Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500,000 patients with type 2 diabetes mellitus.

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Abstract

Importance: The effectiveness of lipid-lowering, blood pressure-lowering, and aspirin treatment for prevention of cardiovascular disease (CVD) differs between individuals with type 2 diabetes (T2DM).

Objectives: To develop and externally validate a Diabetes Lifetime-perspective prediction (DIAL) model, for individualising CVD prevention in people with T2DM by predicting reduction of 10-year CVD-risk and years gained without incident or recurrent myocardial infarction or stroke.

Design: The model was developed using a random 75% of people with T2DM registered in the Swedish National Diabetes Registry (NDR; n=292,024) between 2002 and 2012. Internal validation was performed using the remaining 25% of the Swedish NDR (n=97,342). External validation was performed using data on people with T2DM included in the ADVANCE, ACCORD, ASCOT and ALLHAT-LLT-trials, the SMART and EPIC-NL-cohorts, and the Scottish diabetes register, pooled by geographical region.

Setting: Primary care and hospital-based practice.

Participants: People with T2DM: 389,366 from Sweden, 167,731 from Scotland, 7,742 from other parts of Western-Europe, 2,142 from Eastern-Europe, 14,590 from North-America and 5,580 from Asia and Oceania.

Predictors: Age, sex, current smoking, duration of T2DM, insulin treatment, systolic blood pressure, body mass index, haemoglobin A1c, non-high-density lipoprotein cholesterol, estimated glomerular filtration rate, albuminuria, and history of CVD. Hazard ratios for treatment effects were derived from published meta-analyses.

Main Outcome(s) and Measure(s): CVD-events (vascular mortality, stroke or myocardial infarction), non-vascular mortality, and CVD-free survival derived from two complementary competing risk adjusted Cox proportional hazards functions. Predicted treatment effect in years gained without myocardial infarction, stroke, or death is defined as the difference in median survival with and without treatment.

Results: Predicted and observed CVD-free survival showed good agreement in all validation sets. The c-statistic for the prediction of CVD was 0.83 for internal and 0.64 to 0.65 for external validation.

Treatment effects in CVD-free life years gained can be predicted for individuals with T2DM using an interactive calculator.

Conclusions and Relevance: CVD-free life expectancy and effects of lifelong CVD prevention in terms of CVD-free life years gained can be accurately estimated for people with T2DM using readily available clinical characteristics. The prediction of individual-level treatment effect may facilitate personalised treatment and support informed decision-making and patients' motivation to comply with prescribed treatments.

Introduction

People with T2DM are at up to 2-fold increased risk for cardiovascular disease (CVD) compared to people without T2DM independently from other risk factors.[1] Estimated reductions in life expectancy and quality adjusted life years (QALYs) due to CVD are substantial in people with T2DM especially in people diagnosed with T2DM at young ages.[2 3] International guidelines on CVD prevention recommend lipid-lowering and blood pressure-lowering treatment to achieve cholesterol- and blood pressure targets. As treatment effects may vary greatly between people due to differences in baseline risk, a more individualised approach based on absolute individual CVD-risk should be considered.[4-8] In general, people with higher individual cardiovascular risk will benefit more in absolute terms from lipid-lowering or blood pressure lowering than people with a lower cardiovascular risk. As these treatments are usually used lifelong, it is important to take into account long-term CVD-risk in addition to shorter term risk such as five or 10 year risk as used in many risk scores.[9]

The use of CVD risk prediction models for people with T2DM, such as the UKPDS, ADVANCE, Fremantle, and New Zealand Diabetes risk scores has been recommended in various national guidelines.[10-22] Long-term CVD-risk and CVD-free life expectancy can also be estimated. The latter is the expected number of remaining life years without the occurrence of an incident or recurrent myocardial infarction or stroke, which may be more informative to patients and healthcare providers than an estimate of risk.[23-25] Most existing prediction models predict 5-year risks of CVD[12], however, in people under 50 years of age life expectancy is usually much longer than 5 years. The treatment goal may then be to prevent CVD later in life. As 5-year CVD-risk in younger people is nearly always low, the potential long-term benefit of preventive drug-treatment is frequently underestimated. This may lead to delays in prescribing effective interventions in younger people. As age is such an important risk factor for CVD the majority of older people are eligible for treatment. However, as older people are also at risk for other diseases and mortality from both vascular and non-vascular causes (i.e. competing risks), reductions in CVD-risk may not always result in life years gained. This decreased potential to benefit from preventive

treatment due to competing risks is not taken into account in existing risk models and may contribute to the over-estimation of the effect of preventive treatment in older people.[26 27]

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

Methods

Sources of data

The Swedish National Diabetes Registry (NDR) and the Scottish Care Information (SCI) –Diabetes database are population wide registers. The secondary Manifestation of ARTerial disease (SMART) study and European Prospective Investigation into Cancer-Netherlands (EPIC-NL) are prospective cohort studies and Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE), Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Lipid Lowering Trial component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) are randomised controlled trials, all including people with T2DM. Study details have been described elsewhere.[28-37] The prediction model was developed in the Swedish NDR and externally validated in the remaining datasets. Definitions of T2DM used in each study are provided in supplemental table 1. All use of registers data, cohort and trial studies were approved by institutional review boards and all participants gave written informed consent before taking part in the cohorts and trials.

Participants

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

Outcomes

CVD was defined as a non-fatal myocardial infarction, non-fatal stroke, or vascular mortality. In the Swedish NDR and the SCI –Diabetes database, this is based on linkage to cause of death registers and hospital discharge registers using ICD-10 codes (non-fatal myocardial infarction: ICD-10 code I21; non-fatal stroke ICD-10 code I61, I63, I64; vascular mortality: ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64). For all cohort and trial data, the endpoint definitions are described in supplemental table 1. There was blinding to randomisation group for assessment of outcomes in trial participants. Non-vascular mortality was defined as all deaths other than those with a cardiovascular cause identified in the above list.

Predictors

Predictors were predetermined based on existing diabetes risk scores and availability in routine clinical practice.[13-19 21] Baseline data for people registered in the Swedish NDR and SCI –Diabetes database were data collected in the first year after registration. In the other data sources, the baseline data were measured at study entrance prior to follow-up. Eleven predictors were selected; sex (female/male), current smoking (yes/no), systolic blood pressure (SBP in mmHg), body-mass index (BMI in kg/m^2), haemoglobin A1c (HbA1c in mmol/l), eGFR (ml/min), non-high-density lipoprotein cholesterol (non-HDLc in mmol/l), albuminuria (no/micro/macro), duration of T2DM (years since diagnosis), insulin treatment (yes/no), history of CVD (yes/no). Micro-albuminuria was defined as an albumin/creatinine ratio 3-30 mg/mmol or urine-albumin 20-300mg/l, and macro-albuminuria was defined as an albumin/creatinine ratio

>30mg/mmol or urine-albumin >300mg/l. Prescriptions for preventive medication for CVD were not selected as a predictor, because this would interfere with the predictions of treatment effects of these medication. Socio economic status was not selected due to limited availability in many datasets.

Missing data

To account for missing data in the predictors, single imputation by predictive mean matching was used for each of the original cohorts separately (aregImpute in R, Hmisc package).[38] In the validation cohorts, some predictors were not recorded at all. For cohorts where HbA1c was not measured for any participant (i.e. ALLHAT and ASCOT), values were estimated using available plasma glucose levels assuming measured glucose levels to be average glucose levels (Glucose (mmol/l) = 1.59*HbA1c (%) – 2.59, thus HbA1c (%) = (Glucose (mmol/l)+2.59)/1.59).[39] For all other missing predictors in the validation dataset, data were imputed to the median value of the Swedish NDR. The number, proportions and type of missing data in each dataset are described in the supplemental methods.

Statistical analysis

Handling continuous predictors

Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. Log-linearity of the relationship between continuous predictors and the outcomes was tested with restricted cubic splines and transformations were applied when this improved model fit based on Akaike's Information Criterion.

