the region (if multiple cohorts available). For the high risk region, the Estonian Biobank (n=12,986), Bialystok PLUS/Polaspire (n=219), and REACH Europe high risk region (Hungary, n=836) were used for recalibration; and for the very high risk region, the REACH Registry (Bulgaria, Russia, Lithuania, Romania, Ukraine; n=4,382) was used. Recalibration to regions outside of Europe (North America (n=15,857), Latin America (n=1,446), Asia (excluding Japan, n=5,396), Japan (n=3,745), Australia (n=1,963)) was performed in the REACH Registry.

External validation

Calibration was assessed visually using predicted versus observed risk plots – showing octiles of predicted risks plotted against ASCVD cumulative incidences, rather than Kaplan Meier estimates which may overestimate ASCVD incidence in the presence of competing risks.[16] Where possible, calibration was assessed at 10 years (CPRD, n=240,443; SWEDEHEART, n=67,428; Estonian Biobank, n=12,986) as this is the intended prediction horizon of the SMART2 model. For external validation cohorts with less than 10 years of follow-up, model performance was assessed using the duration of the last complete year with ≥80% endpoint registration, which was 2 or 3 years for the REACH subcohorts (n=46,507, Japan, Latin America, and Europe low risk region 3 years, others 2 years), Nor-COAST (n=497), and Bialystok PLUS/Polaspire (n=219), and 6 years for BACS/BAMI (n=964). For prediction of 2-, 3-, and 6-year risks, the SMART2 predictions were based on the 2-, 3-, and 6-year baseline hazards instead of the 10-year baseline hazard (**Supplementary Table 1**). Discrimination was assessed as an incident C-statistic at 10 years of follow-up if viable, else the same prediction horizon was used as was used calibration. Discrimination results were adjusted for competing risks and calculated using the R-package *timeROC*. For SWEDEHEART and CPRD this was not feasible, and a cumulative C-statistic was used adjusted for competing risks. Results from the same region where pooled using random effects models. The potential clinical value of the SMART2 was evaluated using decision curve analyses. For this, the net benefit of treating all individuals with a predicted SMART2 risk equal greater than the treatment threshold was evaluated across a range of relevant potential treatment thresholds. The clinical benefit was evaluated at 10 years of follow-up and was corrected for competing risks. The analyses were performed using R-function *stdca*.[33] The risk thresholds of 20% up until 50% 10-year risk

of ASCVD events were regarded as clinically relevant for intensified treatment options as stated in 'Step 2' of the 2021 ESC CVD prevention guidelines.[7] Clinical benefit was estimated in all external validation cohorts with at least 10 year maximum follow-up duration (CPRD, SWEDEHEART, Estonian Biobank).[34] Treatment intensification based on predicted residual risk by the SMART2 algorithm was compared to the strategies of treatment intensification in all patients and to performing no treatment intensification. To illustrate the distributions of the predicted risk in the different regions, a simulation was performed using the UCC-SMART data. In this illustration, equal risk factor distributions were assumed in order to make the rates comparable. All analyses were performed with R-statistical programming (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

Sensitivity analyses were performed to evaluate several aspects in model derivation. The methodology of these analyses is described in detail in the Supplementary Methods – validation of all sensitivity analyses was performed in the European REACH data. First, to evaluate the potential benefit of separate model derivation for men and women, the model was derived separately for both sexes. Second, to evaluate whether the discriminative ability of the model predictors was stable over the different anatomical locations of established ASCVD, the model was derived and recalibrated separately for the different locations of established ASCVD (CAD, CevD, and PAD/AAA separately).

Results

Model derivation

In the derivation data, 8,355 patients from UCC-SMART with established ASCVD were included. Mean age at baseline was 61±9 years old, and 74% were male. Detailed patient characteristics are presented in **Table 1**. In a median of 8.2 years of follow-up (IQR 4.2-12.5), 1,706 ASCVD events and 978 non-cardiovascular deaths were observed. The SMART2 risk score subdistribution hazard ratios (SHR) are presented in **Table 2**. There were no or minimal violations of the proportional hazards assumptions as assessed visually based on plotted Schoenfeld residuals. The internal validation C-statistic was 0.696 (95%CI 0.682-0.708) and the internal calibration slope was 1.002 (95%CI 0.984 - 1.019).

Table 1: Patient characteristics of the model derivation population

	UCC-SMART
	n = 8,355
Male sex	6,198 (74%)
Age (years)	61 ± 9
Current smoker	2,504 (30%)
Body mass index (kg/m²)	27 ± 4
Systolic blood pressure (mmHg)	139 ± 20
Diabetes mellitus	1,467 (18%)
Established coronary artery disease	5,215 (62%)
Established peripheral artery disease	1,459 (17%)
Established cerebrovascular disease	2,424 (29%)
Established abdominal aortic aneurysm	706 (8%)
Total cholesterol (mmol/L)	4.6 (3.9-5.5)
HDL-cholesterol (mmol/L)	1.2 (1.0-1.4)
LDL-cholesterol (mmol/L)	2.7 (2.1-3.5)
Triglycerides (mmol/L)	1.4 (1.0-2.0)
Estimated GFR (mL/min/1.73m²)	77 ± 18
hsCRP (mg/dL)	2.0 (1.0-4.4)
Statin	5,764 (69%)
Antiplatelet therapy or anticoagulants	6,494 (78%)
Event rate per 1000 person-years*	24

n (%), mean ± SD, or median (interquartile range; IQR). *Event rate of fatal + non-fatal (MI, stroke) events per 1000 person-years. GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula). ASCVD = cardiovascular disease, hsCRP = C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein

Table 2: Subdistribution hazard ratios of the SMART2 risk score

	Subdistribution hazard ratio (95%CI)
Age†	1.61 (1.50-1.73)
Male sex	1.33 (1.18-1.50)
Current smoking	1.41 (1.27-1.58)
Systolic blood pressure (per 10mmHg)	1.02 (0.99-1.04)
Non-HDL cholesterol (mmol/L)*	1.28 (1.19-1.39)
Established diabetes mellitus	1.37 (1.22-1.54)
Established coronary artery disease	1.34 (1.17-1.55)
Established cerebrovascular disease	1.42 (1.24-1.61)
Established peripheral artery disease	1.25 (1.09-1.43)
Established abdominal aortic aneurysm	1.39 (1.19-1.62)
Years since first ASCVD diagnosis†	1.18 (1.15-1.20)
Estimated glomerular filtration ratio†	0.87 (0.86-0.88)
High sensitivity-CRP*	1.25 (1.17-1.34)

Subdistribution hazard ratios from Fine and Gray models predicting the risk of total (fatal+non-fatal) ASCVD. Predictors marked with (*) are log-transformed ratios, and predictors marked with (†) are squared ratios. For squared (†) or log-transformed (*) ratios, the subdistribution hazard ratios are presented as 3rd versus 1st quartile. ASCVD = Atherosclerotic cardiovascular disease. hsCRP = High-sensitivity C-reactive protein, HDL = high density lipoprotein.

External validation

External validation of risk models involved data from 369,044 individuals with established ASCVD, recruited into 7 cohorts in which 62,807 ASCVD events were observed. Of these, 340,637 (92%) were recruited in Europe. Median follow-up times ranged from 1.9 years (IQR 1.8-1.9) for REACH to 6.5 years (IQR 0.7-9.9) for the Estonian Biobank. Detailed patient characteristics of the included patients are presented in **Table 3**.

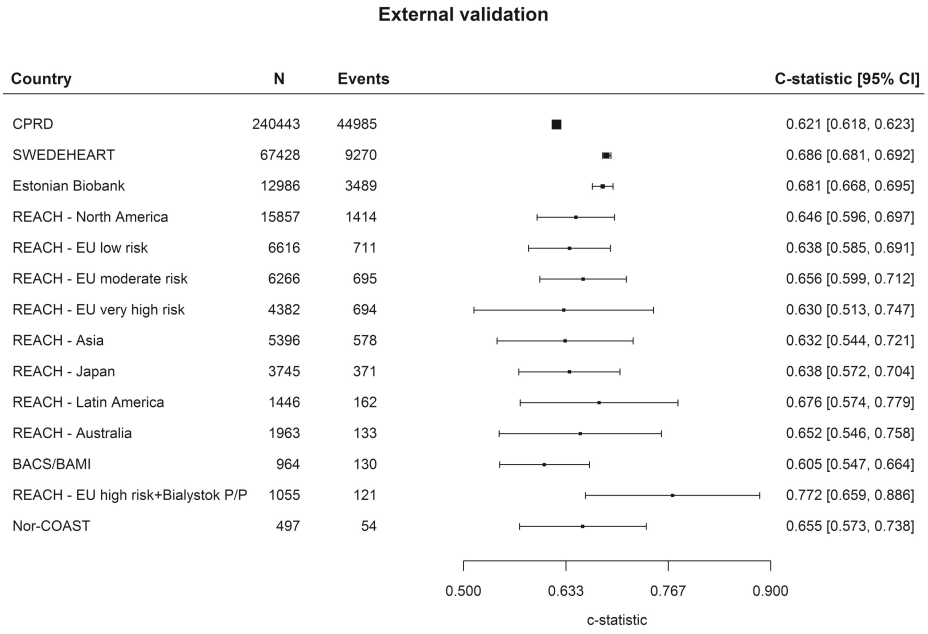
Table 3: Patient characteristics in the external validation populations

	CPRD	SWEDEHEART	Nor-COAST	Bialystok PLUS	BACS/BAMI	Est BB	REACH (EU)	REACH (non-EU)
	n = 240,443	**n = 67,428**	**n = 497**	**n = 219**	**n = 964**	**n= 12,986**	**n = 18,100**	**n = 28,407**
Male sex	149,433 (62%)	50,062 (74%)	306 (62%)	167 (76%)	735 (76%)	5350 (41%)	13,046 (72%)	19,028 (67%)
Age (years)	66 ± 9	62 ± 9	68 ± 9.5	65 ± 8	61 ± 12	63 ± 10	65 ± 9	67 ± 9
Current smoker	46,790 (19%)	8,681 (13%)	62 (12%)	41 (19%)	134 (14%)	2070 (16%)	3,307 (18%)	4,020 (14%)
Body mass index (kg/m^2)	28 ± 5	28 ± 5	27 ± 4	30 ± 5	29 ± 4	29 ± 4	28 ± 4	28 ± 6
Systolic blood pressure (mmHg)	139 ± 20	133 ± 20	139 ± 19	134 ± 20	135 ± 21	135 ± 18	141 ± 20	134 ± 19
Diabetes mellitus	38,346 (16%)	17,690 (26%)	97 (20%)	64 (29%)	232 (24%)	2321 (18%)	5,749 (32%)	11,955 (42%)
Coronary artery disease	152,279 (63%)	67,428 (100%)	83 (17%)	219 (100%)	964 (100%)	10,668 (82%)	12,871 (71%)	20,856 (73%)
Peripheral artery disease	31,803 (13%)	1,142 (2%)	38 (8%)	21 (10%)	36 (4%)	1709 (14%)	3,681 (20%)	3,149 (11%)
Cerebrovascular disease	71,853 (30%)	3,614 (5%)	497 (100%)	17 (8%)	27 (3%)	3314 (25%)	5,951 (33%)	9,385 (33%)
Abdominal aortic aneurysm	6,977 (3%)	474 (1%)	22 (4%)	0 (0%)	4 (0%)	109 (0%)	550 (3%)	930 (3%)
Years since first CVD diagnosis	0.5 (0.5-4.7)	0.2 (0.1-0.2)		2.0 (1.0-5.0)	0.6 (0.5-0.9)	4.8 (2.0-9.5)		
Total cholesterol (mmol/L)	4.7 (4.0-5.6)	4.0 (3.4-4.7)	3.9 (3.4-4.4)	4.0 (3.3-4.7)	3.9 (3.4-4.4)	5.5 (4.8-6.4)	5.2 (4.4-6.0)	4.7 (4.0-5.4)
HDL-cholesterol (mmol/L)	1.3 (1.1-1.6)	1.1 (0.9-1.4)	1.4 (1.1-1.7)	1.2 (1.1-1.6)	1.0 (0.9-1.2)	1.3 (1.0-1.7)		
LDL-cholesterol (mmol/L)		2.1 (1.6-2.7)	2.0 (1.6-2.5)	2.2 (1.7-2.7)	2.0 (1.7-2.4)	3.1 (2.4-3.7)		
Triglycerides (mmol/L)		1.2 (1.0.9-1.7)	1.2 (0.9-1.7)	1.2 (0.8-1.7)	2.6 (2.0-3.6)		1.6 (1.1-2.2)	1.5 (1.1-2.2)
Estimated GFR (mL/min/1.73m^2)	67 ± 18	83 ± 19	78 ± 18	88 ± 21	78 ± 18	81 ± 19	73 ± 21	71 ± 23
hsCRP (mg/dL)		5.0 (2.0-9.0)	1.8 (0.8-3.6)	1.1 (0.5-2.5)	1.8 (0.8-3.6)	2.3 (1.1-5.0)		
Statin		65,075 (95%)	434 (87%)	231 (90%)	914 (94.8%)	4181 (32%)	12,483 (69%)	20,156 (71%)
Antiplatelet therapy or anticoagulants	179,129 (75%)	67,049 (99%)	448 (98%)	211 (96%)	902 (94%)		12,646 (70%)	20,831 (73%)
Follow-up (years)	5.3 (2.2-9.6)	4.0 (1.8-6.9)	2.2 (1.8-2.7)	2.9 (2.5-3.5)	4.7 (2.3-6.7)	6.5 (0.7-9.9)	1.9 (1.8-1.9)	1.9 (1.5-1.9)
CVD events	44,985 (19%)	9,270 (13%)	54 (11%)	20 (9%)	130 (13%)	3489 (39%)	2201 (12%)	2658 (9%)
Eventrate per 1000 person-years*	34	31	51	33	30	48	63	50

All data in n (%), mean ± standard deviation, or median (interquartile range; IQR). *Event rate of fatal + non-fatal (MI, stroke) events per 1000 person-years. GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula). CVD = cardiovascular disease, hsCRP = High-sensitivity C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein.

C-statistics ranged from 0.605 (95%CI 0.547-0.664) in BACS/BAMI, to 0.772 (95%CI 0.659-0.886) in REACH Europe high risk region (**Figure 1**). Most heterogeneity in discrimination results was found in data from Western Europe. The prediction interval of the C-statistics was 0.646 (95%CI 0.581-0.710) in Western Europe, 0.682 (95%CI 0.667-0.697) in Eastern Europe and 0.646 (95%CI 0.613-0.679) in the regions outside of Europe (**Supplementary Figure 2**).

Figure 1: Discrimination in the external validation cohorts



Discrimination in all external validation cohorts based on Harrell's C-statistic.

Prior to recalibration, there was a systematic underestimation of ASCVD risk in most external validation cohorts (**Supplementary Figure 3-5**). After recalibration, in CPRD (low risk), SWEDEHEART (moderate risk), REACH high risk region and very high risk region and the Estonian Biobank (high risk), there were no over- or underestimations in the relevant risk categories (**Figure 2-3**). In REACH Europe low and moderate risk regions, Nor-COAST (moderate risk), and BACS/BAMI (low risk), an underestimation of predicted risks was observed. In all regions outside of Europe, no over- or underestimation was observed of the predicted risks (**Figure 4**). All model parameters used for individual risk prediction or recalibration are shown in **Supplementary Table 1**.

Figure 2: Calibration in external validation cohorts from Western Europe

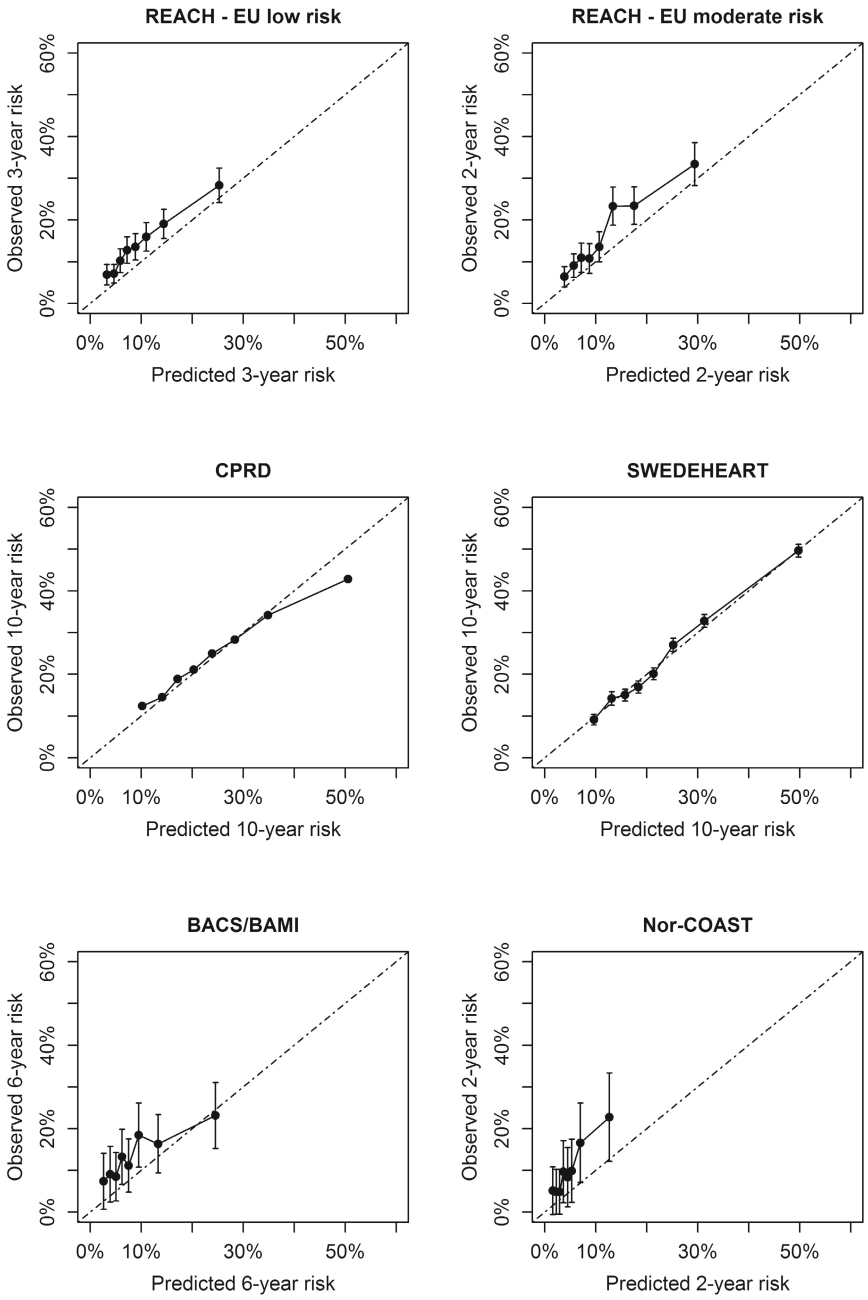


Figure 3: Calibration in external validation cohorts from Eastern Europe

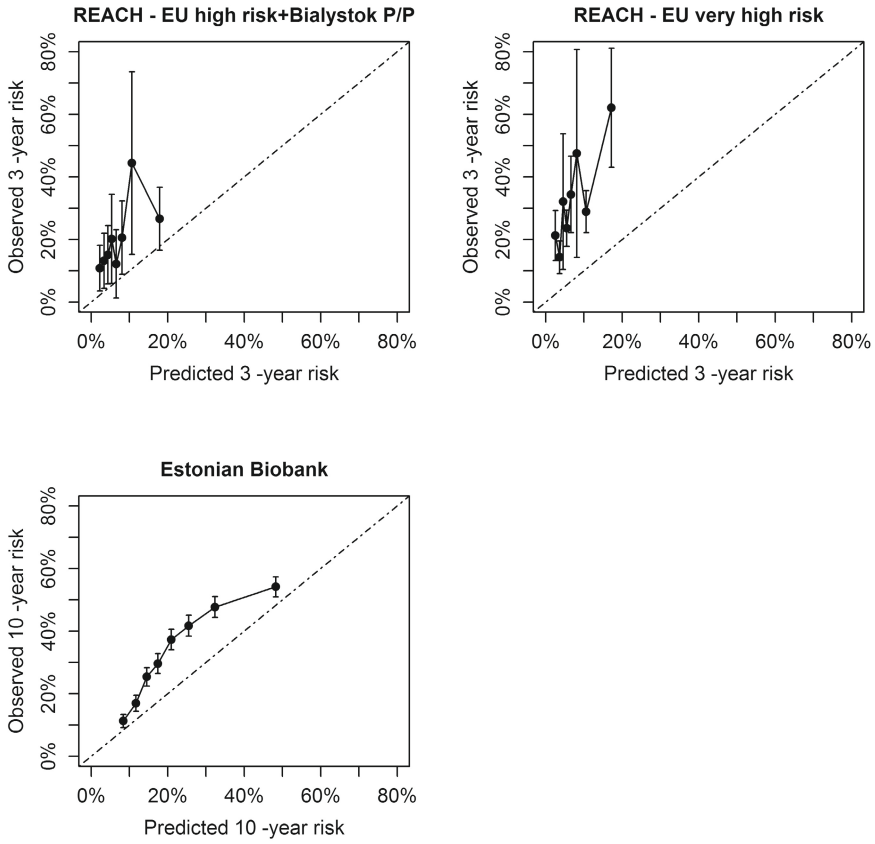
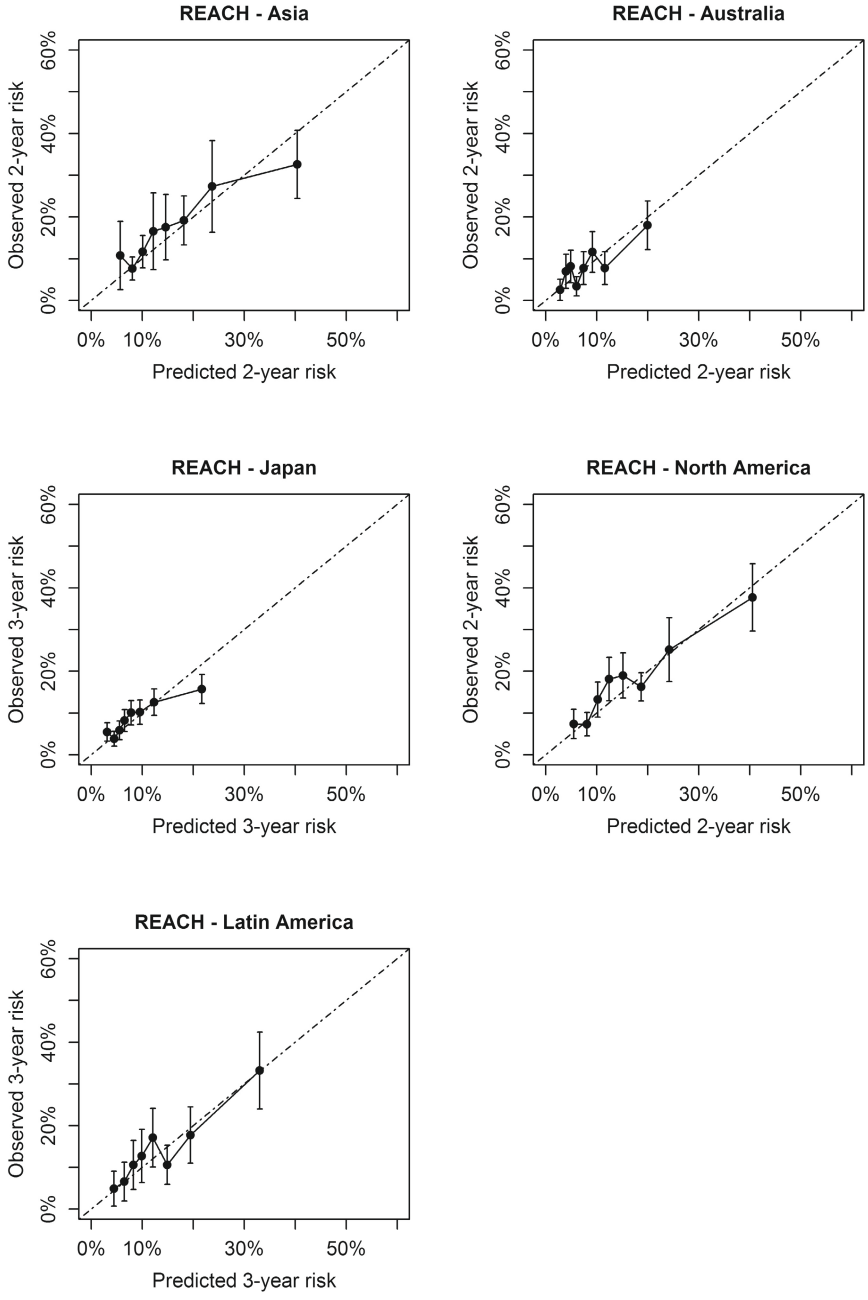


Figure 4: Calibration in Non-European external validation cohorts



Clinical utility

Results from the decision curve analyses are shown in **Supplementary Figure 3**. Clinical utility of treatment intensification based on SMART2 was superior in all three evaluated cohorts to the other evaluated strategies for scenarios where the intervention was indicated for individuals whose risk of recurrence was 20% or greater – up until scenarios where the intervention was indicated for individuals whose risk of recurrence was 50% or greater. Scenarios evaluating treatment thresholds of <15% 10-year ASCVD risk, relevant for interventions with very low costs and almost no harm, showed similar clinical utility of treating all individuals and personalized treatment based on SMART2. For the thresholds above 50%, mostly relevant for interventions with severe disadvantages, clinical utility of SMART2 was similar to performing no additional treatment intensification in CPRD and SWEDEHEART, but inferior to no additional treatment intensification in the Estonian Biobank. The expected proportion of individuals which would be treated using a 20% or 40% treatment threshold in every European risk region is shown in **Supplementary Figure 4**.

Sensitivity analyses

Sensitivity analyses of REACH data from Western Europe (n=12,882) demonstrated that sex-specific and location-specific model derivations and recalibrations did not improve discriminative model performance (**Supplementary Table 3**).

Discussion

The current report describes the development, recalibration, and external validation of the SMART2 risk score for the prediction of recurrent ASCVD in patients with established ASCVD. The model was recalibrated to 4 risk regions within Europe and for regions outside Europe, and external validation was performed in all these regions. The clinical utility of the SMART2 model was demonstrated across a range of clinically relevant treatment thresholds in several of these regions.

The SMART2 risk score includes features that confer advantages compared with the original SMART risk score and other existing tools, such as the SMART-REACH model or the recently published EUROASPIRE risk calculator.[14,35] First, the SMART2 risk score is underpinned by large, and extensive datasets from multiple countries, used for model derivation, recalibration, and validation. Models were derived and externally validated using cohorts and registries with long-term follow-up, during which large numbers of hard vascular endpoints were observed – in total 64,513 CVD events in 377,399 individuals with established ASCVD. The cohorts represent different clinical manifestations of ASCVD, including diseases of the coronary, cerebral and peripheral circulation. This provides greater generalizability of the derived model and validation results and therefore more likely reflects unmet clinical needs particularly in the generalist settings. As both the model derivation and validation populations

of the current study included individuals with polyvascular disease (i.e. those with established ASCVD at multiple locations), the SMART2 risk score can be applied to this high risk population as well.

Moreover, an important strength of the SMART2 risk score is the use of easy-to-measure variables, which are for the most part routinely measured as part of routine clinical practice. This makes it more likely that SMART2 risk tool is clinically applicable to busy, routine practice. Where variables have not been collected in clinical practice, like hsCRP for example, automated imputation of these individual risk factor values is possible by the using mean values of the derivation dataset. This allows estimates of risk to be generated with acceptable prediction metrics,[15,36] a user-friendly function which is already incorporated in online calculators like the ESC CVD risk prediction app or http://U-prevent.com, and the U-Prevent smartphone app. Although the concept of estimating 10 year risk in secondary prevention, with which to guide treatment intensification is relatively new as a concept and has not been formally tested in clinical outcome trials, the increasingly expensive therapeutic armamentarium that is available to treat secondary prevention patients, and the finite resources with which to treat them, makes the use of such risk estimation tools to personalize treatment decisions more attractive. Furthermore, clinicians already use a similar approach in primary prevention with 10 year estimates of CVD risk in order to guide first line therapies. Therefore, using the same approach in secondary prevention and variables that clinicians already measure makes utilization more likely.

Third, possibly the most important update of the SMART2 risk score is that the risk model is geographically recalibrated to multiple different risk regions, both within and outside of Europe. This provides further assurance that the risk model is reliable in local clinical practice settings across multiple geographical locations. On average, the original SMART model performed adequately in contemporary Western European populations, and a systematic underestimation of predicted risk was seen in Eastern European countries,[15,35] similar to what has been observed in primary prevention settings with SCORE. In the current SMART2 update however, the model was recalibrated to 4 European risk regions and to North America, Latin America, Asia (excluding Japan), Japan, and Australia. Results from the current study show External validation in terms of discrimination and calibration was shown in all these regions. In all regions which had a cohort available with a least 10 years of follow-up (Europe's low, moderate and high risk region), clinical utility of the SMART2 risk score was demonstrated across a range of clinically relevant treatment thresholds, indicating the usefulness in clinical practice.

Fourth, the SMART2 risk score accounts for the impact of competing risks – which confers an important advantage in comparison to the original SMART score or the EUROASPIRE risk calculator. As the intended age-range of the SMART2 risk score

reaches 80 years, not accounting for competing risks could greatly overestimate predicted risks and treatment effects, especially in older individuals.[16] Treatment initiation based on overestimated risks may lead to overly optimistic estimates of the individual effect of preventive treatment options.[37] Importantly, competing risk adjusted risk estimates better reflect the way that risk is generally interpreted in clinical practice: the probability of having an ASCVD event in the next 10 years. In contrast, unadjusted risk prediction (ie those originating from Cox proportional hazard models) should be explained as the probability of having an ASCVD event in the hypothetical situation of immortality to other causes of death during the next 10 years.[37,38]

The SMART2 risk algorithm could help resolve clinical uncertainties, and potentially improve clinical practice and treatment inertia by better quantifying risk, thus identifying those patients who may benefit most from additional preventive strategies. Traditionally, all patients with established ASCVD are classified as very high risk, and the same preventive measures are advised for all of them.[2] However, even after treating risk factor levels to evidence based secondary prevention targets, significant residual risk may remain and there is large individual variation of residual risk in this population.[8] The SMART2 risk score may help to identify those at the highest residual risk who are likely to benefit most from treatment intensification. Further intensification of preventive interventions has the advantage of lowering ASCVD risk, but may have disadvantages like polypharmacy, increased costs, and potential harms, like bleeding risks in the case of antithrombotic therapies. By combining 10-year risk predictions with intensified treatment effects from lipid lowering, blood pressure, or anticoagulant therapy, treatment effects can be estimated.[3,39] These treatment effects can be used, together with treatment harms and preferences of both patient and health care provider, to inform the shared decision-making process. Current guidelines suggest to consider intensifying preventive treatment based on residual 10-year risk, although no specific treatment thresholds are recommended.[7,2,7,11] If future guidelines were to include treatment thresholds to guide residual risk reduction, a contemporary well-calibrated model that is generalisable is required. The SMART2 tool provides such a solution.

The potential limitations of our study merit consideration. First, the SMART2 risk model was derived using data from only a low risk country. Ideally, the derivation of the risk model would have involved representative prospective cohort data from all target regions, including high risk regions like Eastern Europe, but this was practically not possible as the different datasets were at different geographical locations and could not be combined into one dataset. However, the effects of predictors on the risk of ASCVD events seemed to be stable across geographical regions,[40,41] and Eastern European discrimination results were comparable to low risk regions, indicating that the relative effects of the risk predictors were transferable to other risk regions. As

the baseline risk of ASCVD events is different across geographical regions, large contemporary datasets from all target regions were used to recalibrate the model intercept to these regions. There may still be a certain extent of variation in CVD incidence within the risk regions used for recalibration. Further recalibration of the SMART2 risk score to more subregions could be a topic for future research. In addition, the data sources that were used for recalibration to every risk region reflect current incidence rates and treatment patterns. Changing cardiovascular incidence rates may warrant updates in the future

Moreover, the model could not be validated on the intended 10-year prediction horizon in all risk regions as this data was only available in Europe's low, moderate and high risk regions. In the other risk regions, a shorter prediction horizon was used to validate the SMART2 risk score. Therefore, the SMART2 risk score may benefit from further long-term validation in these regions. Reassuringly, however, the relative effect of common risk factors on the risk of CVD events is generally stable over time[40] and the validation results in the cohorts with available 10-year follow-up were adequate. In addition, the cohorts in which 10-year validations were viable were very large in comparison to those validated at short prediction horizons.

Another potential limitation is the use of cohort data in several stages of the analysis. Cohorts often have a healthy participant bias and even within risk regions there is always some inter-cohort variation in risk factor levels and disease incidence. These differences in incidence rates are not explainable by risk factor levels alone nor do they necessarily reflect biological differences in disease risk. Often, these differences can be explained by differences in patient selection, arising from varying inclusion criteria or methods or by participation rates. In the low risk region for example, the UCC-SMART cohort represents an outpatient clinic patient population of individuals with stable established ASCVD. ASCVD incidence in UCC-SMART is lower than in Nor-COAST and BACS/BAMI, which are from the same risk region but rather included patients consecutively after recently experiencing stroke or coronary events, leading to higher risk populations. These differences likely explain the underestimation of predicted risk in those cohorts as found in the current study. The SMART2 risk score is intended to inform shared decision-making in patients with established ASCVD, which is often performed in outpatient clinics. Therefore, the model was recalibrated to all risk regions with cohort data resembling outpatient clinic populations where possible.

In conclusion, the derivation, recalibration, and external validation of the SMART2 risk score were shown for the prediction of recurrent ASCVD among patients with established ASCVD. The model was improved by the use of large and contemporary data, recalibration across various regions and adjustment for competing risks. Use of this tool could allow for a more personalized approach to secondary prevention based upon quantitative rather than qualitative estimates of residual risk.

References

1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7
2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106
3. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FLJ. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J. 2014;35(13):837-843. doi:10.1093/eurheartj/ehu004
4. Dorresteijn JAN, Visseren FLJ, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ. 2011;343(oct03 1):d5888-d5888. doi:10.1136/bmj.d5888
5. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-3104. doi:10.1093/eurheartj/ehy339
6. Goff DCJ, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25):S49-73. doi:10.1161/01.cir.0000437741.48606.98
7. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
8. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016;134(19):1419-1429. doi:10.1161/CIRCULATIONAHA.116.021314
9. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377(14):1319-1330. doi:10.1056/NEJMoa1709118
10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664
11. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
12. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013;99(12):866-872. doi:10.1136/heartjnl-2013-303640
13. Simons PCG, Algra A, Van De Laak MF, Grobbee DE, Van Der Graaf Y. Second manifestations of ARTerial disease (SMART) study: Rationale and design. Eur J Epidemiol. 1999;15(9):773-781. doi:10.1023/A:1007621514757
14. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. J Am Heart Assoc. 2018;7(16). doi:10.1161/JAHA.118.009217
15. McKay AJ, Gunn LH, Ference BA, et al. Is the SMART risk prediction model ready for real-world implementation? A validation study in a routine care setting of approximately 380 000 individuals. Eur J Prev Cardiol. Published online June 23, 2021:1-10. doi:10.1093/eurjpc/zwab093

16. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic Models With Competing Risks. Epidemiology. 2009;20(4):555-561. doi:10.1097/EDE.0b013e3181a39056

17. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-836. doi:10.1093/ije/dyv098

18. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA - J Am Med Assoc. 2010;304(12):1350-1357. doi:10.1001/jama.2010.1322

19. Steg G, Bhatt DL, Wilson PWF, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. J Am Med Assoc. 2007;297(11):1197-1206. doi:10.1001/jama.297.11.1197

20. Bhatt DL, Gabriel Steg P, Magnus Ohman E, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. J Am Med Assoc. 2006;295(2):180-189. doi:10.1001/jama.295.2.180

21. Paniczko M, Chlabicz M, Jamiołkowski J, et al. Impact of Pulse Wave Velocity and Parameters Reflecting Android Type Fat Distribution on Left Ventricular Diastolic Dysfunction in Patients with Chronic Coronary Syndromes. J Clin Med. 2020;9(12):3924. doi:10.3390/jcm9123924

22. Leitsalu L, Haller T, Esko T, et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. Int J Epidemiol. 2015;44(4):1137-1147. doi:10.1093/ije/dyt268

23. Carda R, Aceña Á, Pello A, et al. The Prognostic Value of High-Sensitive Troponin I in Stable Coronary Artery Disease Depends on Age and Other Clinical Variables. Cardiology. 2015;132(1):1-8. doi:10.1159/000381259

24. Thingstad P, Askim T, Beyer MK, et al. The Norwegian Cognitive impairment after stroke study (Nor-COAST): study protocol of a multicentre, prospective cohort study. BMC Neurol. 2018;18(1):193. doi:10.1186/s12883-018-1198-x

25. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Heart. 2010;96(20):1617-1621. doi:10.1136/hrt.2010.198804

26. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144

27. Candido dos Reis FJ, Wishart GC, Dicks EM, et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. Breast Cancer Res. 2017;19(1):1-13. doi:10.1186/s13058-017-0852-3

28. Xu Z, Arnold M, Stevens D, et al. Prediction of Cardiovascular Disease Risk Accounting for Future Initiation of Statin Treatment. Am J Epidemiol. Published online February 17, 2021. doi:10.1093/aje/kwab031

29. Collins R, Peto R, Hennekens C, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849-1860. doi:10.1016/S0140-6736(09)60503-1

30. Simes J, Voysey M, O'Connell R, et al. A Novel Method to Adjust Efficacy Estimates for Uptake of Other Active Treatments in Long-Term Clinical Trials. Djulbegovic B, ed. PLoS One. 2010;5(1):e8580. doi:10.1371/journal.pone.0008580

31. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-2454. doi:10.1093/eurheartj/ehab309

32. de Vries TI, Cooney MT, Selmer RM, et al. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455-2467. doi:10.1093/eurheartj/ehab312

33. Decision Curve Analysis. www.decisioncurveanalysis.org

34. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. Diagnostic Progn Res. 2019;3(1):18. doi:10.1186/s41512-019-0064-7

35. De Bacquer D, Ueda P, Reiner Ž, et al. Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE Risk Model. Eur J Prev Cardiol. 2020;32(0). doi:10.1093/eurjpc/zwaa128

36. Berkelmans GFN, Read SH, Gudbjörnsaottir S, et al. Dealing with Missing Patient Characteristics When Using Cardiovascular Prediction Models in Clinical Practice.; 2018.

37. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? Stat Med. 2012;31(11-12):1089-1097. doi:10.1002/sim.4384

38. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28(11):2670-2677. doi:10.1093/ndt/gft355

39. Sundström J, Arima H, Woodward M, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384(9943):591-598. doi:10.1016/S0140-6736(14)61212-5

40. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Heal. 2019;7(10):e1332-e1345. doi:10.1016/S2214-109X(19)30318-3

41. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinol. 2015;3(5):339-355. doi:10.1016/S2213-8587(15)00081-9

Supplementary Materials

Supplementary Methods

External validation cohorts

In the international, prospective REACH Registry, participants were enrolled between 2003 and 2004 from physician outpatient practices in several regions, including Western and Eastern Europe. Participants were followed for a maximum of 4 years for the occurrence of CVD events and mortality. The REACH Registry was used before to assess geographical differences in the risk of recurrent cardiovascular disease.[1] For European regions, the countries were reclassified to the risk regions as used for the SCORE2 project based on standardized CVD mortality rates. Asian and Middle Eastern REACH regions were merged as the number of included Middle Eastern individuals was low and the rates for Asia and the Middle East were very comparable.

Bialystok PLUS/Polaspire included patients in 2016–2018 who were previously hospitalized for acute coronary event or elective percutaneous revascularisation procedure and were followed for a median time of 3 years. Patients were included in the study 12-18 months after the coronary event. Follow-up was performed through return visits at 1 and 3 years after baseline or by linkage to national mortality registers.

The Estonian Biobank is a population-based study from the Estonian Genome Center at the University of Tartu. From this Biobank, all patients were included with established ASCVD prior to inclusion. All biobank participants have signed a broad informed consent form and the study was carried out under ethical approval 1.1-12/624 from the Estonian Committee on Bioethics and Human Research (Estonian Ministry of Social Affairs) and data release N05 from the EstBB. Data analyzes in Estonian dataset were carried out in part in the High-Performance Computing Center of University of Tartu.

In BACS/BAMI, patients were included when admitted at four hospitals in the area of Madrid with either non-ST elevation acute coronary syndrome or ST elevation myocardial infarction between 2006 and 2010. Follow-up for the current study started at this first follow-up visit, 6-12 months after inclusion events.

SWEDEHEART is a large Swedish nationwide myocardial infarction quality registry including all patients treated at coronary care units in Sweden, as well as data on all patients undergoing coronary revascularization (angiography/angioplasty and coronary bypass grafting). Follow-up information was obtained by linkage to national registries. For the current study, all individuals with myocardial were included who had their follow-up visit between 31/01/2005 and 31/12/2016. Risk factor measurements

were used from the follow-up visit 6-10 weeks after this event – follow-up started at this point.

Nor-COAST is a multicentre (5 centres, all in Norway), prospective, cohort study, consecutively including patients with acute stroke between 2015 and 2017. Patients have follow-up visits at 3 and 18 months, and at 3 years. Patients with ischemic stroke were included from 3 months post-stroke – at which point follow-up started for the current study. Follow-up information was obtained by linkage to national registries for cardiovascular disease and mortality.

The Clinical Practice Research Datalink (CPRD) GOLD database is a UK repository containing longitudinal individual primary care patient data collected from 1987 onwards. Over time, 966 primary care centres have contributed data for >20 million patients, with 407 practices actively contributing data for >3 million patients currently. The age, sex and ethnicity distributions of the patient sample broadly reflect those of the general UK population, and linked Hospital Episode Statistics hospital admissions data from English hospitals and Office for National Statistics mortality data, are available. The primary care data are collected during routine general practice activities. The bulk of UK cardiovascular disease prevention work is undertaken in primary care, and (as for other common medical conditions) general practitioners are incentivised to use standard coding procedures to record this activity. The database has previously been used in both derivation and validation of cardiovascular risk prediction tools. For the current study, individuals were eligible to enter the cohort from January 1st 2000 onwards, once they had been registered with the relevant general practice for at least one year (to allow routine reporting to be established), were aged >40 (and <80) years, and were at least six months post their first record of an ASCVD diagnosis.

Recalibration regions

European regions were grouped on the most recently available (assessed July 2020) age- and sex-standardized overall cardiovascular mortality rates per 100,000 (ICD chapters 9, I00-I99, Supplementary Figure 1)[2] as follows: low risk (≤100 CVD deaths per 100,000), moderate risk (>100-150 CVD deaths per 100,000), high risk (>150-300 CVD deaths per 100,000), and very high risk (>300 CVD deaths per 100,000). These rates were obtained from the WHO CVD mortality database[2] to which they were provided by all individual countries.

Missing data

Because complete case analysis may lead to loss of statistical power and possible bias,[3] values of the following variables in the derivation data were imputed by single regression imputation using predictive mean matching: smoking status (n=32, 0.4%),

creatinine (n=31, 0.3%), hsCRP (n=250, 3.2%), SBP (n=18, 0.2%), HDL-c (n=80, 1.0%), and total cholesterol (n=34, 0.4%).

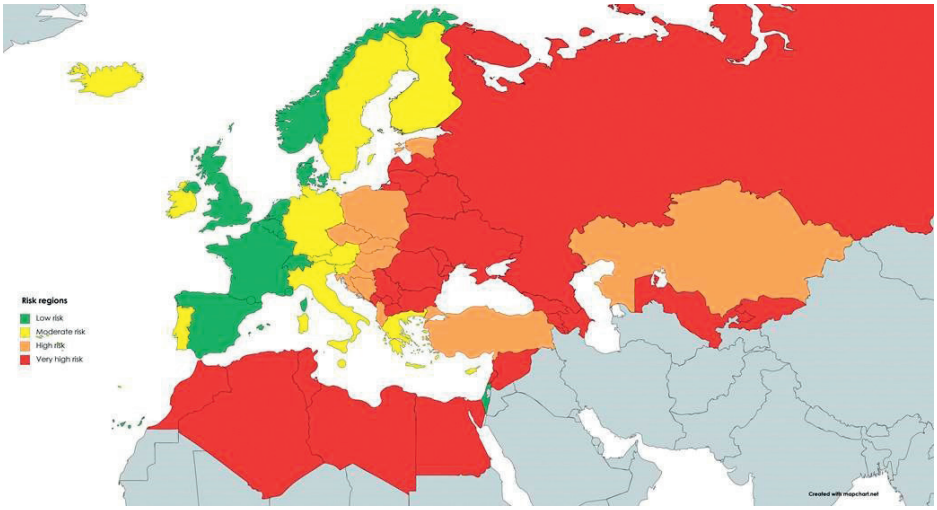
Different approaches were used for sporadically and systematically missing data. Ideally, systematically missing variables were handled using multilevel multiple imputation with fully conditional specification via the mitml-impute package in R (5 imputed datasets). However, as this required the data being transferred to be combined with the other datasets, this was only possible for the REACH Registry (HDL-c, hsCRP, years since first CVD diagnosis). For systematically missing data in other cohorts (Nor-COAST: AAA) the mean of this variable in the derivation data was used, or with systematically missing aspirin treatment data (Estonian Biobank, CPRD) it was assumed all individuals used aspirin or equivalent treatment. Whereas this approach may lead to biased results in studies assessing variable associations, the effect on goodness-of-fit is limited (assuming roughly similar prevalence of systematic missing risk factors in derivation and validation data), and the approach should lead to a conservative estimate of the C-statistic (as not all model parameters are available for risk stratification, discrimination decreases). In cohorts with only sporadically missing data, these were imputed as in the derivation process using single imputation based on predictive mean matching (R-package aregImpute).

Sensitivity analyses

Sensitivity analyses were performed to evaluate several aspects in model derivation. First, to evaluate the potential benefit of separate model derivation for men and women, the whole model derivation process was repeated separately for both sexes. The model was then recalibrated separately for both sexes in the REACH Registry Western Europe (all countries in the low or moderate risk region) similar to the recalibration methodology used for the main model. Model performance was assessed in terms of discrimination, both separately for both sexes and using the complete population.

