Lifetime predictions for individualized vascular disease prevention. Whom and when to treat?

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Lifetime predictions for individualized vascular disease prevention. Whom and when to treat?

Levenslange voorspellingen voor individuele vasculaire preventie.
Wie en wanneer behandelen?
(met een samenvatting in het Nederlands)

Proefschrift

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Contents

1

Chapter 1

General introduction

Prognostication in medicine.

Prognostication originates from the Greek word prognostikos "foreknowing". It was Hippocrates who described that the best way to manage the cure is by foreseeing and foretelling what would happen based on the present state of matters of the sick.[1] Although it is obvious that predicting (disease) outcome both for patients and healthy people is of vital importance for clinical decision making, prognostication is an everlasting struggle for doctors.[2,3] In 1934, Robert Hutchison observed that "of the three great branches of clinical science diagnosis, prognosis, and treatment-prognosis is admittedly the most difficult. It is also that about which least has been written".[4] Prognosis is still not as prominent or explicit a part of medicine as diagnosis and treatment, it is nevertheless fundamental in clinical practice.[5,6] In the last decades, however, substantial improvements in prediction modelling techniques led to an increase in easy-to-use prediction rules. These rules can strongly improve clinical practice by guiding doctors and patients in estimating a prognosis more accurately and objectively. This implies that all doctors should become familiar with prognostic research, obtain a basic understanding of the strengths and weaknesses, and use them appropriately, since "all models are wrong, but some are useful" ~ George Box.[7]

Risk prediction in cardiovascular prevention

Since cardiovascular disease (CVD) is a result of a lifelong exposure to risk factors and involves numerous people, it is utterly important to identify which people are most likely to get CVD in order to prevent or delay disease. Therefore, cardiovascular risk prediction is a keystone in the prevention of CVD and recommended by several guidelines, even among apparently healthy people.[8-10] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline advises to estimate cardiovascular risk in all apparently healthy people without diabetes mellitus or clinical atherosclerotic cardiovascular disease (ASCVD) aged 40 to 79 using the pooled cohort equation.[9] Based on their prognosis, treatment decisions are made. Patients at high risk (≥7.5% 10-year risk), patients with type 2 diabetes mellitus (T2DM), or with a clinical ASCVD should be treated with statins unless their low-density lipoprotein cholesterol (LDL-c) levels are below 1.8 mmol/L.[10] If patients are at low risk (<5% 10-year risk) and between 20-59 years old, there is a possibility to take a 30-year or lifetime risk into account for treatment decision making.[9] In the 2016 European guidelines on cardiovascular disease prevention, in apparently healthy people, the Systematic Coronary Risk Estimation (SCORE) is recommended for the assessment of 10-year risk predictions of fatal CVD. At high risk (≥5% and <10%) or very high risk (≥10%) for fatal CVD, preventive therapy is indicated using LDL-c targets of 2.5 mmol/L and 1.7 mmol/L, respectively. Also, according to current guidelines, risk stratification is not necessary for patients with T2DM or ASCVD because they are all considered to be at high

risk or very high risk of vascular diseases.[8] However not all patients with diabetes mellitus or ASCVD are equally at high risk for (recurrent) cardiovascular disease (CVD).[11-13] Clinical decision making on whether or not to treat patients with preventive therapy could also benefit from risk prediction in these patients. This is especially relevant with the recent availability of promising but expensive preventive therapy, such as proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitors[14], and for patients with T2DM sodium-glucose cotransporter 2 (SGLT2)-inhitors[15] and glucagon-like peptide 1 (GLP1) analogues[16]. Also, risk prediction could support the decision to stop preventive therapy, if the potential future benefit does not outweigh the disadvantage at some point in life.

Towards prediction for the individual patient

Different patients visit the clinic every day, whether this is at the general practitioner's practice or specialist clinic. Let's take a look at two typical patients; Mr. A and Mr. S.
To help us decide whether we should treat Mr. A. and Mr. S. with lipid-lowering therapy, blood pressure-lowering therapy and/or antithrombotic treatment, and what their personal benefit would be, current risk prediction models are insufficient.

Mr. A.
Mr. A. is a 43 year old IT technician, diagnosed with T2DM 5 years ago. He is obese, with a body-mass index of 35 kg/m², does not smoke, and has no other known co-morbidities. His office blood pressure was 150/75 mmHg. Laboratory tests showed a haemoglobin A1c (HbA1c) of 60 mmol/mol, total cholesterol of 6.0 mmol/L, HDL-c of 1.10 mmol/L, and LDL-c of 4.0 mmol/L. His estimated glomerular filtration rate (eGFR) was 70 ml/min/1.73m².

Mr. S.
Mr S. is 75 years old, enjoying his retirement, but recently diagnosed with T2DM. He has a body-mass index of 26 kg/m², does not smoke, and has no other known co-morbidity. His office blood pressure was 140/85 mmHg. He has an HbA1c of 58 mmol/mol, total cholesterol of 5.0 mmol/L, HDL-c of 1.00 mmol/L, and LDL-c of 2.6 mmol/L. Furthermore, because of his age and diagnosed T2DM, his estimated glomerular filtration rate (eGFR) and albumin/creatinine ratio (ACR) was measured. His eGFR was 80 ml/min/1.73m² and he had no albuminuria (ACR < 2.5 mg/mmol).

With the ADVANCE risk calculator, the 5-year risk for cardiovascular events can be estimated in patients with T2DM. However, for the presented case not all required information is available for using this calculator. Whether these patients have retinopathy and/or atrial fibrillation necessary to predict the risks of these patients is not known at time of the clinic visit (table). According to the European guidelines for CVD prevention, there is no need to calculate risk, because a one-size-fits-all approach for all patients with T2DM is proposed, not taking differences between patients in presence of comorbidity into account. Mr. A and Mr. S. are both considered at high risk for CVD without the use of individualized predictions. Lifestyle advice and drug treatment is recommended for all T2DM patients with an LDL-c >2.5 mmol/L and for Mr. A. blood pressure-lowering treatment as well with a systolic blood pressure >150mmHg (table). The ACC/AHA guidelines also recommend drug treatment for both patients, however considering their risk based on the pooled cohort equation, this should be a moderate or intensive statin. According to the ASCVD pooled cohort equation, Mr. A. has a 10-year risk of 7% to develop CVD, with a lifetime risk of 50%. Due to T2DM, a moderate-intensity statin should be considered according to guidelines with a 10-year risk < 7.5%. Mr. S. has a 10-year risk of 50%. Due to a 10-year risk of >7.5% and T2DM, a high-intensity statin should be considered (table). However, whether the risk predictions are accurate remains uncertain since the pooled cohort equation is not validated in a T2DM population. Based on the choice of guidelines and/or risk prediction models chosen, different advises might be applicable for Mr. A. and Mr. S. (table). Although the pooled cohort equation does try to individualize treatment decisions for Mr. A and Mr. S, both guideline strategies (one-size-fits-all or pooled cohort equation) do not provide information on the expected benefit of preventive treatment. A predicted individualized treatment effect of for instance lipid-lowering or blood pressure-lowering would enable weighing benefits and disadvantages of preventive treatment. This improves shared decision making, and could motivate a patient to adhere to preventive medication.

Application of prediction models in cardiovascular prevention

An overwhelming amount of cardiovascular risk prediction models have been developed over the last decades. In the last 15 years, over 250 cardiovascular prediction models were developed for primary prevention only.[17,18] The question arises why only a few of these prediction models are used in clinical practice. There could be several reasons for this. First, most models were derived from, but did not complete all steps of model development. For the development of a prediction model seven steps are described including external validation and model presentation.[19] In only 36% of the models external validation was performed, and most models were reported inadequately for implementation in clinical practice.[17,20] Second, prediction models that are externally validated should be easy to use for clinicians.[21] Factors necessary to predict CVD risk should be available at the

Table: Comparing different risk stratification for our patients.

Risk stratification	Mr. A.	Mr. S.
ADVANCE	*Available characteristics:* - Sex (male) - Age at diabetes diagnosis (38 y) - Known duration of diabetes (5 y) - Systolic and diastolic blood pressure (150/75 mmHg) - HbA1c (60 mmol/mol) - Non-HDL cholesterol (4.9 mmol/L) - Treated hypertension (no)	*Available characteristics:* - Sex (male) - Age at diabetes diagnosis (75 y) - Known duration of diabetes (0 y) - Systolic and diastolic blood pressure (140/85 mmHg) - HbA1c (58 mmol/mol) - Non-HDL cholesterol (4.0 mmol/L) - Treated hypertension (n) - Albumin/creatinine ratio (<22 mg/g)
	Unavailable characteristics: - Waist circumference (cm) - Albumin/creatinine ratio (mg/g) - Retinopathy (y/n) - Atrial fibrillation (y/n)	*Unavailable characteristics:* - Waist circumference (cm) - Retinopathy (y/n) - Atrial fibrillation (y/n)
European guidelines (one size fits all)	- High-risk category based on T2DM, without target organ damage. - Statins are recommended. - Blood pressure-lowering therapy. - LDL-c target 2.0 mmol/L (50% of current LDL-c of 4.0 mmol/L). - No potential treatment effect given.	- High-risk category based on T2DM, without target organ damage. - Statins are recommended. - LDL-c target 1.3 mmol/L (50% of current LDL-c of 2.6 mmol/L). - No potential treatment effect given.
ACC/AHA guidelines (pooled cohort equation not validated in T2DM patients solely)	- 7% 10-year risk for CVD. - 50% lifetime risk for CVD. - moderate-intensity statin - Blood pressure-lowering therapy - no LDL-c target - No potential treatment effect given.	- 50% 10-year risk for CVD. - No lifetime risk given due to age >59 - high-intensity statin - no LDL-c target - No potential treatment effect given.

time of prediction.[6] As more factors are included, the model becomes more complex, time consuming and costly to use because a greater number of risk factors have to be measured to estimate the risk.[22] When these risk factors are available, risk predictions should automatically be provided in electronic patients records at the time and location of decision making.[23] Another option is the availability of user friendly online tools, were clinicians can easily fill in patient characteristics, providing an immediate risk prediction. However, missing patient characteristics necessary to estimate CVD risk will stop a clinician from using such a support tool. Although several techniques have been described for dealing with missing data for the development of prediction models, currently no strategy is available to help clinicians deal with missing patient characteristics at the time of prediction.[24] Thus, with one missing value, a clinician is unable to use the prediction model. Third, the impact of a prediction model should be investigated before use in clinical practice. What does the outcome of a prediction model mean for a patient? And

how does this influence the treatment decision of a clinician? An impact study should quantify the effect of using a model on doctors' behaviour, patient outcome, or cost effectiveness of care compared with not using such a model.[20] If a patients' risk prediction does not change clinical decision making, it is of no use to implement it in daily practice.

Different estimates of individualized treatment effects

The development of risk prediction tools allowed incorporation of established risk factors into multivariable models to predict 10-year risk for CVD. These 10-year risk predictions help to identify patients at high-risk who may benefit most from drug treatment. The magnitude of treatment effects using 10-year risk predictions can be presented as absolute risk reductions (ARR), or number needed to treat (NNT = 1/ARR).[25] However, since CVD is highly age related age is the strongest predictor for CVD in such calculators. This is illustrated by the SCORE table, showing that men under 45 years and women under 55 years are always at low risk for CVD independent of their risk factor levels.[26] For patients older than 70 years, 10-year CVD risks are always high, exceeding the threshold of 7.5%. Two major issues are not taken into account in current prognostic models predicting 10-year risks:

1. The short horizon of 10-years does not adequately reflect the potential long-term risks or benefits of preventive treatment. This could lead to missed treatment opportunities in younger patients, who will not be eligible for preventive treatment based on current risk predictions and guidelines. However, their future long-term exposure to risk factors building up atherosclerosis over a long period of time results in a high lifetime risk for CVD, and therefore a possibly high lifetime benefit of CVD prevention.
2. Competing risks, i.e. death due to other causes such as cancer, are not taken into account in current prediction models. Since risk factor levels related to CVD are also associated with incident cancer, patients at higher risk for CVD are also at higher risk for cancer.[27,28] Most currently available 10-year prediction models assume that patients can only die from CVD for predicting 10-year CVD-risk, which is obviously not reflecting clinical reality. This leads to an overestimation in risk especially for patients at high risk for non-vascular mortality; i.e. the elderly.[29] Therefore, estimated benefits of treatment are overestimated in older patients using conventional 10-year risk prediction tools.

Nowadays, different modelling techniques are available to help stratify patients that benefit most from treatment from a lifetime-perspective. These models take competing risks into account. In younger patients, lifetime risk could overcome issues regarding the potential missed treatment opportunities in the long-term. The presence of two or more

traditional risk factors compared to optimal risk factor levels increased lifetime CVD risk until 95 years with 42% and 63% for women and men, respectively.[30]

Although this information is useful to promote risk factor interventions at younger age, the interpretation of estimated treatment effects is rather difficult.[31] Prevention of CVD at younger age reduces the age-specific CVD rates. By doing so it increases the years of exposure to the risk of CVD. Since CVD rates increase with age, the lifetime risk of CVD might even increase, depending on the increase of relative rate of mortality from competing events.[32] Thus, lifetime risk is useful to estimate whom to treat at younger age. However, since prolonged life expectancy is not taken into account, it is difficult to use lifelong treatment effects in shared-decision making.[31]

Besides lifetime CVD-risk, new methods enable the prediction of life expectancy and the gain in cardiovascular disease-free life years. This can be useful to stratify patients that benefit most from treatment especially in long-term prevention.[33,34] Models predicting CVD-free life expectancy identify patients that are at a high lifetime risk while keeping competing events and prolonged life-expectancy into account (patients with a high lifetime risk have lower life expectancies). These models can estimate the gain in disease-free life years due to treatment combining the model with trial results.[35] The treatment effects are presented in months or years gained without the disease of interest, which are more appealing measures for patients than relative or absolute risk reductions.[36]

Objective of this thesis

The general objective of this thesis is 1) to demonstrate the translations of trial results to the individual patient by predicting individualized CVD risk and treatment benefits for lifelong prevention of CVD, especially in patients with T2DM or a history of CVD and 2) to improve the applicability of prediction models in clinical practise.

Outline of this thesis

In **Chapter 2**, trends in risk factor levels and cardiovascular risk in patients with a history of CVD between 1996 and 2014 are described. It investigates whether the change in cardiovascular risk is solely due to improved risk factor levels and preventive treatments, or whether unmeasured factors play a role in the lower cardiovascular risk. It underscores the need to identify the patients with the highest risk.

In **Chapter 3**, we developed and geographically validated the diabetes lifetime-perspective prediction (DIAL) model for patients with T2DM. Combining the DIAL model with relative treatment effects of trials in an interactive calculator (available at www.u-prevent.com) enables the prediction of individualized treatment effects of lipid, blood

pressure, glucose, and aspirin treatment for prevention of cardiovascular disease (CVD). The individualized treatment effects are given as gain in CVD-free life years, and 10-year absolute risk reduction, facilitating shared decision making.

In **Chapter 4**, the impact of predictions expressed in CVD-free life years compared to 10-year risk reduction is illustrated. In this chapter, the cost-effectiveness of the decision to start PCSK9-inhibitors in patients with a history of CVD based on gain in CVD-free life years is compared to the decision to start PCSK9-inhibitors based on 10-year absolute risk reduction using a microsimulation model.

In **Chapter 5**, the use of prediction models in the presence of missing patient characteristics is investigated. Five different methods dealing with missing characteristics are presented, and results of predictive performances are compared.

Further elaborating on the results of **Chapter 4**, **Chapter 6** describes the influence of postponement of treatment and/or treatment of shorter than lifelong duration. Especially with expensive medication such as PCSK9-inhibitors, it is important to know whether lifelong treatment resulting in high expenses per patient is absolutely necessary for the intended treatment effects. This chapter will describe the appropriate starting point and duration of treatment with PCSK9-inhibitors for patients with a history of CVD.

The general discussion of this thesis is described in **Chapter 7** and summarized in **Chapter 8**.

References

1. Adams CD. Prognosticon part 1. The Genuine Works of Hippocrates 1868.
2. Christakis NA, Iwashyna TJ. Attitude and self-reported practice regarding prognostication in a national sample of internists. Arch Intern Med 1998;158:2389-95.
3. Grover SA, Lowensteyn I, Esrey KL, Steinert Y, Joseph L, Abrahamowicz M. Do doctors accurately assess coronary risk in their patients? Preliminary results of the coronary health assessment study. BMJ 1995;310:975-8.
4. Hutchison R. A Series of Signed Articles contributed by invitation. Lancet 1934;223:697-8.
5. Christakis NA, Sachs GA. The role of prognosis in clinical decision making. J Gen Intern Med 1996;11:422-5.
6. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ 2009;338:b375.
7. Box GEP. Science and Statistics. Journal of the American Statistical Association 1976;71:791-9.
8. 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 (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal 2016;37:2315-81.
9. Goff DC, Jr., 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:S49-73.
10. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1-45.
11. 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;134:1419-29.
12. Kaasenbrood L, Poulter NR, Sever PS, et al. Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus: The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study. Circ Cardiovasc Qual Outcomes 2016;9:213-21.
13. Dorresteijn JA, Boekholdt SM, van der Graaf Y, et al. High-dose statin therapy in patients with stable coronary artery disease: treating the right patients based on individualized prediction of treatment effect. Circulation 2013;127:2485-93.
14. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England journal of medicine 2017;376:1713-22.
15. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 2015;373:2117-28.
16. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine 2016;375:311-22.
17. Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ 2016;353:i2416.
18. van Dieren S, Beulens JW, Kengne AP, et al. Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: a systematic review. Heart 2012;98:360-9.
19. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. European heart journal 2014;35:1925-31.
20. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009;338:b606.
21. James BC. Making it easy to do it right. The New England journal of medicine 2001;345:991-3.

22. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. Journal of the American College of Cardiology 2009;54:1209-27.
23. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ 2005;330:765.
24. Ambler G, Omar RZ, Royston P. A comparison of imputation techniques for handling missing predictor values in a risk model with a binary outcome. Stat Methods Med Res 2007;16:277-98.
25. Jaeschke R, Guyatt G, Shannon H, Walter S, Cook D, Heddle N. Basic statistics for clinicians: 3. Assessing the effects of treatment: measures of association. CMAJ 1995;152:351-7.
26. Cavanaugh-Hussey MW, Berry JD, Lloyd-Jones DM. Who exceeds ATP-III risk thresholds? Systematic examination of the effect of varying age and risk factor levels in the ATP-III risk assessment tool. Prev Med 2008;47:619-23.
27. Rasmussen-Torvik LJ, Shay CM, Abramson JG, et al. Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk In Communities study. Circulation 2013;127:1270-5.
28. Opie L. Cancer and cardiovascular disease: more tightly linked than by chance. Lancet 2015;385:1182.
29. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41:861-70.
30. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791-8.
31. De Backer G, De Bacquer D. Lifetime-risk prediction: a complicated business. Lancet 1999;353:82-3.
32. Rose G, Shipley M. Effects of coronary risk reduction on the pattern of mortality. Lancet 1990;335:275-7.
33. Ferket BS, van Kempen BJ, Heeringa J, et al. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. PLoS Med 2012;9:e1001361.
34. Kassai B, Boissel JP, Cucherat M, Boutitie F, Gueyffier F. Treatment of high blood pressure and gain in event-free life expectancy. Vascular health and risk management 2005;1:163-9.
35. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj-Brit Med J 2016;352.
36. Grisolia JM, Longo A, Hutchinson G, Kee F. Comparing mortality risk reduction, life expectancy gains, and probability of achieving full life span, as alternatives for presenting CVD mortality risk reduction: A discrete choice study of framing risk and health behaviour change. Soc Sci Med 2018;211:164-74.

2

Chapter 2

Decline in risk of recurrent cardiovascular events in the period 1996 to 2014 partly explained by better treatment of risk factors and less subclinical atherosclerosis

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Abstract

Background - To quantify the decline in recurrent major cardiovascular events (MCVE) risk in patients with clinically manifest vascular disease between 1996 and 2014 and to assess whether the improvements in recurrent MCVE-risk can be explained by reduced prevalence of risk factors, more medication use and less subclinical atherosclerosis.

Methods and results - The study was conducted in the Second Manifestations of ARTerial disease (SMART) cohort in patients entering the cohort in the period 1996-2014. The prevalence of risk factors and subclinical atherosclerosis were measured at baseline. Incidence rates per 100 person-years for recurrent MCVE (including stroke, myocardial infarction, retinal bleeding, retinal infarction, terminal heart failure, sudden death, fatal rupture of abdominal aneurysm) were calculated, stratified by the year of study enrolment. For the attributable risk of changes in risk factors, risk factor treatment, and subclinical atherosclerosis on the incidence rates of recurrent MCVE, adjusted rate ratios were estimated with Poisson regression. 7216 patients had a median follow-up of 6.5 years (IQR 3.4-9.9). The crude incidence of recurrent MCVE declined by 53% between 1996 and 2014 (from 3.68 to 1.73 events per 100 person-years) and by 75% adjusted for age and sex. This improvement in vascular prognosis was for 36% explained by changes in risk factors, medication use and subclinical atherosclerosis.

Conclusion - The risk of recurrent MCVE in patients with clinical manifest vascular disease has strongly declined in the period between 1996 and 2014. This is only partly attributable to lower prevalence of risk factors, improved medication use and less subclinical atherosclerosis.

Introduction

The incidence of cardiovascular disease (CVD) has decreased in recent decades, and the 2010 Global Burden of Disease study[1] for Western countries has estimated a 20-50% decrease in the years of life lost due to premature mortality as a result of CVD between 1990 and 2010. However, vascular diseases remain the leading cause of premature death.[2,3] The incidence of cardiovascular morbidity and mortality has decreased due to improved primary prevention and by improved vascular revascularisation.[4-10] For example, the 43% decline in coronary heart disease mortality rates between 2000 and 2010, was 49% attributed to improved revascularization procedures and for 39% attributed to improved risk factor treatment.[11]

In addition, secondary prevention measures have improved over the last 10-20 years. Between 2003 and 2008 in patients hospitalized with coronary artery disease, overall adherence to 6 performance measures (start on aspirin within 24 hours, discharge on aspirin, discharge on beta-blockers, patients with low ejection fraction discharged on ACE inhibitors, smoking cessation counselling, and use of lipid-lowering medications) increased from 72% to 94%.[12] Mean blood pressure and lipid levels decreased between 1999 and 2013 in patients with coronary artery disease.[13] Also, a steady increase in the use of lipid-lowering therapy and aspirin has been observed in the periods 1975-1986 and 1997-2007, which likely contributed to an absolute 5% decrease in 2-year all-cause mortality for patients hospitalized after an acute myocardial infarction[14]. However, it is unknown whether the long-term risk decreased for recurrent major cardiovascular events (MCVE) and for all-cause mortality, and to what extent this is caused by improved risk factor management.

Earlier in life and more widespread use of lipid-lowering and blood pressure-lowering medication for primary and secondary prevention and a decline in smoking may have changed the face of vascular disease to a more benign, stable phenotype. However, as there is a wide variation in the extent of atherosclerotic lesions in the arterial wall between patients with similar risk factors, other factors than the classical risk factors need to be considered.[15] This variation is likely due to a combination of genetic susceptibility, interactions between other risk factors, life-style, and duration of exposure to risk factors.[16] One of the other factors that might give insight into the extent of atherosclerotic lesions might be measures of subclinical atherosclerosis, for example carotid intima-media thickness (cIMT).

The aim of the present study is to quantify the decline in recurrent MCVE-risk in patients with clinically manifest vascular disease between 1996 and 2014 and to assess whether the improvements in recurrent MCVE-risk can be explained by reduced prevalence of risk factors, more medication use and less subclinical atherosclerosis.

Methods

Study population

Patients originated from the SMART (Secondary Manifest of ARTerial disease) study, an ongoing, single-center, prospective cohort study at the University Medical Centre Utrecht (UMCU). A detailed description of the study rationale and design has previously been published.[17] The study commenced in 1996, after which participating patients, aged 18-80 years, referred to the UMCU with clinically manifest atherosclerotic vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm) or cardiovascular risk factors (hyperlipidaemia, diabetes, or hypertension) underwent vascular screening. Screening followed a standardized diagnostic protocol, followed by physical examinations and laboratory testing in the fasting state. For the current study, baseline data of patients included between September 1996 and March 2014, with a history of CVD, were used. Written informed consent was obtained from all participants at baseline. The study was approved by the Medical Ethics Committee of the UMCU.

Follow-up and endpoints

Patients received bi-annual health questionnaires. When a participant reported a possible event, relevant hospital documents, laboratory, and radiologic findings were collected. Cause of death was verified with general practitioners, medical specialists or relatives. All events were audited by three members of the SMART-study endpoint committee, comprised of physicians from different departments. The outcomes for the present analyses are a composite of MCVE, vascular mortality, and all-cause mortality. A composite of MCVE was established including stroke, myocardial infarction, retinal bleeding, retinal infarction, terminal heart failure, sudden death, fatal rupture of abdominal aneurysm.

Follow-up duration was defined as the period between enrolment and first MCVE, death from any cause, date of loss to follow-up, or the preselected date of 1 March 2014. Of the 7216 participants in this study, 419 patients (5.8%) were lost to follow-up due to migration or withdrawal from the study; these patients were censored.

Risk factors and medical treatment of risk factors

Cardiovascular risk factors and the use of medication (antithrombotic, lipid-lowering, or blood pressure-lowering medication) were recorded at baseline, using a standardized diagnostic protocol consisting of a questionnaire, physical examination and laboratory testing in a fasting state. Risk factors measured in this study included age, sex, smoking, pack years, body-mass index (BMI), LDL-c, systolic blood pressure, presence of diabetes mellitus, estimated glomerular filtration rate (eGFR) and duration of CVD. LDL-c in mmol/l was estimated using the Friedewald formula up to triglycerides of 9 mmol/L[18]. Systolic blood pressure was measured every 4 minutes during a total of 25 minutes in supine

position at the right brachial artery until March 1999 and 2 times in the sitting position at the right and left upper arms from March 1999 onward. In both situations, the highest mean of the blood pressure measurements on one arm was taken. Diabetes mellitus was defined as use of glucose lowering-therapy, self-reported diabetes mellitus, or two times a fasting glucose >7.0 mmol/l. eGFR was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations.[19]

Clinical manifest and subclinical atherosclerosis

Clinical manifest vascular disease was registered at baseline (e.g. coronary, cerebrovascular, peripheral artery disease and aortic abdominal aneurysm). Screening for subclinical atherosclerosis comprised of multiple clinical and radiological measurements. Direct measurements of subclinical atherosclerosis were defined as a carotid intima-media thickness (cIMT) >0.9 mm[20], an ankle-brachial index (ABI) <0.9 or greater than 1.3, and an asymptomatic carotid artery stenosis of >50%. With subclinical atherosclerosis-associated measurements were chronic kidney disease (CKD), and a pulse pressure >60mmHg (PP). CKD was defined as either 1) an eGFR <45, 2) an eGFR <60 with >30mg/g albuminuria, or 3) any eGFR with >300mg/g albuminuria.

Data analyses

For the descriptive analysis of baseline characteristics in different time periods, year of vascular screening was split into groups of three years, where in further analyses inclusion year as determinant is used as a continuous variable.

Data of cardiovascular risk factors were missing for systolic blood pressure in 17 patients (0.2%), for glucose measurement in 23 patients (0.3%), for diabetes mellitus status in 19 patients (0.3%), for smoking and pack-years in 42 patients (0.6%), for eGFR in 11 patients (0.2%), and for albuminuria in 258 patients (4%). For atherosclerotic burden, IMT was missing in 208 patients (3%), carotid artery stenosis in 136 patients (2%), ABI in 55 patients (0.8%) and pulse pressure in 48 patients (0.7%). Missing data for risk factors and subclinical atherosclerosis were singly imputed by weighted probability matching on the basis of multivariable regression using covariate and outcome data. Trends in cardiovascular risk factor and subclinical atherosclerosis prevalence were plotted. Crude incidence rates for vascular mortality, all-cause mortality, myocardial infarction, stroke and the composite endpoint of MCVE were calculated stratified for year of vascular screening. To evaluate the effect of cardiovascular risk factors, medication use, subclinical atherosclerosis and duration of CVD on the incidence rates of MCVE and all-cause mortality, adjustment was performed with Poisson regression in multiple models In addition, stratified analyses were performed for different groups of CVD-patients separately (i.e. coronary artery disease, cerebrovascular disease, peripheral artery disease, abdominal aneurysm and polyvascular). To check whether possible non-proportionality during long-term follow-up did not meaningfully influence the results, a sensitivity analysis was performed in

which observations were censored after five year follow-up. All statistical analyses were conducted using R version 3.2.0.

Results

Baseline characteristics

Data of 7,216 patients with a history of CVD included in the SMART cohort between 1996 and 2014 were used for the present analyses. Mean age was 60 ±10 years and 74% of patients were male (table 1). A total of 1,190 recurrent MCVE and 1,324 deaths occurred during a median follow-up of 6.5 (IQR 3.3 - 9.9) years.

Change in prevalence of cardiovascular risk factors between 1996-2014

The percentage of current smokers declined from 43% in 1996 to 25% in 2014 (figure 1). Systolic blood pressure declined from 147 ± 20 mmHg in 1996 to 134 ± 18 mmHg in 2014. The use of blood pressure lowering drugs increased from 59% to 75%. Plasma concentrations of LDL-c declined from 3.7 ± 1.0 mmol/l in 1996 to 2.5 ± 0.9 mmol/l in 2014. The use of lipid-lowering drugs increased from 30% in 1996 to 79% 2014. Mean BMI of patients slightly increased from 26.3 kg/m^2 in 1996 to 27.1 kg/m^2 in 2014.

Change in prevalence of subclinical atherosclerosis between 1996-2014

In the period 1996-2014, the prevalence of asymptomatic carotid artery stenosis decreased from 33% to 6%. In the same period, the prevalence of high IMT >0.9 mm was unchanged: 52% in 1996-1998 and 46% in 2012-2014.The prevalence of CKD decreased from 18% in 1996 to 9% in 2014. The prevalence of ABI <0.9 or >1.3 decreased from 39% in 1996 to 18% in 2014. The prevalence of pulse pressure >60 mmHg, an indicator of arterial stiffness, decreased from 61% in 1996 to 30% in 2014 (figure 1, supplemental table 1).

Change in incidence rates of recurrent MCVE and all-cause mortality for different time periods between 1996-2014

Incidence rates for recurrent MCVE decreased in the period 1996 to 2014 by 53% for recurrent MCVE from 3.68 to 1.73 events per 100 person-years (PY), by 82% for vascular mortality from 2.57 to 0.47 events per 100 PY, and by 82% for all-cause mortality from 4.55 to 0.82 events per 100 PY. Incidence in recurrent MCVE decreased in patients with coronary artery disease, cerebrovascular disease, peripheral artery disease and polyvascular disease, but remained the same for patients with abdominal aortic aneurysm (figure 2; supplemental table 2).

Table 1: Patient characteristics of the study population at baseline according to inclusion periods

	1996-1998	1999-2001	2002-2004	2005-2007	2008-2010	2011-March 2014
	(n = 748)	(n = 1178)	(n = 1333)	(n = 1529)	(n = 1369)	(n = 1059)
Number of fatal and non-fatal vascular events / Person years	284 / 7,724	347 / 12,086	255 / 11,591	175 / 10,603	100 / 5,969	29 / 1,677
Age (y)	61.3 (10.7)	59.9 (10.3)	58.7 (10.5)	59.8 (10.4)	60.8 (10.0)	60.4 (9.9)
Sex (Male)	553 (74%)	915 (78%)	976 (73%)	1,103 (72%)	1,005 (73%)	767 (72%)
Never smoked	120 (16%)	205 (17%)	264 (20%)	334 (22%)	310 (23%)	266 (25%)
History of smoking	309 (41%)	524 (44%)	605 (45%)	775 (51%)	669 (49%)	531 (50%)
Current smoking	319 (43%)	449 (38%)	464 (35%)	420 (27%)	390 (28%)	262 (25%)
Smoking (pack-years)	25 (20)	24 (20.4)	21 (20)	19 (20)	19 (20)	18 (18)
Body mass index (kg/m^2)	26 (3.7)	26 (4)	27 (4)	27 (4)	27 (4)	27 (4)
Diabetes mellitus	175 (23%)	247 (21%)	300 (23%)	349 (23%)	297 (22%)	216 (20%)
Systolic blood pressure (mmHg)	147 (20)	139 (22)	143 (22)	141 (21)	137 (20)	134 (18)
Diastolic blood pressure (mmHg)	79 (11)	80 (11)	83 (12)	83 (11)	81 (11)	79 (11)
Hypertension	611 (82%)	998 (85%)	1,167 (88%)	1,357 (89%)	1,200 (88%)	887 (84%)
Blood pressure-lowering agents	439 (59%)	821 (70%)	973 (73%)	1,200 (78%)	1,092 (80%)	790 (75%)
Anti-platelet / anti-coagulant agents	544 (73%)	866 (74%)	1,040 (78%)	1,322 (86%)	1,260 (92%)	932 (88%)
Statin use	225 (30%)	531 (45%)	896 (67%)	1,178 (77%)	1,138 (83%)	834 (79%)
Total cholesterol (mmol/l)	5.8 (1.1)	5.5 (1.2)	5.0 (1.1)	4.4 (1)	4.5 (1.1)	4.5 (1.1)
HDL-C (mmol/l)	1.1 (0.3)	1.1 (0.3)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)
LDL-C (mmol/l)	3.7 (1.0)	3.4 (1.0)	2.9 (1.0)	2.5 (1.0)	2.6 (0.9)	2.5 (0.9)
Triglycerides (mmol/l)	2.0 (1.2)	2.1 (2.1)	1.8 (1.1)	1.5 (1.3)	1.4 (0.9)	1.6 (1.1)
eGFR (CKDepi)	73 (19)	76 (18)	77 (18)	76 (18)	75 (17)	79 (17)

All data are displayed as mean ± SD, median (interquartile range) or number (%). HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol.

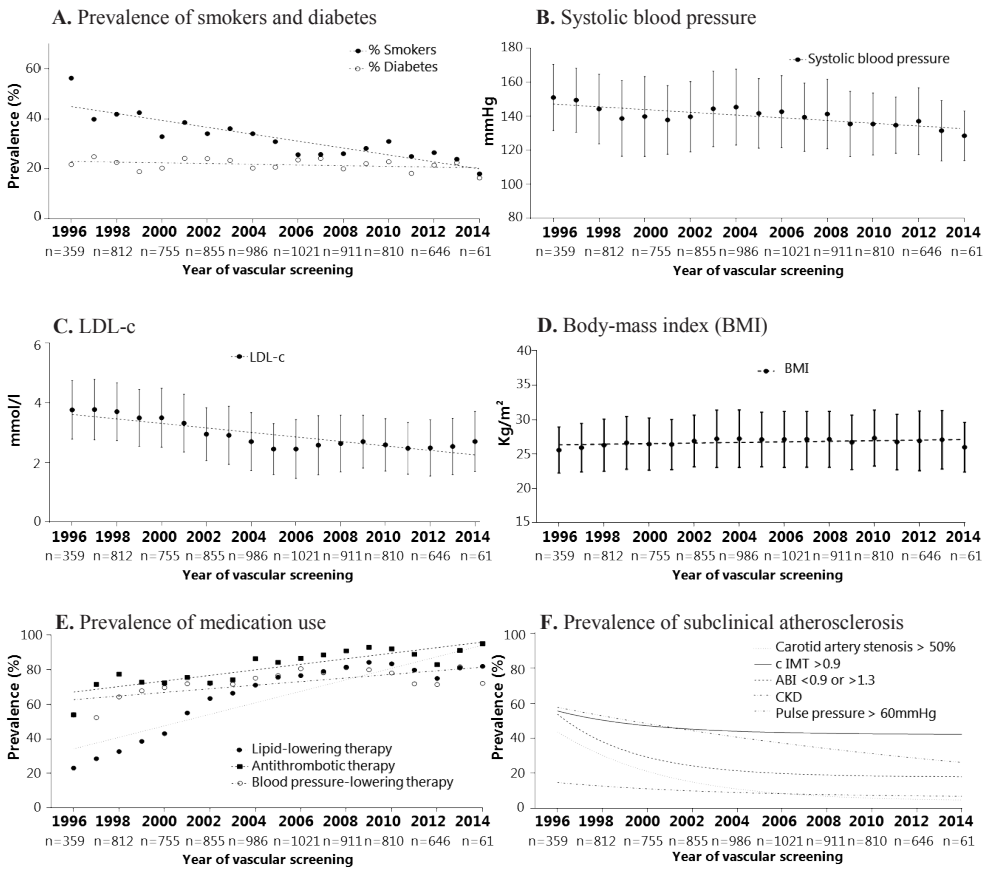


Figure 1: Trends in risk factors (A, B, C and D), risk factor management (E) and subclinical atherosclerotic burden (F) at baseline.

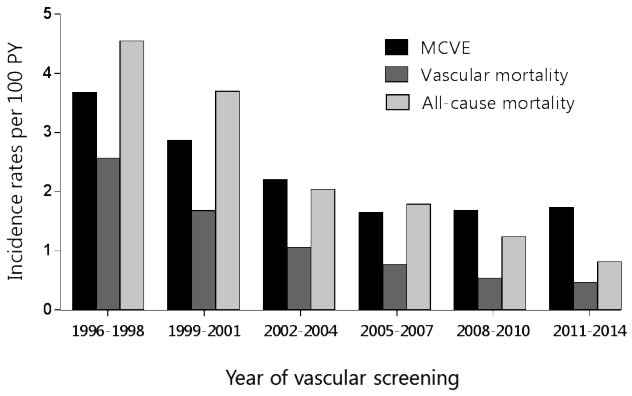


Figure 2: Crude incidence rates of recurrent major cardiovascular events.

Rate ratios of MCVE and all-cause mortality adjusted for changes in risk factor, medication use and subclinical atherosclerosis in different time periods between 1996-2014

The risk for recurrent MCVE adjusted for age and sex changed with -7% per year (rate ratio of 0.93; 95%CI 0.91-0.94). After additional adjustment for risk factors, medication use and subclinical atherosclerosis, the change in risk for recurrent MCVE was -4% per year (adjusted rate ratio 0.96; 95%CI 0.95-0.98). Thus, for MCVE a risk reduction of 3% per year (36% of total) could be explained by changes in risk factors, medication use and subclinical atherosclerosis (figure 3; supplemental table 3).

For vascular mortality, additional adjustment for risk factors, medication use and subclinical atherosclerosis compared to adjustment for age and sex changed the risk from -13% to -7% per year (adjusted rate ratio 0.93; 95%CI 0.91-0.96). Thus, for vascular mortality a risk reduction of 6% per year (49% of total) could be explained by changes in risk factors, medication use and subclinical atherosclerosis.

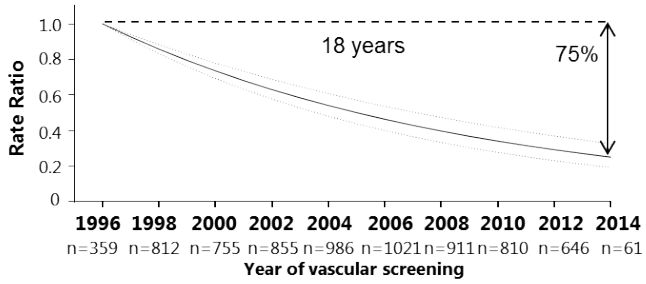
For all-cause mortality, additional adjustment for risk factors, medication use and subclinical atherosclerosis compared to adjustment for age and sex changed the risk from -11% to -6% per year (rate ratio 0.94; 95%CI 0.93-0.96). Thus, for all-cause mortality a risk reduction of 5% per year (48% of total) could be explained by changes in risk factors, medication use and subclinical atherosclerosis (figure 3; supplemental table 3).

For myocardial infarction and stroke separately, similar results were seen as for MCVE after additional adjustment for risk factors, medication use and subclinical atherosclerosis compared to adjustment for age and sex (supplemental table 4).

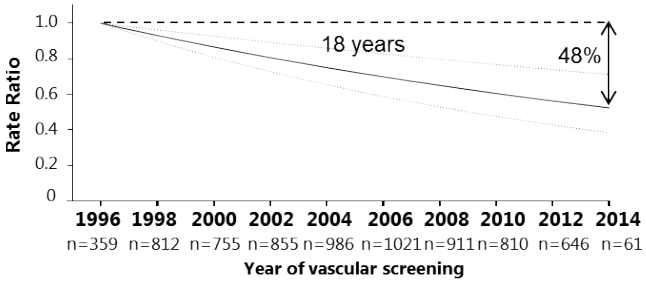
Sensitivity analyses limiting the follow-up to 5 year for each patient after inclusion showed similar results for recurrent MCVE (adjusted rate ratio 0.96; 95%CI 0.93-0.98), for vascular mortality (adjusted rate ratio 0.95; 95%CI 0.92-0.98) and for all-cause mortality (adjusted rate ratio 0.97; 95%CI 0.95-1.00) adjusted for age, sex, cardiovascular risk factors, medication use and subclinical atherosclerosis (supplemental table 5).

Discussion

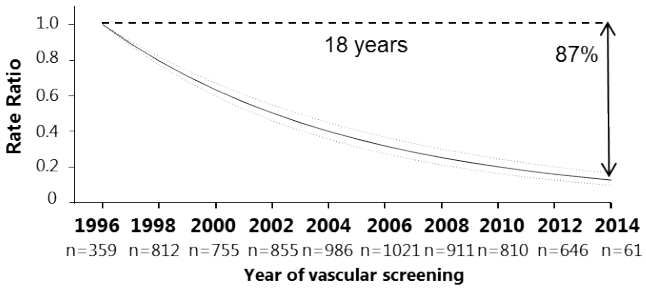
In this cohort study, the risk of recurrent vascular events in patients with clinical manifest vascular disease declined with 53% in the period between 1996 and 2014. The risk of vascular and all-cause mortality both decreased with 82%. These reductions are similar in patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease and polyvascular disease. In patients with abdominal aortic aneurysm a decrease in risk of recurrent events was not observed, possibly due to a small number of patients. During this period, the prevalence of risk factors and prevalence of subclinical atherosclerosis (carotid artery stenosis, cIMT, CKD, ABI, and pulse pressure) declined as well. The observed reductions in recurrent vascular events and all-cause mortality could only partially



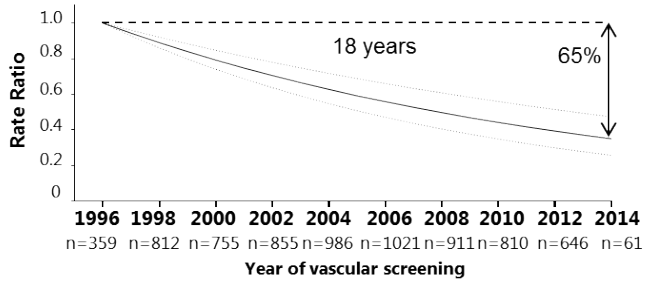
A. Age and sex adjusted rate ratios for recurrent MCVE



B. Risk factor, medication use and subclinical atherosclerosis adjusted rate ratios for recurrent MCVE



C. Age and sex adjusted rate ratios for all-cause mortality



D. Risk factor, medication use and subclinical atherosclerosis adjusted rate ratios for all-cause mortality

Rate ratios (continues line) and 95%CI (dotted line). Reference year of vascular screening is 1996.

Figure 3: Rate ratios of recurrent major cardiovascular events and all-cause mortality in the period 1996 - 2014.

be explained by improved risk factor management and changes in the prevalence of subclinical atherosclerosis.

In the present study, the reduced risk of recurrent CVD is partially explained by improved risk factor management including a decline in the prevalence of smoking as well as a reduction of concomitant subclinical atherosclerosis indicating less advanced stages of atherosclerosis at the time of a clinical vascular event. As expected, over the years, evidence based improvements in risk factor management have resulted in improved outcome after a first cardiovascular event.[3,21 14] The improvement of risk factor management is further supported by the unchanged risk of recurrent events in patients with abdominal aortic aneurysms. In these patients stratified analyses of risk factor levels and prevalence by year of vascular screening showed less improvement in risk factor management (data not shown).