Development of the lifetime model

A random sample of 75% of people from the Swedish NDR (n=292,024) was used as the development dataset. Using these data, we developed two complementary Fine and Gray competing risk adjusted Cox proportional hazard models with left truncation and right censoring: one for the prediction of CVD events using non-vascular mortality as the competing endpoint (i.e. model part A), and another for the prediction

of non-vascular mortality using CVD events as the competing endpoint (i.e. model part B). These statistical methods have been described in detail previously.[23 40] Briefly, age was used as the time-scale and therefore people in the development dataset contributed data to the survival model from their age at study entry until the time of an event or censoring, defined by the age at study exit. As a result, estimates derived from these models are not limited by follow-up time but by the age distribution of study participants. However, predictions are unstable where the number of people and number of events in a specific age group is limited. . The age-range was therefore limited to between 30 and 95 years (number of people <30 years: 2,045, number of people >95 years: 2,501) for estimation of CVD-free life expectancy. The two competing risk adjusted Cox proportional hazard functions were then recalibrated based on the incidence of CVD and incidence of non-vascular mortality using the expected versus observed ratio. The age-specific baseline survival for both Cox proportional hazard functions were centred for continuous variables (BMI of 30 kg/m^2, systolic blood pressure of 140 mmHg, non-HDLc of 3.8 mmol/l, HbA1c of 50 mmol/l, and eGFR of 80 ml/min) for practical reasons and to avoid rounding errors. The proportional hazards assumption was assessed by inspection of the correlation plots between scaled Schoenfeld residuals for the various predictors and age. Transformations and non-proportionality of predictors were described in the supplemental methods. Where interaction existed between a predictor and age, the HR for that predictor is shown for the median age of 65 years. The HR for transformed predictors is shown for the 75th percentile versus the 25th percentile. The sample size was more than sufficient by conventional assessment for prediction models with >1000 endpoints per variable.[41]

Predictions for individual persons

Calculations of CVD-free life expectancy (i.e. median survival without incident or recurrent myocardial infarction, stroke, or vascular death) were based on life-tables with one-year time intervals. An example of such a life-table for an individual person is shown in supplemental table 2. Starting at the current age of an individual with T2DM, the risk of having a CVD-event (a_t) and the risk of dying from non-vascular causes (b_t) were predicted for each future life-year. Next, the cumulative CVD-free survival ($Surv_{t+1}$) was

calculated by multiplying the survival probability at the beginning of each life-year ($Surv_t$) by the CVD-free survival probability during that year ($Surv_t$ - a_t - b_t). Obviously the cumulative CVD-free survival started at 100% at the current age of a person. This process was repeated until the maximum age of 95 years. CVD-free life expectancy of an individual was defined as the median survival without myocardial infarction or stroke or death, which was the age where the estimated cumulative survival drops below 50%. Similarly, 10-year CVD-risk was calculated by summation of the predicted cause-specific CVD risk in the first 10 years from a person's current age onwards. The cause-specific CVD-risk was obtained by multiplication of the chance of survival without a CVD-event at the beginning of each year ($Surv_t$) and the risk of having a CVD-event (a_t) during that year.

Model validation

Internal validation of the lifetime model was performed in the remaining random sample of 25% of people in the Swedish NDR (n=97,342) for 10 year risk predictions. External validation was performed using pooled cohorts based on geographical origin of people originating from the SCI –Diabetes database, SMART, EPIC-NL, ACCORD, ADVANCE, ASCOT, and ALLHAT cohorts. The selected regions were continents, with a subdivision for Europe. Five-year risks were predicted for Western-Europe, Eastern-Europe, North-America, Asia and Oceania, and 10 year risks for Scotland. Although Scotland is part of Western-Europe, this was a separate validation dataset, due to both the longer follow-up and the population-based nature of the dataset. In addition, the comparatively large number of people in Scotland's diabetes register overwhelmed the number of people in other countries in Western-Europe. Supplemental table 3 presents the number of people allocated from each original cohort to each pooled geographical cohort and the number of events occurred in each pooled cohort.

Goodness of fit was assessed for CVD-free survival, vascular event, and non-vascular mortality models separately using calibration plots.[42] The models were recalibrated based on the incidence of CVD and incidence of non-vascular mortality using the expected versus observed ratio in all separate datasets. The

logarithm of the expected versus observed ratio was subtracted from the linear predictor. Discrimination was quantified using c-statistics.

Prediction of individual treatment effect

We combined competing risk adjusted Cox proportional hazard function A for prediction of CVD with hazard ratios from randomised trials or meta-analyses to predict the individual treatment effect and lifetime benefit of treatment. This method of calculating projected individual treatment effects has previously been applied by the American Heart Association and American College of Cardiology in their 'ASCVD risk estimator plus' based on the Pooled Cohort Equations for primary prevention.[43] By using life-tables, any gains in CVD-free survival will automatically be adjusted for competing risks by increasing the time at risk for non-CVD mortality. In this study, we derived estimates of the effect of lipid-lowering, blood pressure-lowering, and aspirin treatment.[44-49] The hazard ratios for different medications used to estimate treatment effects are described in the supplemental methods. The lifetime benefit of treatment for an individual person was calculated as the difference between the predicted median CVD-free life expectancy with and without treatment. Similarly, 10-year absolute CVD-risk reduction for individual persons were estimated by calculating the difference between the predicted 10-year CVD-risk with and without treatment.

Results

The selection of development and validation cohorts from the Swedish NDR is illustrated in figure 1. Of the 292,024 people in the derivation cohort, 21,910 (8%) experienced a CVD event and 45,479 (16%) died of non-vascular causes during follow-up. Of the 97,342 people forming the interval validation dataset, 7,352 (8%) experienced a CVD event and 15,093 (16%) died of non-cardiovascular causes during follow-up. Baseline characteristics of all other study populations are described pooled by geographical origin in table 1, and stratified by original study cohort in supplemental table 4.

Development of the DIAL model

The calculation formulae including the coefficients of the Cox proportional hazard functions, age-specific baseline survivals, and HRs of intended treatment of the model are provided in supplemental table 5 and 6. The hazard ratios (HRs) for Cox proportional hazard functions A and B of the DIAL model are shown in table 2. Cox proportional hazard function B was recalibrated in the internal validation based on the expected versus observed ratio of 0.81 for incidence of non-vascular mortality.

Internal validation

After recalibration for differences in predicted and observed non-vascular death rates predicted 10-year risk for CVD and all-cause mortality (CVD risk and non-vascular mortality risk combined) showed good agreement with the 10-year observed risk in the development dataset (figure 2). Discrimination of the estimated 10-year CVD risk was 0.83 (95% CI 0.83 to 0.84), discrimination of 10-year non-vascular mortality risk was 0.72 (0.72-0.73) and 10-year risk for CVD and all-cause mortality was 0.77 (0.76-0.77).

External validation

The predicted 5-year risk for CVD and all-cause mortality showed good agreement with the observed 5-year CVD-free survival in Western-Europe, Eastern-Europe, North-America and Asia and Oceania (figure 3). Discrimination of the estimated 5-year CVD-risk was between 0.64 and 0.65. C-statistics for 5-year non-vascular mortality risk (range 0.59-0.67) and 5-year risk for CVD and all-cause mortality (range 0.64-0.69) are shown in supplemental table 7. CVD event rates were higher in the Scottish Care Information –Diabetes database (17 per 1000 people per year) compared to the Swedish NDR (11 per 1000 people per year). Recalibration was necessary to take differences in CVD-risk between high and low risk countries, into account. The Cox proportional hazard functions A and B were updated for differences in average predicted and observed event rates in the Scottish diabetes registry with an expected versus observed ratio of 0.17 and 1.34 respectively. After updating the model for differences in predicted and

observed event rates, external validation in Scottish data showed good agreement between the predicted and observed 10-year risk for CVD and all-cause mortality (figure 3). Discrimination of 10-year CVD-risk was 0.64 (95% CI 0.64 to 0.65; supplemental table 7).