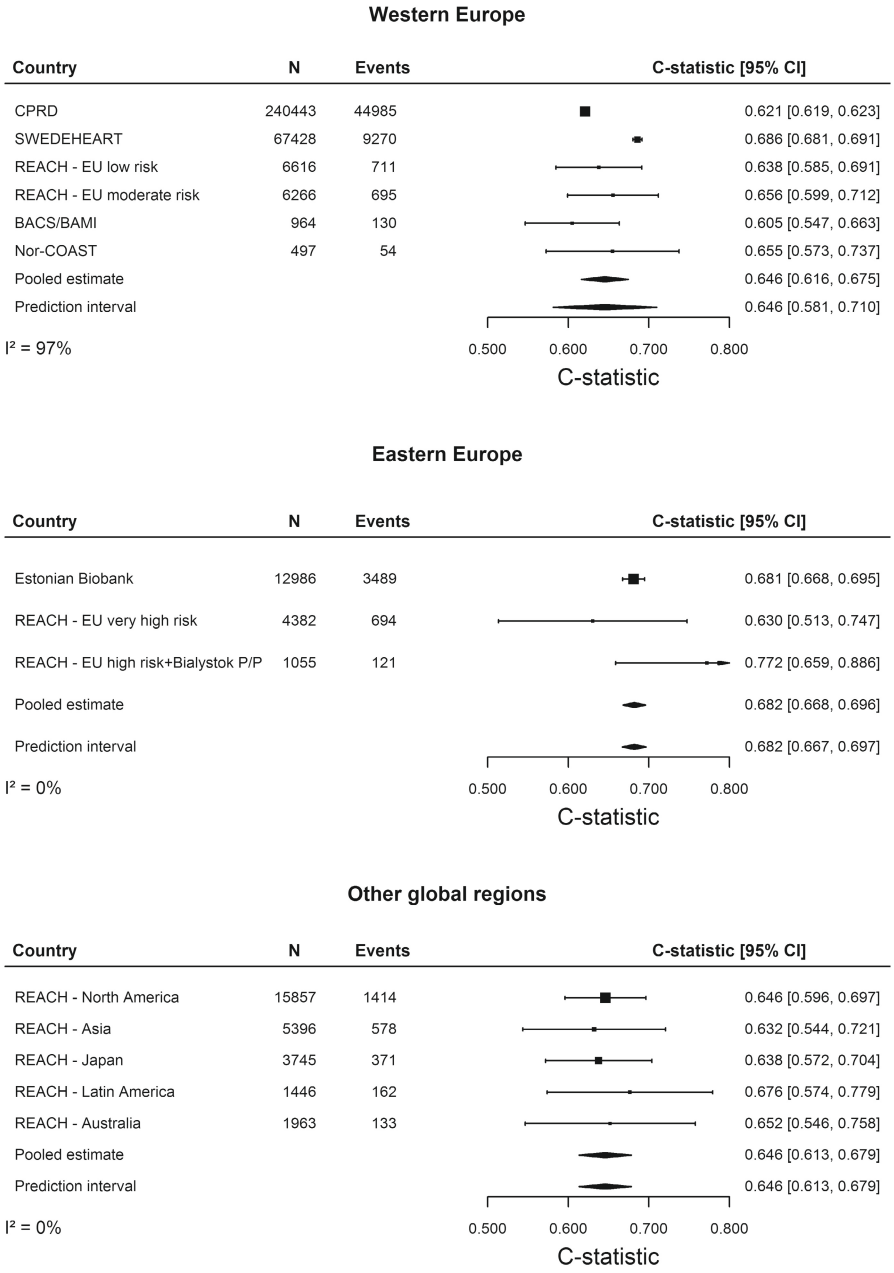
The second sensitivity analyses were similar to the first, but this time derivation and recalibration was performed separate for the different locations of established ASCVD (CAD, CevD, and PAD/AAA separately). Individuals with polyvascular disease contributed to the derivation or recalibration of multiple models (i.e. a subject with both CAD and PAD in UCC-SMART contributed to both the derivation of the CAD-specific and the PAD/AAA-specific model). Individual risk predictions for those with polyvascular disease were calculated by taking the mean of the disease-specific predicted risks (so this individual with CAD and PAD would have two predicted risks: one from the CAD model and one from the PAD/AAA model, the final individual predicted risk is the mean of those two). Model performance was assessed in terms of discrimination, both separately for ASCVD locations and in the complete population.

Supplementary Figure 1: European risk regions – similar to SCORE2 risk regions

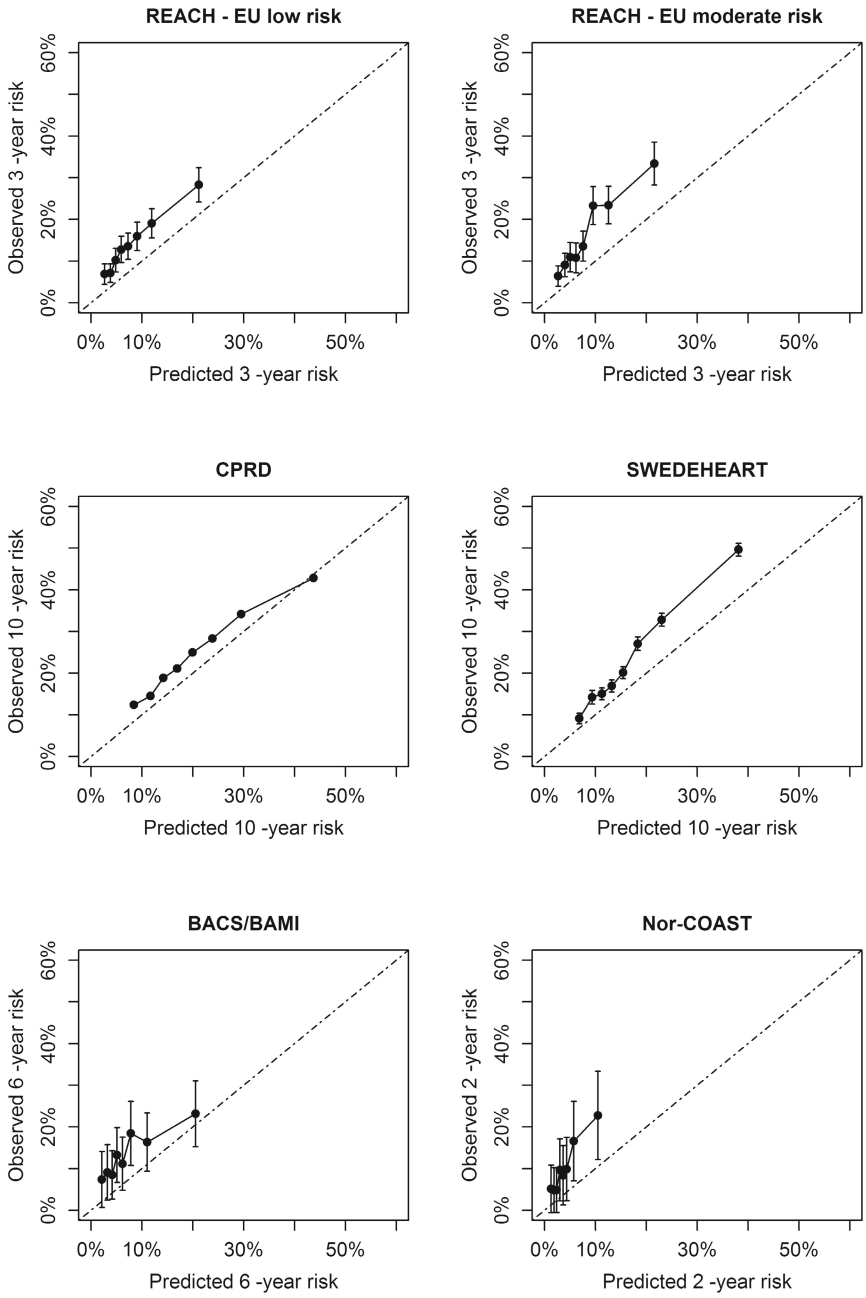


Risk regions based on most recently available age- and sex-standardized overall cardiovascular disease (CVD) mortality rates per 100,000: low risk (≤100 CVD deaths per 100,000), moderate risk (100 to <150 CVD deaths per 100,000), high risk (150 to <300 CVD deaths per 100,000), and very high risk (≥300 CVD deaths per 100,000). Estimates are obtained from the WHO cause specific mortality database (2020).[2]

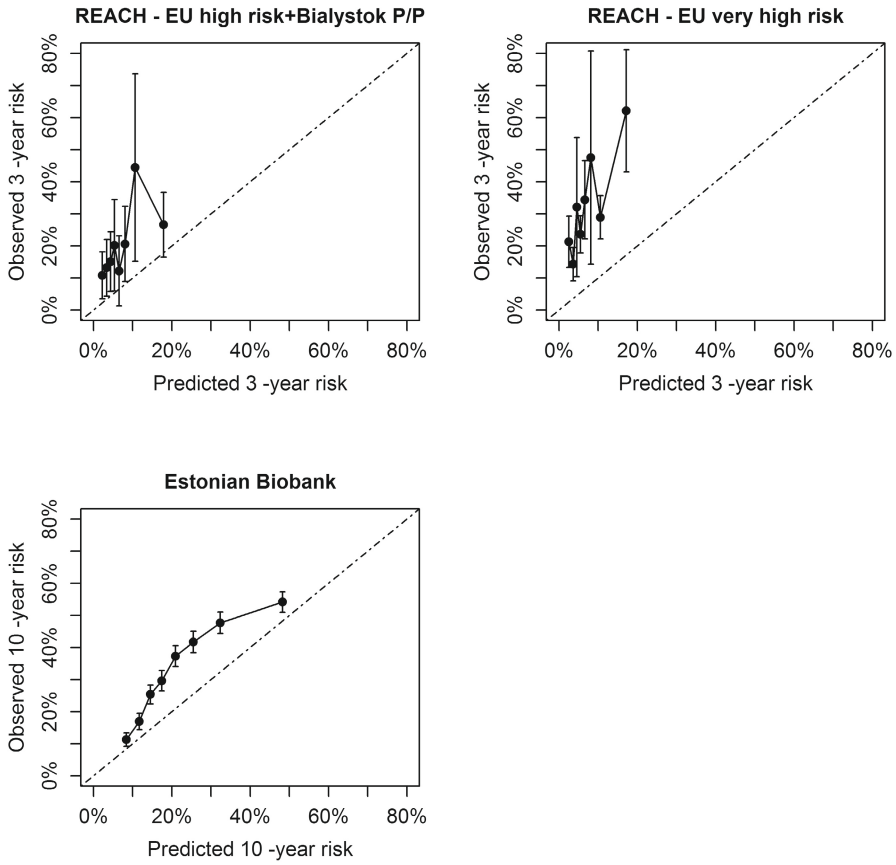
Supplementary Figure 2: Pooled discrimination results per region



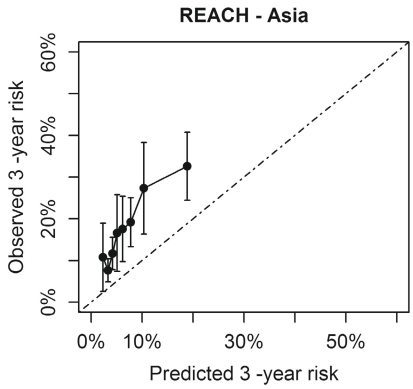
Supplementary Figure 3: Calibration of the SMART2 risk score before recalibration in Western Europe

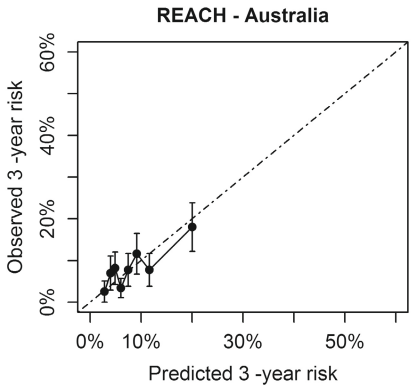


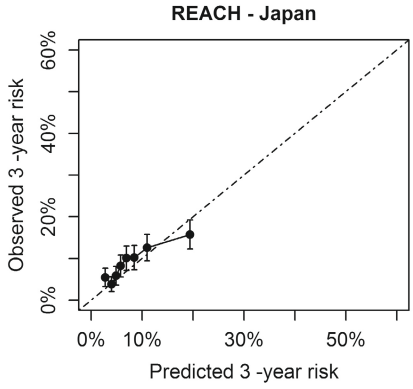
Supplementary Figure 4: Calibration of the SMART2 risk score before recalibration in Eastern Europe

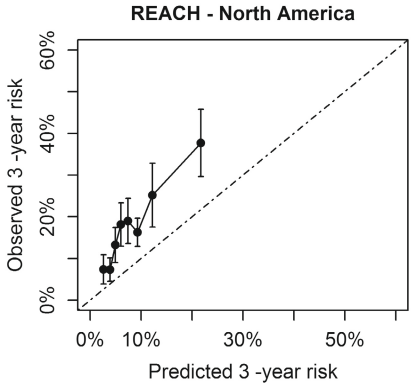


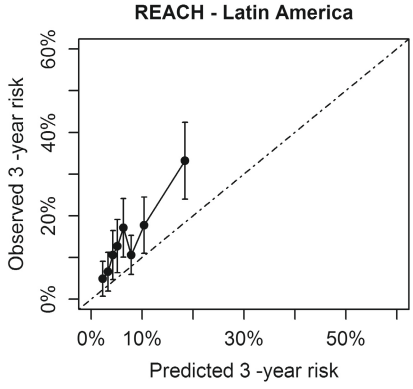
Supplementary Figure 5: Calibration of the SMART2 risk score before recalibration in the Non-European external validation cohorts



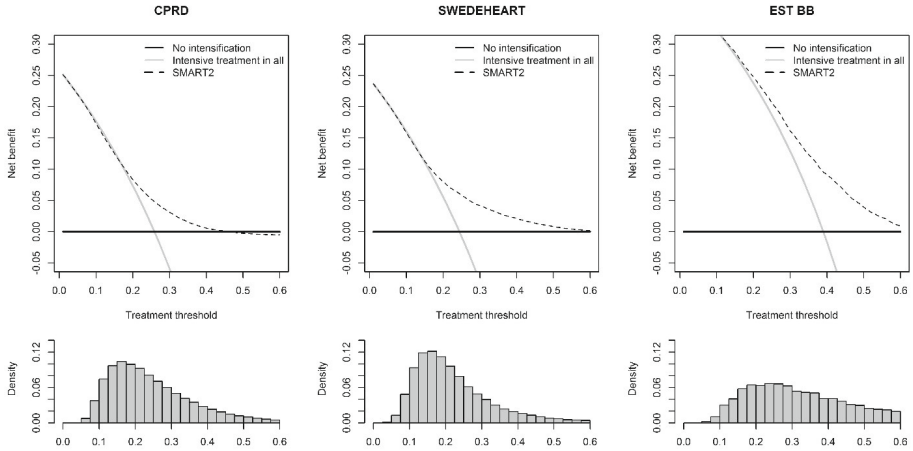






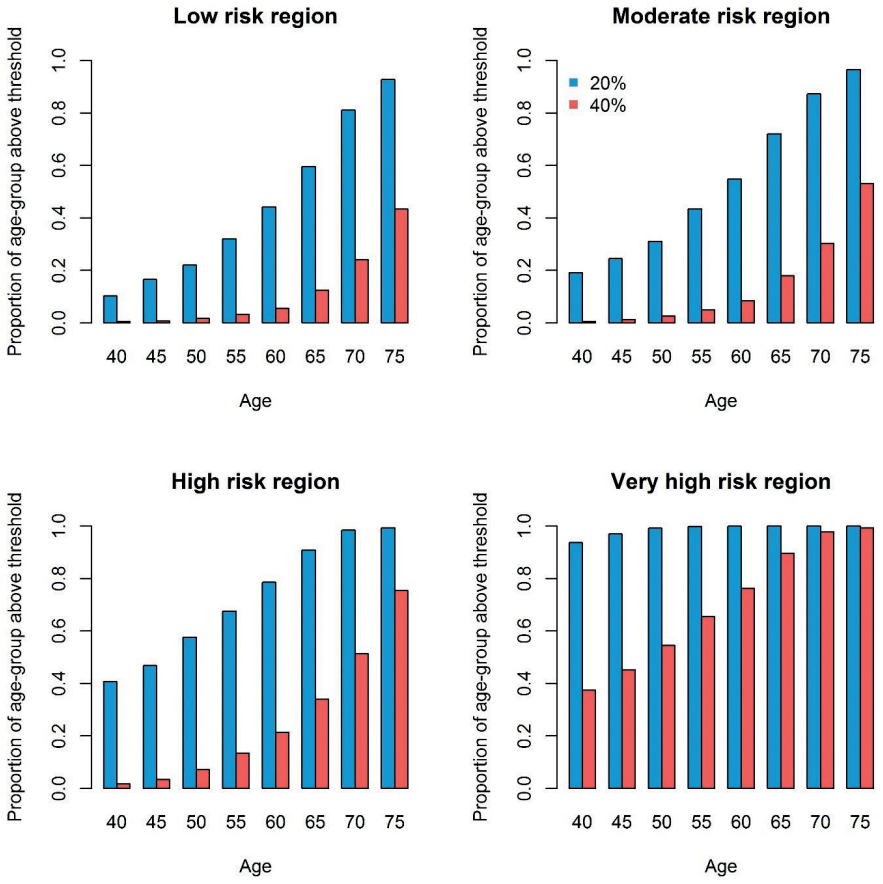


Supplementary Figure 6: Net benefit of treatment intensification based on the SMART2 algorithm



Results from the decision curve analyses in all cohorts with at least 10 years maximum follow-up. Each panel displays the net benefit of treatment intensification based on the SMART2 model (dashed line) against the treat all (gray line) and treat none (black line) approaches.

Supplementary Figure 7: Illustration of the SMART2 risk score recalibrated to the different European regions



Expected proportion of individuals above the 20 and 40% 10 year risk thresholds in every risk region in Europe. Results were based on a simulation in UCC-SMART (n=8,355) assuming equal risk factor distributions across regions.

Supplementary Table 1: Endpoint definitions

Fatal cardiovascular disease	
Endpoints included	ICD10-codes
Hypertensive disease	I10-16
Ischemic heart disease	I20-25
Arrhythmias, heart failure	I46-52
Cerebrovascular disease	I60-69
Atherosclerosis/AAA	I70-73
Sudden death and death within 24h of symptom onset	R96.0-96.1
Excluding the following	
Myocarditis, unspecified	I51.4
Subarachnoid haemorrhage	I60
Subdural haemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I68.2
Moyamoya	I67.5
Non-fatal events	
Non-fatal myocardial infarction	I21-I23
Non-fatal stroke	I60-69
Excluding the following	
Subarachnoid hemorrhage	I60
Subdural hemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I68.2
Moyamoya	I67.5

Endpoint definitions depend on cohort availability but where ideally defined as stated above

Supplementary Table 2: Model parameters and prediction algorithm

Coeficients		Yearly baseline risks		Expected-observed ratio	
Predictor	**Beta**	**Year of follow-up**	**Baseline risk**	**Risk region**	**Ratio**
Abdominal aortic aneurysm	0.330356631	1	0.020867965	Europe, low risk	0.81590
Age, years	-0.03496022	2	0.03481669	Europe, moderate risk	0.6973285
Age squared, years	0.000551072	3	0.047574783	Europe, high risk	0.5085825
Aspirin or equivalent	-0.21072103	4	0.06257936	Europe, very high risk	0.2285371
Coronary artery disease	0.294701954	5	0.07887031	Asia	0.4043255
eGFR (CKDEPI)	-0.03967521	6	0.094891922	Australia	1.0040808
eGFR squared (CKDEPI)	0.000218613	7	0.112217969	Japan	0.8825678
hsCRP (log)	0.151760173	8	0.129898521	North America	0.4714961
Current smoking	0.345583271	9	0.149001544	Latin America	0.5075670
Cerebrovascular disease	0.34831786	10	0.165822797		
Diabetes Mellitus	0.318170659				
Non HDL-c (log)	0.540364249			**Mean linear predictor**	-0.0463729
Peripherial artery disease	0.22446658				
Systolic blood pressure	0.018913154			**Formula to calculate individual risks**	
Male sex	0.287658743			$LP_i = \sum Coef * individual\ risk\ factors$	
Years since first ASCVD diagnosis	0.047699585			$CVDrisk_{10} = 1 - (1 - baserisk_{10})^{exp(LP_i - LP_{mean} - \log(ratio_{region}))}$	
Years since first ASCVD diagnosis, squared	-0.00164973				

All model parameters required for individual predictions. For prediction on horizons shorter than 10 years, the yearly baseline risks of the respective years can be used in the formula. ASCVD = Atherosclerotic cardiovascular disease. hsCRP = High-sensitivity C-reactive protein, HDL = high density lipoprotein, eGFR = Estimated glomular filtration rate, LP = linear predictor, $_i$ = individual.

Supplementary Table 3: Summary of recalibration procedure

Step 1: calculate crude SMART2 risk
First, the non-recalibrated SMART2 10 year risk is predicted for all individuals in the data source. The mean of all these individual predicted risks is the 'expected' incidence.

$$CVDrisk_{10} = 1 - (1 - baserisk_{10})^{\exp(LP_i - LP_{mean})}$$

Step 2: calculate cumulative incidence
In the data source, the cumulative incidence at 10 years is obtained, taking into account competing risks (R function *cuminc, cmprsk package*). This is the 'observed' incidence in the cohort.

Step 3: Expected-observed ratio
Above metrics are combined in the expected-observed ratio.

$$EOratio_{region} = \frac{mean(CVDrisk_{10})}{Cum.inc_{10}}$$

For the high risk region, there was no cohort as large and minimally selected as CPRD (low risk region) or SWEDEHEART (moderate risk region). Therefore, the expected-observed ratios from the individual cohorts were averaged to get a regional recalibration factor.

Step 4: Calculate recalibrated SMART2 risks
Individual recalibrated risks can be calculated by using the natural logarithm of the expected observed ratio.

$$CVDrisk_{10} = 1 - (1 - baserisk_{10})^{\exp(LP_i - LP_{mean} - \ln(EOratio_{region}))}$$

Supplementary Table 4: Discriminative model performance with sex-specific or established ASCVD location-specific model derivation

REACH Western Europe (n=12,882)	**C-statistic (95%CI)**	
	Overall derivation	Sex-specific derivation
Total population	0.644 (0.629-0.659)	0.642 (0.627-0.658)
Men only	0.646 (0.629-0.662)	0.645 (0.629-0.662)
Women only	0.643 (0.623-0.662)	0.639 (0.620-0.658)
	Overall derivation	Location-specific derivation
Total population	0.644 (0.629-0.659)	0.645 (0.630-0.660)
CAD patients only	0.663 (0.645-0.681)	0.661 (0.643-0.679)
CeVD patients only	0.650 (0.609-0.690)	0.650 (0.609-0.690)
PAD/AAA patients only	0.635 (0.606-0.664)	0.634 (0.604-0.663)

External model performance in terms of discrimination when repeating model derivation and validation separately for both sexes (top) and locations of established ASCVD (bottom) in comparison to using the whole dataset. CAD = coronary artery disease, CeVD = cerebrovascular disease, PAD = peripheral artery disease, AAA = abdominal aortic aneurysm.

CHAPTER 9

Residual cardiovascular risk reduction guided by lifetime benefit estimation in patients with symptomatic atherosclerotic disease: effectiveness and cost-effectiveness

Steven HJ Hageman, Jannick AN Dorresteijn, Michiel L Bots, Folkert W Asselbergs, Jan Westerink, Miriam P van der Meulen, Arend Mosterd, Frank LJ Visseren

on behalf of the UCC-SMART studygroup

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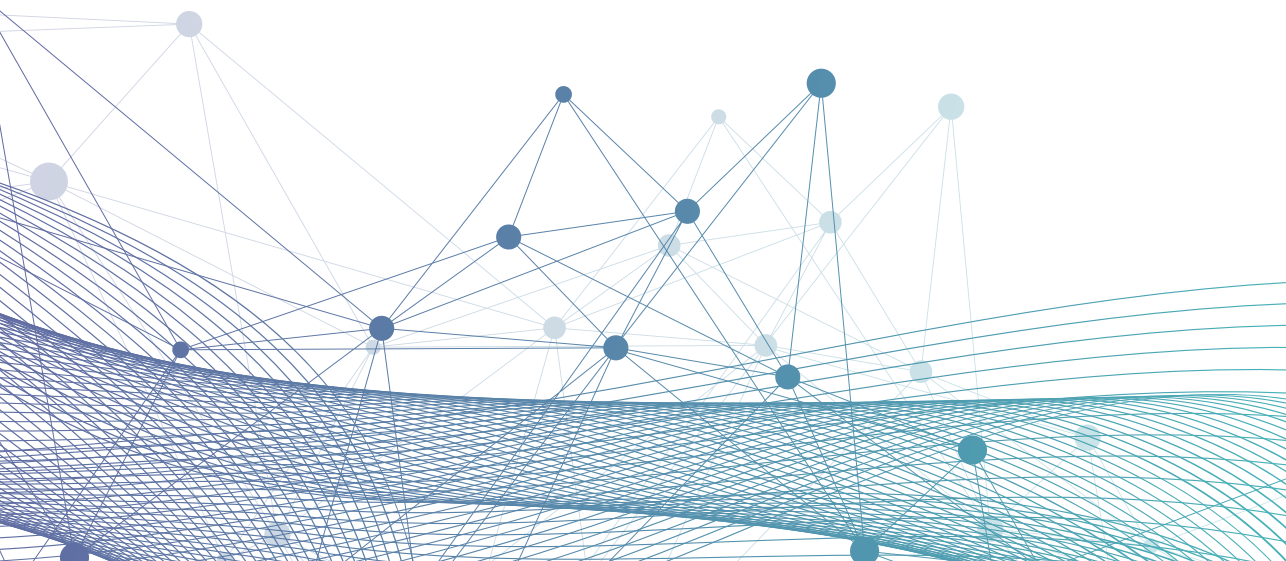


Abstract

Aims: To determine the (cost)-effectiveness of blood pressure lowering, lipid lowering and antithrombotic therapy guided by predicted lifetime benefit compared to risk factor levels in patients with symptomatic atherosclerotic disease.

Methods: For all patients with symptomatic atherosclerotic disease in the UCC-SMART cohort (1996-2018; n = 7,697) two treatment strategies were compared. The lifetime benefit-guided strategy was based on individual estimation of gain in CVD-free life with the SMART-REACH model. In the risk factor-based strategy all patients were treated the following: LDL-c <1.8 mmol/l, systolic blood pressure <140 mmHg, and antithrombotic medication. Outcomes were evaluated for the total cohort using a microsimulation model. Effectiveness was evaluated as total gain in CVD-free life and events avoided, cost-effectiveness as incremental cost-effectivity ratio (ICER).

Results: In comparison to baseline treatment, treatment according to lifetime benefit would lead to an increase of 24,243 CVD-free life years (95%CI 19,980-29,909) and would avoid 940 (95%CI 742-1140) events in the next 10 years. For risk-factor based treatment, this would be an increase of 18,564 CVD-free life years (95%CI 14,225-20,456) and decrease of 857 (95%CI 661-1,057) events. The ICER of lifetime benefit-based treatment with a treatment threshold of ≥1 year additional CVD-free life per therapy was €15,092/QALY gained and of risk factor-based treatment €9,933/QALY gained. In a direct comparison, lifetime benefit-based treatment compared to risk factor-based treatment results in 1871 additional QALYs for the price of €36,538/QALY gained.

Conclusions: Residual risk reduction guided by lifetime benefit estimation results in more CVD-free life years and more CVD events avoided compared to the conventional risk factor-based strategy. Lifetime benefit-based treatment is an effective and potentially cost-effective strategy for reducing residual CVD risk in patients with clinical manifest vascular disease.

Introduction

According to current guidelines all patients with symptomatic atherosclerotic disease are at very high 10 year risk of (recurrent) cardiovascular events.[1,2] Based on this very high risk preventive treatment is advised for all patients, including lipid modifying therapy, blood pressure lowering and antithrombotic therapy. However, even after such therapy is initiated, large variation remains in the residual risk of recurrent cardiovascular disease (CVD).[3] Identification of the patient who benefits most from further risk factor lowering may help to effectively reduce residual risk of CV events in patients with established CVD. It is unknown which is the most (cost)effective method of selecting the right combination of medications for each individual.

With the externally validated SMART risk score, the 10-year risk of CV events can be estimated in patients with clinical manifest vascular disease.[4] As age is one of the most important factors in CVD risk, treatment decisions solely based on 10-year risk can lead to more intensive treatment of the elderly. Due to their limited life expectancy, from both cardiovascular and non-cardiovascular causes, the actual treatment benefit may be overestimated in older patients. Although they may be presumed to have the highest 10 year risk for new CV events, this approach may not be the most (cost) effective method of selecting the right combination of medications. Younger patients on the other hand who may have a high lifetime risk may not be identified for intensive preventive treatment as their 10-year risks are low. To deal with these shortcomings, a more recent development is the possibility to predict CVD-free life expectancy rather than 10-year risk.[5,6] Combining CVD-free life expectancies with hazard ratios (HRs) from trials or meta-analyses opens the possibility of estimating the lifetime treatment benefit, defined as the gain in CVD-free life expectancy from preventive therapy.[7] The highest lifetime treatment benefit can be expected in younger patients (who have the largest life expectancy) with higher levels of vascular risk factors (who have the highest risk to reduce).[7] Intensive or expensive therapies like proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, intensive blood pressure lowering, dual anti-platelet therapy or dual pathway inhibition (DPI) antithrombotic treatment have all proven to effectively reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic disease. These new treatment options are however costly or induce a bleeding risk which makes identification of patients that benefit most a key issue in clinical practice.[8,9] The aim of the current study was to evaluate the effectiveness and cost-effectiveness of blood pressure lowering, lipid lowering and antithrombotic therapy guided by predicted lifetime benefit compared to treatment based on risk factor threshold levels in terms of total gain in CVD-free lifetime and CV events avoided in patients with symptomatic atherosclerotic disease.

Methods

Population

Patients with symptomatic atherosclerotic disease were included from the Utrecht Cardiovascular Cohort - Secondary Manifestations of ARTerial disease (UCC-SMART). UCC-SMART is a single-center ongoing prospective cohort study at the University Medical Center Utrecht, the Netherlands.[10] Patients where included in the period 1996 to 2018 with coronary artery disease, cerebrovascular disease, peripheral artery disease and/or abdominal aortic aneurysm. Patients between the age 45 to 80 years (n = 7,697) were included in the present analyses as the SMART-REACH model is validated for this range.[5] Detailed information about the used definitions, data collection, follow-up procedures and endpoint verification from UCC-SMART can be found in the supplemental methods. The study was approved by the local Medical Ethics Committee and written informed consent was obtained from all patients.

Estimating individual lifetime treatment benefit

First, the CVD-free life expectancy was estimated for all UCC-SMART study participants using the externally validated SMART-REACH model.[5] This competing risk adjusted model uses the following predictors: sex, current smoking, diabetes mellitus, systolic blood pressure (SBP), total cholesterol, creatinine, number of locations of cardiovascular disease (coronary, cerebral and/or peripheral arterial disease), a history of atrial fibrillation and a history of congestive heart failure, more information about the SMART-REACH model can be found in the online supplement. The lifetime treatment benefit is defined as the difference in CVD-free life expectancy with and without medication and can be calculated by incorporating HRs from meta-analyses or trial data in the competing risk models.

Second, to model treatment effect, the SMART-REACH model's predictions are combined with hazard ratios from randomized trials and meta-analyses. For lipid lowering therapies, a decrease in LDL levels is modelled. Meta-analyses have shown an HR of 0.78 (95%CI 0.76 - 0.80) for major vascular events per 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL).[9,11] Moderate-intensity lipid lowering was defined as the use of a low or moderate-intensity statin and was modelled as if simvastatin 40mg was used, lowering LDL by an average 37%.[12] High-intensity lipid lowering was defined as the use of either a high dose statin or the addition of ezetimibe to moderate-intensity lipid lowering. To estimate the treatment effect of high-intensity lipid lowering, an additional LDL reduction of 24% was assumed, equal to the average LDL-reduction achieved by addition of ezetimibe to a moderate dose statin.[11,13] The expected decrease in LDL-c of PCSK9 inhibitors was assumed to be 59%.[14,15]

As the number of classes of antihypertensive drugs are large and the goal of the current analysis was not to compare those classes or a specific strategy combining those, the effect of blood pressure was evaluated through lowering SBP to 130 mmHg or 140 mmHg. The effect of 10mmHg reduction corresponded to an HR of 0.80 (95% CI 0.77-0.83).[16] It was assumed that blood pressure was lowered exactly towards the intended target. The effect of blood pressure lowering was truncated at 130 mmHg, assuming no effect from further reduction.

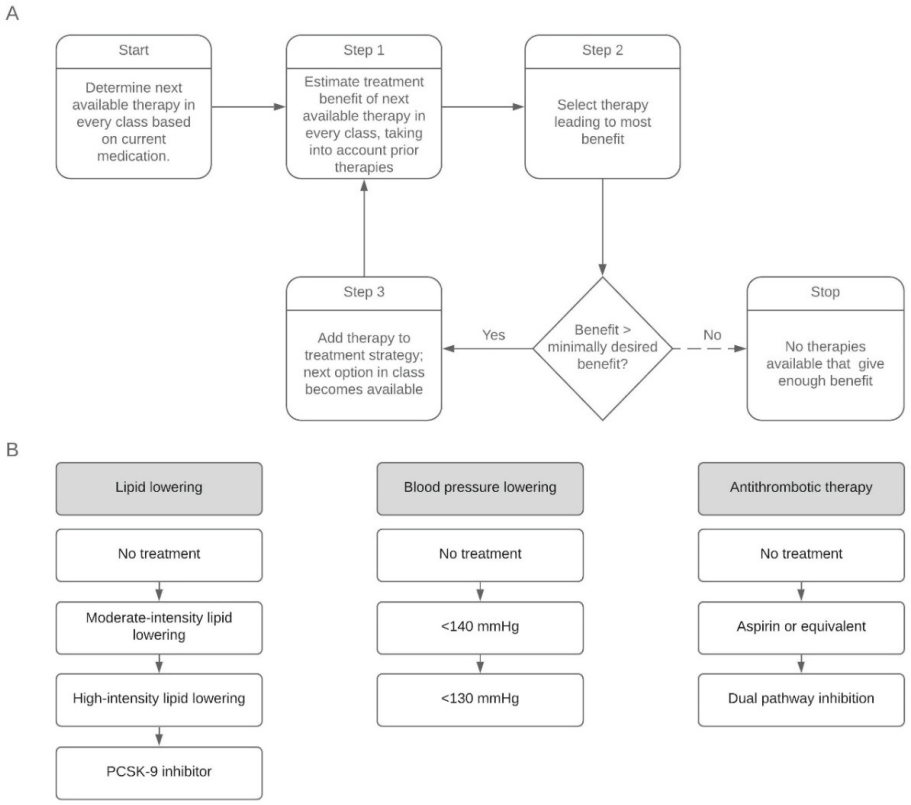
The effect of antithrombotic therapy was directly added to the hazard function for cardiovascular events. For aspirin, an HR of 0.81 (95%CI 0.75-0.87) was used.[17] Addition of a low-dose direct oral anticoagulant (DOAC) to aspirin (i.e. dual pathway inhibition; DPI) was assumed to have an HR of 0.76 (95%CI 0.66-0.86) compared to aspirin alone.[8] Patients with a vitamin K antagonist or a higher-dose DOAC at baseline were assumed to have the risk reduction in CVD events associated with aspirin.

It was assumed that all treatment effects of the different classes were independent of each other[18] and did not affect the risk of non-CVD mortality. No lifestyle interventions such as smoking cessation were evaluated as those should be performed regardless of pharmaceutical interventions. The effect of diabetes-specific medication was not evaluated in the current study.

Lifetime benefit-based treatment decision-algorithm

Clinical decision-making was simulated in this study by following a step-wise decision-algorithm that was run for every individual patient in the study dataset (Figure 1). This decision-algorithm follows an iterative process, estimating therapy benefit in terms of gain in CVD-free life expectancy using the SMART-REACH model. With each iteration, the effect of the first next treatment option in the categories blood pressure lowering, lipid-lowering and antithrombotic therapy is estimated. Out of those three treatment options, the treatment with the highest benefit in terms of extra CVD-free life years gained is compared with the treatment threshold. If the predicted effect of treatment exceeded the threshold, that single therapy was added to the patient's regimen and the algorithm was reiterated with the remaining options. Once there are no remaining treatment options that exceed the treatment threshold, the simulation ends and the total predicted extra CVD-free life years for that specific patient is summed up. For the main analyses, a treatment threshold of 12 months per therapy was evaluated. Treatment thresholds of 6 and 24 months per therapy were evaluated as secondary analyses. In clinical practice, this minimally desired benefit varies from patient to patient and should be part of a shared decision making process, based on preferences of patient and the treating physician.

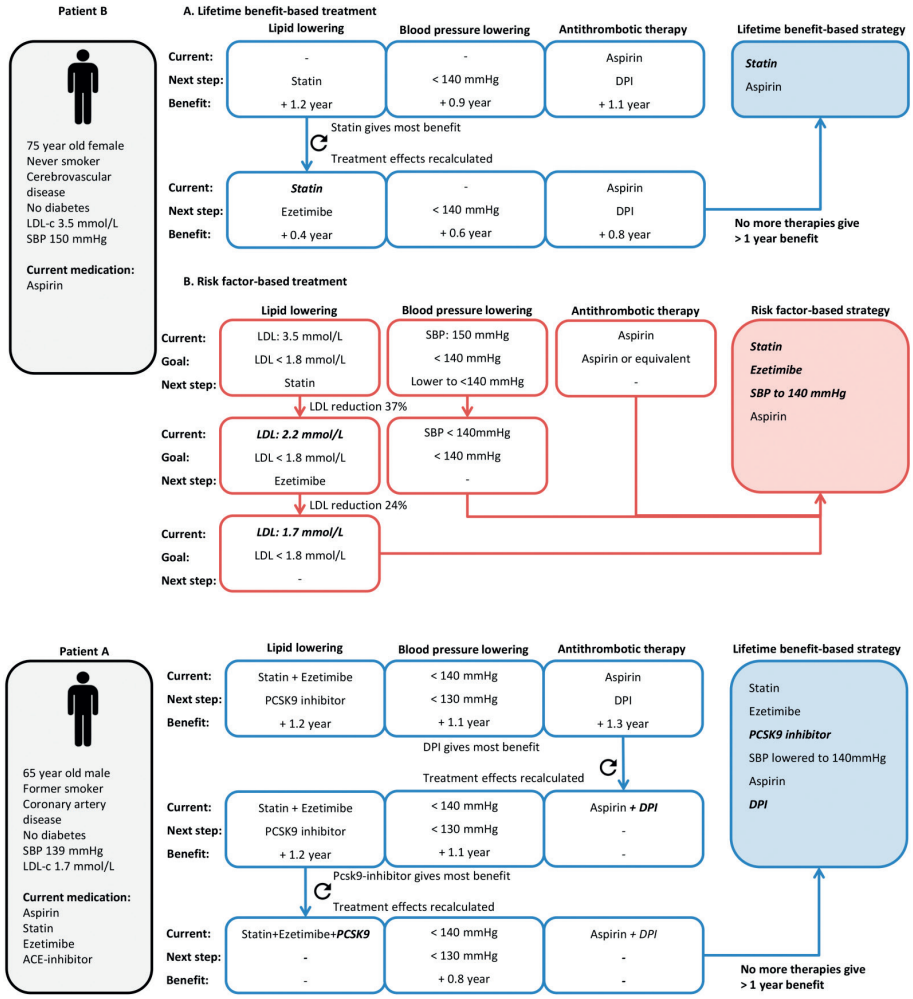
Figure 1: Stepwise decision algorithm of lifetime benefit-based treatment



A) schematic overview over lifetime benefit-based treatment selection. B) shows the possible treatment options in the three different classes. PCSK9 = proprotein convertase subtilisin/kexin type 9.

For example, for a treatment-naïve subject, the next options would be moderate-intensity lipid lowering, SBP lowering <140mmHg, and aspirin. For someone already on high-intensity lipid lowering, the benefit of a PCSK9 inhibitor on top of the high-intensity lipid lowering will be assessed. Next, the therapy benefit was estimated for the next available option in each category (*step 1).* The most effective of these three options was selected (*step 2)* and if the therapy benefit was larger than the minimally desired benefit, the therapy was added to the individual treatment strategy (*step 3*). Then, the first step was repeated, taking into account the therapeutic effect of the selected therapy. In the category of the selected therapy, the therapy benefit of the next available therapy is evaluated. This continues until there are no more therapies that lead to more benefit than the minimally desired benefit (*stop).* Two patient examples are shown in figure 2 and Supplemental Figure S1.

Figure 2: Patient example of lifetime benefit-based treatment



Patient example of a lifetime benefit-based treatment strategy. This patient was already treated according to the current guidelines at baseline. On top of the current medication, cardiovascular prevention could be intensified by adding a PCSK9 inhibitor, dual pathway inhibition or by lowering blood pressure below 130 mmHg. Dual pathway inhibition and a PCSK9 inhibitor led to most benefit and were added to the lifetime benefit-based strategy. SBP = systolic blood pressure, LDL = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin type 9, DPI = dual pathway inhibition

Risk factor-based decision algorithm

The risk factor-based decision algorithm simply consisted of treating all patients according to recommendations for very high risk patients in the current ESC cardiovascular prevention, including the medication that was prescribed at baseline.[1]

For lipid lowering, this meant lowering the LDL-c of all patients to ≤1.8 mmol/L. This was modeled using a stepwise approach: first, all patients with an LDL-c >1.8 mmol/L got assigned moderate-intensity lipid lowering. If the expected post-treatment LDL-c was >1.8 mmol/L, high-intensity lipid-lowering was started. If the expected post-treatment LDL-c was still >1.8 mmol/L, a PCSK9 inhibitor was initiated. SBP was lowered to 140 mmHg for all patients. All patients were treated with aspirin, none were treated with DPI as this is not (yet) recommended in the guidelines. A patient example of a risk factor-based treatment strategy is shown in Supplemental Figure S1.

Microsimulation model

To evaluate outcomes of the different treatment strategies, a microsimulation model was developed to predict quality-adjusted life years (QALYs), costs and clinical outcomes. The model was run three times for all patients in the UCC-SMART cohort, one time with the medication at baseline, one time with risk-based treatment and one with lifetime benefit based treatment. A detailed description of the model and model assumptions can be found in the supplemental methods.

Each year patients had a probability of acute events or death (Supplemental Figure S1). The probabilities of events and death were based on patient characteristics and were modified by treatment effects for the risk factor-based and lifetime benefit-based treatment strategies. All chronic health states were associated with utility, after experiencing an acute event patients would transfer to the chronic health state associated with this event. A chronic 0.0015 reduction in utility was applied per drug used. All costs were discounted with 4%, utilities were discounted with 1.5% as is usual practice in The Netherlands. Costs were calculated from a healthcare perspective. Costs were estimated for acute events, chronic health states and medication based on literature (Supplemental Table 2), recent sources were selected if they were applicable to the Dutch healthcare and included all relevant costs.

Outcomes

Primary effectiveness outcomes were the total gain in CVD-free life-years and cardiovascular events avoided in comparison to treating all patients with the medication as prescribed at baseline. Primary cost-effectiveness outcomes were the difference in QALYs and costs in comparison to baseline treatment. Number of therapies was defined as the sum of different lipid lowering, antihypertensive and antithrombotic drugs and included medication already prescribed at baseline. Confidence intervals and p-values were based on probabilistic sensitivity analyses.

Scenario analyses

Probabilistic scenario analyses were performed to assess robustness of the results, repeating the prior microsimulation model 1000 times for every strategy. In these analyses, drug and event costs, chronic health state utilities, annual event rates

and HRs of all therapies were randomly chosen from beta or gamma distributions. Additionally, several scenario analyses were performed for several model assumptions.

Statistical analysis

Because complete case analysis may lead to loss of statistical power and possible bias,[19] values of the following variables were imputed by single regression imputation: smoking status (n=32, 0.4%), creatinin (n=31, 0.3%), CRP (n=250, 3.2%), SBP (n=18, 0.2%), LDL (n=80, 1.0%) or total cholesterol (n=34, 0.4%). Patients were followed-up until death, lost to follow-up (n=561, 6.1%) or until march 2018. All analyses were performed with R-statistic programming (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of the included patients are presented in Table 1. The mean age of the patients was 62.0 ±8.5 year and 75% was male. At inclusion, 69% of the patients was using a statin and 13% ezetimibe or a high-intensity statin. At baseline, 15% of the population had a LDL ≤1.8 mmol/L, 56% a SBP of ≤140 mmHg, and 84% was treated with aspirin or an equivalent drug.

Effectiveness

In comparison to baseline treatment, treatment according to lifetime benefit with a treatment threshold of 12 months would lead to an increase of 24,243 CVD-free life years (95%CI 19,980-29,909), risk factor-based treatment to an increase of 18,564 CVD-free life years (95%CI 14,225-20,456). In the next ten years, predicted lifetime benefit-based treatment could avoid 940 (95%CI 742-1,140) major adverse cardiovascular events and risk factor-based treatment could avoid 857 (95%CI 661-1,057) events (Table 2).

At baseline, the mean number of preventive therapies was 2.3±1.3. Using a lifetime benefit-based strategy this increased to 4.8±1.8, based on risk factor levels this increased to 4.5±1.5. PCSK9 inhibitors were assigned to 20% of the patients according to the lifetime benefit-based strategy and to 18% of the patients in the risk factor-based strategy, low-dose DOACs were started in 72% of the UCC-SMART population in the lifetime benefit-based treatment strategy. The distribution of the different treatments when using lifetime benefit-based treatment and risk factor-based treatment are presented in Table 3.