EUROASPIRE studies reported similar improved risk factor management and reduced prevalence of risk factors in different time periods (1994-1995, 1999-2000, 2006-2007, and 2012-2013).[13,22] For example, from 1999 and 2000, the prevalence of hypertension (systolic blood pressure >140 and/or diastolic blood pressure >90 mmHg) decreased from 54% to 45% when compared to 2012-2013. The prevalence of LDL-c >2.5 mmol/l decreased by 62% (from 96% to 34%) over the period 1994-2013, as a result of increased use of lipid-lowering therapy in general (18% to 90%) and in the use of high intensity statin regimens (23% to 45%) [13,22]. This is in line with the findings in the present study regarding risk factor prevalence and risk factor management, illustrating the potential gain from adherence to lipid guidelines. In the primary prevention this potential gain from better adherence to guidelines is even larger.[23] The change in prevalence of risk factors and improved risk factor management could be a reflection of improved adherence to guidelines such as the Recommendations of the Task Force of European and other Societies on Coronary Prevention[24,25], lower blood pressure targets, availability of statins, more attention to a healthy life-style, and public health campaigns encouraging to stop smoking.

Besides improved risk factor management and lower risk of recurrent events, it has been shown that the amount of atherosclerotic burden predicts MCVE.[26] In the present study we observed a decreasing atherosclerotic burden at the time of a clinical manifestation of vascular disease in the period 1996 to 2014. Lower atherosclerotic burden at the time of diagnosis could be a reflection of the absolute reduction in risk factors, lower exposure time to risk factors, or a reflection of enhanced detection of cardiovascular disease in an earlier stage of disease. For example, in patients suspected of coronary artery disease troponin has been implemented as a sensitive diagnostic biomarker for the diagnosis of myocardial infarction.[27] Therefore, smaller myocardial infarctions may be detected, which were previously undetected, in patients with less atherosclerotic burden.

An important finding in our study is the still large unexplained reduction in recurrent MCVE after adjustment for cardiovascular risk factors and subclinical vascular disease. A clearer understanding of this unexplained risk reduction could provide new opportunities

to further decrease MCVE risk in patients with clinical manifest vascular disease. Although it could be speculated that part of the unexplained risk reduction could be related to unmeasured improved lifestyle changes such as lower salt intake, less saturated fatty acids or increased physical activity.[28,29] Also, technical improvements in cardiovascular interventions (such as drug-eluting stents), and more frequent performance or revascularization may have contributed to lower risk. Early detection and improved techniques may contribute to a lower need for re-interventions and/or a lower risk for cardiovascular events after an intervention.[30] Despite the large relative reduction in the risk of recurrent MCVE, the incidence in patients with clinical manifest vascular disease remains high. In the present study the recurrent MCVE risk was 1.7 per 100PY, which translates to a 17% 10-year risk. Therefore, it remains of major importance to identify those patients at the highest risk for recurrent MCVE,[31] and find (new) targets for risk reduction. The latest ESC/EAS guidelines of the management of dyslipidaemias suggest even lower LDL-c targets (<1.8 mmol/l for patients with CVD) and stricter life-style recommendations than previous guidelines. Also, drug adherence is an important issue in these guidelines, with important suggestions to improve the adherence to (multiple) drug therapies. These recommendations should further decrease future MCVE-risk.[32]

Incidence of cardiovascular events in patients with and without CVD in the Netherlands decreased by 51% for men and 46% for women between 1997 and 2007. This decrease in CVD is explained for 32% by improved secondary prevention and for 44% by improvement in emergency medicine and is in line with our findings in our cohort.[33] The similarity of findings in our SMART cohort and the Dutch population, show that the SMART cohort is a good representation of patients with manifest vascular disease. Therefore, the findings of our study are generalizable to a population with clinical manifest vascular disease.

The strengths of this study includes the prospective nature of the cohort, yearly inclusion of patients over a substantial time period, long follow-up, and the use of standardized diagnostic protocol, which enabled the direct comparison of risk factors and prevalence of subclinical atherosclerosis in patients included in different time periods without bias due to changed measurement techniques. Some limitations of the study should be considered. Risk factors and subclinical atherosclerosis were only measured at baseline and may have changed during follow-up. However, patients included at the start of the cohort would have had more or improved risk factor therapy during follow-up, which would have led to fewer events during follow-up. Therefore, the event rates of these patients might be underestimated. The actual decrease in risk between patients included at the start of the cohort and patients included later might therefore have been even larger than observed in our study.

Secondly, the measurements used to estimate subclinical atherosclerosis in patients are surrogate, dichotomized measures. This does not completely reflect the biological process and progress of atherosclerosis in patients.

Lastly, the number of patients and number of events in the stratified analyses for different vascular locations are small, especially the group of patients with an AAA. This makes it more difficult to draw conclusions based on these subgroups and should be taken with caution.

In conclusion, in patients with clinically manifest arterial disease, the risk of recurrent MCVE between 1996 and 2014 strongly decreased. This was partially due to lower risk factors and lower prevalence of subclinical atherosclerosis. However, 10-year risk for recurrent events in patients with clinical manifest vascular disease remains high (average 17%) and a better understanding of the in part unexplained reduction in recurrent MCVE may provide new treatment targets.

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References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-128.
2. Haro JM, Tyrovolas S, Garin N, et al. The burden of disease in Spain: results from the global burden of disease study 2010. *BMC Med* 2014; **12**: 236.
3. Murray J, Saxena S, Millett C, Curcin V, de Lusignan S, Majeed A. Reductions in risk factors for secondary prevention of coronary heart disease by ethnic group in south-west London: 10-year longitudinal study (1998-2007). *Family practice* 2010; **27**(4): 430-8.
4. Desai NR, Bradley SM, Parzynski CS, et al. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary Intervention. *Jama* 2015; **314**(19): 2045-53.
5. Capewell S, Beaglehole R, Seddon M, McMurray J. Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. *Circulation* 2000; **102**(13): 1511-6.
6. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004; **109**(9): 1101-7.
7. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. *Circulation* 2015; **132**(11): 997-1002.
8. Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. *Heart* 1999; **81**(4): 380-6.
9. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *The New England journal of medicine* 2002; **347**(18): 1397-402.
10. Sundararajan V, Thrift AG, Phan TG, Choi PM, Clissold B, Srikanth VK. Trends over time in the risk of stroke after an incident transient ischemic attack. *Stroke; a journal of cerebral circulation* 2014; **45**(11): 3214-8.
11. Hotchkiss JW, Davies CA, Dundas R, et al. Explaining trends in Scottish coronary heart disease mortality between 2000 and 2010 using IMPACTSEC model: retrospective analysis using routine data. *BMJ* 2014; **348**: g1088.
12. Kumbhani DJ, Fonarow GC, Cannon CP, et al. Temporal trends for secondary prevention measures among patients hospitalized with coronary artery disease. *The American journal of medicine* 2015; **128**(4): 426 e1-9.
13. Kotseva K, De Bacquer D, Jennings C, et al. Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999-2013. *Glob Heart* 2016.
14. Tisminetzky M, McManus DD, Gore JM, et al. 30-year trends in patient characteristics, treatment practices, and long-term outcomes of adults aged 35 to 54 years hospitalized with acute myocardial infarction. *The American journal of cardiology* 2014; **113**(7): 1137-41.
15. Solberg LA, Strong JP. Risk factors and atherosclerotic lesions. A review of autopsy studies. *Arteriosclerosis* 1983; **3**(3): 187-98.
16. Greenland P, Abrams J, Aurigemma GP, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. *Circulation* 2000; **101**(1): E16-22.
17. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. *European journal of epidemiology* 1999; **15**(9): 773-81.
18. Tremblay AJ, Morrissette H, Gagne JM, Bergeron J, Gagne C, Couture P. Validation of the Friedewald formula for the determination of low-density lipoprotein cholesterol compared with beta-quantification in a large population. *Clin Biochem* 2004; **37**(9): 785-90.
19. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Annals of internal medicine* 2012; **156**(11): 785-95, W-270, W-1, W-2, W-3, W-4, W-5, W-6, W-7, W-8.

20. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European heart journal* 2007; **28**(12): 1462-536.
21. Howard VJ, Furie KL, Wang CH, Sides EG, Toole JF. The changing risk factor profile of participants enrolled in a secondary stroke prevention trial: Vitamin intervention for stroke prevention. *Neuroepidemiology* 2006; **27**(4): 222-9.
22. Reiner Z, De Bacquer D, Kotseva K, et al. Treatment potential for dyslipidaemia management in patients with coronary heart disease across Europe: findings from the EUROASPIRE III survey. *Atherosclerosis* 2013; **231**(2): 300-7.
23. De Backer G, De Bacquer D, Ryden L, et al. Lifestyle and risk factor management in people at high cardiovascular risk from Bulgaria, Croatia, Poland, Romania and the United Kingdom who participated in both the EUROASPIRE III and IV primary care surveys. *European journal of preventive cardiology* 2016; **23**(15): 1618-27.
24. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Atherosclerosis* 1998; **140**(2): 199-270.
25. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *European heart journal* 2003; **24**(17): 1601-10.
26. Lundberg C, Johansson L, Barbier CE, Lind L, Ahlstrom H, Hansen T. Total atherosclerotic burden by whole body magnetic resonance angiography predicts major adverse cardiovascular events. *Atherosclerosis* 2013; **228**(1): 148-52.
27. Ebell MH, Flewelling D, Flynn CA. A systematic review of troponin T and I for diagnosing acute myocardial infarction. *J Fam Pract* 2000; **49**(6): 550-6.
28. Kastarinen M, Laatikainen T, Salomaa V, et al. Trends in lifestyle factors affecting blood pressure in hypertensive and normotensive Finns during 1982-2002. *Journal of hypertension* 2007; **25**(2): 299-305.
29. Alageel S, Wright AJ, Gulliford MC. Changes in cardiovascular disease risk and behavioural risk factors before the introduction of a health check programme in England. *Prev Med* 2016; **91**: 158-63.
30. Naito R, Miyauchi K, Shitara J, et al. Temporal Trends in Clinical Outcomes Following Percutaneous Coronary Intervention in Patients with Renal Insufficiency. *J Atheroscler Thromb* 2016; **23**(9): 1080-8.
31. Goff DC, Jr., 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 2): S49-73.
32. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European heart journal* 2016; **37**(39): 2999-3058.
33. Koopman C, Vaartjes I, van Dis I, et al. De bijdrage van preventie en behandeling in sterfte aan coronaire hartziekten in Nederland tussen 1997 en 2007: naar geslacht. In: Van Dis I, Buddeke J, Vaartjes I, Visseren FLJ, Bots ML. Hart- en vaatziekten in Nederland 2015, cijfers over heden, verleden en toekomst. Den Haag: Hartstichting, 2015.

Supplemental table 1: Subclinical atherosclerosis at baseline for different time periods of vascular screening.

	1996-1998	1999-2001	2002-2004	2005-2007	2008-2010	2011- March 2014
	(n = 748)	(n = 1,178)	(n = 1,333)	(n = 1,529)	(n = 1,369)	(n = 1,059)
Coronary Artery disease	160 (21.4%)	505 (42.9%)	615 (46.1%)	888 (58.1%)	749 (54.7%)	547 (51.7%)
Cerebrovascular disease	179 (23.9%)	222 (18.9%)	276 (20.7%)	321 (21.0%)	293 (21.4%)	258 (24.4%)
Peripheral vascular disease	165 (22.1%)	173 (14.7%)	174 (13.1%)	125 (8.2%)	108 (7.9%)	80 (7.6%)
Aneurysm of abdominal aorta	45 (6.0%)	65 (5.5%)	63 (4.7%)	28 (1.8%)	33 (2.4%)	31 (2.9%)
Polyvascular disease	199 (26.6%)	213 (18.1%)	205 (15.4%)	167 (10.9%)	186 (13.6%)	143 (13.5%)
Carotid artery stenosis <50%	500 (67.3%)	889 (76.8%)	1,119 (86.2%)	1,396 (94.1%)	1,252 (92.5%)	985 (94.4%)
Carotid artery stenosis >50% and <70%	30 (4.0%)	52 (4.5%)	36 (2.8%)	19 (1.3%)	25 (1.9%)	19 (1.8%)
Carotid artery stenosis >70%	213 (28.7%)	217 (18.7%)	143 (11.0%)	69 (4.7%)	77 (5.7%)	39 (3.7%)
Increased IMT (>0.9 mm)**	385 (51.5%)	558 (47.4%)	619 (46.4%)	660 (43.2%)	506 (37.0%)	489 (46.2%)
Kidney function* causing low CVD risk	508 (67.9%)	819 (69.5%)	910 (68.3%)	1,068 (69.9%)	1,009 (73.7%)	820 (77.4%)
Kidney function* causing moderate CVD risk	148 (19.8%)	234 (19.9%)	284 (21.3%)	334 (21.8%)	250 (18.3%)	169 (16.0%)
Kidney function* causing high CVD risk	68 (9.1%)	97 (8.2%)	114 (8.6%)	105 (6.9%)	98 (7.2%)	60 (5.7%)
Kidney function* causing very high CVD risk	24 (3.2%)	28 (2.4%)	24 (1.8%)	22 (1.4%)	12 (0.9%)	10 (0.9%)
Abnormal ABI (<0.9 or >1.3)***	288 (39.3%)	349 (30.1%)	346 (26.1%)	319 (20.9%)	243 (17.8%)	188 (17.9%)
Increased pulse pressure (>60mmHg)	453 (61.0%)	477 (40.7%)	567 (42.5%)	597 (39.1%)	462 (34.1%)	308 (29.5%)

*Classification according to KDIGO clinical practise. Kidney function causing low CVD risk: eGFR >60 and <30 mg/g albuminuria; Kidney function causing moderate CVD risk: (eGFR 45-59 and <30 mg/g albuminuria) or (eGFR >60 and 30-300 mg/g albuminuria); Kidney function causing high CVD risk: (eGFR 30-44 and <30mg/g albuminuria) or (eGFR 45-59 and 30-300 mg/g albuminuria) or (eGFR >60 and >300mg/g albuminuria); Kidney function causing very high CVD risk: (eGFR <30) or (eGFR 30-45 and >30 mg/g albuminuria) or (eGFR 45-59 and >300mg/g albuminuria). **IMT: Intima media Thickness; ***ABI: Ankle-brachial index.

Supplemental table 2: Incidence rates per 100 person-years of recurrent cardiovascular disease stratified for different inclusion diagnosis.

	1996-1998	1999-2001	2002-2004	2005-2007	2008-2010	2011- March 2014
	(n = 748)	(n = 1,178)	(n = 1,333)	(n = 1,529)	(n = 1,369)	(n = 1,059)
Composite of major events						
All patients (n = 7,216)	3.68 (284)	2.87 (347)	2.20 (255)	1.65 (175)	1.68 (100)	1.73 (29)
Coronary artery disease (n = 3,464)	2.44 (48)	2.05 (117)	1.57 (90)	1.51 (94)	1.35 (45)	2.40 (20)
Cerebrovascular disease (n = 1,549)	2.85 (57)	2.82 (63)	2.02 (48)	1.21 (28)	1.70 (21)	0.68 (3)
Peripheral artery disease (n = 825)	3.01 (52)	2.04 (38)	1.86 (28)	1.67 (14)	1.03 (5)	0.00 (0)
Abdominal aortic aneurysm (n = 265)	4.44 (18)	4.98 (27)	4.37 (20)	0.51 (1)	3.52 (5)	6.65 (3)
Polyvascular disease (n = 1,113)	6.71 (109)	5.88 (102)	4.55 (69)	3.62 (38)	3.10 (24)	1.33 (3)
Vascular mortality						
All patients (n = 7,216)	2.57 (218)	1.68 (220)	1.06 (130)	0.77 (84)	0.54 (33)	0.47 (8)
Coronary artery disease (n = 3,464)	1.10 (24)	0.77 (48)	0.55 (33)	0.60 (38)	0.32 (11)	0.35 (3)
Cerebrovascular disease (n = 1,549)	1.76 (38)	1.46 (36)	1.02 (26)	0.59 (14)	0.39 (5)	0.23 (1)
Peripheral artery disease (n = 825)	2.37 (45)	1.43 (28)	0.82 (16)	0.58 (5)	0.61 (3)	0.00 (0)
Abdominal aortic aneurysm (n = 265)	3.28 (15)	4.25 (24)	3.05 (15)	0.51 (1)	1.99 (3)	4.17 (2)
Polyvascular disease (n = 1,113)	5.38 (96)	4.45 (84)	2.54 (43)	2.36 (26)	1.35 (11)	0.88 (2)
All-cause mortality						
All patients (n = 7,216)	4.55 (386)	3.07 (402)	2.04 (251)	1.79 (195)	1.24 (76)	0.82 (14)
Coronary heart disease (n = 3,464)	2.20 (48)	1.58 (98)	1.23 (74)	1.46 (93)	0.91 (31)	0.58 (5)
Cerebrovascular disease (n = 1,549)	3.75 (81)	3.03 (75)	1.93 (49)	1.48 (35)	1.02 (13)	0.90 (4)
Peripheral artery disease (n = 825)	4.47 (85)	3.33 (65)	2.15 (34)	2.32 (20)	1.83 (9)	0.00 (0)
Abdominal aortic aneurysm (n = 265)	6.12 (28)	7.26 (41)	4.47 (22)	2.53 (5)	1.99 (3)	4.17 (2)
Polyvascular disease (n = 1,113)	8.07 (144)	6.52 (123)	4.26 (72)	3.81 (42)	2.46 (20)	1.33 (3)

Numbers are given as incidence rates per 100 PY (number of events)

Supplemental table 3: Rate ratios (95% CI) of recurrent major cardiovascular events for different locations of vascular disease at baseline.

	Rate ratios (95% CI)	
	Model 1	Model 2
Composite of major events		
All patients (n = 7,216)	0.93 (0.91-0.94)	0.96 (0.95-0.98)
Coronary heart disease (n = 3,464)	0.95 (0.92-0.97)	0.96 (0.93-0.99)
Cerebrovascular disease (n = 1,549)	0.95 (0.91-0.98)	1.00 (0.96-1.04)
Peripheral artery disease (n = 825)	0.91 (0.87-0.95)	0.94 (0.89-0.99)
Abdominal aortic aneurysm (n = 265)	0.98 (0.93-1.04)	0.98 (0.91-1.05)
Polyvascular disease (n = 1,113)	0.93 (0.90-0.95)	0.96 (0.93-0.99)
Vascular mortality		
All patients (n = 7,216)	0.87 (0.85-0.89)	0.93 (0.91-0.96)
Coronary heart disease (n = 3,464)	0.89 (0.85-0.92)	0.93 (0.89-0.97)
Cerebrovascular disease (n = 1,549)	0.91 (0.87-0.95)	0.97 (0.91-1.03)
Peripheral artery disease (n = 825)	0.85 (0.80-0.91)	0.89 (0.83-0.96)
Abdominal aortic aneurysm (n = 265)	0.96 (0.90-1.03)	0.97 (0.89-1.05)
Polyvascular disease (n = 1,113)	0.89 (0.86-0.92)	0.93 (0.89-0.96)
All-cause Mortality		
All patients (n = 7,216)	0.89 (0.88-0.91)	0.94 (0.93-0.96)
Coronary heart disease (n = 3,464)	0.91 (0.88-0.93)	0.95 (0.91-0.99)
Cerebrovascular disease (n = 1,549)	0.92 (0.89-0.95)	0.95(0.91-0.99)
Peripheral artery disease (n = 825)	0.91 (0.87-0.94)	0.93 (0.89-0.98)
Abdominal aortic aneurysm (n = 265)	0.94 (0.89-0.99)	0.95 (0.88-1.01)
Polyvascular disease (n = 1,113)	0.91 (0.88-0.93)	0.94 (0.91-0.97)

Model 1: Rate ratios adjusted for age and sex.
Model 2: Rate ratios adjusted for 10-year risk score including age, sex, current smoking, systolic blood pressure, diabetes mellitus, type of cardiovascular disease at inclusion, years since first diagnosis of vascular disease, HDL-c, total cholesterol, eGFR and hs-CRP, and for medication use and subclinical atherosclerosis.

Supplemental table 4: Rate ratios (95% CI) of recurrent myocardial infarction and stroke for different locations of vascular disease at baseline.

	Rate ratios (95% CI)	
	Model 1	Model 2
Myocardial infarction		
All patients (n = 7,216)	0.94 (0.92-0.96)	0.96 (0.94-0.98)
Coronary heart disease (n = 3,464)	0.96 (0.93-0.99)	0.96 (0.92-0.99)
Cerebrovascular disease (n = 1,549)	0.92 (0.87-0.98)	0.98 (0.92-1.06)
Peripheral artery disease (n = 825)	0.91 (0.85-0.98)	0.95 (0.88-1.02)
Abdominal aortic aneurysm (n = 265)	1.02 (0.93-1.11)	1.05 (0.94-1.17)
Polyvascular disease (n = 1,113)	0.95 (0.91-0.98)	0.97 (0.93-1.01)
Stroke		
All patients (n = 7,216)	0.93 (0.91-0.96)	0.98 (0.95-1.01)
Coronary heart disease (n = 3,464)	0.94 (0.88-0.99)	0.98 (0.95-1.05)
Cerebrovascular disease (n = 1,549)	0.97 (0.92-1.01)	0.99 (0.93-1.05)
Peripheral artery disease (n = 825)	0.93 (0.85-1.01)	0.94 (0.84-1.03)
Abdominal aortic aneurysm (n = 265)	1.01 (0.89-1.13)	1.01 (0.87-1.16)
Polyvascular disease (n = 1,113)	0.93 (0.88-0.98)	0.96 (0.91-1.03)

Model 1: Rate ratios adjusted for age and sex.
Model 2: Rate ratios adjusted for 10-year risk score including age, sex, current smoking, systolic blood pressure, diabetes mellitus, type of cardiovascular disease at inclusion, years since first diagnosis of vascular disease, HDL-c, total cholesterol, eGFR and hs-CRP, and for medication use and subclinical atherosclerosis.

Supplemental table 5: Rate ratios of recurrent major cardiovascular events for different locations of vascular disease at baseline with 5 year follow-up cut off.

	Rate ratios (95% CI)	
	Model 1	Model 2
Composite of major events		
All patients (n = 7,216)	0.92 (0.90-0.94)	0.96 (0.93-0.98)
Coronary heart disease (n = 3,464)	0.95 (0.92-1.00)	0.96 (0.92-1.01)
Cerebrovascular disease (n = 1,549)	0.93 (0.88-0.98)	0.96 (0.90-1.02)
Peripheral artery disease (n = 825)	0.91 (0.84-0.97)	0.92 (0.85-0.99)
Abdominal aortic aneurysm (n = 265)	0.96 (0.88-1.05)	0.96 (0.87-1.07)
Polyvascular disease (n = 1,113)	0.94 (0.91-0.98)	0.97 (0.93-1.01)
Vascular mortality		
All patients (n = 7,216)	0.88 (0.86-0.91)	0.95 (0.92-0.98)
Coronary heart disease (n = 3,464)	0.93 (0.87-1.00)	0.98 (0.91-1.06)
Cerebrovascular disease (n = 1,549)	0.93 (0.85-1.00)	0.97 (0.88-1.08)
Peripheral artery disease (n = 825)	0.84 (0.75-0.94)	0.87 (0.76-0.98)
Abdominal aortic aneurysm (n = 265)	0.95 (0.85-1.05)	0.97 (0.85-1.09)
Polyvascular disease (n = 1,113)	0.91 (0.86-0.95)	0.94 (0.89-0.99)
All-cause mortality		
All patients (n = 7,216)	0.92 (0.90-0.94)	0.97 (0.95-1.00)
Coronary heart disease (n = 3,464)	0.96 (0.91-1.01)	1.01 (0.96-1.06)
Cerebrovascular disease (n = 1,549)	0.98 (0.92-1.03)	0.99 (0.92-1.06)
Peripheral artery disease (n = 825)	0.92 (0.86-0.98)	0.94 (0.87-1.01)
Abdominal aortic aneurysm (n = 265)	0.95 (0.87-1.03)	0.95 (0.86-1.05)
Polyvascular disease (n = 1,113)	0.92 (0.89-0.96)	0.97 (0.93-1.01)

Model 1: Rate ratios adjusted for age and sex.
Model 2: Rate ratios adjusted for 10-year risk score including age, sex, current smoking, systolic blood pressure, diabetes mellitus, type of cardiovascular disease at inclusion, years since first diagnosis of vascular disease, HDL-c, total cholesterol, eGFR and hs-CRP, and for medication use and subclinical atherosclerosis.

3

Chapter 3

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

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Abstract

Aim - Although group-level effectiveness of lipid, blood pressure, glucose, and aspirin treatment for prevention of cardiovascular disease (CVD) has been proven by trials, important differences in absolute effectiveness exist between individuals. We aim to develop and validate a prediction tool for individualizing lifelong CVD prevention in people with T2DM predicting life-years gained without myocardial infarction or stroke.

Methods and results - We developed and validated the Diabetes Lifetime-perspective prediction (DIAL)- model, consisting of two complementary competing risk adjusted Cox proportional hazards functions using data from people with T2DM registered in the Swedish National Diabetes Registry (n=389,366). Competing outcomes were: 1) CVD-events (vascular mortality, myocardial infarction or stroke), 2) non-vascular mortality. Predictors were age, sex, smoking, systolic blood pressure, BMI, HbA1c, eGFR, Non-HDLc, albuminuria, T2DM duration, insulin treatment, history of CVD. External validation was performed using data from the ADVANCE, ACCORD, ASCOT and ALLHAT-LLT-trials, the SMART and EPIC-NL-cohorts, and the Scottish diabetes register (total n=197,785). Predicted and observed CVD-free survival showed good agreement in all validation sets. C-statistics for prediction of CVD were 0.83 (95%CI 0.83-0.84) and 0.64 to 0.65 for internal and external validation respectively. We provide an interactive calculator at www.U-Prevent.com that combines model predictions with relative treatment effects from trials to predict individual benefit from preventive treatment.

Conclusions - CVD-free life expectancy and effects of lifelong prevention in terms of CVD-free life years gained can be estimated for people with T2DM using readily available clinical characteristics. Predictions of individual-level treatment effects facilitate translation of trial results to individual patients.

Introduction

People with T2DM are at up to 2-fold increased risk for cardiovascular disease (CVD) compared to people without T2DM independently from other risk factors.[1] Estimated reductions in life expectancy and quality adjusted life years (QALYs) due to CVD are substantial in people with T2DM especially in people diagnosed with T2DM at young ages.[2, 3] International guidelines on CVD prevention recommend lipid-lowering, blood pressure-lowering, and glucose-lowering treatment to achieve the respective targets and for some patients also aspirin use.[4-6] More recently, new drugs have become available to further reduce the burden of CVD in patients with T2DM. These include PCSK9-inhibition, SGLT2-inhibibition and GLP1-analogues.[7,8] Guideline recommendations on the use of these preventive medications are based on the group-level effectiveness of such medication as shown in high-quality trials. Yet, important differences in absolute effectiveness are known to exist between individuals. Clinicians may struggle to identify individuals that benefit most from intensive and newer treatment options as the translation of group-level findings and recommendations to the individual patient level is extremely challenging. As individual effectiveness of preventive treatment is mainly determined by individual baseline CVD-risk, risk estimation could help to individualize treatment.[9] In general, people with higher individual cardiovascular risk will benefit more in absolute terms from lipid-lowering, glucose-lowering, or blood pressure lowering than people with a lower cardiovascular risk.

Therefore, the use of CVD risk prediction models for people with T2DM, such as the UKPDS, ADVANCE, Fremantle, and New Zealand Diabetes risk scores have been recommended in various national guidelines.[10-13] Yet, most existing prediction models predict five-year risks of CVD.[14]

Medications for prevention of CVD, on the other hand, are usually continued life-long and for most patients this means much longer than five years. Therefore, estimates of long-term CVD-risk and CVD-free life expectancy (i.e. expected number of remaining life-years without the occurrence of an incident or recurrent myocardial infarction or stroke) are usually more informative.[15, 16] Several lifetime-perspective models are already available for healthy individuals, but not for patients with T2DM.[17, 18]

The objective of the present study is to develop and externally validate a prediction tool (i.e. the Diabetes Lifetime-perspective prediction (DIAL)-model), for individualizing lifelong CVD prevention with lipid-lowering, anti-hypertensive, glucose-lowering, and aspirin treatment in people with T2DM by predicting treatment effects as gains in 10-year CVD-risk, lifetime risk, and CVD-free life expectancy. Notably, CVD-free life expectancy for a person with a history of CVD should be interpreted as time without recurrent myocardial infarction or stroke.

Methods

Sources of data

The Swedish National Diabetes Registry (NDR) and the Scottish Care Information (SCI) – Diabetes database are population wide registers. The secondary Manifestation of ARTerial disease (SMART) study and European Prospective Investigation into Cancer-Netherlands (EPIC-NL) are prospective cohort studies and Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE), Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Lipid Lowering Trial component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) are randomised controlled trials, all including people with T2DM. Study details have been described elsewhere.[19-27] The lifetime-perspective prediction model was developed in the Swedish NDR and externally validated in the remaining datasets. All use of data from registries, cohorts and trials were approved by institutional review boards and all participants gave written informed consent before taking part in the cohorts and trials. All studies complied with the Declaration of Helsinki.

Participants

Participants were people aged >18 years with a diagnosis of T2DM with or without prevalent CVD. People with a previous diagnosis of cancer (ICD-10 codes C00-C97) or stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate, eGFR <30 mL/min) were excluded. A comprehensive overview of the eligibility criteria and definition of T2DM used for the original cohorts and trials are provided in Supplemental table 1.

Outcomes

CVD was defined as a non-fatal myocardial infarction, non-fatal stroke, or vascular mortality. In the Swedish NDR and the SCI –Diabetes database, this is based on linkage to cause of death registers and hospital discharge registers using ICD-10 codes. All endpoint definitions of all studies are described in Supplemental table 1. Non-vascular mortality was defined as all deaths other than those with an identified cardiovascular cause as described in Supplemental table 1.

Predictors

Based on existing diabetes risk scores and availability in routine clinical practice, eleven selected predictors were: sex (female/male), current smoking (yes/no), systolic blood pressure (SBP in mmHg), body-mass index (BMI in kg/m^2), haemoglobin A1c (HbA1c) measured using the International Federation of Clinical Chemists (IFCC) reference method (in mmol/mol), eGFR estimated by the Chronic Kidney Disease Epidemiology Collaboration equation[28] (CKD-EPI in ml/min/1.73m^2), non-high-density lipoprotein cholesterol (non-

HDLc in mmol/l), albuminuria (no/micro/macro), duration of T2DM (years since diagnosis), insulin treatment (yes/no), history of CVD (yes/no).[10-13, 29] The number, proportion, and type of missing data, and methods dealing with missing data in each dataset are described in the supplementary appendix. No multicollinearity was detected between predictors.

Statistical analysis

Development of the lifetime model

A random sample of 75% of people from the Swedish NDR (n=292,024) was used as the development dataset. Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. Using these data, we developed two complementary Fine and Gray competing risk adjusted Cox proportional hazard models with left truncation and right censoring: one for the prediction of CVD events using non-vascular mortality as the competing endpoint (i.e. model part A), and another for the prediction of non-vascular mortality using CVD events as the competing endpoint (i.e. model part B). Cumulative CVD-free survival was calculated using the complementary models making use of life-tables with one-year time intervals (supplemental table 2). CVD-free life expectancy of an individual was defined as the median survival without myocardial infarction or stroke or death, which was the age where the estimated cumulative survival drops below 50%. 10-year CVD-risk was calculated by summation of the predicted cause-specific CVD risk in the first 10 years from a person's current age onwards. Similarly, lifetime risk was calculated by the summation of the predicted cause-specific CVD risk from a person's current age onwards until the maximum age of 95.[15, 30] A description of the statistical methods is described in the supplementary appendix. The sample size was more than sufficient by conventional assessment for prediction models with >1000 endpoints per variable.[31]

Model validation

Goodness of fit was assessed for vascular events, non-vascular mortality and the combined outcome of CVD-free survival separately using calibration plots for internal and external validation (supplementary appendix).[32] The models were recalibrated based on the incidence of CVD and incidence of non-vascular mortality using the expected versus observed ratio in data from all geographic regions. The logarithm of the expected versus observed ratio was subtracted from the linear predictor. Discrimination was quantified using c-statistics.

Prediction of individual treatment effect

We combined competing risk adjusted Cox proportional hazard function A for prediction of CVD with hazard ratios from randomised trials or meta-analyses to predict the individual treatment effect and lifetime benefit of treatment. The hazard ratio of smoking cessation on non-vascular mortality was added to competing risk adjusted Cox proportional hazard

function B when predicting the effect of smoking cessation. All other predicted treatment effects were assumed to have no effect on non-vascular mortality (i.e. lipid, blood pressure, glucose, and aspirin treatment). This method of calculating projected individual treatment effects has previously been applied by the American Heart Association and American College of Cardiology in their 'ASCVD risk estimator plus' based on the Pooled Cohort Equations for primary prevention.[18] By using life-tables, any gains in CVD-free survival is automatically adjusted for competing risks by increasing the time at risk for non-CVD mortality. In this study, we derived estimates of the effect of lipid-lowering, glucose-lowering, blood pressure-lowering, and aspirin treatment.[8, 33, 34] The hazard ratios for different medications used (statins, ezetimibe, PCSK9-inhibitors, antihypertensive medication, HbA1c-lowering, SGLT2-inhibitors, GLP1analogues, and aspirin) to estimate treatment effects are described in the supplementary appendix. We also derived estimates of the effect of smoking cessation. Smoking cessation was unlike drug therapy assumed to have an effect on both CVD and non-vascular mortality (i.e. cancer mortality).[35, 36]

The lifetime benefit of treatment for an individual person was calculated as the difference between the predicted median CVD-free life expectancy with and without treatment. Similarly, lifetime and 10-year absolute CVD-risk reduction for individual persons were estimated by calculating the difference between the predicted 10-year CVD-risk with and without treatment. 95% CI were calculated for the estimates, representing uncertainty of the model development and relative effects of trial results. This was performed using bootstrap techniques. However, due to computational issues, bags of little bootstraps were necessary. First, 100 random samples without replacement of n^0.8 = 292,024^0.8 = 23,569 patient were computed. In each random sample, 400 bootstrap samples were taken to obtain boundaries of 95% CIs. The average of all 100 upper and lower 95% CI gave the 95% confidence interval around the predicted estimates.[37]

Results

The selection of development and validation cohorts from the Swedish NDR is illustrated in Supplemental figure 1. Baseline characteristics of all study populations are described pooled by geographical origin in table 1, and stratified by original study cohort in Supplemental table 4.

Table 1. Baseline characteristics for study populations used in the DIAL model pooled by geographical origin.

	Derivation	Validation					
	NDR derivation	**NDR validation**	**Western-Europe**	**Eastern-Europe**	**North-America**	**Asia and Oceania**	**Scotland**
Group size	(n = 292,024)	(n = 97,342)	(n = 7,742)	(n = 2,142)	(n = 14,590)	(n = 5,580)	(n = 167,731)
Age (y)	65 (57-74)	65 (57-74)	65 (59-70)	65 (59-71)	63 (58-68)	65 (60-69)	60 (51-68)
Sex (Male)	164,672 (56%)	54,584 (56%)	5,074 (66%)	949 (44%)	8,488 (58%)	3,196 (57%)	96,989 (58%)
Current smoking	48,235 (17%)	16,206 (17%)	1,419 (18%)	377 (18%)	1,989 (14%)	741 (13%)	59,434 (35%)
Duration of diabetes mellitus (y)	2 (0-7)	2 (0-7)	2 (2-5)	7 (3-12)	6 (2-12)	7 (3-12)	0 (0-0)
Insulin treatment	49,388 (17%)	16,639 (17%)	606 (8%)	43 (2%)	3,587 (25%)	84 (2%)	16,373 (10%)
Systolic blood pressure (mmHg)	140 (128-150)	140 (128-150)	150 (137-164)	148 (135-163)	139 (127-150)	141 (128-155)	135 (125-145)
Body mass index (kg/m^2)	29 (26-33)	29 (26-33)	29 (26-32)	30 (27-33)	31 (28-35)	26 (24-29)	32 (28-36)
HbA1c (mmol/mol)	50 (44-59)	50 (44-59)	53 (45-64)	56 (46-69)	63 (55-73)	55 (48-67)	53 (46-65)
Non-HDL (mmol/L)	3.7 (3.0-4.5)	3.7 (3.0-4.5)	3.8 (3.1-4.6)	4.3 (3.6-5.1)	3.9 (3.1-4.6)	3.8 (3.1-4.6)	3.4 (2.7-4.3)
eGFR (mL/min/1.73m^2; CKD-EPI)	84 (68-96)	84 (68-96)	72 (61-86)	70 (59-83)	81 (67-94)	79 (65-92)	83 (68-96)
Micro-albuminuria	43,231 (15%)	14,668 (15%)	2,707 (35%)	560 (26%)	2,892 (20%)	1731 (31%)	24,631 (15%)
Macro-albuminuria	20,526 (7%)	6,832 (7%)	201 (3%)	99 (5%)	761 (5%)	276 (5%)	2,318 (1 %)
History of CVD	55,896 (19%)	18,674 (19%)	2,618 (34%)	771 (36%)	4,948 (34%)	1784 (32%)	24,853 (15%)

All data are shown as median (inter quartile range) or frequency (%). NDR: Swedisch National Diabetes Registry. Micro-albuminuria was defined as an albumin/creatinine ratio 3-30 mg/mmol or urine-albumin 20-300mg/l. Macro-albuminuria was defined as an albumin/creatinine ratio >30mg/mmol or urine-albumin >300mg/l.

Development of the DIAL model

The calculation formulae including the coefficients of the Cox proportional hazard functions, age-specific baseline survivals, and HRs of intended treatment of the model are provided in Supplemental table 5 and Supplemental table 6. The hazard ratios (HRs) for Cox proportional hazard functions A and B of the DIAL model are shown in table 2. Quadratic transformation of continuous predictors was applied for BMI, SBP, HbA1c, non-HDL-c, and eGFR for Cox proportional hazard function A (CVD) and for BMI, SBP, and BMI for Cox proportional hazard function B (non-vascular mortality). Interactions between age and sex, smoking, history of CVD, and treatment with insulin, were added to Cox proportional hazard function A and B. Due to the presence of competing risks, interactions with age and transformations of determinants the coefficients and hazard ratios as presented in table 2 should be interpreted with caution. For example, although the HR of history of CVD in model part B (non-vascular mortality) is 0.25, this should not be interpreted as a protective effect from an etiological perspective. More likely, from a prognostic perspective, increased incidence of vascular events in patients with a history of CVD simply results in a less frequent observation of non-vascular mortality. Also, since history of CVD interacts with age, the HRs are presented for a 65 year old patients and change with changing age. Furthermore, HRs need to be seen in combination with the age specific baseline hazards and are therefore difficult to interpret.

Table 2. Hazard ratios derived from a multi-variable model used in the DIAL model (see footnotes for definitions)

	Cox proportional hazard function A (vascular events)	**Cox proportional hazard function B (non-vascular mortality)**
	HR (95% CI)	**HR (95% CI)**
Male sex*	0.91 (0.88 - 0.94)*	0.89 (0.87 - 0.91)*
Current smoking*	1.04 (1.00 - 1.09)*	1.46 (1.43 - 1.50)*
Duration of T2DM (years)	1.02 (1.01 - 1.02)	1.01 (1.01 - 1.01)
Insulin therapy*	1.02 (0.98 - 1.06)*	1.04 (1.01 - 1.07)*
Systolic blood pressure (mmHg) **	1.06 (0.95 - 1.17)**	1.01 (0.93 - 1.10)**
Body mass index (kg/m^2)**	0.88 (0.81 - 0.97)**	0.89 (0.84 - 0.95)**
HbA1c (mmol/l) **	1.15 (1.05 - 1.26)**	1.00 (1.00 - 1.00)
non-HDL-c (mmol/l) **	1.16 (1.10 - 1.23)**	0.96 (0.92 - 1.00)**
eGFR (ml/min/1.73m^2)**	0.64 (0.60 - 0.69)**	0.99 (0.99 - 0.99)
Micro-albuminuria	1.18 (1.14 - 1.22)	1.17 (1.14 - 1.20)
Macro-albuminuria	1.23 (1.18 - 1.28)	1.24 (1.20 - 1.28)
History of cardiovascular disease	9.99 (9.63 - 10.36)*	0.25 (0.24 - 0.26)*

* Age-dependent variables. Hazard ratios are shown for the median age of 65 years.

** Transformed variables. Hazard ratios are shown for the 75 percentile versus the 25 percentile (Systolic blood pressure: 150 mmHg vs 128 mmHg; Body mass index: 33 kg/m^2 vs 26 kg/m^2; HbA1c: 59 mmol/l vs 44 mmol/l; eGFR: 96 ml/min vs 68 ml/min; Non-HDLc: 4.5 mmol/l vs 3.0 mmol/l).

Internal validation

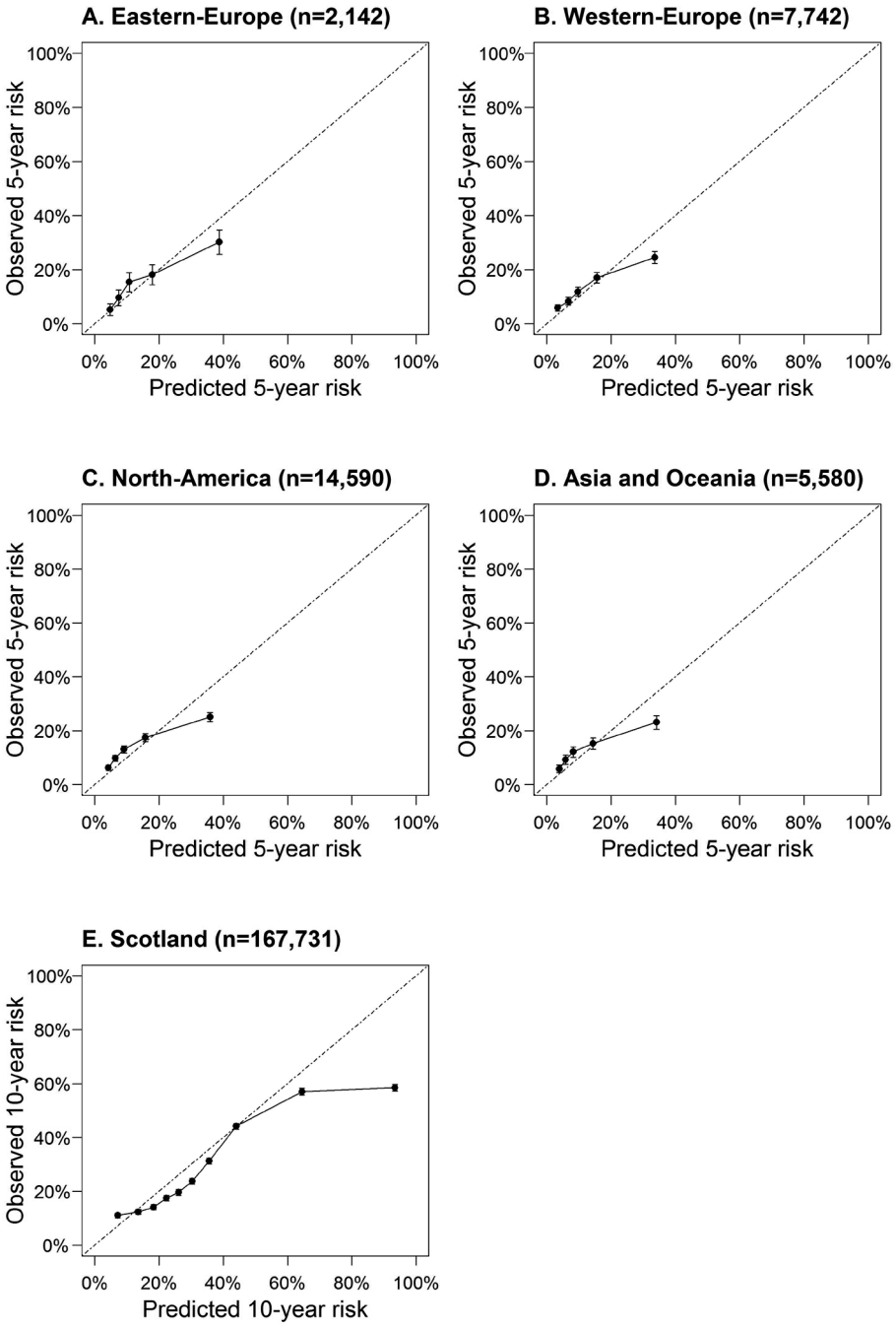
Predicted 10-year risk for CVD and all-cause mortality (CVD risk and non-vascular mortality risk combined) showed good agreement with the 10-year observed risk in the development dataset (Supplemental figure 2). The c-statistics were 0.83 (95% CI 0.83 to 0.84), 0.72 (0.72-0.73) and 0.77 (0.76-0.77) for 10-year CVD-risk, 10-year non-vascular mortality risk, and 10-year CVD-free survival respectively.