Individual lifetime estimates and treatment effects for people with T2DM

Patient characteristics can be entered in the decision support tool together with the intended and current treatment to estimate individual CVD-free survival and CVD-free life years gained of preventive treatment (Appendix: Excel calculator). An example of the differences in expected treatment effect between individuals derived from the decision support tool is that a combination therapy of simvastatin 40mg, ezetimibe 10mg and systolic blood pressure-lowering to 140mmHg, conferred between 0.04 and 12.5 years gained without CVD in people enrolled in the Swedish NDR. People who were 78 years or older, without a history of vascular disease, systolic blood pressure of <140mmHg, and LDL-c of <3.0 mmol/L at baseline gained <0.05 CVD-free years. People aged between 55 and 70 years old, with a history of vascular disease, systolic blood pressure >160 mmHg and LDL-c >3.0 mmol/L at baseline had a lifetime benefit of>10 years. Figure 4 illustrates the results of applying the decision support tool to three additional individual examples of people with T2DM with differing baseline characteristics.

Discussion

In this study we have developed and validated the DIAL model to predict CVD-free life expectancy and 10-year CVD risk in people with T2DM using widely available patient characteristics. This is the first model for people with T2DM that predicts 10-year CVD risk, CVD-free life expectancy, and lifetime benefit in CVD-free life years gained. This enables the identification of likely long-term benefit of preventive treatment for people with T2DM. By taking into account the competing risk of non-CVD mortality, the model can reliably estimate treatment effects. Therefore, the DIAL-model offers additional functionality compared to existing risk scores for people with T2DM (i.e. mainly 5-year absolute risk for people with T2DM) that tend to underestimate risk and benefits of treatment in younger people and

overestimate risk and benefits in older people.[13-19 21] Increasing incidence of T2DM in younger people and the marked increases in prevalence of type 2 diabetes in elderly people means that assessing CVD risk accurately and treating it appropriately is essential for individuals, health systems and societies.

We have validated the DIAL model in populations from different continents and have demonstrated that, after re-calibration, it has the potential to support medical decision-making for CVD prevention in people with T2DM in diverse populations. The discriminative ability of the model was moderate in each external validation dataset consistent with external validation of previous risk scores. For example validation of the ADVANCE risk score in EPIC-NL and SMART gave C-statistics of 0.62 and 0.68 respectively.[22] The cardiovascular event rate was higher in Scotland compared to Sweden, due to differences in multiple factors not taken into consideration in the model, including lifestyle differences. Recalibration of the DIAL model using the expected/observed ratios of incidence of CVD and mortality allows it to be adapted for use in populations with varying levels of CVD risk. Users can choose to apply either the CVD event rate for Sweden (11/1000 people per year) or for Scotland (17/1000 people per year) whichever is more appropriate for their population.

Several studies have convincingly demonstrated the advantage of lifetime prediction compared to traditional 5-year or 10-year risk predictions. A microsimulation model based on 5-year follow-up of the Rotterdam Study showed that the gain in total CVD-free life expectancy increased as risk factor levels increased. The gain in total CVD-free expectancy decreased with advancing age, whereas 10-year risk for CVD mortality, and therefore 10-year risk reduction, increased with age.[50] In other primary prevention settings, the gains from preventive therapy for CVD have been largest in younger people with high lifetime risk for CVD due to high risk factor levels.[23 24 51] For example, smoking cessation at age 60, 50, 40, or 30 years resulted in about 3, 6, 9, and 10 years of life years gained respectively. This indicates that the highest lifetime benefit can be gained by reducing risk factors early in life, ideally with lifestyle interventions but, if necessary, with drug treatment.[52] We illustrate this with our model in figure 3. A younger patient with high risk factor levels (Patient A) has the potential to benefit more from preventive

therapy on the long term compared to an older patient with lower risk factor levels (Patient C), despite the fact that 10-year absolute risk reduction is higher for the older patient in this example.

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

Using the concept of predicting lifetime benefit for making treatment decisions will result in changing characteristics of people eligible for treatment, towards higher proportions of younger people with higher risk factor levels (figure 4). This group of people need to be treated over a longer period of time resulting in higher treatment costs. It is not clear whether stopping treatment in older people would offset these costs and health economic analyses are required to investigate and to establish appropriate thresholds of minimum gain in life-years free of CVD

The strengths of this study include the use of a large number of people from diverse cohorts. Since the Swedish and SCI –Diabetes database are registries with information for over 90% of people with T2DM in both countries, there is limited selection of people with T2DM, in contrast to trial populations.[53] Therefore, these registries are close to true representations of their populations and this increases the generalisability of the DIAL-model to clinical practice. Extensive validation of the DIAL model in large and diverse populations supports the use of the DIAL-model in people with T2DM without chronic kidney disease (eGFR <30) or metastatic cancer in different parts of the world. Also, validation in the population based SCI –Diabetes database made it possible to adapt the model for use in populations with high and low CVD event rates.

Some limitations of the DIAL model should be considered. Although our model can guide the decision to start treatment for the prevention of CVD, it must be emphasised that there are other reasons for people with T2DM to start preventive therapy (e.g. prevention of neuropathy, retinopathy, diabetic nephropathy, or foot ulcers). The DIAL-model predictions do not incorporate these effects and may, therefore, underestimate the total treatment benefits. In addition, some people use preventive medication for other indications. For example, lipid lowering drugs are also used for monogenetic dyslipidaemias, antihypertensive drugs are used to reduce progression of aneurysms, and diuretics are used for heart failure. The DIAL-score may not be applicable to people with such co-morbidities. Additional risk factors such as socio-economic status, coronary calcium scores and ethnicity have not been incorporated in the model and may have improved performance. However, addition of more risk factors to prediction models generally only leads to minor improvements model performance.[54] Finally, the initial and most effective approaches to primary and secondary prevention of T2DM are lifestyle changes, such as smoking cessation or avoidance, sufficient physical activity, healthy diet and, where appropriate, weight loss. Clearly prediction of effects of lifestyle interventions would be valuable. However, it is currently not feasible to include lifestyle factors in prediction models given the lack of robust estimates of the effect size for lifestyle interventions from randomised controlled trials.

Other limitations of the methods used to develop and validate the DIAL model, and to estimate treatment effects should be acknowledged. Baseline predictors such as duration of T2DM, albuminuria, insulin treatment, and HbA1c were missing for some people within the validation data. The use of median, surrogate, and assumed values for these predictors could lead to the underestimation of the accuracy of the model if all data were available. However such data are often missing in clinical practice and prediction tools need to have alternative approaches available for them to be useful in the real world. Second, validation could only be performed for 10-year and 5-year predictions due to the limited follow-up in the included cohorts and trials. Lifetime estimates often go beyond 10-year predictions, and require the assumption that rates will be similar for a current 40 year old in 40 years' time to those of an 80 year old today. This is a major assumption but previous studies have shown that lifetime estimates based on

the methods we used appear to apply for a survival of up to 17 years.[23] Nevertheless, longer-term validation would be preferable and will be possible as follow up data accrue in Sweden and Scotland. Third, a 5-10% overestimation of predicted risk of CVD and mortality combined was observed in people in the highest decile of risk in most external validation datasets. However, in clinical practice, this may not be too problematic, since these people are at high risk anyway and the overestimation does not result in misclassification or incorrect treatment decisions. Furthermore, possible changes in risk factor levels over time were not taken into account. For example, blood pressure and cholesterol were assumed to remain stable over time. Also, the lifetime benefits are calculated assuming immediate, lifelong, successful (i.e. targets reached) and uninterrupted treatment from their current age onwards. Therefore, re-evaluation of CVD-free survival and treatment effects after 5 to 10 years is advised based on our validation to ensure valid predictions to guide treatment decisions.

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

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GB, SG, FV, SW, SF, ASv, YG, SR, BE, and JD contributed to the conception, design, analyses, and interpretation of the work.