Table 1: Patient characteristics of the study population at baseline

	UCC- SMART
	n = 7,697
Male sex	5,774 (75%)
Age (years)	62 ± 8
Current smoker	2,215 (29%)
Former smoker	3,809 (49%)
Body mass index (kg/m2)	26.9 ± 4.0
Systolic blood pressure (mmHg)	140 ± 20
Diabetes mellitus	1,386 (18%)
Coronary artery disease	4,835 (63%)
Peripheral artery disease	1,356 (18%)
Cerebrovascular disease	2,222 (29%)
Abdominal arterial aneurysm	687 (9%)
No. of disease locations	
One	6,484 (84%)
Two	1,050 (14%)
Three	163 (2%)
Total cholesterol (mmol/l)	4.7 (3.9-5.6)
HDL-cholesterol (mmol/l)	1.2 (1.0-1.4)
LDL-cholesterol (mmol/l)	2.7 (2.1-3.5)
Triglycerides (mmol/l)	1.4 (1.0-2.0)
Estimated GFR (ml/min/1.73m2)	76 ± 17
CRP (mg/dL)	2.1 (1.0-4.4)
Medication use	
Statin	5,323 (69%)
High-intensity statin	733 (10%)
Ezetimibe	304 (4%)
Diuretics	1,740 (23%)
ACE inhibitors	2,517 (33%)
Beta-blockers	4,260 (55%)
Calcium channel blockers	1,693 (22%)
Aspirin or equivalent	5,999 (78%)
Oral anticoagulants	862 (11%)

GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula). All data in n (%), mean ± standard deviation, or median (IQR)

Table 2: Effectiveness of predicted lifetime benefit-based treatment and risk-factor based treatment

	Predicted lifetime benefit based			Risk-factor based
N = 7,697	≥6 months	≥12 months	≥24 months	
Total gain in CVD-free lifetime (years)	35,972	24,243	8,806	18,564
Event reduction next 10 years (n)	1,329	940	324	857
Lifetime event reduction (n)	2,597	2,042	1,056	1,584
Mean number of preventive therapies (n)	6.3	4.4	3.0	4.1

The effectiveness of predicted lifetime benefit-based treatment and risk factor-based treatment. Treatment threshold is the minimal number of months gain in CVD life expectancy before a therapy was started, so the threshold of at least 12 months shows the treatment strategy including all preventive treatments leading to at least 1 year gain in CVD-free life expectancy as estimated with the SMART-REACH model. Gain in lifetime and event reduction are all in comparison to treating all patients with their baseline medication. Number of preventive therapies is the sum of the number of lipid lowering, blood pressure lowering or antithrombotic drugs. CVD= cardiovascular disease.

Table 3: Proportion of patients treated with every therapy according to their baseline prescriptions and after lifetime benefit- or risk factor-based treatment intensification

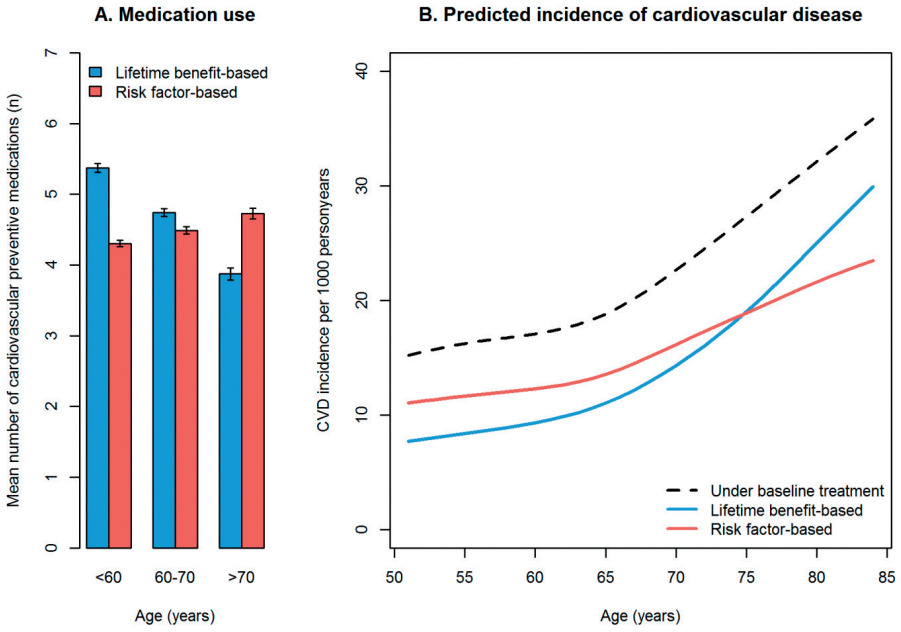
		Treatment intensification based on	
Therapy	**Treatment at baseline**	**Lifetime benefit (>12 months)**	**Risk factor**
Moderate-intensity lipid lowering	69%	93%	99%
High-intensity lipid lowering	13%	23%	52%
PCSK9 inhibitors	0%	20%	18%
SBP target <140 mmHg	43%	77%	88%
SBP target <130 mmHg	0%	8%	0%
Aspirin or equivalent	78%	92%	100%
DPI	0%	72%	0%

Proportion of patients of the UCC-SMART cohort that has a certain therapy assigned at study inclusion or after benefit- or risk factor-based treatment intensification. SBP = systolic blood pressure, PCSK9 = proprotein convertase subtilisin/kexin type 9, DPI = dual pathway inhibition.

In younger patients (<60 year), lifetime benefit-based treatment with a treatment threshold of 12 months led to treatment with median 5.4±1.7 therapies and risk factor-based to 4.3±1.4 therapies in comparison to 2.4±1.4 at baseline. In patients >75 year, lifetime benefit-based treatment led to a median of 3.4±1.8 therapies and risk factor-based treatment to 4.8±1.7 therapies, in comparison to 1.8±1.2 at baseline (Figure 3A). The mean age of a PCSK9 inhibitor user was 57±7 years when treating lifetime benefit-based and 62±9 years old when treating risk factor-based. Treating according to lifetime benefit would lead to a decreased incidence of CVD in patients up to 75 years old, but a higher incidence in patients older than 75 year (Figure 3B).

When using a treatment threshold of 6 months gain in CVD-free life expectancy rather than 12 months, more events could be avoided and more CVD-free life years could be won (Table 3). However, this would be at the cost of increased medication use. In a treatment strategy with a threshold of 24 months per therapy, fewer medications would be started, but this would result in fewer events avoided and less CVD-free life won.

Figure 3: Medication use and predicted incidence of CVD when treating lifetime benefit-based or risk factor-based per age group



Medication use and predicted incidence of CVD when treating lifetime benefit-based (threshold >12 months) or riskfactor-based per agegroup. A) Medication use includes baseline use of medication and is the sum of the number of treatments for lipid lowering, blood pressure lowering and antithrombotic therapy. B) Predicted incidence was calculated by combining the treatment effects per strategy with the observed incidence (dashed line).

Cost-effectiveness

Lifetime benefit-based treatment with a treatment threshold of 12 months led to 9,664 additional QALYs, risk factor-based treatment led to 7,793 additional QALYs compared to treatment as at baseline. The additional costs for the lifetime benefit-based strategy were €145.8 million and for risk factor-based treatment €77.4 million. The ICER of lifetime benefit-based treatment was €15,092/QALY gained and of risk factor-based treatment €9,933/QALY gained (table 4). A lifetime benefit-based treatment approach was 90% likely to be cost-effective under the Dutch threshold

of €20,000/QALY gained compared to treatment as at baseline (supplemental figure S3). For a risk factor-based treatment approach, this was >99%. The results when using a treatment threshold of 6 or 24 months are in table 4. When directly comparing lifetime benefit-based treatment to risk factor-based treatment, the ICER was €36,538/QALY gained, which was 20% probable to be cost-effective under the threshold of €20,000/QALY. A direct comparison for other commonly used cost-effectiveness thresholds is shown in supplemental Table 3. When discounting both costs and utilities with 3% as is usual in several other countries, the ICER for lifetime benefit-based treatment was €24,432/QALY gained. Excluding DPI led to an ICER of €19,529 for lifetime benefit-based treatment. When doubling the chronic disutility per drug used to 0.003 to account for side effects, the ICER increased to €16,281/QALY gained. The results of all scenario analyses are shown in supplemental Figure S4 and supplemental Table 4.

Table 4: Cost-effectiveness of lifetime benefit-based and risk factor-based treatment

	Baseline treatment	**Predicted lifetime benefit based**			**Risk-factor based**
N = 7,697		≥6 months	≥12 months	≥24 months	
Total costs (mln €)	442.1	818.2	587.9	472.0	519.4
CVD event costs (mln €)	182.4	107.7	130.4	161.4	138.5
Chronic care costs (mln €)	246.8	296.4	278.1	259.8	273.1
Therapeutic costs (mln €)	12.8	414.1	179.4	50.8	107.8
Total QALYs (x1000)	74.4	90.0	84.0	78.7	82.2
Total lifeyears (x1000)	149.2	176.0	164.9	155.8	161.9
Total events (MACE)	9,633	7,061	7,591	8,602	8,049
ICER vs current practice (€/QALY)		25,327	15,092	8,217	9,933
ICER vs risk-factor based (€/QALY)		38,340	36,585	13,775	
Prob. of cost-effectiveness (<20,000 €/QALY)		0.16	0.90	>0.99	>0.99

Cost-effectiveness results of the different strategies. All results are on cohort level on a lifetime perspective. Treatment threshold is the minimal number of months gain in CVD life expectancy before a therapy was started, so the threshold of at least 12 months shows the treatment strategy including all preventive treatments leading to at least 1 year gain in CVD-free life expectancy as estimated with the SMART-REACH model. ICER is in comparison to baseline treatment. Probability of cost-effectiveness is defined as the probability that the treatment strategy costs less than 20,000 euro per QALY. QALY = quality-adjusted lifeyear, ICER = incremental cost-effectiveness ratio.

Discussion

Results from the current study show that lifetime benefit-based treatment is an effective for reducing residual CVD risk in patients with clinical manifest vascular disease. In direct comparison to risk factor-based treatment, treating lifetime benefit-based can avoid more cardiovascular events and can lead to more CVD-free life years

with a similar amount of started preventive therapies, although at a higher price. Depending on the willingness-to-pay threshold, lifetime benefit-based treatment is potentially cost-effective.

Residual risk reduction based on predicted lifetime benefit leads to more intensive treatment of younger patients compared to the conventional risk factor-based strategy. As cardiovascular events are prevented at a younger age, a larger gain of CVD-free life expectancy can be obtained. However, this comes with the cost of longer treatment durations as preventive treatment is usually initiated lifelong, with increased costs and potential side effects. On the other hand, lifetime benefit based treatment may reduce overtreatment of older patients. Even though absolute risk reduction from preventive therapy can be substantial in older patients, the actual increase in life expectancy can be limited due to the high remaining risk of both CVD and non-CVD mortality. On top of that, this group has the highest rates of adverse events and interactions with other medications due to the high rates of polypharmacy, even further reducing the net-benefit this group has from preventive treatment.[20]

In the current study, only intensification of preventive treatment was evaluated. Overtreatment in older patients may be prevented even further by evaluating whether currently prescribed medication still leads to sufficient benefit. It should be noted that only pharmaceutical interventions were evaluated in the current study, as lifestyle improvements should be performed regardless of pharmaceutical interventions. Especially smoking cessation, of which the absolute risk reduction and gain in CVD-free life expectancy are often much greater than from any of the pharmaceutical interventions mentioned in the current study, should be recommended in clinical practice prior to considering pharmaceutical treatment intensification.

In the current study, a minimally desired benefit of 12 months gain in CVD-free life expectancy was primarily used in order to make an analysis on a population scale. However, in clinical practice it is unlikely that one threshold for treatment benefit can be used in all patients. Secondary analyses showed that the use of a smaller threshold like 6 months more events can be avoided, but at the cost of more intensive treatment. There is much variation in how much benefit patients and physicians consider enough in order to start or intensify risk factor treatment.[21] Deciding whether the expected therapy benefit is enough should be the result of shared decision making between patient and healthcare professional. As the benefit in terms of gain in CVD-free life-expectancy is an intuitive measure, it is very suitable to be used in shared decision-making and should be used alongside the expected treatment duration and side effects.

A previous study found that lifetime benefit-based treatment is more cost-effective than a 10-year risk-based approach for PCSK9 inhibitors for patients with symptomatic

atherosclerotic disease.[22] To our knowledge, there are no other studies assessing the effectiveness or cost-effectiveness of treatment decisions based on lifetime benefit or directly comparing an individual risk factor-based and lifetime benefit-based approach in the secondary prevention of cardiovascular disease. Results from the current study show that residual CV risk reduction based on lifetime benefit is an effective alternative to risk factor-based treatment as advocated in guidelines for patients with established atherosclerotic vascular disease.[1]

Both the lifetime benefit-based and risk factor-based strategies are cost-effective strategies in comparison to current practice. In direct comparison, it depends on the treatment threshold for lifetime benefit based treatment and the willingness-to-pay threshold used which strategy is most likely cost-effective. In the Netherlands, willingness-to-pay thresholds range from €20,000 to €80,000 per QALY gained.[23,24] Under the most conservative threshold of 20,000€/QALY, often used in The Netherlands when evaluating prevention programs, only the 24 month threshold was cost-effective. However, at a willingness-to-pay threshold of 50,000€/QALY lifetime benefit-based strategies are likely to be cost effective regardless of the individual treatment threshold used.

In the current ESC guidelines, all patients with symptomatic atherosclerotic disease are in the very high risk category.[1] As a consequence, treatment targets for SBP and LDL are equal for all patients with cardiovascular disease and all patients are advised to use an antiplatelet drug. In a recent ESC position paper it is suggested that lifetime benefit can facilitate communication concerning treatment decisions and, after additional validation of the methodology, may play a more central role in future treatment recommendations in guidelines.[25] By prediction of treatment effects, cardiovascular prevention can be more precisely tailored to the individual patient, which can be more or less intensive than treatment advised in current guidelines.

A strength of the current study is the use of a large, real-world cohort with patients with different types of symptomatic cardiovascular disease. CV event- and (total) mortality rates could be accurately modelled in the cost-effectiveness analysis due to the extensive follow-up in the UCC-SMART cohort. Treatment selection was done using the externally validated SMART-REACH model. This model is competing-risk adjusted and left truncation allows the model to perform accurate predictions beyond the scope of the observed follow-up time, making it very suitable for evaluating the long-term effectiveness of interventions.[7] Also, extensive sensitivity analyses were performed to confirm the robustness and validity of the assumptions of the cost-effectiveness analysis, including probabilistic analyses and one-way scenario analyses. Finally, 'lifetime benefit-based treatment' as used in this study can be applied directly in clinical practice. Both the SMART-REACH model and (soon) the

tool that was used for the individual treatment selection are available in an online calculator (www.u-prevent.com).

Limitations of the study should also be considered. Treatment effects were assumed to be constant for lifetime duration. Especially for more novel treatments like PCSK9 inhibitors and low-dose DOACs, this required extrapolation beyond the maximum follow-up of the relevant RCTs. Long-term results of treatment with those agents are not yet available, long-term efficacy and safety should be validated in future studies with longer follow-up durations. For PCSK9 inhibitors, the actual effect of long-term LDL-c reduction may be even larger than modelled, since the causal effect of LDL-c lowering on cardiovascular outcomes is cumulative and increases over time.[26,27] For DPI such evidence unfortunately does not exist yet. Treatment algorithms like the one shown in the current study should be continuously adapted to growing knowledge and potentially changing priorities. Moreover, the effectivity of long-term treatment in individuals developing additional comorbidities may be altered. As these long term effects are often not captured in trials due to the limited follow-up duration, treatment effects from trials may become less applicable to the target population as time passes. Another limitation is that two variables of the SMART-REACH model, presence of atrial fibrillation and congestive heart failure, were not recorded at baseline in the UCC-SMART study. However, repeating the analysis on a simulated population resembling the UCC-SMART population including age- and sex- corrected prevalence rates of atrial fibrillation and congestive heart failure showed similar results as the main analysis.

In conclusion, residual CV risk reduction guided by lifetime benefit estimation is an effective and potentially cost-effective strategy which can lead to more CVD-free life years and event reduction compared to treating according to risk factor threshold based treatment in patients with established vascular disease. Treatment benefit expressed as gain in extra CVD-free life is an intuitive measure to be used in the shared decision making process, which can help to tailor preventive treatment to the individual patient.

References

1. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2016; 37: 2315–2381.
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *J Am Coll Cardiol* 2019; 74: e177–e232.
3. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. *Circulation* 2016; 134: 1419–1429.
4. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart* 2013; 99: 866–872.
5. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: The SMART-REACH model. *J Am Heart Assoc*; 7. Epub ahead of print 2018. DOI: 10.1161/JAHA.118.009217.
6. Jaspers NEM, Blaha MJ, Matsushita K, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. *Eur Heart J* 2019; 31: 1–10.
7. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. *BMJ* 2016; 352: i1548.
8. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med* 2017; 377: 1319–1330.
9. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; 376: 1713–1722.
10. Simons PCG, Algra A, Van De Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: Rationale and design. *Eur J Epidemiol* 1999; 15: 773–781.
11. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010; 376: 1670–1681.
12. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; 326: 1423–0.
13. Leiter LA, Betteridge DJ, Farnier M, et al. Lipid-altering efficacy and safety profile of combination therapy with ezetimibe/statin vs. statin monotherapy in patients with and without diabetes: an analysis of pooled data from 27 clinical trials. *Diabetes, Obes Metab* 2011; 13: 615–628.
14. Zhang XL, Zhu QQ, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: A meta-analysis of 25 randomized, controlled trials. *BMC Med*; 13. Epub ahead of print 2015. DOI: 10.1186/s12916-015-0358-8.
15. Bonaca MP, Nault P, Giugliano RP, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease. *Circulation* 2018; 137: 338–350.
16. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet* 2016; 387: 957–967.
17. Collins R, Peto R, Hennekens C, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849–1860.
18. Sundström J, Gulliksson G, Wirén M. Synergistic effects of blood pressure-lowering drugs and statins: systematic review and meta-analysis. *BMJ Evidence-Based Med* 2018; 23: 64–69.

19. Donders ART, van der Heijden GJMG, Stijnen T, et al. Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; 59: 1087–1091.

20. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. *Br J Clin Pharmacol* 2015; 80: 796–807.

21. Jaspers NEM, Visseren FLJ, Numans ME, et al. Variation in minimum desired cardiovascular disease-free longevity benefit from statin and antihypertensive medications: A cross-sectional study of patient and primary care physician perspectives. *BMJ Open* 2018; 8: 1–9.

22. Berkelmans GFN, Greving JP, Van Der Graaf Y, et al. P4388Treatment decisions based on individual estimated lifetime benefit versus individual estimated 10-year absolute risk reduction: a cost-effectiveness analyses with PCSK9 inhibition. *Eur Heart J*; 39. Epub ahead of print August 2018. DOI: 10.1093/eurheartj/ehy563.P4388.

23. Stadhouders N, Koolman X, Dijk C, et al. The marginal benefits of healthcare spending in the Netherlands: Estimating cost-effectiveness thresholds using a translog production function. *Health Econ* 2019; 28: 1331–1344.

24. Reckers-Droog VT, van Exel NJA, Brouwer WBF. Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands. *Health Policy (New York)* 2018; 122: 621–629.

25. Piepoli MF, Abreu A, Albus C, et al. Update on cardiovascular prevention in clinical practice: A position paper of the European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Prev Cardiol* 2019; 204748731989303.

26. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017; 38: 2459–2472.

27. Ference BA, Bhatt DL, Catapano AL, et al. Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure with Lifetime Risk of Cardiovascular Disease. *JAMA - J Am Med Assoc* 2019; 322: 1381–1391.

Supplementary Materials

UCC-SMART cohort

Study patients of the UCC-SMART cohort are newly referred patients to the University Medical Center Utrecht with atherosclerotic disease or an increased risk for atherosclerotic disease and were included between January 1996 and March 2018. Coronary artery disease was defined as a history of a clinical diagnosis of angina pectoris, myocardial infarction, cardiac arrest, or coronary revascularization (coronary bypass surgery or coronary angioplasty), cerebrovascular disease as a clinical diagnosis of a transient ischemic attack or ischemic or hemorrhagic stroke, peripheral artery disease as a symptomatic and documented obstruction of distal arteries of the leg (ankle brachial index ≤0.90), a revascularization procedure of the leg (percutaneous transluminal angioplasty or bypass surgery) or a prior amputation and an abdominal aortic aneurysm as an abdominal aortic anteroposterior diameter of ≥3 cm at baseline screening.

All baseline characteristics were determined at baseline using a standardized screening protocol consisting of questionnaires, physical examination and laboratory testing. Smoking and the amount of pack-years were self-reported. Medication use was self-reported. Office systolic blood pressure was used, which was measured in sitting position twice in the both arms, the highest mean of the measurements on one arm was used. Diabetes mellitus (DM) at baseline was either self-reported DM type 1 or 2 or a fasting glucose of >7.0 mmol/L at baseline screening. LDL-c was calculated using the Friedewald formula. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

To evaluate possible endpoints, patients received biannual questionnaires. Whenever a possible event was reported, hospital discharge letters, GP letters, and results of relevant laboratory and radiology examinations were collected and the endpoint was verified by three independent experienced physicians from the UMC Utrecht.

SMART-REACH model

The CVD-free life expectancy was estimated for all UCC-SMART study participants using the externally validated SMART-REACH model.[5] This competing risk adjusted model uses the following predictors: sex, current smoking, diabetes mellitus, systolic blood pressure (SBP), total cholesterol, creatinine, number of locations of cardiovascular disease (coronary, cerebral and/or peripheral arterial disease), a history of atrial fibrillation and a history of congestive heart failure, These predictors are used for two Fine and Gray competing risk-models for cause specific estimates for cumulative incidence, one for CVD and one for non-CVD mortality. With age as an underlying time-scale, life-tables are made, calculating the risk for every 1-year

interval. The CVD-free life expectancy can be read from this table as the median survival without CVD, the age at which the cumulative survival is 0.5. The lifetime treatment benefit is defined as the difference in CVD-free life expectancy with and without medication and can be calculated by incorporating HRs from meta-analyses or trial data in the competing risk models.

Microsimulation model

To model (cost-)effectiveness, a discrete-time microsimulation was run for all patients in the UCC-SMART cohort with 1-year time intervals. Costs were calculated from a healthcare perspective and did not include indirect patient costs. All acute and chronic health states were associated with certain costs and utilities, based on trials, observational studies or registries. All costs were derived from Dutch sources with comparable population to the population used in the current study. Event costs include the costs of the event and post-event care.. All costs were discounted with 4%, utilities were discounted with 1.5% as is usual practice in The Netherlands.[1] As a sensitivity analysis, both utilities and costs were discounted 3% as is practice in several other geographical regions. The incremental cost-effectiveness ratio (ICER) was defined as the costs spend per QALY gained for every approach .in comparison to the scenario in which all patients were treated according to their baseline medication.

Event probabilities

In the model, all patients start in the chronic health state according to their clinical history. Every year, a patient has a certain probability of acute events (coronary revascularizations, major adverse limb events (MALE), myocardial infarctions, strokes or hospitalizations for heart failure) and death. The model was run until all patients had died. After experiencing an acute event, patients would transfer to the chronic healthstate associated with this event (supplemental figure S1).

Annual event probabilities were based on the UCC-SMART cohort or trials (supplemental table S1). Even probabilities were corrected for age, sex, SBP, presence of diabetes mellitus, smoking status and total cholesterol. Case-fatality rates of acute events were obtained from Dutch registries and are age- and sex-dependent (supplemental table S1).[2,3] Treatment effects were implemented in the microsimulation model by multiplying the cardiovascular event probabilities for every year with the combined HR of all therapies in the lifetime benefit-based or risk factor-based strategy. Treatment effects were assumed not to affect non-CVD mortality.

Costs

The costs of the different treatment options were based on the cheapest available alternative in that class in the Netherlands (supplemental table S2). Pharmaceutical costs included costs of the therapy itself, one outpatient physician consult per started therapy (€96), and a pharmacy dispensing fee of €7 per 3 months for every therapy.[1]

For blood pressure lowering, the number of standard dosses of antihypertensive required was based on the pre-treatment blood pressure according to a trial-based formula.[4] To model the effect of blood pressure, it was assumed that blood pressure lowering from a standard dose was the same regardless of the antihypertensive class. Costs per standard dose were calculated using a weighted average of the cheapest available agent in any class, weighted by prescription frequency in the UCC-SMART cohort since 2009. Costs of novel preventive medications were assumed to reduce 25% in price after patent expiry (2024 for Rivaroxaban, 2029 for Evolocumab). All costs were updated to 2019 levels using the Dutch consumer price indices.[1]

Utilities

QALYs were calculated by the time spent in a health state multiplied by the utility that is associated with that particular health state (supplemental table S2). In the used sources, this utility is determined by EQ-5D questionnaires and varies between 0.0 (death) and 1.0 (perfect health).5 In the base case analysis, the median utility for all chronic health states was used. As only patients were used with prior cardiovascular disease, all patients would start in a chronic health state. For all acute events, a 0.1 disutility was assumed for one month.6 After experiencing an acute event, the chronic utility value for this individual would decrease up to a random value between the current utility and the lower bound of the event-associated chronic health state. A chronic 0.0015 disutility was substracted per used medication in the base case scenario.

Sensitivity analyses

Probabilistic scenario analyses were performed to assess robustness of the (cost) effectivity results, repeating the prior microsimulation model 1000 times. HRs of all treatment effects, annual event rates and utilities were randomly chosen in every repitition from beta distributions, costs were randomly chosen from gamma distributions. These random distributions were selected a priori based on relevant literature and prior cost-effectivity analyses.[7–11] For treatment effects, annual event rates, the 95% confidence interval was used as the random distribution. For utilities, the interquartile ranges were used surrounding the median that was used in the base case. Costs were chosen from a range from -25% to +25% of the base case costs. Primary outcome of the probabilistic analyses was the probability if cost-effectiveness for every willingness to pay.

Additionally, several scenario analysis were performed, assessing the sensitivity to variation of single assumptions of the model. These scenario analyses included an analysis in which DPI was left out of the analysis and an analysis assuming a statin intolerance of 10% of the population. As congestive heart failure (CHF) and atrial fibrillation (AF) were not recorded at baseline in the UCC-SMART cohort, an analysis was performed with a simulated population based on the UCC-SMART cohort. In

this simulated population, presence of CHF or AF at baseline was randomly sampled using age- and sex dependent prevalence rates.[12,13] Finally, an analysis was performed to account for disutility due to medication use and side effects. In this analysis, a disutility 0.003 per therapy was subtracted for every lifeyear for every patient.[14]

Supplemental Table 1. Event risks, costs and utilities

Parameter	Base case	Source	Reference
Annual event risk (%) *			
Revascularization	2.17	Observational study	[15]
Myocardial infarction	1.08	Observational study	[15]
Stroke	0.72	Observational study	[15]
Major adverse limb event	1.68	Observational study	[15]
Hospitalization for heart failure	1.16	Registry	[16]
Death	0.93	Observational study	[15]
Case fatality rates (%) *			
Myocardial infarction	22	Registry	[2]
Stroke	13	Registry	[3]
Hospitalization for heart failure	16	Registry	[3]

Mean annual event risks and fatality rates for a 60 year old female patient with mean risk factor levels. Fatality rates were dependent on age and sex, annual event risks depended on age, sex, systolic blood pressure, smoking status and total cholesterol and were predicted using Cox proportional hazard models (supplemental Table 3).

Supplemental Table 2. Costs and utilities

Parameter	Base case	Lower bound	Upper bound	Source	Reference
Event costs					
Revascularization	€ 18,284	€ 13,713	€ 22,855	RCT	[17]
Myocardial infarction	€ 5,544	€ 4,158	€ 6,930	Registry	[18]
Stroke	€ 20,409	€ 15,306	€ 25,511	Observational study	[19]
Major adverse limb event	€ 7,914	€ 5,935	€ 9,892	Observational study	[20]
Hospitalization for heart failure	€ 6,528	€ 4,896	€ 8,160	Registry	[21]
Chronic care costs					
Coronary artery disease	€ 3,214	€ 2,411	€ 4,018	Registry	[22]
Cerebrovascular disease	€ 3,430	€ 2,573	€ 4,288	Registry	[22]
Peripheral artery disease	€ 2,451	€ 1,838	€ 3,064	Registry	[23]
Chronic heart failure	€ 4,023	€ 3,018	€ 5,029	Registry	[22]
Medication costs					
Statin	€ 14.24	€ 10.68	€ 17.80	Official tariff	[24]
Ezetimibe	€ 20.27	€ 15.20	€ 25.34	Official tariff	[24]
PCSK9 inhibitor	€ 5,547.56	€ 4,160.67	€ 6,934.45	Official tariff	[24]
Blood pressure lowering*	€ 10.63	€ 7.97	€ 13.29	Estimated tariff	[24]
Aspirin	€ 8.63	€ 6.47	€ 10.79	Official tariff	[24]
Low-dose DOAC	€ 859.59	€ 644.69	€ 1,074.49	Official tariff	[24]
Pharmacy	€ 7	€ 5.52	€ 9.20	Official tariff	[1,24]
Doctor's visit	€ 96	€ 71.73	€ 119.53	Official tariff	[1]
*per standard dose					
Utilities					
Coronary artery disease	0.70	0.59	0.80	Observational study	[5]
Cerebrovascular disease	0.66	0.19	0.78	Observational study	[5]
Peripheral artery disease	0.73	0.62	0.80	Observational study	[5]
Chronic heart failure	0.62	0.19	0.73	Observational study	[5]
Death	0			Definition	

PCSK9 = proprotein convertase subtilisin/kexin type 9, DOAC = direct oral anticoagulant.

Supplemental Table 3: Direct comparison between lifetime benefit-based treatment and risk factor-based treatment

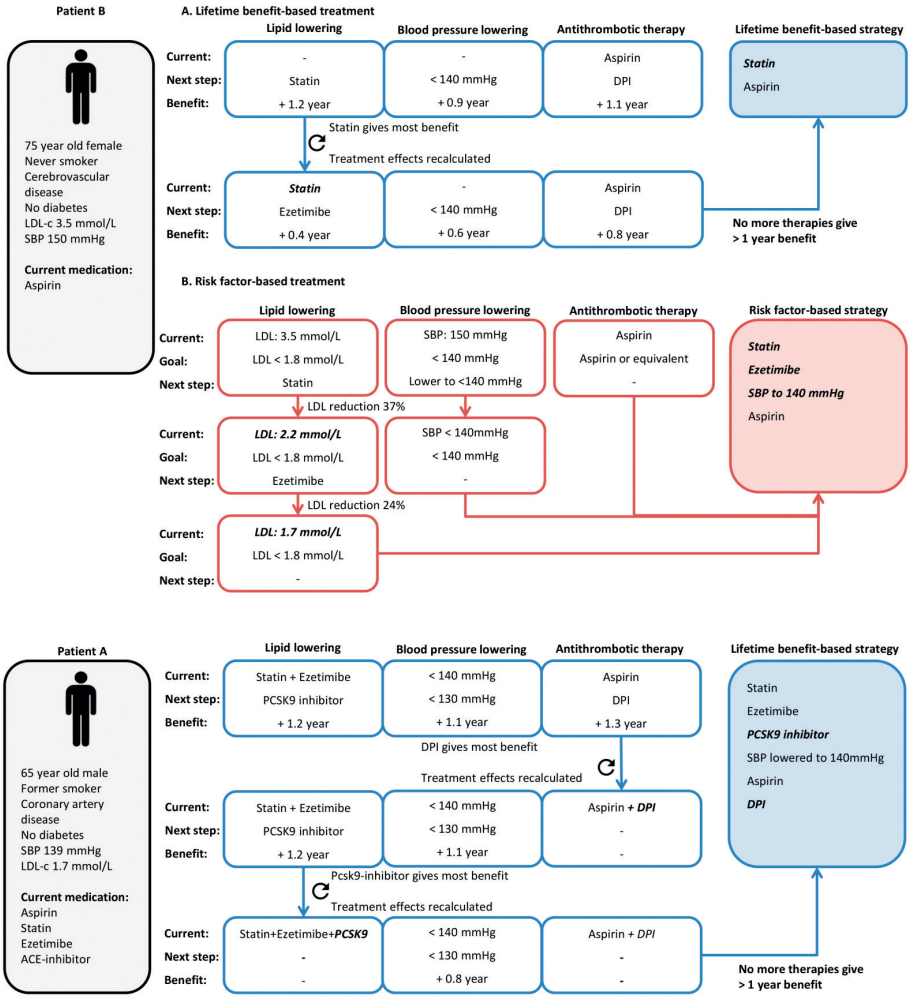
	Predicted lifetime benefit based		
N = 7,697	**≥6 months**	**≥12 months**	**≥24 months**
ICER vs risk-factor based (€/QALY)	38,340	36,585	13,775
Prob. of cost-effectiveness (<20,000 €/QALY)	0.004	0.204	0.974
Prob. of cost-effectiveness (<50,000 €/QALY)	0.845	0.829	>0.99
Prob. of cost-effectiveness (<80,000 €/QALY)	>0.99	0.937	>0.99

Supplemental Table 4: Results from the scenario analyses

	Lifetime benefit-based			Risk factor- based		
Scenario	Incremental costs (mln Euros)	Incremetnal QALYs	ICER	Incremental costs (mln Euros)	Incremetnal QALYs	ICER
Medication costs + 25%	€ 180.1	9114	€ 19,756	€ 88.3	6421	€ 13,752
Medication costs - 25%	€ 101.7	9114	€ 11,162	€ 46.5	6421	€ 7,240
Event probabilities +25%	€ 151.5	11,769	€ 12,869	€ 78.1	8637	€ 9,040
Event probabilities -25%	€ 136.6	7206	€ 18,959	€ 60.4	4683	€ 12,904
Mortality +25%	€ 136.4	8178	€ 16,677	€ 61.3	5086	€ 12,063
Mortality -25%	€ 167.8	12,598	€ 13,316	€ 89.7	9066	€ 9,895
Utilities lower limit	€ 140.9	5841	€ 24,122	€ 67.4	3626	€ 18,586
Utilities upper limit	€ 140.9	10,620	€ 13,267	€ 67.4	7544	€ 8,934
Medication efficacy lower bounds	€ 141.0	11,665	€ 12,084	€ 73.5	7883	€ 9,329
Medication efficacy upper bounds	€ 139.6	6840	€ 20,412	€ 73.8	6080	€ 12,132
Similar discount cost/benefit (3%)	€ 160.5	6634	€ 24,191	€ 76.7	4806	€ 15,960
Undiscounted	€ 260.9	12,887	€ 20,241	€ 125.1	8830	€ 14,167
Event penalties 0.1	€ 140.9	9666	€ 14,577	€ 67.4	6883	€ 9,792
75% price reduction after patent expiry	€ 88.3	9114	€ 9,689	€ 47.4	6421	€ 7,379
No price reduction after patent expiry	€ 167.2	9114	€ 18,344	€ 77.4	6421	€ 12,055
Statin intolerance 10% of population	€ 145.2	8705	€ 16,685	€ 104.0	6604	€ 15,744
Simulated population with AF and CHF	€ 151.2	9496	€ 15,925	€ 66.1	7042	€ 9,383
Excluding Dual pathway inhibition	€ 131.6	6819	€ 19,294			
Simulated bleeding probabilities	€ 139.5	8319	€ 16,765	€ 68.0	6306	€ 10,791
No disutility from medication	€ 140.9	9444	€ 14,919	€ 67.4	6680	€ 10,089
Double disutility for medication	€ 140.9	8786	€ 16,036	€ 67.4	6163	€ 10,936
70% DPI in risk-factor based treatment				€ 123.3	10,513	€ 11,725
100% DPI in risk-factor based treatment				€ 142.7	12,021	€ 11,874
Reduced DOAC effectivity after 10 years	€ 145.3	8573	€ 16,946			
Only patients over 75 years	€ 1.5	451	€ 3,266	€ 4.9	621	€ 7,825
Only patients below 75 years	€ 146.1	9844	€ 14,845	€ 76.1	7780	€ 9,775

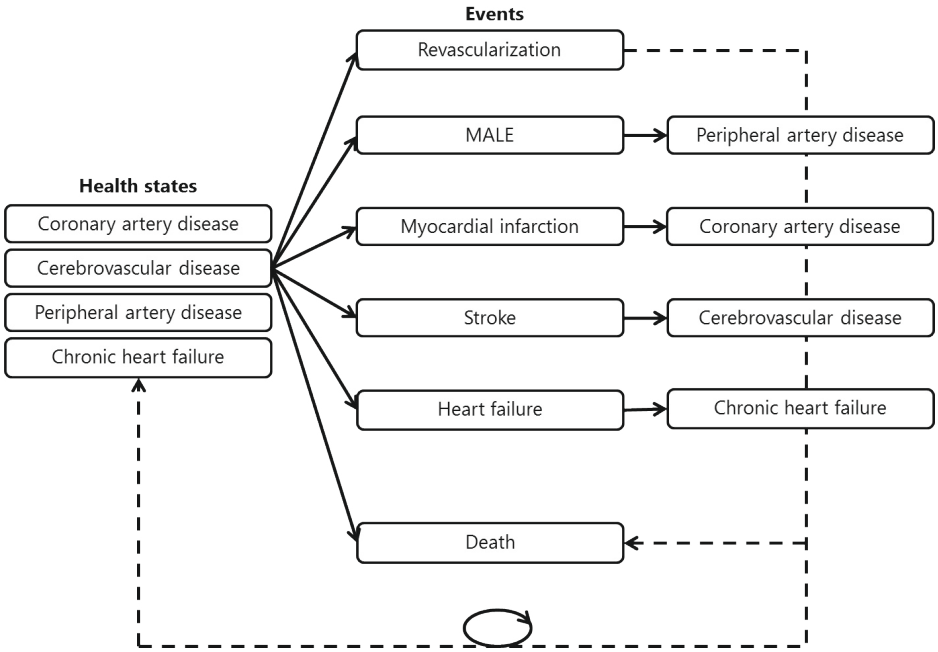
Results from all scenario sensitivity analyses for lifetime benefit-based treatment and risk factor-based treatment.

Supplemental figure S1: Patient example of benefit- and risk factor-based treatment



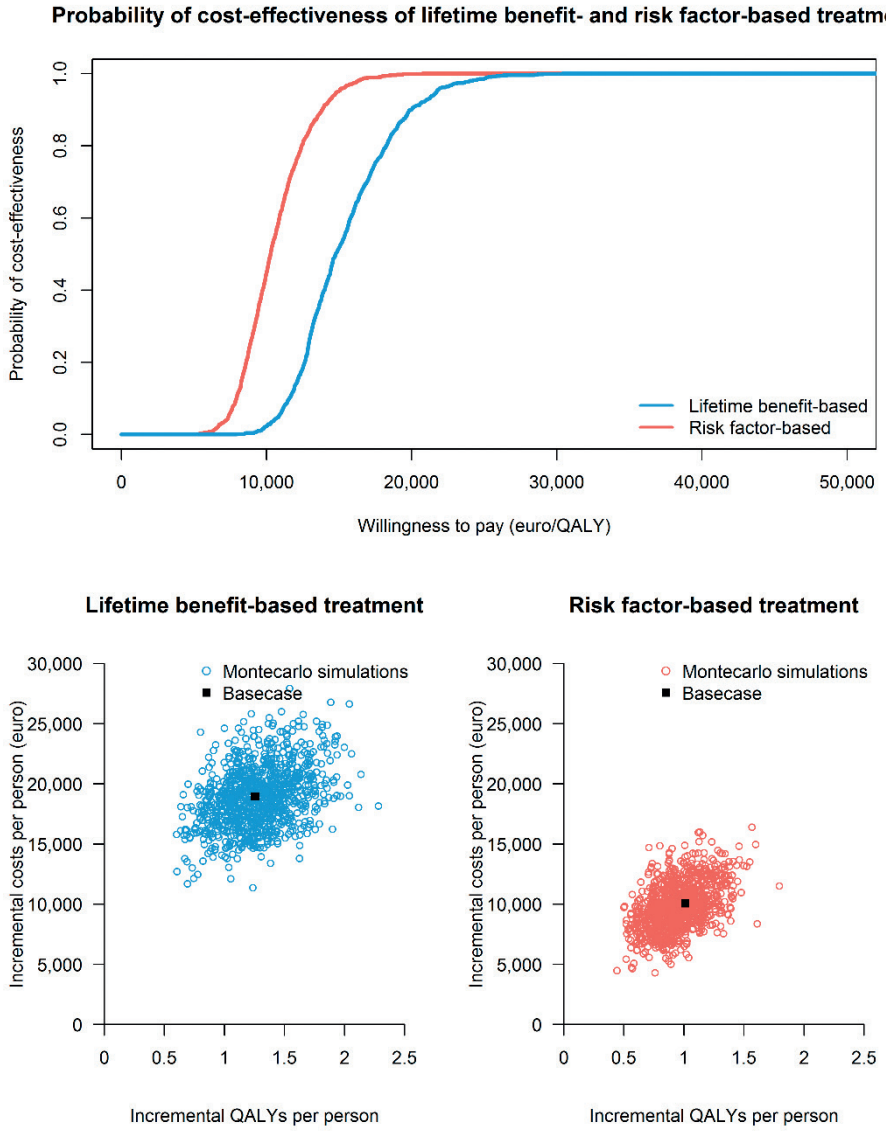
Patient example of a lifetime benefit-based and risk factor-based treatment strategy. At baseline, this patient was only treated with aspirin. Only a statin or dual pathway inhibition would lead to an increase of more than 1 year in CVD-free life expectancy. According to the risk factor-based strategy, additional therapy for lipids and blood pressure would be considered. SBP = systolic blood pressure, LDL = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin type 9, DPI = dual pathway inhibition.

Supplemental figure S2: schematic overview of the microsimulation model



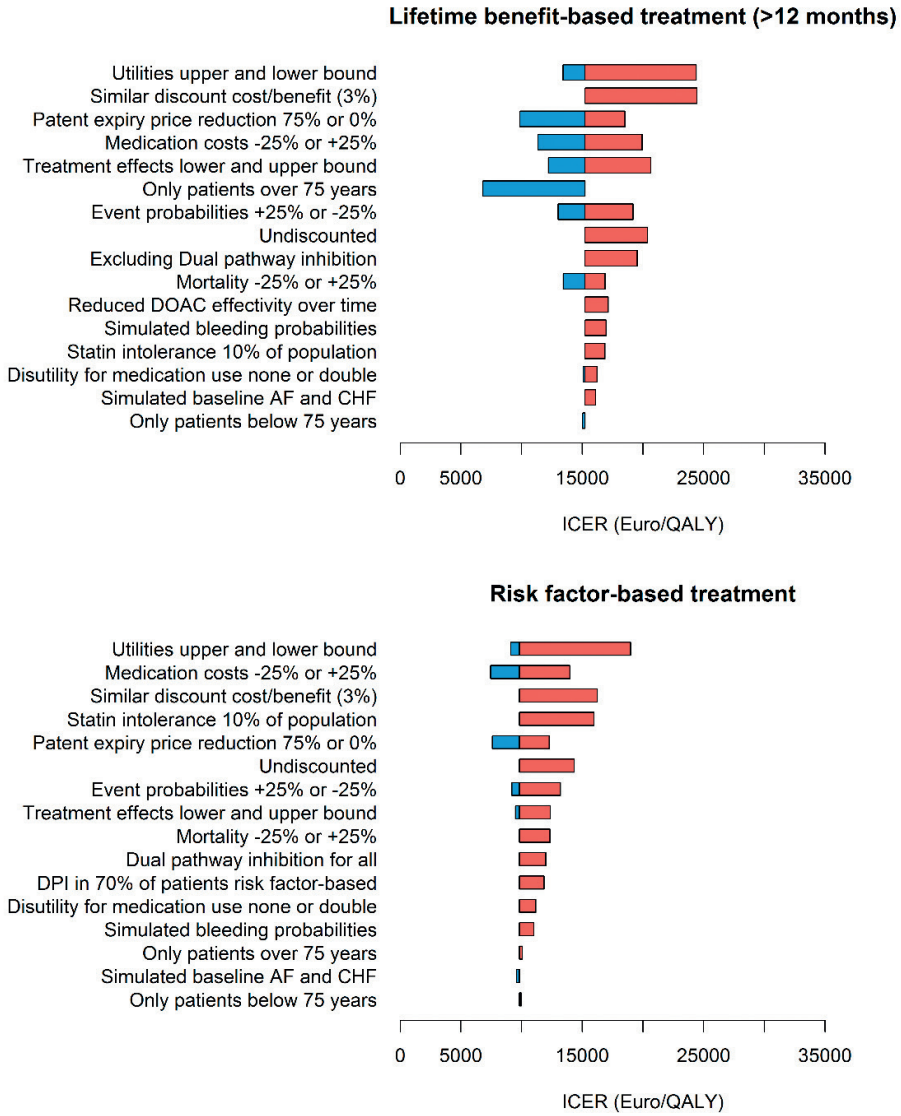
Supplemental figure S2: schematic overview of the microsimulation model which was run for a lifetime horizon with 1-year intervals. All patients started in the health state present in their medical history and had a certain probability of having an acute event every year, thereby transferring to the associated healthstate. MALE = major adverse limb event.

Supplemental figure S3: Probabilistic sensitivity analyses of benefit- and risk factor-based treatment



Supplemental figure S3: Probabilistic sensitivity analyses presented in cost-effectiveness planes and cost-effectiveness acceptability curves. Results are from a treatment threshold of 12 months. Upper: the probability of cost-effectiveness of benefit- or risk factor-based treatment in comparison to treatment at baseline for different thresholds of willingness to pay per QALY. Lower: Incremental costs and QALYs benefit or risk factor-based treatment in comparison to treatment at baseline. Each dot is 1 of 1000 Monte Carlo simulations. QALY = quality adjusted lifeyear.

Supplemental figure S4: One-way sensitivity analyses for lifetime benefit-based and risk factor-based treatment



Supplemental figure S4: Scenario analyses varying model assumptions for benefit- and risk factor-based treatment. AF = atrial fibrillation, CHF = congestive heart failure, ICER = incremental cost-effectivity ratio, QALY = quality adjusted lifeyear. DPI = Dual pathway inhibition.

