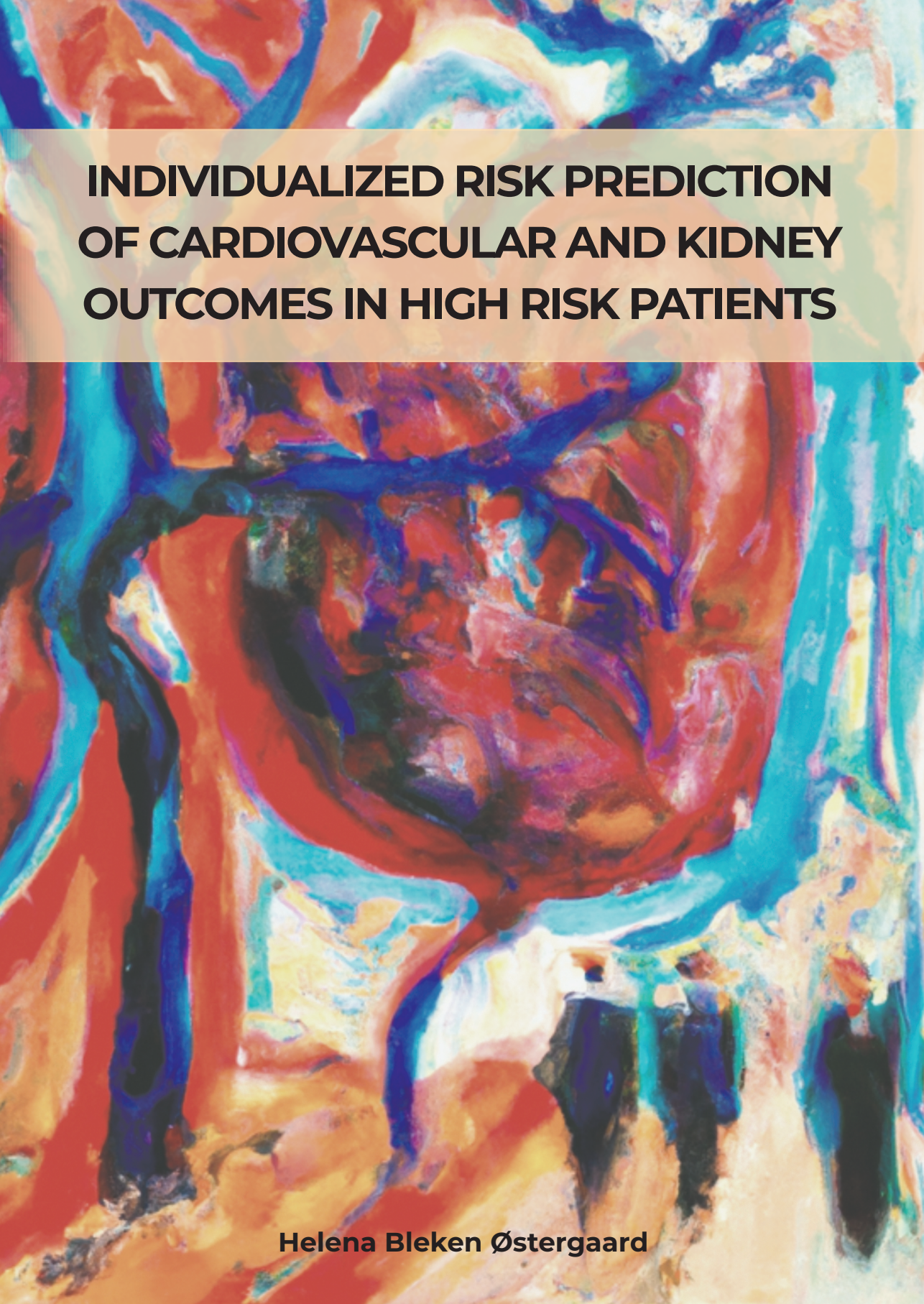


INDIVIDUALIZED RISK PREDICTION OF CARDIOVASCULAR AND KIDNEY OUTCOMES IN HIGH RISK PATIENTS

Helena Bleken Østergaard

INDIVIDUALIZED RISK PREDICTION OF CARDIOVASCULAR AND KIDNEY OUTCOMES IN HIGH RISK PATIENTS

Helena Bleken Østergaard

ISBN: 978-94-6458-962-7
Cover design: Julia Bleken Krøjer
Lay-out: Publiss | www.publiss.nl
Print: Ridderprint | www.ridderprint.nl

Individualized risk prediction of cardiovascular and kidney outcomes in high risk patients

Geïndividualiseerde risicovoorspelling van cardiovasculaire en nieruitkomsten bij hoogrisicopatiënten

(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college door promoties in het openbaar te verdedigen op dinsdag 16 mei 2023 des middags te 2:15 uur

door

Helena Bleken Østergaard

Geboren op 7 mei 1990 te Aarhus, Denemarken

Promotor:	Prof. dr. F.L.J. Visseren
Co-promotoren:	Dr. J. van der Leeuw
	Dr. J. Westerink
Beoordelingscommissie:	Prof. dr. M.L. Bots
	Prof. dr. R.T. Gansevoort
	Prof. dr. M. Nieuwdorp
	Prof. dr. F.H. Rutten
	Prof. dr. M.C. Verhaar

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Table of contents

CHAPTER 1

General introduction

General introduction

"*Declare the past, diagnose the present, foretell the future.*"[1] Hippocrates (460 B.C. - 370 B.C.), the "father of medicine", already stated this more than 2000 years ago, and to this day it is still something physicians strive for in patient encounters. The focus in clinical practice is, however, most often on the first two - obtaining a medical history, diagnosing and treating the present disease. Foretelling the future of a patient is just as important in order to prevent potential future diseases, individualize treatment and promote shared decision making. Even though more than 2000 years have passed, the question still remains: Can we predict the future of a patient, including predictions of patient risks and treatment benefits in clinical practice?

Type 2 diabetes, CVD and kidney disease – three pieces of the same puzzle

Worldwide, the prevalence of non-communicable diseases, including type 2 diabetes, cardiovascular disease (CVD) and chronic kidney disease is growing.[2] Atherosclerotic CVD takes first place in common non-communicable diseases, being responsible for 17.8 million deaths annually worldwide. Chronic kidney disease is responsible for 1.2 million deaths and type 2 diabetes is the fourth most common non-communicable disease and responsible for 1 million deaths worldwide.

The increasing number of individuals with CVD, kidney disease and/or type 2 diabetes is due to several factors, including increased survival of patients with disease as well as an ageing population who have more opportunity to develop disease. Also, it will come as no surprise that these diseases are strongly intertwined with shared risk factors such as obesity and sedentary behaviour while at the same time the presence of one of the mentioned diseases increases the risk of the others. For example, diabetes accounts for more than 40% of kidney failure cases,[3] and the risk of CVD is 2-3 times higher in people with type 2 diabetes compared to people without.[4] Also, CVD confers a 4-fold increased risk of developing chronic kidney disease[5] and the risk of CVD increases with declining kidney function.[6]

Risk factors for cardiovascular and kidney disease

Before foretelling the future, i.e. predicting a patient's risk of disease, we need to *"diagnose the present"*, which involves identifying risk factors that are causally

related to cardiovascular and kidney disease. Many amendable risk factors have already been manifested, including type 2 diabetes,[4, 7] hypertension,[8] obesity and sedentary behaviour, dyslipidemia[9] and smoking.[10, 11] However, amendable risk factors are primarily investigated in low-risk populations and their effect may differ in high-risk patients with established CVD and/or chronic kidney disease, since the pathogenesis might involve different pathways in certain high-risk populations. For example, a previous study reported that the reduction in relative risk of major vascular events with statin-based treatment to lower LDL-c weakened with declining eGFR, suggesting other pathogenic factors play a bigger part in patients with worse kidney function.[12] Therefore, the effect of amendable risk factors on cardiovascular and kidney disease must also be assessed in high-risk patients.

In patients with type 2 diabetes there is still a residual risk for CVD even when traditional risk factors are optimally controlled. Therefore, there is increasing interest in discovering novel, potentially amendable, causally related risk factors for CVD in people with type 2 diabetes. One such potential risk factor proposed is the hemoglobin glycation index (HGI). The HGI is to be understood as a possible marker of interindividual differences in haemoglobin glycosylation.[13] It is defined as the difference between observed HbA_{1c} and predicted HbA_{1c} as calculated by the population linear regression equation of HbA_{1c} and a wide discordance has been proposed as being causally linked to increased risk of diabetes-related outcomes, including CVD.[14] However, before such novel potential risk factors, e.g. the HGI, are introduced as a possible part of the pathophysiological pathway and integrated as a risk factor in clinical practice, they need to be thoroughly examined to identify whether there is in fact a causal link.

Predicting cardiovascular and kidney outcomes in individuals with type 2 diabetes

As touched upon previously, type 2 diabetes is considered a severe threat for global health, with a current global prevalence of 9% and a staggering number of 578 million people expected to have diabetes in 2030.[15] Type 2 diabetes is not only associated with increased risk for cardiovascular and kidney disease, but also other outcomes such as neuropathy and retinopathy. Even more people are estimated to have pre-diabetes, and people often already have significant

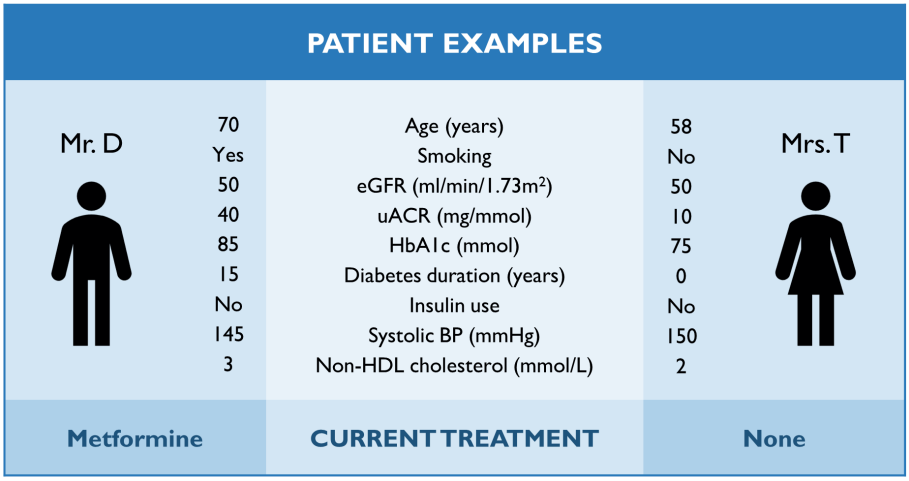
macro- and microvascular damage at time of diagnosis and treatment.[16] As the prevalence of type 2 diabetes keeps increasing, so does the diversity of this group of patients. Thus, a lot of different patients with type 2 diabetes visit the clinic everyday, whether at the general practitioner or a specialist out-patient clinic. Two such patients that may be seen are Mr. D and Mrs. T (*Figure 1*).

Mr. D is a 70-year old male, recently retired and looking forward to slowing down and spending more time with his family. 15 years ago, he was diagnosed with type 2 diabetes. He takes oral glucose-lowering medication every morning and evening (when his wife reminds him) and tries to cut down on fast sugars, but more often than not can't resist desserts. Ideally, he should lose 25 kg, but on the other hand exercise was never really part of his sedentary corporate lifestyle. His biggest vice is the daily pack of cigarettes, but he enjoys them too much to actually quit. During his last visit at the out-patient diabetes clinic, the doctor did mention something about proteinuria and a declining kidney function, and dyslipidemia, but he doesn't really see the need for taking more pills when he generally feels healthy. Thus, he attends his annual check-ups, but is not otherwise concerned with it.

Mrs. T is a 58-year old female, enjoying her grown-up kids and living an active, social life. She was recently diagnosed with type 2 diabetes during a routine visit at her general practitioner, which came as quite a shock to her. The doctor also mentioned something about protein in her urine and an elevated blood pressure, but she didn't really think more of this. She's determined to change the disease course and immediately opts her already healthy diet and increases exercise. She finds herself way too young to start taking pills chronically, even though this was what the doctor recommended.

A main question that arises in the encounters with both Mr. D and Mrs. T is; What is their individual risk of developing diabetes-related outcomes, including cardiovascular and kidney disease? This risk estimate is the starting point for a personalised discussion of the disease course and pros and cons of starting treatment. Generally, patients with type 2 diabetes, especially those with target organ damage or several major risk factors, are deemed at (very) high risk for both (recurrent) cardiovascular and kidney disease. However, also in this group of patients there is significant variation in risk depending on disease severity, duration and concomitant risk factors.[17, 18] Should both Mr. D and Mrs. T be prescribed the same treatment even though risks and benefits may differ widely?

Figure 1. Example of two patients with type 2 diabetes; Mr. D and Mrs. T



BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; uACR = urine-Albumine/Creatinine ratio.

Several prediction models for predicting cardiovascular and kidney disease in people with type 2 diabetes exist,[19, 20] and other models aim to predict neuropathy, retinopathy and all-cause mortality.[21, 22] Optimally, such models should be used in clinical practice to identify patients at high risk who are anticipated to derive greatest benefit from treatment and to promote shared decision making on treatment decisions. In order to do so, it is important that the predictions are accurate and applicable to the specific clinical situation. However, most of the prediction models for cardiovascular and kidney disease in people with type 2 diabetes have several methodological shortcomings. For example, most models only predict outcomes over a short time span, e.g. 5 to 10-year predictions. These predictions are mostly driven by age, and since younger people have lower short-term risks even in the presence of high risk factor levels, they will mostly not receive preventive therapy, although their lifetime benefit may be very high. Also, in order to reliably use these prediction models in clinical practice, the models should be well calibrated so that predicted risks match the actual disease incidence for the individual of interest, and this should be proven in independent data that is representative of the target population. Outcome incidences in people with type 2 diabetes vary over geographical regions and over periods of time beyond what can be explained by risk factors alone. Recent advances in geographical recalibration methods using average

risk factor levels and incidence rates from nationally representative registry data allow for contemporary and geographic recalibration of models[23, 24] and may thus aid in accuracy of predictions.

Individual benefit from preventive treatment

Several more questions arise in our encounters with Mr. D and Mrs. T: How to best prevent cardiovascular and kidney disease for Mr. D and Mrs. T? Is it for example appropriate to initiate glucose-lowering and blood pressure-lowering therapy? And, what does the patient think of taking medications on a daily basis? Fortunately, several effective treatment options to prevent or delay cardiovascular and kidney disease in individuals with type 2 diabetes exist, including lifestyle interventions such as smoking cessation[10] and intensive glucose- and blood pressure lowering and lowering of LDL-cholesterol.[8, 25] Furthermore, treatment with angiotensin-converting enzyme-inhibitors (ACEi) or Angiotensin-II Receptor Blockers (ARB) has proven to lower the risk of progressive kidney function decline and end-stage kidney disease[26] and more novel agents such as sodium-glucose cotransporter-2 inhibitors (SGLT2i)[27, 28] and glucagon-like peptide-1 receptor agonists (GLP-1 RA)[27, 29] reduce both cardiovascular and kidney disease risk. But how do we know what the benefit of these various treatments is for different individual patients?

Other questions that may emerge in our patients encounters: Are they themselves worried about cardiovascular and kidney disease associated with their diagnosis of type 2 diabetes? Or are they perhaps worried about possible side effects? Is the treatment covered by health insurance? The absolute benefit an individual may derive in terms of risk reduction from these treatments depends on several different factors including risk factor burden, duration of treatment and overall life expectancy. Thus, even though many treatment options are effective in reducing cardiovascular and kidney disease at a population level, disadvantages like adverse side-effects, polypharmacy and costs need to be taken into consideration and even intensive lifestyle factor modification may not be beneficial for all individuals with type 2 diabetes.[30] Therefore, treatment should only be recommended to those who are expected to benefit most from therapy while of course also accounting for patient preferences.

The 2021 European Society of Cardiology prevention guidelines introduced a two-step approach as an individualized prevention strategy.[31] A first line

approach of treatment is applicable to all individuals with type 2 diabetes and includes smoking cessation, lifestyle interventions and management of HbA1c. In step two, intensified preventive treatment should be considered at an individual level, and here it is especially important to also consider possible side effects, more frequent clinical visits, increased costs, predicted risks and patient preferences.

In conclusion, even with the lack of a future foretelling crystal ball, individual risk estimations of cardiovascular and kidney disease and potential benefit from treatment in people with type 2 diabetes can be obtained. This, however, needs to be done using risk scores with longer time span estimates that are in line with the latest methodological standards, including external validation. Such risk scores will help ensure accurate predictions and estimate benefit from treatment. This will help Mr. D and Mrs. T, in collaboration with their treating physician, choose the interventions most beneficial for their risk profile and personal preferences.

Thesis objective

The objectives of this thesis are to individualize predictions of cardiovascular and kidney outcomes in high risk patients with type 2 diabetes or established CVD. Therefore, the general objectives are:

1. To identify risk factors associated with kidney and cardiovascular outcomes in high risk patients with type 2 diabetes and/or established CVD.
2. To improve the accuracy and clinical utility of risk prediction by increasing the time span of individual estimates of cardiovascular and kidney disease risk and to estimate individual benefit from treatment in people with type 2 diabetes.

Thesis outline

Part 1 focuses on risk factors for development of (recurrent) CVD and kidney disease, including kidney function decline and end-stage kidney disease in high-risk patients with established CVD and/or type 2 diabetes. In **chapter 2** the relationship between several amendable risk factors and end-stage kidney

disease is investigated in patients with established CVD from the UCC-SMART cohort. In **chapter 3** change in lifestyle factors, including smoking, exercise, alcohol consumption and obesity markers, over 10 years and the effect on kidney function decline is examined in patients with established CVD. In **chapter 4** the relation between HGI and risk of CVD in patients with type 2 diabetes from the UCC-SMART cohort is examined. Part 2 of this thesis focuses on prediction of cardiovascular risk and risk of end-stage kidney disease in people with type 2 diabetes. In **chapter 5** cardiovascular risk and lifetime benefit from preventive treatment is investigated in a cohort of people with type 2 diabetes spanning 13 different countries. In **chapter 6** a prediction model for end-stage kidney disease in people with type 2 diabetes is derived and validated using data from approximately 1,000,000 individuals with type 2 diabetes. In **chapter 7** a comprehensive update of the DIAL model, a lifetime prediction model for CVD in people with type 2 diabetes, is derived and validated including geographical recalibration. **Chapter 8** describes the derivation and validation of a prediction model for estimating 10-year risk of CVD in people with type 2 diabetes according to the latest methodological advancements. The main findings of this thesis are discussed in **chapter 9**.

References

1. Hippocrates tbFA. On Epidemics; 1849.
2. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-1788.
3. Levey AS, Coresh J. Chronic kidney disease. Lancet 2012;379:165-80.
4. Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med 2004;164:1422-6.
5. Liu JH, Lin SY, Hsu CY, Lin HH, Liang CC, Sung FC, Huang CC. The risk for chronic kidney disease in patients with heart diseases: a 7-year follow-up in a cohort study in Taiwan. BMC Nephrol 2012;13:77.
6. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073-81.
7. Kramer A, Boenink R, Stel VS, Santiuste de Pablos C, Tomović F, Golan E, Kerschbaum J, Seyahi N, Ioanou K, Beltrán P, Zurriaga O, Magaz Á, Slon Roblero MF, Gjorgjievski N, Garneata L, Arribas F, Galvão AA, Bell S, Ots-Rosenberg M, Muñoz-Terol JM, Winzeler R, Hommel K, Åsberg A, Spustova V, Palencia García M, Vazelov E, Finne P, Ten Dam M, Lopot F, Trujillo-Alemán S, Lassalle M, Kolesnyk MO, Santhakumaran S, Idrizi A, Andrusev A, Comas Farnés J, Komissarov K, Resić H, Palsson R, Kuzema V, Garcia Bazaga MA, Ziginskiene E, Stendahl M, Bonthuis M, Massy ZA, Jager KJ. The ERA-EDTA Registry Annual Report 2018: a summary. Clin Kidney J 2021;14:107-123.
8. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-967.
9. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.
10. Xia J, Wang L, Ma Z, Zhong L, Wang Y, Gao Y, He L, Su X. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Nephrol Dial Transplant 2017;32:475-487.
11. Mons U, Müezzinler A, Gellert C, Schöttker 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. 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.
12. Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellström B, Jardine AG, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray MJ, Keech A, Simes J, Collins R, Baigent C. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol 2016;4:829-39.
13. Hempe JM, Gomez R, McCarter RJ, Jr., Chalew SA. High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. J Diabetes Complications 2002;16:313-20.

14. Hempe JM, Liu S, Myers L, McCarter RJ, Buse JB, Fonseca V. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. Diabetes Care 2015;38:1067-74.
15. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract 2019;157:107843.
16. Beulens J, Rutters F, Rydén L, Schnell O, Mellbin L, Hart HE, Vos RC. Risk and management of pre-diabetes. Eur J Prev Cardiol 2019;26:47-54.
17. Howard BV, Best LG, Galloway JM, Howard WJ, Jones K, Lee ET, Ratner RE, Resnick HE, Devereux RB. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. Diabetes Care 2006;29:391-7.
18. Paynter NP, Mazer NA, Pradhan AD, Gaziano JM, Ridker PM, Cook NR. Cardiovascular risk prediction in diabetic men and women using hemoglobin A1c vs diabetes as a high-risk equivalent. Arch Intern Med 2011;171:1712-8.
19. Slieker RC, van der Heijden A, Siddiqui MK, Langendoen-Gort M, Nijpels G, Herings R, Feenstra TL, Moons KGM, Bell S, Elders PJ, t Hart LM, Beulens JWJ. Performance of prediction models for nephropathy in people with type 2 diabetes: systematic review and external validation study. Bmj 2021;374:n2134.
20. van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FL. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J 2014;35:837-43.
21. Dagliati A, Marini S, Sacchi L, Cogni G, Teliti M, Tibollo V, De Cata P, Chiovato L, Bellazzi R. Machine Learning Methods to Predict Diabetes Complications. J Diabetes Sci Technol 2018;12:295-302.
22. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925-33.
23. Pennells L, Kaptoge S, Wood A, Sweeting M, Zhao X, White I, Burgess S, Willeit P, Bolton T, Moons KGM, van der Schouw YT, Selmer R, Khaw KT, Gudnason V, Assmann G, Amouyel P, Salomaa V, Kivimaki M, Nordestgaard BG, Blaha MJ, Kuller LH, Brenner H, Gillum RF, Meisinger C, Ford I, Knuiman MW, Rosengren A, Lawlor DA, Völzke H, Cooper C, Marín Ibañez A, Casiglia E, Kauhanen J, Cooper JA, Rodriguez B, Sundström J, Barrett-Connor E, Dankner R, Nietert PJ, Davidson KW, Wallace RB, Blazer DG, Björkelund C, Donfrancesco C, Krumholz HM, Nissinen A, Davis BR, Coady S, Whincup PH, Jørgensen T, Ducimetiere P, Trevisan M, Engström G, Crespo CJ, Meade TW, Visser M, Kromhout D, Kiechl S, Daimon M, Price JF, Gómez de la Cámara A, Wouter Jukema J, Lamarche B, Onat A, Simons LA, Kavousi M, Ben-Shlomo Y, Gallacher J, Dekker JM, Arima H, Shara N, Tipping RW, Roussel R, Brunner EJ, Koenig W, Sakurai M, Pavlovic J, Gansevoort RT, Nagel D, Goldbourt U, Barr ELM, Palmieri L, Njølstad I, Sato S, Monique Verschuren WM, Varghese CV, Graham I, Onuma O, Greenland P, Woodward M, Ezzati M, Psaty BM, Sattar N, Jackson R, Ridker PM, Cook NR, D'Agostino RB, Thompson SG, Danesh J, Di Angelantonio E. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. Eur Heart J 2019;40:621-631.
24. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Health 2019;7:e1332-e1345.

25. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, Hayward RA, Craven T, Coleman RL, Chalmers J. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431-437.
26. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D, Rosano GM, Davis BR, Ridao M, Zaragoza A, Montero-Corominas D, Tobías A, de la Fuente-Honrubia C, Tabarés-Seisdedos R, Hutton B. Cardiovascular and Renal Outcomes of Renin-Angiotensin System Blockade in Adult Patients with Diabetes Mellitus: A Systematic Review with Network Meta-Analyses. PLoS Med 2016;13:e1001971.
27. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, Tunnicliffe D, Ruospo M, Natale P, Saglimbene V, Nicolucci A, Johnson DW, Tonelli M, Rossi MC, Badve SV, Cho Y, Nadeau-Fredette AC, Burke M, Faruque LI, Lloyd A, Ahmad N, Liu Y, Tiv S, Millard T, Gagliardi L, Kolanu N, Barmanray RD, McMorrow R, Raygoza Cortez AK, White H, Chen X, Zhou X, Liu J, Rodríguez AF, González-Colmenero AD, Wang Y, Li L, Sutanto S, Solis RC, Díaz González-Colmenero F, Rodriguez-Gutierrez R, Walsh M, Guyatt G, Strippoli GFM. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. Bmj 2021;372:m4573.
28. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol 2021;6:148-158.
29. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021.
30. de Vries TI, Dorresteijn JAN, van der Graaf Y, Visseren FLJ, Westerink J. Heterogeneity of Treatment Effects From an Intensive Lifestyle Weight Loss Intervention on Cardiovascular Events in Patients With Type 2 Diabetes: Data From the Look AHEAD Trial. Diabetes Care 2019;42:1988-1994.
31. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-3337.

PART I

Risk factors for cardiovascular and kidney disease

CHAPTER 2

End-stage kidney disease in patients with clinically manifest vascular disease; incidence and risk factors: results from the UCC-SMART cohort study

Helena Bleken Østergaard
Jan Westerink
Marianne C Verhaar
Michiel L Bots
Folkert W Asselbergs
Gert J de Borst
L Jaap Kappelle
Frank LJ Visseren
Joep van der Leeuw
on behalf of the UCC-SMART studygroup

J Nephrol. 2021 Oct;34(5):1511-1520

Abstract

Background: Patients with cardiovascular disease are at increased risk of end-stage kidney disease. Insights in the incidence and role of modifiable risk factors for end-stage kidney disease may provide means for prevention in patients with cardiovascular disease.

Methods: We included 8,402 patients with stable cardiovascular disease. Incidence rates for end-stage kidney disease were determined stratified according to vascular disease location. Cox proportional hazard models were used to assess the risk of end-stage kidney disease for the different determinants.

Results: 65 events were observed with a median follow-up of 8.6 years. The overall incidence rate of end-stage kidney disease was 0.9/1000 person-years. Patients with polyvascular disease had highest incidence rate (1.8/1000 person-years). Smoking (HR 1.87; 95%CI 1.10-3.19), type 2 diabetes (HR 1.81; 95%CI 1.05-3.14), higher systolic blood pressure (HR 1.37; 95%CI 1.24-1.52/10 mmHg), lower estimated glomerular filtration rate (HR 2.86; 95%CI 2.44-3.23/10 mL/min/1.73m^2) and higher urine albumin/creatinine ratio (HR 1.19; 95%CI 1.15-1.23/10 mg/mmol) were independently associated with elevated risk of end-stage kidney disease. Body mass index, waist circumference, non-HDL-cholesterol and exercise were not independently associated with risk of end-stage kidney disease.

Conclusions: Incidence of end-stage kidney disease in patients with cardiovascular disease varies according to vascular disease location. Several modifiable risk factors for end-stage kidney disease were identified in patients with cardiovascular disease. These findings highlight the potential of risk factor management in patients with manifest cardiovascular disease.

Introduction

Chronic kidney disease (CKD) is a growing health problem worldwide, predicted to be the 5th most common cause of life-years lost by 2040.[1] The rise in CKD is mainly due to the increasing prevalence of type 2 diabetes and hypertension in the presence of increasing life expectancy.[2] CKD is irreversible and in most cases progressive and the consequences include progression to end-stage kidney disease (ESKD), as well as an increased risk for cardiovascular disease (CVD) and mortality.[3, 4] The relation between CVD and CKD is bidirectional and patients with manifest CVD are at increased risk for adverse kidney outcomes.[5, 6]

Early identification and treatment of modifiable risk factors is the first-line strategy to reduce CKD progression in patients at high risk for developing ESKD, including patients with CVD at baseline. Known modifiable risk factors for ESKD include hypertension,[7, 8] type 2 diabetes,[9, 10] kidney function,[11] obesity,[12] dyslipidemia,[13] smoking[14-16] and exercise.[17] However, these risk factors for ESKD are primarily investigated in low-risk populations and the effect of these risk factors may differ in patients with vascular disease, especially in more advanced cases. To the best of our knowledge, no previous study investigated the relation between modifiable risk factors for CVD and occurrence of ESKD in a high-risk population cohort with different manifestations of CVD, including cerebrovascular disease, coronary artery disease (CAD), peripheral artery disease (PAD) or polyvascular disease.

The aim of this study is two-fold. First, we set out to determine the incidence of ESKD in patients with stable manifest CVD according to vascular disease location. The second aim was to assess the relation between modifiable risk factors for kidney disease and incident ESKD in a contemporary population cohort with stable manifest vascular disease.

Materials and methods

Study population

The study population consisted of patients included in the Utrecht Cardiovascular Cohort - Second Manifestations of Arterial Disease (UCC-SMART) study. The UCC-SMART study is an ongoing single-center prospective cohort study conducted in Utrecht, the Netherlands including patients from 18 years of age. A description of the study protocol has been provided elsewhere.[18] Study participants were

patients newly referred to the University Medical Centre Utrecht with established CVD or an increased risk hereof, and were enrolled from September 1996 to February 2018. For this analysis, all patients with manifest cerebrovascular disease, CAD, symptomatic PAD and/or abdominal aortic aneurysm (AAA) were included. For definitions of CVD see *Supplementary table 1*. Patients with ESKD at baseline were excluded (n = 20). The UCC-SMART study was approved by the local Medical Ethics Committee and written informed consent was obtained from all patients.

Collection of data

All patients underwent vascular screening at baseline, including a health questionnaire, a standardized physical examination and collection of fasting blood samples. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[19] Systolic blood pressure (SBP) was measured three times on both arms in supine position and the mean of the last two measurements of the highest arm was used. Type 2 diabetes was defined as either a referral or self-reported diagnosis of type 2 diabetes, or a fasting plasma glucose ≥ 7 mmol/L at study inclusion with initiation of glucose-lowering treatment within 1 year, or baseline use of antihyperglycemic agents or insulin. Non-HDL-cholesterol was calculated as total cholesterol minus HDL-cholesterol and LDL-cholesterol was calculated using the Friedewald formula up to triglyceride-values of 8.0 mmol/L. Smoking was self-reported and categorized as current smoking, former smoker or never smoker. Exercise was also self-reported as number of hours per week for sports, walking, cycling, and gardening, and this was multiplied by a specific metabolic equivalent of task (MET) derived from the Compendium of Physical activity,[20] resulting in a number of MET hours per week per activity. The total amount of physical activity was the sum of MET hours per week of all activities.

Participants were asked to fill out a questionnaire twice a year. If an event was reported, hospital discharge letters, relevant laboratory results and radiological examinations were collected. With this additional information, all events were audited by three members of the UCC-SMART study endpoint committee, comprising physicians from various departments. The outcome of interest for this study was ESKD, defined according to Kidney Disease Improving Global Outcomes[21] as CKD stage 5 (sustained eGFR <15 ml/min/1.73 m^2), long-term dialysis or kidney transplantation.

Data analyses

Data in the baseline table are presented as counts (percentages) for categorical values, as mean ± standard deviation (SD) for normally distributed variables and as median with interquartile range (IQR) for skewed distributions. The cohort was stratified according to previous vascular disease location. Vascular disease location was specified to either only cerebrovascular disease, only CAD, only PAD and/or AAA, or polyvascular disease defined as ≥2 locations.

To prevent loss of statistical power and potential bias,[22] missing data were imputed by single regression imputation using all covariate and outcome data: eGFR (0.4%), urine albumin to creatinine ratio (uACR) (3%), smoking (0.4%), SBP (0.2%), BMI (0.2%), waist circumference (12%), non-HDL-cholesterol (0.6%) and exercise (23%). Incidence rates (IR) and 95% confidence intervals (CI) were determined according to subgroups of vascular disease location. Kaplan-Meier survival curves were fitted to determine ESKD-free survival over time. To test for significant differences in ESKD-free survival between the groups, the Peto's log-rank test[23] was performed. In addition, survival curves based on an unadjusted Cox proportional hazard model was fitted with age at baseline and age at event as time-axis instead of follow-up time. This was done in order to illustrate the possible difference in life-expectancy free of ESKD between the subgroups of vascular disease location. The latter survival curve only included patients with a baseline age ≥50 years.

To assess the association between smoking, type 2 diabetes, SBP, BMI, waist circumference, non-HDL-cholesterol, eGFR, uACR and weekly exercise and ESKD, Cox proportional hazard models were constructed to determine hazard ratios (HRs) and 95%CIs. For eGFR as determinant, the inverse hazard ratio was determined (1/HR) in order to report risk of ESKD associated with decrease of eGFR. The linearity assumption between determinants and the log-hazard of ESKD was not violated based on visual inspection of restricted cubic splines. Satisfaction of the proportional-hazards assumption was confirmed by visual inspection of Schoenfeld residual plots. To adjust for confounding, three models were constructed: the first model was adjusted for sex and age and the second model was further adjusted for smoking, type 2 diabetes, SBP, BMI, non-HDL-cholesterol and exercise (if not determinant of interest). A third model was constructed with addition of use of glucose-lowering medication, antihypertensive medication and lipid-lowering medication to the second model. All analyses were performed with R-statistic programming (version

3.5.1, R Foundation for Statistical Computing, Vienna, Austria). All p-values were two-sided, with statistical significance set at 0.05.

Sensitivity analyses

Since eGFR and uACR are part of the causal pathway in the relation between determinants and risk of ESKD, we did not include them as confounders in the main analyses. However, since these markers of kidney function may also partly act as confounders in the causal pathway, we performed analyses with these added to model 1. Also we show the hazard ratios of the crude data. Furthermore, for sensitivity analyses, the association between risk factors and ESKD was assessed in patients who were treated with RAS-inhibitors, as this is often used as treatment to prevent kidney function decline in high-risk patients and may thus act as an effect modifier in the relation between determinants and risk of ESKD. Also, as all-cause mortality constitutes a competing risk for ESKD, a Fine and Gray competing risk regression analysis was done with all-cause mortality as competing risk. Lastly, IR were calculated stratified according to sex and age groups and interaction with sex and age, respectively, in the relation between determinants and risk of ESKD was examined.

Results

Baseline characteristics

A total of 8,402 patients were included with a total follow-up of 75,131 person-years (median follow-up 8.6 years, IQR 4.7-12.8 years). Baseline characteristics of patients are shown in *Table 1*. *Supplementary table 2* shows the distribution of determinants and incidence rates for total mortality in patients who reached ESKD and in patients who did not. The mean age was 60 ± 10 years, 74% percent of the patients were male, 1848 (22%) had a history of only cerebrovascular disease, 4119 (49%) had a history of only CAD, 1227 (15%) had a history of only PAD and 1208 (14%) had a history of polyvascular disease. Patients with CAD or polyvascular disease were more often treated with antihypertensive and lipid-lowering medication. Patients with PAD were more often smokers and patients with PAD and polyvascular disease had on average higher SBP and lower levels of physical exercise. Patients with polyvascular disease had overall lower eGFR and higher uACR. Overall mortality risk during follow-up was 23% (IR 26/1000 person-years, 95%CI 25-27) and CVD risk was 19% (IR 22/1000 person-years, 95%CI 21-23).

Table 1. Baseline table

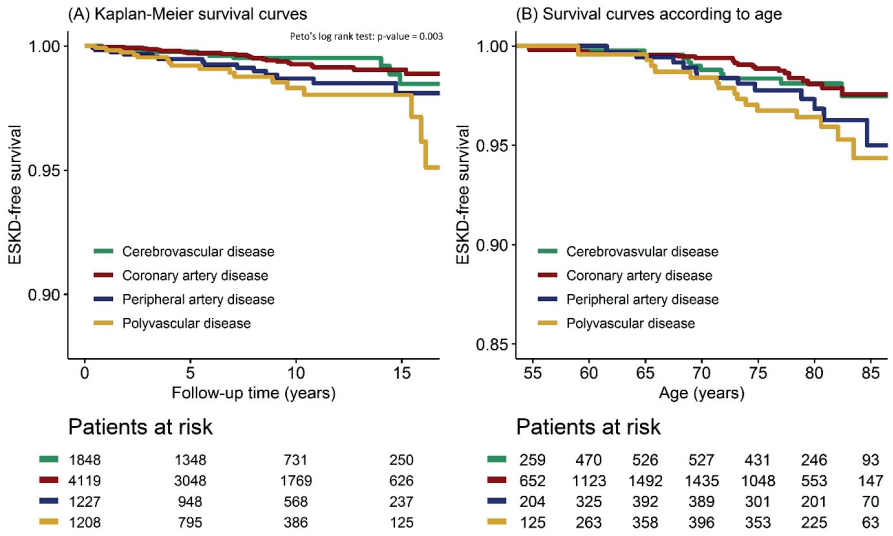
	Total (n = 8402)	Cerebrovascular disease (n = 1848)	Coronary artery disease (n = 4119)	Peripheral artery disease (n = 1227)	Polyvascular disease (n = 1208)
Gender, male [*n* (%)]	6199 (74%)	1059 (57%)	3341 (81%)	826 (67%)	973 (81%)
Age (years)	60 ± 10	58 ± 11	60 ± 10	59 ± 11	63 ± 9
Smoking, current [*n* (%)]	2561 (30%)	596 (32%)	930 (23%)	650 (53%)	385 (32%)
Type 2 diabetes [*n* (%)]	1386 (17%)	221 (12%)	718 (17%)	175 (14%)	272 (23%)
Physical exercise (MET hours/week)	34 (17-63)	35 (18-61)	42 (22-70)	26 (10-51)	28 (11-52)
Systolic blood pressure (mmHg)	138 ± 21	140 ± 22	135 ± 19	143 ± 21	142 ± 21
Diastolic blood pressure (mmHg)	81 ± 11	82 ± 12	80 ± 11	83 ± 12	80 ± 12
Body mass index (kg/m^2)	25.9 ± 4.1	25.4 ± 4.2	26.3 ± 3.8	25.0 ± 4.3	26.0 ± 4.0
Waist circumference (cm)	95.8 ± 11.8	92.6 ± 12.4	97.0 ± 11.3	94.6 ± 11.7	97.9 ± 11.7
HbA1c (%)	5.9 ± 0.8	5.7 ± 0.7	5.9 ± 0.8	6.0 ± 1.0	6.1 ± 1.0
Total cholesterol (mmol/L)	4.8 ± 1.2	5.0 ± 1.2	4.5 ± 1.1	5.5 ± 1.3	4.8 ± 1.1
LDL cholesterol (mmol/L)	2.8 ± 1.0	3.0 ± 1.1	2.6 ± 0.9	3.4 ± 1.1	2.8 ± 1.0
Non-HDL cholesterol (mmol/L)	3.6 ± 1.2	3.6 ± 1.2	3.3 ± 1.1	4.2 ± 1.3	3.7 ± 1.1
Triglycerides (mmol/L)	1.4 (1.0-2.0)	1.3 (0.9-1.8)	1.4 (1.0-1.9)	1.5 (1.1-2.2)	1.5 (1.1-2.2)
Serum creatinine (µmol/l)	87 (76-99)	83 (73-95)	88 (78-99)	85 (74-98)	92 (80-108)
eGFR (mL/min/1.73 m^2)	77 ± 18	79 ± 18	78 ± 17	78 ± 19	71 ± 19
Albuminuria (micro) [*n* (%)]	1007 (12%)	204 (11%)	363 (9%)	199 (16%)	241 (20%)
Albuminuria (macro) [*n* (%)]	138 (1.6%)	23 (1.2%)	52 (1.3%)	33 (2.7%)	30 (2.5%)
Albumine/creatinine-ratio (mg/mmol)	2.6 ± 11.5	2.3 ± 9.7	2.0 ± 10.5	3.5 ± 14.3	4.2 ± 13.8
Use of antidiabetic medication [*n* (%)]	1129 (13%)	175 (9%)	601 (15%)	135 (11%)	218 (18%)
Use of insulin [*n* (%)]	378 (4%)	41 (2%)	203 (5%)	44 (4%)	90 (7%)
Use of antihypertensive medication [*n* (%)]	6297 (75%)	994 (54%)	3775 (92%)	543 (44%)	985 (82%)
Use of RASi medication [*n* (%)]	3579 (43%)	630 (34%)	1995 (48%)	343 (28%)	611 (51%)
Use of lipid-lowering medication [*n* (%)]	4508 (54%)	789 (43%)	2584 (63%)	415 (34%)	720 (60%)

Abbreviations: MET = metabolic equivalent of task, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, LDL = low density lipoprotein, HDL = high density lipoprotein, RASi = renin angiotensin system inhibition.

Incidence rates of ESKD according to vascular disease location

A total of 65 ESKD-events were observed during follow-up (IR 0.9/1000 person-years, 95%CI 0.7-1.1). In patients with only cerebrovascular disease, 10 ESKD-events occurred (IR 0.6/1000 person-years, 95%CI 0.3-1.1). In patients with only CAD, 24 ESKD-events occurred (IR 0.6/1000 person-years, 95%CI 0.4-1.0). In patients with only PAD, 14 ESKD-events occurred (IR 1.2/1000 person-years, 95%CI 0.6-2.0) and in patients with polyvascular disease, 17 ESKD-events occurred (IR 1.8/1000 person-years, 95%CI 1.0-2.9). Overall absolute risk of ESKD was relatively small over time (*Figure 1a*), and at the age of 50 years, patients with polyvascular disease had a shorter life-expectancy free of ESKD compared to patients with only cerebrovascular disease or only CAD (*Figure 1b*).

Figure 1. End-stage kidney disease-free survival according to vascular disease location at baseline

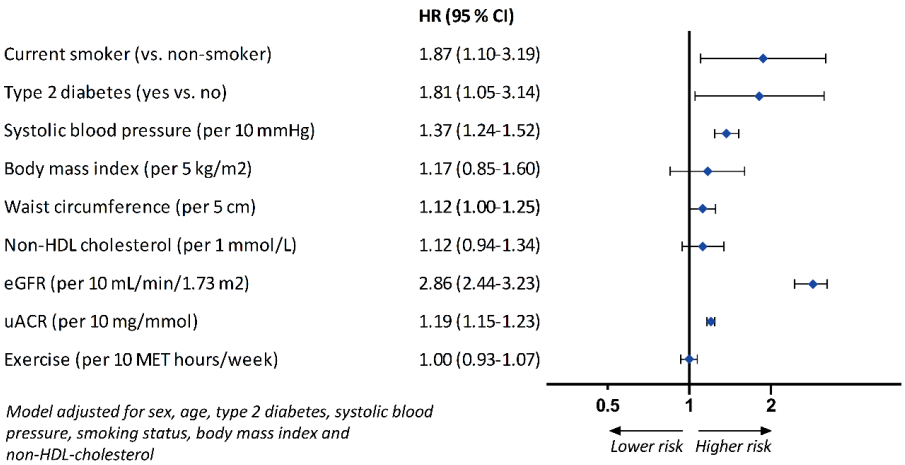


Relation between risk factors and risk of ESKD

Using the model with clinical covariates, current smoking was independently associated with an elevated risk of ESKD (HR 1.87; 95%CI 1.10-3.19) and patients with type 2 diabetes had higher risk of ESKD (HR 1.81; 95%CI 1.05-3.14). An increase in SBP was associated with an increase in the risk of ESKD (HR 1.37; 95%CI 1.24-1.52 per 10 mmHg). A 10 ml/min/1.73m^2 lower eGFR increased the

risk of ESKD (HR 2.86; 95%CI 2.44-3.23) and a 10 mg/mmol higher uACR was significantly associated with higher risk of ESKD (HR 1.19; 95%CI 1.15-1.23) (*Figure 2*).

Figure 2. Relation between determinants and risk of end-stage kidney disease



No significant independent relation was observed between physical exercise (HR 1.00; 95%CI 0.93-1.07), BMI (HR 1.16; 95%CI 0.85-1.60 per 5 kg/m^2), waist circumference (1.12, 95%CI 1.00-1.25) and non-HDL-cholesterol (HR 1.12; 95%CI 0.94-1.34) and risk of ESKD. The magnitude and direction of the HR was not materially different compared with the model only adjusted for sex and age (*Table 2*), except that relations between non-HDL-cholesterol and risk of ESKD (HR 1.21; 95%CI 1.03-1.42) and waist circumference (HR 1.15, 95%CI 1.03-1.28) and risk of ESKD were significant. Further adjusting for use of medication added to the second model did not alter the HR meaningfully.

Sensitivity analyses

Adjusting for eGFR and uACR did not meaningfully alter the direction of the hazard ratios, except for type 2 diabetes as determinant which became insignificant (*Supplementary table 3*). When performing the analyses with all-cause mortality as a competing risk, the direction and magnitude of the hazard ratios did not change substantially (*Supplementary table 4*). Furthermore, in patients who were using RAS-inhibitors, the hazard ratios for the relation between risk factors and ESKD also did not change considerably (*Supplementary*

table 5). IR for ESKD were higher in men (1.0/1000 person-years) compared to women (0.5/1000 person-years) and in subjects older than 70 years of age compared to subjects younger than 70 years of age (*Supplementary table 6*). However, no interaction between sex and age, respectively, and any of the determinants was observed (data not shown).

Table 2. Relation between determinants and risk of end-stage kidney disease

	Hazard ratios and 95%CI		
	Model 1	**Model 2**	**Model 3**
Current smoking (yes vs no)	1.90 (1.13-3.20)	1.87 (1.10-3.19)	1.93 (1.13-3.30)
Type 2 diabetes (yes vs no)	2.07 (1.21-3.54)	1.81 (1.05-3.14)	1.74 (1.00-3.01)
Systolic blood pressure (per 10 mmHg)	1.39 (1.26-1.54)	1.37 (1.24-1.52)	1.37 (1.24-1.51)
Body mass index (per 5 kg/m^2)	1.23 (0.90-1.70)	1.16 (0.85-1.60)	1.12 (0.81-1.55)
Waist circumference (per 5 cm)	1.15 (1.03-1.28)	1.12 (1.00-1.25)	1.11 (0.99-1.24)
Non-HDL cholesterol (per mmol/L)	1.21 (1.03-1.42)	1.12 (0.94-1.34)	1.12 (0.96-1.30)
eGFR (per 10 mL/min/1.73 m^2)	2.94 (2.50-3.33)	2.86 (2.44-3.23)	2.86 (2.44-3.33)
Albumine/creatinine-ratio (per 10 mg/mmol)	1.23 (1.19-1.27)	1.19 (1.15-1.23)	1.17 (1.13-1.22)
Exercise (per 10 MET hours/week)	0.97 (0.91-1.04)	1.00 (0.93-1.07)	1.00 (0.93-1.07)

Model 1: Parameters included in the model are sex and age.
Model 2: Parameters included in the model are sex, age, type 2 diabetes, systolic blood pressure, current smoking, body mass index, non-HDL cholesterol and exercise.
Model 3: Parameters included in the model are sex, age, type 2 diabetes, systolic blood pressure, current smoking, body mass index, non-HDL cholesterol, exercise, antihypertensive medication, lipid-lowering medication and glucose-lowering medication (except for type 2 diabetes as determinant, which was not adjusted for use of glucose-lowering medication)

Discussion

The present study shows that incidence of ESKD in patients with stable manifest CVD varies according to vascular disease location. A higher incidence of ESKD and lower life expectancy free of ESKD was observed in patients with polyvascular disease or only PAD compared to patients with only cerebrovascular disease or only CAD. With respect to risk factors for ESKD in patients with stable manifest CVD, current smoking, type 2 diabetes, systolic hypertension, lower eGFR and higher uACR were all independently associated with increased risk of ESKD.

It is well known that the heart and kidneys are intertwined, in which dysfunction in one organ may induce dysfunction and increase the risk of disease in the

other.[3, 4] The majority of previous studies examining the cardiorenal syndrome have focused on the relation between heart failure and CKD.[24] We expand on these previous findings by including patients with stable CVD with manifestations in different vascular beds.

The incidences of ESKD observed in the current study are higher than IR reported in general population cohorts,[11, 25, 26] indicating that patients with stable vascular disease have a higher risk of ESKD. A study performed in the CKD Prognosis Consortium cohorts found an IR for ESKD of 1.83/1000 person-years in populations with previous CVD or at increased risk of vascular disease.[11] A study examining the risk of ESKD after hospitalization with an incident CVD event reported an overall incidence of ESKD of 3.3/1000 person-years.[27] The incidence for ESKD in our study (overall IR of 0.9/1000 person-years) is lower, which might be due to the fact that the cohort consisted of patients who were overall intensively treated in terms of cardiovascular risk factors. Also, differences in case mix may strongly influence the incidence numbers across the studies.

In a broader perspective, approximately 1,550,000 people in the Netherlands are living with CVD.[28] Assuming the incidence rate found in this study, this will result in 1395 incident cases of ESKD per year. This agrees well with the incidence of ESKD-events within the Dutch population.[29] Since ESKD is associated with mortality and severe morbidity, reduced quality of life and increased health-care costs, this is a considerable number of events and focus on the prevention of ESKD in high-risk patients with manifest CVD is important.

This study identified patients with PAD and polyvascular disease as patients at highest risk for ESKD. These findings may result from identification of a population with more advanced general atherosclerosis, which also affects the aorta, kidney arteries and the kidneys themselves, resulting in a higher risk of ESKD. The disparities in incidence of ESKD between men and women, with men having a higher IR than women, are complex and may relate to a faster decline of kidney function in men hypothesized to be related to protective hormonal effects in women and differences in lifestyle factors.[30]

In the current study, several modifiable risk factors for ESKD in patients with stable CVD were identified. We observed a higher risk of ESKD in patients who were current smokers, patients with type 2 diabetes and patients with higher SBP. A previous study using general population cohorts found a relative risk for

ESKD in subjects who were current smokers to be very similar to our results.[15] This underlines the importance of encouraging smoking cessation for both prevention of cardiovascular and kidney outcomes. Also, type 2 diabetes and SBP showed similar associations with ESKD as in the general population,[8, 31] warranting close follow-up and treatment of these patients.

A previous meta-analysis found lower eGFR and higher uACR to be associated with increased risk of ESKD, independent of traditional CVD risk factors,[11] and albuminuria has previously been shown to be associated with increased risk of ESKD.[32] eGFR and albuminuria are measures of glomerular and tubular function and therefore intuitively important risk factors for ESKD. Also, a lower eGFR and higher uACR can both partly be attributed to the causal pathway between other risk factors and the development of ESKD. However, a lower eGFR is also associated with accumulation of uremic toxins, which increases progression of both CKD and CVD.[33] Specific treatment strategies, for example prescription of RAS-inhibitors,[34] glucose lowering drugs[35] and lifestyle interventions,[36] may alter this long term process by diminishing eGFR decline and reduce proteinuria. Increased awareness of these kidney function measures is likely to lead to better risk stratification and treatment in these high-risk patients.

Previous studies generally show obesity to be associated with increased risk of ESKD,[12, 37-39] but little is known about the pathophysiology behind this relation. In the present study, larger waist circumference was found to be significantly associated with risk of ESKD when only adjusted for sex and age as confounders. A larger waist circumference is associated with higher insulin resistance,[40] potentially leading to type 2 diabetes, which is a risk factor for ESKD. Thus, type 2 diabetes is likely part of the causal pathway in the relation between waist circumference and risk of ESKD. This was also suggested in our study, where the relation between waist circumference and risk of ESKD was slightly reduced when adjusting for type 2 diabetes. Furthermore, BMI was not found to be significantly associated with risk of ESKD. A recent study found a larger waist circumference to be associated with increased risk of ESKD, but no significant relation between BMI and risk of ESKD, as was also observed in the present study.[41] Since BMI is a composite measure of muscle- and bone mass as well as adipose tissue, waist circumference might be a more specific marker for adiposity. Also, as higher BMI is somewhat protective of CVD and ESKD in individuals at risk for malnutrition,[42] such as people with advanced CKD or

CVD, this might lead to reverse causality in the relation between BMI and risk of ESKD. These results indicate that obesity is a potential risk factor for ESKD in patients with manifest stable CVD, and waist circumference might be a better indicator for obesity when assessing this risk.

The major strengths of this prospective cohort study include the large number of patients with manifest CVD with extensive phenotyping of risk factors at baseline and a long and complete follow-up. Furthermore, the cohort is very contemporary as demonstrated by the high prevalence of preventive drug prescriptions. Also, the UCC-SMART cohort consists of patients referred with a broad spectrum of vascular disease, making the results applicable to patients with various manifestations of CVD. Lastly, as patients with kidney disease often die of cardiovascular causes, we performed additional analyses to account for competing events and demonstrated similar results. Some limitations must also be considered. Baseline characteristics were only recorded at the start of the study but may have changed during the course of follow-up. Also, as ESKD develops over a longer time period there was a limited number of outcomes, thereby reducing the power of the study to find specific subgroup effects. Assessment of parameters known to influence vascular calcification, e.g. phosphate, calcium and serum levels of parathyroid hormone as risk factors for ESKD could also be relevant, but were unavailable in this study. However, their absence does not affect the validity of our findings.

In conclusion, the incidence of ESKD in patients with vascular disease is relatively low compared to vascular events and varies according to vascular disease location, being higher in patients with PAD or polyvascular disease. Modifiable risk factors for development of ESKD in patients with stable CVD include current smoking, type 2 diabetes, systolic hypertension, low eGFR and high uACR. These findings highlight the potential of risk factor management in this high-risk patient group not only to prevent recurring vascular disease, but also to reduce progression to ESKD. This is in particular important when discussing risk factor management with patients and may enhance shared decision making by showing the importance of lifestyle changes and medication in the prevention of both recurrent CVD and ESKD.

References

1. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW, Brown JC, Friedman J, He J, Heuton KR, Holmberg M, Patel DJ, Reidy P, Carter A, Cercy K, Chapin A, Douwes-Schultz D, Frank T, Goettsch F, Liu PY, Nandakumar V, Reitsma MB, Reuter V, Sadat N, Sorensen RJD, Srinivasan V, Updike RL, York H, Lopez AD, Lozano R, Lim SS, Mokdad AH, Vollset SE, Murray CJL. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet 2018;392:2052-2090.
2. Burrows NR, Vassalotti JA, Saydah SH, Stewart R, Gannon M, Chen S-C, Li S, Pederson S, Collins AJ, Williams DE. Identifying High-Risk Individuals for Chronic Kidney Disease: Results of the CHERISH Community Demonstration Project. American journal of nephrology 2018;48:447-455.
3. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 2010;31:703-11.
4. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013;382:339-52.
5. Liu M, Li XC, Lu L, Cao Y, Sun RR, Chen S, Zhang PY. Cardiovascular disease and its relationship with chronic kidney disease. European review for medical and pharmacological sciences 2014;18:2918-2926.
6. Kuwahara M, Takehara E, Sasaki Y, Azetsu H, Kusaka K, Shikuma S, Akita W. Effects of Cardiovascular Events on End-Stage Renal Disease and Mortality in Patients With Chronic Kidney Disease Before Dialysis. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2016;20:12-19.
7. Bae EH, Lim SY, Han K-D, Oh TR, Choi HS, Kim CS, Ma SK, Kim SW. Association Between Systolic and Diastolic Blood Pressure Variability and the Risk of End-Stage Renal Disease. Hypertension (Dallas, Tex. : 1979) 2019;74:880-887.
8. Hsu C-y, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Archives of internal medicine 2005;165:923-928.
9. Nasri H, Rafieian-Kopaei M. Diabetes mellitus and renal failure: Prevention and management. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2015;20:1112-1120.
10. Lin Y-C, Chang Y-H, Yang S-Y, Wu K-D, Chu T-S. Update of pathophysiology and management of diabetic kidney disease. Journal of the Formosan Medical Association = Taiwan yi zhi 2018;117:662-675.
11. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Chronic Kidney Disease Prognosis C. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney international 2011;80:93-104.

12. Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, Gutierrez OM, Hosseinpanah F, Iseki K, Kenealy T, Klein B, Kronenberg F, Lee BJ, Li Y, Miura K, Navaneethan SD, Roderick PJ, Valdivielso JM, Visseren FLJ, Zhang L, Gansevoort RT, Hallan SI, Levey AS, Matsushita K, Shalev V, Woodward M, Consortium CKDP. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. BMJ (Clinical research ed.) 2019;364:k5301-k5301.
13. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, Buring JE, Gaziano JM. Cholesterol and the risk of renal dysfunction in apparently healthy men. Journal of the American Society of Nephrology : JASN 2003;14:2084-2091.
14. Alba MM, Citarelli AN, Menni F, Agricola M, Braicovich A, De Horta E, De Rosa F, Filanino G, Gaggiotti R, Junqueras N, Martinelli S, Milan A, Morales ME, Setti S, Villalba DO. Tobacco and end stage renal disease: a multicenter, cross-sectional study in Argentinian Northern Patagonia. Tobacco induced diseases 2015;13:28-28.
15. Xia J, Wang L, Ma Z, Zhong L, Wang Y, Gao Y, He L, Su X. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2017;32:475-487.
16. Wesson DE. The relationship of cigarette smoking to end-stage renal disease. Seminars in nephrology 2003;23:317-322.
17. Pike M, Taylor J, Kabagambe E, Stewart TG, Robinson-Cohen C, Morse J, Akwo E, Abdel-Kader K, Siew ED, Blot WJ, Ikizler TA, Lipworth L. The association of exercise and sedentary behaviours with incident end-stage renal disease: the Southern Community Cohort Study. BMJ open 2019;9:e030661-e030661.
18. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol 1999;15:773-81.
19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
20. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Jr., Schmitz KH, Emplaincourt PO, Jacobs DR, Jr., Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498-504.
21. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-100.
22. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-91.
23. Peto R, Peto J. Asymptotically Efficient Rank Invariant Test Procedures. Journal of the Royal Statistical Society 1972;A135:185-207.
24. House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, Kasiske BL, Deswal A, deFilippi CR, Cleland JGF, Anker SD, Herzog CA, Cheung M, Wheeler DC, Winkelmayer WC, McCullough PA. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:1304-1317.

25. van Blijderveen JC, Straus SM, Zietse R, Stricker BH, Sturkenboom MC, Verhamme KM. A population-based study on the prevalence and incidence of chronic kidney disease in the Netherlands. Int Urol Nephrol 2014;46:583-92.
26. Collins G, Altman D. Predicting the risk of chronic kidney disease in the UK: an evaluation of QKidney® scores using a primary care database. Br J Gen Pract 2012;62:e243-50.
27. Ishigami J, Cowan LT, Demmer RT, Grams ME, Lutsey PL, Carrero JJ, Coresh J, Matsushita K. Incident Hospitalization with Major Cardiovascular Diseases and Subsequent Risk of ESKD: Implications for Cardiorenal Syndrome. J Am Soc Nephrol 2020;31:405-414.
28. A.R. de Boer IvD, F.L.J. Visseren, I. Vaartjes, M.L. Bots. Hart- en vaatziekten in Nederland 2019. https://www.hartstichting.nl/getmedia/41cf66bf-2107-44d6-b2c3-739fc465ec73/cijferboek-hartstichting-hart-vaatziekten-nederland-2019-rp92.pdf 2019.
29. T. Hoekstra FWD, K. Cransberg, W.J. Bos, M. van Buren and M.H. Hemmelder. RENINE annual report 2018. https://www.nefrovisie.nl/wp-content/uploads/2019/12/20191212_RENINE-annual-report-2018.pdf 2018.
30. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nat Rev Nephrol 2018;14:151-164.
31. Johnson ES, Smith DH, Thorp ML, Yang X, Juhaeri J. Predicting the risk of end-stage renal disease in the population-based setting: a retrospective case-control study. BMC Nephrol 2011;12:17.
32. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, Jong PE, Coresh J, Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, de Jong PE, Coresh J, El-Nahas M, Eckardt KU, Kasiske BL, Wright J, Appel L, Greene T, Levin A, Djurdjev O, Wheeler DC, Landray MJ, Townend JN, Emberson J, Clark LE, Macleod A, Marks A, Ali T, Fluck N, Prescott G, Smith DH, Weinstein JR, Johnson ES, Thorp ML, Wetzels JF, Blankestijn PJ, van Zuilen AD, Menon V, Sarnak M, Beck G, Kronenberg F, Kollerits B, Froissart M, Stengel B, Metzger M, Remuzzi G, Ruggenenti P, Perna A, Heerspink HJ, Brenner B, de Zeeuw D, Rossing P, Parving HH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int 2011;79:1331-40.
33. Tonelli M, Karumanchi SA, Thadhani R. Epidemiology and Mechanisms of Uremia-Related Cardiovascular Disease. Circulation 2016;133:518-36.
34. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
35. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016;375:323-34.
36. Chang A, Van Horn L, Jacobs DR, Jr., Liu K, Muntner P, Newsome B, Shoham DA, Durazo-Arvizu R, Bibbins-Domingo K, Reis J, Kramer H. Lifestyle-related factors, obesity, and incident microalbuminuria: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Am J Kidney Dis 2013;62:267-75.

37. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006;144:21-8.
38. Vivante A, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, Calderon-Margalit R. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Arch Intern Med 2012;172:1644-50.
39. Mohammedi K, Chalmers J, Herrington W, Li Q, Mancia G, Marre M, Poulter N, Rodgers A, Williams B, Perkovic V, Coresh J, Woodward M. Associations between body mass index and the risk of renal events in patients with type 2 diabetes. Nutr Diabetes 2018;8:7.
40. Racette SB, Evans EM, Weiss EP, Hagberg JM, Holloszy JO. Abdominal adiposity is a stronger predictor of insulin resistance than fitness among 50-95 year olds. Diabetes Care 2006;29:673-8.
41. Kramer H, Gutiérrez OM, Judd SE, Muntner P, Warnock DG, Tanner RM, Panwar B, Shoham DA, McClellan W. Waist Circumference, Body Mass Index, and ESRD in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. Am J Kidney Dis 2016;67:62-9.
42. Kalantar-Zadeh K, Rhee CM, Chou J, Ahmadi SF, Park J, Chen JL, Amin AN. The Obesity Paradox in Kidney Disease: How to Reconcile it with Obesity Management. Kidney Int Rep 2017;2:271-281.

Supplementary material

Supplementary table 1. Definitions of cardiovascular disease

Cerebrovascular disease	A clinical diagnosis of a transient ischemic attack or ischemic or hemorrhagic stroke.
Coronary artery disease	A clinical diagnosis of angina pectoris, myocardial infarction, cardiac arrest or coronary revascularization.
Peripheral artery disease	Symptomatic and documented obstruction of distal arteries of the leg (ankle brachial index ≤ 0.90), a revascularization procedure of the leg (percutaneous transluminal angioplasty or bypass surgery) or a prior amputation.
Abdominal aortic aneurism	A history of abdominal aortic surgery or an abdominal aortic anteroposterior diameter of ≥ 3 cm at baseline.

Supplementary table 2. Distribution of determinants and incidence rates for total mortality in patients who did not reach ESKD and patients who did

	ESKD outcome (n = 65)	**No ESKD outcome (n = 8337)**
Current smoking [*n* (%)]	26 (40%)	2535 (30%)
Type 2 diabetes [*n* (%)]	19 (29%)	1367 (16%)
Systolic blood pressure (mmHg)	158 ± 23	139 ± 21
Body mass index (kg/m^2)	27.3 ± 4.3	26.9 ± 4.0
Waist circumference (cm)	99.6 ± 11.4	95.8 ± 11.8
Non-HDL cholesterol (mmol/L)	4.0 ± 1.4	3.6 ± 1.2
eGFR (mL/min/1.73 m^2)	45.7 ± 22.0	77.5 ± 17.4
Albumine/creatinine-ratio (mg/mmol)	27.4 ± 63.5	2.4 ± 9.9
Physical exercise (MET hours/week)	22 (7-55)	35 (17-63)
Incidence rate of mortality	83/1000 person-years	26/1000 person-years

Supplementary table 3. Relation between determinants and risk of ESKD; crude data and markers of kidney function included as confounders

N = 8402, ESKD events = 65	**HR (95%CI)**	
	Model 1	**Model 2**
Current smoking (yes vs no)	1.41 (0.85-2.31)	1.81 (1.06-3.10)
Type 2 diabetes (yes vs no)	2.29 (1.34-3.91)	1.47 (0.85-2.55)
Systolic blood pressure (per 10 mmHg)	1.40 (1.28-1.53)	1.21 (1.10-1.34)
Body mass index (per 5 kg/m^2)	1.17 (0.87-1.57)	1.15 (0.84-1.58)
Waist circumference (per 5 cm)	1.17 (1.05-1.30)	1.15 (1.03-1.28)
Non-HDL cholesterol (mmol/L)	1.16 (0.99-1.35)	1.13 (0.93-1.39)
eGFR (per 10 mL/min/1.73 m^2)	2.79 (2.42-3.21)	2.76 (2.38-3.19)
Albumine/creatinine-ratio (per 10 mg/mmol)	1.21 (1.17-1.25)	1.10 (1.06-1.14)
Physical exercise (per 10 MET hours/week)	0.98 (0.92-1.05)	1.03 (0.97-1.09)

Supplementary model 1: Crude data
Supplementary model 2: Parameters included in the model are sex, age, eGFR and albumine/creatinine ratio.

Supplementary table 4. Relation between determinants and ESKD in competing risk analyses with all-cause mortality as competing risk

ESKD outcome (n = 65)	**Subdistribution HR (95%CI)**
Current smoking (yes vs no)	1.67 (1.00-2.80)
Type 2 diabetes (yes vs no)	1.73 (1.01-2.95)
Systolic blood pressure (per 10 mmHg)	1.36 (1.24-1.49)
Body mass index (per 5 kg/m^2)	1.16 (0.85-1.59)
Waist circumference (per 5 cm)	1.11 (1.00-1.24)
Non-HDL cholesterol (mmol/L)	1.12 (0.95-1.33)
eGFR (per 10 mL/min/1.73 m^2)	0.39 (0.33-0.46)
Albumine/creatinine-ratio (per 10 mg/mmol)	1.16 (1.13-1.18)
Physical exercise (per 10 MET hours/week)	1.00 (0.93-1.08)

Parameters included in the model are sex, age, type 2 diabetes, systolic blood pressure, smoking status, body mass index, non-HDL-cholesterol and exercise.

Supplementary table 5. Relation between determinants and risk of ESKD in patients treated with RAS-inhibitors

N = 3579, ESKD events = 39	**HR (95%CI)**
Current smoking (yes vs no)	1.31 (0.64-2.68)
Type 2 diabetes (yes vs no)	1.75 (0.90-3.39)
Systolic blood pressure (per 10 mmHg)	1.35 (1.20-1.53)
Body mass index (per 5 kg/m^2)	1.27 (0.87-1.86)
Waist circumference (per 5 cm)	1.13 (0.99-1.29)
Non-HDL cholesterol (mmol/L)	1.11 (0.84-1.45)
eGFR (per 10 mL/min/1.73 m^2)	0.35 (0.28-0.43)
Albumine/creatinine-ratio (per 10 mg/mmol)	1.18 (1.13-1.23)
Physical exercise (per 10 MET hours/week)	0.96 (0.88-1.06)

Parameters included in the model are sex, age, type 2 diabetes, systolic blood pressure, smoking status, body mass index, non-HDL-cholesterol and exercise.

Supplementary table 6. Incidence of ESKD stratified according to sex and age

	Incidence rates per 1000 person-years (95% confidence intervals)			
Sex:	**Males** (n = 6199)	**Females** (n = 2203)		**P-value***
	1.0 (0.7-1.3)	0.5 (0.3-1.0)		0.08
Age:	**< 50 years** (n = 1335)	**50-70 years** (n = 5635)	**> 70 years** (n = 1432)	
	0.6 (0.3-1.2)	0.8 (0.6-1.1)	1.3 (0.7-2.3)	0.10

**P-value is based on the Peto's log rank test for testing difference between survival curves between the specific subgroups.*

CHAPTER 3

Lifestyle changes and kidney function: A ten year follow-up study in patients with manifest cardiovascular disease

Helena Bleken Østergaard
Imre Demirhan
Jan Westerink
Marianne C Verhaar
Folkert W Asselbergs
Gert J de Borst
L Jaap Kappelle
Frank LJ Visseren
Joep van der Leeuw
on behalf of the UCC-SMART studygroup.

Eur J Clin Invest. 2022 Sep;52(9):e13814

Abstract

Background: Patients with cardiovascular disease (CVD) are at higher risk of kidney function decline. The aim of the current study was to examine the association of lifestyle changes on kidney function decline in patients with manifest CVD.

Methods: 2,260 patients from the UCC-SMART cohort with manifest CVD who returned for a follow-up visit after a median of 9.9 years were included. The relation between change in lifestyle factors (smoking, alcohol consumption, physical activity and obesity) and change in kidney function (eGFR and uACR) was assessed using linear regression models.

Results: Increase in body mass index (β -2.81; 95%CI -3.98;-1.63per 5 kg/m^2) and for men also increase in waist circumference (β -0.87; 95%CI -1.28;-0.47per 5 cm) were significantly associated with a steeper decline in eGFR over 10 years. Continuing smoking (β -2.44, 95%CI -4.43;-0.45) and recent smoking cessation during follow-up (β -3.27; 95%CI -5.20;-1.34) were both associated with a steeper eGFR decline compared to patients who remained as non- or previous smokers from baseline. No significant association was observed between physical exercise or alcohol consumption and kidney function decline. No significant relation between any lifestyle factor and change in uACR was observed.

Conclusions: In patients with CVD, continuing smoking, recent smoking cessation and an increase in obesity markers were related to a steeper kidney function decline. Although no definite conclusions from this study can be drawn, the results support the importance of encouraging weight loss and smoking cessation in high-risk patients as a means of slowing down kidney function decline.

Introduction

The number of patients with chronic kidney disease (CKD) is increasing worldwide with a current global prevalence in adults of 13%.[1] This development is mainly due to increasing prevalence of lifestyle related conditions including hypertension and type 2 diabetes in combination with increasing life expectancy.[2] CKD can progress to end-stage kidney disease (ESKD) and both conditions are associated with decreased life expectancy, loss in quality of life and high healthcare costs.[3] Several chronic diseases contribute to increased risk of CKD, including cardiovascular disease (CVD) which confers a 4-fold increased risk of developing CKD.[4] Furthermore, the risk of both ESKD and CVD increases with declining kidney function, and monitoring eGFR decline can predict time to onset of kidney failure and guide interventions aimed at altering kidney function decline.[5]

Fortunately, progressive loss of kidney function can be diminished by a number of interventions, including prescription of a RAS-inhibitor,[6] SGLT2-inhibitor,[7] adequate control of known risk factors such as diabetes mellitus and hypertension, and lifestyle interventions, including smoking cessation,[8] weight loss,[9] lower alcohol consumption[10] and physical exercise.[11] Reduced intake of sodium has also been shown to lower kidney function decline.[12] These lifestyle factors are especially encouraged in patients with CVD, who often visit the out-patient clinic frequently, and an improvement in almost all risk factors will have beneficial impact on both CKD and CVD risk. Since patients with CVD are at increased risk of kidney function decline compared to patients without,[13] improvement in risk factors including lifestyle changes is likely to have greater benefit in patients with CVD. To the best of our knowledge, no previous study examined the effect of changes in these lifestyle factors on kidney function decline in a high risk cohort of patients with manifest CVD.

The aim of the current study was to evaluate the relation between lifestyle changes (change in smoking status, alcohol consumption, markers of obesity and physical exercise) and kidney function decline (assessed by change in eGFR and urine-albumine/creatinine ratio (uACR)) over a 10-year time span in patients with manifest CVD.

Methods

Study population

The cohort consisted of patients from the Utrecht Cardiovascular Cohort – Second Manifestations of ARTerial disease (UCC-SMART), which is an ongoing prospective cohort study including patients from 18 years of age. Study design and rationale have previously been described in detail.[14] Study inclusion for the cohort used for this study occurred between 1996 and 2012. From 2006 and onwards, patients with at least 4 years of follow-up were invited once for a second visit with reassessment of baseline measurements (UCC-SMART 2). Thus, all participants in UCC-SMART 2 had one visit at baseline and further one follow-up visit at least four years after baseline visit. The UCC-SMART study was approved by the local Medical Ethics Committee and written informed consent was obtained from all patients. Reporting of the study conforms to broad EQUATOR guidelines.[15]

Patients with manifest cardiovascular disease at baseline who returned for a second measurement and with eGFR levels ≥15 ml/min/1.73m2 at baseline were included (n = 2,260). Manifest CVD was defined as cerebrovascular disease, coronary artery disease, symptomatic peripheral artery disease and/or abdominal aortic aneurysm (AAA). For specific definitions of CVD see *Supplementary table 1*. After baseline visit, advice on lifestyle improvements was given according to general clinical practice, and no specific lifestyle intervention was performed in this observational study.

Collection of data

Data collection at baseline and follow-up visit was identical, acquired using a standardized protocol. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[16] Information on smoking status (never, former or current, including number of pack-years) and alcohol consumption (no alcohol,<1, 1–10, 11–20, 21–30, or >30 units per week) was obtained with a questionnaire. A previously validated questionnaire suitable for ranking subjects[17] was used for measuring physical activity, with one additional question on the intensity of sports activity. Number of hours per week reported by patients for sports, walking, cycling, and gardening was multiplied by a specific metabolic equivalent of task (MET), resulting in a number of MET hours per week per activity. The total amount of physical activity was the sum of the MET hours per week of all activities. Visceral adipose tissue (VAT) thickness was

measured as the distance between the lumbar spine and the peritoneum, and subcutaneous adipose tissue (SAT) thickness was measured as the distance between the linea alba and the skin. Both were measured using a previously validated ultrasound technique.[18]

Lifestyle changes

Lifestyle factors were assessed at baseline and follow-up regarding smoking, body mass index (BMI), waist circumference, VAT and SAT, physical activity and alcohol consumption. Change in eGFR (ΔeGFR) was calculated by subtracting eGFR at baseline from eGFR at follow-up and dividing the difference by follow-up time in years and multiplied by a factor 10 to account for change over 10 years (median follow-up time was 10 years). The same approach was done for change in uACR (ΔuACR). Thus, a negative ΔeGFR indicates a fall in eGFR and a positive ΔuACR indicates an increase in uACR over 10 years. The same approach was done for Δpack-years, Δphysical exercise, ΔBMI, Δwaist circumference, ΔVAT and ΔSAT. Changes in smoking status was defined as either smoking cessation at any point during follow-up, smoking start at any point during follow-up, continued smoking or remained as non-smoker or previous smoker (if patient had a history of smoking at baseline). Heavy alcohol consumption was defined as > 20 units/week for men and > 10 units/week for women, and change in alcohol consumption was defined as persistent heavy alcohol consumer, persistent no/light alcohol consumer, stopped heavy alcohol consumption or started heavy alcohol consumption.

Registration of events during follow-up

Events were assessed from baseline visit onwards by patients receiving biannual questionnaires obtaining information on incident cardiovascular disease, bleeding events, diabetes mellitus and end-stage kidney disease. If an affirmative answer was given, additional information from hospital or general practitioner's data was gathered. All clinical events were independently evaluated by an endpoint committee consisting of three physicians and conflicting decisions were discussed.

Data analyses

Descriptive statistics were assessed by a baseline table and histograms over distribution of change in eGFR and uACR and change in lifestyle factors between

baseline and follow-up. Change in eGFR according to baseline eGFR and baseline age, respectively, was evaluated by plotting mean difference (standard error of the mean (SEM)) stratified according to baseline eGFR and age category.

In order to account for missing data and avoid potential bias, missing data (eGFR, smoking, pack-years, alcohol consumption and BMI < 1%, uACR 3%, physical exercise 27%, waist circumference 6%, VAT 16% and SAT 16%) was imputed using multiple imputation by predicted mean matching (MICE package) with 10 imputation datasets. Results from the imputed datasets were pooled using Rubin's rule.[19]

Continuous variables and change in these were winsorized to the 1st and 99th percentile to diminish the effect of outliers. In order to investigate the relation between lifestyle changes and kidney function decline over time, linear regression analyses were performed, with ΔeGFR and ΔuACR, respectively, as dependent variables and change in each lifestyle factor (smoking, alcohol use, physical exercise and markers of obesity) as independent variables. For the categorical independent variables, remaining no/light alcohol consumer and remaining non-smoker, respectively, were set as reference categories. For continuous independent variables, pack-years was assessed per pack year increase, physical exercise was assessed per 10 METh/week increase, BMI per 5 kg/m2 increase, waist circumference and VAT per 5 cm increase and SAT per cm increase.

In order to account for potential confounding, models were adjusted for baseline eGFR and uACR, respectively, since the change over time might depend on baseline levels. Furthermore, model 1 was adjusted for sex and age, model 2 further for type 2 diabetes status and systolic blood pressure at baseline, and model 3 was further adjusted for BMI, smoking status, alcohol consumption and physical exercise at baseline (if not determinant of interest). For the main analyses, model 3 was used. The confounders for all models were pre-specified.

Type 2 diabetes status, RASi medication, sex and age were assessed as potential effect modifiers by examining these as interaction terms with each determinant. Since a significant interaction was found between waist circumference and sex (p-value 0.01) and the effect on eGFR decline, the analyses for this determinant was stratified according to sex.

Regarding assumptions of linear regression, linearity between independent variable and outcome, normality of residuals and homoscedasticity were all

assessed by visual inspection and no violations were observed. P-values were two-sided, with statistical significance set at 0.05. All analyses were performed with R-statistic programming (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

To evaluate whether time since change in smoking status acted as an effect modifier in the relation between change in smoking status and eGFR decline and uACR change, respectively, an interaction term between change in smoking status and time since smoking status was added to the models. Exploratory models were evaluated with the addition of blood pressure lowering medication, lipid lowering medication as well as education level at baseline added to model 3. Since it has been substantially debated whether to adjust for baseline variables in regression models using change as dependent variable,[20] we also performed the analyses without adjusting for baseline variables for eGFR and uACR, respectively, and the results did not change substantially (data not shown). Furthermore, due to the difference in follow-up between patients, we performed the analyses for the categorical determinants (change in smoking status and change in alcohol intake) adjusted for follow-up time as confounder. Baseline characteristics for patients in SMART2 (thus patients who returned for a follow-up visit) vs. patients in SMART1 (who did not return for a follow-up visit) are shown in *Supplementary table 2*.

Results

Baseline characteristics

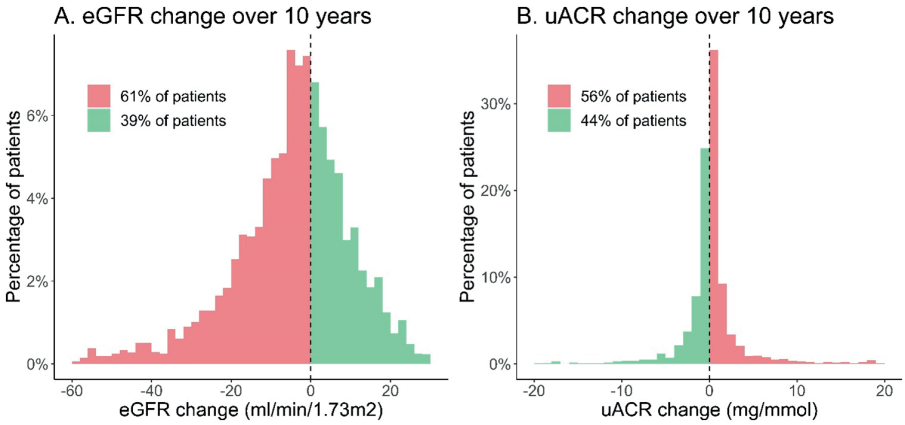
A total of 2,260 patients with clinically manifest CVD were included in the study. Mean age at visit 1 was 58 years and the majority were men (78%). Median follow-up (time between first and follow-up visit) was 9.9 years (IQR 8.7-10.8, range 2.9-16.8 years). Patient characteristics for both visits are shown in *Table 1*. Median eGFR was 79.3 ml/min/1.73m2 (IQR 68.4-90.0) at baseline and 77.0 ml/min/1.73m2 (IQR 64.7-87.7) at follow-up, and 61% of patients experienced an unfavorable change in eGFR over 10 years (*Figure 1A*). Median uACR was 0.82 mg/mmol (IQR 0.47-1.63) at baseline and 0.96 mg/mmol (IQR 0.59-1.75) at follow-up, and 56% of patients experienced an unfavorable change in uACR over 10 years (*Figure 1B*).

Table 1. Baseline table

n = 2,260	Baseline	Follow-up
Sex (male)	1,752 (78%)	1,752 (78%)
Age (years)	58 ± 9	66 ± 9
History of cerebrovascular disease	589 (26%)	640 (28%)
History of coronary artery disease	1,453 (64%)	1,540 (68%)
History of peripheral artery disease	355 (16%)	418 (19%)
History of abdominal aortic aneurism	119 (5%)	161 (7%)
Type 2 diabetes	287 (13%)	494 (22%)
Metabolic syndrome[b]	1,097 (49%)	1,233 (55%)
Smoking	653 (29%)	377 (17%)
Packyears	19 ± 19	23 ± 21
Alcohol use (>10 units for women and > 20 units for men)	312 (14%)	224 (10%)
Physical exercise (MET hours/week)	53 ± 39	53 ± 38
Education level		
Low	1040 (46%)	974 (43%)
Middle	598 (26%)	629 (28%)
High	622 (28%)	657 (29%)
Blood-pressure lowering medication	1,665 (74%)	1,812 (80%)
Lipid lowering medication	1,541 (68%)	1,944 (86%)
Anti-platelet therapy	1,875 (83%)	2,078 (92%)
RASi medication	757 (34%)	1,247 (55%)
Body Mass Index (kg/m2)	27 ± 4	27 ± 4
Waist circumference (cm)	95 ± 11	99 ± 12
Systolic blood pressure (mmHg)	139 ± 20	139 ± 17
Diastolic blood pressure (mmHg)	82 ± 11	79 ± 10
eGFR (ml/min/1.73m2)[a]	79 (68-90)	77 (65-88)
u-Albumine/creatinine ratio (mg/mmol)	0.82 (0.47-1.63)	0.96 (0.59-1.75)
Cholesterol (mmol/L)	4.9 ± 1.2	4.5 ± 1.1
Triglycerides (mmol/L)	1.4 (1.0-2.0)	1.3 (0.9-1.8)
HDL-cholesterol (mmol/L)	1.2 ± 0.4	1.3 ± 0.4
LDL-cholesterol (mmol/L)	2.9 ± 1.0	2.6 ± 0.9
Microalbuminuria	188 (8%)	268 (12%)
Macroalbuminuria	23 (1%)	30 (1%)
Visceral adipose tissue thickness (cm)	9.0 ± 2.5	9.3 ± 2.6
Subcutaneous adipose tissue thickness (cm)	2.5 ± 1.3	2.3 ± 1.1

Median time between visits was 9.9 years (IQR 8.7–10.8 years).
Data are mean ± SD for normally distributed variables or median (interquartile range) for skewed distributions. Categorical variables are presented as number (%).