GB, FV, YG, and JD contributed to data acquisition (SMART-cohort)

SG, SF, ASv, and BE contributed to data acquisition (Swedish NDR)

SW and SR contributed to data acquisition (SCI –Diabetes database)

JC and MW contributed to data acquisition (ADVANCE-trial)

BD and SP contributed to data acquisition (ALLHAT)

NP and AG contributed to data acquisition (ASCOT)

ASp and YS contributed to data acquisition (EPIC-NL)

All authors drafted or critically revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Licence statement

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

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

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

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

	Cox proportional hazard function A (vascular events)	**Cox proportional hazard function B (non-vascular mortality)**
	HR (95% CI)	**HR (95% CI)**
Male sex*	0.91 (0.88 - 0.94)*	0.89 (0.87 - 0.91)*
Current smoking*	1.04 (1.00 - 1.09)*	1.46 (1.43 - 1.50)*
Duration of T2DM (years)	1.02 (1.01 - 1.02)	1.01 (1.01 - 1.01)
Insulin therapy*	1.02 (0.98 - 1.06)*	1.04 (1.01 - 1.07)*
Systolic blood pressure (mmHg) **	1.06 (0.95 - 1.17)**	1.01 (0.93 - 1.10)**
Body mass index (kg/m²)**	0.88 (0.81 - 0.97)**	0.89 (0.84 - 0.95)**
HbA1c (mmol/l) **	1.15 (1.05 - 1.26)**	1.00 (1.00 - 1.00)
non-HDL-c (mmol/l) **	1.16 (1.10 - 1.23)**	0.96 (0.92 - 1.00)**
eGFR (ml/min/1.73m²)**	0.64 (0.60 - 0.69)**	0.99 (0.99 - 0.99)
Micro-albuminuria	1.18 (1.14 - 1.22)	1.17 (1.14 - 1.20)
Macro-albuminuria	1.23 (1.18 - 1.28)	1.24 (1.20 - 1.28)
History of cardiovascular disease	9.99 (9.63 - 10.36)*	0.25 (0.24 - 0.26)*

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

** Transformed variables. Hazard ratios are shown for the 75 percentile versus the 25 percentile (Systolic blood pressure: 150 mmHg vs 128 mmHg; Body mass index: 33 kg/m² vs 26 kg/m²; HbA1c: 59 mmol/l vs 44 mmol/l; eGFR: 96 ml/min vs 68 ml/min; Non-HDLc: 4.5 mmol/l vs 3.0 mmol/l).

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

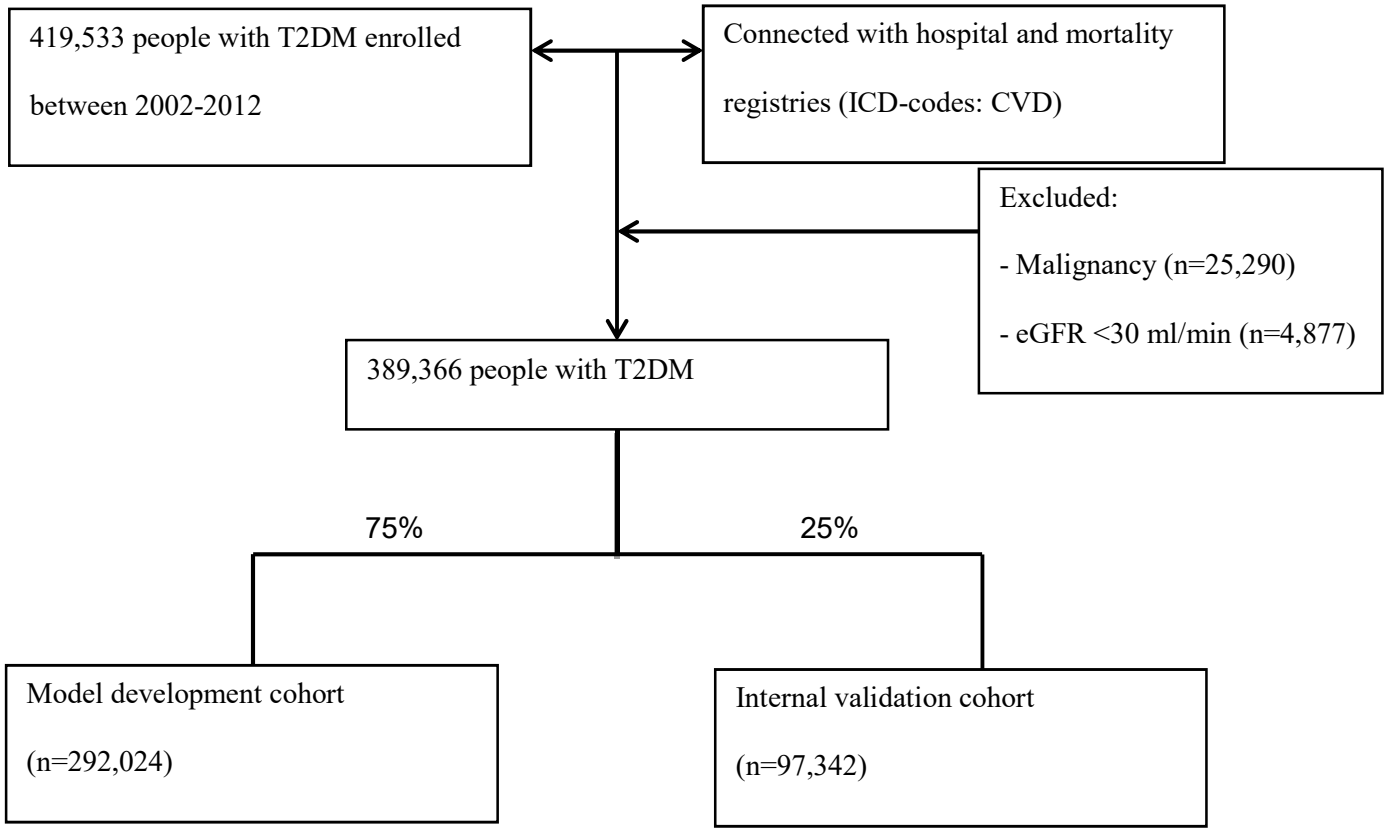
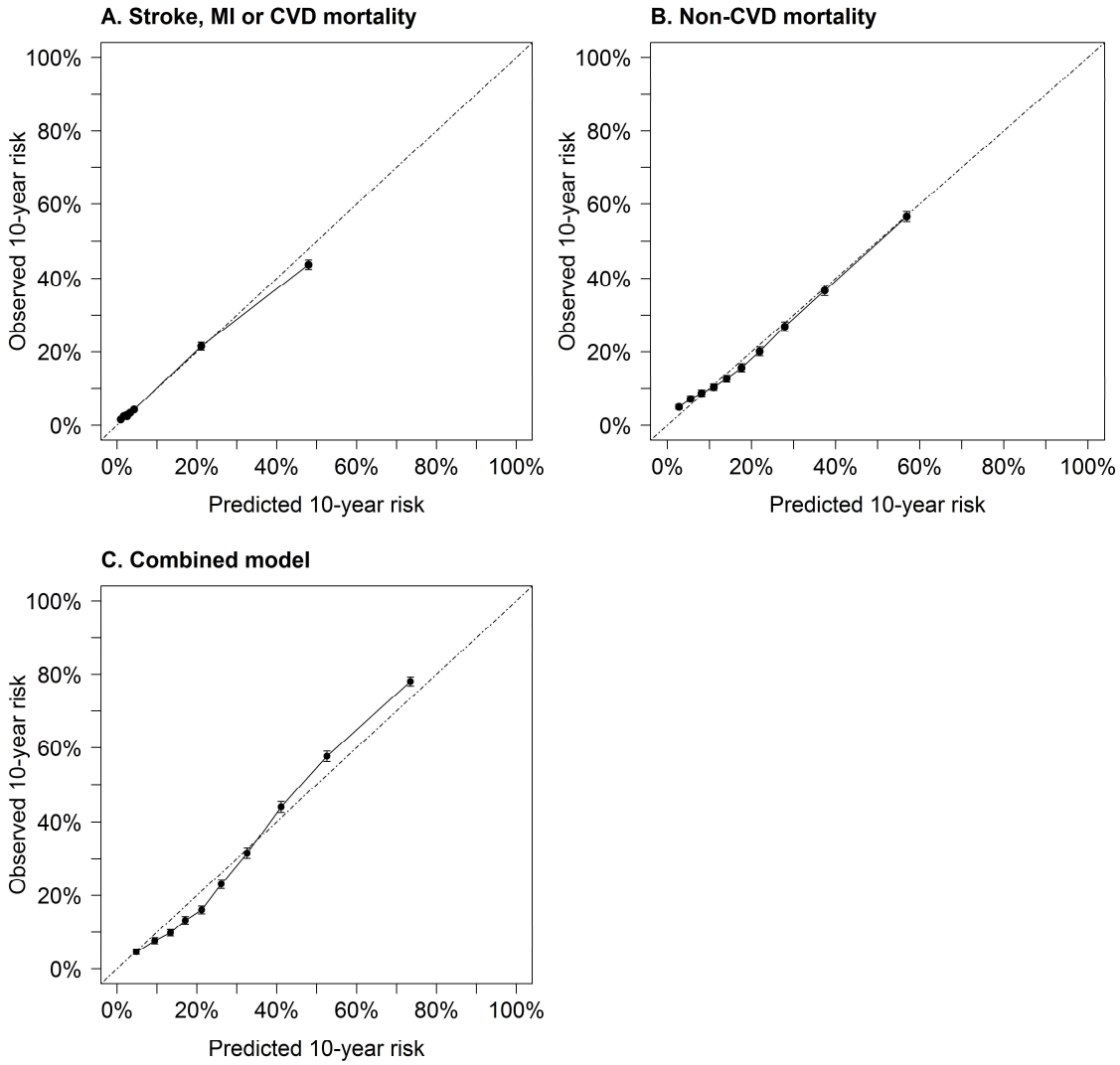