References

1. Hakkaart-van Roijen, L., van der Linden, N., Bouwmans, C., Kanters, T. & Swan Tan, S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. (2015).
2. Koopman, C., van Dis, I., Visseren, F. L. J., Vaartjes, I. & Bots, M. L. Hart- en vaatziekten in Nederland 2012 Cijfers over risicofactoren, ziekte en sterfte Gegevens. (2012).
3. Buddeke J, Valstar GB, van Dis I, Visseren FLJ, Bots ML, den Ruijter HM, V. I. Hart- en vaatziekten in Nederland 2017, cijfers over leefstijl, risicofactoren, ziekte en sterfte. (2017).
4. Law, M. R., Morris, J. K. & Wald, N. J. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* **338**, b1665–b1665 (2009).
5. Sullivan, P. W., Slejko, J. F., Sculpher, M. J. & Ghushchyan, V. Catalogue of EQ-5D Scores for the United Kingdom. *Med. Decis. Mak.* **31**, 800–804 (2011).
6. Bress, A. P. *et al.* Cost-Effectiveness of Intensive versus Standard Blood-Pressure Control. *N. Engl. J. Med.* **377**, 745–755 (2017).
7. Briggs, A. Probabilistic Analysis of Cost-Effectiveness Models: Statistical Representation of Parameter Uncertainty. *Value Heal.* **8**, 1–2 (2005).
8. Mantopoulos, T., Mitchell, P. M., Welton, N. J., McManus, R. & Andronis, L. Choice of statistical model for cost-effectiveness analysis and covariate adjustment: empirical application of prominent models and assessment of their results. *Eur. J. Heal. Econ.* **17**, 927–938 (2016).
9. Berkelmans, G. F. N., Greving, J. P., van der Graaf, Y., Visseren, F. L. J. & Dorresteijn, J. A. N. Would treatment decisions about secondary prevention of CVD based on estimated lifetime benefit rather than 10-year risk reduction be cost-effective? *Diagnostic Progn. Res.* **4**, 4 (2020).
10. Stam-Slob, M. C., van der Graaf, Y., de Boer, A., Greving, J. P. & Visseren, F. L. J. Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease. *Int. J. Cardiol.* **253**, 148–154 (2018).
11. Briggs, A., Sculpher, M. & Claxton, K. *Decision Modelling for Health Economic Evaluation*. (Oxford University Press, 2006).
12. Bui, A. L., Horwich, T. B. & Fonarow, G. C. Epidemiology and risk profile of heart failure. *Nat. Rev. Cardiol.* **8**, 30–41 (2011).
13. Heeringa, J. *et al.* Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur. Heart J.* **27**, 949–953 (2006).
14. Hutchins, R., Pignone, M. P., Sheridan, S. L. & Viera, A. J. Quantifying the utility of taking pills for preventing adverse health outcomes: a cross-sectional survey. *BMJ Open* **5**, e006505–e006505 (2015).
15. Simons, P. C. G., Algra, A., Van De Laak, M. F., Grobbee, D. E. & Van Der Graaf, Y. Second manifestations of ARTerial disease (SMART) study: Rationale and design. *Eur. J. Epidemiol.* **15**, 773–781 (1999).
16. Vidal-Petiot, E. *et al.* Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* **388**, 2142–2152 (2016).
17. Osnabrugge, R. L. *et al.* Cost-effectiveness of percutaneous coronary intervention versus bypass surgery from a Dutch perspective. *Heart* **101**, 1980–1988 (2015).
18. Soekhlal, R. R., Burgers, L. T., Redekop, W. K. & Tan, S. S. Treatment costs of acute myocardial infarction in the Netherlands. *Netherlands Hear. J.* **21**, 230–235 (2013).
19. van Eeden, M. *et al.* The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year poststroke. *BMJ Open* **5**, e008220 (2015).

20. van den Houten, M. M. L. *et al.* Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication. *Br. J. Surg.* **103**, 1616–1625 (2016).

21. Stevanovic, J., Denee, L., Koenders, J. M. & Postma, M. J. Incidence Description and Costs of Acute Heart Failure in the Netherlands. *Value Heal.* **17**, A328 (2014).

22. RIVM. volksgezondheidenzorg.info. https://www.volksgezondheidenzorg.info/.

23. Zorginstituut Nederland. Verbetersignalement Perifeer arterieel vaatlijden. 1–76 (2016).

24. Zorginstituut Nederland. medicijnkosten.nl. https://www.medicijnkosten.nl/.

CHAPTER 10

Risk stratification in patients with ischemic stroke and residual cardiovascular risk with current secondary prevention

Mari Nordbø Gynnild, Steven H. J. Hageman, Jannick A. N. Dorresteijn, Olav Spigset, Stian Lydersen, Torgeir Wethal, Ingvild Saltvedt, Frank L. J. Visseren, Hanne Ellekjær

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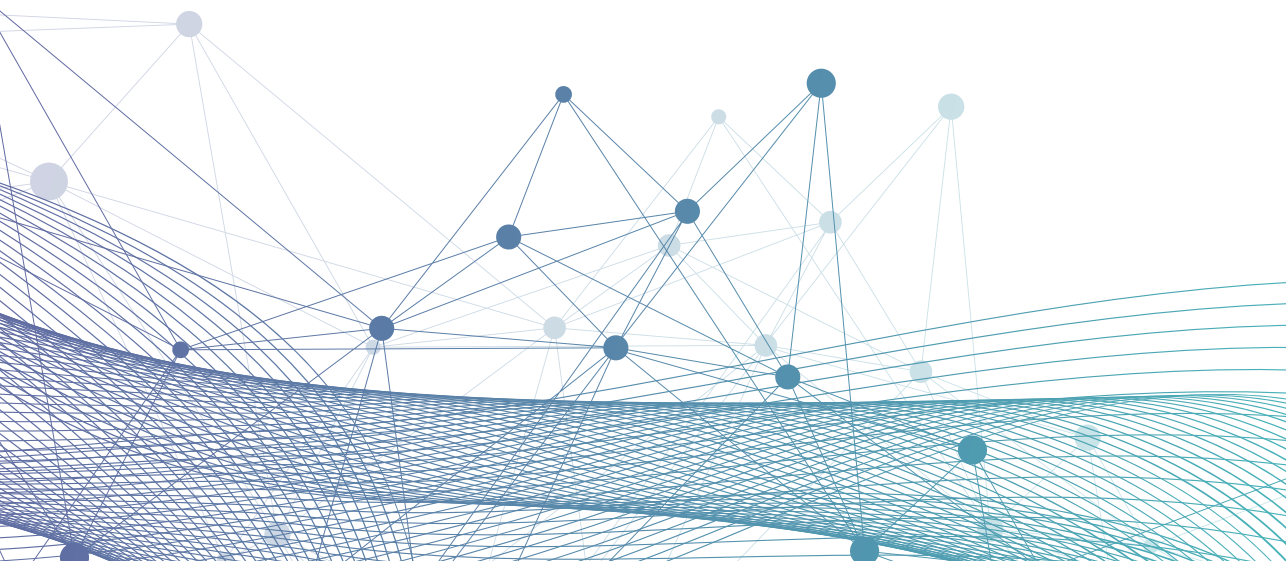


Abstract

Purpose: Suboptimal secondary prevention in patients with stroke causes a remaining cardiovascular risk desirable to reduce. We have validated a prognostic model for secondary preventive settings and estimated future cardiovascular risk and theoretical benefit of reaching guideline recommended risk factor targets.

Patients and methods: The SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model for 10-year and lifetime risk of cardiovascular events was applied to 465 patients in the Norwegian Cognitive Impairment After Stroke (Nor-COAST) study, a multicenter observational study with two-year follow-up by linkage to national registries for cardiovascular disease and mortality. The residual risk when reaching recommended targets for blood pressure, low-density lipoprotein cholesterol, smoking cessation and antithrombotics was estimated.

Results: In total, 11.2% had a new event. Calibration plots showed adequate agreement between estimated and observed 2-year prognosis (C-statistics 0.63, 95% confidence interval 0.55-0.71). Median estimated 10-year risk of recurrent cardiovascular events was 42% (Interquartile range (IQR) 32-54%) and could be reduced to 32% by optimal guideline-based therapy. The corresponding numbers for lifetime risk were 70% (IQR 63-76%) and 61%. We estimated an overall median gain of 1.4 (IQR 0.2-3.4) event-free life years if guideline targets were met.

Conclusions: Secondary prevention was suboptimal and residual risk remains elevated even after optimization according to current guidelines. Considerable interindividual variation in risk exists, with a corresponding variation in benefit from intensification of treatment. The SMART-REACH model can be used to identify patients with the largest benefit from more intensive treatment and follow-up.

Introduction

Patients with ischemic stroke have an increased risk of recurrent cardiovascular events.[1] Secondary prevention aims to reduce the risk of recurrence, but implementation of guideline recommendations in clinical practice is suboptimal with poor risk factor control and low adherence to medications.[2-5] Consequently, the residual cardiovascular risk remains elevated. However, there is a substantial interindividual variation in the risk of recurrent events among patients with established cardiovascular disease (CVD).[6-8] This variation results from a composite of several prognostic features like age, genetics, cardiovascular risk factors, effectiveness of preventive therapy, competing risks and remaining life-expectancy.[6,9,10] Appropriate identification of patients at high risk is important because they most likely gain greatest clinical benefit from intensive treatment of cardiovascular risk factors, novel therapies on top of standard treatment[9,11,12] and a more intensive and multidisciplinary follow-up.

Patients with stroke are heterogeneous and systemic atherosclerotic disease and overlapping stroke etiologies are common.[13-15] Existing risk stratification tools for stroke patients often focus on short-time risk of recurrent stroke [16-18], while recent long-term follow-up studies have shown that risk of a fatal recurrent stroke and a fatal cardiac event is similar.[1] The SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model[19] is a previously derived, externally validated model estimating individual residual 10-year risk and lifetime risk for recurrent stroke, myocardial infarction and vascular death. The model is intended for use in all patients with clinically manifest atherosclerotic vascular disease and may be useful in routine clinical stroke care. However, it is unknown if this model gives reliable prognostic risk information in a stroke population. Our aim is to estimate future cardiovascular risk using the SMART-REACH model for secondary preventive settings after first validating the model in a stroke cohort. Furthermore, we aim to estimate the theoretical benefit of reaching guideline-recommended risk factor targets.

Material and methods

Study population

We included 729 home-dwelling patients admitted with acute ischemic stroke in the Nor-COAST (Norwegian Cognitive Impairment After Stroke) Study, a multicenter, prospective cohort study consecutively including patients at five Norwegian stroke units from May 2015 to March 2017. Details have been reported previously.[2,20]

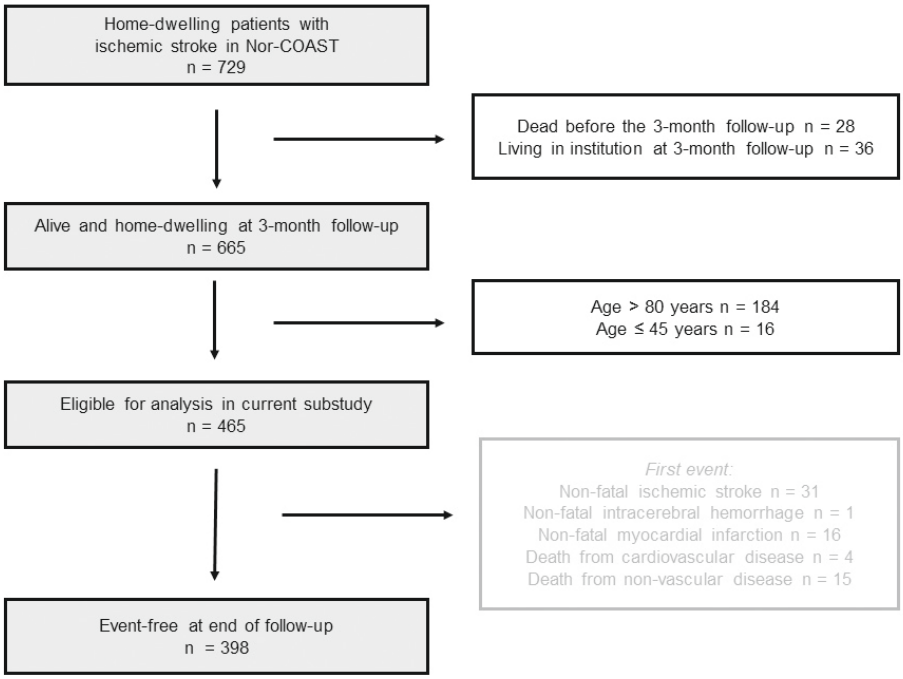
Follow-up for the current substudy started at 3 months poststroke and patients who died before the scheduled 3-month visit (n = 28) were excluded. Since patients expected to have difficulties returning for follow-up visits and patients not dependent in daily activities were excluded in the original SMART-REACH derivation and validation cohorts[19] and the model is intended for patients with stable vascular disease in which additional preventive therapy is considered, we excluded patients living in nursing homes (n = 36). As the SMART-REACH model was derived in patients aged 45 to 80 years, patients outside this age range were excluded, leaving 465 patients eligible for analysis (**Figure 1**). Patients were assessed with self-report questionnaires, clinical assessments and blood sampling 3 months poststroke at the outpatient clinic. Patients unable to attend were assessed by telephone or by proxy information. The Regional Committee for Medical and Health Research Ethics in North Norway (REC number 2015/171 and 2017/1462) approved the study. All participants gave their written informed consent before inclusion or by proxy if unable. This study was conducted in accordance with the Declaration of Helsinki.

Outcomes

We defined recurrent cardiovascular events as stroke, myocardial infarction (MI) or cardiovascular death, whichever occurred first. All hospitalized events from 3 months poststroke (stable phase) to 31 December 2018 were identified by linkage to the Norwegian Stroke Registry and the Norwegian Cardiovascular Disease Registry. The Norwegian Causes of Death Registry provided follow-up information on primary cause of death.

We defined recurrent stroke as either registration in the Norwegian Stroke Registry or the Norwegian Cardiovascular Disease Registry (main diagnosis)[21] according to the International Classification of Diseases, 10th revision (ICD-10); I61, I63 and I64. Admission with main or secondary diagnosis of MI (ICD-10; I21, I22 and I24) according to the Norwegian Cardiovascular Disease Registry was defined as subsequent MI[22]. Cardiovascular death was defined as ICD-code I00-I99 registered as primary cause of death or death within 28 days after a recurrent stroke or MI. The quality of the information in the registries have been described previously[21,22] (Supplementary methods).

Figure 1: Flowchart of inclusion and exclusion of patients



Residual cardiovascular risk

The SMART-REACH model[19] was used to predict residual cardiovascular risk after initial treatment. The model is a Fine and Gray competing risk model for 10-year and lifetime predictions of cardiovascular events (non-fatal stroke, non-fatal MI and CVD mortality) and non-cardiovascular mortality, where age is used as the underlying time function.[9,19] The model uses the following predictors: age, sex, current smoking, diabetes mellitus, history of heart failure, history of atrial fibrillation, systolic blood pressure (BP), serum creatinine concentration, number of locations of CVD (cerebrovascular, coronary and peripheral artery disease) and total and low-density lipoprotein cholesterol (LDL-C). Risks were estimated based on clinical measurements at the 3-month visit since the model is intended for patients with stable CVD in which additional therapy is considered. This timepoint also roughly corresponds to the guideline recommendations to examine risk factors and initiate or modify treatment at 1-3 months after an acute event.[23] Table S1 show detailed definitions of all variables included in the SMART-REACH model and more information about the SMART-REACH model can be found in Supplementary Methods.

External validation

The external validity of the SMART-REACH model was assessed for risks at 2 years of follow-up. We expressed discrimination (the extent to which patients who develop an event also had higher estimated risk than those who were event-free) with Harrell's C-statistic.[24] We showed the agreement between predicted and observed 2-year risk (calibration) in a flexible calibration curve based on local polynomial regression fitting (*loess* function in R).[25] First, the cohort was divided in 100 quantiles of predicted risk. Then, a local regression was used to smoothly explain the observed cumulative incidence per group by the mean predicted risk per group. The smooth calibration plot and confidence bounds were subsequently predicted from this model over the whole range of relevant predicted risks (cohort predicted risk quantile 0.025 up to 0.975). As event rates vary between geographic locations [8,26] and may be influenced by selection of study participants, recalibration to the population of interest is often necessary.[6,19,25] The intercept of the SMART-REACH model for both CVD events and non-CVD mortality was recalibrated ("calibration-in-the-large") to Nor-COAST by subtracting the expected-observed ratio from the linear predictor (Supplementary Methods).[25,27]

Impact of optimization of risk factors

Reaching the recommended targets according to Norwegian guidelines[23] for systolic BP (≤140 mmHg), LDL-C (≤1.8 mmol/L), smoking cessation and use of antithrombotic agents was defined as optimization of risk factor control and possible benefits if each risk factor was controlled was quantified by the SMART-REACH model.

The relative effect of treating risk factors to recommended targets was retrieved from meta-analyses[28-30] (details described in Table S2) and combined with the competing risk-adjusted Cox proportional hazard function from the SMART-REACH model according to previously described methods.[9,10,19] A hazard ratio (HR) of 0.80 was assumed per 10 mmHg reduction in systolic BP[29] and a HR of 0.78 was assumed per 1.0 mmol/L reduction in LDL-C[28] regardless of whether this was achieved by lifestyle changes or medication. Smoking cessation was assumed to reduce the risk of both CVD events (HR 0.60)[31] and non-CVD mortality (HR 0.73).[32] We assumed that no use of antithrombotic therapy was associated with the inverse effect of starting (at least) aspirin (HR 1/0.81 = 1.23).[30] Patients who had already achieved an individual target at 3 months were modeled with a HR of 1.00 for that target.

To estimate the benefit of reaching the guideline-recommended risk factor targets, the cardiovascular risk was estimated twice with the SMART-REACH model for each individual. First, we estimated the risk with the 3-month risk factor levels and treatment, and next we estimated the risk with the assumption that all risk factors met the guideline-recommended targets. The difference between estimated risk with 3-month risk factor levels and estimated risk when risk factors are at target

corresponds to an individual's estimated absolute risk reduction (ARR). We obtained the following estimates from the model: 1) 10-year risk of CVD events, 2) lifetime risk of CVD events, defined as the risk of having an event before the 90th life-year, and 3) the life-expectancy free of CVD events. We calculated the following treatment effects: 1) absolute CVD risk reduction in the next 10 years, 2) absolute lifetime CVD risk reduction and 3) gain in CVD-free life expectancy. The therapy benefits from achieving treatment targets for BP, LDL-C and smoking were first estimated separately. Next, the overall benefit of achieving optimal control of all targets (including use of antithrombotic therapy) was modelled and the relevant ARRs calculated.

Statistics

Baseline characteristics at the index stroke event were described by means with standard deviations (SD) and proportions as appropriate. Estimated risks and ARRs are reported as median with interquartile range (IQR). We visually compared the distribution of estimated risk on current treatment and estimated risk with risk factor(s) at targets in density plots. We imputed missing data for clinical measurements at 3 months for prediction of CVD risk by means of single imputation using predictive mean matching, including all variables used in the analyses. Details and amount of missing data are shown in Table S3. All analyses were conducted using Stata version 16.1 or R statistical software V.4.0.2 (www.r-project.org, packages Hmisc, Survival, Cmprsk, Rms, Pec).

Results

Table 1 shows characteristics at index stay and **Table 2** presents achieved risk factor levels 3 months poststroke. Mean LDL-C was 2.1 mmol/L (SD 0.8), mean % relative LDL-C reduction from index stay to 3 months was 24% (SD 33) and 43% reached the target at 3 months. Mean systolic BP was 140 mmHg (SD 19), 51% reached the BP target and 50% (55/109) of smokers quitted smoking at 3 months. Antithrombotic drugs were used by 98%, corresponding numbers for lipid-lowering and antihypertensive drugs were 89% and 73%. Detailed information on cardiovascular medications in use is shown in Table S4. In total, 80% (302/376) reported high adherence at 3 months defined as a score of 4 on Morisky Medication Adherence Scale 4.[2,33]

In total, 52 cardiovascular events and 15 non-cardiovascular deaths were observed from 3 months poststroke during a follow-up of median 2.20 years (IQR 1.79 to 2.62), totally 991 patient-years (**Figure 1**). In total, 61% (n = 32) of the patients with a recurrent cardiovascular event had a non-fatal stroke, 31% (n = 16) experienced a non-fatal MI and 8% (n = 4) died due to cardiovascular causes.

Table 1: Characteristics at the index stay (N = 465)

	n (% of N) or mean (SD)
Age	69.0 (8.1)
Sex, male	287 (62%)
Atrial fibrillation	101 (22%)
Diabetes mellitus	92 (20%)
History of hypertension	252 (54%)
History of hypercholesterolemia	253 (54%)
Previous cerebrovascular disease	108 (23%)
Coronary artery disease	79 (17%)
Peripheral artery disease	35 (8%)
Number of vascular areas affected[a] 1, 2 or 3	369 (79%), 78 (17%), 18 (4%)
Heart failure	11 (2%)
Current smoker	109 (24%)
Previous smoker	174 (38%)
Estimated GFR[b] (ml/min/1.73 m^2)	79 (16)
Body Mass Index (kg/m^2)	26.6 (4.2)
High-sensitive CRP concentration (mg/L)	9.6 (18.0)
Stroke subtype[c] (n = 450)	
Large artery disease	49 (11%)
Cardioembolic	103 (23%)
Small vessel disease	105 (23%)
Other causes	12 (3%)
Unknown or multiple causes	181 (40%)
NIHSS[d] at discharge (n = 437)	1.7 (2.4)
Charlson Comorbidity Index	3.7 (1.9)
Frail[e]	34 (7%)
Cognitive impairment[f]	13 (3%)

Notes: [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]GFR calculated by CKD-EPI equation. [c]According to TOAST: Trial of ORG 10172 in Acute Stroke Treatment. [d]Stroke severity according to National Institutes of Health Stroke Scale (NIHSS). [e]Measured by the 5-item Fried criteria. [f]Defined as score ≥ 3 on Global Deterioration Scale. Detailed definitions in supplementary methods.
Abbreviations: CRP; C-reactive protein, eGFR; Estimated glomerular filtration rate.

Estimated risk of recurrent events

The average observed 2-year risk in Nor-COAST was higher than the average predicted 2-year risk with the SMART-REACH model (Figure S1) (expected-observed ratio 0.54). After recalibration, the calibration curve showed adequate agreement

between predicted and observed risk and modest discrimination (C-statistics 0.63, 95% CI 0.55 to 0.71) (Figure 2). Discrimination was slightly lower when excluding patients with cardioembolic stroke etiology (C-statistics 0.61, 95% CI 0.53 to 0.70, Figure S2). Sex-specific analyses showed C-statistics 0.65 (95% CI 0.56 to 0.73) for men and 0.57 (95% CI 0.41 to 0.74) for women (Figure S3).

Median estimated 10-year risk of recurrent events was 42% (IQR 32 to 54) (Table 3, Figure 3 and Figure S4-S6). Median lifetime risk was 70% (IQR 63 to 76). Ten-year cardiovascular risk increased with age, while lifetime risk was highest in younger patients (Figure S7, Table S5-S6). In total, 56% of the patients in the highest 10-year risk quartile had polyvascular disease (Table S5) and 22% were smoking; the corresponding proportions for patients in the lowest risk quartile were 2% and 5%, respectively.

Table 2: Risk factor levels at the index stay and the 3-month visit (n = 465)

	Index stay[a]	**3-month visit**
Systolic blood pressure (mmHg)	140 (20)	140 (19)
Diastolic blood pressure (mmHg)	80 (13)	83 (12)
LDL-C (mmol/L)	3.1 (1.1)	2.1 (0.8)
HDL-C (mmol/L)	1.4 (0.5)	1.5 (0.5)
Total cholesterol (mmol/L)	4.9 (1.3)	4.0 (0.9)
Current smoking	109 (23%)	55 (12%)
Use of secondary preventive medications		
Lipid-lowering drugs[b]	415 (89%)	412 (89%)
Antihypertensive drugs[c]	320 (69%)	338 (73%)
Antithrombotic drugs[d]	456 (98%)	455 (98%)

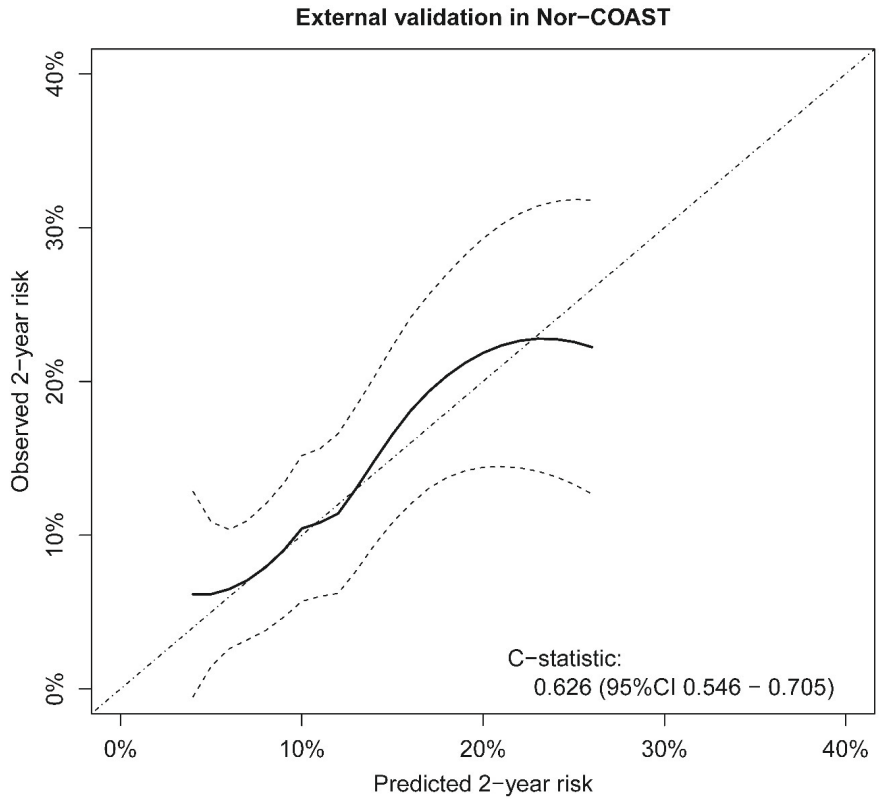
Notes: Values are mean (standard deviation) or n (%). Missing values are imputed by single imputation using predictive mean matching. [a]Concentrations of cholesterol were measured the first day after admission and blood pressure levels at day 7 or at the day of discharge. [b]Use of lipid-lowering drugs as discharge was defined as use of drugs belonging to ATC group C10. [c]Use of antihypertensive drugs at discharge was defined as use of drugs belonging to ATC groups C03A, C07, C08, C09A/B, C09C/D, C02A, C02C and C02D. [d]Use of antithrombotic drugs at discharge was defined as use of drugs belonging to ATC group B01A. Detailed information about types of medications in use are shown in Supplementary Table S4.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ATC, *Anatomical Therapeutic Chemical* classification system.

Estimated benefit from optimization of risk factors

Figure S4-S6 shows the benefits from achieving targets for LDL-C, systolic BP and smoking cessation separately. Median 10-year ARR if patients with elevated LDL-C reached the target was 4% (IQR 2 to 7) and gain in CVD-free life-years was 0.8 years (IQR 0.4 to 1.6) (Figure S4b). Median 10-year ARR if patients with elevated BP reached the target was 8% (IQR 3 to 14) and 1.6 CVD-free life-years gained (IQR 0.6 to 3.1)

(Figure S5b). Smoking cessation led to 14% (IQR 12 to 16) 10-year ARR and median 3.4 CVD-free life-years gained (IQR 2.4 to 4.3) (Figure S6).

Figure 2: Flexible calibration curve showing the agreement between quantiles of estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model versus observed 2-year risk after recalibration



If all targets were achieved, the overall median 10-year ARR was 6% (IQR 1 to 14) and lifetime ARR was 6% (IQR 1 to 15) (Table 3 and Figure 3). The population could gain median 1.4 (IQR 0.2 to 3.4) CVD-free life years. After optimization, the residual median 10-year risk had decreased to 32% (IQR 24 to 44) and lifetime CVD risk had decreased to 61% (IQR 49 to 70) with a CVD-free life expectancy of 82.2 (IQR 78.9 to 85.4) years. If all targets were reached, the 10-year risk would be < 20% for 16% of the patients and < 30% for 43%. Treatment benefits in terms of gain in CVD-free life years were highest in younger patients with elevated risk factor levels (Table S8).

Table 3: Estimated prognosis and benefits of optimal guideline-therapy

	Total (n = 465)	**SBP > 140 mmHg (n = 226)**	**LDL-C > 1.8 mmol/L (n = 265)**	**Smokers (n = 55)**	**No antithrombotics (n = 10)**
Current estimated risk					
10-year CVD risk (%)	42 (32 to 54)	44 (34 to 54)	41 (32 to 52)	52 (39 to 66)	53 (46 to 65)
Lifetime CVD risk[a] (%)	70 (63 to 76)	67 (61 to 75)	69 (63 to 75)	76 (74 to 81)	77 (68 to 84)
CVD-free life expectancy[b] (years)	80.4 (76.4 to 83.5)	81.8 (78.9 to 84.3)	80.7 (76.8 to 83.6)	75.3 (72.2 to 80.1)	79.2 (75.8 to 82.3)
Remaining CVD-free life-years[c]	9.9 (7.2 to 13.5)	9.5 (7.2 to 12.3)	10.0 (7.4 to 13.3)	7.6 (4.8 to 9.9)	8.1 (6.3 to 9.7)
Treatment benefits from optimal guideline therapy[d]					
10-year ARR (%)	6 (1 to 14)	12 (6 to 20)	9 (3 to 16)	17 (15 to 25)	17 (8 to 34)
Lifetime ARR (%)	6 (1 to 15)	14 (7 to 23)	11 (3 to 19)	15 (10 to 30)	22 (4 to 47)
Gain in CVD-free life expectancy (years)	1.4 (0.2 to 3.4)	2.6 (1.2 to 4.6)	2.0 (0.7 to 4.1)	4.4 (2.9 to 8.0)	5.1 (1.2 to 8.8)

Notes: Values are median (interquartile range). [a]Defined as risk of having an event before the 90th life-year. [b]Median life expectancy without a CVD event or death. [c]Number of years without a CVD-event due to current treatment. [d]Defined as systolic blood pressure 140 mmHg, LDL-C 1.8 mmol/L, smoking cessation and use of antithrombotic medications.
Abbreviations; LDL-C, Low density lipoprotein cholesterol; CVD, Cardiovascular disease; ARR, Absolute risk reduction.

Discussion

In this observational study of patients with ischemic stroke, we found that a notable proportion suffered from a recurrent event the first 2 years poststroke and showed substantial variation in estimated future cardiovascular risk and treatment benefit from intensification of secondary prevention. We revealed a remaining preventive potential by reaching the guideline-recommended treatment targets and demonstrated that the SMART-REACH model generates prognostic risk information reasonably well in stroke patients.

Studies quantifying future cardiovascular risk in stroke populations are scarce. However, comparable findings of risk and potential benefit variations have been shown in patients with established CVD in general.[6,19,34] The residual risk in Nor-COAST is quite high compared to other studies [6,19,34]. However, Nor-COAST included solely patients with stroke while other cohorts also included transient ischemic attacks.[7,19] Moreover, the consecutive inclusion of stroke patients minimizes healthy participant bias [35] and higher-risk patients are more likely to be included. Although high residual risk might be explained by non-modifiable factors such as age, already severely progressed atherosclerosis or genetic disposition, modifiable risk factors like inflammation or further reduction of BP and LDL-C are of importance [23,28,29]. Mean risk factor levels in Nor-COAST are not far from targets and more in line with guideline recommendations compared to other populations,[2-4] yielding less possibilities for benefit based on current cut-offs. However, BP and LDL-C are continuously related to CVD risk [28,29] and an individual patient could still benefit from further reduction.

The predicted 2-year risk corresponded adequately with the observed risk in Nor-COAST after recalibration. Discrimination was acceptable and in line with other prognostic tools already in clinical use[7,16,18] and previous validations of the SMART-REACH model have shown comparable results.[19,34] Moreover, sex-specific analyses showed lower c-statistics for women; however, these results should be interpreted with caution due to lack of statistical power. Stroke is a heterogeneous condition with multiple possible etiologies where stroke classification is crucial. Performance of the model may be different in patients with cardioembolic stroke etiology, especially if the burden of atherosclerosis and associated risk factors is low or absent. Due to the limited sample size, the performance in this subgroup could not be evaluated. Still, the large overlap between underlying etiologies and other cardiovascular entities[13-15] illustrate the need for optimal atherosclerotic risk factor control in general. Although some short-term risk prediction models developed separately for stroke patients already exist,[16-18] the SMART-REACH[19] model can be used in individuals with any type of atherosclerotic disease, also multiple manifestations, which often is the case in clinical practice. The SMART-REACH model is readily available via online calculators

such as u-prevent.com. However, ideally the geographic correction factor should be applied when using the model in clinical practice for similar populations.

Strengths and limitations

The strengths of this study include the multicenter design, valid registry data, an up-to-date time period and prospective consecutive inclusion of patients reflecting current clinical practice.[35] Another strength is using a prediction tool that estimates both 10-year risk and lifetime risk adjusting for competing risks and remaining life-expectancy. As secondary prevention presumably is continued lifelong, it may be more intuitive to use a lifetime risk prediction model. Furthermore, adjusting for death of other causes avoids overestimating CVD risk and treatment benefit in older individuals [19]. The observed 2-year event rate in Nor-COAST (Figure S8) corresponds reasonably well with event rates in a recent meta-analysis[1] and the Nor-COAST population has characteristics in line with patients in the Norwegian stroke registry.[2,35] Generalization at least to Norwegian stroke patients and comparable stroke populations is therefore plausible.

Not including the oldest patients is a significant limitation and performing external validation and recalibration based on 2-year predictions might be a weakness. However, previous studies have shown that lifetime estimates based on similar methods appear to be reliable for predictions up to at least 17 years.[9] C-statistics for discrimination are moderate. However, demonstrating adequate calibration might be a more relevant measure since knowing that the predicted risk reflects the actual risk is important for clinical treatment decisions.[8,36] We did not account for changes in risk factor levels over time. However, changes in risk factor levels after 3 months are not likely to affect predictive performance.[37] We have previously published detailed data on how adherence to medications and risk factor control changes from discharge to 18 months poststroke in Nor-COAST,[2] which showed that risk factor levels remain relatively unchanged. Risk factor levels also often deteriorate over time due to decrease in drug adherence and healthy lifestyle habits.[2,5] Missing data for clinical measurements at the 3-month follow-up might however be a weakness. The relative effects of BP and LDL-C lowering are based on large meta-analyses synthesizing evidence from primary and secondary preventive settings and benefits might be smaller or larger depending on specific stroke characteristics. However, relative effect estimates are broadly similar across several subgroups of patients [28,29]. Therefore, we consider these relative effects valid for our population. We did not account for disadvantages and harm of pharmacotherapy like adverse reactions and costs. At last, risk prediction models include varying degrees of uncertainty and cannot replace good clinical judgment but help structure and guide clinicians in their medical decision-making process.[8]

Conclusions

Current risk factor control after ischemic stroke is suboptimal. The predicted future risk is high but with considerable individual variation and a corresponding variation in the benefit from intensification of secondary prevention. An available risk prediction tool such as the SMART-REACH model can be used to identify patients with the largest benefit from intensification of treatment and more intensive short-term or multidisciplinary follow-up. We believe the model can be a useful tool for more personalized surveillance of patients in both stroke units and other clinical settings like general practice. More research is needed to assess potential strategies for further lowering of the high residual cardiovascular risk in these patients, and selection of patients by risk stratification may help improve focus and efficiency in future trials.

References

1. Boulanger M, Béjot Y, Rothwell PM, Touzé E. Long-Term Risk of Myocardial Infarction Compared to Recurrent Stroke After Transient Ischemic Attack and Ischemic Stroke: Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2018;7(2):e007267. doi:10.1161/JAHA.117.007267
2. Gynnild MN, Aakerøy R, Spigset O, et al. Vascular risk factor control and adherence to secondary preventive medication after ischaemic stroke. J Intern Med. Aug 2 2020;doi:10.1111/joim.13161
3. Brewer L, Mellon L, Hall P, et al. Secondary prevention after ischaemic stroke: The ASPIRE-S study. Article. BMC Neurol. 2015;15(1)216. doi:10.1186/s12883-015-0466-2
4. Heuschmann PU, Kircher J, Nowe T, et al. Control of main risk factors after ischaemic stroke across Europe: data from the stroke-specific module of the EUROASPIRE III survey. Eur J Prev Cardiol. Oct 2015;22(10):1354-62. doi:10.1177/2047487314546825
5. Norrving B, Barrick J, Davalos A, et al. Action Plan for Stroke in Europe 2018–2030. European Stroke Journal. 2018/12/01 2018;3(4):309-336. doi:10.1177/2396987318808719
6. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016;134(19):1419-1429.
7. Dorresteijn JA, Visseren FL, Wassink AM, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. Jun 2013;99(12):866-72. doi:10.1136/heartjnl-2013-303640
8. Rossello X, Dorresteijn JA, Janssen A, et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). Eur Heart J Acute Cardiovasc Care. Jun 25 2019:2048872619858285. doi:10.1177/2048872619858285
9. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. BMJ. 2016;352:i1548. doi:10.1136/bmj.i1548
10. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FL. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J. Apr 2014;35(13):837-43. doi:10.1093/eurheartj/ehu004
11. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. Article. N Engl J Med. 2017;377(14):1319-1330. doi:10.1056/NEJMoa1709118
12. Giugliano Robert P, Pedersen Terje R, Saver Jeffrey L, et al. Stroke Prevention With the PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Evolocumab Added to Statin in High-Risk Patients With Stable Atherosclerosis. Stroke. 2020/05/01 2020;51(5):1546-1554. doi:10.1161/STROKEAHA.119.027759
13. Hoshino T, Sissani L, Labreuche J, et al. Prevalence of Systemic Atherosclerosis Burdens and Overlapping Stroke Etiologies and Their Associations With Long-term Vascular Prognosis in Stroke With Intracranial Atherosclerotic Disease. JAMA Neurol. Feb 1 2018;75(2):203-211. doi:10.1001/jamaneurol.2017.3960
14. Sirimarco G, Lavallée Philippa C, Labreuche J, et al. Overlap of Diseases Underlying Ischemic Stroke. Stroke. 2013/09/01 2013;44(9):2427-2433. doi:10.1161/STROKEAHA.113.001363
15. Gongora-Rivera F, Labreuche J, Jaramillo A, Steg Philippe G, Hauw J-J, Amarenco P. Autopsy Prevalence of Coronary Atherosclerosis in Patients With Fatal Stroke. Stroke. 2007/04/01 2007;38(4):1203-1210. doi:10.1161/01.STR.0000260091.13729.96

16. Kernan Walter N, Viscoli Catherine M, Brass Lawrence M, et al. The Stroke Prognosis Instrument II (SPI-II). Stroke. 2000/02/01 2000;31(2):456-462. doi:10.1161/01.STR.31.2.456

17. Ay H, Gungor L, Arsava EM, et al. A score to predict early risk of recurrence after ischemic stroke. Neurology. Jan 12 2010;74(2):128-35. doi:10.1212/WNL.0b013e3181ca9cff

18. Weimar C, Diener HC, Alberts MJ, et al. The Essen stroke risk score predicts recurrent cardiovascular events: a validation within the REduction of Atherothrombosis for Continued Health (REACH) registry. Stroke. Feb 2009;40(2):350-4. doi:10.1161/strokeaha.108.521419

19. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. J Am Heart Assoc. Aug 21 2018;7(16):e009217. doi:10.1161/jaha.118.009217

20. Thingstad P, Askim T, Beyer MK, et al. The Norwegian Cognitive impairment after stroke study (Nor-COAST): study protocol of a multicentre, prospective cohort study. BMC Neurol. 2018/11/26 2018;18(1):193. doi:10.1186/s12883-018-1198-x

21. Varmdal T, Bakken IJ, Janszky I, et al. Comparison of the validity of stroke diagnoses in a medical quality register and an administrative health register. Scand J Public Health. Mar 2016;44(2):143-9. doi:10.1177/1403494815621641

22. Govatsmark RES, Janszky I, Slørdahl SA, et al. Completeness and correctness of acute myocardial infarction diagnoses in a medical quality register and an administrative health register. Scand J Public Health. Feb 2020;48(1):5-13. doi:10.1177/1403494818803256

23. Norwegian Guideline for Prevention of Cardiovascular Disease. The Norwegian Directorate of Health. Updated 5 March 2018. Accessed February 23, 2021. https://www.helsedirektoratet.no/retningslinjer/forebygging-av-hjerte-og-karsykdom

24. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. Feb 28 1996;15(4):361-87.

25. Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW. Calibration: the Achilles heel of predictive analytics. BMC Med. Dec 16 2019;17(1):230. doi:10.1186/s12916-019-1466-7

26. Ducrocq G, Bhatt DL, Labreuche J, et al. Geographic differences in outcomes in outpatients with established atherothrombotic disease: results from the REACH Registry. European Journal of Preventive Cardiology. 2014/12/01 2013;21(12):1509-1516. doi:10.1177/2047487313501278

27. Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. Stat Med. Aug 30 2004;23(16):2567-86. doi:10.1002/sim.1844

28. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. Nov 13 2010;376(9753):1670-81. doi:10.1016/s0140-6736(10)61350-5

29. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. Mar 05 2016;387(10022):957-67. doi:10.1016/s0140-6736(15)01225-8

30. Antithrombotic Trialists C. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet. 2009;373(9678):1849-1860. doi:10.1016/S0140-6736(09)60503-1

31. Mons U, Müezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ. Apr 20 2015;350:h1551. doi:10.1136/bmj.h1551

32. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. Arch Intern Med. Jun 11 2012;172(11):837-44. doi:10.1001/archinternmed.2012.1397

33. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. Jan 1986;24(1):67-74.

34. de Vries TI, Eikelboom JW, Bosch J, et al. Estimating individual lifetime benefit and bleeding risk of adding rivaroxaban to aspirin for patients with stable cardiovascular disease: results from the COMPASS trial. Eur Heart J. Dec 7 2019;40(46):3771-3778a. doi:10.1093/eurheartj/ehz404

35. Kuvås KR, Saltvedt I, Aam S, Thingstad P, Ellekjær H, Askim T. The Risk of Selection Bias in a Clinical Multi-Center Cohort Study. Results from the Norwegian Cognitive Impairment After Stroke (Nor-COAST) Study. Clin Epidemiol. 2020;12:1327-1336. doi:10.2147/clep.S276631

36. Cook Nancy R. Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction. Circulation. 2007/02/20 2007;115(7):928-935. doi:10.1161/CIRCULATIONAHA.106.672402

37. Xu Z, Arnold M, Stevens D, et al. Prediction of Cardiovascular Disease Risk Accounting for Future Initiation of Statin Treatment. Am J Epidemiol. 2021;doi:10.1093/aje/kwab031

Supplementary Materials

Supplementary Methods

Definitions of variables in Table 1

Hypertension was defined as self-reported hypertension or use of antihypertensive drugs at admission (Anatomical Therapeutic Chemical Classification System codes (ATC): C03A, C07, C08, C09A/B, C09C/D, C02A, C02C and C02D). Hypercholesterolemia was defined by use of lipid lowering drugs at admission (ATC -code: C10). Previous stroke (before the index event) or transient ischemic attack (TIA) was defined as previous ischemic stroke, TIA, hemorrhagic stroke or stroke of undetermined subtype as reported by doctor (based on review of medical records) / patient. GFR (Glomerular filtration rate) was based on the CKD-EPI equation (based on gender, age and the serum creatinine concentration measured at first day during admission).[2] Blood tests were taken the first day after admission. Stroke subtype was defined according to the TOAST Trial of ORG 10172 in Acute Stroke Treatment classification.[38] Stroke severity was assessed by National Institutes of Health Stroke Scale (NIHSS). Prestroke cognitive impairment was defined as score ≥ 3 on Global Deterioration Scale assessed by study nurses' interviews of caregivers during hospital stay.[2] Frailty was measured using a modified version of the five-item Fried criteria,[2] based on reduced grip strength, slow gait speed, self-reported fatigue, low physical activity and unintentional weight loss, where 3-5 criteria present corresponds to frail. Definitions of variables also included in the SMART-REACH model are described in Table S1.

Registry data

The Norwegian Stroke Registry is a medical quality register where all Norwegian hospitals have been obligated to enter medical data on all residents > 18 years of age admitted to hospital with acute stroke (ICD-10 codes I61, I61 and I64). The Norwegian Stroke Registry had a coverage (completeness) of 87% in 2018,[35,39] we therefore also linked Nor-COAST data to the Norwegian Cardiovascular Disease Registry which is more complete.[21] The Norwegian Cardiovascular Disease Registry is an administrative health register based on data from the Norwegian Patient Register, containing information on all admissions to hospital (main and second diagnosis), both private and public, included in the public reimbursement policy in Norway since 2008. For stroke endpoints we restricted analyses to main diagnoses of stroke which give more correct registrations.[21] For myocardial infarction endpoints we used both main and second diagnoses for higher completeness.[22] The Norwegian Causes of Death Registry provided follow-up information on cardiovascular disease as the primary cause of death. All registries are regulated according to the Act relating to Personal Health Data Registries. The quality of information in the registries have previously been described.[21,22]

The use of the SMART-REACH Fine and Gray competing risk model in Nor-COAST

The SMART-REACH risk model is a competing-risk adjusted Fine and Gray model, which can be used for estimation of both 10-year and lifetime risk of major cardiovascular events and non-cardiovascular mortality in patients with clinically manifest vascular disease. The underlying model formulas and methodology were published in the original SMART-REACH publication.[19] With age as underlying timescale, lifetables calculating risks for every 1-year interval are made beginning at the starting age of each individual[9,19] and repeated up to the maximum age of 90 years. The model was derived using adapted Fine and Gray models to allow for left truncation and right censoring.[40]

For better judgement of the calibration, less influenced by arbitrary grouping in comparison to a traditional calibration plot, we showed a flexible calibration curve based on local polynomial regression fitting (*loess*, function R).[25,41,42] First, the cohort was divided in 100 quantiles of predicted risk. Then, a local regression was used to smoothly explain the observed cumulative incidence per group by the mean predicted risk per group. The smooth calibration plot and confidence bounds were subsequently predicted from this model over the whole range of relevant predicted risks (cohort predicted risk quantile 0.025 up to 0.975). A curve close to the diagonal indicates that predicted risks correspond well with the observed proportion of events.[25]

Recalibration of the model was considered based on the calibration plot and performed using "calibration-in-the-large" by subtracting the expected-observed ratio from the linear predictor for both the CVD hazard function as for the non-CVD mortality function.[25,27] The expected-observed ratio was calculated by dividing the expected incidence (mean of all predicted 2-year risks) by the observed incidence (cumulative incidence in the study population at 2 years, corrected for competing risks).