External validation

Predicted 5-year risk for CVD and all-cause mortality showed good agreement with the observed 5-year CVD-free survival in Western-Europe, Eastern-Europe, North-America and Asia and Oceania (figure 1). The c-statistic of the estimated 5-year CVD-risk was between 0.64 and 0.65 in all geographically pooled datasets. C-statistics for 5-year non-vascular mortality risk (range 0.59-0.67) and 5-year risk for CVD and all-cause mortality (range 0.64-0.69) are shown in Supplemental table 7. CVD event rates were higher in the Scottish Care Information –Diabetes database (17 per 1000 people per year) compared to the Swedish NDR (11 per 1000 people per year). After recalibrating the model for differences in predicted versus observed event rates, external validation in Scottish data showed good agreement between the predicted and observed 10-year risk for CVD and all-cause mortality (figure 1). Discrimination of 10-year CVD-risk was 0.64 (95% CI 0.64 to 0.65; Supplemental table 7).

Individual lifetime estimates and treatment effects for people with T2DM

An interactive calculator is provided at www.U-Prevent.com. Patient characteristics and current medication can be entered in this decision support tool to estimate individual risk and CVD-free survival. Also the individual effect from medication changes can be modelled in terms of CVD-free life years gained, absolute risk reduction and individual number needed to treat. Absolute treatment effects vary widely between individuals. As an example, we modelled that a combination therapy of simvastatin 40mg, ezetimibe 10mg and systolic blood pressure-lowering to 140mmHg, conferred between 0.04 (95% CI 0.01 - 0.04) and 12.5 (95% CI 11.0 - 21.2) years gained without CVD-events in people enrolled in the Swedish NDR. Treatment effect was lowest (<0.05 CVD-free years) in people who were 78 years or older, without a history of vascular disease, systolic blood pressure of <140mmHg, and LDL-c of <3.0 mmol/L at baseline. Treatment effect was highest (>10 CVD-free years) in people aged 55 to 70, with a history of vascular disease, systolic blood pressure >160 mmHg and LDL-c >3.0 mmol/L at baseline. As another illustration example, figure 2 shows the expected result of starting the same treatment (i.e. simvastatin 40 mg) in three different people with T2DM.



Predicted versus observed 5-year risk of CVD and all-cause mortality according to the DIAL-model in quintiles of risk in A) Eastern-Europe, B) Western-Europe, C) North-America, and D) Asia and Oceania. E) Predicted versus observed 10-year risk of CVD and all-cause mortality according to the DIAL-model in deciles of risk in Scotland.

Figure 1. Calibration plots in external dataset pooled by geographical region.

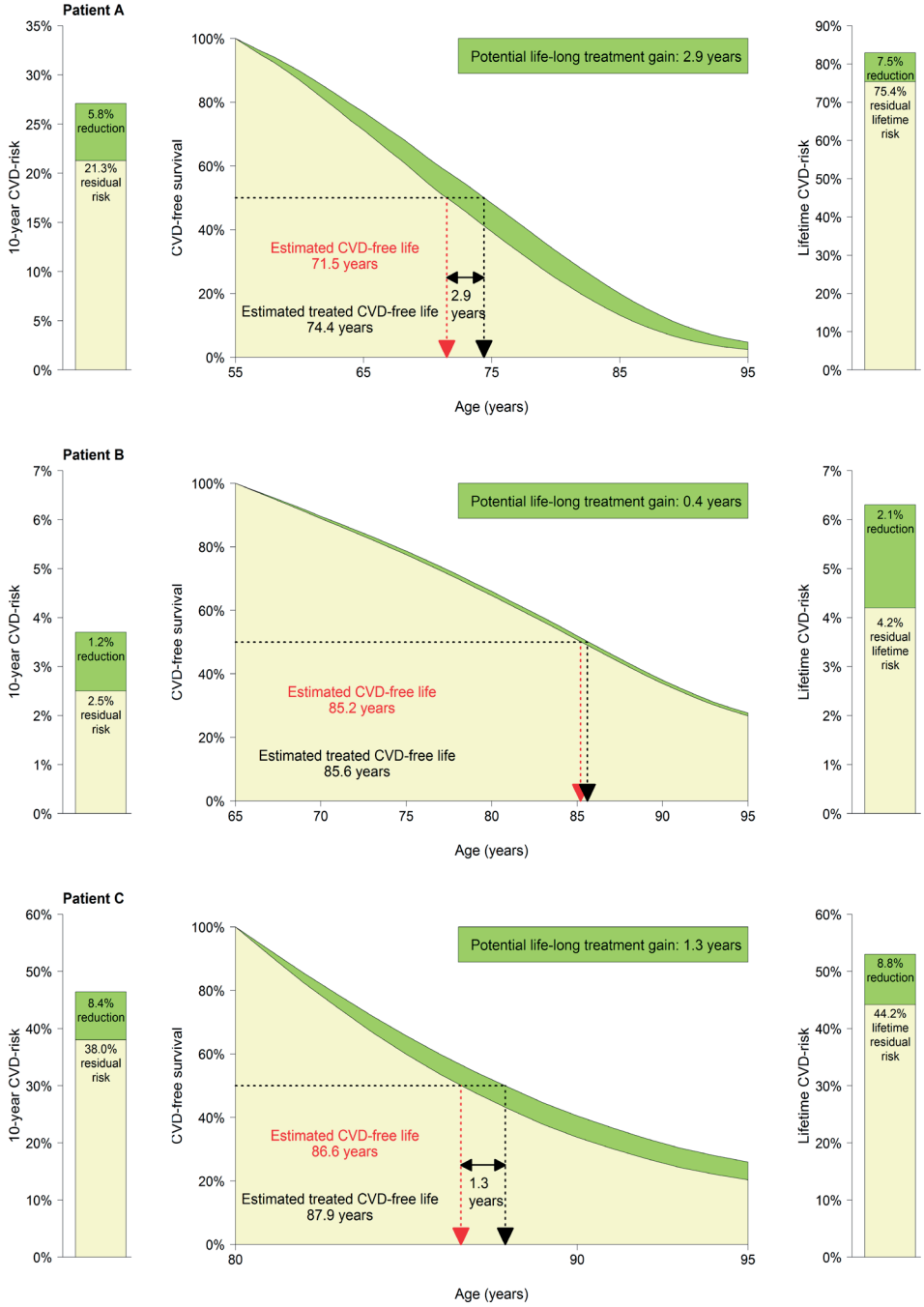


Figure 2. Examples of treatment effects of simvastatin 40 mg versus no treatment in people with different characteristics.

	Patient A	Patient B	Patient C
Age (years)	55	65	80
Sex	male	female	female
Smoking status	no	no	no
Duration of T2DM (y)	5	5	10
Insulin therapy	no	no	no
Systolic blood pressure (mmHg)	150	145	140
Body-mass index (kg/m^2)	27	27	30
HbA1c (mmol/mol)	55	55	55
Non-HDL-c (mmol/l)	5	6	5
eGFR (ml/min/1.73m^2)	70	70	60
Albuminuria	no	no	micro-albuminuria
History of CVD	yes	no	yes
LDL-c (mmol/l)	3.0	4.5	3.0
10 year-risk (%)	27.1 (20.1 - 31.5)	3.7 (2.7 - 4.6)	46.4 (37.9 - 53.4)
10-year ARR (%)	5.8 (4.4 - 6.7)	1.2 (0.9 - 1.6)	8.4 (7.0 - 9.4)
10-year NNT	17 (15 - 23)	83 (64 - 115)	12 (11 - 14)
CVD-free survival (y)	71.5 (70.0 - 73.9)	85.2 (84.2 - 86.6)	86.6 (85.6 - 87.7)
Lifetime gain free of CVD (y)	2.9 (2.3 - 3.4)	0.4 (0.3 - 0.6)	1.3 (0.9 - 1.5)
Lifetime CVD risk (% until 95 years)	82.9 (74.7 - 86.1)	6.3 (5.1 - 8.8)	53.0 (43.6 - 60.4)

Discussion

In this study we have developed and validated the DIAL model to predict CVD-free life expectancy, lifetime risk and 10-year CVD risk in people with T2DM using widely available patient characteristics. The novelty of this tool compared to previous models is that it not only predicts 5 of 10-year risk, but also long-term perspective outcomes. In addition the DIAL-model takes competing non-cardiovascular mortality into account and can, therefore, be used to estimate unbiased lifetime benefits of preventive treatment when combined with trial-findings. Therefore, the DIAL model may help clinicians to translate group-level trial findings to the individual patient. The interactive calculator at www.U-Prevent.com facilitates the actual use of the DIAL-model in clinical practice. We have validated the DIAL model in populations from different continents and have demonstrated that, after re-calibration, it has the potential to support medical decision-making for CVD prevention in people with T2DM in diverse populations. The discriminative ability of the model was moderate in each external validation dataset consistent with external validation of previous risk scores. For example validation of the ADVANCE risk score in EPIC-NL and SMART gave C-statistics of 0.62 and 0.68 respectively.[38] The cardiovascular event rate was higher in Scotland compared to Sweden, due to differences in multiple factors not taken into consideration in the model, including lifestyle differences. Recalibration of the DIAL

model allows it to be adapted for use in populations with varying levels of CVD risk. Users can choose to apply either the low-risk CVD event rate (based on the Swedish cohort, i.e. 11/1000 people per year) or the high-risk event rate (based on the Scottish cohort, i.e.17/1000 people per year), whichever is more appropriate for their population. Although calibration plots show an overestimation for patients at the highest risk, in clinical practice this is unlikely to lead to erroneous clinical decisions. Overestimation occurs in patients with 5-year risks of >20% (corresponding to 10-year risks of >40%). Even though overestimated, the true observed risk in these patients is still very high and should urge for intensive medical therapy anyway. Also, overestimation of risk in the high-risk patient category is not a specific limitation of the DIAL-model, but in line with previous validation studies of CVD-risk models in diabetes patients.[38]

Several studies have convincingly demonstrated the advantage of lifetime prediction compared to traditional 5-year or 10-year risk predictions. A microsimulation model based on 5-year follow-up of the Rotterdam Study showed that the gain in total CVD-free life expectancy increased as risk factor levels increased. The gain in total CVD-free expectancy decreased with advancing age, whereas 10-year risk for CVD mortality, and therefore 10-year risk reduction, increased with age.[39] In other primary prevention settings for example, smoking cessation at age 60, 50, 40, or 30 years resulted in about 3, 6, 9, and 10 years of life years gained respectively. This indicates that the highest lifetime benefit can be gained by reducing risk factors early in life, ideally with lifestyle interventions but, if necessary, with drug treatment.[40]

In clinical practice, prediction of lifetime benefit in CVD-free life years gained would enable patients (as well as clinicians) to better understand the potential benefits of treatment. Such information could help patients to participate in the decision-making process about treatment and may also motivate them to adhere to therapy. Clinicians and patients can balance the benefit and possible disadvantages of treatment, to decide whether preventive medication should be started or stopped. Also, the ability to estimate which preventive therapy is most effective (e.g. lipid-lowering, glucose-lowering, blood pressure-lowering, or aspirin treatment) can help to decide what treatment should be initiated first, and what treatment can be postponed or not prescribed to avoid excessive polypharmacy.

Using the concept of predicting lifetime benefit for making treatment decisions will result in changing characteristics of people eligible for treatment, towards higher proportions of younger people with higher risk factor levels. This group of people need to be treated over a longer period of time resulting in higher treatment costs. Prediction based treatment using the DIAL-model could theoretically also lead to higher cost-effectiveness of treatment on a group level. This, of course, should be confirmed by future cost-effectiveness studies. Also, it is not clear whether stopping treatment in older people would offset these costs and health economic analyses are required to investigate and to establish appropriate thresholds of minimum gain in life-years free of CVD.

The strengths of this study include the use of a large number of people from diverse cohorts. Since the Swedish and SCI –Diabetes database are registries with information for over 90% of people with T2DM in both countries, there is limited selection of people with T2DM, in contrast to trial populations.[41] Therefore, these registries are close to true representations of their populations and this increases the generalizability of the DIAL-model to clinical practice. Extensive validation of the DIAL model in large and diverse populations supports the use of the DIAL-model in people with T2DM without chronic kidney disease (eGFR <30) or metastatic cancer in different parts of the world. However, new external validation studies using data of other and new trials including T2DM patients could further enhance the validity of the DIAL-model.

Some limitations of the DIAL model should be considered. Although our model can guide the decision to start treatment for the prevention of CVD, it must be emphasized that there are other reasons for people with T2DM to start preventive therapy (e.g. prevention of neuropathy, retinopathy, diabetic nephropathy, or foot ulcers). The DIAL-model predictions do not incorporate these effects and may, therefore, underestimate the total treatment benefits. In addition, some people use preventive medication for other indications. For example, lipid lowering drugs are also used for monogenetic dyslipidaemias, antihypertensive drugs are used to reduce progression of aneurysms, and diuretics are used for heart failure. The DIAL-score may not be applicable to people with such co-morbidities. Additional risk factors such as socio-economic status, coronary calcium scores and ethnicity have not been incorporated in the model and may have improved performance. However, addition of more risk factors to prediction models generally only leads to minor improvements model performance.[42] Finally, the initial and most effective approaches to primary and secondary prevention of T2DM are lifestyle changes, such as sufficient physical activity, healthy diet and, where appropriate, weight loss. Clearly prediction of effects of lifestyle interventions would be valuable. However, it is currently not feasible to include lifestyle factors in prediction models given the lack of robust estimates of the effect size for lifestyle interventions from randomized controlled trials.

Other limitations of the methods used to develop and validate the DIAL model, and to estimate treatment effects should be acknowledged. Validation could only be performed for 10-year and 5-year predictions due to the limited follow-up in the included cohorts and trials. Lifetime estimates often go beyond 10-year predictions, and require the assumption that rates will be similar for a current 40 year old in 40 years' time to those of an 80 year old today. This is a major assumption but previous studies have shown that lifetime estimates based on the methods we used appear to apply for a survival of up to 17 years.[15] Nevertheless, longer-term validation would be preferable and will be possible as follow up data accrue in Sweden and Scotland. Also, the lifetime benefits are calculated assuming immediate, lifelong, successful (i.e. targets reached) and uninterrupted treatment from their current age onwards. The estimated treatment effects are the

maximum potential benefit with treatment (i.e. full adherence, usage as prescribed). In clinical practice treatment adherence to preventive medication is reported to be 50% primary and 66% in secondary cardiovascular prevention settings.[43] Yet the DIAL-model is intended to support medical decision-making by providing estimates about what a patient and health care professional can expect when adhering to a treatment as prescribed. The predicted treatment effects are based on the results of large randomized clinical trials in which adherence to treatment usually is about 80%. Furthermore, possible changes in risk factor levels over time were not taken into account. For example, blood pressure and cholesterol were assumed to remain stable over time. Therefore, re-evaluation of CVD-free survival and treatment effects after 5 to 10 years is advised based on our validation to ensure valid predictions to guide treatment decisions.

In conclusion, CVD-free life expectancy as well as the effect of lifelong lipid-lowering, glucose-lowering, blood pressure-lowering, and aspirin treatment in terms of CVD-free life years gained can be reliably predicted for people with T2DM using readily available characteristics. The DIAL model may facilitate personalized treatment and support shared decision-making and patients' motivation to adhere to prescribed drug-treatments to reduce CVD risk.

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References

1. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;**375**(9733):2215-22.
2. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. Jama 2003;**290**(14):1884-90.
3. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. Diabetes care 1998;**21**(7):1138-45.
4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF, American College of Cardiology/American Heart Association Task Force on Practice G. 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 2):S49-73.
5. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). European heart journal 2012;**33**(13):1635-701.
6. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Torbicki A, Wijns W, Windecker S, De Backer G, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Betteridge J, Ceriello A, Funck-Brentano C, Gulba DC, Kjekshus JK, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Reiner Z, Sattar N, Schachinger V, Scheen A, Schirmer H, Stromberg A, Sudzhaeva S, Viigimaa M, Vlachopoulos C, Xuereb RG. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). European heart journal 2013;**34**(39):3035-87.
7. Sattar N, Preiss D, Robinson JG, Djedjos CS, Elliott M, Somaratne R, Wasserman SM, Raal FJ. Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data. The lancet Diabetes & endocrinology 2016;**4**(5):403-10.
8. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: A systematic review and meta-analysis. Jama 2018;**319**(15):1580-1591.
9. Rabar S, Harker M, O'Flynn N, Wierzbicki AS, Guideline Development G. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ 2014;**349**:g4356.
10. Davis WA, Knuiman MW, Davis TM. An Australian cardiovascular risk equation for type 2 diabetes: the Fremantle Diabetes Study. Internal medicine journal 2010;**40**(4):286-92.
11. Elley CR, Robinson E, Kenealy T, Bramley D, Drury PL. Derivation and validation of a new cardiovascular risk score for people with type 2 diabetes: the new zealand diabetes cohort study. Diabetes care 2010;**33**(6):1347-52.

12. Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S, Chalmers J, Colagiuri S, Grobbee DE, Hamet P, Heller S, Neal B, Woodward M, Group AC. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil 2011;**18**(3):393-8.
13. Stevens RJ, Kothari V, Adler AI, Stratton IM. 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):671-9.
14. van Dieren S, Beulens JW, Kengne AP, Peelen LM, Rutten GE, Woodward M, van der Schouw YT, Moons KG. Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: a systematic review. Heart 2012;**98**(5):360-9.
15. Dorresteijn JAN, Kaasenbrood L, Cook NR, van Kruijsdijk RCM, van der Graaf Y, Visseren FLJ, Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj-Brit Med J 2016;**352**.
16. Leening MJ, Berry JD, Allen NB. Lifetime Perspectives on Primary Prevention of Atherosclerotic Cardiovascular Disease. Jama 2016.
17. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014;**100 Suppl 2**:ii1-ii67.
18. Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelser C, Gulati M, Masoudi FA, Goff DC, Jr. Estimating Longitudinal Risks and Benefits From Cardiovascular Preventive Therapies Among Medicare Patients: The Million Hearts Longitudinal ASCVD Risk Assessment Tool: A Special Report From the American Heart Association and American College of Cardiology. Circulation 2017;**135**(13):e793-e813.
19. Beulens JW, Monninkhof EM, Verschuren WM, van der Schouw YT, Smit J, Ocke MC, Jansen EH, van Dieren S, Grobbee DE, Peeters PH, Bueno-de-Mesquita HB. Cohort profile: the EPIC-NL study. Int J Epidemiol 2010;**39**(5):1170-8.
20. Committee AM. Study rationale and design of ADVANCE: action in diabetes and vascular disease--preterax and diamicron MR controlled evaluation. Diabetologia 2001;**44**(9):1118-20.
21. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, Investigators A. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;**366**(9489):895-906.
22. Group AS, Buse JB, Bigger JT, Byington RP, Cooper LS, Cushman WC, Friedewald WT, Genuth S, Gerstein HC, Ginsberg HN, Goff DC, Jr., Grimm RH, Jr., Margolis KL, Probstfield JL, Simons-Morton DG, Sullivan MD. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. The American journal of cardiology 2007;**99**(12A):21i-33i.
23. Gudbjornsdottir S, Cederholm J, Nilsson PM, Eliasson B, Steering Committee of the Swedish National Diabetes R. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes care 2003;**26**(4):1270-6.
24. Officers A, Coordinators for the ACRGTA, Lipid-Lowering Treatment to Prevent Heart Attack T. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Jama 2002;**288**(23):2981-97.
25. Patel A, Group AC, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;**370**(9590):829-40.
26. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. European journal of epidemiology 1999;**15**(9):773-81.
27. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. The New England journal of medicine 2008;**358**(24):2545-59.

28. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI. A new equation to estimate glomerular filtration rate. Annals of internal medicine 2009;**150**(9):604-12.
29. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjornsdottir S. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes care 2008;**31**(10):2038-43.
30. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics 2011;**67**(1):39-49.
31. Austin PC, Allignol A, Fine JP. The number of primary events per variable affects estimation of the subdistribution hazard competing risks model. J Clin Epidemiol 2017;**83**:75-84.
32. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;**21**(1):128-38.
33. Cholesterol Treatment Trialists C, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;**371**(9607):117-25.
34. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. Journal of hypertension 2017;**35**(5):922-944.
35. Gellert C, Schottker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. Arch Intern Med 2012;**172**(11):837-44.
36. Mons U, Muezzinler A, Gellert C, Schottker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, Kromhout D, Kuulasmaa K, Laatikainen T, O'Doherty MG, Bueno-de-Mesquita B, Orfanos P, Peters A, van der Schouw YT, Wilsgaard T, Wolk A, Trichopoulou A, Boffetta P, Brenner H, Consortium C. 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**:h1551.
37. Kleiner A, Talwalkar A, Sarkar P, Jordan MI. A scalable bootstrap for massive data. J R Stat Soc B 2014;**76**(4):795-816.
38. van der Leeuw J, van Dieren S, Beulens JW, Boeing H, Spijkerman AM, van der Graaf Y, van der AD, Nothlings U, Visseren FL, Rutten GE, Moons KG, van der Schouw YT, Peelen LM. The validation of cardiovascular risk scores for patients with type 2 diabetes mellitus. Heart 2015;**101**(3):222-9.
39. Ferket BS, van Kempen BJ, Heeringa J, Spronk S, Fleischmann KE, Nijhuis RL, Hofman A, Steyerberg EW, Hunink MG. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. PLoS Med 2012;**9**(12):e1001361.
40. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;**328**(7455):1519.
41. Saunders C, Byrne CD, Guthrie B, Lindsay RS, McKnight JA, Philip S, Sattar N, Walker JJ, Wild SH, Scottish Diabetes Research Network Epidemiology G. External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? Diabetic medicine : a journal of the British Diabetic Association 2013;**30**(3):300-8.
42. Austin PC, Pencinca MJ, Steyerberg EW. Predictive accuracy of novel risk factors and markers: A simulation study of the sensitivity of different performance measures for the Cox proportional hazards regression model. Stat Methods Med Res 2017;**26**(3):1053-1077.
43. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. The American journal of medicine 2012;**125**(9):882-7 e1.

Supplementary appendix

Expanded methods

Predictors and missing data.

Predictors were predetermined based on existing diabetes risk scores and availability in routine clinical practice. Baseline data for people registered in the Swedish NDR and SCI – Diabetes database were data collected in the first year after registration. In the other data sources, the baseline data were measured at study entrance prior to follow-up. Micro-albuminuria was defined as an albumin/creatinine ratio 3-30 mg/mmol or urine-albumin 20-300mg/l, and macro-albuminuria was defined as an albumin/creatinine ratio >30mg/mmol or urine-albumin >300mg/l. Prescriptions for preventive medication for CVD were not selected as a predictor, because this would interfere with the predictions of treatment effects of these medication.

In the Swedish National Diabetes Registry (NDR) proportions of missing data was 0% for age, sex, and outcome status, 15% for systolic blood pressure (SBP), 11% for Haemoglobin A1c (HbA1c), 12% for duration of T2DM, 22% for smoking status, 25% for body mass index (BMI), 21% for estimated glomerular filtration rate (eGFR), 31% for total cholesterol, 40% for high-density lipoprotein cholesterol (HDLc) and 42% for albuminuria. In the SCI –Diabetes database proportions of missing data were 0% for age, sex, and outcome status, 9% for SBP, 10% for HbA1c, 12% for eGFR, 22% for smoking status, 32% for non-HDLc, 35% for BMI, and 43% for albuminuria. Duration of T2DM was not missing, because the population was limited to an incident cohort. In SMART missing data for cholesterol, eGFR, history of CVD and albuminuria ranged from 0.05% to 6%. In EPIC-NL missing data was 1% for SBP and history of CVD, 3.6% for duration of T2DM, 11.5% for HbA1c, eGFR, cholesterol, HDLc, and 24.8% for type of diabetes treatment. In the ACCORD and ADVANCE-trial, missing data ranged from <1% for SBP to 4.5% for albuminuria. In the ASCOT-trial missing data was 8.3% for plasma glucose and 33.6% for eGFR. In the ALLHAT-LLT-trial missing data was <2.0% for BMI, cholesterol, HDLc, and eGFR, and 20.9% for plasma glucose. To account for missing data in the predictors, single imputation by predictive mean matching was used for each of the original cohorts separately (aregImpute in R, Hmisc package).[1]

In EPIC-NL, ASCOT, and ALLHAT-LLT, data was not available for duration of T2DM (ASCOT, ALLHAT-LLT), albuminuria (EPIC-NL, ALLHAT-LLT), treatment of T2DM with insulin (ASCOT, ALLHAT-LLT) and HbA1c. For cohorts where HbA1c was not measured for any participant (i.e. ALLHAT and ASCOT), values were estimated using available plasma glucose levels assuming measured glucose levels to be average glucose levels (Glucose (mmol/l) = 1.59*HbA1c (%) – 2.59, thus HbA1c (%) = (Glucose (mmol/l)+2.59)/1.59).[2] For all other missing predictors in the validation dataset, data were imputed to the median value of the Swedish NDR (i.e. 2.0 years duration of T2DM, 17% insulin treatment, 15% micro-albuminuria, and 7% macro-albuminuria).

Transformations and non-proportionality of predictors.

Log-linearity of the relationship between continuous predictors and the outcomes was tested with restricted cubic splines and transformations were applied when this improved model fit based on Akaike's Information Criterion. Quadratic transformation of continuous predictors was applied for BMI, SBP, HbA1c, non-HDL-c and eGFR for the CVD Cox proportional hazard function and for BMI, SBP, and BMI for the non-vascular mortality Cox proportional hazard function. Non-proportionality was observed for sex, smoking, history of CVD and treatment with insulin, in both parts of the Cox proportional hazard functions (i.e. for CVD and non-vascular mortality). These predictors are of increasing or decreasing importance with increasing age. Therefore, interactions with these predictors and age were included in the model. Supplemental figure 3 (CVD) and supplemental figure 4 (non-vascular mortality) visualize the HRs of transformed predictors and HRs of predictors depending on age.

Statistical analyses

Development of the lifetime model

Two complementary Fine and Gray competing risk adjusted Cox proportional hazard models with left truncation and right censoring: one for the prediction of CVD events using non-vascular mortality as the competing endpoint (i.e. model part A), and another for the prediction of non-vascular mortality using CVD events as the competing endpoint (i.e. model part B). Age was used as the time-scale and therefore people in the development dataset contributed data to the survival model from their age at study entry until the time of an event or censoring, defined by the age at study exit. As a result, estimates derived from these models are not limited by follow-up time but by the age distribution of study participants.[3 4] However, predictions are unstable where the number of people and number of events in a specific age group is limited. The age-range was therefore limited to between 30 and 95 years (number of people <30 years: 2,045, number of people >95 years: 2,501) for estimation of CVD-free life expectancy. The two competing risk adjusted Cox proportional hazard functions were then recalibrated based on the incidence of CVD and incidence of non-vascular mortality using the expected versus observed ratio. The age-specific baseline survival for both Cox proportional hazard functions were centered for continuous variables (BMI of 30 kg/m2, systolic blood pressure of 140 mmHg, non-HDLc of 3.8 mmol/l, HbA1c of 50 mmol/l, and eGFR of 80 ml/min) for practical reasons and to avoid rounding errors. The proportional hazards assumption was assessed by inspection of the correlation plots between scaled Schoenfeld residuals for the various predictors and age. Transformations and non-proportionality of predictors were described in the supplementary appendix. Where interaction existed between a predictor and age, the HR for that predictor is shown for the median age of 65 years. The HR for transformed predictors is shown for the 75th percentile versus the 25th percentile.

Predictions for individual persons

Calculations of CVD-free life expectancy (i.e. median survival without incident or recurrent myocardial infarction, stroke, or vascular death) were based on life-tables with one-year time intervals. An example of such a life-table for an individual person is shown in Supplemental table 2. Starting at the current age of an individual with T2DM, the risk of having a CVD-event (a_t) and the risk of dying from non-vascular causes (b_t) were predicted for each future life-year. Next, the cumulative CVD-free survival ($Surv_{t+1}$) was calculated by multiplying the survival probability at the beginning of each life-year ($Surv_t$) by the CVD-free survival probability during that year ($Surv_t - a_t - b_t$). Obviously the cumulative CVD-free survival started at 100% at the current age of a person. This process was repeated until the maximum age of 95 years. CVD-free life expectancy of an individual was defined as the median survival without myocardial infarction or stroke or death, which was the age where the estimated cumulative survival drops below 50%. 10-year CVD-risk was calculated by summation of the predicted cause-specific CVD risk in the first 10 years from a person's current age onwards. The cause-specific CVD-risk was obtained by multiplication of the chance of survival without a CVD-event at the beginning of each year ($Surv_t$) and the risk of having a CVD-event (a_t) during that year. Similarly, lifetime risk was calculated by the summation of the predicted cause-specific CVD risk from a person's current age onwards until the age of 95.

Validation

Internal validation of the lifetime model was performed in the remaining random sample of 25% of people in the Swedish NDR (n=97,342) for 10 year risk predictions. Although bootstrap-based internal validation would be the most efficient method for internal validation, we have chosen for the split-sample validation for feasibility reasons. Due to the large number of patients and endpoints per variable of >1000, this will not lead to biased results.[5]

External validation was performed using pooled cohorts based on geographical origin of people originating from the SCI –Diabetes database, SMART, EPIC-NL, ACCORD, ADVANCE, ASCOT, and ALLHAT cohorts. The selected regions were continents, with a subdivision for Europe. Five-year risks were predicted for Western-Europe, Eastern-Europe, North-America, Asia and Oceania, and 10 year risks for Scotland. Although Scotland is part of Western-Europe, this was a separate validation dataset, due to both the longer follow-up and the population-based nature of the dataset. In addition, the comparatively large number of people in Scotland's diabetes register overwhelmed the number of people in other countries in Western-Europe. Supplemental table 3 presents the number of people allocated from each original cohort to each pooled geographical cohort and the number of events occurred in each pooled cohort.

Relative treatment effects of meta-analyses and trials translated to lifelong treatment benefit in CVD-free life years gained

Lipid-lowering treatment:
The effect of lipid-lowering treatment on CVD depends on estimated reduction in low-density lipoprotein cholesterol (LDLc) compared to baseline. A reduction of 1 mmol/l LDLc is related to a hazard ratio of 0.78.[6 7] The percentage decrease of baseline LDLc for different statins and/or ezetimibe for people with T2DM are described in meta-analyses.[8 9] For proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, the percentage decrease of baseline LDLc is 59% in patients with T2DM.[10]

The individual expected relative risk reduction of CVD is calculated by $0.78^{\text{LDL-reduction in mmol/l}}$, where LDL-reduction in mmol/l is defined as Baseline LDL-c multiplied by the expected percentage LDL-c reduction due to intended treatment.

Blood pressure-lowering treatment:
The effect of blood pressure-lowering treatment is estimated as a hazard ratio of 0.74 per 10 mmHg for people with T2DM with a baseline blood pressure of 130mmHg or higher.[11] There is no relative risk reduction assumed of lowering blood pressure under 130 mmHg.[12] The individual expected relative risk reduction of CVD is calculated by $0.74^{(\text{Blood pressure reduction in mmHg}/10)}$, where blood pressure reduction in mmHg is the blood pressure of the patient minus the target blood pressure. This only applies for people with a blood pressure above 130 mmHg. The hazard ratio for blood pressure changes under 130mmHg is assumed to be 1.

Glucose-lowering treatment:
The effect of glucose-lowering treatment is estimated as a hazard ratio of 0.91 per 10 mmol/mol reduction in HbA1c.[13] There is no relative risk reduction assumed of lowering HbA1c under 53 mmol/mol. The individual expected relative risk reduction of CVD is calculated by $0.91^{(\text{HbA1c reduction in mmol per mol}/10)}$, where HbA1c reduction in mmol/mol is the HbA1c of the patient minus the target HbA1c. This only applies for HbA1c levels above 53 mmol/mol, whereas HbA1c changes under 53 mmol/mol correspond to a hazard ratio of 1. Besides HbA1c levels, individual effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) analogues can be estimated. The effect of SGLT2 inhibitors and GLP1 analogues are assumed to be independent of HbA1c levels. For SGLT2, the effect is estimated as a hazard ratio of 0.88. For GLP1, the effect is estimated as a hazard ratio of 0.91.[14]

Aspirin treatment:
The effect of aspirin treatment on CVD differs between people with and without a history of CVD. The hazard ratio of aspirin treatment in people without a history of CVD is 0.88 and for patient with a history of CVD 0.81.[15 16]

Smoking cessation:
Smoking cessation is assumed to reduce the hazard ratio for cardiovascular events of current smokers versus never smokers (hazard ratio 1.98) to that of ex-smokers versus never smokers (hazard ratio 1.18).[17] The resulting hazard ratio for cardiovascular events of current to ex-smoking, thus, is 0.60. Also, smoking cessation is assumed to reduce the hazard ratio for non-vascular mortality of current smokers versus never smokers (hazard ratio 1.83) to that of ex-smokers versus never smokers (hazard ratio 1.34).[18] The resulting hazard ratio for non-vascular mortality of current to ex-smoking, thus, is 0.73.

Combined individualized treatment effects:
The hazard ratios of lipid-lowering, blood pressure-lowering, and aspirin treatment are multiplied to calculate the relative individualized risk reduction for the combination of treatments. This hazard ratio of intended treatment is used in the Cox proportional hazard function for vascular events (A) as shown in supplemental table 5 for the estimation of individualized treatment effects.

Supplemental table 1. In- and exclusion criteria of the original cohorts and trials and definition of type 2 diabetes mellitus (T2DM).

In- and exclusion criteria of the study populations

	Inclusion criteria	Exclusion criteria
Swedish NDR[19]	People aged 18 years or older with T2DM, registered between 2002 and 2012	
Scottish Care Information – Diabetes database	People aged 18 years or older with T2DM, registered between January 2004 and June 2016.	
SMART[20]	People aged 18-79 years with T2DM, included between 1996 and 2015.	-Terminal malignancy -Not independent in daily activities (Rankin scale >3) -Not sufficiently fluent in Dutch - Estimated glomerular filtration rate (eGFR) < 30 ml/min
EPIC-NL[21]	People originated from the MORGEN and PROSPECT cohort. PROSPECT is a prospective cohort study among women aged 49–70. The MORGEN cohort consists of a general population sample of men and women aged 20–59 years. People with a confirmed diagnosis of T2DM were eligible for this study.	- Estimated glomerular filtration rate (eGFR) < 30 ml/min
ACCORD[22]	Patient aged 40-79 with T2DM	- A medical condition likely to limit survival to <3 years or a malignancy other than non-melanoma skin cancer within the past 2 years - Currently participating in another clinical trial - Estimated glomerular filtration rate (eGFR) < 30 ml/min
ADVANCE[23]	People aged 55 years and older with a diagnosis of T2DM at the age of 30 or older.	A definite indication for long-term insulin therapy. - Estimated glomerular filtration rate (eGFR) < 30 ml/min
ASCOT[24]	People aged 40-79 with T2DM and two other cardiovascular risk factors	Previous myocardial infarction, currently treated angina, heart failure, or a cerebrovascular event within the previous 3 months. - Estimated glomerular filtration rate (eGFR) < 30 ml/min
ALLHAT[25]	People aged 55 and older with T2DM	Symptomatic myocardial infarction or stroke within the past 6 months or diseases likely to lead to non-cardiovascular death over the course of the study - Estimated glomerular filtration rate (eGFR) < 30 ml/min

Definition of T2DM

Swedish NDR[19]	The definition of T2DM was treatment with 1) diet only, 2) oral hypoglycaemic agents only, or 3) insulin only or combined with oral agents, and onset age of diabetes ≥40 years
Scottish Care Information – Diabetes database	T2DM was defined using an algorithm which uses information from the clinician recorded diabetes type, prescription data (use of and timing of sulphonylureas and insulin) and age at diagnosis.
SMART[20]	A referral diagnosis of T2DM, self-reported T2DM, a fasting serum glucose ≥7.0 mmol/L at inclusion with initiation of glucose lowering treatment within one year, or the use of oral anti-hyperglycaemic agents or insulin at baseline. Participants with known type 1 diabetes mellitus were excluded.
EPIC-NL[21]	Diagnosis of T2DM was self-reported at baseline.
ACCORD[22]	1) Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/l. Casual was defined as any time of day without regard to time since last meal. The classic symptoms of T2DM include polyuria, polydipsia, and unexplained weight loss for ≥3 months. 2) Fasting plasma glucose ≥7.0 mmol/l. Fasting is defined as no caloric intake for at least 8 h for ≥3 months. 3) Stable diabetes therapy for >3 months. 4) An HbA1c level 7.5%-11% more than 3 months before randomization.
ADVANCE[23]	People diagnosed with non-insulin-dependent T2DM at age 30 years or older.
ASCOT[24]	1) Fasting plasma glucose ≥7 mmol/l and/or random glucose ≥11 mmol/l, 2) Self-reported T2DM and receiving dietary or drug therapy, or 3) Presence of both impaired fasting glucose (≥6 mmol/l) and glucosuria in absence of above two criteria.
ALLHAT[25]	History of treatment with insulin or oral hypoglycaemic agents during the 2 years preceding randomization, a fasting baseline glucose level >7.8 mmol/l, or a non-fasting baseline glucose level >11.1 mmol/l.

Definition of endpoints.

Swedish NDR[19]	Outcome evaluation: All CVD and non-cardiovascular causes of death endpoints were retrieved by data linkage with the Swedish Cause of Death Register and the Hospital Discharge Register (National Board of Health and Welfare, Sweden). CVD was defined as a myocardial infarction, stroke or vascular mortality (ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64).
	Myocardial infarction: Hospitalization due to non-fatal myocardial infarction or cardiac arrest. ICD-10 codes: I21, I46.0, I46.1, I46.9.
	Stroke: Hospitalization due to non-fatal stroke. ICD-10 codes: I61,I63, I64
	Cardiovascular mortality: ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64.
Scottish Care Information – Diabetes database	Outcome evaluation: All CVD and non-cardiovascular causes of death endpoints were retrieved by data linkage with the National Records of Scotland death registrations and the national hospitalization register (Scottish Morbidity Record, SMR01). CVD was defined as a myocardial infarction, stroke or vascular mortality (ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64).
	Myocardial infarction: Hospitalization due to non-fatal myocardial infarction or cardiac arrest. ICD-10 codes: I21, I46.0, I46.1, I46.9.
	Stroke: Hospitalization due to non-fatal stroke. ICD-10 codes: I61,I63, I64
	Cardiovascular mortality: ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64.
SMART[20]	Outcome evaluation: During follow-up, people were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. If a vascular event was reported, hospital discharge letters and results of laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evaluated by three members of the endpoint committee, comprising physicians from different clinical departments.
	Myocardial infarction: Fatal and non-fatal myocardial infarction, characterized by at least two of the following criteria: 1. Chest pain for at least 20 minutes not disappearing after administration of nitrates 2. ST-elevation >1 mm in two following leads or a left bundle branch block on the ECG * 3. CK elevation of at least two times the normal value of CK and an MB-fraction >5% of the total CK
	Stroke: Relevant clinical features which have caused an increase in handicap of at least one grade on the modified Rankin scale, accompanied by a fresh infarct on a repeat CT scan.
	Cardiovascular mortality: -Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms or within 24 hours given convincing circumstantial evidence -Death from ischemic stroke -Death from congestive heart failure -Death from myocardial infarction -Death from rupture of abdominal aortic aneurysm -Vascular death from other cause, i.e. sepsis following stent placement

EPIC-NL[21]	Outcome evaluation: Vital status was identified using the municipal population register with a loss-to-follow-up of 2.6%. For participants who died, information on the cause of death was obtained from Statistics Netherlands. Morbidity data were provided by the national hospital discharge register (HDR). Causes of death and morbidity have been coded according to the Ninth Revision of the International Classification of Diseases (ICD-9) until 1996, and after that according to the Tenth Revision of the International Statistical Classification of Diseases (ICD-10).
	Myocardial infarction: Hospitalization due to non-fatal myocardial infarction or cardiac arrest. ICD-10 codes I20-I25, I46 or ICD-9 code 410
	Stroke: Hospitalization due to stroke. ICD-10 codes I60-I63, I65, G45 or ICD-9 codes 430, 431, 432, 433, 434, 435
	Cardiovascular mortality: ICD-10 codes I20-I25, I46, I60-I63, I65, R96, G45 and ICD-9 codes 410, 430, 431, 432, 433, 434, 435
ACCORD[22]	Outcome evaluation: Outcomes were adjudicated by a central committee whose members were unaware of study-group assignments on the basis of predefined criteria.
	Myocardial infarction: The diagnosis of MI is based on the occurrence of a compatible clinical syndrome associated with diagnostic elevation of cardiac enzymes (ie, an increase in troponin T or troponin I to a level indicating myonecrosis and/or an increase in creatine-kinase–myocardial band to a level more than twice the upper limit of normal). Q-wave MI is defined as the development of new significant Q waves. Silent MI is diagnosed when new (compared with the previous 12-lead electrocardiogram) significant Q waves are detected by surveillance electrocardiography performed every 2 years and at study end in all participants.
	Stroke: Stroke is diagnosed by a focal neurologic deficit that lasts >24 hours, associated with evidence of brain infarction or haemorrhage by computed tomography, MRI, or autopsy.
	Cardiovascular mortality: Cardiovascular causes of death include fatal MI, congestive heart failure, documented arrhythmia, death after invasive cardiovascular interventions, death after non-cardiovascular surgery, fatal stroke, unexpected death presumed to be due to ischemic CVD occurring <24 hours after the onset of symptoms, and death due to other vascular diseases (eg, pulmonary emboli, abdominal aortic aneurysm rupture).
ADVANCE[23]	Outcome evaluation: An Endpoint Adjudication Committee, masked to treatment allocation, reviewed source documentation for all individuals who had a suspected primary endpoint or who died during follow-up. Outcomes were coded according to the 10th revision of the International Classification of Diseases.
	Myocardial infarction: ICD-10 codes I20-I25, I46
	Stroke: ICD-10 codes I60-I63, I65, G45
	Cardiovascular mortality: ICD-10 codes I20-I25, I46, I60-I63, I65, R96, G45
ASCOT[24]	Outcome evaluation: Each possible study endpoint was reviewed by at least two members of an independent Endpoint Committee blinded tot the study treatments following standardized study criteria, definitions and algorithms.
	Myocardial infarction: Non-fatal (including silent) myocardial infarction
	Stroke: Any stroke
	Cardiovascular mortality: Death due to any cardiovascular disease (not further specified)

ALLHAT[25]	Outcome evaluation: The diagnosis of an endpoint was classified by the physician-investigator at the clinical site based on death certificates or hospital discharge summaries. For a random 10% subset of hospitalized (fatal and nonfatal) myocardial infarctions and strokes, the Clinical Trials Center will request more detailed information. For this subset, in hospital ECGs and enzyme levels (for myocardial infarctions), and neurologists' reports and computed tomography (CT) or magnetic resonance imaging (MRI) reports (for strokes) will be evaluated by the study Endpoints Committee and the accuracy of the discharge diagnoses assessed.
	Myocardial infarction: Non-fatal myocardial infarction based on hospital discharge summaries classified by the physician investigator.
	Stroke: Non-fatal stroke based on hospital discharge summaries classified by the physician investigator.
	Cardiovascular mortality: Any death classified by the physician-investigator as caused due to cardiovascular disease.

Supplemental table 2. Example of a life-table.