Figure 1. Change in eGFR and uACR during follow-up in the study population



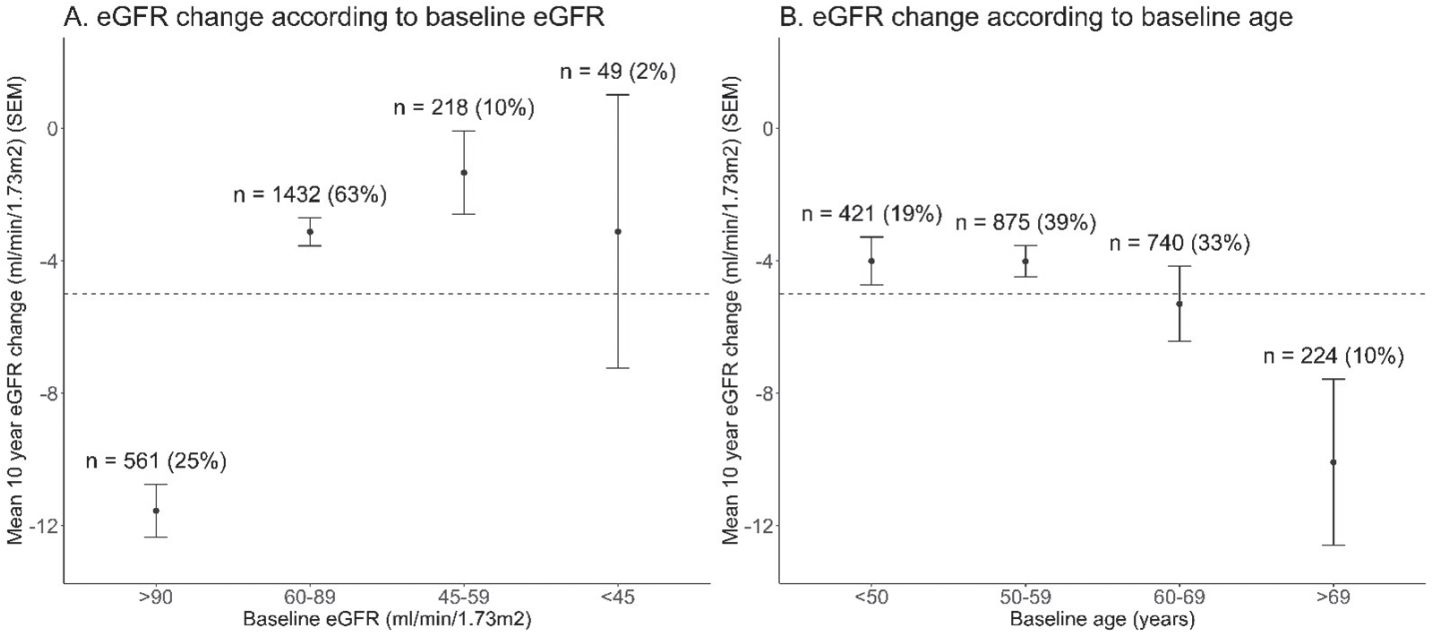
Red color indicates unfavourable change (A. decrease in eGFR and B. increase in uACR over 10 years) and green color indicates favorable change (A. increase in eGFR and B. decrease in uACR over 10 years). Legend represents frequency of patients with unfavourable and favourable change, respectively.

Overall mean eGFR decline over 10 years was 5.0 ml/min/1.73m2 (SEM 0.26) and overall mean uACR increase was 0.04 mg/mmol (SEM 0.6). A steeper eGFR decline was observed in patients with normal kidney function at baseline (>90 ml/min/1.73m2) and in patients with CKD 3b or higher at baseline (p-value <0.01) (*Figure 2A*). Patients with higher baseline age also had steeper eGFR decline, especially patients ≥70 years (p-value <0.01) (*Figure 2B*). Change in lifestyle factors between baseline and follow-up is shown in *Figure 3*.

Relation between change in smoking status and kidney function decline

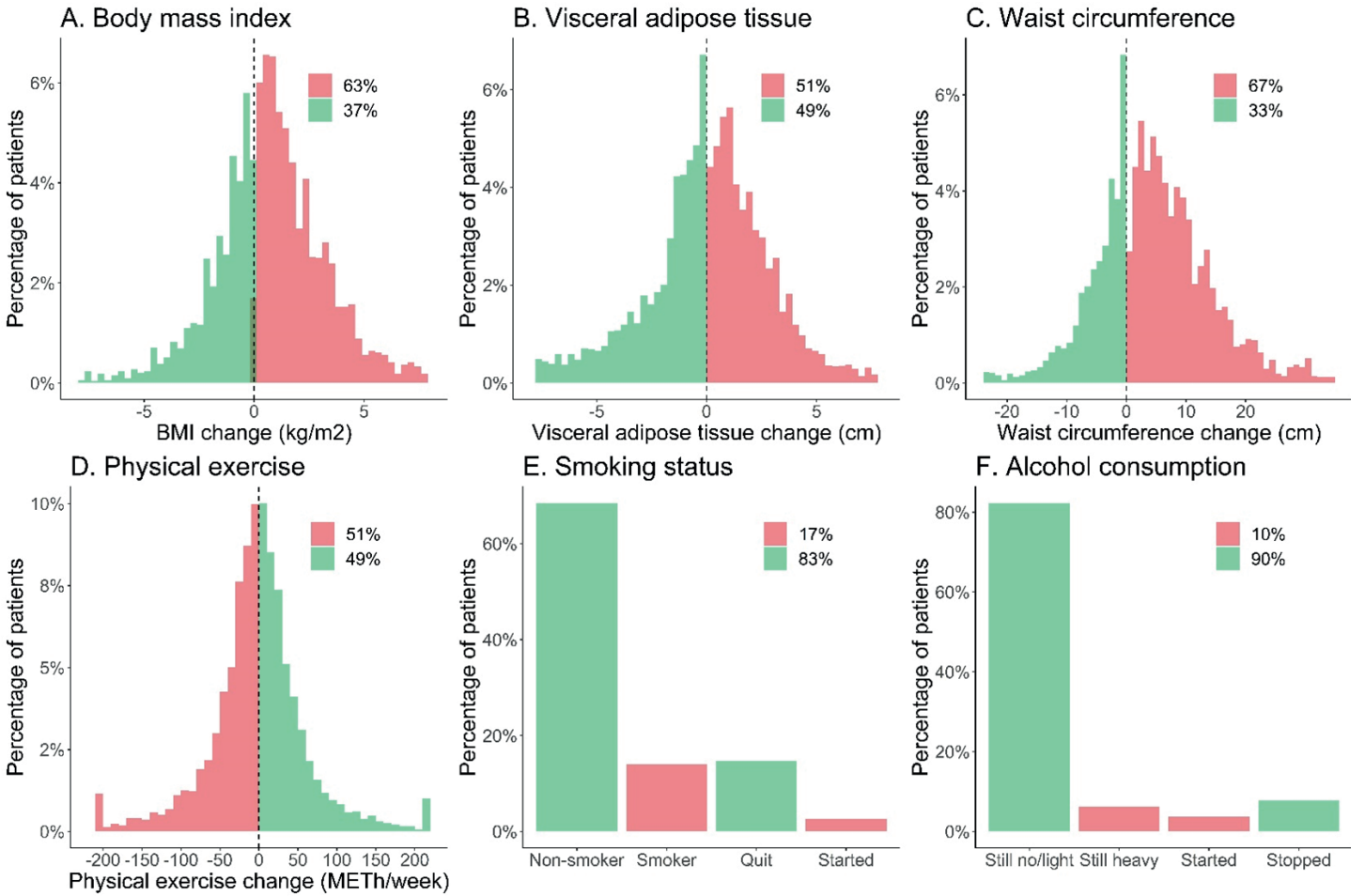
Mean 10 year eGFR decrease for patients who remained non- or previous smoker was 4.3 ml/min/1.73m^2 (SEM 0.3) (reference category). When adjusting for sex, age, eGFR, type 2 diabetes status, systolic blood pressure, alcohol consumption, exercise and BMI at baseline, patients who continued smoking (n = 319) had a significant additional eGFR decline compared to patients who remained non- or previous smoker of 2.44 ml/min/1.73m^2 over 10 years (β = -2.44; 95%CI -4.43, -0.45) (*Figure 4*). Patients who stopped smoking during follow-up (n = 333) also had a significantly steeper decrease in eGFR of 3.27 ml/min/1.73m^2 over 10 years compared to patients who remained non- or previous smoker (β = -3.27; 95%CI -5.20, -1.34). The same trend was seen in patients who started smoking during follow-up (n = 59) (β = -2.82; 95%CI -7.08, 1.43),

Figure 2. eGFR change during follow-up according to A. baseline eGFR and B. age at baseline



Dots represent mean 10 year eGFR change per group, errorbars represent standard errors. Number above errorbars represent number (%) of patients belonging to that specific group. Dotted line is overall eGFR decline over 10 years (-5.0 ml/min/1.73m2).

Figure 3. Change in lifestyle factors during follow-up in the study population



Red color indicates unfavourable change, and green color indicates favourable change. Legend represents frequency of patients with unfavorable and favorable change, respectively.

although this relation was not significant. Per 1 unit increase in pack-years, eGFR decline was 0.10 steeper (β = -0.10; 95%CI -0.17, -0.04). The results were not substantially different when only adjusting for sex and age or when adjusting for the aforementioned confounders excluding lifestyle factors (*Supplementary table 3*). Concerning change in smoking status and change in uACR, no significant relation was seen, although a trend of continuing smoking or starting smoking and an increase in uACR was observed.

Relation between change in markers of obesity and kidney function decline

Regarding measures of obesity, the effect of change in waist circumference on change in eGFR was different for men and women. Overall mean change in BMI over 10 years was 0.8 kg/m^2 (SEM 0.02). Overall mean change in waist circumference was 4.4 cm (SEM 1.1) for men and 5.6 cm (SEM 1.0) for women. For VAT and SAT, overall mean change was 0.2 cm (SEM 0.08) and -0.2 cm (SEM 0.04), respectively. Per 5 units increase in BMI, eGFR decline steepened with 2.81 ml/min/1.73m2 (β = -2.81; 95%CI -3.98, -1.63). Per 5 cm increase in waist circumference, eGFR decline for men was 0.87 ml/min/1.73m2 steeper (β = -0.87; 95%CI -1.28, -0.47) (*Figure 2*). No significant relation was observed between change in waist circumference and eGFR decline in women, and also overall no significant relation was observed between 10 year change in VAT or SAT and eGFR decline. Adjusting for only sex and age or the aforementioned confounders excluding lifestyle factors did not significantly alter the results (*Supplementary table 3*). No significant relation was observed between changes in markers of obesity and change in uACR.

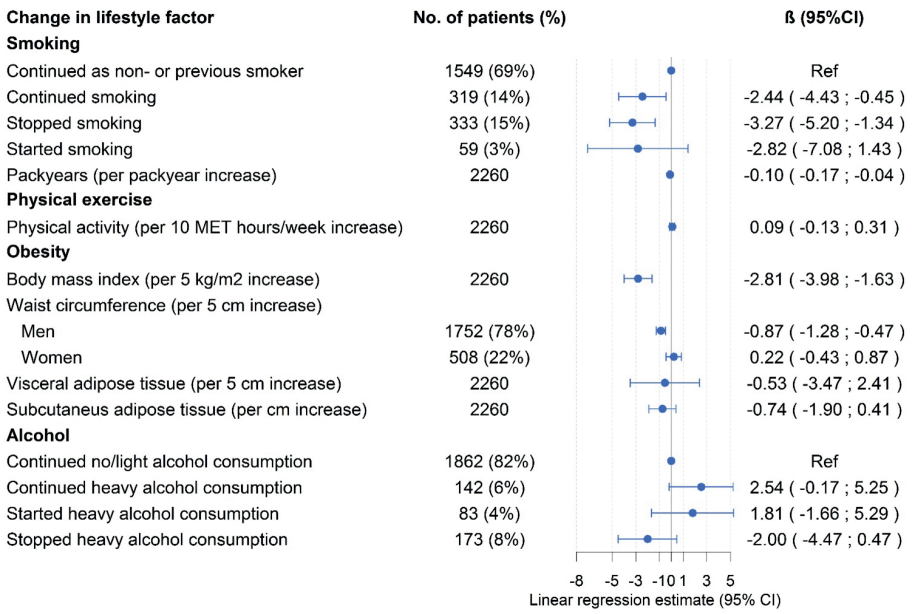
Relation between change in alcohol consumption and kidney function decline

Mean 10 year eGFR decline in patients who remained no/light alcohol consumers was 4.9 ml/min/1.73m^2 (SEM 0.25). No significant relation was observed between continuing, starting or stopping heavy alcohol consumption and eGFR decline compared to patients who remained no/light alcohol consumers. Adjusting for fewer confounders did not significantly change the results. No significant relation was observed between change in alcohol consumption and change in uACR.

Relation between change in physical exercise and kidney function decline

Mean 10-year change in physical activity was -1.8 METh/week (SEM 10.2). No significant relation was observed between change in physical exercise and eGFR decline (β = 0.09; 95%CI -0.13, 0.31) or change in uACR (β = -0.06; 95%CI -0.14, 0.01).

Figure 4. Relation between change in lifestyle factors and eGFR decline over 10 years



Adjusted for sex, age, type 2 diabetes status, systolic blood pressure, smoking status, number of alcohol units per week, exercise and body mass index at baseline (if not determinant of interest) and eGFR at baseline and stratified according to sex for waist circumference as determinant.

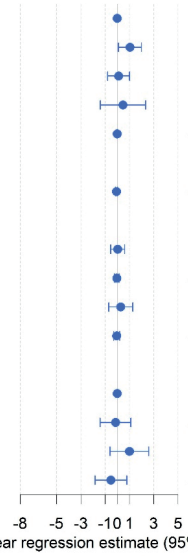
Sensitivity analyses

The results did not change substantially when adding lipid-lowering medication, blood pressure lowering medication and education level to model 3 (*Supplementary table 3 and 4*). Furthermore, no indication of an interaction with smoking status and time since smoking status was found (p-value 0.11 for eGFR decline and 0.42 for change in uACR). Also, no interaction was observed between type 2 diabetes, or age, respectively, and eGFR decline or uACR

change. No interaction between RASi medication use at baseline and eGFR decline or uACR change was observed. When performing the analyses for change in smoking status and change in alcohol intake adjusted for follow-up time, the results did not change significantly (data not shown).

Figure 5. Relation between change in lifestyle factors and change in uACR over 10 years

Change in lifestyle factor	No. of patients (%)	ß (95%CI)
Smoking		
Continued as non- or previous smoker	1549 (69%)	Ref
Continued smoking	319 (14%)	1.05 (0.10 ; 2.01)
Stopped smoking	333 (15%)	0.12 (-0.79 ; 1.02)
Started smoking	59 (3%)	0.47 (-1.39 ; 2.33)
Packyears (per packyear increase)	2260	-0.01 (-0.04 ; 0.02)
Physical exercise		
Physical activity (per 10 MET hours/week increase)	2260	-0.06 (-0.14 ; 0.01)
Obesity		
Body mass index (per 5 kg/m2 increase)	2260	0.04 (-0.53 ; 0.61)
Waist circumference (per 5 cm increase)	2260	-0.03 (-0.22 ; 0.16)
Visceral adipose tissue (per 5 cm increase)	2260	0.29 (-0.70 ; 1.27)
Subcutaneus adipose tissue (per cm increase)	2260	-0.05 (-0.30 ; 0.20)
Alcohol		
Continued no/light alcohol consumption	1862 (82%)	Ref
Continued heavy alcohol consumption	142 (6%)	-0.14 (-1.41 ; 1.13)
Started heavy alcohol consumption	83 (4%)	1.00 (-0.59 ; 2.60)
Stopped heavy alcohol consumption	173 (8%)	-0.52 (-1.83 ; 0.79)



Adjusted for sex, age, type 2 diabetes status, systolic blood pressure, smoking status, number of alcohol units per week, exercise and body mass index at baseline (if not determinant of interest) and uACR at baseline.

Discussion

The current study found that in a population of patients with manifest vascular disease, the majority of patients improved in lifestyle factors regarding smoking and alcohol consumption, however markers of obesity worsened over a 10 year follow-up period. A steeper eGFR decline over 10 years was observed for patients who continued smoking or recently stopped smoking during follow-up compared to patients who remained non- or previous smokers. Also, an increase in BMI, and for men increase in waist circumference, was associated with a steeper eGFR decline over 10 years.

Continuing smoking and recent smoking cessation compared to continuing as non- or previous smoker was associated with accelerated eGFR decline in the present study. Also, a negative trend regarding eGFR decline was observed in patients who started smoking compared to patients who continued being non- or previous smokers. These findings are in line with several previous studies that found an increased risk of CKD in current or former smokers compared to non-smokers.[8, 21] The pathophysiology behind smoking aggravating kidney function decline is caused by several underlying mechanisms, including kidney-vascular disease due to endothelial cell injury.[22] It is also worth noting that smoking cessation occurred at an unknown time between baseline and follow-up and could be very recent, which possibly explains the accelerated eGFR decline observed in the group who stopped smoking.

The current study found an increase over 10 years in BMI to be associated with a steeper eGFR decline in patients with CVD. Furthermore, an increase in waist circumference was associated with a steeper eGFR decline in men with CVD, however this association was attenuated in women. Previous studies have found higher baseline BMI to be associated with increased risk of CKD.[9, 23, 24] The exact reason for the differences found in men and women is not fully understood, although this observation was also observed in previous studies.[23] It is well known that men have a faster decline in kidney function compared to women, and these findings have been stipulated as due to protective effects of endogenous estrogens in women.[25] Possibly, several of the biological mechanisms attributed to the relation between obesity and kidney disease[26] are also affected by sex hormones, explaining sex as an effect modifier in the relation between waist circumference and accelerated eGFR decline. Furthermore, creatinine depends on muscle tissue, and with increase in obesity markers, muscle mass also increases, resulting in an increase in creatinine and thus lower eGFR. This might cause some overestimation in the relation between increase in obesity markers and eGFR decline observed in this study.

Change in physical activity in our study was not associated with kidney function decline in patients with manifest cardiovascular disease. Previous studies have found higher physical activity to be associated with decreased risk of rapid eGFR decline.[11] Physical inactivity indirectly influences risk of CKD through development of obesity, diabetes and hypertension, which were all adjusted for in our main analyses. Also, serum creatinine concentrations and muscle

mass are in general higher in active people than in sedentary people,[27] which could disguise the beneficial effects of increase in physical activity on kidney function decline.

Counterintuitively, the current study found a trend towards a less steep eGFR decline in patients who continued or started heavy alcohol consumption (> 10 units per week for women and > 20 units per week for men) compared to patients who remained no/light alcohol consumers, however not significant. It is well known that alcohol consumption has severe detrimental effects on overall health and mortality, including cardiovascular disease.[28] Previous studies examining alcohol consumption and kidney function decline have shown controversial results,[29] and some studies indicated a possible inverse association.[10, 30] However, the findings in our study are most likely due to epidemiologic fallacies playing a role in the inverse relation between change in alcohol consumption on kidney function decline. Since patients who have a more rapid eGFR decline often have several comorbidities, they might be less prone to continue or start heavy alcohol consumption, and the trend found in this study might thus partly be due to reverse causality. Furthermore, very few people started (4%) or continued (6%) heavy alcohol consumption, reducing the power of finding an effect in these groups.

The strengths of the current study include a large study population of patients with manifest CVD at baseline and the repeated and complete measurement of lifestyle factors and eGFR and uACR concentrations over substantial follow-up time. Also, as demonstrated by the high prevalence of preventive drug prescriptions, the cohort is very contemporary. Furthermore, the cohort consists of patients with a broad spectrum of vascular disease, making the results widely applicable to other patients with vascular disease. Potential limitations also need consideration. eGFR was used as an estimate for kidney function, however some determinants may have inherent effects on eGFR not associated with kidney function, why the causal relations should be interpreted with this in mind. Patients were assessed at baseline and follow-up, which might not be fully representative for the follow-up period. For example, it could have been that some patients quitted and restarted smoking, heavy alcohol consumption or certain medication, which would then not have been reflected in the follow-up data. Furthermore, the standardized questionnaires regarding smoking and alcohol intake were not specifically validated for lifestyle habits.

Also, social desirability bias and recall bias could have influenced the answers concerning physical activity, smoking and alcohol consumption, potentially leading to an underestimation of these relations with kidney function decline. As with all etiologic studies, unmeasured confounding might be present, e.g. social class, although the relations did not change when further adjusting for level of education. Furthermore, patients eligible for the study had to return for a follow-up visit approximately 10 years after the first visit, possibly resulting in selection bias. However, one would expect this to also result in underestimation of the relations between healthy lifestyle changes and kidney function decline, as the healthier subjects, and thus subjects with a less steep eGFR decline, would return for a follow-up visit. In the current study, the duration of RASi usage before baseline or time of initiation or cessation of RASi during follow-up was not known, and since initiation of a RASi is potentially associated with an acute decrease in eGFR, this could potentially have an effect on eGFR change. However, in the current study, treatment with a RASi was not shown to be an effect modifier in the relation between any lifestyle factor and eGFR decline. Also, very few patients in the cohort started smoking or started heavy alcohol consumption during follow-up, thereby reducing the power of the study to find specific effects in these groups. Lastly, the majority of the cohort had normoalbuminuria both at baseline and follow-up and thus very low uACR values, making it difficult to detect an effect on change in uACR.

In conclusion, in patients with CVD, continuing smoking and recent smoking cessation, and for men also increase in obesity markers, was related to a steeper kidney function decline. Although no definite conclusions from this study can be drawn, the results support the importance of encouraging weight loss and smoking cessation in high-risk patients as a means of slowing down kidney function decline.

References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):e0158765.
2. Burrows NR, Vassalotti JA, Saydah SH, Stewart R, Gannon M, Chen S-C, Li S, Pederson S, Collins AJ, Williams DE. Identifying High-Risk Individuals for Chronic Kidney Disease: Results of the CHERISH Community Demonstration Project. Am J Nephrol. 2018;48(6):447-455.
3. Wan EYF, Chin WY, Yu EYT, Wong ICK, Chan EWY, Li SX, Cheung NKL, Wang Y, Lam CLK. The Impact of Cardiovascular Disease and Chronic Kidney Disease on Life Expectancy and Direct Medical Cost in a 10-Year Diabetes Cohort Study. Diabetes Care. 2020;43(8):1750-1758.
4. Liu JH, Lin SY, Hsu CY, Lin HH, Liang CC, Sung FC, Huang CC. The risk for chronic kidney disease in patients with heart diseases: a 7-year follow-up in a cohort study in Taiwan. BMC Nephrol. 2012;13:77.
5. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4s):S1-s115.
6. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851-860.
7. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-39.
8. Xia J, Wang L, Ma Z, Zhong L, Wang Y, Gao Y, He L, Su X. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Nephrol Dial Transplant. 2017;32(3):475-487.
9. Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, Gutierrez OM, Hosseinpanah F, Iseki K, Kenealy T, Klein B, Kronenberg F, Lee BJ, Li Y, Miura K, Navaneethan SD, Roderick PJ, Valdivielso JM, Visseren FLJ, Zhang L, Gansevoort RT, Hallan SI, Levey AS, Matsushita K, Shalev V, Woodward M, Consortium CKDP. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. BMJ. 2019;364:k5301-k5301.
10. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Brabec BA, O'Corragain OA, Edmonds PJ, Erickson SB. High alcohol consumption and the risk of renal damage: a systematic review and meta-analysis. Qjm. 2015;108(7):539-548.
11. Chang PY, Lyu SY, Lin YF, Huang CC. High Level of Physical Activity Reduces the Risk of Renal Progression in Hypertensive Patients. Int J Environ Res Public Health. 2020;17(5).
12. McMahon EJ, Campbell KL, Bauer JD, Mudge DW, Kelly JT. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database Syst Rev. 2021;6(6):Cd010070.
13. Elsayed EF, Tighiouart H, Griffith J, Kurth T, Levey AS, Salem D, Sarnak MJ, Weiner DE. Cardiovascular disease and subsequent kidney disease. Arch Intern Med. 2007;167(11):1130-1136.

14. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol. 1999;15(9):773-781.
15. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. Eur J Clin Invest. 2010;40(1):35-53.
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
17. Pols MA, Peeters PH, Ocké MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol. 1997;26 Suppl 1:S181-189.
18. Stolk RP, Meijer R, Mali WP, Grobbee DE, van der Graaf Y. Ultrasound measurements of intraabdominal fat estimate the metabolic syndrome better than do measurements of waist circumference. Am J Clin Nutr. 2003;77(4):857-860.
19. Rubin DB. Multiple Imputation for Nonresponse in Surveys.: John Wiley & Sons Inc., New York.; 2004.
20. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. Am J Epidemiol. 2005;162(3):267-278.
21. Shankar A, Klein R, Klein BE. The association among smoking, heavy drinking, and chronic kidney disease. Am J Epidemiol. 2006;164(3):263-271.
22. Lhotta K, Rumpelt HJ, König P, Mayer G, Kronenberg F. Cigarette smoking and vascular pathology in renal biopsies. Kidney Int. 2002;61(2):648-654.
23. Shankar A, Leng C, Chia KS, Koh D, Tai ES, Saw SM, Lim SC, Wong TY. Association between body mass index and chronic kidney disease in men and women: population-based study of Malay adults in Singapore. Nephrol Dial Transplant. 2008;23(6):1910-1918.
24. Garofalo C, Borrelli S, Minutolo R, Chiodini P, De Nicola L, Conte G. A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney Int. 2017;91(5):1224-1235.
25. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nat Rev Nephrol. 2018;14(3):151-164.
26. Lastra G, Manrique C, Sowers JR. Obesity, cardiometabolic syndrome, and chronic kidney disease: the weight of the evidence. Adv Chronic Kidney Dis. 2006;13(4):365-373.
27. Banfi G, Del Fabbro M, Lippi G. Serum creatinine concentration and creatinine-based estimation of glomerular filtration rate in athletes. Sports Med. 2009;39(4):331-337.
28. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018;392(10152):1015-1035.
29. Yuan HC, Yu QT, Bai H, Xu HZ, Gu P, Chen LY. Alcohol intake and the risk of chronic kidney disease: results from a systematic review and dose-response meta-analysis. Eur J Clin Nutr. 2021.
30. Koning SH, Gansevoort RT, Mukamal KJ, Rimm EB, Bakker SJ, Joosten MM. Alcohol consumption is inversely associated with the risk of developing chronic kidney disease. Kidney Int. 2015;87(5):1009-1016.

Supplementary material

Supplementary table 1. Definitions of cardiovascular disease

Cerebrovascular disease	A clinical diagnosis of a transient ischemic attack or ischemic or hemorrhagic stroke.
Coronary artery disease	A clinical diagnosis of angina pectoris, myocardial infarction, cardiac arrest or coronary revascularization.
Peripheral artery disease	Symptomatic and documented obstruction of distal arteries of the leg (ankle brachial index ≤ 0.90), a revascularization procedure of the leg (percutaneous transluminal angioplasty or bypass surgery) or a prior amputation.
Abdominal aortic aneurism	A history of abdominal aortic surgery or an abdominal aortic anteroposterior diameter of ≥ 3 cm at baseline.

Supplementary table 2. Responders (SMART2) and non-responders (SMART1)

	SMART2 (n = 2260)	**SMART1 (n = 6537)**
eGFR (ml/min/1.73)[a]	79 (68-90)	78 (65-90)
u-Albumine/creatinine ratio (mg/mmol)	0.82 (0.47-1.63)	0.85 (0.50-1.74)
Sex (male)	1,752 (78%)	4,742 (73%)
Age (years)	58 ± 9	62 ± 10
History of cerebrovascular disease	589 (26%)	2001 (31%)
History of coronary artery disease	1,453 (64%)	4000 (61%)
History of peripheral artery disease	355 (16%)	1161 (18%)
History of abdominal aortic aneurism	119 (5%)	614 (9%)
Type 2 diabetes	287 (13%)	1164 (18%)
Metabolic syndrome[b]	1,097 (49%)	3084 (55%)
Smoking	653 (29%)	1991 (31%)
Packyears	19 ± 19	20 ± 20
Alcohol use (>10 units for women and > 20 units for men)	312 (14%)	777 (12%)
Physical exercise (MET hours/week)	53 ± 39	54 ± 44
Education level		
Low	1040 (46%)	1997 (44%)
Middle	598 (26%)	1132 (25%)
High	622 (28%)	1440 (32%)
Medication		
Blood-pressure lowering medication	1,665 (74%)	4973 (76%)
Lipid lowering medication	1,541 (68%)	4578 (70%)
Anti-platelet therapy	1,875 (83%)	5479 (84%)

Supplementary table 2. Continued

	SMART2 (n = 2260)	SMART1 (n = 6537)
RASi medication	757 (34%)	2995 (46%)
Physical examination		
Body Mass Index (kg/m2)	27 ± 4	27 ± 4
Waist circumference (cm)	95 ± 11	96 ± 13
Visceral adipose tissue thickness (cm)	9.0 ± 2.5	9.1 ± 2.6
Subcutaneous adipose tissue thickness (cm)	2.5 ± 1.3	2.4 ± 1.2
Systolic blood pressure (mmHg)	139 ± 20	138 ± 21
Diastolic blood pressure (mmHg)	82 ± 11	81 ± 12
Laboratory measurements		
HbA1c (mmol/mol)	5.9 ± 0.8	5.9 ± 0.9
Cholesterol (mmol/L)	4.9 ± 1.2	4.8 ± 1.2
Triglycerides (mmol/L)	1.4 (1.0-2.0)	1.4 (1.0-2.0)
HDL cholesterol (mmol/L)	1.2 ± 0.4	1.2 ± 0.4
LDL cholesterol (mmol/L)	2.9 ± 1.0	2.8 ± 1.0
Microalbuminuria	188 (8%)	768 (12%)
Macroalbuminuria	23 (1%)	123 (2%)

Data are mean ± SD for normally distributed variables or median (interquartile range) for skewed distributions. Categorical variables are presented as number (%).

Supplementary table 3. Relation between lifestyle changes and eGFR decline

Lifestyle factor	Crude model	Model 1	Model 2	Model 3	Model 4
Still non-smoker (n = 1549)	Ref	Ref	Ref	Ref	Ref
Still smoking (n = 319)	-1.63 (-3.63; 0.37)	-3.11 (-5.17; -1.05)	-2.59 (-4.55; -0.64)	-2.44 (-4.43; -0.45)	-1.79 (-3.80; 0.22)
Smoking cessation (n = 333)	-2.92 (-4.96; -0.89)	-3.91 (-5.98; -1.85)	-3.35 (-5.27; -1.43)	-3.27 (-5.20; -1.34)	-2.7 (-4.63; -0.77)
Smoking start (n = 59)	-3.03 (-7.57; 1.51)	-4.00 (-8.54; 0.53)	-3.13 (-7.37; 1.12)	-2.82 (-7.08; 1.43)	-2.18 (-6.43; 2.06)
Packyears increase (per packyear) (n = 2260)	-0.13 (-0.20; -0.06)	-0.13 (-0.20; -0.06)	-0.1 (-0.17; -0.04)	-0.1 (-0.17; -0.04)	-0.1 (-0.17; -0.03)
Physical activity increase (per 10 MET hours/week) (n = 2260)	0.15 (-0.06; 0.36)	0.13 (-0.09; 0.35)	0.09 (-0.13; 0.31)	0.09 (-0.13; 0.31)	0.1 (-0.11; 0.31)
Body mass index increase (per 5 kg/m2) (n = 2260)	-3.00 (-4.24; -1.76)	-3.35 (-4.60; -2.11)	-2.96 (-4.14; -1.78)	-2.82 (-4.00; -1.65)	-2.7 (-3.87; -1.53)
Waist circumference increase (per 5 cm)					
Men (n = 1752)	-0.96 (-1.39; -0.53)	-1.01 (-1.43; -0.58)	-0.91 (-1.30; -0.51)	-0.87 (-1.28; -0.47)	-0.84 (-1.26; -0.43)
Women (n = 508)	-0.09 (-0.61; 0.78)	0.09 (-0.61; 0.79)	0.25 (-0.41; 0.91)	0.22 (-0.43; 0.87)	0.23 (-0.42; 0.87)
Visceral adipose fat increase (per 5 cm) (n = 2260)	-0.49 (-3.70; 2.71)	-0.61 (-3.66; 2.45)	-0.55 (-3.64; 2.55)	-0.53 (-3.47; 2.41)	-0.49 (-3.30; 2.33)
Subcutaneus abdominal fat (per cm) (n = 2260)	-0.72 (-2.00; 0.56)	-0.73 (-1.99; 0.52)	-0.73 (-1.98; 0.52)	-0.74 (-1.90; 0.41)	-0.77 (-1.83; 0.29)
Still no/light alcohol consumption (n = 1862)	Ref	Ref	Ref	Ref	Ref
Still heavy alcohol consumption (n = 142)	1.21 (-1.65; 4.07)	1.02 (-1.83; 3.87)	2.2 (-0.54; 4.94)	2.54 (-0.17; 5.25)	2.57 (-0.12; 5.27)
Started heavy alcohol consumption (n = 83)	0.67 (-2.98; 4.33)	0.54 (-3.10; 4.19)	1.21 (-2.27; 4.68)	1.81 (-1.66; 5.29)	1.29 (-2.17; 4.74)
Stopped heavy alcohol consumption (n = 173)	-2.67 (-5.26; -0.08)	-2.80 (-5.38; -0.21)	-2.17 (-4.62; 0.29)	-2.00 (-4.47; 0.47)	-1.82 (-4.27; 0.64)

Model 1: Adjusted for sex and age

Model 2: Adjusted for sex, age, type 2 diabetes, systolic blood pressure and eGFR at baseline

Model 3: Adjusted for sex, age, type 2 diabetes, systolic blood pressure, smoking, excessive alcohol use, exercise and body mass index (if not determinant of interest) and eGFR at baseline

Model 4: Adjusted for sex, age, type 2 diabetes, systolic blood pressure, smoking, excessive alcohol use, exercise and body mass index (if not determinant of interest), lipid lowering therapy and blood pressure lowering therapy and eGFR at baseline

Mean eGFR decline over 10 years for patients who remained non-smokers was 4.3 ml/min/1.73m2 and for patients who remained no/light alcohol consumers mean 10 year eGFR decline was 4.9 ml/min/1.73m2.

Supplementary table 4. Relation between lifestyle changes and change in uACR

Lifestyle factor	Crude data	Model 1	Model 2	Model 3	Model 4
Still non-smoker (n = 1549)	Ref	Ref	Ref	Ref	Ref
Still smoking (n = 319)	-0.15 (-1.23; 0.93)	0.26 (-0.86; 1.39)	0.98 (0.02; 1.93)	1.05 (0.10; 2.01)	1.04 (0.08; 2.01)
Smoking cessation (n = 333)	-0.85 (-1.94; 0.24)	-0.6 (-1.68; 0.49)	0.06 (-0.85; 0.97)	0.12 (-0.79; 1.02)	0.11 (-0.80; 1.01)
Smoking start (n = 59)	-1.07 (-3.34; 1.21)	-0.89 (-3.16; 1.39)	0.43 (-1.42; 2.29)	0.47 (-1.39; 2.33)	0.45 (-1.42; 2.31)
Packyears increase (per packyear) (n = 2260)	-0.03 (-0.07; 0.01)	-0.04 (-0.08; 0.00)	-0.01 (-0.04; 0.02)	-0.01 (-0.04; 0.02)	-0.01 (-0.04; 0.02)
Physical activity increase (per 10 MET hours/week) (n = 2260)	-0.03 (-0.12; 0.06)	-0.03 (-0.12; 0.06)	-0.06 (-0.14; 0.02)	-0.06 (-0.14; 0.01)	-0.06 (-0.14; 0.01)
Body mass index increase (per 5 kg/m2) (n = 2260)	-0.06 (-0.76; 0.63)	0.07 (-0.61; 0.75)	0.08 (-0.50; 0.66)	0.04 (-0.53; 0.61)	0.04 (-0.54; 0.61)
Waist circumference increase (per 5 cm) (n = 2260)	-0.03 (-0.28; 0.22)	0 (-0.25; 0.24)	-0.02 (-0.21; 0.16)	-0.03 (-0.22; 0.16)	-0.03 (-0.22; 0.15)
Visceral adipose fat increase (per 5 cm) (n = 2260)	0.09 (-1.23; 1.41)	0.14 (-1.25; 1.53)	0.29 (-0.69; 1.27)	0.29 (-0.70; 1.27)	0.29 (-0.69; 1.27)
Subcutaneus abdominal fat (per cm) (n = 2260)	-0.07 (-0.49; 0.34)	-0.06 (-0.51; 0.40)	-0.04 (-0.29; 0.20)	-0.05 (-0.30; 0.20)	-0.05 (-0.30; 0.20)
Still no/light alcohol consumption (n = 1862)	Ref	Ref	Ref	Ref	Ref
Still heavy alcohol consumption (n = 142)	-1.05 (-2.61; 0.51)	-0.94 (-2.49; 0.62)	-0.11 (-1.38; 1.16)	-0.14 (-1.41; 1.13)	-0.17 (-1.45; 1.10)
Started heavy alcohol consumption (n = 83)	1.16 (-0.74; 3.07)	1.29 (-0.61; 3.19)	1.07 (-0.51; 2.65)	1 (-0.59; 2.60)	1.03 (-0.57; 2.63)
Stopped heavy alcohol consumption (n = 173)	-1.25 (-2.88; 0.39)	-1.23 (-2.86; 0.40)	-0.47 (-1.80; 0.86)	-0.52 (-1.83; 0.79)	-0.55 (-1.85; 0.76)

Model 0: Crude data

Model 1: Adjusted for sex and age

Model 2: Adjusted for sex, age, type 2 diabetes, systolic blood pressure and uACR at baseline

Model 3: Adjusted for sex, age, type 2 diabetes, systolic blood pressure, smoking, excessive alcohol use, exercise and body mass index (if not determinant of interest) and uACR at baseline

Model 4: Adjusted for sex, age, type 2 diabetes, systolic blood pressure, smoking, excessive alcohol use, exercise and body mass index (if not determinant of interest), lipid lowering therapy and blood pressure lowering therapy and uACR at baseline

Mean uACR increase over 10 years for patients who remained non-smokers was 0.26 mg/mmol and for patients who remained no/light alcohol consumers mean 10 year uACR increase was 0.21 ml/min/1.73m2.

CHAPTER 4

Limited benefit of Hemoglobin Glycation Index as risk factor for cardiovascular disease in type 2 diabetes patients

Helena Bleken Østergaard
Thomas Mandrup-Poulsen
Gijs FN Berkelmans
Yolanda van der Graaf
Frank LJ Visseren
Jan Westerink
on behalf of the UCC-SMART study group.

Diabetes Metab. 2019;45(3):254-260

Abstract

Background: The Hemoglobin Glycation Index (HGI) has been proposed as a marker of inter-individual differences in haemoglobin glycosylation. Previous studies showed a relation between high HGI and risk of cardiovascular disease (CVD) in patients with diabetes. However, no studies investigated the role of previous CVD in regards to this association.

Methods: The cohort consisted of patients with type 2 diabetes (n = 1910) included in the Second Manifestations of ARTerial disease (SMART) study. The relation between HGI or HbA_{1c} and composite of cardiovascular events as primary outcome and mortality, cardiovascular mortality, myocardial infarction and stroke as secondary outcomes was investigated using Cox proportional hazards models. Similar analyses were performed after stratification for previous CVD.

Results: A one unit higher HGI was associated with a 29% higher risk of the composite of cardiovascular events (HR 1.29, 95% CI 1.06-1.57) in patients without previous CVD. No such relation was seen in patients with previous CVD (HR 0.96, 95% CI 0.86-1.08). The direction and magnitude of the hazard ratios of HGI and HbA_{1c} in relation to outcomes were similar. Additional adjustment for HbA_{1c} in the relation between HGI and outcomes decreased the magnitude of the hazard ratios.

Conclusions: Similar to HbA_{1c}, a higher HGI is related to a higher risk of cardiovascular events in patients with type 2 diabetes without cardiovascular disease. As HbA_{1c} was shown to be a comparable risk factor, and obtaining and interpreting HGI is difficult, the added benefit of HGI in a clinical setting seems limited.

Introduction

Type 2 diabetes is a major global health problem with approximately 422 million patients diagnosed worldwide.[1] Patients with type 2 diabetes have a two-fold greater risk of cardiovascular disease (CVD)[2] and increased risk of microvascular complications.[3] Since glycosylated haemoglobin (HbA_{1c}) was discovered in the late 1960s, HbA_{1c} has become the standard test for monitoring glycaemic control, a cornerstone in the treatment of type 2 diabetes.[4] In 2002, the Hemoglobin Glycation Index (HGI) was for the first time proposed as a marker of inter-individual differences in haemoglobin glycosylation,[5] and has since been investigated in a number of studies.[6-10] HGI is the difference between observed HbA_{1c} and predicted HbA_{1c} calculated from the linear population regression equation of HbA_{1c} on blood glucose.

A high discordance between observed and predicted HbA_{1c} was indeed shown to be associated with a 3-fold higher risk of retinopathy and a 6-fold greater risk of nephropathy in patients with type 1 diabetes included in the Diabetes Control and Complications Trial (DCCT).[7] A sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study investigated effect modification by HGI on the relation between strict glycaemic control (HbA_{1c} <6.0%[11]) and cardiovascular outcome and mortality. Strict glycaemic control was shown to be associated with a 14% higher risk of mortality in patients with a high HGI (thus with a higher HbA_{1c} than predicted based on fasting plasma glucose) when compared to patients with low and moderate HGI.[8] However, there has also been opposition to adopting HGI as a marker of inter-individual differences in haemoglobin glycosylation arguing that HGI is a surrogate for HbA_{1c} or a reflection of other factors such as insulin use, duration of diabetes, and glycaemic variability.[12, 13]

The purpose of the current study was to examine the relation between HGI and cardiovascular events and mortality in patients with type 2 diabetes with and without a history of CVD and whether this relation differed from that of HbA_{1c}. We also investigated whether previous CVD at baseline was an effect modifier in the relation between HGI and cardiovascular events.

Materials and Methods

Study population

The cohort consisted of 1910 patients with type 2 diabetes included in the Second Manifestations of ARTerial disease (SMART) study. Type 2 diabetes was

defined as a referral diagnosis of type 2 diabetes, or a self-reported diagnosis of type 2 diabetes, or a fasting plasma glucose ≥7 mmol/L at study inclusion with initiation of glucose-lowering treatment within 1 year, or baseline usage of anti-hyperglycemic medicine or insulin. Participants with known type 1 diabetes mellitus were excluded. Patients were enrolled from September 1996 to February 2015. The SMART study is an ongoing single-center prospective cohort study in the University Medical Center Utrecht (UMCU), the Netherlands. Inclusion criteria in the SMART study were manifest vascular disease or risk factors associated with CVD and an age between 18 and 80 years. All patients included in the SMART study underwent a vascular screening at baseline including a health questionnaire, a standardized physical examination and collection of fasting blood samples as described previously.[14]

The study was approved by the Medical Ethics Committee of the UMCU and written informed consent was obtained from all participants (approval number 13-597/D NL45885.041.13).

Follow-up of patients

The participants of the SMART study were asked to fill out a questionnaire twice a year. If a possible event was noted, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Using the additional information, all events were audited by three members of the SMART study Endpoint Committee, consisting of physicians from different departments. The primary outcome of interest for this study was the composite of a major vascular event (composite of myocardial infarction, stroke (infarction or hemorrhagic), retinal infarction, terminal heart failure (death as cause of heart failure), sudden death and vascular mortality), and secondary outcomes included total mortality, cardiovascular mortality, myocardial infarction and stroke (*Supplementary Table 1*).

Measurement of variables

HbA_{1c} was measured at baseline in all patients enrolled in the SMART study. HbA_{1c} was measured on an automated HA8180 HPLC analyzer (Menarini Diagnostics, Florence, Italy). Fasting plasma glucose (FPG) was measured at baseline in all patients using a glucose hexokinase method on an AU 5811 routine chemistry analyzer (Beckman Coulter, Brea, California). Estimated glomerular filtration rate (eGFR) was estimated in ml/min/1.73m^2 using the Modification of Diet in Renal Disease (GFR (mL/min/1.73 m^2) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if

female) × (1.212 if African American) (MDRD) equation. Proteinuria was defined as a urine-albumin/creatinine ratio (uACR) of 3-30 mg/mmol (microalbuminuria) or a uACR ≥30 mg/mmol (macroalbuminuria). Information about duration of diabetes, alcohol consumption, level of education and smoking was obtained through a patient questionnaire.

Calculation of the HGI

Baseline and time matched FPG and HbA_{1c} data from the cohort were used to estimate the linear relationship between FPG and HbA_{1c} in the study population (*Supplementary figure 1*). The linear approach was chosen in concordance with previous studies,[6-9] although the linear correlation between FPG and HbA_{1c} was not strong (R^2 = 0.39). A predicted HbA_{1c} was calculated for each individual by inserting FPG in the linear population regression equation (Predicted HbA_{1c} = 0.28 * FPG (mmol/L) + 4.68). Baseline HGI was calculated as the difference between observed HbA_{1c} at baseline and the predicted HbA_{1c} (Observed HbA_{1c} – Predicted HbA_{1c}).

Data analyses

The baseline characteristics are presented as mean ± standard deviation (SD) in case of a normal distribution or as median with interquartile range (IQR) in case of variables with a skewed distribution. Categorical variables are presented as frequency. For continuous variables, we used Independent Samples *t* Tests for normally distributed variables and Kruskal-Wallis tests for non-normally distributed variables, and χ^2 tests for categorical variables. Baseline characteristics were also compared in terms of HGI tertiles (low, moderate and high HGI subgroups) and among HbA_{1c} tertiles (low, moderate and high HbA_{1c} subgroups).

Missing data for HbA_{1c} (n = 133, 7.0%), FPG (n = 33, 0.2%) and for the confounders history of CVD (n = 81, 4.2%), body mass index (BMI) (n = 4, 0.2%), systolic blood pressure (SBP) (n = 4, 0.2%), total cholesterol (n = 10, 0.5%), HDL-cholesterol (n = 14, 0.7%), eGFR (n = 9, 0.5%) and level of education (n = 877, 45.9%) were singly imputed by weighted probability matching based on multivariable linear regression using all covariate and outcome data.

Analyses were performed to assess the relation between HGI and the occurrence of primary and secondary outcomes (*Supplementary table 1*). Similar analyses were performed with HbA_{1c} as determinant. If a patient had

multiple events, the first event was used in the analyses. Cox proportional hazard models were used to determine hazard ratios and 95% confidence intervals. The proportional hazards assumption was satisfied based on visual inspection of Schoenfeld residual plots.

In order to assess the relation between HGI and cardiovascular events and mortality, we built four models. Model I was adjusted for sex and age. Model II was additionally adjusted for BMI, diabetes duration, non-HDL-cholesterol level, eGFR, use of insulin and SBP. The confounders were both included based on previous investigations and on univariate linear regression between HGI and different covariates (data not shown).

Exploratory models were constructed with HbA_{1c} or level of education added to model II (model III and IV, respectively). Similar models, with the exception of model III, were constructed with HbA_{1c} as determinant.

To test for effect modification, we added the cross-product of sex, age, insulin use, duration of diabetes, eGFR, level of education and previous CVD, respectively, and HGI to the Cox proportional hazard models with composite of cardiovascular events as outcome.

Sensitivity analyses were performed excluding patients with missing HbA1c, FPG, or history of CVD to ensure that the relation was not influenced by imputation methods. All analyses were performed using IBM SPSS Statistics 21.0, IBM Corp., Armonk, New York and RStudio 3.3.2 (R-packages Hmisc and survival).

Results

Baseline characteristics are presented in *Table 1*. Patients with type 2 diabetes had an average follow-up time of 9.6 years (IQR 5.6-13.4), in which 380 (19.9%) patients experienced a cardiovascular event (myocardial infarction, stroke (infarction or hemorrhagic), retinal infarction, terminal heart failure, sudden death or vascular mortality) and 436 (22.8%) died, of whom 243 (12.7%) died of a vascular cause. 127 (6.6%) patients experienced a myocardial infarction, and 97 (5.1%) experienced a stroke. 140 (7.3%) of the patients where lost to follow-up. Mean age was 60 ± 10 years, 70% of the patients were male, and 69% of the patients had a history of CVD. Baseline characteristics of the study population divided in tertiles of HGI and HbA_{1c}, respectively, are shown in *Supplementary table 2 and 3*.

Table 1. Baseline characteristics

	All patients (n = 1910)	Previous CVD (n = 1260)	No previous CVD (n = 569)	p-value*
HGI	-0.00 ± 1.00	-0.08 ± 0.93	0.2 ± 1.1	< 0.001
Sex (male,%)	1329 (70%)	948 (75%)	338 (59%)	< 0.001
Age (years)	60 ± 10	63 ± 9	55 ± 11	< 0.001
Current alcohol usage (%)	860 (46%)	585 (47%)	238 (43%)	0.03
Current smoking (%)	464 (25%)	321 (26%)	126 (22%)	< 0.001
Level of education				0.04
Low (%)	365 (35%)	259 (35%)	85 (34%)	
Moderate (%)	410 (40%)	302 (41%)	90 (36%)	
High (%)	258 (25%)	175 (24%)	73 (29%)	
Duration of diabetes (years)	4 (1-10)	4 (1-10)	3 (0-7)	< 0.001
Weight (kg)	87 ± 17	86 ± 15	91 ± 20	< 0.001
Body mass index (kg/m2)	29 ± 5	28 ± 4	30 ± 6	< 0.001
Waist circumference (cm)	101 ± 13	101 ± 12	102 ± 15	0.07
Systolic blood pressure (mmHg)	145 ± 21	145 ± 21	146 ± 21	0.21
Diastolic blood pressure (mmHg)	83 ± 12	81 ± 11	86 ± 12	< 0.001
Use of insulin (%)	455 (24%)	302 (24%)	134 (24%)	0.85
Use of only metformin (%)	371 (19%)	247 (19%)	106 (18%)	0.63
Use of glucose lowering agents (%)	1262 (66%)	822 (65%)	388 (68%)	0.22
Glucose (mmol/L)	8.7 ± 2.9	8.5 ± 2.7	9.2 ± 3.2	< 0.001
HbA_{1c} (%)	7.1 ± 1.3	6.9 ± 1.1	7.5 ± 1.5	< 0.001
Insulin (mU/L)	13.0 (8.0-20.0)	13.0 (8.0-20.0)	13.0 (9.0-22.0)	0.36
eGFR (ml/min/1.73 m^2)	78.5 ± 22.1	75.9 ± 21.0	85.1 ± 22.6	< 0.001
Proteinuria				0.66
Micro (%)	368 (21%)	249 (22%)	107 (21%)	
Macro (%)	61 (4%)	41 (4%)	14 (3%)	
Total cholesterol (mmol/L)	4.8 ± 1.4	4.6 ± 1.2	5.3 ± 1.6	< 0.001
Non-HDL-cholesterol (mmol/L)	3.7 ± 1.4	3.5 ± 1.2	4.1 ± 1.7	< 0.001
HDL-cholesterol (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.4	0.001
LDL-cholesterol (mmol/L)	2.8 ± 1.1	2.6 ± 1.0	3.0 ± 1.1	< 0.001
Triglycerides (mmol/L)	1.7 (1.2-2.5)	1.6 (1.2-2.4)	1.8 (1.2-2.7)	< 0.001
Hemoglobin (mmol/L)	8.7 ± 0.9	8.7 ± 0.9	8.9 ± 0.8	< 0.001

**p-value is the p-value for the difference between patients with previous CVD and patients without previous CVD.*

HGI = Hemoglobin Glycation Index, CVD = cardiovascular disease. Microalbuminuria is defined as an albumin/creatinine ratio (ACR) 3-30 mg/mmol. Macroalbuminuria is defined as a urine-albumin/creatinine ratio ≥30 mg/mmol.

Relation of HGI and HbA_{1c} with cardiovascular events and mortality in patients with type 2 diabetes with and without cardiovascular disease at baseline

As previous CVD was proven to be the only effect modifier (p-value for interaction by CVD at baseline = 0.02) in the relation between HGI and composite of cardiovascular events, all analyses were stratified according to presence or absence of previous CVD.

In patients with previous CVD, an inverse relation between HGI and myocardial infarction was seen when adjusting for confounders (model II; HR 0.78, 95% CI 0.63-0.96). No statistical significant relation was seen between HGI and composite of cardiovascular events, total mortality, cardiovascular mortality or stroke (*Table 2*). No significant relation was seen between HbA_{1c} and any of the outcomes in patients with previous CVD (*Table 3*).

In patients without previous CVD, a significant relation between HGI and composite of cardiovascular events was seen when adjusting for confounders (model II; HR 1.29, 95% CI 1.06-1.57). No significant relation was observed between HGI and total mortality, cardiovascular mortality, myocardial infarction or stroke (*Table 2*).

A significant relation between HbA_{1c} and composite of cardiovascular events was observed in patients without previous CVD when adjusting for confounders (model II; HR 1.23, 95% CI 1.04-1.45), although here the p-value for interaction was not significant (p-value = 0.14). There was no significant relation between HbA_{1c} and total mortality, cardiovascular mortality, myocardial infarction or stroke (*Table 3*).

Sensitivity analyses in patients without missing HbA_{1c}, fasting plasma glucose, or history of CVD did not alter our results. Although the inverse effects of HGI and myocardial infarction was not significant, this is probably due to a lack of power when excluding 123 of 1313 patients with type 2 diabetes (*Supplementary table 4*).

Additional adjustment for HbA_{1c} and level of education

In order to evaluate whether the relation between HGI and cardiovascular events and mortality would be influenced by HbA_{1c}, we additionally adjusted for HbA_{1c}.

Table 2. Relation between HGI and cardiovascular events and mortality in patients with type 2 diabetes with and without cardiovascular disease

	All patients (n=1910)	**Previous CVD (n=1313)**	**No previous CVD (n=597)**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Composite of cardiovascular events			
Events:	n = 380 (19.9%)	n = 315 (24.0%)	n = 65 (10.9%)
Model I	1.04 (0.94-1.14)	1.01 (0.90-1.13)	1.30 (1.08-1.56)*
Model II	1.00 (0.90-1.11)	0.96 (0.86-1.08)	1.29 (1.06-1.57)*
Model III	0.93 (0.80-1.08)	0.89 (0.75-1.05)	1.17 (0.86-1.59)
Model IV	0.99 (0.89-1.10)	0.95 (0.85-1.07)	1.30 (1.07-1.57)*
Total mortality			
Events:	n = 436 (22.8%)	n = 345 (26.3%)	n = 91 (15.2%)
Model I	1.12 (1.03-1.22)*	1.14 (1.03-1.26)*	1.19 (1.01-1.40)*
Model II	1.07 (0.97-1.17)	1.07 (0.96-1.18)	1.14 (0.96-1.36)
Model III	0.99 (0.86-1.13)	0.96 (0.82-1.13)	1.09 (0.83-1.42)
Model IV	1.07 (0.97-1.17)	1.07 (0.97-1.19)	1.14 (0.96-1.36)
Cardiovascular mortality			
Events:	243 (12.7%)	n = 205 (15.6%)	n = 38 (6.4%)
Model I	1.05 (0.94-1.19)	1.03 (0.90-1.19)	1.34 (1.07-1.69)*
Model II	1.00 (0.88-1.13)	0.97 (0.84-1.11)	1.27 (0.99-1.63)
Model III	0.92 (0.76-1.10)	0.82 (0.67-1.01)	1.38 (0.91-2.08)
Model IV	0.99 (0.87-1.12)	0.95 (0.82-1.10)	1.30 (1.02-1.65)*
Myocardial infarction			
Events:	127 (6.6%)	n = 106 (8.1%)	n = 21 (3.5%)
Model I	0.87 (0.72-1.04)	0.81 (0.66-1.01)	1.26 (0.91-1.74)
Model II	0.82 (0.68-0.99)*	0.78 (0.63-0.96)*	1.33 (0.92-1.91)
Model III	0.78 (0.60-1.01)	0.74 (0.56-0.99)*	1.10 (0.64-1.89)
Model IV	0.82 (0.68-0.99)*	0.78 (0.63-0.96)*	1.35 (0.94-1.94)
Stroke			
Events:	97 (5.1%)	n = 79 (6.0%)	n = 18 (3.0%)
Model I	1.11 (0.92-1.33)	1.11 (0.90-1.38)	1.25 (0.88-1.78)
Model II	1.09 (0.90-1.33)	1.06 (0.85-1.33)	1.42 (0.97-2.08)
Model III	1.04 (0.78-1.40)	1.05 (0.75-1.48)	1.22 (0.65-2.29)
Model IV	1.06 (0.87-1.29)	1.01 (0.81-1.27)	1.37 (0.95-1.99)

Model I is adjusted for sex and age. Model II is adjusted for sex, age, body mass index, insulin use, duration of diabetes, non-HDL-cholesterol, eGFR and systolic blood pressure. In model III, HbA_{1c} is added to model II, and in model IV level of education is added to model II.
** indicates a p-value < 0.05.*

Table 3. Relation between HbA_{1c} and cardiovascular events and mortality in patients with type 2 diabetes with and without cardiovascular disease

	All patients (n=1910)	Previous CVD (n=1313)	No previous CVD (n=597)
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Composite of cardiovascular event			
Events:	380 (19.9%)	n = 315 (24.0%)	n = 65 (10.9%)
Model I	1.07 (0.99-1.16)	1.07 (0.98-1.17)	1.23 (1.06-1.42)*
Model II	1.04 (0.95-1.13)	1.02 (0.92-1.12)	1.23 (1.04-1.45)*
Model IV	1.03 (0.94-1.12)	1.01 (0.92-1.12)	1.24 (1.05-1.45)*
Total mortality			
Events:	436 (22.8%)	n = 345 (26.3%)	n = 91 (15.2%)
Model I	1.12 (1.05-1.20)*	1.15 (1.06-1.25)*	1.15 (1.01-1.30)*
Model II	1.08 (1.00-1.16)	1.09 (1.00-1.20)	1.11 (0.97-1.28)
Model IV	1.08 (1.00-1.16)	1.10 (1.01-1.20)*	1.11 (0.96-1.28)
Cardiovascular mortality			
Events:	243 (12.7%)	n = 205 (15.6%)	n = 38 (6.4%)
Model I	1.09 (0.99-1.20)	1.12 (1.01-1.25)*	1.16 (0.96-1.41)
Model II	1.05 (0.94-1.16)	1.06 (0.94-1.19)	1.13 (0.90-1.42)
Model IV	1.04 (0.93-1.15)	1.05 (0.93-1.19)	1.15 (0.92-1.43)
Myocardial infarction			
Events:	127 (6.6%)	n = 106 (8.1%)	n = 21 (3.5%)
Model I	0.96 (0.84-1.11)	0.94 (0.79-1.11)	1.24 (0.95-1.60)
Model II	0.92 (0.79-1.07)	0.88 (0.73-1.05)	1.29 (0.97-1.72)
Model IV	0.92 (0.79-1.07)	0.88 (0.74-1.06)	1.30 (0.98-1.72)
Stroke			
Events:	97 (5.1%)	n = 79 (6.0%)	n = 18 (3.0%)
Model I	1.10 (0.95-1.27)	1.11 (0.93-1.32)	1.22 (0.94-1.58)
Model II	1.08 (0.92-1.27)	1.04 (0.86-1.27)	1.30 (0.98-1.71)
Model IV	1.05 (0.89-1.24)	1.01 (0.83-1.23)	1.27 (0.97-1.66)

Model I is adjusted for sex and age. Model II is adjusted for sex, age, BMI, insulin use, duration of diabetes, non-HDL cholesterol, eGFR and systolic blood pressure. In model IV level of education is added to model II.
** indicates a p-value < 0.05.*

The magnitude of the hazard ratios decreased, for example from 1.29 (95% CI 1.06-1.57) to 1.17 (95% CI 0.86-1.59) with composite of cardiovascular events as outcome in patients without previous CVD. Additional adjustment for level of education did not change the direction or the magnitude of the hazard ratios.

When performing the same analyses with HbA_{1c} as determinant instead of HGI, the hazard ratios closely resembled those of HGI as determinant (*Table 2 and 3*).

The linear relationship between HGI and HbA_{1c} showed a correlation of R^2 = 0.61, indicating a close relation between HGI and HbA_{1c} (*Supplementary figure 2*).

The group without previous CVD and the group with previous CVD differed in regards to the association between HGI and outcomes. In the study, we used the same linear regression for calculating HGI in both groups, since it is a population regression equation based on the whole cohort, also coherent with previous studies of HGI.

Discussion

The current study showed that a higher HGI was associated with a higher risk of cardiovascular events in patients with type 2 diabetes but without previous CVD. The same was seen with HbA_{1c} and risk of cardiovascular events in patients with type 2 diabetes but without previous CVD. An inverse relation between higher HGI and myocardial infarction was seen in the group with previous CVD. As the direction and magnitude of the hazard ratios of HGI and outcomes closely resembled the hazard ratios of HbA_{1c} and outcomes and adjustment for HbA_{1c} decreased the magnitude of the hazard ratios, HGI closely resembles HbA_{1c} as a risk factor for cardiovascular morbidity and mortality.

Although the correlation between blood glucose and HbA_{1c} measurements is generally good,[15] this is not always the case. The relation between blood glucose levels and HbA_{1c} may be influenced by factors influencing haemoglobin glycosylation such as age,[16] race,[17, 18] genetic variations,[19] differences in erythrocyte life span and environment,[7] as well as iron deficiency and anemia.[20] One way of approaching this discordance is the HGI;[5] the difference between observed HbA_{1c} and predicted HbA_{1c} calculated from the population regression equation of HbA_{1c} on FPG. A high and low HGI thus represent HbA_{1c} levels that are higher or lower, respectively, than predicted compared to other patients with similar (fasting) plasma glucose levels. In addition, a single fasting plasma glucose may not always correlate with HbA_{1c} due to day-to-day changes in fasting plasma glucose and postprandial glucose excursions.

To the best of our knowledge, this is the first prospective study to investigate the relation between both HGI and HbA_{1c} as separate determinants and their association with cardiovascular events in patients with type 2 diabetes with and without stable cardiovascular disease at baseline. Several previous studies have investigated the relation between HGI and micro- and macrovascular complications of diabetes. A sub-study of the ACCORD trial found increased mortality and increased risk of hypoglycemia with intensive treatment in the high HGI tertile compared with low and moderate HGI.[8] This might be due to the fact that patients with a high HGI often had more pronounced glucose excursions with frequent lower blood glucose levels compared to their HbA_{1c}, and thus were more exposed to the detrimental factors related to episodic hypoglycemia.[21] However, in view of our results, it is important to note that in the original ACCORD trial, patients in the intensive treatment arm with a higher HbA_{1c} also had increased risk of mortality compared to patients with a lower $HbA_{1c.}$[22] The similar results of HGI and HbA_{1c}, respectively, as risk factors for mortality in the ACCORD study could indicate that the HGI is a proxy for HbA_{1c}.

In a study from the DCCT, a high HGI was associated with a three-fold increase in the risk for retinopathy and a six-fold increase in the risk for nephropathy in patients with type 1 diabetes.[7] A critical oponent to this study performed analyses with the DCCT data including HbA_{1c} as covariate, and here the results were non-significant.[12] A recent study from the AleCardio trial found increased risk for cardiovascular mortality and total mortality in patients with a high HGI.[23] A one percent increase in HGI was associated with a 16% higher risk of cardiovascular mortality. However, this association was no longer evident after additional adjustment for HbA_{1c}, while the hazard ratios for the relation between HGI and outcomes were comparable to those seen between HbA_{1c} and outcomes. A study from the ADVANCE trial compared HGI and HbA_{1c} as predictors for cardiovascular disease in two groups with intensive and standard glucose control.[24] They found that a higher HGI was associated with an increased risk of macro- and microvascular diabetes complications and mortality. However, when using the same confounders, HbA_{1c} was a stronger predictor.

We expand on this data by showing that this not only applies to a trial population but also to a stable real-life population of patients with type 2 diabetes with and without CVD. These data put together indicate that HGI is no more than a surrogate for $HbA_{1c.}$

A recent study from South Korea showed a significant relation between the high HGI tertile and cardiovascular events in patients with pre-diabetes or type 2 diabetes,[9] while another study from South Korea in patients with type 2 diabetes found no significant relation between HGI and any diabetic complication.[10] A recent study conducted in non-diabetic Caucasian Italians found that a high HGI was associated with a significant increase in carotid intima media thickness, an indicator of subclinical atherosclerosis, in non-diabetic individuals predisposed for type 2 diabetes.[6] However, none of these studies took potential effect modification by cardiovascular disease at baseline into account, and only one study performed additional analyses with HbA_{1c} as a confounder.[9] The previous studies of HGI as risk factor for CVD also differ in regards to patient population and the type of measurement of blood glucose, making the results difficult to interpret.

It is previously shown that hyperglycemia (a high HbA_{1c}) increases the risk of mortality and cardiovascular disease in patients with type 2 diabetes, since it is associated with abnormalities in coagulation, dyslipidemia, and other known risk factors associated with increased risk of cardiovascular disease,[25] mainly because of the formation of glycosylation end products.[26] If HGI is no more than a surrogate for HbA_{1c}, the results obtained in studies that showed a relation between high HGI and increased risk of cardiovascular disease and mortality might simply be due to the fact that patients with a high HGI simultaneously had a high HbA_{1c}. The clinical use of HGI is furthermore hampered by the need to construct a linear relation between blood glucose and HbA_{1c}, as the linear population regression equation used to calculate predicted HbA_{1c} differs between populations across different studies.

Furthermore, there are several factors that need to be taken into consideration when interpreting HGI, which we will briefly discuss. Glycemic variability, understood as fluctuations in blood glucose, has been proposed as a risk factor for diabetic complications.[27-30] A high HGI could in theory be a reflection of high glycemic variability, and thus the association between a high HGI and increased risk of CVD might simply reflect this phenomenon. Insulin use affects fasting or postprandial glucose levels, but does not affect HbA_{1c} to the same extent,[13] which might also lead to a higher HGI. Furthermore, the use of glucose-lowering agents has been shown to alter the relation between FPG and HbA_{1c}, with a smaller increase in HbA_{1c} for every unit increase in FPG.[31] A higher HGI

may thus in theory also reflect higher daytime or postprandial glucose levels compared to FPG or the use of insulin or glucose-lowering agents.

Another problem to consider in using the HGI is the measurement of blood glucose. Although a study showed correlation between HGI calculated from fasting plasma glucose and HGI calculated from all glucose data,[5] patients with type 2 diabetes may be subject to a "doctor-pleasing" attitude, achieving a lower FPG at the time of the clinical visit with a still higher than expected $HbA_{1c,}$ thus resulting in a higher HGI. However, when adding level of education to the model, as a marker of socio-economic status related to compliance, no change in the risk was seen.

In the analysis, we divided the cohort into patients with and without previous CVD. However, the patients without previous CVD were still high-risk patients, as all patients were enrolled during hospitalization and they all had at least one risk factor for CVD.

The effect modification of previous CVD can be caused by a number of factors. One possible explanation is that in patients with previous CVD, a high HGI (and thus a high HbA_{1c}) is not the main factor for endothelial damage leading to a cardiovascular event. It could very well be that other known risk factors for CVD (e.g. hypertension and dyslipidemia) play a larger role in the pathogenesis of CVD in patients with established CVD. This could indicate that there is a need for individual treatment in patients with type 2 diabetes, especially in the high-risk group.

The inverse relation between HGI and myocardial infarction in patients with previous CVD is possibly due to the fact that a low HGI (and thus a low HbA_{1c}) might be an indicator of frequent hypoglycemia and thus increased risk of morbidity and mortality,[21, 32, 33] and patients with previous CVD might be more at risk of myocardial infarction with a lower HGI (and thus a low HbA_{1c}). The relation between HbA_{1c} and risk of myocardial infarction was of the same direction as the relation between HGI and myocardial infarction, although it was not statistically significant.

There are several strengths of the present study including the prospective design, the large number of events because of the substantial follow-up time and the large cohort size. Furthermore, the completeness of the data decreases

the risk of information bias. However, some study limitations also need to be considered. The predicted HbA_{1c} used to calculate the HGI was based on only one value of FPG, which is a limitation to the study in regards to a precise calculation of HGI, as mean blood glucose in participants could be higher or lower. Ideally, more measurements of blood glucose, including postprandial measurements should be used to calculate HGI. Further, the linear regression equation used to calculate predicted HbA_{1c} cannot be extrapolated to other populations; thus a new equation will have to be made for each population. Also, the SMART study is conducted in a central academic university hospital, meaning that the diversity of the cohort is limited to almost only Caucasian individuals. Finally, there were not a lot of events for the secondary outcomes stroke and myocardial infarction, raising caution regarding the validity of the results for these outcomes.

Conclusion

In conclusion, in patients with type 2 diabetes but without cardiovascular disease, a higher HGI is related to a higher risk of cardiovascular events, and in patients with previous cardiovascular disease, a higher HGI is related to a lower risk of myocardial infarction. However, since HbA_{1c} confers similar risk and because of the strong correlation between HGI and HbA_{1c} in patients, the added benefit of HGI as a risk factor for cardiovascular events seems limited.

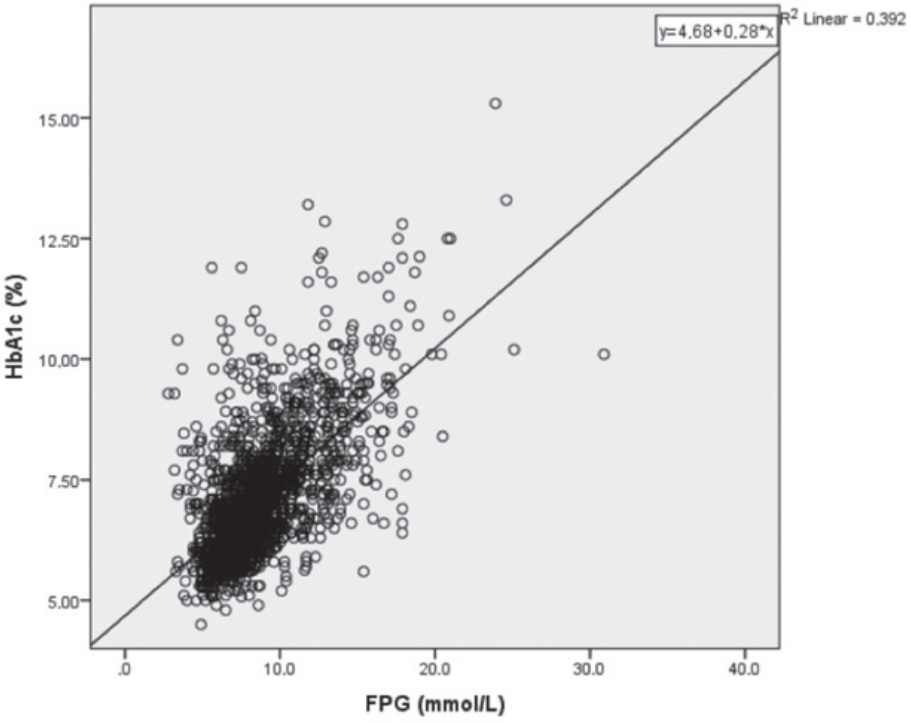
References

1. WHO. Diabetes Fact Sheet, http://www.who.int/mediacentre/factsheets/fs312/en/: WHO; 2016 [visited June 12, 2017].
2. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet (London, England). 2010;375(9733):2215-22.
3. Nazimek-Siewniak B, Moczulski D, Grzeszczak W. Risk of macrovascular and microvascular complications in Type 2 diabetes: results of longitudinal study design. J Diabetes Complications. 2002;16(4):271-6.
4. Gillery P. A history of HbA1c through Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med. 2013;51(1):65-74.
5. Hempe JM, Gomez R, McCarter RJ, Jr., Chalew SA. High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. J Diabetes Complications. 2002;16(5):313-20.
6. Marini MA, Fiorentino TV, Succurro E, et al. Association between hemoglobin glycation index with insulin resistance and carotid atherosclerosis in non-diabetic individuals. PloS one. 2017;12(4):e0175547.
7. McCarter RJ, Hempe JM, Gomez R, Chalew SA. Biological variation in HbA1c predicts risk of retinopathy and nephropathy in type 1 diabetes. Diabetes Care. 2004;27(6):1259-64.
8. Hempe JM, Liu S, Myers L, McCarter RJ, Buse JB, Fonseca V. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. Diabetes Care. 2015;38(6):1067-74.
9. Ahn CH, Min SH, Lee DW, et al. Hemoglobin Glycation Index Is Associated with Cardiovascular Diseases in People with Impaired Glucose Metabolism. J Clin Endocrinol Metab. 2017.
10. Kim MK, Jeong JS, Kwon HS, Baek KH, Song KH. Concordance the hemoglobin glycation index with glycation gap using glycated albumin in patients with type 2 diabetes. J Diabetes Complications. 2017.
11. Gerstein HC, Miller ME, Genuth S, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011;364(9):818-28.
12. Lachin JM, Genuth S, Nathan DM, Rutledge BN. The hemoglobin glycation index is not an independent predictor of the risk of microvascular complications in the Diabetes Control and Complications Trial. Diabetes. 2007;56(7):1913-21.
13. Riddle MC, Gerstein HC. Comment on Hempe et al. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. Diabetes Care 2015;38:1067-1074. Diabetes Care. 2015;38(10):e170-1.
14. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol. 1999;15(9):773-81.
15. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA1c goals. Diabetes Care. 2014;37(4):1048-51.
16. Pani LN, Korenda L, Meigs JB, et al. Effect of aging on A1C levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001-2004. Diabetes Care. 2008;31(10):1991-6.
17. Herman WH, Cohen RM. Racial and ethnic differences in the relationship between HbA1c and blood glucose: implications for the diagnosis of diabetes. J Clin Endocrinol Metab. 2012;97(4):1067-72.

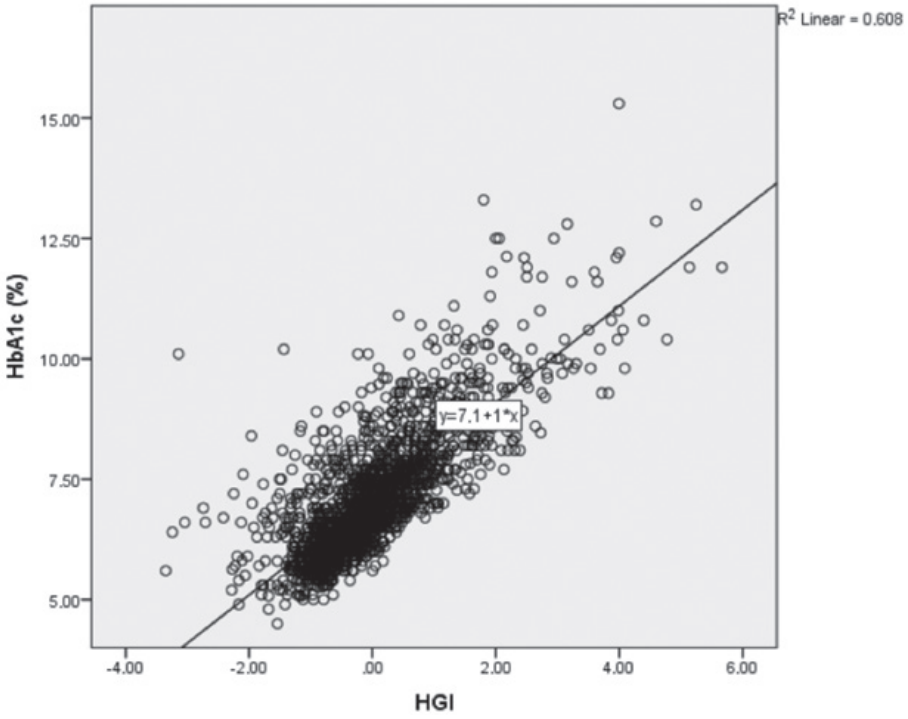
18. Bergenstal RM, Gal RL, Connor CG, et al. Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A1c Levels. Ann Intern Med. 2017;167(2):95-102.
19. Snieder H, Sawtell PA, Ross L, Walker J, Spector TD, Leslie RD. HbA(1c) levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. Diabetes. 2001;50(12):2858-63.
20. English E, Idris I, Smith G, Dhatariya K, Kilpatrick ES, John WG. The effect of anaemia and abnormalities of erythrocyte indices on HbA1c analysis: a systematic review. Diabetologia. 2015;58(7):1409-21.
21. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes. 2014;63(5):1738-47.
22. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care. 2010;33(5):983-90.
23. van Steen SC, Schrieks IC, Hoekstra JB, et al. The haemoglobin glycation index as predictor of diabetes-related complications in the AleCardio trial. Eur J Prev Cardiol. 2017;24(8):858-66.
24. van Steen SC, Woodward M, Chalmers J, et al. Haemoglobin glycation index and risk for diabetes-related complications in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia. 2018;61(4):780-9.
25. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care. 1995;18(2):258-68.
26. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation. 2006;114(6):597-605.
27. Satya Krishna SV, Kota SK, Modi KD. Glycemic variability: Clinical implications. Indian J Endocrinol Metab. 2013;17(4):611-9.
28. Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R. Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus: the Verona Diabetes Study. Circulation. 1997;96(6):1750-4.
29. Suh S, Kim JH. Glycemic Variability: How Do We Measure It and Why Is It Important? Diabetes Metab. 2015;39(4):273-82.
30. Smith-Palmer J, Brandle M, Trevisan R, Orsini Federici M, Liabat S, Valentine W. Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(3):273-84.
31. Ramachandran A, Riddle MC, Kabali C, Gerstein HC. Relationship between A1C and fasting plasma glucose in dysglycemia or type 2 diabetes: an analysis of baseline data from the ORIGIN trial. Diabetes Care. 2012;35(4):749-53.
32. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. Diabetologia. 2002;45(7):937-48.
33. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;57(12):3169-76.

Supplementary material

Supplementary figure 1. The linear population regression equation of HbA_{1c} as a function of FPG used to calculate predicted HbA_{1c} in the cohort (HGI = observed HbA_{1c}– predicted HbA_{1c})



Supplementary figure 2. The linear regression equation between HGI and HbA_{1c} for the entire cohort



Supplementary table 1. Outcome events in this study

Composite of cardiovascular events	Composite of myocardial infarction, stroke (infarction or hemorrhagic), retinal infarction, terminal heart failure, sudden death and vascular mortality
Total mortality	Death from any cause
Cardiovascular mortality	Death caused by stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death of other causes
Myocardial infarction	Two or more of the following criteria: (I) Chest pain for at least 20 minutes, not disappearing after administration of nitrates (II) ST-elevation > 1 mm in two following leads or a left bundle branch block on the electrocardiogram (III) Troponin elevation above clinical cut-off values or creatinine kinase (CK) elevation of at least two times the normal value of CK and a myocardial band-fraction > 5% of the total CK Sudden death: unexpected cardiac death occurring within one hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Stroke	Relevant clinical features ≥ 24 hours causing an increase in impairment of at least one grade on the modified ranking scale, with a new cerebral infarction on CT or MRI Relevant clinical features ≥ 24 hours causing an increase in impairment of at least one grade on the modified ranking scale, without a new (hemorrhage) cerebral infarction on CT or MRI

Supplementary table 2. Baseline table grouped by HGI tertile

	Low HGI (n =637)	Moderate HGI (n =637)	High HGI (n =636)	p-value
HGI	-0.9 ± 0.4	-0.2 ± 0.2	1.1 ± 0.9	< 0.001
Sex, male (%)	475 (73%)	439 (70%)	415 (66%)	0.001
Age (years)	61 ± 10	62 ± 10	59 ± 10	< 0.001
Weight (kg)	86 ± 16	88 ± 17	88 ± 18	0.06
Body mass index (kg/m2)	28 ± 5	29 ± 5	30 ± 5	< 0.001
Waist circumference (cm)	100 ± 13	102 ± 12	102 ± 14	0.08
Duration of diabetes (years)	2 (0-8)	4 (1-10)	5 (1-11)	< 0.001
Systolic blood pressure (mmHg)	145 ± 21	146 ± 20	144 ± 21	0.17
Diastolic blood pressure (mmHg)	83 ± 12	83 ± 11	82 ± 12	0.57
Current alcohol usage (%)	331 (53%)	288 (46%)	241 (38%)	< 0.001
Current smoking (%)	150 (23%)	138 (22%)	176 (28%)	0.01
History of CVD (%)	441 (73%)	441 (72%)	378 (62%)	< 0.001
Level of education				0.33
Low (%)	113 (34%)	141 (36%)	111 (36%)	
Moderate (%)	125 (39%)	165 (40%)	120 (41%)	
High (%)	95 (27%)	90 (24%)	73 (24%)	
Use of insulin (%)	90 (14%)	129 (20%)	236 (37%)	< 0.001
Use of only metformin (%)	138 (22%)	149 (23%)	84 (13%)	< 0.001
Use of glucose lowering agents (%)	393 (62%)	448 (70%)	421 (66%)	0.005
Glucose (mmol/L)	8.8 ± 2.9	8.2 ± 2.4	9.1 ± 3.2	< 0.001
HbA_{1c} (%)	6.2 ± 0.7	6.8 ± 0.7	8.3 ± 1.3	< 0.001
Insulin (mU/L)	13.0 (8.0-19.0)	12.0 (8.0-19.0)	14.0 (9.0-24.0)	< 0.001
eGFR (ml/min/1.73 m^2)	77.6 ± 21.3	77.2 ± 22.1	80.7 ± 22.9	0.01
Albuminuria				0.002
Micro (%)	103 (17%)	115 (20%)	150 (26%)	
Macro (%)	14 (2%)	21 (4%)	26 (5%)	
Total cholesterol (mmol/L)	4.8 ± 1.2	4.7 ± 1.3	4.9 ± 1.5	0.07
Non-HDL-cholesterol (mmol/L)	3.7 ± 1.2	3.6 ± 1.3	3.8 ± 1.5	0.02
HDL-cholesterol (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.03
LDL-cholesterol (mmol/L)	2.8 ± 1.0	2.7 ± 1.1	2.8 ± 1.1	0.04
Triglycerides (mmol/L)	1.6 (1.1-2.4)	1.7 (1.2-2.4)	1.8 (1.3-2.6)	0.03
Hb (mmol/L)	8.8 ± 0.9	8.7 ± 0.8	8.7 ± 0.9	0.02

HGI = Hemoglobin Glycation Index, CVD = cardiovascular disease. Microalbuminuria is defined as a urine-albumin/creatinine ratio of 3-30 mg/mmol. Macroalbuminuria is defined as a urine-albumin/creatinine ratio ≥30 mg/mmol.