Table S1. Definitions of variables included in the SMART-REACH model 7 and sources

Variable	Source when used in present study
Age (years)	As recorded in medical journals
Sex (male/female)	As recorded in medical journals
Current smoking (yes/no)	Patient response to smoking status at 3 months
Diabetes mellitus (yes/no)	Self-reported diabetes or HbA1c ≥ 48 mmol/mol at admission or prescribed antidiabetic drugs at admission or discharge
Congestive heart failure (yes/no)	History of heart failure as reported by doctor (based on review of medical records) / patient
Atrial fibrillation (yes/no)	Self-reported or documented on electrocardiogram or telemetry during admission
Systolic blood pressure (mmHg)	Measured thrice by the same physician at 3 months with one-minute intervals and the average of the second and third measurements was used in the analysis
Creatinine (µmol/L)	Serum concentration at 3 months
Total cholesterol (mmol/L)	Non-fasting serum concentrations from venous blood measured in fresh samples at 3 months
LDL cholesterol (mmol/L)	Non-fasting serum concentrations from venous blood measured in fresh samples at 3 months
History of cerebrovascular disease (yes/no)	All patients were registered with cerebrovascular disease, since stroke was an inclusion criterion in the Nor-COAST study.
History of coronary heart disease (yes/no)	Previous angina pectoris, myocardial infarction or coronary revascularization (coronary bypass surgery or percutaneous coronary intervention) as reported by doctor (based on review of medical records) / patient
History of peripheral artery disease (yes/no)	Symptomatic or documented obstruction of distal arteries of the leg or surgery of the leg or documented surgery of aorta as reported by doctor (based on review of medical records) / patient
Use of antithrombotic drugs (yes/no)	Use of aspirin or equivalent drug belonging to the Anatomical Therapeutic Chemical (ATC) Classification System group B01A at 3 months. As reported by the patient or doctor, if information regarding medications in use were missing, we contacted general practitioners, home care services or used the electronic summary care record for safer healthcare in Norway.

Abbreviations: HbA1c; Hemoglobin A1c. Nor-COAST; Norwegian Cognitive Impairment after Stroke.

Table S2. Guideline recommended targets and effect measures from meta-analyses used when calculating treatment benefits from optimization of risk factors

Risk factor target	Guideline defined treatment and target	Effect measures and literature references	Comments
Lipid targets	LDL-C ≤ 1.8 mmol/L [23]	A hazard ratio (HR) of 0.78 was assumed per 1.0 mmol/L reduction in LDL-C [28]. Patients who had already achieved the target were modelled with a HR of 1.00, regardless whether this was achieved by lifestyle or medication. LDL-C reduction in mmol/L was defined as the 3-month LDL-C level minus 1.8 mmol/L. We assumed no further risk reduction from lowering LDL-C below 1.8 mmol/L.	We used the effect measure from a meta-analysis with patients from both primary and secondary preventive settings, where subgroup analyses have shown that the relative risk reduction is more or less the same across several groups of patients suggesting broadly generalizable benefits. We therefore assume these effects also are valid in subgroups of stroke patients.
Blood pressure targets	Systolic blood pressure ≤ 140 mmHg [23]	A 10 mmHg reduction in systolic BP was assumed to correspond to a cardiovascular specific HR of 0.80 [29]. Patients who had already achieved this target were modelled with a HR of 1.00, regardless whether this was achieved by lifestyle or medication. BP reduction in mmHg was defined as the 3-month systolic BP minus the target systolic BP of 140. We assumed no further risk reduction from lowering BP below 140 mmHg.	We used the effect measure from a meta-analysis with patients from both primary and secondary preventive settings (including stroke patients), where subgroup analyses have shown that the relative risk reduction is more or less the same across several groups of patients. A HR of 0.80 for the combined endpoint of major cardiovascular events was used. However, the relative effect for stroke separately seems to be larger (HR 0.73) [29].
Antithrombotic treatment	Aspirin or other equivalent antiplatelet drugs. Anticoagulation if non-valvular atrial fibrillation [23]	Estimated risk is based on the assumption that standard care is provided. Such standard care (HR 1.00) included aspirin or equivalent type of antithrombotic therapy, including vitamin K antagonists or DOACs, regardless of number of antithrombotic drugs in use. We assumed that no use of antithrombotic therapy was associated with the inverse effect of starting (at least) aspirin (i.e., HR 1/0.81 = 1.23) [43].	The HR for long-term aspirin (0.81) monotherapy in secondary preventive setting from the meta-analysis [43] was used. The estimate is based on 16 secondary preventive trials from whom 10 was in stroke or patients with transient ischemic attack. The benefit of different antithrombotic regimens was not assessed since the proportion not using antithrombotic drugs was low.
Smoking target	Smoking cessation [23]	The effect of smoking cessation was estimated in current smokers and was assumed to reduce the risk of both CVD events and non-CVD mortality. The HR for CVD events for current smokers when converting to ex-smoker was assumed to be 0.60 [31]. The HR for non-CVD mortality for current smokers who are now ex-smokers was assumed to be 0.73 [32].	In absence of evidence from RCTs, the effect of smoking cessation was estimated from observational studies, using the hazard ratio between current and former smoking.

Abbreviations: LDL, Low-density lipoprotein; BP, blood pressure; DOACs, Direct Oral Anticoagulants; RCTs, Randomized Controlled Trials; TIA, Transient ischemic attack

Table S3. Overview of missing values at index stay and 3-month visit (n=465)

	n (%) missing at index stay	**n (%) missing at 3-month visit**
Age	0	0
Sex	0	0
Current smoking	1 (0.2%)	68 (15%)
Diabetes mellitus	0	0
Systolic blood pressure	34 (7%)	72 (15%)
Total cholesterol	8 (2%)	113 (24%)
HDL cholesterol	12 (3%)	117 (25%)
LDL cholesterol	15 (3%)	115 (25%)
Creatinine	2 (0.4%)	119 (26%)
Coronary artery disease	0	0
Peripheral artery disease (incl. AAA)	0	0
Heart failure	0	0
Atrial fibrillation	0	0
Information about medications	5 (1%)	32 (7%)

Missing values for current smoking, systolic blood pressure, cholesterol, creatinine and information about medications were imputed using single imputation by predictive mean matching for the purpose of CVD risk prediction and assessment of changes in risk factor levels from index stay to 3-months follow-up. With this method, the imputed value is taken randomly from a set of observed values whose predicted values are closest to the predicted value from a specified regression model. For the baseline characteristics age, sex, history of diabetes, coronary artery disease, peripheral artery disease, heart failure and atrial fibrillation, we assumed that registrations at index stay also were valid at the 3-month visit. Abbreviations: eGFR; Estimated glomerular filtration rate. AAA; Abdominal aortic aneurism, HDL; High-density lipoprotein, LDL; Low-density lipoprotein.

Table S4. Cardiovascular medications at discharge from index stay and at 3 months of follow-up for patients with available detailed data on medications in use

	Discharge (n = 460)	3-month visit (n = 433)
Antithrombotic drugs		
No[a]	9 (2%)	8 (2%)
Single antiplatelet therapy	111 (24%)	130 (30%)
Dual antiplatelet therapy	189 (41%)	150 (35%)
Anticoagulation monotherapy	107 (23%)	114 (25%)
Anticoagulation in combination with antiplatelet agent(s)	44 (10%)	31 (7%)
Number of antihypertensive drugs		
0[a]	144 (31%)	118 (27%)
1	167 (36%)	160 (37%)
2	105 (23%)	101 (23%)
3	33 (7%)	43 (10%)
>3	11 (2%)	11 (3%)
Lipid-lowering drugs		
No[a]	45 (10%)	42 (10%)
Any statin monotherapy	407 (88%)	381 (88%)
Low-moderate intensity statin[b]	142 (30%)	133 (31%)
High intensity statin[b]	265 (58%)	248 (57%)
Ezetimibe monotherapy	3 (1%)	6 (1%)
Statin + ezetimibe	5 (1%)	4 (1%)

[a]Of patients with available follow-up information about medications in use at both discharge and 3 months (n=429), 5 out of 8 patients not using (any) antithrombotic drugs (ATC code: B01A) at discharge started antithrombotic treatment between 0 and 3 months, while 4 out of 421 prescribed antithrombotic drugs at discharge discontinued between 0 and 3 months. For antihypertensive drugs (ATC codes: C03A, C07, C08, C09A/B, C09C/D, C02A, C02C and C02D), corresponding numbers were 28 / 133 and 12 / 296. For lipid-lowering drugs (ATC code: C10), corresponding numbers were 12 / 40 and 11 / 389. [b]High-intensity statin was defined as atorvastatin ≥40 mg/d or other equivalent drug as described previously [2]. Low-moderate intensity statin was defined as <40 mg atorvastatin or other equivalent drug. Abbreviations: ATC, Anatomical Therapeutic Chemical classification system

Figure S1. Flexible calibration curve showing the agreement between estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model and observed 2-year risk before recalibration

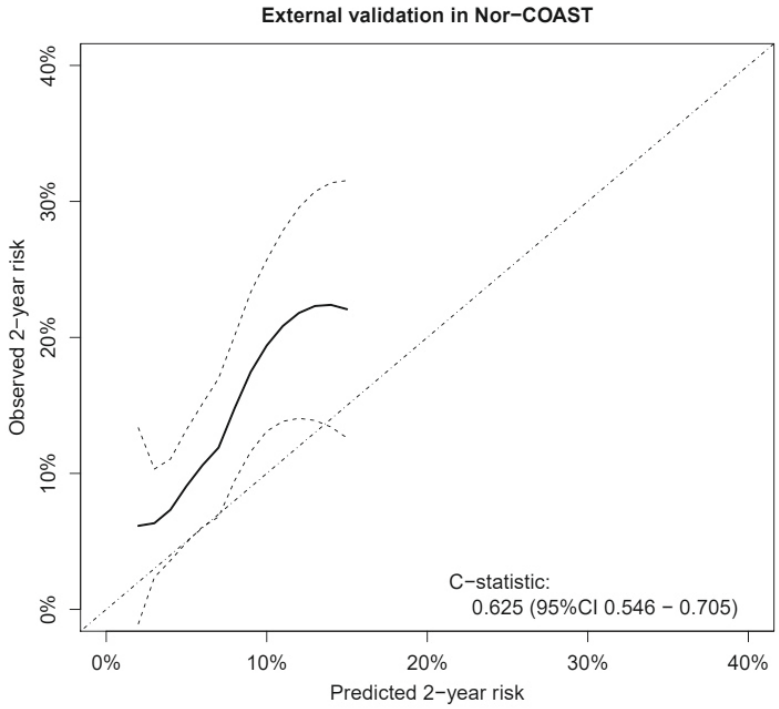


Figure S2: Flexible calibration curve showing the agreement between estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model versus observed 2-year risk when excluding patients with cardioembolic stroke etiology according to the TOAST-classification

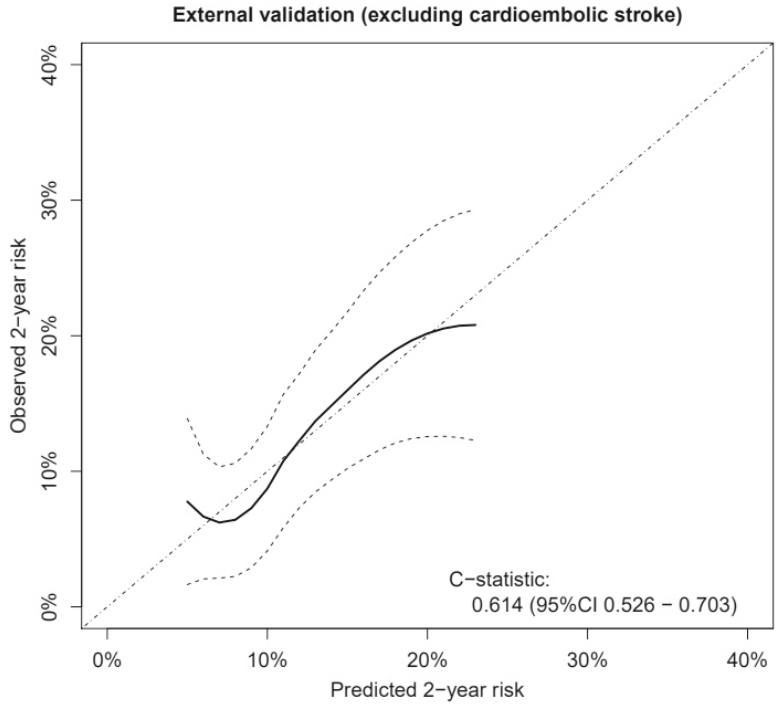
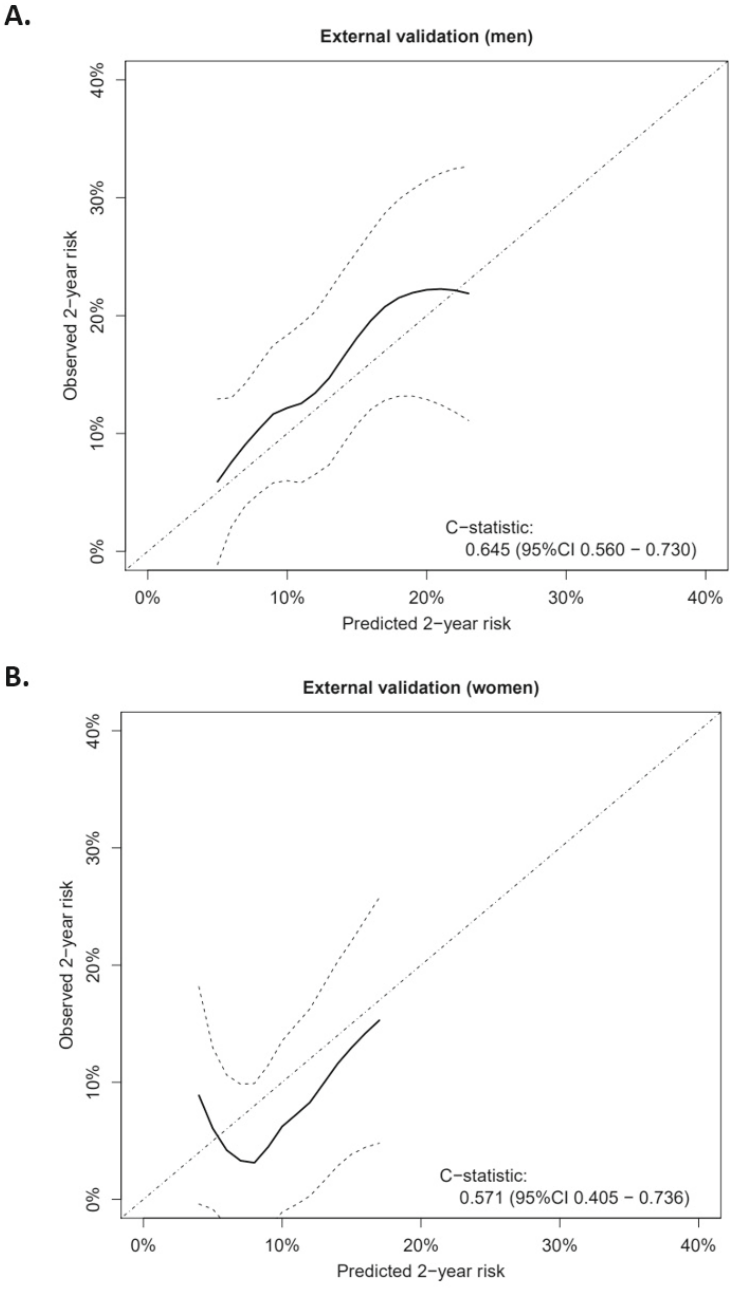
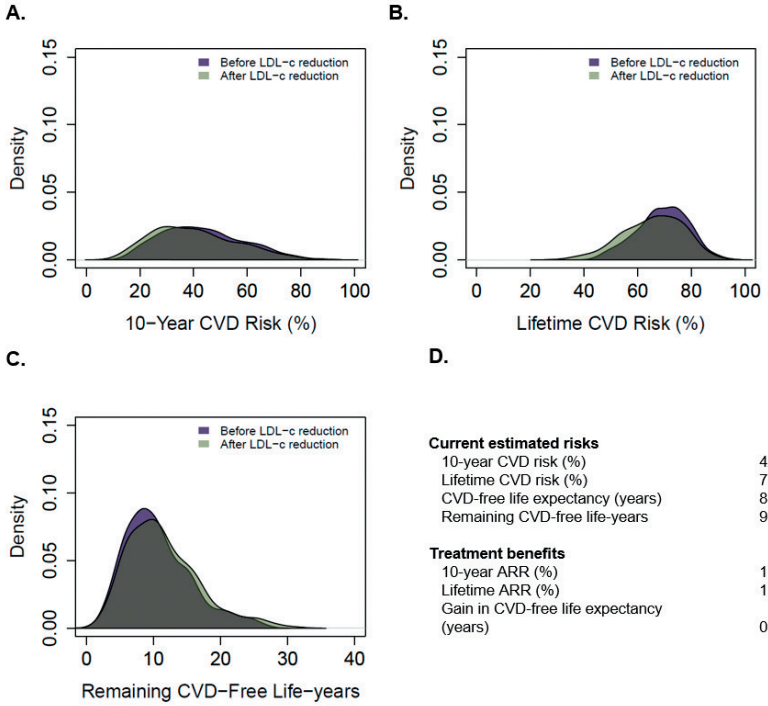


Figure S3. Sex-specific flexible calibration curves showing the agreement between estimated risk of stroke, myocardial infarction or vascular death by the SMART-REACH model versus observed 2-year risk for a) men (n=278) and b) women (n=178).



Notes: Number of CVD events for men and women were n=34 and n=18, respectively. Number of non-CVD related deaths were n=10 and n=5 for men and women respectively.

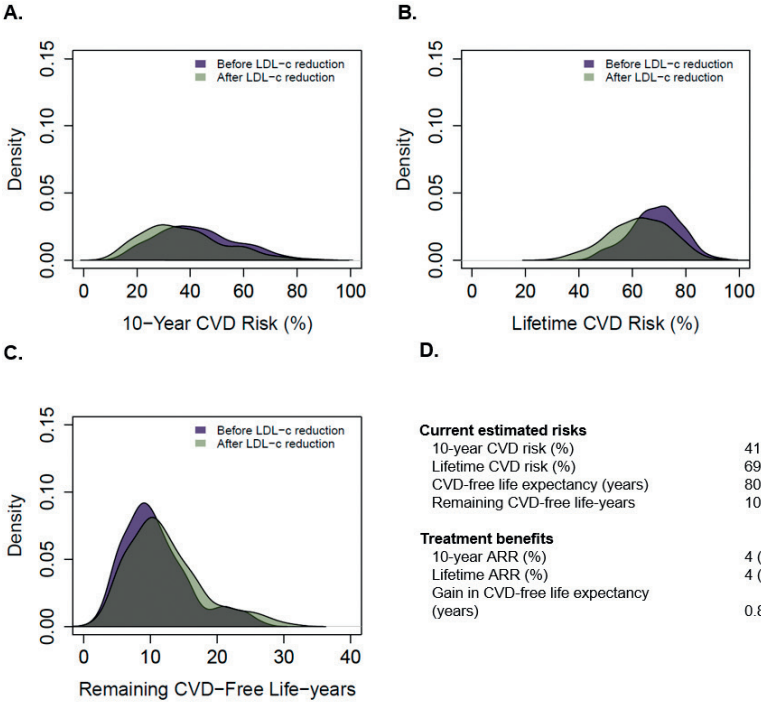
Figure S4a: Current cardiovascular risk and potential benefit from optimization of LDL-C levels (n = 465)



Current estimated risks	
10-year CVD risk (%)	42 (32 to 54)
Lifetime CVD risk (%)	70 (63 to 76)
CVD-free life expectancy (years)	80.4 (76.4 to 83.5)
Remaining CVD-free life-years	9.9 (7.2 to 13.5)
Treatment benefits	
10-year ARR (%)	1 (0 to 4)
Lifetime ARR (%)	1 (0 to 5)
Gain in CVD-free life expectancy (years)	0.2 (0 to 1)

Distributions of **A.** Ten-year cardiovascular disease risk, **B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D**. Current estimated risks and treatment benefits (median (interquartile range)) from optimization of LDL-C level to ≤1.8 mmol/L in all patients. Abbreviations: LDL-C; Low density lipoprotein cholesterol, CVD; Cardiovascular disease, ARR: Absolute risk reduction

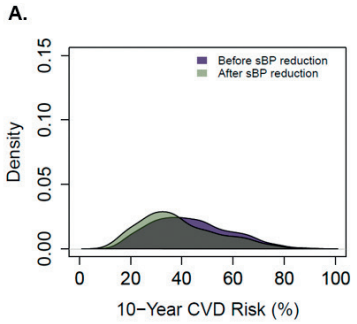
Figure S4b: Current cardiovascular risk and potential benefit from optimization of LDL-C levels in patients with LDL-C > 1.8 mmol/L (n = 265)

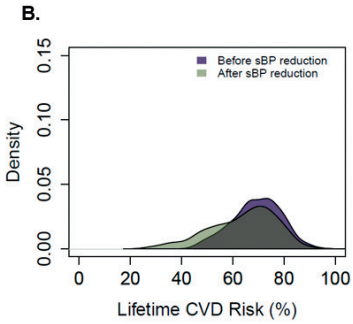


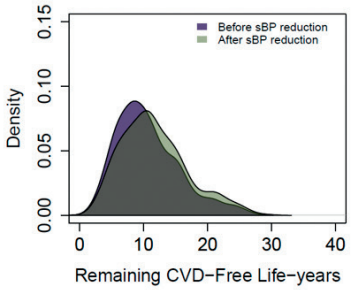
Current estimated risks	
10-year CVD risk (%)	41 (32 to 52)
Lifetime CVD risk (%)	69 (63 to 75)
CVD-free life expectancy (years)	80.7 (76.8 to 83.6)
Remaining CVD-free life-years	10.0 (7.4 to 13.3)
Treatment benefits	
10-year ARR (%)	4 (2 to 7)
Lifetime ARR (%)	4 (2 to 9)
Gain in CVD-free life expectancy (years)	0.8 (0.4 to 1.6)

Distributions of **A**. Ten-year cardiovascular disease risk, **B**. Lifetime CVD risk, **C.** Remaining CVD-free life-years, **D**. Current estimated risks and treatment benefits (median (interquartile range)) from optimization of LDL-C level to 1.8 mmol/L in patients with LDL-C > 1.8 mmol/L. Abbreviations: LDL-C; Low density lipoprotein cholesterol, CVD; Cardiovascular disease, ARR: Absolute risk reduction

Figure S5a. Current cardiovascular risk and potential benefit from optimization of systolic blood pressure levels (n = 465)





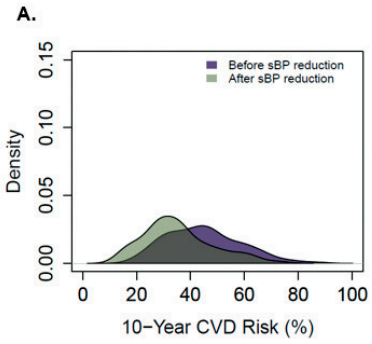


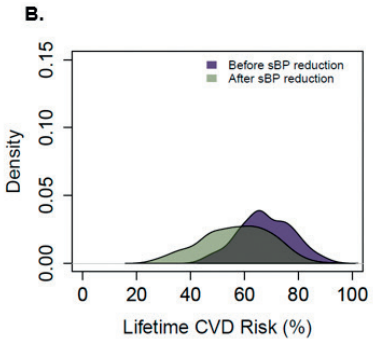
D.

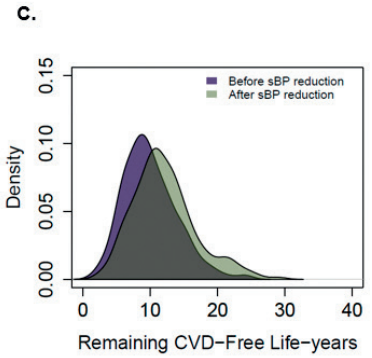
Current estimated risks	
10-year CVD risk (%)	42 (32 to 54)
Lifetime CVD risk (%)	70 (63 to 76)
CVD-free life expectancy (years)	80.4 (76.4 to 83.5)
Remaining CVD-free life-years	9.9 (7.2 to 13.5)
Treatment benefits	
10-year ARR (%)	0 (0 to 7)
Lifetime ARR (%)	0 (0 to 9)
Gain in CVD-free life expectancy (years)	0 (0 to 1.5)

Distributions of **A**. Ten-year cardiovascular disease risk**, B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D.** Current estimated risks and treatment benefits (median (interquartile range)) from optimization of sBP level to ≤140 mmHg in all patients. Abbreviations: sBP; Systolic blood pressure, CVD; Cardiovascular disease, ARR: Absolute risk reduction

Figure S5b. Current cardiovascular risk and potential benefit from optimization of systolic blood pressure levels (n = 226) in patients with levels above 140 mmHg.





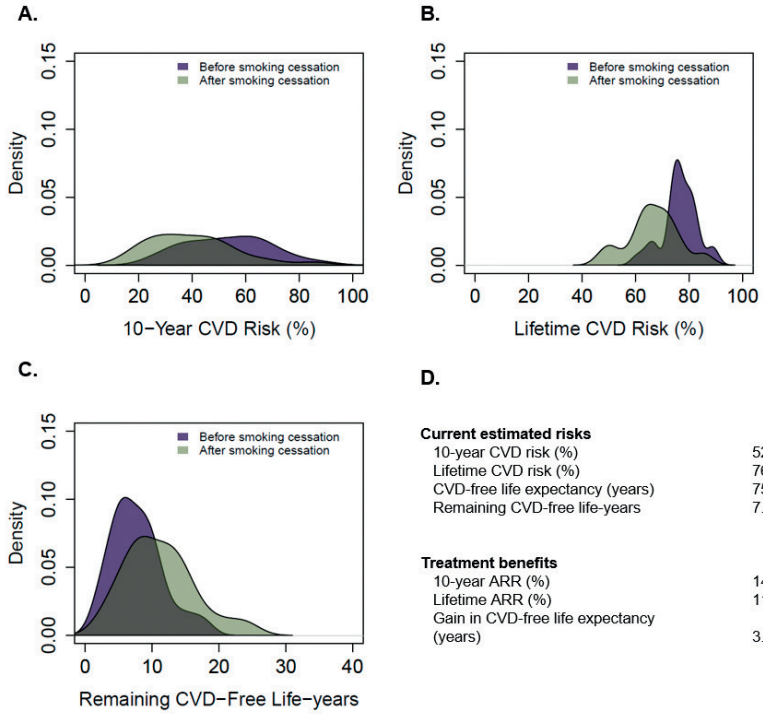


D.

Current estimated risks	
10-year CVD risk (%)	44 (34 to 54)
Lifetime CVD risk (%)	67 (61 to 75)
CVD-free life expectancy (years)	81.8 (78.9 to 84.3)
Remaining CVD-free life-years	9.5 (7.2 to 12.3)
Treatment benefits	
10-year ARR (%)	8 (3 to 14)
Lifetime ARR (%)	9 (3 to 16)
Gain in CVD-free life expectancy (years)	1.6 (0.6 to 3.1)

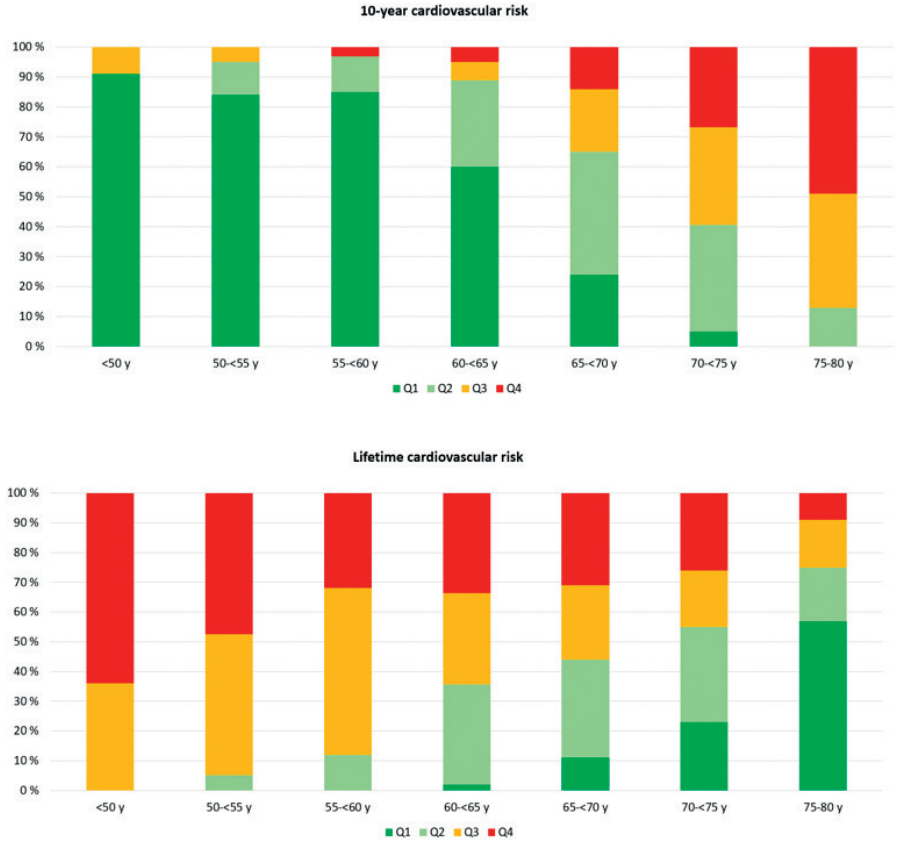
Distributions of **A**. Ten-year cardiovascular disease risk**, B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D.** Current estimated risks and treatment benefits (median (interquartile range)) from optimization of sBP level to 140 mmHg in patients with sBP > 140 mmHg (n = 226). Abbreviations: sBP; Systolic blood pressure, CVD; Cardiovascular disease, ARR: Absolute risk reduction

Figure S6: Current cardiovascular risk and potential benefit from smoking cessation in smokers (n = 55)



Distributions of **A**. Ten-year cardiovascular disease risk**, B**. Lifetime CVD risk, **C**. Remaining CVD-free life-years, **D.** Current estimated risks and treatment benefits (median (interquartile range)) from smoking cessation in patients smoking at 3 months. Abbreviations: ARR: Absolute risk reduction, CVD; Cardiovascular disease

Figure S7. Age-specific subgroups of estimated 10-year and lifetime risk of a recurrent vascular event by the SMART REACH model in patients with ischemic stroke in the Nor-COAST study.



Age-specific subgroups of estimated 10-year and lifetime risk of a recurrent vascular event by the SMART REACH model in patients with ischemic stroke in the Nor-COAST study. Data are shown as quartiles of risk where Q1 corresponds to lowest risk quartile and Q4 the highest risk quartile.

Table S5. Patient characteristics stratified by quartiles (Q1 – Q4) of estimated 10-year risk of recurrent vascular events and mortality

	10-year CVD risk			
	Q1 (n = 117)	**Q2 (n = 116)**	**Q3 (n = 116)**	**Q4 (n = 116)**
Median (IQR) estimated 10-year risk, %	26 (21 to 29)	37 (34 to 39)	48 (44 to 50)	66 (58 to 68)
Age, y	59.5 (6.2)	68.8 (5.6)	73.0 (5.6)	74.9 (4.5)
Female sex	46 (39%)	49 (42%)	45 (39%)	38 (33%)
Atrial fibrillation	7 (6%)	14 (12%)	30 (26%)	50 (43%)
Diabetes mellitus	2 (2%)	13 (11%)	19 (16%)	58 (50%)
≥ 2 vascular areas[a] affected	2 (2%)	9 (8%)	20 (17%)	65 (56%)
Current smoker[b]	5 (5%)	11 (10%)	13 (11%)	26 (22%)
Systolic blood pressure (mmHg) [b]	137 (16)	139 (15)	144 (18)	140 (25)
Total cholesterol[b], mmol/L	4.0 (0.8)	4.1 (1.0)	4.1 (1.0)	3.9 (0.8)
LDL cholesterol[b], mmol/L	2.1 (0.8)	2.2 (0.8)	2.1 (0.8)	2.0 (0.7)
eGFR (ml/min/1.73 m^2)[b, c]	87 (12)	81 (13)	75 (15)	65 (18)
Frail[d]	3 (3%)	6 (5%)	9 (8%)	16 (14%)
Prestroke dementia[e]	0 (0%)	1 (1%)	3 (3%)	9 (8%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

Table S6. Patient characteristics stratified by quartiles (Q1 – Q4) of estimated lifetime risk of recurrent vascular events and mortality

	Lifetime CVD risk			
	Q1 (n = 117)	**Q2 (n = 116)**	**Q3 (n = 116)**	**Q4 (n = 116)**
Median (IQR) estimated life-time risk, %	58 (54 to 61)	67 (65 to 68)	73 (71 to 74)	80 (78 to 83)
Age, y	75.6 (3.7)	69.9 (5.9)	65.7 (8.6)	64.8 (8.8)
Female sex	67 (57%)	49 (42%)	32 (28%)	30 (26%)
Atrial fibrillation	18 (15%)	28 (24%)	23 (20%)	32 (28%)
Diabetes mellitus	0 (0%)	9 (8%)	29 (25%)	55 (47%)
≥ 2 vascular areas[a] affected	6 (6%)	17 (14%)	26 (23%)	47 (41%)
Current smoker[b]	2 (2%)	6 (5%)	18 (16%)	29 (25%)
Systolic blood pressure (mmHg)[b]	144 (16)	142 (19)	136 (18)	138 (23)
Total cholesterol[b], mmol/L	4.2 (0.8)	4.2 (1.0)	4.0 (0.9)	3.8 (0.9)
LDL cholesterol[b], mmol/L	2.2 (0.8)	2.2 (0.8)	2.1 (0.8)	2.0 (0.7)
eGFR (ml/min/1.73 m^2)[b, c]	77 (12)	79 (15)	81 (15)	71 (22)
Frail[d]	11 (9%)	10 (9%)	4 (3%)	9 (8%)
Prestroke dementia[e]	5 (4%)	4 (4%)	0 (0%)	4 (4%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

Table S7. Patient characteristics stratified by quartiles (Q1 – Q4) of estimated 10-year ARR of recurrent vascular events and mortality

	10-year ARR			
	Q1 (n = 117)	**Q2 (n = 116)**	**Q3 (n = 116)**	**Q4 (n = 116)**
Median (IQR) estimated 10-year ARR, %	0% (0 to 0)	3% (2 to 4)	10% (8 to 12)	21% (16 to 27)
Age, y	67.4 (8.5)	67.5 (8.8)	69.4 (7.5)	71.7 (6.8)
Female sex	42 (36%)	42 (36%)	41 (35%)	53 (46%)
Atrial fibrillation	31 (27%)	22 (19%)	22 (19%)	26 (22%)
Diabetes mellitus	17 (15%)	21 (18%)	23 (20%)	31 (27%)
≥ 2 vascular areas[a] affected	18 (16%)	27 (23%)	20 (17%)	31 (27%)
Current smoker[b]	0 (0%)	1 (1%)	8 (7%)	46 (40%)
Systolic blood pressure (mmHg) [b]	128 (10)	132 (12)	146 (13)	155 (23)
Total cholesterol[b], mmol/L	3.4 (0.6)	3.9 (0.5)	4.3 (0.8)	4.5 (1.2)
LDL cholesterol[b], mmol/L	1.6 (0.3)	2.1 (0.4)	2.3 (0.8)	2.6 (1.0)
eGFR (ml/min/1.73 m^2)[b, c]	80 (14)	77 (18)	77 (16)	75 (17)
Frail[d]	6 (5%)	7 (6%)	7 (6%)	14 (12%)
Prestroke dementia[e]	2 (2%)	5 (4%)	2 (2%)	4 (4%)

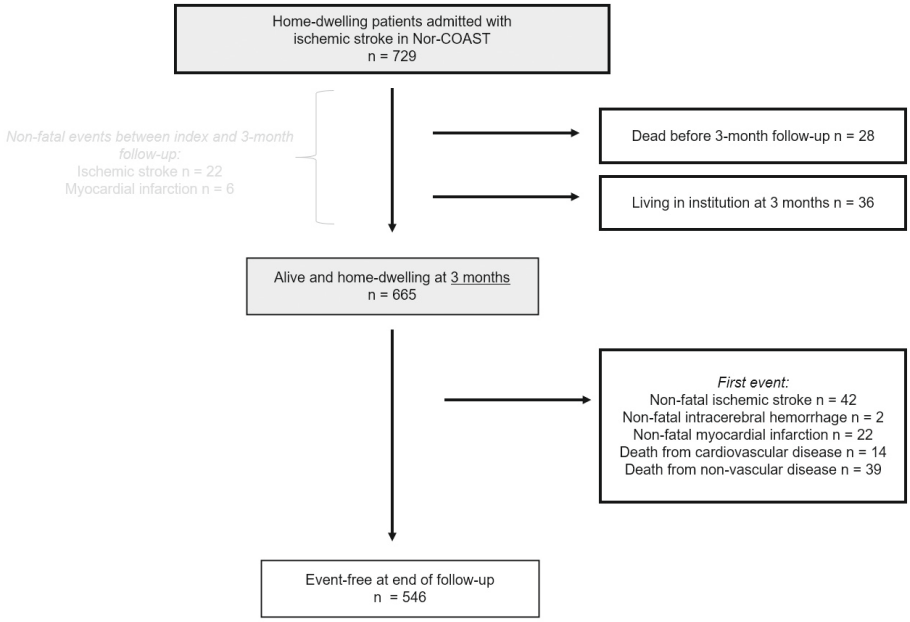
Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: IQR, Interquartile range; ARR, Absolute risk reduction; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

Table S8. Patient characteristics stratified by quartiles (Q1 – Q4) of lifetime benefit from optimization of risk factors

	Gain in CVD-free life years			
	Q1 (n = 122)	**Q2 (n = 117)**	**Q3 (n = 113)**	**Q4 (n = 113)**
Median (IQR) lifetime benefit (in terms of CVD-free life years)	0 (0 to 0)	0.6 (0.4 to 1.0)	2.3 (1.8 to 2.8)	5.3 (4.3 to 7.1)
Age, y	68.6 (8.2)	69.2 (7.9)	71.2 (7.1)	66.0 (8.7)
Female sex	41 (34%)	43 (37%)	43 (38%)	51 (45%)
Atrial fibrillation	34 (28%)	23 (20%)	25 (22%)	19 (17%)
Diabetes mellitus	22 (18%)	24 (21%)	25 (22%)	21 (19%)
≥ 2 vascular areas[a] affected	25 (20%)	29 (25%)	22 (19%)	20 (18%)
Current smoker[b]	0 (0%)	2 (2%)	16 (14%)	37 (33%)
Systolic blood pressure (mmHg)[b]	128 (10)	133 (14)	143 (17)	157 (19)
Total cholesterol[b], mmol/L	3.4 (0.6)	3.9 (0.6)	4.2 (0.8)	4.6 (1.1)
LDL cholesterol[b], mmol/L	1.6 (0.3)	2.0 (0.4)	2.3 (0.7)	2.7 (1.0)
eGFR (ml/min/1.73 m^2)[b, c]	78 (15)	73 (19)	78 (13)	79 (19)
Frail[d]	8 (7%)	8 (7%)	8 (7%)	10 (9%)
Prestroke dementia[e]	2 (2%)	6 (5%)	4 (4%)	1 (1%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; eGFR, Estimated Glomerular Filtration Rate.

Figure S8. Recurrent stroke, myocardial infarction and death in home-dwelling patients with ischemic stroke in Nor-COAST regardless of age.

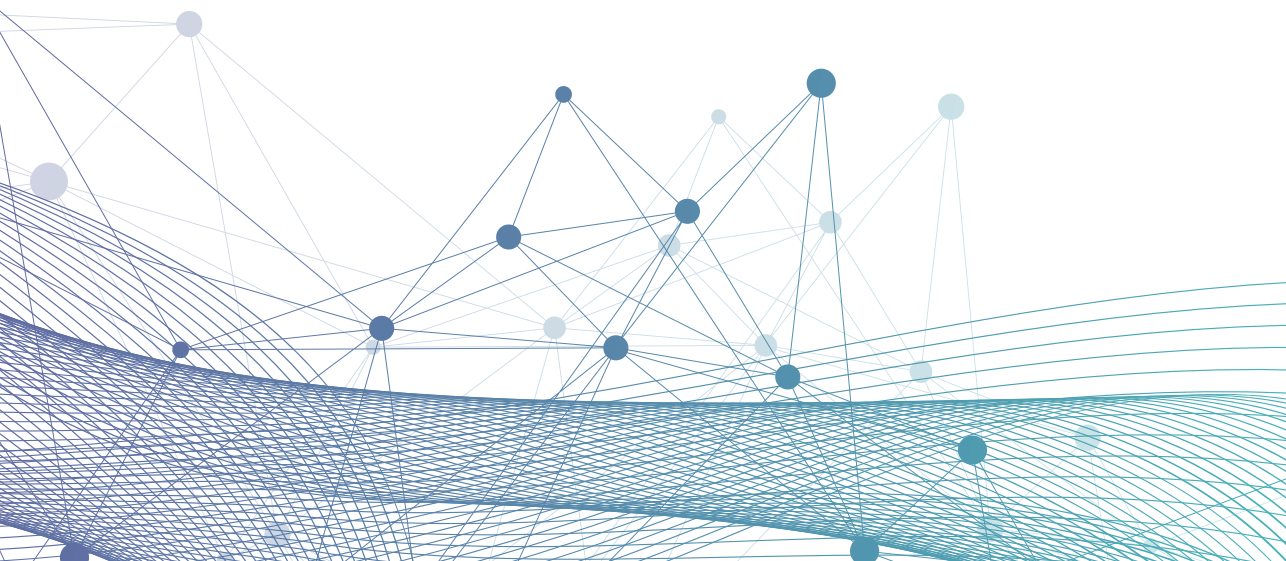


CHAPTER 11

Use of lipid-lowering therapy after stroke and expected benefit from intensification of treatment

Mari Nordbø Gynnild, Steven H. J. Hageman, Olav Spigset, Stian Lydersen, Ingvild Saltvedt, Jannick A. N. Dorresteijn, Frank L. J. Visseren, Hanne Ellekjær

Open Heart, Online ahead of print



Abstract

Background: Elevated low-density lipoprotein cholesterol (LDL-C) increases the risk of recurrent cardiovascular disease (CVD) events. We examined prescription patterns for lipid-lowering therapy (LLT) following ischemic stroke, and estimated benefits from guideline-based up-titration of LLT.

Methods: The Norwegian COgnitive Impairment After STroke (Nor-COAST) study, a multicenter prospective cohort study, collected data on LLT use, dose intensity, and LDL-C levels for 462 home-dwelling patients with ischemic stroke. We used the SMART-REACH (Secondary Manifestations of Arterial Disease – Reduction of Atherothrombosis for Continued Health) model to estimate expected benefit of up-titrating LLT.

Results: At discharge, 92% received LLT (97% statin monotherapy). Patients with prestroke dementia and cardioembolic stroke etiology were less likely to receive LLT. Older patients (coefficient -3 mg atorvastatin per 10 years, 95% CI -6 to -0.5) and women (coefficient -5.1 mg atorvastatin, CI -9.2 to -0.9) received lower doses, while individuals with higher baseline LDL-C, ischemic heart disease, and large artery stroke etiology received higher dose intensity. At 3 months, 45% reached LDL-C ≤1.8 mmol/L, and we estimated that 81% could potentially reach the target with statin and ezetimibe, resulting in median 5 (interquartile range (IQR) 0 to 12) months of CVD-free life gain and median 2% 10-year absolute risk reduction (IQR 0 to 4) with large interindividual variation.

Conclusion: Potential for optimization of conventional LLT use exists in ischemic stroke patients. Awareness of groups at risk of undertreatment and objective estimates of the individual patient's benefit of intensification can help personalize treatment decisions and reduce residual cholesterol risk.

Introduction

Patients with ischemic stroke are at high risk of recurrent cardiovascular disease (CVD) events.[1] Drugs lowering low-density lipoprotein cholesterol (LDL-C) concentrations reduce the risk of recurrent events[2-6] and statins are first-line lipid-lowering therapy (LLT) with the addition of ezetimibe or other novel drugs in patients with persistently elevated LDL-C levels or patients intolerant to statins.[3,7] Although the optimal LDL-C target after stroke remains unclear,[3] recent studies indicate that lower treatment targets are more beneficial,[5,8,9] especially in stroke patients with atherosclerotic disease.

There has been an increase in both statin use and dose over time,[10,11] but gaps still exist between recommendations in guidelines[3,7,12,13] and current practice with suboptimal target achievement for LDL-C.[3,10,14-16] Therefore, stroke patients may not gain the full potential benefit from use of LLT. This gap could be associated with both patient-related factors, such as poor adherence and persistence to prescribed treatment and perceived side-effects,[6,13,14,17] and physician-related factors like the choice of drug type and dose intensity.[6,13,14,17] Awareness of an individual patient's risk of CVD events, perceived risk of adverse effects and the expected harm-benefit ratio may also influence how LLT is prescribed and used.[3,6,12,13,16,18]

Little is known about current use of LLT among patients with a recent ischemic stroke and factors influencing prescribing patterns. Moreover, stroke patients show considerable interindividual variation in risk of recurrent events, competing risks and remaining life expectancy,[1] with a corresponding variation in the net benefit from more intensive LLT.[1,19] Objective estimates of an individual patient's benefit of intensification of LLT might assist in making well-balanced decisions on whether to intensify treatment or not, in light of potential costs, adverse effects and remaining life-expectancy. Our study therefore aimed to address two sets of questions. First, how do current prescription patterns and achieved LDL-C reduction differ in subgroups of stroke patients? Next, what is the expected treatment benefit when theoretically up-titrating LLT according to guideline recommendations?