Life years	Cumulative survival	% CVD risk	% non-CVD mortality
55	1.00	2.48%	0.11%
56	0.97	2.50%	0.13%
57	0.95	2.28%	0.13%
58	0.93	2.82%	0.15%
59	0.90	2.99%	0.18%
60	0.87	3.38%	0.20%
61	0.84	3.55%	0.23%
62	0.81	3.65%	0.27%
63	0.78	4.02%	0.26%
64	0.74	3.67%	0.32%
65	0.71	4.26%	0.37%
66	0.68	4.42%	0.42%
67	0.65	4.36%	0.45%
68	0.62	5.05%	0.51%
69	0.58	5.31%	0.60%
70	0.55	5.42%	0.62%
71	0.51	4.80%	0.72%
72	0.49	5.36%	0.79%
73	0.46	6.03%	0.92%
74	0.42	6.18%	0.99%
75	0.39	6.43%	1.22%
76	0.36	6.79%	1.32%
77	0.33	7.18%	1.54%
78	0.30	7.86%	1.79%
79	0.28	7.92%	1.92%
80	0.25	7.80%	2.33%
81	0.22	8.70%	2.51%
82	0.20	8.79%	2.87%
83	0.18	9.57%	3.29%
84	0.15	9.54%	3.91%
85	0.13	9.83%	4.28%
86	0.11	9.84%	4.83%
87	0.10	9.73%	5.42%
88	0.08	10.64%	6.01%
89	0.07	9.67%	6.46%
90	0.06	9.51%	6.89%
91	0.05	9.31%	7.47%
92	0.04	8.94%	7.83%
93	0.03	7.24%	7.58%
94	0.03	6.14%	7.94%

Life-table is of patient example A (figure 2), a 55-year old male, who does not smoke, T2DM since 5 years, a systolic blood pressure of 150 mmHg, BMI of 27 kg/m2, HbA1c of 55 mmol/mol, Non-HDL-c of 5 mmol/l, eGFR of 70 ml/min/1.73m2, no albuminuria, and a history of CVD. This patient has a median survival free of CVD of 71.5 years and a 10-year CVD-risk of 27.1%.

Supplemental table 3. Number of people, recruitment period, follow-up, and number of events.

Study characteristics				Development		Geographical validation				
Cohort	**Recruit-ment period**	**Follow-up (years)**	**People after exclusion**	**Derivation**	**Internal validation**	**Wesern-Europe**	**Eastern-Europe**	**North-America**	**Asia & Oceania**	**Scotland**
Swedish NDR (n=419,533)	2002-2012	6.1 (4.1 to 8.5)	389,366	292,024	97,342					
SMART (n=1,910)	1996-2014	6.8 (3.5 to 10.5)	1,876			1,876				
EPIC (n=524)	1993-1997	14.5 (12.1 to 15.9)	522			522				
ACCORD (n=10,251)	2001-2003	4.8 (4.0 to 5.7)	10,242					10,242		
ADVANCE (n=11,139)	2001-2002	5.0 (4.5 to 5.7)	11,062			2,921	2,126	433	5,580	
ASCOT (n=4,646)	1998-2000	5.5 (5.0 to 6.0)	4,629			2,354				
ALLHAT (n=3,903)	1994-1998	4.6 (3.8 to 5.7)	3,865					3,865		
SCI –Diabetes database (n=167,731)	2004-2016	5.3 (2.0 to 8.0)	167,731							167,731
		CVD events		21,910 (8%)	7,352 (8%)	935 (12%)	243 (11%)	1,540 (11%)	575 (10%)	15,288 (9%)
		Non-vascular deaths		45,579 (16%)	15,093 (16%)	562 (7%)	92 (4%)	285 (5%)	183 (3%)	11,576 (7%)

NDR: National Diabetes Registry; SMART: Secondary Manifestation of ARTerial disease study; EPIC-NL: European Prospective Investigation into Cancer-Netherlands; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and vascular disease: preterAx and diamicroN-MR Controlled Evaluation; ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial; ALLHAT-LLT: Lipid Lowering Trial component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. SCI: Scottish Care Information.
Follow-up years are shown as median (inter quartile range).

Supplemental table 4. Baseline characteristics of original cohort and trial data.

	Swedish NDR	SMART	EPIC-NL	ACCORD	ADVANCE	ASCOT	ALLHAT-LLT	SCI –Diabetes database
Group size	(n = 394,152)	(n = 1,910)	(n = 524)	(n = 10,251)	(n = 11,139)	(n = 4,646)	(n = 3,903)	(n = 167,731)
Age (y)	65 (57-74)	61 (54-68)	59 (53-64)	62 (58-67)	66 (61-70)	64 (58-70)	65 (60-71)	60 (51-68)
Sex (Male)	221,372 (56%)	1,329 (70%)	95 (18%)	6,299 (61%)	6,406 (58%)	3,306 (71%)	1,869 (48%)	96,989 (58%)
Current smoking	65,135 (17%)	466 (24%)	129 (25%)	1,429 (14%)	1,682 (15%)	887 (19%)	500 (13%)	59,434 (35%)
Duration of diabetes mellitus (y)	2 (0-7)	2 (2-2)	5 (2-11)	10 (5-15)	7 (3-11)	2 (2-2)	2 (2-2)	0 (0-0)
Insulin treatment	67,872 (17%)	455 (24%)	125 (24%)	3,582 (35%)	159 (1%)	0 (0%)	0 (0%)	16,373 (10%)
Systolic blood pressure (mmHg)	140 (128-150)	143 (130-157)	140 (127-156)	135 (125-147)	144 (130-158)	163 (152-176)	146 (137-158)	135 (125-145)
Body mass index (kg/m^2)	29 (26-33)	28 (25-32)	29 (26-32)	32 (28-36)	28 (25-31)	30 (27-33)	30 (27-34)	32 (28-36)
HbA1c (mmol/mol)	50 (44-59)	51 (44-61)	62 (50-77)	65 (60-74)	55 (48-66)	49 (41-63)	52 (41-70)	53 (46-65)
Non-HDL (mmol/L)	3.7 (3.0-4.5)	3.5 (2.8-4.4)	3.5 (3.0-4.2)	3.5 (2.9-4.2)	3.8 (3.2-4.6)	4.4 (3.7-5.1)	4.6 (4.1-5.1)	3.4 (2.7-4.3)
eGFR (CKD-EPI)	84 (67-96)	79 (64-92)	100 (92-108)	83 (69-95)	75 (62-88)	67 (59-77)	74 (62-87)	83 (68-96)
Micro-albuminuria	59,301 (15%)	452 (24%)	0 (0%)	2,766 (27%)	3,181 (29%)	2,848 (61%)	0 (0%)	24,631 (15%)
Macro-albuminuria	29,462 (7%)	83 (4%)	0 (0%)	752 (7%)	513 (5%)	0 (0%)	0 (0%)	2,318 (1 %)
History of CVD	50,615 (13%)	1,317 (69%)	63 (12%)	3,609 (35%)	3,589 (32%)	642 (14%)	1,168 (30%)	24,853 (15%)

All data are shown as median (inter quartile range) or frequency (%). NDR: National Diabetes Registry. SCI: Scottish Care Information. Micro-albuminuria was defined as an albumin/creatinine ratio 3-30 mg/mmol or urine-albumin 20-300mg/l. Macro-albuminuria was defined as an albumin/creatinine ratio >30mg/mmol or urine-albumin >300mg/l.

Supplemental table 5. Calculation formulas of cause-specific 1-year survivals.

Vascular Cox proportional hazard function (A)

1-year survival = (age-specific 1-yr baseline survival¥)^exp(A)

A = -2.432709 (if male) + 0.035983*age (if male) - 0.08603257*(BMI - 30) + 0.001155281*(*squared* BMI - 30^2) - 0.6910912 (if smoking) + 0.01127745*age (if smoking) - 0.02365684*(SBP-140) + 0.00009386*(*squared* SBP - 140^2) + 0.2632915*(nonHDL-3.8) - 0.02153226*(*squared* nonHDL - 3.8^2) + 0.02274024*(HbA1c-50) - 0.0001292752*(*squared* HbA1c - 50^2) - 0.01172895*(eGFR-80) - 0.00002497421*(*squared* eGFR - 80^2) + 0.1654953 (if micro-albuminuria) + 0.2061535 (if macro-albuminuria) + 0.01650379*(diabetes duration) - 0.4734714 (if history of CVD) + 0.04268836*age (if history of CVD) - 0.8525590 (if insulin treatment) + 0.01344922*age (if insulin treatment) + LN(Hazard Ratio of intended treatment)§ + 1.763233 (if high risk county)

Non-vascular mortality Cox proportional hazard function (B)

1-year survival = (age-specific 1-yr baseline survival¥)^exp(B)

B = -1.933780 (if male) + 0.02801824*age (if male) - 0.1325985*(BMI - 30) + 0.001977846*(*squared* BMI - 30^2) - 0.08033368 (if smoking) + 0.004628002*age (if smoking) - 0.02241861*(SBP-140) + 0.00008235097*(*squared* SBP - 140^2) + 0.1612940*(nonHDL-3.8) - 0.01791413*(*squared* nonHDL - 3.8^2) + 0.002996913*(HbA1c-50) - 0.008377349*(eGFR-80) + 0.1574689 (if micro-albuminuria) + 0.2131683 (if macro-albuminuria) + 0.007551427*(diabetes duration) - 3.783736 (if history of CVD) + 0.03680227*age (if history of CVD) - 0.3656307 (if insulin treatment) + 0.006264885*age (if insulin treatment) + 0.2164599 (if low risk country) - 0.07736502 (if high risk county)

¥ Age-specific baseline survivals are shown in table S6 for both Cox proportional hazard functions.
§ LN(Hazard ratio of intended treatment) is 0 if there is no estimation of treatment effects. The calculation of the hazard ratio of intended treatment is explained in the methods and supplementary appendix.
BMI: Body mass index in kg/m^2; SBP: Systolic blood pressure in mmHg; non-HDLc: non-high-density cholesterol in mmol/l; HbA1c: Hemoglobin A1c in mmol/l; eGFR: estimated glomerular filtration rate in ml/min.

Supplemental table 6. Age-specific baseline survivals.

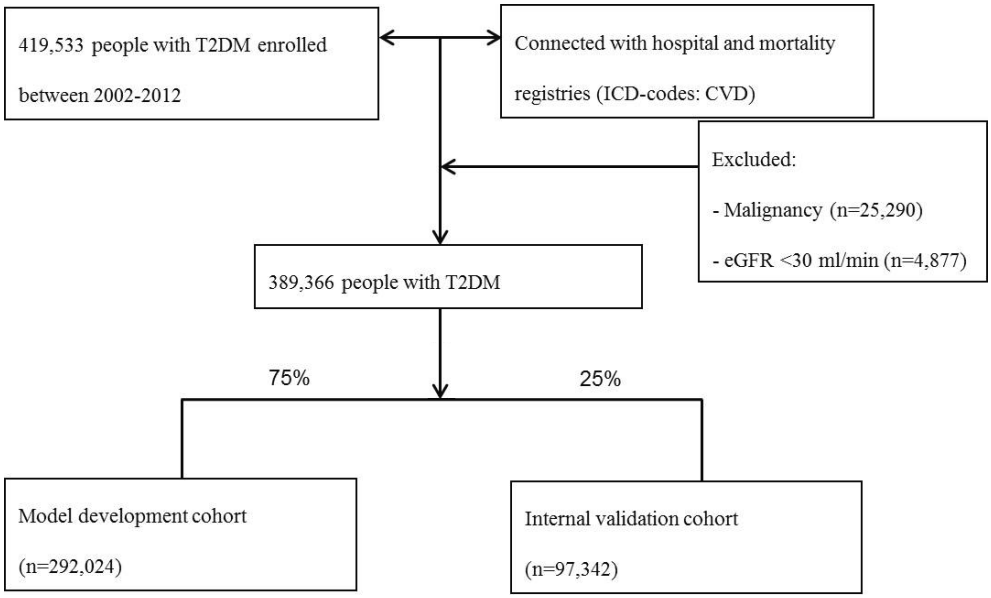
Age	1-year survival free of stroke or MI*	1-year survival for non-cardiovascular mortality**	Age	1-year survival free of stroke or MI*	1-year survival for non-cardiovascular mortality**
30	0.99828	0.99567	63	0.99670	0.99118
31	1.00000	1.00000	64	0.99722	0.99009
32	1.00000	0.99662	65	0.99700	0.98919
33	0.99883	0.99860	66	0.99712	0.98854
34	1.00000	0.99685	67	0.99738	0.98835
35	0.99910	0.99835	68	0.99718	0.98756
36	0.99857	0.99906	69	0.99726	0.98650
37	0.99825	0.99843	70	0.99741	0.98692
38	1.00000	0.99766	71	0.99789	0.98557
39	1.00000	0.99591	72	0.99782	0.98523
40	0.99929	0.99778	73	0.99772	0.98390
41	0.99815	0.99707	74	0.99784	0.98374
42	0.99922	0.99625	75	0.99792	0.98132
43	0.99824	0.99535	76	0.99796	0.98098
44	0.99781	0.99678	77	0.99800	0.97924
45	0.99770	0.99579	78	0.99797	0.97734
46	0.99857	0.99615	79	0.99811	0.97722
47	0.99807	0.99548	80	0.99828	0.97400
48	0.99757	0.99531	81	0.99822	0.97375
49	0.99696	0.99481	82	0.99834	0.97187
50	0.99793	0.99433	83	0.99832	0.96976
51	0.99722	0.99507	84	0.99845	0.96625
52	0.99692	0.99452	85	0.99852	0.96537
53	0.99684	0.99457	86	0.99863	0.96327
54	0.99626	0.99429	87	0.99875	0.96126
55	0.99621	0.99389	88	0.99873	0.95968
56	0.99647	0.99322	89	0.99894	0.95926
57	0.99702	0.99382	90	0.99907	0.95922
58	0.99659	0.99312	91	0.99913	0.95844
59	0.99665	0.99210	92	0.99923	0.95911
60	0.99649	0.99200	93	0.99943	0.96285
61	0.99659	0.99134	94	0.99955	0.96348
62	0.99676	0.99049			

Age-specific baseline survivals for centered continues variables with a systolic blood pressure of 140 mmHg, BMI of 30 kg/m^2, HbA1c of 50 mmol/l, non-HDL-c of 3.8 mmol/l, and eGFR of 80 ml/min. *Based on Cox proportional hazard function A for cardiovascular disease. **Based on Cox proportional hazard function B for non- cardiovascular mortality

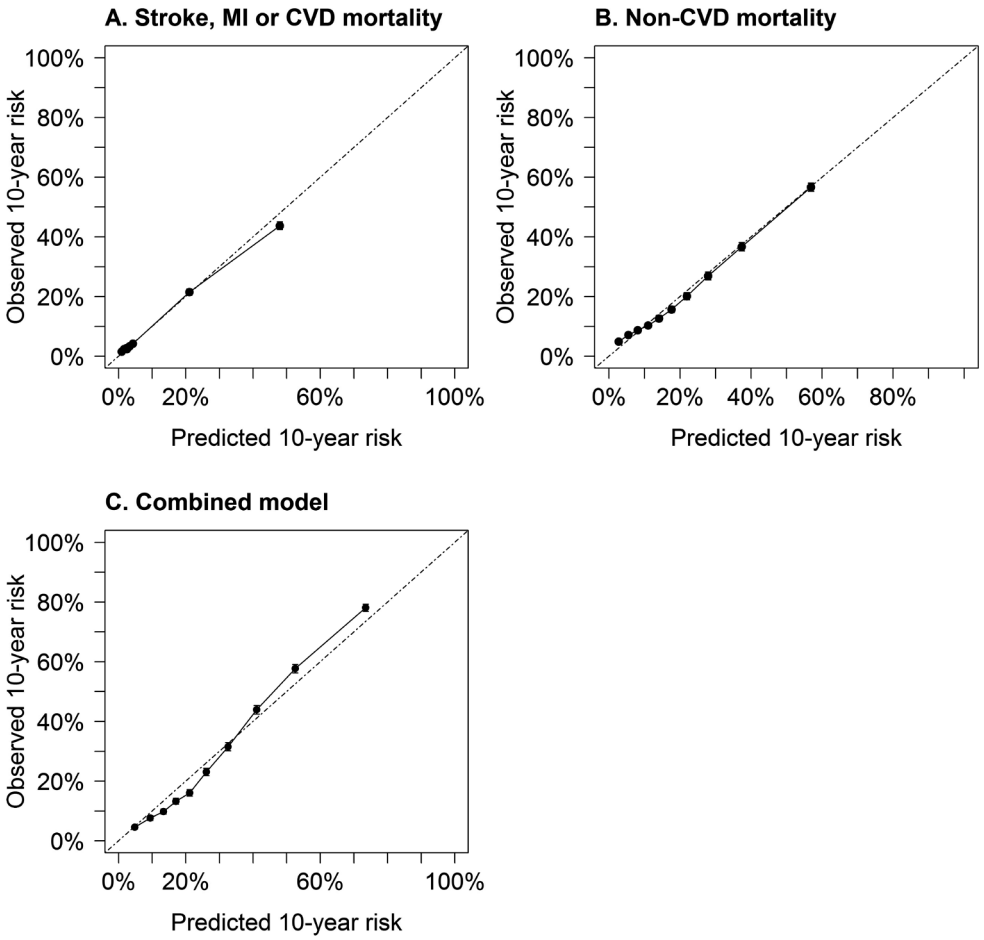
Supplemental table 7. Discrimination of the DIAL model and Cox proportional hazard functions A and B for internal (10-year risks) and external validation (5-year risks, except Scotland: 10-year risks).

	Discrimination of estimated vs observed risk		
	A. Cardiovascular disease	B. Non-vascular mortality	C. Combined model (DIAL model)
Validation cohort			
Swedish NDR (n=97,324)	0.83 (0.83-0.84)	0.72 (0.72-0.73)	0.77 (0.76-0.77)
Western-Europe (n=7,742)	0.65 (0.63-0.67)	0.62 (0.60-0.65)	0.66 (0.64-0.67)
Eastern-Europe (n=2,142)	0.64 (0.60-0.67)	0.59 (0.52-0.66)	0.68 (0.65-0.71)
North-America (n=14,590)	0.64 (0.62-0.65)	0.61 (0.58-0.63)	0.64 (0.63-0.66)
Asia and Oceania (n=5,580)	0.64 (0.62-0.66)	0.61 (0.57-0.66)	0.65 (0.63-0.67)
SCI –Diabetes database (n=167,731)	0.64 (0.64-0.65)	0.67 (0.67-0.68)	0.69 (0.69-0.70)

NDR: National Diabetes Registry. SCI: Scottish Care Information.

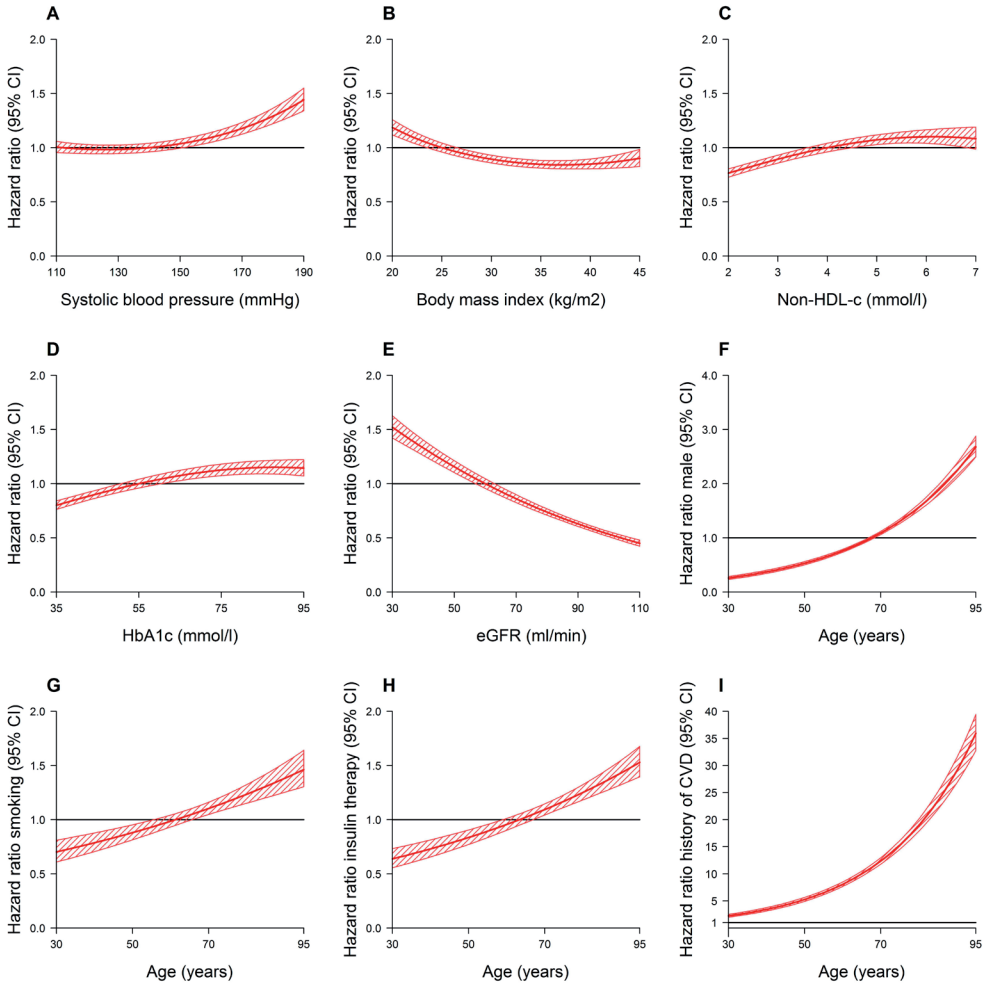


Supplemental figure 1. Flowchart describing cohort selection from the Swedish National Diabetes Registry.



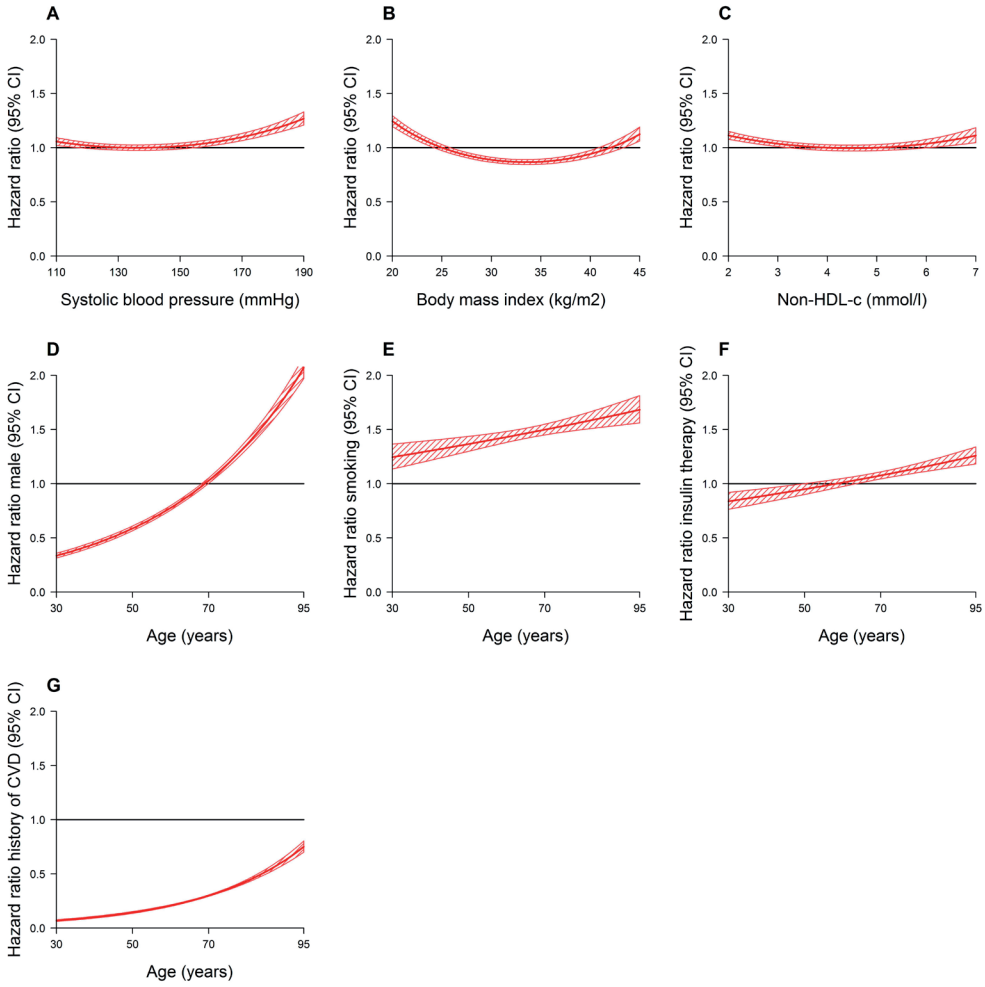
A) Predicted versus observed 10-year risk of the cause-specific CVD risk (Cox proportional hazard function A). B) Predicted versus observed 10-year risk of the non-vascular mortality risk (Cox proportional hazard function B; after recalibration). C). Predicted versus observed 10-year risk of CVD and all-cause mortality (DIAL-model).
Dots represent mean risks with 95% confidence intervals of people grouped by deciles of predicted risk.

Supplemental figure 2. Internal validation (n=97,342) of the predicted 10-year risk.



A-E. Quadratic relation between cardiovascular disease (CVD) and A) systolic blood pressure; B) Body-mass index; C) Non-HDL-c; D) HbA1c; E) eGFR.
F-I: Relation between age and the effect of F) sex; G) smoking; H) insulin therapy; I) history of CVD on the risk of CVD.

Supplemental figure 3. Hazard ratios and 95% CI for transformed and age-dependent variables of the cause-specific cumulative incidence model for cardiovascular disease.



A-C. Quadratic relation between non-cardiovascular mortality and A) systolic blood pressure; B) Body-mass index; C) Non-HDL-c.
D-G: Relation between age and the effect of D) sex; E) smoking; F) insulin therapy; G) history of CVD on the risk of non-cardiovascular mortality.

Supplemental figure 4. Hazard ratios and 95% CI for transformed and age-dependent variables of the cause-specific cumulative incidence model for non-cardiovascular mortality.

References

1. Masconi KL, Matsha TE, Erasmus RT, et al. Effects of Different Missing Data Imputation Techniques on the Performance of Undiagnosed Diabetes Risk Prediction Models in a Mixed-Ancestry Population of South Africa. PLoS One 2015;**10**(9):e0139210.
2. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. Diabetes care 2008;**31**(8):1473-8.
3. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj-Brit Med J 2016;**352**.
4. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics 2011;**67**(1):39-49.
5. Austin PC, Steyerberg EW. Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. Stat Methods Med Res 2017;**26**(2):796-808.
6. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, 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.
7. Cholesterol Treatment Trialists C, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;**371**(9607):117-25.
8. 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.
9. 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, obesity & metabolism 2011;**13**(7):615-28.
10. Sattar N, Preiss D, Robinson JG, et al. Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data. The lancet Diabetes & endocrinology 2016;**4**(5):403-10.
11. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. Jama 2015;**313**(6):603-15.
12. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. Journal of hypertension 2017;**35**(5):922-44.
13. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;**52**(11):2288-98.
14. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: A systematic review and meta-analysis. Jama 2018;**319**(15):1580-91.
15. Antithrombotic Trialists C, Baigent C, Blackwell L, 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):1849-60.
16. Xie M, Shan Z, Zhang Y, et al. Aspirin for primary prevention of cardiovascular events: meta-analysis of randomized controlled trials and subgroup analysis by sex and diabetes status. PLoS One 2014;**9**(10):e90286.
17. 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**:h1551.
18. Gellert C, Schottker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. Arch Intern Med 2012;**172**(11):837-44.
19. Gudbjornsdottir S, Cederholm J, Nilsson PM, et al. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes care 2003;**26**(4):1270-6.

20. Simons PC, Algra A, van de Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: rationale and design. European journal of epidemiology 1999;**15**(9):773-81.
21. Beulens JW, Monninkhof EM, Verschuren WM, et al. Cohort profile: the EPIC-NL study. Int J Epidemiol 2010;**39**(5):1170-8.
22. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. The New England journal of medicine 2008;**358**(24):2545-59.
23. Patel A, Group AC, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;**370**(9590):829-40.
24. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;**366**(9489):895-906.
25. Officers A, Coordinators for the ACRGTA, Lipid-Lowering Treatment to Prevent Heart Attack T. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Jama 2002;**288**(23):2981-97.

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Chapter 4

Cost-effectiveness of treatment decisions based on individual estimated lifetime benefit in life years gained versus individual estimated 10-year absolute risk reduction: The PCSK9 inhibition example

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Submitted

Abstract

Objective - To assess whether treatment decisions based on gain in cardiovascular disease (CVD)-free life-expectancy is cost-effective compared to decisions based on conventional 10-year CVD-risk estimates.

Study design and settings - A microsimulation model was constructed for 10,000 patients with stable cardiovascular disease (CVD). Costs and quality adjusted life years (QALYs) due to recurrent cardiovascular events and (non)vascular death were estimated for lifetime benefit-based compared to 10-year risk-based treatment, with PCSK9 inhibition as an illustration example. Lifetime benefit in months gained and 10-year absolute risk reduction were estimated using the REACH-SMART model, including an individualized treatment effect of PCSK9 inhibition based on baseline low-density lipoprotein cholesterol. For different cut-off values (i.e. the 5%, 10%, and 20% of patients with the highest estimated benefit of both strategies), cost-effectiveness was assessed using the incremental cost-effectiveness ratio (ICER), indicating additional costs per QALY gain.

Results - Lifetime benefit-based treatment of 5%, 10%, and 20% of patients resulted in an ICER of €37,200/QALY, €39,800/QALY, or €41,500/QALY. 10-Year risk-based treatment decisions of 5%, 10%, and 20% of patients resulted in an ICER of €47,700/QALY, €54,800/QALY, or €52,100/QALY.

Conclusion - Treatment decisions based on estimated lifetime benefit are more cost-effective than treatment decisions based on estimated 10-year benefits.

Introduction

Recent guidelines for cardiovascular prevention all recommend estimating an individual patient's risk (10-year risk of cardiovascular disease) for decision-making on whether or not to start preventive interventions.[1-4] According to the United States guidelines for primary prevention, if 10-year risk for fatal cardiovascular disease (CVD) is ≥ 7.5%, patients between 20 and 80 years old are considered high risk and eligible for intensive lipid-lowering therapy.[4] These patients with a ≥ 7.5% fatal CVD-risk benefit most from statin therapy.[5] However, in patients under 40 years of age, 10-year risk for fatal CVD is always lower than 7.5%, despite risk factors. For example, a 40 year old smoking male with a blood pressure of 180 mmHg and cholesterol of 8 mmol/L, has a 10-year risk for fatal CVD of 4% and would not be treated according to guidelines. However, it seems contra-intuitive to withhold treatment for this patient, since his lifetime risk for CVD is high.[6, 7] This example shows that specifically in younger patients, the 10-year risk horizon does not adequately reflect the potential long-term benefit of preventive treatment.[8-10] This may lead to missed treatment opportunities.

A recently developed prediction model, the REACH-SMART model, is able to estimate individual benefit of medication for prevention of CVD in patients with a history of stable CVD as 10-year risk reduction or as months gained from a lifetime perspective, the lifetime benefit (supplementary appendix).[11] Estimation of treatment effects expressed by a lifetime benefit could overcome some disadvantages of the 10-year risk based strategies. The younger patients with a low 10-year risk, but high risk factor levels, will have a high estimated lifetime benefit because lifetime prediction models take long-term exposure of risk factors and follow-up time into account.[12] On the other hand, in patients older than 70 years of age, the high estimated 10-year risk for fatal CVD may falsely suggest large estimated 10-year risk reduction of preventive treatment. As older patients are also at risk for non-CVD mortality, any reductions in CVD-mortality may be counterbalanced by a high risk for non-CVD mortality. This may result in 10-year risk estimations leading to an overestimation of the potential benefit of preventive treatment in older patients.[13]

Although it is tempting to assume estimations from a lifetime perspective could be useful in the identification of patients that benefit most from preventive treatment and interventions, there is no evidence on the cost-effectiveness of lifetime benefit assessment for guiding pharmacological therapy decisions.[1] Also, starting preventive interventions at a younger age means longer treatment duration and, therefore higher costs and more harm. The differences in efficacy and costs between risk classification of patients using a lifetime prediction model and a 10-year risk model can be compared using a microsimulation model with a lifetime horizon.[14] As an illustration example, Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition treatment will be used. PCSK9 inhibitors are a new class of drugs that effectively reduce low-density lipoprotein cholesterol (LDL-c) levels with 50-60%, and reduce CVD.[15-18]

We aimed to assess whether treatment decisions based on lifetime benefit-based treatment lead to more cost-effectiveness compared to 10-year risk-based treatment, using PCSK9 inhibition treatment as an illustration example.

Methods

A stepwise summary of the methods is shown in figure 1.

Study population

In order to get a representation of a national population of patients with stable CVD, a hypothetical population was created by repeatedly sampling from correlated probability distributions of risk factors. The correlated probability distribution used to create this hypothetical population was subtracted of the Second Manifestation of ARTerial disease (SMART) cohort described elsewhere.[19] In brief, the SMART cohort exists of 7,519 patients with clinical manifest vascular disease included between 1996 and 2015. Of these patients, baseline measurements of risk factors were performed using a standardized protocol. For our study, a population of 10,000 hypothetical patients was sampled using these baseline risk factor variables and the distribution among patients of age, sex, smoking, diabetes mellitus, systolic blood pressure, total cholesterol, LDL-c, creatinine, and number of locations with vascular disease. Baseline variables of atrial fibrillation and chronic heart failure were not available in the SMART cohort. Therefore, the sampling distributions of atrial fibrillation and chronic heart failure were established from literature and only aged and sex dependent.[20, 21]

Individual treatment effect estimations

Individualized 10-year risk reduction and life time benefit treatment effects were estimated using the REACH-SMART model.[11] The REACH-SMART model is a model to estimate life-expectancy free of a recurrent CVD in patients with a history of CVD. It is based on the competing risk model of Fine and Gray and the age of patients is used as the time scale (left truncation).[22] To estimate individual treatment effects of PCSK9 inhibition on recurrent CVD in this study, a coefficient based on the relative risk reduction of trials or meta-analyses was added to the model. The number of CVD-free life-years gained by therapy was calculated as the difference between the estimated life-expectancy free of recurrent CVD with treatment and without treatment is the lifetime benefit of the treatment. The difference between the expected 10-year risk with treatment and without treatment resulted in the 10-year absolute risk reduction (supplementary appendix).

Our assumption on the effect of PCSK9 inhibitors was based on the expected LDL-c reduction, which is conditional to the baseline LDL-c level.[17] On average, PCSK9 inhibitors

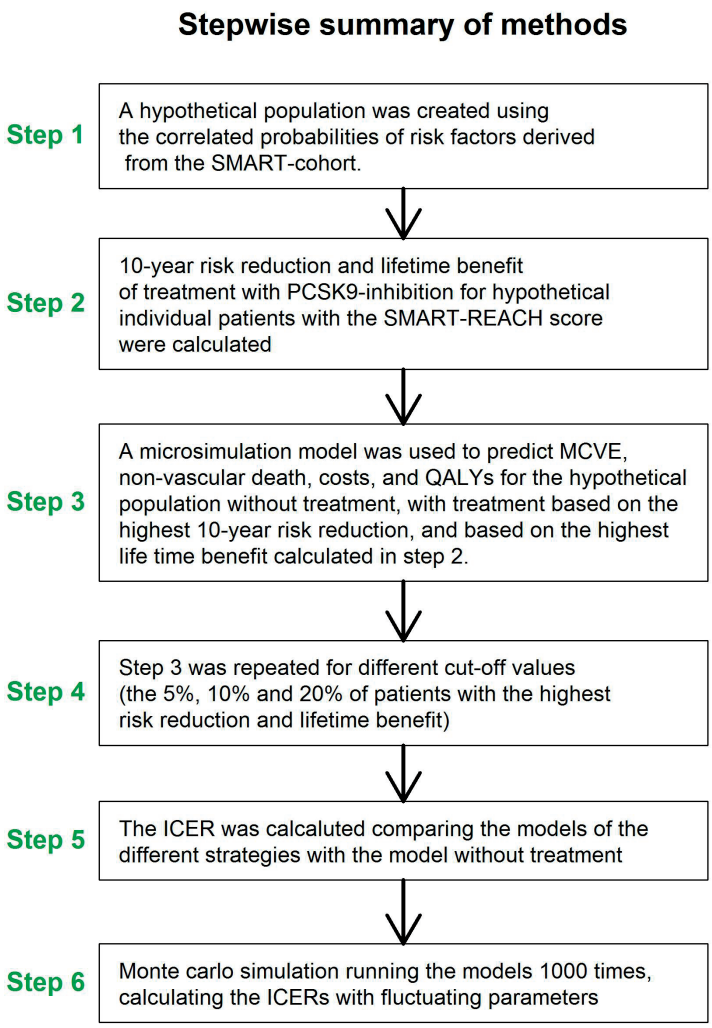


Figure 1. A brief explanation of the methods.

have been shown to reduce LDL-c levels by 50-60%.[18] In the present study, a conservative estimate of treatment benefit of 50% LDL-c reduction was assumed. The results of the recent PSCK9 inhibitor outcome trial correspond with the more robust results from large meta-analyses showing a hazard ratio of 0.78 (95% CI 0.76-0.80) for major vascular events per 1 mmol/L LDL-c reduction.[15, 16] There was no indication of a decreasing effect size when LDL-c were reduced below 2 mmol/L.[15] Thus, for our study the individualized relative treatment effect of PCSK9 inhibition on CVD based on expected LDL-c reduction was defined as $0.78^{0.5*\text{LDL-c}}$. Individualized hazard ratios (HRs) were calculated for each study participant. We assumed that LDL-c reduction has no effect on non-vascular mortality.[15]

Microsimulation model design

A microsimulation model was developed to predict major cardiovascular events (MACE), (non)vascular death, costs and quality-adjusted life years (QALYs) for risk-based treatment and life-time-benefit-based treatment, using treatment with PCSK9 inhibitors as an example.[14] Treatment of patients within the study population with the highest predicted treatment effect based on 10-year absolute risk reduction and lifetime benefit were compared, using different cut-off values (i.e. the best 5%, 10%, and 20% % of patients with the highest estimated benefit). The microsimulation model contained three health states: 'stable cardiovascular disease', 'recurrent MACE' and 'death'. All hypothetical patients started in the 'stable cardiovascular disease' health state. Patients could stay in their health state or transit to another health state each year (Figure 2). Patients transit to the recurrent MACE state if they experienced a MACE in the particular year, namely a myocardial infarction, ischemic stroke or haemorrhagic stroke. Patients transit to the 'death' health state whenever they died of any cause and remained in that health state. The simulation ran until all hypothetical patients had died, i.e. for a lifetime horizon.

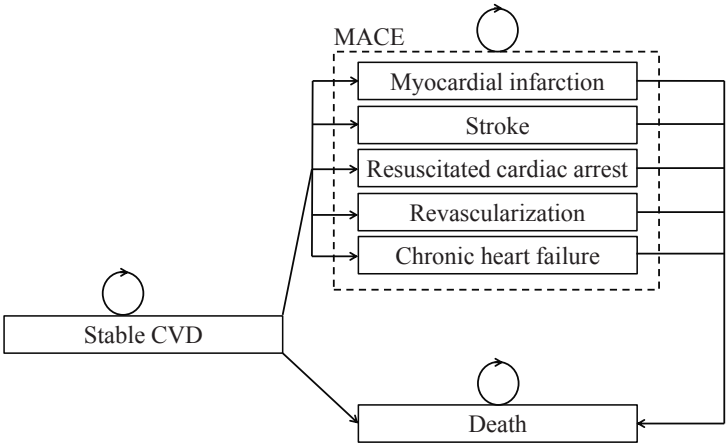


Figure 2. Diagrammatic representation of the micro-simulation model with health states (boxes) and possible transitions (arrows).

Model variables

Transition risks

This economic evaluation was performed from a health care perspective, meaning that only medical and not societal costs and effects were evaluated. The probabilities of transition from the stable CVD health state to the MACE health state were based on mean annual cardiovascular event risks. Mean annual event risks for myocardial infarction, stroke and revascularization without PCSK9 treatment were derived from the SMART

cohort (supplemental table 1).[19] Mean annual event risks for resuscitated cardiac arrest and heart failure without PCSK9 treatment were derived from the intensive treatment arm of the TNT trial (supplemental table 1).[23] The individualized event risks changed with age according to an existing 10-year risk score for patients with CVD (supplemental figure 1), systolic blood pressure, current smoking, and diabetes mellitus.[24] The annual event rates were multiplied by the HR to obtain an e individualized expected treatment effect when a patient was treated with PCSK9 inhibitors. Case-fatality rates for myocardial infarction and stroke were age-dependent and obtained from Dutch nationwide registries for in- and outside hospital deaths.[25-27] The probability of non-vascular death for patients with stable CVD or patients in the post-event health state was estimated by multiplying the age-adjusted probability of non-vascular death in the general population by a disease-specific mortality multiplier (supplemental table 1).[28-34]

Health outcomes

The amount of life years and QALYs for each patient was estimated for the different treatment strategies (treatment of patients within the study population with the highest predicted treatment effect based on 10-year absolute risk reduction and lifetime benefit). QALYs were calculated by summing up the multiplication of the time a person spent in a certain health state by the utility associated with that particular health state (supplemental table 2). A utility is a quality of life weight varying between 1.0 (perfect health) and 0.0 (death). In the present study, all patients start with a utility of 0.78, since all patients included have stable CVD. Utilities were derived from published data and measured with multi-attribute health status classification systems, mostly EQ-5D questionnaires[35-37]. Patients who experienced a revascularization were assumed to have the same quality of life as patients with stable CVD.

Costs

The costs of the cheapest available PCSK9 inhibitors (Alirocumab) in the Netherlands were taken as base case scenario.[38] Event costs and lifetime health care costs associated with vascular events were derived from observational studies in the Netherlands and from Dutch nationwide registries. Lifetime costs made in the hospital, nursing home and at the general practitioner were included.[39-43] Mean costs for a revascularization procedure were estimated as the weighted average for a PCI and a CABG.[26] Costs of pharmacist's and laboratory tests for all patients were modelled. The cost of one extra doctor's visit each year for prescription of PCSK9 inhibitors was included.[40] Costs in euro's were updated to 2016 with the Dutch consumer price indices (supplemental table 2).[27]

Data analyses

The microsimulation model was run with a lifetime horizon for all 10,000 hypothetical patients within the described cohort for different scenarios: 1) treat no one, 2) lifetime

benefit-based treatment of the most eligible 5%, 10%, and 20% of patients, and 3) 10-year risk-based treatment of the most eligible 5%, 10%, and 20% of patients. Similar cut-off values were used to obtain equal numbers of treated patients. Mean costs, life years and QALYs per patient were estimated for each of these scenarios and cut-off values. Incremental costs and QALYs were estimated for comparison between these scenarios. To calculate the incremental cost-effectiveness ratio (ICER) the incremental costs was divided by the incremental QALYs, expressed as costs spend per QALY gain. Discount rates of 4.0% for costs and 1.5% for health outcomes were applied.[44]

Scenario analyses

Scenario analyses were done to test the robustness of our results, based on the treatment of 10% of the patients with the highest 10-year risk reduction and highest lifetime benefit. Scenarios were based on variations in drug costs, event probabilities, event costs, treatment effects of PCSK9 inhibitors, discount rates, mortality multipliers and utilities, fluctuating one parameter at a time (supplemental table 1 and supplemental table 2; lower and upper bound).

Sensitivity analyses

Probabilistic sensitivity analyses were run a 1,000 times using Monte Carlo simulation, in which all parameters could fluctuate at the same time. For every simulation, event probabilities, hazard ratios for lowering LDL-c by PCSK9 inhibitors and utilities were randomly chosen from beta distributions, mortality multipliers and costs from gamma distributions. The individualized expected effect of PCSK9 inhibition was recalculated with the randomly chosen HRs. The probability that risk based and/or benefit based treatment for different cut-off values is cost-effective compared to no treatment with PCSK9 inhibitors is displayed in graphs for varying thresholds of euros willing to pay per QALY gained.

Results

The baseline characteristics of our hypothetical study population of 10,000 patients are shown in table 1. Notable, patients selected for treatment based on the highest lifetime benefit are more than 10 years younger compared to patients selected based on the highest absolute 10-year CVD-risk reduction.

Table 1. Baseline characteristics.