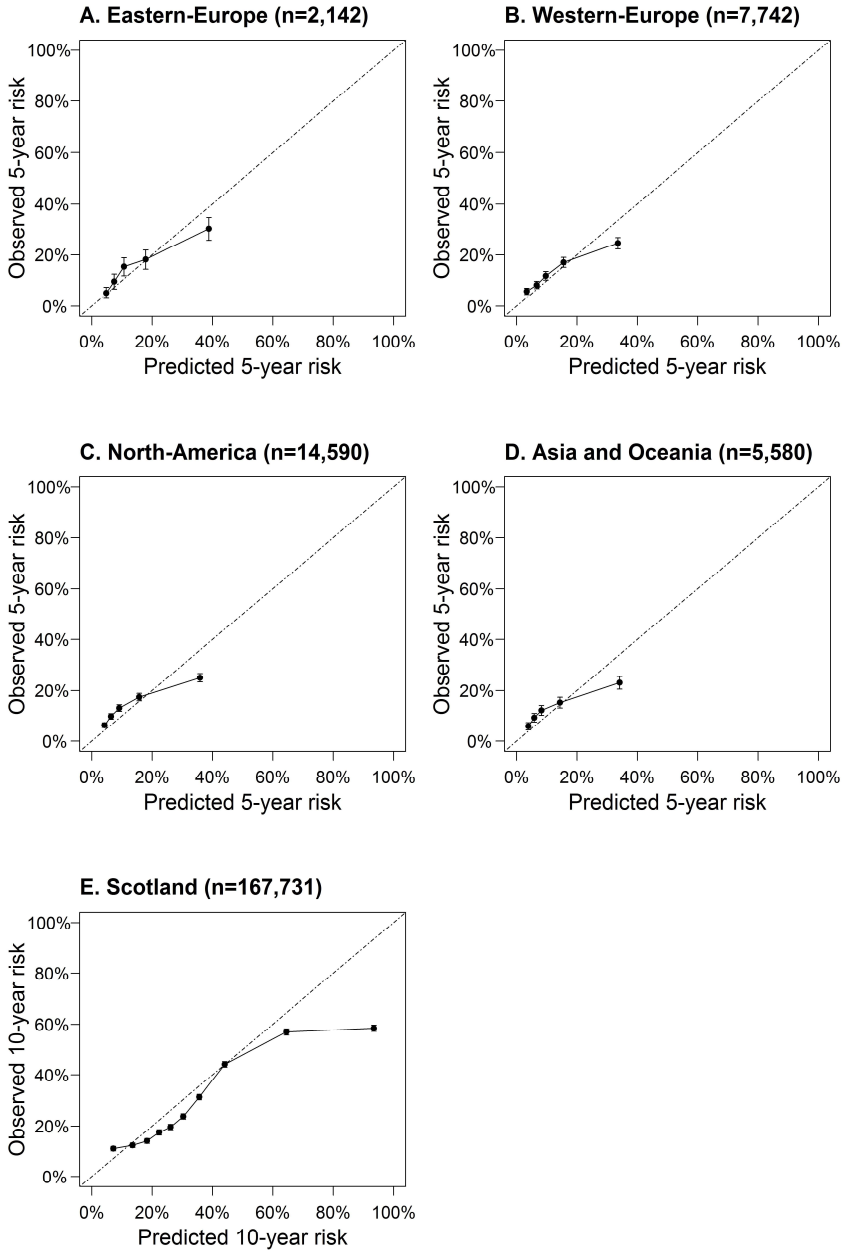
Figure 2: Internal validation (n=97,342) of the predicted 10-year risk.



A) Predicted versus observed 10-year risk of the cause-specific CVD risk (Cox proportional hazard function A). B) Predicted versus observed 10-year risk of the non-vascular mortality risk (Cox proportional hazard function B; after recalibration). C). Predicted versus observed 10-year risk of CVD and all-cause mortality (DIAL-model).

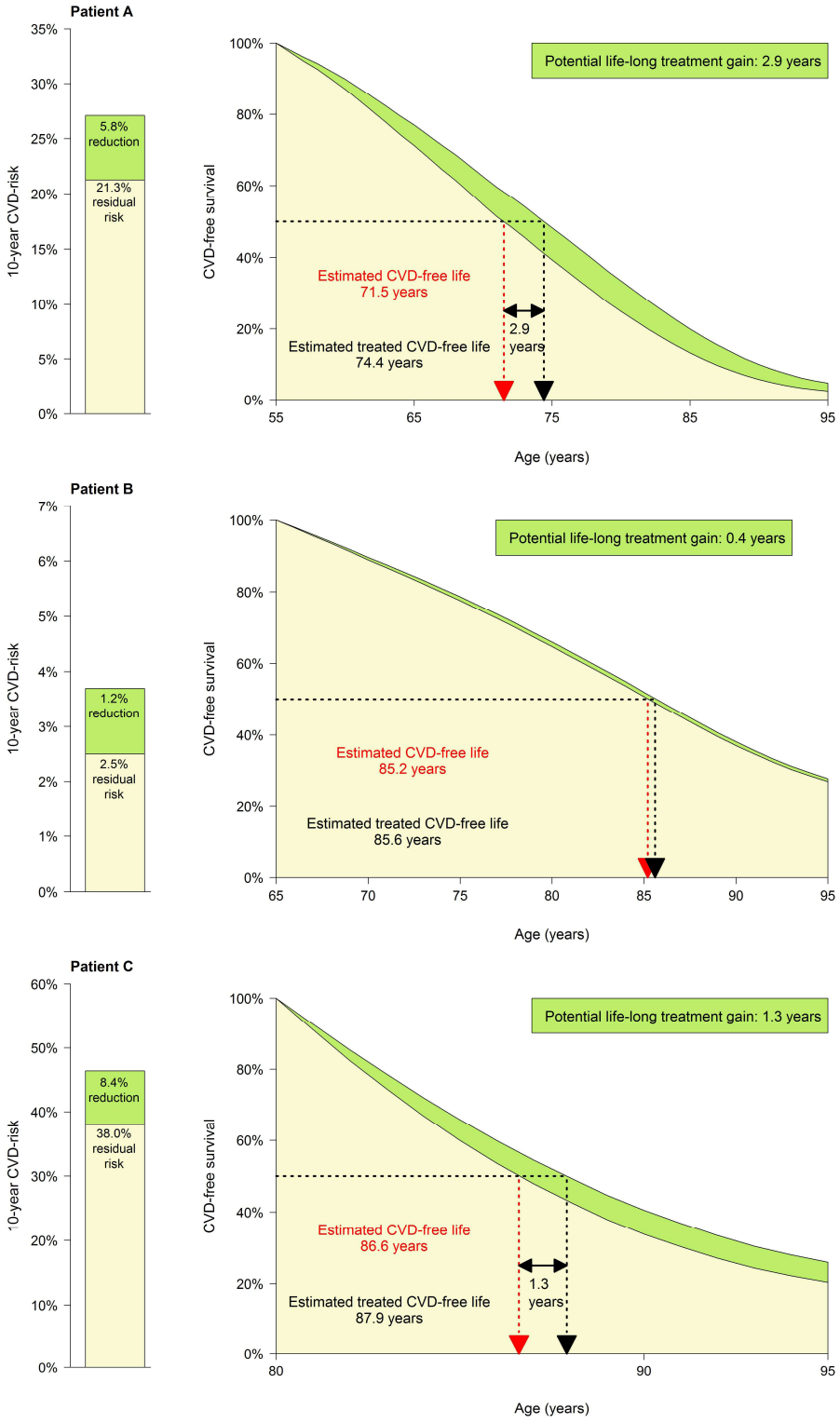
Dots represent mean risks with 95% confidence intervals of people grouped by deciles of predicted risk.