Methods

Study population

Home-dwelling patients from the Nor-COAST (Norwegian Cognitive Impairment After Stroke) study, a multicenter observational cohort study, were included (n=729), Figure S1. In Nor-COAST, patients admitted with acute ischemic stroke at five Norwegian stroke units were consecutively included between May 2015 and March 2017.[20] Patients were assessed with self-report questionnaires, clinical examinations, and blood sampling after 3 and 18 months at outpatient clinics. Patients unable to attend were assessed by telephone interview or by proxy information. Detailed information about definitions used and data collection in Nor-COAST can be found in Supplementary Methods. For all analyses, we excluded patients who died within the first 3 months poststroke (n = 29), patients living in nursing homes at 3 months poststroke (n = 36) and patients lacking information about medications at all time points (n = 3). Patients between 45 and 80 years (n=462) were included in the present analyses as we used a cardiovascular risk prediction model derived and validated in this age range.[1,19] All participants in Nor-COAST gave written informed consent or by proxy if the participant was unable to cooperate. The Norwegian Regional Committee for Medical and Health Research Ethics North (REC numbers 2015/171 and 2017/1462) approved the study.

Assessment of use of lipid-lowering therapy

Trained health professionals obtained information about medications in use by clinical interview of patients and caregivers at the index stay, 3 and 18 months. If information regarding medications was missing, we contacted general practitioners and / or home care services or used the electronic summary care record for safer healthcare in Norway. LLT was identified using the following Anatomical Therapeutic Chemical (ATC) classification system codes defined by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology [21]: C10AA (HMG-CoA reductase inhibitors (statins)), C10AC (bile acid sequestrants), C10AX (other lipid modifying agents) and C10B (combinations of lipid-lowering drugs). Statins included atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. We used the Defined Daily Doses (DDDs),[21] which are 20 mg for atorvastatin, 30 mg for simvastatin, 10 mg for rosuvastatin, 60 mg for fluvastatin and 30 mg for pravastatin, to convert the doses to atorvastatin equivalent doses by the following formula: (Dose of statin / DDD for that statin) x DDD for atorvastatin = atorvastatin equivalent dose. High-intensity statin (HIS) treatment was defined as drugs known to lower LDL-C by approximately 50%, which corresponds to ≥ 40 mg atorvastatin, ≥ 20 mg rosuvastatin or 80 mg simvastatin per day.[3] Other statins were defined as non-high-intensity treatment. We measured medication adherence by the 4-item Morisky Medication Adherence Scale (MMAS4), where a score of 4 points was defined as high adherence.[22]

LDL-C target achievement at 3 months and expected LDL-C levels with up-titration of LLT

LDL-C ≤1.8 mmol/L was defined as target attainment[7,12] and 3-month levels were used as the basis for theoretical intensification as this timepoint roughly corresponds to the guideline recommended control after an acute event where risk factors should be examined and prevention intensified if indicated.[7] Guidelines recommend statins at maximally tolerated dose as first-line therapy (**Step 1**) and use of ezetimibe (**Step 2**) in patients who are unable to achieve the LDL-C target with statins alone or are statin intolerant.[3,7,12] While statins and ezetimibe are well-established treatments available at low costs, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are more potent and expensive and mainly considered for patients still not reaching targets (**Step 3**).[3,7]

We included patients receiving LLT at discharge in these analyses. When information of drug and dose was missing at 3 months (6%), we used the drug and dose prescribed at discharge.[14] We estimated the effect of hypothetically up-titrating current LLT, defined as drug and dose used at the 3-month visit, using a stepwise approach.[7] The mean percent reduction in LDL-C derived from randomized clinical trials, as previously presented and validated specifically for each drug and dose, was used[23] (**Supplementary Methods, Table S1**). First, all patients with LDL-C > 1.8 mmol/L not using HIS was up-titrated to HIS, assuming a 50.2% mean reduction in LDL-C corresponding to the effect of atorvastatin 80 mg. [23] If the expected LDL-C then was > 1.8 mmol/L, ezetimibe was added on top, assuming a mean 22.7% reduction in LDL-C.[23] We also estimated the effect of adding ezetimibe without increased statin doses, assuming that all patients already were on maximally tolerated statin dose and patients using ezetimibe monotherapy were statin intolerant.

Estimated potential benefit from up-titration of LLT

We estimated individual benefit of the abovementioned approach from a lifetime perspective expressed in terms of gain in months free of recurrent stroke, myocardial infarction or cardiovascular mortality[19] and as 10-year absolute risk reduction (ARR), by using the externally validated SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model.[19] The model is a competing risk-adjusted lifetime risk model previously validated in Nor-COAST,[1] which uses the following predictors: sex, current smoking, diabetes mellitus, systolic blood pressure, total cholesterol, serum creatinine concentration, number of locations of cardiovascular disease (coronary, cerebral and/or peripheral arterial disease), atrial fibrillation, and heart failure (**Supplementary Methods** and **Table S2**).

We first calculated the life expectancy without recurrent cardiovascular events based on 3-month levels of predictors in the model, defined as the median estimated survival without a recurrent event [19]. We next estimated potential treatment benefit

defined as the difference in CVD-free life expectancy with and without up-titration of LLT. CVD-free life expectancy with achieved LDL-C level after up-titration was calculated by incorporating a hazard ratio of 0.78 for major cardiovascular events per 1.0 mmol/L reduction in LDL-C[2] in the competing risk model. For 10-year ARRs, we first calculated the 10-year CVD risk based on 3-month LDL-C levels, and next, we calculated the 10-year CVD risk with achieved LDL-C levels after up-titration, where the difference corresponds to the individuals' ARRs. Patients were assigned to intensification only if they had not attained the LDL-C target. Since it is uncertain how well the SMART-REACH model performs in the subgroup with cardioembolic stroke[1] with otherwise low levels of atherosclerotic risk factors, we did additional analyses excluding patients with cardioembolic stroke etiology.

Statistical analysis

We report characteristics by LLT use and intensity at discharge by means with standard deviations (SD) and proportions as appropriate. We also reported descriptive statistics for patient characteristics in categories defined by quartiles of percent LDL-C reduction from discharge to 3 months. Logistic and linear regression was used with LLT prescription (yes/no) and atorvastatin equivalent dose (mg/d) as dependent variables, respectively, to identify variables predictive of LLT use and intensity. Potential predictors were selected a priori based on previous studies[10,11,17,24] and clinical reasoning, leading to inclusion of the following covariates, first one at a time, and next, adjusted for age and sex: age, sex, LDL-C (measured the first day after admission), prestroke use of LLT, frailty by a modified version of the 5-item Fried criteria[14] as a continuous variable from 0 (robustness) to 5 (frail), the Global Deterioration Scale (GDS) as continuous variable from 1 (normal cognitive function) to 7 (severe dementia). A history of ischemic heart disease was included as a categorical variable (yes/no) and was defined as angina pectoris, myocardial infarction, and/or coronary revascularization (coronary bypass surgery or percutaneous coronary intervention). Stroke subtype was divided into five categories according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification: large artery disease, cardioembolic stroke, small vessel disease, other etiology, and undetermined strokes. As the subtype "other etiology" comprised a small number, it was grouped with "undetermined". We report coefficients or odds ratios (OR) with 95% confidence intervals (CI) where relevant. Two-sided p-values <0.05 were regarded as statistically significant. However, due to multiple comparisons, p-values between 0.01 and 0.05 should be interpreted with caution. Estimated CVD risks and benefits were reported as medians with interquartile ranges (IQRs). We visually compared distribution of estimated risk with current treatment and estimated risk after LLT intensification in histograms. Since an available case analysis might lead to bias and loss of power, we imputed missing data for LDL-C and covariates to predict CVD risk by means of single imputation using predictive mean matching. The extent of missing data for relevant variables is described in **Table S2**. We included all variables to be used in the

analyses in the imputation model. Data analysis was performed using Stata version 16 or R version 4.0.2.

Results

Baseline characteristics and prescription patterns at discharge

The analysis included 462 home-dwelling patients with mean age 69.0 years (SD 8.1), 38% were female, 24% were smoking and 27% were physically active. At hospital admission, 35% (n=161) were already using LLT in terms of statins (n=153), ezetimibe monotherapy (n=5) or combination (n=3). The mean atorvastatin equivalent dose was 34 mg (SD 22) and 37% used HIS.

At discharge, 92% (n=427) were prescribed LLT, of whom 422 received statins, either alone (n=414) or in combination with ezetimibe (n=8), whereas five patients were receiving ezetimibe alone. The most frequently prescribed statin was atorvastatin (77%), mean statin dose was 41 mg (SD 21) atorvastatin equivalent dose and 64% (n=276) received HIS. Type and doses of LLT are shown in **Table S3**. In total, 65% of those using LLT prestroke received the same LLT intensity at discharge.

Table 1: Clinical characteristics at index stay by lipid-lowering therapy use at discharge

	Prescribed lipid-lowering therapy (n = 427)			**Not prescribed lipid-lowering therapy (n = 35)**	**Total population (n = 462)**
	Non-high intensity statin (n=146)	**High-intensity statin[a] (n=276)**	**Any[b] (n=427)**		
Demographics					
Age (years)	70.4 (8.0)	68.0 (8.0)	68.8 (8.1)	70.7 (8.2)	69.0 (8.1)
Sex, female	57 (39)	105 (38)	163 (38)	14 (40)	177 (38)
Education	12.3 (3.8)	12.6 (3.7)	12.6 (3.7)	11.5 (3.4)	12.5 (3.7)
Home care services	7 (5)	5 (3)	15 (4)	5 (14)	20 (4)
Cardiovascular characteristics					
Atrial fibrillation	38 (26)	46 (17)	84 (20)	16 (46)	100 (22)
Diabetes mellitus	32 (22)	50 (18)	84 (20)	6 (17)	90 (20)
History of hypertension	84 (58)	146 (53)	233 (55)	17 (49)	250 (54)
Prestroke lipid-lowering therapy	69 (47)	89 (32)	160 (37)	1 (3)	161 (35)
Previous cerebrovascular disease	41 (28)	52 (19)	97 (23)	10 (29)	107 (23)
Ischemic heart disease	30 (21)	46 (17)	77 (18)	2 (6)	79 (17)
Peripheral artery disease	15 (10)	19 (7)	34 (8)	0 (0)	34 (7)
Heart failure	2 (1)	6 (2)	8 (2)	3 (9)	11 (2)

Table 1 (continued)

	Prescribed lipid-lowering therapy (n = 427)			Not prescribed lipid-lowering therapy (n = 35)	Total population (n = 462)
	Non-high intensity statin (n=146)	High-intensity statin[a] (n=276)	Any[b] (n=427)		
Glomerular Filtration Rate (ml/min/1.73 m²)	79 (15)	78 (16)	79 (16)	77 (21)	79 (16)
Body Mass Index (kg/m²)	26.2 (4.2)	27.0 (4.3)	26.7 (4.2)	26.0 (3.7)	26.7 (4.2)
Current smoker	34 (23)	101 (37)	100 (24)	9 (26)	109 (24)
Physically active	36 (25)	77 (28)	115 (27)	8 (23)	123 (27)
Lipid levels at index stay					
Total cholesterol (mmol/L)	4.6 (1.2)	5.1 (1.3)	5.0 (1.3)	4.7 (1.4)	5.0 (1.3)
LDL cholesterol (mmol/L)	2.8 (0.9)	3.3 (1.1)	3.1 (1.1)	3.0 (1.3)	3.1 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.6)	1.4 (0.6)	1.4 (0.6)	1.3 (0.4)	1.4 (0.5)
Stroke characteristics and other comorbidities					
NIHSS discharge	1.4 (1.8)	1.7 (2.4)	1.6 (2.2)	2.0 (3.9)	1.7 (2.4)
Stroke subtype (n = 447)					
Large artery disease	10 (7)	38 (14)	48 (12)	1 (3)	49 (11)
Cardioembolic	34 (24)	54 (20)	88 (21)	15 (43)	103 (23)
Small vessel disease	35 (25)	62 (24)	99 (24)	5 (14)	104 (23)
Other cause	5 (4)	6 (2)	11 (3)	1 (3)	12 (3)
Undetermined or multiple causes	59 (41)	104 (39)	166 (40)	13 (37)	179 (40)
Charlson Comorbidity Index	3.8 (1.7)	4.3 (1.9)	3.6 (1.8)	4.1 (1.9)	3.6 (1.8)
Frail	14 (10)	16 (6)	30 (7)	2 (6)	32 (7)
Cognitive impairment	3 (2)	4 (2)	7 (2)	6 (17)	13 (3)
Independent functional status at discharge[c]	102 (70)	196 (71)	303 (71)	21 (60)	324 (70)
Other secondary preventive drugs at discharge					
Antithrombotic drugs	144 (99)	275 (100)	424 (99)	34 (97)	458 (99)
Antihypertensive drugs	113 (77)	205 (74)	321 (75)	25 (71)	346 (75)
Total number of medications	5.3 (2.6)	5.2 (2.4)	5.2 (2.5)	4.0 (3.0)	5.1 (2.6)

Values are n (%) or mean (standard deviation) (n observations). [a] Defined as ≥ 40 mg atorvastatin, ≥ 20 mg rosuvastatin or 80 mg simvastatin per day. [b] 5 patients received ezetimibe monotherapy. [c] Defined as ≤2 on Modified Rankin Scale. Abbreviations: LDL; Low density lipoprotein, HDL; High density lipoprotein; NIHSS, National Institutes of Health Stroke Scale. Detailed definitions in supplementary methods.

Unadjusted and age- and sex-adjusted associations between patient characteristics and prescription of LLT (yes/no) at discharge are shown in **Table S4**. Prestroke cognitive impairment and cardioembolic stroke etiology were associated with no

prescription**.** Patient characteristics associated with dose intensity at discharge are shown in **Table 2**. In analyses excluding cardioembolic stroke, the effect estimates were mostly the same as in Table 2, but there was no significant association between age and statin dose intensity (data not shown).

Table 2: Linear regression with statin dose intensity (mg) a as dependent variable, for participants prescribed statin monotherapy at discharge (n = 414)

	Unadjusted analysis			**Age- and sex adjusted analysis**	
	n	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Age, years	414	-0.30 (-0.55 to -0.05)	0.019	-0.26 (-0.51 to -0.01)	0.039
Sex, female	414	-5.1 (-9.2 to -0.9)	0.017	-4.5 (-8.6 to -0.3)	0.036
LDL-C[b], mmol/L	414	2.7 (0.9 to 4.5)	0.004	2.8 (0.9 to 4.6)	0.003
Prestroke use of LLT	414	-2.4 (-6.6 to 1.8)	0.268	-1.8 (-6.1 to 2.4)	0.402
Frailty[c]	414	0.2 (-2.0 to 2.3)	0.889	1.3 (-0.9 to 3.5)	0.249
Cognitive impairment[d]	408	0.2 (-3.0 to 3.4)	0.918	0.8 (-2.4 to 4.0)	0.626
Ischemic heart disease	414	6.1 (0.8 to 11.4)	0.024	6.7 (1.3 to 12.1)	0.016
Index stroke etiology[e]	399				
Large artery disease		Reference category		Reference category	
Cardioembolic stroke		-11.8 (-19.4 to -4.2)	0.002	-11.6 (-19.1 to -4.1)	0.003
Small vessel disease		-11.3 (-18.8 to -3.8)	0.003	-11.3 (-18.8 to -3.9)	0.003
Undetermined or multiple causes		-9.2 (-16.2 to -2.3)	0.010	-9.4 (-16.3 to -2.4)	0.008

[a]Atorvastatin equivalent dose. [b]Measured at first day after admission [c]Measured by modified Fried Frailty criteria with 0 as reference corresponding to robust, and 5 to frail. [d]Prestroke, measured by Global deterioration scale with 1 as reference corresponding to normal cognitive function and 7 to severe dementia. [e]Classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. Abbreviations: LDL-C, Low-density lipoprotein cholesterol.

Achieved LDL-C levels and LLT at follow-up

For patients prescribed LLT at discharge (n=427), mean LDL-C decreased from 3.1 (SD 1.1) to 2.1 (SD 0.7) mmol/L from index stay to 3 months poststroke. For LLT naïve patients the corresponding decreases were from 3.5 (SD 1.0) to 2.0 (SD 0.7) mmol/L and for those receiving prestroke LLT from 2.4 (SD 1.0) to 2.1 (SD 0.7) mmol/L, respectively. In total, 45% (n=193) achieved the LDL-C target of ≤1.8 mmol/L and 33% of these had reached the target by receiving non-HIS, 62% by HIS, 1% by ezetimibe monotherapy, 2% by statin plus ezetimibe and 2% without LLT (discontinued). In total, 14 patients had discontinued statins between discharge and 3 months. For patients not at target, the mean distance to the target was 0.7 (SD 0.6) mmol/L. In total, 58% (n=249) had LDL-C ≤2.0 mmol/L, 11% (n=45) ≤1.4 mmol/L and 2% (n=10) ≤1.0 mmol/L and 78% reported high medication adherence.

Lipid profiles according to subgroups of stroke patients are shown in **Table S5,** where women, younger patients and patients with no prestroke LLT had higher LDL-C at admission. LLT for patients not reaching the target by subgroups of stroke patients is shown in **Table S6**. Target attainment in different subgroups of LLT regimens is shown in **Figure S2,** target attainment was observed in less than half of patients in all LLT intensity groups.

Table 3 shows characteristics in categories defined by quartiles of relative LDL-C reduction. Patients with the largest reduction were younger, had higher LDL-C at index stay, 82% were prescribed HIS and 86% reported optimal adherence. Among patients with the smallest LDL-C reduction, 78% had prestroke LLT. In total, 28% had achieved ≥50% reduction in LDL-C, mean relative reduction in LDL-C for patients initiating HIS (with no prestroke LLT) was 42.5 % (SD 26).

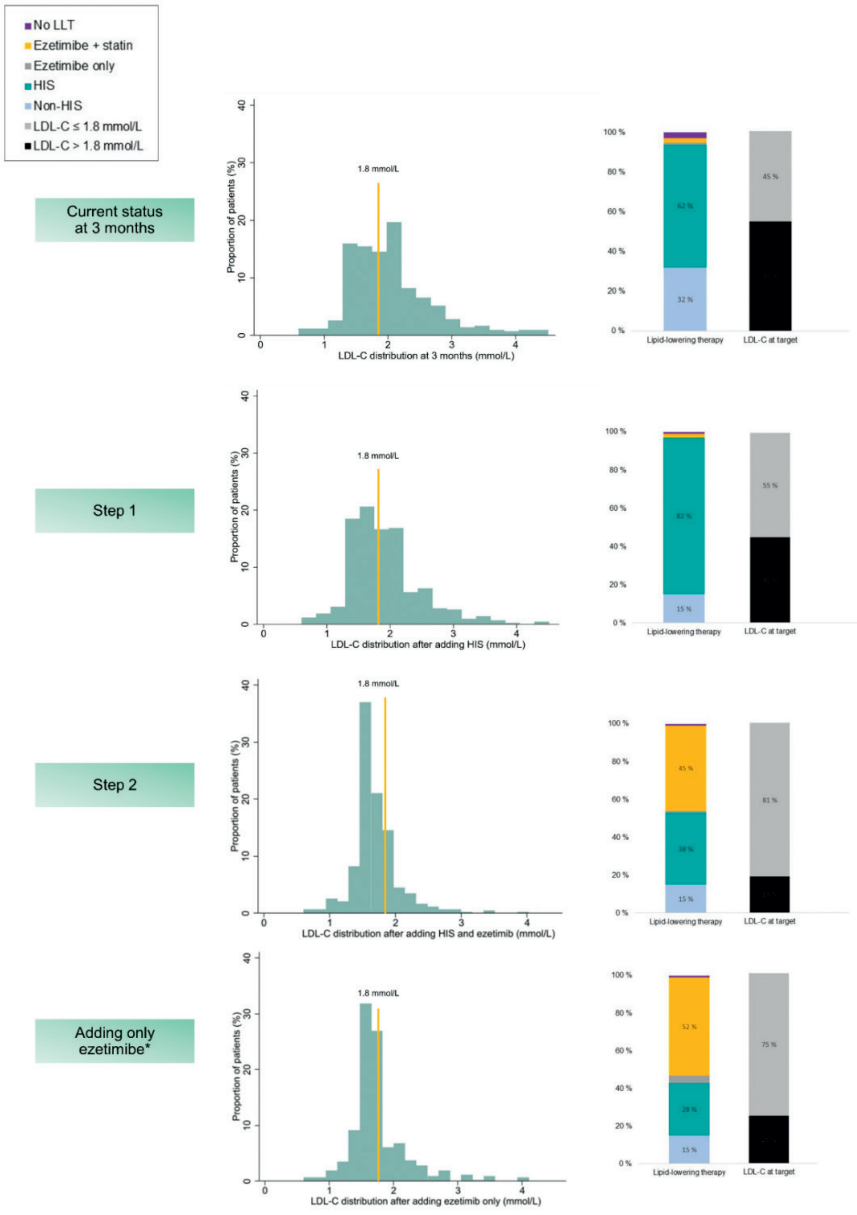
In total, 73% of the 352 patients with available medication lists at 18 months reported high medication adherence and 11% (n=38) had discontinued statins (10% of men and 13% of women, p=0.337, 9% with HIS and 14% with non-HIS, p=0.229), of whom 4 had switched to ezetimibe monotherapy. Treatment patterns for those still persistent to statins are shown in **Figure S3**. Of patients with no LLT use at discharge or 3 months (n=26), six patients had started with LLT after more than 3 months.

Expected LDL-C levels when theoretically up-titrating LLT

Figure 1 shows LDL-C distribution after theoretically up-titrating LLT according to guidelines, proportions achieving the guideline target for each step and proportions at different LLT. Of the 55% (n=234) of patients not at target at 3 months, 63% (n=147) were already receiving HIS whereas 37% (n=87) could undergo up-titration to HIS **(Step 1), Supplementary Figure S4.** Up-titration in these 87 subjects would result in an additional 18% (n=43) achieving an LDL-C level ≤ 1.8 mmol/L (overall cohort with LDL-C ≤ 1.8 mmol/L, 55% at this stage). Of the remaining 45% (n=191) not at the LDL-C target, six patients were already receiving concomitant ezetimibe. Ezetimibe could be added to the remaining 44% (n=185) receiving HIS who were not at the target **(Step 2).** After this step, an additional 26% would have reached the target (total at target, 81% (n=347)).

After intensification, mean LDL-C changed from 2.1 mmol/L (SD 0.7) to 1.7 mmol/L (SD 0.4). Mean LDL-C for those not reaching the target after intensification (n=80) was 2.2 mmol/L (SD 0.4). Assuming all patients were already using maximally tolerated statin dose and only ezetimibe could be added to current treatment, 75% (n=319) could potentially reach the treatment target.

Figure 1. Distribution of LDL-C, proportions at target ≤1.8 mmol/L and LLT in use at 3 months and after hypothetically up-titrating LLT according to guideline-recommendations



first (step 1) by adding / up-titrating to high intensity statin, and next (step 2) by adding ezetimibe.*Assuming already on maximally tolerated statin dose. Proportions are n of the total population (n=427). Patients with no LLT, are patients who have discontinued prescribed LLT between discharge and 3 months. Abbreviations: LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; HIS, high-intensity statin.

Table 3: Characteristics in categories defined by quartiles of % LDL-cholesterol reduction from index stay to the 3-month visit for patients prescribed LLT at discharge (n=427)

	≤Q1 < 8% reduction (n=107)	**Q1 to Q2 9 to 35% reduction (n=107)**	**Q2 to Q3 36 to 51% reduction (n=107)**	**Q3 >51% reduction (n=106)**
Median % reduction (IQR)	-6 (-28 to 0)	23 (16 to 29)	44 (39 to 48)	57 (54 to 61)
Age, mean (SD)	70.3 (8.1)	69.3 (7.8)	68.9 (8.3)	66.9 (7.9)
Sex, female	28 (26)	42 (39)	44 (41)	49 (46)
Body Mass Index (kg/m^2), mean (SD)	26.7 (4.1)	26.6 (4.8)	26.5 (4.1)	27.0 (3.9)
Current smoker at admission	26 (24)	22 (21)	23 (22)	29 (27)
Hypertension	81 (76)	66 (62)	44 (41)	42 (40)
Prestroke use of LLT	83 (78)	51 (48)	18 (17)	8 (8)
Diabetes mellitus	28 (26)	20 (19)	19 (18)	17 (16)
History of ischemic heart disease	41 (28)	19 (18)	13 (12)	4 (4)
Prior stroke	45 (42)	29 (27)	11 (10)	12 (11)
Charlson Comorbidity Index	4.3 (1.8)	3.8 (2.0)	3.2 (1.4)	3.1 (1.8)
Frail	7 (7)	9 (8)	6 (6)	8 (8)
Cognitive impairment	4 (4)	3 (3)	0 (0)	0 (0)
Stroke subtype (n=412)				
Large artery disease	10 (9)	14 (14)	13 (12)	11 (11)
Cardioembolic stroke	33 (31)	24 (24)	18 (17)	13 (13)
Small vessel disease	19 (18)	24 (24)	27 (26)	29 (29)
Other	3 (3)	3 (3)	5 (5)	0 (0)
Undetermined	40 (38)	36 (35)	43 (41)	47 (47)
LDL-C at index stay, mean (SD)	2.1 (0.8)	2.8 (0.8)	3.5 (0.9)	4.0 (0.9)
LDL-C at 3 months, mean (SD)	2.4 (0.8)	2.1 (0.6)	2.0 (0.5)	1.7 (0.4)
10-year CVD risk (%)[a], median (IQR)	50 (38 to 63)	43 (33 to 54)	40 (30 to 52)	37 (29 to 49)
Discontinued statin between 0 and 3 months	7 (7)	6 (6)	1 (1)	0 (0)
Optimal medication adherence[b] (n=351)	70/87 (81)	67/87 (77)	69/90 (77)	75/87 (86)
Non-high intensity statin	50 (47)	37 (35)	37 (35)	19 (18)
High-intensity statin	50 (47)	64 (60)	69 (64)	87 (82)
At target at 3 months	29 (27)	41 (38)	47 (44)	76 (72)

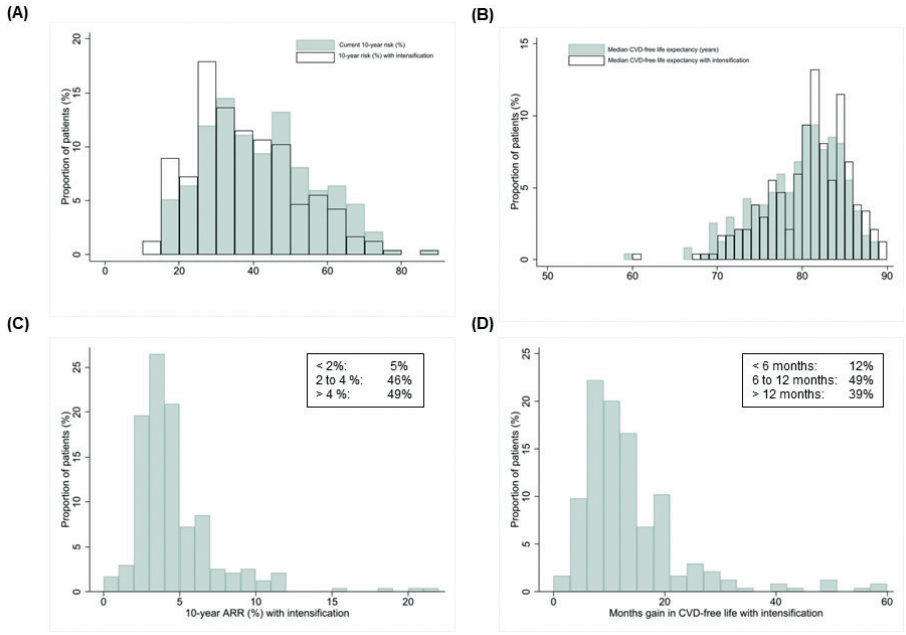
Values are n/N (%) if other not specified. [a]Estimated by the SMART-REACH model. [b]Corresponding to score 4 on Morisky Medication Adherence Scale 4. Abbreviations: LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; LLT, lipid-lowering therapy; CVD, cardiovascular disease; SD, standard deviation; IQR, interquartile range. Detailed definitions of variables in Supplementary Methods.

Expected benefit when theoretically up-titrating LLT

For all patients prescribed LLT (n=427), the median 10-year CVD risk was 42% (IQR 31 to 54%) and lifetime risk was 70% (IQR 64 to 76%). Median CVD-free life expectancy was 80.2 years (IQR 76.2 to 83.2). The median estimated lifetime benefit when up-titrating LLT for those not at target was 5 months (IQR 0 to 12). Median CVD-free life gain was < 6 months for 52% (n=220), 6 to 12 months for 27% (n=115) and > 12 months for 22% (n=92). Estimated median 10-year ARR was 2% (IQR 0 to 4%).

For patients with LDL-C above 1.8 mmol/L (n= 234), the median estimated lifetime benefit by up-titrating LLT was 11 months (IQR 7 to 17), with 39% having > 12 months of estimated CVD-free life gain (**Figure 2, panel D).**

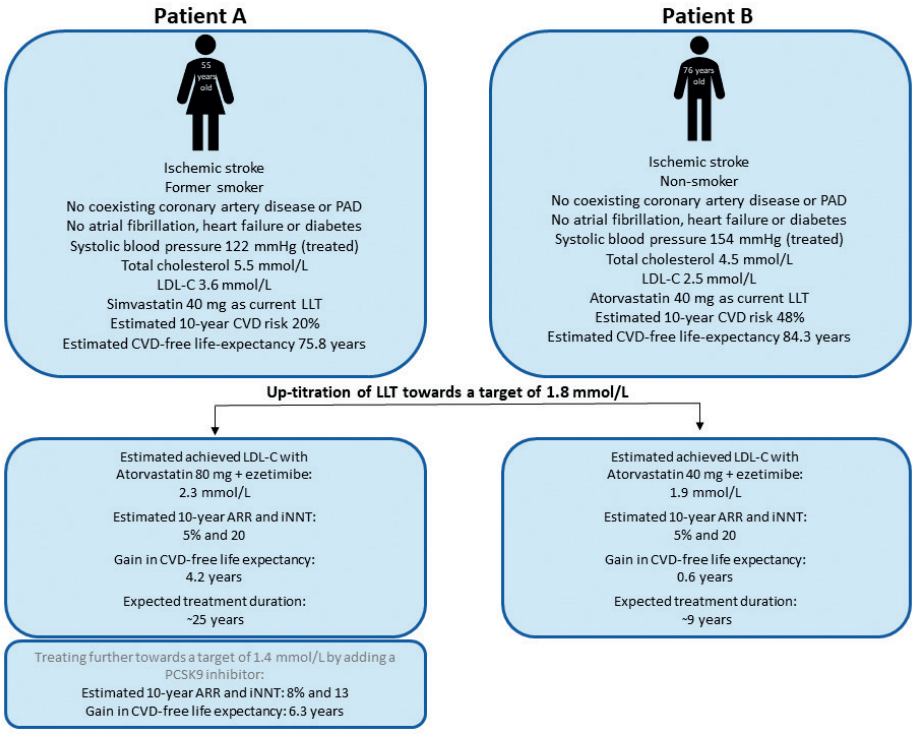
Figure 2. Estimated prognostic impact of intensification of lipid-lowering therapy according to the guideline-recommendations for patients with LDL-C above 1.8 mmol/L at 3 months (n=234).



The top row shows (A) the distribution of the estimated 10-year CVD before and after intensification and (B) estimated median life-expectancy free from CVD events before and after intensification. The bottom row shows (C) distribution of estimated 10-year ARRs with intensification and (D) distribution in gain in months free from CVD events with intensification. Abbreviations: LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; ARR, absolute risk reduction

Characteristics for patients stratified by tertiles of months of gain in CVD-free life are shown in **Supplementary Table S7**. Estimated 10-year ARR for these patients was median 4% (IQR 3 to 5%), and the median 10-year risk level could be reduced from 40% (IQR 31 to 52%) to 35% (IQR 27 to 46%). Estimated lifetime benefit when excluding patients with cardioembolic stroke etiology (n=51) was 11 months (IQR 7 to 17) and median 10-year ARR was 4% (IQR 3 to 5%). Further up-titration to the LDL-C target 1.4 mmol/L would lead to median 17 months (IQR 11 to 25) of estimated lifetime benefit (**Supplementary Figure S5**). Two illustrative patient examples are shown in **Figure 3**.

Figure 3. Patient examples



The benefit of intensification of current lipid-lowering therapy estimated by the SMART-REACH model for patients aged 55 years versus 76 years and expected treatment duration. Abbreviations: PAD, peripheral artery disease; LLT, lipid-lowering therapy; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; ARR, absolute risk reduction; iNNT, individual number-needed-to-treat (1 divided by ARR); PCSK9, proprotein convertase subtilisin/kexin type 9.

Discussion

In this observational study of patients ≤80 years discharged home after relatively minor ischemic strokes, we showed high LLT prescription rates, and although LDL-C levels in many cases were not far from target, less than half of patients reached the target of 1.8 mmol/L. Age, sex, index stroke etiology and baseline LDL-C were related to LLT intensity prescribed; however, target attainment was observed in approximately 40-50% irrespective of age, sex, prestroke LLT, subtypes of stroke and LLT intensity subgroups. Younger patients, women and patients receiving HIS had larger % LDL-C reduction. We estimated that 81% could potentially reach the target with well-established low-cost drugs leading to median of 11 months CVD-free life-gain for patients with elevated LDL-C, but with large interindividual variation.

The prescription rates and mean statin doses were higher in the present study than in other studies.[10,15,16,24-27] In total, 63% of those not reaching the target reported using HIS, illustrating that many patients with established CVD do not reach treatment targets by the highest tolerated statin monotherapy dose.[13,15] However, a previous study has noted that LDL-C levels down to a mean of 1.4 mmol/L is possible to achieve if adherence to therapy is optimal and optimized dose of conventional LLT (including ezetimibe) is prescribed.[28] Although the Nor-COAST study was conducted between 2015 and 2018 and most physicians were treating towards a target of LDL-C < 2.0 mmol/L[29] (reached by 58% of patients), most patients with dose adjustments had their dose reduced, in line with other studies,[30] few used alternative LLT and although reason for discontinuation was not known, 11% discontinued statins within 18 months.

In a previous study also including patients > 80 years, female sex and younger age were associated with poor LDL-C control,[14] while higher statin dose was associated with better LDL-C control. As shown in the current analyses, multiple factors might interfere with choice of dose intensity. As in other studies,[10,11,24,26,30,31] female sex and advanced age were associated with lower dose intensity and females also had higher LDL-C levels at admission. Other studies have shown that females less often receive evidence-based CVD drugs and often experience more adverse drug reactions than men and also more often have lower awareness of their CVD risk.[1]. Current prescription patterns in the elderly might be explained by the large heterogeneity in underlying health status and life-expectancy,[3,18,32] as well as age and polypharmacy being risk factors for adverse effects and interactions.[3] Although emerging evidence supports similar relative risk reductions for major CVD events regardless of age, including those ≥ 75 years,[32] previous guidelines have been less concise in their recommendations. The absolute risk reduction with intensified LLT can be substantial in the elderly. At the same time, the actual increase in life-expectancy might be limited due to risk of both CVD events and competing risks (**Figure 3**).[3,18,32]

Cardioembolic stroke was associated with no LLT prescription, while large artery disease etiology was associated with higher dose intensity. Coexisting ischemic heart disease was associated with higher dose intensity. Evidence has historically been more robust for patients with ischemic heart disease and large artery disease,[4,5,15,16] and previous studies have reported that patients with ischemic heart disease receive LLT and HIS more often than patients with peripheral and cerebrovascular disease.[15,16] However, the large overlap between ischemic stroke subtypes and the high prevalence of atherosclerosis regardless of stroke etiology illustrate the need for optimal lipid control in all subtypes.[33] Furthermore, consistent relative treatment effects across multiple subgroups of patients have been demonstrated in landmark meta-analyses[2,3] and observational studies show reduced risk of CVD events and mortality with statins also in cardioembolic stroke.[34,35] Though, some of these patients might not have atherosclerosis and treating lipids less intensively might better harmonize with the individual patients' expected benefit.

Concordance with guidelines might not be the ultimate marker of successful treatment for all patients.[36] However, not achieving targets might well be influenced by lack of familiarity with guidelines, physicians' and patients' preferences and uncertainty of clinical benefit of LLT which might lead to misinterpretations about the benefit-harm tradeoffs.[13,15-18,30] Statin intolerance and narrow reimbursement criteria for PCSK9-inhibitors might also be important reasons.[16,17] Moreover, levels are often not far from targets; the physicians might then take a more pragmatic approach. When hypothetically up-titrating LLT, 81% was expected to reach LDL-C ≤1.8 mmol/L with safe, effective low-cost drugs, a proportion similar to large simulation studies.[23,37] Though, the efficiency of LLT is likely to be lower in real-life settings (**Supplementary Table S8**) and PCSK9 inhibitors would be required for a certain proportion especially if aiming for more stringent treatment targets.[3,13,23] However, the estimated individual net benefit of a more intensive approach varies, depending on baseline CVD risk, level of LDL-C, remaining life-expectancy and competing risks.[3,12,19] Benefit on group level was largest in younger patients with relatively high LDL-C levels, however, younger age also means longer treatment duration and thereby higher costs to achieve those benefits (**Figure 3**). The amount of benefit considered meaningful is also highly subjective and conditional on side effects, costs, and patient preferences.[38] Furthermore, only estimating further up-titration for patients with LDL-C above 1.8 mmol/L underestimated the actual potential benefit of intensified LLT, since CVD risk is linearly related to LDL-C reduction[2,3] (**Supplementary Figure S5**).

Strengths and limitations

The strengths of this study include prospective consecutively inclusion and assessing LLT intensity three time-points post an acute event,[3,7] whereas previous studies are hampered by retrospective design[10,25] with data collected a long period after an event[10,25,30] or solely at discharge.[11,24,26] We add knowledge about factors

influencing LLT use in patients with stroke, which is a less studied group compared to i.e., ischemic heart disease.[15] Although proportions with frailty and dementia were low, including detailed clinical information about these features and ischemic stroke etiology is a strength that previous studies lack or have based on registry data and diagnostic codes only.[10,11] Using a lifetime risk prediction model adjusted for competing risk avoids overestimating treatment benefit in older individuals and underestimation of benefit in younger individuals.[19] The Nor-COAST study participants have characteristics comparable to patients in the Norwegian Stroke Registry[39] and generalization at least to Norwegian stroke patients and comparable populations is plausible, however, it should be noted that we excluded the oldest patients from these analyses.

Several limitations merit considerations. Self-reported use of LLT and medication adherence might overestimate the actual use and might lead to a conservative estimate of the expected LDL-C levels achieved with intensification of treatment in these analyses. We did not account for the large interindividual variations in percentage LDL-C reduction achieved with the same drug dose.[3,13] Whereas most variables only had limited missingness, there was considerable missing for LDL-C at 3 months (24%). In addition, the findings of the current study could further have improved if information regarding drug-related adverse effects or patient preferences was available, as these data might be the reason for non-adherence and reduction in dose intensity. Our cohort does by no means represent a randomized controlled trial setting, from which the LDL-C reductions and hazard ratio were retrieved. Although ischemic stroke has more heterogeneous etiology than, i.e., ischemic heart disease, we assumed all subtypes of stroke had the same relative benefit of LDL-C reduction. However, the SMART-REACH model may perform differently in patients with cardioembolic stroke etiology.[1] Moreover, these results give an indication of the impact of conventional LLT but need to be put into the perspective of a patient's estimated life-expectancy, multimorbidity, polypharmacy and functional impairments.[12,36]

In **conclusion**, in a cohort with recent ischemic stroke ≤ 80 years, almost all patients received LLT at discharge from hospital, but below half of the patients reached the guideline-based LDL-C treatment target. We show potential for improving LDL-C control and reducing residual cholesterol risk with safe, effective well-established low-cost lipid-lowering therapies. Awareness of patient groups at risk of undertreatment, like women, and awareness of an individual patient's risk of CVD events and the benefits of intensifying treatment might help avoid under- and overtreatment. To overcome uncertainties regarding individuals' clinical benefit of further intensification of treatment, the SMART-REACH model can be used to objectively estimate expected benefit. When benefits are known, these can be balanced against potential costs and perceived side-effects, to assist physicians and patients in well-informed treatment decisions.

References

1. Gynnild MN, Hageman SHJ, Dorresteijn JAN, Spigset O, Lydersen S, Wethal T, et al. Risk Stratification in Patients with Ischemic Stroke and Residual Cardiovascular Risk with Current Secondary Prevention. Clin Epidemiol. 2021;13:813-23.
2. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.
4. Amarenco P, Bogousslavsky J, Callahan Iii A, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549-59.
5. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y, et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med. 2020;382(1):9.
6. Khunti K, Danese MD, Kutikova L, Catterick D, Sorio-Vilela F, Gleeson M, et al. Association of a Combined Measure of Adherence and Treatment Intensity With Cardiovascular Outcomes in Patients With Atherosclerosis or Other Cardiovascular Risk Factors Treated With Statins and/or Ezetimibe. JAMA Netw Open. 2018;1(8):e185554.
7. Norwegian Guideline for Prevention of Cardiovascular Disease: The Norwegian Directorate of Health; 2017 [updated 5 March 2018. Available from: https://www.helsedirektoratet.no/retningslinjer/forebygging-av-hjerte-og-karsykdom.
8. Amarenco P, Hobeanu C, Labreuche J, Charles H, Giroud M, Meseguer E, et al. Carotid Atherosclerosis Evolution When Targeting a Low-Density Lipoprotein Cholesterol Concentration <70 mg/dL After an Ischemic Stroke of Atherosclerotic Origin. Circulation. 2020;142(8):748-57.
9. Giugliano Robert P, Pedersen Terje R, Saver Jeffrey L, Sever Peter S, Keech Anthony C, Bohula Erin A, et al. Stroke Prevention With the PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Evolocumab Added to Statin in High-Risk Patients With Stable Atherosclerosis. Stroke. 2020;51(5):1546-54.
10. Yang Z, Edwards D, Massou E, Saunders CL, Brayne C, Mant J. Statin use and high-dose statin use after ischemic stroke in the UK: a retrospective cohort study. Clin Epidemiol. 2019;11:495-508.
11. Sjolander M, Eriksson M, Glader E-L. Social stratification in the dissemination of statins after stroke in Sweden. Eur J Clin Pharmacol. 2013;69(5):1173-80.
12. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2021.
13. Averna M, Banach M, Bruckert E, Drexel H, Farnier M, Gaita D, et al. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. Atherosclerosis. 2021;325:99-109.
14. Gynnild MN, Aakerøy R, Spigset O, Askim T, Beyer MK, Ihle-Hansen H, et al. Vascular risk factor control and adherence to secondary preventive medication after ischaemic stroke. J Intern Med. 2020.
15. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. European Journal of Preventive Cardiology. 2020.

16. Xian Y, Navar AM, Li S, Li Z, Robinson J, Virani SS, et al. Intensity of Lipid Lowering With Statin Therapy in Patients With Cerebrovascular Disease Versus Coronary Artery Disease: Insights from the PALM Registry. J Am Heart Assoc. 2019;8(19):e013229.

17. Hirsh BJ, Smilowitz NR, Rosenson RS, Fuster V, Sperling LS. Utilization of and Adherence to Guideline-Recommended Lipid-Lowering Therapy After Acute Coronary Syndrome: Opportunities for Improvement. J Am Coll Cardiol. 2015;66(2):184-92.

18. Ko DT, Mamdani M, Alter DA. Lipid-Lowering Therapy with Statins in High-Risk Elderly Patients: The Treatment-Risk Paradox. J Am Med Assoc. 2004;291(15):1864-70.

19. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB, Sr., Massaro JM, et al. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. J Am Heart Assoc. 2018;7(16):e009217.

20. Thingstad P, Askim T, Beyer MK, Bråthen G, Ellekjær H, Ihle-Hansen H, et al. The Norwegian Cognitive impairment after stroke study (Nor-COAST): study protocol of a multicentre, prospective cohort study. BMC Neurol. 2018;18(1):193.

21. WHO. World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology 2020 [Available from: http://www.whocc.no/atcdddindex.

22. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.

23. Cannon CP, Khan I, Klimchak AC, Reynolds MR, Sanchez RJ, Sasiela WJ. Simulation of Lipid-Lowering Therapy Intensification in a Population With Atherosclerotic Cardiovascular Disease. JAMA Cardiology. 2017;2(9):959-66.

24. Canavero I, Cavallini A, Perrone P, Magoni M, Sacchi L, Quaglini S, et al. Clinical factors associated with statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry. BMC Neurol. 2014;14:53.

25. Heuschmann PU, Kircher J, Nowe T, Dittrich R, Reiner Z, Cifkova R, et al. Control of main risk factors after ischaemic stroke across Europe: data from the stroke-specific module of the EUROASPIRE III survey. Eur J Prev Cardiol. 2015;22(10):1354-62.

26. Ovbiagele B, Schwamm LH, Smith EE, Hernandez AF, Olson DM, Pan W, et al. Recent nationwide trends in discharge statin treatment of hospitalized patients with stroke. Stroke. 2010;41(7):1508-13.

27. Ní Chróinín D, Ní Chróinín C, Akijian L, Callaly EL, Hannon N, Kelly L, et al. Suboptimal lipid management before and after ischaemic stroke and TIA—the North Dublin Population Stroke Study. Ir J Med Sci. 2018;187(3):739-46.

28. Munkhaugen J, Sverre E, Peersen K, Kristiansen O, Gjertsen E, Gullestad L, et al. Is the novel LDL-cholesterol goal <1.4 mmol/L achievable without a PCSK9 inhibitor in a chronic coronary population from clinical practice? European Journal of Preventive Cardiology. 2020.

29. National guideline for treatment and rehabilitation in stroke: The Norwegian Directorate of Health; 2010, updated 2017 [updated 2017. Available from: https://www.helsedirektoratet.no/retningslinjer/hjerneslag.

30. De Backer G, Jankowski P, Kotseva K, Mirrakhimov E, Reiner Ž, Rydén L, et al. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. Atherosclerosis. 2019;285:135-46.