	All patients	% Patients with the highest lifetime benefit			% Patients with the highest 10-year risk reduction		
	n = 10000	n = 500	n = 1000	n = 2000	n = 500	n = 1000	n = 2000
Age (years)	61 (8)	51 (5)	52 (5)	54 (6)	65 (8)	64 (8)	64 (8)
Male gender	7366 (74%)	274 (55%)	598 (60%)	1259 (63%)	346 (69%)	718 (72%)	1479 (74%)
Current smoking	3137 (31%)	116 (23%)	240 (24%)	531 (27%)	242 (48%)	471 (47%)	907 (45%)
Type 2 diabetes mellitus	1775 (18%)	46 (9%)	105 (11%)	210 (11%)	144 (29%)	280 (28%)	506 (25%)
Systolic blood pressure (mmHg)	140 (20)	142 (21)	141 (21)	140 (21)	150 (22)	148 (22)	146 (22)
Total cholesterol (mmol/L)	4.7 (4.0 - 5.6)	6.6 (5.9 - 7.2)	6.2 (5.6 - 6.9)	5.9 (5.2 - 6.6)	6.9 (6.3 - 7.6)	6.4 (5.8 - 7.1)	6.0 (5.3 - 6.7)
Creatinine (umol/L)	89 (70 - 111)	90 (75 - 108)	90 (74 - 111)	90 (72 - 110)	107 (86 - 129)	106 (85 - 128)	103 (84 - 125)
1 location of CVD	7929 (79%)	414 (83%)	828 (83%)	1636 (82%)	284 (57%)	602 (60%)	1288 (64%)
2 location of CVD	1998 (20%)	86 (17%)	172 (17%)	359 (18%)	211 (42%)	386 (39%)	696 (35%)
3 location of CVD	73 (1%)	0 (0%)	0 (0%)	5 (0%)	5 (1%)	12 (1%)	16 (1%)
Coronary heart disease	6191 (62%)	314 (63%)	627 (63%)	1253 (63%)	339 (68%)	659 (66%)	1295 (65%)
Cerebrovascular disease	3110 (31%)	140 (28%)	299 (30%)	600 (30%)	155 (31%)	314 (31%)	663 (33%)
Peripheral artery disease	1924 (19%)	84 (17%)	163 (16%)	344 (17%)	130 (26%)	258 (26%)	467 (23%)
Abdominal aortic aneurysm	919 (9%)	48 (10%)	83 (8%)	172 (9%)	97 (19%)	179 (18%)	303 (15%)
Atrial fibrillation	278 (3%)	1 (0%)	3 (0%)	6 (0%)	32 (6%)	65 (7%)	106 (5%)
Chronic heart faillure	486 (5%)	7 (1%)	15 (2%)	42 (2%)	61 (12%)	117 (12%)	190 (10%)

All data are displayed as mean ± SD, median (Inter quartile range) or n (%).

* Locations of CVD: The number of locations of vascular disease (i.e. Coronary heart disease, cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysm and combinations).

Treatment of the 5%, 10%, and 20% most eligible patients according to the lifetime benefit-based treatment strategy resulted in selection of patients with >4.8 years, >4.2 years, and >3.5 years CVD life-years gain respectively. Treatment of the 5%, 10%, and 20% most eligible patients according to the 10-year risk-based treatment strategy resulted in selection of patients with >12.3%, >10.9% and >9.2% 10-year absolute risk reduction of CVD, respectively. 72 patients (14%) selected according to the 5% highest lifetime benefit-based treatment strategy were also selected according to the 5% highest 10-year risk-based treatment strategy. 200 patients (20%) selected according to the 10% highest lifetime benefit-based treatment strategy were also selected according to the 10% highest 10-year risk-based treatment strategy. 612 patients (31%) selected according to the 20% highest lifetime benefit-based treatment strategy were also selected according to the 20% highest 10-year risk-based treatment strategy.

Compared to standard of care, the incremental costs for treatment with PCSK9 inhibitors was similar for lifetime benefit-based treatment strategy and 10-year risk-based treatment strategy. However, the QALYs gained treated with PCSK9 inhibitors were higher for the lifetime benefit-based treatment strategy compared to 10-year risk-based treatment strategy (table 2). Overall, lifetime benefit-based treatment was more cost-effective compared to 10-year risk-based treatment. For a treatment of 5% of all patients, the ICER for lifetime benefit-based treatment was €37,200 /QALY whereas for 10-year risk-based treatment this was €47,700 /QALY. For a treatment of 10% of all patients, the ICER for lifetime benefit-based treatment was €39,800 /QALY whereas for 10-year risk-based treatment this was €54,800/QALY. For a treatment of 20% of all patients, the ICER for lifetime benefit-based treatment was €41,500 /QALY whereas for 10-year risk-based treatment this was €52,100/QALY (table 2).

Scenario analyses

Scenario analyses showed a substantial influence of change in event probabilities, change in annual drug cost, and change in discount. Therapy becomes less cost-effective if CVD event rates are lower than estimated and more cost-effective if CVD event rates are higher. If therapy is less expensive, treatment becomes more cost-effective, while with more expensive therapy, treatment becomes less cost-effective.

A 5% higher or lower discount for both costs and health outcomes and undiscounted analyses showed an increase in ICER for both strategies (figure 3).

Table 2. ICER for patients with the highest lifetime benefit-based treatment estimates and the highest 10-year risk-based treatment estimates. Costs and QALYs are given for the scenario of 10,000 patients. QALYs: quality-adjusted life years; ICER: Incremental cost-effectiveness ratio.

Cut-off value	**5% of patients treated**			**10% of patients treated**			**20% of patients treated**		
	Costs	QALYs	ICER (€/QALY)	Costs	QALYs	ICER (€/QALY)	Costs	QALYs	ICER (€/QALY)
No treatment	€111,727,411	65,897	-	€111,732,871	65,935	-	€111,620,058	65,893	-
Lifetime benefit-based treatment	€153,997,681	67,057	€37,200	€194,164,605	68,014	€39,800	€269,495,928	69,704	€41,500
10-year risk-based treatment	€153,071,526	66,755	€47,700	€192,212,131	67,443	€54,800	€266,326,909	68,846	€52,100

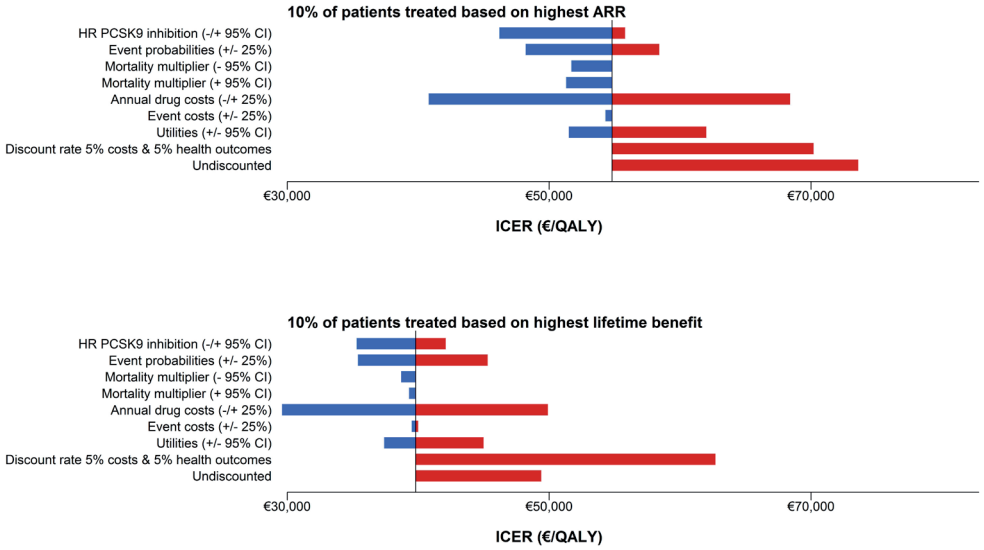


Figure 3. Scenario analyses estimating the influence of different model assumptions on A) the ICER of the lifetime benefit-based treatment strategy of 10% of the patients vs. no treatment and B) the ICER of the 10-year risk-based treatment strategy of 10% of the patients vs no treatment.

Sensitivity analyses

Irrespective of the strategy used, treatment with PCSK9-therapy is always more expensive than no treatment for all. The probability of treatment being cost-effective therefore depends on the willingness to pay; generally €50,000 per additional QALY is considered acceptable.[45] For this level of willingness to pay, the probability that lifetime benefit-based treatment of 5%, 10%, and 20% of patients is cost-effective compared to no treatment at all is 69.0%, 77.2%, and 84.1% respectively (figure 4, 5, and 6). Similarly, the probability that the 10-year risk-based treatment of the 5%, 10%, and 20% most eligible patients is cost-effective compared to no treatment at all is 51.6%, 47.3%, and 38.8% respectively (figure 4, 5, and 6). The level of willingness to pay, however, can be debated. The lower bound of willingness to pay for which treatment is >50% certain cost-effective was €35,900/QALY, €38,400/QALY and €41,700/QALY for 5%, 10% and 20% most eligible patients based on the lifetime benefit-based treatment strategy and approximately €47,800/QALY, €51,300/QALY and €53,100/QALY for 5%, 10% and 20% most eligible patients based on the 10-year risk-based treatment strategy.

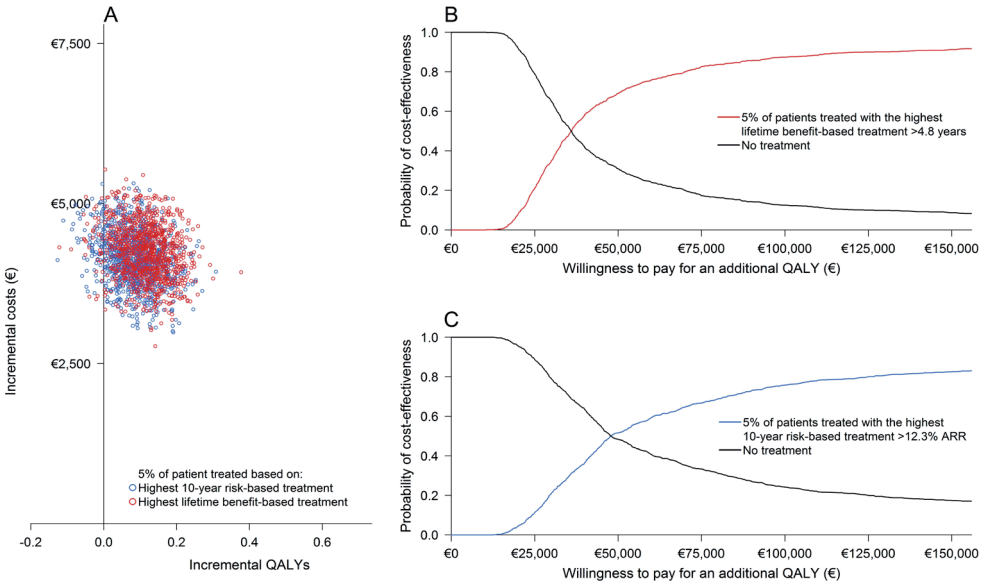


Figure 4. Incremental cost-effectiveness plane of the lifetime benefit-based strategy and the 10-year risk-based treatment strategy for 5% of patients treated with PCSK9 inhibition (A). Additional cost-effectiveness acceptability curves for both strategies separately (B: Lifetime benefit-based treatment; C: 10-year risk-based treatment).

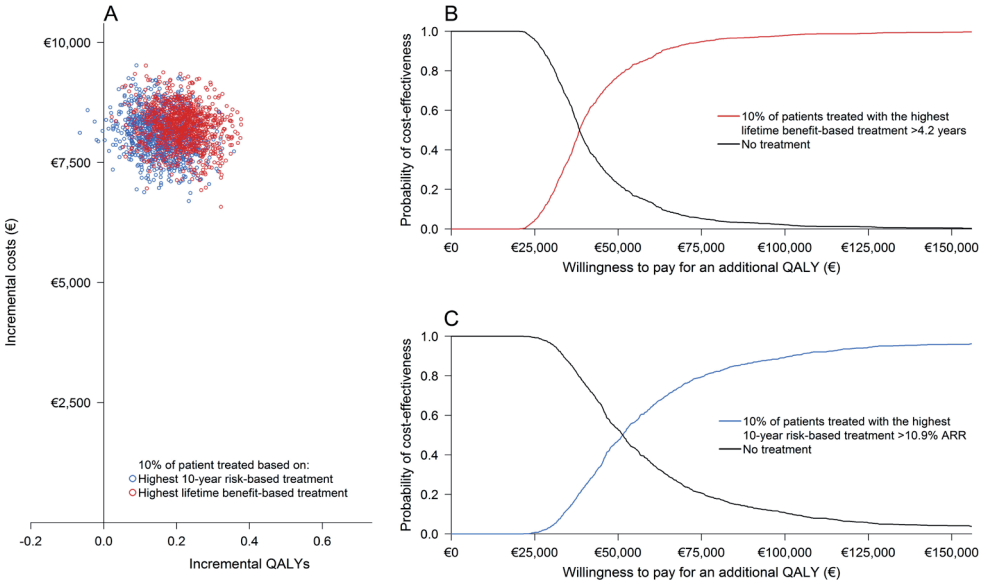


Figure 5. Incremental cost-effectiveness plane of the lifetime benefit-based strategy and the 10-year risk-based treatment strategy for 10% of patients treated with PCSK9 inhibition (A). Additional cost-effectiveness acceptability curves for both strategies separately (B: Lifetime benefit-based treatment; C: 10-year risk-based treatment).

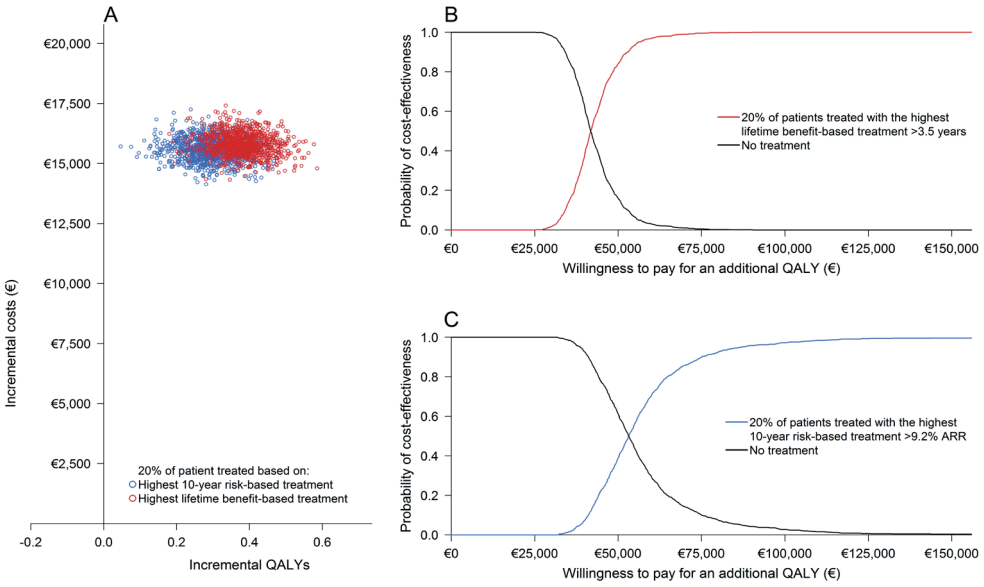


Figure 6. Incremental cost-effectiveness plane of the lifetime benefit-based strategy and the 10-year risk-based treatment strategy for 20% of patients treated with PCSK9 inhibition (A). Additional cost-effectiveness acceptability curves for both strategies separately (B: Lifetime benefit-based treatment; C: 10-year risk-based treatment).

Discussion

In the present study it is shown that lifetime benefit-based treatment decisions results in lower costs per QALY gained than 10-year risk-based treatment decisions, at least in this illustration example of PSCK9 inhibition in patients with stable CVD. The expected costs per QALY gained for treatment of 10% of patients based on the highest lifetime benefit was €39,800/QALY and based on the highest absolute risk reduction was €54,300/QALY. Although the results are sensitive to the assumptions made, our scenario analyses show that treating patients the lifetime benefit based treatment strategy remained favourable compared to the traditional absolute risk reduction based treatment strategy in all scenarios.

Increasing evidence suggests that estimation of lifetime benefit may help to identify a group of patients with previously underappreciated long-term potential for benefiting from preventive treatment. A large pooled survival analysis with more than 900,000 person-years using data from 5 community-based cohort studies from 1964 through 2008 showed that individuals with an index age of 45 with at least 2 risk factors lose 14 life-years free of CVD compared to individuals with optimal risk factor profiles. The loss in life-years free of CVD for individuals with an index age of 75 was only 4 years, compared to

individuals with optimal risk factors. This suggests that long-term exposure to risk factors at younger age has more impact on life-years lost, despite the fact that 10-year CVD-risk is still low.[6, 46]

These findings are also in line with a modelling study on of aspirin use in healthy women.[10] That study showed that aspirin use is associated with the highest lifetime benefit in younger women with otherwise high risk factor levels. In contrast, the women with the highest 10-year CVD-risk, who were generally older, experienced a lower lifetime benefit of aspirin use to prevent CVD. It was suggested that treatment decision making for the highest treatment effect based on lifetime benefit improved health outcomes.[9, 47, 48] In a microsimulation based on a population based cohort of individuals aged 55 year and older, it has been shown that the youngest individuals with high risk factor levels have the highest CVD free gain in life-expectancy with statin therapy.[9] However, based on these studies the question remains whether improvements in health outcomes would outweigh the costs of longer treatment duration in these younger patients.

Our findings provide evidence that the improved health outcomes due to treatment decisions based on the highest lifetime benefit do outweigh the costs of longer treatment duration compared to treatment decisions based on the highest risk reduction. This raises the question whether or not lifetime benefit-based strategies should be recommended for other treatments and in other patient populations. The scenario analyses estimating the influence of different assumptions in the model gives a sense of changing parameters, but it is merely speculating whether the lifetime benefit-based treatment strategy is superior to the 10-year risk-based treatment strategy in other settings. Whether the cost-effectiveness of the lifetime benefit based treatment decisions are generalizable in other populations, for instance in a primary prevention setting, should be established in other studies. Additional, before lifetime benefit can be used to guide clinical decision making in other settings, thresholds at which treatment is recommended should be investigated. For a specific preventive intervention, a cost-effectiveness analysis can be performed to establish a threshold of disease free lifetime benefit gained at which an intervention is cost-effective. For PCSK9 inhibition in a population with stable CVD and a willingness to pay €50,000 per additional QALY, lifetime benefit-based treatment is cost-effective for patients with a lifetime benefit of >3.1 years.

Strengths of this study include the use of the microsimulation model, in which a cohort of patients can be exposed to multiple strategies with a lifetime horizon. It also made it possible to simulate the effect of multiple strategies for individual patients instead of simulations on a population level. Also, we based our assumptions on recent peer-reviewed literature and adjusted event probabilities and risk of death for the age and cardiovascular history of patients. Furthermore, we performed various scenario analyses and sensitivity analyses that showed the effect of assumption on the cost-effectiveness.

Some limitations should be considered. First, in this cost-effectiveness analysis, we used PCSK9 inhibitions as an example. It is unsure whether our results are generalizable

for other treatments. Hypothetically, selection of patients based on lifetime benefit is even more cost-effective compared to 10-year risk based selection for less expensive treatments with similar efficacy, for example statins. However, longer treatment duration with different medication also results in more adverse effects. It is merely speculation whether this outweigh the potential gain in QALYs. It would be reassuring to find similar results with for example statin therapy in primary prevention setting, statin therapy in patients with diabetes mellitus, or PCSK9 inhibition in patients with familiar hypercholesterolemia. Secondly, we only modelled the effect of treatment on first recurrent events, but not on subsequent ones. This might have led to slight underestimation of the cost-effectiveness of both strategies. However, taking subsequent event into account would only have led to a more prominent difference between them and, thus, would not change our conclusions. Third, the possibility to postpone treatment to an older age was not taken into account. For the selection of patients with the highest lifetime benefit, the possibility to postpone treatment will not influence the selection, since the life-year gained only decrease with postponed treatment. For the selection of patients with the highest 10-year risk reduction, there could be a difference in patient selection due to increasing 10-year risk with age, and aligned with that an increased 10-year risk reduction. However, the results of our study would not be different, since the utility gain and the costs for treatment in patients with a postponed treatment will be similar to the relative older patients selected at the start of the simulation.

Finally, the harm and disutility of PCSK9 inhibition was not incorporated in the model. Assuming that harm is independent of the cardiovascular risk and benefit of the treatment, this would be similar for the patients treated based on the highest lifetime benefit and the patients treated based on the highest absolute risk reduction. However, patients with the highest lifetime benefit are treated for a longer duration. Since PCSK9 inhibitors are a new class of drugs, there is limit information on the harm of PCSK9 inhibition, especially on the long run. Therefore the microsimulation analyses should be re-adjusted including harm of treatment whenever any risk of harm is observed.

In conclusion, lifetime benefit-based treatment decisions for patients are cost-effective compared to treatment decisions guided by 10-year risk estimates, at least in this example for PCSK9 inhibition in patients with stable CVD.

References

1. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice G. 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:S49-73.
2. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, European Association for Cardiovascular P, Rehabilitation and Guidelines ESCCfP. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European heart journal*. 2012;33:1635-701.
3. Robinson JG and Stone NJ. The 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk: a new paradigm supported by more evidence. *European heart journal*. 2015;36:2110-2118.
4. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1-45.
5. Egan BM, Li J, White K, Fleming DO, Connell K, Hernandez GT, Jones DW, Ferdinand KC and Sinopoli A. 2013 ACC/AHA Cholesterol Guideline and Implications for Healthy People 2020 Cardiovascular Disease Prevention Goals. *Journal of the American Heart Association*. 2016;5.
6. Doll R, Peto R, Boreham J and Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004;328:1519.
7. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A and Hemingway H. 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;383:1899-911.
8. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA and Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791-8.
9. Ferket BS, van Kempen BJ, Heeringa J, Spronk S, Fleischmann KE, Nijhuis RL, Hofman A, Steyerberg EW and Hunink MG. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. *PLoS Med*. 2012;9:e1001361.
10. Dorresteijn JAN, Kaasenbrood L, Cook NR, van Kruijsdijk RCM, van der Graaf Y, Visseren FLJ and Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. *Bmj-Brit Med J*. 2016;352.
11. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB, Massaro JM, van der Graaf Y, Cramer MJM, Kappelle LJ, de Borst GJ, Steg PG and Visseren FLJ. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. *Journal of the American Heart Association*. 2018.
12. Leening MJ, Berry JD and Allen NB. Lifetime Perspectives on Primary Prevention of Atherosclerotic Cardiovascular Disease. *Jama*. 2016.

13. Wolbers M, Koller MT, Witteman JC and Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology*. 2009;20:555-61.
14. Rutter CM, Zaslavsky AM and Feuer EJ. Dynamic microsimulation models for health outcomes: a review. *Med Decis Making*. 2011;31:10-8.
15. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J and Collins R. 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;376:1670-81.
16. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *The New England journal of medicine*. 2017;376:1713-1722.
17. Soran H, Schofield JD and Durrington PN. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. *European heart journal*. 2015;36:2975-83.
18. Zhang XL, Zhu QQ, Zhu L, Chen JZ, Chen QH, Li GN, Xie J, Kang LN and Xu B. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Med*. 2015;13:123.
19. Simons PC, Algra A, van de Laak MF, Grobbee DE and van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. *European journal of epidemiology*. 1999;15:773-81.
20. Bui AL, Horwich TB and Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*. 2011;8:30-41.
21. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY and Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *European heart journal*. 2006;27:949-53.
22. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. *Biometrics*. 2011;67:39-49.
23. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK and Treating to New Targets I. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *The New England journal of medicine*. 2005;352:1425-35.
24. Dorresteijn JA, Visseren FL, Wassink AM, Gondrie MJ, Steyerberg EW, Ridker PM, Cook NR and van der Graaf Y. 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;99:866-72.
25. Koopman CV, I. van Dis, I. Visser, MC. Bots, ML. Beroerte, met uitsplitsing naar subarachnoïdale bloeding, intracerebrale bloeding en herseninfarct. *In: Koopman C, van Dis I, Vaartjes I, Visseren FLJ, Bots ML Hart- en vaatziekten in Nederland 2014, cijfers over kwaliteit van leven, ziekte en sterfte Den Haag: Hartstichting, 2014*.
26. Koopman CB, ML.; van Oeffelen, AAM.; van Dis, I.; Verschuren, WMM.; Engelfriet, PM.; Capewell, S.; Vaartjes, I. Trends in incidentie van acuut hartinfarct in de Nederlandse bevolking, 1998-2007. *Hart- en vaatziekten in Nederland 2012, cijfers over risicofactoren, ziekte en sterfte Den Haag: Hartstichting, 2012*. 2012.
27. Dutch nationwide registries. http://statline.cbs.nl. Accessed on: 22-09-2016.
28. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT and Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke; a journal of cerebral circulation*. 1993;24:796-800.
29. Criqui MH, Denenberg JO, Langer RD and Fronek A. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. *Vasc Med*. 1997;2:221-6.
30. Eldrup N, Budtz-Lilly J, Laustsen J, Bibby BM and Paaske WP. Long-term incidence of myocardial infarct, stroke, and mortality in patients operated on for abdominal aortic aneurysms. *Journal of vascular surgery*. 2012;55:311-7.
31. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A and Grobbee DE. The prognosis of heart failure in the general population: The Rotterdam Study. *European heart journal*. 2001;22:1318-27.
32. Bronnum-Hansen H, Jorgensen T, Davidsen M, Madsen M, Osler M, Gerdes LU and Schroll M. Survival and cause of death after myocardial infarction: the Danish MONICA study. *J Clin Epidemiol*. 2001;54:1244-50.

33. Lampe FC, Whincup PH, Wannamethee SG, Shaper AG, Walker M and Ebrahim S. The natural history of prevalent ischaemic heart disease in middle-aged men. *European heart journal*. 2000;21:1052-62.
34. Komocsi A, Simon M, Merkely B, Szuk T, Kiss RG, Aradi D, Ruzsa Z, Andrassy P, Nagy L, Lupkovics G, Koszegi Z, Ofner P and Janosi A. Underuse of coronary intervention and its impact on mortality in the elderly with myocardial infarction. A propensity-matched analysis from the Hungarian Myocardial Infarction Registry. *International journal of cardiology*. 2016;214:485-90.
35. Deasy C, Bray J, Smith K, Harriss L, Bernard S, Cameron P and Committee VS. Functional outcomes and quality of life of young adults who survive out-of-hospital cardiac arrest. *Emerg Med J*. 2013;30:532-7.
36. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, Farje MR, Moncada G, Dutta A, Sazawal S, Dyer A, Seiler J, Aboyans V, Baker L, Baxter A, Benjamin EJ, Bhalla K, Bin Abdulhak A, Blyth F, Bourne R, Braithwaite T, Brooks P, Brugha TS, Bryan-Hancock C, Buchbinder R, Burney P, Calabria B, Chen H, Chugh SS, Cooley R, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, Davis A, Degenhardt L, Diaz-Torne C, Dorsey ER, Driscoll T, Edmond K, Elbaz A, Ezzati M, Feigin V, Ferri CP, Flaxman AD, Flood L, Fransen M, Fuse K, Gabbe BJ, Gillum RF, Haagsma J, Harrison JE, Havmoeller R, Hay RJ, Hel-Baqui A, Hoek HW, Hoffman H, Hogeland E, Hoy D, Jarvis D, Karthikeyan G, Knowlton LM, Lathlean T, Leasher JL, Lim SS, Lipshultz SE, Lopez AD, Lozano R, Lyons R, Malekzadeh R, Marcenes W, March L, Margolis DJ, McGill N, McGrath J, Mensah GA, Meyer AC, Michaud C, Moran A, Mori R, Murdoch ME, Naldi L, Newton CR, Norman R, Omer SB, Osborne R, Pearce N, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Pourmalek F, Prince M, Rehm JT, Remuzzi G, Richardson K, Room R, Saha S, Sampson U, Sanchez-Riera L, Segui-Gomez M, Shahraz S, Shibuya K, Singh D, Sliwa K, Smith E, Soerjomataram I, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Taylor HR, Tleyjeh IM, van der Werf MJ, Watson WL, Weatherall DJ, Weintraub R, Weisskopf MG, Whiteford H, Wilkinson JD, Woolf AD, Zheng ZJ, Murray CJ and Jonas JB. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2129-43.
37. Sullivan PW, Lawrence WF and Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. *Med Care*. 2005;43:736-49.
38. Dutch Health Care Insurance Board. Drug costs 2016. www.medicijnkosten.nl. Accessed on: 22-09-2016.
39. Dutch nationwide registries. www.kostenvanziekten.nl. Accessed on: 22-09-2016.
40. Greving JP, Visseren FL, de Wit GA and Algra A. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. *BMJ*. 2011;342:d1672.
41. Ringborg A, Nieuwlaat R, Lindgren P, Jonsson B, Fidan D, Maggioni AP, Lopez-Sendon J, Stepinska J, Cokkinos DV and Crijns HJ. Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. *Europace*. 2008;10:403-11.
42. Soekhlal RR, Burgers LT, Redekop WK and Tan SS. Treatment costs of acute myocardial infarction in the Netherlands. *Neth Heart J*. 2013;21:230-5.
43. van Mastrigt GA, Heijmans J, Severens JL, Fransen EJ, Roekaerts P, Voss G and Maessen JG. Short-stay intensive care after coronary artery bypass surgery: randomized clinical trial on safety and cost-effectiveness. *Crit Care Med*. 2006;34:65-75.
44. Dutch guideline for economic evaluations in healthcare 2016. www.zorginstituutnederland.nl. Accessed on: 23-09-2016.
45. Dutch National Health Care Institute. Costeffectiveness in practice. 2015. https://www.zorginstituutnederland.nl/publicaties/rapport/2015/06/26/kosteneffectiviteit-in-de-praktijk.
46. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR and Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *Jama*. 2012;308:1795-801.
47. Dehmer SP, Maciosek MV, Flottemesch TJ, LaFrance AB and Whitlock EP. Aspirin for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: A Decision Analysis for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2016.
48. Schievink B, Kropelin T, Mulder S, Parving HH, Remuzzi G, Dwyer J, Vemer P, de Zeeuw D and Lambers Heerspink HJ. Early renin-angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes. *Diabetes, obesity & metabolism*. 2016;18:64-71.

Supplementary appendix

REACH-SMART model[1]

The REACH-SMART model is a prediction model with a lifetime horizon. It has been developed in the REduction of Atherothrombosis for Continued Health (REACH) and external validated in the Secondary Manifestations of ARTerial disease (SMART) cohort. REACH and SMART are prospective cohort studies of patients with clinical vascular disease or vascular risk factors. Study details have been described elsewhere.[2 3] The statistical methods of the model were previously described in detail.[4 5] In short, two Fine and Gray competing risk models were fitted for cause specific estimates of the cumulative incidence, one for recurrent vascular events (stroke, MI, or vascular death) and one for non-vascular mortality. Age was used as the underlying time function (i.e., left-truncation). This enables lifetime predictions across the age range from the youngest age at study entry to the highest age at study exit. Predictors were pre-specified based on existing prediction models and on availability in both datasets. Nine predictors were used for both Fine and Gray models: sex, current smoking (yes/no), diabetes mellitus (yes/no), systolic blood pressure (mmHg), total cholesterol (mmol/L), creatinine (umol/L), number of locations of vascular disease (i.e., CAD, CVD, and PAD), history of atrial fibrillation (yes/no) and history of congestive heart failure (yes/no).

Beginning at the starting age of each individual, the cumulative survival free of myocardial infarction (MI) and stroke was estimated for each subsequent year. The estimated survival free of MI and stroke at the beginning of each life-year was multiplied by the survival probability during that year. The survival probability was obtained by subtracting vascular risk and non-vascular mortality risk from one.

Life-expectancy free of stroke or MI of an individual person was defined as the median estimated survival, which is the age where the predicted individual survival curve equals 50%. The REACH-SMART model can estimate 10-year CVD-risks, by truncating cause-specific estimates of vascular risk at 10 years after the starting age. An individual's benefit from lifelong treatment was estimated as the difference between the estimated survival with and without treatment.

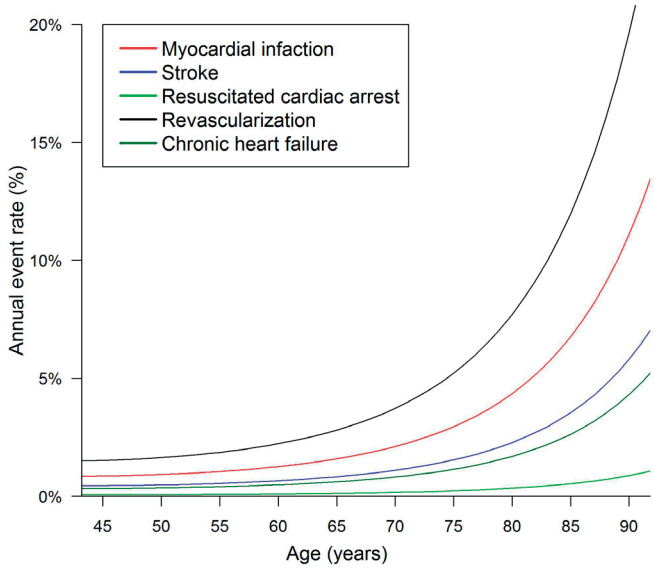
Supplemental table 1. Annual event risks and mortality multipliers.

	Base case	Lower bound	Upper bound	Source	Reference
Mean annual event risk*(%)					
Myocardial infarction	1.26			Observational study	[3]
Stroke	0.66			Observational study	[3]
Resuscitated cardiac arrest	0.10			RCT	[6]
Revascularization	2.23			Observational study	[3]
Chronic heart failure	0.49			RCT	[6]
Mortality multipliers					
Stable CVD					
Coronary artery disease	2.5	2.3	2.7	Observational study	[7]
Cerebrovascular disease	2.3	2.0	2.7	Observational study	[8]
Peripheral artery disease	3.1	1.9	4.9	Observational study	[9]
Abdominal aortic aneurysm	1.7	1.6	1.8	Observational study	[10]
Myocardial infarction	2.4	2.1	2.7	Observational study	[3]
Stroke	1.9	1.6	2.2	Observational study	[3]
Resuscitated cardiac arrest	2.4	2.1	2.7	Observational study	[3]
Revascularization	1.6	1.3	2.1	Observational study	[11]
Chronic heart failure	2.1	1.8	2.7	Observational study	[12]

*Mean annual event risk is the risk for a 60 year old patient.

Supplemental table 2. Costs and utilities.

	Base Case	Lower bound	Upper bound	Source	Reference
Costs					
Drug (annual costs for 1 patient)					
PCSK9 inhibitors	€ 5,981	€ 4,486	€ 7,476	Official tariff	[13]
Event					
Myocardial infarction	€ 5,037	€ 3,778	€ 6,296	Observational study	[14]
Stroke	€ 19,030	€ 14,273	€ 23,788	Dutch registries	[15]
Resuscitated cardiac arrest	€ 28,636	€ 21,477	€ 35,795	Observational study	[16]
Revascularization	€ 6,944	€ 5,009	€ 8,349	Observational study	[14 16 17]
Post-event care					
Stroke	€ 9,827	€ 7,370	€ 12,284	Dutch registries	[15]
Chronic heart failure	€ 6,569	€ 4,927	€ 8,211	Dutch registries	[15]
Other costs					
Doctor's visit	€ 109	€ 69	€ 157	Official tariff	[18]
Pharmacy	€ 26	€ 11	€ 52	Official tariff	[18]
Laboratory	€ 25	€ 17	€ 37	Official tariff	[18]
Utilities					
Stable CVD	0.78	0.69	0.83	Observational study	[19]
Myocardial infarction	0.65	0.56	0.70	Observational study	[19]
Stroke	0.64	0.55	0.69	Observational study	[19]
Resuscitated cardiac arrest	0.65	0.42	0.75	Observational study	[20]
Chronic heart failure	0.63	0.51	0.72	Observational study	[21]



Supplemental figure 1. Age-adjusted annual event rates in percentage.

References

1. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. Journal of the American Heart Association 2018.
2. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. Jama 2006;**295**(2):180-9.
3. Simons PC, Algra A, van de Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: rationale and design. European journal of epidemiology 1999;**15**(9):773-81.
4. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj-Brit Med J 2016;**352**.
5. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics 2011;**67**(1):39-49.
6. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. The New England journal of medicine 2005;**352**(14):1425-35.
7. Bronnum-Hansen H, Jorgensen T, Davidsen M, et al. Survival and cause of death after myocardial infarction: the Danish MONICA study. J Clin Epidemiol 2001;**54**(12):1244-50.
8. Dennis MS, Burn JP, Sandercock PA, et al. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. Stroke; a journal of cerebral circulation 1993;**24**(6):796-800.
9. Criqui MH, Denenberg JO, Langer RD, et al. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. Vasc Med 1997;**2**(3):221-6.
10. Eldrup N, Budtz-Lilly J, Laustsen J, et al. Long-term incidence of myocardial infarct, stroke, and mortality in patients operated on for abdominal aortic aneurysms. Journal of vascular surgery 2012;**55**(2):311-7.
11. Komocsi A, Simon M, Merkely B, et al. Underuse of coronary intervention and its impact on mortality in the elderly with myocardial infarction. A propensity-matched analysis from the Hungarian Myocardial Infarction Registry. International journal of cardiology 2016;**214**:485-90.
12. Mosterd A, Cost B, Hoes AW, et al. The prognosis of heart failure in the general population: The Rotterdam Study. European heart journal 2001;**22**(15):1318-27.
13. Dutch Health Care Insurance Board. Drug costs 2016. www.medicijnkosten.nl. Accessed on: 22-09-2016.
14. Soekhlal RR, Burgers LT, Redekop WK, et al. Treatment costs of acute myocardial infarction in the Netherlands. Neth Heart J 2013;**21**(5):230-5.
15. Dutch nationwide registries. www.kostenvanziekten.nl. Accessed on: 22-09-2016.
16. Ringborg A, Nieuwlaat R, Lindgren P, et al. Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. Europace 2008;**10**(4):403-11.
17. van Mastrigt GA, Heijmans J, Severens JL, et al. Short-stay intensive care after coronary artery bypass surgery: randomized clinical trial on safety and cost-effectiveness. Crit Care Med 2006;**34**(1):65-75.
18. Greving JP, Visseren FL, de Wit GA, et al. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ 2011;**342**:d1672.
19. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Med Care 2005;**43**(7):736-49.
20. Deasy C, Bray J, Smith K, et al. Functional outcomes and quality of life of young adults who survive out-of-hospital cardiac arrest. Emerg Med J 2013;**30**(7):532-7.
21. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012;**380**(9859):2129-43.

5

Chapter 5

Dealing with missing patient characteristics when using cardiovascular prediction models in clinical practice

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Abstract

Background - Individual risk prediction can be used to optimize and support treatment decisions regarding cardiovascular disease (CVD) prevention in clinical practice. Estimating patient risk using prediction models such as the Swedish National Diabetes register (NDR) CVD risk prediction model may be limited by incomplete patient data, a common occurrence in clinical practice.

Purpose - To compare the validity of five methods for handling missing patient characteristics required to estimate CVD risk using the Swedish National Diabetes Registry (NDR) risk prediction model.

Methods - The performance of the missing data methods was assessed using data from the Swedish NDR (n=419,533) and Scottish Care Information (SCI) - Diabetes register (n=226,953). Five methods for handling missing data were compared: 1) Reduced model method. Development of 2^n models, one model for each possible combination of available characteristics. 2) Hybrid model method. With one missing variable this method is similar to the reduced model method. With >1 predictor missing, the median value of a predictor was imputed to use multiple reduced models, taking the average as risk. 3) Conditional single imputation. 4) Median imputation. 5) The naïve approach. Baseline population survival adjusted by factors determined by independent risk ratio and population prevalence of available characteristics. The validity of each method for handling missing data was compared using calibration plots and c-statistics.

Results - There was no difference in terms of calibration or discrimination with identical c-statistics by missing data method (0.82 (95% CI 0.82-0.83) in NDR and 0.74 (95% CI 0.74-0.75) in SCI-Diabetes database) . Analyses of patients of the NDR with complete data after randomly deletion of variables, lowered c-statistics of median imputation and naïve approach when age was excluded. C-statistics were 0.75 (95% CI 0.74 - 0.75) compared to 0.80 (95% CI 0.80-0.81) of other methods dealing with missing data.

Conclusion - Pragmatic imputation of missing values by median values resulted in reliable predictions, though were less reliable for imputing important characteristics such as age.

Introduction

Several prediction models are currently recommended by national clinical guidelines [1-3], and is expected to increase in the future.[4-6] Unfortunately, an important barrier to their use in clinical practice is the potential unavailability of the necessary patient data required to estimate risk. Due to this problem, healthcare providers may choose against using the risk prediction tool leading to possible suboptimal care. Options for addressing incomplete data in the clinical setting are limited. One approach is to replace the missing value with the median value for a given population but the validity of this approach is unknown and in general, missing data are not randomly missing. Existing, inflexible prediction models incapable of overcoming this barrier do not match the requirements of clinical practice and limit the use of prediction models.

Extensive research has been conducted to investigate the effect of and methods for handling missing data in large datasets. Much of the work conducted in the risk prediction field has been primarily focused upon the effect of different imputation methods on risk prediction model development where missing data occurs in the development cohort.[7-9] There is limited evidence on methods to deal with missing patient characteristics in individual cases. In examples with classification trees and logistic models, reduced modelling approaches seem to be the most accurate way of deal with missing data, however this is not shown for cox proportional hazard models.[10] Reduced modelling is a method in which new models are derived for each combination of missing variables. In cases where the number of available variables is low then each available variable becomes more important, with different coefficients in each model. Reduced modelling, however, comes at a cost, either in terms of storage or computation time. Therefore, an accurate and more efficient method is preferred. Other proposed method for handling incomplete data in this setting are the hybrid model method[10], conditional single imputation, mean/median imputation[11], or the naïve approach.[12] The hybrid method is similar to reduced modelling if only 1 (or 2 variables) are missing. New models are derived for each combination of variables, assuming a maximum of missing variables. However, exceeding the maximum number of missing variables will be solved by imputation of the mean/median value of the additional missing variables. With the naïve approach predictions are based upon the population baseline survival. The naïve approach does not use regression modelling to predict individual risks. If no characteristics are known of an individual patient, the mean population risk is the most accurate estimate of risk for that patient. For every additional characteristic known, a more accurate risk prediction can be estimated by combining the population baseline survival with the population prevalence of that characteristic and the independent hazard ratios of that characteristic.

The objective of the present study is to compare the validity of 5 methods for dealing with missing patient characteristics in a cardiovascular disease (CVD) prevention setting for patient with type 2 diabetes mellitus (T2DM) using an update of the 5-year risk equation from the Swedish National Diabetes Registry (NDR) as an example.[13]

Methods

Study population

Data for this study were obtained from the Swedish NDR and the Scottish Care Information-Diabetes (SCI-Diabetes) database. Patients were aged >18 years with a diagnosis of T2DM registered in the Swedish NDR[14] between 2002 and 2012 or in the SCI-Diabetes register between 2004 and 2016. The definition of T2DM in the Swedish NDR was treatment with 1) diet only, 2) oral hypoglycaemic agents only, or 3) insulin only or combined with oral agents, and onset age of diabetes ≥40 years. In the SCI – Diabetes database T2DM was defined using an algorithm which uses information from the clinician recorded diabetes type, prescription data (use of and timing of sulphonylureas and insulin) and age at diagnosis. People with a previous diagnosis of cancer (ICD-10 codes C00-C97) were excluded, due to their increased risk of mortality and CVD.[15] Use of each register's data was approved by institutional review boards.

Baseline characteristics

Clinical characteristics at baseline for patients registered in the Swedish NDR and SCI –Diabetes database were data collected in the first year after registration. Clinical characteristics included in the updated Swedish NDR risk score? were age (years), sex (female/male), age at onset of T2DM (years), smoking status (yes/no), body-mass index (BMI in kg/m^2), systolic blood pressure (SBP in mmHg), haemoglobin A1c (HbA1c in mmol/mol), non-high-density lipoprotein cholesterol (non-HDLc in mmol/l), albuminuria (no/micro/macro), estimated glomerular filtration rate (eGFR in ml/min/1.73 m^2), retinopathy (yes/no), and a history of CVD (yes/no) and atrial fibrillation (yes/no). Micro-albuminuria was defined as an albumin/creatinine ratio 3-30 mg/mmol or urine-albumin 20-300mg/l, and macro-albuminuria was defined as an albumin/creatinine ratio >30mg/mmol or urine-albumin >300mg/l.

Methods handling missing data

In addition to an update of the Swedish NDR risk equation[13] (supplemental methods), a random 25% of patients of the Swedish NDR (development dataset) was used to generate the necessary framework for each method for handling missing data. These five developed methods were:

1. Reduced model method. Starting with a model including all predictors (full model), all other possible models with a combination of fewer predictors was developed. The full model consists of 13 predictors. Therefore, for the reduced model method, 2^13 = 8192 models were developed within the development dataset.
2. Hybrid model method. Starting with a full model including all predictors, all other possible models with one predictor missing (with the exception of age

and sex) were developed. When more than 1 predictor is missing, the median value for continues variables or mean value for categorical variables of the other predictor in the development dataset was used. This approach generates multiple predictions (one for every missing value), which were averaged to end with a single risk prediction.