Figure 3: Calibration plots in external dataset pooled by geographical region.



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

Figure 4: Examples of treatment effects of simvastatin 40 mg versus no treatment in people with different characteristics.



	Patient A	**Patient B**	**Patient C**
Age (years)	55	65	80
Sex	male	female	female
Smoking status	no	no	no
Duration of T2DM (y)	5	5	10
Insulin therapy	no	no	no
Systolic blood pressure (mmHg)	150	145	140
Body-mass index (kg/m²)	27	27	30
HbA1c (mmol/mol)	55	55	55
Non-HDL-c (mmol/l)	5	6	5
eGFR (ml/min/1.73m²)	70	70	60
Albuminuria	no	no	micro-albuminuria
History of CVD	yes	no	yes
LDL-c (mmol/l)	3.0	4.5	3.0
10 year-risk (%)	27.1	3.7	46.4
10-year ARR (%)	5.8	1.2	8.4
10-year NNT	17	83	12
CVD-free survival (y)	71.5	85.2	86.6
Lifetime gain free of CVD (y)	2.9	0.4	1.3

Supplemental material

Supplemental methods:

Missing data.

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

In EPIC-NL, ASCOT, and ALLHAT-LLT, data was not available for duration of T2DM (ASCOT, ALLHAT-LLT), albuminuria (EPIC-NL, ALLHAT-LLT), treatment of T2DM with insulin (ASCOT, ALLHAT-LLT) and HbA1c. For validation, duration of T2DM, treatment with insulin, and albuminuria were imputed by the median values in Swedish NDR (i.e. 2.0 years duration of T2DM, 17% insulin treatment, 15% micro-albuminuria, and 7% macro-albuminuria).

Transformations and non-proportionality of predictors.

Quadratic transformation of continuous predictors was applied for BMI, SBP, HbA1c, non-HDL-c and eGFR for the CVD Cox proportional hazard function and for BMI, SBP, and BMI for the non-vascular mortality Cox proportional hazard function. Non-proportionality was observed for sex, smoking, history

of CVD and treatment with insulin, in both parts of the Cox proportional hazard functions (i.e. for CVD and non-vascular mortality). These predictors are of increasing or decreasing importance with increasing age. Therefore, interactions with these predictors and age were included in the model. Supplemental figure 1 (CVD) and supplemental figure 2 (non-vascular mortality) visualize the HRs of transformed predictors and HRs of predictors depending on age.

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

Lipid-lowering treatment:

The effect of lipid-lowering treatment on CVD depends on estimated reduction in low-density lipoprotein cholesterol (LDLc) compared to baseline. A reduction of 1 mmol/l LDLc is related to a hazard ratio of 0.78.[44 45] The percentage decrease of baseline LDLc for different statins and/or ezetimibe for people with T2DM are described in meta-analyses.[47 48] The individual expected relative risk reduction of CVD is calculated by $0.78^{\text{LDL-reduction in mmol/l}}$, where LDL-reduction in mmol/l is defined as
Baseline LDL-c multiplied by the expected percentage LDL-c reduction due to intended treatment.

Blood pressure-lowering treatment:

The effect of blood pressure-lowering treatment is estimated as a hazard ratio of 0.74 per 10 mmHg for people with T2DM with a baseline blood pressure of 140mmHg or higher.[46] There is no relative risk reduction assumed of lowering blood pressure under 140 mmHg.[49]

The individual expected relative risk reduction of CVD is calculated by $0.74^{(\text{Blood pressure reduction in mmHg}/10)}$, where blood pressure reduction in mmHg is the blood pressure of the patient minus the target blood pressure. This only applies for people with a blood pressure above 140 mmHg. The hazard ratio for blood pressure changes under 140mmHg is assumed to be 1.

Aspirin treatment:

The effect of aspirin treatment on CVD differs between people with and without a history of CVD. The hazard ratio of aspirin treatment in people without a history of CVD is 0.88 and for patient with a history of CVD 0.81.[55 56]

Combined individualized treatment effects:

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

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

A. In- and exclusion criteria of the study populations

	Inclusion criteria	Exclusion criteria
Swedish NDR[32]	People aged 18 years or older with T2DM, registered between 2002 and 2012	
Scottish Care Information – Diabetes database	People aged 18 years or older with T2DM, registered between January 2004 and June 2016.	
SMART[36]	People aged 18-79 years with T2DM, included between 1996 and 2015.	-Terminal malignancy -Not independent in daily activities (Rankin scale >3) -Not sufficiently fluent in Dutch - Estimated glomerular filtration rate (eGFR) < 30 ml/min
EPIC-NL[28]	People originated from the MORGEN and PROSPECT cohort. PROSPECT is a prospective cohort study among women aged 49–70. The MORGEN cohort consists of a general population sample of men and women aged 20–59 years. People with a confirmed diagnosis of T2DM were eligible for this study.	- Estimated glomerular filtration rate (eGFR) < 30 ml/min
ACCORD[37]	Patient aged 40-79 with T2DM	- A medical condition likely to limit survival to <3 years or a malignancy other than nonmelanoma skin cancer within the past 2 years - Currently participating in another clinical trial - Estimated glomerular filtration rate (eGFR) < 30 ml/min
ADVANCE[34]	People aged 55 years and older with a diagnosis of T2DM at the age of 30 or older.	A definite indication for long-term insulin therapy. - Estimated glomerular filtration rate (eGFR) < 30 ml/min
ASCOT[30]	People aged 40-79 with T2DM and two other cardiovascular risk factors	Previous myocardial infarction, currently treated angina, heart failure, or a cerebrovascular event within the previous 3 months. - Estimated glomerular filtration rate (eGFR) < 30 ml/min
ALLHAT[33]	People aged 55 and older with T2DM	Symptomatic myocardial infarction or stroke within the past 6 months or diseases likely to lead to non-cardiovascular death over the course of the study - Estimated glomerular filtration rate (eGFR) < 30 ml/min

B. Definition of T2DM

Swedish NDR[32]	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.
SMART[36]	A referral diagnosis of T2DM, self-reported T2DM, a fasting serum glucose ≥7.0 mmol/L at inclusion with initiation of glucose lowering treatment within one year, or the use of oral anti-hyperglycemic agents or insulin at baseline. Participants with known type 1 diabetes mellitus were excluded.
EPIC-NL[28]	Diagnosis of T2DM was self-reported at baseline.
ACCORD[37]	1) Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/l. Casual was defined as any time of day without regard to time since last meal. The classic symptoms of T2DM include polyuria, polydipsia, and unexplained weight loss for ≥3 months. 2) Fasting plasma glucose ≥7.0 mmol/l. Fasting is defined as no caloric intake for at least 8 h for ≥3 months. 3) Stable diabetes therapy for >3 months. 4) An HbA1c level 7.5%-11% more than 3 months before randomization.
ADVANCE[34]	People diagnosed with non-insulin-dependent T2DM at age 30 years or older.
ASCOT[30]	1) Fasting plasma glucose ≥7 mmol/l and/or random glucose ≥11 mmol/l, 2) Self-reported T2DM and receiving dietary or drug therapy, or 3) Presence of both impaired fasting glucose (≥6 mmol/l) and glucosuria in absence of above two criteria.
ALLHAT[33]	History of treatment with insulin or oral hypoglycemic agents during the 2 years preceding randomization, a fasting baseline glucose level >7.8 mmol/l, or a non-fasting baseline glucose level >11.1 mmol/l.