Supplementary table 3. Baseline table grouped by HbA_{1c} tertile

	Low HbA_{1c} (n =637)	Moderate HbA_{1c} (n =637)	High HbA_{1c} (n =636)	p-value
HbA_{1c} (%)	5.9 ± 0.3	6.8 ± 0.3	8.5 ± 1.1	< 0.001
HGI	-0.7 ± 0.4	-0.2 ± 0.6	0.9 ± 1.1	< 0.001
Sex, male (%)	469 (74%)	441 (69%)	419 (66%)	0.01
Age (years)	61 ± 10	61 ± 10	59 ± 10	< 0.001
Weight (kg)	85 ± 16	87 ± 16	89 ± 18	0.001
Body mass index (kg/m2)	28 ± 5	29 ± 5	30 ± 6	< 0.001
Waist circumference (cm)	100 ± 12	101 ± 12	103 ± 14	< 0.001
Duration of diabetes (years)	2 (0-6)	4 (1-10)	6 (1-12)	< 0.001
Systolic blood pressure (mmHg)	144 ± 20	146 ± 21	145 ± 20	0.06
Diastolic blood pressure (mmHg)	82 ± 11	83 ± 12	83 ± 11	0.88
Current alcohol usage (%)	347 (55%)	296 (47%)	217 (35%)	< 0.001
Current smoking (%)	142 (22%)	142 (22%)	180 (29%)	0.01
History of CVD (%)	449 (75%)	442 (72%)	369 (60%)	< 0.001
Level of education				0.03
Low (%)	134 (34%)	141 (38%)	90 (34%)	
Moderate (%)	152 (38%)	148 (40%)	110 (42%)	
High (%)	110 (28%)	86 (23%)	62 (24%)	
Use of insulin (%)	58 (9%)	144 (23%)	253 (40%)	< 0.001
Use of only metformin (%)	174 (27%)	130 (20%)	67 (11%)	< 0.001
Use of glucose lowering agents (%)	409 (64%)	453 (71%)	404 (64%)	0.004
Glucose (mmol/L)	7.1 ± 1.5	8.3 ± 2.0	10.7 ± 3.5	< 0.001
Insulin (mU/L)	12.0 (8.0-18.0)	13.0 (8.0-20.0)	15.0 (10.0-26.0)	< 0.001
eGFR (ml/min/1.73 m^2)	76.2 ± 20.2	77.6 ± 21.8	81.7 ± 23.9	< 0.001
Albuminuria				0.001
Micro (%)	101 (17%)	121 (19%)	146 (25%)	
Macro (%)	14 (2%)	20 (3%)	27 (5%)	
Total cholesterol (mmol/L)	4.7 ± 1.2	4.6 ± 1.3	5.1 ± 1.6	< 0.001
Non-HDL-cholesterol (mmol/L)	3.6 ± 1.2	3.5 ± 1.3	4.0 ± 1.6	< 0.001
HDL-cholesterol (mmol/L)	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.002
LDL-cholesterol (mmol/L)	2.8 ± 1.1	2.6 ± 1.0	2.9 ± 1.1	< 0.001
Triglycerides (mmol/L)	1.5 (1.1-2.2)	1.6 (1.1-2.5)	1.9 (1.3-2.8)	< 0.001
Hb (mmol/L)	8.8 ± 0.9	8.7 ± 0.9	8.8 ± 0.9	0.51

HGI = Hemoglobin Glycation Index, CVD = cardiovascular disease. Microalbuminuria is defined as a urine-albumin/creatinine ratio of 3-30 mg/mmol. Macroalbuminuria is defined as a urine-albumin/creatinine ratio ≥30 mg/mmol.

Supplementary table 4. Relation between HGI and cardiovascular events and mortality in patients with type 2 diabetes with and without cardiovascular disease. Only cases with complete data for previous CVD, FPG and HbA_{1c} are included

	All patients (n=1784)	**Previous CVD (n=1190)**	**No previous CVD (n=594)**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Composite of cardiovascular events			
Events:	n = 323 (18.1%)	n = 258 (21.7%)	n = 65 (10.9%)
Model I	1.08 (0.98-1.20)	1.05 (0.93-1.19)	1.30 (1.09-1.56)*
Model II	1.04 (0.94-1.16)	1.00 (0.88-1.13)	1.30 (1.07-1.58)*
Model III	0.97 (0.83-1.14)	0.92 (0.76-1.11)	1.14 (0.84-1.55)
Model IV	1.03 (0.92-1.15)	0.99 (0.87-1.12)	1.30 (1.07-1.58)*
Total mortality			
Events:	n = 374 (21.0%)	n = 283 (23.8%)	n = 91 (15.3%)
Model I	1.17 (1.07-1.28)*	1.21 (1.08-1.35)*	1.19 (1.01-1.40)*
Model II	1.11 (1.01-1.22)*	1.12 (1.00-1.26)*	1.15 (0.97-1.37)
Model III	0.99 (0.86-1.15)	0.95 (0.80-1.13)	1.06 (0.82-1.39)
Model IV	1.11 (1.01-1.22)*	1.13 (1.01-1.27)	1.15 (0.97-1.37)
Cardiovascular mortality			
Events:	206 (11.5%)	n = 168 (14.1%)	n = 38 (6.4%)
Model I	1.10 (0.96-1.25)	1.08 (0.92-1.26)	1.34 (1.07-1.69)*
Model II	1.04 (0.91-1.19)	1.00 (0.85-1.17)	1.28 (0.98-1.64)
Model III	0.95 (0.77-1.16)	0.82 (0.65-1.03)	1.36 (0.90-2.05)
Model IV	1.03 (0.90-1.17)	0.98 (0.84-1.15)	1.30 (1.02-1.65)*
Myocardial infarction			
Events:	104 (5.8%)	n = 83 (7.0%)	n = 21 (3.5%)
Model I	0.92 (0.76-1.13)	0.86 (0.68-1.09)	1.26 (0.91-1.75)
Model II	0.87 (0.71-1.06)	0.81 (0.64-1.02)	1.33 (0.93-1.92)
Model III	0.78 (0.59-1.04)	0.73 (0.53-1.01)	1.06 (0.62-1.82)
Model IV	0.86 (0.70-1.06)	0.81 (0.64-1.02)	1.35 (0.94-1.94)
Stroke			
Events:	84 (4.7%)	n = 66 (5.1%)	n = 18 (3.0%)
Model I	1.12 (0.92-1.36)	1.12 (0.88-1.42)	1.25 (0.88-1.77)
Model II	1.12 (0.91-1.38)	1.09 (0.85-1.39)	1.42 (0.97-2.08)
Model III	1.12 (0.81-1.56)	1.17 (0.79-1.75)	1.18 (0.63-2.23)
Model IV	1.08 (0.88-1.33)	1.03 (0.81-1.32)	1.37 (0.95-1.98)

Model I is adjusted for sex and age. Model II is adjusted for sex, age, body mass index, insulin use, duration of diabetes, non-HDL cholesterol, eGFR and systolic blood pressure. In model III, HbA_{1c} is added to model II, and in model IV level of education is added to model II.
** indicates a p-value < 0.05.*

PART II

Individual prediction and benefit from treatment

CHAPTER 5

Cardiovascular risk and lifetime benefit from preventive treatment in type 2 diabetes: A post hoc analysis of the CAPTURE study

Helena Bleken Østergaard
Valerie Humphreys
Ellen Margo Hengeveld
Julie Broe Honore
François Mach
Frank L. J. Visseren
Jan Westerink
Gourav Yadav
Ofri Mosenzon
on behalf of the CAPTURE investigators

Diabetes Obes Metab. 2023 Feb;25(2):435-443

Abstract

Aim: CAPTURE was a non-interventional, cross-sectional, multinational study collecting clinical characteristics on 9823 adults with type 2 diabetes, aiming to estimate cardiovascular disease (CVD) prevalence and treatment patterns. This post hoc analysis aimed to assess gain in life-years free of (recurrent) CVD event with optimal cardiovascular risk management (CVRM) and initiation of glucose-lowering agents with proven cardiovascular benefit.

Materials and Methods: The diabetes lifetime-perspective prediction model was used for calculating individual 10-year and lifetime CVD risk. Distribution of preventive medication use was assessed according to predicted CVD risk and stratified for history of CVD. For estimation of absolute individual benefit from lifelong preventive treatment, including optimal CVRM and addition of glucagon-like peptide-1 receptor agonist (GLP-1 RA) and sodium–glucose co-transporter-2 inhibitor (SGLT-2i), the model was combined with treatment effects from current evidence.

Results: GLP-1 RA or SGLT-2i use did not greatly differ between patients with and without CVD history, while use of blood pressure-lowering medication, statins and aspirin was more frequent in patients with CVD. Mean (standard deviation [SD]) lifetime benefit from optimal CVRM was 3.9 (3.0) and 1.3 (1.9) years in patients with and without established CVD, respectively. Further addition of GLP-1 RA and SGLT-2i in patients with CVD gave an added mean (SD) lifetime benefit of 1.2 (0.6) years.

Conclusion: Life-years gained free of (recurrent) CVD by optimal CVRM and addition of GLP-1 RA or SGLT-2i is dependent on baseline CVD status. These results aid individualizing prevention and promote shared decision-making in patients with type 2 diabetes.

Introduction

The prevalence of type 2 diabetes is rapidly increasing worldwide and the current global prevalence is 9%.[1] Furthermore, patients with type 2 diabetes have a two-fold excess risk of cardiovascular disease (CVD), independent of other risk factors, compared with people without type 2 diabetes.[2] CVD is the main cause of disability and death in patients with type 2 diabetes, and is also associated with reduced health-related quality of life and increased healthcare costs.[3] Assessing risk and preventing CVD in patients with type 2 diabetes is therefore highly important.

Available glucose-lowering agents (GLAs) with proven cardiovascular (CV) benefits include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT-2is).[4, 5] The results of several randomized controlled trials indicate that these treatments provide specific benefits for patients with a history of CVD, above and beyond glycaemic control.[6, 7] Therefore, current guidelines advocate their use in high-risk patients,[8-11] although implementation of these therapies remains limited.[12, 13] Guidelines recommend regular cardiovascular risk management (CVRM) as the first-line treatment strategy: the effects of lipid-lowering,[14, 15] glucose-lowering[16] and blood pressure-lowering medications,[17, 18] aspirin use (in secondary prevention)[19] and smoking cessation[20] are all highly significant in CVD risk reduction, and their use is monitored.

There is a wide distribution in terms of individual benefit from optimal CVRM and preventive treatment in patients with type 2 diabetes, based on risk factor burden, baseline risk and duration of treatment. The diabetes lifetime-perspective prediction (DIAL) model predicts CVD risk in patients with type 2 diabetes while adjusting for non-CVD mortality as a competing risk.[21] Furthermore, the model allows incorporation of treatment effects (hazard ratios [HRs] from trials or meta-analyses) to assess the number of life-years gained without a (recurrent) CVD event with the initiation of preventive medication strategies. The individual CVD risk and benefit from preventive treatment initiation can be discussed in clinical practice, and enhances shared decision-making between the patient and clinician.

CAPTURE was a non-interventional, cross-sectional study that collected demographic and clinical characteristics for 9823 adults with type 2 diabetes

across 13 countries worldwide in 2019,[13] aiming to estimate CVD risk distribution and assess treatment patterns. The aim of this post hoc analysis of data from CAPTURE was to estimate the potential gain in the number of life-years free of a (recurrent) CVD event with CVRM and initiation of GLAs with proven CV benefits.

Materials and methods

Study population

All patients included in the CAPTURE cohort attended a single, routine clinical visit in a primary or specialist care setting. Owing to the functionality of the DIAL model, regions were defined solely based on geography and did not account for inter-regional differences, for example in healthcare systems. Regions were defined as Latin America (Argentina, Brazil and Mexico), Western Europe (Italy and France), Eastern Europe (Turkey, the Czech Republic and Hungary), Australia, East Asia (China and Japan) and the Middle East (Saudi Arabia and Israel). Baseline characteristics were described as mean ± standard deviation (SD) for continuous variables, median (interquartile range [IQR]) for skewed variables and count (percentage) for categorical variables.

Missing data in the cohort were imputed using single imputation by predicted mean matching (aregImpute algorithm in R, Hmisc package, version 4.5-0). Imputation was performed with stratification according to region. The proportion of patients with missing data was: 0% for sex, age, region, history of CVD and medication use; 0.1% for diabetes duration; 2% for systolic blood pressure and body mass index; 7% for glycated haemoglobin (HbA1c) level; 22% for non-high-density lipoprotein (HDL)-cholesterol level; 19% for eGFR; 1% for smoking status; and 34% for albuminuria. Non-imputed baseline data, including numbers of missing values, are provided in *Supplementary table 1*.

The DIAL model is suitable for CVD risk prediction for patients with T2D aged 30–85 years who have an estimated glomerular filtration rate (eGFR) above 30 mL/min/1.73 m^2. Therefore, CAPTURE participants younger than 30 years and older than 85 years were excluded (n = 169), as were those with an eGFR below 30 mL/min/1.73 m^2 (n = 250); including 12 patients in both categories. Exclusion was done after imputation of missing data. This resulted in a cohort

for CVD risk prediction of 9416 patients with type 2 diabetes, 2901 with a history of CVD and 6515 without a history of CVD (*Supplementary figure 1*).

DIAL model for estimating CVD risk and treatment benefit

The DIAL model has previously been described in detail,[21] and is available via an online interactive calculator (www.u-prevent.com). Individual 10-year and lifetime CVD risks were calculated using previously validated life-table methods.[22] The model was combined with HRs from meta-analyses on the effect of GLP-1 RA and SGLT-2i, respectively, on CV outcomes,[4, 5] to estimate individual absolute benefit from treatment in terms of gain in life-years free of (recurrent) CVD event.

Definition of individual optimal preventive treatment

Individuals were stratified into risk groups (moderate, high or very high CVD risk) according to the 2021 European Society of Cardiology (ESC) guidelines (*Supplementary table 2*).[10] Optimal treatment was likewise assessed in line with these guidelines. The main analyses were based on CVRM according to step 2 of the ESC guidelines two-step approach. *Supplementary figure 2* shows life-years gained free of (recurrent) CVD with optimal CVRM according to step 1 and step 2, stratified for history of CVD. Lifetime benefit was calculated individually for all patients using the scenario that those who were currently smoking would stop, and that all patients would reach their respective risk group targets for low-density lipoprotein (LDL)-cholesterol level, HbA1c concentration and systolic blood pressure. It was also assumed that treatment with aspirin, GLP-1 RAs and/or SGLT-2is was initiated, if appropriate, following the aforementioned guidelines. GLP-1 RA and SGLT-2i therapy was therefore assigned to all patients classified as being at very high CVD risk. Definitions of targets are provided in *Supplementary table 3*.

Prediction of individual CVD risk and lifetime benefit from preventive treatment

Patient-level data from the CAPTURE study (age, sex, body mass index, smoking status, HbA1c level, history of CVD, duration of type 2 diabetes, non-HDL-cholesterol level, insulin use, eGFR, albuminuria and region) were used for predicting individual CVD risk using the DIAL model. In line with the original

DIAL model, Eastern Europe was set as a high-risk region and the remaining regions were defined as low-risk regions.

Predicted risk was calculated taking current antiplatelet medication, GLP-1 RA and SGLT-2i use into consideration using HRs from current best available evidence.[4, 5, 19] Current treatment with lipid-lowering and antihypertensive medication was assumed to act by reducing non-HDL-cholesterol level and systolic blood pressure, respectively, both of which were included as predictors in the DIAL model. Treatment effects of GLP-1 RAs (HR of 0.85 in patients with CVD and 1.00 in those without CVD)[4] and SGLT-2is (HR of 0.89 in patients with CVD and 1.00 in those without CVD),[5] as well as HRs for reduction of blood pressure, HbA1c level and LDL-cholesterol level, aspirin treatment and smoking cessation, were combined with the DIAL model to estimate individual lifetime benefit free of (recurrent) CVD with initiation of preventive treatment.[23] HRs were based on three-component major adverse CV events (including myocardial infarction, stroke and CV death) as outcome. *Supplementary table 4* provides a full list of HRs for treatment effects.

Distribution of predicted CVD risk, current use of preventive medication and lifetime benefit

Distributions of predicted 10-year and lifetime risk of a (recurrent) CVD event were stratified according to history of CVD. A high CVD risk was defined as a 10-year risk of CVD of greater than 10%[10] and a lifetime risk of CVD as greater than 50%. Distributions of the use of preventive GLAs with proven CV benefit (GLP-1 RAs and SGLT-2is) were stratified by history of CVD and according to deciles of predicted lifetime CVD risk. Distributions of the use of CVRM medications (antihypertensive medication, statins and aspirin) were assessed in the same way.

Distributions of numbers of life-years gained without a (recurrent) CVD event with optimal CVRM and the addition of GLP-1 RAs and SGLT-2is were stratified by history of CVD and assessed according to deciles of predicted lifetime risk. All analyses were performed with R-statistical programming (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

Given that there was a substantial amount of missing data, we performed all the analyses as a complete case analysis. Baseline tables for patients with and

without CVD were also stratified by lifetime CVD risk decile. Furthermore, the use of GLP-1 RAs and SGLT-2is was assessed according to geographical region and stratified according to history of CVD. Gain in the number of life-years free of (recurrent) CVD with optimal CVRM and addition of GLP-1 RA and SGLT-2i according to age was also evaluated. Lastly, the current ESC guidelines recommend considering a GLP-1 RA or SGLT-2i in patients with type 2 diabetes without established CVD but at high risk of CVD.[10] Therefore, we assessed the lifetime benefit of adding GLP-1 RA and SGLT-2i to current treatment in patients without CVD, using the overall HR from the meta-analyses (HR for GLP-1 RA of 0.86[4] and HR for SGLT-2i of 0.90[5]) for patients at high CVD risk.

Results

Study population

Baseline characteristics stratified according to history of CVD are shown in *Table 1*. The cohort comprised 2901 patients with CVD (31%) and 6515 patients without CVD (69%). Generally, compared with patients without CVD, those with CVD were older, were more often male, had a longer duration of type 2 diabetes, and more often had microvascular complications of type 2 diabetes. Furthermore, patients with CVD more often used CV preventive medication and insulin.

Distribution of CVD risk

Distributions of 10-year and lifetime CVD risk stratified according to history of CVD are shown in *Figure 1*. There was a wide distribution of both 10-year and lifetime risk, with higher risk in patients with a history of CVD than in those without CVD. Two peaks were observed in patients with CVD; one at approximately 30% 10-year and 65% lifetime CVD risk, and one at approximately 95% 10-year and 98% lifetime CVD risk. Patients with T2D and a history of CVD with lower predicted risks were generally older, had lower risk factor levels and had higher frequency of preventive CV medication use. The majority of patients with type 2 diabetes and a history of CVD at very high predicted CVD risk belonged to a high-risk region. Among patients with a history of CVD, 96% had a 10-year risk of recurrent CVD over 10%, and 80% had a lifetime risk of recurrent CVD over 50%. In patients without a history of CVD, 14% had a 10-year risk of a first CV event over 10%, and only 0.4% had a lifetime risk of a first CV event over 50%.

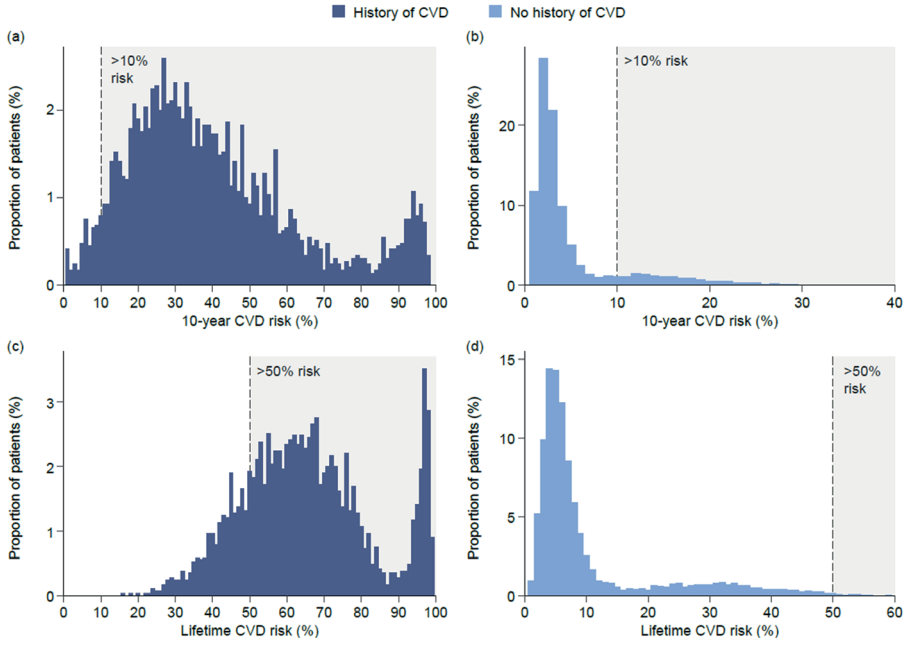
Table 1. Baseline characteristics of the CAPTURE study population included in this analysis (N = 9416)

Characteristic	History of CVD (n = 2901)	No history of CVD (n = 6515)
Demographics and medical history		
Age, years	67 ± 9	61 ± 11
Sex, men	1831 (63)	3303 (51)
Diabetes duration, years, median (IQR)	13 (7–20)	10 (5–16)
Smoking, current	428 (15)	888 (14)
Nephropathy	800 (28)	1081 (17)
Retinopathy	697 (24)	1028 (16)
Neuropathy	874 (30)	1243 (19)
Cardiovascular medication use		
Blood pressure-lowering medication	2240 (77)	3498 (54)
Lipid-lowering medication	1947 (67)	2845 (44)
Antiplatelet medication	1790 (62)	1309 (20)
Glucose-lowering agent use		
Metformin	2163 (75)	5208 (80)
Insulin	1323 (46)	2208 (34)
DPP-4i	802 (28)	2015 (31)
Sulfonylurea	642 (22)	1525 (23)
SGLT-2i	517 (18)	1062 (16)
GLP-1 RA	281 (10)	715 (11)
Clinical characteristics and laboratory values		
Systolic blood pressure, mmHg	132 ± 17	132 ± 15
Diastolic blood pressure, mmHg	76 ± 11	78 ± 10
Body mass index, kg/m^2	30 ± 6	30 ± 6
eGFR, mL/min/1.73 m^2, median (IQR)	76 (59–90)	84 (68–96)
Microalbuminuria	870 (30)	1432 (22)
Macroalbuminuria	237 (8)	370 (6)
HbA1c, mmol/mol	62 ± 17	60 ± 18
HbA1c, %, mean	7.8	7.6
Cholesterol, mmol/L	4.2 ± 1.2	4.6 ± 1.1
HDL-cholesterol, mmol/L	1.2 ± 0.3	1.2 ± 0.3
LDL-cholesterol, mmol/L	2.3 ± 0.9	2.6 ± 0.9
Non-HDL-cholesterol, mmol/L	2.4 ± 1.0	2.6 ± 1.2
Predicted risks		
Mean 10-year risk of CVD, %	40.1	4.9
Mean lifetime risk of CVD, %	65.0	10.2

Data are presented as n (%) or mean ± SD unless otherwise stated.

Abbreviations: CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Figure 1. Predicted 10-year CVD risk for patients (A) with CVD and (B) without CVD, and predicted lifetime CVD risk for patients (C) with CVD and (D) without CVD in the CAPTURE study



CVD, cardiovascular disease

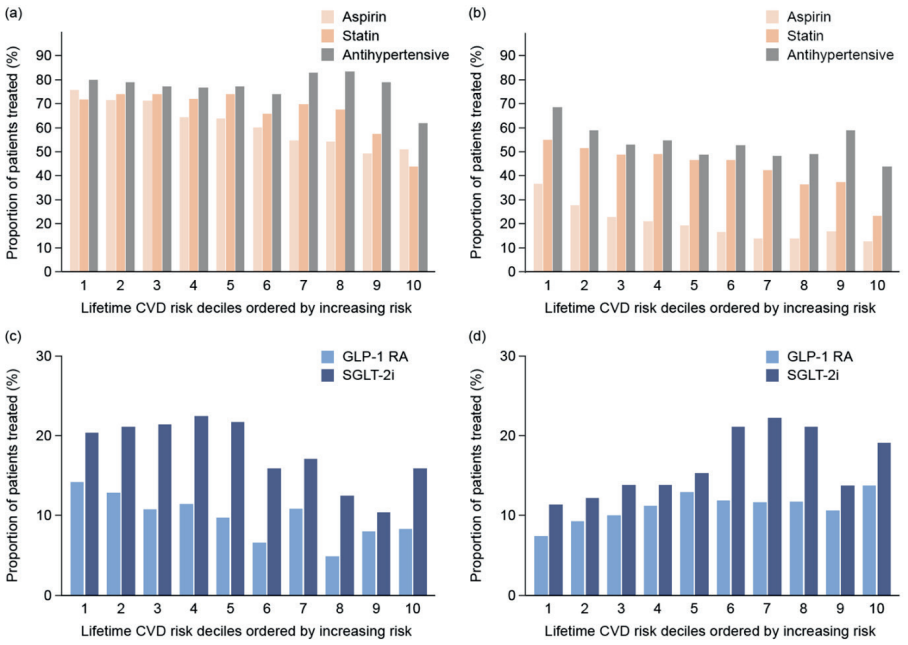
Distribution of preventive CVD treatment

Distribution of preventive medication use stratified by history of CVD and according to decile of predicted lifetime CVD risk is shown in *Figure 2*. Larger proportions of patients with CVD were using blood pressure-lowering medication, statins and aspirin than those of patients without CVD (*Figure 2A,B*). Among patients with and without CVD, those with a higher predicted lifetime CVD risk generally had lower statin and aspirin use. Patients with CVD and at higher predicted CVD risk had higher use of antihypertensive medication. GLP-1 RA use (10% in patients with CVD and 11% in patients without CVD) was lower than SGLT-2i use (18% in patients with CVD and 16% in patients without CVD). Overall, the proportion of patients with T2D using GLP-1 RA or SGLT-2i did not greatly differ between patients with and without a history of CVD (*Figure 2C,D*). In patients with a history of CVD, there was a trend for both GLP-1 RA and SGLT-2i use to be lower in individuals with a higher predicted CVD risk. In patients without CVD, no clear pattern according to risk decile was observed.

Distribution of lifetime benefit from preventive treatment

The distribution of the number of life-years gained without (recurrent) CVD with optimal CVRM and addition of GLP-1 RAs and SGLT-2is is shown in *Figure 3*. In patients with CVD, mean (SD) number of life-years gained without recurrent CVD was 0.9 (0.5) years (*Figure 3A*) with addition of GLP-1 RA and 0.6 (0.4) years with addition of SGLT-2i (*Figure 3B*). The lifetime benefit from optimal CVRM was higher in patients with CVD (overall mean [SD] lifetime benefit gained 3.9 [3.0] years) (*Figure 3C*) than in those without CVD (overall mean [SD] lifetime benefit gained 1.3 [1.9] years) (*Figure 3D*). In patients with CVD, higher predicted CVD risk was associated with greater lifetime benefit from optimal CVRM, except for in the highest lifetime CVD risk decile. In patients with CVD, addition of both GLP-1 RAs and SGLT-2is to optimal CVRM led to an overall mean (SD) gain in the number of life-years free of a (recurrent) CVD event of 1.2 (0.6) years, which increased with rising lifetime CVD risk.

Figure 2. Distribution of current preventive medication use according to predicted lifetime CVD risk stratified by history of CVD. CVRM in patients (A) with CVD and (B) without CVD. GLA treatment in patients (C) with CVD and (D) without CVD

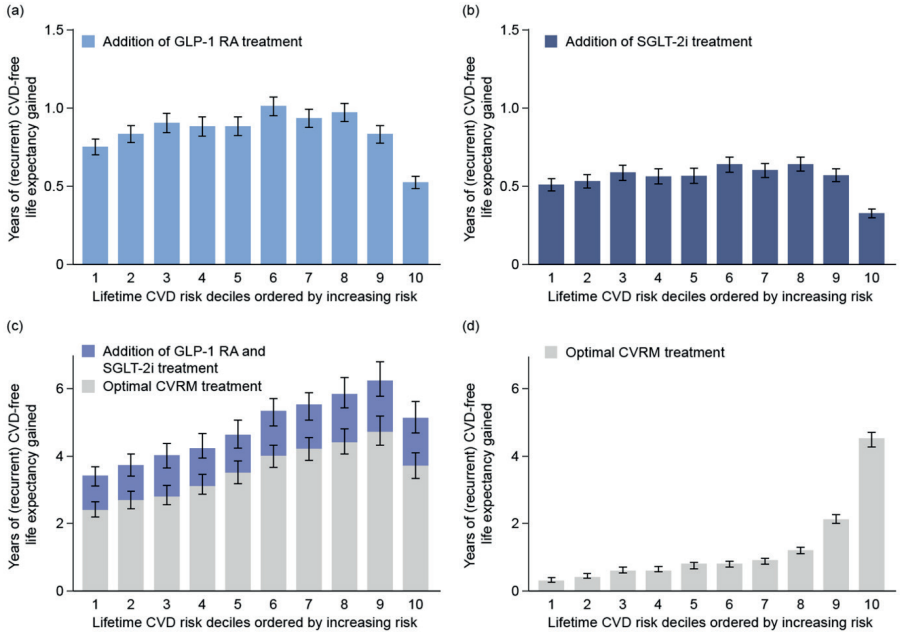


CVD, cardiovascular disease; CVRM, cardiovascular risk management; GLA, glucose-lowering agent; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium glucose co-transporter-2 inhibitor

Sensitivity analyses

When performing the analyses as a complete case analysis (n = 3532), the results did not change substantially (data not shown). Baseline tables stratified by history of CVD and lifetime CVD risk decile are shown in *Supplementary tables 5 and 6*. There was a wide distribution in the use of GLP-1 RA and SGLT-2i according to geographical region (*Supplementary figure 3*). Younger age at treatment initiation was associated with a larger gain in number of life-years free of (recurrent) CVD with optimal treatment and further addition of GLP-1 RA and SGLT-2i (*Supplementary figure 4*). Lastly, when assessing lifetime benefit of adding GLP-1 RA and SGLT-2i to current treatment in patients without CVD but at high CVD risk, a higher predicted CVD risk was associated with more benefit from treatment (*Supplementary figure 5*).

Figure 3. Distribution of the number of predicted life-years gained without (recurrent) CVD with the addition of (A) GLP-1 RA and (B) SGLT-2i treatment in patients with CVD, and with optimal CVRM, in patients (A, B, C) with CVD and (D) without CVD



Optimal CVRM includes smoking cessation (if the patient was a smoker), reaching specified target goals for LDL-cholesterol level, HbA1c level and systolic blood pressure, and initiation of aspirin treatment if appropriate. Panel C also shows the number of predicted life-years gained without (recurrent) CVD with the addition of SGLT-2is and GLP-1 RAs to CVRM. Error bars represent 95% confidence intervals. CVD, cardiovascular disease; CVRM, cardiovascular risk management; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Discussion

This post hoc analysis of the CAPTURE data showed a wide distribution of predicted CVD risk in patients with and without a history of CVD. The use of preventive medication varied across lifetime CVD risk deciles. Antihypertensive medication, statins and aspirin use was much more common in patients with CVD; however, no clear difference in GLP-1 RA and SGLT-2i use was seen between patients with and without CVD. When adding GLP-1 RA and SGLT-2i to current treatment, a wide distribution of gain in number of life-years without a (recurrent) CVD event was observed. The benefit of adding these GLAs to optimal CVRM was considerably smaller. Higher lifetime benefits of preventive treatment were seen in patients with type 2 diabetes with a higher predicted CVD risk, and younger patients had a higher lifetime benefit from preventive treatment.

Use of prediction models in the field of CV medicine is increasing.[24] Well-performing models allow individualized predictions and tailored risk management based on a series of easily obtainable clinical values and patient characteristics. Translating CVD risk into lifetime CVD risk and life-years free of CVD with and without initiation of specific treatments is clear and relatable for patients, and may promote shared decision-making. Patients with type 2 diabetes are often the primary managers of their condition, and such discussion may aid adherence to treatment or lifestyle changes, provided that the treating physician tailors communication to the individual.

Several CVD prediction models have been developed for patients with type 2 diabetes;[25, 26] however, we chose the DIAL model because it is contemporary and also allows assessment of absolute risk reduction and gain in life-years without (recurrent) CVD with preventive treatment. Furthermore, the model accounts for non-CV mortality as a competing risk and allows for longer prediction time spans (including lifetime predictions). The model was derived and externally validated in large, contemporary population-based type 2 diabetes cohorts from various regions, making it applicable to general type 2 diabetes populations in routine clinical settings in various countries and regions.

We observed two peaks in the distribution of predicted risk of recurrent CVD in patients with CVD. Patients with type 2 diabetes and a history of CVD with lower predicted risks were generally older, and thus possibly causing a healthy

survivor effect. Furthermore, as would be expected, risk factor levels were lower and there was a higher frequency of preventive CV medication use in these patients. The second peak could be attributed to the fact that the majority of patients with type 2 diabetes and a history of CVD at very high predicted CVD risk belonged to a high-risk region, as was seen in the predicted risk stratified baseline table.

Prescriptions of aspirin and statins appeared to be less frequent in patients with increasing predicted lifetime risk of CVD. These patients at highest risk of CVD are likely to be poorly treated in terms of CVRM, and therefore have higher CVD risk. GLP-1 RA and SGLT-2i provide significant CVD risk reduction independent of glucose lowering. Meta-analyses in patients with type 2 diabetes and a history of CVD have found a 15% lower risk of major CVD outcomes with a GLP-1 RA[4] and a 11% lower risk with an SGLT-2i,[5] compared with placebo. In the present study, there was a trend for patients with CVD at higher predicted CVD risk to have a lower frequency of both GLP-1 RA and SGLT-2i use. Only a small proportion of patients with CVD in the CAPTURE cohort used these therapies, and no substantial difference was seen between patients with and without CVD; even though these GLAs are recommended for patients with CVD in current guidelines.[10, 11] The present study did not consider other reasons contributing to the low GLP-1 RA and SGLT-2i use, including lack of reimbursement from healthcare providers or contraindications in high-risk patients. Furthermore, the CAPTURE data were collected in 2019, and rates of GLP-1 RA and SGLT-2i use may have changed since then. We applied the CV treatment effects of GLP-1 RA and SGLT-2i only to patients with established CVD, because a significant effect was observed only in this patient group in the meta-analyses.[4, 5] It should be acknowledged that these preventive GLAs will likely also be effective in patients with CVD risk factors only, rather than established CVD, and interaction with established CVD in the meta-analyses was non-significant for both GLP-1 RA and SGLT-2i.[4, 5] Current guidelines recommend considering GLP-1 RA and SGLT-2i in patients with type 2 diabetes without established CVD but at high risk of CVD;[10] however, because there is still limited evidence that this effect is significant in patients with CVD risk factors only, we chose not to incorporate this in our main analyses.

CVRM remains the primary focus in reducing CVD risk in patients with type 2 diabetes, including smoking cessation, lowering of lipid levels, blood pressure

and blood glucose concentrations, aspirin use and lifestyle interventions;[11] however, the level of evidence for efficacy of these interventions differs. Optimal CVRM is difficult to achieve in a large percentage of patients with type 2 diabetes,[27] and these patients will benefit from GLP-1 RA or SGLT-2i in terms of years gained free of (recurrent) CVD. In the present study, we combined HRs for several preventive treatments according to best available current evidence, to show the absolute benefit an individual patient may gain from treatment, both with optimal CVRM and with the addition of GLP-1 RA and SGLT-2i. We observed a wide distribution of the gain in (recurrent) CVD-free life expectancy. Patients with established CVD at higher CVD risk gained more life-years free of (recurrent) CVD, except for those in the highest decile, most likely owing to lower overall life expectancy in this group of patients and lower lifelong benefit from treatment. We previously used the DIAL model to demonstrate the benefit of adding semaglutide treatment for high-risk patients, which also showed a wide distribution in the number of life-years gained without (recurrent) CVD and a greater gain in patients with type 2 diabetes at higher CVD risk.[28] Furthermore, this approach has been used in other populations, including apparently healthy people[29] and patients with vascular disease.[30] By using an external cohort of patients with type 2 diabetes spanning various regions and including preventive treatment, we have expanded on these previous studies.

The cohort with type 2 diabetes included patients from various regions, making our results applicable worldwide. However, the original CAPTURE study involved a selected population, with inclusion of patients from both specialist care and general practice, which might not represent the general type 2 diabetes population in each specific country; the use of preventive medication is likely to be higher than that in the general population with type 2 diabetes. This may also lead to a degree of selection bias, and participants in the CAPTURE study may have been at higher CVD risk than the general population of patients with type 2 diabetes. Furthermore, owing to the functionality of the DIAL model, the geographical regions were based solely on country location and did not represent inter-regional differences in healthcare systems. Also, since the DIAL model only allows for prediction of CVD as the outcome, no assessment could be performed regarding risk of chronic kidney disease and hospitalization for heart failure, which are also highly relevant outcomes in people with type 2 diabetes. With the data on people with type 2 diabetes

currently available, it is not feasible to validate the DIAL model for longer than 10-year time span predictions, because this would require a cohort with a lifetime follow-up. The DIAL model has shown reasonable discrimination and calibration for 10-year risk of cardiovascular disease in different populations;[21, 28] however, as data on populations with type 2 diabetes accrues, the model will benefit from longer time span validations. Substantial amounts of data were missing for some predictors, which might have affected the results; however, imputation was used to reduce the risk of bias and a complete case analysis was also performed, which did not alter the results substantially. Furthermore, because data were collected cross-sectionally and no follow-up was available, we were unable to geographically recalibrate the model to the current cohort. Recalibration according to the geographical regions from the original DIAL model was therefore used. HRs of preventive treatment are constant, so patients were assumed to experience the same clinical benefit for the remainder of their life expectancy.

Conclusions

We found a wide distribution of lifetime CVD risk in patients with type 2 diabetes from the CAPTURE study. There was also a wide distribution in benefit from preventive treatment, in terms of both optimal CVRM and the addition of GLP-1 RA and SGLT-2i. Translating CVD risk into lifetime risk and expressing the benefit of preventive treatment as gain in (recurrent) CVD-free life expectancy aids in individualizing prevention in patients with type 2 diabetes and shared decision-making in the clinical setting.

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843.
2. 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;375:2215–2222.
3. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol 2018;17:83.
4. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653–662.
5. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–158.
6. Minze MG, Will KJ, Terrell BT, Black RL, Irons BK. Benefits of SGLT2 inhibitors beyond glycemic control - a focus on metabolic, cardiovascular and renal outcomes. Curr Diabetes Rev 2018;14:509–517.
7. Vergès B, Bonnard C, Renard E. Beyond glucose lowering: glucagon-like peptide-1 receptor agonists, body weight and the cardiovascular system. Diabetes Metab 2011;37:477–488.
8. Sattar N, McMurray JJ, Cheng AY. Cardiorenal risk reduction guidance in diabetes: can we reach consensus? Lancet Diabetes Endocrinol 2020;8:357–360.
9. Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL, Jr, Kalyani RR, Kosiborod M, Magwire M, Morris PB, Neumiller JJ, Sperling LS. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020;76:1117–1145.
10. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–3337.
11. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes – 2021. Diabetes Care 2021;44:S125–S150.
12. Nargesi AA, Jeyashanmugaraja GP, Desai N, Lipska K, Krumholz H, Khera R. Contemporary National Patterns of Eligibility and Use of Novel Cardioprotective Antihyperglycemic Agents in Type 2 Diabetes Mellitus. J Am Heart Assoc 2021;10:e021084.

13. Mosenzon O, Alguwaihes A, Leon JLA, Bayram F, Darmon P, Davis TME, Dieuzeide G, Eriksen KT, Hong T, Kaltoft MS, Lengyel C, Rhee NA, Russo GT, Shirabe S, Urbancova K, Vencio S. CAPTURE: a multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries. Cardiovasc Diabetol 2021;20:154.
14. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, 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;376:1670–1681.
15. 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;371:117–125.
16. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298.
17. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967.
18. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615.
19. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–1860.
20. Mons U, Müezzinler A, Gellert C, Schöttker 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. 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.
21. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, Wild SH, Franzen S, Chalmers J, Davis BR, Poulter NR, Spijkerman AM, Woodward M, Pressel SL, Gupta AK, van der Schouw YT, Svensson AM, van der Graaf Y, Read SH, Eliasson B, Dorresteijn JAN. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. Eur Heart J 2019;40:2899–2906.
22. Dorresteijn JA, Kaasenbrood L, Cook NR, van Kruijsdijk RC, van der Graaf Y, Visseren FL, Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj 2016;352:i1548.
23. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31–39.

24. Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, Cobain M, Piepoli MF, Visseren FL, Dendale P, Terra SG. Risk prediction tools in cardiovascular disease prevention: a report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). Eur J Prev Cardiol 2019;26:1534–1544.
25. 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;101:671–679.
26. D'Agostino RBS, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–753.
27. Wang L, Li X, Wang Z, Bancks MP, Carnethon MR, Greenland P, Feng YQ, Wang H, Zhong VW. Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999-2018. JAMA 2021;326:1–13.
28. Westerink J, Matthiessen KS, Nuhoho S, Fainberg U, Lyng Wolden M, Østergaard HB, Visseren F, Sattar N. Estimated Life-Years Gained Free of New or Recurrent Major Cardiovascular Events With the Addition of Semaglutide to Standard of Care in People With Type 2 Diabetes and High Cardiovascular Risk. Diabetes Care 2022;45:1211-1218.
29. Jaspers NEM, Blaha MJ, Matsushita K, van der Schouw YT, Wareham NJ, Khaw KT, Geisel MH, Lehmann N, Erbel R, Jöckel KH, van der Graaf Y, Verschuren WMM, Boer JMA, Nambi V, Visseren FLJ, Dorresteijn JAN. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Eur Heart J 2020;41:1190–1199.
30. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB, Sr, Massaro JM, van der Graaf Y, Cramer MJM, Kappelle LJ, de Borst GJ, Steg PG, Visseren FLJ. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: the SMART-REACH model. J Am Heart Assoc 2018;7:e009217.

Supplementary material

Supplementary table 1. Baseline table for non-imputed data with the number of missing values per variable (*N* = 9416)

Characteristic	History of CVD (*n* = 2901)	No history of CVD (*n* = 6515)	Missing values, *n* (%)[a]
Demographics and medical history			
Age, years	67 ± 9	61 ± 11	0
Sex, men	1831 (63)	3303 (51)	0
Diabetes duration, years, median (IQR)	13 (7–20)	10 (5–16)	11 (0.1)
Smoking, current	424 (15)	876 (14)	97 (1)
Nephropathy	797 (28)	1080 (17)	5 (<0.1)
Retinopathy	696 (24)	1028 (16)	5 (<0.1)
Neuropathy	872 (30)	1242 (19)	6 (<0.1)
Cardiovascular medication use			
Blood-pressure-lowering medication	2240 (77)	3498 (54)	0
Lipid-lowering medication	1947 (67)	2845 (44)	0
Antiplatelet medication	1790 (62)	1309 (20)	0
Glucose-lowering-agent use			
Metformin	2163 (75)	5208 (80)	0
Insulin	1323 (46)	2208 (34)	0
DPP-4i	802 (28)	2015 (31)	0
Sulfonylurea	642 (22)	1525 (23)	0
SGLT-2i	517 (18)	1062 (16)	0
GLP-1 RA	281 (10)	715 (11)	0
Clinical characteristics and laboratory values			
Systolic blood pressure, mmHg	132 ± 17	132 ± 16	199 (2)
Diastolic blood pressure, mmHg	76 ± 11	78 ± 10	201 (2)
Body mass index, kg/m^2	30 ± 6	30 ± 6	204 (2)
eGFR, mL min^{-1} [1.73 m]$^{-2}$, median (IQR)	75 (59–90)	84 (68–95)	1834 (19)
Microalbuminuria	612 (31)	917 (22)	3205 (34)
Macroalbuminuria	175 (9)	266 (6)	3205 (34)
HbA_{1c}, mmol/mol	61 ± 17	60 ± 18	672 (7)
HbA_{1c}, %, mean	7.7	7.6	–
Total cholesterol, mmol/L	4.2 ± 1.2	4.6 ± 1.2	1473 (16)
HDL-cholesterol, mmol/L	1.2 ± 0.3	1.2 ± 0.4	1772 (19)
LDL-cholesterol, mmol/L	2.3 ± 0.9	2.6 ± 0.9	1644 (17)
Non-HDL-cholesterol, mmol/L	2.4 ± 1.1	2.6 ± 1.3	2044 (22)

[a]*From the total of 9416 patients.*

Data are presented as n (%) or mean ± SD unless otherwise stated.

CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Supplementary table 2. Classification of patients with type 2 diabetes in CAPTURE according to 2021 ESC guidelines

CVD risk group	Definition in CAPTURE study population	*n* (%)
Very high risk	Type 2 diabetes with: • ASCVD and/or • Severe target organ damage defined as either: o eGFR <45 mL min^{-1} [1.73 m]$^{-2}$ o eGFR 45–59 mL min^{-1} [1.73 m]$^{-2}$ and albuminuria A2 (uACR 30–299 mg/g) o Albuminuria A3 (uACR ≥300 mg/g) o Microalbuminuria and retinopathy and neuropathy	3820 (41%)
High risk	Type 2 diabetes with: • No ASCVD and • No severe target organ damage and • Not fulfilling moderate risk criteria	5424 (58%)
Moderate risk	Type 2 diabetes with all of the following: • Type 2 diabetes duration <10 years and • Well controlled type 2 diabetes: o HbA_{1c} <53 mmol/mol (7%) • No evidence of TOD: o No neuropathy o No retinopathy o No albuminuria and eGFR >60 mL min^{-1} [1.73 m]$^{-2}$ • No additional ASCVD risk factors: o Systolic blood pressure <140 mmHg o LDL-cholesterol ≤2.6 mmol/L o Body mass index ≤30 kg/m^2 o Non-smoker	172 (2%)

Derived from Visseren et al.[1]

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HbA_{1c}, glycated haemoglobin; LDL, low-density lipoprotein; TOD, target organ damage; uACR, urine albumin–creatinine ratio.

Supplementary table 3. Treatment targets according to CVD risk group derived from the 2021 ESC guidelines

	Very high risk	High risk	Moderate risk
SGLT-2i	Yes	No	No
GLP-1 RA	Yes	No	No
Aspirin	Yes	No	No
Systolic blood pressure			
Step 1	140 mmHg	140 mmHg	No further reduction
Step 2	130 mmHg	130 mmHg	No further reduction
HbA_{1c}, mmol/mol	64	53	No further reduction
HbA_{1c}, %	8	7	–
LDL-cholesterol			
Step 1	1.8 mmol/L	2.6 mmol/L	No further reduction
Step 2	1.4 mmol/L	1.8 mmol/L	No further reduction
Smoking cessation	Yes	Yes	Already non-smoker

Derived from Visseren et al.[1]

CVD, cardiovascular disease; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; LDL, low-density lipoprotein; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Supplementary table 4. Treatment effects used for calculating lifetime benefit from optimal treatment

Treatment	Hazard ratio of treatment	
	Patients with history of CVD	Patients without history of CVD
Lipid-lowering treatment		
1 mmol/L LDL-cholesterol reduction	0.78[2]	0.78[2]
Blood-pressure-lowering treatment		
10 mmHg SBP reduction	0.80[3]	0.80[3]
Glucose-lowering treatment		
10 mmol/mol HbA_{1c} reduction	0.91[4]	0.91[4]
Aspirin or equivalent	0.81[5]	0.88[5]
Smoking cessation		
CVD outcome	0.60[6]	0.60[6]
Non-CVD mortality outcome	0.73[7]	0.73[7]
SGLT-2i	0.89[8]	1.00[8]
GLP-1 RA	0.85[9]	1.00[9]

CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; LDL, low-density lipoprotein; SBP, systolic blood pressure; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Supplementary table 5. Baseline table stratified by decile of predicted lifetime CVD risk in patients with CVD

	Lifetime CVD risk decile									
	1 (*n* = 291)	**2 (*n* = 290)**	**3 (*n* = 290)**	**4 (*n* = 290)**	**5 (*n* = 291)**	**6 (*n* = 291)**	**7 (*n* = 288)**	**8 (*n* = 290)**	**9 (*n* = 290)**	**10 (*n* = 290)**
Demographics and medical history										
Age, years	72 ± 10	68 ± 10	68 ± 10	68 ± 9	67 ± 9	65 ± 9	65 ± 9	65 ± 8	65 ± 10	63 ± 8
Sex, men	93 (32)	147 (51)	183 (63)	193 (67)	198 (68)	222 (76)	216 (75)	211 (73)	193 (67)	175 (60)
High-risk region, yes	0	0	0	0	0	0	0	2 (0.7)	100 (34)	290 (100)
Diabetes duration, years, median (IQR)	9 (5–16)	10 (5–16)	10 (6–18)	12 (7–19)	14 (8–20)	14 (8–20)	15 (9–21)	19 (12–25)	167 (10–22)	13 (8–20)
Smoking, current	22 (8)	37 (13)	44 (15)	51 (18)	42 (14)	59 (20)	54 (19)	39 (13)	30 (10)	50 (17)
Nephropathy	32 (11)	41 (14)	44 (15)	72 (25)	63 (22)	92 (32)	102 (35)	129 (44)	133 (46)	92 (32)
Retinopathy	38 (13)	46 (16)	38 (13)	65 (22)	58 (20)	61 (21)	75 (26)	101 (35)	100 (34)	115 (40)
Neuropathy	51 (18)	82 (28)	68 (23)	80 (28)	79 (27)	87 (30)	86 (30)	93 (32)	107 (37)	141 (49)
Cardiovascular medication use										
Blood-pressure-lowering medication	233 (80)	229 (79)	224 (77)	223 (77)	225 (77)	216 (74)	239 (83)	242 (83)	229 (79)	180 (62)
Lipid-lowering medication	209 (72)	215 (74)	215 (74)	209 (72)	216 (74)	192 (66)	201 (70)	196 (68)	167 (58)	127 (44)
Antiplatelet medication	221 (76)	208 (72)	207 (71)	187 (64)	186 (64)	175 (60)	158 (55)	157 (54)	143 (49)	148 (51)
Glucose-lowering-agent use										
Metformin	236 (81)	232 (80)	224 (77)	222 (77)	227 (78)	211 (73)	208 (72)	204 (70)	191 (66)	208 (72)
Insulin	47 (16)	74 (26)	94 (32)	115 (40)	134 (46)	150 (52)	160 (56)	189 (65)	189 (65)	171 (59)
DPP-4i	69 (24)	72 (25)	80 (28)	90 (31)	82 (28)	86 (30)	81 (28)	75 (26)	89 (31)	78 (27)
Sulfonylurea	62 (21)	64 (22)	50 (17)	69 (24)	62 (21)	86 (30)	70 (24)	70 (24)	67 (23)	42 (14)
SGLT-2i	59 (20)	61 (21)	62 (21)	65 (22)	63 (22)	46 (16)	49 (17)	36 (12)	30 (10)	46 (16)
GLP-1 RA	41 (14)	37 (13)	31 (11)	33 (11)	28 (10)	19 (7)	31 (11)	14 (5)	23 (8)	24 (8)

Supplementary table 5. Continued

	Lifetime CVD risk decile									
	1 (*n* = 291)	**2 (*n* = 290)**	**3 (*n* = 290)**	**4 (*n* = 290)**	**5 (*n* = 291)**	**6 (*n* = 291)**	**7 (*n* = 288)**	**8 (*n* = 290)**	**9 (*n* = 290)**	**10 (*n* = 290)**
Clinical characteristics and laboratory values										
Systolic blood pressure, mmHg	131 ± 14	131 ± 15	131 ± 15	130 ± 15	134 ± 17	133 ± 16	133 ± 18	133 ± 19	136 ± 18	134 ± 18
Diastolic blood pressure, mmHg	75 ± 10	75 ± 10	75 ± 11	75 ± 10	75 ± 11	75 ± 11	76 ± 11	77 ± 11	77 ± 10	78 ± 11
Body mass index, kg/m^2	30 ± 5	30 ± 6	29 ± 5	29 ± 5	29 ± 6	29 ± 5	29 ± 6	29 ± 5	30 ± 6	31 ± 5
eGFR, mL min^{-1} [1.73 m]$^{-2}$, median (IQR)	90 (79–103)	90 (76–102)	85 (67–95)	82 (66–91)	78 (63–90)	73 (60–87)	69 (55–79)	60 (49–73)	60 (48–77)	72 (59–88)
Microalbuminuria	54 (19)	64 (22)	76 (26)	86 (30)	98 (34)	107 (37)	110 (38)	109 (38)	107 (37)	59 (20)
Macroalbuminuria	2 (0.7)	3 (1)	5 (2)	15 (5)	13 (4)	23 (8)	40 (14)	50 (17)	56 (19)	30 (10)
HbA_{1c}, mmol/mol	54 ± 13	57 ± 15	57 ± 14	58 ± 14	62 ± 17	63 ± 17	65 ± 16	68 ± 18	65 ± 18	66 ± 18
HbA_{1c}, %, mean	7.1	7.4	7.4	7.5	7.8	7.9	8.1	8.4	8.1	8.2
Total cholesterol, mmol/L	4.1 ± 1.0	4.1 ± 1.1	3.9 ± 1.1	4.0 ± 1.0	4.1 ± 1.2	4.1 ± 1.2	4.2 ± 1.0	4.3 ± 1.1	4.7 ± 1.4	4.7 ± 1.3
HDL-cholesterol, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.3
LDL-cholesterol, mmol/L	2.2 ± 0.9	2.2 ± 1.0	2.1 ± 0.9	2.1 ± 0.8	2.2 ± 0.9	2.2 ± 0.9	2.2 ± 0.8	2.3 ± 0.9	2.6 ± 1.1	2.7 ± 1.0
Non-HDL-cholesterol, mmol/L	2.2 ± 0.6	2.2 ± 0.7	2.2 ± 0.7	2.3 ± 0.8	2.3 ± 0.8	2.3 ± 0.9	2.4 ± 0.9	2.6 ± 1.0	2.9 ± 1.3	2.8 ± 1.4
Predicted risks										
Mean 10-year risk of CVD, %	22.3	25.3	29.1	31.6	34.4	35.3	38.5	44.5	58.0	82.5
Mean lifetime risk of CVD, %	37.2	47.0	52.7	57.3	61.8	66.0	70.3	75.6	86.1	97.1

Data are presented as n (%) or mean ± SD unless otherwise stated.

CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Supplementary table 6. Baseline table stratified by decile of predicted lifetime CVD risk in patients without CVD

	Lifetime CVD risk decile									
	1 (*n* = 654)	**2 (*n* = 651)**	**3 (*n* = 655)**	**4 (*n* = 648)**	**5 (*n* = 663)**	**6 (*n* = 642)**	**7 (*n* = 649)**	**8 (*n* = 650)**	**9 (*n* = 652)**	**10 (*n* = 651)**
Demographics and medical history										
Age, years	75 ± 7	67 ± 9	63 ± 10	61 ± 10	59 ± 10	58 ± 10	57 ± 9	56 ± 10	62 ± 10	56 ± 9
Sex, men	194 (30)	304 (47)	347 (53)	344 (53)	396 (60)	356 (55)	374 (58)	376 (58)	276 (42)	336 (52)
High-risk region, yes	0	0	0	0	0	0	0	20 (3)	514 (79)	651 (100)
Diabetes duration, years, median (IQR)	9 (5–15)	9 (4–16)	9 (5–15)	9 (4–15)	9 (5–16)	10 (5–17)	10 (6–16)	11 (7–19)	10 (5–16)	10 (5–15)
Smoking, current	40 (6)	71 (11)	102 (16)	81 (13)	101 (15)	82 (13)	87 (13)	102 (16)	82 (13)	140 (22)
Nephropathy	65 (10)	66 (10)	70 (11)	75 (12)	103 (16)	106 (17)	116 (18)	181 (28)	123 (19)	176 (27)
Retinopathy	68 (10)	78 (12)	77 (12)	73 (11)	98 (15)	102 (16)	99 (15)	138 (21)	128 (20)	167 (26)
Neuropathy	86 (13)	90 (14)	90 (14)	78 (12)	123 (19)	118 (18)	117 (18)	151 (23)	165 (25)	225 (35)
Cardiovascular medication use										
Blood-pressure-lowering medication	449 (69)	384 (59)	348 (53)	354 (55)	323 (49)	339 (53)	313 (48)	318 (49)	385 (59)	285 (44)
Lipid-lowering medication	359 (55)	335 (51)	319 (49)	318 (49)	309 (47)	299 (47)	275 (42)	236 (36)	243 (37)	152 (23)
Antiplatelet medication	239 (37)	181 (28)	149 (23)	136 (21)	127 (19)	106 (17)	89 (14)	90 (14)	110 (17)	82 (13)
Glucose-lowering agent use										
Metformin	500 (76)	527 (81)	533 (81)	532 (82)	552 (83)	532 (83)	517 (80)	483 (74)	523 (80)	509 (78)
Insulin	93 (14)	143 (22)	185 (28)	190 (29)	213 (32)	232 (36)	283 (44)	324 (50)	241 (37)	304 (47)
DPP-4i	212 (32)	224 (34)	212 (32)	210 (32)	193 (29)	225 (35)	204 (31)	185 (28)	177 (27)	173 (27)
Sulfonylurea	153 (23)	177 (27)	163 (25)	168 (26)	191 (29)	179 (28)	144 (22)	135 (21)	120 (18)	95 (15)
SGLT-2i	74 (11)	79 (12)	90 (14)	89 (14)	101 (15)	135 (21)	144 (22)	137 (21)	89 (14)	124 (19)
GLP-1 RA	48 (7)	60 (9)	65 (10)	72 (11)	85 (13)	76 (12)	75 (12)	76 (12)	69 (11)	89 (14)

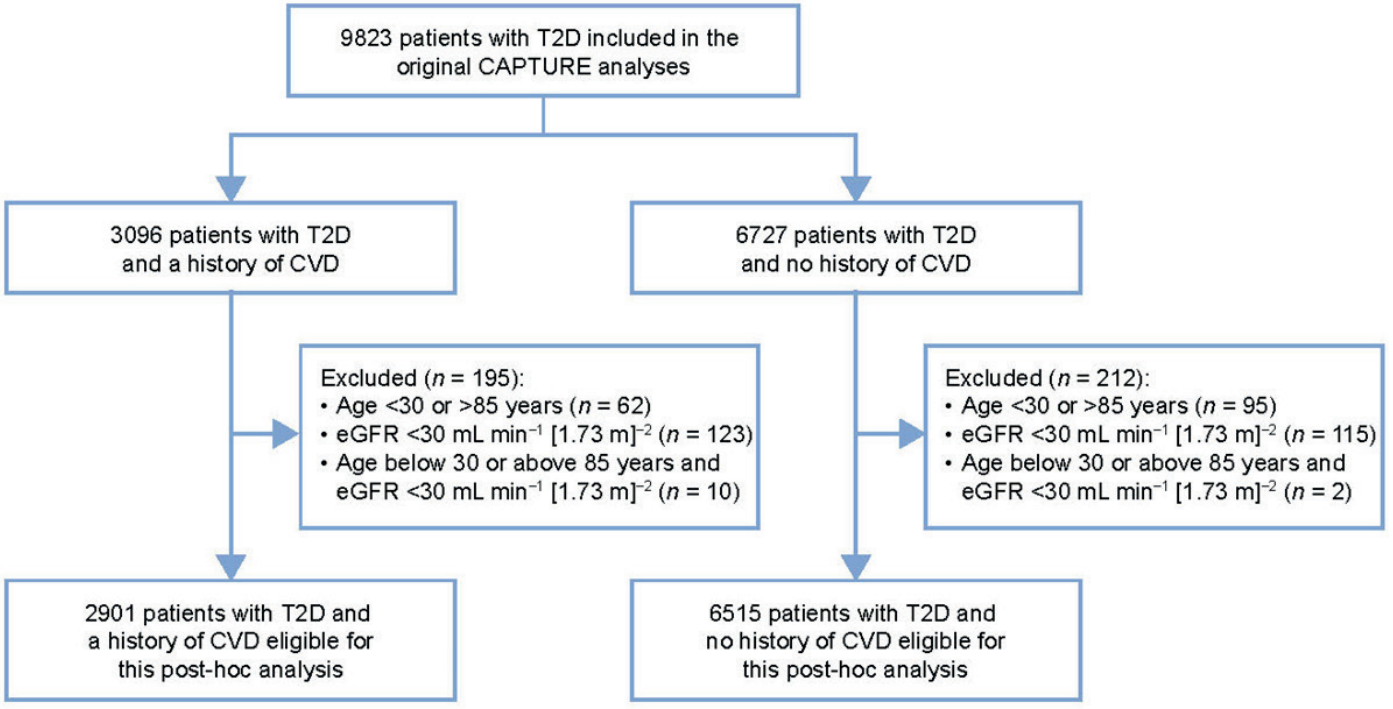
Supplementary table 6. Continued

	Lifetime CVD risk decile									
	1 (*n* = 654)	**2 (*n* = 651)**	**3 (*n* = 655)**	**4 (*n* = 648)**	**5 (*n* = 663)**	**6 (*n* = 642)**	**7 (*n* = 649)**	**8 (*n* = 650)**	**9 (*n* = 652)**	**10 (*n* = 651)**
Clinical characteristics and laboratory values										
Systolic blood pressure, mmHg	133 ± 15	131 ± 13	131 ± 15	132 ± 15	131 ± 15	130 ± 15	132 ± 16	134 ± 18	134 ± 16	132 ± 16
Diastolic blood pressure, mmHg	75 ± 9	77 ± 9	77 ± 10	77 ± 10	77 ± 9	78 ± 10	78 ± 10	79 ± 11	79 ± 10	79 ± 10
Body mass index, kg/m^2	30 ± 6	30 ± 6	30 ± 6	30 ± 6	29 ± 6	30 ± 6	29 ± 6	29 ± 6	31 ± 6	32 ± 6
eGFR, mL min^{-1} [1.73 m]$^{-2}$, median (IQR)	86 (71–97)	89 (73–104)	90 (75–107)	89 (71–102)	88 (72–100)	86 (69–95)	79 (65–90)	70 (57–81)	82 (62–95)	84 (67–92)
Microalbuminuria	86 (13)	120 (18)	115 (18)	132 (20)	164 (25)	164 (26)	168 (26)	218 (34)	118 (18)	147 (23)
Macroalbuminuria	17 (3)	13 (2)	16 (2)	18 (3)	28 (4)	36 (6)	44 (7)	79 (12)	61 (9)	58 (9)
HbA_{1c}, mmol/mol	53 ± 12	54 ± 13	56 ± 15	58 ± 15	60 ± 16	62 ± 17	66 ± 17	67 ± 18	59 ± 19	64 ± 18
HbA_{1c}, %, mean	7.0	7.1	7.3	7.5	7.6	7.8	8.2	8.3	7.5	8.0
Total cholesterol, mmol/L	4.3 ± 1.0	4.4 ± 1.0	4.4 ± 1.0	4.4 ± 1.1	4.5 ± 1.0	4.6 ± 1.1	4.7 ± 1.1	4.9 ± 1.2	4.9 ± 1.3	5.2 ± 1.3
HDL-cholesterol, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.3
LDL-cholesterol, mmol/L	2.4 ± 0.8	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.6 ± 0.9	2.6 ± 0.9	2.8 ± 1.0	2.9 ± 1.0	3.1 ± 1.0
Non-HDL-cholesterol, mmol/L	2.2 ± 0.7	2.2 ± 0.8	2.3 ± 0.8	2.3 ± 0.9	2.4 ± 0.8	2.6 ± 1.0	2.7 ± 1.0	3.1 ± 1.2	2.6 ± 1.2	3.5 ± 1.6
Predicted risks										
Mean 10-year risk of CVD, %	1.7	2.1	2.2	2.4	2.6	2.8	3.2	4.20	10.8	16.8
Mean lifetime risk of CVD, %	2.3	3.4	4.1	4.8	5.5	6.4	7.5	9.60	20.7	37.7

Data are presented as n (%) or mean ± SD unless otherwise stated.

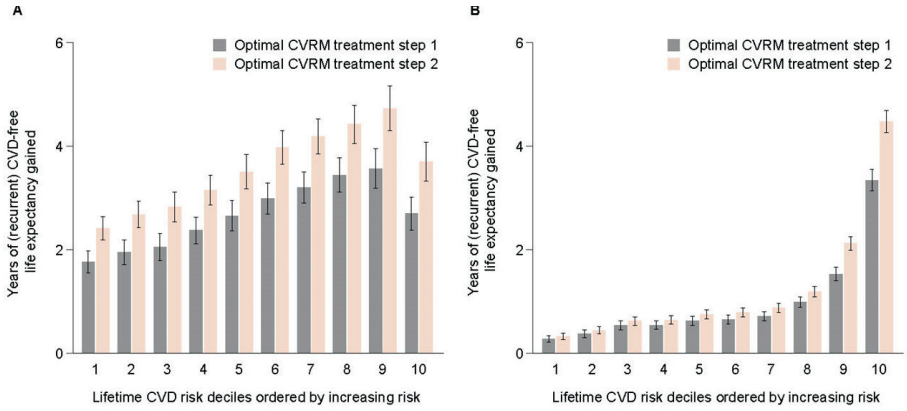
CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Supplementary figure 1. Cohort selection for patients with type 2 diabetes eligible for this post-hoc analysis stratified for history of CVD



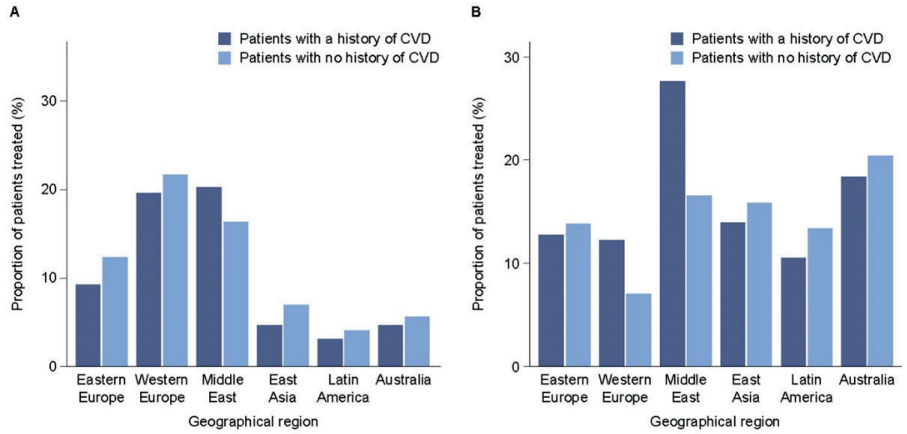
CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes.

Supplementary figure 2. Life-years free of (recurrent) CVD with optimal CVRM according to step 1 and step 2 of treatment targets in patients (*A*) with a history of CVD and (*B*) with no history of CVD



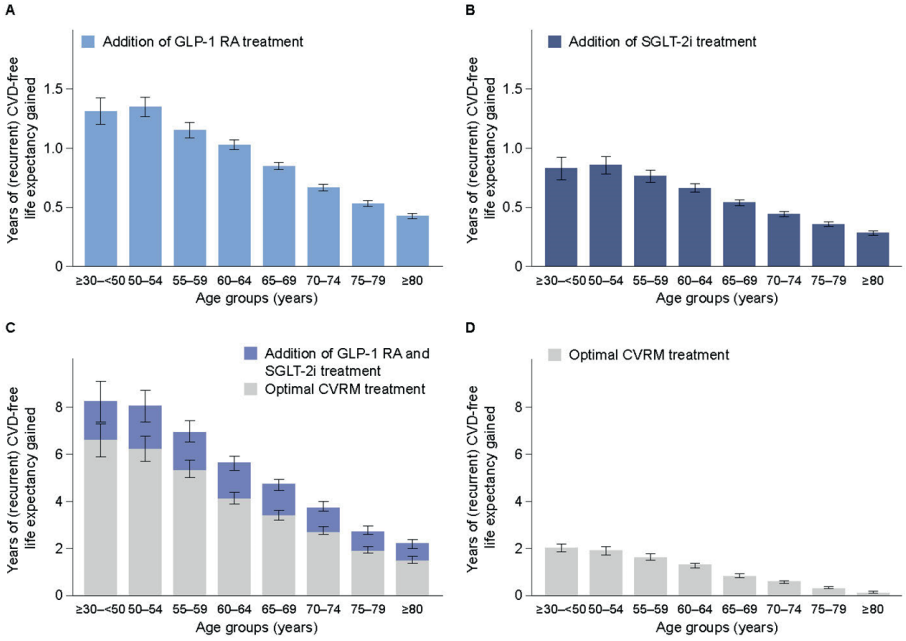
CVD, cardiovascular disease; CVRM, cardiovascular risk management.

Supplementary figure 3. Distribution of preventive medication for (*A*) GLP-1 RA and (*B*) SGLT-2i and according to geographical region stratified according to history of CVD



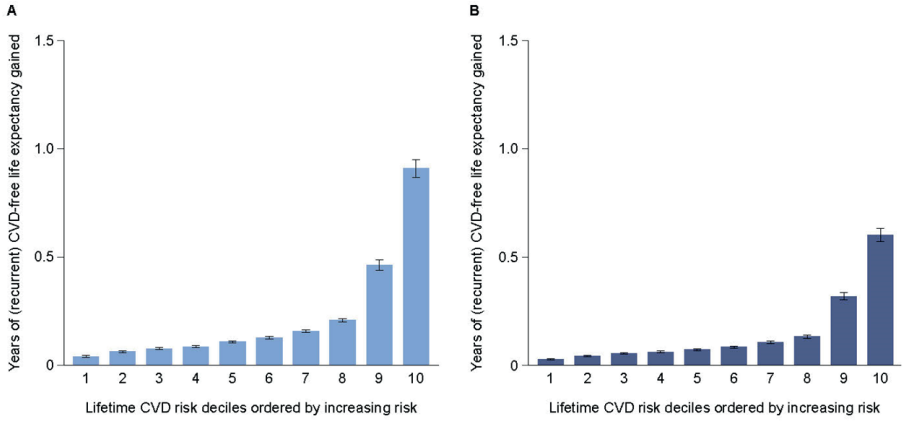
CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Supplementary figure 4. Distribution of predicted life-years gained without (recurrent) CVD with optimal CVRM treatment and addition of GLP-1 RA and SGLT-2i according to age at baseline in patients (*A, B, C*) with a history of CVD and (*D*) with no history of CVD



CVD, cardiovascular disease; CVRM, cardiovascular risk management; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

Supplementary figure 5. Distribution of predicted life-years gained without (recurrent) CVD with addition of (*A*) GLP-1 RA and (*B*) SGLT-2i



CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodiumglucose co-transporter-2 inhibitor.

References, supplementary material

1. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227–3337.
2. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, 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;376:1670–1681.
3. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957–967.
4. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288–2298.
5. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–1860.
6. Mons U, Müezzinler A, Gellert C, Schöttker 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. 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.
7. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Arch Intern Med* 2012;172:837–844.
8. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–158.
9. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653–662.

CHAPTER 6

Development and Validation of a Lifetime Risk Model for End-Stage Kidney Disease and Treatment Benefit in Type 2 Diabetes: 10-Year and Lifetime Risk Prediction Models

Helena Bleken Østergaard
Stephanie Read
Naveed Sattar
Stefan Franzén
Nynke Halbesma
Jannick AN Dorresteijn
Jan Westerink
Frank LJ Visseren
Sarah H. Wild*
Björn Eliasson*
Joep van der Leeuw*

*Contributed equally

Clin J Am Soc Nephrol. 2022;17(12):1783-1791.

Abstract

Background and objectives: Individuals with type 2 diabetes are at higher risk of developing end-stage kidney disease (ESKD). The objective of this study was to develop and validate a decision support tool for estimating 10-year and lifetime risk of ESKD in individuals with type 2 diabetes as well as estimating individual treatment effects of preventive medication.

Design, setting, participants, and measurements: The prediction algorithm was developed in 707,077 individuals with prevalent and incident type 2 diabetes from the Swedish National Diabetes Register for 2002-2019. Two Cox proportional regression functions for ESKD (first occurrence of either kidney transplantation, long-term dialysis or persistent estimated glomerular filtration rate <15 ml/min/1.73m^2) and all-cause mortality as respective endpoints were developed using routinely available predictors. These functions were combined into life-tables to calculate predicted survival without ESKD, while using all-cause mortality as competing outcome. The model was externally validated in 256,265 individuals with incident type 2 diabetes from the Scottish Care Information Diabetes database between 2004 and 2019.

Results: During a median follow-up of 6.8 years (IQR 3.2-10.6), 8,004 (1.1%) of individuals with type 2 diabetes in the Swedish National Diabetes Register cohort developed ESKD and 202,078 (29%) died. The model performed well with a c-statistic for ESKD of 0.89 (95%CI 0.88-0.90) for internal validation and 0.74 (95%CI 0.73-0.76) for external validation. Calibration plots showed good agreement in observed vs. predicted 10-year risk of ESKD for both internal and external validation.

Conclusions: This study derived and externally validated a prediction tool for estimating 10-year and lifetime risk of ESKD as well as life-years free of ESKD gained with preventive treatment in individuals with type 2 diabetes using easily available clinical predictors.

Introduction

Worldwide, the prevalence of type 2 diabetes is rapidly increasing.[1] Individuals with type 2 diabetes have three to five times higher risk of developing end-stage kidney disease (ESKD) compared with individuals without type 2 diabetes.[2] Treatment options to prevent or delay ESKD in individuals with type 2 diabetes include smoking cessation,[3] intensive glucose- and blood pressure (BP)-lowering,[4, 5] treatment with angiotensin-converting enzyme-inhibitors (ACEi) or Angiotensin-II Receptor Blockers (ARB),[6] sodium-glucose cotransporter-2 inhibitors (SGLT2i)[7] and glucagon-like peptide-1 receptor agonists (GLP1-RA).[7] The absolute benefit an individual may derive in terms of ESKD risk reduction from these treatments depends on several different factors including risk factor burden, duration of treatment and overall life expectancy.

Few prediction models exist for ESKD in individuals with type 2 diabetes.[8-11] These models have important limitations since they predict risk over a relatively short time period and often predict intermediate outcomes such as doubling of serum creatinine,[8] which might be less relatable to an individual than ESKD as a hard outcome. Notably, shared risk factors associated with ESKD also contribute to a high cardiovascular disease and mortality risk.[12] Therefore it is crucial to take all-cause mortality into account as a competing risk to avoid overestimation of ESKD risk, since most individuals with type 2 diabetes will die from other causes before developing ESKD. These gaps highlight the need to develop prediction models for long-term risk of ESKD in individuals with type 2 diabetes.

Therefore, the aim of the current study was to develop and validate a prediction model for risk of ESKD in large population-based cohorts of individuals with type 2 diabetes. Further, we aimed to predict life expectancy free of ESKD and include treatment effects of preventive therapy.

Methods

Data sources and participants

The prediction model was developed and internally validated in the Swedish National Diabetes Register (NDR) (n = 707,077), which includes individuals with both incident and prevalent type 2 diabetes. Participants in NDR were included from January 1st 2002 until 25th September 2019.

The model was externally validated in an extract of the Scottish Care Information (SCI)-Diabetes database (n = 256,265), which includes individuals with incident type 2 diabetes. Participants from SCI-Diabetes were included if their date of diagnosis of diabetes was between January 1st 2004 and January 1st 2019. Both registers have close to complete coverage of the population with a diagnosis of type 2 diabetes during the study period. Register details for both cohorts have been described elsewhere.[13, 14] All participants were aged >30 years at cohort entry with a diagnosis of type 2 diabetes (*Supplementary table 1*) without ESKD at baseline. All use of data from these registers received appropriate local data governance approvals and all studies complied with the Declaration of Helsinki.

Predictor and outcome variables

ESKD was defined as chronic kidney disease (CKD) stage 5 (sustained estimated glomerular filtration rate (eGFR) <15ml/min/1.73 m^2), long-term dialysis or kidney transplantation,[15] and all-cause mortality was defined as death from any cause. Linkage of the NDR and SCI-Diabetes to national death registrations and hospital admission/discharge registries enabled the identification of ESKD using ICD-10 and procedure codes (*Supplementary table 2*).

Predictors were pre-selected based on existing risk scores for ESKD[9-11] and their availability in clinical practice. Pre-selection of variables was applied to prevent overfitting.[16] The predictors included age, sex (male/female), current smoking (yes/no), systolic BP, body mass index (BMI), Hemoglobin A1c, eGFR,[17] non-high-density lipoprotein (HDL) cholesterol, albuminuria (none/moderate/severe), duration of type 2 diabetes (years since diagnosis), insulin treatment (yes/no) and history of cardiovascular disease (yes/no) (*Supplementary table 1*). Non-HDL-cholesterol was chosen as single marker to represent lipid profile.[18] Albuminuria was defined as a urine-albumin/creatinine ratio (UACR) of 3-30 mg/mmol for moderate albuminuria and UACR >30mg/mmol for severe albuminuria. An individual's baseline was set as the date of the first eGFR measurement following enrollment in NDR or diagnosis of diabetes in SCI-Diabetes and the values of other predictors were defined at the first measurement within 12 months after this date.

Statistical analyses

Baseline characteristics are described as median and interquartile range (IQR) for continuous variables and as count (%) for categorical variables.

Development of the prediction model

A split-sample approach was used for development and internal validation of the prediction model. A random sample of 75% of participants from NDR (n=530,308) was used as the development dataset. Missing data were imputed using single imputation with predictive mean matching. Details are described in the *Supplementary material, Predictors and missing data*.

In the derivation dataset, two Cox proportional hazards functions with left truncation and right censoring were developed using age as the time-axis: one for prediction of ESKD events (function A) and one for prediction of all-cause mortality (function B).

Baseline hazards for ESKD (function A) were derived using 1-year intervals (due to the low amount of ESKD events) and thereafter smoothed and interpolated to 3-month intervals. Baseline hazards for all-cause mortality (function B) were derived using 3-month intervals (*Supplementary figure 1)*.

By combining the coefficients from the Cox proportional hazards functions A and B and the smoothed baseline hazards, ESKD-free survival, 10-year and lifetime risk of ESKD and all-cause mortality were calculated using previously validated life-tables.[19] 10-year risk of ESKD was calculated by summation of the predicted ESKD and all-cause mortality risk, respectively, in the first 10 years and beyond from a person's age at cohort entry. Similarly, lifetime risk of ESKD was calculated by the summation of the predicted ESKD risk from an individual's age at cohort entry until the maximum age of 95 years. All analyses were performed with R-statistic programming (version4.0.3,R Foundation for Statistical Computing, Vienna,Austria). A detailed description of statistical methods is provided in the *Supplementary material, Statistical analyses*.

Model validation for 10-year predictions

Goodness-of-fit was assessed in the remaining 25% of NDR by calibration plots. Observed risks of ESKD were calculated using cumulative incidence functions with the competing event being all-cause mortality. For external validation in SCI-Diabetes, the models were recalibrated based upon the incidence of ESKD and all-cause mortality, using the expected vs. observed ratios. The logarithm of the expected vs. observed ratio was subtracted from the linear predictor for both outcomes. Discrimination was quantified using Harrell's c-statistic for

survival data.[20] Our approach to model development and validation complies with PROBAST guidelines[21] and TRIPOD.[22]

Prediction of treatment effects

To estimate the individual treatment benefit, the linear predictor for function A was combined with hazard ratios (HRs) from the most recent high quality meta-analyses describing effect sizes for each intervention. For the current study, we derived estimates of the effect of glucose-lowering, BP-lowering, GLP1-RA, SGLT2i, ACEi/ARB treatment and smoking cessation as described in the *Supplementary material, Relative treatment effects*. The HR of smoking cessation, BP-lowering and initiation of GLP1-RA or SGLT2i for all-cause mortality were added to the linear predictor for model B.[5, 23-25]

The lifetime benefit of treatment was calculated as the difference between predicted median ESKD-free life expectancy with and without treatment. Similarly, 10-year absolute risk reduction was estimated by calculating the difference between the predicted 10-year ESKD risk with and without treatment. This same approach was used for estimating lifetime ESKD risk reduction with initiation of treatment. All model assumptions are provided in *Supplementary table 9*.

Sensitivity analyses

To incorporate the natural decline of eGFR in the predictions of ESKD-risk several sensitivity analyses were performed to incorporate functions of eGFR over time, see *Supplementary materials, Sensitivity analyses*.

Results

Baseline characteristics

Selection of the development and the validation cohorts in NDR is illustrated in *Supplementary figure 2*. The NDR cohort consisted of 401,433(57%) men, median(IQR) age was 65(57-74) years and median(IQR) eGFR was 85(68-97) ml/min/1.73m^2 (*Table 1*). In SCI-Diabetes, 145,753(57%) were men, median(IQR) age was 61(52-70) years and median(IQR) eGFR was 83(68-96) ml/min/1.73m^2. In NDR, median(IQR) follow-up was 6.8(3.2-10.6) years with 8004 individuals(1.1%) developing incident ESKD and 202,078(29%) deaths. In SCI-Diabetes, median(IQR) follow-up was 5.9(2.6-9.6) years with 1653(0.7%) ESKD-events and 45,056(18%) deaths.