3. Conditional single imputation to impute variables based on the available characteristics. All missing values were estimated with one linear or one logistic regression model in R for continuous and categorical predictors respectively. In the case of multiple missing variables, imputation consisted of 30 iterations.
4. Median imputation method whereby median values for continuous predictors and mean values for categorical predictors from the development dataset were imputed.
5. The naïve approach. The baseline population survival of the development dataset, the prevalence of each categorical predictor, and the mean values of the continuous predictors were stored. Also, the independent hazard ratios for all predictors were gathered from the updated risk equation. This enabled calculation of individual risk based on the formula: baseline population survival^(hazard ratio/population relative risk), where the population relative risk is equal to (prevalence of a factor)*HR of the factor + (1-prevalence) * 1.0 for categorical variables. For continues variables, the (hazard ratio/population relative risk) is equal to the (hazard ratio*individual continues value)/(hazard ratio*median value of population).

Validation of methods dealing with missing data

In the remaining 75% of patients (test dataset) from the Swedish NDR, real-world missing data was available to compare the methods for handling missing data. Each method for handling missing data was applied in the estimation of five-year risk for all patients using the updated Swedish NDR risk equation. The effect of missing data on the predictive accuracy of risk predictions was quantified by comparing C-statistics and calibration plots, stratified by the number of missing variables. For additional analyses, in patients without missing data, missing patient characteristics were introduced in two ways. First, one patient characteristic was assumed missing at one time for all patients. This resulted in predictions for patients with 12 of 13 characteristics available. All 13 characteristics were excluded one by one, which enabled observations of accuracy of methods dealing with missing characteristics influenced by important and less important predictors in the subset of patients with complete data only.

Second, for all patients with complete data, patient characteristics were randomly excluded. However, the number of missing patient characteristics was fixed. This resulted in 13 analyses with 1 up until 13 missing patient characteristics. Thus, the first analysis performed this way included all patients with complete data, with 1 randomly

excluded variable in these patients. The second analysis was performed in all patients with complete data, introducing 2 randomly excluded variables. This continued for any number of randomly excluded variables until all 13 patient characteristics were missing.

External validation of methods dealing with missing data

For external validation of the methods, data from the SCI-diabetes database with real-world missing data were used. Recalibration of the Swedish NDR 5-year risk equation for the Scottish population was performed in an imputed 25% of the patient data to take into account differences in baseline hazards (supplemental methods). The methods for dealing with missing patient characteristics were applied in the remaining 75% of the patients with real-world missing data. Predictions were based on imputations and population means derived from the Swedish NDR development data. This was done for the hybrid model method, conditional single imputation method, median imputation method, and naïve approach. The reduced model method was not feasible due to necessary recalibration of 8,192 developed (reduced) models. All statistical analyses were conducted using R version 3.4.1.

Results

Baseline characteristics

The baseline characteristics (including percentage of missing characteristics) of patients in the Swedish NDR development dataset (n = 104,883), the Swedish NDR test dataset (n = 314,650) and the external validation SCI-diabetes database (n = 170,215) are shown in table 1. Notably, in the Swedish NDR and the SCI-diabetes database, age, sex, history of CVD, and history of atrial fibrillation were always available (0% missing), and also age at onset of T2DM and retinopathy was never missing in the SCI-diabetes database. The remaining missing data were not missing completely at random. Patients without missing data tend to be younger (median age of patients: 65 years versus 66 years without versus with missing data). Also, patients without missing data had a longer duration of diabetes, with a difference in median duration of 2 years.

Table 1: Baseline characteristics

	Development dataset Swedish NDR		**Internal validation dataset Swedish NDR**		**External validation dataset SCI-diabetes database**	
	(n = 104,883)		(n = 314,650)		(n =170,215)	
	Median/frequency	Missing	Median/frequency	Missing	Median/frequency	Missing
Age (y)	66 (57-75)	0 (0%)	66 (58-75)	0 (0%)	61 (52-71)	0 (0%)
Sex (Male)	58557 (56%)	0 (0%)	176051 (56%)	0 (0%)	95869 (56%)	0 (0%)
Current smoking	13111 (16%)	23030 (22%)	39591 (16%)	68839 (22%)	29634 (17%)	41892 (25%)
Age at onset of T2DM (y)	60 (52-69)	12794 (12%)	61 (52-69)	38054 (12%)	61 (52-71)	0 (0%)
Systolic blood pressure (mmHg)	140 (128-150)	15473 (15%)	140 (128-150)	46283 (15%)	135 (125-145)	21003 (12%)
Body mass index (kg/m2)	29 (26-33)	26824 (26%)	29 (26-33)	80221 (25%)	31 (28-36)	65145 (38%)
HbA1c (mmol/mol)	50 (44-59)	11842 (11%)	50 (44-59)	35611 (11%)	53 (45-65)	23207 (14%)
Non-HDL-c (mmol/l)	3.7 (3.0-4.4)	42240 (40%)	3.7 (3.0-4.4)	127107 (40%)	3.1 (2.7-4.2)	60971 (36%)
eGFR (ml/min/1.73m^2)	82 (67-95)	22059 (21%)	83 (66-95)	66912 (21%)	81 (66-95)	29052 (17%)
Micro-albuminuria	9106 (15%)	43862 (42%)	27499 (15%)	132091 (42%)	14637 (9%)	77099 (45%)
Macro-albuminuria	4712 (8%)		14090 (8%)		1553 (1%)	
Retinopathy	7249 (21%)	70718 (67%)	21800 (21%)	212485 (68%)	20958 (12%)	0 (0%)
Atrial fibrillation	7582 (7%)	0 (0%)	23208 (7%)	0 (0%)	8311 (5%)	0 (0%)
History of CVD	13952 (13%)	0 (0%)	41117 (13%)	0 (0%)	27919 (16%)	0 (0%)

All data are shown as median (inter quartile range) or frequency (%). NDR: National Diabetes Registry. SCI: Scottish Care Information. Micro-albuminuria was defined as an albumin/creatinine ratio 3-30 mg/mmol or urine-albumin 20-300mg/l. Macro-albuminuria was defined as an albumin/creatinine ratio >30mg/mmol or urine-albumin >300mg/l.

Validity of methods dealing with missing patient characteristics in the Swedish NDR

In the test dataset of the Swedish NDR with real-world missing patient characteristics, the predicted 5-year risks using any of the methods dealing with missing data showed good agreement with 5-year observed risks (figure 1). There was no difference in discriminative power as evaluated by c-statistics of 0.82 (95% CI 0.82-0.83) for all methods. Also, when stratified for the number of missing characteristics, no differences in c-statistics between the methods were observed (figure 2). Even with 9 missing patient characteristics (only age, sex, history of CVD, and atrial fibrillation available), c-statistics remained high with 0.81 (95% CI 0.78-0.83)

The results were different in a dataset of randomly introduced missing data in the subset of patients of the Swedish NDR with complete data (n = 46,971). When the most important variable (i.e. age; supplemental table 1) was missing, the single imputation method, reduced model method, and hybrid model method resulted in c-statistics of 0.80 (95% CI 0.80-0.81) versus c-statistics of only 0.75 (95% CI 0.74 - 0.75) achieved by median imputation or the naïve approach (figure 3). Missingness in the most important variables (i.e. age or history of CVD based on the chi-squares of model variables; supplemental table 1) resulted in 5% underestimation of predicted risk in the highest quintile of observed risk when median imputation or the naïve approach was applied (supplemental figure 1). The observed and predicted risk showed adequate agreement when applying the other methods.

With the introduction of multiple random missing characteristics, the single imputation method and reduced model method were more accurate than the hybrid method, median imputation, and naïve approach. C-statistics of single imputation and reduced model method compared with the other methods remained higher with increasing numbers of randomly excluded missing characteristics (figure 4). The largest difference in c-statistics between single imputation and reduced model method compared to the other methods was observed with 10 missing variables (c-statistic of 0.68 versus 0.62). Also, calibration plots showed that the hybrid method, median imputation, and naïve approach underestimated predicted 5-year risks compared to observed 5-year risks with increasing number of missing variables (supplemental figure 2).

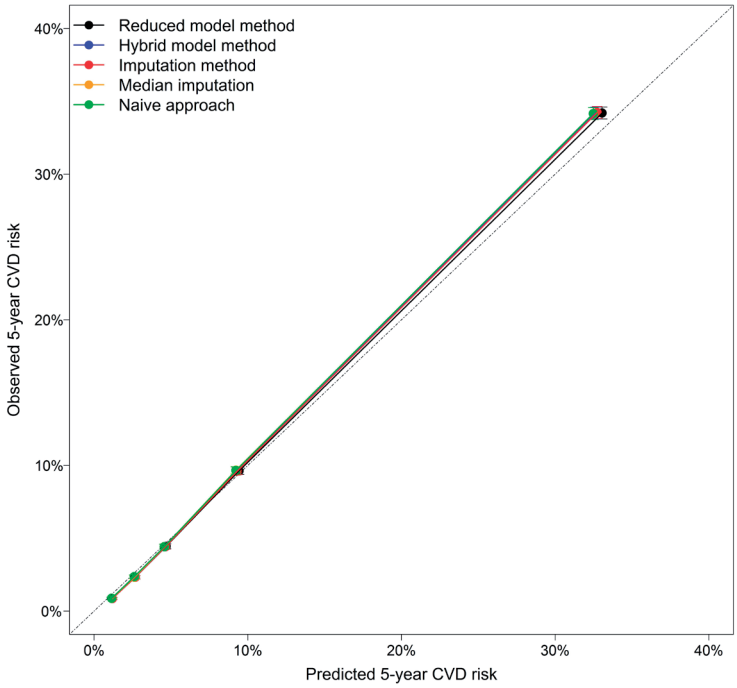


Figure 1: Calibration plot of observed versus predicted risk among patients in the Swedish national diabetes register (n = 314,650) with real-world missing patient characteristics by five methods for dealing with missing characteristics.

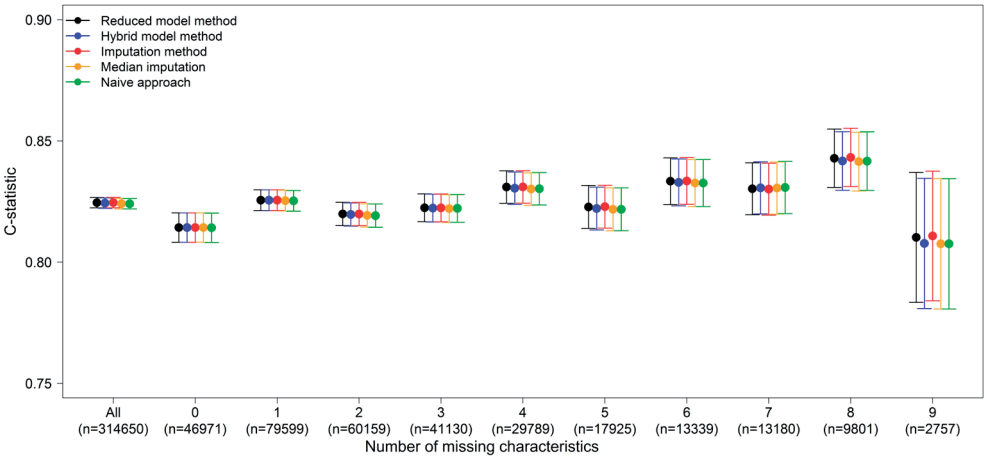


Figure 2: C-statistics for each method for handling missing patient characteristics in the Swedish national diabetes register (n = 314,650) using by number of missing patient characteristics.

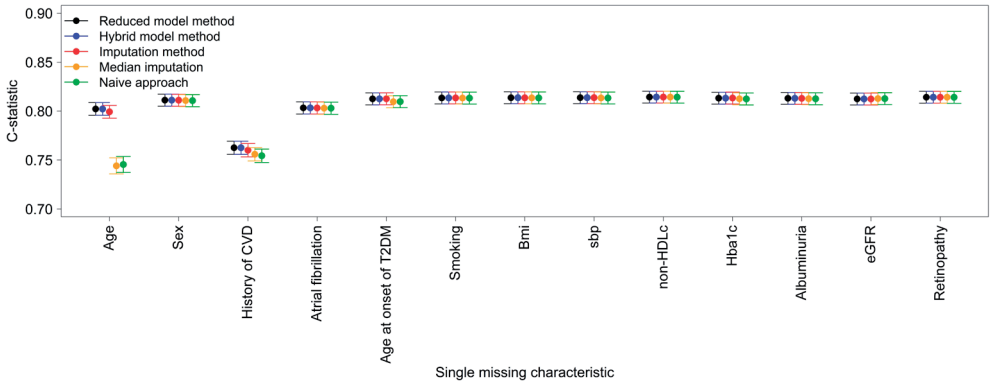


Figure 3: C-statistics for each method for handling missing patient data among a subset of people with complete data and in whom missing data were introduced for each missing characteristic separately from the Swedish national diabetes registry (n=46,971).

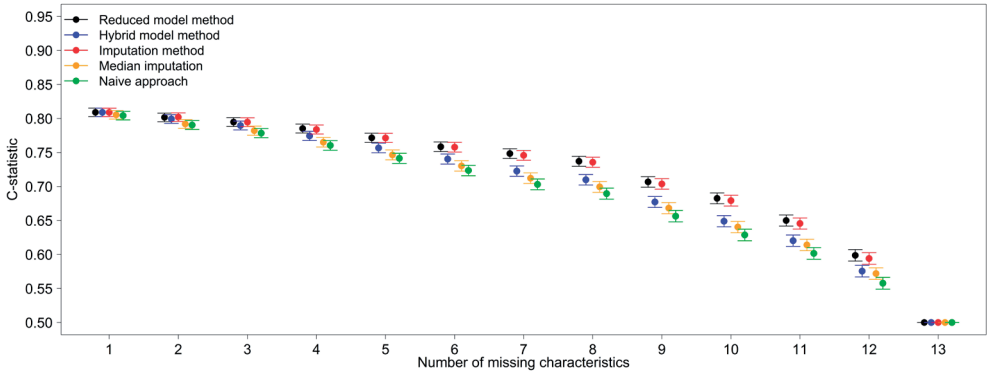


Figure 4: C-statistics for each method for handling missing patient data among a subset of people with complete data and in whom missing data were randomly introduced from Swedish national diabetes registry (n=46,971) by number of missing patient characteristics introduced.

External validity of methods dealing with missing patient characteristics in the SCI-diabetes database

After recalibration of the Swedish NDR risk equation (supplemental methods), in the clinical data of the SCI-diabetes database (n = 170,215), there was no difference in discriminative ability between the hybrid method, single imputation, median imputation, or naïve approach with c-statistics of 0.74 (95% CI 0.74-0.75; figure 5). Predicted 5-year risk was similar to observed 5-year risk for the patients with a risk <30% using each of the five methods for handling missing data. In patients with an observed risk >30%, all methods overestimated risk as expected based on the recalibration curve (supplemental figure 3).

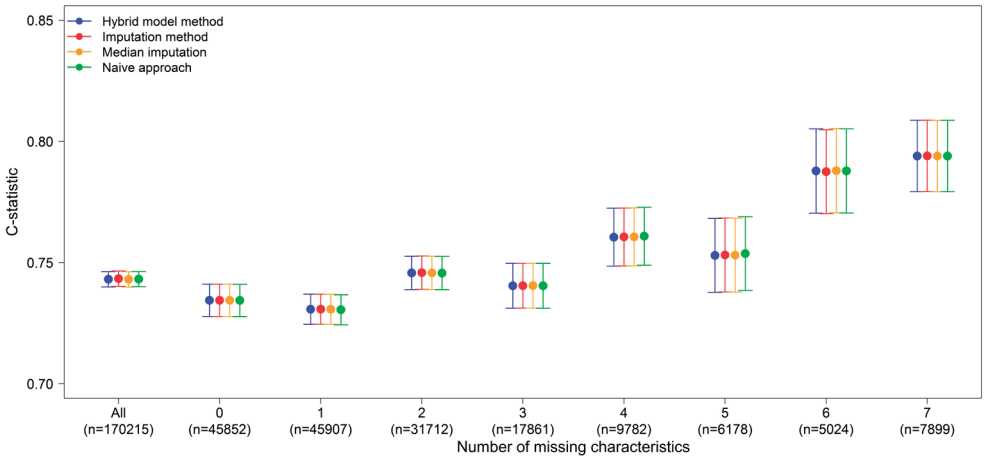


Figure 5: C-statistics for each method for handling missing data among people in the Scottish Care Information - diabetes database (n=170,250) by number of missing characteristics.

Discussion

In this study, five methods for dealing with missing patient characteristics were developed and validated in real-world test datasets with missing characteristics and in data with randomly introduced missing characteristics. The hybrid model method, single imputation, median imputation, and naïve approach all showed similar discrimination and good calibration compared to the reduced model method. When important predictor variables were missing, such as age and history of CVD, the most optimal accuracy was achieved by single imputation or the reduced model method. Here, when age, history of CVD, atrial fibrillation, and sex were available and 9 out of 13 variables were imputed using any of the five methods tested, the individual predictions were reliable.

The results of this study are comparable to previous studies in a diagnostic setting.[11] In a study with a diagnostic prediction model for deep venous thrombosis (DVT), the authors compared multiple imputation to other strategies for handling missing data. In the absence of a D-dimer test (strongest predictor for the diagnosis of DVT), multiple imputation was the best way for dealing with missing characteristics. In the absence of calf circumference, which is a weak predictor for the diagnosis of DVT, all strategies had similar results in terms of calibration and c-statistics. However, it must be emphasized that in the clinical setting for diagnosing DVT, only a few variables are needed in the model that are usually available. In prediction models predicting CVD usually 6 to 16 variables are needed for predictions and therefore the chance of missing variables becomes higher.[16]

In our study, the results did not differ by missing data method when handling incomplete weak predictors since these weak predictors have limited effect on predictive

accuracy. Therefore, any of the proposed method were able to adequately deal with missing weak predictor [17 18] The opposite is true when strong predictors are missing. In the case of missing strong predictors, the method resulting in the closest estimate of the true value of the strong predictor is more likely to have the highest predictive accuracy compared to other methods. Thus, for dealing with missing strong predictors, the median imputation and the naïve approach are insufficient.

These findings should encourage the addition of imputation models within apps or web-based calculators to handle incomplete data to enable physicians to reliably use risk prediction models in the presence of missing patient characteristics. Although imputation solves a problem of missing characteristics in clinical practice, it should be emphasized that it is still preferred to have complete data available. Any method for dealing with missing data using prediction models results in a small loss of predictive accuracy.

While the reduced model method, hybrid model method, single and median imputation methods, provide actual numbers for missing data, the naïve approach uses the population baseline hazard and the hazard ratios from the risk equation to estimate individual risks.[12] Interestingly, this fundamental difference in methods did not lead to differences in c-statistics or calibration. Thus, with all characteristics available, the naïve approach was as accurate as predictions using Cox proportional hazard models. This could provide further opportunities when other important patient information is available in addition to predictors in a risk model, such as coronary calcium score[19] or family history[20]. Both are mentioned in the ESC guidelines to downgrade or upgrade the risk in intermediate risk categories.[21] With the naïve approach, this information could be added to an existing model if the hazard ratio from large studies, ideally adjusted for all predictors in the model, and prevalence in the population is known.

Some strengths and limitations of the present study should be considered. The large number of patients, observational nature, and the methods to gather patient data in the Swedish NDR and the SCI-diabetes database allowed for analyses in clinical data with real-world missing characteristics that can be generalized to clinical practice. Whether the findings of this study could also be generalized to other fields in medicine is uncertain. However, the use of imputation as the most accurate way to deal with missing characteristics in a DVT example suggests that this method applies for prediction models in general. Although five methods were developed, only four methods were externally validated in the SCI-diabetes database. The reduced model method was not included for the analyses in the SCI-diabetes database due to long computation time, as 8,192 models were computed for the Swedish NDR that could not be stored, recalibrated, and used in an external dataset. Therefore, the reduced model method, despite being one of the most accurate methods for handling missing data, may not be suitable for clinical use when the number of predictors is high.

In conclusion, pragmatic imputation of missing values by median values resulted in reliable predictions, though were less reliable for imputing important characteristics such

as age and history of CVD. The clinical use of cardiovascular prediction tools in clinical practice could be facilitated by automatic imputation of missing patient characteristics other than age and history of CVD by median values.

Acknowledgements

For the Swedish national diabetes registry, we thank all of the clinicians who were involved in the care of patients with diabetes for collecting data, and staff at the Swedish National Diabetes Registry.

We acknowledge with gratitude the contributions of people and organisations involved in providing data, setting up, maintaining and overseeing SCI-Diabetes, including the Scottish Diabetes Research Network that is supported by National Health Service (NHS) Research Scotland, a partnership involving Scottish NHS Boards and the Chief Scientist Office of the Scottish Government.

References

1. Goff DC, Jr., 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 2):S49-73.
2. Ryden L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). European heart journal 2013;34(39):3035-87.
3. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57(2):75-89.
4. Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ 2016;353:i2416.
5. Kleinrouweler CE, Cheong-See FM, Collins GS, et al. Prognostic models in obstetrics: available, but far from applicable. Am J Obstet Gynecol 2016;214(1):79-90 e36.
6. Noble D, Mathur R, Dent T, et al. Risk models and scores for type 2 diabetes: systematic review. BMJ 2011;343:d7163.
7. Engels JM, Diehr P. Imputation of missing longitudinal data: a comparison of methods. J Clin Epidemiol 2003;56(10):968-76.
8. Gorelick MH. Bias arising from missing data in predictive models. J Clin Epidemiol 2006;59(10):1115-23.
9. Shrive FM, Stuart H, Quan H, et al. Dealing with missing data in a multi-question depression scale: a comparison of imputation methods. BMC Med Res Methodol 2006;6:57.
10. Saar-Tsechansky M, Provost F. Handling Missing Values when Applying Classification Models. Journal of machine learning research [1532-4435] 2007;8(July):1623.
11. Janssen KJ, Vergouwe Y, Donders AR, et al. Dealing with missing predictor values when applying clinical prediction models. Clin Chem 2009;55(5):994-1001.
12. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Statistics in medicine 2004;23(7):1111-30.
13. Zethelius B, Eliasson B, Eeg-Olofsson K, et al. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). Diabetes Res Clin Pract 2011;93(2):276-84.
14. Gudbjornsdottir S, Cederholm J, Nilsson PM, et al. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes care 2003;26(4):1270-6.
15. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 2001;19(13):3163-72.
16. Wessler BS, Lai Yh L, Kramer W, et al. Clinical Prediction Models for Cardiovascular Disease: Tufts Predictive Analytics and Comparative Effectiveness Clinical Prediction Model Database. Circ Cardiovasc Qual Outcomes 2015;8(4):368-75.
17. Austin PC, Pencinca MJ, Steyerberg EW. Predictive accuracy of novel risk factors and markers: A simulation study of the sensitivity of different performance measures for the Cox proportional hazards regression model. Stat Methods Med Res 2017;26(3):1053-77.
18. Austin PC, Steyerberg EW. Predictive accuracy of risk factors and markers: a simulation study of the effect of novel markers on different performance measures for logistic regression models. Statistics in medicine 2013;32(4):661-72.
19. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. Jama 2010;303(16):1610-6.
20. Superko HR, Roberts R, Garrett B, et al. Family coronary heart disease: a call to action. Clin Cardiol 2010;33(12):E1-6.

21. 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 (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal 2016;37(29):2315-81.
22. Liao P, Zeng R, Zhao X, et al. Prognostic value of non-high-density lipoprotein cholesterol for mortality in patients with coronary heart disease: A systematic review and meta-analysis. International journal of cardiology 2017;227:950-55.
23. Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes care 2003;26(1):16-23.

Supplementary appendix

Update of the Swedish national diabetes registry (NDR) risk equation[1]
Development of an update of the Swedish NDR risk equation was performed in a random 25% of patients (development dataset) using a Cox Proportional hazard regression model.

Cardiovascular outcome definitions
CVD was defined as a non-fatal coronary heart disease (CHD), non-fatal stroke, or vascular mortality. This is based on linkage to cause of death registers and hospital discharge registers using ICD-10 codes Non-fatal CHD was defined as non-fatal myocardial infarction (ICD-10 code I21), cardiac arrest (ICD-10 code I46), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention and/or coronary artery bypass. Non-fatal stroke was defined as intra-cerebral haemorrhage, cerebral infarction, or unspecified stroke (ICD-10 code I61, I63, and I64). Vascular mortality was defined as any death due to CVD (ICD-10 code I20-I25, I46, I61, I63, I64).

Model development
The risk equation of the Swedish NDR was updated including predictors of the original risk equation (age, sex, age at onset of diabetes, smoking status, BMI, SBP, HbA1c, total cholesterol and high-density lipoprotein ratio which will be replaced for non-HDLc[2] [3], albuminuria, atrial fibrillation, history of CVD and additional risk factors (eGFR and retinopathy). Missing data of the development dataset was single imputed. Continuous predictors will be truncated at the 1st and 99th percentile to limit the effect of outliers. Log-linearity of the relationship between continuous predictors and the outcome will be tested with restricted cubic splines and transformation is applied when this improves model fit based on Akaike's Information Criterion (AIC). The proportional hazard assumption will be assessed by inspection of the Schoenfeld residuals.

Validation of the updated Swedish NDR risk equation
The updated Swedish NDR risk equation was internal and external validated in the Swedish NDR and the SCI-diabetes database. Model validation was performed assessing goodness of fit with calibration plots comparing 5-year predicted and observed risks. Discrimination was quantified using a bootstrap method to calculate c-statistics with 95% confidence intervals.

Results of updated Swedish NDR risk equation
In the random 25% development dataset (n=104,883) of the Swedish NDR a number of 11,446 cardiovascular events occurred in a median follow up of 5.6 years (IQR 3.7-8.3 years). In the remaining 75% internal validation dataset (n=314,650) of the Swedish NDR a number of 34,394 cardiovascular events occurred in equal follow up duration. In

the random 25% SCI-diabetes database recalibration dataset (n=56,738) a total of 8,826 cardiovascular events occurred in a median follow up of 4.8 years (IQR 2.3-7.9 years). In the remaining 75% SCI-diabetes database external validation dataset (n=170,215) a total of 26,352 cardiovascular events occurred in a median follow up of 4.8 years (IQR 2.2-7.9 years). The calculation formula of the updated Swedish NDR risk equation is provided in supplemental table 2. Based on the AIC, SBP and HbA1c were quadratic terms in to the risk equation. eGFR was log-transformed based on the AIC. Interaction between history of CVD and age significantly improved model fit (p-value <0.001) and was therefore added to the model.

Internal validation

After updating the risk equation, predicted 5-year risk showed good agreement with the observed 5-year risk in the development dataset (supplemental figure 4). C-statistic was 0.82 (95% CI 0.82-0.83).

External validation

After recalibration of the Swedish NDR risk equation using 25% of the patients' data in the SCI-diabetes database, the predicted 5-year risks showed good agreement with 5-year observed risks (supplemental figure 5). For external validation, the c-statistic was 0.73 (95% CI 0.73-0.74).

Supplemental table 1: Chi-squares of variables in the updated NDR risk equation. Age and history of vascular disease are the most important variables in the model, based on the highest chi-square.

Variables of updated Swedish NDR risk equation	Chi-square
Age (years)	7437
Sex (female/male)	551
Age at onset of T2DM (years)	398
Smoking status (yes/no)	46
Body-mass index (kg/m^2)	99
Systolic blood pressure (mmHg)	408
Haemoglobin A1c (mmol/mol)	187
Non-HDLc (mmol/l)	127
Albuminuria (no/micro/macro)	313
eGFR (ml/min/1.73 m^2)	197
Retinopathy (yes/no)	3
History of CVD (yes/no)	5898
Atrial fibrillation (yes/no)	1792
Age*history of CVD (interaction term)	421

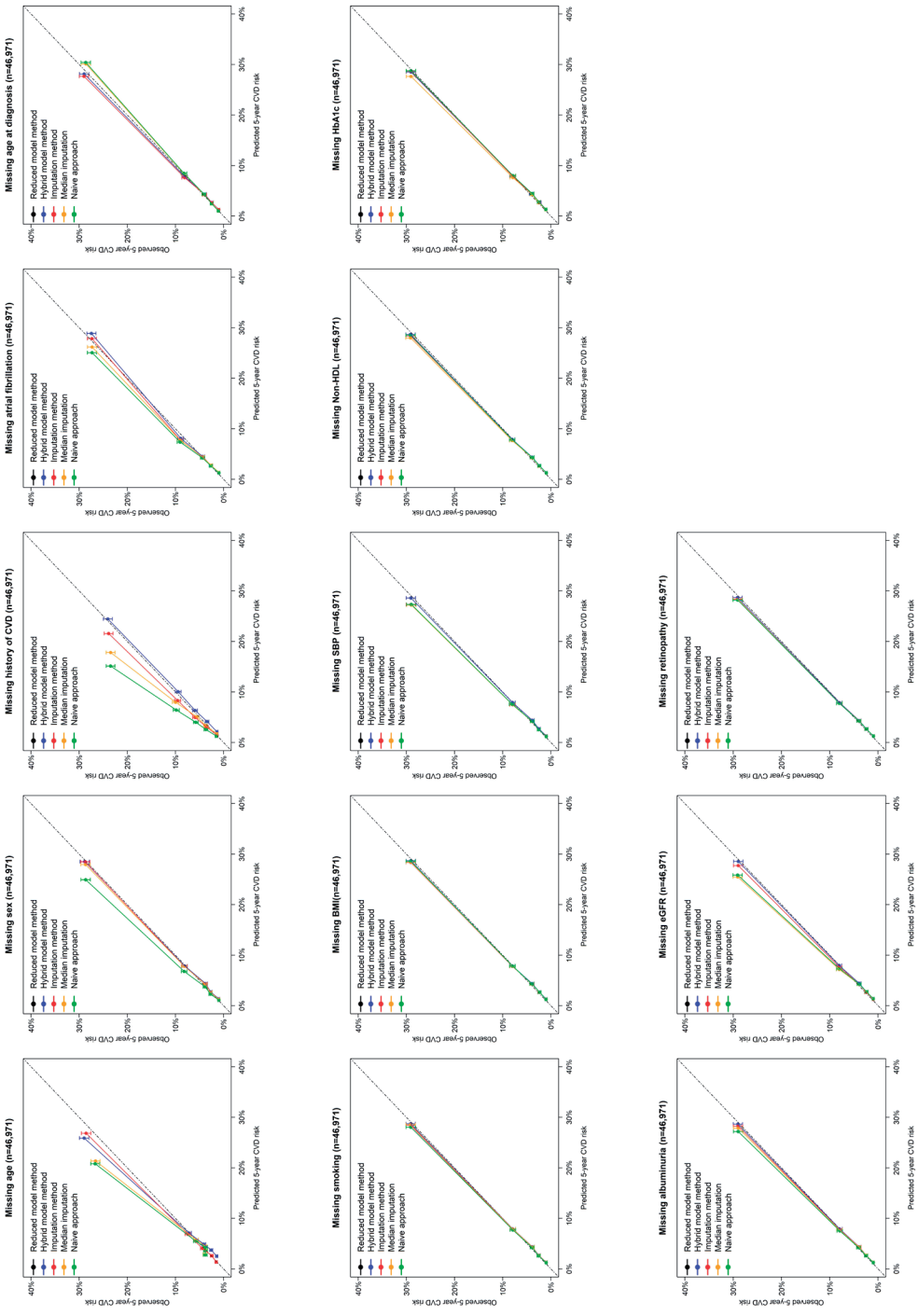
Supplemental table 2: Calculation formula of 5-year cardiovascular disease (CVD) risk.

5-year risk prediction for CVD with the Swedish NDR risk equation (%)

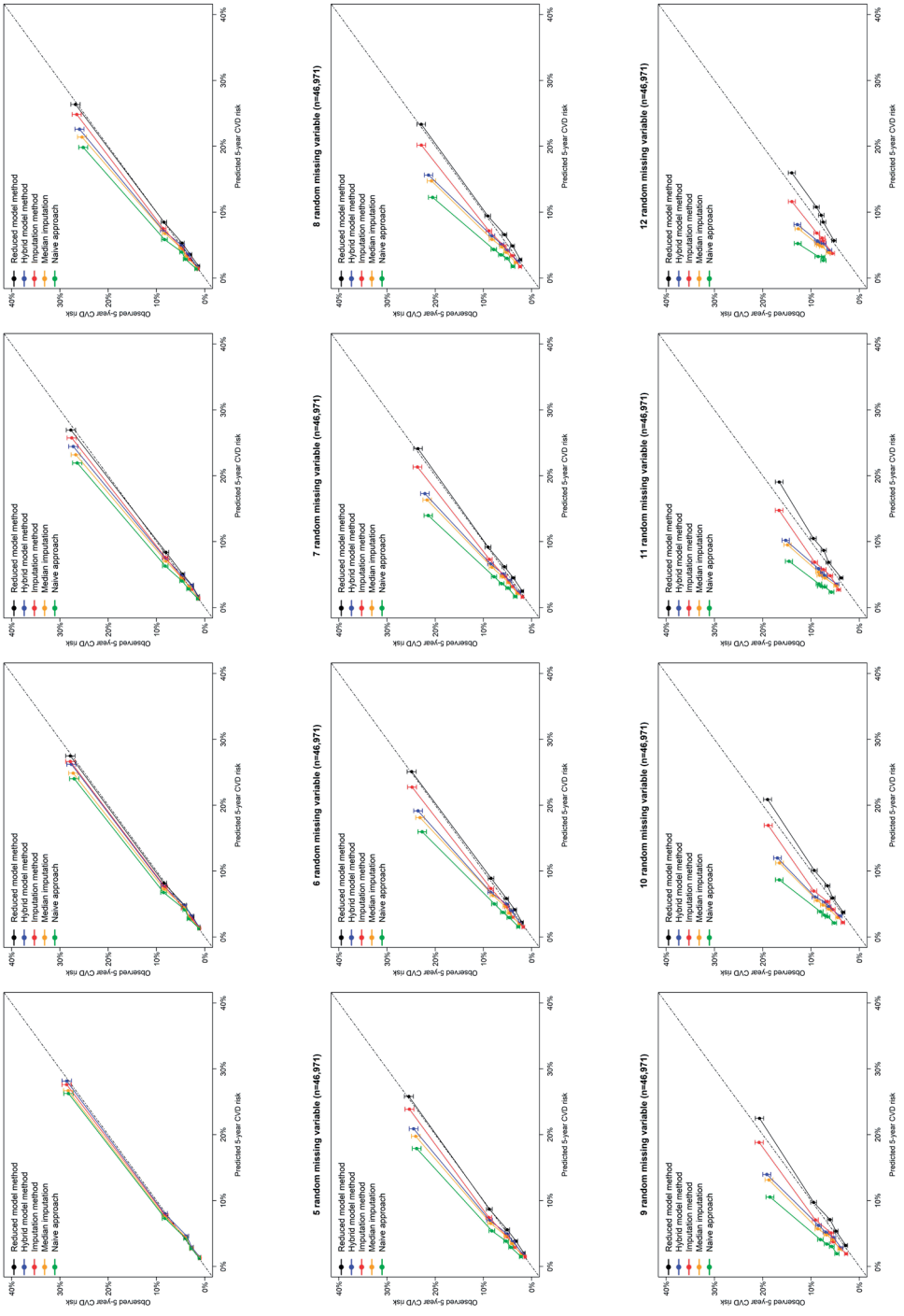
Sweden: $(1 - 0.973^{\exp(LP)}) * 100\%$
Scotland: $(1 - 0.964^{\exp(LP+0.053848)}) * 100\%$

LP = linear predictor = 0.0838 * (age in years) + 0.2639 (if male) - 0.0174 * (age at onset of T2DM) + 0.1582 (if current smoker) + 0.0081 * (body mass index in kg/m^2) - 0.0447 * (systolic blood pressure in mmHg) + 0.0001 * (systolic blood pressure in mmHg)^2 + 0.0295 * (hba1c in mmol/mol) - 0.0002 (hba1c in mmol/mol)^2 + 0.0081 * (non-HDLc in mmol/l) + 0.1050 (if micro-albuminuria) + 0.2291 (if macro-albuminuria) + 0.7732 (if atrial fibrillation) - 0.5170 * log(eGFR in ml/min/1.73m^2) + 0.0317 (if retinopathy) + 4.4345 (if history of CVD) - 0.0386 * (age in years if history of CVD)

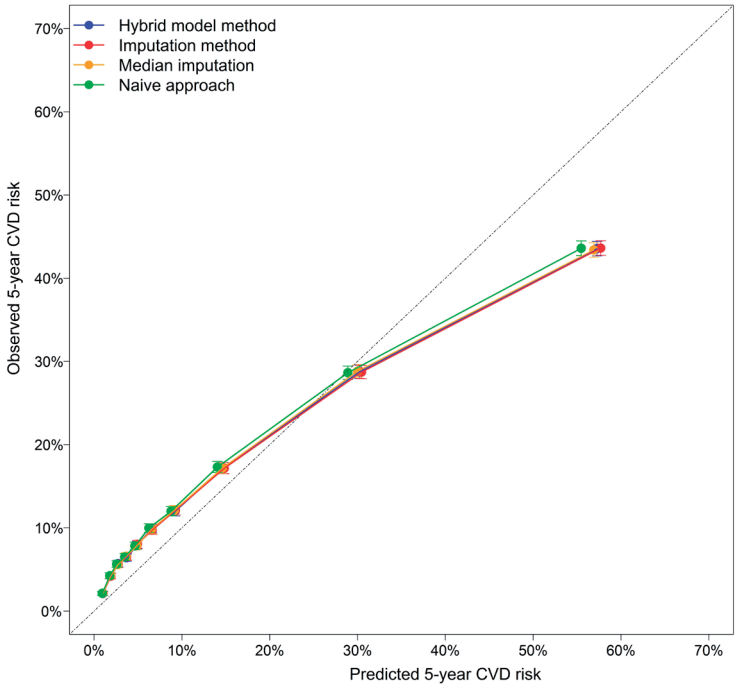
NDR: National diabetes registry. T2DM: Type 2 diabetes mellitus. CVD: Cardiovascular disease.



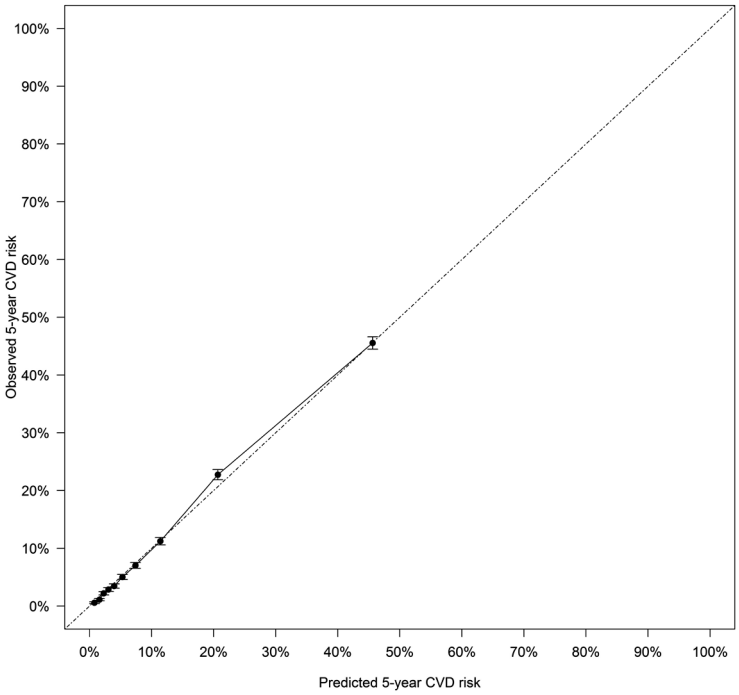
Supplemental figure 1: Calibration of randomly introduced single missing variables in all complete cases of the Swedish national diabetes registry (NDR)



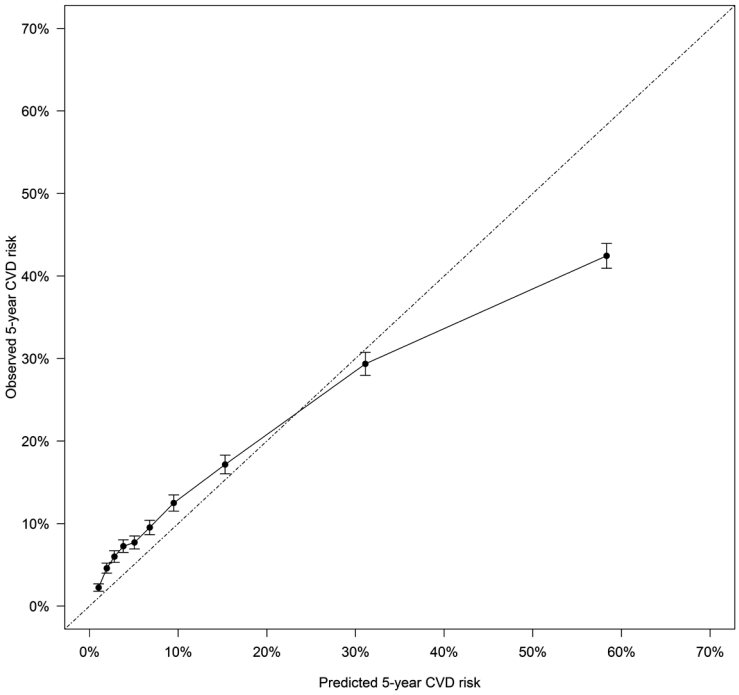
Supplemental figure 2: Calibration of randomly introduced single missing variables in all complete cases of the Swedish national diabetes registry (NDR)



Supplemental figure 3: Calibration of the Swedish NDR risk equation in the clinical data with real-world missing patient characteristics in the Scottish Care Information-diabetes register. Dots represent mean risks with 95% confidence intervals of patients grouped by deciles of predicted risk.



Supplemental figure 4: Calibration of the updated Swedish NDR risk equation (internal validation of risk score). Dots represent mean risks with 95% confidence intervals of patients grouped by deciles of predicted risk.



Supplemental figure 5: Calibration of the Swedish NDR risk equation in the recalibration data of the Scottish Care Information-diabetes register (external validation of risk score). Dots represent mean risks with 95% confidence intervals of patients grouped by deciles of predicted risk.

References

1. Zethelius B, Eliasson B, Eeg-Olofsson K, et al. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). Diabetes Res Clin Pract 2011;**93**(2):276-84.
2. Liao P, Zeng R, Zhao X, et al. Prognostic value of non-high-density lipoprotein cholesterol for mortality in patients with coronary heart disease: A systematic review and meta-analysis. International journal of cardiology 2017;**227**:950-55.
3. Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes care 2003;**26**(1):16-23.

6

Chapter 6

Lifelong PCSK9-monoclonal antibody treatment vs. a limited treatment period at some stage in life to reduce cardiovascular risk in patients with vascular disease

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Abstract

Background - Maximum benefit from intensive lipid-lowering therapy to prevent cardiovascular disease (CVD) is achieved by lifelong treatment, but high financial costs of PCSK9 monoclonal antibodies (mAbs) urge for consideration of alternative treatment strategies. One option is to postpone treatment to later in life, a period associated with higher CVD risk. Another option is to treat patients earlier in life, but for shorter treatment duration.

Objective - To estimate the effect of postponed and/or shortened treatment durations compared to lifelong treatment with PCSK9-mAbs in patients with a history of CVD.

Methods - Patients included were 45 to 75 years with a history of CVD originating from the SMART cohort. Using a lifetime perspective prediction model (SMART-REACH model), lifetime benefit in life years gained was estimated based on CVD-risk, baseline LDL-c, and expected 59% reduction in LDL-c with PCSK9-mAbs. Life years gained was calculated for postponed and shorter durations of treatment with and without a presumed legacy effect.

Results - 10-year postponement of treatment resulted in a loss of treatment benefit of 0.2 CVD-free life-years for 5-year, 0.5 years for 10-year and and 1.9 years for lifelong treatment. When patients are treated at their current age, the lifetime benefit increases with 1.1 CVD-free life-years per 10-year additional treatment duration when no legacy effect is assumed. Lifetime benefit of treatment assuming a constant legacy effect is 2.6 years independent of treatment duration. With an assumed declining legacy effect, a treatment duration of 10 year would result in 2.5 year lifetime gain compared to a lifetime gain of 3.6 year when treated lifelong.