C. Definition of endpoints.

Swedish NDR[32]	*Outcome evaluation:* All CVD and non-cardiovascular causes of death endpoints were retrieved by data linkage with the Swedish Cause of Death Register and the Hospital Discharge Register (National Board of Health and Welfare, Sweden). CVD was defined as a myocardial infarction, stroke or vascular mortality (ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64).
	Myocardial infarction: Hospitalization due to non-fatal myocardial infarction or cardiac arrest. ICD-10 codes: I21, I46.0, I46.1, I46.9.
	Stroke: Hospitalization due to non-fatal stroke. ICD-10 codes: I61,I63, I64
	Cardiovascular mortality: ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64.
Scottish Care Information – Diabetes database	*Outcome evaluation:* All CVD and non-cardiovascular causes of death endpoints were retrieved by data linkage with the National Records of Scotland death registrations and the national hospitalization register (Scottish Morbidity Record, SMR01). CVD was defined as a myocardial infarction, stroke or vascular mortality (ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64).
	Myocardial infarction: Hospitalization due to non-fatal myocardial infarction or cardiac arrest. ICD-10 codes: I21, I46.0, I46.1, I46.9.
	Stroke: Hospitalization due to non-fatal stroke. ICD-10 codes: I61,I63, I64
	Cardiovascular mortality: ICD-10 codes I20-I25, I46.0, I46.1, I46.9, I61, I63, and I64.
SMART[36]	*Outcome evaluation:* During follow-up, people were asked biannually to complete a standardized questionnaire on hospital admissions and outpatient clinic visits. If a vascular event was reported, hospital discharge letters and results of laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the treating specialist. All possible events were independently evaluated by three members of the endpoint committee, comprising physicians from different clinical departments.
	Myocardial infarction: Fatal and non-fatal myocardial infarction, characterized by at least two of the following criteria: 1. Chest pain for at least 20 minutes not disappearing after administration of nitrates 2. ST-elevation >1 mm in two following leads or a left bundle branch block on the ECG * 3. CK elevation of at least two times the normal value of CK and an MB-fraction >5% of the total CK
	Stroke: Relevant clinical features which have caused an increase in handicap of at least one grade on the modified Rankin scale, accompanied by a fresh infarct on a repeat CT scan.
	Cardiovascular mortality: -Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms or within 24 hours given convincing circumstantial evidence -Death from ischemic stroke -Death from congestive heart failure -Death from myocardial infarction -Death from rupture of abdominal aortic aneurysm -Vascular death from other cause, i.e. sepsis following stent placement
EPIC-NL[28]	*Outcome evaluation:* Vital status was identified using the municipal population register with a loss-to-follow-up of 2.6%. For participants who died, information on

	the cause of death was obtained from Statistics Netherlands. Morbidity data were provided by the national hospital discharge register (HDR). Causes of death and morbidity have been coded according to the Ninth Revision of the International Classification of Diseases (ICD-9) until 1996, and after that according to the Tenth Revision of the International Statistical Classification of Diseases (ICD-10).
	Myocardial infarction: Hospitalization due to non-fatal myocardial infarction or cardiac arrest. ICD-10 codes I20-I25, I46 or ICD-9 code 410
	Stroke: Hospitalization due to stroke. ICD-10 codes I60-I63, I65, G45 or ICD-9 codes 430, 431, 432, 433, 434, 435
	Cardiovascular mortality: ICD-10 codes I20-I25, I46, I60-I63, I65, R96, G45 and ICD-9 codes 410, 430, 431, 432, 433, 434, 435
ACCORD[37]	*Outcome evaluation:* Outcomes were adjudicated by a central committee whose members were unaware of study-group assignments on the basis of predefined criteria.
	Myocardial infarction: The diagnosis of MI is based on the occurrence of a compatible clinical syndrome associated with diagnostic elevation of cardiac enzymes (ie, an increase in troponin T or troponin I to a level indicating myonecrosis and/or an increase in creatine kinase–myocardial band to a level more than twice the upper limit of normal). Q-wave MI is defined as the development of new significant Q waves. Silent MI is diagnosed when new (compared with the previous 12-lead electrocardiogram) significant Q waves are detected by surveillance electrocardiography performed every 2 years and at study end in all participants.
	Stroke: Stroke is diagnosed by a focal neurologic deficit that lasts >24 hours, associated with evidence of brain infarction or hemorrhage by computed tomography, MRI, or autopsy.
	Cardiovascular mortality: Cardiovascular causes of death include fatal MI, congestive heart failure, documented arrhythmia, death after invasive cardiovascular interventions, death after noncardiovascular surgery, fatal stroke, unexpected death presumed to be due to ischemic CVD occurring <24 hours after the onset of symptoms, and death due to other vascular diseases (eg, pulmonary emboli, abdominal aortic aneurysm rupture).
ADVANCE[34]	*Outcome evaluation:* An Endpoint Adjudication Committee, masked to treatment allocation, reviewed source documentation for all individuals who had a suspected primary endpoint or who died during follow-up. Outcomes were coded according to the 10th revision of the International Classification of Diseases.
	Myocardial infarction: ICD-10 codes I20-I25, I46
	Stroke: ICD-10 codes I60-I63, I65, G45
	Cardiovascular mortality: ICD-10 codes I20-I25, I46, I60-I63, I65, R96, G45
ASCOT[30]	*Outcome evaluation:* Each possible study endpoint was reviewed by at least two members of an independent Endpoint Committee blinded tot the study treatments following standardized study criteria, definitions and algorithms.
	Myocardial infarction: Non-fatal (including silent) myocardial infarction
	Stroke: Any stroke
	Cardiovascular mortality: Death due to any cardiovascular disease (not further specified)
ALLHAT[33]	*Outcome evaluation:* The diagnosis of an endpoint was classified by the physician-investigator at the clinical site based on death certificates or hospital discharge summaries. For a random 10% subset of hospitalized (fatal and nonfatal) myocardial infarctions and strokes, the Clinical Trials Center will request more detailed information. For this subset, in hospital ECGs and enzyme levels (for myocardial

	infarctions), and neurologists' reports and computed tomography (CT) or magnetic resonance imaging (MRI) reports (for strokes) will be evaluated by the study Endpoints Committee and the accuracy of the discharge diagnoses assessed.
	Myocardial infarction: Non-fatal myocardial infarction based on hospital discharge summaries classified by the physician investigator.
	Stroke: Non-fatal stroke based on hospital discharge summaries classified by the physician investigator.
	Cardiovascular mortality: Any death classified by the physician-investigator as caused due to cardiovascular disease.

Supplemental table 2. Example of a life-table.

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

Life-table is of patient example A (figure 3), a 55-year old male, who does not smoke, T2DM since 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, no albuminuria, and a history of CVD. This patient has a median survival free of CVD of 71.5 years and a 10-year CVD-risk of 27.1%.

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

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

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

Follow-up years are shown as median (inter quartile range).

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

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

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

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

Vascular Cox proportional hazard function (A)

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

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

Non-vascular mortality Cox proportional hazard function (B)

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

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

¥ Age-specific baseline survivals are shown in Supplemental Table 6 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 supplemental methods

BMI: Body mass index in kg/m^2; SBP: Systolic blood pressure in mmHg; non-HDLc: non-high-density cholesterol in mmol/l; HbA1c: Hemoglobin A1c in mmol/l; eGFR: estimated glomerular filtration rate in ml/min.

Supplemental table 6. Age-specific baseline survivals.