31. Peters SAE, Colantonio LD, Zhao H, Bittner V, Dai Y, Farkouh ME, et al. Sex Differences in High-Intensity Statin Use Following Myocardial Infarction in the United States. J Am Coll Cardiol. 2018;71(16):1729-37.

32. Gencer B, Marston NA, Im K, Cannon CP, Sever P, Keech A, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. Lancet. 2020;396(10263):1637-43.

33. Sirimarco G, Lavallée Philippa C, Labreuche J, Meseguer E, Cabrejo L, Guidoux C, et al. Overlap of Diseases Underlying Ischemic Stroke. Stroke. 2013;44(9):2427-33.

34. Park H-K, Lee JS, Hong K-S, Cho Y-J, Park J-M, Kang K, et al. Statin therapy in acute cardioembolic stroke with no guidance-based indication. Neurology. 2020;94(19):e1984.

35. Choi J-Y, Seo W-K, Kang SH, Jung J-M, Cho K-H, Yu S, et al. Statins Improve Survival in Patients With Cardioembolic Stroke. Stroke. 2014;45(6):1849-52.

36. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age Ageing. 2013;42(1):62-9.

37. Allahyari A, Jernberg T, Hagström E, Leosdottir M, Lundman P, Ueda P. Application of the 2019 ESC/EAS dyslipidaemia guidelines to nationwide data of patients with a recent myocardial infarction: a simulation study. Eur Heart J. 2020;41(40):3900-9.

38. Jaspers NEM, Visseren FLJ, Numans ME, Smulders YM, van Loenen Martinet FA, van der Graaf Y, et al. Variation in minimum desired cardiovascular disease-free longevity benefit from statin and antihypertensive medications: a cross-sectional study of patient and primary care physician perspectives. BMJ Open. 2018;8(5):e021309.

39. Kuvås KR, Saltvedt I, Aam S, Thingstad P, Ellekjær H, Askim T. The Risk of Selection Bias in a Clinical Multi-Center Cohort Study. Results from the Norwegian Cognitive Impairment After Stroke (Nor-COAST) Study. Clin Epidemiol. 2020;12:1327-36.

Supplementary Material

Supplementary Methods

Data collection and definitions used in Nor-COAST

Atrial fibrillation was defined by self-report or documented on electrocardiogram or telemetry during admission. Prestroke diabetes mellitus was defined as self-reported diabetes or HbA1c ≥ 48 mmol/mol at index stay or prescribed antidiabetic drugs at admission. Hypertension was defined as self-reported hypertension or use of antihypertensive drugs. Prestroke use of lipid-lowering therapy was defined as use of ATC classes: C10AA, C10B, C10AC or C10AX. Prevalence of previous cerebrovascular disease and coronary heart disease was retrieved from hospital medical records. Estimated glomerular filtration rate was based on the CKD-EPI equation.[40] Physically active was defined as self-reported adherence to physical activity guidelines defined as minimum 75 min per week of high-intensity exercise or minimum 150 min per week of moderate intensity exercise. Stroke severity was measured according to National Institutes of Health Stroke Scale (NIHSS). Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification by experienced stroke physicians [41]. Frailty was measured by a modified version of the Fried frailty criteria,[42] giving a score from 0 (robustness) to 5 (frail) based on reduced grip strength, slow gait speed, self-reported fatigue, low physical activity and unintentional weight loss. Cognitive impairment was defined as score ≥ 3 on Global Deterioration Scale[43], a global measure of cognitive function and ability to perform daily life activities. Trained study nurses used all available information from interviews with caregivers during hospital stay to give a score from 1 (normal cognitive function) to 7 (severe dementia). Independent functional status was defined as Modified Rankin Scale ≤2.

Estimation of achievable LDL-C levels when up-titrating LLT according to guideline recommendations

We used the mean percentage change in LDL-C reduction with statins and ezetimibe as presented and validated by Cannon et al.[23] (as shown in **Supplementary table S1**) to estimate potentially achievable LDL-C levels when up-titrating therapy for those not already at the target at 3 months. For patients already using a high-intensity statin (HIS), achieved LDL-C levels at 3 months were used when calculating the effect of adding ezetimibe. For patients using non-high intensity statins, we calculated additional LDL-C reduction (based on LDL-C levels achieved at 3 months) by switching from non-high intensity statin to HIS, for example for switching from atorvastatin 10 mg (associated with 35.5% LDL-C reduction) to atorvastatin 80 mg (associated with 50.2% LDL-C reduction), the assumed additional LDL-C reduction was 23% (1-(1-0.502)/(1-0.355)).[23] After up-titrating all to a high-intensity statin, we assumed a mean 22.7% reduction in LDL-C when adding ezetimibe.[23,44]

Assessment of cardiovascular risk and benefit of LDL-C lowering by the SMART-REACH model

The SMART-REACH model is a Fine and Gray model consisting of two complementary competing-risk-adjusted cause specific hazard functions; one for vascular events, and one for non-vascular mortality, where age is used as the underlying time function.[19] The model uses the following predictors: age, sex, current smoking, diabetes mellitus, systolic BP, history of heart failure, history of atrial fibrillation, creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and number of locations of vascular disease (cerebrovascular, coronary and peripheral artery disease). Since the model is intended for use in patients with stable cardiovascular disease, clinical measurements at the 3-month visit were used in the analysis. Detailed definition of the variables in the model have been previously published when validating the model in Nor-COAST.[1] Missing data for the relevant variables and mean levels at 3 months are shown in **Supplementary Table S2.**

The SMART-REACH model was used to estimate life expectancy (years) without a recurrent cardiovascular event for individual patients and 10-year risk of CVD events by calculating the cumulative cause-specific event-risk truncated at 10 years after age at baseline.[19,45] To estimate the benefit of the guideline-recommended intensification of LLT, the cardiovascular risk was estimated twice with the SMART-REACH model for each individual. First, we estimated the risk with the 3-month LDL-C levels, and next we estimated the risk with the achieved LDL-C levels after intensification. The difference between estimated 10-year risk and healthy life-expectancy with 3-month LDL-C levels and estimated risk after intensification corresponds to the individuals' absolute benefit.

The effect of LLT on CVD events depends on the estimated reduction in LDL-C compared to baseline. A hazard ratio of **0.78 was assumed per 1.0 mmol/L reduction in LDL-C**.[2] The individuals' expected relative risk reduction was calculated by $0.78^{\text{LDL-C reduction in mmol/L}}$. LDL-C reduction in mmol/L was defined as the 3-month LDL-C level minus achieved LDL-C level after intensification.

Figure S1: Flowchart of inclusion and exclusion of participants in current analysis

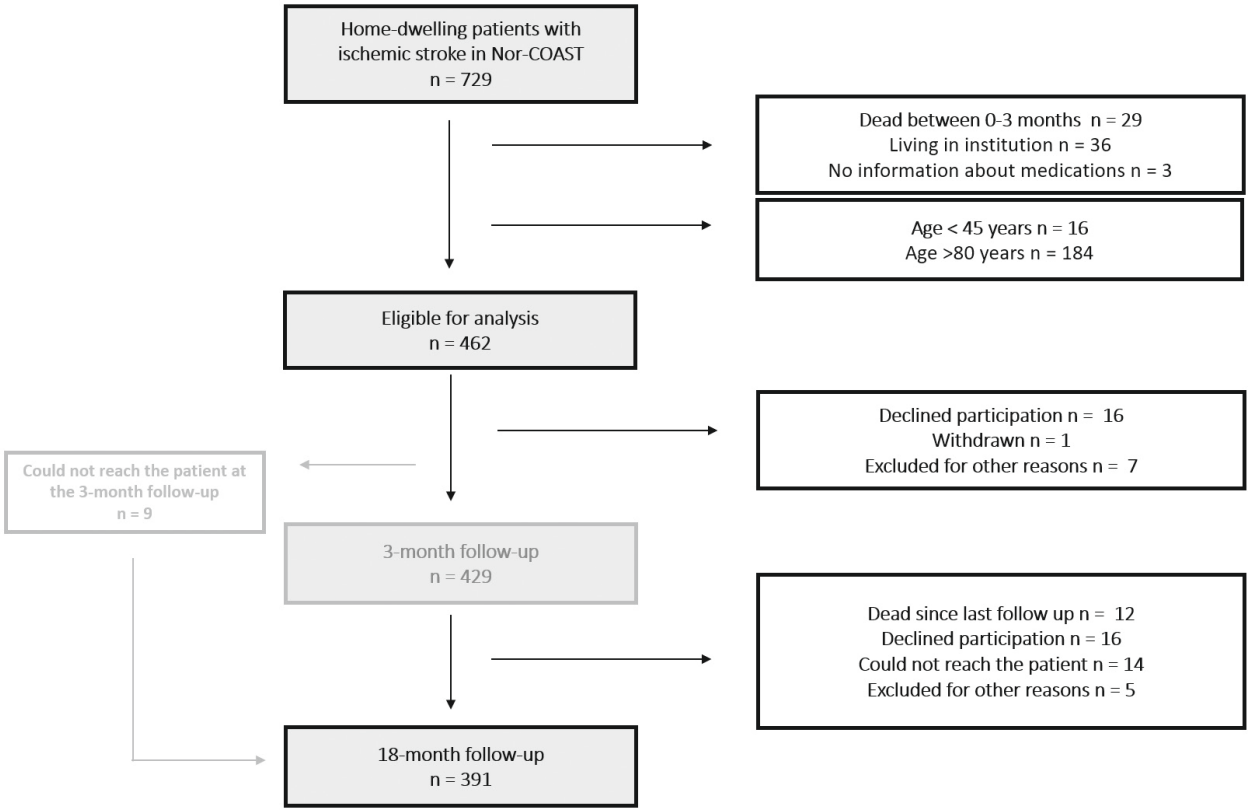


Table S1: Mean and standard deviation (SD) percentage change in LDL-C reduction with statins and ezetimibe, as presented and validated by Cannon et al. (5)

Drug	Dose, mg	Mean (reference)	SD (reference)
Atorvastatin	10	35.5% [46]	10.6% [23,47]
	20	41.4% [46]	13.5% [23,47]
	40	46.2% [46]	12.5% [23,47]
	80	50.2% [46]	13.8% [23,47]
Fluvastatin	20	17.0% [47]	8.0% [47]
	40	23.0% [47]	10.0% [47]
	80	26.0% [47]	9.0% [47]
Lovastatin	10	21.0% [48]	10.1% [23]
	20	24.0% [49]	11.0% [49]
	40	30.0% [49]	11.0% [49]
	60	34.5% [23]	11.7% [23]
Pravastatin	10	20.0% [47]	11.0% [47]
	20	24.0% [47]	11.0% [47]
	40	30.0% [47]	13.0% [47]
	80	33.0% [48]	11.2% [23]
Rosuvastatin	5	38.8% [46]	13.2% [23]
	10	44.1% [46]	12.5% [23,47]
	20	49.5% [46]	13.3% [23,47]
	40	54.7% [46]	12.9% [23,47]
Simvastatin	5	23.0% [48]	11.0% [23,47]
	10	27.4% [46]	13.7% [23,47]
	20	33.0% [46]	10.4% [23,47]
	40	38.9% [46]	14.0% [23,47]
	80	45.0% [46]	11.7% [23,47]
Ezetimibe	10	22.7% [44]	16.5% [50]

Table S2: Levels of cardiovascular risk factors at 3 months for variables included in the SMART-REACH model (7) and n (%) missing for the relevant variables at 3 months (N=462)

	Mean (SD) or n (%)	n (%) missing at 3 months
Age, years	69.0 (8.1)	0 (0%)
Sex, female	177 (38%)	0 (0%)
Current smoking[b]	54 (12%)	65 (14%)
Diabetes mellitus	90 (20%)	0 (0%)
Congestive heart failure	11 (2%)	0 (0%)
Atrial fibrillation	100 (22%)	0 (0%)
Systolic blood pressure (mmHg)	140 (19)	69 (15%)
Creatinine (µmol/L)	82 (22)	116 (25%)
Total cholesterol (mmol/L)	4.0 (0.9)	110 (24%)
LDL cholesterol (mmol/L)	2.1 (0.7)	112 (24%)
Cerebrovascular disease	462 (100%)	0 (0%)
History of ischemic heart disease	79 (17%)	0 (0%)
History of peripheral artery disease	34 (7%)	0 (0%)

Abbreviations: LDL, low-density lipoprotein

Table S3: Types and daily doses of statins and ezetimibe for patients using lipid lowering drugs at discharge and 18 months (n)

	Discharge* (n = 427)	18 months** (n = 321)
Simvastatin n (%)	80 (19%)	56 (17%)
10 mg	3	4
20 mg	18	11
40 mg	56	33
80 mg	3	6
Unknown dose	0	2
Pravastatin n (%)	6 (1%)	6 (2%)
10 mg	1	0
20 mg	4	3
40 mg	0	2
80 mg	1	1
Atorvastatin n (%)	328 (77%)	245 (76%)
10 mg	5	17
20 mg	52	55
40 mg	191	121
60 mg	0	2
80 mg	80	48
Unknown dose	0	2
Rosuvastatin n (%)	3 (1%)	4 (1%)
5 mg	2	2
10 mg	0	1
20 mg	1	1
40 mg	0	0
Fluvastatin n (%)	5 (1%)	3 1%)
20 mg	2	0
40 mg	1	2
80 mg	2	1
Ezetimibe 10 mg monotherapy n (%)	5 (1%)	7 (2%)
Ezetimibe 10 mg in addition to statin n (%)	8 (2%)	13 (4%)

*In total, 412 were prescribed statins at discharge, while 10 patients received statins between 0-3 months, which was defined as statins at discharge. In addition, 5 patients received ezetimibe monotherapy. **Type and dose regardless of prescription at discharge or not. No patients used PCSK9-inhibitors.

Table S4: Logistic regression with prescription of lipid-lowering therapy at discharge as dependent variable (n= 462)

		Unadjusted analysis		Age- and sex adjusted analysis	
	n	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age, years	462	0.97 (0.92 to 1.02)	0.185	0.97 (0.92 to 1.01)	0.191
Sex, female	462	0.93 (0.46 to 1.88)	0.831	1.00 (0.50 to 2.10)	0.989
LDL-C[a] (mmol/L)	462	1.13 (0.83 to 1.55)	0.439	1.09 (0.79 to 1.51)	0.584
Prestroke LLT	462	20.4 (2.76 to 150.30)	0.003	23.6 (3.18 to 175.39)	0.002
Frailty[b]	462	0.77 (0.56 to 1.07)	0.123	0.80 (0.57 to 1.13)	0.205
Cognitive impairment[c] prestroke	456	0.59 (0.43 to 0.80)	0.001	0.60 (0.44 to 0.83)	0.002
History of ischemic heart disease	462	3.63 (0.85 to 15.5)	0.081	4.30 (0.99 to 18.7)	0.051
Index stroke etiology[d]	447				
Cardio embolic stroke		Reference category		Reference category	
Large artery disease		8.18 (1.04 to 63.8)	0.045	8.09 (1.03 to 63.27)	0.046
Small vessel disease		3.38 (1.17 to 9.66)	0.023	3.24 (1.13 to 9.30)	0.029
Undetermined or multiple causes		2.16 (1.00 to 4.66)	0.051	2.06 (0.95 to 4.48)	0.068

[a]Measured at first day after admission [b]Measured by modified Fried Frailty criteria with 0 as reference corresponding to robust, and 5 to frail. [c]Measured by Global deterioration scale with 1 as reference corresponding to normal cognitive function and 7 to severe dementia. [d]Classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. There were no patients with large artery disease as stroke etiology not receiving lipid-lowering therapy at discharge. Abbreviations: OR, odds ratio; LDL-C, Low-density lipoprotein cholesterol.

Table S5: Lipid profile according to subgroups of stroke patients at index stay and 3 months follow-up (n=427)

	Index stay				3-month follow-up				
	Total-C (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	LDL-C ≤1.8 mmol/L	Total-C (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	LDL-C ≤1.8 mmol/L	Mean distance from target[c]
All (n=427)	5.0 (1.3)	3.1 (1.1)	1.4 (0.6)	53 (12%)	4.0 (0.8)	2.1 (0.7)	1.5 (0.5)	193 (45%)	0.7 (0.6)
Men (n=264)	4.7 (1.2)	3.0 (1.1)	1.3 (0.5)	39 (15%)	3.8 (0.8)	2.1 (0.7)	1.4 (0.5)	115 (44%)	0.7 (0.6)
Women (n=163)	5.3 (1.3)	3.3 (1.1)	1.6 (0.6)	14 (9%)	4.2 (0.8)	2.1 (0.6)	1.7 (0.5)	78 (48%)	0.7 (0.6)
Age groups									
45 – 59 years (n=61)	5.2 (1.2)	3.3 (1.0)	1.4 (0.5)	6 (10%)	3.9 (0.8)	2.1 (0.7)	1.5 (0.5)	25 (41%)	0.8 (0.6)
60 – 69 years (n=135)	5.2 (1.3)	3.4 (1.2)	1.4 (0.5)	9 (7%)	3.9 (0.8)	2.1 (0.7)	1.4 (0.6)	60 (44%)	0.7 (0.6)
70 – 80 years (n=231)	4.7 (1.2)	2.9 (1.0)	1.5 (0.6)	38 (17%)	4.0 (0.8)	2.0 (0.6)	1.6 (0.5)	108 (47%)	0.7 (0.6)
No prestroke LLT (n=267)	5.4 (1.1)	3.5 (1.0)	1.5 (0.5)	9 (3%)	3.9 (0.8)	2.0 (0.7)	1.6 (0.5)	122 (46%)	0.7 (0.6)
Prestroke LLT (n=160)[a]	4.2 (1.1)	2.4 (1.0)	1.4 (0.6)	44 (28%)	4.0 (0.8)	2.1 (0.7)	1.4 (0.5)	71 (44%)	0.7 (0.8)
Stroke subtype									
Large artery disease (n=48)	5.0 (1.2)	3.1 (1.1)	1.4 (0.7)	5 (10%)	3.8 (0.8)	2.0 (0.6)	1.5 (0.4)	25 (52%)	0.6 (0.4)
Cardioembolic stroke (n=88)	4.7 (1.2)	2.9 (1.1)	1.4 (0.4)	15 (17%)	4.0 (0.8)	2.2 (0.8)	1.4 (0.4)	37 (42%)	0.8 (0.7)
Small vessel disease (n=99)	5.1 (1.3)	3.2 (1.2)	1.6 (0.6)	12 (12%)	4.0 (0.8)	2.0 (0.7)	1.6 (0.7)	48 (49%)	0.7 (0.6)
Undetermined or other (n=177)	5.1 (1.2)	3.2 (1.1)	1.4 (0.5)	19 (11%)	4.0 (0.80)	2.1 (0.6)	1.5 (0.5)	77 (44%)	0.6 (0.6)

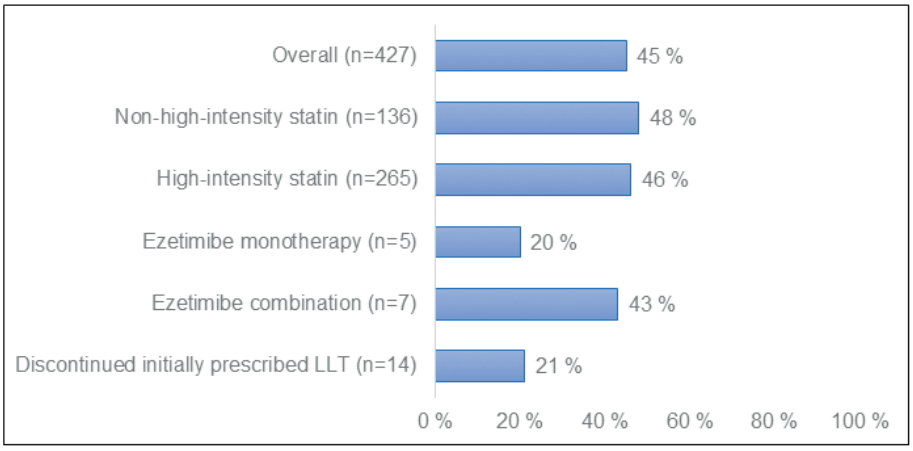
Values are mean (SD) or n (%). [a]39% of men were using LLT at admission and 34% of women. [b]According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. [c]Mean (SD) distance (mmol/L) from the LDL-C target 1.8 mmol/L for patients not at target. Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

Table S6: Lipid-lowering therapy (LLT) at 3 months for patients prescribed LLT at discharge not reaching the target (n=234) by subgroups of stroke patients

	Discontinued LLT[a]	Non-HIS	HIS	Ezetimibe monotherapy	Ezetimibe + statin[c]
All	11 (5%)	71 (30%)	144 (61%)	4 (2%)	4 (2%)
Men (n=149)	8 (5%)	46 (31%)	87 (58%)	4 (3%)	4 (3%)
Women (n=85)	3 (4%)	25 (29%)	57 (67%)	0 (0%)	0 (0%)
Age groups (years)					
<60 (n=36)	2 (6%)	9 (25%)	25 (69%)	0 (0%)	0 (0%)
60 – 69 (n=75)	4 (5%)	19 (25%)	50 (67%)	1 (1%)	1 (1%)
70 – 80 (n=123)	5 (4%)	43 (35%)	60 (56%)	3 (3%)	3 (2%)
Stroke subtype[b]					
Large artery disease (n=23)	0 (0%)	4 (17%)	17 (74%)	0 (0%)	2 (9%)
Cardioembolic stroke (n=51)	3 (6%)	19 (37%)	29 (57%)	0 (0%)	0 (0%)
Small vessel disease (n=51)	7 (8%)	22 (43%)	24 (47%)	1 (2%)	0 (0%)
Undetermined or other (n=100)	4 (4%)	25 (25%)	66 (66%)	3 (3%)	2 (2%)

[a]Discontinued LLT between discharge and 3 months. [b]According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. [c]3 out of 4 received high-intensity statin. Abbreviations: LLT, lipid-lowering therapy; HIS, high-intensity statin; LDL-c, low-density lipoprotein cholesterol

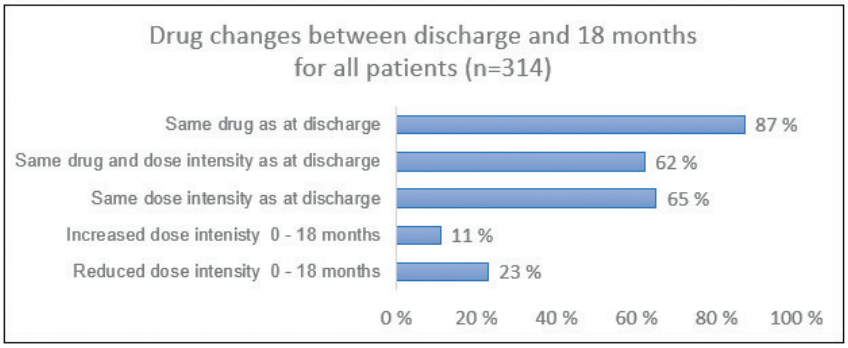
Supplementary figure S2: Proportions at LDL-C target at 3 months in subgroups of lipid-lowering therapy regimen.



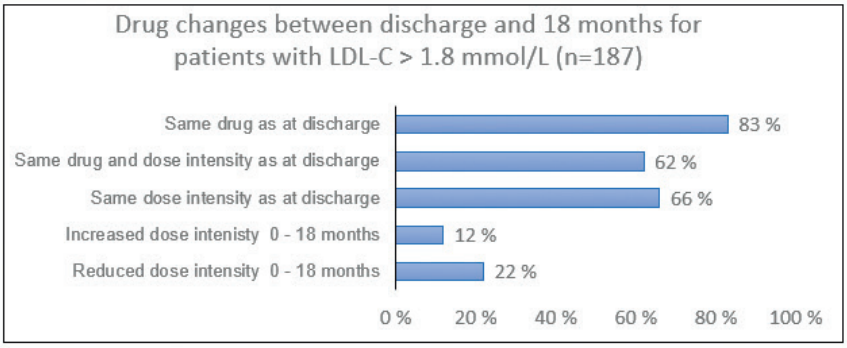
Abbreviations: LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol

Supplementary Figure S3: Statin drug type and dose intensity at 18 months follow-up compared to discharge

a)

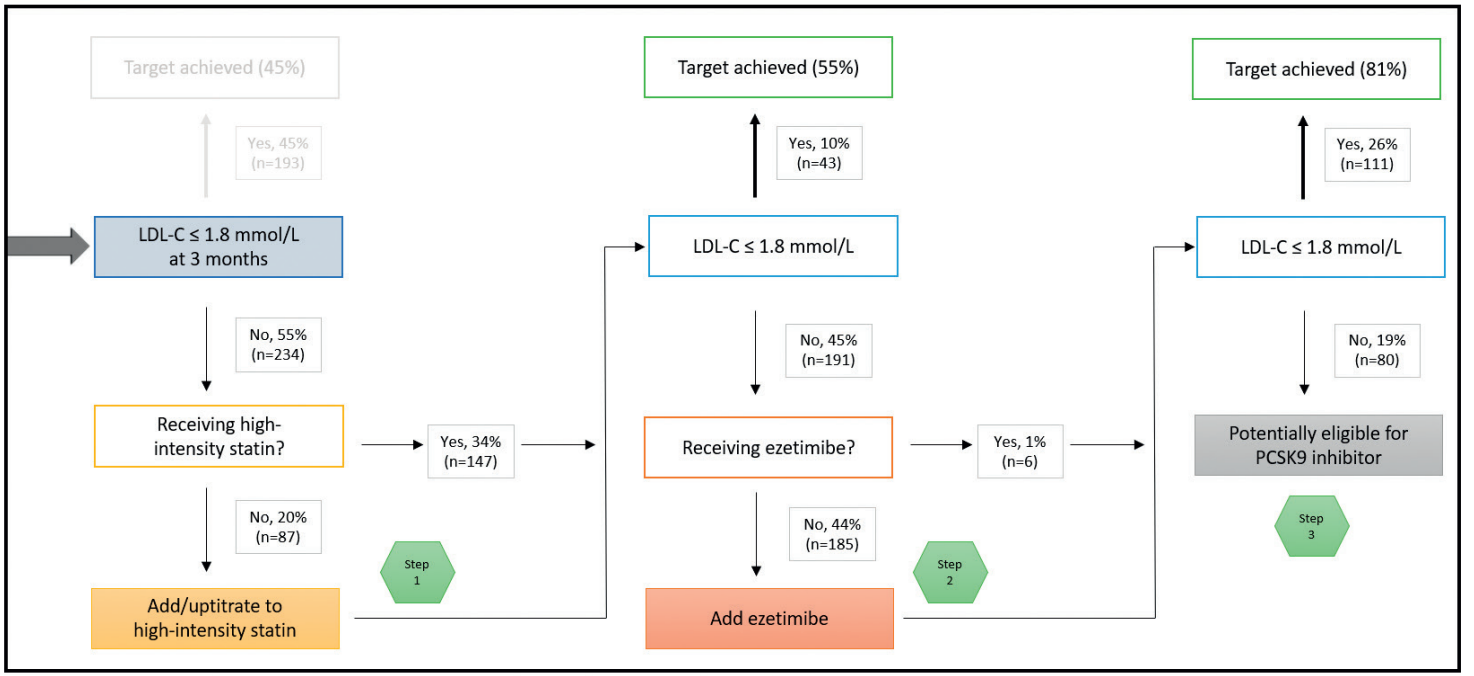


b)



For a) all patients with information on medications in use and persistent to statins at 18 months (n=314) and b) patients still not reaching the LDL-C target ≤1.8 mmol/L at 18 months (n=187). A total of 352 patients prescribed statins at discharge had medication lists at 18 months follow-up (18% missing).

Figure S4: Estimation of effect of up-titration of lipid lowering treatment according to guideline recommendations and proportion of patients reaching LDL-C ≤1.8 mmol/L



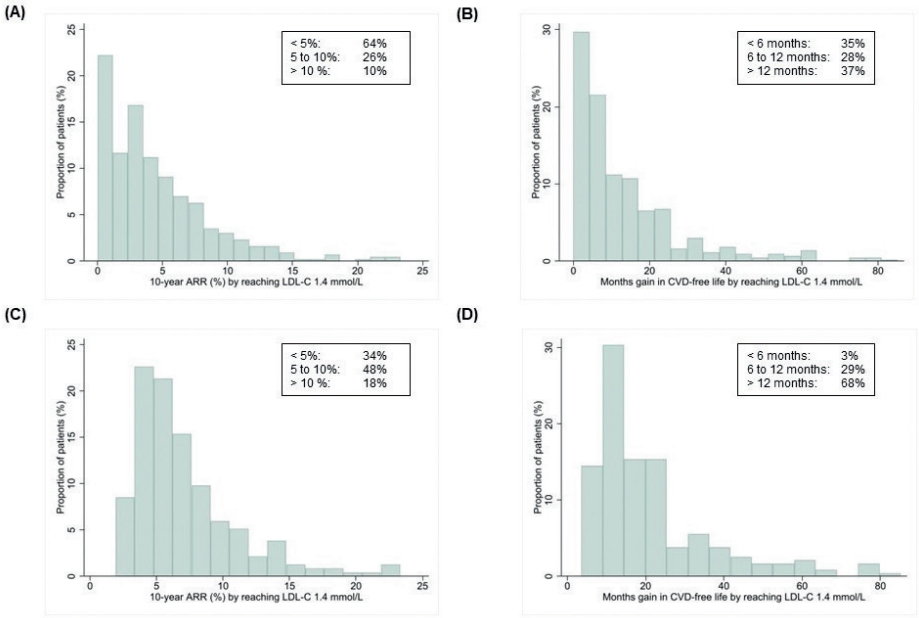
With Step 1; Adding / up-titrating to high intensity statin, Step 2; Adding ezetimibe. Proportions are n of the total population (n=427). Abbreviations: LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

Table S7: Characteristics for patients according to tertiles (T1 to T3) of months gain in CVD-free life by up-titrating lipid-lowering therapies according to the stepwise guideline-recommendation for patients with LDL-C above the guideline recommended target 1.8 mmol/L (n=234)

	T1 (n=79)	**T2 (n=79)**	**T3 (n=76)**
Median CVD-free life months (IQR)	6.0 (4.8 to 7.2)	10.8 (9.6 to 12)	18.6 (16.8 to 25.8)
Age, y	73.1 (5.6)	69.1 (6.8)	63.2 (9.5)
Sex, female	19 (24%)	36 (46%)	30 (39%)
Diabetes mellitus	26 (33%)	12 (15%)	7 (9%)
≥ 2 vascular areas[a] involved	31 (39%)	13 (16%)	8 (11%)
Current smoker at 3 months	12 (15%)	6 (8%)	7 (9%)
Systolic blood pressure (mmHg)[b]	141 (22)	142 (15)	141 (18)
Total Cholesterol[b], mmol/L	4.0 (0.5)	4.3 (0.6)	4.8 (0.8)
HDL Cholesterol[b], mmol/L	1.5 (0.7)	1.5 (0.4)	1.4 (0.4)
LDL Cholesterol[b], mmol/L	2.1 (0.3)	2.4 (0.4)	2.9 (0.7)
Estimated GFR (ml/min/1.73 m^2)[b, c]	70 (16)	78 (16)	85 (16)
High sensitive CRP (mg/L)[b]	3.3 (7.3)	3.1 (4.1)	3.7 (8.0)
Frail[d]	2 (3%)	6 (8%)	2 (3%)
Prestroke dementia[e]	4 (5%)	1 (1%)	0 (0%)
Ischemic stroke subtype			
Large artery disease	9 / 75 (12%)	10 / 75 (13%)	4 / 75 (5%)
Cardioembolic stroke	18 / 75 (24%)	16 / 75 (21%)	17 / 75 (23%)
Small vessel disease	20 / 75 (27%)	10 / 75 (13%)	21 / 75 (28%)
Other, undetermined or unknown	28 / 75 (37%)	39 / 75 (52%)	33 / 75 (44%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; HDL, High density lipoprotein; GFR, Glomerular Filtration Rate; CRP, C-reactive protein.

Figure S5: Estimated prognostic impact of reaching an LDL-C level of 1.4 mmol/L



The top row shows (A) distribution of estimated 10-year ARRs (B) distribution in gain in months free from CVD events for all patients prescribed LLT (n=427) when reacing LDL-C 1.4 mmol/L. The bottom row shows (C) distribution of estimated 10-year ARRs and (D) distribution in gain in months free from CVD events for patients with LDL-C above 1.8 mmol/L at 3 months (n=234) when reaching LDL-C 1.4 mmol/L. Abbreviations: LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; ARR, absolute risk reduction.

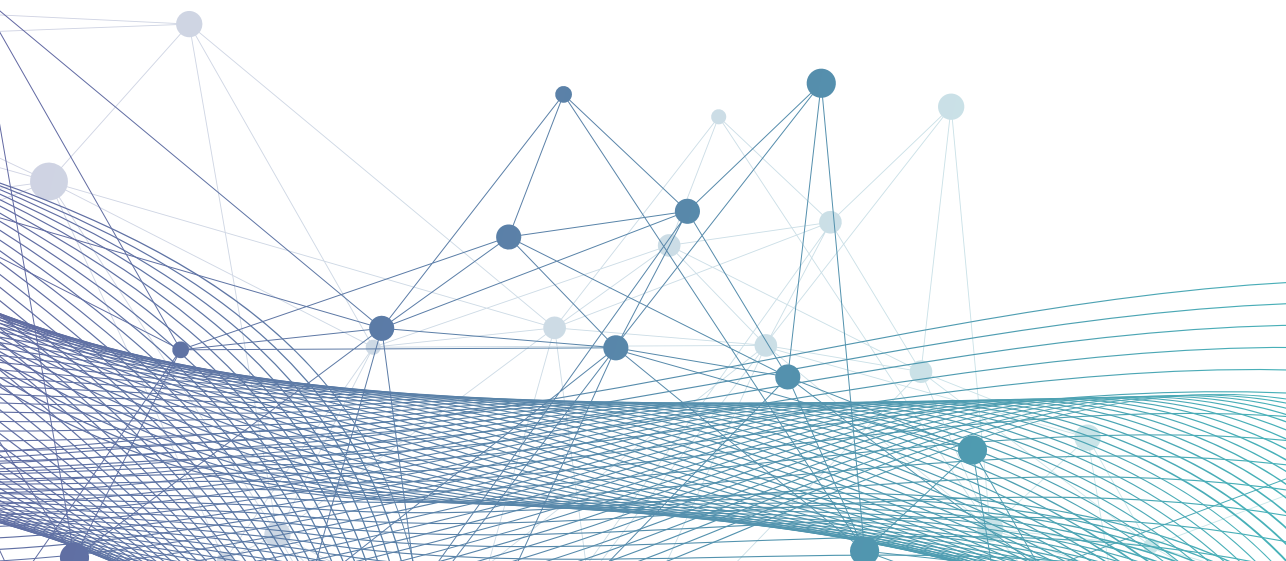
Table S8: Sensitivity analysis using other effect estimates for % LDL-C reduction when intensifying LLT

	% estimated at target at 3 months with HIS only	Mean LDL-C (mmol/L) (SD) obtained after adding HIS	% estimated at target when adding ezetimibe	Mean LDL-C (mmol/L) (SD) obtained after adding HIS and ezetimib
Main analysis	55%	1.9 (0.6)	81%	1.7 (0.4)
Using LDL-C values at index stay	58%	1.9 (0.7)	84%	1.7 (0.4)
Using % reduction obtained by Rosuvastatin 40 mg[c]	58%	1.9 (0.6)	82%	1.7 (0.4)
Using mean % reduction obtained in Nor-COAST[a]	49%	2.0 (0.6)	68%	1.8 (0.5)
Using % reduction obtained in SWEDEHEART [37b]	48%	2.0 (0.6)	66%	1.8 (0.5)

[a]Mean % reduction for patients prescribed HIS at discharge not at LLT prestroke (n=181) was 42.5% (SD 26), for ezetimibe naïve (n=5) the mean % reduction was 16.2%. [b]Mean % reduction in LDL-C obtained with high-intensity statin in SWEDEHEART was 39.7% (SD 15.7)[37], when adding ezetimibe 14.7% (SD 21.3). [c]Rosuvastatin 40 mg is assumed to reduce LDL-C by 54.7% and ezetimibe 22.7%. Abbreviations: HIS, high-intensity statin; LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

CHAPTER 12

General discussion



General discussion

In this thesis, the general objective were to improve upon the accuracy and clinical applicability of prediction-based treatment by developing or updating cardiovascular disease (CVD) risk prediction algorithms in apparently healthy individuals and patients with established atherosclerotic cardiovascular disease (ASCVD), and to evaluate the effectiveness of prediction-based treatment strategies.

Prediction reliability

In order to reliably use risk predictions in the shared decision process to decide upon treatment initiation, the predicted risks should match the actual probability of disease in order to avoid systematic under- or overoptimistic expectations from the benefit of preventive treatment. Since the incidence of CVD greatly varies over geographical regions and over periods of time, geographic and temporal recalibration in relevant populations is an absolute necessity to get reliable individual predicted risks.[1]

Historically, the recalibration of models is often performed in cohort data. However, cohort data per definition reflects a past period of time which was necessary for data collection, and generally has a certain degree of healthy participant bias.[2] Therefore, to ensure the most accurate risks for individuals in clinical practice, the SCORE2 and SCORE2-OP models were recalibrated to four European risk region using nationally representative registry data (**chapter 2 and 3**). The use of registry data allowed to circumvent healthy participant bias in cohorts. In addition, the methodology allows for future rapid adaption of predicted risks with trends in CVD incidence. The recalibration strategy was one of the major advancements in the SCORE2 model as this ensured accurately calibrated risks to all European risk regions (**chapter 2**). This methodology was later adapted to allow for systematic recalibration of lifetime models (**chapter 6**). For the SMART2 risk score, such an approach was unfortunately not possible due to the lack of reliable aggregate data on risk factor levels and disease incidence representative to individuals with established ASCVD. However, with powerful and contemporary cohort data, geographical differences across Europe and several other global regions were accounted for as best as possible with currently existing data to allow for accurate prediction of residual risk in all these regions (**chapter 8**).

The clinical benefit of prediction-based treatment is also affected by how well high-risk and low-risk individuals can be discriminated from each other, the model discrimination. There are many factors which may influence in a single population, including the risk distribution[3], quality of predictor and endpoint ascertainment, the number of the risk factors and the predictive performance of these risk factors.[3] Model calibration is often reduced when transferring a prediction model to a different geographical region due to differences in CVD incidence between populations. However, as the relative effect of prognostic factors on the risk of CVD events is

relatively stable across geographical areas, discrimination is much less affected by this.[4,5] This is in line with previous studies, showing limited geographical heterogeneity in the relative effect of risk factor on the risk of CVD events.[5] For all CVD prediction models shown in the current thesis, there was also no evidence of any reduced transferability of relative risk factors effects based on the discrimination results (**chapter 2, 3, 6, and 8**). The models presented in the current thesis showed similar or slightly improved discrimination in comparison to pre-existing prediction models (**chapter 2, 3, and 8**). With the flexible methodology introduced in **chapter 4**, the discrimination of existing risk models can be further improved with the addition of clinically relevant risk predictors not included in the original model.

In the SCORE2, SCORE2-OP, and SMART2 risk models (**chapter 2, 3, and 8**), one of the improvements in comparison to predecessors was the adjustment for competing risks. Not accounting for competing risks may lead to overestimation of predicted CVD risks (**chapter 5**). This overestimation is especially important in persons at high risk of non-cardiovascular causes of death, such as older persons or those with severe comorbidities. The use of these unadjusted risk predictions may lead to overestimated, risks and thus to wrong treatment decisions as estimated risk for individual patient influences the shared decision making process between health care provider and patient. In **chapter 5**, it was shown that individuals identified for treatment based on a prediction model not adjusted for competing risks are expected to benefit slightly less from preventive treatment in comparison to individuals identified by a model that was adjusted for competing risks.

Clinical applicability

For apparently healthy individuals, the SCORE2 and SCORE2-OP models presented in this thesis are important improvements to more relevant predictions of CVD event risk (**chapter 2 and 3**). The SCORE2 and SCORE2-OP predict the risk of fatal and non-fatal CVD events, whereas the original SCORE model predicted only the risk of fatal CVD events. As the main burden of CVD events in younger individuals consists of non-fatal CVD events, it is important to take the combined risk of non-fatal and fatal CVD events into account in the shared decision process.

Moreover, the confidence in 10-year CVD risk predictions by health care providers and patients could be improved by taking into account additional relevant risk factors, which are known in clinical practice but not implemented in CVD prediction models, for example family history for premature myocardial infarction, a coronary calcium score, or albuminuria. In those situations where such a risk factor is known for an individual, but not used in the prediction of CVD event risk, healthcare providers and patients may decide to ignore a risk model's prediction, because they feel the patient profile is not fully captured by the algorithm. In the 2021 ESC CVD prevention guidelines several of these factors are mentioned as potential risk modifiers, such

as a coronary calcium score or a parental history of myocardial infarction.[6] Generally, no specific notions are given about how to handle the presence of such factors quantitatively, apart from ethnicity and inflammatory conditions (multiply with a specific factor). Implementation of many of these factors are named under 'gaps in the evidence', similar to the general methodology on incorporating potential risk markers into conventional models.[6] In **chapter 4** a solution is presented on how to implement such risk factors in predictions from existing models. The methodology was shown to improve upon the accuracy of predicted risks and may potentially increase confidence in model predictions in those situations where additional risk modifiers are present.

For individuals with established ASCVD, the SMART2 risk score improves upon both the currently recommended models, the SMART risk score and the EUROASPIRE risk calculator. In comparison to the SMART risk score, most improvements are in terms of accuracy by using more powerful and more contemporary data, while adjusting for competing risks and for geographical differences in disease incidence (**chapter 8**).[7] In comparison to the EUROASPIRE calculator, one of the relevant advantages of the SMART2 risk score is the prediction horizon. The EUROASPIRE calculator only predicts 2-year risks,[8] whereas the SMART2 risk score can predict the 10-year risk of recurrent ASCVD events, which is a more relevant horizon as preventive therapy is often initiated for a longer duration. Moreover, all predictors required for the SMART2 risk score are routinely available in clinical practice, for example no time-consuming questionnaires on mental health are required.

Apart from the all model-specific improvements which may increase clinical applicability, presented in this thesis, the clinical applicability of prediction-based treatment has improved in parallel due to external factors in the past few years. One important development is the increased interest in shared decision making based on predicted risks as recommended in the 2021 ESC CVD prevention guidelines.[6] In these guidelines, the recommendations on risk-based treatment were extended from apparently healthy people to apparently healthy older persons, those with established ASCVD, and patients with diabetes mellitus. All risk scores discussed in the current thesis are readily available in clinical practice via easy online calculators like www.u-prevent.com or the ESC CVD risk prediction app.

Total CVD burden

In the current thesis, multiple composite CVD endpoints are used in various predictions models which aim to capture an as relevant as possible portion of the total CVD burden. As stated above, one of the major improvements in the SCORE2 and SCORE2-OP models is the prediction of 'non-fatal + fatal CVD events' (**chapter 2 and 3**), which was 'CVD mortality' in the original SCORE model.[9] The non-fatal component of the SCORE2 and SCORE2-OP models includes non-fatal myocardial

infarction and non-fatal stroke. The fatal component is equal to the original SCORE CVD mortality endpoint.

Even though in the early stages of the SCORE2 project, the endpoint was often referred to as 'total CVD event risk', the SCORE2 endpoint still only captures a certain proportion of the total CVD burden.[10] Different scores for apparently healthy people have used slightly different composite endpoints to try to capture this. The QRISK3 score, derived and recommended in the UK, includes as well transient ischemic attacks, angina pectoris and chronic ischemic heart disease on top of the SCORE2 endpoint.[11] The original LIFE-CVD model included as well the component of resuscitated cardiac arrest,[12] which was left out of the recalibrated model to allow for the systematic recalibration with registry data that did not include this endpoint (**chapter 6**). For individuals with established ASCVD, the SMART2 risk score can be used the predict the endpoint similar to SCORE2 (**chapter 8**). An adaption was made to the original SMART score to include coronary interventions as well.[13] The EUROASPIRE risk calculator predicted a similar outcome as the SMART2 risk score, but includes both coronary interventions as well as heart failure in this composite CVD endpoint.[8]

All these different composite outcomes capture different, largely overlapping parts of the total CVD burden, although none captured all of it. All models predict the risk of the first CVD event in the period of interest, ignoring the potential of multiple events in a single subject. Including those requires much more sophisticated methodology, requiring additional assumptions regarding the relationship between subsequent events, which may not be met.[14] In addition, including those events would only have a small effect on the relationship between risk factors and the outcome, likely identifying the same individuals as high risk of CVD events.[14] Moreover, other relevant clinical atherosclerotic outcomes are not named in any of these risks models, for example the risk of major adverse limb events. These events have been shown to be frequent among individuals with established ASCVD and may cause significant morbidity (**chapter 7**).

The choice of the exact endpoint is especially important when it influences decisions on treatment, which was the case in the transition from SCORE to SCORE2. As case-fatality rates of CVD events have a clear relation with age, and are much lower in younger individuals, CVD mortality is very rare among the young. Non-fatal events may cause substantial morbidity and the risk can be effectively reduced with adequate risk factor reduction.[10,15,16] Including these non-fatal CVD events in the SCORE2 definition will lead to increased treatment of younger individuals in comparison to SCORE, thereby targeting these individuals at very high risk of morbidity but not (yet) of high fatal CVD events (**chapter 2**).

The different endpoints were likely selected based on the weighing of the objectiveness and transferability of certain endpoints versus the completeness of the endpoint in capturing the full disease burden. CVD mortality is a relatively objective diagnosis, although there is a bit of heterogeneity between geographical areas or periods of time.[17] Data on non-fatal events is generally more scarce than on fatal events, especially in Eastern Europe and shows substantially more heterogeneity. Therefore, a multiplier approach was used to estimate nationally representative incidences of non-fatal disease for SCORE2 and SCORE2-OP (**chapter 2 and 3**). The inclusion of coronary interventions in the composite outcome, like in the EUROASPIRE calculator, may require thorough geographical and temporal validation. This is because this endpoint not only includes the CVD disease itself, but also the treating physician's handling to it - based on personal experience and current guidelines. This may lead to substantial geographical variation in intervention rates among similar patients even within countries.[18] In addition, the inclusion of less severe components in the endpoint, like interventions, may complicate the interpretation of the predicted risk. It may be unclear which part of the predicted risk consists of severe CVD events like a major stroke, and which part of planned interventions.