Conclusion - Postponement of intensive lipid-lowering therapy in patients with vascular disease always leads to loss of treatment efficacy. Given the likelihood of a legacy effect, it could be considered to discontinue treatment after a treatment period of 3 to 10 years, especially in older patients or patients with lower life-expectancy and already low LDL-c levels.

Introduction

Several guidelines recommend lipid-lowering treatment for patients at high risk of cardiovascular disease (CVD).[1,2] When a patient is considered at high risk of CVD, lipid lowering treatments such as statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9-mAbs) are prescribed usually lifelong. However, these guidelines provide no recommendations for stopping lipid lowering treatment at a certain age for futility. High financial costs of PCSK9-mAbs urge for consideration of alternative treatment strategies. One option is to postpone treatment to a higher age, which is associated with higher risk of CVD, and therefore results in higher absolute benefit. Another option is to treat patients earlier in life, but for a limited treatment duration., which affects lifelong CVD risk.

A recent study has shown that elderly patients have less benefit from lipid-lowering treatment with high number needed to treat, depending on their medical history and clinical characteristics.[3] Also, there is evidence for a legacy effect of statins, with a persistent effect after 5-year therapy up to 20 years after discontinuation.[4-6] Thus, benefits of statin treatment do not instantly stop when the drugs are stopped. Although these findings suggest that patients may benefit from shorter treatment durations, it is unknown what on the optimal moment in life to start or the optimal limited treatment duration of PCSK9-mAbs.

PCSK9-mAbs are a class of drugs that effectively reduce low-density lipoprotein cholesterol (LDL-c) levels with 50-60%, and reduce the risk of CVD.[7-9] Considering the high costs of PCSK9-mAbs[10], it could be considered to start treatment later in a patient's life or shorten the treatment period and still receive sizeable benefit in terms of CVD risk reduction, especially when a legacy effect is assumed due to atherosclerosis stabilization.[11]

Recently developed prediction models are able to estimate lifetime individual benefit of medication for prevention of CVD in patients with manifest vascular disease expressed as years gained from a lifetime perspective, the lifetime benefit.[12] The statistical methods of these prediction models allow for alterations to estimate effects of postponed preventive treatment. It also gives the opportunity to estimate the lifetime benefit of stopping medication with or without a legacy effect.

The objective of the present study is to estimate the effect of starting treatment later in life and/or a short treatment period compared to lifelong treatment with PCSK9-mAbs in patients with clinical evident CVD, to lower the risk of recurrent CVD with and without an assumed legacy effect.

Methods

Study population

Baseline characteristics were used of patients originated from The Secondary Manifest of ARTerial disease (SMART) cohort included between 1996 and 2016. The SMART cohort is an ongoing, single-center, prospective cohort study.[13] For the current study, patients included were between 45 and 75 years of age with clinical manifest vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, or abdominal aortic aneurysm). Patients with baseline low-density lipoprotein cholesterol (LDL-c) lower than 1.8mmol/L were excluded, since these patients do not need an intensified cholesterol lowering treatment according to current guidelines.

Individual treatment effect estimates of lifelong treatment

Individualized lifetime benefit of treatment is estimated using the REACH-SMART model (www.U-Prevent.com). The REACH-SMART model is a prediction model with a lifetime horizon. It has been developed in the REduction of Atherothrombosis for Continued Health (REACH) and external validated in the Secondary Manifestations of ARTerial disease (SMART) cohort. REACH and SMART are prospective cohort studies of patients with clinical vascular disease or vascular risk factors. Study details have been described elsewhere.[13,14] The statistical methods of the model were previously described in detail.[15,16] In short, two Fine and Gray competing risk models were fitted for cause specific estimates of the cumulative incidence, one for recurrent vascular events (stroke, myocardial infarction, or vascular death) and one for non-vascular mortality. Age was used as the underlying time function (i.e., left-truncation). This enables lifetime predictions across the age range from the youngest age at study entry to the highest age at study exit. Beginning at the starting age of each individual, the cumulative survival free of myocardial infarction (MI) and stroke was estimated for each subsequent year. The estimated survival free of MI and stroke at the beginning of each life-year was multiplied by the survival probability during that year. The survival probability was obtained by subtracting vascular risk and non-vascular mortality risk from one.

Life-expectancy free of stroke or MI of an individual person was defined as the median estimated survival, which is the age where the predicted individual survival curve equals 50%. To estimate the life-expectancy free of stroke or MI with treatment, an individualized hazard ratio PCSK9 inhibition (explained below) is added to the Fine and Gray competing risk model for recurrent vascular events. Due to the complementary risk model for non-vascular death, reducing risk for recurrent CVD results in a larger absolute risk for non-vascular death. An individual's benefit from lifelong treatment was estimated as the difference between the median estimated survival with and without treatment.

Treatment effects for treatments at some stage in life with or without a legacy effect

To estimate treatment effects that are of limited duration at any stage in life, the individualized hazard ratio for therapy can be added only at the years of treatment to the competing risk model for recurrent CVD. Similarly, a legacy effect can be added to the model after treatment has been stopped. To estimate an individual's benefit of treatments at some stages in life, the estimated survival curves are divided in parts equal to duration of postponed treatment, treatment duration, and treatment withdraw. The differences in median survival of these separate parts are estimated, multiplied by the proportion of the survival curve, and added up. A simplified example of a survival curve for a 50 year old individual patient is given in figure 1. The postponement of treatment for this patient results in no difference between median survivals for the first 20% of the survival curve. Starting a 15 year treatment after 5 year, will diverge the survival curves with and without treatment. The number of years gained in this part is measured at a survival level of 0.62, because this is the median between 0.8 (i.e. survival chance at the beginning of this treatment interval) and 0.44 (i.e. survival chance at the end of this treatment interval). The number of years gained in this part is 3.0 years multiplied by the respective proportion of the survival curve (i.e from 0.8 and 0.44 = 0.36). This equals 0.36*3.0 = 1.08 year lifetime benefit. After the treatment interval, therapy is stopped, which will converge the survival curves. However, there is still benefit in this part (i.e. 4.5 years), shown by a difference in median survivals. This difference is also multiplied by the respective proportion of the survival curve (i.e. 44%) and this results in an additional 0.44*4.5 = 1.98 years lifetime benefit. The total expected lifetime benefit of treatment in this simplified individual patient example would, thus, be 0 + 1.08 + 1.98 = 3.06 years.

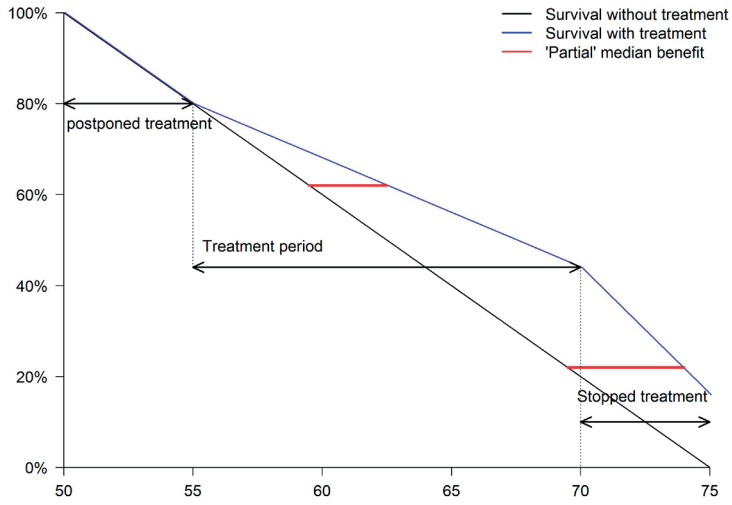

Figure 1: Median expected lifetime benefit with postponed and shorter duration of treatment.

Individual hazard ratios of PCSK9 inhibitors

Our assumption on the effect of PCSK9-inhibition was based on the expected LDL-c reduction, which is conditional to the baseline LDL-c level.[8] On average, PCSK9-mAbs have been shown to reduce LDL-c levels by 59%.[9] The results of the recent PSCK9-mAbs outcome trial correspond with the more robust results from large meta-analyses showing a hazard ratio of 0.78 (95% CI 0.76-0.80) for major vascular events per 1 mmol/L LDL-c reduction.[7,17] There was no indication of a decreasing effect size when LDL-c were reduced below 2 mmol/L.[17] Thus, for our study the individualized relative treatment effect of PCSK9 inhibition on CVD based on expected LDL-c reduction was defined as $0.78^{0.59*\text{LDL-c}}$. Individualized hazard ratios (HRs) were calculated for each study participant. We assumed that LDL-c reduction has no effect on non-vascular mortality.[17]

Legacy effect of lipid-lowering therapy

The West of Scotland Coronary Prevention Study (WOSCOPS) showed a reduction of cardiovascular events with a HR of 0.79 after 20-years follow-up[5], although after 10-year follow-up the use of statins was shown to be equal with 35.2% in the original placebo group and 38.7% treatment group.[18] Based on these results and the reached difference in LDL-c of 1.3 mmol/L during the original placebo controlled double blinded trial[19], a scenario of the legacy effect of lipid-lowering therapy was a remaining effect of therapy with a HR of 0.84 per 1 mmol/L LDL-c over the remaining lifespan.

To take in to account treatment duration and possible overestimation of the legacy effect, another scenario modelled was a decaying legacy effect of lipid-lowering therapy. The effect of lipid-lowering therapy in this scenario is assumed to be equal as on treatment effects (HR 0.78 per mmol/L) for half of the on-treatment period. Afterwards, the effect of lipid-lowering treatment was reduced with a half-life every half on-treatment period. This results in a logaritmic decaying treamtent effect with a HR of $0.78^{\wedge(0.5^{\wedge}0)} = 0.78$, $0.78^{\wedge(0.5^{\wedge}1)} = 0.88$, $0.78^{\wedge(0.5^{\wedge}2)} = 0.94$, $0.78^{\wedge(0.5^{\wedge}3)} = 0.97$ etc. for every passed half on-treatment period after stopping treatment. These two scenario's of treatment effects including legacy effects are compared with a scenario were there is no assumed legacy effect.

Statistical analyses

Predictions of the lifetime benefit of PCSK9-mAbs were estimated for all study patients. First, this was performed for lifelong, 5 year, and 10 year treatment durations. The predictions are made with and without assumed legacy effects. Mean lifetime benefits were plot against age to inspect the influence of increasing age of patients on the lifetime benefit. The effect of age on the lifetime benefit independent of 10-year risk and LDL-c was quantified using linear regression analyses. In addition, a graphical representation of lifetime benefit was shown stratified for age groups (45-55 year, 55-65 year, 65-75 year), risk groups (10%-20%, 20-30%, 30-40%, >40%), and LDL-c (1.8-2.5 mmol/L, 2.5-3.5 mmol/L, >3.5 mmol/L).

To investigate the effect of postponed treatment, the years of postponement between 0 years (meaning immediate start of treatment at a patient's current age) and 10 years were randomly assigned to the study patients to avoid differences in distributions of age, risk, or risk factors. The effect of postponed treatment on the lifetime benefit of a patient was calculated for lifelong, 5-year, and 10-year treatment with and without legacy effects. The lifetime benefit of patients was inspected with a graphical representation. To quantify the effect of postponed treatment independent of a patient's age, 10-year risk, or LDL-c, a linear regression analyses was performed with lifetime benefit as the dependent variable. Similarly, the effect of a shortened duration of treatment was investigated by randomly assignment of treatment durations between 1 and 20 years, quantifying the effect using linear regression models. All statistical analyses were conducted using R version 3.4.1.

Results

Data from 5,739 patients with a history of CVD were used for the present analyses. Mean age was 60 ± 8 years and 74% of the patients were male (table 1). Median 10-year risk for CVD estimated using the REACH-SMART model was 27% (IQR 22% - 36%).

Table 1: Baseline characteristics

	n = 5,739
Age (years)	61 (54 - 67)
Male	4263 (74%)
Current smoking	1830 (32%)
Type 2 diabetes mellitus	901 (16%)
Systolic blood pressure (mmHg)	138 (126 - 152)
Total cholesterol (mmol/L)	4.9 (4.2 - 5.7)
LDL-c (mmol/L)	2.9 (2.3 - 3.6)
Creatinine (umol/L)	88 (77 - 100)
1 location of CVD	4864 (85%)
2 location of CVD	768 (13%)
3 location of CVD	107 (2%)
Atrial fibrillation	148 (3%)
Heart faillure	285 (5%)
Lipid-lowering medication	3810 (66%)

All data are displayed as median (Inter quartile range) or n (%).
LDL-c: low-density lipoprotein cholesterol
* Locations of CVD: The number of locations of vascular disease (i.e. Coronary heart disease, cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysm and combinations).

Relation between age at start of PCSK9-mAbs and benefit of treatment

In general, more lifetime benefit can be gained in younger patients than in older patients. Also, lifetime benefit increases with start at young age and longer treatment durations, with the highest lifetime benefit for younger patients treated lifelong (figure 2). Lifetime benefit of a limited duration of treatment is higher with larger assumed legacy effect (figure 2). Compared to lifelong treatment delaying start of PCSK9-mAbs treatment with 10 year results in a decrease of 1.8 year (95% CI 1.7 – 1.8 year) CVD free life benefit (for example starting at age 70-years instead of starting at age 70-year). This lower benefit is adjusted for 10-year risk and LDL-c which is typically higher in older patients (table 2). It is also adjusted for life-expectancy, which is higher in younger patients with a median of 68 year (IQR 65-73) for patients of 45 to 50 years old, and 81 (IQR 79 – 83) for patients of 70 to 75 years old. Thus, lifelong treatment for young patients would mean treating for about 20 years, and for older patients that would be treating for approximately 10 years. Limited treatment durations of 5 or 10 year have the same lifetime benefit irrespective of age at start of PCSK9-mAbs therapy, assuming no legacy effect (figure 2). However, it must be noted, that this is independent of increasing 10-year risks and LDL-c at older age. When assuming a legacy effect, short durations of treatment starting at younger age always results in more lifetime benefit, with increasing lifetime benefit with increasing assumed legacy effects (table 2).

Exploratory analyses which group of patients benefit most from lifelong treatment, and thus without legacy effect, are shown in figure 3. Notably, younger patients with the highest LDL-c have the most benefit from lifelong treatment.

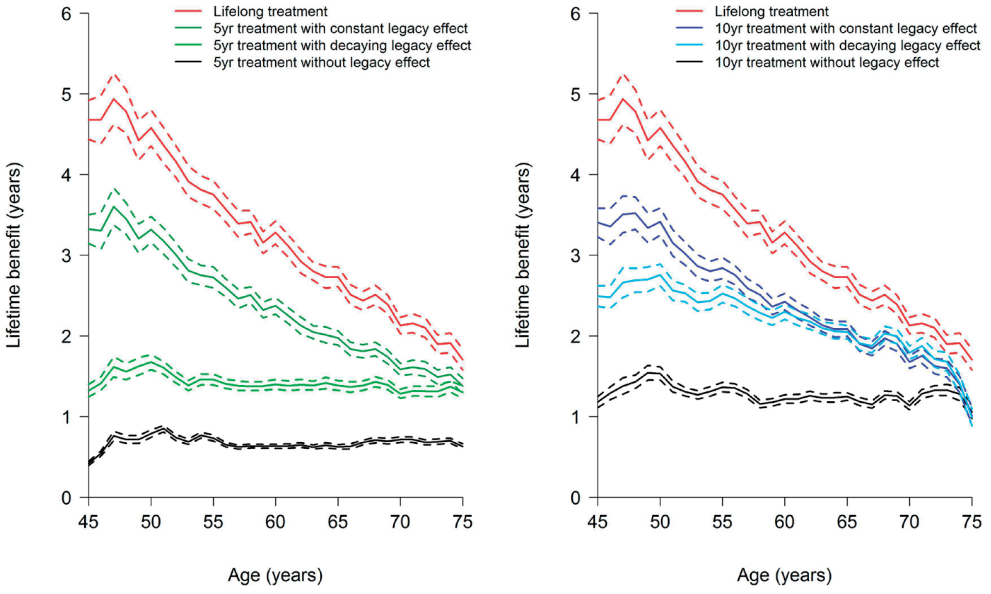

Figure 2: Effect of age of patients on lifetime benefit in life years gained for lifelong and five year treatment duration (left) and lifelong and ten year treatment durations (right), with and without assumed legacy effects.

Table 2: Relation between age at start of PCSK9-mAbs and benefit of treatment.

	Treatment duration						
	Lifelong	Five year			Ten year		
Legacy effect	**NA**	**Without**	**Constant**	**Decay**	**Without**	**Constant**	**Decay**
Age (per +10 years)	-1.8 (-1.8 - -1.7)	0.0 (0.0 - 0.0)	-1.3 (-1.3 - -1.2)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	-1.2 (-1.2 - -1.1)	-0.3 (-0.3 - -0.2)
10-year CVD-risk (per +10%)	0.15 (0.13 - 0.18)	0.1 (0.1 - 0.1)	0.1 (0.1 - 0.2)	0.0 (0.0 - 0.0)	0.1 (0.1 - 0.1)	0.2 (0.1 - 0.2)	0.0 (0.0 - 0.0)
Median life expectancy (per +10-years)	1.3 (1.2 - 1.3)	-0.1 (-0.1 - -0.1)	0.9 (0.8 - 0.9)	-0.2 (-0.3 - -0.2)	-0.1 (-0.2 - -0.1)	0.7 (0.6 - 0.7)	-0.2 (-0.2 - -0.1)
LDL-c (per +1 mmol/L)	1.0 (1.0 - 1.0)	0.2 (0.2 - 0.2)	0.8 (0.8 - 0.8)	0.4 (0.4 - 0.4)	0.4 (0.4 - 0.4)	0.8 (0.7 - 0.8)	0.7 (0.6 - 0.7)

Effect of differences in patient's current age, CVD-risk, life-expectancy and LDL-c level on lifetime benefit in life years gained from PCSK9-inhibition with different treatment durations, with and without assumed legacy effects. Differences were adjusted for one-another and, thus, independent (i.e. age-differences are adjusted for CVD-risk, life-expectancy and LDL-c level). Data are displayed as life years gained with 95% CI. LDL-c: low-density lipoprotein cholesterol. Data are displayed as life years gained with 95% CI; LDL-c: low-density lipoprotein cholesterol.

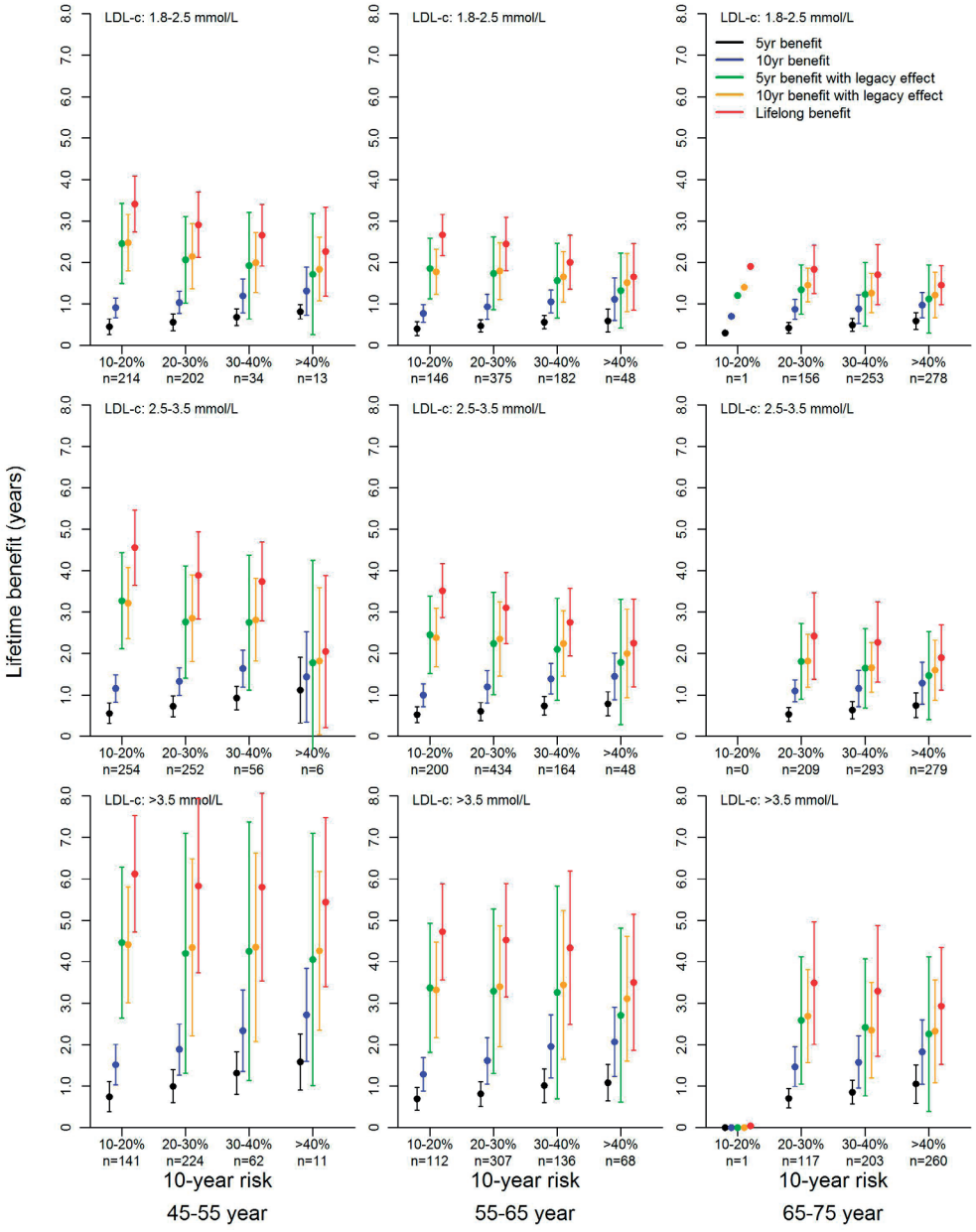

Figure 3: Lifetime benefit of lifelong treatment with PCSK9-mAbs stratified for age groups, LDL-c levels, and CVD-risk. Lifelong treatment of younger patients with high LDL-c levels results in the highest lifetime benefit.

Relation between delaying the start of treatment and lifetime benefit

As shown in figure 4, postponement of treatment results in a decrease in lifetime benefit in any of the scenarios (lifelong treatment, 5-year treatment with and without legacy effect, or 10-year treatment with and without legacy effect). The largest decrease due to delaying treatment was seen in the lifelong treated patients with a decrease of 1.9 year (95% CI 1.8 – 1.9 years) in lifetime benefit per 10-year postponed treatment. For example a 45 year old patient, who would start PCSK9-mAbs treatment at 55 years leads to 1.9 year less gain in lifetime benefit.

Adjusted for age, LDL-c, life-expectancy, and 10-year risk, postponement of treatment was least disadvantageous on the lifetime benefit with a 0.2 year (95% CI 0.2 – 0.2 years) lower lifetime benefit per 10-year postponed treatment (table 3).

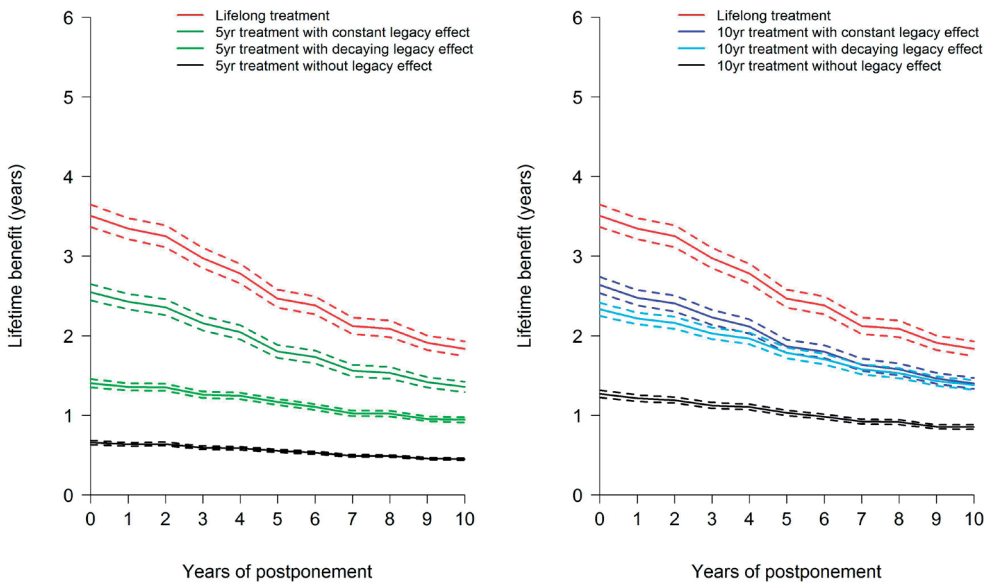

Figure 4: Effect of postponement of 5-year treatment (left) and 10-year treatment (right) compared to lifelong treatment (red lines) with and without a presumed legacy effect.

Relation between duration of PCSK9-mAbs treatment and lifetime benefit

The expected average lifetime benefit of patients randomly assigned to a treatment duration varying from 1 to 20 years is plotted against lifetime benefit (figure 5). Naturally, maximum treatment effects can be achieved by lifelong treatment with an average CVD-free life years gained of 3.6 years, and this scenario can be used as a comparison for the effect of shortened treatment strategies. When treatment duration is shorter, the impact of the treatment duration on the lifetime benefit depends on the assumption of a legacy effect. Without a legacy effect, the lifetime benefit of patients is 1.1 year (95% CI 1.1 - 1.2) more for each 10-year longer treatment duration, presumably until lifelong treatment.

Table 3: Relation between delaying the start of treatment and lifetime benefit

	Treatment duration						
	Lifelong	Five year			Ten year		
Legacy effect	**NA**	**Without**	**Cosntant**	**Decay**	**Without**	**Constant**	**Decay**
Postponed treatment (per +10-years)	-1.9 (-1.9 - -1.8)	-0.2 (-0.2 - -0.2)	-1.3 (-1.3 - -1.2)	-0.5 (-0.5 - -0.5)	-0.5 (-0.5 - -0.5)	-1.3 (-1.4 - -1.3)	-1.0 (-1.1 - -1.0)
Age (per +10 years)	-1.7 (-1.8 - -1.7)	0.0 (0.0 - 0.0)	-1.2 (-1.2 - 1.1)	-0.1 (-0.1 - 0.0)	-0.1 (-0.1 - -0.1)	-1.1 (-1.1 - -1.0)	-0.4 (-0.5 - -0.4)
10-year CVD risk (per +10%)	0.2 (0.1 - 0.2)	0.0 (0.0 - 0.0)	0.1 (0.1 - 0.2)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.1 (0.1 - 0.1)	-0.1 (-0.1 - 0.0)
Median life expectancy (per +10-years)	1.4 (1.3 - 1.5)	0.0 (0.0 - 0.0)	0.9 (0.8 - 1.0)	-0.1 (-0.1 - 0.0)	0.0 (-0.1 - 0.0)	0.7 (0.7 - 0.8)	0.1 (0.1 - 0.1)
LDL-c (per +1 mmol/L)	0.8 (0.8 - 0.8)	0.1 (0.1 - 0.2)	0.6 (0.6 - 0.6)	0.3 (0.3 - 0.3)	0.3 (0.3 - 0.3)	0.6 (0.6 - 0.6)	0.6 (0.5 - 0.6)

Effect of delaying treatment for a certain number of years or until a later age, higher level of CVD-risk, higher LDL-c level or shorter life-expectancy on lifetime benefit in life years gained from PCSK9-inhibition with different treatment durations, with and without assumed legacy effects. Data are displayed as life years gained with 95% CI. LDL-c: low-density lipoprotein cholesterol. Data are displayed as life years gained with 95% CI; LDL-c: low-density lipoprotein cholesterol

With a constant legacy effect as assumed based on the WOSCOPS[5], the lifetime benefit is 0.2 year (95% CI 0.2 – 0.2 years) higher for each 10 year longer treatment duration (table 4). However, most of the CVD-free gain in life years with a constant legacy effect is expected to be at the moment treatment has started (figure 5), and does not depend on treatment duration. When the legacy effect decays conditional on treatment duration, the lifetime benefit is 2.5 year (95% CI 2.4 – 2.5 years) higher with a treatment duration between 1 and 10 year and 0.75 year (95% CI 0.73 – 0.76 years) higher between 10 and 20 year treatment duration (table 4). The most lifetime benefit is gained in the first 10-years of treatment (figure 5).

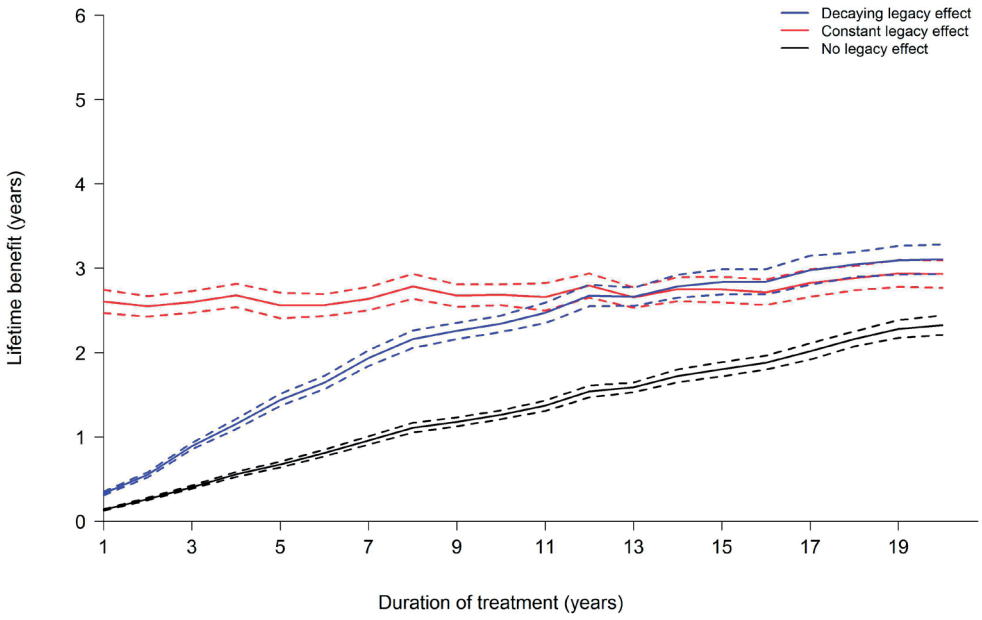

Figure 5: Effect of different treatment durations with and without legacy effect. Lifelong treatment was not shown in this figure.

Table 4: Relation between duration of PCSK9-mAbs treatment and lifetime benefit

	Legacy effect		
	Without	**Constant**	**Decay**
Duration of treatment (per + 10-year)	1.1 (1.1 - 1.2)	0.2 (0.2 - 0.2)	1.1 (1.1 - 1.1)*
Age (per +10 years)	-0.1 (-0.2 - -0.1)	-1.3 (-1.2 - -1.3)	0.0 (-0.1 - 0.0)
10-year CVD risk (per +10%)	0.1 (0.1 - 0.1)	0.2 (0.2 - 0.2)	0.1 (0.0 - 0.1)
Median life expectancy (per +10-years)	-0.1 (-0.1 - 0.0)	0.8 (0.7 - 0.9)	0.1 (0.0 - 0.1)
LDL-c (per +1 mmol/L)	0.4 (0.4 - 0.4)	0.9 (0.9 - 0.9)	0.7 (0.7 - 0.7)

Regression coefficients of the effect of treatment durations on lifetime benefit in life years gained independent of age, 10-year CVD risk, life-expectancy, and LDL-c levels. Maximum benefit of lifelong durations was on average 3.6 years. Data are displayed as life years gained with 95% CI. LDL-c: low-density lipoprotein cholesterol. * per 1 log(duration in years).

Discussion

This study shows that starting PCSK9-mAbs treatment later in life and limited treatment duration results in lower lifetime benefit in terms of CVD free life in CVD patients. Younger patients with high LDL-c levels have the highest expected lifetime benefit from lifelong treatment. Postponement of treatment in patients eligible for treatment will always results in loss of efficacy and efficiency of treatment to prevent a recurrent myocardial infarction, stroke, or vascular death, independent of the treatment duration or an assumed legacy effect. Also, lifelong treatment durations always result in the highest lifetime benefit. However, depending on the legacy effect, the gain in lifetime benefit is not constant with the duration of treatment. Assuming a constant legacy effect, most of the benefit of treatment is obtained in the first years of treatment. As shown in figure 5, the lifetime benefit of treatment assuming a constant legacy effect is 2.6 years at a duration of only 1 year, compared to a maximum of 3.6 years gain when treated lifelong treatment. With an assumed declining legacy effect, a treatment duration of 10 year would result in 2.5 year lifetime gain compared to a lifetime gain of 3.6 year when treated lifelong, which is on average 20 years of treatment. If there is no assumed legacy effect, the gain in benefit is constant with the duration of treatment.

Legacy effects have been suggested for lipid-lowering and blood-pressure lowering treatment, and for glucose-lowering treatment in patients with diabetes mellitus.[20] For lipid-lowering therapy, the legacy effect during extended open-label study follow-up ranged from an odds ratio of 0.82 to 1.06, with an overall odds ratio of 0.88 based on 8 studies (average 6 years of follow-up after trial ending).[21] The effect of blood pressure-lowering therapy during extended follow-up without differences in treatment ranged

from an odds ratio of 0.57 to 1.07, with an overall odds ratio of 0.85 based on 18 studies.[22] For glucose-lowering therapy, evidence is contradicting. The risk for CVD is reduced in extended follow-up of the Diabetes Control and Complications Trial (DCCT)[23] and UKPDS trail, but not for patients included in the ADVANCE trial.[24] However, the legacy effect of glucose-lowering therapy did reduce risk of end-stage renal disease in all trials.[20] Also, when bariatric surgery is performed in patients with type 2 diabetes, patients with a transient period of type 2 diabetes remission compared to patients without a remission have a lower long-term microvascular disease risk. The length of time spend in remission was related to the risk reduction of microvascular disease, with a 19% reduction in risk for every additional year spend in remission.[25] All these examples provide evidence of a legacy effect, however, the magnitude of the estimated legacy effects varies between studies. The duration of a legacy effect is unknown. In the present study we assumed a lifelong legacy effect as well as a decaying legacy effect. The legacy effect seen in these studies might be explained by vascular biology. When comparing carotid intimal medial thickness (CIMT) between patients on statins and placebo, after a mean treatment duration of 26 months, there was a significant regression of CIMT in patients using statins.[26] Also, a combination of ezetimibe and statin therapy showed greater coronary plaque regression compared to statin monotherapy.[27] Thus, patients treated with lipid-lowering therapy do not only have a hold in progression of atherosclerotic plaques, but a regression of the plaques. Therefore, it would be only logical to state that treated patients are not at a similar risk after treatment cessation as patients who were not treated, which is the underlying mechanism of a legacy effect.

The importance of risk factor management in younger patients due to higher lifetime risks leading to higher lifetime benefits have also been described previously. In line with our study, PCSK9-mAbs are most effective in younger patients with high cholesterol levels and high 10-year CVD risks.[28] In a simulation study investigating the effect of lipid-lowering treatment with statins, there was a larger gain in CVD-free life expectancy in younger patients. Increasing CVD-free life expectancy was observed with increasing CVD risk due to increased blood pressure, unfavorable lipid levels, and body mass index.[29] Vice versa, the absence of established risk factors at 50 years of age is associated with a very low lifetime risk and longer survival.[30] This is not limited to lipid-lowering treatments. A study investigating longitudinal patterns of change in systolic blood pressure observed that exposure to elevated systolic blood pressure at any point in midlife results in higher CVD event rates even if systolic blood pressure is lowered later in life. This suggests that blood pressure levels should be maintained below guideline recommendations during life, advocating an early treatment of elevated blood pressure.[31]

Implications for clinical practice are that it might be beneficial to prescribe PCSK9-mAbs, only for a short period of time, between 3 and 10 years, starting at relatively young age. This would result in more patients being treated using the same amount of resources, while the loss of treatment effect in years gained per patient due to early cessation is compensated by a legacy effect.

Strengths of this study include the use of an external validated competing risk adjusted lifetime risk model. Such a model enables estimates of lifetime benefit that are not overestimated due to non-vascular mortality, which is important for estimating long-term treatment effects. Also, the hazard ratios used to estimate the effects of PCSK9-mAbs are based on large trial data and adjusted for LDL-c levels of individual patients. Furthermore, the use of real-world patient data of the SMART cohort instead of simulated data provides results that are generalizable to clinical practice.

Some limitations should be considered. In our study, baseline characteristics of patients with a history of CVD were used to estimate the lifetime benefit of treatment based on their LDL-c levels. However, on a population level, LDL-c increases between 18 years and 70 years of age, and decrease when patients become older than 70 years old. This could have led to an underestimation of treatment benefit especially later in life. Second, since the magnitude of a legacy effect is a crucial factor to estimate the most optimal duration of therapy, an accurate estimate of a legacy effect is necessary for accurate estimates of lifetime benefits. It would be interesting to study this phenomenon in more detail by following-up participants of recently published PCSK9-mAbs trials over a much longer period after the trial period. This would enable to more accurately quantify the legacy effect of preventive therapy, especially if information of clinical characteristics and therapy use after the trial is known. Cost-effectiveness analyses of alternative strategies could reveal whether treating more patients for a shorter period of time is more effective in terms of costs per quality adjusted life-year gained than treating less patients lifelong.

In conclusion, postponement of intensive lipid-lowering therapy in patients with vascular disease always leads to loss of treatment efficacy. Given the likelihood of a legacy effect, it could be considered to discontinue treatment after a period of 3 to 10 years, especially in older patients or patients with lower life-expectancy and already low LDL-c levels. Such a treatment strategy would advocate to treat more patients with PCSK9-mAbs for a short period compared to treating less patients lifelong leading to more benefit on population level. On an individual level lifelong treatment always results in more life years gained without recurrent CVD events.

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References

1. 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 (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal 2016;37:2315-81.
2. Goff DC, Jr., 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:S49-73.
3. Stam-Slob MC, Visseren FL, Wouter Jukema J, et al. 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.
4. Heart Protection Study Collaborative G. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Lancet 2011;378:2013-20.
5. Kashef MA, Giugliano G. Legacy effect of statins: 20-year follow up of the West of Scotland Coronary Prevention Study (WOSCOPS). Glob Cardiol Sci Pract 2016;2016:e201635.
6. Lv HL, Jin DM, Liu M, Liu YM, Wang JF, Geng DF. Long-term efficacy and safety of statin treatment beyond six years: a meta-analysis of randomized controlled trials with extended follow-up. Pharmacol Res 2014;81:64-73.
7. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England journal of medicine 2017;376:1713-22.
8. Soran H, Schofield JD, Durrington PN. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. European heart journal 2015;36:2975-83.
9. 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 2015;13:123.
10. Arrieta A, Hong JC, Khera R, Virani SS, Krumholz HM, Nasir K. Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers: Insights Derived From the FOURIER Trial. JAMA Cardiol 2017;2:1369-74.
11. Robinson JG, Heistad DD, Fox KA. Atherosclerosis stabilization with PCSK-9 inhibition: An evolving concept for cardiovascular prevention. Atherosclerosis 2015;243:593-7.
12. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. Journal of the American Heart Association 2018.
13. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. European journal of epidemiology 1999;15:773-81.
14. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. Jama 2006;295:180-9.
15. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj-Brit Med J 2016;352.
16. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics 2011;67:39-49.
17. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, 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;376:1670-81.
18. Ford I, Murray H, Packard CJ, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. The New England journal of medicine 2007;357:1477-86.
19. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. The New England journal of medicine 1995;333:1301-7.

20. Khunti K, Kosiborod M, Ray KK. Legacy benefits of blood glucose, blood pressure and lipid control in individuals with diabetes and cardiovascular disease: Time to overcome multifactorial therapeutic inertia? Diabetes, obesity & metabolism 2018;20:1337-41.
21. Kostis WJ, Moreyra AE, Cheng JQ, Dobrzynski JM, Kostis JB. Continuation of mortality reduction after the end of randomized therapy in clinical trials of lipid-lowering therapy. J Clin Lipidol 2011;5:97-104.
22. Kostis WJ, Thijs L, Richart T, Kostis JB, Staessen JA. Persistence of mortality reduction after the end of randomized therapy in clinical trials of blood pressure-lowering medications. Hypertension 2010;56:1060-8.
23. Writing Group for the DERG, Orchard TJ, Nathan DM, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. Jama 2015;313:45-53.
24. Zhang X, Liu Y, Zhang F, Li J, Tong N. Legacy Effect of Intensive Blood Glucose Control on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Very High Risk or Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized Controlled Trials. Clin Ther 2018;40:776-88 e3.
25. Coleman KJ, Haneuse S, Johnson E, et al. Long-term Microvascular Disease Outcomes in Patients With Type 2 Diabetes After Bariatric Surgery: Evidence for the Legacy Effect of Surgery. Diabetes care 2016;39:1400-7.
26. Bedi US, Singh M, Singh PP, et al. Effects of statins on progression of carotid atherosclerosis as measured by carotid intimal--medial thickness: a meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol Ther 2010;15:268-73.
27. Tsujita K, Sugiyama S, Sumida H, et al. Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. Journal of the American College of Cardiology 2015;66:495-507.
28. Kaasenbrood L, Ray KK, Boekholdt SM, et al. Estimated individual lifetime benefit from PCSK9 inhibition in statin-treated patients with coronary artery disease. Heart 2018.
29. Ferket BS, van Kempen BJ, Heeringa J, et al. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. PLoS Med 2012;9:e1001361.
30. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791-8.
31. Petruski-Ivleva N, Viera AJ, Shimbo D, et al. Longitudinal Patterns of Change in Systolic Blood Pressure and Incidence of Cardiovascular Disease: The Atherosclerosis Risk in Communities Study. Hypertension 2016;67:1150-6.

7

Chapter 7

General discussion

Trial results and individual treatment effects

For the prevention of cardiovascular disease (CVD), numerous options of treatments exist, i.e. lipid-lowering[1-3], blood pressure-lowering[4], and antithrombotic[5], and glucose-lowering therapy[6 7] for patients with type 2 diabetes mellitus (T2DM). The positive effects of these cardiovascular preventive therapies are shown in various large randomized clinical trials. However, trials report an average effect based on the difference between two groups which does not apply to all individual patients matching eligibility criteria of the trial.[8 9] The absolute treatment effect in trials varies across individual patients, and depends on a patient's baseline CVD risk . The basic concept is the greater the baseline CVD risk, the greater the treatment effects of preventive treatment.[10 11] Also, if a patient's baseline risk declines, therapy becomes less effective to prevent CVD in absolute effects and might not even outweigh potential disadvantages.

Chapter 2 of this thesis showed a decline in residual risk for recurrent CVD in patients with a history of CVD. This decline in CVD risk is also shown for patients with T2DM.[12] Furthermore, patients with a history of CVD or T2DM are not all equally at high risk for (recurrent) CVD.[13-15] Therefore, it could be questioned whether these patients are still all at very high risk. Based on the concept that greater baseline or residual CVD risk leads to greater preventive treatment effect, it could be more beneficial from a health care perspective to use baseline risk stratification in order to identify patients that reduce their risk of CVD most and least from (additional) preventive treatment. Also, patients and their clinicians can weigh the benefits in terms of CVD risk reduction and possible harm from side effects. Based on this risks and benefits of treatment, it could enable risk based treatment decisions regarding (expensive) preventive treatment in these "very high risk" populations.