Table 1. Baseline characteristics of participants identified from the Swedish National Diabetes Register and Scottish Care Information - Diabetes cohort after imputation of missing data

	Swedish National Diabetes Register (n = 707,077)	Scottish Care information - Diabetes cohort (n = 256,265)
Sex (male)	401,433 (57%)	145,753 (57%)
Age (years)	65 (57-74)	61 (52-70)
Current smoking	110,630 (16%)	57,702 (23%)
Duration of diabetes mellitus (years)	2 (0-7)	0 (0-0)
Incident type 2 diabetes	229,635 (32%)	256,265 (100%)
Insulin treatment	133,661 (19%)	25,227 (10%)
History of cardiovascular disease	155,806 (22%)	43,012 (17%)
eGFR (mL/min/1.73m^2)	85 (68-97)	83 (68-96)
Moderate albuminuria	104,227 (15%)	49,536 (19%)
Severe albuminuria	43,454 (6%)	5,353 (2%)
Systolic blood pressure (mmHg)	138 (126-150)	135 (124-144)
Body mass index (kg/m^2)	29 (26-33)	31 (28-36)
HbA1c (%)	6.7 (6.2-7.6)	6.9 (6.3-7.9)
HbA1c (mmol/mol)	50 (44-60)	52 (45-63)
Non HDL cholesterol (mmol/L)	3.6 (2.9-4.4)	3.3 (2.6-4.2)
Prescribed RASi medication	299,559 (42%)	38,769 (15%)

Variables are displayed as median (IQR) for continuous variables and counts (%) for categorical variables. Abbreviations: eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, HDL = high-density-lipoprotein, RASi = Renin-angiotensin-system inhibition medication

Prediction model and validation

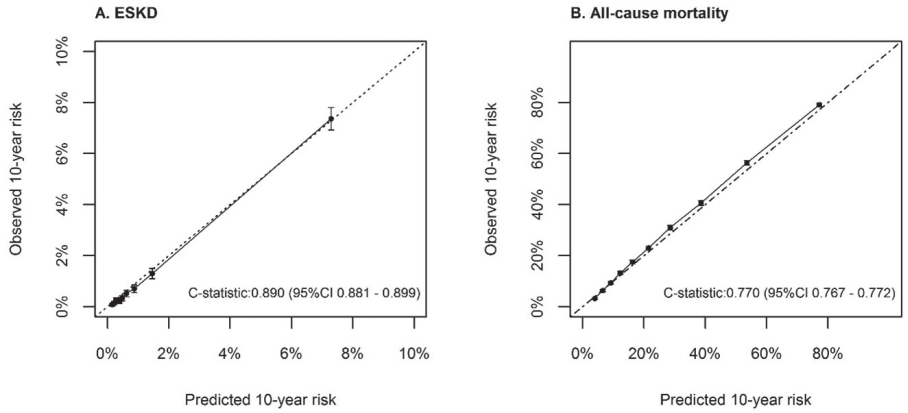
Supplementary table 3 shows the HRs and 95% confidence intervals (95%CI) for functions A and B. The formulae for calculating survival for 3-month intervals, including coefficients and age-specific baseline hazards are included in *Supplementary tables 4 and 5*.

Predicted 10-year risk for ESKD and all-cause mortality showed good agreement with the 10-year observed risk in the internal validation dataset (*Figure 1*). Internal model performance in terms of discrimination was good, reflected in c-statistics of 0.89(95%CI 0.88-0.90) for ESKD and 0.77(95%CI 0.77-0.77) for all-cause mortality.

Incidence rates for ESKD and all-cause mortality were higher in NDR than in SCI-Diabetes *(Table 2)*. Due to the difference in event rates, the model was recalibrated according to predicted vs. observed ESKD and all-cause mortality rates. Predicted 10-year risk for ESKD and all-cause mortality showed good

agreement with the 10-year observed risk in SCI-Diabetes (*Figure 2*), although risk in the highest decile was overestimated. The model performed well regarding discrimination with c-statistics of 0.74 (95% CI 0.73-0.76) for ESKD and 0.77 (95% CI 0.77-0.77) for all-cause mortality. A table of baseline characteristics stratified for incident versus prevalent type 2 diabetes in NDR is provided as *Supplementary table 6.* A baseline table for predictors stratified according to predicted ESKD risk is provided in *Supplementary table 7*.

Figure 1. Calibration plots for internal validation in a random sample of 25% from the Swedish National Diabetes Register (n = 170,114)



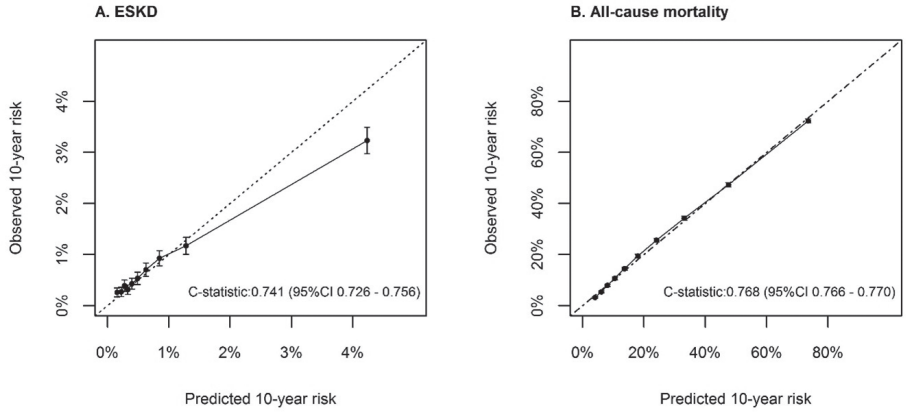
Calibration slope for end-stage kidney disease as outcome 1.02, slope for all-cause mortality as outcome 1.04. ESKD = end-stage kidney disease.

Table 2. Outcomes and results for the Swedish National Diabetes Register and the Scottish Care Information – Diabetes database

	Swedish National Diabetes Register (n = 707,077)	**Scottish Care information - Diabetes cohort (n = 256,265)**
Median follow-up (IQR) (years)	6.8 (3.2-10.6)	5.9 (2.6-9.6)
ESKD events (n, (%))	8004 (1.1%)	1653 (0.7%)
All-cause mortality events (n, (%))	202,078 (29%)	45,056 (18%)
Incidence rate, ESKD	1.6/1,000 person-years	1.0/1,000 person-years
Incidence rate, all-cause mortality	39.5/1,000 person-years	28.0/1,000 person-years
C-statistic for ESKD	0.89 (0.88-0.90)	0.74 (0.73-0.76)
C-statistic for all-cause mortality	0. 77 (0.77-0.77)	0.77 (0.77-0.77)

For individuals with incident type 2 diabetes in Swedish National Diabetes Register cohort (n = 229,635;32%), incidence rates were 0.7/1000 person-years for ESKD and 27/1000 person-years for all-cause mortality. ESKD = end-stage kidney disease; IQR = interquartile range.

Figure 2. Calibration plots for external validation in SCI-Diabetes cohort (n = 256,265)



Calibration slope for end-stage kidney disease as outcome 0.73, slope for all-cause mortality as outcome 0.99 after recalibration. ESKD = end-stage kidney disease.

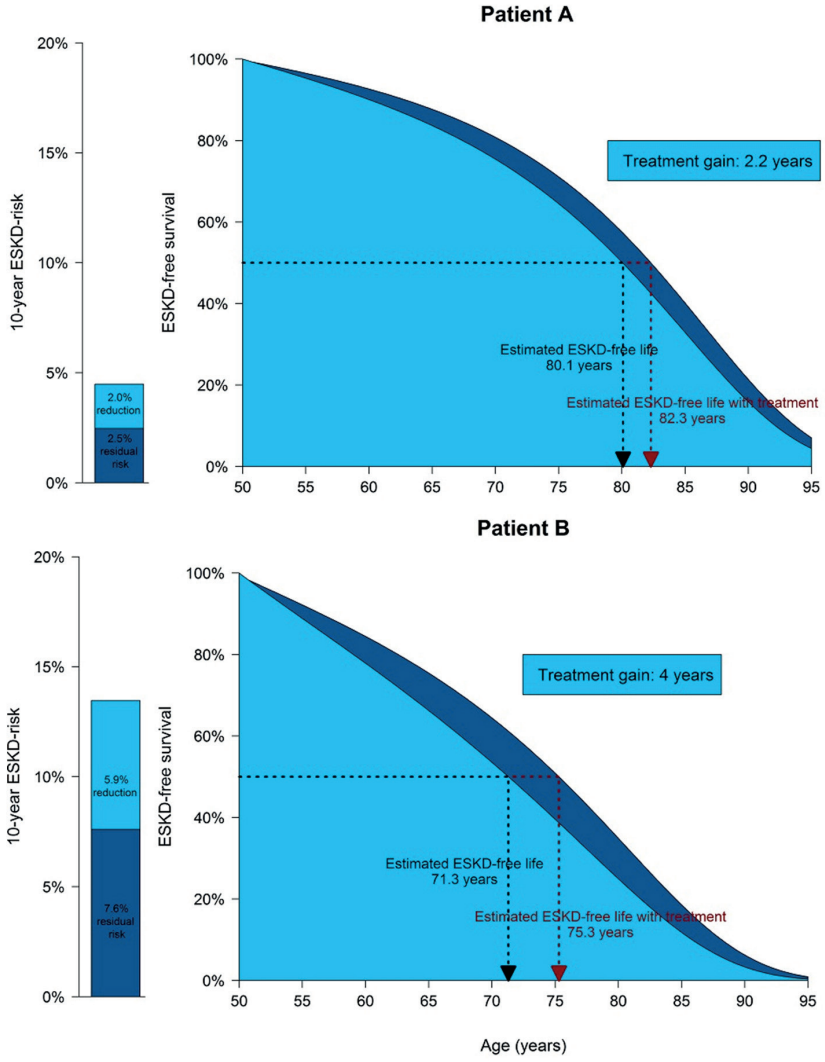
Individual lifetime estimation of risk and treatment effects

An interactive user-friendly calculator is provided as *supplementary file* and will be provided at www.U-Prevent.com. Individual effects from medication initiation can be modelled in terms of ESKD-free life years gained and absolute risk reduction. *Figure 3* illustrates ESKD-free life expectancy and 10-year ESKD risk for two individual examples with and without initiation of preventive medication.

Sensitivity analyses

When incorporating the natural decline of eGFR in the predictions of ESKD-risk, model performance did not improve for 10-year predictions (*Supplementary material, Sensitivity analyses*).

Figure 3. Example of 10-year ESKD risk, life-years free of ESKD and benefit from preventive treatment in two patient scenarios



Effect of initiation of RAS-inhibitor and SGLT2i on ESKD-free lifetime expectancy for two patient examples

Patient A; a 50-year old male, non-smoker, 5 years diabetes duration, no history of cardiovascular disease, no insulin use, systolic blood pressure 140 mmHg, BMI 33 kg/m2, eGFR 60 ml/min/1.73m2, moderate albuminuria, non HDL cholesterol 3.0 mmol/L, HbA1c 8.1% (65 mmol/mol).

Patient B; a 65-year old female, non-smoker, 2 years diabetes duration, history of cardiovascular disease, no insulin use, systolic blood pressure 150 mmHg, BMI 25 kg/m2, eGFR 50 ml/min/1.73m2, severe albuminuria, non HDL cholesterol 4.0 mmol/L, HbA1c 7.5% (58 mmol/mol).

Discussion

The current study describes the development and external validation of a prediction model for estimation of 10-year and lifetime risk of ESKD using data from almost one million individuals with type 2 diabetes. Furthermore, the model allows estimation of individual benefit of treatment with medication most often used for kidney protection in individuals with type 2 diabetes expressed as life-years gained free of ESKD with treatment initiation. The prediction tool is available as *Supplementary material* and will be provided as a calculator at www.U-Prevent.com to allow use in clinical practice.

Existing ESKD prediction models developed in individuals with type 2 diabetes are based on shorter prediction horizons of up to eight years.[9-11, 26-28] These shorter term predictions remain relevant for use in some patient groups, i.e. those already having advanced kidney damage, for intensifying follow-up and timing of kidney replacement therapy.[29] However, for patients with lower short-term risk, including younger patients, longer-term predictions will be valuable to support decisions about preventive treatment. All models failed to adjust for competing risks. This is critical to avoid overestimating predicted ESKD risks and treatment effects,[30] especially in older individuals and individuals at low risk for ESKD, who are likely to die before developing ESKD. Furthermore, only two previous ESKD risk prediction models in individuals with type 2 diabetes performed external validation. Elley et al. performed external validation for 5-year risk of ESKD in 5,877 individuals with type 2 diabetes arising from the same geographical region as the derivation cohort with a c-statistic of 0.89 and reasonable calibration.[11] Basu et al. performed external validation for 10-year risk of ESKD in 1,018 individuals with type 2 diabetes with a c-statistic for ESKD of 0.54 and did not perform calibration of this specific outcome.[27] In the current model, c-statistics dropped from 0.89 for internal validation to 0.74 for external validation. The lower discrimination ability in the external validation is likely due to the categorical definitions of albuminuria used rather than continuous data that may provide a better predictor, as well as the lower availability of albuminuria in the validation cohort (54% missing data). Also, diabetes duration is a relevant predictor in NDR (since this was a cohort with both prevalent and incident type 2 diabetes), however not in SCI-Diabetes (since this was a cohort with incident type 2 diabetes).

In the current study, the event rates for both ESKD and all-cause mortality in individuals with type 2 diabetes were higher in Sweden compared to Scotland. The difference in ESKD event rates is likely explained by the use of an incident cohort from SCI-Diabetes who were almost five years younger at cohort entry than the population of individuals with prevalent and incident diabetes identified from NDR, despite the potential for survival bias in the NDR cohort. More individuals in the NDR had severe albuminuria and a history of cardiovascular disease and the prevalence of treatment with insulin was higher. Moreover, the prevalence of RASi medication prescription was higher in NDR. This may be due to differences in antihypertensive treatment algorithms with a more prominent role for RASi treatment in Swedish guidelines as compared to Scottish guidelines.[31, 32] Furthermore, since SCI-Diabetes was a cohort with incident type 2 diabetes, prescription of RASi-medication is likely to have increased after diagnosis.[33] Future validation and recalibration of the model will be valuable as data on individuals with type 2 diabetes with sufficient follow-up accrue, also to account for differences in baseline risk due to changing patterns of medication use.

The current model is intended for use in clinical practice to assess ESKD risk in individuals with type 2 diabetes as well as likely benefits from preventive treatment. The model is underpinned by two very large and contemporary type 2 diabetes population-based cohorts with limited selection of participants. Large databases with extensive follow-up are important in order to ensure sufficient power with an adequate amount of ESKD events, since the incidence of ESKD is relatively low as compared with cardiovascular outcomes and mortality in these populations. In external validation of the current model, a slight overestimation of ESKD risk for patients at highest risk of ESKD was observed, which could indicate a modest degree of overfitting in the highest risk group. However, in clinical practice this is unlikely to lead to erroneous decisions regarding treatment, as the true observed risk in these patients is still high and justifies intensive medical therapy. The model was developed for the entire range of eGFR. Individuals with type 2 diabetes and CKD stage 3 or 4 are likely already managed as a high-risk group where preventive treatment is indicated. However, also in these groups progression of kidney function decline may take several years and the model can still act as a suitable tool to aid adherence and shared decision making in the prevention of ESKD.

The current model emphasizes lifetime benefit from treatment, which may support initiation of preventive treatment if absolute benefit is deemed appropriate. Contrary, the model may support not starting or postponement of preventive drug treatment if the absolute benefit is too low and focus on lifestyle changes might be a more appropriate initial treatment choice. In this way lifetime risk predictions inform shared decision making while lowering the risk of side effects and polypharmacy. Furthermore, trials are often not powered to detect an effect on ESKD risk, and albuminuria, eGFR slopes or a combined kidney event are often used as proxies for hard kidney outcomes.[34] With lifetime predictions for ESKD, a better alternative for translating absolute ESKD risk reduction with initiation of preventive treatment is provided.

We chose to also incorporate effect on all-cause mortality of treatment initiation where there was substantial evidence for this, since this leads to longer life expectancy and thus also more years to develop ESKD. However, it should be noted that ESKD-free life years gained in individuals with a low risk of ESKD is mostly derived from the effect on all-cause mortality. Treatment should always be considered and initiated according to current guidelines,[35, 36] and the ESKD prediction tool can help support these decisions. It should further be emphasized that preventive treatment in individuals with type 2 diabetes might be initiated for other reasons than prevention or postponement of ESKD (e.g. prevention of cardiovascular outcomes or heart failure) that were not incorporated into the current model. The model therefore underestimates the total benefit of treatment. Ideally, the model should be combined with models predicting risk of cardiovascular disease to fully capture treatment benefit.[37]

The model assumes that predictors follow a natural course over time that matches the course of predictors in the derivation cohort, and model predictions are based on the current predictor levels of a patient. However, follow-up in the derivation cohort was not sufficient to incorporate the natural course of predictors over the entire lifetime span, which might be particularly important for eGFR as a strong predictor for ESKD that is known to decline with increasing age. The different methodological approaches that we used to account for this general eGFR decline with age (e.g. incorporating standardized annual eGFR decline and modelled decline) did not improve model performance. Furthermore, the model assumes that other baseline risk factor levels follow the natural course captured in the dataset, which might

not always be appropriate. However, previous studies have validated methods of estimating lifetime predictions for up to 17 years.[19] Since all risk factors are subject to change after baseline and because of the general decline of eGFR with increasing age, lifetime estimations should be repeated when decisions about new treatment approaches are required.

Potential limitations of the study merit consideration. Internal and external validation was performed for 10-year risk as it is not possible to perform validation over an individual's lifetime. Also, diabetes duration is calculated as time since diabetes diagnosis, which is unlikely to be fully accurate as some people are likely to have developed diabetes some time before a clinical diagnosis is made.

We did not have information on ethnicity, so were not able to include this as predictor in the model. It is possible that the use of ICD-10 codes to identify outcomes may have resulted in misclassification, particularly underestimation of sustained eGFR <15ml/min/1.73m2 in the absence of long-term dialysis or transplantation as reported in a previous study.[38] It is not possible to validate the ICD-codes in the study populations used for this analysis or to estimate the likely effect of misclassification on the estimated discrimination and calibration of the risk models without knowing whether the degree of misclassification varies with different levels of risk factors.

We performed single imputation due to computational feasibility, which might slightly underestimate the true variability of outcome measures as opposed to multiple imputation. However, no conclusions are drawn based on the significance of the model's coefficients. Also, we chose for a split-sample approach for model development, while resampling methods would have been preferred. Model development was however still performed in >500,000 individuals with type 2 diabetes making the power of the study more than sufficient. Another assumption made is full adherence to preventive treatment for the remaining lifetime. However, since lack of adherence is a common problem, this current model might be used in aiding communication and addressing the importance of adherence to preventive treatment. Since ESKD is a rare outcome and studies are often underpowered, treatment effects for glucose-lowering and BP-lowering were estimated using the best available evidence and should be interpreted with this in mind. Further research is

needed to investigate to what extent the model is used in clinical practice and whether its use improves outcomes.

In conclusion, 10-year and lifetime risk of ESKD as well as ESKD-free life expectancy and life-years free of ESKD gained with treatment initiation can be estimated for individuals with type 2 diabetes using readily available characteristics. Assessment of individual risk and gain from treatment facilitates personalized medicine and shared-decision in the management of long-term outcomes in clinical practice.

References

1. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. Jama. 2003;290(14):1884-1890.
2. Kramer A, Boenink R, Stel VS, Santiuste de Pablos C, Tomović F, Golan E, Kerschbaum J, Seyahi N, Ioanou K, Beltrán P, Zurriaga O, Magaz Á, Slon Roblero MF, Gjorgjievski N, Garneata L, Arribas F, Galvão AA, Bell S, Ots-Rosenberg M, Muñoz-Terol JM, Winzeler R, Hommel K, Åsberg A, Spustova V, Palencia García M, Vazelov E, Finne P, Ten Dam M, Lopot F, Trujillo-Alemán S, Lassalle M, Kolesnyk MO, Santhakumaran S, Idrizi A, Andrusev A, Comas Farnés J, Komissarov K, Resić H, Palsson R, Kuzema V, Garcia Bazaga MA, Ziginskiene E, Stendahl M, Bonthuis M, Massy ZA, Jager KJ. The ERA-EDTA Registry Annual Report 2018: a summary. Clin Kidney J. 2021;14(1):107-123.
3. Xia J, Wang L, Ma Z, Zhong L, Wang Y, Gao Y, He L, Su X. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Nephrol Dial Transplant. 2017;32(3):475-487.
4. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, Hayward RA, Craven T, Coleman RL, Chalmers J. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol. 2017;5(6):431-437.
5. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-967.
6. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D, Rosano GM, Davis BR, Ridao M, Zaragoza A, Montero-Corominas D, Tobías A, de la Fuente-Honrubia C, Tabarés-Seisdedos R, Hutton B. Cardiovascular and Renal Outcomes of Renin-Angiotensin System Blockade in Adult Patients with Diabetes Mellitus: A Systematic Review with Network Meta-Analyses. PLoS Med. 2016;13(3):e1001971.
7. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, Tunnicliffe D, Ruospo M, Natale P, Saglimbene V, Nicolucci A, Johnson DW, Tonelli M, Rossi MC, Badve SV, Cho Y, Nadeau-Fredette AC, Burke M, Faruque LI, Lloyd A, Ahmad N, Liu Y, Tiv S, Millard T, Gagliardi L, Kolanu N, Barmanray RD, McMorrow R, Raygoza Cortez AK, White H, Chen X, Zhou X, Liu J, Rodríguez AF, González-Colmenero AD, Wang Y, Li L, Sutanto S, Solis RC, Díaz González-Colmenero F, Rodriguez-Gutierrez R, Walsh M, Guyatt G, Strippoli GFM. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. Bmj. 2021;372:m4573.
8. Slieker RC, van der Heijden AAWA, Siddiqui MK, Langendoen-Gort M, Nijpels G, Herings R, Feenstra TL, Moons KGM, Bell S, Elders PJ, t Hart LM, Beulens JWJ. Performance of prediction models for nephropathy in people with type 2 diabetes: systematic review and external validation study. BMJ (Clinical research ed). 2021;374:n2134-n2134.
9. Wan EYF, Fong DYT, Fung CSC, Yu EYT, Chin WY, Chan AKC, Lam CLK. Prediction of new onset of end stage renal disease in Chinese patients with type 2 diabetes mellitus - a population-based retrospective cohort study. BMC Nephrol. 2017;18(1):257.
10. Lin CC, Li CI, Liu CS, Lin WY, Lin CH, Yang SY, Li TC. Development and validation of a risk prediction model for end-stage renal disease in patients with type 2 diabetes. Sci Rep. 2017;7(1):10177.

11. Elley CR, Robinson T, Moyes SA, Kenealy T, Collins J, Robinson E, Orr-Walker B, Drury PL. Derivation and validation of a renal risk score for people with type 2 diabetes. Diabetes Care. 2013;36(10):3113-3120.
12. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-2081.
13. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care. 2003;26(4):1270-1276.
14. Cunningham S, McAlpine R, Leese G, Brennan G, Sullivan F, Connacher A, Waller A, Boyle DI, Greene S, Wilson E, Emslie-Smith A, Morris AD. Using web technology to support population-based diabetes care. J Diabetes Sci Technol. 2011;5(3):523-534.
15. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67(6):2089-2100.
16. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation and Updating. New York, USA: Springer; 2009.
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
18. Arsenault BJ, Rana JS, Stroes ES, Després JP, Shah PK, Kastelein JJ, Wareham NJ, Boekholdt SM, Khaw KT. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol. 2009;55(1):35-41.
19. Dorresteijn JA, Kaasenbrood L, Cook NR, van Kruijsdijk RC, van der Graaf Y, Visseren FL, Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj. 2016;352:i1548.
20. Harrell FE, Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. Jama. 1982;247(18):2543-2546.
21. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med. 2019;170(1):51-58.
22. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Bmj. 2015;350:g7594.
23. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. Arch Intern Med. 2012;172(11):837-844.
24. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021;6(2):148-158.
25. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653-662.

26. Wysham CH, Gauthier-Loiselle M, Bailey RA, Manceur AM, Lefebvre P, Greenberg M, Duh MS, Young JB. Development of risk models for major adverse chronic renal outcomes among patients with type 2 diabetes mellitus using insurance claims: a retrospective observational study. Curr Med Res Opin. 2020;36(2):219-227.
27. Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS. Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. Lancet Diabetes Endocrinol. 2017;5(10):788-798.
28. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013;56(9):1925-1933.
29. Eckardt KU, Bansal N, Coresh J, Evans M, Grams ME, Herzog CA, James MT, Heerspink HJL, Pollock CA, Stevens PE, Tamura MK, Tonelli MA, Wheeler DC, Winkelmayer WC, Cheung M, Hemmelgarn BR. Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2018;93(6):1281-1292.
30. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology. 2009;20(4):555-561.
31. Landstinget Sörmland L. Behandlingsriktlinjer hypertoni. 2016.
32. Scotland HI. Risk estimation and the prevention of cardiovascular disease. 2017.
33. Wright AK, Suarez-Ortegon MF, Read SH, Kontopantelis E, Buchan I, Emsley R, Sattar N, Ashcroft DM, Wild SH, Rutter MK. Risk Factor Control and Cardiovascular Event Risk in People With Type 2 Diabetes in Primary and Secondary Prevention Settings. Circulation. 2020;142(20):1925-1936.
34. Greene T, Ying J, Vonesh EF, Tighiouart H, Levey AS, Coresh J, Herrick JS, Imai E, Jafar TH, Maes BD, Perrone RD, Del Vecchio L, Wetzels JFM, Heerspink HJL, Inker LA. Performance of GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Statistical Simulation. J Am Soc Nephrol. 2019;30(9):1756-1769.
35. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021.
36. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4s):S1-s115.
37. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, Wild SH, Franzen S, Chalmers J, Davis BR, Poulter NR, Spijkerman AM, Woodward M, Pressel SL, Gupta AK, van der Schouw YT, Svensson AM, van der Graaf Y, Read SH, Eliasson B, Dorresteijn JAN. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. Eur Heart J. 2019;40(34):2899-2906.
38. Norton JM, Grunwald L, Banaag A, Olsen C, Narva AS, Marks E, Koehlmoos TP. CKD Prevalence in the Military Health System: Coded Versus Uncoded CKD. Kidney Med. 2021;3(4):586-595.e581.

Supplementary material

Expanded methods

Predictors and missing data

Predictors were predetermined and selected based on existing risk scores for end-stage kidney disease (ESKD) in people with type 2 diabetes, literature and availability in routine clinical practice. Baseline date was set as first date where an eGFR value was registered, and if no eGFR value was registered for an individual, eGFR was set as missing. Baseline data for the remaining predictors for Swedish National Diabetes Register (NDR) and Scottish Care Information(SCI) - Diabetes cohort were collected as first registered measured value in the first year after baseline date.

For missing data, single imputation was performed using predictive mean matching (aregImpute-algorithm in R, Hmisc package) with weighted probability based on all available non-missing patient characteristics and outcomes. In the Swedish NDR, percentage of imputed data was 0% for age, sex and history of cardiovascular disease, 13% for smoking, 3% for eGFR, 27% for albuminuria, 5% for SBP, 15% for body mass index (BMI), 23% for non-HDL-cholesterol (non-HDL-c), 3% for HbA1c, 1% for insulin use and 9% for duration of diabetes. In the SCI-Diabetes cohort, percentage of imputed data was 0% for sex, age, history of cardiovascular disease and insulin use, 22% for current smoking, 21% for BMI, 15% for HbA1c, 36% for non-HDL-c and 54% for albuminuria. Duration of diabetes was set to 0 since the population was an incident type 2 diabetes cohort. Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers.

Restricted cubic splines were performed to test for log-linearity of the relationship between continuous predictors and the outcomes and transformations were applied when this improved model fit based on Akaike's Information Criterion. Quadratic transformation of continuous predictors was applied for eGFR, BMI, HbA1c and non-HDL-c for the ESKD Cox proportional hazard function (function A) and for eGFR, BMI, SBP, non-HDL-c and HbA1c for the all-cause mortality Cox proportional hazard function (function B). The hazard ratios (HR) for transformed predictors is shown for the 75th percentile versus the 25th percentile.

Statistical analyses

Development of the lifetime model

A random sample of 75% (n = 530,308) from the Swedish NDR was chosen for the derivation of the model. Two complementary Cox proportional hazards models were developed; one for the prediction of ESKD events (function A), and another for the prediction of all-cause mortality (function B). To enable lifetime predictions, age was used as the time-scale by adapting left truncation and right censoring to the models. Hereby, patients 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 age at study exit. Due to the relatively low number of people and events in patients <30 years and >95 years, the development cohort was restricted to patients 30-95 years of age. Age-specific baseline survivals for both Cox proportional hazards functions were centred for continuous predictors using the population mean of that specific predictor (BMI of 30 kg/m^2, systolic blood pressure of 138 mmHg, non-HDLc of 3.7 mmol/l, HbA1c of 55 mmol/l, and eGFR of 82 ml/min). Baseline hazards for the Cox proportional hazards model predicting ESKD were derived per 1 year intervals due to the relatively low number of ESKD events and thereafter smoothed and interpolated to 3-month intervals using a local regression smoother with a span of 0.7 (Supplementary figure 2). To account for the lower risk during a 3-month interval compared to a 1-year interval, baseline hazards were exponentiated to ¼. Baseline hazards for the Cox proportional hazards model predicting all-cause mortality were derived per 3-month intervals and smoothed using an exponential function. The proportional hazards assumption was assessed by visual inspection of Schoenfeld residuals plots for the various predictors and age, and no violations were found.

Predictions for individual persons

Next, these models were used to calculate life expectancy free of ESKD (median survival without ESKD) and ESKD risk for individual patients. Predictions were based on lifetable calculations.[1-3] Starting at the current age of an individual with type 2 diabetes, the risk of having an ESKD event (a_t) combined with the risk of dying from all causes (b_t) were predicted for each future 3-month interval. Next, the cumulative ESKD free survival ($Surv_{t+1}$) was calculated by multiplying the survival probability at the beginning of each 3-month interval ($Surv_t$) by the ESKD free survival probability during those 3 months ($Surv_t * a_t - b_t$), allowing for

adjustment of all-cause mortality as competing risk. Logically the cumulative ESKD free survival started at 100% at the current age of a person. This process was repeated until the maximum age of 95 years. An example of such a life-table for an individual person is shown in *Supplementary table 8*. ESKD free life expectancy of an individual was defined as the median survival without ESKD, determined as the age where the estimated cumulative survival drops below 50%. 10-year ESKD risk was calculated by summation of the attributable ESKD risk in the first 10 years from a person's current age onwards. The attributable ESKD risk was obtained by multiplication of the probability of survival without an ESKD event at the beginning of each 3-month interval ($Surv_t$) and the risk of having an ESKD event (a_t) during that 3-month interval. Similarly, lifetime risk was calculated by the summation of the attributable ESKD risk from a person's current age onwards until the age of 95. The life table approach was used in order to be able to estimate lifetime predictions by projecting 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 = 170,114) for 10 year risk predictions. The split-sample validation approach was chosen for feasibility reasons. Due to the large number of patients and a more than sufficient number of endpoints per variable this approach will not lead to biased results.[4] External validation was performed using the SCI-Diabetes cohort. Recalibration of prediction models for external validation is most often necessary due to the difference in event rates between populations and cohorts,[5] thus for external validation the intercept of the two Cox proportional hazards functions were recalibrated based on the incidence of ESKD and incidence of all-cause mortality, respectively, using the specific expected versus observed ratios in the SCI-Diabetes cohort.

Relative treatment effects to estimate lifelong treatment benefit in ESKD-free life years gained

SGLT-2 inhibition treatment

HR of SGLT-2 inhibition treatment is estimated as 0.71.[6] This HR is based on ESKD as outcome as defined in the trials of the meta-analyses. An independent effect of SGLT-2 inhibition therapy in addition to HbA1c lowering is assumed. Furthermore, SGLT-2 inhibition treatment is assumed to have an effect on all-cause mortality with a HR of 0.87.[7] Because the use of SGLT2-inhibition was

negligible in the development cohort (<1%), it was assumed that all patients were non-users and thus the HR for not using SGLT-2 inhibition was set to 1.

GLP-1 receptor agonists (RA) treatment

HR of GLP-1 RA treatment is estimated as 0.78.[6] This HR is based on ESKD as outcome as defined in the trials of the meta-analyses. An independent effect of GLP-1 RA therapy in addition to HbA1c lowering is assumed. Furthermore, GLP-1 RA treatment is assumed to have an effect on all-cause mortality with a HR of 0.88.[8] Because the use of GLP-1 RA was negligible in the development cohort (<1%), it was assumed that all patients were non-users and thus the HR for not using GLP-1 RA was set to 1.

RAS inhibition treatment

The effect of starting treatment with RASi (Renine-Angiotensin-System inhibition) treatment (an angiotensin-converting-enzyme inhibitor or angiotensin2-receptor-blocker) is estimated as a hazard ratio of 0.71[9] if starting treatment. This HR is based on ESKD as outcome as defined in the trials of the meta-analyses. Since there is no evidence that one treatment is superior to the other,[9] this was the pooled HR for ACEi and ARB treatment, which were reported separately. An independent effect of RASi therapy in addition to lowering of blood pressure is assumed.

Treatment with RASi medication is widely used in a population with type 2 diabetes, and in the Swedish NDR 42% of the cohort were using RASi medication at baseline. This of course impacts baseline risk, so the current ESKD model estimates the risk of ESKD for a person with a 42% usage of RASi. We accounted for this using the naïve method,[10, 11] where this risk for the individual is calculated back to the real world scenario, being either no RASi use (0%) or RASi use (100%). This is done by adjusting the causal effect implemented to the current prevalence of RASi usage in the derivation cohort. The treatment-HR for ESKD risk is thus lowered for users (HR of using RASi at baseline was 0.81 (0.71/(0.58*1+0.42*0.71)) and raised for non-users (HR of not using RASi at baseline was 1.14 (1/(0.58*1+0.42*0.71)). Thereby, the proportional ratio between the two is exactly 0.71.[10, 11]

Blood-pressure lowering treatment

The effect of blood-pressure lowering treatment on the risk of ESKD is estimated as a HR of 0.88 per 10 mmHg reduction in systolic blood pressure in people with type

2 diabetes.[12] This HR is based on ESKD as outcome as defined in the trials of the meta-analyses. No relative risk reduction is assumed for lowering systolic blood pressure below 130 mmHg. Individual expected relative risk reduction of ESKD is thereby calculated as $0.88^{(\text{Blood pressure reduction in mmHg}/10)}$, blood pressure reduction being the current systolic blood pressure of the patient minus the target systolic blood pressure. Furthermore, lowering of systolic blood pressure in people with type 2 diabetes is assumed to have an effect on all-cause mortality with a HR of 0.87 per 10 mmHg lowering[12], so calculated as $0.87^{(\text{Blood pressure reduction in mmHg}/10)}$. HR for systolic blood pressure changes below 130 mmHg is assumed to be 1.

Glucose-lowering treatment

There is abundant evidence that intensive HbA1c lowering has a beneficial effect on the risk of chronic kidney disease progression.[13, 14] However, due to limited power and heterogeneity of trials, the exact percentage of ESKD risk reduction per unit HbA1c is unknown. Observational studies examining the causal relation between HbA1c and risk of ESKD are also of limited value to determine the treatment effect, since they are often performed in specific subgroups of patients with type 2 diabetes[15] or only assess HbA1c as categorical variable.[16] Therefore, we calculated the treatment effect using a Cox proportional hazards model with HbA1c as determinant and ESKD as outcome in the development cohort from the Swedish NDR. All predictors from the model were used as confounders, and no violations in regards to the assumptions of Cox proportional hazards models were observed. This led to a HR of 0.95 per 5 mmol/mol HbA1c reduction. No relative risk reduction is assumed for lowering HbA1c below 53 mmol/mol. Individual expected relative risk reduction of ESKD is thereby calculated as $0.95^{(\text{HbA1c reduction in mmol per mol}/5)}$, HbA1c reduction being current HbA1c of the patient minus target HbA1c. HR for HbA1c changes below 53 mmol/mol is assumed to be 1.

Smoking cessation

Smoking cessation is assumed to reduce the HR for ESKD events of current smokers versus never smokers (HR 1.91) to that of former smokers versus never smokers (HR 1.44).[17] The resulting HR for ESKD events when stopping smoking is thus 0.75. Furthermore, smoking cessation is assumed to have an effect on all-cause mortality with a HR for current smokers versus never smokers of 1.83, and a HR for former smokers versus never smokers of 1.34,[18] resulting in a HR for smoking cessation on all-cause mortality of 0.73.

Combined individual treatment effect

The relative individualized risk reduction for the combination of added therapy is calculated by multiplying the hazard ratios of the intended treatments. Thereby the assumption is made that the different treatments are independent of one another. In the SGLT2i and GLP-1 RA trials, almost all subjects were using RASi medication at baseline, indicating an independent effect on ESKD risk reduction with these therapies. The combined hazard ratio is used in the lifetables for the function for ESKD events and the HR for smoking cessation, SGLT2i and GLP-1 RA on all-cause mortality is used in the lifetables for the function of all-cause mortality in order to estimate lifetime benefit with treatment (*Supplementary table 8*).

Sensitivity analyses

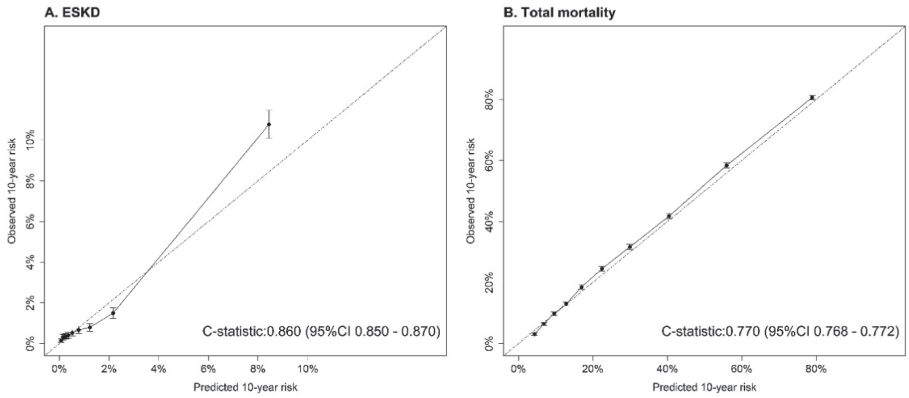
It is well known that eGFR has a natural decline during the course of one's lifetime, with an estimated eGFR decline per year of 0.5-1 ml/min/1.73m^2.[19] An important assumption in the ESKD prediction model is that predictors follow a natural course over time (i.e. age) that matches the course of predictors in the derivation cohort, and model predictions are based on the current predictor levels of a patient. Predictor levels might change with age (e.g. a decrease in eGFR), but this happened during the follow-up period in the derivation cohort as well. As long as the change in predictor levels follows the same course over time as in the derivation cohort and the derivation cohort has substantial follow-up time, no adjustment is needed. However, for lifetime predictions, follow-up time is not sufficient, and the lifetime predictions therefore need careful interpretation, especially in younger patients.

In the Swedish NDR cohort, longitudinal laboratory values are included, and thus also eGFR obtained at different time points per subject. The dataset consisted of 3,758,796 eGFR measurements, a mean of 5.5 eGFR measurements per subject (range 1 to 19 eGFR measurements and > 3months between measurements). In order to incorporate natural eGFR slope over the whole course of one's lifetime, we tried several methodological adjustments in the derivation of the model.

eGFR incorporated as age- and sex specific percentile in the derivation of the model

With this methodological adjustment we aimed to depict the predictor for individual eGFR as age- and sex specific eGFR percentile.

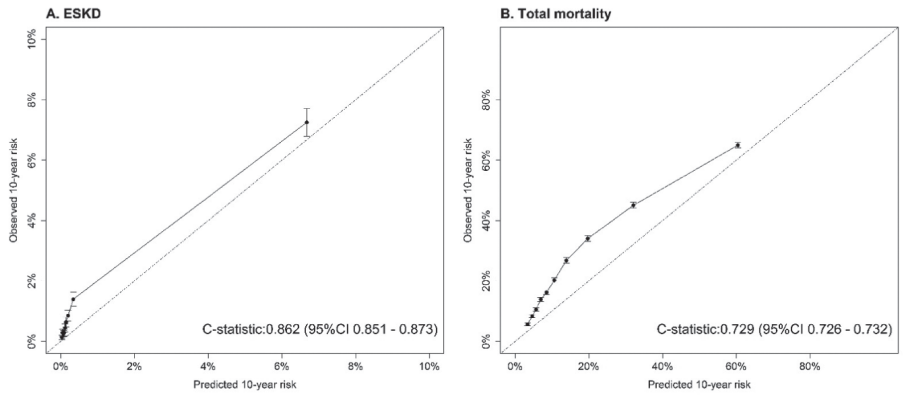
The individual age- and sex specific eGFR percentile was obtained according to previously described methods.[20] First, the percentiles for the overall population were calculated by modelling the mean of the eGFR distribution as a function of age for each sex using a local regression smoother with a smoothing span of 0.7. For each individual eGFR observation, the corresponding estimated eGFR value was then subtracted. The pooled residuals from this model were ranked, and the jth percentile for each of j=1…100 of the residuals were calculated. When adding these to the fitted eGFR value for a particular age and sex an estimated percentile for eGFR was calculated. Instead of eGFR as predictor in the Cox proportional hazards model, we used the calculated age- and sex specific percentile for eGFR. For validation of the model, individual age and sex specific eGFR percentiles were similarly calculated using the model obtained in the derivation cohort. All other steps in derivation and validation remained the same (as previously described). The internal validation of the model for 10-year predictions when adapting this methodology is shown below.



Incorporating individual eGFR decline in lifetables when calculating ESKD risk

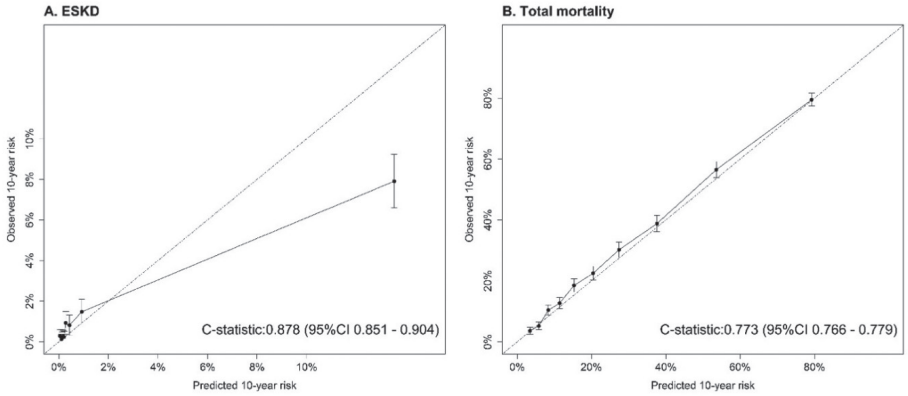
A further modification of the methodology to account for natural eGFR decline was to incorporate predicted individual eGFR slope in the lifetables when calculating individual ESKD risk and ESKD-free survival. First, in the derivation of the model, eGFR as predictor was specified as a time-varying covariate. Second, we aimed to estimate individual eGFR slope per year. This was done by first fitting a linear mixed model on the effect of age (as time axis) on eGFR

with a random intercept and random slope in the derivation cohort. Thereby individual eGFR slope was derived.[21] The second step was to fit a linear model of eGFR slope (ml/min/1.73m2 per year) as a function of baseline age and baseline eGFR. This model was then used in the validation of the model for predicting individual eGFR slope based on age and baseline eGFR, and this was incorporated in the lifetables, so that eGFR declined per year correspondingly. The internal validation of the model for 10-year predictions when incorporating estimated individual eGFR slope is shown below.



Incorporating an overall eGFR decline of 0.5 ml/min/1.73m²

The internal validation of the model for 10-year predictions when incorporating an overall eGFR decline of 0.5 ml/min/1.73m2 per individual in the lifetables is shown below.



Interpretation of different approaches to incorporate continuous eGFR decline

When looking at 10-year predictions, the model without methodological modifications performed very well both in regards to discrimination and calibration, indicating that the natural eGFR decline is incorporated in the model for 10-year predictions (as would be expected with the sufficient follow-up time in the cohorts for this time frame). However, it is not achievable to test the validity of lifetime predictions, since no cohort has sufficient follow-up for this. Since the above methodological modifications also introduce assumptions and the continuous eGFR measurements in the Swedish NDR dataset are subject to selection bias (people with type 2 diabetes with more eGFR measurements are likely to be more ill and have more frequent clinical controls and thus accelerated eGFR decline), we chose to incorporate the original methodology in the main article. However, the lifetime predictions for ESKD should be interpreted with caution, especially in younger individuals, and predictions for the individual person with type 2 diabetes should be repeated every e.g. 10 years.

Supplementary table 1. Definition of type 2 diabetes and history of cardiovascular disease in Swedish National Diabetes Register and Scottish Care Information - Diabetes Database

Dataset	Definition of type 2 diabetes	Definition of history of cardiovascular disease
Swedish National Diabetes Register	The definition of type 2 diabetes was treatment with 1) diet only, 2) oral hypoglycemic agents only, or 3) insulin only or combined with oral agents, and onset age of diabetes ≥40 years	History of cardiovascular disease was defined as a history of myocardial infarction, stroke, peripheral vascular disease, PCI or CABG (ICD10-codes I20-25, I46, I61, I63, I64, I70.2, I71).
Scottish Care Information - Diabetes Database	Type 2 diabetes 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.	

Supplementary table 2. Definition of ESKD and all-cause mortality outcomes in Swedish National Diabetes Register and Scottish Care Information - Diabetes Database

Dataset	Definition of outcomes
Swedish National Diabetes Register	*Outcome evaluation:* All ESKD and all-cause mortality 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). ESKD was defined as kidney transplantation, long-term dialysis or chronic kidney disease stage 5.
	Kidney transplantation: Allogenic kidney transplantation from living or deceased donor. KVA-codes: KAS10, KAS20
	Long-term dialysis: Long-term haemodialysis or long-term peritoneal dialysis. KVA-codes: DR012, DR013, DR014, DR016, DR024, DR055, DR056, DR060, DR061
	Chronic kidney disease stage 5: Sustained eGFR <15 ml/min/1.73m2. ICD-10 codes: N18.5, N18.6
Scottish Care Information - Diabetes Database	*Outcome evaluation:* All ESKD and all-cause mortality endpoints were retrieved by data linkage with the National Records of Scotland death registrations and the national hospitalization register (Scottish Morbidity Record, SMR01). ESKD was defined as kidney transplantation, long-term dialysis or chronic kidney disease stage 5.
	Kidney transplantation: Allogenic kidney transplantation from living or deceased donor. ICD-10 codes: Z94.0. OPCS4 codes: M01.2, M01.3, M01.4, M01.5
	Long-term dialysis: Long-term haemodialysis or long-term peritoneal dialysis. ICD-10 codes: Z49.1, Z99.2. OPCS4 codes: X40.1, X40.2, X40.3, X40.4, X40.5, X40.6.
	Chronic kidney disease stage 5: Sustained eGFR <15 ml/min/1.73m2. ICD-10 codes: N18.5

Supplementary table 3. Hazard ratios and 95% confidence intervals derived from multivariable Cox proportional hazard models

	HR for ESKD (95 % CI)	**HR for all-cause mortality (95 % CI)**
Sex (male)	1.70 (1.61-1.80)	1.32 (1.30-1.33)
Current smoking	1.45 (1.35-1.55)	1.71 (1.69-1.74)
Systolic blood pressure (mmHg)	1.10 (1.10-1.10)[b]	0.91 (0.91-0.92)[a]
Body mass index (kg/m2)	1.14 (1.09-1.19)[a]	1.01 (1.00-1.02)[a]
eGFR (ml/min/1.73m2)	0.41 (0.41-0.41)[a]	1.09 (1.09-1.09)[a]
HbA1c mmol/mol	1.08 (1.07-1.09)[a]	1.07 (1.07-1.08)[a]
Non-HDL-cholesterol	1.02 (0.88-1.17)[a]	1.03 (1.00-1.07)[a]
Moderate albuminuria	2.69 (2.51-2.88)	1.26 (1.24-1.27)
Severe albuminuria	5.43 (5.08-5.83)	1.46 (1.44-1.49)
Duration of type 2 diabetes mellitus (years)	1.01 (1.01-1.02)	1.01 (1.01-1.01)
History of cardiovascular disease	0.96 (0.91-1.02)	1.38 (1.36-1.39)
Insulin treatment	1.30 (1.23-1.38)	1.32 (1.30-1.34)

[a]*Transformed variable. Hazard ratios are presented as 75th percentile vs. 25th percentile (eGFR: 96.4 ml/min vs. 68.4 ml/min; systolic blood pressure: 150 mmHg vs. 126 mmHg; body mass index: 30 kg/m2 vs. 26 kg/m2; HbA1c: 7.6% (60 mmol/mol) vs. 6.2% (44 mmol/mol); non-HDL-cholesterol: 4.4 mmol/L vs. 2.9 mmol/L)*

[b]*Hazard ratio is presented per 10 mmHg increase*

Supplementary table 4. Calculation formulas of 3-month interval survivals

ESKD Cox proportional hazard function (A)
3-month survival = (age-specific 3-month baseline survival¥)^exp(A)
A = 0.5295829868 (if male) -0.0302637391*(BMI - 30) + 0.0008332090*(*squared* BMI - 30^2) + 0.3696540712 (if smoking) + 0.0089130229*(SBP-138) - 0.1905498619*(nonHDL-3.7) + 0.0275638175*(*squared* nonHDL - 3.7^2) - 0.0088094561*(HbA1c-55) + 0.0001317019*(*squared* HbA1c - 55^2) - 0.1345453423*(eGFR-82) + 0.0006241907*(*squared* eGFR - 82^2) + 0.9890738792 (if micro-albuminuria) + 1.6925027125 (if macro-albuminuria) + 0.0167046698*(diabetes duration) - 0.0392162074 (if history of cardiovascular disease) + 0.2643295233 (if insulin treatment) + LN(Hazard Ratio of intended treatment)§
All-cause mortality Cox proportional hazard function (B)
3-month survival = (age-specific 3-month baseline survival¥)^exp(B)
B = 0.2740189 (if male) - 0.146682*(BMI - 30) + 0.002494125*(*squared* BMI - 30^2) + 0.5383219 (if smoking) - 0.04837925*(SBP-138) + 0.0001616799*(*squared* SBP - 138^2) - 0.007339466*(nonHDL-3.7) + 0.003946654*(*squared* nonHDL - 3.7^2) + 0.001541359*(HbA1c-55) + 0.00002801039(*squared* HbA1c - 55^2) - 0.03773463*(eGFR-82) + 0.0002479993*(*squared* eGFR - 82^2) + 0.2272037 (if micro-albuminuria) + 0.3796535 (if macro-albuminuria) + 0.008351482*(diabetes duration) + 0.3194937 (if history of cardiovascular disease) - 0.2789714 (if insulin treatment) + LN(Hazard Ratio of intended treatment)§

¥ Age-specific baseline survivals are shown in table S4 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 methods.

BMI: Body mass index in kg/m²; SBP: Systolic blood pressure in mmHg; non-HDLc: non-high-density cholesterol in mmol/l; HbA1c: Hemoglobin A1c in mmol/mol; eGFR: estimated glomerular filtration rate in ml/min/1.73m2.

Supplementary table 5. Age-specific baseline survivals per 3-month interval

Age (years)	3-month survival free of ESKD*	3-month survival for all-cause mortality**	Age (years)	3-month survival free of ESKD*	3-month survival for all-cause mortality**
30,00	0,999989994	0,9996502	39,75	0,9999468	0,9996049
30,25	0,999988484	0,9996495	40,00	0,9999461	0,9996029
30,50	0,999986998	0,9996489	40,25	0,9999454	0,9996009
30,75	0,999985534	0,9996482	40,50	0,9999447	0,9995988
31,00	0,999984092	0,9996475	40,75	0,9999441	0,9995966
31,25	0,999982673	0,9996468	41,00	0,9999434	0,9995944
31,50	0,999981277	0,9996461	41,25	0,9999428	0,9995921
31,75	0,999979902	0,9996453	41,50	0,9999422	0,9995898
32,00	0,99997855	0,9996446	41,75	0,9999416	0,9995873
32,25	0,99997722	0,9996438	42,00	0,999941	0,9995848
32,50	0,999975911	0,999643	42,25	0,9999405	0,9995822
32,75	0,999974624	0,9996421	42,50	0,99994	0,9995796
33,00	0,999973359	0,9996412	42,75	0,9999394	0,9995768
33,25	0,999972115	0,9996404	43,00	0,999939	0,999574
33,50	0,999970892	0,9996394	43,25	0,9999385	0,9995711
33,75	0,99996969	0,9996385	43,50	0,999938	0,9995681
34,00	0,99996851	0,9996375	43,75	0,9999376	0,9995651
34,25	0,99996735	0,9996365	44,00	0,9999372	0,9995619
34,50	0,99996621	0,9996355	44,25	0,9999368	0,9995586
34,75	0,999965091	0,9996344	44,50	0,9999364	0,9995553
35,00	0,999963993	0,9996333	44,75	0,999936	0,9995518
35,25	0,999962914	0,9996322	45,00	0,9999357	0,9995482
35,50	0,999961856	0,999631	45,25	0,9999353	0,9995446
35,75	0,999960817	0,9996298	45,50	0,999935	0,9995408
36,00	0,999959798	0,9996286	45,75	0,9999347	0,9995369
36,25	0,999958799	0,9996273	46,00	0,9999345	0,9995329
36,50	0,99995782	0,999626	46,25	0,9999342	0,9995287
36,75	0,99995686	0,9996246	46,50	0,999934	0,9995245
37,00	0,999955919	0,9996232	46,75	0,9999338	0,9995201
37,25	0,999954998	0,9996218	47,00	0,9999336	0,9995156
37,50	0,999954096	0,9996203	47,25	0,9999335	0,9995109
37,75	0,999953212	0,9996188	47,50	0,9999334	0,9995061
38,00	0,999952348	0,9996173	47,75	0,9999333	0,9995012
38,25	0,999951503	0,9996156	48,00	0,9999332	0,9994961
38,50	0,999950676	0,999614	48,25	0,9999331	0,9994909
38,75	0,999949868	0,9996123	48,50	0,9999331	0,9994855
39,00	0,999949079	0,9996105	48,75	0,9999331	0,99948
39,25	0,999948309	0,9996087	49,00	0,9999331	0,9994742
39,50	0,999947557	0,9996068	49,25	0,9999332	0,9994684

Supplementary table 5. Continued

Age (years)	3-month survival free of ESKD*	3-month survival for all-cause mortality**	Age (years)	3-month survival free of ESKD*	3-month survival for all-cause mortality**
49,50	0,999933257	0,9994623	59,25	0,9999367	0,9990127
49,75	0,999933372	0,9994561	59,50	0,9999366	0,998993
50,00	0,999933516	0,9994496	59,75	0,9999366	0,9989728
50,25	0,99993369	0,999443	60,00	0,9999366	0,9989519
50,50	0,99993389	0,9994362	60,25	0,9999365	0,9989304
50,75	0,999934114	0,9994292	60,50	0,9999364	0,9989083
51,00	0,999934357	0,9994219	60,75	0,9999364	0,9988855
51,25	0,999934611	0,9994145	61,00	0,9999363	0,9988621
51,50	0,999934867	0,9994068	61,25	0,9999362	0,9988379
51,75	0,999935117	0,9993989	61,50	0,9999361	0,998813
52,00	0,999935352	0,9993908	61,75	0,9999361	0,9987874
52,25	0,999935421	0,9993824	62,00	0,999936	0,998761
52,50	0,999935485	0,9993738	62,25	0,9999359	0,9987338
52,75	0,999935698	0,9993649	62,50	0,9999359	0,9987058
53,00	0,999935893	0,9993557	62,75	0,9999358	0,998677
53,25	0,999935943	0,9993463	63,00	0,9999358	0,9986473
53,50	0,999935985	0,9993366	63,25	0,9999357	0,9986167
53,75	0,999936157	0,9993266	63,50	0,9999357	0,9985852
54,00	0,999936314	0,9993163	63,75	0,9999357	0,9985528
54,25	0,999936339	0,9993057	64,00	0,9999356	0,9985194
54,50	0,999936354	0,9992948	64,25	0,9999356	0,998485
54,75	0,999936493	0,9992835	64,50	0,9999356	0,9984496
55,00	0,999936623	0,999272	64,75	0,9999356	0,9984132
55,25	0,999936619	0,99926	65,00	0,9999356	0,9983756
55,50	0,999936607	0,9992478	65,25	0,9999356	0,9983369
55,75	0,999936721	0,9992351	65,50	0,9999356	0,9982971
56,00	0,99993683	0,9992221	65,75	0,9999356	0,9982561
56,25	0,999936799	0,9992087	66,00	0,9999356	0,9982139
56,50	0,99993676	0,9991948	66,25	0,9999356	0,9981704
56,75	0,999936854	0,9991806	66,50	0,9999357	0,9981256
57,00	0,999936942	0,999166	66,75	0,9999357	0,9980794
57,25	0,999936885	0,9991509	67,00	0,9999357	0,9980319
57,50	0,999936821	0,9991353	67,25	0,9999358	0,997983
57,75	0,999936884	0,9991193	67,50	0,9999359	0,9979326
58,00	0,999936933	0,9991028	67,75	0,9999359	0,9978808
58,25	0,999936853	0,9990858	68,00	0,999936	0,9978274
58,50	0,99993677	0,9990684	68,25	0,9999361	0,9977723
58,75	0,999936798	0,9990503	68,50	0,9999362	0,9977157
59,00	0,999936812	0,9990318	68,75	0,9999363	0,9976574

Supplementary table 5. Continued

Age (years)	3-month survival free of ESKD*	3-month survival for all-cause mortality**	Age (years)	3-month survival free of ESKD*	3-month survival for all-cause mortality**
69,00	0,999936409	0,9975973	78,75	0,9999472	0,9931591
69,25	0,999936561	0,9975354	79,00	0,9999477	0,9929658
69,50	0,999936721	0,9974717	79,25	0,9999481	0,9927667
69,75	0,999936827	0,9974061	79,50	0,9999486	0,9925618
70,00	0,999936939	0,9973386	79,75	0,999949	0,9923508
70,25	0,999937123	0,997269	80,00	0,9999495	0,9921337
70,50	0,999937314	0,9971974	80,25	0,99995	0,9919101
70,75	0,999937449	0,9971236	80,50	0,9999505	0,99168
71,00	0,999937592	0,9970477	80,75	0,999951	0,9914431
71,25	0,999937806	0,9969695	81,00	0,9999515	0,9911992
71,50	0,999938025	0,996889	81,25	0,999952	0,9909482
71,75	0,999938192	0,996806	81,50	0,9999525	0,9906898
72,00	0,999938366	0,9967206	81,75	0,999953	0,9904238
72,25	0,999938608	0,9966327	82,00	0,9999535	0,99015
72,50	0,999938855	0,9965422	82,25	0,9999541	0,9898682
72,75	0,999939106	0,9964489	82,50	0,9999546	0,9895781
73,00	0,999939362	0,9963529	82,75	0,9999552	0,9892795
73,25	0,999939623	0,9962541	83,00	0,9999558	0,9889722
73,50	0,99993989	0,9961523	83,25	0,9999563	0,9886559
73,75	0,999940163	0,9960475	83,50	0,9999569	0,9883304
74,00	0,999940443	0,9959396	83,75	0,9999575	0,9879954
74,25	0,99994073	0,9958285	84,00	0,9999581	0,9876506
74,50	0,999941023	0,9957141	84,25	0,9999587	0,9872957
74,75	0,999941325	0,9955963	84,50	0,9999593	0,9869305
75,00	0,999941633	0,995475	84,75	0,9999599	0,9865546
75,25	0,99994195	0,9953501	85,00	0,9999606	0,9861678
75,50	0,999942274	0,9952215	85,25	0,9999612	0,9857698
75,75	0,999942607	0,9950891	85,50	0,9999618	0,9853602
76,00	0,999942947	0,9949528	85,75	0,9999625	0,9849388
76,25	0,999943295	0,9948124	86,00	0,9999631	0,9845051
76,50	0,999943651	0,9946679	86,25	0,9999638	0,9840588
76,75	0,999944016	0,9945191	86,50	0,9999645	0,9835996
77,00	0,999944389	0,9943659	86,75	0,9999652	0,9831272
77,25	0,999944769	0,9942082	87,00	0,9999659	0,982641
77,50	0,999945158	0,9940458	87,25	0,9999666	0,9821409
77,75	0,999945555	0,9938787	87,50	0,9999673	0,9816264
78,00	0,99994596	0,9937066	87,75	0,999968	0,981097
78,25	0,999946374	0,9935294	88,00	0,9999687	0,9805524
78,50	0,999946795	0,9933469	88,25	0,9999694	0,9799921

Supplementary table 5. Continued

Age (years)	3-month survival free of ESKD*	3-month survival for all-cause mortality**
88,50	0,99997015	0,9794158
88,75	0,999970893	0,978823
89,00	0,999971643	0,9782132
89,25	0,999972401	0,9775859
89,50	0,999973167	0,9769407
89,75	0,99997394	0,9762772
90,00	0,999974721	0,9755947
90,25	0,99997551	0,9748929
90,50	0,999976306	0,9741711
90,75	0,99997711	0,9734289
91,00	0,999977922	0,9726656
91,25	0,999978742	0,9718808
91,50	0,999979569	0,9710739
91,75	0,999980404	0,9702442
92,00	0,999981246	0,9693912
92,25	0,999982096	0,9685143
92,50	0,999982954	0,9676129
92,75	0,99998382	0,9666862
93,00	0,999984693	0,9657337
93,25	0,999985575	0,9647547
93,50	0,999986463	0,9637484
93,75	0,99998736	0,9627143
94,00	0,999988264	0,9616516
94,25	0,999989176	0,9605596
94,50	0,999990096	0,9594376
94,75	0,999991024	0,9582847

*Age-specific baseline survivals for centered continuous variables with a systolic blood pressure of 138 mmHg, BMI of 30 kg/m^2, HbA1c of 55 mmol/l, non-HDL-c of 3.7 mmol/l, and eGFR of 82 ml/min. *Based on Cox proportional hazard function A for ESKD. **Based on Cox proportional hazard function B for all-cause mortality.*

Supplementary table 6. Baseline characteristics of participants from the Swedish National Diabetes Register stratified according to incident or prevalent type 2 diabetes after imputation of missing data

	Proportion with incident type 2 diabetes	**Proportion with prevalent type 2 diabetes**
Number of participants	229,635 (32%)	477,442 (68%)
Sex (male)	132624 (58%)	268809 (56%)
Age (years)	64 (54-72)	66 (58-75)
Current smoking	37099 (16%)	73531 (15%)
Duration of diabetes mellitus (years)	0 (0-0)	4 (2-10)
Insulin treatment	18245 (8%)	115416 (24%)
History of CVD	43879 (19%)	111927 (23%)
eGFR (mL/min/1.73m^2)	88 (73-99)	83 (66-95)
Moderate albuminuria	28452 (12%)	75775 (16%)
Severe albuminuria	8210 (4%)	35244 (7%)
Systolic blood pressure (mmHg)	135 (125-145)	140 (128-150)
Body mass index (kg/m^2)	30 (27-34)	29 (26-33)
HbA1c (mmol/mol)	50 (44-60)	51 (44-60)
Non-HDL-c (mmol/L)	3.8 (3.1-4.6)	3.6 (2.9-4.3)
Prescribed RASi medication	102883 (45%)	196676 (41%)

Variables are displayed as median (IQR) for continuous variables and counts (%) for categorical variables. Abbreviations: CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, non-HDL-c = non-high-density-lipoprotein cholesterol, RASi = Renin-angiotensin-system inhibition medication

Supplementary table 7. Baseline variables in the internal validation dataset (n = 170,114) stratified according to predicted 10-year ESKD risk

	1st risk decile (n = 17,035)	2nd risk decile (n = 16,996)	3rd risk decile (n = 17,011)	4th risk decile (n = 17,035)	5th risk decile (n = 16,984)	6th risk decile (n = 17,020)	7th risk decile (n = 17,002)	8th risk decile (n = 17,009)	9th risk decile (n = 17,011)	10th risk decile (n = 17,011)
Mean 10-year risk of ESKD (%)	0.16%	0.22%	0.28%	0.33%	0.40%	0.48%	0.62%	0.88%	1.46%	7.29%
Sex (male)	1907 (11%)	5844 (34%)	9888 (58%)	11,262 (66%)	11,839 (70%)	11,640 (68%)	11,181 (66%)	11,126 (65%)	11,310 (67%)	11,655 (69%)
Age (years)	67 (54-77)	64 (54-72)	63 (54-71)	63 (54-70)	62 (55-70)	63 (55-71)	64 (56-72)	66 (58-73)	67 (59-74)	70 (62-76)
Current smoking	708 (4%)	1893 (11%)	1905 (11%)	2375 (14%)	3235 (19%)	3694 (22%)	3697 (22%)	3261 (19%)	3446 (20%)	3307 (19%)
Duration of diabetes mellitus (years)	1 (0-3)	1 (0-4)	1 (0-4)	1 (0-5)	1 (0-6)	2 (0-7)	2 (0-8)	3 (0-8)	4 (1-10)	7 (1-14)
Insulin treatment	812 (5%)	1318 (8%)	1552 (9%)	2036 (12%)	2660 (16%)	3321 (20%)	3888 (23%)	4067 (24%)	4938 (29%)	7418 (44%)
History of CVD	3295 (19%)	3271 (19%)	3209 (19%)	3016 (18%)	3215 (19%)	3285 (19%)	3364 (20%)	3944 (23%)	4354 (26%)	5684 (33%)
eGFR (mL/min/1.73m^2, CKD-EPI)	93 (85-101)	92 (84-100)	92 (83-100)	91 (81-99)	88 (78-98)	84 (73-96)	78 (67-94)	74 (62-92)	70 (56-90)	53 (41-69)
Micro-albuminuria	27 (0.2%)	72 (0.4%)	107 (0.6%)	265 (1.6%)	588 (3.5%)	1189 (7%)	2713 (16%)	5736 (34%)	7727 (45%)	6325 (37%)
Macroalbuminuria	0	0	0	0	10 (0.1%)	22 (0.1%)	106 (0.6%)	529 (3.1%)	2215 (13%)	7214 (42%)
Systolic blood pressure (mmHg)	130 (120-140)	130 (120-140)	132 (125-140)	135 (126-145)	138 (130-148)	140 (130-150)	140 (130-150)	140 (130-150)	140 (130-153)	140 (130-159)
Body mass index (kg/m^2)	28 (25-31)	29 (26-33)	29 (26-32)	30 (27-33)	30 (27-33)	30 (27-34)	30 (27-34)	30 (27-34)	30 (27-34)	30 (27-34)
HbA1c (mmol/mol)	47 (42-52)	48 (43-54)	48 (43-55)	49 (44-57)	50 (44-60)	52 (45-63)	52 (45-66)	52 (45-65)	54 (46-67)	56 (47-69)
Non-HDL-c (mmol/L)	3.5 (2.9-4.2)	3.6 (2.9-4.3)	3.6 (2.9-4.3)	3.6 (2.9-4.4)	3.7 (3.0-4.4)	3.7 (3.0-4.5)	3.7 (3.0-4.5)	3.7 (3.0-4.5)	3.6 (2.9-4.4)	3.6 (2.9-4.4)

Variables are displayed as median (IQR) for continuous variables and counts (%) for categorical variables. Abbreviations: CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, non-HDL-c = non-high-density-lipoprotein cholesterol

Supplementary table 8. Example of a life table

Age	Cumulative survival	% ESKD risk	% Mortality risk	% Attributable ESKD risk	% Sum attributable ESKD risk
55.00	1.000000	0.111	0.206	0.111	0.111
55.25	0.996829	0.111	0.210	0.110	0.221
55.50	0.993634	0.111	0.213	0.110	0.331
55.75	0.990415	0.111	0.217	0.110	0.441
56.00	0.987173	0.110	0.220	0.109	0.550
56.25	0.983907	0.110	0.224	0.109	0.659
56.50	0.980613	0.111	0.228	0.108	0.767
56.75	0.977292	0.110	0.232	0.108	0.875
57.00	0.973944	0.110	0.236	0.107	0.982
57.25	0.970569	0.110	0.241	0.107	1.089
57.50	0.967163	0.110	0.245	0.107	1.196
57.75	0.963725	0.110	0.250	0.106	1.302
58.00	0.960257	0.110	0.254	0.106	1.408
58.25	0.956757	0.110	0.259	0.106	1.514
58.50	0.953223	0.111	0.264	0.105	1.619
58.75	0.949653	0.110	0.269	0.105	1.724
59.00	0.946049	0.110	0.274	0.105	1.829
59.25	0.942409	0.111	0.280	0.104	1.933
59.50	0.938730	0.111	0.285	0.104	2.037
59.75	0.935012	0.111	0.291	0.104	2.141
60.00	0.931255	0.111	0.297	0.103	2.244
60.25	0.927458	0.111	0.303	0.103	2.347
60.50	0.923618	0.111	0.309	0.103	2.450
60.75	0.919735	0.111	0.316	0.102	2.552
61.00	0.915808	0.111	0.322	0.102	2.654
61.25	0.911837	0.112	0.329	0.102	2.756
61.50	0.907818	0.112	0.336	0.101	2.857
61.75	0.903752	0.112	0.343	0.101	2.958
62.00	0.899638	0.112	0.351	0.101	3.059
62.25	0.895475	0.112	0.359	0.100	3.159
62.50	0.891260	0.112	0.367	0.100	3.259
62.75	0.886995	0.112	0.375	0.100	3.359
63.00	0.882676	0.112	0.383	0.099	3.458
63.25	0.878303	0.112	0.392	0.099	3.557
63.50	0.873876	0.112	0.401	0.098	3.655
63.75	0.869392	0.112	0.410	0.098	3.753
64.00	0.864852	0.113	0.419	0.097	3.850

Supplementary table 8. Continued

Age	Cumulative survival	% ESKD risk	% Mortality risk	% Attributable ESKD risk	% Sum attributable ESKD risk
64.25	0.860253	0.113	0.429	0.097	3.947
64.50	0.855594	0.113	0.439	0.096	4.043
64.75	0.850875	0.113	0.449	0.096	4.139
65.00	0.846094	0.113	0.460	0.095	4.234
75.00	0.591590	0.102	1.278	0.060	7.414
75.25	0.583427	0.101	1.313	0.059	7.473
75.50	0.575175	0.101	1.349	0.058	7.531
75.75	0.566835	0.100	1.386	0.057	7.588
76.00	0.558408	0.100	1.425	0.056	7.644
76.25	0.549896	0.099	1.464	0.055	7.699
76.50	0.541301	0.099	1.505	0.053	7.752
76.75	0.532623	0.098	1.546	0.052	7.804
77.00	0.523866	0.097	1.589	0.051	7.855
77.25	0.515030	0.097	1.634	0.050	7.905
77.50	0.506120	0.096	1.679	0.049	7.954
77.75	0.497136	0.095	1.726	0.047	8.001
78.00	0.488082	0.094	1.774	0.046	8.047
78.25	0.478961	0.094	1.824	0.045	8.092
78.50	0.469776	0.093	1.875	0.044	8.136
78.75	0.460530	0.092	1.928	0.042	8.178
79.00	0.451228	0.092	1.982	0.041	8.219
79.25	0.441873	0.091	2.037	0.040	8.259
79.50	0.432469	0.090	2.095	0.039	8.298
79.75	0.423021	0.089	2.154	0.038	8.336
80.00	0.413533	0.088	2.214	0.037	8.373
91.00	0.057784	0.039	7.558	0.002	9.044
91.25	0.053394	0.037	7.769	0.002	9.046
91.50	0.049226	0.036	7.986	0.002	9.048
91.75	0.045277	0.034	8.209	0.002	9.050
92.00	0.041545	0.033	8.438	0.001	9.051
92.25	0.038026	0.031	8.672	0.001	9.052
92.50	0.034716	0.030	8.913	0.001	9.053
92.75	0.031612	0.028	9.160	0.001	9.054
93.00	0.028707	0.027	9.414	0.001	9.055

Supplementary table 8. Continued

Age	Cumulative survival	% ESKD risk	% Mortality risk	% Attributable ESKD risk	% Sum attributable ESKD risk
93.25	0.025997	0.025	9.674	0.001	9.056
93.50	0.023475	0.024	9.941	0.001	9.057
93.75	0.021136	0.022	10.215	0.000	9.057
94.00	0.018973	0.021	10.495	0.000	9.057
94.25	0.016977	0.019	10.783	0.000	9.057
94.50	0.015143	0.017	11.078	0.000	9.057
94.75	0.013463	0.016	11.381	0.000	9.057

Life-table of a patient example: a 55-year old male, who does not smoke, duration of type 2 diabetes of 5 years, a systolic blood pressure of 150 mmHg, BMI of 27 kg/m^2, HbA1c of 55 mmol/mol, non-HDL-C of 5 mmol/l, eGFR of 70 ml/min/1.73m^2, severe albuminuria, no insulin use, and a history of cardiovascular disease.

ESKD-risk (%) and all-cause mortality risk (%) are derived using the equations depicted in Supplementary table 4. ESKD-free life expectancy is the age at which the cumulative survival drops below 0.50, for this patient ESKD-free life expectancy is thus 78 years. The patient further has a 10-year risk of ESKD of 4.2% and a lifetime risk of ESKD of 9.1%.

Attributable risk = ESKD risk / (all-cause mortality risk + ESKD risk)(cumulative survival at beginning of current life-year – cumulative survival at beginning of next life-year).*

For feasibility reasons, some parts of the lifetable has been omitted in this example (indicated with the dotted line), for the calculations of course the lifetable in its full is used.

Supplementary Table 9. Model assumptions

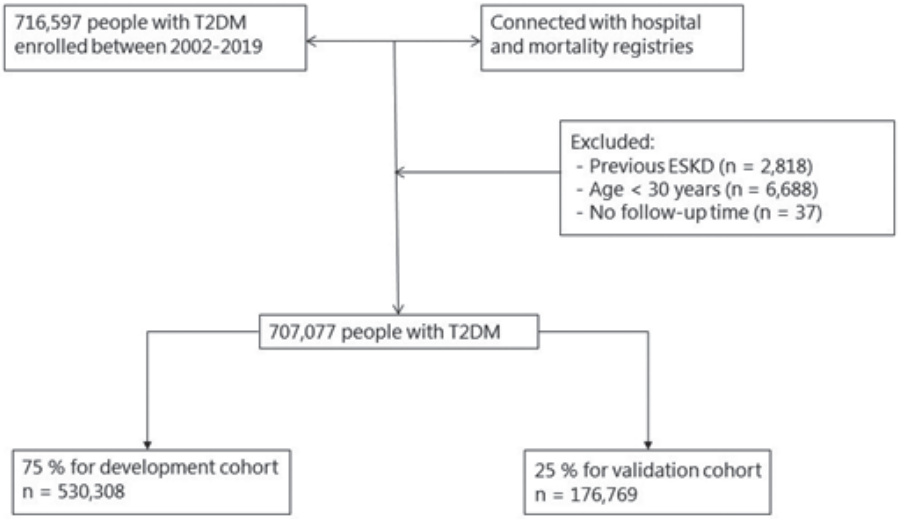
Assumption	Explanation
Lifetime prediction	
Proportional hazards	The model assumes proportional hazards for all predictors, meaning that hazard ratios are assumed to be constant over time. Since age is used as time scale, the assumption is made that hazard ratios are constant over age (e.g. the hazard ratio for male sex at age 50 years is the same as at age 80 years). The proportional hazards assumption is tested using Schoenfeld residuals, and visual inspection of hazard ratios plotted against age. If a hazard ratio for a predictor significantly changes with age, an interaction term between this predictor and age is included in the model.
Linearity of the predictor-outcome relation	The model assumes a linear relationship between continuous predictors and the outcome. For all continuous predictors in relation to the outcome, it is assessed whether a logarithmic or quadratic transformation of the predictor substantially improves model fit. If the AIC decreases by ≥ 2 points, the transformation is included in the final model.
Natural course of predictors	The model assumes that predictors follow a natural course over time (i.e. age) that matches the course of predictors in the derivation cohort. Model predictions are based on the current predictor levels of a patient (e.g. an eGFR of 80 ml/min/1.73m2). Predictor levels might change with age (e.g. a decrease in eGFR), but this happened during the follow-up period in the derivation cohort as well. As long as the change in predictor levels follows the same course over time as in the derivation cohort and the derivation cohort has substantial follow-up time, no adjustment is needed. However, for lifetime predictions, follow-up time is not sufficient, and these results should be interpreted with caution, especially in younger patients.
Stationarity of baseline hazards	The model assumes that the baseline survival for each age interval is equal for all patients, during that interval. It assumes that the baseline survival for an age interval (e.g. between 60 years and 60 years and 3 months) is equal for patients currently within that interval (i.e. patients who just turned 60 years old) as well as patients entering that interval in the future (e.g. 50-year olds who will turn 60 in 10 years). It is assumed that the baseline survivals are stationary over time (i.e. baseline survival for a 60-year old now is equal to baseline survival for a 60-year old in the future).
Treatment effects	
Equal relative treatment effect	It is assumed that relative treatment effects (i.e. the hazard ratios derived from meta-analyses) are equal for all patients for whom a treatment is recommended (e.g. the HR of SGLT2i therapy for ESKD is 0.71 for all patients with type 2 diabetes). This assumption is made since subgroup analyses from trials and meta-analyses mostly have not identified significant differences in relative treatment effects between eligible patients with varying characteristics. Also, subgroup analyses are underpowered for the detection of heterogeneity in relative treatment effects.

Supplementary table 9. Continued

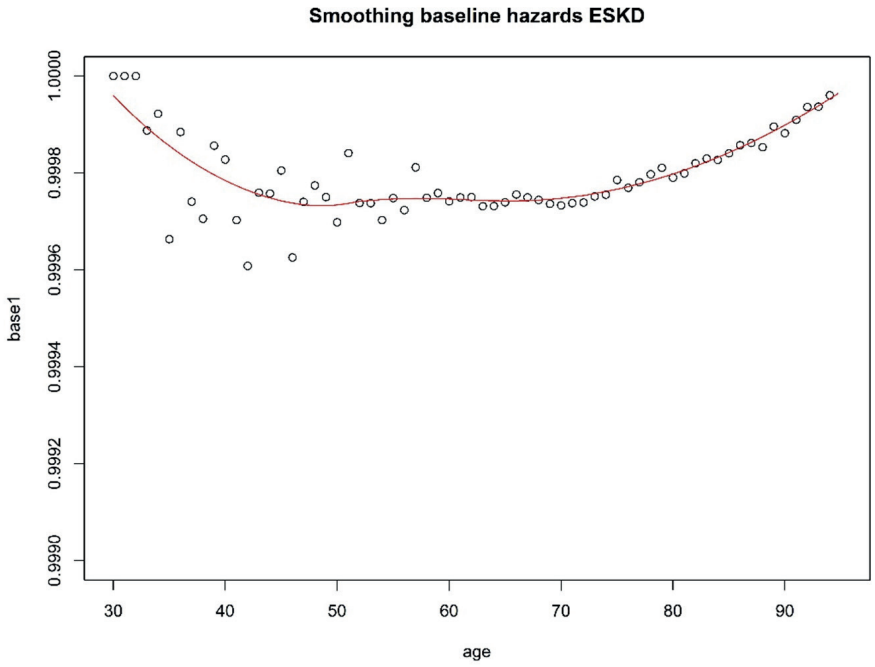
Assumption	Explanation
Constant treatment effect over time	It is assumed that the relative treatment effects remain constant over time, so that therapy benefits continue to accrue over lifetime exposure. In other words, it is assumed that the hazard ratios found in actual trials or meta-analyses are equal to hazard ratios that would have been found in trials with lifelong follow-up.
Additive benefits	It is assumed that benefits of individual therapies are multiplicative when used simultaneously.
Adequate adherence	It is assumed that patients remain adherent to the prescribed therapies for their remaining lifetimes. Reassuring in this regard is that data have shown that clustered initiation of recommended therapies is safe,[22] and that adding new therapies to extensive background therapy does not result in more serious adverse events. Also, adherence in trials is mostly also not 100%.

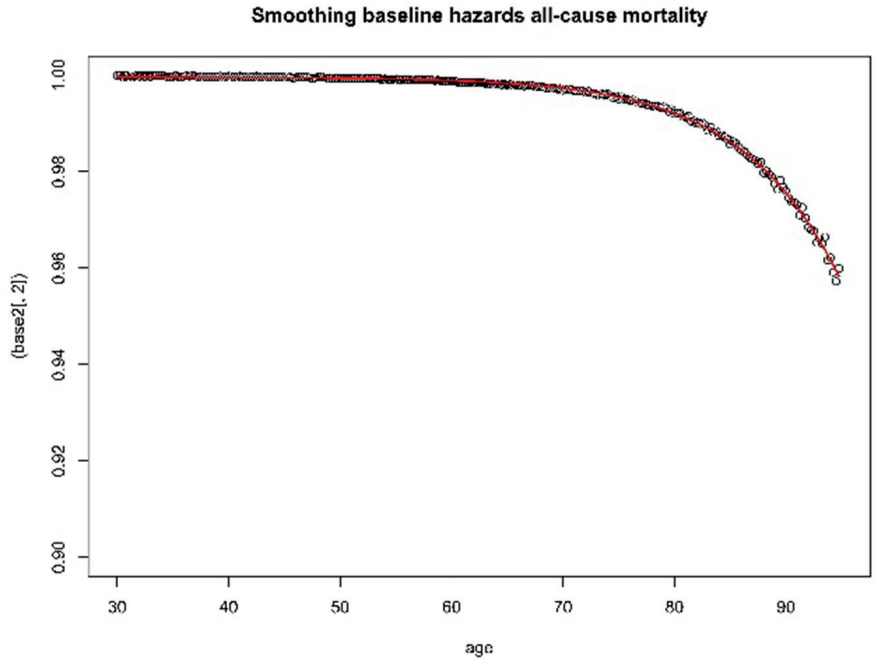
Abbreviations: AIC = Akaike Information Criterion, HR = hazard ratio, SGLT2 = sodium/glucose cotransporter 2.

Supplementary figure 1. Selection of cohort Swedish National Diabetes Register



Supplementary figure 2. Smoothing and interpolation of baseline hazards





References, supplementary material

1. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. Bmj. 2010;341:c6624.
2. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014;100 Suppl 2:ii1-ii67.
3. Dorresteijn JA, Kaasenbrood L, Cook NR, van Kruijsdijk RC, van der Graaf Y, Visseren FL, Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj. 2016;352:i1548.
4. 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.
5. 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.
6. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, Tunnicliffe D, Ruospo M, Natale P, Saglimbene V, Nicolucci A, Johnson DW, Tonelli M, Rossi MC, Badve SV, Cho Y, Nadeau-Fredette AC, Burke M, Faruque LI, Lloyd A, Ahmad N, Liu Y, Tiv S, Millard T, Gagliardi L, Kolanu N, Barmanray RD, McMorrow R, Raygoza Cortez AK, White H, Chen X, Zhou X, Liu J, Rodríguez AF, González-Colmenero AD, Wang Y, Li L, Sutanto S, Solis RC, Díaz González-Colmenero F, Rodriguez-Gutierrez R, Walsh M, Guyatt G, Strippoli GFM. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. Bmj. 2021;372:m4573.
7. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021;6(2):148-158.
8. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653-662.
9. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D, Rosano GM, Davis BR, Ridao M, Zaragoza A, Montero-Corominas D, Tobías A, de la Fuente-Honrubia C, Tabarés-Seisdedos R, Hutton B. Cardiovascular and Renal Outcomes of Renin-Angiotensin System Blockade in Adult Patients with Diabetes Mellitus: A Systematic Review with Network Meta-Analyses. PLoS Med. 2016;13(3):e1001971.
10. Berkelmans GFN, Read SH, Gudbjörnsdottir S, Wild SH, Franzen S, van der Graaf Y, Eliasson B, Visseren FLJ, Paynter NP, Dorresteijn JAN. Population median imputation was noninferior to complex approaches for imputing missing values in cardiovascular prediction models in clinical practice. J Clin Epidemiol. 2022;145:70-80.
11. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111-1130.
12. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-967.

13. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, Hayward RA, Craven T, Coleman RL, Chalmers J. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol. 2017;5(6):431-437.
14. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, Arima H, Monaghan H, Joshi R, Colagiuri S, Cooper ME, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Lisheng L, Mancia G, Marre M, Matthews DR, Mogensen CE, Perkovic V, Poulter N, Rodgers A, Williams B, MacMahon S, Patel A, Woodward M. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med. 2014;371(15):1392-1406.
15. Navaneethan SD, Schold JD, Jolly SE, Arrigain S, Winkelmayer WC, Nally JV, Jr. Diabetes Control and the Risks of ESRD and Mortality in Patients With CKD. Am J Kidney Dis. 2017;70(2):191-198.
16. Liao LN, Li CI, Liu CS, Huang CC, Lin WY, Chiang JH, Lin CC, Li TC. Extreme Levels of HbA1c Increase Incident ESRD Risk in Chinese Patients with Type 2 Diabetes: Competing Risk Analysis in National Cohort of Taiwan Diabetes Study. PLoS One. 2015;10(6):e0130828.
17. Xia J, Wang L, Ma Z, Zhong L, Wang Y, Gao Y, He L, Su X. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Nephrol Dial Transplant. 2017;32(3):475-487.
18. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. Arch Intern Med. 2012;172(11):837-844.
19. Grams ME, Sang Y, Ballew SH, Matsushita K, Astor BC, Carrero JJ, Chang AR, Inker LA, Kenealy T, Kovesdy CP, Lee BJ, Levin A, Naimark D, Pena MJ, Schold JD, Shalev V, Wetzels JFM, Woodward M, Gansevoort RT, Levey AS, Coresh J. Evaluating Glomerular Filtration Rate Slope as a Surrogate End Point for ESKD in Clinical Trials: An Individual Participant Meta-Analysis of Observational Data. J Am Soc Nephrol. 2019;30(9):1746-1755.
20. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006;113(1):30-37.
21. Heerspink HJL, Jongs N, Chertow GM, Langkilde AM, McMurray JJV, Correa-Rotter R, Rossing P, Sjöström CD, Stefansson BV, Toto RD, Wheeler DC, Greene T. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9(11):743-754.
22. Cai Y, Shi W, Xu G. The efficacy and safety of SGLT2 inhibitors combined with ACEI/ARBs in the treatment of type 2 diabetes mellitus: A meta-analysis of randomized controlled studies. Expert Opin Drug Saf. 2020;19(11):1497-1504.

CHAPTER 7

Estimating individual lifetime risk of incident cardiovascular events in adults with type 2 diabetes: an update and geographical calibration of the DIAbetes Lifetime perspective model (DIAL2)

Helena Bleken Østergaard*
Steven H J Hageman*
Stephanie H Read*
Owen Taylor*
Lisa Pennells
Stephen Kaptoge
Carmen Petitjean
Zhe Xu
Fanchao Shi
John William McEvoy
William Herrington
Frank L J Visseren
Angela Wood
Björn Eliasson†
Naveed Sattar†
Sarah H. Wild†
Emanuele Di Angelantonio†
Jannick A N Dorresteijn†

† Contributed equally
* Contributed equally

Eur J Prev Cardiol. 2023 Jan 11;30(1):61-69

Abstract

Background: The 2021 ESC cardiovascular disease (CVD) prevention guidelines recommend the use of (lifetime) risk prediction models to aid decisions regarding intensified preventive treatment options in adults with type 2 diabetes, e.g. the DIAbetes Lifetime perspective model (DIAL model). The aim of this study was to update the DIAL-model using contemporary and representative registry data (DIAL2) and to systematically calibrate the model for use in other European countries.

Methods and Results: The DIAL2 model was derived in 467,856 people with type 2 diabetes without a history of CVD from the Swedish National Diabetes Register, with a median follow-up of 7.3 years (IQR 4.0-10.6 years) and comprising 63,824 CVD (including fatal CVD, nonfatal stroke and nonfatal myocardial infarction) events and 66,048 non-CVD mortality events. The model was systematically recalibrated to Europe's low and moderate risk region using contemporary incidence data and mean risk factor distributions. The recalibrated DIAL2 model was externally validated in 218,267 individuals with type 2 diabetes from the Scottish Care Information – Diabetes (SCID) and Clinical Practice Research Datalink (CPRD). In these individuals, 43,074 CVD events and 27,115 non-CVD fatal events were observed. The DIAL2 model discriminated well, with C-indices of 0.732 (95%CI 0.726-0.739) in CPRD and 0.700 (95%CI 0.691-0.709) in SCID.

Interpretation: The recalibrated DIAL2 model provides a useful tool for the prediction of CVD-free life expectancy and lifetime CVD risk for people with type 2 diabetes without previous CVD in the European low and moderate risk regions. These long-term individualized measures of CVD risk are well suited for shared decision making in clinical practice as recommended by the 2021 CVD ESC prevention guidelines.

Introduction

Type 2 diabetes is a common chronic disease, with a worldwide prevalence of currently more than 6%.[1] Despite major advances in treatment, cardiovascular disease (CVD, defined as myocardial infarction, stroke and fatal cardiovascular disease) remains the main cause of morbidity and premature mortality in this population.[2] One consideration in the primary prevention of CVD is the use of (lifetime) risk prediction tools. The 2021 European Society of Cardiology (ESC) prevention guidelines introduced a two-step approach as an individualized CVD prevention strategy. A first line approach of treatment is applicable to all people with type 2 diabetes. In step two, intensified preventive treatment should be considered for each individual while taking into account personal preferences, expected side effects and predicted 10-year CVD risk and/or lifetime prediction measures.[3] Lifetime prediction measures can be useful for supporting shared-decision making and projecting the lifetime effect of preventive treatment.

Different risk scores are available for use in people with type 2 diabetes. For estimating recurrent CVD risk in people with type 2 diabetes and established CVD, who are classified as being at 'very high risk' for a recurrent CVD event,[3] the SMART2-risk score[4] (10-year risk) and SMART-REACH model[5] (lifetime risk) can be used. However, in people with type 2 diabetes without established CVD the individual level of 10-year or lifetime CVD risk varies considerably ranging from low to very high depending on individual and regional risk factors.[6] The 2021 ESC CVD prevention guidelines suggest the use of the ADVANCE risk score or DIAL-model for estimating CVD risk in this group of people,[3] as these models include diabetes-specific variables and have been externally validated.[7, 8]

The DIAL model estimates 10-year and lifetime CVD risk, life expectancy free of (recurrent) CVD and lifetime treatment benefit from risk factor treatment in people with type 2 diabetes aged 30 to 85 years.[8] The model is available via the ESC CVD risk calculation app and as an interactive online calculator www.U-Prevent.com. The DIAL model was developed in a cohort of people with type 2 diabetes from the Swedish National Diabetes Register (NDR) included up until 2012. However, the continuous and ongoing inclusion of people with type 2 diabetes in the Swedish NDR provides the opportunity to use more recent data and longer follow-up for derivation of a more contemporary model that is

capable of predicting 10-year and lifetime risks of CVD. Also, recent advances in geographical recalibration methods using aggregated age- and sex-specific average risk factor levels and CVD incidence rates and non-CVD mortality rates from nationally representative registry data[9, 10] allow for contemporary and geographic recalibration of the model.

The aim of this current study was to update and externally validate the DIAL prediction model (i.e. DIAL2) for estimation of lifetime risk of incident CVD in people with type 2 diabetes without established CVD, and to calibrate the DIAL2 model to different geographical risk regions using an approach to easily update and enhance the accuracy of risk predictions with changing epidemiology of CVD in the future.

Methods

Study populations

The target population for the DIAL2 model consists of people with type 2 diabetes *without* established CVD (defined as coronary heart disease, stroke and peripheral artery disease) and aged 30-85 years. The DIAL2 model was developed using the Swedish NDR, which includes people with both incident and prevalent type 2 diabetes and has close to complete coverage of the population with a diagnosis of type 2 diabetes in Sweden during the study period (currently approximately 95% coverage). Details of the Swedish NDR have been described elsewhere.[11] For this study, all participants registered in the Swedish NDR on January 1st 2008 as well as participants registering up until January 1st 2018 were included. Baseline date was set as January 1st 2008 for those already registered in the Swedish NDR on this date and as date of enrollment for those registered after this date. All baseline characteristics were determined at baseline date, and if missing at this date, a time frame of inclusion of measurements of two years prior and six months after baseline was allowed (*Supplementary Figure 1*).

For external validation, we used the Scottish Care Information -Diabetes database[12] (SCID, n = 143,042) and the Clinical Practice Research Datalink (CPRD) for England[13] (n = 72,215). SCID is a dynamic population-based register of people with a diagnosis of diabetes in Scotland that has had almost complete coverage since 2006 from which research extracts are linked to national population-based

hospital and death records. Ethical and data governance approval for use of the linked database for research was obtained from the Scotland A multi-center research ethics committee (reference: 11-AL-0225) and the Public Benefit and Privacy Panel for health and social care in Scotland (reference: 1617-0147). CPRD is an ongoing primary care database of anonymized medical records from general practitioners, with coverage of over 11.3 million patients from 674 practices in the UK.[12] With 4.4 million active (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included and patients are broadly representative of the UK general population in terms of age, sex and ethnicity. The CPRD data used for this study is restricted to the region of England. Model validation used records from both the SCID and the CPRD obtained for individuals with diabetes during the period on 1st of June 2008 with risk factors recorded nearest to this date, included during the prior two years or following 6 months. Endpoints were obtained by linkage with Hospital Episode Statistics (HES) and death records from the Office of National Statistics (ONS). From these cohorts, all people with type 2 diabetes and without established CVD aged 30 to 85 years were included. The definition of type 2 diabetes diagnosis in all data sources can be found in *Supplementary Table 1*.

Predictors and outcome variables

Two versions of the DIAL2 model were derived, a core model and an extended model including additional diabetes-specific risk factors. The predictors for the core DIAL2 model were predefined based on clinical availability and included age, sex, current smoking status (yes/no), systolic blood pressure (SBP) (mmHg), total cholesterol, high-density-lipoprotein-cholesterol (HDL-c), estimated glomerular filtration rate (eGFR) (estimated using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation, CKD-EPI[14]), HbA1c and age at onset of type 2 diabetes (years). Furthermore, we derived an extended model with the aforementioned predictors as well as additional diabetes specific risk factors with sufficient availability in the development cohort. These additional variables were albuminuria (urine-albumin/creatinine ratio of <3 mg/mmol for none to mild albuminuria, 3-30 mg/mmol for moderate albuminuria and >30mg/mmol for severe albuminuria[15]), body mass index (kg/m^2), retinopathy (yes/no) and insulin use (yes/no). Previous research has shown that the associations of these risk factors with CVD decline with increasing age,[10] therefore interactions with baseline age for all predictors were added. To assess the association of

continuous predictors with outcome variables, visual inspection of restricted cubic splines was used and this led to a log transformation of eGFR.

The outcomes of interest were CVD and non-CVD mortality, respectively. CVD was defined as a composite of nonfatal myocardial infarction, nonfatal stroke or cardiovascular mortality (death due to coronary heart disease, heart failure, stroke and sudden death). Non-CVD mortality was defined as death from any non-CVD cause. Endpoints were obtained by linkage to hospital records and mortality registers using ICD-10 codes (*Supplementary Table 2*), and did not include events observed in primary care practices.

Derivation of the DIAL2 algorithm

To account for differences in the relative effects of certain predictors between men and women, the models were derived separately for men and women. The coefficients for the DIAL2 model were estimated by fitting two cause-specific Cox proportional hazards models with left truncation and right censoring thereby using age as the time-scale; one was developed with CVD-event as outcome (function A) and another for non-CVD mortality as outcome (function B). Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. Missing data were imputed by single imputation by predicted mean matching, further details regarding missing data are described in the *Supplementary Methods*. Baseline hazards for both functions were derived using 1-year intervals and smoothed using a LOESS function. By combining the coefficients from the cause-specific Cox proportional hazards functions A and B and the smoothed baseline hazards, lifetime risk of CVD and non-CVD mortality was estimated. This was done by adapting previously validated lifetable methods.[16] Hereby, cumulative survival for both outcomes combined was calculated using one-year predictions for all future life years of an individual, enabling adjustment for competing risks. Lifetime risk of CVD was then calculated as the cumulative risk from an individual's current age onwards until the maximum age of 95 years. A detailed description of statistical methods is provided in the statistical section in the *Supplementary material*.

Geographical recalibration

The DIAL2 model was systematically recalibrated to the European risk regions defined in the 2021 ESC Cardiovascular Prevention Guidelines (*Supplementary*

Figure 2), using similar methods as were used for recalibration of SCORE2 and SCORE2-OP.[17, 18] The methodology as well as the necessary adaptations of these methods for lifetime models and the population of patients with diabetes are explained in detail in *Supplementary methods*. In short, mean region-, age- and sex-specific risk factor values for individuals with diabetes and no prior CVD were obtained using CPRD data for low risk region and from the Swedish NDR data for moderate risk region. Annual CVD and non-CVD mortality rates were extracted from WHO global burden of disease database.[19] Previously published SCORE2 multipliers were used to convert WHO CVD mortality rates of the total population to incidence of fatal and non-fatal CVD in people not having established CVD, including both apparently healthy people and people with diabetes[17]. Secondly, incidence of fatal and non-fatal CVD in people not having established CVD was converted to incidence of fatal and non-fatal CVD in people with type 2 diabetes using the SCORE2/SCORE2-OP hazard ratio (HR) of having diabetes for the respective event, adjusted for the age- and sex-specific prevalence of diabetes.[20, 21] The same approach was used to convert WHO non-CVD mortality rates to non-CVD mortality rates in individuals with diabetes. Prevalence of type 2 diabetes was obtained from the NCDRisc risk factors collaboration. Hazard ratios for diabetes on CVD and non-CVD mortality were obtained from SCORE2[17] and SCORE2-OP[18] (*Supplementary figure 3*).

Model validation

Discrimination was quantified using Harrell's C-statistic corrected for competing risks.[22] Calibration was assessed visually by plotting predicted 10-year risks against 10-year CVD cumulative incidences adjusted for competing risks. Our approach to model development and validation complies with PROBAST guidelines[23] and TRIPOD.[24]

Absolute risk reduction of CVD event from risk factor treatment

A theoretical application of the DIAL2 model is the estimation of individualized benefit from cardiovascular risk factor management.[25] This process is described in detail in *Supplementary material, methods*. To estimate the effect of blood pressure and cholesterol lowering on CVD risk, average relative treatment effects estimated in large meta-analyses may be combined with DIAL2 predictions. Examples of this include the effect of lowering SBP using a HR of

0.80 per 10 mmHg SBP reduction[26] or the effect of LDL reduction with an HR of 0.78 per 1 mmol/L.[27] All analyses were performed with R-statistic programming (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 16.1, StataCorp, College Station, Texas).

Sensitivity analyses

Since 40% of the derivation population were on lipid-lowering agents, we performed sensitivity analyses assessing discrimination of the core model in the external validation cohorts in people with and without use of lipid-lowering agents, respectively. Also, we validated the original DIAL model and the ADVANCE risk score for 10-year predictions of CVD in the Swedish NDR cohort and the SCID cohort. It was not feasible to validate these models in the CPRD cohort due to several predictors not being available.

Results

Model derivation

The Swedish NDR cohort used for derivation comprised of 467,856 people with type 2 diabetes and without established CVD. Mean age at baseline was 63 years and 55% were male. Median age at type 2 diabetes diagnosis was 58 years (IQR 50-67 years). Baseline characteristics are presented in *Table 1*. Median follow-up was 7.3 years (IQR 4.0-10.6 years), in which 63,824 incident CVD events and 66,048 non-CVD mortality events were observed. For the core model, the C-statistic in the derivation dataset was 0.709 (95% CI 0.703-0.714) for CVD events and 0.723 (95% CI 0.718-0.728) for non-CVD mortality events. For the extended model, the C-statistic in the derivation dataset was 0.713 (95% CI 0.708-0.718) for CVD events (*Supplementary table 6*). All parameters necessary for individual predictions are listed in the *Supplementary Materials*: coefficients for individual predictions for both the core and extended model are shown in *Supplementary Table 3*, and shown graphically across different ages in *Supplementary Figure 4*. The age-specific baseline hazards are provided in *Supplementary Table 4*. The smoothed baseline hazards are shown in *Supplementary Figure 5*.

Geographical recalibration

The DIAL2 model was recalibrated to the low and moderate risk regions using the age-, sex-, and region-specific risk factor levels and CVD incidence rates

and non-CVD mortality incidences. After recalibration, the DIAL2 incidence rates observed well with the incidence rates for recalibrating the CVD events (*Supplementary Figure 6*) and the rates for recalibrating non-CVD mortality (*Supplementary Figure 7*). The rescaling factors derived for geographical recalibration are provided in *Supplementary Table 5*. Distributions of all individual prediction measures from DIAL2 in Swedish NDR are shown in *Figure 1*. Individuals below 70 years of age had relatively low 10-year CVD event risks in comparison to older individuals, but higher lifetime CVD risks (*Figure 1*).

Table 1. Baseline characteristics of the Swedish National Diabetes Register cohort for derivation after imputation

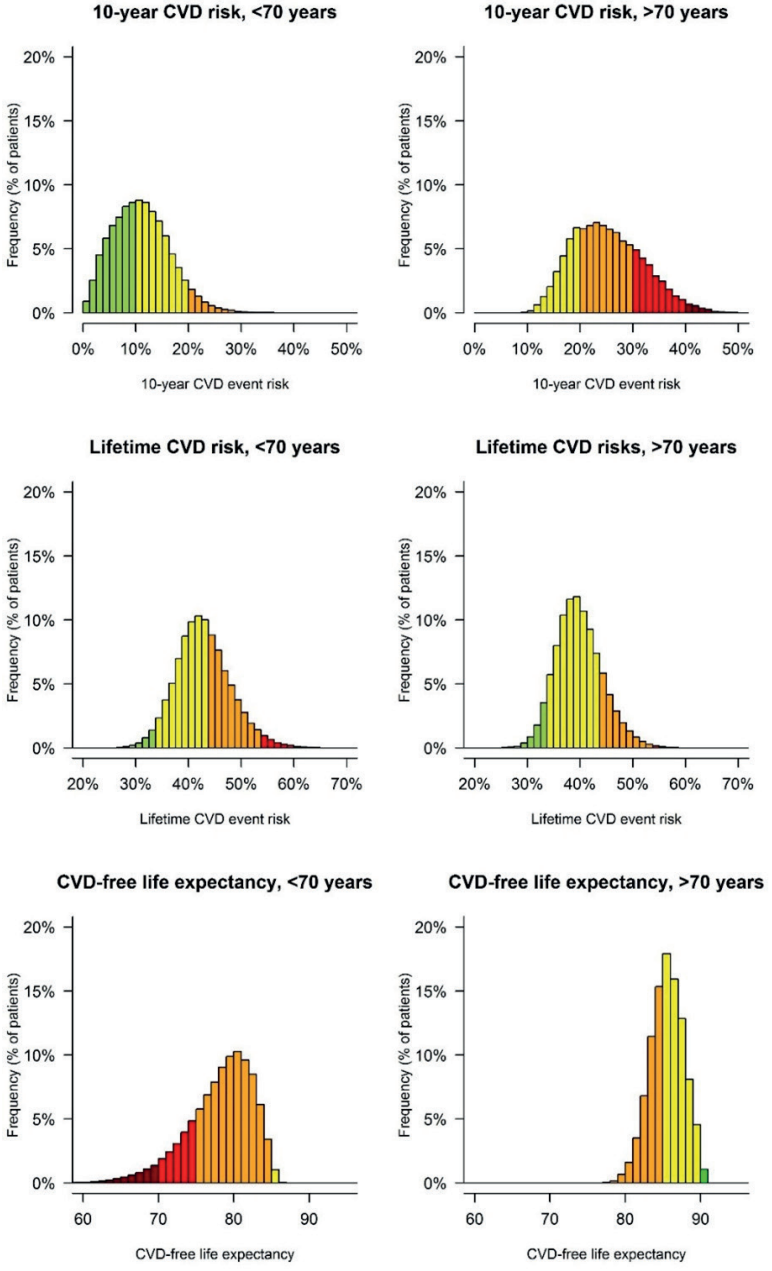
	Women (n = 211,761; 45%)	**Men (n = 256,095; 55%)**
Age (years)	65 ± 12	62 ± 12
Current smoking	31,503 (15%)	42,871 (17%)
Insulin use	36,619 (17%)	48,577 (19%)
Age at T2D onset	60 (51-69)	57 (49-65)
Antihypertensive medication use	138,869 (66%)	155,513 (61%)
Lipid-lowering medication use	83,560 (40%)	99,996 (39%)
Antiplatelet medication use	45,268 (21%)	57,536 (23%)
Systolic blood pressure (mmHg)	138 ± 17	138 ± 16
Diastolic blood pressure (mmHg)	78 ± 10	80 ± 10
Body mass index (kg/m2)	31 ± 6	30 ± 5
eGFR (ml/min/1.73m2)	85 (68-97)	90 (76-100)
Moderate albuminuria	26,937 (13%)	41,793 (16%)
Severe albuminuria	9,371 (4%)	16,450 (6%)
HbA1c (mmol/mol)	54 ± 15	56 ± 17
Triglycerides (mmol/L)	1.8 ± 1.2	2.0 ± 1.7
Total cholesterol (mmol/L)	5.2 ± 1.1	5.0 ± 1.1
HDL-c (mmol/L)	1.4 ± 0.4	1.2 ± 0.3
LDL-c (mmol/L)	3.0 ± 1.0	2.9 ± 1.0

Data are shown as mean ± SD or n (%) or median (IQR). eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, T2D = type 2 diabetes. Albuminuria was defined as a urine-albumin/creatinine ratio of < 3 mg/mmol for none to mild albuminuria, 3-30 mg/mmol for moderate albuminuria and urine-albumin/creatinine ratio >30mg/mmol for severe albuminuria.

Validation of the model

After recalibration, the DIAL2 model was validated in the data from CPRD, in SCID (both low risk region) and the Swedish NDR (moderate risk region).

Figure 1. Distribution of 10-year and lifetime CVD prediction measures in individuals younger and older than 70 years in Swedish NDR



Distribution of individual prediction measures from the DIAL2 model in Swedish NDR after recalibration to the moderate risk region.

Detailed characteristics of the individuals included in the external validation are shown in *Table 2*. In CPRD, validation included 75,215 individuals with type 2 diabetes comprising 7,286 CVD events and 5,236 non-CVD fatal events during a median follow-up of 6.1 years (IQR 0.8-11). In the validation performed in SCID, 143,042 individuals with type 2 diabetes were included, comprising 35,788 CVD events and 21,879 non-CVD fatal events during a median follow-up of 11.0 years (IQR 6.7-11.0). For predicting CVD events, the C-statistics were 0.732 (95%CI 0.726-0.739) and 0.700 (95%CI 0.691-0.709) in CPRD and SCID, respectively (*Figure 2*). C-statistics for predicting the outcome of non-CVD mortality are also shown in *Figure 2*.

Table 2. Baseline characteristics of the external validation cohorts

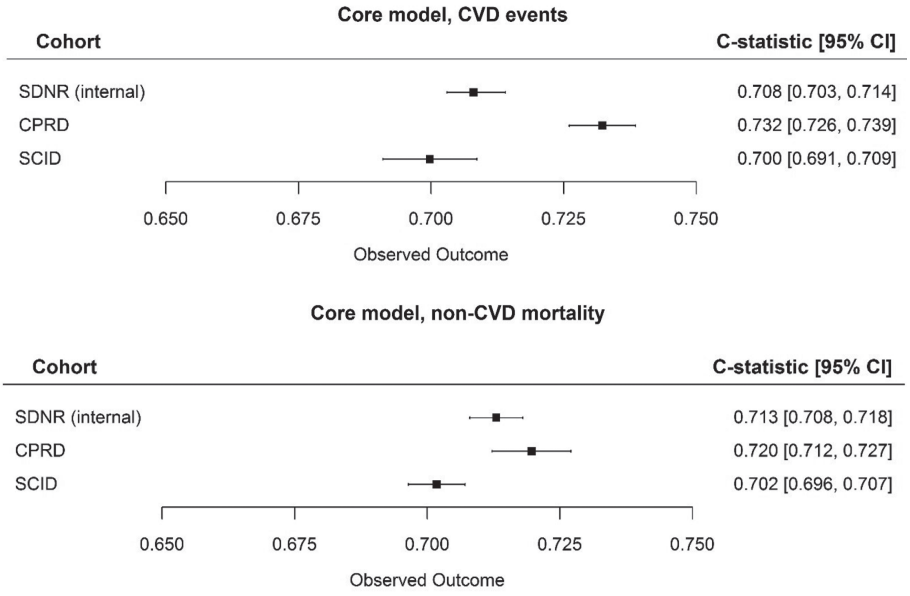
	CPRD (n = 75,215)	**SCID (n = 143,042)**
Age (years), mean ± SD	63 ± 12	63 ± 13
Male sex, n (%)	39,708 (53%)	75,797 (53%)
Current smoking, n (%)	11,999 (21%)	27,383 (19.1%)
Insulin use		44,303 (30.9%)
Age at T2D onset, median (IQR)	57 (49-66)	58 (49-66)
Antihypertensive medication use		78,744 (55.0%)
Lipid-lowering medication use		70,007 (49.0%)
Antiplatelet medication use		48,714 (34.1%)
Systolic blood pressure (mmHg), mean ± SD	136 ± 16	135.6 ± 16.3
Diastolic blood pressure (mmHg)		87.1 ± 5.9
Body mass index (kg/m2)		32.5 ± 6.6
eGFR (ml/min/1.73m2), median (IQR)	75 (61-90)	79.8 (67.2-98.0)
Moderate albuminuria		26,319 (18.4%)
Severe albuminuria		3,969 (2.7%)
HbA1c (mmol/mol), mean ± SD	59 ± 17	58.0 ± 17.1
Triglycerides (mmol/L)		2.3 ± 1.3
Total cholesterol (mmol/L), mean ± SD	4.4 ± 1.1	4.4 ± 1.1
HDL-c (mmol/L), mean ± SD	1.2 ± 0.4	1.2 ± 0.4
LDL-c (mmol/L)		2.3 ± 0.8

Data are shown as mean ± SD or n (%) or median (IQR). eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, T2D = type 2 diabetes. Albuminuria was defined as a urine-albumin/creatinine ratio of 3-30 mg/mmol for moderate albuminuria and urine-albumin/creatinine ratio >30mg/mmol for severe albuminuria.

For the extended model, the C-statistic for predicting CVD events was 0.705 (0.695-0.714) in the SCID (*Supplementary Table 6*). Validation of the extended

model in CPRD was not feasible since all additional variables were not available in this dataset. Predicted 10-year CVD risks from the core DIAL2 model corresponded well with observed incidences up until 70 years of age in Swedish NDR and CPRD (*Supplementary Figure 8*). In older individuals, predictions were adequate in Swedish NDR but underestimated in CPRD. In SCID, observed incidence was higher than predicted CVD risks. 10-year predictions of non-CVD mortality corresponded well with observed incidences in Swedish NDR and SCID but were overestimated in CPRD (*Supplementary Figure 9*).

Figure 2. C-indices of the core DIAL2 model for assessing CVD events and non-CVD mortality

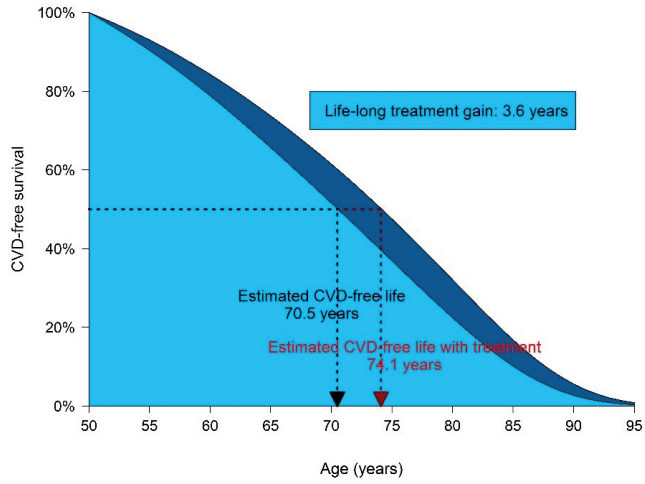


Absolute CVD event risk reduction from risk factor management

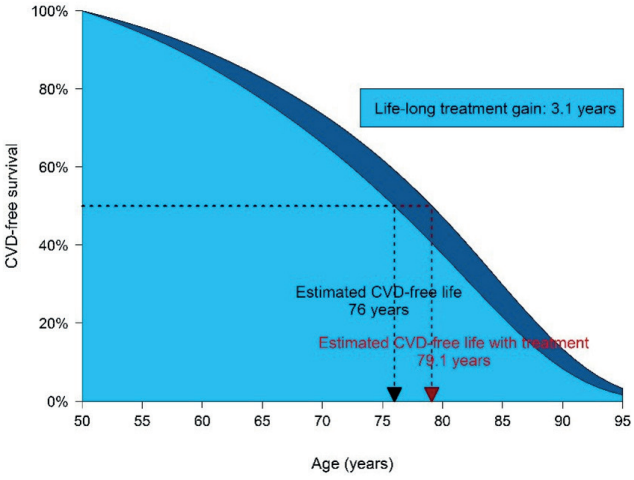
Figure 3 displays the estimated CVD-free life expectancy and gain in CVD-free life expectancy from a 10 mmHg SBP reduction and 1.5 mmol/L LDL-c reduction for two individuals with type 2 diabetes, both men from a moderate risk region and aged 50 years both of whom have the following conventional risk factor levels: non-smoker, SBP of 140 mmHg, total cholesterol of 5.5 mmol/L, HDL cholesterol of 1.3 mmol/L. Example A additionally has an HbA1c of 75 mmol/mol, diagnosis of type 2 diabetes 10 years prior to current age and an eGFR of 70 ml/min/1.73m2. Example B has an HbA1c of 50 mmol/mol, newly diagnosed type 2 diabetes and an eGFR of 70 ml/min/1.73m2.

Figure 3. Theoretical example of lifetime benefit from 10 mmHg reduction in systolic blood pressure and 1.5 mmol/L reduction in LDL-c in two individuals with type 2 diabetes

Individual A:



Individual B:



Theoretical example of combining predicted CVD-free life expectancy with trial evidence on therapy benefit. Estimated CVD-free life expectancy and gain in CVD-free life expectancy from a 10 mmHg systolic blood pressure reduction and 1.5 mmol/L LDL-c for two individuals with type 2 diabetes, both men from a moderate risk region and aged 50 years with conventional risk factor levels (non-smoker, systolic blood pressure of 140 mmHg, total cholesterol of 5.5 mmol/L, HDL cholesterol of 1.3 mmol/L). Example A has an HbA1c of 75 mmol/mol, diagnosis of type 2 diabetes 10 years prior to current age and an eGFR of 70 ml/min/1.73m2. Example B has an HbA1c of 50 mmol/mol, newly diagnosed type 2 diabetes and an eGFR of 70 ml/min/1.73m2.

Sensitivity analyses

Discriminative performance of the core model was comparable among those on lipid lowering therapy and those not on lipid lowering therapy (*Supplementary Table 7*). C-statistic for the original DIAL model for CVD events was 0.558 (0.555-0.560) in the Swedish NDR and 0.556 (0.538-0.574) in SCID. C-statistic for the ADVANCE risk score for CVD events was 0.673 (0.670-0.675) in the Swedish NDR and 0.674 (0.656-0.692) in SCID (*Supplementary Table 8*).

Discussion

This paper described the development and external validation of the DIAL2 model for predicting lifetime risk of CVD in people with type 2 diabetes without established CVD. The model further allows for estimating CVD-free life expectancy to aid in individualized cardiovascular risk management. The updated DIAL2 model was recalibrated and validated using data from Europe's low and moderate risk regions.

The DIAL2 model has several advantages and added clinical relevance as compared to the previously published DIAL model and other CVD risk prediction models for individuals with type 2 diabetes. The DIAL2 model showed improved discrimination for 10-year predictions as compared to the original DIAL model and the ADVANCE risk score. The low C-statistic for the original DIAL model is likely due to the model being derived in people with and without established CVD together, with the majority of events happening in the group of people with type 2 diabetes and established CVD. This affected discrimination in people with type 2 diabetes but without established CVD negatively, underlining the importance of updating the model. Furthermore, the key advantage of the DIAL2 model in comparison to its predecessors is the recalibration using contemporary and representative data on CVD and non-CVD mortality incidence and risk factor levels translated to populations with type 2 diabetes. This enables the use of the DIAL2 model across countries with different levels of CVD risk. By using a recalibration approach based on registry data, the model can be readily updated to reflect future CVD incidence and risk factor profiles as updated data become available. Due to a lack of reliable risk factors and external validation data in the high and very high risk region, the model was only recalibrated to the low and moderate risk region

at this point. However, the updated DIAL2 model is ready for recalibration to the high and very-high European risk regions as soon as such data become available for these countries. Previous CVD risk prediction models in people with type 2 diabetes did not perform recalibration to different populations or were recalibrated based on small cohorts or trial data, which may not reflect contemporary region-specific CVD and non-CVD mortality rates.

Additionally, the DIAL2 model accounts for non-CVD mortality as competing risk, an asset that is crucial in preventing overestimation of risks and treatment benefits, especially in older individuals.[22] Moreover, the extended DIAL2 model performed slightly better than the core model in terms of discrimination and further incorporates several diabetes-specific risk factors, including albuminuria which is a very important risk factor in people with type 2 diabetes.[28] For individuals with such risks factors available in clinical practice the extended model therefore allows for more accurate predictions.

Furthermore, model derivation, recalibration and validation was performed in large and contemporary cohorts, enhancing accuracy and generalizability to individuals with type 2 diabetes without established CVD across different European countries, and minimizing the risk of model overfitting. The recalibrated model performed well both in regards to discriminating risk in individuals with type 2 diabetes in all data sources and showed generally adequate agreement between predicted and observed CVD risks both in the low and moderate risk region, underlining the validity of the recalibrated model. After recalibration to the low risk region, a systematic underestimation of CVD event risks was observed in Scottish data from SCID. These findings can likely be explained by the fact that the UK as a whole is considered low risk of CVD mortality, but Scotland is an outlier within the UK in having higher rates.[29] These differences between countries also highlight the need for country-specific recalibration. Should high-quality data in specific countries be available, then the methodology as described in the current paper could be used to tailor the risk score to these specific countries.

The DIAL2 model can be used to estimate several prediction measures including CVD-free life expectancy. In contrary to the original DIAL model, 10-year risk is not predicted with the DIAL2 model as this will be possible with the SCORE2-Diabetes model which has been developed in parallel, featuring

the same risk regions, predictors and similar recalibration methodology. As these key features have been streamlined between the two models, 10-year predictions from SCORE2-Diabetes and lifetime predictions from DIAL2 can be consistently used in parallel, allowing easy implementation in clinical practice and use of prediction parameters deemed most relevant for every individual.

Since age is the primary driver of 10-year CVD risk, lifetime measures might at times be a suitable additional measure to help make treatment decisions, especially in younger and older individuals with type 2 diabetes. In younger people, 10-year CVD risks will often be considered low, although lifelong benefit from long-term use of preventive treatment may be substantial.[30] On the other hand, older persons almost always have very high 10-year CVD risks, but due to their limited remaining life expectancies, their benefit from preventive therapy may be small. Lifetime predictions, including CVD-free life expectancy, directly relate to life expectancy and are furthermore adjusted for competing risks, making them more suitable for individualized risk assessment and treatment in younger and older individuals.[3]

The 2021 ESC prevention guidelines recommend a two-step approach as an individualized CVD prevention strategy in each individual with type 2 diabetes. Step 1 includes prevention goals for all, i.e. stop smoking, lifestyle recommendations, and Hba1c <53 mmol/mol. In addition, patients with a diabetes duration >10 years but no established CVD or severe target organ damage are recommended to lower SBP <140 to 130 mmHg and LDL-c to <2.6 mmol/L. In addition, step 2 prevention goals should be considered in all patients, taking into account personal preferences, expected side effects and predicted 10-year CVD risk and/or lifetime prediction measures.[3] Step 2 prevention goals are SBP <130 mmHg, LDL-c <1.8 mmol/L, and initiation of SGLT2-i or GLP1-RA. Lifetime prediction measures can be useful for supporting shared-decision making on these step 2 prevention goals and to project the lifetime effect of preventive treatment. These interventions are to be initiated in a shared-decision making process, which requires a good understanding of these risk measures by both patient and physician. Lifetime risks and gain in CVD-free life years by initiation of preventive treatment have been shown to be an intuitive concept for individuals when considering preventive treatment.[31]

Several limitations of the current study merit consideration. First of all, a validation was only performed for up to 10 years, since the cohort data did

not have longer follow-up. Although previous studies have shown the validity of lifetime predictions for up to 17 years,[16] predictors may change during the course of a lifetime and as long-term follow-up data become available, the model will benefit from longer timeframe validations to further validate the methodology.

Furthermore, ideally more data should be used for both estimating the mean risk factor levels for people with type 2 diabetes in each region and for the diabetes-specific CVD and non-CVD mortality event rates. This is currently not feasible with the lack of diabetes-specific representative and contemporary cohorts. However, the current methodology using general population data adapted to the diabetes-specific situation has been shown to lead to adequate calibration and can be used until high quality data with national coverage are available specifically for people with diabetes.

Another limitation is that model derivation was only performed in Swedish data from the Swedish NDR data, and ideally this would have involved data from all relevant regions in which the model is intended for usage. Reassuringly, previous studies have found the relative effects of model coefficients to be stable over geographical areas.[10, 32] Also, information on ethnicity, family history of premature CVD and socio-economic status was not available in the Swedish NDR used for model derivation, so we were not able to incorporate these predictors, even though they may be of added relevance in clinical practice. For estimation of the rescaling factors used for geographical recalibration, region-specific mean risk factor levels were obtained from country-specific cohorts, which may not be representative for the whole region. However, the recalibrated DIAL2 model performed well in cohorts from both the low- and moderate risk regions.

It should also be emphasized that the DIAL2 model does not predict other adverse outcomes in people with type 2 diabetes, such as incident heart failure or progression to kidney failure, which may also be key indications to initiate preventive treatment. The model may thus underestimate the total benefit from treatment which may also differ for different preventive agents.

In conclusion, lifetime CVD risk as well as CVD-free life expectancy can be estimated based on readily available patient characteristics using the DIAL2 model. The DIAL2 model is calibrated accounting for geographical differences

in CVD incidence and mortality for European low and moderate risk regions, and is ready for further recalibration to high and very high risk regions as soon as the relevant data become available. The DIAL2 model may be used to support shared decision making in clinical practice as recommended by the 2021 CVD ESC prevention guidelines.

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health 2020;10:107-111.
2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol 2018;17:83.
3. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-3337.
4. Hageman SHJ, McKay AJ, Ueda P, Gunn LH, Jernberg T, Hagström E, Bhatt DL, Steg PG, Läll K, Mägi R, Nordbø Gynnild M, Ellekjær H, Saltvedt I, Tuñón J, Mahíllo I, Aceña Á, Kaminski K, Chlabicz M, Sawicka E, Tillman T, McEvoy JW, Di Angelantonio E, Graham I, De Bacquer D, Ray KK, Dorresteijn JAN, Visseren FLJ. Estimation of recurrent atherosclerotic cardiovascular event risk in patients with established cardiovascular disease: the updated SMART2 algorithm. Eur Heart J 2022.
5. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB, Sr., Massaro JM, van der Graaf Y, Cramer MJM, Kappelle LJ, de Borst GJ, Steg PG, Visseren FLJ. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. J Am Heart Assoc 2018;7:e009217.
6. van Staa TP, Gulliford M, Ng ES, Goldacre B, Smeeth L. Prediction of cardiovascular risk using Framingham, ASSIGN and QRISK2: how well do they predict individual rather than population risk? PLoS One 2014;9:e106455.
7. 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. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil 2011;18:393-8.
8. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, Wild SH, Franzen S, Chalmers J, Davis BR, Poulter NR, Spijkerman AM, Woodward M, Pressel SL, Gupta AK, van der Schouw YT, Svensson AM, van der Graaf Y, Read SH, Eliasson B, Dorresteijn JAN. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. Eur Heart J 2019;40:2899-2906.
9. Pennells L, Kaptoge S, Wood A, Sweeting M, Zhao X, White I, Burgess S, Willeit P, Bolton T, Moons KGM, van der Schouw YT, Selmer R, Khaw KT, Gudnason V, Assmann G, Amouyel P, Salomaa V, Kivimaki M, Nordestgaard BG, Blaha MJ, Kuller LH, Brenner H, Gillum RF, Meisinger C, Ford I, Knuiman MW, Rosengren A, Lawlor DA, Völzke H, Cooper C, Marín Ibañez A, Casiglia E, Kauhanen J, Cooper JA, Rodriguez B, Sundström J, Barrett-Connor E, Dankner R, Nietert PJ, Davidson KW, Wallace RB, Blazer DG, Björkelund C, Donfrancesco C, Krumholz HM, Nissinen A, Davis BR, Coady S, Whincup PH, Jørgensen T, Ducimetiere P, Trevisan M, Engström G, Crespo CJ, Meade TW, Visser M, Kromhout D, Kiechl S, Daimon M, Price JF, Gómez de la Cámara A, Wouter Jukema J, Lamarche B, Onat A, Simons LA, Kavousi M, Ben-Shlomo Y, Gallacher J, Dekker JM, Arima H, Shara N, Tipping RW, Roussel R, Brunner EJ, Koenig W, Sakurai M, Pavlovic J, Gansevoort RT, Nagel D, Goldbourt U, Barr ELM, Palmieri L, Njølstad I, Sato S, Monique Verschuren WM, Varghese CV, Graham I, Onuma O, Greenland P, Woodward M, Ezzati M, Psaty BM, Sattar N, Jackson R, Ridker PM, Cook NR, D'Agostino RB, Thompson SG, Danesh J, Di Angelantonio E. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. Eur Heart J 2019;40:621-631.

10. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Health 2019;7:e1332-e1345.
11. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care 2003;26:1270-6.
12. Cunningham S, McAlpine R, Leese G, Brennan G, Sullivan F, Connacher A, Waller A, Boyle DI, Greene S, Wilson E, Emslie-Smith A, Morris AD. Using web technology to support population-based diabetes care. J Diabetes Sci Technol 2011;5:523-34.
13. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827-36.
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
15. Group KDIGOKCW. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl, 3 2013:pp. 1-150.
16. Dorresteijn JA, Kaasenbrood L, Cook NR, van Kruijsdijk RC, van der Graaf Y, Visseren FL, Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. Bmj 2016;352:i1548.
17. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J 2021.
18. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J 2021.
19. Organization. WH. WHO Mortality Database. In; Accessed May 7, 2020., https://apps.who.int/healthinfo/statistics/mortality/whodpms/.
20. Kooter AJ, Kostense PJ, Groenewold J, Thijs A, Sattar N, Smulders YM. Integrating information from novel risk factors with calculated risks: the critical impact of risk factor prevalence. Circulation 2011;124:741-5.
21. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23:1111-30.
22. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology 2009;20:555-61.
23. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, Reitsma JB, Kleijnen J, Mallett S. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med 2019;170:51-58.
24. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Bmj 2015;350:g7594.
25. Dorresteijn JA, Visseren FL, Ridker PM, Wassink AM, Paynter NP, Steyerberg EW, van der Graaf Y, Cook NR. Estimating treatment effects for individual patients based on the results of randomised clinical trials. Bmj 2011;343:d5888.
26. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-967.
27. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, 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.

28. Fangel MV, Nielsen PB, Kristensen JK, Larsen TB, Overvad TF, Lip GY, Jensen MB. Albuminuria and Risk of Cardiovascular Events and Mortality in a General Population of Patients with Type 2 Diabetes Without Cardiovascular Disease: A Danish Cohort Study. Am J Med 2020;133:e269-e279.
29. Scotland PH. https://beta.isdscotland.org/find-publications-and-data/conditions-and-diseases/heart-disease-and-blood-vessels/heart-disease-statistics/.
30. Jaspers NEM, Blaha MJ, Matsushita K, van der Schouw YT, Wareham NJ, Khaw KT, Geisel MH, Lehmann N, Erbel R, Jöckel KH, van der Graaf Y, Verschuren WMM, Boer JMA, Nambi V, Visseren FLJ, Dorresteijn JAN. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Eur Heart J 2020;41:1190-1199.
31. Jaspers NEM, Visseren FLJ, van der Graaf Y, Smulders YM, Damman OC, Brouwers C, Rutten G, Dorresteijn JAN. Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial. BMJ Open 2021;11:e041673.
32. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, Azizi F, Cifkova R, Di Cesare M, Eriksen L, Farzadfar F, Ikeda N, Khalili D, Khang YH, Lanska V, León-Muñoz L, Magliano D, Msyamboza KP, Oh K, Rodríguez-Artalejo F, Rojas-Martinez R, Shaw JE, Stevens GA, Tolstrup J, Zhou B, Salomon JA, Ezzati M, Danaei G. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinol 2015;3:339-55.

Supplementary material

Expanded methods

Missing data

Missing data were singly imputed using predictive mean matching method (aregImpute-algorithm in R, Hmisc package) that involved taking probability weighted means of non-missing characteristics closest to the predicted value of a missing data point in regression model fitted to the observed data. Missing data in the Swedish NDR were infrequent: 3% for each of sex, age, eGFR, HbA1c and systolic blood pressure, 4% for smoking, 7% for total cholesterol, 10% for HDL-C and 12% for age at diabetes diagnosis.

Statistical analyses

Development of the lifetime model

The interlinked stages of model derivation and recalibration are summarized in *Supplementary Methods, Figure 1*. An overview of the process is as follows:

Box 1. Risk model derivation

The Swedish NDR dataset was used to derive risk prediction models for men and women with diabetes separately, without history of cardiovascular disease (CVD). Two cause-specific Cox proportional hazards models were fitted: one for the event of interest (incident CVD) and another for the competing event (non-CVD mortality), using age as the time scale with left truncation and right censoring. Participants contributed data to the survival models from their age at study entry until the time of a respective event or censoring, defined by age at study exit. Continuous predictors were standardised by subtracting the mean and dividing by the standard deviation. Age-specific baseline survivals were calculated in 1-year intervals from age 30 to 94 years for the two Cox proportional hazard models and smoothed using a local regression smoother (*Supplementary methods figure 2*). Interactions between predictors and age at risk (e.g. age for calculating yearly risk in the lifetables) were included to allow for expected age-dependent associations.

Box 2. Yearly cause-specific mortality risk in four previously defined risk regions

We aimed to update DIAL2 following a similar approach as used in the SCORE2 CVD risk algorithm that has been recommended for CVD risk assessment in people without diabetes in four risk regions of Europe.[1] The four risk regions were defined by grouping countries according to age-standardized CVD mortality rates calculated from the WHO mortality database. CVD-mortality comprised fatal events in the CVD endpoints considered, and non-CVD mortality comprised all other fatal events not in the CVD endpoint (for definitions see *Supplementary Table 2*). Region-level estimates of CVD and non-CVD mortality rates were obtained as the medians of country-specific rates by sex and 5-year age groups within the relevant region.

For the DIAL2 model development we similarly obtained the region-level CVD and non-CVD mortality rates, but using 1-year age groups. The cause-specific mortality rates were then converted to 1–year mortality risks (r) using the formula:

$$r = 1\ e^{-(-\text{fatal}_{\text{rateagegroup-and sex specific}})}$$

As the WHO rates cover 1-year intervals already, no interpolation was needed.

Box 3. Converting mortality rates to incidence estimates

To convert 1-year mortality estimates to incidence estimates, age- and sex-specific multiplication factors estimated previously for the SCORE2 model development were subsumed.

$$\text{multiplier} = \frac{\text{Cumulative 1 year incidence total CV events}_{\text{without prior CVD}}}{\text{Cumulative 1 year incidence fatal CV events}_{\text{entire population}}}$$

This was done to convert population level mortality statistics (calculated among the whole population regardless of prior disease status) into first event incidence estimates (which are representative of the target primary population without prior CVD). To be as consistent as possible to the SCORE2 methodology, no new multipliers were derived, and the multipliers from SCORE2 were applied to these 1-year mortality rates. The validity of this assumption was assessed by comparing the cumulative incidence of CVD mortality rates and CVD events at 1-year and 10-years in large-scale population-based data sources (*Supplementary Methods Figure 3*).

Multiplication factors were assumed to be stable within each region and over time which was additionally verified in several analyses in SCORE2.[1]

Box 4. Estimating yearly CVD incidence for patients with type 2 diabetes

The yearly incidence of first CVD event in the general population in people without prior CVD (Box 3) was translated to yearly incidence among people with type 2 diabetes using a naïve method[2] that assumes that the general population incidence rate is a weighted average of the incidence rates in people with and without diabetes. Thus it modifies predicted risks based on the population prevalence of diabetes and the hazard ratio (HR) for diabetes.

We used the NCD risk factor collaboration data to calculate the population prevalence of type 2 diabetes in each region. For the HR of diabetes on CVD event we used the age-specific estimates derived in the SCORE2 model[1] for people ≤ 65 years and estimates derived in the SCORE-OP model for people > 65 years[3] (*Supplementary Figure 3*).

We similarly calculated the HR for non-CVD mortality with diabetes in the dataset used for derivation of SCORE2 (sex-specific Fine and Gray model stratified by cohort fit using ERFC and UK Biobank data), with non-CVD mortality as primary endpoint and CVD event as competing endpoint. All predictors, including age interactions, were the same as in SCORE2.

Population relative risk was calculated using the prevalence of type 2 diabetes per region (from the NCD data) as:

$$\text{Population RR} = \text{T2D prevalence}_{\text{region}} * \text{HR for diabetes} + (1 - \text{T2D prevalence}_{\text{region}})$$

Risks were thereafter modified as follows:

$$\text{One-year risk in T2D} = 1 - (1 - (\text{one - year risk}))^{\text{HR for T2D}/(\text{population RR})}$$

Box 5. Recalibration of the DIAL-2 model

Predicted (uncalibrated) 1-year risks of CVD events and non-CVD mortality were estimated by applying the uncalibrated DIAL2 model to age- and sex-specific means of predictor variables within each region for every year of age from age 40 years. The means of predictors were obtained from cohorts of people with type 2 diabetes in each region: CPRD for low-risk region and Swedish NDR for moderate-risk region.

Recalibration of the core DIAL2 model was completed separately for each risk region and sex using the previously published and validated process[1] as described in *Supplementary Methods Figure 2*. Expected age- and sex- specific

1-year risks (Box 4) were regressed on the DIAL-2 model predicted 1-year risks (Box 5) with transformations to derive rescaling factors (the intercept and slope of the resulting regression line) for recalibration in each risk region. Since the age-groups of 35 and 40 years were observed to be outliers and due to the low prevalence of events in these age-groups (<2%) in the dataset used for derivation of coefficients and baseline hazards (for esti-mating predicted CVD-risk), we did not include these in the calculation of the rescaling factors.

Predictions for individual persons

In order to calculate CVD-free life expectancy (median survival without CVD) and CVD risk, life-tables were estimated with 1-year time intervals. Starting at the current age of an individual with T2D, the risk of having a CVD-event (a_t) combined with the risk of a non-CVD mortality event (b_t) were predicted for each future 1-year interval. Next, the cumulative CVD-free survival ($Surv_{t+1}$) was calculated by multiplying the survival probability at the beginning of each 1-year interval ($Surv_t$) by the CVD-free survival probability during that 1 year ($Surv_t * a_t - b_t$). Logically 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 CVD, determined as the age where the estimated cumulative survival drops below 50%. The attributable CVD-risk was obtained by multiplication of the probability of survival without a CVD-event at the beginning of the 1-year interval ($Surv_t$) and the risk of having a CVD-event (a_t) during that year. Similarly, lifetime risk was calculated by the summation of the attributable CVD risk from a person's current age onwards until the age of 95.

Predicting treatment effects from risk factor treatment using DIAL2

It has previously been shown that risk estimations can be combined with relative treatment effects from trials to calculate absolute individualized treatment effects.[4,5] To show the potential use of using DIAL2 in daily clinical practice, we included an example on the individual absolute benefit of blood pressure lowering and lipid lowering in people with type 2 diabetes. To estimate the effect of blood pressure lowering on CVD, average relative treatment effects were added to DIAL2, using a hazard ratio (HR) of 0.80 per 10 mmHg SBP reduction taken from a large meta-analysis for blood pressure lowering, and estimating the benefit from a 10 mmHg blood pressure lowering for a patient example.

For lipid lowering, an HR of 0.78 per 1 mmol/L LDL reduction was used and the treatment benefit of a 1.5 mmol/L lowering was likewise estimated for a patient example. For both treatment effects, it was assumed that the HR can be applied across the entire age range. Indeed, no evidence for heterogeneity of these treatment effects across different age ranges has been found.

Treatment benefit was calculated for the respective risk factor treatment by combining the HR with the individualized estimated CVD event risks as used in the lifetable (here an example shown for a HR per 10 mmHg SBP reduction):

$$\text{Risk}_{\text{with treatment}} = 1 - (1 - \text{risk}_{\text{original}})^{\exp(\log(HR)\times((\text{SBP reduction})/10))}$$

Treatment effects are calculated in the lifetable for every 1-year separately, thereby taking into account the probability of having a CVD event or non-CVD fatal event before the moment of interest.

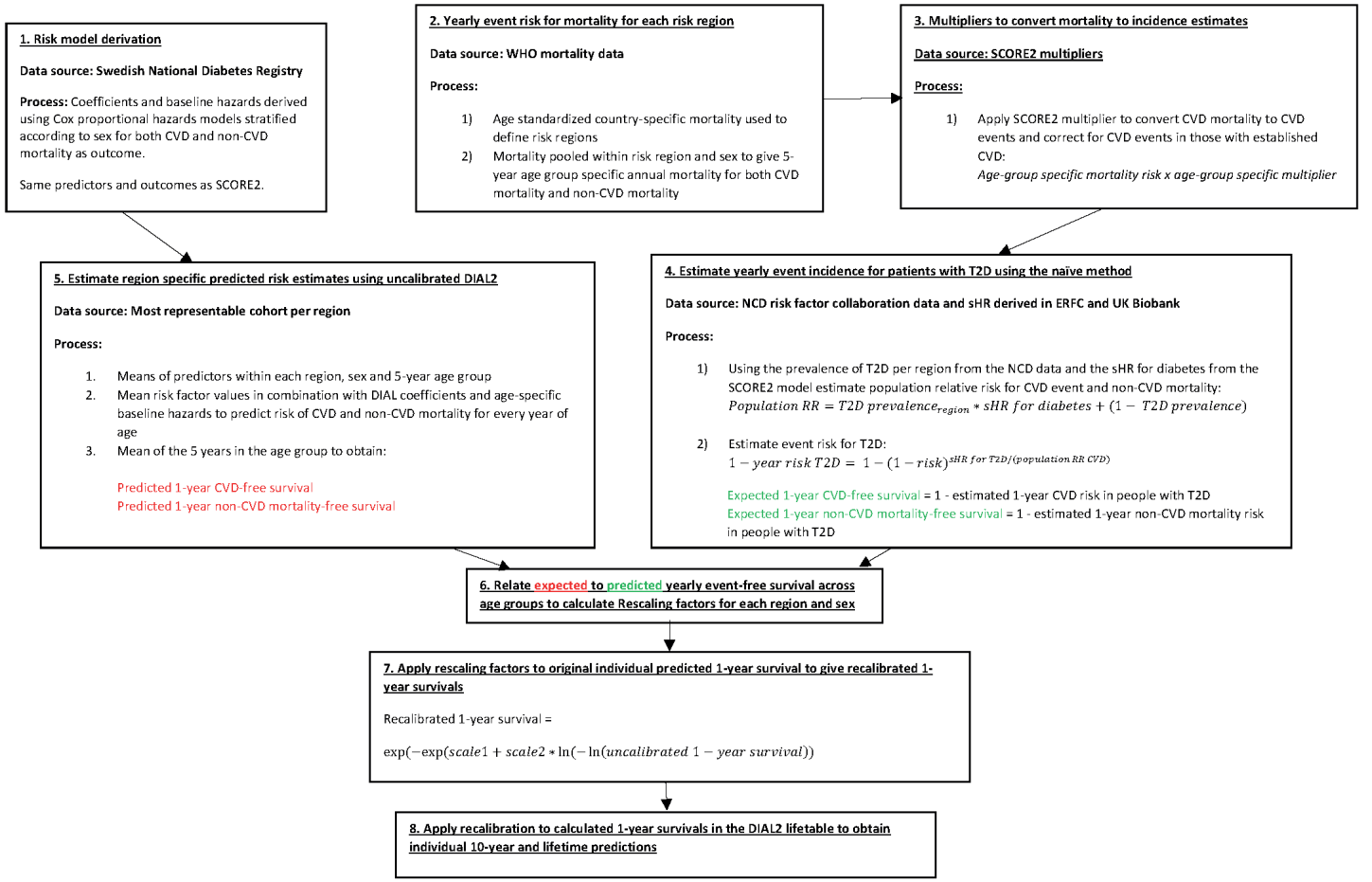
Treatment benefit for individual patients is defined as the gain in life years with the initiated treatment:

Gain in CVDfree life years=median CVDfree life expectancy-treated median CVDfree life expectancy

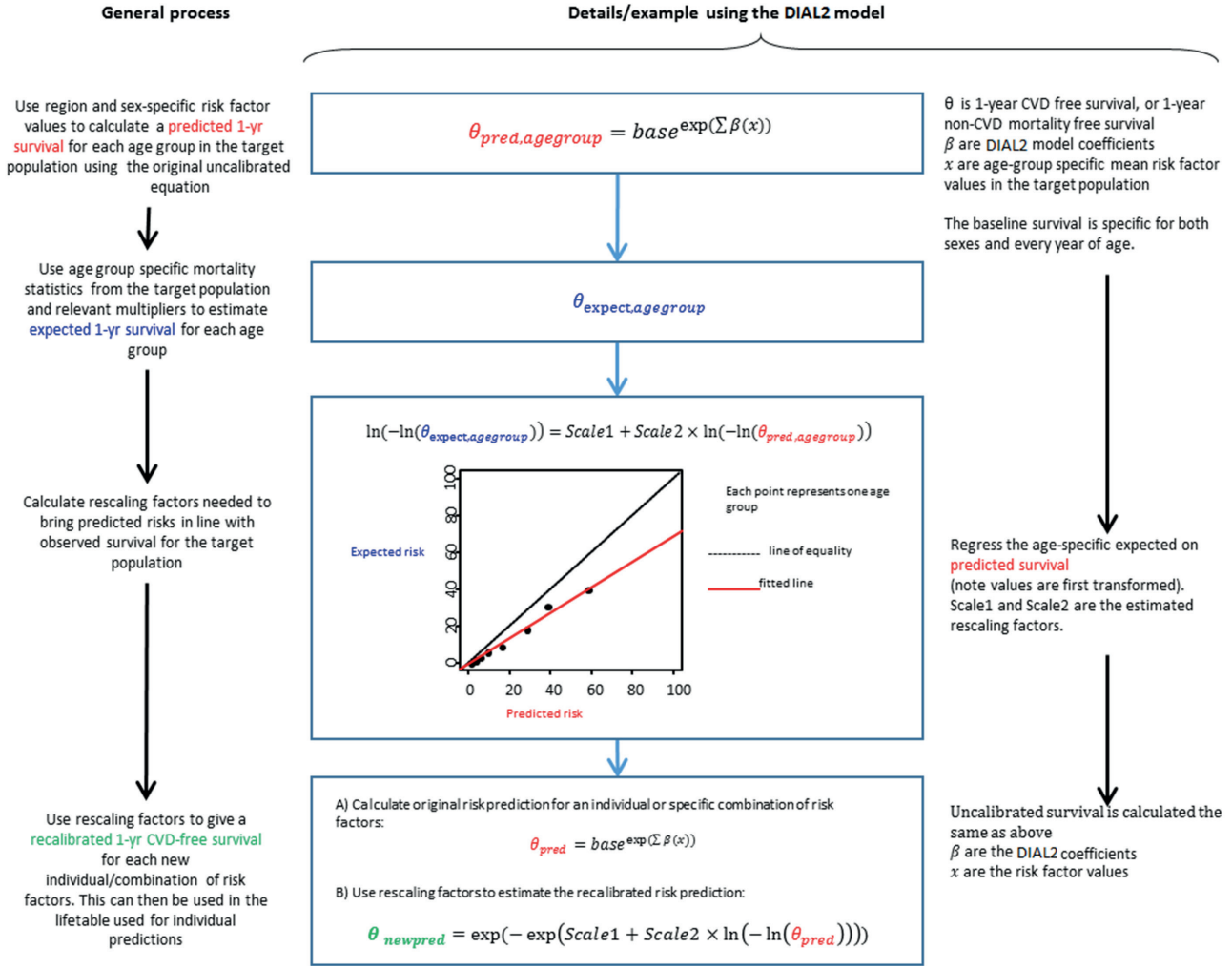
References, Supplementary material

1. Hageman S, Pennells L, Ojeda F, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-2454. doi:10.1093/eurheartj/ehab309
2. Berkelmans GFN, Read SH, Gudbjörnsaottir S, et al. Dealing with Missing Patient Characteristics When Using Cardiovascular Prediction Models in Clinical Practice.; 2018.
3. de Vries TI, Cooney MT, Selmer RM, et al. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455-2467. doi:10.1093/eurheartj/ehab312
4. Dorresteijn JAN, Visseren FLJ, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ. 2011;343(oct03 1):d5888-d5888. doi:10.1136/bmj.d5888
5. Jaspers NEM, Blaha MJ, Matsushita K, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Eur Heart J. 2019;31:1-10. doi:10.1093/eurheartj/ehz23

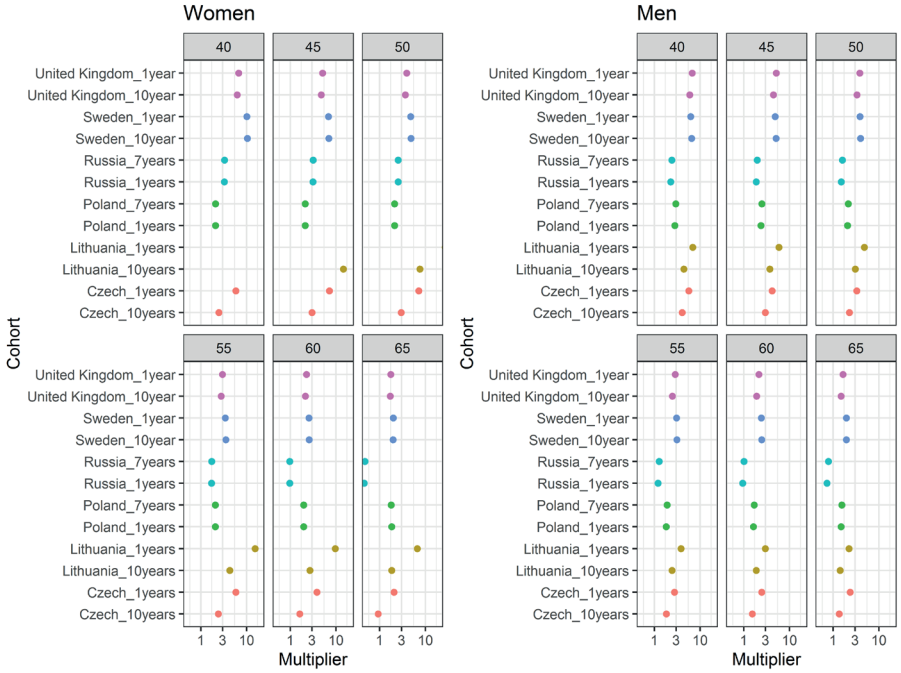
Supplementary Methods, Figure 1. Model recalibration process



Supplementary Methods, Figure 2. Methods used for recalibration of risk scores



Supplementary Methods, Figure 3. Comparison of 10-year versus 1-year multipliers



Supplementary Table 1. Definition of type 2 diabetes in the different cohorts

Cohort	Definition of type 2 diabetes
Swedish National Diabetes Registry	The definition of T2DM was treatment with 1) diet only, 2) oral hypoglycemic 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.

Supplementary Table 2. Endpoint definitions

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

Supplementary Table 3. Coefficients for individual predictions for the DIAL2 model

	Transformed variable	Coefficients for CVD		Coefficients for non-CVD mortality	
Core model		**Men**	**Women**	**Men**	**Women**
Smoking	-	0.43613704	0.54527701	0.674543628	0.728291130
Systolic blood pressure (per mmHg)	(sbp-138)/17	0.12921558	0.14219108	-0.026938046	-0.028290246
eGFR (per ml/min/1.73m2)	(log(egfr)-4.4)/0.26	-0.18938779	-0.18455476	-0.150284234	-0.189683460
Total cholesterol (per mmol/L)	(chol-5.1)/1.1	0.08772782	0.09169500	-0.047992832	-0.012281223
HDL-cholesterol (per mmol/L)	(hdl-1.3)/0.4	-0.13786297	-0.18063757	0.047784488	-0.001272966
HbA1c (per mmol/L)	(hba1c-55)/16	0.14216289	0.19429348	0.098037317	0.131909277
Age at diabetes diagnosis (years)	(age.diab-58)/12	-0.24439230	-0.33419381	-0.206644824	-0.207464980
Age interactions					
Smoking	((age-63)/12)*smoking	-0.09903685	-0.14932562	-0.171190819	-0.124903591
Systolic blood pressure (per mmHg)	((age-63)/12)*((sbp-138)/17)	-0.05898188	-0.05351348	-0.048826237	-0.028008013
eGFR (per ml/min/1.73m2)	((age-63)/12)*((log(egfr)-4.4)/0.26)	0.01406480	0.02185866	0.060655025	0.092678739
Total cholesterol (per mmol/L)	((age-63)/12)*((chol-5.1)/1.1)	-0.02829846	-0.03486721	0.044609913	-0.025594853
HDL-cholesterol (per mmol/L)	((age-63)/12)*((hdl-1.3)/0.4)	0.02557480	0.07303232	-0.018204521	0.022638760
HbA1c (per mmol/L)	((age-63)/12)*((hba1c-55)/16)	-0.01188235	-0.04922785	-0.010890054	-0.011887602
Age at diabetes diagnosis (years)	((age-63)/12)*((age.diab-58)/12)	0.06790247	0.10063012	-0.009980081	-0.021117448

Supplementary Table 3. Continued

	Transformed variable	Coefficients for CVD		Coefficients for non-CVD mortality	
Extended model		**Men**	**Women**	**Men**	**Women**
Smoking	-	0.426163707	0.536555603	0.656927583	0.718503526
Systolic blood pressure (per mmHg)	(sbp-138)/17	0.105694636	0.122158576	-0.052399885	-0.042062178
eGFR (per ml/min/1.73m2)	(log(egfr)-4.4)/0.26	-0.139847937	-0.148879183	-0.079995915	-0.134596547
Total cholesterol (per mmol/L)	(chol-5.1)/1.1	0.099339006	0.102412373	-0.032139301	-0.001121771
HDL-cholesterol (per mmol/L)	(hdl-1.3)/0.4	-0.129172714	-0.171915791	0.059017712	0.005940174
HbA1c (per mmol/L)	(hba1c-55)/16	0.103724172	0.14594887	0.037718786	0.055748479
Age at diabetes diagnosis (years)	(age.diab-58)/12	-0.140508597	-0.21504671	-0.041976912	-0.060554158
Insulin	-	0.194380243	0.209076623	0.436969318	0.439157259
Retinopathy	-	0.180182801	0.220946877	0.069238813	0.090139141
BMI	(bmi-30)/5.5	0.035881631	0.016383435	0.067030039	0.052120498
Albuminuria, micro	-	0.235989829	0.279704202	0.260268018	0.351453551
Albuminuria, macro	-	0.393796527	0.455902698	0.545166611	0.584011076
Age interactions					
Smoking	((age-63)/12)*smoking	-0.09681524	-0.173752434	-0.161786041	-0.133776676
Systolic blood pressure (per mmHg)	((age-63)/12)*((sbp-138)/17)	-0.050592585	-0.046846111	-0.039173329	-0.021980773
eGFR (per ml/min/1.73m2)	((age-63)/12)*((log(egfr)-4.4)/0.26)	0.009662798	0.015341663	0.024231812	0.062065795
Total cholesterol (per mmol/L)	((age-63)/12)*((chol-5.1)/1.1)	-0.027419758	-0.039953058	0.035694689	-0.028354887
HDL-cholesterol (per mmol/L)	((age-63)/12)*((hdl-1.3)/0.4)	0.026182374	0.066213833	-0.025048738	0.014944265
HbA1c (per mmol/L)	((age-63)/12)*((hba1c-55)/16)	-0.014041355	-0.047804281	0.012003378	0.017159838
Age at diabetes diagnosis (years)	((age-63)/12)*((age.diab-58)/12)	0.049610996	0.065202031	-0.088836001	-0.089520632
Insulin use	(age-63)/12)*insulin	-0.005178553	-0.011897452	-0.205280046	-0.195825407
Retinopathy*age	(age-63)/12)*rethinopathy	-0.016295981	-0.053153035	-0.038174003	-0.070142231
BMI	((age-63)/12)*((bmi-30)/5.5)	-0.015549964	-0.026042501	-0.048739152	-0.035110721
Albuminuria, micro	((age-63)/12)*microalb	-0.017560561	-0.011779919	-0.094955851	-0.109803836
Albuminuria, macro	((age-63)/12)*macroalb	-0.019131199	-0.062941404	-0.171143613	-0.122520344

Supplementary Table 4. Age-specific baseline hazards for individual predictions for the DIAL2 model

Core model

Age	Baseline hazards for CVD		Baseline hazards for non-CVD mortality	
	Men	Women	Men	Women
30	0.9998293	0.9998565	0.9994517	1
31	0.9997662	0.999854	0.9992266	0.9999997
32	0.9996901	0.9998489	0.9990281	0.9996788
33	0.9996019	0.9998397	0.9988527	0.9993951
34	0.9995023	0.9998255	0.9986977	0.9991462
35	0.9993913	0.999806	0.9985618	0.9989295
36	0.9992691	0.9997819	0.9984439	0.9987445
37	0.9991352	0.999755	0.9983447	0.9985923
38	0.9989872	0.9997294	0.9982671	0.9984744
39	0.9988238	0.9996981	0.9982163	0.9983979
40	0.9986793	0.9996267	0.9981685	0.9983665
41	0.9985078	0.9995375	0.9980773	0.9983094
42	0.9983092	0.999423	0.9979703	0.9982468
43	0.9981005	0.9992745	0.9978316	0.998208
44	0.997873	0.9991081	0.9976819	0.9981554
45	0.9976122	0.9989359	0.9975508	0.9980506
46	0.9973142	0.9987595	0.9974513	0.9979352
47	0.9969843	0.9985751	0.9973646	0.9978421
48	0.9966384	0.9983841	0.997278	0.9977632
49	0.9962791	0.9981962	0.9971717	0.997687
50	0.995904	0.9980184	0.9970235	0.9975903
51	0.9955246	0.9978511	0.9968283	0.9974611
52	0.995151	0.9976868	0.9965986	0.9972861
53	0.9947816	0.9975215	0.996327	0.9970572
54	0.994387	0.9973424	0.9959967	0.9967986
55	0.9939475	0.9971368	0.9956019	0.9965327
56	0.9934664	0.9969031	0.9951759	0.9962605
57	0.9929383	0.9966428	0.9947575	0.9959449
58	0.9923644	0.9963401	0.9943528	0.995566
59	0.9917537	0.9959813	0.9939268	0.995153
60	0.9910945	0.9955634	0.993446	0.9947426
61	0.9903806	0.9950855	0.9929045	0.9943342
62	0.989642	0.9945521	0.9923196	0.993883

Supplementary Table 4. Continued

Age	Baseline hazards for CVD		Baseline hazards for non-CVD mortality	
	Men	Women	Men	Women
63	0.9888947	0.9939677	0.9916917	0.9933427
64	0.9881741	0.9933402	0.9909887	0.9927154
65	0.9874773	0.9926821	0.9901786	0.9920471
66	0.9867378	0.991968	0.9892775	0.9913655
67	0.9859176	0.9912046	0.9883097	0.9906735
68	0.9849895	0.9903964	0.9872678	0.9899269
69	0.9839251	0.9895306	0.9860997	0.9890634
70	0.9827127	0.988576	0.9847445	0.9881015
71	0.9813333	0.9874698	0.9831778	0.9870408
72	0.9797778	0.9862148	0.9814194	0.9858311
73	0.9780527	0.9848419	0.9794554	0.9844413
74	0.9761649	0.9833537	0.9772473	0.9828348
75	0.9741417	0.9817054	0.9747013	0.9809881
76	0.9719586	0.9798273	0.971754	0.9788992
77	0.9695478	0.977632	0.9683471	0.9765357
78	0.9668429	0.9750382	0.964308	0.9738093
79	0.9637983	0.9720317	0.9595616	0.9705838
80	0.9604942	0.9686439	0.9540458	0.9667519
81	0.9568775	0.9649187	0.9476512	0.9622104
82	0.9527988	0.9608883	0.9404653	0.9569748
83	0.9482612	0.9566166	0.9324025	0.9510166
84	0.9432077	0.9520183	0.9231998	0.9442042
85	0.9377561	0.9471244	0.9128504	0.9362527
86	0.932045	0.9419826	0.9017291	0.9269463
87	0.9261494	0.9364888	0.8887435	0.9159623
88	0.9198165	0.9307792	0.87377	0.9033584
89	0.9130291	0.9248601	0.856952	0.8891999
90	0.9058059	0.9187206	0.8383406	0.8734926
91	0.8981605	0.9123523	0.817949	0.8562255
92	0.8901037	0.9057563	0.7957676	0.8373831
93	0.8816344	0.8989348	0.7717645	0.8169509
94	0.8727474	0.8918909	0.7458921	0.7949127

Supplementary Table 4. Continued

Extended model

Age	Baseline hazards for CVD		Baseline hazards for non-CVD mortality	
	Men	Women	Men	Women
30	0.99981682	0.999841605	1	1
31	0.999745449	0.999833396	0.999990171	0.999990171
32	0.999662585	0.999823888	0.999650585	0.999650585
33	0.999569233	0.999811444	0.999354685	0.999354685
34	0.999466106	0.999794978	0.999099913	0.999099913
35	0.999353288	0.999774361	0.998883294	0.998883294
36	0.999230963	0.999750236	0.998704231	0.998704231
37	0.999098455	0.999724764	0.998563939	0.998563939
38	0.998953177	0.999702344	0.998464105	0.998464105
39	0.998793252	0.999674522	0.998413151	0.998413151
40	0.998656499	0.999603385	0.998415774	0.998415774
41	0.998495451	0.999514588	0.998391432	0.998391432
42	0.998309113	0.999402421	0.998360012	0.998360012
43	0.998115425	0.999258185	0.998353153	0.998353153
44	0.997905438	0.999098003	0.998331679	0.998331679
45	0.997664761	0.998934176	0.998255594	0.998255594
46	0.997389305	0.998768334	0.998167316	0.998167316
47	0.997084942	0.998597677	0.998100925	0.998100925
48	0.996768502	0.998423401	0.998048773	0.998048773
49	0.996443782	0.998254679	0.99799871	0.99799871
50	0.996109087	0.998098206	0.997929869	0.997929869
51	0.995774505	0.997954063	0.997833818	0.997833818
52	0.995448895	0.997815399	0.997700975	0.997700975
53	0.995131225	0.997678226	0.997524097	0.997524097
54	0.994795624	0.997530004	0.997323005	0.997323005
55	0.994424927	0.997358787	0.997115296	0.997115296
56	0.994022102	0.997164108	0.996902224	0.996902224
57	0.993581649	0.996948197	0.996653809	0.996653809
58	0.99310471	0.99669659	0.996353938	0.996353938
59	0.992599479	0.996396599	0.996026256	0.996026256
60	0.992055322	0.996046126	0.995700166	0.995700166
61	0.991466123	0.995644647	0.995374137	0.995374137
62	0.990858402	0.995196653	0.995010591	0.995010591
63	0.990246405	0.994705948	0.994571431	0.994571431

Supplementary Table 4. Continued

Age	Baseline hazards for CVD		Baseline hazards for non-CVD mortality	
	Men	Women	Men	Women
64	0.989660437	0.994179814	0.994058246	0.994058246
65	0.989097587	0.993629998	0.993509088	0.993509088
66	0.988500545	0.993035685	0.992946311	0.992946311
67	0.987837683	0.992403063	0.992372283	0.992372283
68	0.987088259	0.991736871	0.991750607	0.991750607
69	0.986230488	0.991027744	0.991030236	0.991030236
70	0.98525524	0.990250832	0.990226477	0.990226477
71	0.984146864	0.989354655	0.9893375	0.9893375
72	0.982898154	0.988341489	0.988319339	0.988319339
73	0.981514839	0.987235751	0.987144274	0.987144274
74	0.980002732	0.986038091	0.985778612	0.985778612
75	0.978385381	0.984711305	0.98419872	0.98419872
76	0.976643363	0.983198005	0.982399046	0.982399046
77	0.974720638	0.981424828	0.980346611	0.980346611
78	0.97256165	0.979322626	0.977960403	0.977960403
79	0.970126547	0.976878407	0.975115004	0.975115004
80	0.967482965	0.974117192	0.971707593	0.971707593
81	0.964591803	0.971076317	0.967639592	0.967639592
82	0.961332805	0.967783266	0.962917524	0.962917524
83	0.957708816	0.964288909	0.957497413	0.957497413
84	0.953673792	0.960516339	0.951235994	0.951235994
85	0.949325046	0.956484839	0.943847267	0.943847267
86	0.944782568	0.95223702	0.935113241	0.935113241
87	0.940070604	0.947685092	0.924691219	0.924691219
88	0.934975357	0.942932386	0.912614233	0.912614233
89	0.929487413	0.93798461	0.898951256	0.898951256
90	0.923624021	0.93283321	0.883711484	0.883711484
91	0.917396703	0.927471854	0.866885797	0.866885797
92	0.910813616	0.921901412	0.848458964	0.848458964
93	0.903872778	0.916123649	0.828415247	0.828415247
94	0.896568211	0.910140428	0.806736339	0.806736339

Supplementary Table 5. Region-specific recalibration scales for calculation of the 1-year CVD event and non-CVD mortality risks

	Male		Female	
	Scale 1	**Scale 2**	**Scale 1**	**Scale 2**
CVD events				
Low risk region	-1.1963	0.7686	-0.7647	0.8626
Moderate risk region	-0.7944	0.7906	-0.2967	0.9083
Non-CVD mortality				
Low risk region	0.0596	0.9920	0.6679	1.1289
Moderate risk region	-0.2930	0.9002	0.3085	1.0426

Rescaling factors for the DIAL2 model to scale individual predicted risks within the life table to the target population, based on recent nationally representative estimates of incident cardiovascular disease and risk factor levels.

Supplementary Table 6. Discrimination of both the core and extended model

Cohort	**C-statistic core model (95%CI)**		**C-statistic extended model (95%CI)**	
	CVD	**Non-CVD mortality**	**CVD-events**	**Non-CVD mortality**
Swedish NDR	0.709 (0.703-0.714)	0.723 (0.718-0.728)	0.713 (0.708-0.718)	0.720 (0.718-0.722)
SCID	0.700 (0.691-0.709)	0.702 (0.696-0.707)	0.705 (0.695-0.714)	0.700 (0.692-0.706)
CPRD	0.732 (0.726-0.739)	0.720 (0.712-0.727)	NA	NA

The extended model was not externally validated in CPRD as all additional variables necessary for validation of the extended model were not available in this validation dataset.