Generally, the endpoint should be as complete as possible, capturing a large and representative portion of the CVD burden, while being as objective and standardized as possible. The endpoint of non-fatal myocardial infarction, non-fatal stroke and CVD mortality as used in several risk scores used in this thesis likely meets those criteria. However, for specific groups, even more relevant combinations of endpoints may be included, like the risk of major adverse limb events for those with peripheral artery disease (**chapter 7**).

Lifetime versus 10-year prediction horizon

In the current thesis, CVD prediction models have been presented which can estimate the risk developing CVD in 5 years, 10 years or even on a lifetime perspective. Of the models named in the 2021 ESC CVD prevention guidelines, some have even shorter prediction horizons like the ADVANCE model for individuals with type 2 diabetes mellitus or the EUROASPIRE risk calculator for patients with coronary artery disease.[8,19] Most physicians likely have most experience in using 10-year CVD event risks with the SCORE model,[20] but it is unclear what the 'optimal' prediction horizon would be or whether this even exists.

If there would be an optimal prediction horizon, this is horizon would have to meet several criteria. First, the horizon would need to be representative of the intended treatment duration. The individual who benefits most on the short term is not necessarily the same that benefits on the long term (**chapter 6 and 9**). Since medication to prevent CVD is generally initiated for a long-term period,[6] perhaps even on a lifetime perspective, this would favor a lifetime prediction horizon.

Second, the prediction horizon should be relevant in comparison to the remaining life expectancy. For younger individuals, even a 10-year risk is often very low in absolute terms (**chapter 2**), whereas their potential benefit of lifelong risk factor reduction can be substantial (**chapter 6**). The very old, on the other hand, may only have a limited remaining life expectancy, which better suits a shorter prediction interval, like the 5-year risk charts provided for the SCORE2-OP model (**chapter 3**). The advantage of a lifetime approach is that the life expectancy of an individual is taken into account automatically and relevant treatment benefits are presented for all age groups (**chapter 6**). With the 2021 ESC CVD prevention guidelines, age-specific treatment thresholds were introduced.[6] As treatment thresholds are lower for younger individuals, 10-year risks can be more effectively used to identify young individuals at high CVD risk in comparison to their age-peers. On the short term, these individuals may not benefit as much as older individuals in who treatment is recommended, but on a lifetime perspective these individuals may have a substantial treatment benefit (**chapter 6 and 10**). On the other side, the use of higher treatment targets in older persons may limit treatment in those at high short-term risk but a limited gain in life expectancy due to intensified prevention (**chapter 6 and 10**). The use of age-specific treatment thresholds circumvents some of the disadvantages of treatment based on 10-year risk. However, as the life expectancy is also highly affected by smoking status, geographical region and sex, the use of lifetime measures may more accurately identify those who benefit on the long run.

Third, for the most reliable treatment decisions, predictions need to be as accurate as possible. As predicting at short horizons is easier than at longer horizons (similar to the weather, which is easier to predict for tomorrow than it is to predict exactly 1 month from now), using short-term predictions could be the most accurate alternative. In addition, the lifetime models SMART-REACH (**chapter 9**) and LIFE-CVD (**chapter 6**) have been derived using a more sophisticated approach which allows for predictions beyond the duration of the original derivation data follow-up time. This approach has been thoroughly validated to be accurate at least up until 17 years in the future[21], but requires the additional assumptions to be made that further extrapolation is possible, and an individual's risk factors stay relatively stable over time.

Finally, the prediction measure should be easy to interpret. To really participate in the shared decision process on whether to start or intensify preventive treatment, a good understanding of the communicated prediction measure is vital. A predicted risk for example, though commonly used, can be very hard to really understand.[22] A lifetime risk is even more difficult to explain and may be even counterintuitive as it relies not only on CVD risk factors, but also strongly on an individual's life expectancy.. Solely reducing one's risk of mortality due to non-cardiovascular causes would actually *increase* the lifetime CVD risk because there is a longer remaining lifetime duration in which CVD events may arise. Luckily, both short-term and long-term predictions can

be translated to substantially easier measures by combining these with treatment effects. The 10-year risk can be transformed to an individual number needed to treat ("In a group of individuals with exactly your risk factor levels, we would need to treat 12 individuals to prevent one CVD event"). This is often considered an easy measure, but may also be misinterpret by patients.[22] Combining the predictions from lifetime models with treatment effects results in another intuitive measure: lifetime treatment benefit, defined as the gain in CVD-free life expectancy from preventive therapy. This can be explained to the individual patient as "In group of individuals with exactly your risk factor levels is expected to live on average 1.5 year longer without cardiovascular disease with this treatment". This measure has not only been shown to be an effective and cost effective measure to use for treatment decisions in individuals with established ASCVD (**chapter 9**), but also to lower the decisional conflict in individuals considering preventive treatment.[23]

Treatment thresholds for individuals with established ASCVD

For apparently healthy individuals, the 2021 ESC CVD prevention guidelines have introduced age-specific CVD risk thresholds for SCORE2 and SCORE2-OP predicted risks to signal individuals who are 'very high risk of CVD'.[6] For those individuals above these risk thresholds, it is recommended to initiate risk factor management, either through lifestyle recommendations or through preventive therapy. This has been common practice for this population as previous guidelines have had similar recommendations on the SCORE model.[20,24] The prediction of CVD risk in individuals with established ASCVD has a different place in the guidelines. First, it is recommended to perform the most relevant risk factor treatment options in all patients ('Step 1': stop smoking and lifestyle recommendations, reduce SBP between 130 and 140 mmHg, reduce LDL-c by >50% and below 1.8 mmol/L and start antithrombotic medication).[6] After this step, several intensified treatment options remain ('Step 2'), for example dual pathway inhibition (DPI), colchicine, further reduction of blood pressure or LDL-c levels. These intensive treatment options have been shown to be effective, but are not recommended to all individuals with established ASCVD due to high costs or the risk of side effects including the risk of major bleeding. An individual approach is recommended in identifying those patients who may benefit from further prevention. Several measures are named to aid in identifying these patients the shared decision process, including predicted residual CVD risk or lifetime benefit. Both of these measures can be used to determine the benefit of treatment initiation for the individual patient (**chapter 8, 9 and 10**). In contrary to the preventive strategies in apparently healthy people, there is no mentioning on specific thresholds for these measures on when to initiate therapy in current guidelines.[6] The exception on this is the indication for dual pathway inhibition by Zorginsituut Nederland for individuals with a SMART-risk score of 20% or greater.[25]

The development of certain CVD risk or treatment benefit thresholds for this population would have several advantages. First, this would simplify the process of further therapy intensification, giving guidance to both patient and the treating physician on the fact that the patient's predicted residual risk is regarded as high enough to initiate further treatment intensification. Clear information on whether to intensify treatment with a certain predicted CVD risk or treatment benefit can especially be useful for those clinicians not yet familiar with CVD risk or treatment benefit prediction in this patient population. This is because knowledge about the risk distribution is required in order to judge whether the patient in front of you has a relatively high risk in comparison to other individuals with established ASCVD. With a certain risk threshold, a similar guidance is given. In addition, a clear verdict on whether the predicted CV risk or treatment benefit is regarded 'high' or 'low' can help reduce the time needed to explain the meaning of the predicted risk in clinical practice. Reduced time requirements and increased access for those not yet so familiar could both lead to increased use of prediction measures for treatment decisions in clinical practice, which has been shown to be an effective strategy for determining treatment eligibility in this population (**chapter 8 and 9**). Second, using clear treatment thresholds enhances the standardization of treatment intensification. This may help to reduce the differences in the treatment patterns of similar patients (**chapter 11**). As these targets allow for population-based analyses of (cost-) effectiveness (**chapter 9 and 10**) of certain treatment strategies, these could be very important in determining evidence based reimbursement strategies of expensive novel treatment options.

Individualized treatment without specific risk thresholds also has some advantages. There are many factors which have to be taken into account in the decision on whether to intensify treatment, including frailty, comorbidities, and the preferences of patient and physician. The characteristics of individual situations require different amounts of treatment benefit in order to outweigh the treatment harms. A single threshold may not fully capture this heterogeneity. The use of a clear-cut threshold may also limit further shared decision making, as it is much faster in the busy clinical practice to decide upon a single threshold rather than to weigh all individual conditions. Moreover, analyses of (cost-)effectiveness are dependent on the geographical location and have not been performed in most countries for most treatment options. Using a too low threshold to determine eligibility could lead to large increases in healthcare costs on a population level (**chapter 9**). Using a model with methodological shortcomings, like ignoring the possibility of competing risks, may also lead to much more individuals qualifying for treatment than expected beforehand (**chapter 5**).

Should future treatment thresholds be developed for those with established ASCVD, these may be most effective if based on therapy benefit rather than on a measure of CVD risk.[26] For two individuals with exactly the same risk, the expected absolute risk

reduction from a single blood pressure agent is larger in the one with the higher blood pressure.[16] Similarly, the largest benefits of lipid lowering therapy is in those with higher lipid levels (**chapter 11**). This therapy benefit could for example be expressed as absolute risk reduction or gain in CVD-free life expectancy. The direct use of therapy benefit, does not only help to effectively identify patients who would benefit much from further prevention, but also to select the right treatment for the individual patients (**chapter 9**).

Likely, most potential disadvantages of a treatment threshold for individuals with established ASCVD can be accounted for in future analyses. As treatment decisions based on predicted residual risk or benefit are an effective way of determining treatment eligibility, the population of individuals with established ASCVD will likely benefit from this. The evidence presented in **chapter 8 and 9** can help to determine these treatment thresholds for both 10-year residual CVD risk as well as for gain in CVD-free life expectancy. These threshold likely depend on the treatment of interest and the available budget for expensive preventive drugs. For an expensive, yet effective therapy like PCSK9 inhibition, it could be considered to recommend this to individuals with a measured LDL of ≥1.8 mmol/L and a predicted SMART2 10-year risk of 30% or greater. For the Dutch population, this would lead to approximately 20% of the individuals with established ASCVD being eligible for treatment – the 20% of the population with likely the highest treatment benefit (**chapter 8**).

Concluding remarks

In the future, the accuracy and clinical applicability of prediction models may be improved even further. Within Europe, most room for improvement of predictive accuracy may be in Eastern Europe: the predictions done by all models presented in this thesis can only be as good as the data available during model development. Whereas the recalibration to Western European countries was based on abundant cohort or registry data, reliable data especially of non-fatal events in Eastern Europe are relatively scarce. Even within Western Europe, technical advancements may further improve prediction accuracy by incorporating real-world 'big data' electronic health records or by linking national registries on CVD incidence, mortality or risk factor data. Similar linkage in other countries could further fuel prediction research in these countries. Several of the risk models presented in the current thesis were validated in large, care-as-usual datasets like the Clinical Practice Research Datalink from the United Kingdom. In future risk prediction algorithms, these are likely to play an even more central role due to their enormous power and region- or countrywide implementation. Especially when combined with sophisticated machine learning algorithms, the accuracy of such models may be further improved.

Clinical applicability of prediction models may benefit from further technical advancements, for example by linking CVD prediction algorithms to individual

electronic health records. This reduces time and chance of mistakes required for entering predictors in the algorithm, leaving additional time to explain the interpretation of the predictions and to discuss whether the potential benefit of treatment outweighs the treatment harm.

It is unclear whether future risk algorithms will calculate a certain measure of uncertainty surrounding individual predictions, like for example is offered for the SCORE2-OP risk charts (**chapter 3**). Currently, it is unclear how such an uncertainty interval should be defined, and which exact uncertainty should be incorporated. Should this interval contain the true value for the individual of interest with 95% certainty? This may be complicated, because an individual will in the end always either have, or not have an event. As soon as it is clear how to define these intervals, these may make the shared decision process more informed by giving an indication of the accuracy on individual predictions. On the other hand, the shared decision process might also become a lot more complicated: the point estimate of a risk prediction is already very difficult to explain to an individual patient, and the confidence interval makes this process even harder. Therefore, the shared decision process in only improved if an informative measure of uncertainty is used, which can be well understood by the patient. Until then, treatment decisions are best informed by using the best estimate available, in this case the point estimate of the predicted risk.

A lot of progress has been made in the individualized strategies for the prevention of cardiovascular disease. Prediction models for cardiovascular disease have become more reliable than ever before and are better suited to use in more clinical situations and patient populations, including those with established ASCVD. The relevance of prediction-based treatment has substantially increased with the latest 2021 ESC CVD prevention guidelines, which may help to effectively target those who may benefit most from preventive treatment.

Highlights of this thesis

- The 10-year risk of CVD events can be accurately predicted for apparently healthy individuals in four European risk regions using the updated SCORE2 model, which was systematically recalibrated using contemporary and representative aggregate data (**chapter 2**).
- To communicate CVD event risks and potential benefits of risk factor treatment to older persons, the competing risk adjusted SCORE2-OP model was developed. This may facilitate shared decision-making in the CVD risk management in older persons (**chapter 3**).
- Additional risk factors present in clinical practice can be flexibly implemented in risk predictions from existing risk factors. The methods were shown to be accurate

using a broad range of potential risk modifiers and was accurate even when using multiple risk factors. This improves upon clinical applicability and accuracy of existing prediction models (**chapter 4**).

- CVD events and potential benefits from risk factor treatment those situations where individuals are not only at risk of CVD events, but also of non-cardiovascular mortality, this should be accounted for in the development, recalibration and validation of CVD prediction models. Ignoring this possibility may lead to overestimated CVD event risks and with that, to overoptimistic expectations of benefit from preventive treatment (**chapter 5**).
- The systematic recalibration methodology using contemporary and representative aggregate data as applied in the SCORE2 model was adapted to the lifetime setting to recalibrate the life-CVD model. This allows for accurate estimations of CVD-free life expectancy in four European risk regions (**chapter 6**).
- The 'classic' cardiovascular risk factors smoking, systolic blood pressure and non-HDL cholesterol also increase the risk of major adverse limb events in individuals with established ASCVD. As these events are common and may severely impact quality of life, this further underlines risk factor management in these patients (**chapter 7**).
- With the updated SMART2 risk score, the 10-year residual risk of CVD events in individuals with established ASCVD can be accurately estimated. This can help to identify those individuals that benefit most from further therapy intensification (**chapter 8**).
- Alternatively, further residual CVD risk reduction guided by lifetime benefit estimation is an effective and potentially cost-effective strategy which can lead to more CVD-free life years and event reduction compared to treating according to risk factor threshold based treatment in patients with established ASCVD (**chapter 9 and 10**).
- Even though almost all stroke patients get prescribed lipid lowering medication, many of those do not reach guideline-specified LDL targets. Recurrent event risks may be lowered by optimization of lipid lowering therapy (**chapter 11**).

References

1. Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J*. 2019;40(7):621-631. doi:10.1093/eurheartj/ehy653
2. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am J Epidemiol*. 2017;186(9):1026-1034. doi:10.1093/aje/kwx246
3. Cook NR. Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction. *Circulation*. 2007;115(7):928-935. doi:10.1161/CIRCULATIONAHA.106.672402
4. Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J*. 2019;40(7):621-631. doi:10.1093/eurheartj/ehy653
5. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Heal*. 2019;7(10):e1332-e1345. doi:10.1016/S2214-109X(19)30318-3
6. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
7. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart*. 2013;99(12):866-872. doi:10.1136/heartjnl-2013-303640
8. De Bacquer D, Ueda P, Reiner Ž, et al. Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE Risk Model. *Eur J Prev Cardiol*. 2020;32(0). doi:10.1093/eurjpc/zwaa128
9. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. *Eur Heart J*. 2003;24(11):987-1003. doi:10.1016/S0195-668X(03)00114-3
10. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7
11. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357(May):j2099. doi:10.1136/bmj.j2099
12. Jaspers NEM, Blaha MJ, Matsushita K, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. *Eur Heart J*. 2019;31:1-10. doi:10.1093/eurheartj/ehz239
13. Klooster CC van t., Bhatt DL, Steg PG, et al. Predicting 10-year risk of recurrent cardiovascular events andcardiovascular interventions in patients with established cardiovascular disease: results from UCC-SMART and REACH. *Int J Cardiol*. 2021;325:140-148. doi:10.1016/j.ijcard.2020.09.053
14. de Vries TI, Westerink J, Bots ML, Asselbergs FW, Smulders YM, Visseren FLJ. Relationship between classic vascular risk factors and cumulative recurrent cardiovascular event burden in patients with clinically manifest vascular disease: results from the UCC-SMART prospective cohort study. *BMJ Open*. 2021;11(3):e038881. doi:10.1136/bmjopen-2020-038881
15. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326(7404):1423-0. doi:10.1136/bmj.326.7404.1423

16. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338(may19 1):b1665-b1665. doi:10.1136/bmj.b1665

17. World Health Organization. WHO Mortality Database. Accessed May 7, 2020. https://apps.who.int/healthinfo/statistics/mortality/whodpms/

18. Baig SS, Altman DG, Taggart DP. Major geographical variations in elective coronary revascularization by stents or surgery in England. *Eur J Cardio-Thoracic Surg*. 2015;47(5):855-859. doi:10.1093/ejcts/ezu276

19. Kengne AP, Patel A, Marre M, et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. *Eur J Cardiovasc Prev Rehabil*. 2011;18(3):393-398. doi:10.1177/1741826710394270

20. Conroy RM, Group on behalf of the S project, Pyörälä K, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24(11):987-1003. doi:10.1016/S0195-668X(03)00114-3

21. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. *BMJ*. 2016;352:i1548. doi:10.1136/bmj.i1548

22. Dickinson R, Raynor DK, Knapp P, MacDonald J. Providing additional information about the benefits of statins in a leaflet for patients with coronary heart disease: a qualitative study of the impact on attitudes and beliefs. *BMJ Open*. 2016;6(12):e012000. doi:10.1136/bmjopen-2016-012000

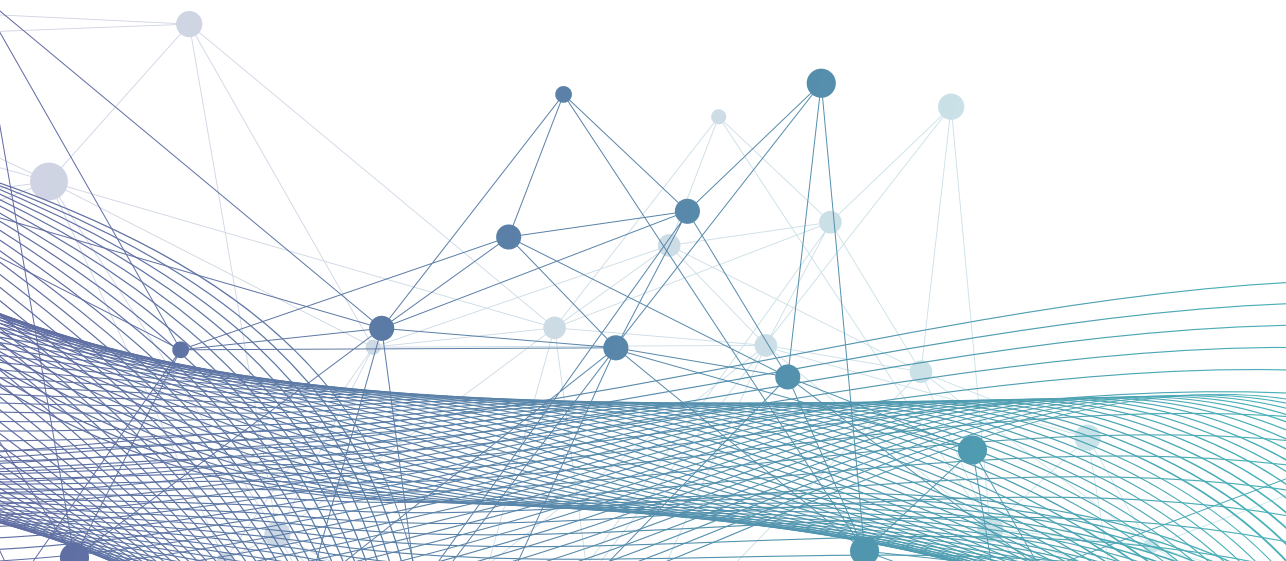
23. Jaspers NEM, Visseren FLJ, van der Graaf Y, et al. Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial. *BMJ Open*. 2021;11(7):e041673. doi:10.1136/bmjopen-2020-041673

24. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106

25. Zorginstituut Nederland. FK preparaattekst Rivaroxaban. Accessed October 27, 2021. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/r/rivaroxaban

26. Berkelmans GFN, Greving JP, van der Graaf Y, Visseren FLJ, Dorresteijn JAN. Would treatment decisions about secondary prevention of CVD based on estimated lifetime benefit rather than 10-year risk reduction be cost-effective? *Diagnostic Progn Res*. 2020;4(1):4. doi:10.1186/s41512-020-00072-5

APPENDIX



Summary

Cardiovascular disease (CVD), including coronary heart disease and cerebrovascular disease, are the most common non-communicable diseases globally. In the prevention of CVD events, effective strategies have been developed by reduction of the most important modifiable risk factors: smoking, systolic blood pressure and cholesterol. Whereas all these treatment options are effective in reducing CVD risk on a population level, most of these therapies also have disadvantages like the costs or the risk of adverse events. To most effectively target such preventive measures, individuals who benefit most are often identified using prediction models that predict an individual's cardiovascular event risk. In this thesis, we improve upon such predictions of cardiovascular event risk by updating existing models, or by the development of new models.

Chapter 2 discusses the development, systematic recalibration and validation of the SCORE2 (Systematic COronary Risk Evaluation 2). The SCORE2 model is the successor to the widely used SCORE model and can be used to predict the 10-year risk of CVD events for apparently healthy people from age 40-70 years. Important improvements compared to the original model are the use of large, contemporary datasets, and the inclusion of non-fatal cardiovascular diseases in the prediction outcomes. The In **chapter 2**, it was shown that the SCORE2 model was well-tailored to the clinical practice in four European risk regions, and could discriminate well between high-risk and low-risk individuals, which enhances the identification of individuals at higher risk of developing CVD across Europe.

The counterpart of SCORE2 for predicting cardiovascular disease risk in people older than 70 is the SCORE2-OP (Systematic COronary Risk Evaluation 2 - Older Persons) model, which is discussed on **chapter 3**. Similar to the SCORE2 model, SCORE2-OP was systematically recalibrated to four European risk regions, and was shown to be able to discriminate between high-risk and low-risk older persons. These models can be used for communicating the risk of CVD and potential benefit from risk factor treatment, and may facilitate shared decision making between clinicians and patients in CVD risk management in older persons.

In clinical practice, often additional prognostic factors are known which are not directly incorporated in cardiovascular risk prediction models, like albuminuria, education level, or coronary calcium score. In **chapter 4**, a solution was presented on how to integrate such possible risk modifying characteristics in existing CVD risk models for the prediction of CVD event risk in apparently healthy people. This flexible methodology improves the accuracy of predicted risks and increases applicability of prediction models for individuals with known additional risk modifiers

Many models developed for predicting the risk of cardiovascular disease (CVD), are adjusted for the competing risk of non-CVD mortality, which has been suggested to reduce potential overestimation of cumulative incidence in populations where the risk of competing events is high. In **chapter 5**, this was illustrated for a high risk population with individuals with established atherosclerotic CVD. The predictions unadjusted for competing risks were shown to overestimate the cumulative incidence of CVD events, which was most apparent in the highest risk quartiles and in older persons.

The systematic recalibration methodology using contemporary and representative aggregate data, as applied to the SCORE2 model, was adapted to the lifetime setting to recalibrate the life-CVD model in **chapter 6**. After applying the recalibrated risk prediction models to external validation cohorts, predicted risks matched the observed cumulative incidence, and the discrimination of the model was shown to be adequate. By taking into account geographical differences in CVD incidence, the recalibrated LIFE-CVD model provides a more accurate tool for the prediction of lifetime risk and CVD-free life expectancy.

Major adverse limb events, atherosclerotic complications in the lower limb, may cause substantial morbidity in individuals in individuals with peripheral artery disease. In **chapter 7**, the incidence of major adverse limb events was shown to differs according to vascular disease location, and shown to be associated with non-HDL cholesterol, systolic blood pressure and smoking. These findings underline the importance of risk factor management in patients with vascular disease.

In **chapter 8**, the development and validation of the SMART2 risk score for the prediction of 10-year CVD event risk in individuals with established atherosclerotic CVD was shown. To broaden generalizability across regions, the SMART2 risk score was recalibrated to four European risk regions and to Asia (excluding Japan), Japan, Australia, North America, and Latin America using contemporary cohort data from each target region. Use of this tool could allow for a more personalized approach to secondary prevention based upon quantitative rather than qualitative estimates of residual risk.

In **chapter 9**, it was shown that residual CVD risk reduction guided by lifetime benefit estimation, as predicted with the previously published SMART-REACH model, is an effective and potentially cost-effective strategy in individuals with established atherosclerotic CVD. Based on the results of a microsimulation model, this strategy led to more CVD-free life years and fewer CVD events compared to treating according to risk factor thresholds. This SMART-REACH model was further validated in stroke patients in **chapter 10.** The SMART-REACH model was shown to accurately predict CVD event risk. In addition, the SMART-REACH model was used to show that the residual risk in these stroke patients was substantial, and that there was much

interindividual variation in CVD risk, with a corresponding variation in benefit from intensification of treatment.

In **chapter 11**, prescription patterns for lipid-lowering therapy (LLT) following ischemic stroke, and estimated benefits from guideline-based up-titration of LLT were evaluated. It was shown that women and older adults were prescribed lower doses of lipid lowering therapy, and that most stroke patients (81%) are expected to be able to reach guideline targets (<1.8 mmol/L) with only statins and ezetimibe, whereas these are currently only met in 45% of the stroke patients.

Samenvatting (voor niet-ingewijden)

Hart- en vaatziekten zijn wereldwijd de belangrijkste oorzaak van ziekte en sterfte. Deze kunnen in belangrijke mate voorkomen worden door het behandelen van de risicofactoren. Gezien deze (medicamenteuze) behandelingen vaak nadelen hebben zoals het risico op bijwerkingen of hoge kosten, is het belangrijk om mensen te identificeren die het meest baat hebben bij deze preventieve maatregelen. Bij mensen zonder eerdere vaatziekten wordt dit gedaan middels het voorspellen van het risico op hart- en vaatziekten. Modellen waarmee dit kan, maken gebruik van een algoritme om met risicofactoren als leeftijd, geslacht, rookstatus of bloeddruk een zo nauwkeurig mogelijke schatting te maken van het risico. Deze behandelstrategie wordt momenteel aangeraden bij mensen zonder eerdere vaatziekten. Deze effectieve manier van behandelen is echter momenteel gebaseerd op modellen die al in iets ouder zijn, terwijl sinds er sinds toen nieuwe ontwikkelingen op methodologisch gebied zijn, en de incidentie van hart- en vaatziekten fors is afgenomen. Daarom was het doel van de huidige thesis om de voorspellingen op het risico van hart- en vaatziekten te verbeteren, middels het door vernieuwen van bestaande modellen te verbeteren of door nieuwe modellen te maken.

In **hoofdstuk 2** wordt de ontwikkeling van het SCORE2 (Systematic COronary Risk Evaluation 2) model besproken, de opvolger van het veelal gebruikte SCORE model. Het SCORE model was al jaren de basis is voor het cardiovasculaire risicomanagement van mensen zonder eerdere vaatziekten, in zowel Nederland als de rest van Europa. Het algoritme kan het 10-jaars risico op hart- en vaatziekten voorspellen op basis van risicofactoren als roken, bloeddruk en cholesterol bij mensen onder de 70. SCORE2-OP (Systematic COronary Risk Evaluation 2 - Older Persons), besproken in **hoofdstuk 3** is de tegenhanger hiervan voor het voorspellen van het risico op hart- en vaatziekten voor mensen boven de 70. Belangrijke verbeteringen ten opzichte van het originele model zijn het gebruik van een stuk modernere data, het feit dat nu ook niet-fatale hart- en vaatziekten worden voorspeld en het feit dat nu ook rekening wordt gehouden met het feit dat mensen ook aan andere oorzaken kunnen overlijden. Voor de algoritmes is relevante data van meer dan 700,000 individuen gebruikt. Deze mensen zijn lange tijd gevolgd. De meer dan 30.000 events van hart- en vaatziekten die deze mensen kregen zijn gebruikt om zo precies mogelijk te kunnen voorspellen hoe hoog het risico op hart- en vaatziekten is bij welke mensen. Middels het gebruik van grootschalige data van miljoenen Europese individuen zijn de algoritmes zo precies mogelijk afgesteld op de klinische praktijk in vier Europese regio's, de laag, gemiddeld, hoog en zeer hoog risico gebieden. Nederland valt in het 'laag risico' gebied.

Een andere belangrijke methodologische verbetering van de hierboven genoemde modellen, is de correctie voor 'concurrerende risico's': de kans dat iemand overlijdt

aan iets anders dan vaatziekten. Aanpassing voor concurrerende risico's wordt beschouwd als een methodologische vooruitgang om het risico op vaatziekten beter te schatten. In **hoofdstuk 4** wordt de klinische impact van het corrigeren voor concurrerende risico's geïllustreerd. In deze illustratie blijkt dat indien hier niet voor gecorrigeerd wordt, er een overschatting kan ontstaan van de voorspelde risico's, met name bij oudere mensen met een hoog risico op vaatziekten. Dit zou ook kunnen leiden tot een overschatting van het behandeleffect.

In **hoofdstuk 5** wordt gekeken naar hoe er bij het voorspellen van het risico op hart- en vaatziekten het best gebruik kan worden gemaakt van bekende risicofactoren, die niet gebruikt worden in bestaande predictiemodellen. Voorbeelden hiervan zijn een coronaire calciumscore, of iemand waarbij hart- en vaatziekten op jonge leeftijd voorkomen in de familie. Hiervoor is in **hoofdstuk 5** een flexibele methode geïntroduceerd om deze factoren betrekken bij voorspellingen. Met gebruik van deze factoren, werden de modellen iets beter in het schatten van de risico's. Daarnaast werd de klinische toepasbaarheid van de modellen ook groter, gezien alle relevante voorspellers nu kunnen worden meegenomen.

Om zo goed mogelijk rekening te kunnen houden met regionale verschillen in het voorkomen van hart- en vaatziekten, is het belangrijk dat modellen goed aangepast worden naar de lokale situatie ('recalibratie'). In **hoofdstuk 6** wordt de manier van recalibratie, zoals beschreven in **hoofdstuk 2 en 3**, aangepast zodat deze ook werkt voor modellen met een levelslange voorspelhorizon, in plaats van 10 jaar. Vervolgens wordt de methodologie ook toegepast op het eerder gepubliceerde LIFE-CVD model, zodat in vier Europese risico regio's accurate voorspellingen gedaan kunnen worden van de levensverwachting vrij van vaatziekten, en de verwachte winst hierop door risicofactorbehandeling als stoppen met roken of cholsterolverlaging.

In **hoofdstuk 7** wordt er gekeken naar het effect van klassieke risico factoren op amputaties en ander vaatingrepen aan het been, welke kunnen leiden tot grote afhankelijkheid en ziektelast. Deze problemen zijn met name bekend bij patiënten met perifeer arterieel vaatlijden ("etalagebenen"), maar kunnen ook optreden bij mensen met vaatziekten op andere locaties. Middels data van 8139 patiënten uit het UCC-SMART cohort onderzoeken wij hoe vaak deze ingrepen precies voorkomen bij patiënten met verschillende typen vaatziekten en wat het effect van cholesterol, bloeddruk en roken hierop is. Cholesterol lijkt een minder grote rol te spelen bij het ontstaan van amputaties en vaatingrepen. Een hogere bloeddruk geeft een duidelijk hoger risico hierop. Het grootste effect is echter van roken – mensen die vroeger hebben gerookt, hebben een drie keer zo hoog risico als personen die nooit hebben gerookt. Mensen die nog steeds roken hebben zelfs een zever keer zo grote kans op amputaties en vaatingrepen. Dit onderzoek toont aan dat het ook voor amputaties en vaatingrepen aan de benen zeer belangrijk is om niet te roken en een verhoogde bloeddruk te behandelen.

Momenteel kan het risico op vaatziekten bij mensen met eerder vaatziekten geschat worden met de SMART risk score. In **hoofdstuk 8** wordt deze risicoscore vernieuwd, waarbij diverse methodologische verbeteringen worden doorgevoerd en meer data wordt gebruikt om nog preciezere schattingen te maken. Een van de verbeteringen is het corrigeren voor concurrerende risicos (**hoofdstuk 4**). Voor de vernieuwde SMART2 risicoscore wordt gebruik gemaakt van 8355 mensen met eerdere vaatziekten die geïncludeerd zijn vanuit het UMC Utrecht, welke mensen zijn lange tijd gevolgd. Deze lange termijn data is gebruikt voor de update, en de score is daarna verder gevalideerd in 369,044 uit diverse regio's binnen Europa en daarbuiten.

Voor mensen met vaatziekten kunnen ook voorspellingen van cardiovasculair risico worden gedaan met een levenslang perspectief, dit kan met het eerder gepubliceerde SMART-REACH model. In **hoofdstuk 9** is gekeken of behandelbeslissingen genomen op basis van deze voorspellingen effectief en kosteneffectief zijn. Middels een simulatie worden dergelijke behandelbeslissingen vergeleken met het volgen van huidige richtlijnen. Uit de resultaten blijkt dat het gebruiken van de toename in vaatziekte-vrije overleving een effectieve maat is om te gebruiken voor behandelbeslissingen, dit kan leiden tot meer vaatziekte-vrije levensjaren en het voorkomen van meer cardiovasculaire events.

Het model dat gebruikt werd in **hoofdstuk 9**, is in **hoofdstuk 10** aangepast voor gebruik in patiënten met eerdere beroertes uit Noorwegen. Na aanpassing van de onderliggende risico's van het SMART-REACH model, kwamen de voorspelde risico's goed overeen met de risico's zoals geobserveerd werden. Nu dit model goed aansloot op de lokale praktijk, kon geschat worden hoeveel winst de Noorse patiënten zouden hebben in het theoretische geval dat ze exact volgens de richtlijnen behandeld zouden worden. Daaruit bleek dat er aanzienlijke winst te halen viel, die kan leiden tot 1.4 jaar langere levensduur zonder vaatziekten voor een doorsnee patiënt.

In hoofdstuk 11 wordt nog wat dieper ingegaan op de behandelingen gericht op het verlagen van cholesterol in dezelfde groep patiënten met een eerdere beroerte uit Noorwegen. Het doel was om te kijken welke mensen op dit moment mogelijk worden onder behandeld en hoe veel baat deze mensen zouden hebben bij intensievere behandeling. Hieruit bleek dat met name ouderen en vrouwen minder intensief werden behandeld om hun cholesterol te verlagen. Zelfs zonder het gebruik van moderne, dure cholesterolverlagers zou ruim 80% van de patiënten de cholesteroldoelen uit de richtlijnen kunnen halen, waar nu slechts 45% dit haalt. De levenswinst die hieruit behaald kan worden verschilt veel van persoon tot persoon, maar kan erg groot zijn voor sommige individuen. Dit pleit voor een individuele behandelstrategie, zoals bijvoorbeeld beschreven in **hoofdstuk 9** of **hoofdstuk 8.**

List of publications

Publications included in this thesis

Hageman SHJ, Pennells L, Ojeda F, Kaptoge S, Kuulasmaa K, de Vries T, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-2454.

Hageman SHJ, Pennells L, Ojeda F, Kaptoge S, Dorresteijn J, Di Angelantonio E. SCORE2 models allow consideration of sex-specific cardiovascular disease risks by region. Eur Heart J. 2022;43(3):241-242.

de Vries TI, Cooney MT, Selmer RM, **Hageman SHJ**, Pennells LA, Wood A, et al. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455-2467.

Hageman SHJ, de Borst GJ, Dorresteijn JAN, Bots ML, Westerink J, Asselbergs FW, et al. Cardiovascular risk factors and the risk of major adverse limb events in patients with symptomatic cardiovascular disease. Heart. 2020;106(21):1686-1692.

Hageman SHJ, McKay AJ, Ueda P, Gunn LH, Jernberg T, Hagström E, et al. Estimation of recurrent atherosclerotic cardiovascular event risk in patients with established cardiovascular disease: the updated SMART2 algorithm. Eur Heart J. 2022. Online ahead of print.

Hageman SHJ, Dorresteijn JAN, Bots ML, Asselbergs FW, Westerink J, van der Meulen MP, et al. Residual cardiovascular risk reduction guided by lifetime benefit estimation in patients with symptomatic atherosclerotic disease: effectiveness and cost-effectiveness. Eur J Prev Cardiol 2021. Online ahead of print.

Gynnild MN, **Hageman SHJ**, Dorresteijn JA, Spigset O, Lydersen S, Wethal T, et al. Risk Stratification in Patients with Ischemic Stroke and Residual Cardiovascular Risk with Current Secondary Prevention. Clin Epidemiol. 2021;Volume 13(September):813-823.

Gynnild MN, **Hageman SHJ**, Spigset O, Lydersen S, Saltvedt, I, et al. Use of lipid-lowering therapy after stroke and expected benefit from intensification of treatment. Open Heart 2022. Online ahead of print.

Publications not included in this thesis

Hageman SHJ, Kovalchuk MO, Sleutjes BTHM, van Schelven LJ, van den Berg LH, Franssen H. Sodium-potassium pump assessment by submaximal electrical nerve stimulation. Clin Neurophysiol. 2018;129(4):809-814.

Hageman SHJ, Dorresteijn JAN, Visseren FLJ. Comment to: Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE risk model. Eur J Prev Cardiol. 2021;31:139-140.

Contributing authors

Abdonas Tamosiunas	Institute of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania
Adam D Timmis	William Harvey Research Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK
Ailsa J McKay	Department of Primary Care and Public Health, Imperial College London, United Kingdom
Álvaro Aceña	Department of Cardiology, Fundación Jiménez Díaz, Madrid, Autónoma University, Madrid
Andreas Stang	Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
Andrzej Pająk	Department of Epidemiology and Population Studies, Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Kraków, Poland
Angela Wood	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Arend Mosterd	Department of Cardiology, Meander Medical Centre, Amersfoort, The Netherlands.
Börge Schmidt	Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
Brian A Ference	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Christopher J Bulpitt	School of Public Health, Imperial College London, London, UK
Deepak L Bhatt	Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA, USA
Dirk De Bacquer	Department of Public Health and Primary Care, Ghent University, Ghent, Belgium
Emanuele Di Angelantonio	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Emil Hagström	Department of Medical Sciences, Uppsala University, Uppsala Clinical Research Center, Uppsala, Sweden
Emilia Sawicka	Department of Population Medicine and Lifestyle Diseases Prevention, Medical University of Bialystok, Poland
Folkert W Asselbergs	Department of Cardiology, University Medical Center Utrecht, Utrecht, Netherlands
Francisco Ojeda	University Heart & Vascular Center, Hamburg, Germany
Frank Kee	School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, Northern Ireland
Frank Visseren	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
Gert J de Borst	Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
Giovanni Veronesi	Research Center in Epidemiology and Preventive Medicine, Department of Medicine and Surgery, University of Insubria, Varese, Italy

Grethe S Tell	Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway and Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway
Haakon E Meyer	Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway and Department of Community Medicine and Global Health, Institute of Health and Society, University of Oslo, Oslo, Norway
Hanne Ellekjær	Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU – Norwegian University of Science and Technology, Trondheim, Norway; Department of Stroke, Clinic of Medicine, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway
Hynek Pikhart	Department of Epidemiology and Public Health, University College London, London, UK
Ian Graham	School of Medicine, Trinity College Dublin, The University of Dublin, College Green, Dublin, Ireland
Ignacio Mahíllo	Department of Epidemiology, Fundación Jiménez Díaz, Madrid
Inger Ariansen	Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway
Ingvild Saltvedt	Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU – Norwegian University of Science and Technology, Trondheim, Norway; Department of Geriatrics, Clinic of Medicine, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway
Jan Westerink	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
Jannick Dorresteijn	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
Jannicke Igland	Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
John W McEvoy	National Institute for Prevention and Cardiovascular Health, Ireland; National University of Ireland Galway, Galway, Ireland.
José Tuñón	Department of Cardiology, Fundación Jiménez Díaz, Madrid, Autónoma University, Madrid
Kari Kuulasmaa	THL-Finnish Institute for Health and Welfare, Helsinki, Finland
Karl-Heinz Jöckel	Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
Karol Kaminski	Department of Population Medicine and Lifestyle Diseases Prevention, Medical University of Bialystok, Poland
Kausik K Ray	Department of Primary Care and Public Health, Imperial College London, United Kingdom
Kjersti S. Rabanal	Department of Public Health, Faculty of Health Sciences, University of Stavanger, Stavanger, Norway and Research Department, Stavanger University Hospital, Stavanger, Norway
Kristi Läll	Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia
Kunihiro Matsushita	Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

Laura H Gunn	Department of Public Health Sciences and School of Data Science, University of North Carolina at Charlotte, USA; Department of Primary Care and Public Health, Imperial College London, United Kingdom
Lisa Pennells	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Maarten van Smeden	Julius Center for Health Science and Primary Care, University Medical Center Utrecht, University of Utrecht, Utrecht, the Netherlands.
Majon Muller	Department of Internal Medicine, section Geriatric Medicine, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Cardiovascular Sciences, the Netherlands
Malgorzata Chlabicz	Department of Population Medicine and Lifestyle Diseases Prevention, Medical University of Bialystok, Poland
Mari Nordbø Gynnild	Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU – Norwegian University of Science and Technology, Trondheim, Norway; Department of Stroke, Clinic of Medicine, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway
Marie Therese Cooney	St Vincent's University Hospital and School of Medicine, University College Dublin, Dublin, Ireland
Marielle H Emmelot-Vonk	Department of Geriatrics, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
Martin Bobak	Department of Epidemiology and Public Health, University College London, London, UK
Martin Halle	University Hospital ´Klinikum rechts der Isar´, Technical University of Munich, Munich, Germany
Michael Blaha	Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins Hospital, Baltimore, USA.
Michiel Bots	Julius Center for Health Sciences and Primary Care, Utrecht, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
Miriam van der Meulen	Julius Center for Health Sciences and Primary Care, Utrecht, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
Nigel Beckett	Imperial Clinical Trials Unit, Imperial College London, London, UK
Nils Lehmann	Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
Olaf H Klungel	Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
Olav Spigset	Department of Clinical Pharmacology, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway
Panos Vardas	Heraklion University Hospital, Crete, Greece
Patrick C Souverein	Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
Paul Dendale	Hasselt University, Hasselt, Belgium
Peter Ueda	Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

Ph. Gabriel Steg	Université de Paris, French Alliance for Cardiovascular Trials,; Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Paris, France INSERM Unité, 1148 Paris, France
Raimund Erbel	Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
Randi M Selmer	Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway
Reedik Mägi	Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia
Riitta Antikainen	Center for Life Course Health Research/Geriatrics and Medical Research Center Oulu, University of Oulu, Oulu, Finland
Robyn L McClelland	Department of Biostatistics, University of Washington, Seattle, WA
Romin Pajouheshnia	Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
Ruth Peters	School of Public Health, Imperial College London, London, UK and Psychology, University of New South Wales, Sydney, Australia & Neuroscience Research Australia, Sydney, Australia
Ruzena Kubinova	National Institute of Public Health, Czech Republic
Ryan Chung	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Sara Schramm	Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
Sofia Malyutina	Research Institute of Internal and Preventive Medicine, Branch of "Federal Research Center Institute of Cytology and Genetics"(IC&G), Siberian Branch of RAS, Novosibirsk, Russia
Stefan Blankenberg	University Heart & Vascular Center Hamburg, Hamburg, Germany, and German Centre for Cardiovascular Disease (DZHK), Hamburg
Stella Trompet	Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands and Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
Stephen Kaptoge	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Stian Lydersen	Department of Mental Health, Faculty of Medicine and Health Sciences, NTNU – Norwegian University of Science and Technology, Trondheim, Norway
Taavi Tillman	Institute of Family Medicine and Public Health, University of Tartu, Estonia
Tamar de Vries	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
Thomas Bolton	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Tomas Jernberg	Department of clinical sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
Torgeir Wethal	Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU – Norwegian University of Science and Technology, Trondheim, Norway
Veikko Salomaa	THL-Finnish Institute for Health and Welfare, Helsinki, Finland

Vijay Nambi	Center for Cardiovascular Disease Prevention, Michael E DeBakey Veterans Affairs Hospital, Houston, USA; Department of Medicine, Baylor College of Medicine, Houston, USA
Wentian Lu	Department of Epidemiology and Public Health, University College London, London, UK
WM Monique Verschuren	Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment, Bilthoven
Wouter Jukema	Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
Yvonne T van der Schouw	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
Zhe Xu	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

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Curriculum vitae

Steven was born on the 9th of November 1992 in Nijmegen, the Netherlands. After graduating from the 'Stedelijk Gymnasium Arnhem' in 2011, he studied Medicine at the University of Utrecht. His first experience with research was a research internship at the Department of Neurology in the UMC Utrecht during his, regarding the electrophysiological properties of the sodium-potassium pump. In the final year of his master degree, he did another research internship, this time at the Department of Endocrinology. This research was about the risk of stroke in individuals with acromegaly. During his Master's degree, he did a clinical internship at the University of Malaya, in Kuala Lumpur, Malaysia and his senior internship at the St. Antonius Hospital in Nieuwegein.

After obtaining his medical degree early 2018, he started to work in the St. Antonius Hospital in Utrecht, mainly at the department of Internal Medicine. In September 2018, he started working on this PhD thesis ('*Individualized cardiovascular disease prevention, clinical implementation of risk prediction*') at the department of Vascular Medicine Internal Medicine, UMC Utrecht, under the supervision of prof. dr. F.L.J. Visseren, prof. dr. E. di Angelantonio and dr. J.A.N. Dorresteijn. At the European Society of Cardiology Congress in 2020, he was nominated for the Young Investigator Award for a presentation on the contents presented in Chapter 9 of this thesis. He combined his PhD research with the post-graduate master Clinical Epidemiology, from which he graduated in November 2020. After this thesis, he will start to work as a post-doctoral researcher at the UMC Utrecht.

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