Conventional way of risk stratification and effects of prevention for CVD

The most conventional way of risk stratification used in guidelines for primary prevention of CVD is 10-year risk for CVD. These 10-year risks are based on individual patient characteristics using validated risk scores.[16 17] Above a certain threshold (10% in the European ESC/EAS guideline and 7.5% in the American College of Cardiology/American Heart Association; ACC/AHA guidlines)[18 19], patients qualify for pharmacologic treatment. However, to deliberate with a patient whether or not preventive treatment is desirable, an individual measure of effectiveness of therapy is necessary. Combining the validated risk scores with relative treatment effects of trials enable estimation of treatment effects in 10-year absolute risk reductions (ARR).[20] Although 10-year ARR gives a hunch on the effectiveness of preventive treatment, patients eligible for preventive CVD treatment usually live much longer than 10 years (depending on their current age). Therefore, 10-year

ARR does not reflect the true benefit during the lifespan of patients.[21 22] Also, as mentioned in the introduction of this thesis, the risk scores used in the ACC/AHA guidelines do not take competing risks into account. The risk of CVD in conventional risk scores predicts the possibility of a CVD in the upcoming 10 years. However, especially in elderly patients, the chance of other diseases leading to death (competing events such as infectious disease or cancer) are also increased compared to younger patients. Thus as a simplified example, a patients actual life-expectancy based on the competing events might only be 5-years. When not taken into account, this will result in an overestimation of risk for CVD (the risk for CVD between the 6th and 10th year for a 10-year CVD risk prediction). And because a higher baseline (or residual) risk for CVD leads to greater preventive treatment effects, this could lead to overestimated treatment effects.[23 24]

Let's take a look at our patients described in the introduction of this thesis, Mr. A. and Mr. S. Blood pressure-lowering therapy is indicated for Mr. A. due to his systolic blood pressure of 150mmHg. According to the developed DIAL model in **Chapter 3**, Mr. A has a predicted 10-year CVD risk of 2% assuming absence of albuminuria (**Chapter 5;** figure 1). Mr. S. has a predicted 10-year CVD risk of 3% (figure 2). Both patients are categorized as low-risk patients according to cut-off values of current guidelines. However, according to the ASCVD pooled cohort equation Mr. S. has a 50% 10-year CVD risk and should be motivated to use cholesterol-lowering therapy. Starting a moderate dose statin (e.g. simvastatin 40mg) according to current guidelines would result in an estimates 10-year ARR of 12.5%. Using the DIAL model, keeping competing risks into account, the estimated 10-year ARR would only be 0.6%. There are two major reasons for the overestimation of the ARR of 12%. First, it is important to notice that the ASCVD is not developed in a population of patients with T2DM, but in a general population with T2DM as a determinant. Therefore, it might be that the ASCVD is not able to distinguish low and/or high risk T2DM patients. Second, competing risks is as mentioned before of huge importance in older patients. To make this clear, the use of the LIFE-CVD model[25] (also developed for apparently healthy people in primary prevention setting), estimates for Mr. S. a 10-year risk of 15%. The difference between 15% and 50% 10-year CVD risk is solely due to competing risks.

Absolute risk reduction, a difficult measure to understand

The main reasons to use prediction models are to inform individuals about the future course of their risk of developing illness and to guide doctors and patients in joint decisions on further treatment.[26] Therefore, individualized 10-year CVD risk prediction in patients with T2DM or CVD is a step forward compared to the "one-size-fits-all" approach, where all these patients are classified in the high or very high CVD-risk category. However, it remains difficult for patients and their physicians to understand 10-year risks and effectiveness of therapy expressed as ARR or number needed to treat (NNT = 1/ARR).

Thus, it is important to consider outcomes of prediction models that are more easy to understand, since one of the main goals of prediction models is to inform individuals. In studies with medical students, 30% of the students could not correctly answer 3 items testing numeracy, which was similar to surgical residents. The innumeracy was related to misunderstanding of risks addressing the need for further training.[27 28] Although the authors suggest a systematic problem in the medical training, it must be emphasized that these students are all highly educated compared to most of the patients in clinical practice. It is recognized that in order to understand health-related information, patients must have a certain level of numeracy.[29] To understand risks and benefits, patients need to understand their baseline risks as a reference and their relative or absolute risk reduction as a result of preventive treatments of CVD.[30] However, the method of presentation of treatment benefits can influence its interpretation by patients.[31] To help patients make better informed decisions, only the most important information should be presented in the most easy way. Less relevant information should be avoided, since it leads to worse decisions. Also, presenting information in which a higher number means better outcomes helps patients make better choices. For example, baseline risks where higher numbers represent worse health outcomes are more difficult to interpret than reductions of risks, where larger numbers represent better health outcomes.[32]

A different approach to estimate treatment effects of CVD prevention, time for a change?

For several decades, 10-year risk stratification of patients enabled individual predictions of CVD risk and CVD risk reduction to inform patients of their risk and guide clinical decision making. One of the first risk scores available was the Framingham risk score published in 1987[33], and many CVD risk prediction scores followed.[34] However, although these CVD risk scores made it possible to personalize vascular medicine, tailoring CVD management to individual patients, some limitation of 10-year risk models should be noted. Most important limitations are 1) the 10-year risks are mainly driven by age[35], 2) do not take competition of other causes of death in to account[23 24], and 3) are difficult to interpret.[29] As a result of these limitations, older patients are usually advised to be treated in primary prevention with for instance statin therapy due to a high risk caused by their age, while treatment effects are overestimated as shown in previous mentioned examples. On the other hand, younger patients with for instance high risk LDL-c levels are advised not to be treated, due to their low 10-year risk caused by their young age. However, CVD is a result of long-term exposure to risk factors. An early intervention could stop the process of atherosclerotic disease in an early stage to prevent CVD in the long run.[36] This example is contra-intuitive from a clinicians perspective, which contributes to the difficulty to interpret risk and risk reduction. Newly available techniques in prognostic research can

deal with these limitations to further improve individual risk predictions. Therefore, it is time for a change. The first question one would like to answer before starting preventive therapy is ´What is the individual benefit of preventive treatment?´. The second question could be ´What is the necessary investment to reach the benefit?´. Thus, if clinicians prescribe preventive treatment indefinitely, it would only be logical that the expected benefit of this investment would represent the same time span. In other words, the expected treatment benefit should be a lifetime benefit for treatment that is prescribed lifelong, while taking competing risks into account. Therefore, new techniques enabling estimates of long-term CVD-risk and CVD-free life expectancy (i.e. expected number of remaining life-years without the occurrence of an incident or recurrent myocardial infarction or stroke) are more appropriate.[37 38]

The DIAL model presented in **Chapter 3** enables the prediction of CVD-free life expectancy for patients with T2DM. Also, the effectiveness of preventive treatment can be predicted for lipid-lowering, blood pressure-lowering, glucose-lowering, and antithrombotic treatment in terms of lifetime benefit. For Mr. A. and Mr. S. the CVD-free life expectancy without treatment can be predicted. Mr. A. has a predicted CVD-free life expectancy of 81 years. Lifelong treatment with simvastatin 40mg and blood pressure-lowering therapy from 150mmHg to 140mmHg, is estimated to result in 1.1 years gain without CVD. To achieve this gain, he needs to use simvastatin and blood pressure-lowering therapy for an estimated 39 years (figure 1). Mr. S. has a predicted CVD-free life expectancy of 87 years. His blood pressure is 140mmHg, thus according to guidelines there is no need for blood pressure-lowering therapy. His lifetime benefit in years gained without CVD due to simvastatin 40mg is estimated to be 0.1 years. To achieve this, he would need to take his medication for his remaining life expectancy of 12 years (figure 2).

Based on simulation studies, using lifetime benefit as a measure of treatment effect results in a shift of patients being treated, towards higher proportions of younger people with higher risk factor levels.[21 22] However, this group of people needs to be treated over a longer period of time resulting in higher treatment costs and potential side effects. In **Chapter 4** is shown that the lifetime benefit from using lifetime benefit as predicted by the SMART-REACH model to identify patients that benefit the most from PCSK9 monoclonal antibody treatment outweighs the higher costs of longer treatment duration in patients with a history of CVD. Although this is a result that might be generalizable for all lifetime benefit based decisions, it would be reassuring when more studies were performed and resulted in similar conclusions.

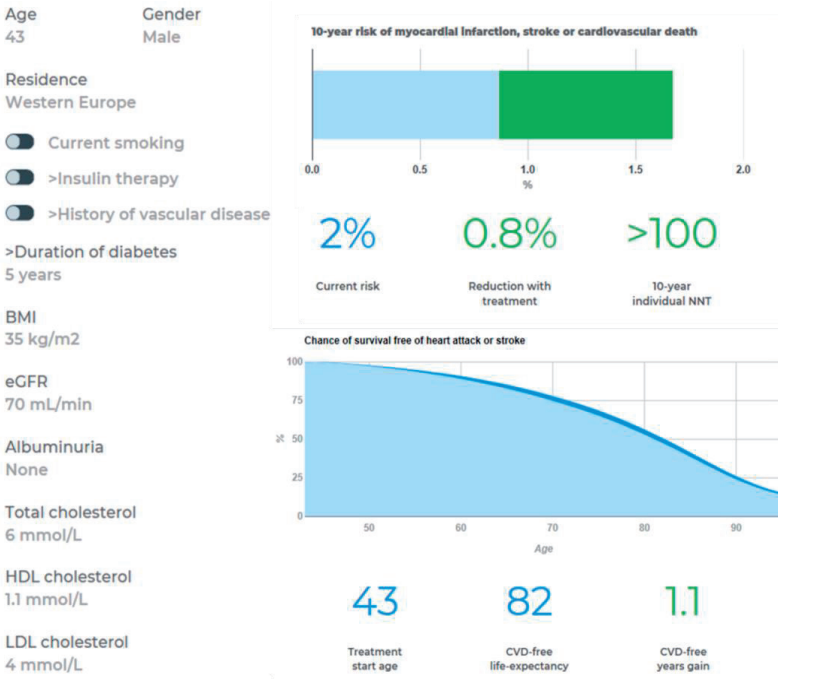

Figure 1: Mr. A his personal risk profile, 10-year CVD risk, and lifetime benefit of simvastatin 40mg and blood pressure-lowering therapy from 150mmHg to 140mmHg.

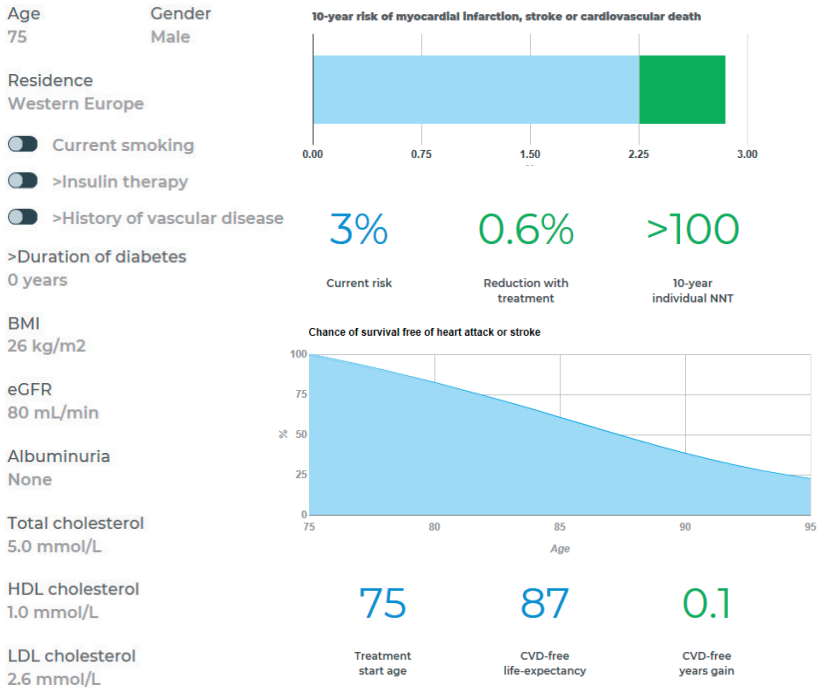

Figure 2: Mr. S his personal risk profile, 10-year CVD risk, and lifetime benefit of simvastatin 40mg.

Benefit-based treatment, back to treating risk factors

Recent decades, cardiovascular prevention has taken a shift from risk factor treatment towards treatment based on 10-year CVD risk.[39 40] This shift towards 10-year risk prediction was based on the concept that risk factors often exert a cumulative effect on absolute CVD risk. Thus, an individual with multiple mildly abnormal risk factors may be at a higher level of absolute risk for CVD than an individual with just one high abnormal risk factor. And since patients with a high absolute risk, also have a high absolute risk reduction, this was seen as a beneficial strategy from a health care perspective.[41 42] However, based on the findings in this thesis, and other recently published studies[21 22], this might leave long-term effects of high risk factor levels in younger patients out of the equation. The use of benefit-based treatment decisions results in the selection of patients with the most gain in CVD-free life years from preventive treatment. Patients with the highest benefit are either patients with high risk factor levels at young age and, thus, a low 10-year CVD risk based on their age, or patients with a high short-term (10-year) CVD risk, without a high chance of competing events. Typical patients in this category are patients with a history of CVD combined with high risk factor levels. Due to the addition of treatment effects conditional on the baseline risk factors treated, the benefit-based treatment tools predict highest benefit of for instance lipid-lowering treatment in patients with high cholesterol levels, while patients with high blood pressure will benefit most from blood pressure-lowering treatment. Therefore, the use of benefit based treatment decisions will support clinicians to treat high risk factors of individual patients that have a high risk of CVD somewhere in life, also when patients are not yet at a high 10-year risk for CVD due to a young age.

What does the patient want?

Benefit-based treatment tools were recently developed for cardiovascular prevention in primary prevention[25], T2DM patients (**Chapter 3**), and patients with a history of CVD[43] (www.U-Prevent.com) using state of the art prognostic modelling techniques. The use of these or other prediction models in clinical practice should be facilitated to help inform patients and clinical decision making. However, this is often precluded by missing patient characteristics. Therefore, less important patient characteristics should be automatically imputed with median values when missing by web or app based prediction tools (**Chapter 5**). Although, it should be noted that predictions are most accurate when all requested patient characteristics are available.

One of the questions remaining using benefit based treatment decision is: "What does the patient want?". With the newly developed benefit-based treatment tools, doctors are able to communicate the return on investment from preventive pharmacological CVD therapy with their patients. However, there is a large variation in the desired benefit of

preventive therapy.[44] If we take a look at our two patient examples, it is imaginable that patients are not willing to take medication for a gain in CVD-free life of 0.1 year treatment. On the other hand, a patient might not experience any harm from medication and decide to agree on prevention for a gain of 1.1 year. One could even look at the expected benefit when treatment is postponed or shortened (**Chapter 6**) to further individualize preventive treatment and shared decision making. This would also help patients and clinicians decide to stop preventive treatment for CVD due to low expected benefit in a patient's remaining life. While the benefit of treatment compared to 10-year ARR is easier to understand, the effect of communicating these measures of vascular prognosis and treatment benefits on patients understanding[45], adherence to medication, or quality of life, should be investigated by clinical trials.

Future clinical perspective

With the availability of www.U-Prevent.com as online support tool to estimate cardiovascular prognosis and benefit from preventive treatment, new possibilities arise to inform patients for shared decision making regarding preventive treatment. Due to improved understanding of the benefit of preventive medication, it could lead to improved adherence, which is currently poor in both primary and secondary prevention settings.[46] There is also a possibility that the use of benefit-based estimates lead to a reduction in patients using preventive medication. Expected benefits could be disappointing for patients, resulting in a decision to stop preventive treatment. To incorporate benefit based treatments in guidelines, it should be clear whom and when to treat our patients. For inexpensive preventive therapy such as most blood pressure-lowering medication and statin therapy, patients preferences could guide treatment decisions. However for expensive therapy such as PCSK9 monoclonal antibodies, the role of benefit based treatment guiding treatment decisions is not completely clear. Several possibilities are imaginable, such as establishment of cut-off values of lifetime benefit, age, or LDL-cholesterol levels of patients to select those patients were benefit outweigh costs of treatment. Another option is presentation of a gain in CVD-free life expectancy per 10 year treatment, as an indication of cost-effectiveness.

Future research

In the near future studies may focus on the clinical applicability and clinical impact of benefit-based treatments. It would be reassuring if benefit based decisions change daily clinical practice, reduce the risk of (recurrent) vascular events, and improve patients health perception.[47] Also, regular updating of underlying prediction models remain necessary.

The accuracy of the models are based on assumptions that baseline hazards of the derivation population is similar to patients for which the models are used. However, since vascular event rates decline over the last decades (**Chapter 2**), this is by definition not true. Thus, updating prediction models to newer populations of different geographical areas are necessary when available.[48]

In the distant future, different techniques based on big data analytics and machine learning algorithms might further improve personalized medicine. Analyses could be extended by including a large number of risk factors, and by using all available data of electronic health records to assess cardiovascular risk. Although feasibility and acceptability of these methods are still far away from clinical practice, with increasing computational capacity in health care systems, the opportunities for machine learning techniques will become a realistic option in the future.[49 50]

In conclusion, studies presented in this thesis showed the following:

The cardiovascular event rates declined over the last decades in patients with a history of CVD, although residual 10-year recurrent CVD risk remained high (17%). However, this trend in declining risks underscores the need of residual risk stratification in patient populations at very-high risk.

The DIAL model predicts 10-year absolute risk and CVD-free life expectancy for patients with T2DM. Also, the DIAL model enables the predictions of treatment benefit in terms of 10-year ARR and lifetime benefit in CVD-free life years gained. The use of lifetime benefit results in a shift of patients being treated, towards higher proportions of younger people with higher risk factor levels.

Using lifetime benefit as a decision threshold for PCSK9 inhibitor treatment in patients with a history of CVD is cost-effective compared to decision thresholds based on the highest 10-year ARR. The quality adjusted life years (QALYs) gained from early treatment due to lifetime benefit based decisions outweigh the costs of longer treatment duration.

Pragmatic imputation of missing values by median values results in reliable predictions, but important characteristics must be available. The clinical use of cardiovascular prediction tools in clinical practice could be facilitated by automatic imputation of missing patient characteristics other than age and history of CVD by median values.

Postponement of intensive lipid-lowering therapy in patients with vascular disease always leads to loss of treatment efficacy. Given that statin therapy is likely to have a legacy effect after discontinuation, it could be considered to discontinue treatment after a period of 3 to 10 years, especially in older patients or patients with short life-expectancy and already low LDL-c levels. These findings could further improve personalized treatment decisions and shared decision making.

References

1. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, 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.
2. 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, obesity & metabolism 2011;**13**(7):615-28.
3. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England journal of medicine 2017;**376**(18):1713-22.
4. 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):957-67.
5. Antithrombotic Trialists C, Baigent C, Blackwell L, 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):1849-60.
6. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;**52**(11):2288-98.
7. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: A systematic review and meta-analysis. Jama 2018;**319**(15):1580-91.
8. Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. BMJ 1995;**311**(7016):1356-9.
9. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. Jama 2007;**298**(10):1209-12.
10. van der Leeuw J, Ridker PM, van der Graaf Y, et al. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. European heart journal 2014;**35**(13):837-43.
11. Dorresteijn JA, Visseren FL, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ 2011;**343**:d5888.
12. Rawshani A, Rawshani A, Franzen S, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. The New England journal of medicine 2017;**376**(15):1407-18.
13. 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):1419-29.
14. Kaasenbrood L, Poulter NR, Sever PS, et al. Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus: The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study. Circ Cardiovasc Qual Outcomes 2016;**9**(3):213-21.
15. Dorresteijn JA, Boekholdt SM, van der Graaf Y, et al. High-dose statin therapy in patients with stable coronary artery disease: treating the right patients based on individualized prediction of treatment effect. Circulation 2013;**127**(25):2485-93.
16. Conroy RM, Pyorala 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.
17. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. Jama 2014;**311**(14):1406-15.
18. Goff DC, Jr., 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 2):S49-73.

19. 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 (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal 2016;**37**(29):2315-81.
20. Lloyd-Jones DM, Huffman MD, Karmali KN, et al. Estimating Longitudinal Risks and Benefits From Cardiovascular Preventive Therapies Among Medicare Patients: The Million Hearts Longitudinal ASCVD Risk Assessment Tool: A Special Report From the American Heart Association and American College of Cardiology. Circulation 2017;**135**(13):e793-e813.
21. Kaasenbrood L, Ray KK, Boekholdt SM, et al. Estimated individual lifetime benefit from PCSK9 inhibition in statin-treated patients with coronary artery disease. Heart 2018.
22. Ferket BS, van Kempen BJ, Heeringa J, et al. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. PLoS Med 2012;**9**(12):e1001361.
23. Andersen PK, Geskus RB, de Witte T, et al. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;**41**(3):861-70.
24. Wolbers M, Koller MT, Witteman JC, et al. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology 2009;**20**(4):555-61.
25. Jaspers N, Blaha M, Matsushita K, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Manuscript draft 2018.
26. Moons KG, Royston P, Vergouwe Y, et al. Prognosis and prognostic research: what, why, and how? BMJ 2009;**338**:b375.
27. Johnson TV, Abbasi A, Schoenberg ED, et al. Numeracy among trainees: are we preparing physicians for evidence-based medicine? J Surg Educ 2014;**71**(2):211-5.
28. Thornton H. Doctors' numeracy and communication skills need to improve. BMJ 2012;**344**:e3069.
29. Webster R, Heeley E. Perceptions of risk: understanding cardiovascular disease. Risk Manag Healthc Policy 2010;**3**:49-60.
30. Natter HM, Berry DC. Effects of presenting the baseline risk when communicating absolute and relative risk reductions. Psychology, Health & Medicine 2005;**10**(4):326-34.
31. Covey J. A meta-analysis of the effects of presenting treatment benefits in different formats. Med Decis Making 2007;**27**(5):638-54.
32. Peters E, Hibbard J, Slovic P, et al. Numeracy skill and the communication, comprehension, and use of risk-benefit information. Health Aff (Millwood) 2007;**26**(3):741-8.
33. Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). The American journal of cardiology 1987;**59**(14):91G-94G.
34. Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ 2016;**353**:i2416.
35. Leening MJG, Cook NR, Ridker PM. Should we reconsider the role of age in treatment allocation for primary prevention of cardiovascular disease? European heart journal 2017;**38**(20):1542-47.
36. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. Journal of the American College of Cardiology 2012;**60**(25):2631-9.
37. Leening MJ, Berry JD, Allen NB. Lifetime Perspectives on Primary Prevention of Atherosclerotic Cardiovascular Disease. Jama 2016.
38. Dorresteijn JAN, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj-Brit Med J 2016;**352**.
39. WHO. *Prevention of cardiovascular disease : guidelines for assessment and management of total cardiovascular risk*. http://www.who.int/iris/handle/10665/43685: Geneva : World Health Organization, 2007.
40. Wallis EJ, Ramsay LE, Jackson PR. Cardiovascular and coronary risk estimation in hypertension management. Heart 2002;**88**(3):306-12.

41. Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Heart 1998;**80 Suppl 2**:S1-29.
42. Grundy SM, Pasternak R, Greenland P, et al. AHA/ACC scientific statement: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Journal of the American College of Cardiology 1999;**34**(4):1348-59.
43. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. Journal of the American Heart Association 2018.
44. 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**(5):e021309.
45. Grisolia JM, Longo A, Hutchinson G, et al. Comparing mortality risk reduction, life expectancy gains, and probability of achieving full life span, as alternatives for presenting CVD mortality risk reduction: A discrete choice study of framing risk and health behaviour change. Soc Sci Med 2018;**211**:164-74.
46. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. The American journal of medicine 2012;**125**(9):882-7 e1.
47. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart 2012;**98**(9):691-8.
48. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Annals of internal medicine 1999;**130**(6):515-24.
49. Krittanawong C, Zhang H, Wang Z, et al. Artificial Intelligence in Precision Cardiovascular Medicine. Journal of the American College of Cardiology 2017;**69**(21):2657-64.
50. Weng SF, Reps J, Kai J, et al. Can machine-learning improve cardiovascular risk prediction using routine clinical data? PLoS One 2017;**12**(4):e0174944.

8

Chapter 8

Summary
Samenvatting (voor niet ingewijden)
Dankwoord
List of publications
Curriculum Vitae

Summary

Since cardiovascular disease (CVD) is a result of a lifelong exposure to risk factors and involves numerous people, it is utterly important to identify which people are most likely to get CVD in order to prevent or delay disease. Therefore, cardiovascular risk prediction is a keystone in the prevention of CVD to help identify patients at high-risk who may benefit most from drug treatment. An overwhelming of 250 risk prediction models are made over the last 15 years, but only a few are used in clinical practice. Besides a lack of applicability of these prediction models, two major issues are not taken into account in current prognostic models predicting 10-year risks. First, the short horizon of 10-years does not adequately reflect the potential long-term risks or benefits of preventive treatment. However, in younger patients, their future long-term exposure to risk factors building up atherosclerosis over a long period of time results in a high lifetime risk for CVD, and therefore a possibly high lifetime benefit of CVD prevention. Second, competing risks, i.e. death due to other causes such as cancer, are not taken into account in current prediction models. This leads to an overestimation in risk especially for patients at high risk for non-vascular mortality; i.e. the elderly. Therefore, the aim of this thesis was 1) to demonstrate the translations of trial results to the individual patient by predicting individualized CVD risk and treatment benefits for lifelong prevention of CVD, especially in patients with T2DM or a history of CVD and 2) to improve the applicability of prediction models in clinical practice.

In **Chapter 2**, we described the risk of recurrent major cardiovascular events (MCVE) in patients with clinically manifest arterial disease over the last decades. The study was conducted in the Second Manifestations of ARTerial disease (SMART) cohort in patients entering the cohort in the period 1996-2014. The recurrent MCVE risk in these patients strongly declined with 53% from 3.68 to 1.73 events per 100 person-years. This was partially due to lower risk factors and lower prevalence of subclinical atherosclerosis. However, the 10-year risk for recurrent events remained high with an average of 17%. This underscores the need to identify the patients with the highest risk.

In **Chapter 3** we aimed to predict treatment effects of individual life years gained without CVD from pharmacological preventive treatment in patients with type 2 diabetes mellitus (T2DM). The Diabetes Lifetime-perspective prediction (DIAL)- model, consisting of two complementary competing risk adjusted Cox proportional hazards functions was developed using the Swedish National Diabetes Registry (n=389,366). External

validation of the model was performed using data from the ADVANCE, ACCORD, ASCOT, and ALLHAT-LTT –trial, the SMART and EPIC-NL-cohorts, and the Scottish Care Information (SCI) –Diabetes database, with patients selected by geographical region. Calibration of the model was adequate and discrimination was modest with c-statistics of 0.64 to 0.69 for the external validation regions. Individual treatment effects of pharmacological treatment were predicted by addition of hazard ratios from randomized trials or meta-analyses to the competing risk adjusted cox proportional hazard function predicting CVD outcomes. The (complementary) competing risk adjusted cox proportional hazard function predicting non-cardiovascular mortality outcomes were not influenced by pharmacological treatment. However, for the prediction of the effect of smoking cessation, a hazard ratio was added to both the adjusted cox proportional hazard function outcomes, since smoking cessation also influences non-CVD mortality (e.g. cancer). The model developed and validated, with the addition of treatment effects was the groundwork for the DIAL-model as presented in the interactive web-based calculator at www.U-prevent.com. Using the concept of predicting lifetime benefit for making treatment decisions will result in changing characteristics of people eligible for treatment, towards higher proportions of younger people with higher risk factor levels.

Chapter 4 compared the cost-effectiveness of decisions based on lifetime benefit predictions, and therefore, treatment of younger people for a much longer period in life, with treatment decisions based on 10-year absolute risk reductions. In this microsimulation study, 10,000 hypothetical patients representing a population of patients with stable CVD was created by repeatedly sampling from correlated probability distributions of risk factors. The correlated probability distribution used to create this hypothetical population was subtracted of the SMART cohort. As an example, treatment of patients with the highest lifetime benefit or highest absolute risk reduction was simulated using the treatment effects and costs of expensive PCSK9-inhibition with monoclonal antibodies. Individual predictions of treatment effects (both in life years gained and 10-year absolute risk reduction) were calculated using the SMART-REACH model available at www.U-prevent.com.

When treating the same proportion of patients (5%, 10%, and 20%), the costs were higher for the lifetime benefit based treatment decisions compared to 10-year absolute risk reduction based decisions, as expected. However, the quality adjusted life years (QALYs) gained due to treatment with PCSK9-inhibition were also higher for the lifetime benefit based treatment decisions. The incremental cost-effectiveness ratio (ICER) in euro per QALY gain, the decisions based on the highest lifetime benefit resulted in ICERs of €37,200, €39,800, and €41,500 for 5%, 10%, and 20% of patients treated. The decisions based on highest absolute risk reduction resulted in ICERs of €47,700, €54,800, and €52,100. Thus, lifetime benefit-based treatment decisions for patients are cost-effective compared to treatment decisions guided by 10-year risk estimates, at least in this example for PCSK9 inhibition in patients with stable CVD.

Chapter 5 focused on the applicability of CVD prediction models. Estimating patient risk using prediction models may be limited by incomplete patient data, a common occurrence in clinical practice. Therefore, five methods handling missing patient characteristics required to estimate CVD risk were compared on their validity. 1) Reduced model method. Development of 2^n models, one model for each possible combination of available characteristics. 2) Hybrid model method. With one missing variable this method is similar to the reduced model method. With >1 predictor missing, the median value of a predictor was imputed to use multiple reduced models, taking the average as risk. 3) Conditional single imputation. 4) Median imputation. 5) The naïve approach. Baseline population survival adjusted by factors determined by independent risk ratio and population prevalence of available characteristics. These five methods were used on missing data of the Swedish NDR and SCI-Diabetes database for patients to estimate there individual risk of CVD using an updated version of the Swedish NDR risk prediction model. There was no difference in terms of calibration or discrimination by missing data method with identical c-statistics of 0.82 (95% CI 0.82-0.83) for patients of the NDR and 0.74 (0.74-0.75) for patients of the SCI-Diabetes database. However, when missing data was randomly introduced in important variables that were always available (such as age or history of CVD), median imputation and the naïve approach were inferior to the other methods dealing with missing data. These findings recommend the use of pragmatic imputation of missing values by median values, as long as important characteristics such as age are available.

Chapter 6 builds on findings of **chapter 4**. Although **Chapter 4** shows an cost-effective treatment decision by lifetime benefit predictions, the absolute costs of treatment using PCSK9-inhibition was higher compared to the 10-year absolute risk reduction. Investing in younger patients treated lifelong is therefore costly on a population level. However, it is reasonable to assume some legacy effect of pharmacological CVD prevention. **Chapter 6** demonstrated different treatment strategies for treatment of individual patients with stable cardiovascular disease using PCSK9 monoclonal antibodies in which a legacy effect is and is not assumed. It shows that lifelong treatment always results in higher life years gained without CVD (lifetime benefit). Also, treating patients younger is always more beneficial than later in life. However, depending on an assumed legacy effect, treatment cessation would only result in a small loss of lifetime benefit. Implications for clinical practice are that it might be beneficial to prescribe PCSK9 monoclonal antibodies, only for a short period of time, between 3 and 10 years, starting at relatively young age. This would result in more patients being treated using the same amount of resources, while the loss of treatment effect in years gained per patient due to early cessation is compensated by a legacy effect. Such a treatment strategy would lead to more benefit on population level, while on an individual level lifelong treatment always results in more life years gained without recurrent CVD events.

Samenvatting (voor niet ingewijden)

Hart- en vaatziekten is het gevolg van een levenslange blootstelling aan risicofactoren waarmee slagaderverkalking wordt opgebouwd, en komt bij meer dan een miljoen mensen in Nederland voor. Voor de preventie is het belangrijk de mensen te kunnen selecteren die de hoogste kans hebben op het krijgen van hart- en vaatziekten. Er wordt daarbij traditioneel onderscheid gemaakt tussen mensen die geen vaatziekten hebben (primaire preventie), mensen met vaatziekten (secundaire preventie) en mensen met diabetes. Ondanks het feit dat wetenschappelijk onderzoek naar nieuwe medicatie altijd een gemiddelde effecten rapporteert, is gebleken dat de patiënten met het hoogste risico, de patiënten zijn die het meeste baat hebben bij preventieve medicamenteuze therapieën, zoals cholesterolverlagers, bloeddrukverlagers, of aspirine. Daarom is het kunnen voorspellen (predictie) van de risico's bij mensen een van de bouwstenen voor de preventie van hart- en vaatziekten. Dat blijkt mede uit het feit dat in de huidige richtlijnen in de primaire preventie behandeladviezen worden gegeven op basis van het risico van patiënten.

In de laatste 15 jaar zijn er meer dan 250 voorspel modellen (predictie modellen) gemaakt om het 10-jaars risico op hart- en vaatziekten van mensen in de primaire preventie, maar worden er maar een aantal gebruikt in de klinische praktijk. De vraag die we onszelf daarbij kunnen stellen is waarom er zo weinig gebruik wordt gemaakt van deze ontwikkelingen. Daarbij is het belangrijk te weten waar een predictie model aan moet voldoen om risico's te kunnen voorspellen. Allereerst, om een predictie model af te leiden is een reeks gegevens noodzakelijk over de risicofactoren van patiënten en moeten zij vervolg worden in de tijd om te kijken wie er wel of niet hart- en vaatziekten gaat krijgen. Met die gegevens kan een model worden afgeleid die voorspeld of patiënten een hoog- of laagrisico profiel hebben. Daarna is het van belang te zien of dat de voorspellingen van het patiënten uit andere gegevensbronnen ook daadwerkelijk overeenkomen met het geobserveerde risico op hart- en vaatziekten (externe validatie). Ten tweede zou een model voor een clinicus praktisch moeten zijn in het gebruik. Dit kan door middel van gebruiksvriendelijke (online) calculators, waarin alleen de benodigde gegevens ingevoerd hoeven te worden, waarna de clinicus alle gevraagde gegevens te zien krijgt. Echter, bij ontbrekende patiënten gegevens is er tijdens het gebruik van een risico model kan er momenteel geen risico voorspelling worden gedaan voor een individuele patiënt.

Het gebruik van de meest voorkomende 10-jaars predictie modellen opent de mogelijkheid om de patiënten te selecteren die (op relatief korte termijn) hart- en vaatziekten gaan ontwikkelen. Daarbij kan er berekend worden wat er verwacht wordt van

medicamenteuze behandelingen als absolute vermindering van het 10-jaars risico door de behandeling. Er zijn echter belangrijke keerzijden van het voorspellen van 10-jaars risico. Zoals in de inleiding van deze samenvatting al aangegeven, is hart- en vaatziekten een gevolg van een levenslange blootstelling aan risicofactoren. Daarom geeft 10 jaar een onjuist beeld van het effect van preventieve behandeling. Een goed voorbeeld hiervan zijn hele jonge mensen met veel risicofactoren. Van deze mensen wordt er op basis van hun leeftijd niet verwacht dat zij de eerste 10 jaar hart- en vaatziekten zullen ontwikkelen. Omdat het risico gerelateerd is aan het behandeleffect van preventieve therapie (absolute risico reductie), zal de absolute reductie in procenten afname ook laag zijn (een heel klein risico kan nooit veel kleiner worden). Wanneer we bij deze mensen zouden kijken naar het effect op de langer termijn, dan zou er juist heel veel winst te halen zijn door het tegengaan van de opbouw van slagaderverkalking, en daarmee hart- en vaatziekten. Er zijn echter ook mensen met een levensverwachting korter dan 10 jaar mede door "concurrerende" ziekten anders dan hart- en vaatziekten. Bij deze vaak oudere mensen wordt het risico op hart- en vaatziekten hierdoor vaak overschat, en daarmee wordt ook het gerelateerde behandeleffect overschat. Met huidige nieuwe technieken kunnen deze nadelen worden weggenomen.

In dit proefschrift richten we ons daarom op 1) het vertalen van gemiddelde behandeleffecten van wetenschappelijke bevindingen naar individuele patiënten door het voorspellen van individuele hart- en vaatziekten risico's en behandeleffecten voor levenslange preventie, met name voor patiënten met diabetes of hart- en vaatziekten. En 2) op het verbeteren van het gebruik van predictie modellen in de klinische praktijk.

In **Hoofdstuk 2** van dit proefschrift beschrijven het risico op een terugkerende hart- en vaatziekten bij patiënten met hart- en vaatziekten over de afgelopen decennia. Hiervoor hebben we de gegevens van patiënten uit het Second Manifestations of ARTerial disease (Tweede manifestatie van slagaderverkalking; SMART) cohort gebruikt. Daarin laten we zien dat het risico op een volgende uiting van hart- en vaatziekten met 53% is afgenomen in de periode tussen 1996 en 2014. Dit was deels verklaard door een afname in risicofactoren en een toename in preventieve medicatie. Echter het absolute risico bleef hoog met een gemiddelde van 17% over 10 jaar (dus gemiddeld 17 van de 100 patiënten krijgt een volgende uiting van hart- en vaatziekten in de komende 10 jaar). Dit hoge gemiddelde onderstreept het belang van het maken van onderscheid tussen de patiënten met een heel hoog en een minder hoog risico.

In **Hoofdstuk 3** hadden we als doel om zelf een predictie model te maken, waarbij we de levenslange behandeleffecten van preventieve medicatie in jaren winst zonder een (nieuw) hartinfarct of herseninfarct konden bereken voor patiënten met diabetes. Dit predictie model (DIAL-model) hebben we afgeleid en extern gevalideerd in verschillende gegevens van patiënten uit de hele wereld, waarvan de meeste gegevens uit Zweden

en Schotland. De behandeleffecten van grote trials voor het verlagen van cholesterol, bloeddruk, en glucose, het behandelen met aspirine, en het effect van stoppen met roken hebben we toegevoegd aan het predictie model. Dit is de basis geweest voor het DIAL-model zoals dat te vinden is binnen de interactieve calculator op www.U-prevent.com. Wanneer er individueel gekeken wordt naar de winst in 10-jaar risico reductie ten opzichte van levenslange winst in jaren zonder hart- en vaatziekten, dan wordt er een verschuiving gezien in de patiënten karakteristieken . Op basis van de levenslange winst komen vaker jongere patiënten in aanmerking voor behandeling met hogere waarden van risicofactoren.

Hoofdstuk 4 vergelijkt of de kosten-baten verhouding van behandeladviezen op basis van de hoogste levenswinst waarbij meer jongere patiënten voor een langere tijd worden behandeld, lager is dan de huidige manier om behandeladviezen te geven op basis van het 10-jaars risico reductie. Om dit te doen is er gebruik gemaakt van een simulatie studie waarin 10,000 fictieve patiënten met hart- en vaatziekten met behulp van de ene of andere methode behandeladviezen kregen voor een duur cholesterolverlagend middel, PCSK9-remmers. 5%, 10% en 20% van deze patiënten met de hoogste levenslange winst werden behandeld binnen de simulatie, en vergeleken met de behandeling van 5%, 10%, en 20% patiënten op basis van de hoogste 10-jaars risico reductie. Zoals verwacht lagen de kosten van de behandeladviezen op basis van levenslange winst hoger, maar leverde dit ook meer gezondheidswinst op. Deze gezondheidswinst was zodanig groter voor de levenslange behandelbeslissingen, dat dit de kosten-baten verhouden goedkoper maakten dan de beslissingen op basis van de 10-jaars risico reductie. Kortom, dit is dus voor de maatschappij een efficiëntere manier om patiënten te selecteren, in ieder geval in het gebruikte voorbeeld van patiënten met al bestaande hart- en vaatziekten en PCSK9-remmers.

Hoofdstuk 5 richt zich op het verbeteren van de toepasbaarheid van een predictie model. In dit hoofdstuk hebben we gekeken naar vijf verschillende methodes om met missende patiënten gegevens om te gaan tijdens het gebruik van een predictie model. Daarbij hebben we gekeken welk van de methode het meest nauwkeurige voorspellingen gaf. Het model dat we daarvoor hebben gebruikt is het Zweedse 5-jaars risico model voor het voorspellen van hart- en vaatziekten. De methodes zijn getest op hun nauwkeurigheid om voorspellingen te kunnen blijven doen door risico's te voorspellen voor patiënten met missende gegevens uit Zweden en uit Schotland te gebruiken (externe validatie). Daarnaast hebben we zelf missende waarden geïntroduceerd door willekeurig gegevens de verwijderen en vervolgens te kijken wat de methodes deden op de voorspellingen. Het bleek dat het invoeren van een gemiddelde waarden uit de gehele populatie afdoende was om nauwkeurige voorspellingen te geven, mits leeftijd, geslacht, en de voorgeschiedenis of een patiënt hart- en vaatziekte had maar aanwezig waren. Kortom,

deze bevindingen kunnen ervoor zorgen dat clinici voorspellingen op het krijgen van hart- en vaatziekten ook kunnen doen, terwijl minder belangrijke gegevens ontbreken die nodig zijn voor het invullen van het predictie model.

Hoofdstuk 6 komt deels voort uit de bevindingen in **Hoofdstuk 4.** In **hoofdstuk 4** werd gezien dat de kosten-baten analyses in het voordeel uitvielen voor levenslange schattingen. Er moet daarbij wel gezegd worden dat de kosten die geïnvesteerd moeten worden om alle patiënten levenslang te behandelen, wel hoger zijn bij de beslissingen op basis van levensjaren winst. **Hoofdstuk 6** laat diverse strategieën zien waarop patiënten kunnen worden behandeld met cholesterolverlagende medicatie. Daarbij wordt in ogenschouw genomen dat het gebruik van cholesterolverlagende (en mogelijk ook andere preventieve) medicatie een effect zou kunnen hebben, wat langer doorwerkt dan daadwerkelijk de medicijnen worden gebruikt. Dit zou betekenen dat er nog gezondheidswinst is lang nadat de medicatie gestopt is. De diverse strategieën met en zonder aanhoudende gezondheidswinst laten een aantal interessante bevindingen zien. Allereerst levert levenslang behandelen, vanaf het moment waarop besloten wordt dat dit zinvol zou kunnen zijn het meest levenswinst zonder hart- en vaatziekten op. Uitstellen van behandeling is daarbij ongunstig voor het effect op levenswinst. Afhankelijk van de grote van de aanhoudende gezondheidswinst zou korter behandelen (op jongere leeftijd), waarna gestopt wordt, leiden tot relatief weinig verlies van gezondheid. Dit impliceert dat we daarom voor dezelfde kosten meer patiënten kunnen behandelen op jongere leeftijd, waarna zij na tussen de 3 en 10 jaar zouden kunnen stoppen met behandeling. Dit zou op populatie niveau de meeste winst opleveren tegen dezelfde kosten, ondanks het feit dat op individueel niveau levenslang behandelen altijd het meeste gezondheidswinst oplevert.

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List of publications not included in this thesis

D Kofink, SA Muller, RS Patel, JAN Dorresteijn, **GFN Berkelmans**, MCH de Groot, WW v Solinge, S Haitjema, T Leiner, FLJ Visseren, IE Hoefer, FW Asselbergs, on behalf of the SMART study group. Routinely measured hematological parameters and prediction of recurrent vascular events in patients with clinically manifest vascular disease. *Accepted Plos one*.

GFN Berkelmans, S Kuipers, BE Westerhof, AME Spoelstra-de Man, YM Smulders. Comparing volume-clamp method and intra-arterial blood pressure measurements in patients with atrial fibrillation admitted to the intensive or medium care unit. *J Clin Monit Comput. 2018 Jun;32(3):439-446*.

HB Østergaard, T Mandrup-Poulsen, **GFN Berkelmans**, Y vd Graaf; FLJ Visseren, J Westerink, on behalf of the SMART Study Group. Limited benefit of haemoglobin glycation index as risk factor for cardiovascular disease in type 2 diabetes patients. *Diabetes Metab. 2018 May 8. pii: S1262-3636(18)30083-1*.

RK Feenstra, CP Allaart, **GFN Berkelmans**, BE Westerhof, YM Smulders. Accuracy of oscillometric blood pressure measurement in atrial fibrillation. *Blood Press Monit. 2018 Apr;23(2):59-63*.

JOM Zaat, **GFN Berkelmans**, Y vd Graaf. Niet mijn pakkie-an of toch de barricade op? *NTvG, 2017 dec*.

GFN Berkelmans, FLJ Visseren, NEM Jaspers, W Spiering, Y vd Graaf, JAN Dorresteijn. SPRINT trial: It's not just the blood pressure! *Eur J Prev Cardiol. 2017 Sep;24(14):1482-1484*.

Curriculum Vitae

Gijs Berkelmans was born on 18 April 1987 in Maarssen, the Netherlands. After graduation from the "Gymnasium Baken Park" in Almere 2005, he studied Medical Natural Sciences and Medicine at the Vrije Universiteit Amsterdam. He finished both studies and obtained his medical degree in 2013 after a senior internship in Internal Medicine at the "Zaans Medisch Centrum". In his year of work as doctor at the department of Internal Medicine of the Diakonessenhuis in Utrecht, he met Jannick Dorresteijn as a colleague. Under supervision of Jannick Dorresteijn, Frank Visseren, and Yolanda van der Graaf, he started working in 2015 on this thesis at the department of Vascular Medicine, University Medical Center Utrecht (UMCU). He combined his PhD research with the post-graduate master Clinical Epidemiology from which he graduated in August 2017. He will start his residency in Internal Medicine in December 2018 in the Diakonessenhuis in Utrecht.