Supplementary Table 7. C-indices (95%CI) for validation of the core DIAL2 model in people with and without use of statin therapy in the external validation cohorts

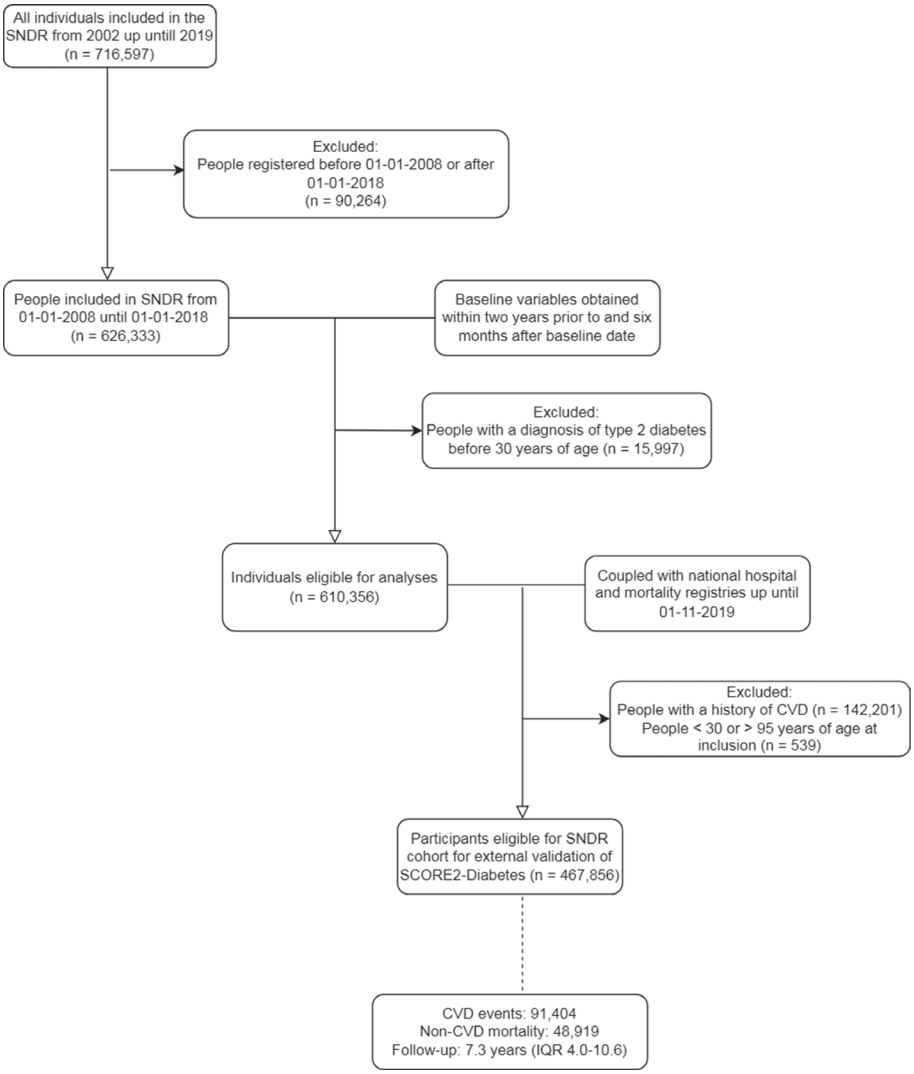
	SCI-Diabetes		**CPRD**	
	Statin-users (n = 70,007, 49%)	**No statin-users (n = 73,035, 51%)**	**Statin-users (n = 61,981)**	**No statin-users (n = 13,234)**
CVD events	0.697 (0.689-704)	0.705 (0.688-0.722)	0.739 (0.733-0.745)	0.790 (0.773-0.806)
Non-CVD mortality events	0.695 (0.689-0.702)	0.703 (0.687-0.719)	0.725 (0.718-0.732)	0.733 (0.718-0.748)

Supplementary Table 8. C-indices (95%CI) for the original DIAL model and the ADVANCE risk score as well as the current DIAL2 model for 10-year CVD predictions in the Swedish NDR cohort and the SCI-Diabetes cohort

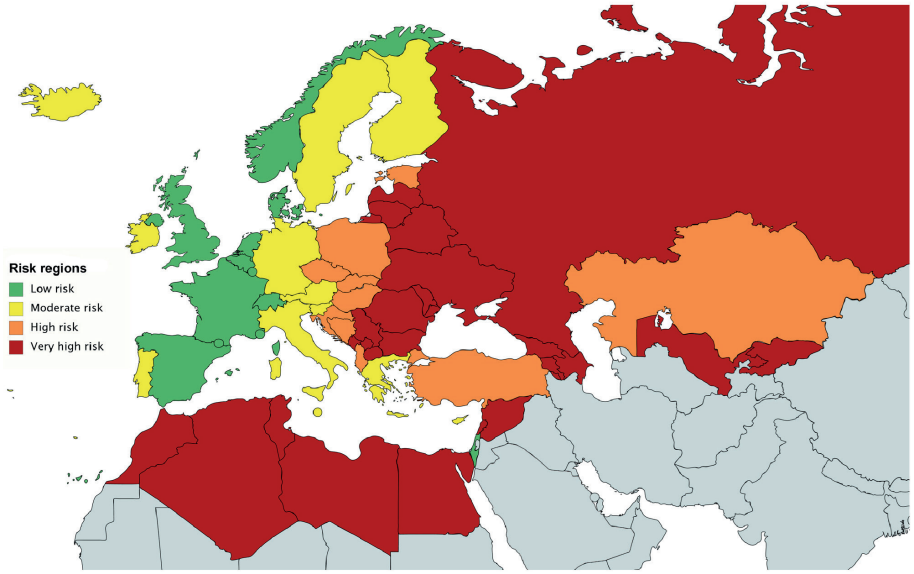
	Swedish NDR	**SCI-Diabetes**
DIAL	0.558 (0.555-0.560)	0.556 (0.538-0.574)
ADVANCE	0.673 (0.670-0.675)	0.674 (0.656-0.692)
DIAL2	0.708 (0.703-0.714)	0.700 (0.691-0.709)

These models were not externally validated in CPRD as several variables necessary for validation were not available in this dataset.

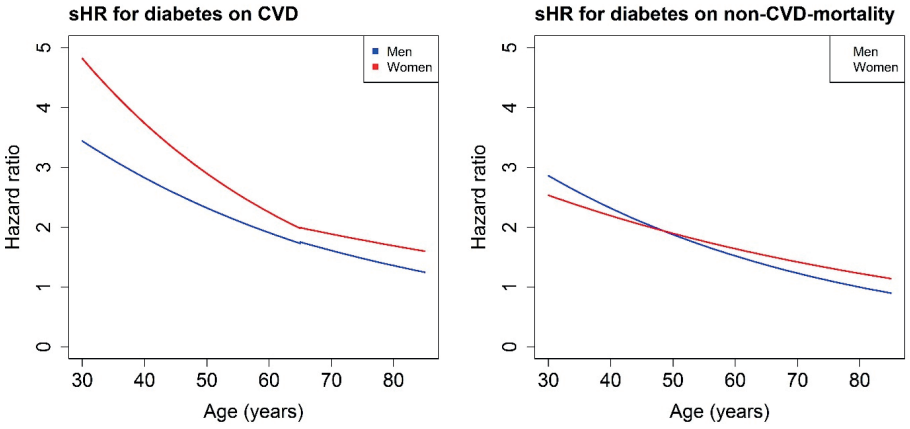
Supplementary Figure 1. Flowchart over selection of the Swedish National Diabetes Register derivation cohort



Supplementary Figure 2. Risk regions based on standardised CVD mortality rates (from SCORE2, *Hageman et al* 2021)

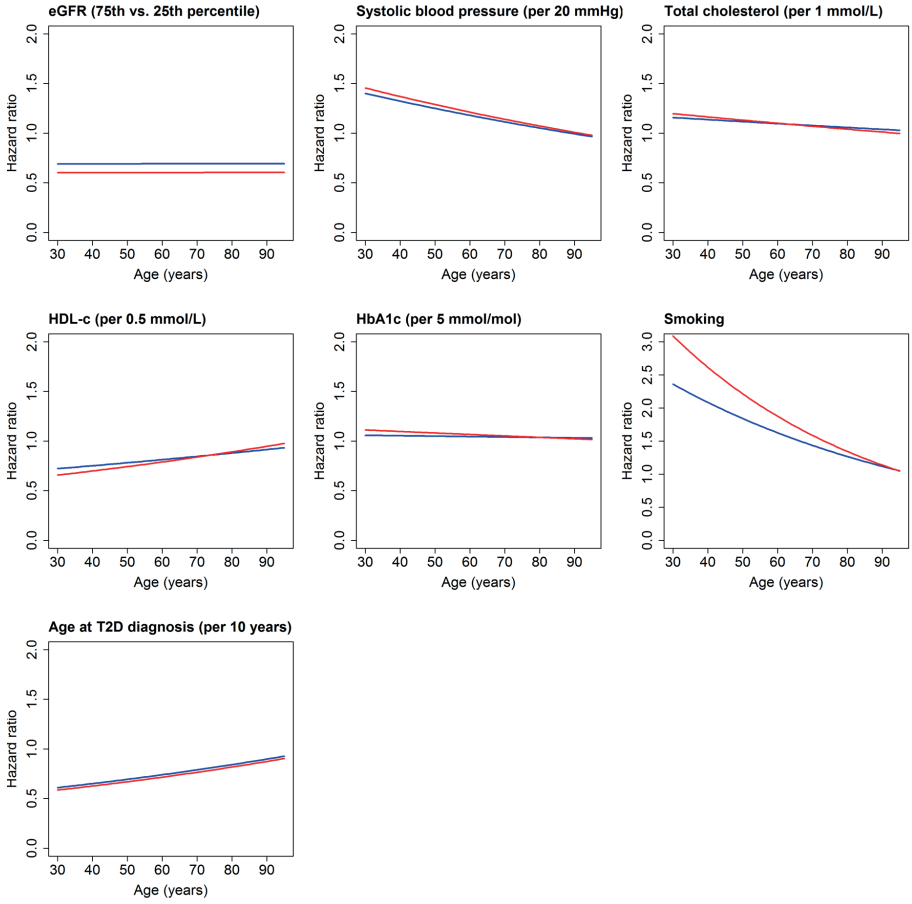


Supplementary Figure 3. sHR for diabetes on CVD and non-CVD mortality according to age used for estimating diabetes-specific CVD incidences in expected risks



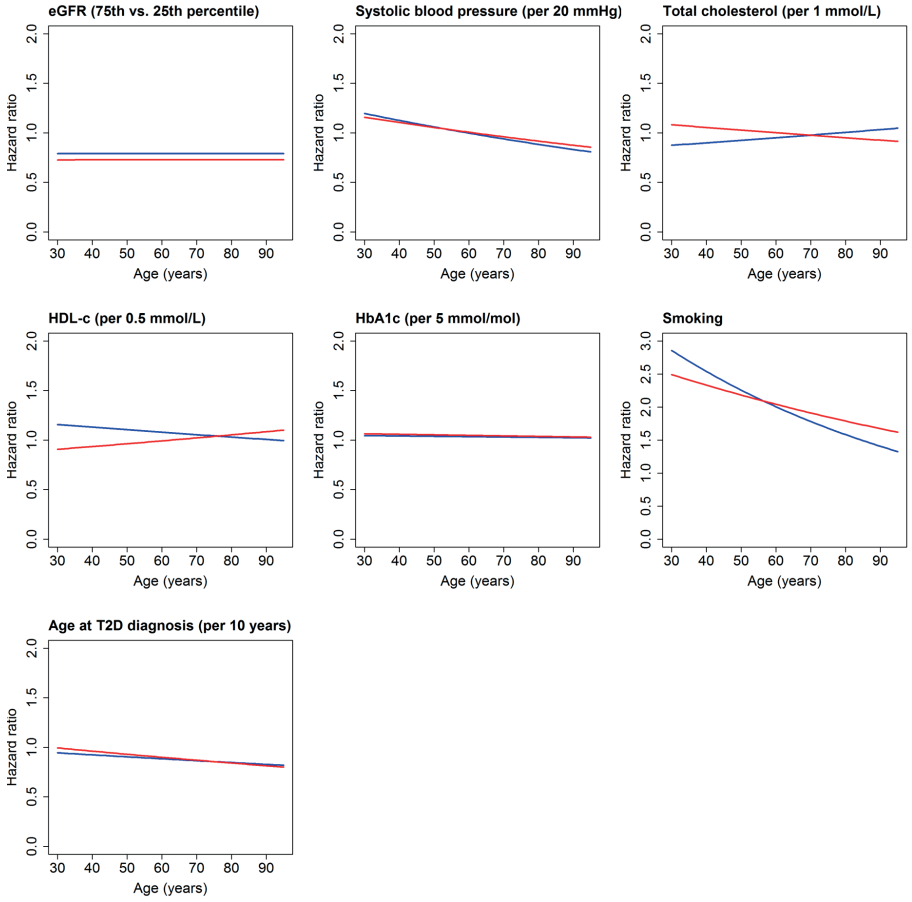
Supplementary figure 4. Relative effect of risk factors across different ages

Hazard ratios for CVD events:



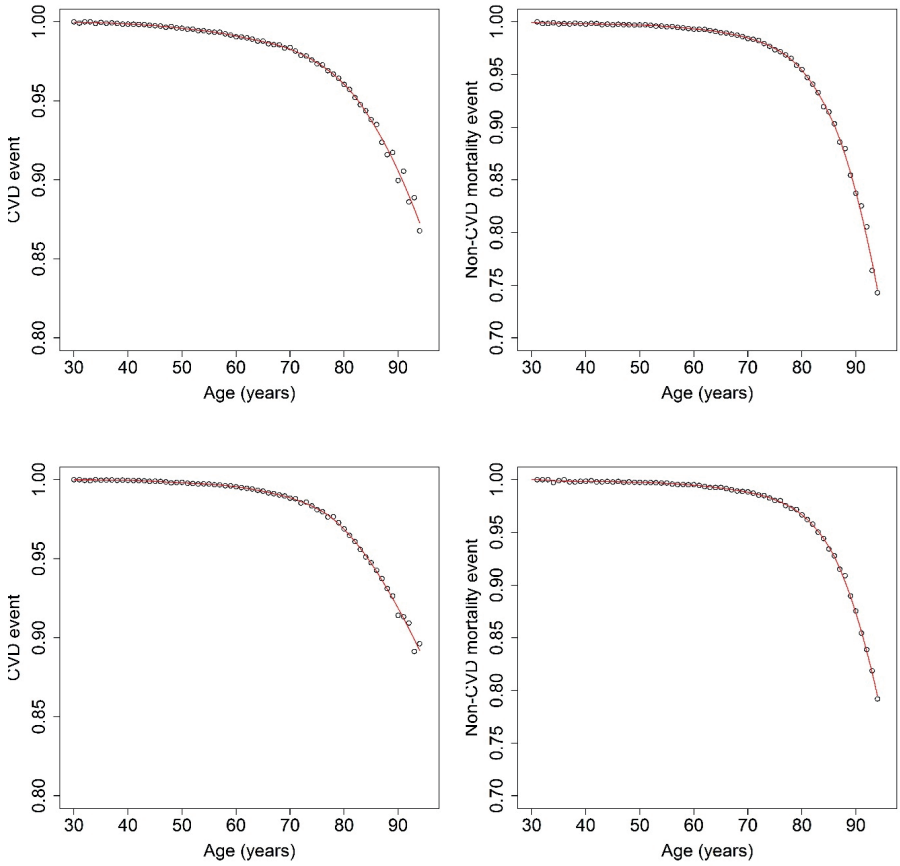
Supplementary figure 4. Continued

Hazard ratios for non-CVD mortality:

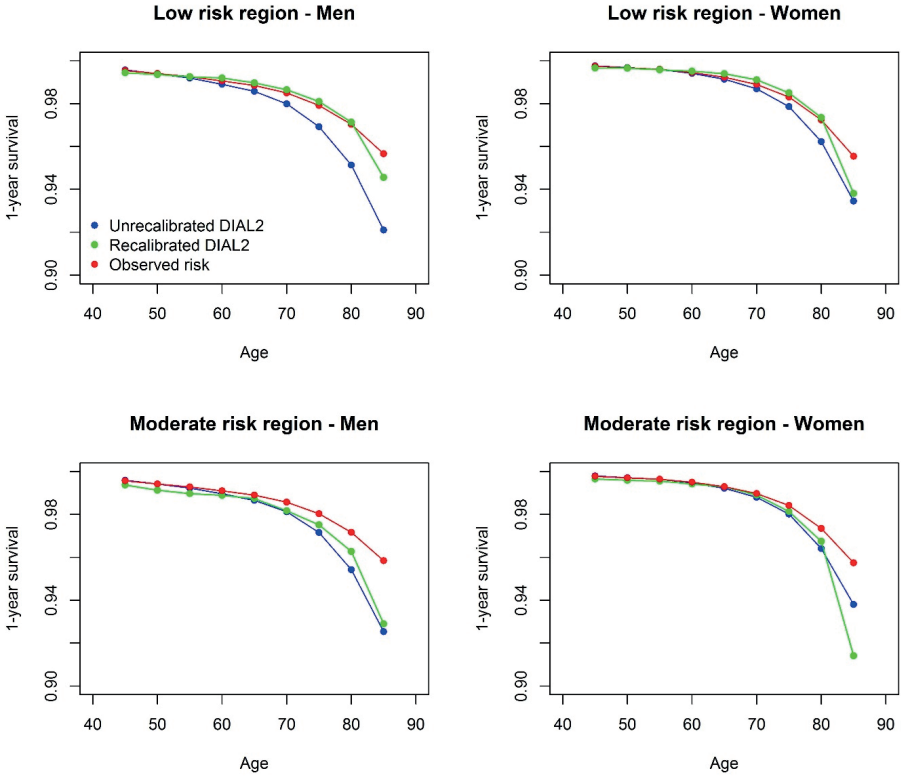


All predictors of the core model, graphically across the relevant age-range. The plotted line is a summary of both the main effect estimate and the age-interaction at every age.

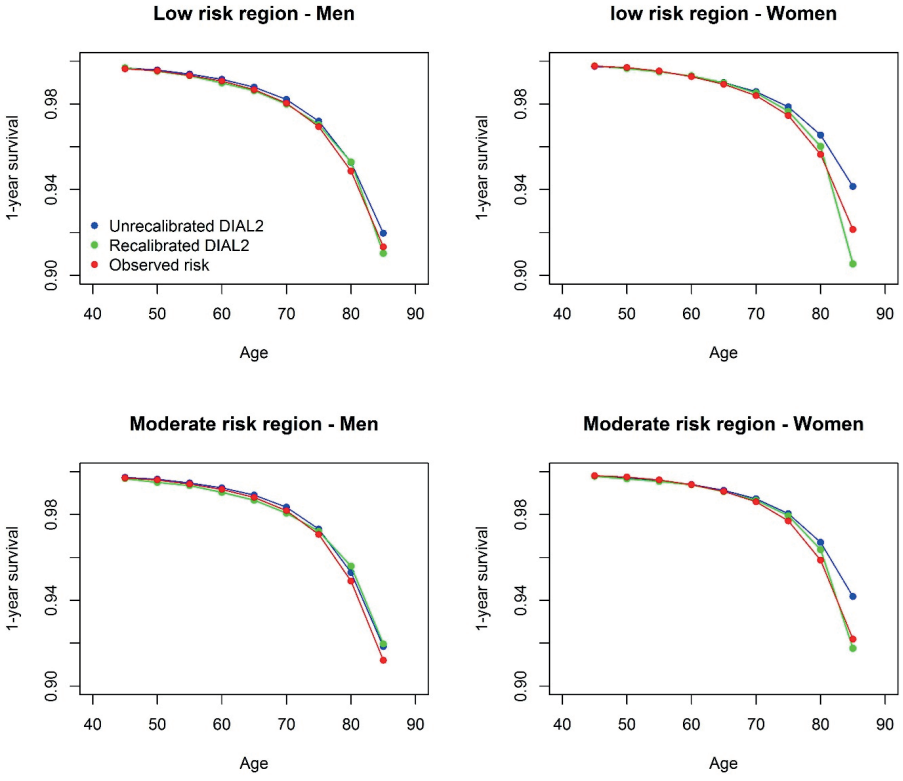
Supplementary Figure 5. Smoothing of age-specific baseline survivals for (A) 1-year CVD baseline survival and (B) 1-year non-CVD mortality baseline survival. Black dots indicate the original baseline survivals based on the observed events per life-year, the red lines show the predicted progression of baseline survivals from the age of 30 years to 95 years



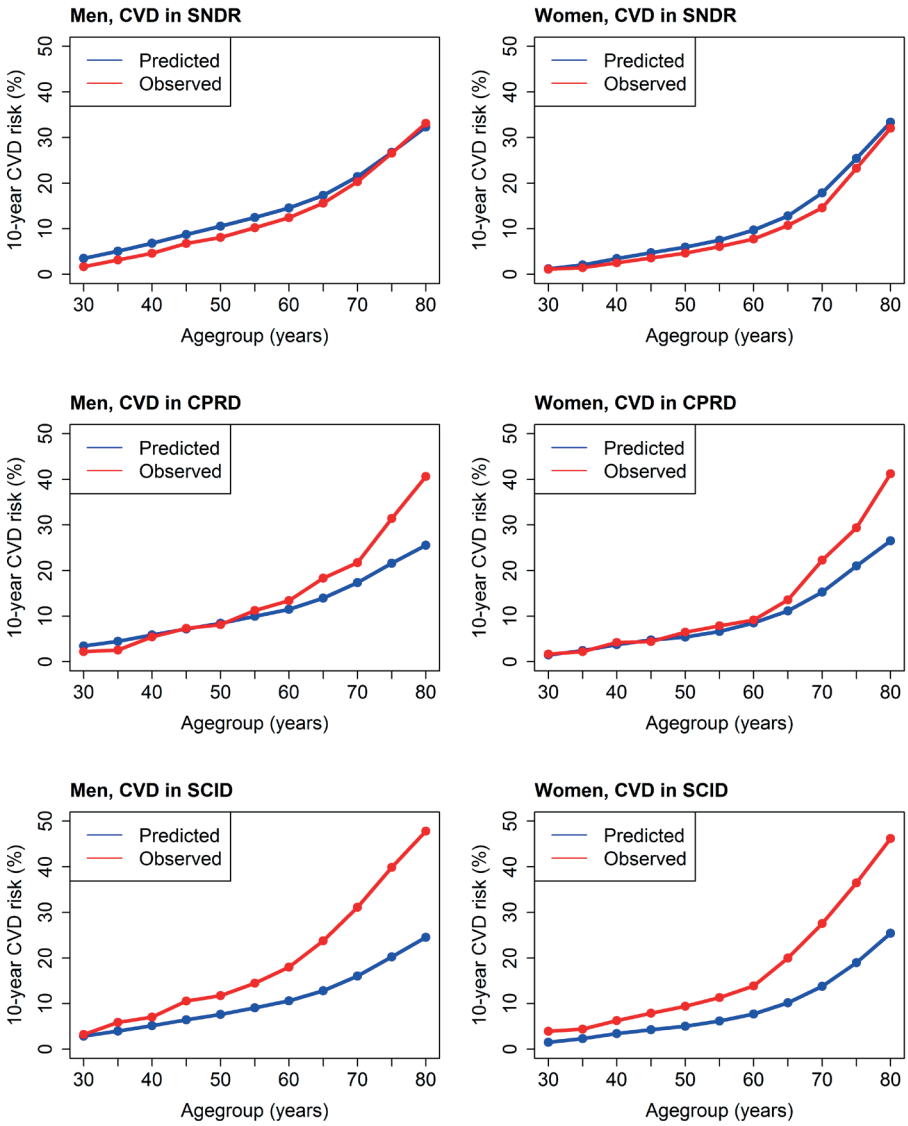
Supplementary Figure 6. Agreement of the DIAL2 yearly CVD event rates with registry data before and after recalibration



Supplementary Figure 7. Agreement of the DIAL2 yearly non-CVD mortality rates with registry data before and after recalibration

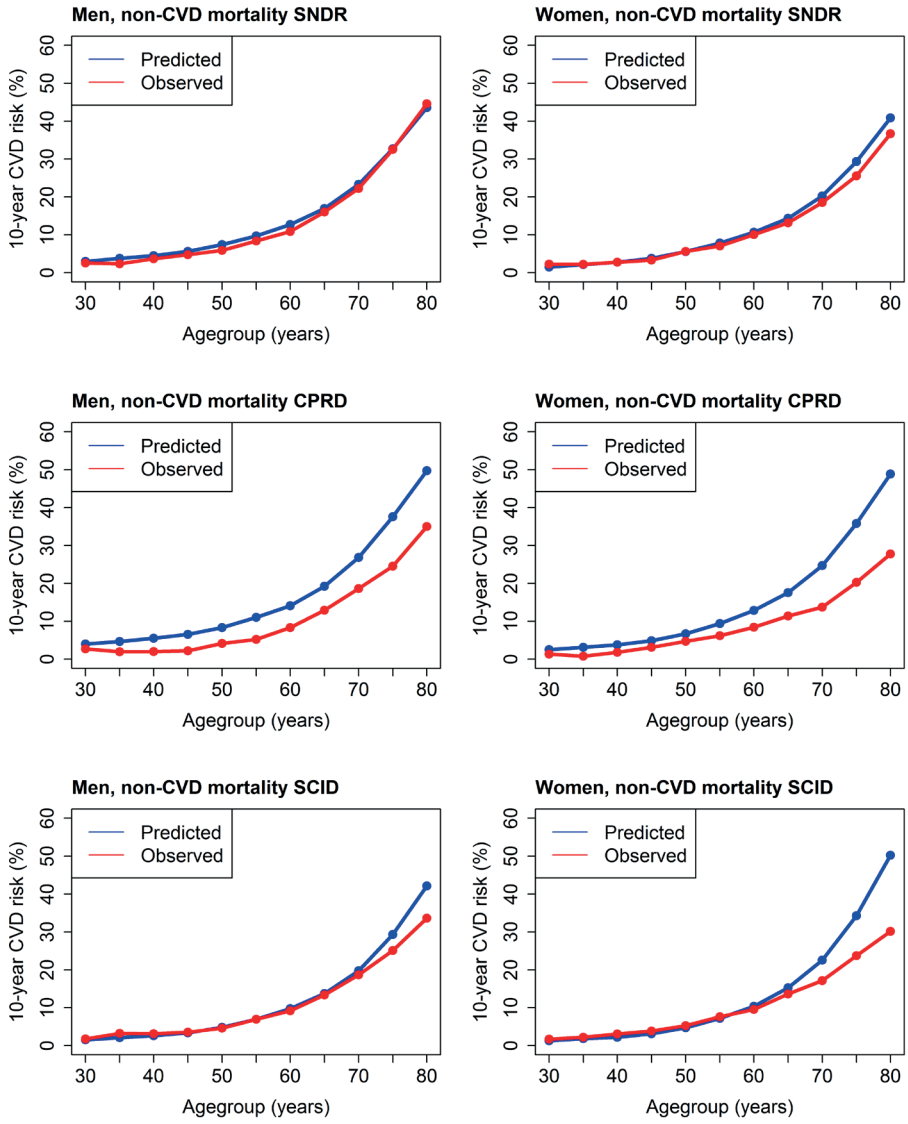


Supplementary Figure 8. Calibration of the core DIAL2 model for predicting the 10-year risk of CVD events



Calibration of the DIAL2 risk model. Predicted risks are obtained as the mean 10-year risk per age-group obtained using the recalibrated DIAL2 model. Observed risks are the mean 10-year cumulative incidences adjusted for non-CVD mortality as competing risk according to age-groups.

Supplementary Figure 9. Calibration of the core DIAL2 model for predicting the 10-year risk of non-CVD mortality



Calibration of the DIAL2 risk model. Predicted risks are obtained as the mean 10-year risk per age-group obtained using the recalibrated DIAL2 model. Observed risks are the mean 10-year cumulative incidences adjusted for CVD as competing risk according to age-groups.

CHAPTER 8

SCORE2-Diabetes: new calibrated models to estimate 10-year risk of cardiovascular disease in individuals with type 2 diabetes in Europe

SCORE2-Diabetes working group and the ESC Cardiovascular Risk Collaboration

Lisa Pennells*
Stephen Kaptoge*
Helena Bleken Østergaard*
Stephanie H Read*
Fabrizio Carinci*
Josep Franch-Nadal
Carmen Petitjean
Owen Taylor
Steven H.J. Hageman
Zhe Xu
Fanchao Shi
Brian Ference
Dirk De Bacquer
Martin Halle
Radu Huculeci
John William McEvoy
Adam Timmis
Panagiotis Vardas
Jannick A. N. Dorresteijn
Ian Graham
Angela Wood
Björn Eliasson
William Herrington
John Danesh
Dídac Mauricio
Massimo Massi Benedetti‡
Naveed Sattar‡
Frank L.J. Visseren‡
Sarah Wild‡
Emanuele Di Angelanto‡

*Contributed equally
‡Contributed equally

On behalf of all other authors of the SCORE2 prediction algorithm, who are listed at the end of the chapter.

Accepted, Eur Heart J.

Abstract

Aims: To develop and validate a recalibrated prediction model (SCORE2-Diabetes) to estimate 10-year risk of cardiovascular disease (CVD) in individuals with type 2 diabetes in Europe.

Methods and results: SCORE2-Diabetes was developed by extending SCORE2 algorithms using individual-participant-data from four large-scale datasets comprising 229,460 participants (43,706 CVD events) with type 2 diabetes and without previous CVD. We used sex-specific competing risk-adjusted models including conventional risk factors (i.e., age, smoking, systolic blood pressure, total- and HDL-cholesterol), as well as diabetes-related variables (i.e., age-at-diabetes diagnosis, glycated haemoglobin [HbA1c] and creatinine-based estimated glomerular filtration rate [eGFR]). Models were recalibrated to CVD incidence in four European risk regions. External validation included 216,980 further individuals (38,594 CVD events), and showed good discrimination, and improvement over SCORE2 (C-index change from 0.009 to 0.031). Regional calibration was satisfactory. SCORE2-Diabetes risk predictions varied several-fold, depending on individuals' levels of diabetes-related factors. For example, in the moderate risk region, the estimated 10-year CVD risk was 11% for a 60-year-old man, non-smoker, with type 2 diabetes, average conventional risk factors, HbA1c of 50 mmol/mol, eGFR of 90ml/min/1.73m^2, and age-at-diabetes diagnosis of 60 years. By contrast, the estimated risk was 17% in a similar man, with HbA1c of 70 mmol/mol, eGFR of 60 ml/min/1.73m^2, and age-at-diagnosis of 50 years. For a woman with the same characteristics, risk was 8% and 13%, respectively.

Conclusions: SCORE2-Diabetes, a new algorithm developed, calibrated, and validated to predict 10-year risk of CVD in individuals with type 2 diabetes, enhances identification of individuals at higher risk of developing CVD across Europe.

Introduction

Cardiovascular diseases (CVD) remain a major cause of morbidity and mortality in Europe with almost 13 million new cases recorded in 2019 alone.[1] Type 2 diabetes mellitus is a major risk factor for CVD. Individuals with diabetes from high-income countries have, on average, 2-fold greater risk of developing CVD outcomes compared to counterparts without diabetes.[2] The European Society of Cardiology (ESC) provides guidelines and advocates estimation of CVD risk in individuals with type 2 diabetes to inform treatment decisions.[3]

Risk prediction models used in the primary prevention of CVD in general populations usually estimate individual risk over a 10-year period by integrating information on measured levels of conventional CVD risk factors (i.e., age, smoking status, systolic blood pressure, and total- and HDL-cholesterol) and information on diabetes status.[4-6] To help account for substantial variation in risk across individuals with diabetes, however, additional diabetes-related information (e.g., age at diagnosis of diabetes, glycated haemoglobin [HbA1c], and markers of kidney function) have been included in several published risk models.[7-10] Nonetheless, available diabetes-specific models have important potential limitations. In particularly, they may not be optimal for use across Europe's diverse populations since they have been developed from a narrow set of observational studies and/or intervention trials, and have not been systematically 'recalibrated' (i.e. statistically adapted) to reflect the substantial variation in CVD rates across different European countries.[1,10,11] To address these limitations, the ESC has convened an effort to extend the regionally recalibrated European SCORE2 10-year risk models[12], enabling use in individuals with type 2 diabetes.

Here, we describe development, validation, and illustration of SCORE2-Diabetes to estimate 10-year risk of non-fatal myocardial infarction, stroke or any CVD mortality in individuals with diabetes but without previous CVD, aged over 40 years, in four different European risk regions.

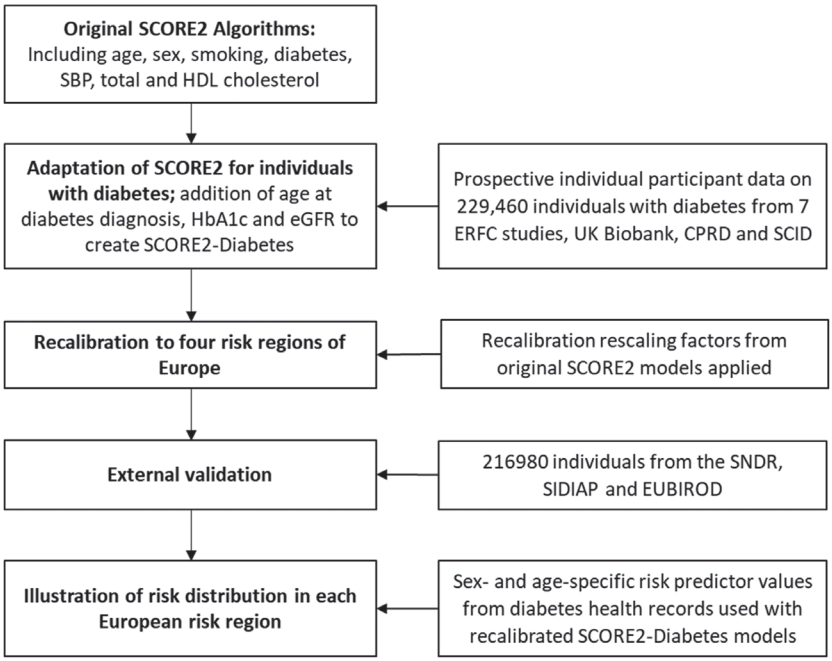
Methods

Study design

The SCORE2-Diabetes project involved several interrelated components and data sources (*Figure 1*). First, the original SCORE2 risk prediction models for fatal and non-fatal CVD outcomes were adapted for use in individuals with type 2

diabetes using individual-participant data from four population data sources (Scottish Care Information – Diabetes [SCID], Clinical Practice Research Datalink [CPRD], UK Biobank [UKB], Emerging Risk Factors Collaboration [ERFC]) across 7 countries (England, Wales, Scotland, France, Germany, Italy and the USA). Second, we recalibrated the derived risk models to each European risk region, applying methods previously used to develop SCORE2. Third, we completed external validation in individuals with type 2 diabetes across four countries (Sweden, Spain, Croatia and Malta) using data from the Swedish National Diabetes Register (SNDR), the Information System for Research in Primary Care (SIDIAP, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària), and two contributing registries from the EUropean Best Information through Regional Outcome in Diabetes (EUBIROD). Fourth, we illustrated the variation of CVD risk in individuals with type 2 diabetes across European regions by applying the recalibrated models to data from contemporary populations in each risk region.

Figure 1. Study design



ERFC: Emerging Risk Factors Collaboration, CPRD: Clinical Practice Research Datalink, SCID: Scottish Care Information – Diabetes, SNDR: Swedish National Diabetes Register, SIDIAP: Information System for Research in Primary Care, EUBIROD: EUropean Best Information through Regional Outcome in Diabetes.
eGFR: estimated Glomerular Filtration Rate, HbA1c: glycated haemoglobin

Data sources and procedures

For model derivation, we used individual-participant data from patients with type 2 diabetes, without previous CVD, aged over 40 years, from SCID, CPRD, UKB, and 7 cohorts from the ERFC with available information on diabetes-related variables. SCID is a dynamic population-based register of people with a diagnosis of diabetes in Scotland that has had almost complete coverage since 2006.[13] CPRD is an ongoing primary care database of anonymised medical records from general practitioners, with coverage of over 11.3 million patients from 674 practices in the UK[14]. With 4.4 million active (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included and patients are broadly representative of the UK general population in terms of age, sex and ethnicity. The data used for this study is restricted to the region of England.

Model derivation datasets for the SCID and the CPRD involved individuals with diabetes on 1st June 2008 and risk factor measurements recorded during the period from 30th June 2006 to 31st December 2008. Follow-up was to 1st June 2019 for SCID and 31st December, 2019 for CPRD, with incident nonfatal events obtained from linkage with Scottish Morbidity Records and English Hospital Episode Statistics and deaths from National Records of Scotland and Office for National Statistics. The UKB is a single large prospective cohort study with individual-participant data on approximately 500,000 participants aged over 40 years recruited across 23 UK based assessment centres during 2006-2010, and followed-up for cause-specific morbidity and mortality through linkages to routinely available national datasets and disease-specific registers.[15] The ERFC has collated and harmonised individual-participant data from many long-term prospective cohort studies of CVD risk factors and outcomes.[16] Prospective studies in the ERFC were included in this analysis if they met all the following criteria: had recorded baseline information on CVD risk factors necessary to derive risk prediction models (i.e., age, sex, smoking status, systolic blood pressure, total- and HDL-cholesterol, history of diabetes mellitus (defined by self-report plus medication and/or biochemical criteria[2,17]), age at diabetes diagnosis, HbA1c and creatinine or estimated glomerular filtration rate [eGFR]); were approximately population-based (i.e., did not select participants on the basis of having previous disease [e.g., case-control studies] and were not active treatment arms of intervention studies); had a median year of baseline

survey after 1990; and had recorded cause-specific deaths and/or non-fatal CVD events (i.e., non-fatal myocardial infarction or stroke) for at least five-years of follow-up. Data selection for model adaptation/derivation is shown in *Supplementary Figure 1*. Details of contributing data sources are provided in *Supplementary Tables 1 and 2*.

For recalibration of models, recalibration factors from the SCORE2 risk models were used. SCORE2 has been systematically recalibrated to reflect risk of the entire population (including those with diabetes) in four risk regions of Europe. Hence, adapting SCORE2 for use in individuals with type 2 diabetes (i.e., SCORE2-Diabetes) does not require additional data and recalibration for diabetes-specific populations. Data from the SNDR, SIDIAP and EUBIROD were used for external validation (*Supplementary Table 3*). SNDR is a national registry that has close to complete coverage of the population with a diagnosis of type 2 diabetes in Sweden.[18] As with data used in model derivation, we used records from individuals with diabetes during the period from 30th June 2006 to 31st December 2008, and no previous history of CVD. Follow-up was to 31st December, 2019 with incident nonfatal events obtained from linkage to hospital and mortality records. SIDIAP is a primary care electronic health records database managed by the Catalan Health Institute, covering around 75% of individuals (>5 million) in the Catalonia region of Spain across 328 primary care centres, and is representative of this population in terms of age, sex and geographic distribution[19,20]. For this analysis, we used individuals with type 2 diabetes from a randomly selected 400,000 individuals whose records were linked to hospital and specific cause of death records to obtain CVD outcomes. Individuals had been included in SIDIAP for at least 1 year prior to 1st January 2010 and were subsequently followed up until 2017. EUBIROD is the largest network of diabetes registries and data sources in Europe[21], sharing a common dataset[22] and open source software[23] to analyse individual data in a privacy-enhanced distributed infrastructure.[24-26] Data on people with type 2 diabetes with baseline records between January 2013 and June 2015 were independently processed at each of the 8 participating countries (Belgium, Croatia, Denmark, Germany, Hungary, Latvia, Malta and Slovenia), and analysed using R source code embedded in the EUBIROD NeuBIRO software. Where available, follow-up for CVD events was obtained through linkage to hospital and death records over the subsequent 5 years, enabling validation. Only aggregate data were

made available by each participating centre to the study coordinators. Risk factor data from CPRD, SNDR, SIDIAP, EUBIROD and the 2017/18 extraction from the National Diabetes Audit (NDA) were used to illustrate SCORE2-Diabetes predicted risk distributions in each European risk region. The NDA is an annually updated registry covering more than 98% of individuals with a recorded diabetes diagnosis from primary healthcare providers in England and Wales and specialist care healthcare providers in England.[27]

The primary outcome was CVD events, defined as a composite of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. Follow-up was until the first non-fatal myocardial infarction, non-fatal stroke, death or end of the study or registration period. Deaths from non-CVD were treated as competing events. Details of the different ICD-10 codes included in both the fatal and non-fatal components of the endpoint are provided in *Supplementary Table 4*. In all data sources, individuals with a known history of previous CVD at baseline were excluded, as defined in *Supplementary Table 5*.

Statistical analysis

Details of statistical analysis are provided in *Supplementary Methods*. For model derivation, the SCORE2 models were extended by addition of diabetes-related variables: HbA1c, age at diabetes diagnosis and eGFR. These predictors were selected due to their predictive ability based on previous literature as well as their wide availability in clinical practice and in available datasets used for model derivation. Coefficients for the variables already included in SCORE2 derivation (i.e., age, current smoking, history of diabetes mellitus, systolic blood pressure, and total- and HDL-cholesterol) were fixed at the same values used in the SCORE2 models and included as an offset in Fine and Gray competing risk-adjusted models used to estimate additional sex-specific coefficients (i.e., sub-distribution hazard ratios [SHRs]). Additional coefficients were then estimated for each of the SCORE2 variables, to allow their effects to vary among individuals with diabetes, as well as for the newly added diabetes-related variables included in SCORE2-Diabetes. All newly derived coefficients were estimated separately by data source and pooled using fixed effects meta-analysis. Since previous research showed that associations of these variables with CVD decline with increasing age, age-interactions were added for all predictors. A quadratic term was also included for eGFR to allow for its non-

linear association with CVD outcomes (*Supplementary Methods Figure*). There were no (or very minimal) violations of the proportional hazards assumptions, as assessed by inclusion of time varying coefficients.

Risk models were recalibrated to risk regions using recalibration factors previously derived for SCORE2 and SCORE2-OP models (*Supplementary Methods Table 1*). Similarly, the grouping of European countries into risk regions was defined according to WHO CVD mortality rates following SCORE2 and SCORE2-OP methodology (*Supplementary Table 6, Supplementary Figure 2*). For validation we assessed discrimination using Harrell's C-index, adjusted for competing risk,[28] and examined improvement when comparing use of SCORE2-Diabetes versus SCORE2. Where data were available we compared SCORE2-Diabetes with the ADVANCE risk model for individuals with diabetes.[10] We use ADVANCE as a comparison as it is recommended by the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice[3] and it is designed to predict CVD risk. To provide clinical context, we compared incremental improvements afforded by diabetes-related information included in SCORE2-Diabetes with those afforded by total and HDL cholesterol, biomarkers commonly used in CVD risk assessment. Improvements in risk prediction were also quantified by the continuous net reclassification index (NRI), which summarises appropriate directional change in risk predictions for those who do (cases) and do not (non-cases) experience an event during follow-up (with increases in predicted risk being appropriate for cases and decreases being appropriate for non-cases). Similarly, the categorical NRI was also applied to summarise the appropriate movement between risk categories of <5%, 5-10%, 10-15%, 15-20% and >25%. Calibration was assessed by comparing the observed and predicted risks.

To compare the proportion of the population with diabetes at different levels of CVD risk according to the SCORE2-Diabetes models, predicted risk distributions were estimated using age- and sex-specific risk factor values from the CPRD, NDA, SNDR and all contributing EUBIROD populations, with the region-specific recalibrated versions of SCORE2-Diabetes. To ensure that the SCORE2 recalibration factors were applicable in recalibration of SCORE2-Diabetes we assessed that the average sex- and age-specific SCORE2-Diabetes risk predictions matched the expected risks for each risk region, and that the average sex- and age-specific risk predictions were similar in the

whole population, as well as in individuals with diabetes, when using SCORE2 and SCORE2-Diabetes. We also ensured similar risk predictions were obtained when using both the 2009 and 2021[29] versions of the CKD-EPI eGFR equations to ensure interchangeability of the two measures in clinical practice. Finally, SHRs were also estimated without inclusion of ERFC/UK Biobank data to ensure no sensitivity to potential minor overlap in individuals contributing to UK based studies and the CPRD.

Missing data were imputed for derivation datasets, SNDR and SIDIAP using methods described in the *Supplementary Methods*. We adopted analytical approaches and reporting standards recommended by the PROBAST guidelines and TRIPOD.[30] Analyses were performed with R-statistic programming (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 16.1, StataCorp, College Station, Texas). The study was designed and completed by the SCORE2-Diabetes Working Group in collaboration with the ESC Cardiovascular Risk Collaboration.

Ethical approval

Relevant ethical approval and participant consent were already obtained in all studies that contributed data to this work (*Supplementary study-specific information*).

Results

Model derivation involved a total of 229,460 participants with diabetes and without history of CVD at baseline from SCID, CPRD, and ERFC/UKB. Mean age (SD) at baseline was 65 (11) years for SCID, 60 (8) years for CPRD and 64 (11) years for ERFC/UKB. A total of 122,543 (53.4%) participants were male across all data sources (*Table 1*). Median (5^{th}, 95^{th} percentile) follow-up in years was 10.9 (6.8, 11.0) in SCID, 6.0 (0.8, 11.0) in CPRD, and 11.3 (2.8, 13.6) in ERFC/UKB, during which a total of 43,706 CVD events and 28,226 non-CVD deaths were recorded. SHRs are shown in *Table 2*. The association of the diabetes-related variables decreased with increasing age of participants (*Supplementary Methods Figure*). Associations were similar when excluding ERFC/UKB data (*Supplementary Table 7*).

Table 1. Summary of available data on individuals with diabetes used in SCORE2-Diabetes risk model derivation

	N (%) or mean (SD)		
	SCID	**ERFC/UKB**	**CPRD**
Participants	136,192	20,517	72,751
Male sex	72,525 (53%)	11,485 (56%)	38,599 (53%)
SCORE2 variables			
Age (years)	65 (11)	60 (8)	64 (11)
Current smoker	24,447 (18%)	2353 (12%)	11,423 (21%)
Systolic blood pressure (mmHg)	136 (16)	142 (17)	136 (16)
Total cholesterol (mmol/L)	4.3 (1.0)	4.7 (1.1)	4.4 (1.0)
HDL-cholesterol (mmol/L)	1.3 (0.4)	1.2 (0.3)	1.2 (0.4)
SCORE2-Diabetes additional variables			
Diabetes age of diagnosis (per 5-years)	58 (12)	53 (9)	58 (11)
HbA1c (mmol/mol)	58 (17)	55 (20)	52 (19)
eGFR (ml/min/1.73m^2)	74 (20)	88 (17)	76 (17)
Follow-up (years, median (5^{th}/95^{th} percentile))	10.9 (6.8, 11.0)	11.3 (2.8, 13.6)	6.0 (0.8, 11.0)
Cardiovascular events	34,595	1,864	7,247
Non-cardiovascular deaths	21,062	1,953	5,211

SCID: Scottish Care Information – Diabetes, ERFC: Emerging Risk Factors Collaboration, UKB: UK Biobank, CPRD: Clinical Practice Research Datalink
eGFR: estimated Glomerular Filtration Rate, calculated using the CKD-EPI 2009 equations; HbA1c: glycated haemoglobin, in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units
Table shows summary statistics for datasets before imputation (which was carried out during analysis). A summary of missing data, by data source and variable, is provided in Supplementary Table 2

The C-indices in the derivation datasets were 0.704 (95% CI 0.701, 0.706), 0.733 (0.727-0.739) and 0.666 (0.653, 0.678) in SCID, CPRD and ERFC/UKB respectively (Figure 2). In external validation, the C-index for SCORE2-Diabetes was 0.670 (0.667, 0.673) using data from 168,585 individuals with diabetes (34,944 CVD events) from the SNDR and 0.658 (0.648, 0.669) using 21,698 individuals with diabetes (2464 CVD events) from SIDIAP. Using EUBIROD datasets including 3,876 individuals from Malta and 22,821 individuals from Croatia with complete information on all risk predictors, the C-index was 0.661 (0.622) and 0.688 (0.672, 0.705) respectively (*Supplementary Figure 3*).

In comparison to SCORE2, SCORE2-Diabetes showed improved risk discrimination in individuals with diabetes, with increases in C-indices (95% CI) of 0.021 (0.020,

0.022), 0.023 (0.020, 0.026) and 0.026 (0.018, 0.034) in SCID, CPRD and ERFC/UKB, respectively. Somewhat smaller improvements were observed in SNDR, and SIDIAP with increases in C-index of 0.009 (0.007, 0.010) and 0.009 (0.005, 0.014) respectively (*Figure 2*). In EUBIROD datasets from Malta and Croatia, increases in C-indices were of 0.031 (0.011, 0.050) and 0.013 (0.006, 0.021), respectively (*Supplementary Figure 3*).

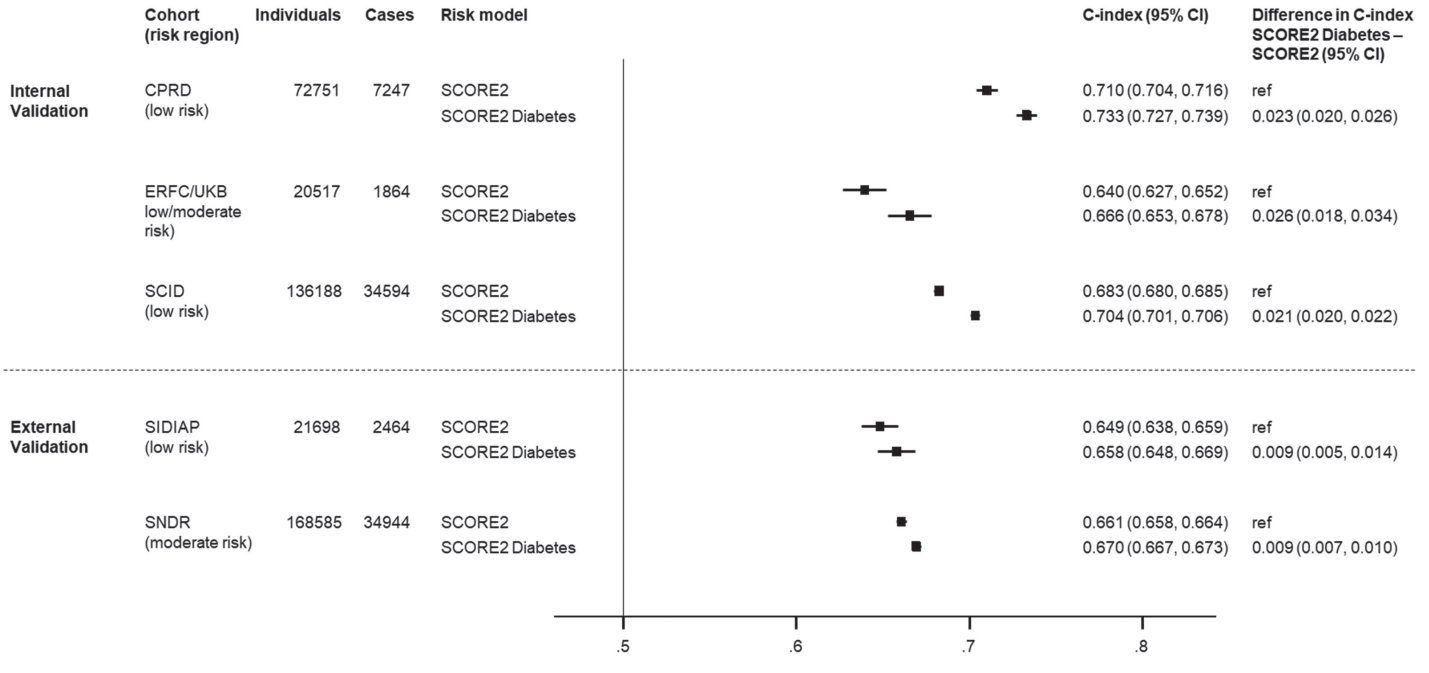
Table 2. Subdistribution hazard ratios for predictor variables in the SCORE2-Diabetes risk models

	Men		Women	
	Main effect	**Age interaction term**	**Main effect**	**Age interaction term**
SCORE2 variables				
Age (per 5 years)	1.71 (1.66, 1.76)	-	1.94 (1.88, 2.00)	-
Current smoking	1.61 (1.53, 1.70)	0.94 (0.91, 0.96)	1.85 (1.73, 1.98)	0.89 (0.87, 0.92)
Systolic blood pressure (per 20mmHg)	1.14 (1.11, 1.17)	0.97 (0.96, 0.99)	1.15 (1.12, 1.19)	0.98 (0.97, 1.00)
Total cholesterol (per 1 mmol/L)	1.12 (1.10, 1.14)	0.98 (0.97, 0.99)	1.12 (1.09, 1.15)	0.98 (0.97, 0.99)
HDL cholesterol (per 0.5 mmol/L)	0.90 (0.86, 0.93)	1.01 (0.99, 1.03)	0.85 (0.82, 0.89)	1.02 (1.00, 1.04)
History of diabetes mellitus	1.91 (1.81, 2.01)	0.91 (0.88, 0.93)	2.25 (2.11, 2.40)	0.88 (0.85, 0.91)
SCORE2-DM2 additional variables				
Diabetes age at diagnosis (per 5-years)	0.90 (0.89, 0.91)		0.89 (0.88, 0.90)	
HbA1c (per SD mmol/mol)	1.10 (1.09, 1.11)	0.99 (0.98, 0.99)	1.12 (1.11, 1.14)	0.98 (0.98, 0.98)
ln eGFR (per SD ln(ml/min/1.73m2))	0.94 (0.93, 0.96)	1.01 (1.01, 1.01)	0.94 (0.92, 0.95)	1.02 (1.01, 1.02)
ln eGFR2 (quadratic term)	1.01 (1.00, 1.01)		1.01 (1.00, 1.01)	

Sex-specific subdistribution hazard ratios from Fine and Gray models predicting the risk of fatal and non-fatal CVD events as derived for SCORE2 and adapted in individuals with diabetes from ERFC, UK Biobank, CPRD, SCID to include adjustments to SCORE2 effects and SCORE2-DM2 additional variables. Age was centered at 60 years, systolic blood pressure at 120 mmHg, total cholesterol at 6 mmol/L, HDL cholesterol at 1.3 mmol/L, age at diabetes onset at 50 years HbA1c at 31 mmol/mol and eGFR 90 ml/min/1.73^2 (i.e. Ln-eGFR of 4.5). The median baseline survival at 10 years in the derivation cohorts was 0.9625 for men and 0.9795 for women. For HbA1c, 1 SD = 9.34 mmol/mol and for eGRF 1SD=0.15 ln(ml/min/1.73m^2)

**Values shown are the combination of original SCORE2 coefficients and additional coefficients which modify the associations for individuals with diabetes. See Supplementary methods for full sets of component effects for each risk predictor*

Figure 2. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from each data source



CPRD: Clinical Practice Research Datalink; ERFC: Emerging Risk Factors Collaboration; UKB: UK Biobank; SCID: Scottish Care Information – Diabetes; SIDIAP: Information System for Research in Primary Care; SNDR: Swedish National Diabetes Register.

Significant improvements in C-indices were also seen in both men and women, and within 10-year age groups (*Supplementary Figures 4 to 7*). C-indices were similar when eGFR was calculated using different equations (*Supplementary Figure 8*), but were slightly attenuated when excluding individuals with eGFR <45 ml/min/1.73m^2 (*Supplementary Figure 9*). Improvements in risk discrimination provided by the additional diabetes-related variables included in SCORE2-Diabetes (i.e., age of diabetes diagnosis, HbA1c, and eGFR) were greater than that provided by total and HDL-cholesterol concentration in the same model. SCORE2-Diabetes also showed slightly improved discrimination over the ADVANCE risk score (*Supplementary Table 8*).

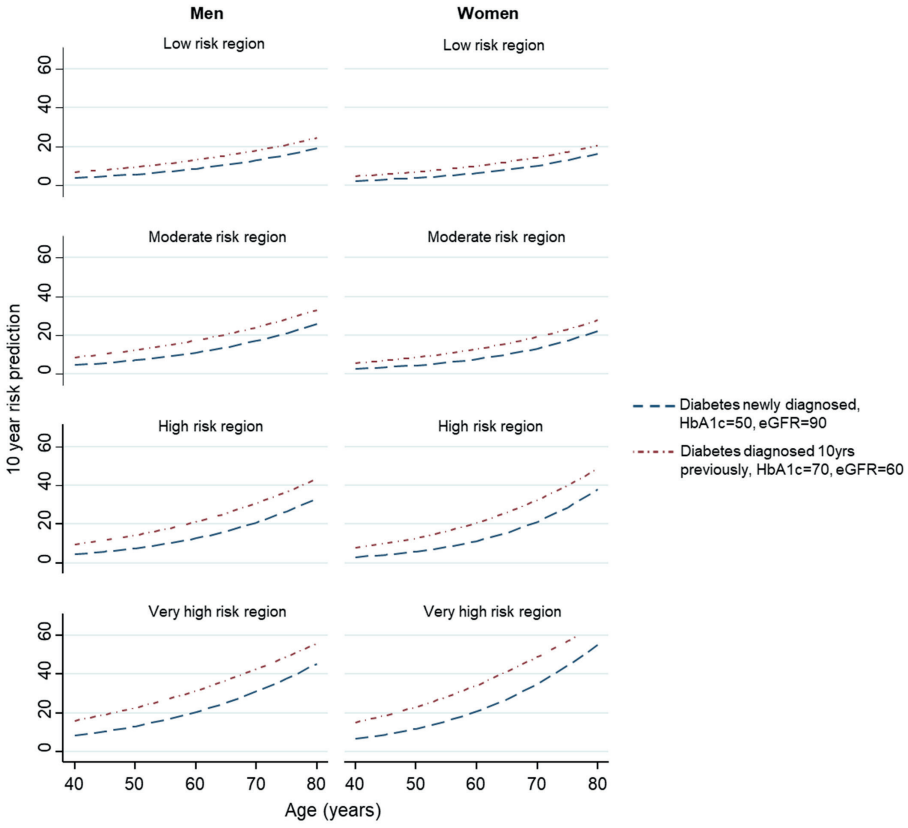
Using SCORE2-Diabetes rather than SCORE2 improved risk classification, yielding a continuous NRI of 25.2 (95% CI, 22.4, 28.0) in the CPRD and 28.7 (27.7, 29.8) in the SNDR. Similarly, using SCORE2-Diabetes rather than SCORE2 yielded a categorical NRI of 24.6 (22.5, 26.8) in the CPRD and 13.7 (12.9, 14.5) in the SNDR, with a respective net of 44.8% (43.0%, 46.7%) and 31.9% (31.2%, 32.6%) cases being appropriately reclassified (*Supplementary Table 9*).

After recalibration, the SCORE2-Diabetes predicted risks showed good agreement with the expected 10-year CVD incidence in each risk region (*Supplementary Figure 7*), and were similar on average within each age-group to those produced using SCORE2 (*Supplementary Figure 8*). SCORE2-Diabetes predicted risks also agreed with observed risks in individuals with diabetes from nationally representative datasets with 10-year of follow-up (*Supplementary Figure 9 and 10*), and showed improved calibration over SCORE2 (*Supplementary Figure 10*).

The SCORE2-Diabetes algorithms for CVD risk estimation in four European risk regions are shown in the *Supplementary Methods Table 1*. The estimated absolute risk for a given age and combination of conventional CVD risk factors differed substantially according to levels of the diabetes-related variables (*Figure 3*). For example, when using the moderate risk region version of SCORE2-Diabetes, the estimated 10-year CVD risk for a 60-year-old non-smoking man with a history of diabetes, average levels of conventional risk factors (i.e., systolic blood pressure of 140 mm Hg, total cholesterol of 5.5 mmol/L and HDL cholesterol of 1.3 mmol/L), HbA1c of 50 mmol/mol, eGFR of 90ml/min/1.73m^2, and age-at-diabetes diagnosis of 60 years, was 11.0%. For a

similar man with less favourable diabetes-related risk factors (i.e., of HbA1c of 70 mmol/mol, eGFR of 60 ml/min/1.73m^2, and age at diagnosis of 50 years), the estimated risk was 17.2%. For a woman with the same characteristics, risk was 7.9% and 12.7%, respectively. Risk estimates also varied across European risk regions due to recalibration, with a man or woman with the latter risk factor values having an estimated risk of 12.9% and 8.4% respectively in the low-risk region, and 31.3% and 34.0% in the very high-risk region (*Figure 3*).

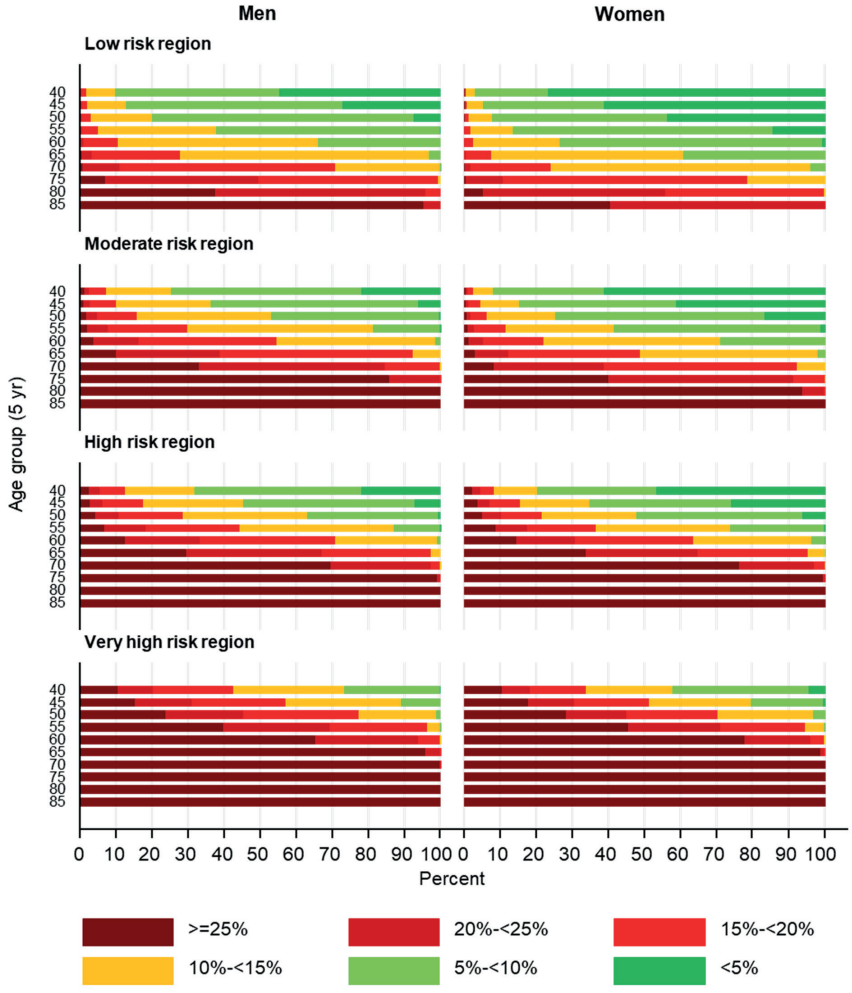
Figure 3. Predicted sex- and age-specific SCORE2-Diabetes 10-year cardiovascular disease risks for an individual with diabetes and different levels of type 2 diabetes risk factors from four European Risk Regions



Estimates are for non-smokers with systolic blood pressure of 140 mm Hg, total cholesterol of 5.5 mmol/L and HDL cholesterol of 1.3 mmol/L
eGFR: estimated Glomerular Filtration Rate (ml/min/1.73m^2) calculated using the CKD-EPI 2009 equations; HbA1c (mmol/mol): glycated haemoglobin, in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units

When we applied recalibrated SCORE2-Diabetes models to simulated data representing populations from each risk region, the proportion of individuals aged 40–79 years with an estimated risk greater than 10% varied substantially by region, from 61% in the low-risk region to 96% in the very-high risk region in men and from 51% to 94% respectively in women, with proportions increasing with age as expected (*Figure 4*).

Figure 4. Distribution of sex- and age-specific 10-year CVD risk according to recalibrated SCORE2-Diabetes models across European risk regions



*The proportion of individuals expected in each risk category was estimated to reflect the age-group and sex-specific risk factor values in each risk region (**Supplementary methods**)*

Discussion

Compared with existing risk scores, SCORE2-Diabetes, an extension of the SCORE2 risk models tailored to individuals with type 2 diabetes across Europe's diverse populations, should help better support allocation of preventative interventions, as it involves several advantages.

First, SCORE2-Diabetes has been systematically recalibrated to four distinct European regions defined by varying CVD risk levels, using the most contemporary and representative CVD rates available.[12] This improves on previous CVD risk prediction models for individuals with diabetes which either have not incorporated any recalibration to different populations, or have been recalibrated based on sparse cohort or country-level data on individuals with diabetes, which may not accurately reflect the CVD rates and risk factor levels of populations in each region.[9-11] Our analysis illustrates that three- to four-fold variation in estimated CVD risk for a given set of risk factors can be seen as a result of recalibration. Without recalibration this substantial variation in risk across Europe would be ignored. Because the recalibration approach we used is based on registry data, the model can be readily updated to reflect future CVD incidence and risk factor profiles of any target population to be screened, including those with diabetes. This means that if descriptive age- and sex-specific epidemiological data are available from individual European countries (or within-country regions), they can be readily incorporated to revise models at a country-level. This is an important feature of the current risk score since there have been considerable changes in CV risk over time and region in people with type 2 diabetes, necessitating contemporary risk estimation.

A second -and related advantage- is that, rather than being developed solely in data from individuals with diabetes, SCORE2-Diabetes extends SCORE2 models that were developed in all individuals without previous CVD, including both those with and without diabetes (although the ESC does not recommend SCORE2 for use in those with diabetes). A key advantage of this approach is that it allows recalibration of the models using risk factor data and incidence rates from the general population, rather than requiring data specifically from individuals with diabetes, which are currently not available systematically across European countries. By extending SCORE2 we also ensure harmonization of risk estimation for individuals with and without diabetes across Europe, aiding

communication and interpretation of risk estimates. The existing ESC CVD Risk Calculation App[31] and the "HeartScore" website[32] will be updated to include SCORE2-Diabetes to facilitate risk estimation and communication between health professionals and individuals with type 2 diabetes.

Third, SCORE2-Diabetes shows good ability to discriminate risk among individuals with type 2 diabetes, that was higher than that observed with ADVANCE and SCORE2, mainly due to the addition of risk predictors relevant to type 2 diabetes, such as age of diabetes diagnosis, HbA1c and kidney function. SCORE2-Diabetes risk estimations could therefore be used to help guide clinicians and patients for considering the intensity of existing treatment (such as lipid lowering therapies) as well as additional interventions to prevent CVD (such as sodium-glucose co-transporter-2 inhibitors [SLGT2i] or glucagon like peptide-1 receptor agonists [GLP-1 RA]).

Fourth, development, calibration, validation, and illustration of the SCORE2-Diabetes models have been underpinned by powerful, extensive and complementary datasets of contemporary relevance to individuals with type 2 diabetes across European populations. In particular, SCORE2-Diabetes was developed and validated using data on a total of almost 450,000 individuals from 8 countries, which should enhance the accuracy, generalizability and validity of the approach.

Fifth, the approach used in SCORE2-Diabetes accounts for the impact of the competing risk of non-CVD death. This statistical adjustment should prevent any overestimation of CVD risk, thereby reducing the chances of over-estimating the potential benefits of CVD-risk modifying treatments. This adjustment particularly benefits treatment decisions in older individuals, and those from high or very-high risk regions, where the risk of competing non-CVD death is high.

Finally, our analysis has illustrated the performance of SCORE2-Diabetes with simulated data on individuals with type 2 diabetes from different European risk regions, showing that the proportions of individuals across different risk categories are strikingly different across regions. This finding suggests that our risk estimates should assist policy makers to make more appropriate and locally informed decisions about the allocation of resources.

The potential limitations of this study merit consideration. We extended the SCORE2 risk prediction models by estimating additional relative risks for the diabetes-related variables using data sources from European regions and populations at low- or moderate- CVD risk. Ideally, relative risk estimation for use in high and very high-risk countries would have involved large nationally representative, prospective cohorts in these countries, coupled with prolonged follow-up and validation of fatal and non-fatal CVD endpoints. Unfortunately, such data do not yet exist. Indeed, even in low- and moderate-risk regions, the data sources involved may not be nationally or regionally representative, reflecting past periods of time, 'healthy' volunteers contributing to cohort studies, or, in the case of registry data, individuals with increased tendency to seek medical attention. However, while such biases can lead to misleading levels of absolute risk, relative risks are generally unaffected.[2,33,34] Furthermore, our analyses identified little heterogeneity in model coefficients across studies used in model derivation, suggesting transferability of model coefficients across different populations, as evidenced by good discrimination in all populations tested. Crucially, SCORE2-Diabetes models were recalibrated using nationally representative incidence rates, an important step not commonly considered in development of other CVD risk scores for individuals with diabetes[10,11], avoiding the limitations of mis-calibration provided by potentially non-representative incidence rates in derivation datasets.

The rescaling factors used in recalibration of SCORE2-Diabetes were identical to those used in recalibration of the SCORE2 risk models. This approach assumes that the additional measurement of diabetes age at diagnosis, HbA1c and eGFR among individuals with diabetes does not importantly change the average sex and age-specific risk predictions for the regional target population (including those with and without diabetes). We have tested this assumption using several datasets mostly from the low and moderate risk regions, but further testing should be completed if the relevant data become available in the future. Likewise, more accurate representation of the potential predicted risk distributions in each European risk region could be achieved by applying the recalibrated SCORE2-Diabetes models to risk factor levels from the diabetes-specific populations from additional representative datasets in each risk region. In parallel to the analysis presented in the current study, we have developed methods and statistical codes that will allow future validation and illustration of SCORE2-Diabetes in diabetes-specific registries as data becomes available.[21,35]

While fatal outcomes for heart failure and peripheral vascular disease were included in SCORE2-Diabetes outcome, data on non-fatal incident heart failure, peripheral artery disease and microvascular complications were not uniformly recorded in available derivation and recalibration data sources and it has therefore not been possible to include these outcomes. Previous research suggests that discrimination of SCORE2-Diabetes for these outcomes is still likely to be good[7], however, estimates of CVD risk from SCORE2-Diabetes could be conservative and may underestimate the potential benefits of CVD-risk modifying treatments that also reduce heart failure risk.

It is assumed that many individuals using SCORE2-Diabetes will already be taking medication that affects CVD risk, and this assumption is respected by inclusion of such individuals in datasets used to derive and recalibrate the models. In addition, some individuals in our model derivation cohorts may have initiated preventative treatment (e.g., statin) during follow-up and accounting for this could improve model calibration and discrimination. However previous analyses have suggested that inclusion of information on statin-initiation during follow-up provides only limited improvement in risk prediction.[36] Furthermore, comprehensive individual-participant-data on medication use were unavailable in all data sources used for model development and recalibration. This was also the case with family history of CVD, socio-economic status, ethnicity, and albuminuria meaning interpretation of SCORE2-Diabetes estimates may require clinical judgement, especially for individuals for whom these factors may be relevant (e.g., those with a family history of premature CVD, or in higher-risk socio-economic and non-white ethnic groups) as well as in older age groups where additional consideration of multi-morbidities and life expectancy may be needed.[9,37] While the SCORE2-Diabetes models are broadly applicable across all European countries, there remains a place for country-specific risk calculators that consider the specific characteristics relevant to that population (ideally incorporating information on socio-economic status and ethnicity). More generally, better quality data collection, both in terms of risk factors and outcomes will serve to improve the quality of risk prediction, and should be integral to the evolution of electronic health records and their linkage.

We compared the performance of SCORE2-Diabetes with the ADVANCE model in the SNDR dataset since this dataset is considered nationally representative of the diabetes population in Sweden. However, due to lack of data availability

albuminuria was used as a binary rather than continuous variable and atrial fibrillation was not included, meaning that the full predictive ability of ADVANCE may not have been observed in the current analysis. Further comparison with other risk models already developed for use in individuals with type 2 diabetes was generally not possible because these models contain variables often not available in datasets. Similarly, data availability for recalibration is very limited, making such models less appropriate for use across different risk regions. Furthermore, previous analyses have suggested that only minor differences exist in risk discrimination among guideline-recommended risk prediction models including those developed in the whole population and those developed specifically within individuals with diabetes.[7,38] By contrast, the clinical performance of risk prediction models depends importantly on differing ability to predict the correct level of risk in the target population (i.e., extent of 'calibration').[38] We, therefore, ensured SCORE2-Diabetes was well-calibrated to current absolute risk levels for each European region.

In summary, we have derived, recalibrated, validated and illustrated SCORE2-Diabetes, a 10-year risk model tailored to individuals with diabetes in European populations to predict 10-year risk of first-onset CVD. This will assist future guidelines on CVD prevention in individuals with type 2 diabetes, by providing an appropriate risk estimation system to enhance the accuracy, practicability, and sustainability of CVD prevention strategies and help guide preventive treatment.

References

1. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, Gale CP, Maggioni AP, Petersen SE, Huculeci R, Kazakiewicz D, de Benito Rubio V, Ignatiuk B, Raisi-Estabragh Z, Pawlak A, Karagiannidis E, Treskes R, Gaita D, Beltrame JF, McConnachie A, Bardinet I, Graham I, Flather M, Elliott P, Mossialos EA, Weidinger F, Achenbach S; Atlas Writing Group, European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J Qual Care Clin Outcomes. 2022.
2. Emerging Risk Factors Collaboration, 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):2215-2222.
3. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337.
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 Guidelines. 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-S73.
5. Group WCRCW. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Health. 2019;7(10):e1332-e1345.
6. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357.
7. Dziopa K, Asselbergs FW, Gratton J, Chaturvedi N, Schmidt AF. Cardiovascular risk prediction in type 2 diabetes: a comparison of 22 risk scores in primary care settings. Diabetologia. 2022;65(4):644-656.
8. Read SH, van Diepen M, Colhoun HM, Halbesma N, Lindsay RS, McKnight JA, McAllister DA, Pearson ER, Petrie JR, Philip S, Sattar N, Woodward M, Wild SH; Scottish Diabetes Research Network Epidemiology Group. Performance of Cardiovascular Disease Risk Scores in People Diagnosed With Type 2 Diabetes: External Validation Using Data From the National Scottish Diabetes Register. Diabetes Care. 2018;41(9):2010-2018.
9. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, Wild SH, Franzen S, Chalmers J, Davis BR, Poulter NR, Spijkerman AM, Woodward M, Pressel SL, Gupta AK, van der Schouw YT, Svensson AM, van der Graaf Y, Read SH, Eliasson B, Dorresteijn JAN. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. Eur Heart J. 2019;40(34):2899-2906.

10. 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; ADVANCE Collaborative Group. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil. 2011;18(3):393-398.
11. Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study G. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond). 2001;101(6):671-679.
12. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-2454.
13. McKnight JA, Morris AD, Cline D, Peden N, Fischbacher C, Wild S; Scottish Diabetes Survey Monitoring Group. Implementing a national quality assurance system for diabetes care: the Scottish Diabetes Survey 2001-2006. Diabet Med. 2008;25(6):743-746.
14. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-836.
15. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
16. Emerging Risk Factors Collaboration, Danesh J, Erqou S, Walker M, et al. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. Eur J Epidemiol. 2007;22(12):839-869.
17. Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, et al. Association of Cardiometabolic Multimorbidity With Mortality. JAMA. 2015;314(1):52-60.
18. 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):1270-1276.
19. Mata-Cases M, Mauricio D, Real J, Bolibar B, Franch-Nadal J. Is diabetes mellitus correctly registered and classified in primary care? A population-based study in Catalonia, Spain. Endocrinol Nutr. 2016;63(9):440-448.
20. Bolíbar B, Fina Avilés F, Morros R, Garcia-Gil Mdel M, Hermosilla E, Ramos R, Rosell M, Rodríguez J, Medina M, Calero S, Prieto-Alhambra D; Grupo SIDIAP. [SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research]. Med Clin (Barc). 2012;138(14):617-621.
21. Carinci F, Štotl I, Cunningham SG, et al. Making Use of Comparable Health Data to Improve Quality of Care and Outcomes in Diabetes: The EUBIROD Review of Diabetes Registries and Data Sources in Europe. Frontiers in Clinical Diabetes and Healthcare. 2021;2.
22. Cunningham SG, Carinci F, Brillante M, Leese GP, McAlpine RR, Azzopardi J, Beck P, Bratina N, Bocquet V, Doggen K, Jarosz-Chobot PK, Jecht M, Lindblad U, Moulton T, Metelko Ž, Nagy A, Olympios G, Pruna S, Skeie S, Storms F, Di Iorio CT, Massi Benedetti M. Core Standards of the EUBIROD Project. Defining a European Diabetes Data Dictionary for Clinical Audit and Healthcare Delivery. Methods Inf Med. 2016;55(2):166-176.

23. EUBIROD. NeuBIRO Software http://www.eubirod.eu/academy/software.html. Accessed.
24. Di Iorio CT, Carinci F, Oderkirk J, Smith D, Siano M, de Marco DA, de Lusignan S, Hamalainen P, Benedetti MM. Assessing data protection and governance in health information systems: a novel methodology of Privacy and Ethics Impact and Performance Assessment (PEIPA). J Med Ethics. 2020.
25. Di Iorio CT, Carinci F, Brillante M, Azzopardi J, Beck P, Bratina N, Cunningham SG, De Beaufort C, Debacker N, Jarosz-Chobot P, Jecht M, Lindblad U, Moulton T, Metelko Ž, Nagy A, Olympios G, Pruna S, Røder M, Skeie S, Storms F, Massi Benedetti M. Cross-border flow of health information: is 'privacy by design' enough? Privacy performance assessment in EUBIROD. Eur J Public Health. 2013;23(2):247-253.
26. Di Iorio CT, Carinci F, Azzopardi J, Baglioni V, Beck P, Cunningham S, Evripidou A, Leese G, Loevaas KF, Olympios G, Federici MO, Pruna S, Palladino P, Skeie S, Taverner P, Traynor V, Benedetti MM. Privacy impact assessment in the design of transnational public health information systems: the BIRO project. J Med Ethics. 2009;35(12):753-761.
27. Holman N, Knighton P, Wild SH, Sattar N, Dew C, Gregg EW, Khunti K, Valabhji J, Young B. Cohort profile: National Diabetes Audit for England and Wales. Diabet Med. 2021;38(9):e14616.
28. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology. 2009;20(4):555-561.
29. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, Grams ME, Greene T, Grubb A, Gudnason V, Gutiérrez OM, Kalil R, Karger AB, Mauer M, Navis G, Nelson RG, Poggio ED, Rodby R, Rossing P, Rule AD, Selvin E, Seegmiller JC, Shlipak MG, Torres VE, Yang W, Ballew SH, Couture SJ, Powe NR, Levey AS; Chronic Kidney Disease Epidemiology Collaboration. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-1749.
30. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015;162(1):55-63.
31. European Society of Cardiology https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app. Accessed2022.
32. European Society of Cardiology https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/HeartScore. Accessed2022.
33. Batty GD, Gale CR, Kivimaki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ. 2020;368:m131.
34. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schöttker B, Shankar A, Shlipak M, Tonelli M, Townend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Ärnlöv J; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3(7):514-525.

35. Cunningham SG, Carinci F, Brillante M, Leese GP, McAlpine RR, Azzopardi J, Beck P, Bratina N, Bocquet V, Doggen K, Jarosz-Chobot PK, Jecht M, Lindblad U, Moulton T, Metelko Ž, Nagy A, Olympios G, Pruna S, Skeie S, Storms F, Di Iorio CT, Massi Benedetti M. Core Standards of the EUBIROD Project. Defining a European Diabetes Data Dictionary for Clinical Audit and Healthcare Delivery. Methods Inf Med. 2016;55(2):166-176.
36. Xu Z, Arnold M, Stevens D, Kaptoge S, Pennells L, Sweeting MJ, Barrett J, Di Angelantonio E, Wood AM. Prediction of Cardiovascular Disease Risk Accounting for Future Initiation of Statin Treatment. Am J Epidemiol. 2021;190(10):2000-2014.
37. SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455-2467.
38. Pennells L, Kaptoge S, Wood A, Emerging Risk Factors Collaboration, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. Eur Heart J. 2019;40(7):621-631.

Authors List

Lisa Pennells* (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Stephen Kaptoge* (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Helena Bleken Østergaard* (Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands); Stephanie H Read* (Usher Institute, University of Edinburgh, Edinburgh, UK); Fabrizio Carinci* (Department of Statistical Sciences, University of Bologna, Italy); Josep Franch-Nadal (Center for Biomedical Research on Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Barcelona, Spain. Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gorina (IDIAPJGol), Barcelona, Spain. Primary Health Care Center Raval Sud, Institut Català de la Salut, Barcelona, Spain); Carmen Petitjean (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Owen Taylor (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Steven H.J. Hageman (Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands); Zhe Xu (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Fanchao Shi (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Sarah Spackman (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Stefano Gualdi (Internet Express, Pescara, Italy); Naomi Holman (Department of Epidemiology and Biostatistics, Imperial College London, UK); Rui Bebiano Da Providencia E Costa (UCL Institute for Health Informatics Research, University College London, London, UK); Fabrice Bonnet (University of Rennes 1, Rennes CHU, Rennes, France); Hermann Brenner (Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany. Network Aging Research, University of Heidelberg, Heidelberg, Germany); Richard F Gillum (Howard University Hospital, Washington DC, DC, USA); Stefan Kiechl (Department of Neurology, Medical University Innsbruck, Innsbruck, Austria); Deborah A Lawlor (MRC Integrative Epidemiology Unit at the University of Bristol, UK; Population Health Science, Bristol Medical School, Bristol University, UK); Louis Potier (Université Paris City, Bichat Hospital, AP-HP, INSERM U1151 INEM, Paris, France); Ben Schöttker (Division of Clinical Epidemiology and Aging

Research, German Cancer Research Center, Heidelberg, Germany. Network Aging Research, University of Heidelberg, Heidelberg, Germany); Reecha Sofat (UCL Institute for Health Informatics Research, University College London, London, UK); Henry Völzke (Institute for Community Medicine, University Medicine Greifswald, Germany); Johann Willeit (Department of Neurology, Medical University Innsbruck, Innsbruck, Austria); Zane Baltane (The Centre for Disease Prevention and Control of Latvia); Stephen Fava (University of Malta); Sandor Janos (University of Debrecen); Astrid Lavens (Sciensano, Belgium); Santa Pildava (The Centre for Disease Prevention and Control of Latvia); Tamara Poljicanin MD, PhD (Croatian Institute of Public Health, Rockefellerova 7, Zagreb, Croatia); Ivan Pristas MD, PhD (Croatian Institute of Public Health, Rockefellerova 7, Zagreb, Croatia); Peter Rossing (Steno Diabetes Center, Gentofte, Denmark); Reiff Sascha (Ministry of Health, Malta); Christa Scheidt-Nave (Robert Koch Institute); Iztok Stotl (Department of Endocrinology, Diabetes and Metabolic Diseases,University Medical Centre Ljubljana, Ljubljana, Slovenia); Gail Tibor (University of Debrecen); Vlima Urbančič-Rovan (Department of Endocrinology, Diabetes and Metabolic Diseases,University Medical Centre Ljubljana, Ljubljana, Slovenia Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia); An-Sofie Vanherwegen (Sciensano, Belgium); Dorte Vistisen (Steno Diabetes Center, Gentofte, Denmark); Yong Du (Robert Koch Institute); Matthew R Walker (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Peter Willeit (Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Brian Ferenece (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Dirk De Bacquer (Ghent University, Ghent, Belgium); Martin Halle (University Hospital ´Klinikum rechts der Isar´, Technical University of Munich, Munich, Germany); Radu Huculeci (European Society of Cardiology, Brussels, Belgium); John William McEvoy (National University of Ireland Galway, Galway, Ireland); Adam Timmis (William Harvey Research Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK); Panagiotis Vardas (Heraklion University Hospital, Crete, Greece); Jannick A. N. Dorresteijn (Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands); Ian Graham (School of Medicine, Trinity College Dublin, The University of Dublin, College Green,

Dublin, Ireland); Angela Wood (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Björn Eliasson (Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden; The Swedish National Diabetes Register, Gothenburg, Sweden); William Herrington (Medical Research Council Population Health Research Unit at the University of Oxford, Nuffield Department of Population Health, University of Oxford, Oxford, UK); John Danesh (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK); Dídac Mauricio (Department of Endocrinology & Nutrition, Hospital de la Santa Creu i Sant Pau, and Sant Pau Biomedical Research Institute, Barcelona, Spain. Center for Biomedical Research on Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Barcelona, Spain. Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gorina (IDIAPJGol), Barcelona, Spain. Departament of Medicine, Central University of Catalonia, Vic, Spain); Massimo Massi Benedetti‡ (Hub for International Health Research, Perugia,Italy); Naveed Sattar‡ (Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK); Frank L.J. Visseren‡ (Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands); Sarah Wild‡ (Usher Institute, University of Edinburgh, Edinburgh, UK); Emanuele Di Angelantonio‡ (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK, Health Data Science Centre, Human Technopole, Milan, Italy).