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

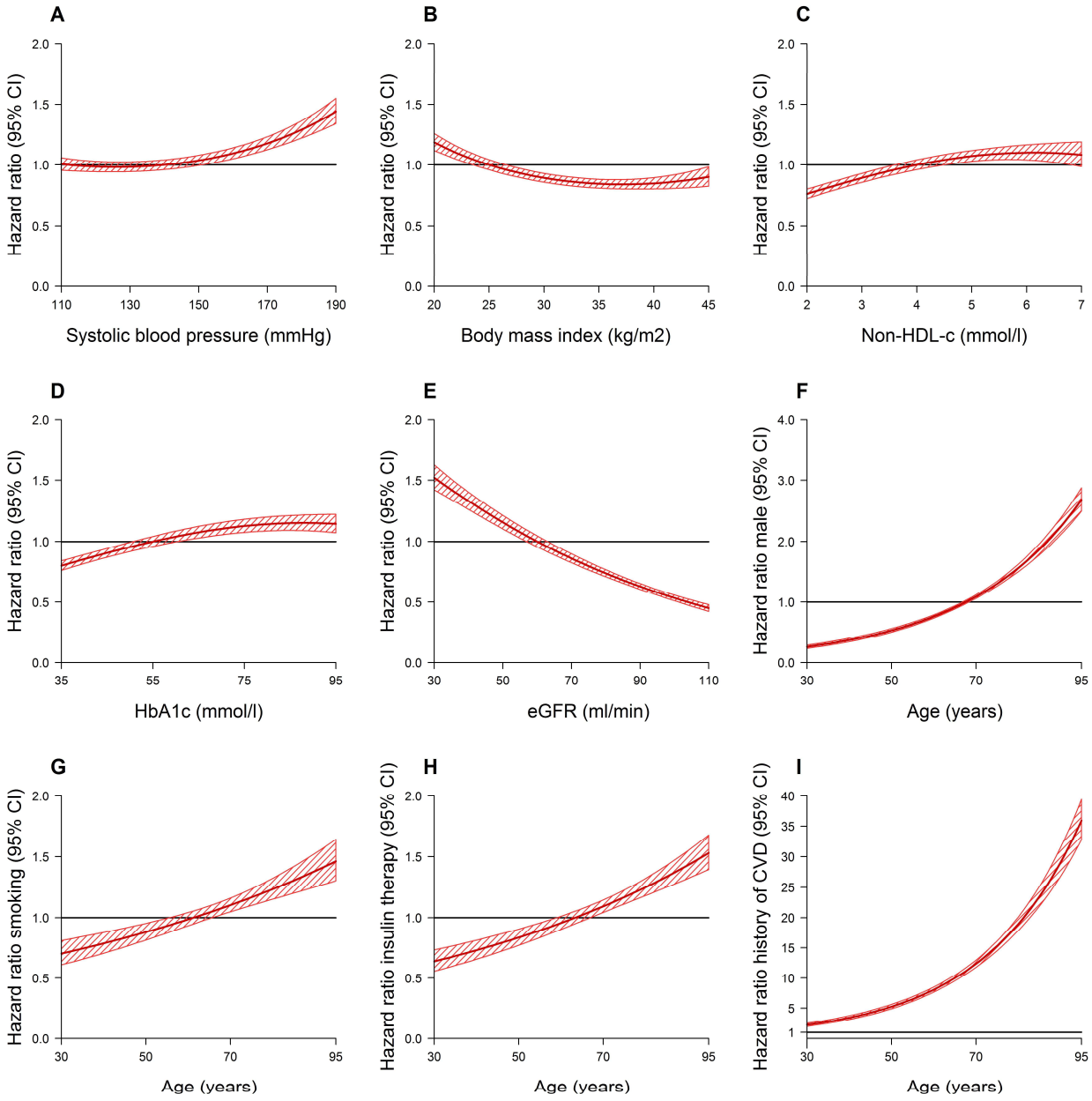
Age-specific baseline survivals for centered continues variables with a systolic blood pressure of 140 mmHg, BMI of 30 kg/m², HbA1c of 50 mmol/l, non-HDL-c of 3.8 mmol/l, and eGFR of 80 ml/min. *Based on Cox proportional hazard function A for cardiovascular disease. **Based on Cox proportional hazard function B for non- cardiovascular mortality

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

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

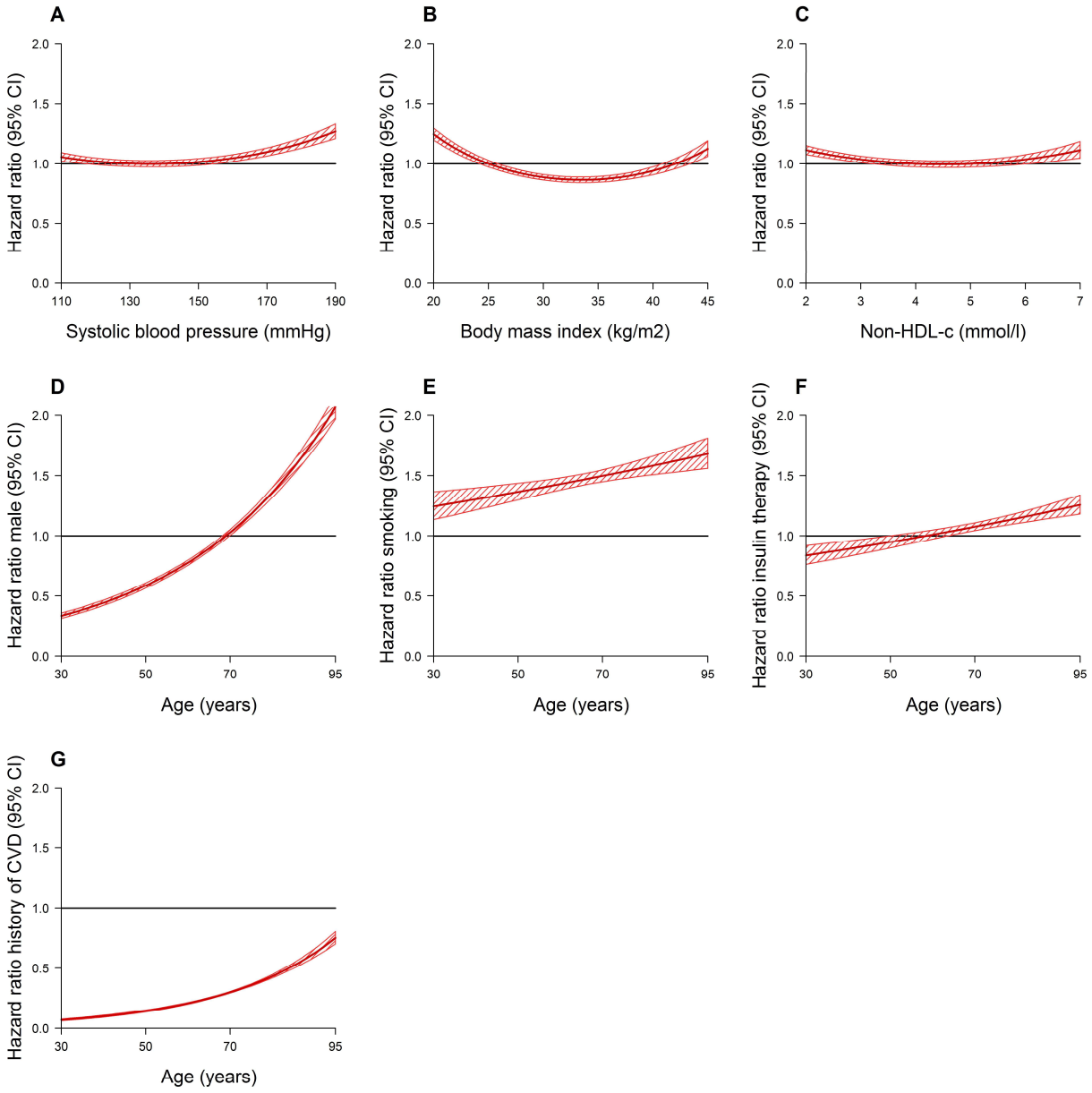
NDR: National Diabetes Registry. SCI: Scottish Care Information.

Supplemental figure 1. Hazard ratios and 95% CI for transformed and age-dependent variables of the cause-specific cumulative incidence model for cardiovascular disease.



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

Supplemental figure 2. Hazard ratios and 95% CI for transformed and age-dependent variables of the cause-specific cumulative incidence model for non-cardiovascular mortality.



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