*Contributed equally; ‡Contributed equally

Supplementary material

Supplementary Methods

SCORE2-Diabetes derivation

SCORE2-Diabetes is an extension of the SCORE2 models for CVD risk prediction in Europe, to include additional information needed to estimate CVD risk in individuals with diabetes. The original SCORE2 models were derived using 44 studies from the Emerging Risk Factors Collaboration (ERFC) and the UK Biobank (UKB), and were recalibrated to four risk regions defined by CVD mortality rates, using risk factor averages and estimated incidence for each region. The 45 derivation cohorts included individuals with and without diabetes and the SCORE2 models included an adjustment for diabetes status.

Original SCORE2 risk models

The SCORE2 risk models take the following form.

1) Uncalibrated_score2 = 1-$s_o(10)^{\exp(LP\_score2)}$

Where, using the transformed variables defined in *Supplementary Methods table 1*:

LP_score2= β_1*cages + β_2*smoking + β_3*csbp + β_4*ctchol + β_5*chdl + β_6*hxdiabetes + β_7*cages*smoking + β_8* cages *csbp + β_9* cages * ctchol + β_{10}* cages *chdl + β_{11} * cages*hxdiabetes

$\beta_{1\text{-}11}$ are the sex-specific log HR estimates from the original SCORE2 derivation data

$s_o(10)$ is the baseline sex-specific survival estimate from the derivation data

2) Recalibrated_score2 = 1-exp(-exp(scale1 + scale2 * ln(-ln(1 – uncalibrated_score2)))), where scale1 and scale2 are the region and sex-specific recalibration factors estimated for each of the four risk regions

Extension of SCORE2 to add new risk predictor effects specific to improving risk prediction for individuals with diabetes: The SCORE2-Diabetes model

The SCORE2-Diabetes prediction models are structured as follows:

Uncalibrated_score2_DM2 = 1 - $s_o(t)^{LP_{score2}+LP_{DM}+SCORE2vars}$, where

LP_{score2} and $s_o(t)$ are exactly as defined for SCORE2

LP_{DM} = β_{12} *cagediab + β_{13} *chba1c + β_{14} *cages*chba1c + β_{15} *clnegfr + β_{16} *clnegfr*clnegfr + β_{17} *cages*clnegfr

SCORE2vars = β_{18} * cages + β_{19} *Smoking + β_{20} *csbp + β_{21} *ctchol + β_{22} *chdl + β_{23} *Diabetes + β_{24} *cages*Smoking + β_{25} *cages*csbp + β_{26} *cages*ctchol + β_{27} *cages*chdl β_{28} *cages*Diabetes

$\beta_{12\text{-}28}$ are the sex-specific log SHR estimates from the new derivation data

The additional inclusion of SCORE2 variables (as well as their use in the offset term) enabled inclusion of interactions between baseline age and the new variables of interest, corrected for any residual correlation/confounding between the conventional SCORE2 variables and the additional SCORE2-Diabetes variables, and allowed the SCORE2 predictor effects to be modified for individuals with diabetes.

This process was completed separate for each sex and data source and the estimates of $\beta_{12\text{-}28}$ pooled using fixed effect meta-analysis, yielding the final model for use in clinical practice.

The final SCORE2-Diabetes models and estimation process are summarized in *Supplementary Methods Table 1*, which displays the combined effects of $\beta_{1\text{-}11}$ and $\beta_{12\text{-}28}$ for the conventional SCORE2 risk predictors (mathematically identical to applying the two sets individually). The full set of $\beta_{1\text{-}11}$ with $\beta_{12\text{-}28}$ from the derivation models are provided for information in *Supplementary Methods Table 2.*

Missing Data

Missing data in all model derivation datasets, in the Swedish National Diabetes Register (SNDR) and in the Information System for Research in Primary Care (SIDIAP) were imputed using multiple chained equations with predictive mean matching with 10 imputations, including in the imputation model all risk predictors and Nelson-Aalen estimators for both the CVD, and non-CVD death, outcomes.

Estimation of regionally representative predicted risk distributions

To compare the proportion of the population at different levels of CVD risk according to the SCORE2-Diabetes algorithm in the four risk regions, predicted risk distributions were estimated by rescaling individual participant data in CPRD according to estimated relative differences in age- and sex-specific means and prevalences of risk factors values in each region, compared to the low risk region.

The region-specific risk factor means and prevalences were estimated by pooling summary data from CPRD, NDA, SNDR, SIDIAP and contributing registries from EUBIROD using a linear mixed model with fixed effects for sex, 5-year age group, risk region, interactions of sex with 5-year age group and risk region, and random effect for country.

Ratios corresponding to expected relative differences in risk factor means and prevalences in comparison to the low risk region were calculated and applied to rescale individual level data in CPRD to estimate region-specific risk distributions. This approach accounted for expected regional differences in risk factor levels, but assumed risk factor correlations were broadly similar to those observed in the CPRD dataset.

Supplementary Methods table 1. Calculation of 10-year CVD risk using SCORE2-Diabetes

1) Calculation of Linear Predictor			
Risk factor (units)	**Transformed Risk factor**	**Log SHR**	
		Men	**Women**
SCORE2 variables			
Age (yrs)	cage = (age - 60)/5	0.5368	0.6624
Smoking (current vs. other)	smallbin	0.4774	0.6139
SBP (mm Hg)	csbp = (sbp - 120)/20	0.1322	0.1421
Diabetes (yes vs. no)	hxdiabbin	0.6457	0.8096
Total cholesterol (mmol/L)	ctchol = (tchol - 6)/1	0.1102	0.1127
HDL cholesterol (mmol/L)	chdl = (hdl - 1.3)/0.5	-0.1087	-0.1568
Smoking interaction with age	cage*smallbin	-0.0672	-0.1122
SBP interaction with age	cage*csbp	-0.0268	-0.0167
Diabetes interaction with age	cage*hxdiabbin	-0.0983	-0.1272
TCHOL interaction with age	cage*ctchol	-0.0181	-0.0200
HDL interaction with age	cage*chdl	0.0095	0.0186
SCORE2-DM2 additional variables			
Diabetes age at diagnosis (yrs)	cagediab=(agediab - 50)/5 if hxdiabbin=1, else 0.	-0.0998	-0.118
HbA1c (mmol/mol)	chba1c=(hba1c - 31)/9.34	0.0955	0.1173
Ln eGFR (ml/min/1.73m^2)	clnegfr=(lnegfr - 4.5)/0.15	-0.0591	-0.0640
Ln eGFR^2	clnegfr* clnegfr	0.0058	0.0062
HbA1c interaction with age	chba1c*cage	-0.0134	-0.0196
Ln eGFR interaction with age	clnegfr*cage	0.0115	0.0169
Linear predictor= Σ (transformed risk factor x log SHR)			

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

Men	**Women**
Uncalibrated risk = 1-0.9605 $^{\exp(\text{linear predictor})}$	Uncalibrated risk = 1-0.9776 $^{\exp(\text{linear predictor})}$

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

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

Risk region	**Male**	**Female**
Low	1-exp(-exp(-0.5699+0.7476 x ln(-ln(1 un-calibrated 10-yr risk))))	1-exp(-exp(-0.7380+0.7019 x ln(-ln(1- un-calibrated 10-yr risk))))
Moderate	1-exp(-exp(-0.1565+0.8009 x ln(-ln(1- un-calibrated 10-yr risk))))	1-exp(-exp(-0.3143+0.7701 x ln(-ln(1- un-calibrated 10-yr risk))))
High	1-exp(-exp(0.3207+0.9360 x ln(-ln(1- un-calibrated 10-yr risk))))	1-exp(-exp(0.5710+0.9369 x ln(-ln(1 un-calibrated 10-yr risk))))
Very high	1-exp(-exp(0.5836+0.8294 x ln(-ln(1- un-calibrated 10-yr risk))))	1-exp(-exp(0.9412+0.8329 x ln(-ln(1- un-calibrated 10-yr risk))))

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

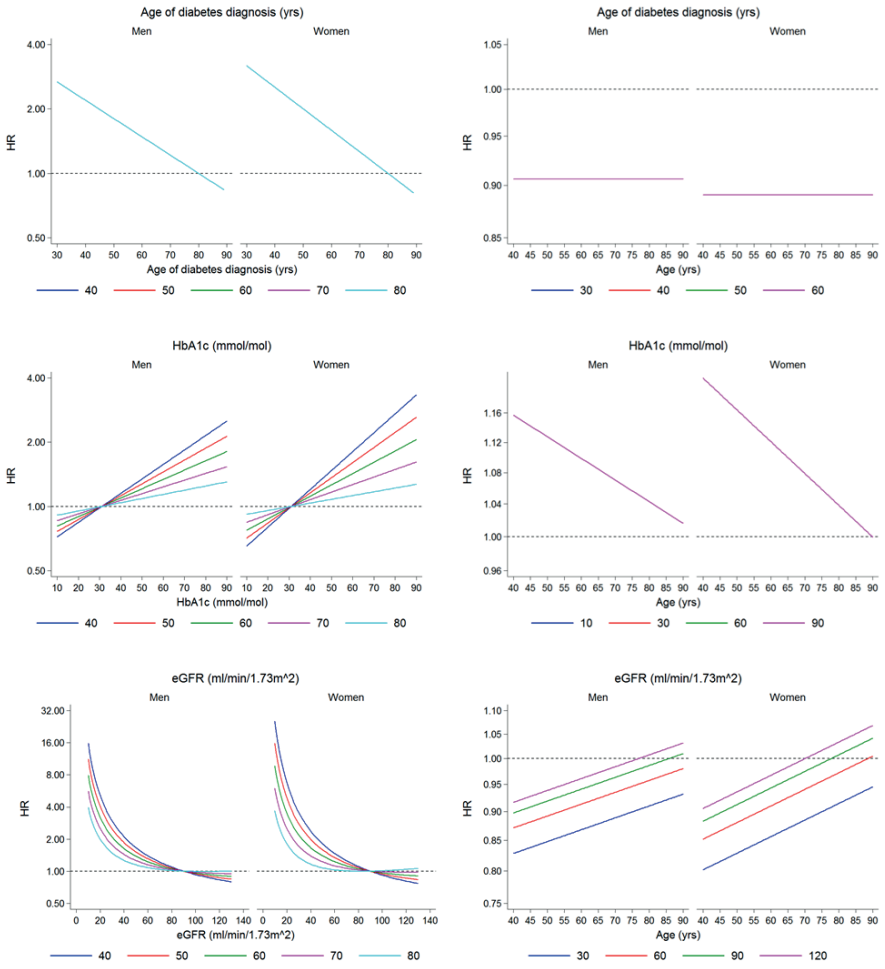
eGFR: estimated Glomerular Filtration Rate (ml/min/1.73m^2) calculated using the CKD epi 2009 equations; HbA1c (mmol/mol): glycated haemoglobin, in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units

Supplementary Methods Table 2. Subdistribution Hazard ratios estimated during derivation of SCORE2-Diabetes

	SCORE2 variables				SCORE2-Diabetes variables		
	Main effects from SCORE2	**Age interaction terms from SCORE2**	**Adjustment to SCORE2 main effects for individuals with diabetes***	**Adjustment to SCORE2 age interaction terms for individuals with diabetes***		**Main effects**	**Age interaction terms**
Men							
Age (per 5 years)	1.47 (1.44, 1.49)	-	1.18 (1.15, 1.20)		Diabetes age at diagnosis (per 5-years)	0.90 (0.89, 0.91)	
Current smoking	1.88 (1.81, 1.95)	0.92 (0.91, 0.94)	0.88 (0.85, 0.92)	1.01 (0.99, 1.02)	HbA1c (per 9.34 mmol/mol)	1.10 (1.09, 1.11)	0.99 (0.98, 0.99)
SBP (per 20mmHg)	1.32 (1.29, 1.34)	0.98 (0.97, 0.98)	0.86 (0.85, 0.88)	1.00 (0.99, 1.01)	ln eGFR (per 0.15 ln(ml/min/1.73m2))	0.94 (0.93, 0.96)	1.01 (1.01, 1.01)
Total cholesterol (per 1 mmol/L)	1.16 (1.15, 1.17)	0.98 (0.97, 0.98)	0.97 (0.95, 0.98)	1.01 (1.00, 1.02)	Ln eGFR2 (quadratic term)	1.01 (1.00, 1.01)	
HDL cholesterol (per 0.5 mmol/L)	0.76 (0.74, 0.78)	1.05 (1.03, 1.06)	1.17 (1.14, 1.21)	0.97 (0.96, 0.98)			
History of diabetes mellitus*	1.93 (1.82, 2.04)	0.91 (0.88, 0.94)					
Women							
Age (per 5 years)	1.62 (1.59, 1.65)	-	1.22 (1.19, 1.25)	-	Diabetes age at diagnosis (per 5-years)	0.89 (0.88, 0.90)	
Current smoking	2.25 (2.15, 2.37)	0.89 (0.86, 0.91)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	HbA1c (per 9.34 mmol/mol)	1.12 (1.11, 1.14)	0.98 (0.98, 0.98)
SBP (per 20mmHg)	1.36 (1.33, 1.39)	0.97 (0.96, 0.98)	0.84 (0.82, 0.86)	1.01 (1.00, 1.02)	ln eGFR (per 0.15 ln(ml/min/1.73m2))	0.94 (0.92, 0.95)	1.02 (1.01, 1.02)
Total cholesterol (per 1 mmol/L)	1.10 (1.08, 1.12)	0.98 (0.97, 0.99)	1.01 (0.99, 1.03)	1.00 (1.00, 1.01)	Ln eGFR2	1.01 (1.00, 1.01)	
HDL cholesterol (per 0.5 mmol/L)	0.76 (0.74, 0.78)	1.06 (1.04, 1.08)	1.11 (1.07, 1.15)	0.96 (0.95, 0.97)			
History of diabetes mellitus*	2.35 (2.18, 2.53)	0.88 (0.84, 0.91)		-			

eGFR: estimated Glomerular Filtration Rate (ml/min/1.73m²) calculated using the CKD epi 2009 equations; HbA1c (mmol/mol): glycated haemoglobin, in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units

Supplementary Methods Figure 1. Association of Diabetes-associated variables with CVD outcomes in the SCORE2-Diabetes risk models; shown by age



Graphs on the left hand side show the shape of the association between each risk predictor and CVD outcomes, with each line representing a different baseline age. Graphs on the right hand side show how each risk predictor effect changes with age, with each line representing a different level of the relevant risk predictor.

Supplementary Table 1. Summary of data sources used in SCORE2-Diabetes development

Data source	Country	study	Median year of recruitment	Number of Participants	Ages Mean (SD)	Age range: min, max	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean (SD)	Total cholesterol (mmol/L) Mean (SD)	HDL cholesterol (mmol/L) Mean (SD)	Age of diabetes diagnosis	HbA1c (mmol/mol) Mean (SD)	eGFR mean (SD)	Median follow-up years (IQR)	Number of CV events	Number of competing events (non-CVD death)
CPRD	UK	CPRD	2008	72,751	64 (11)	41-90	38,599 (53)	11,423 (21)	136 (16)	4.39 (1.0)	1.24 (0.36)	58 (11)	52 (19)	76 (17)	6.0 (0.8, 11.0)	7247	5211
SCID	Scotland	-	2008	136,192	65 (11)	40-89	72,525 (53)	24,447 (18)	135.6 (16)	4.4 (1.0)	1.24 (0.40)	58 (17)	74 (20)	74 (20)	10.9 (6.8, 11.0)	34595	21062
ERFC	France	DESIR	1995	253	55 (7)	41-66	155 (61)	69(27)	144 (19)	6.1 (1.3)	1.42 (0.34)	48 (8)	49 (16)	80 (13)	5.5 (0.0 to 9.2)	8	0
ERFC	Germany	ESTHER	2001	933	63 (6)	49-75	473 (51)	151 (17)	144 (20)	5.6 (1.3)	1.23 (0.35)	56 (8)	53 (15)	83 (20)	5.0 (1.2 to 6.0)	41	11
ERFC	Germany	SHIP	1999	367	64 (10)	41-81	210 (57)	70 (19)	151 (20)	5.9 (1.2)	1.26 (0.39)	55 (10)	55 (15)	74 (16)	0.0 (0.0 to 11.5)	7	0
ERFC	Italy	BRUN	1990	28	68 (9)	52-79	13 (46)	4 (14)	165 (24)	5.6 (1.0)	1.29 (0.32)	59 (12)	56 (19)	76 (15)	12.5 (4.4 to 20.5)	10	11
ERFC	UK	BWHHS	2000	136	69 (5)	60-79	0 (0)	16 (12)	155 (25)	6.1 (1.1)	1.45 (0.37)	61 (8)	50 (16)	66 (12)	12.1 (4.3 to 13.4)	19	31
ERFC	USA	NHANES3	1990	936	64 (12)	40-89	383 (41)	179 (19)	141 (21)	5.6 (1.2)	1.21 (0.40)	55 (12)	63 (23)	66 (22)	13.1 (1.6 to 22.0)	264	400
ERFC	USA	WHS	1994	715	57 (7)	46-76	0 (0)	87 (12)	136 (13)	5.7 (1.2)	1.14 (0.36)	50 (9)	58 (21)	92 (17)	17.6 (3.7 to 20.0)	107	6
UK Biobank	UK	ZZUKBIOBANK	2009	17,149	60 (7)	40-76	10251 (60)	1808 (11)	142 (17)	4.53 (1.03)	1.21 (0.32)	53 (8)	55 (20)	90 (16)	11.4 (5.1 to 13.1)	1408	1493
TOTAL ERFC/UKB			-	20,517	60 (8)	40-89	11,485 (56)	2353 (12)	142 (17)	4.70 (1.14)	1.21 (0.33)	53 (9)	55 (20)	88 (17)	11.3 (2.8 to 13.6)	1864	1953

Supplementary Table 2. Summary of missing data in cohorts used for model derivation

			N(%) missing								
Data source	**Study**	**Total number of participants**	**Ages**	**Sex**	**Smoking**	**Systolic BP**	**Total cholesterol**	**HDL cholesterol**	**Age of diabetes diagnosis**	**HbA1c**	**eGFR**
SCID		136192	0 (0)	0 (0)	7653 (5.6)	6347 (4.7)	7704 (5.7)	28298 (20.8)	0 (0)	9142 (6.7)	19521 (14.3)
CPRD		72751	0 (0)	0 (0)	17936(24.7)	3413 (4.7)	4201 (5.8)	9270 (12.7)	0 (0)	5550 (7.3)	4266 (5.9)
ERFC	DESIR	253	0 (0)	0 (0)	1 (0.6)	1 (0.6)	0 (0)	8 (5.2)	39 (25.3)	0 (0)	1 (0.6)
ERFC	ESTHER	933	0 (0)	0 (0)	21 (2.3)	22 (2.4)	5 (0.6)	347 (38.2)	313 (34.4)	10 (1.1)	5 (0.6)
ERFC	SHIP	367	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.3)	1 (0.3)	125 (34.4)	0 (0)	2 (0.6)
ERFC	BRUN	28	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ERFC	BWHHS	136	0 (0)	0 (0)	0 (0)	13 (9.6)	18 (13.2)	19 (14)	7 (5.1)	17 (12.5)	18 (13.2)
ERFC	NHANESIII	936	0 (0)	0 (0)	2 (0.2)	18 (1.9)	517 (55.3)	526 (56.3)	39 (4.2)	511 (54.7)	526 (56.3)
ERFC	WHS	715	0 (0)	0 (0)	0 (0)	28 (3.9)	9 (1.3)	9 (1.3)	37 (5.2)	2 (0.3)	9 (1.3)
UK Biobank	ZZUKBIOBANK	17149	0 (0)	0 (0)	66 (0.4)	39 (0.2)	1184 (6.9)	2545 (14.8)	263 (1.5)	1390 (8.1)	1198 (7)
Total ERFC/UKB		20517	0 (0)	0 (0)	0 (0)	122 (0.6)	1734 (8.5)	3455 (16.9)	823 (4)	1930 (9.5)	1759 (8.6)

ERFC: Emerging Risk Factors Collaboration, CPRD: Clinical Practice Research Datalink, SCID: Scottish Care Information – Diabetes

Supplementary Table 3. Summary of data used in SCORE2-Diabetes validation

Cohort/ data source	Country	Median year of study recruitment	No of Participants	Ages Mean (SD)	Age range: min, max	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean (SD)	Total cholesterol (mmol/L) Mean (SD)	HDL cholesterol (mmol/L) Mean (SD)	Age of diabetes diagnosis median (IQR)	HbA1c (mmol/mol) median (IQR)	eGFR (ml/min/1.73m^2) median (IQR)	Median follow-up years (IQR)	Number of CV events	Number of competing events (non-CVD death)
SNDR	Sweden	2008	168585	66 (11)	40-90	90321 (54)	22672 (15)	138 (17)	4.9 (1.0)	1.3 (0.4)	57 (49-65)	54 45-59)	85 (69-95)	11.4(6.8-11.4)	34944	41379
SIDIAP	Spain	2010	21754	69 (12)	40-110	11008 (51)	3194 (15)	136 (16)	5.1 (1.0)	1.3 (0.3)	62.3 (17.3)	48 (19)	79 (27)	7.0 (5.2-7.0)	2472	3097
EUBIROD*	Malta	2015	3876	68 (11)	40-90	2102 (54)	634 (16)	142 (19)	4.6 (1.1)	1.4 (0.4)	58 (13)	52 (18)	101 (28)	4.8 (0.9)	239	291
EUBIROD*	Croatia	2015	22821	66 (10)	40-90	10651 (47)	4112 (18)	136 (15)	5.3 (1.2)	1.3 (0.3)	61 (14)	51 (16)	94 (29)	2.9 (0.3)	947	1128

**Summary statistics for EUBIROD are for the complete case dataset used in validation analysis*
Missing data (imputed) by variable for SNDR were smoking: 9%, SBP:4%, total cholesterol: 16%, HDL cholesterol: 24% age of diabetes diagnosis: 7%, HbA1c: 3%, eGFR: 9%
Missing data (imputed) by variable for SIDIAP were smoking: 0%, SBP:24%, total cholesterol: 31%, HDL cholesterol: 40% age of diabetes diagnosis: 0%, HbA1c: 35%, eGFR: 33%
SNDR: Swedish National Diabetes Register (SNDR), SIDIAP: Information System for Research in Primary Care, EUBIROD: EUropean Best Information through Regional Outcome in Diabetes

Supplementary Table 4. Endpoint definitions

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

Supplementary Table 5. Definition of history of vascular disease at baseline

Prior disease	**ICD code**
Coronary heart disease	I20-I25
Stroke	I60-69
TIA	G45
Peripheral artery disease	I70-71

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

Country	Age and sex standardised CVD mortality per 100 000 person years, ICD chapter 9	Year collected
Low risk region		
France	70.9	2014
Israel	76.7	2015
Spain	89.4	2015
Netherlands	89.9	2016
Switzerland	90.2	2015
Denmark	90.4	2015
Norway	90.8	2015
Luxembourg	92.9	2015
Belgium	99.2	2015
United Kingdom	99.7	2015
Moderate risk region		
Iceland	101.0	2016
Portugal	107.9	2014
Sweden	109.0	2016
Italy	110.1	2015
San Marino	-	
Ireland	111.5	2014
Cyprus	111.5	2016
Finland	128.5	2015
Austria	130.9	2016
Malta	133.3	2015
Greece	138.8	2015
Germany	139.0	2015
Slovenia	143.3	2015
High risk region		
Albania	184.5	2010
Czech Republic	195.0	2016
Turkey	199.5	2015
Kazakhstan	214.0	2015
Croatia	214.6	2016
Poland	223.8	2015
Estonia	234.8	2015
Slovakia	239.2	2014
Hungary	274.1	2016
Bosnia and Herzegovina	279.2	2014

Supplementary Table 6. Continued

Country	Age and sex standardised CVD mortality per 100 000 person years, ICD chapter 9	Year collected
Very high risk region		
Armenia	306.3	2016
Lithuania	309.0	2016
Georgia	309.6	2015
Latvia	327.2	2015
Serbia	329.1	2015
Romania	330.5	2016
Montenegro	348.4	2009
Russian Federation	368.8	2015
TFYR Macedonia	387.8	2013
Belarus	395.4	2014
Azerbaijan	416.5	2007
Bulgaria	421.2	2014
Republic of Moldova	442.2	2016
Ukraine	476.7	2015
Kyrgyzstan	476.9	2015
Uzbekistan	478.6	2014
Egypt	543.7	2015
Morocco	-	
Syria	-	
Tunisia	-	
Lebanon	-	
Algeria	-	
Libya	-	

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

Supplementary Table 7. Subdistribution hazard ratios for predictor variables in the SCORE2-Diabetes risk models when using CPRD and SCID data only

	Men		Women	
	Main effect	**Age interaction term**	**Main effect**	**Age interaction term**
SCORE2 variables				
Age (per 5 years)	1.72 (1.68, 1.77)	-	1.95 (1.90, 2.01)	-
Current smoking	1.63 (1.55, 1.71)	0.93 (0.91, 0.96)	1.86 (1.74, 1.98)	0.90 (0.87, 0.92)
Systolic blood pressure (per 20mmHg)	1.14 (1.11, 1.17)	0.97 (0.96, 0.98)	1.15 (1.12, 1.19)	0.98 (0.97, 0.99)
Total cholesterol (per 1 mmol/L)	1.12 (1.10, 1.14)	0.98 (0.97, 0.99)	1.12 (1.10, 1.15)	0.98 (0.97, 0.99)
HDL cholesterol (per 0.5 mmol/L)	0.90 (0.86, 0.93)	1.01 (0.99, 1.02)	0.85 (0.82, 0.89)	1.02 (1.00, 1.04)
History of diabetes mellitus	1.91 (1.84, 1.98)	0.91 (0.89, 0.93)	2.25 (2.15, 2.35)	0.88 (0.86, 0.90)
SCORE2-DM2 additional variables				
Diabetes age at diagnosis (per 5-years)	0.90 (0.89, 0.91)		0.89 (0.88, 0.90)	
HbA1c (mmol/mol)	1.10 (1.09, 1.11)	0.99 (0.98, 0.99)	1.13 (1.11, 1.14)	0.98 (0.98, 0.98)
Ln eGFR (ml/min/1.73m2)	0.94 (0.93, 0.96)	1.01 (1.01, 1.02)	0.94 (0.93, 0.96)	1.02 (1.01, 1.02)
Ln eGFR2 (quadratic term)	1.01 (1.00, 1.01)		1.01 (1.01, 1.01)	

Sex-specific subdistribution hazard ratios from Fine and Gray models predicting the risk of fatal and non-fatal CVD events as derived for SCORE2 and adapted in individuals with diabetes from CPRD and SCID to include adjustments to SCORE2 effects and SCORE2-DM2 additional variables. Age was centered at 60 years, systolic blood pressure at 120 mmHg, total cholesterol at 6 mmol/L, HDL cholesterol at 1.3 mmol/L, age at diabetes onset at 50 years HbA1c at 31 mmol/mol and eGFR 90 ml/min/1.73^2 (i.e. Ln-eGFR of 4.5). The median baseline survival at 10 years in the derivation cohorts was 0.9625 for men and 0.9795 for women.

**Values shown are the combination of original SCORE2 coefficients and additional coefficients which modify the associations for individuals with diabetes. See Supplementary methods for full sets of component effects for each risk predictor*

Supplementary Table 8. Change in discrimination: SCORE2-Diabetes vs SCORE2, SCORE2-Diabetes vs SCORE2-Diabetes without lipids, and SCORE2-Diabetes vs ADVANCE

Result for CPRD

Risk model	C-index	Difference in C-index (95% CI)
SCORE2-Diabetes	0.733 (0.727, 0.739)	reference
SCORE2-Diabetes with lipid values removed	0.730 (0.724, 0.736)	-0.0035 (-0.0046 ,-0.0025)
SCORE2	0.710 (0.704, 0.716)	-0.0228 (-0.0198, -0.0259)

Result for SNDR

Risk model	C-index	Difference in C-index (95% CI)
SCORE2-Diabetes	0.670 (0.667, 0.673)	reference
SCORE2-Diabetes with lipid values removed	0.665 (0.662, 0.668)	-0.0046 (-0.0061, -0.0031)
SCORE2	0.661 (0.658, 0.664)	-0.0088 (-0.0102, -0.0074)
ADVANCE	0.665 (0.662, 0.668)	-0.0046 (-0061, -0.0031)

Supplementary Table 9. Net reclassification when using SCORE2 diabetes versus SCORE2

A. Using the Prospective continuous NRI

Data source	Expected net appropriate reclassification of CVD events occurring before 10-years (%)	Expected net appropriate reclassification of individuals CVD event free at 10-years	Continuous NRI
SNDR	56.9 (56.0, 57.9)	-28.2 (-28.8, -27.6)	28.7 (27.7, 29.8)
CPRD	62.4 (60.0, 64.8)	-37.2 (-38.1, -36.4)	25.2 (22.4, 28.0)

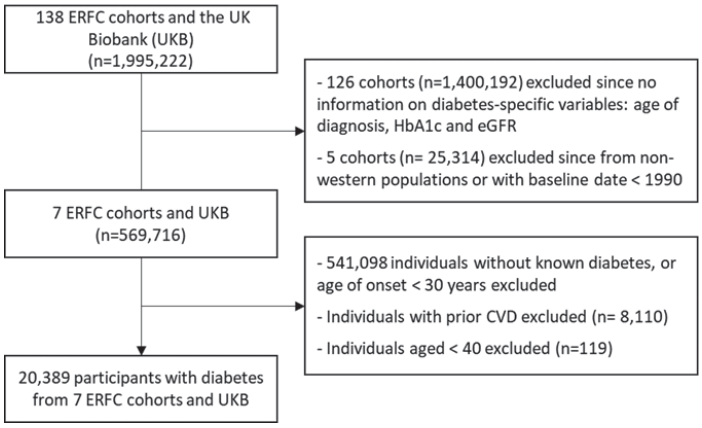
B. Using the Prospective categorical NRI, with risk thresholds, 5, 10, 15, 20 and 25% CVD risk

Data source	Expected net appropriate reclassification of CVD events occurring before 10-years (%)	Expected net appropriate reclassification of individuals CVD event free at 10-years (%)	Categorical NRI
SNDR	31.9 (31.2, 32.6)	-18.2 (-18.6, -17.9)	13.7 (12.9, 14.5)
CPRD	44.8 (43.0, 46.7)	-20.2 (-20.8, -19.6)	24.6 (22.5, 26.8)

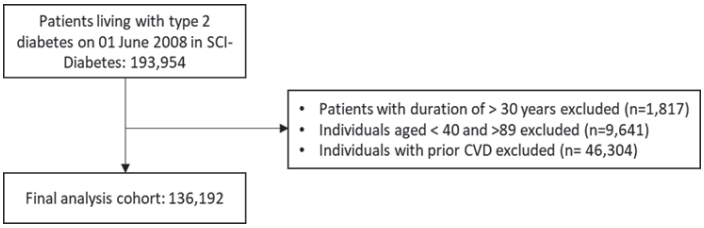
CPRD: Individuals with diabetes from the Clinical Practice Research Datalink
SNDR: Swedish National Diabetes Register

Supplementary Figure 1. Selection of studies and individuals for SCORE2-Diabetes model derivation

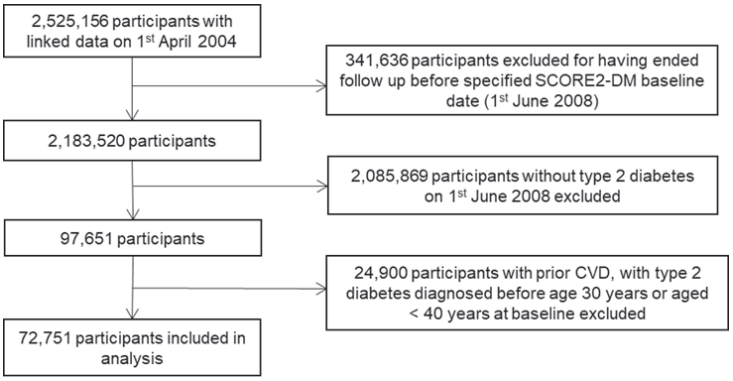
Emerging Risk Factors Collaboration/UK Biobank



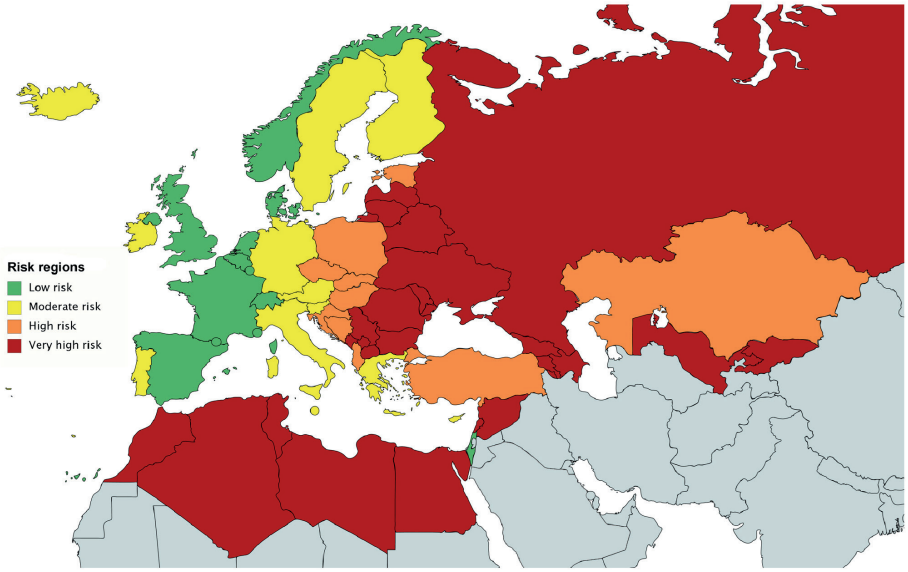
Scottish Care Information- Diabetes



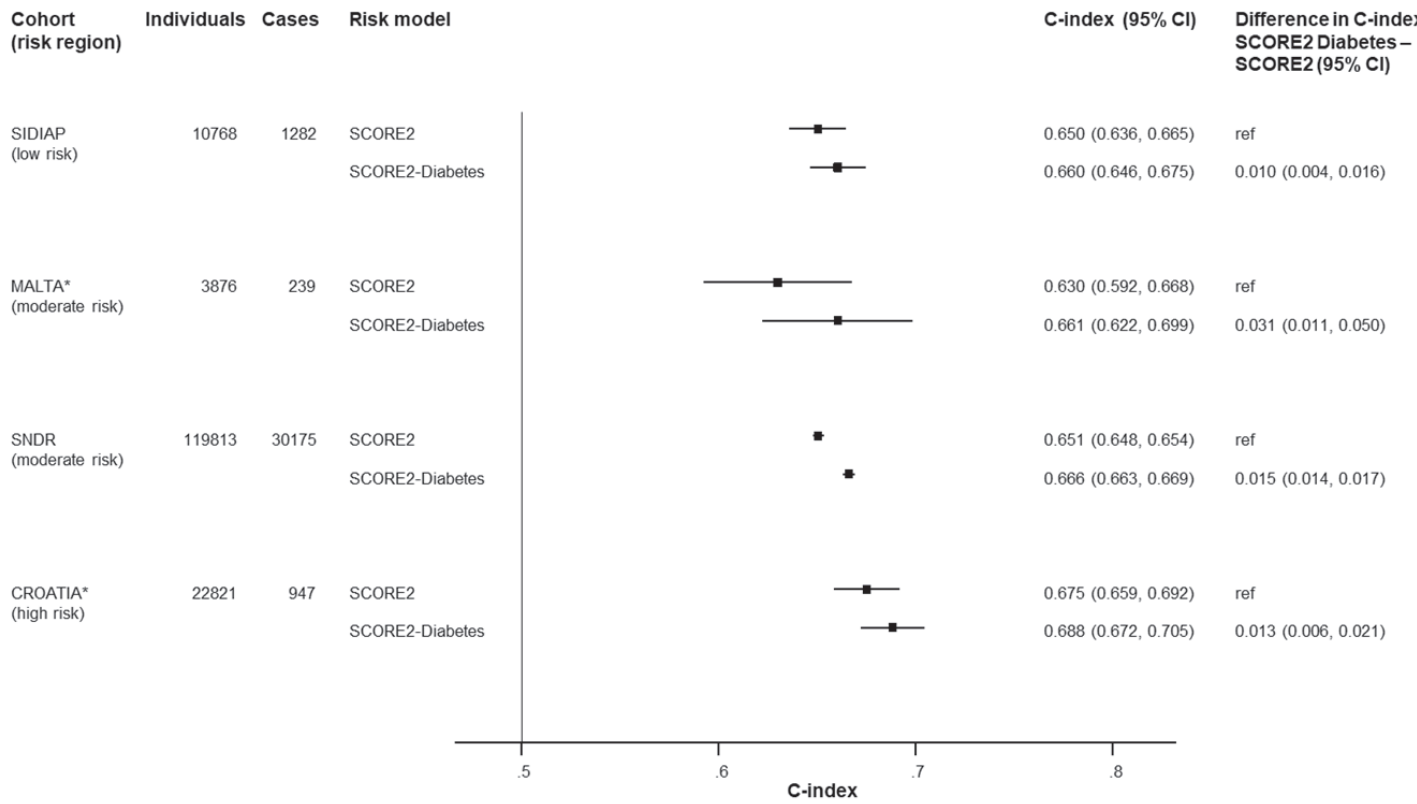
Clinical Practice Research Datalink



Supplementary Figure 2. Risk regions for SCORE2-Diabetes application

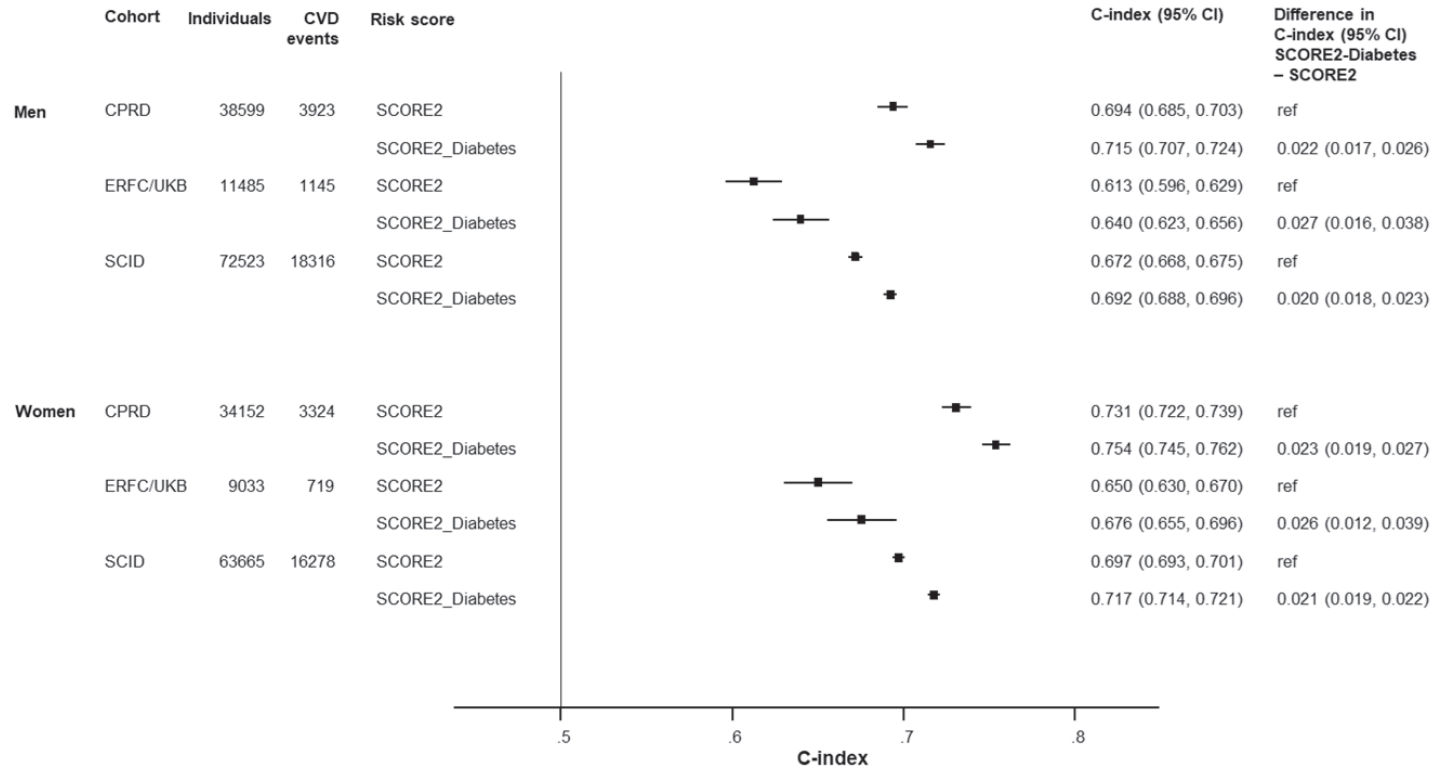


Supplementary Figure 3. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from external data sources using complete case datasets



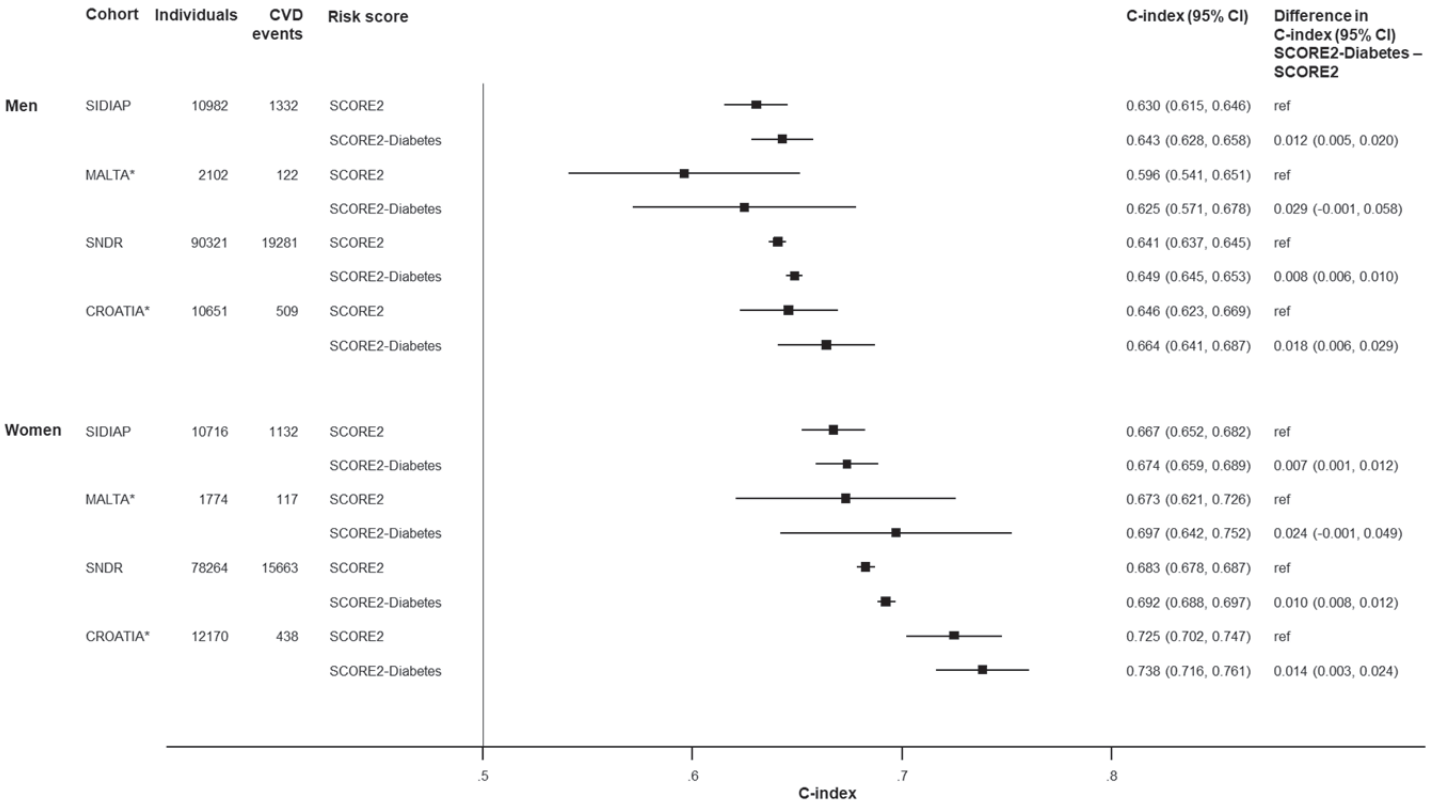
**Data source from EUBIROD (EUropean Best Information through Regional Outcome in Diabetes)*
SIDIAP: Information System for Research in Primary Care; SNDR: Swedish National Diabetes Register (SNDR)

Supplementary Figure 4. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from derivation datasets, by sex



CPRD: Clinical Practice Research Datalink, ERFC: Emerging Risk Factors Collaboration, UKB: UK Biobank, SCID: Scottish Care Information-Diabetes

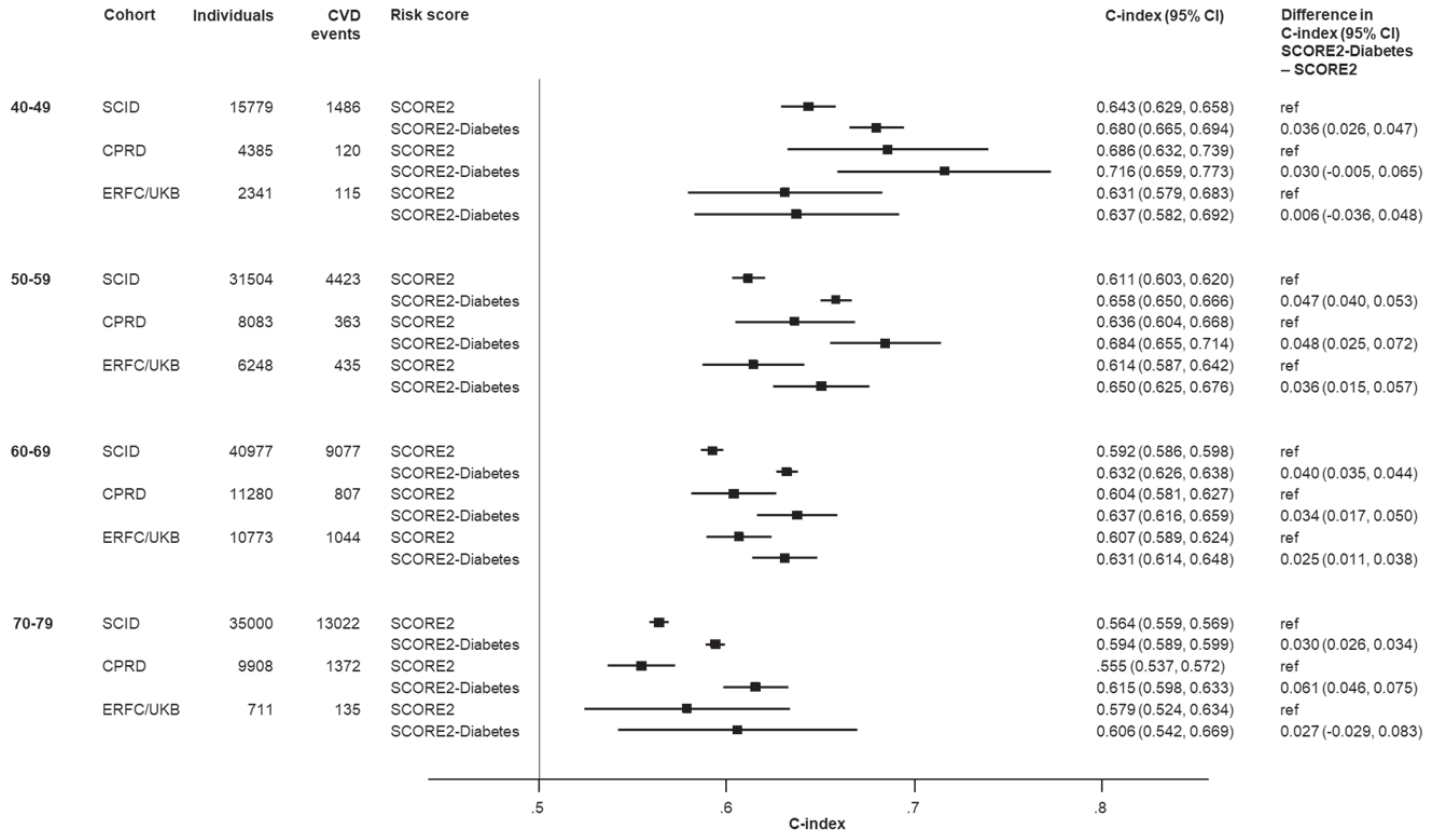
Supplementary Figure 5. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from external validation datasets, by sex



**Complete case data source from EUBIROD (EUropean Best Information through Regional Outcome in Diabetes, MALTA represents the moderate and CROATIA the high risk region).*

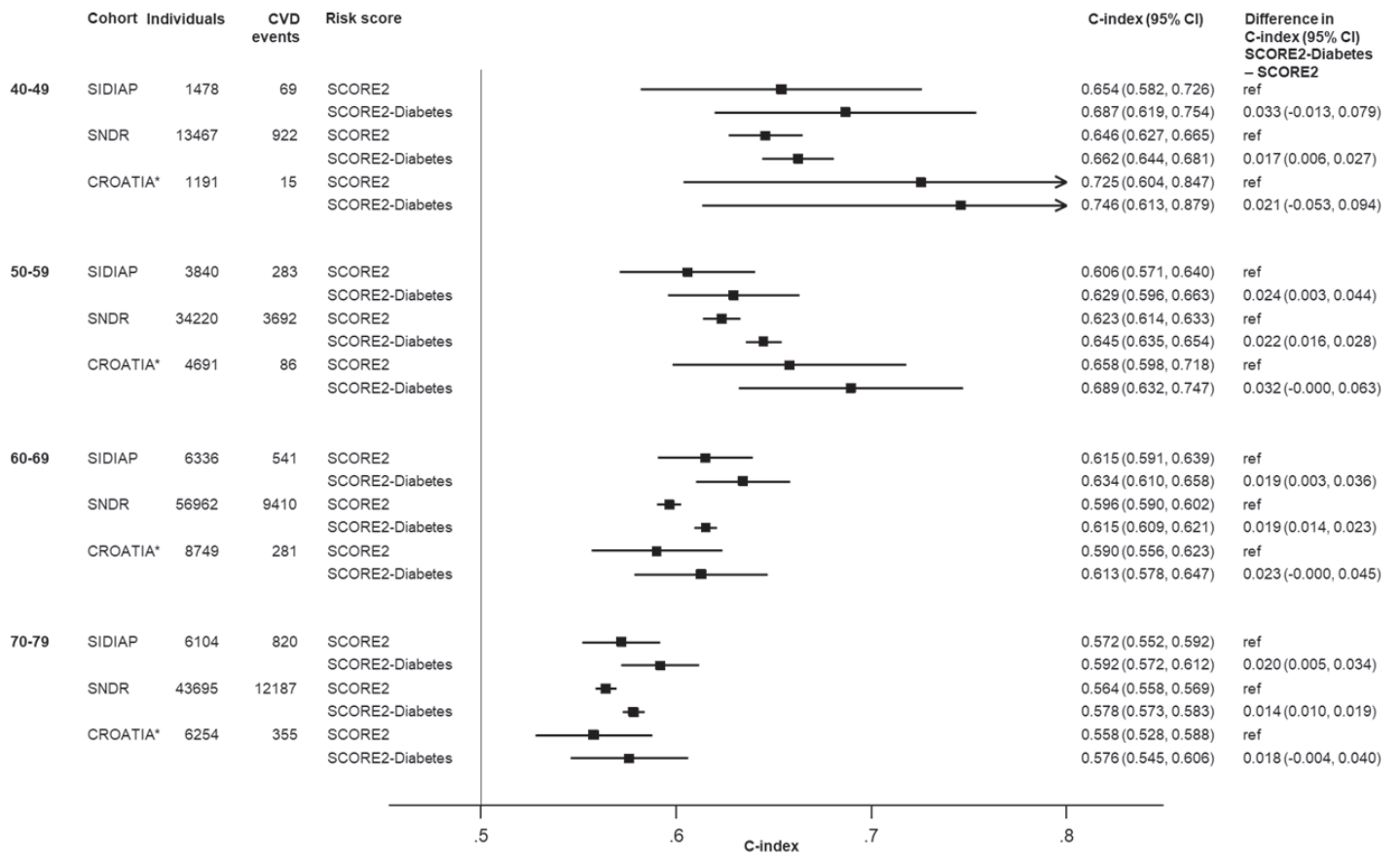
SIDIAP: Information System for Research in Primary Care (low risk region); SNDR: Swedish National Diabetes Register (moderate risk region)

Supplementary Figure 6. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from derivation datasets, by age-group



CPRD: Clinical Practice Research Datalink, ERFC: Emerging Risk Factors Collaboration, UKB: UK Biobank, SCID: Scottish Care Information-Diabetes

Supplementary Figure 7. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from external validation datasets, by age-group

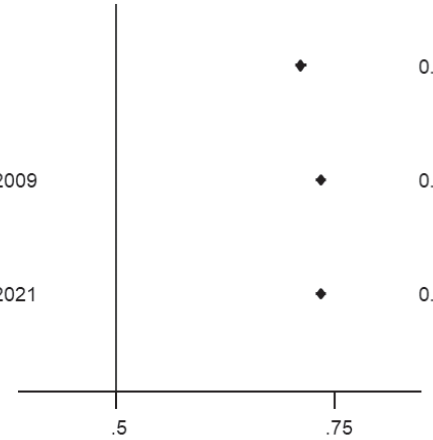


** Complete case data source from EUBIROD (EUropean Best Information through Regional Outcome in Diabetes, CROATIA represents the high risk region).*

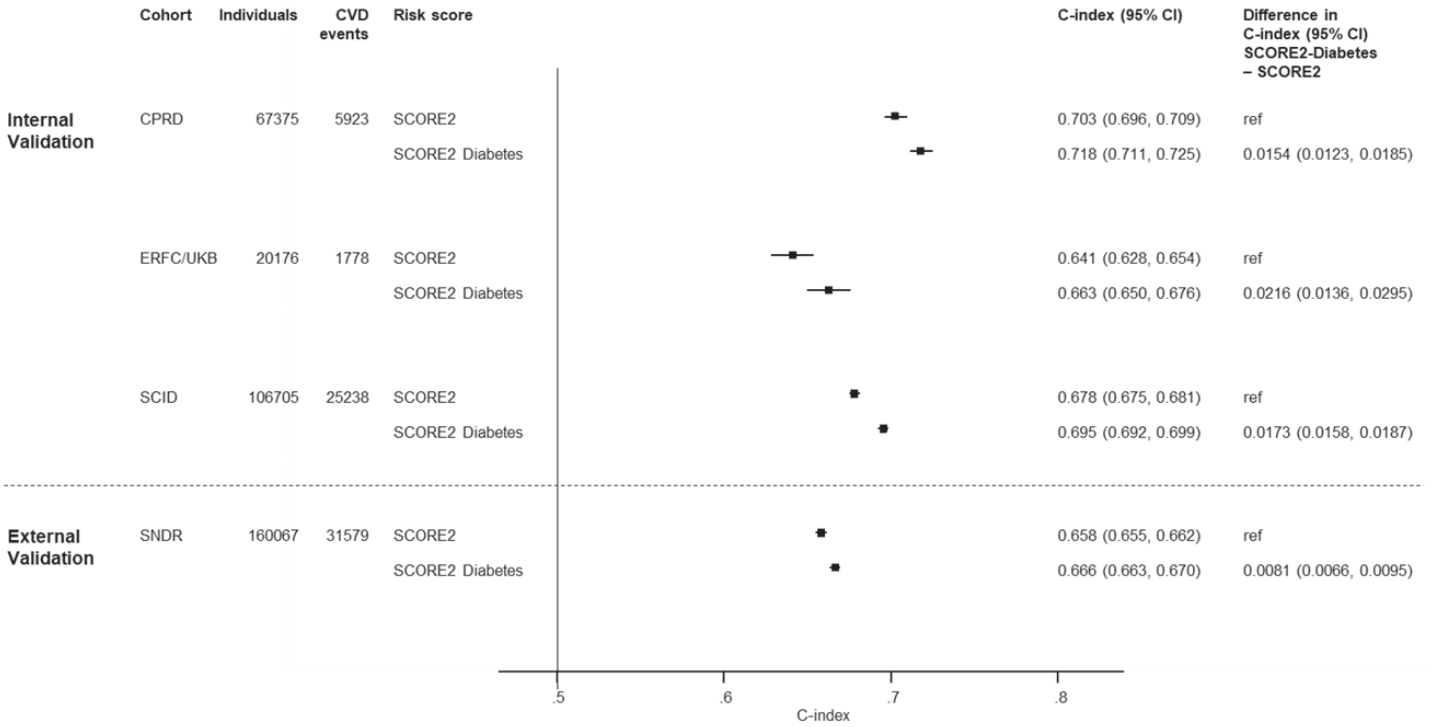
SIDIAP: Information System for Research in Primary Care (low risk region); SNDR: Swedish National Diabetes Register (moderate risk region)

Supplementary Figure 8. C-index for SCORE2-Diabetes, when using alternative eGFR CKD-Epi calculations

Risk estimation used	C-index (95% CI)	Difference1 (95% CI)	Difference2 (95% CI)
SCORE2	0.7103 (0.7043, 0.7164)	Ref.	
SCORE2-Diabetes using CKD-Epi 2009	0.7332 (0.7272, 0.7391)	0.0228 (0.0198, 0.0259)	Ref.
SCORE2-Diabetes using CKD-Epi 2021	0.7330 (0.7271, 0.7389)	0.0227 (0.0197, 0.0257)	-0.0002 (-0.0003, -0.0000)

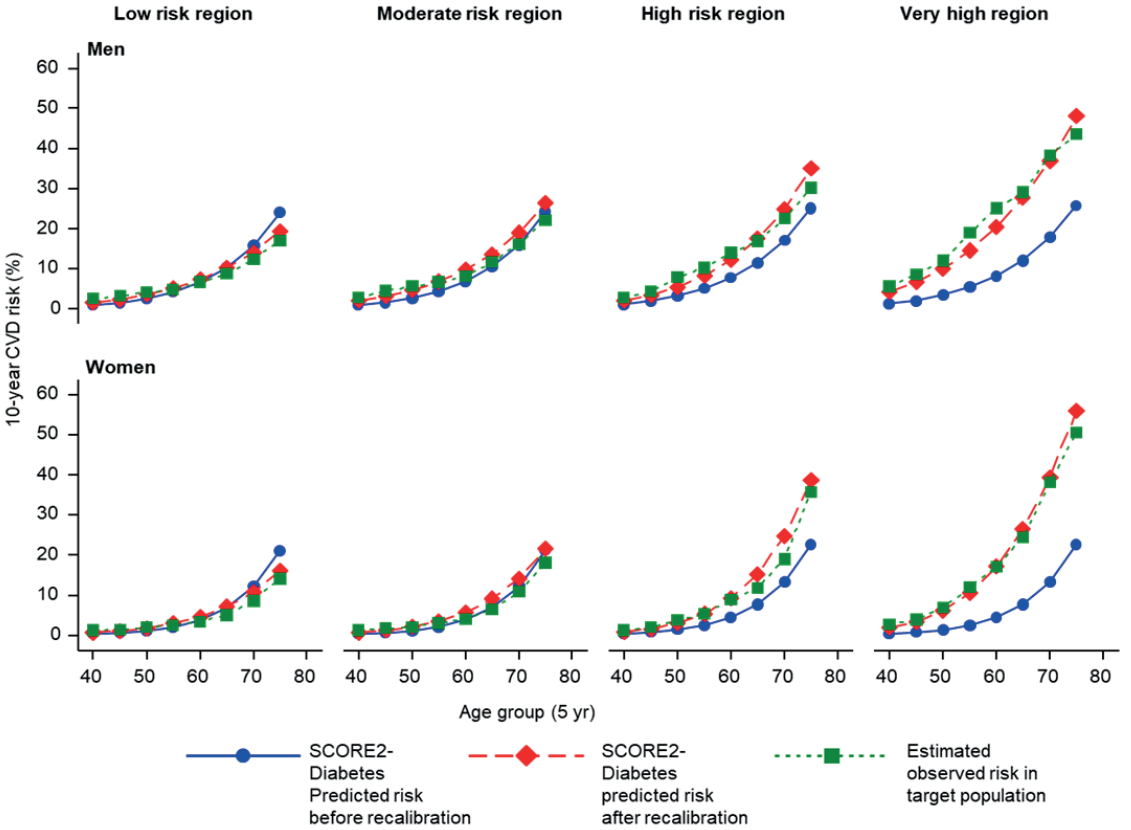


Supplementary Figure 9. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes and eGFR >45 ml/min/1.73m^2



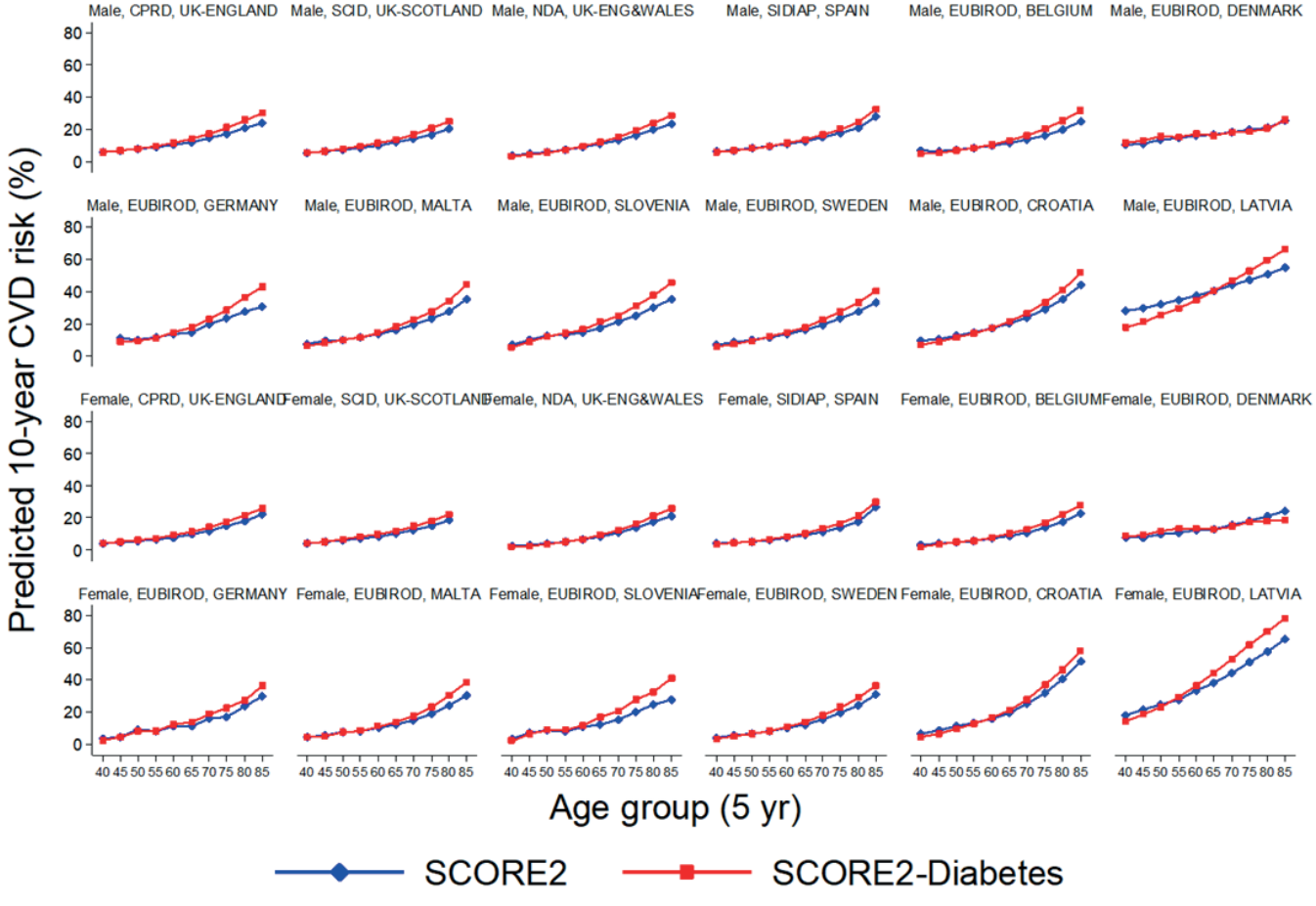
CPRD: Clinical Practice Research Datalink, ERFC: Emerging Risk Factors Collaboration, UKB: UK Biobank, SNDR: Swedish National Diabetes Register, SCID: Scottish Care Information- Diabetes

Supplementary Figure 10. SCORE2-Diabetes predicted risks and expected risks by risk region, before and after recalibration



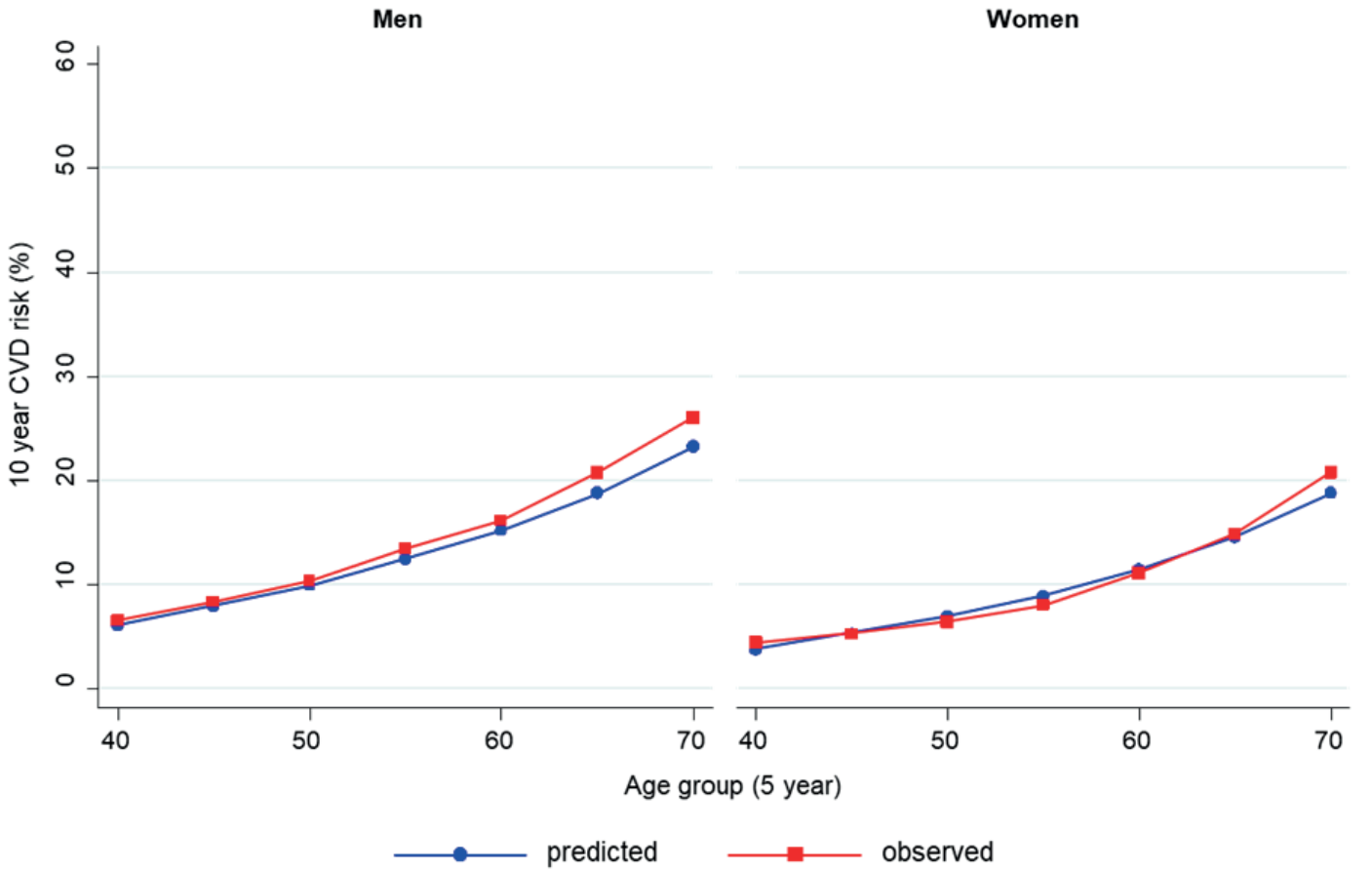
Estimated sex and age specific risk is in the whole population based on WHO mortality converted to total competing risk adjusted 10-year CVD incidence, using multipliers derived in representative data from each risk region, as used in the recalibration of SCORE2. Predicted risk is based on sex and age specific conventional risk factor means from NCD_Risc as used in the recalibration of SCORE2 and Diabetes related variable means from CPRD, applied proportionately according to the proportion with diabetes in each age group.

Suplementary Figure 11. Agreement in average age group specific risks estimated with SCORE2 and SCORE2-Diabetes in individuals with diabetes

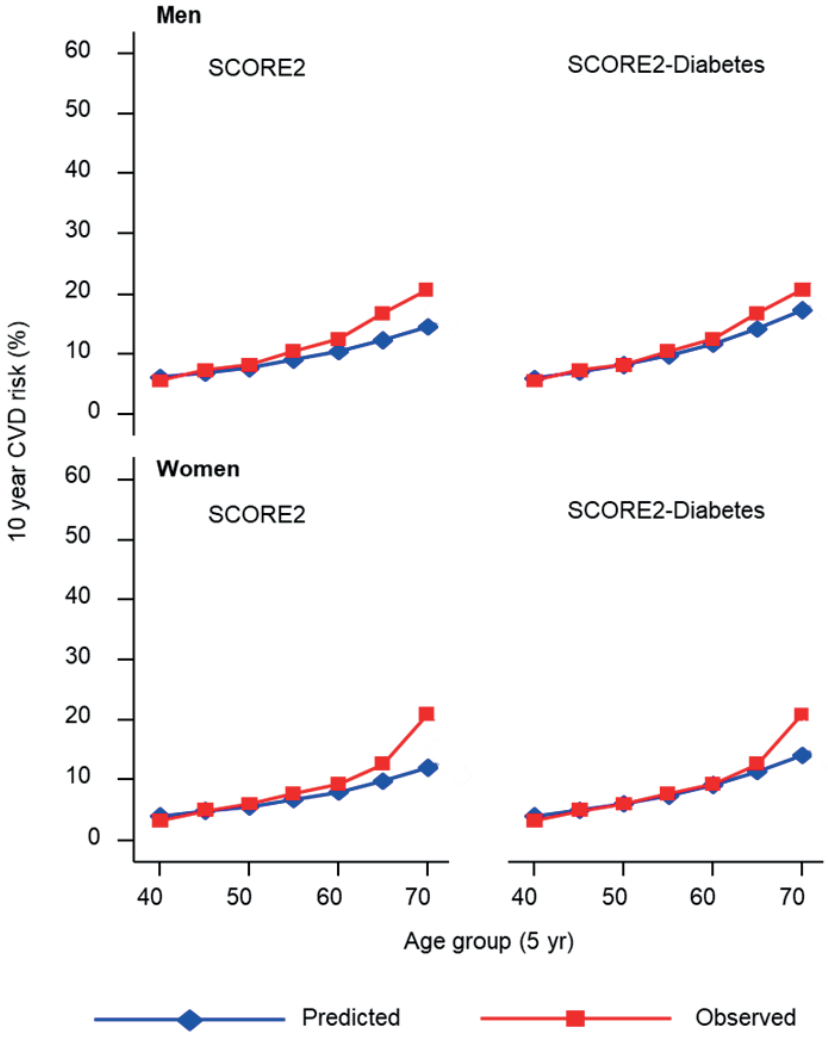


CPRD: Clinical Practice Research Datalink, NDA: National Diabetes Audit, SNDR: Swedish National Diabetes Register, SIDIAP: Information System for Research in Primary Care; SNDR: Swedish National Diabetes Register (SNDR), SCID: Scottish Care Information- Diabetes; EUBIROD (EUropean Best Information through Regional Outcome in Diabetes)

Supplementary Figure 12. Calibration of SCORE2-Diabetes using individual participant data from the Swedish National Diabetes Registry



Supplementary Figure 13. Calibration of SCORE2-Diabetes and SCORE2 using individual participant data from individuals with diabetes from the CPRD



CHAPTER 9

General discussion

General discussion

In this thesis, several risk factors associated with cardiovascular and kidney disease in high-risk patients with type 2 diabetes and/or established cardiovascular disease (CVD) were investigated. Furthermore, three risk prediction tools for individualized prediction of cardiovascular and kidney disease in people with type 2 diabetes were developed in line with the latest advancements in methodology. These prediction tools enhance the time horizon and precision of predictions, allow for estimation of benefit from treatment and thus promote shared decision making in clinical practice.

As mentioned in the introduction, the prevalence of non-communicable diseases, including type 2 diabetes, CVD and chronic kidney disease, is growing at a rapid speed.[1] The management of these diseases is associated with a high burden on the health care system and, of course, for the individual patient. It is therefore important to look at risk factors and assess risk specifically in high-risk patients and not just the general population, as some risk factors are of more importance in this patient group.

Risk factors for kidney disease in patients with established cardiovascular disease

Several amendable risk factors for end-stage kidney disease (ESKD) are already integrated in clinical practice, including kidney function, blood pressure, obesity, smoking, cholesterol and exercise. These factors and the attributable risks are, however, primarily investigated in low-risk populations. However, patients with established CVD are at a 4-fold increased risk of developing chronic kidney disease,[2] potentially leading to ESKD. This very high a priori risk could be a reason why the aforementioned risk factors may differ in the size of attributable risk in this already high risk patient population. In patients with established CVD, smoking, type 2 diabetes, a higher systolic blood pressure, lower eGFR and higher uACR were all significantly associated with higher risk of ESKD (**Chapter 2**). The focus on amendable risk factors is thus especially important in patients with established CVD, not only to prevent recurrent CVD, but also to reduce progression to ESKD.

A cornerstone in the management of kidney protection in high-risk patients in clinical practice is amendable lifestyle factors, including smoking, alcohol,

exercise and weight management. Monitoring eGFR decline can predict time to onset of kidney failure and guide interventions aimed at reducing kidney function decline.[3] In **Chapter 3**, we found that in a cohort of patients with established CVD, most patients improved in lifestyle factors regarding smoking and alcohol consumption, however markers of obesity worsened over a 10 year follow-up period. A steeper eGFR decline over 10 years was observed for patients who continued smoking or recently stopped smoking during follow-up compared to patients who remained non- or previous smokers. Also, an increase in body mass index, and for men especially increase in waist circumference, was associated with a steeper eGFR decline over 10 years. Patients with established CVD and chronic kidney disease are prone to have more nontraditional CVD risk factors, including uremia-related ones i.e. inflammation, oxidative stress and promotors of vascular calcification, making it even more important to prevent a rapid decline in kidney function in this patient group. Changes in lifestyle, as shown in **Chapter 3**, may potentially prevent a rapid decline in kidney function, both via regular risk pathways and non-traditional pathways. Still, assessing the causal relation between lifestyle factors and outcomes remains a challenge. For example, it is near impossible to eliminate residual confounding, as confounding associated with lifestyle is very difficult to measure precisely, e.g. socio-economic status, diet and genetics may play a role.[4] Furthermore, reporting and recall bias is almost always present. Next, a main obstacle in improving lifestyle factors as a means of preventing chronic kidney disease as well as CVD is implementation in clinical practice. Several public health campaigns have sought to improve lifestyle factors for the population, however implementation remains difficult and most patients do not reach lifestyle targets.[5] Another main barrier is adherence to lifestyle changes. More research is thus needed to seek to diminish residual confounding as much as possible and to develop effective strategies for implementing and enhancing adherence to lifestyle improvements.

Measures of glycemic control and risk for cardiovascular disease in patients with type 2 diabetes

Despite implementation of international guidelines focused on managing important amendable risk factors for CVD in people with type 2 diabetes,[6, 7] the risk of CVD in this patient group remains two-fold higher compared to counterparts without diabetes.[8] In people with type 2 diabetes, blood-pressure

lowering, glucose-lowering, lipid-lowering and smoking cessation have long been the cornerstone of cardiovascular risk management (CVRM).[9, 10] Optimal CVRM of known risk factors may not always be reached for all patients with type 2 diabetes (**Chapter 5**). Therefore, there is ongoing interest to find novel potential drivers of CVD risk in people with type 2 diabetes, and one such potential risk factor is the hemoglobin glycation index (HGI). The HGI has been proposed as a marker of interindividual differences in hemoglobin glycosylation and is calculated as the difference between observed HbA1c and predicted HbA1c, where predicted HbA1c is obtained by the population linear regression equation of HbA1c as a function of blood glucose.[11] The HGI has previously been proposed as being an independent risk factor for CVD and microvascular outcomes in people with diabetes. A higher HGI was associated with a higher risk of CVD in people with type 2 diabetes and without established CVD, however not in people with type 2 diabetes with established CVD (**Chapter 4**). Similar results were seen when assessing HbA1c as determinant on risk of CVD, also only significant in people with type 2 diabetes without established CVD. Thus, the HGI is likely simply a surrogate for HbA1c and obtaining and interpreting the HGI is complicated. These results thus indicate a limited benefit of applying the HGI as a risk factor for CVD in people with type 2 diabetes in a clinical setting. HbA1c is the standard measure for glucose control in patients with type 2 diabetes in clinical practice and has been associated with both macro- and microvascular outcomes.[12] Thus, HbA1c should be used for glycemic control, as also recommended by international guidelines on diabetes management.[7] However, HbA1c does not identify interday glucose variations, and with the increase in continuous glucose monitoring, new methods for glucose monitoring, such as time in range (TIR), have emerged. TIR denotes the amount of time that the glucose level remains within the specific target for glycemic control (3.9-10.0 mmol/L)[13] and thus allows for direct observations for glycemic excursions. TIR has been associated with microvascular diabetic complications in patients with type 2 diabetes.[14] Also, a study found good correlation between HbA1c and TIR.[15] Thus, TIR is a promising addition to HbA1c as marker for glycemic control. However, future studies should be conducted assessing TIR as a glycemic marker and its association with diabetic complications in patients with type 2 diabetes, also in high-risk patients who also have established CVD and/or chronic kidney disease.

Treatment strategies for reducing risk of cardiovascular and kidney disease in patients with established CVD or type 2 diabetes

Even with optimal management of lifestyle factors, there is still a substantial (residual) risk for CVD and kidney disease in high-risk patients with established CVD and/or type 2 diabetes. Fortunately, several treatment strategies exist for reducing the risk of (recurrent) CVD events and kidney disease. International guidelines provide guidance for reaching specific treatment targets for LDL-c, blood pressure and, for patients with type 2 diabetes, HbA1c and recommendations for pharmacotherapy.[3, 6, 7] Lowering of LDL-c is recommended to as low as 1.4 mmol/L in very high risk patients.[6] Previous studies have found a 21% lower risk for CVD per 1 mmol/L LDL-c lowering[16] and a reduction in risk of kidney disease by 39% with statin use compared to non-statin users.[17] Lowering systolic blood pressure has been shown associated with a 20% reduction of CVD risk per 10 mmHg lowering.[18] For patients with type 2 diabetes, a main preventive treatment goal for both CVD and kidney disease is management of HbA1c to values below 53 mmol/mol, however targets should be individualized according to diabetes duration, age and comorbidities.[19, 20] Furthermore, treatment with ACEi or ARB has proven to lower the risk of progressive kidney function decline and kidney failure by 23%.[21]

Novel anti-diabetic treatments

A major break-through in reducing risk of CVD and kidney disease in people with type 2 diabetes is the introduction of new glucose-lowering therapies, such as sodium-glucose transport protein 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor analogues (GLP-1 RA). SGLT2i have proven beneficial in reducing risk of CVD by 14% and risk of kidney outcomes by 38% in people with type 2 diabetes.[22] GLP-1 RAs are proven effective in reducing CVD risk and risk of kidney outcomes by 10% and 21%, respectively, in people with type 2 diabetes.[23] Current international guidelines recommend treatment with SGLT2i and GLP-1 RA in patients with type 2 diabetes at high risk for CVD.[6, 7] Even though the use of these medications is increasing, implementation still remains limited, as was also shown in **Chapter 5**. In a cohort of people with type 2 diabetes spanning 13 countries worldwide, the use of GLP-1 RA and SGLT2i did not greatly differ between patients with and without established CVD. Less than one out of five patients with CVD were treated with an SGLT2i

and only one in ten patients with CVD were treated with a GLP-1 RA. Use of blood-pressure lowering medication, statins and aspirin was more frequent in patients with type 2 diabetes with CVD. Worth noting is that the data for the cohort was collected in 2019 and did not consider reasons for not prescribing these treatments, however more recent data suggest that the prevalence of people with established CVD and type 2 diabetes receiving SGLT2i and GLP-1 RA has not improved.[24] These results thus indicate that there is still a lot to be gained on a population level in terms of implementation. SGLT2i and GLP-1 RAs have been studied as glucose-lowering drugs, which could have impeded uptake by other specialists, i.e. cardiologists and nephrologists, even though both drugs have been shown to lower risk of CVD and kidney disease independent of their glucose-lowering abilities.[25, 26] Also, there may still be a lot to be gained in terms of reimbursement from health care providers. Furthermore, fear of side-effects or contraindications due to limited research in high-risk patients (e.g. an eGFR <25-30 ml/min/1.73m2 for SGLT2i treatment) may abstain treating physicians from prescribing SGLT2i and GLP-1 RA. The ongoing gain of knowledge from several trials assessing risk reduction for different outcomes with SGLT2i and GLP-1 RA in different patient populations may result in an improved implementation of these medications. Also, as we'll touch upon later in this chapter, prediction tools assessing individual benefit from preventive treatment may aid in deciding which patients will benefit the most, while also outweighing the risk of side-effects.

Risk prediction in patients with type 2 diabetes

So with the increasing evolutions in treatments to reduce risk of adverse outcomes, should we just treat all patients and with all the treatments available? Most would agree that that would not be a very beneficial approach, neither for the individual patient nor society. All medication have a risk of adverse events, add to the pill-burden for patients, and some of the therapies are associated with high costs, why from an economic health care perspective it should be given to the patients with highest treatment benefits. Patient preferences are also very important, and adherence decreases as the amount of treatments given to the individual patient increases. Thus, how do we figure out who, when and how to treat? Previously, patients with established CVD and/or type 2 diabetes were all assumed to be at (very) high risk of CVD and kidney disease, however such a one size fits all approach is too simplistic. Future risk can be estimated using individualized risk

prediction models, both in primary and secondary prevention and can be used to guide treatment decisions in shared decision making in clinical practice.

Let's return to our two patients described in the introduction of this thesis; Mr. D and Mrs. T (*Figure 1*). According to the ESC 2021 prevention guidelines,[6] they are both at high risk of a CVD event since both have type 2 diabetes and target organ damage in the form of albuminuria. But what is their individual risk for CVD? And what about microvascular outcomes such as ESKD? Of course, Mr. D should lose weight, obtain a healthier diet, exercise more and definitely stop smoking! But what about Mrs. T who already has a healthy lifestyle? Should an SGLT2i or GLP-1 RA be considered? According to the guidelines yes, but what is their individual gain when initiating these treatments? In terms of shared decision making, shouldn't we be frank about potential gains of treatment? And how should treatments be prioritized?

Prediction models can inform individuals on their expected course of disease, estimate risk of developing a disease and guide clinicians and patients when deciding on future interventions and treatments.[27] Many prediction models exist, with more and more being developed and there is increasing focus on risk prediction in secondary prevention. Risk prediction tools aimed at a target population allow for inclusion of specific predictors relevant for this population, and this will result in more accurate risk estimations. For example, several risk models include diabetes as a predictor, however using a model targeted at patients with diabetes will include diabetes-specific risk factors (such as HbA1c and the duration of diabetes). Several risk prediction models in secondary prevention exist, including the SMART2 risk score for people with established CVD[28] and the ADVANCE[29] and UKPDS risk engines[30] for people with type 2 diabetes. The Kidney Failure Risk Equation (KFRE) predicts short-term ESKD risk in patients with chronic kidney disease,[31] however this risk equation was developed specifically for people with an eGFR <60 ml/min/1.73m2 and does not account for type 2 diabetes. In **Chapter 6, 7 and 8** we developed prediction models to assess individual risk and treatment benefit for CVD and ESKD in people with type 2 diabetes.

Reliability of predictions

Over the years, ongoing advancements in methodology for prediction tools have allowed for more accurate predictions, providing a significant step forward. For risk predictions to be reliable in clinical practice, the prediction

estimates must match the actual probability of disease. Most of the prediction models for cardiovascular and kidney disease in people with type 2 diabetes have several methodological shortcomings.

Adjustment for competing risks

One methodological shortcoming in most prediction models within this field is the failure to adjust for competing risks. For example, none of previous ESKD prediction models in people with type 2 diabetes adjusted for all-cause mortality as competing risk.[32] Adjusting for (non-CVD) mortality as competing risk avoids overestimations of risks and treatment effects.[33] This is especially important in older individuals and other persons at high risk of death and also for individuals at low risk for the outcome, who are likely to die before developing said outcome. The overestimated risks and treatment benefits caused by not accounting for competing risks may lead to higher than real expected benefit and may cause an inaccurate weighing of benefits and harms in the shared decision making process. Therefore, all risk scores predicting outcomes that have relevant competing risks (so in reality all outcomes except for all-cause mortality) should be adjusted for competing risks, since this is methodologically feasible and avoids overestimation of risks and treatment benefits. In SCORE2-DM, DIAL2 and DIAL-ESKD (**Chapters 6, 7 and 8**), one of the improvements in comparison to their predecessors was the adjustment for all-cause mortality as competing risk when predicting ESKD as outcome and non-CVD mortality when predicting CVD as outcome.

Geographical recalibration

The incidence of most diseases, including CVD and kidney disease, varies between different populations, over geographical regions and over periods of time beyond what can be explained by risk factors alone. Therefore, when possible, geographic and temporal recalibration of prediction models in the populations for intended use should be performed. The majority of existing prediction models for people with type 2 diabetes failed to perform external validation and recalibration.[34] Furthermore, recalibration is most often performed using cohort data which may reflect past periods of time and are subject to some degree of healthy participant bias. A recent advancement in geographical recalibration is the usage of nationally representative registry data.[35, 36] In **Chapter 8**, this methodology was adapted to people with type 2 diabetes. In **Chapter 7**, we updated the existing DIAL model and adapted the methodology for systematic recalibration of lifetime CVD risks in

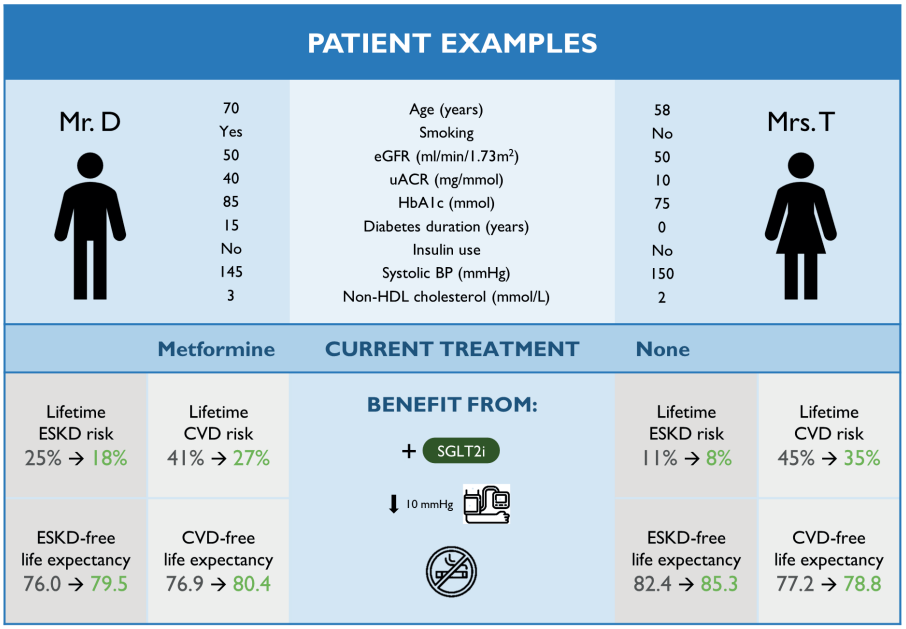
people with type 2 diabetes. For the DIAL-ESKD model in **Chapter 6**, this approach was not possible due to the lack of reliable aggregate data on diabetes-specific risk factor levels and incidence of ESKD in individuals with type 2 diabetes. Also, since ESKD is a much less common outcome than for example CVD in people with type 2 diabetes, large databases with extensive follow-up are important in order to ensure sufficient power with an adequate amount of events. We developed and validated the model in two different, recent and large representative databases. However, future validation and recalibration of the model will be valuable as data on individuals with type 2 diabetes with sufficient follow-up accrue.

Prediction time spans

Most prediction models predict risk over a limited time horizon, up to e.g. 10 years. The ADVANCE model was developed for predicting 4-year risk of CVD[29] and the KFRE up to 5-year risks of ESKD.[31] Furthermore, existing ESKD prediction models developed in individuals with type 2 diabetes are based on shorter prediction horizons of up to eight years.[37-42] Short-term predictions are mostly driven by age, and since younger people have lower short-term risks even in the presence of high risk factor levels, they will mostly not receive preventive therapy, although their lifetime benefit may be very high. Also, vascular damage and kidney impairment usually develops gradually over the course of many years, and short-term prediction may underestimate long-term gains. For some patient groups, shorter term predictions remain relevant. For example, for predicting ESKD as outcome, shorter time span predictions in patients already having advanced kidney damage may be relevant for intensifying follow-up and timing of work-up for kidney replacement therapy.[43] However, for patients with lower short-term risk, including younger patients, longer-term predictions will be valuable to support decisions about preventive treatment. The DIAL-ESKD model in **Chapter 6** and the DIAL2 model in **Chapter 7** both emphasize lifetime risk predictions.

Returning to our patients, Mr. D and Mrs. T with type 2 diabetes at our out-patient clinic. Using the DIAL-ESKD model in **Chapter 6** and the DIAL2 model in **Chapter 7**, we can estimate their lifetime risks of a CVD event and ESKD (*Figure 1*). Mr. D has a lifetime risk of a CVD event of 41% and a lifetime risk of ESKD of 25%. Mrs. T has a lifetime risk of CVD of 45% and a lifetime risk of ESKD of 11%. Lifetime risk of CVD for Mrs. T is thus larger, even though Mr. D's cardiovascular risk factor burden is intuitively larger. However, Mrs. T is younger and thus has more years to develop CVD.

Figure 1. Lifetime risk estimates and treatment benefit for end-stage kidney disease and cardiovascular disease for two examples of patients with type 2 diabetes; Mr. D and Mrs. T



BP = blood pressure; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; SGLT2i = sodium glucose cotransporter 2 inhibitor; uACR = urine-Albumine/Creatinine ratio.

Individual benefit from treatment interventions

Fortunately, several preventive treatments exist for lowering risk of both cardiovascular and kidney disease in people with type 2 diabetes and international guidelines can provide recommendations on who, how and when to treat. However, these treatments may not be applicable to all and should be given to individuals with type 2 diabetes who will benefit the most. As shown in **Chapter 5** there is a wide range of predicted benefit from different treatment options in people with type 2 diabetes, why estimating individual benefit from treatment is important to choose the right treatment for the right patient. The relative treatment effects that stem from trials apply to the group level, thus the average patient. However, clinicians treat individual, not average, patients, and applying this relative risk to individuals in clinical practice is not always informative regarding absolute benefit. A treatment may be associated with a considerable reduction in relative risk but result in a modest reduction in absolute risk when the absolute baseline risk of the outcome is low, and vice versa.[44, 45] In **chapters 5, 6, 7 and 8**, the inclusion of

treatment effects allowed for estimating individual gain from preventive treatment, expressed as gain in CVD- or ESKD-free life years or absolute risk reduction (ARR). In this way, the relative risk reduction from trials is translated to individual benefit and this helps distinguish which patients may benefit the most. An older person may have high risk of a CVD or kidney outcome, but will have less benefit from an intervention, while a younger patient may have low risk of a CVD or kidney outcome, but high benefit from an intervention when taken life-long. Identifying which patients will benefit the most will enhance effective drug use, especially for expensive medication. It may also prevent unnecessary polypharmacy, while still ensuring that patients with a high-risk and significant treatment benefit are treated. When making decisions on treatments, patient preferences is of course also of key importance, and patients have reported it easier to comprehend gain in healthy life years than a relative risk.[46] The estimations of individual treatment benefit is likely to aid in shared decision making and adherence. In time, incorporation of additional relevant treatment effects should be possible, including exercise, adapting a healthier diet and losing weight, which might also act as a motivator for the individual patient. However, as mentioned previously, the risk on outcomes associated with changes in lifestyle is difficult to investigate and define.

What does this mean for our two patients? If Mr. D was to stop smoking, obtain a 10 mmHg reduction in his systolic blood pressure and initiate treatment with an SGLT2i, his lifetime CVD risk is estimated to be 27% (ARR 14%) with a gain of 3.5 CVD-free life years (**Chapter 7**), while his lifetime risk of ESKD would be 18% (ARR 7%) and a gain of 3.5 ESKD-free life years (**Chapter 6**). If Mrs. T was to lower her systolic blood pressure with 10 mmHg and initiate treatment with SGLT2i, her lifetime risk of CVD would be 35% (ARR 10%) with a gain of 1.6 CVD-free life-years, while her lifetime risk of ESKD would be 8% (ARR 3%) with a gain in ESKD-free life years of 2.9 (*Figure 1*). These measures can be used in clinical practice to promote adherence and shared decision making. Perhaps Mr. D is more willing to cut out his daily pack of cigarettes if he knows he will have an extra 3.5 disease-free years to spend with his grandchildren? Or that Mrs. T will be more keen to start blood-pressure lowering medication, despite her initial aversion, if she knows her estimated gain?

Risk prediction in clinical practice

Accurate and reliable predictions and treatment benefit estimations are worth nothing if not being used by the health care providers and the actual individual

patients. Several factors are important for a prediction model to be easily implementable in clinical practice. First of all, predictors required in the model should be routinely available. In SCORE2-DM, DIAL2 and DIAL-ESKD (**Chapter 6, 7 and 8**) all predictors are most often available in patients with type 2 diabetes. Second, the model should be easy and not time-consuming to use. The models developed in this thesis will shortly be available as inter-active online user-friendly calculators via www.u-prevent.com. Future innovations should focus on further implementing risk prediction models, for example in a way that information from electronic health records is directly transferred to the risk prediction model. This will free time in clinical practice to explain and discuss the risk and benefit estimates as well as treatment strategies with patients based on their individual predictions to support the shared decision making process.

Concluding remarks

Cardiovascular disease, kidney disease and type 2 diabetes remain some of the most common non-communicable diseases and are associated with increased risk of several adverse outcomes, despite advances in management and treatment. Prediction tools with a lifetime scope for cardiovascular and kidney disease allow for individualizing risk assessment and choosing between treatments together with better informed patients. Prediction models for a number of outcomes and in different patient populations, also some presented in this thesis, are available on www.U-prevent.com. With the recent methodological advancements and the ongoing improvements in data collection, the accuracy of prediction models will likely improve even more. Also, future advancements of allowing linkage to individual electronic health records will enhance clinical applicability of prediction models. The latest 2021 ESC cardiovascular disease prevention guidelines have put a lot more focus on individual risk based treatment, and perhaps so far we've only seen the top of the iceberg when it comes to estimating individual risk and treatment benefits. So even though we cannot predict the exact future for our patients, accuracy and reliability of risk estimates continue to progress.

Key findings of this thesis

- In patients with established cardiovascular disease, the incidence of ESKD varies according to vascular disease location and is highest in patients with polyvascular disease. Several modifiable risk factors

are associated with a higher risk of ESKD in patients with established cardiovascular disease, including smoking, type 2 diabetes, higher systolic blood pressure, lower eGFR and higher uACR (**Chapter 2**).

- Continuing smoking and recent smoking cessation and for men also an increase in obesity markers are associated with a steeper kidney function decline over 10 years in patients with established CVD (**Chapter 3**).
- A higher Hemoglobin Glycation Index (as a marker of interindividual differences in hemoglobin glycosylation) is related to a higher risk of cardiovascular disease in people with type 2 diabetes, however only in those without established CVD. However, as HbA_{1c} has proved to be a comparable risk factor, and obtaining and interpreting the HGI is complicated, any additional benefit of applying the HGI in clinical settings is likely to be limited (**Chapter 4**).
- In people with type 2 diabetes, GLP-1 RA or SGLT2i does not greatly differ between patients with and without CVD history, while use of blood pressure-lowering medication, statins and aspirin is more frequent in patients with CVD. Life-years gained free of (recurrent) CVD by optimal cardiovascular risk management and addition of GLP-1 RA and SGLT2i is dependent on baseline CVD risk and has a wide range in people with type 2 diabetes (**Chapter 5**).
- To estimate and communicate risk of ESKD and potential benefit with nephroprotective treatments in people with type 2 diabetes, a competing risk adjusted lifetime model was developed. This may promote shared decision making in the clinical practice (**Chapter 6**).
- With the updated DIAL2 model, the lifetime risk of CVD events in people with type 2 diabetes can be estimated. The model was updated to align with recent methodological advancements in recalibration to low- and moderate risk regions in Europe (**Chapter 7**).
- Using the SCORE2-DM risk score, 10-year risk of CVD events in people with type 2 diabetes can be estimated. The model can aid in identifying individuals at high CVD risk that will benefit most from treatment (**Chapter 8**).

References

1. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1736-1788.
2. Liu JH, Lin SY, Hsu CY, Lin HH, Liang CC, Sung FC, Huang CC. The risk for chronic kidney disease in patients with heart diseases: a 7-year follow-up in a cohort study in Taiwan. *BMC Nephrol* 2012;13:77.
3. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2020;98:S1-s115.
4. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am J Epidemiol* 2007;166:646-55.
5. Evangelidis N, Craig J, Bauman A, Manera K, Saglimbene V, Tong A. Lifestyle behaviour change for preventing the progression of chronic kidney disease: a systematic review. *BMJ Open* 2019;9:e031625.
6. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227-3337.
7. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;41:255-323.
8. 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;375:2215-22.
9. Pyörälä K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice: recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Atherosclerosis* 1994;110:121-61.
10. The recognition and management of hyperlipidaemia in adults: A policy statement of the European Atherosclerosis Society. *Eur Heart J* 1988;9:571-600.
11. Hempe JM, Gomez R, McCarter RJ, Jr., Chalew SA. High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. *J Diabetes Complications* 2002;16:313-20.
12. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Bmj* 2000;321:405-12.
13. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ, 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care* 2019;42:1593-1603.

14. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, Lu W, Zhu W, Bao Y, Vigersky RA, Jia W. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. *Diabetes Care* 2018;41:2370-2376.
15. Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. *Diabetes Technol Ther* 2019;21:81-85.
16. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581-90.
17. Esmeijer K, Dekkers OM, de Fijter JW, Dekker FW, Hoogeveen EK. Effect of different types of statins on kidney function decline and proteinuria: a network meta-analysis. *Sci Rep* 2019;9:16632.
18. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957-967.
19. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288-98.
20. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, Hayward RA, Craven T, Coleman RL, Chalmers J. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017;5:431-437.
21. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D, Rosano GM, Davis BR, Ridao M, Zaragoza A, Montero-Corominas D, Tobías A, de la Fuente-Honrubia C, Tabarés-Seisdedos R, Hutton B. Cardiovascular and Renal Outcomes of Renin-Angiotensin System Blockade in Adult Patients with Diabetes Mellitus: A Systematic Review with Network Meta-Analyses. *PLoS Med* 2016;13:e1001971.
22. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol* 2021;6:148-158.
23. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021.
24. Mahtta D, Ramsey DJ, Lee MT, Chen L, Al Rifai M, Akeroyd JM, Vaughan EM, Matheny ME, Santo K, Navaneethan SD, Lavie CJ, Birnbaum Y, Ballantyne CM, Petersen LA, Virani SS. Utilization Rates of SGLT2 Inhibitors and GLP-1 Receptor Agonists and Their Facility-Level Variation Among Patients With Atherosclerotic Cardiovascular Disease and Type 2 Diabetes: Insights From the Department of Veterans Affairs. *Diabetes Care* 2022;45:372-380.
25. Minze MG, Will KJ, Terrell BT, Black RL, Irons BK. Benefits of SGLT2 Inhibitors Beyond Glycemic Control - A Focus on Metabolic, Cardiovascular and Renal Outcomes. *Curr Diabetes Rev* 2018;14:509-517.
26. Vergès B, Bonnard C, Renard E. Beyond glucose lowering: glucagon-like peptide-1 receptor agonists, body weight and the cardiovascular system. *Diabetes Metab* 2011;37:477-88.

27. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *Bmj* 2009;338:b375.
28. Hageman SHJ, McKay AJ, Ueda P, Gunn LH, Jernberg T, Hagström E, Bhatt DL, Steg PG, Läll K, Mägi R, Gynnild MN, Ellekjær H, Saltvedt I, Tuñón J, Mahíllo I, Aceña Á, Kaminski K, Chlabicz M, Sawicka E, Tillman T, McEvoy JW, Di Angelantonio E, Graham I, De Bacquer D, Ray KK, Dorresteijn JAN, Visseren FLJ. Estimation of recurrent atherosclerotic cardiovascular event risk in patients with established cardiovascular disease: the updated SMART2 algorithm. *Eur Heart J* 2022;43:1715-1727.
29. 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. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. *Eur J Cardiovasc Prev Rehabil* 2011;18:393-8.
30. 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;101:671-9.
31. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, Levin A, Levey AS. A predictive model for progression of chronic kidney disease to kidney failure. *Jama* 2011;305:1553-9.
32. Slieker RC, van der Heijden A, Siddiqui MK, Langendoen-Gort M, Nijpels G, Herings R, Feenstra TL, Moons KGM, Bell S, Elders PJ, t Hart LM, Beulens JWJ. Performance of prediction models for nephropathy in people with type 2 diabetes: systematic review and external validation study. *Bmj* 2021;374:n2134.
33. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009;20:555-61.
34. van der Leeuw J, van Dieren S, Beulens JW, Boeing H, Spijkerman AM, van der Graaf Y, van der AD, Nöthlings 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;101:222-9.
35. Pennells L, Kaptoge S, Wood A, Sweeting M, Zhao X, White I, Burgess S, Willeit P, Bolton T, Moons KGM, van der Schouw YT, Selmer R, Khaw KT, Gudnason V, Assmann G, Amouyel P, Salomaa V, Kivimaki M, Nordestgaard BG, Blaha MJ, Kuller LH, Brenner H, Gillum RF, Meisinger C, Ford I, Knuiman MW, Rosengren A, Lawlor DA, Völzke H, Cooper C, Marín Ibañez A, Casiglia E, Kauhanen J, Cooper JA, Rodriguez B, Sundström J, Barrett-Connor E, Dankner R, Nietert PJ, Davidson KW, Wallace RB, Blazer DG, Björkelund C, Donfrancesco C, Krumholz HM, Nissinen A, Davis BR, Coady S, Whincup PH, Jørgensen T, Ducimetiere P, Trevisan M, Engström G, Crespo CJ, Meade TW, Visser M, Kromhout D, Kiechl S, Daimon M, Price JF, Gómez de la Cámara A, Wouter Jukema J, Lamarche B, Onat A, Simons LA, Kavousi M, Ben-Shlomo Y, Gallacher J, Dekker JM, Arima H, Shara N, Tipping RW, Roussel R, Brunner EJ, Koenig W, Sakurai M, Pavlovic J, Gansevoort RT, Nagel D, Goldbourt U, Barr ELM, Palmieri L, Njølstad I, Sato S, Monique Verschuren WM, Varghese CV, Graham I, Onuma O, Greenland P, Woodward M, Ezzati M, Psaty BM, Sattar N, Jackson R, Ridker PM, Cook NR, D'Agostino RB, Thompson SG, Danesh J, Di Angelantonio E. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J* 2019;40:621-631.

36. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health* 2019;7:e1332-e1345.
37. Lin CC, Li CI, Liu CS, Lin WY, Lin CH, Yang SY, Li TC. Development and validation of a risk prediction model for end-stage renal disease in patients with type 2 diabetes. *Sci Rep* 2017;7:10177.
38. Wan EYF, Fong DYT, Fung CSC, Yu EYT, Chin WY, Chan AKC, Lam CLK. Prediction of new onset of end stage renal disease in Chinese patients with type 2 diabetes mellitus - a population-based retrospective cohort study. *BMC Nephrol* 2017;18:257.
39. Elley CR, Robinson T, Moyes SA, Kenealy T, Collins J, Robinson E, Orr-Walker B, Drury PL. Derivation and validation of a renal risk score for people with type 2 diabetes. *Diabetes Care* 2013;36:3113-20.
40. Wysham CH, Gauthier-Loiselle M, Bailey RA, Manceur AM, Lefebvre P, Greenberg M, Duh MS, Young JB. Development of risk models for major adverse chronic renal outcomes among patients with type 2 diabetes mellitus using insurance claims: a retrospective observational study. *Curr Med Res Opin* 2020;36:219-227.
41. Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS. Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. *Lancet Diabetes Endocrinol* 2017;5:788-798.
42. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia* 2013;56:1925-33.
43. Eckardt KU, Bansal N, Coresh J, Evans M, Grams ME, Herzog CA, James MT, Heerspink HJL, Pollock CA, Stevens PE, Tamura MK, Tonelli MA, Wheeler DC, Winkelmayer WC, Cheung M, Hemmelgarn BR. Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2018;93:1281-1292.
44. Rothwell PM. Can overall results of clinical trials be applied to all patients? *Lancet* 1995;345:1616-9.
45. Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. *Bmj* 1995;311:1356-9.
46. Jaspers NEM, Visseren FLJ, van der Graaf Y, Smulders YM, Damman OC, Brouwers C, Rutten G, Dorresteijn JAN. Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial. *BMJ Open* 2021;11:e041673.

CHAPTER 10

Summary

The prevalence of type 2 diabetes, cardiovascular disease (CVD) and chronic kidney disease is growing at a rapid speed due to several factors, including increased survival of patients with disease, and an ageing population with more chance to develop disease. At the same time, the aforementioned diseases are strongly intertwined with shared risk factors, and the presence of one of the diseases increases the risk of the other two. The management of cardiovascular and kidney outcomes associated with both type 2 diabetes, chronic kidney disease and CVD is related to a high burden on the health care system and for the individual patient. Even with optimal management of lifestyle factors, there is still a substantial risk for CVD and kidney disease in "high-risk patients" with already established CVD and/or type 2 diabetes. Fortunately, several treatment strategies exist for reducing this risk, including lowering of LDL-c and blood pressure and for patients with type 2 diabetes lowering of HbA1c. Also, international guidelines recommend certain pharmacotherapy to reduce this risk. However, as these treatments are associated with a risk of adverse events, add to the pill-burden of patients and the fact that some of the therapies are associated with high costs, it is important to be able to precisely identify which patients are at higher risk and which will benefit most from preventive therapy.

This thesis consists of two parts: **Part 1** focuses on traditional and novel risk factors for CVD and kidney outcomes in high-risk patients with established CVD and/or type 2 diabetes. **Part 2** focuses on the prediction of cardiovascular and kidney disease in patients with type 2 diabetes.

Part 1. Risk factors for cardiovascular and kidney disease

Patients with established CVD are at increased risk of kidney disease, including end-stage kidney disease (ESKD). In **chapter 2**, it was shown that in 8,402 patients with established CVD from the UCC-SMART cohort, the incidence rate of ESKD differed according to vascular disease location and was highest in patients with polyvascular disease (1.8/1000 person-years). Several modifiable risk factors were associated with an increased risk of developing ESKD, including smoking (HR 1.87; 95%CI 1.10-3.19), type 2 diabetes (HR 1.81; 95%CI 1.05-3.14), higher systolic blood pressure (HR 1.37; 95%CI 1.24-1.52/10 mmHg), lower estimated glomerular filtration rate (HR 2.86; 95%CI 2.44-3.23/10 mL/min/1.73m^2) and higher urine albumin/creatinine ratio (HR 1.19; 95%CI 1.15-1.23/10 mg/mmol).

Chapter 3 investigates the relation between changes in lifestyle factors, including smoking, alcohol consumption, exercise and obesity markers, and change in kidney function over a 10 year follow-up period in patients with established CVD. We found that an increase in body mass index (β -2.81; 95%CI -3.98;-1.63per 5 kg/m^2) and for men also increase in waist circumference (β -0.87; 95%CI -1.28;-0.47per 5 cm) were associated with a steeper decline in eGFR over 10 years. Continuing smoking (β -2.44, 95%CI -4.43;-0.45) and recent smoking cessation during follow-up (β -3.27; 95%CI -5.20;-1.34) were also both associated with a steeper eGFR decline compared to patients who remained as non- or previous smokers from baseline. The findings from **chapter 2 and 3** highlight the potential of risk factor management for preventing ESKD and the importance of encouraging especially weight loss and smoking cessation in patients with established CVD.

Despite implementation of international guidelines focused on managing important amendable risk factors for CVD in people with type 2 diabetes, there is still a substantial risk of CVD. Therefore, there is ongoing interest in finding novel potential drivers of CVD risk in this patient group. In **chapter 4**, we investigated one such potential risk factor, the Hemoglobin Glycation Index (HGI). The HGI has been proposed as a marker of interindividual differences in hemoglobin glycosylation and is calculated as the difference between observed HbA1c and predicted HbA1c, where predicted HbA1c is obtained by the population linear regression equation of HbA1c as a function of blood glucose. However, our findings were not supportive of integrating HGI as a risk factor in clinical practice, since HbA_{1c} was shown to be a comparable risk factor, and obtaining and interpreting HGI is difficult.

Part 2. Individual prediction and benefit from treatment

New glucose-lowering therapies, such as sodium-glucose transport protein 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor analogues (GLP-1 RA), show promising results in reducing CVD risk and kidney disease risk in people with type 2 diabetes. In **chapter 5**, we found that in a cohort of 9,823 patients with type 2 diabetes spanning 13 countries, the use of GLP-1 RA or SGLT2i did not greatly differ between patients with and without a CVD history, while use of blood pressure-lowering medication, statins and aspirin was more frequent in patients with CVD. Also, we showed that life-years gained free of (recurrent)

CVD by optimal cardiovascular risk management and addition of GLP-1 RA and SGLT2i is dependent on baseline CVD risk and has a wide range in people with type 2 diabetes.

Prediction models for predicting cardiovascular and kidney outcomes in people with type 2 diabetes should be used in clinical practice to identify high-risk patients who are expected to benefit most from treatment. This ultimately helps in shared decision-making on treatment decisions. To do this, however, it is important that predictions are accurate and applicable to the specific clinical situation. In **chapter 6** we developed and validated the DIAL-ESKD; a competing risk adjusted model for predicting individual 10-year and lifetime risk of ESKD (defined as first occurrence of either kidney transplantation, long-term dialysis or persistent estimated glomerular filtration rate <15 ml/min/1.73m^2) in people with type 2 diabetes. Development and validation was performed in more than 1,000,000 people with type 2 diabetes from large, contemporary and representative regional cohorts, stemming from Sweden and Scotland. Performance of the model was good (c-statistic 0.89; 95%CI 0.88-0.90 for internal validation and 0.74; 95%CI 0.73-0.76 for external validation) and calibration plots showed good agreement in observed vs. predicted 10-year risk of ESKD. The model also allows for estimation of potential individual benefit from nephroprotective treatments and is intended for use in clinical practice to promote shared decision making.

Chapter 7 describes the development and geographical recalibration of the DIAL2 model, a competing risk adjusted prediction tool for predicting lifetime risk of CVD in people with type 2 diabetes and without established CVD. The model was developed in 467,856 people with type 2 diabetes and was systematically recalibrated to Europe's low and moderate risk region using contemporary incidence data and mean risk factor distributions. External validation of the recalibrated model in 218,267 people with type 2 diabetes was well (C-indices of 0.732; 95%CI 0.726-0.739 and 0.700; 95%CI 0.691-0.709). The DIAL2 model provides a useful tool for the prediction of CVD-free life expectancy and lifetime CVD risk for people with type 2 diabetes without previous CVD in the European low and moderate risk regions.

The counterpart of the DIAL2 model is the SCORE2-DM risk score discussed in **chapter 8**. The SCORE2-DM model can be used in clinical practice to

predict 10-year risk of CVD events in people with type 2 diabetes and without established CVD. The model was developed by extending SCORE2 algorithms using individual-participant-data from four large-scale datasets (229,460 individuals with type 2 diabetes) and recalibrated to CVD incidence in four European risk regions (low, moderate, high and very high risk regions). External validation included 216,980 further individuals and showed good discrimination with regional calibration being satisfactory. The model can aid in identifying individuals with type 2 diabetes at high CVD risk that will benefit most from treatment.

To conclude, prediction tools for cardiovascular and kidney outcomes in "high risk"-patients developed in line with recent advances in methodology allow for improved individualized risk assessment and estimation of treatment benefits. This promotes a stronger foundation for shared-decision leading to higher patient commitment and potentially better adherence in clinical practice. With the ongoing improvements in data collection, the accuracy of prediction models will likely improve even more in the future.

Nederlandse samenvatting (voor niet ingewijden)

Het aantal patiënten met diabetes type 2, hart- en vaatziekten en chronische nierziekten neemt wereldwijd in snel tempo toe. Dit als gevolg van onder andere een vergrijzende samenleving met toegenomen levensverwachting en daarbij meer kans om een ziekte te ontwikkelen. Het behandelen van diabetes type 2, chronische nierziekten en hart- en vaatziekten gaat gepaard met een hoge belasting voor de gezondheidszorg en de individuele patiënt. Tegelijkertijd zijn bovengenoemde ziekten sterk met elkaar verweven, met gedeelde risicofactoren en de aanwezigheid van een van de ziekten verhoogt het risico op het krijgen van de anderen. Gelukkig bestaan er verschillende behandelingen om dit risico te verminderen, waaronder verlaging van cholesterol, bloeddruk en bloedsuiker (voor patiënten met diabetes type 2) en internationale richtlijnen geven aanbevelingen voor bepaalde medicatie voor patiënten met een bijzonder hoog risico. Deze behandelingen gaan echter gepaard met een risico op bijwerkingen, een toename van het aantal pillen dat patiënten moeten slikken en, voor sommige therapieën, hoge kosten. Daarom is het belangrijk te kunnen vaststellen welke patiënten een verhoogd risico lopen en welke het meeste baat hebben bij preventieve medicatie.

Dit proefschrift bestaat uit twee delen: Deel 1 richt zich op traditionele en nieuwe risicofactoren voor hart- en vaatziekten en nierziekten bij risicopatiënten met vastgestelde hart- en vaatziekten en/of type 2 diabetes. Deel 2 richt zich op de voorspelling van hart- en vaatziekten en nierziekten bij patiënten met diabetes type 2.

Deel 1. Risicofactoren voor hart- en vaatziekten en nierziekten

Patiënten met vastgestelde hart- en vaatziekten lopen een verhoogd risico op nierziekten, waaronder eindstadium nierfalen. In **hoofdstuk 2** werd aangetoond dat in deze patiëntenpopulatie, de incidentie van eindstadium nierfalen verschilt naar gelang van de plaats waar de vaatziekte zich manifesteert, en het hoogst was bij patiënten met vaatziekten op meerdere plekken in het lichaam. Verschillende aanpasbare risicofactoren werden in verband gebracht met een verhoogd risico op het ontwikkelen van eindstadium nierfalen, waaronder roken, diabetes type 2, hogere bloeddruk, en lagere nierfunctie.

Hoofdstuk 3 onderzoekt de relatie tussen veranderingen in leefstijlfactoren, waaronder roken, alcoholgebruik, lichaamsbeweging en obesitasmarkers,

en verandering in nierfunctie gedurende een follow-up periode van 10 jaar bij patiënten met vastgestelde hart- en vaatziekten. Er werd gevonden dat een toename van de body mass index (BMI) en voor mannen ook een toename van de middelomtrek samenhangt met een sterkere daling van de nierfunctie over een periode van 10 jaar. Blijven roken tijdens de follow-up was geassocieerd met een steilere daling van de nierfunctie in vergelijking met patiënten die vanaf de uitgangswaarde niet rookten. De bevindingen van **hoofdstuk 2 en 3** benadrukken het potentieel van risicofactorbeheer voor het voorkomen van eindstadium nierfalen en het belang van het aanmoedigen van met name gewichtsverlies en stoppen met roken bij patiënten met vastgestelde hart- en vaatziekten.

Ondanks de toepassing van internationale richtlijnen die gericht zijn op het management van belangrijke risicofactoren voor hart- en vaatziekten bij mensen met diabetes type 2, is het risico op het ontstaan hiervan nog steeds aanzienlijk. In **hoofdstuk 4** werd één zo'n potentiële risicofactor onderzocht: de Hemoglobin Glycation Index (HGI). De HGI wordt berekend als het verschil tussen waargenomen HbA1c (lange termijn bloedsuiker) en voorspeld HbA1c. De bevindingen ondersteunen echter niet de integratie van HGI als risicofactor in de klinische praktijk, aangezien HbA1c een vergelijkbare risicofactor blijkt te zijn. Ook is het verkrijgen en interpreteren van HGI moeilijk.

Deel 2. Individuele voorspelling en voordeel van de behandeling

Nieuwe medicatie voor het verlagen van de bloedsuikerwaarde (SGLT2i en GLP-1 RA) laten veelbelovende resultaten zien bij het verminderen van het risico op hart- en vaatziekten en nierziekten bij mensen met diabetes type 2. In **hoofdstuk 5** vonden wij dat in patiënten met diabetes type 2, verspreid over 13 landen, het gebruik van deze medicijnen niet veel verschilde tussen patiënten met en zonder hart- en vaatziekten in het verleden, terwijl het gebruik van bloeddrukverlagende en cholesterolverlagende medicatie vaker voorkwam bij patiënten met hart- en vaatziekten. Ook werd gezien dat het aantal levensjaren zonder (terugkerende) hart- en vaatziekten door optimaal management van risicofactoren en bij toevoeging van GLP-1 RA en SGLT2i afhankelijk is van het baseline risico voor hart- en vaatziekten en een grote spreiding kent bij mensen met diabetes type 2.

Voorspellingsmodellen voor het voorspellen van hart- en vaatziekten en nierziekten bij mensen met diabetes type 2 moeten in de klinische praktijk worden

gebruikt om patiënten met een hoog risico te identificeren en van wie wordt verwacht dat zij de meeste baat hebben bij behandeling. Dit helpt uiteindelijk in het bevorderen van gedeelde besluitvorming over behandelingsbeslissingen. Daartoe is het echter van belang dat de voorspellingen nauwkeurig zijn en van toepassing op de specifieke klinische situatie. In **hoofdstuk 6** hebben wij het DIAL-ESKD model ontwikkeld en gevalideerd voor het voorspellen van het individuele 10-jaars- en levenslange risico op eindstadium nierfalen bij mensen met diabetes type 2. De ontwikkeling en validatie werd uitgevoerd bij meer dan 1.000.000 mensen met diabetes type 2 uit grote en representatieve regionale cohorten, afkomstig uit Zweden en Schotland. Een belangrijke component van het model is dat er ook rekening wordt gehouden met het feit dat mensen met diabetes type 2 vaak overlijden voordat zij eindstadium nierfalen krijgen. De prestaties van het model in externe data waren goed. Het model maakt ook een schatting mogelijk van het potentiële individuele voordeel van behandelingen bedoeld om nierziekten te voorkomen bij mensen met diabetes type 2. Daardoor is het model bedoeld voor gebruik in de klinische praktijk ter bevordering van gedeelde besluitvorming.

Hoofdstuk 7 beschrijft de ontwikkeling en geografische herijking van het DIAL2-model voor het voorspellen van het levenslange risico op hart- en vaatziekten bij mensen met diabetes type 2 en zonder reeds vastgestelde hart- en vaatziekten. Het model werd ontwikkeld in bijna 500,000 mensen met diabetes type 2. Middels het gebruik van grootschalige data van mensen met diabetes type 2 in Europa en regionale incidentie van hart- en vaatziekten is het model zo precies mogelijk afgestemd op de klinische praktijk in de laag- en gemiddeld-risico gebieden in Europa (Nederland hoort bij het gebied met een laag risico). De prestaties van het model in externe data waren voldoende. Het DIAL2-model vormt een nuttig instrument voor de voorspelling van de levensverwachting zonder hart- en vaatziekten en het levenslange risico op hart- en vaatziekten voor mensen met diabetes type 2 zonder eerdere hart- en vaatziekten.

De tegenhanger van het DIAL2-model is de in **hoofdstuk 8** besproken SCORE2-DM risicoscore. Het SCORE2-DM-model kan in de klinische praktijk worden gebruikt om het risico op hart- en vaatziekten in 10 jaar tijd te voorspellen bij mensen met diabetes type 2 zonder vastgestelde hart- en vaatziekten. Het model is ontwikkeld door de veelal gebruikte en recente SCORE2-algoritme

uit te breiden met gegevens van individuele deelnemers met diabetes type 2 uit vier grootschalige datasets. Het werd opnieuw aangepast naar de incidentie van hart- en vaatziekten in vier Europese risicogebieden; laag, gemiddeld, hoog en zeer hoog. In externe data was de prestatie van SCORE2-DM voldoende. Het model kan helpen bij het identificeren van personen met diabetes type 2 met een hoog risico op hart- en vaatziekten die het meest gebaat zijn bij behandeling.

Kortom, voorspellingsinstrumenten voor hart- en vaatziekten en nierziekten bij patiënten met diabetes type 2, i.e. patiënten met een hoog risico, maken het mogelijk de risicobeoordeling te individualiseren en het voordeel van de behandeling zo nauwkeurig mogelijk in te schatten. Dit bevordert gedeelde besluitvorming in de klinische praktijk met beter geïnformeerde patiënten. Met de voortdurende verbeteringen in de gegevensverzameling zal de nauwkeurigheid van de voorspellingsmodellen in de toekomst waarschijnlijk nog verder verbeteren.

Contributing authors

Emanuele Di Angelantonio	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK Health Data Science Centre, Human Technopole, Milan, Italy
Folkert W Asselbergs	Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom
Dirk De Bacquer	Ghent University, Ghent, Belgium
Zane Baltane	The Centre for Disease Prevention and Control of Latvia
Rui Bebiano Da Providencia E Costa	UCL Institute for Health Informatics Research, University College London, London, UK
Massimo Massi Benedetti	Hub for International Health Research, Perugia, Italy
Gijs FN Berkelmans	Department of Vascular Medicine, University Medical Centre Utrecht, the Netherlands
Fabrice Bonnet	University of Rennes 1, Rennes CHU, Rennes, France
Gert J de Borst	Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands
Michiel L Bots	Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
Hermann Brenner	Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany. Network Aging Research, University of Heidelberg, Heidelberg, Germany
Fabrizio Carinci	Department of Statistical Sciences, University of Bologna, Italy

John Danesh	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Imre Demirhan	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
Jannick A. N. Dorresteijn	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
Yong Du	Robert Koch Institute, Germany
Björn Eliasson	Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden; The Swedish National Diabetes Register, Gothenburg, Sweden
Stephen Fava	University of Malta
Brian Ference	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Josep Franch-Nadal	Center for Biomedical Research on Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Barcelona, Spain.
Stefan Franzén	Swedish National Diabetes Register, Center of Registers in Region, Gothenburg, Sweden Health Metric Unit, Sahlgrenska Academy, Gothenburg Unversity, Sweden
Richard F Gillum	Howard University Hospital, Washington DC, DC, USA
Yolanda van der Graaf	Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, the Netherlands
Ian Graham	School of Medicine, Trinity College Dublin, The University of Dublin, College Green, Dublin, Ireland
Stefano Gualdi	Internet Express, Pescara, Italy
Steven H.J. Hageman	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
Nynke Halbesma	Usher Institute University of Edinburgh, UK and on behalf of the Scottish Diabetes Research Network Epidemiology Group

Martin Halle	University Hospital ´Klinikum rechts der Isar´, Technical University of Munich, Munich, Germany
Ellen Margo Hengeveld	Novo Nordisk A/S, Søborg, Denmark
William Herrington	Medical Research Council Population Health Research Unit at the University of Oxford, Nuffield Department of Population Health, University of Oxford, Oxford, UK
Naomi Holman	Department of Epidemiology and Biostatistics, Imperial College London, UK
Julie Broe Honore	Novo Nordisk A/S, Søborg, Denmark
Radu Huculeci	European Society of Cardiology, Brussels, Belgium
Valerie Humphreys	Diabetes Ireland Advocacy Group, Dublin, Ireland
Sandor Janos	University of Debrecen
L Jaap Kappelle	Department of Neurology, University Medical Center Utrecht, Utrecht, the Netherlands
Stephen Kaptoge	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Stefan Kiechl	Department of Neurology, Medical University Innsbruck, Innsbruck, Austria
Astrid Lavens	Sciensano, Belgium
Deborah A Lawlor	MRC Integrative Epidemiology Unit at the University of Bristol, UK; Population Health Science, Bristol Medical School, Bristol University, UK
Joep van der Leeuw	Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, the Netherlands Department of Internal Medicine, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands
François Mach	Cardiology Division, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Thomas Mandrup-Poulsen	Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
Dídac Mauricio	Department of Endocrinology & Nutrition, Hospital de la Santa Creu i Sant Pau, and Sant Pau Biomedical Research Institute, Barcelona, Spain.
John William McEvoy	National University of Ireland Galway, Galway, Ireland
Ofri Mosenzon	Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel
Lisa Pennells	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Carmen Petitjean	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Santa Pildava	The Centre for Disease Prevention and Control of Latvia
Tamara Poljicanin	Croatian Institute of Public Health, Zagreb, Croatia
Louis Potier	Université Paris City, Bichat Hospital, AP-HP, Paris, France
Ivan Pristas	Croatian Institute of Public Health, Zagreb, Croatia
Stephanie H Read	Usher Institute, University of Edinburgh, Edinburgh, UK
Peter Rossing	Steno Diabetes Center, Gentofte, Denmark
Reiff Sascha	Ministry of Health, Malta
Naveed Sattar	Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK
Christa Scheidt-Nave	Robert Koch Institute, Germany
Ben Schöttker	Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany. Network Aging Research, University of Heidelberg, Heidelberg, Germany.
Fanchao Shi	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

Reecha Sofat	UCL Institute for Health Informatics Research, University College London, London, UK
Sarah Spackman	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Iztok Stotl	Department of Endocrinology, Diabetes and Metabolic Diseases,University Medical Centre Ljubljana, Ljubljana, Slovenia
Owen Taylor	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Gail Tibor	University of Debrecen, Hungary
Adam Timmis	William Harvey Research Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK
Vlima Urbančič-Rovan	Department of Endocrinology, Diabetes and Metabolic Diseases,,University Medical Centre Ljubljana, Ljubljana, Slovenia Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
Sofie Vanherwegen	Sciensano, Belgium
Panagiotis Vardas	Heraklion University Hospital, Crete, Greece
Marianne C Verhaar	Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, the Netherlands
Frank L.J. Visseren	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
Dorte Vistisen	Steno Diabetes Center, Gentofte, Denmark
Henry Völzke	Institute for Community Medicine, University Medicine Greifswald, Germany
Matthew R Walker	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Jan Westerink	Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands

Sarah Wild	Usher Institute, University of Edinburgh, Edinburgh, UK
Johann Willeit	Department of Neurology, Medical University Innsbruck, Innsbruck, Austria
Peter Willeit	Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Angela Wood	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Zhe Xu	Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
Gourav Yadav	Novo Nordisk Global Business Services, Bengaluru, India

List of publications

Østergaard HB*, Hageman SHJ*, Read SH*, Taylor O*, Pennells L, Kaptoge S, Petitjean C, Xu Z, Shi F, McEvoy JW, Herrington W, Visseren FLJ, Wood A, Eliasson B†, Sattar N†, Wild SH†, Di Angelantonio E†, Dorresteijn JAN†, †Contributed equally, *Contributed equally. Estimating individual lifetime risk of incident cardiovascular events in adults with type 2 diabetes: an update and geographical calibration of the DIAbetes Lifetime perspective model (DIAL2). Eur J Prev Cardiol. 2023 Jan 11;30(1):61-69.

Østergaard HB, Read SH, Sattar N, Franzén S, Halbesma N, Dorresteijn JAN, Westerink J, Visseren FLJ, Wild SH, Eliasson B, van der Leeuw J. Development and Validation of a Lifetime Risk Model for Kidney Failure and Treatment Benefit in Type 2 Diabetes: 10-Year and Lifetime Risk Prediction Models. Clin J Am Soc Nephrol. 2022;17(12):1783-1791.

Østergaard HB, Humphreys V, Hengeveld EM, Honoré JB, Mach F, Visseren FLJ, Westerink J, Yadav G, Mosenzon O. Cardiovascular risk and lifetime benefit from preventive treatment in type 2 diabetes: A post hoc analysis of the CAPTURE study. Diabetes Obes Metab. 2023 Feb;25(2):435-443.

Østergaard HB, Demirhan I, Westerink J, Verhaar MC, Asselbergs FW, de Borst GJ, Kappelle LJ, Visseren FLJ, van der Leeuw J. Lifestyle changes and kidney function: A 10-year follow-up study in patients with manifest cardiovascular disease. Eur J Clin Invest. 2022;52(9):e13814.

Østergaard HB, Westerink J, Verhaar MC, Bots ML, Asselbergs FW, de Borst GJ, Kappelle LJ, Visseren FLJ, van der Leeuw J. End-stage kidney disease in patients with clinically manifest vascular disease; incidence and risk factors: results from the UCC-SMART cohort study. J Nephrol. 2021;34(5):1511-1520.

Østergaard HB, van der Leeuw J, Visseren FLJ, Westerink J. Comment on Vistisen et al. A Validated Prediction Model for End-Stage Kidney Disease in Type 1 Diabetes. Diabetes Care 2021;44:901-907. Diabetes Care. 2021;44(6):e139.

Westerink J, Matthiessen KS, Nuhoho S, Fainberg U, Lyng Wolden M, **Østergaard HB**, Visseren F, Sattar N. Estimated Life-Years Gained Free of New or Recurrent Major Cardiovascular Events With the Addition of Semaglutide to Standard of Care in People With Type 2 Diabetes and High Cardiovascular Risk. Diabetes Care. 2022;45(5):1211-1218.

Østergaard HB, Mandrup-Poulsen T, Berkelmans GFN, van der Graaf Y, Visseren FLJ, Westerink J. Limited benefit of haemoglobin glycation index as risk factor for cardiovascular disease in type 2 diabetes patients. Diabetes Metab. 2019;45(3):254-260.

Kjær AS, **Østergaard HB**. [HIV may be cured]. Ugeskr Laeger. 2015;177(17).

Dankwoord/takkeord

So, here we are, at the end of a long winding road; promoveren! It has been three years filled with ups and downs, challenges, frustrations, self-development, a lot of knowledge gained and friendships made, which all culminated in this thesis. I am beyond proud of the result and my own perseverance, but apparently it does take a village to write a PhD. This thesis isn't complete without deeply thanking my 'village' of people who supported me through this and whom I couldn't have done it without.

Als eerste wil ik mijn promotieteam heel erg bedanken; mijn promotor prof. dr. F.L.J. Visseren en mijn copromotoren dr. J. van der Leeuw en dr. J. Westerink.

Prof. dr. F.L.J. Visseren, beste Frank. Allereerst, bedankt dat je mij de kans gaf om bij jou en in de Vascu groep te promoveren en om de master klinische epidemiologie te volgen. Je bent altijd heel laagdrempelig bereikbaar geweest, zowel voor de grote als kleine dingen. Verder weet je ook altijd tijd voor iedereen te maken. Ik snap niet altijd hoe je dit doet, alhoewel, terwijl de meeste mensen hun tijd in het vliegtuig gebruiken om door de filmkeuze te browsen, gebruik jij die om manuscripten nauwkeurig te bekijken. Jij bent altijd heel positief en enthousiast, zowel binnen de onderzoekswereld als in de klinische praktijk, en je scherpe vragen en opmerkingen vereisten dat ik overal extra goed over na moest denken. Ook buiten werk vind je tijd voor gezelligheid om de afdeling nog hechter te maken en arrangeer je barbecues en thanksgiving diners bij jou thuis.

Dr. J. van der Leeuw, beste Joep. Ik ben heel blij en voel mij vereerd dat ik jouw eerste promovendus ben. Manuscripten werden altijd heel grondig doorgenomen en je feedback was altijd 'spot-on'. Door je (vaak kritische) opmerkingen en vragen bij overleggen werden de projecten altijd stuk beter en duidelijker. Jij wist altijd tijd voor me te maken, ook ondanks jouw drukke schema. Er gebeurden voor ons allebei meerdere grote events tijdens mijn promotietijd (we zijn een paar verhuizingen en een paar kinderen verder), en tegelijkertijd hebben wij dit mooie resultaat bereikt.

Dr. J. Westerink, beste Jan. Eigenlijk moet ik jou bedanken dat ik nu in Nederland vastzit, met een man, kind en huis ;-) Bedankt dat je mij onder je hoede nam jaren geleden, toen je een e-mail kreeg van een of andere random

Deense geneeskundestudent. Ook bedankt voor het vertrouwen waarmee je mij daarna bij de Vascu binnen hebt weten te loodsen. Vanaf dag een was je een super begeleider. Je hebt een hele scherpe blik op zowel onderzoek als de kliniek, en daarnaast ook vooral in hoe je die twee weet te combineren. Jij weet het onderzoek naar een hoger niveau te brengen, maar ook heb ik van jou veel geleerd over, onder andere, de oorsprong van verschillende Germaanse woorden en (Duitse) metaaldetector vondsten.

Dr. J.A.N. Dorresteijn, beste Jannick, ook jou wil ik graag bedanken voor je onmisbare begeleiding op het gebied van predictie, voor het DIAL-ESKD model en natuurlijk voor de succesvolle samenwerking met DIAL2 en SCORE2-DM. Het was af en toe pittig met vele politieke belangen, maar met jouw aanwezigheid, enthousiasme en kritische blik hebben we een zeer mooie resultaat kunnen neerzetten.

De andere collega's van de afdeling Vasculaire geneeskunde, Wilko, Stan, Jan-Steven, Thomas, Jorn, Melvin, Jean-Paul, Manon en Corine, bedankt voor de prettige samenwerking en fijne sfeer op de afdeling en veel kennis bij de wekelijkse poli-bespreking. Margie, the machine that keeps it all going, dankjewel voor al je hulp en je altijd positieve karakter.

Corina, Sara en Inge, bedankt voor alle leuke gesprekken en jullie persoonlijke interesse. Ik vond het altijd ontzettend gezellig en prettig om met jullie samen te mogen werken op de researchpoli.

UCC-SMART medewerkers, beste Ursula, Ank, Lies, Loes, Yvonne, Hetty, Baukje, Angela en Rutger, bedankt voor de fijne samenwerking bij SMART en voor al jullie harde inzet voor de UCC-SMART studie.

De hooggeleerde leden van de beoordelingscommissie prof. dr. M. Bots, prof. dr. M. Verhaar, prof. dr. F.H. Rutten, prof. dr. R. Gansevoort en prof. dr. M. Nieuwdorp dank ik voor hun tijd en bereidheid dit proefschrift te beoordelen. Ik kijk er naar uit om mijn proefschrift met jullie te bespreken.

Prof. dr. Michiel Bots en prof. dr. Yvonne van der Schouw, jullie ook bedankt voor de begeleiding en beoordeling van het researchproject tijdens de master epidemiologie.

I would like to thank all co-authors for their invaluable inputs and fruitful

collaborations that contributed to a large part of this PhD. Especially thanks to Sarah Wild, Björn Eliasson, Naveed Sattar, Emanuele Di Angelantonio, Stephanie Read, Stephen Kaptoge and Lisa Pennells for the collaborations on the prediction models presented in this thesis and for the many meetings and discussions.

Thank you to all patients and participants from various cohorts and trials, both domestic and international. Your contributions are essential and without it this PhD would not have seen the light of day.

To the many peer-reviewers, thank you for the insightful and critical comments and feedback that helped improve the manuscripts even more.

Mede Vascu-collega onderzoekers, wat heb ik toch geluk gehad om in zo'n leuke groep te landen! Wij zijn echt een goed team, helpen en steunen elkaar en ik had jullie voor geen goud willen missen! Dankjulliewel voor alle gezellige momenten; vrijmibo's, weekendjes naar Sevilla, Breukelen en Lissabon, vele koffie-sessies, mentale steun, woordgrappen (die meestal zo slecht waren dat zelfs ik ze begreep), voor het helpen met de Nederlandse taal en het meedoen aan al mijn gekke Deense tradities!

Tamar, echte Vascu-mama, ik ken niemand die zo efficiënt kan werken als die dan eenmaal werkt! Jouw aanwezigheid maakte het altijd een stuk gezelliger, met je humor, goede verhalen en praatjes! Ook bedankt dat je mij kilometers op een board door het water meegesleept hebt toen ik mijn paddle kwijt raakte tijdens het SUP'en in Breukelen. Ook zijn jouw karaoke-skills benijdbaar. Cilie, ik vond het super leuk en gezellig om samen met je te werken en heb veel respect voor hoe je wist door te werken van 's morgens vroeg tot 's avonds laat. Ik vind het nog leuker dat jij ook in de oosterse buitenwijken van Utrecht bent beland en ik denk dat Berend en Lasse hele goede vrienden gaan worden! Britt, mijn mede-vascu "partner in crime", wij konden het altijd heel goed over alle PhD ups en downs hebben, maar ook alle andere grote en kleine dingen in het leven. Ik heb heel veel respect voor hoe hard je werkt en je doorzettingsvermogen, en tegelijkertijd ben je gewoon een fantastisch persoon (ook ben ik dankbaar voor je flexibele ruggengraat, dit maakte de "uit de hand gelopen" borrels altijd een stuk gezelliger). Mocht je ooit een bijbaantje zoeken dan doe je het uitstekend als nep-Deense voetbalfan! Steven, ons fenomeen, dat ben je wel echt! Niet alleen ben je predictie en – buiten proporties – R-expert, je bent

ook heel behulpzaam en ik heb ontzettend genoten van alle samenwerkingen op werk, en uiteraard alle gezellige momenten buiten werk. Met jou was het nooit saai, en je toonde ook oprecht medeleven als je zag dat het even tegen zat. Maria, in het begin was je echt een soort mythe voor me, alle collega's hadden het de hele tijd over "Maria de Winter" terwijl ik geen idee had over wie ze het hadden. Toen ontmoette ik jou, en ik snapte gelijk waarom. Ik heb heel veel respect voor hoe veel je weet te combineren en tegelijkertijd ben je super sociaal. De "koele-kast" sessies waren altijd een feest! Ik heb genoten van alle praatjes, etentjes, feestjes, borrels en hardloop-sessies! Eline, mede-epi-master, zonder jou was de epi een stuk saaier geweest. Sorry dat je vaak helemaal niks aan me had als je weer een wiskundige formule volledig wilden begrijpen. Jij en Maria hebben ook cavia's voor mij naar een heel nieuw niveau gebracht. Ik bewonder hoe hard jij werkt, je oog voor detail, jouw empathie en je smaak in wijn (en muziek uiteraard)! De interne geneeskunde heeft een grote aanwinst met jou gekregen. Pascal, jij begon in een rare tijd met lock-down etc., maar daarna hadden wij gelukkig veel plezier van je droge humor en je vaardigheden in het schrijven van reviews over hotels. Ook bedankt voor al je hulp en het sparren over predictie-dingen. Ik ken niemand die zo lang, zo geconcentreerd (zonder noise-cancelling!) kan werken in een kamer waar er meer of minder geschreeuwd wordt. Marga, ook jij was een echte toevoeging voor de Vascu! Altijd zo lief en bedachtzaam, jij denkt echt aan alle mensen om je heen! Ook ken ik niemand die zo veel structuur heeft, zowel op werk als in het leven. Uiteraard ben je ook super gezellig en altijd borrel-klaar! Nadia, super leuk dat je na je onderzoeksstage een promotie kwam doen. Bedankt voor alle gezelligheid bij lunches, koffies en borrels. Met jouw talent laat je het lijken alsof promoveren een eitje is (ook al weet ik dat dat niet altijd zo is natuurlijk). Iris, werken met jou was nooit saai! Jouw enthousiasme, openheid en lach zijn besmettelijk, en ik heb heel veel respect voor hoe je dingen aanpakt en voor elkaar weet te krijgen! Katrien, ik dacht dat ik de Nederlandse taal redelijk onder de knie had, maar toen kwam jij bij de Vascu promoveren en een hele nieuwe wereld van hilarische uitspraken opende zich voor me! Jij hebt een onbreekbaar werkethos en tegelijkertijd ben je super sociaal, leuk en gezellig! Lukas, jouw vuurdoop was meteen een weekend met z'n allen weg, en wat hebben wij sindsdien mogen genieten van je energie, positivisme en enthousiasme! Super knap hoe je zo'n moeilijke trial hebt weten op te zetten. Joris, wij werkten niet lang samen, maar ik kan nu al zeggen dat je een

enorme aanwinst voor de Vascu bent! Bomvol energie en een brein dat sneller werkt dan van de meesten, het gaat met jou helemaal goed komen. Milena, ook met jou heb ik weinig gewerkt, maar ik vond het altijd gezellig! Infectie-mensen, Patrick, Jesper en Bianca, ook jullie bedankt voor alle gezelligheid in de afgelopen jaren.

Nederlandse vrienden, emigreren wordt een stuk leuker en makkelijker met zo veel leuke mensen om je heen! Nicole, we met each other during my research-internship a couple of years ago. With the addition of motherhood, I've really found a lot of support in you and I cherish our friendship. Nina, fellow "expat-fell-in-love-with-a-Dutch-guy", I'm very thankful that we now both live in Utrecht, and I always enjoy our talks and times together, let there be many more to come! Maria, fellow Dane og fodbold-fan der også forvildede sig til Holland, virkelig hyggeligt I også er i Utrecht omegn (for nu i hvert fald). Marlous, van trim-hockey en avontuurclubje, jij bent echt een heel leuk en sociaal persoon. Volgens mij zou je op de Noordpool kunnen zitten en nog steeds vrienden maken, je hebt mijn leven in Utrecht echt een stuk gezelliger gemaakt. PNS/P1/plus de rest; Jochem en Job, jullie hebben mij meteen met open armen ontvangen toen ik vele weekendjes in jullie huis kwam logeren, dank daarvoor! Samen met, Floor, Anna, Wouter, Patrick, Lieke, Nick, Dorine, Daan en Tessa vind ik jullie echt een leuke groep en ik geniet altijd ontzettend van alle momenten samen! Dankjulliewel voor al jullie hulp met het huis!

CP-groepje, Marlous, Elske, Annemie, Ingrid, Janne, Roos, Lisette en de rest, moeder worden en verhuizen naar Zeist was echt een stuk zwaarder geweest zonder jullie! Ik kan met jullie altijd goed relativeren en sparren over van alles; van groot tot klein. Dankjulliewel voor alle gezellige koffie (uiteraard met taart) en cocktail momentjes!

Mia, en sjælden gang imellem møder man et menneske, og så siger det bare klik – sådan var det med dig! Jeg har været så glad for at sparre med dig de sidste par år, både over PhD-struggles, men også alle andre op- og nedture. Du er så stærk, sej, sjov og omsorgsfuld, og jeg priser mig lykkelig for, at vi valgte lige præcis dig som roomie til vores hollandsk-inspirerede "lej-vores-værelse-jobsamtale" på Nørrebro! Julia, fra unge, blå og uvidende første semesters medicin-studerende på KU til læger, flittige PhD-studerende og mødre i hvert sit land. Jeg nyder altid, når vi snakker sammen og ses. Emilie, du er altid god til

at perspektivere og dejlig at snakke med, lad os blive ved med det. Catherina, hold fast vi har været igennem meget sammen, fra Hunsur, København, Hammerfest, Utrecht og ikke mindst verdens navle, aka Faaborg ;-) Selvom vi begge er lidt af nogle nomader, ved jeg, vi bliver ved med at holde kontakten – sådan er det jo med pure-sisses! Folkeskolepigerne, Siri, Sarah, Anna-Louise og Cecilie, vi har formået at holde kontakten, og selvom der går længe mellem vi ses, føles det altid så naturligt og hyggeligt, når det sker. Anne, 'dying frog', der er sket meget i vores liv siden vi mødtes i en tipi i Canada! Din latter er så smitsom, og heldigvis er du gavmild med den, og jeg nyder virkelig, når det lykkes at ses. Camilla, fra parfume-produktion på Rørvangen (begriber stadig ikke at vores salgstal ikke var højere) til hus og barn i henholdsvis Thorsager og Zeist. Du har så meget viljestyrke, empati og humor, og jeg værdsætter virkelig vores venskab. Gry og Louise, vi rejste alle på udveksling før gymnasitet, unge og uvidende, og blev derefter veninder. Selvom livet er gået i alle mulige forskellige retninger for os, har vi vidst at holde sammen, og det er jeg meget taknemmelig for.

Schoonfamilie, wat heb ik toch geluk met jullie! Lieve schoonouders, Joop en Marieke, bedankt voor alle gezellige momenten en reizen in de afgelopen jaren. Jullie zijn een onmisbare steun en staan echt altijd voor ons klaar en dat waardeer ik enorm. Jullie hebben een gezin gecreëerd met heel veel liefde en warmte en ik heb het genoegen er nu deel van uit te maken. Wisse, Esther, Dirk en Pannie, ik vind het altijd super leuk met jullie en wat kunnen wij samen goed lachen! Dankjulliewel voor alle fijne en gezellige momenten; verjaardagen, Sinterklaas, borrels etc.! Ik kijk uit naar nog veel meer mooie momenten in de toekomst!

Kære familie, tak for jeres fantastiske støtte og opbakning gennem denne PhD-rejse. Jeg ved godt, det ikke altid er optimalt at skulle krydse landegrænser for at ses, men ikke desto mindre er det så så meget mere hyggeligt, når vi ses! Vi har det altid utroligt sjovt, når vi er sammen, og jeg glæder mig til mange flere hyggelige stunder i fremtiden.

Mor, tak for din evige støtte, dit store hjerte og enorme empati. Du har altid bakket mig op i alt, hvad jeg har foretaget mig. Når det hele blev lidt for meget, vidste jeg altid, hvem jeg skulle ringe til. Far, du har altid været en kilde til utrolig meget inspiration og et forbillede for mig. Dit drive, entusiasme og gå-på-mod er intet mindre end beundringsværdigt, og jeg har altid lært utrolig

meget af dig. Samtidig er du en utrolig god støtte og far! Bettina, tak for mange hyggelige stunder, både i Århus og Utrecht!

Julia, verdens bedste lillesøster, tak for bare at være dig. Din humor, omsorg, energi og ukuelighed beundrer jeg virkelig meget, og jeg er sindssygt stolt af dig. Tusind tak for hjælpen med forsiden til bogen! Dig og Sinas har virkelig skabt et hjem med så meget hjertevarme. Sinas, tak for dit rolige væsen og for altid at tage imod os med åbne arme. Teodor, fantastiske lille nevø, med din livsglæde, stædighed og charme kommer du til at kunne opnå alt, hvad du sætter dig for. Jeg elsker at være din moster og se dig vokse op. Kommende niece, jeg glæder mig så meget til at møde dig! Andreas, tak for at være verdens bedste lillebror. Du er så livsklog og har samtidig en utrolig god (og til tider lidt sort) humor. Du er intelligent og samtidig så empatisk, og uanset hvad du giver dig i kast med, "winger" du den bare. Du gør din storesøster helt vildt stolt. Tak for din hjælp til rigtig mange figurer, graphical abstracts etc. i denne her PhD! Freja, tak for dig, dit rolige, sjove og charmerende væsen (og bagværk) er virkelig en fantastisk tilføjelse til vores familie.

Lieve Sef, waar moet ik beginnen? Van "braaien" en wine-tours in Zuid-Afrika tot huisje, boompje en baby in Zeist. Het leven met jou is een groot avontuur en ik ben elke dag gelukkig en dankbaar dat ik jou naast me heb. Jouw steun en optimisme gedurende mijn promotietraject waren essentieel, en je wist mij altijd te "grounden" als ik weer een kleine break-down had over super-computers of afgewezen manuscripten. Jouw liefde, energie en openheid zijn bewonderingswaardig en ik ben zo trots op hoe je in het leven staat. Tijdens mijn promotietijd waren er meerdere life-events; opleiding, bruiloft, huis kopen, ouders worden, wat het ook af en toe een klein beetje stressvol maakte, maar wij wisten en weten altijd samen te lachen. Je bent een geweldige man en vader en ik hou heel veel van je.

Lasse, du har været med mig i nogle ret afgørende øjeblikke i løbet af denne PhD. Først inde i maven og derefter siddende i bæreselen på mit bryst, hoppende på en yoga-bold. Du kom, vendte vores verden på hovedet, og jeg har aldrig følt større kærlighed. Du er så fantastisk en lille mand, så nysgerrig på livet, viljestærk, åben og lattermild. En dag finder du måske denne bog støvet på reolen, og jeg håber, du alligevel vil være lidt stolt af, at din mor engang skrev en bog. Jeg elsker dig til månen og tilbage igen.

"Wherever there is love for medicine, there is love for humanity."
Hippocrates (460 B.C. - 370 B.C.)

Acknowledgements (English translation)

So, here we are, at the end of a long winding road; promoveren! It has been three years filled with ups and downs, challenges, frustrations, self-development, a lot of knowledge gained and friendships made, which all culminated in this thesis. I am beyond proud of the result and my own perseverance, but apparently it does take a village to write a PhD. This thesis isn't complete without deeply thanking my "village" of people who supported me through this and whom I couldn't have done it without.

First of all, I would like to sincerely thank my PhD team; my supervisor prof. dr. F.L.J. Visseren and my co-supervisors dr. J. van der Leeuw and dr. J. Westerink.

Prof. dr F.L.J. Visseren, dear Frank. First of all, thank you for giving me the opportunity to do my PhD with you and in the Vascu group and to pursue the master's degree in clinical epidemiology. You have always been very approachable, both for the big and small things. Furthermore, you always manage to make time for everyone. I don't always get how you do this, but then again, while most people use their time on the plane to browse through the in-flight movie selection, you use it to thoroughly look at manuscripts. You are always very positive and enthusiastic, both within research and clinical practice, and your insightful questions and comments required me to think about everything extra carefully. Even outside work, you find time for sociability to make the department even more united, arranging barbecues and thanksgiving dinners at your house.

Dr. J. van der Leeuw, dear Joep. I am very happy and honored to be your first PhD student. Manuscripts were always reviewed very thoroughly and your feedback was always 'spot-on'. Your (often critical) comments and questions during meetings always made the projects much better and clearer. You always managed to make time for me, even despite your busy schedule. Several big events happened for both of us during my PhD period (we are a couple of moves and a couple of kids down the road), and at the same time we achieved this great result.

Dr J. Westerink, dear Jan. Actually, I have you to thank for the fact that I am now stuck in the Netherlands, with a husband, child and house ;-) Thank you for taking me under your wing years ago, when you received an e-mail from some

random Danish medical student. Thank you for the confidence with which you managed to get me into the Vascu afterwards. From day one, you were an amazing supervisor. You have a very keen eye for both research and the clinic, and especially in how you manage to combine the two. You know how to take research to the next level, but you also taught me a lot about other things, such as the origin of various Germanic words and (German) metal detector finds.

Dr. J.A.N. Dorresteijn, dear Jannick, I would also like to thank you for your indispensable guidance in the field of prediction, for the DIAL-ESKD model and of course for the successful collaboration with DIAL2 and SCORE2-DM. It was challenging at times, but with your presence, enthusiasm and critical eye we were able to achieve a very good result.

The other colleagues of the Vascular Medicine department, Wilko, Stan, Jan-Steven, Thomas, Jorn, Melvin, Jean-Paul, Manon and Corine, thank you for the pleasant cooperation and great atmosphere in the department and a lot of knowledge at the weekly outpatient meeting. Margie, the machine that keeps it all going, thank you for all your help and your always positive character.

Corina, Sara and Inge, thank you for all the nice conversations and your personal interest. I always found it incredibly pleasant and enjoyable to work with you at the research clinic.

UCC-SMART staff, dear Ursula, Ank, Lies, Loes, Yvonne, Hetty, Baukje, Angela and Rutger, thank you for the nice cooperation with SMART and for all your hard work for the UCC-SMART study.

I thank the highly learned opponents of the review committee, prof. dr. M. Bots, prof. dr. M. Verhaar, prof. dr. F.H. Rutten, prof. dr. R. Gansevoort and prof. dr. M. Nieuwdorp for their time and willingness to review this thesis. I look forward to discussing my thesis with you.

Prof. dr. Michiel Bots and prof. dr. Yvonne van der Schouw, thank you for your guidance and assessment of the research project during the master clinical epidemiology.

I would like to thank all co-authors for their invaluable inputs and fruitful collaborations that contributed to a large part of this PhD. Especially thanks to Sarah Wild, Björn Eliasson, Naveed Sattar, Emanuele Di Angelantonio,

Stephanie Read, Stephen Kaptoge and Lisa Pennells for the collaborations on the prediction models presented in this thesis and for the many meetings and discussions.

Thank you to all patients and participants from various cohorts and trials, both domestic and international. Your contributions are essential and without it this PhD would not have seen the light of day.

To the many peer-reviewers, thank you for the insightful and critical comments and feedback that helped improve the manuscripts even more.

Fellow Vascu researchers, I consider myself very lucky to land in such a great group! We really are a good team, helping and supporting each other and I wouldn't have missed you for anything! Thank you so much for all the good times; 'vrij-mi-bo's', weekends to Sevilla, Breukelen and Lisbon, many coffee sessions, mental support, word jokes (which were usually so bad that even I understood them), for helping me with the Dutch language and participating in all my crazy Danish traditions!

Tamar, true 'Vascu-mama', I don't know anyone who can work as efficiently once they actually do work! Your presence always made it a lot more pleasant, with your humor, good stories and small talk. Thank you for dragging me along for miles on a board through the water when I lost my paddle while SUP'ing in Breukelen. Also, your karaoke skills are enviable. Cilie, I really enjoyed working with you and have a lot of respect for how you managed to work through from early morning to late evening. I enjoy even more that you also ended up in the eastern suburbs of Utrecht and I think Berend and Lasse are going to become very good friends! Britt, my fellow vascu 'partner in crime', we always had really good talks about all the PhD ups and downs, but also all the other big and small things in life. I have a lot of respect for how hard you work and your perseverance, and at the same time you are just a fantastic person (also, I am grateful for your flexible backbone, this always made the 'out of control' borrels a lot more fun). Should you ever look for a side job, you do an excellent job as a fake Danish football supporter! Steven, our phenomenon, you really are! Not only are you prediction and - disproportionately - R-expert, you're also very helpful and I've immensely enjoyed all the collaborations at work, and of course all the pleasant moments outside work. With you it was never boring, and you also showed genuine compassion when you saw that things were not quite on the right

track. Maria, in the beginning you really were like a myth to me, all colleagues talked about "Maria de Winter" all the time while I had no idea who they were talking about. Then I met you, and I immediately understood why. I have a lot of respect for how much you manage to combine and at the same time you are super social. The 'koele kast' sessions were always a treat! I enjoyed all the chats, dinners, parties, get-togethers and running sessions! Eline, fellow epi master, without you the epi would have been a lot more boring. My excuses that you often had absolutely no use of me when you wanted to fully understand another mathematical formula. You and Maria have also taken guinea pigs to a whole new level for me. I admire how hard you work, your eye for detail, your empathy and your taste in wine (and music of course)! Internal medicine has gained a great asset with you. Pascal, you started in a weird time with lock-down etc., but after that we happily enjoyed your dry humor and your skills in writing reviews about hotels. Thank you for all your help and discussions on prediction matters. I don't know anyone who can work so long, so concentrated (without noise-cancelling!) in a room where people are more or less screaming. Marga, you too were a real addition to the Vascu! Always so sweet and thoughtful, you really think of everyone around you! Also, I don't know anyone who has so much structure, both at work and in life. Of course, you are also super social and always 'borrel'-ready! Nadia, super nice that you came to do a PhD after your research internship. Thanks for all the sociability at lunches, coffees and borrels. With your talent, you make it seem like doing a PhD is a walk in the park (even though I know it's not always like that). Iris, working with you was never boring! Your enthusiasm, openness and smile are contagious, and I have a lot of respect for how you tackle things and manage to get things done! Katrien, I thought I had pretty much mastered the Dutch language, but then you came to do a PhD at the Vascu and a whole new world of hilarious sayings opened up to me! You have an unbreakable work ethic and at the same time you are super social, fun and likable! Lukas, your baptism of fire was immediately a weekend away together with colleagues, and we have really had the pleasure of your energy, positivism and enthusiasm ever since! Respect for how you managed to set up such a difficult trial. Joris, we didn't work together for long, but I can already say that you are a huge asset to the Vascu! Packed with energy and a brain that works faster than most, you are going to do just fine. Milena, I didn't work with you much either, but I always enjoyed it! Infection people, Patrick, Jesper and Bianca, thank you too for all the nice moments over the past years.

Dutch friends, emigrating becomes a lot more fun and easy with so many nice people around you! Nicole, we met each other during my research-internship a couple of years ago. With the addition of motherhood, I've really found a lot of support in you and I cherish our friendship. Nina, fellow "expat-fell-in-love-with-a-Dutch-guy", I'm very thankful that we now both live in Utrecht, and I always enjoy our talks and times together, let there be many more to come! Maria, fellow Dane and football-supporter, amazing that you are also currently living in the surroundings of Utrecht (for now, that is). Marlous, from trim-hockey and 'avontuur-club', you really are a very nice and social person. I think you could be sitting at the North Pole and still make friends, you have really made my life in Utrecht a lot more fun. PNS/P1/plus the rest; Jochem and Job, you immediately welcomed me with open arms when I came to stay in your house for numerous weekends, thank you for that! Together with Floor, Anna, Wouter, Patrick, Lieke, Nick, Dorine, Daan and Tessa, I think you are a really nice group and I always enjoy our times together! Thank you for all your work on the house!

CP group, Marlous, Elske, Annemie, Ingrid, Janne, Roos, Lisette and the rest, becoming a mother and moving to Zeist would really have been a lot more difficult without you! With you I can always relate well and spar about everything; from big to small. Thank you for all the great coffee (with cake of course) and cocktail moments!

Mia, once in a while you meet a person and it just clicks - that's how it was with you! I've been so happy to spar with you over the last few years, both over PhD struggles, but also all other ups and downs. You are so strong, amazing, funny and caring, and I consider myself extremely lucky that we chose you as a roomie for our Dutch-inspired "rent-our-room-job-interview" at Nørrebro! Julia, from young and ignorant first-semester medical students at KU to doctors, diligent PhD students and mothers in each our country. I always enjoy when we talk and see each other. Emilie, you are always good at giving perspective and great to talk to, let's keep that up. Catherina, we've been through a lot together, from Hunsur, Copenhagen, Hammerfest, Utrecht and not to mention the hub of the world, aka Faaborg ;-) Even though we're both a bit of nomads, I know we'll keep in touch - that's how it is with pure-sisses! Folkeskolepigerne, Siri, Sarah, Anna-Louise and Cecilie, we've managed to keep in touch and even though there are often long gaps between seeing each other, I always

find it very natural and 'hyggeligt' when it happens. Anne, 'dying frog', a lot has happened in our lives since we met in a tipi in Canada! Your laughter is so contagious, and thankfully you are generous with it, and I really enjoy when we manage to get together. Camilla, from perfume production at Rørvangen (still can't believe our sales figures weren't higher) to house and child in Thorsager and Zeist, respectively. You have so much willpower, empathy and humor and I really appreciate our friendship. Gry and Louise, we all travelled on exchange before high school, young and naive, and straight afterwards became friends. Although life has gone in all sorts of different directions for us, we have known how to stick together and for that I am very grateful.

In-laws, how lucky I am to have you! Dear parents-in-law, Joop and Marieke, thank you for all the good times and trips over the past years. You are an indispensable support and are always there for us and I really appreciate that. You have created a family with a lot of love and warmth and I feel privileged to now be a part of it. Wisse, Esther, Dirk and Pannie, I always have a great time with you and we're extremely good at laughing together! Thank you very much for all the nice and 'gezellig' moments; birthdays, Sinterklaas, borrels, etc.! I am looking forward to many more great moments in the future!

Dearest family, thank you for your amazing support and backing me up through this PhD journey. I know it's not always optimal to have to cross borders to see each other, but nevertheless it makes it so much nicer when we do! We always have a great time when we are together and I am looking forward to many more pleasant moments in the future.

Mom, thank you for your constant support, big heart and enormous empathy. You have always supported me in everything I have taken on. When it all got a little too much, I always knew who to call. Dad, you have always been a source of incredible inspiration and a role model for me. Your drive, enthusiasm and 'go-getter' attitude are admirable and I have always learned so much from you. At the same time, you are an incredible support and father. Bettina, thank you for many nice moments, both in Aarhus and Utrecht!

Julia, the best little sister in the world, thank you for just being you. I really admire your humor, care, energy and resilience, and I'm insanely proud of you. Thank you so much for helping with the cover of the book! You and Sinas have really created a home with so much love and warmth. Sinas, thank you for your

calm nature and for always welcoming us with open arms. Teodor, amazing little nephew, with your zest for life, stubbornness and charm you will be able to achieve everything you set your mind to. I love being your aunt and watching you grow up. Future niece, I am so excited to meet you! Andreas, thank you for being the best little brother in the world. You are so wise to life and at the same time have an amazing (and sometimes a little dark) sense of humor. You are intelligent and at the same time so kind at heart, and whatever you set out to do, you just "wing it". You make your big sister so proud. Thanks for your help with so many figures, graphical abstracts, etc. in this PhD! Freja, your calm, funny and charming nature (and baked goods) are truly a wonderful addition to our family.

Dear Sef, where do I start? From "braaien" and wine-tours in South Africa to house, tree and baby in Zeist. Life with you is a great adventure and every day I am happy and grateful to have you beside me. Your support and optimism throughout my PhD journey were essential, and you always knew how to ground me when I had another little break-down over super-computers or rejected manuscripts. Your love, energy and openness are admirable and I am so proud of how you go about life. During my PhD period, there were multiple life-events; education, wedding, buying a house, becoming parents, which also made it a little bit stressful at times, but we always knew and managed to laugh together. You are an amazing husband and father and I love you very much.

Lasse, you've been with me during some pretty pivotal moments during this PhD. First inside my belly and then sitting in the baby carrier on my chest, bouncing on a yoga ball. You came, turned our world upside down, and I've never felt more love. You are such an amazing little man, so curious about life, will-powered, open and full of laughter. Someday you might find this book dusty on the bookshelf, and I hope you will be somewhat proud that your mother once wrote a book. I love you to the moon and back.

"Wherever there is love for medicine, there is love for humanity."
Hippocrates (460 B.C. - 370 B.C.)

Curriculum Vitae

Helena Bleken Østergaard was born on May 7th, 1990 in Aarhus, Denmark. After graduating from Risskov Gymnasium in 2010, she spent five months in Karnataka, India doing volunteer work teaching English and mathematics at a local school for tribal children. In 2011, she moved to Copenhagen to study medicine at the University of Copenhagen. During her Master's programme she spent five months in Cape Town, South Africa, for an internship in thoracic surgery and internal medicine. In her last year, she did a research internship at the Department of Internal Vascular Medicine under the supervision of Jan Westerink and Frank Visseren. She obtained her medical degree in 2018 and had her residency as a medical doctor at the department of acute medicine and department of nephrology at Aarhus University Hospital. Subsequently, she was given the opportunity to work as a research physician at the Department of Vascular Medicine, University Medical Center Utrecht under the supervision of Frank Visseren, Joep van der Leeuw and Jan Westerink, and she started working on this thesis in July 2019 (*'Individual prediction of cardiovascular and kidney outcomes in high risk patients'*). The PhD research was combined with the post-graduate master Clinical Epidemiology, from which she graduated in August 2021. Helena is currently working as a medical doctor in geriatrics and internal medicine at the 'Diakonessenhuis' in Utrecht and Zeist. Helena lives with her husband and son in Zeist, the Netherlands, and spends her free time being with family and friends, running, spinning, travelling, reading and visiting the ocean as often as possible.