












# 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)

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## Aims

The 2021 European Society of Cardiology 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 (interquartile range: 4.0–10.6 years) and comprising 63 824 CVD (including fatal CVD, non-fatal stroke and non-fatal myocardial infarction) events and 66 048 non-CVD mortality events. The model was systematically recalibrated to Europe's low- and moderate-risk regions 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% confidence interval (CI) 0.726–0.739] in CPRD and 0.700 (95% CI 0.691–0.709) in SCID.

## Conclusion

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.

## Keywords

Type 2 diabetes • cardiovascular disease • prediction

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## Introduction

Type 2 diabetes is a common chronic disease, with a worldwide prevalence of currently more than 6%.<sup>1</sup> Despite major advances in treatment, cardiovascular disease (CVD, defined as myocardial infarction, stroke, and fatal CVD) remains the main cause of morbidity and premature mortality in this population.<sup>2</sup> 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 2, 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.<sup>3</sup> 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,<sup>3</sup> the SMART2-risk score<sup>4</sup> (10-year risk) and SMART-REACH model<sup>5</sup> (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.<sup>6</sup> 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,<sup>3</sup> as these models include diabetes-specific variables and have been externally validated.<sup>7,8</sup>

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 30–85 years.<sup>8</sup> The model is available via the ESC CVD risk calculation app and as an interactive online calculator [www.U-Prevent.com](http://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 the 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<sup>9,10</sup> 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 the 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.<sup>11</sup> For this study, all participants registered in the Swedish NDR on 1 January 2008 as well as participants registering

up until 1 January 2018 were included. The baseline date was set as 1 January 2008 for those already registered in the Swedish NDR on this date and as the date of enrolment for those registered after this date. All baseline characteristics were determined at the baseline date, and if missing at this date, a time frame of inclusion of measurements of 2 years prior and 6 months after baseline was allowed (see [Supplementary material online, Figure S1](#)).

For external validation, we used the Scottish Care Information—Diabetes (SCID) database<sup>12</sup> ( $n = 143\,042$ ) and the Clinical Practice Research Datalink (CPRD) for England<sup>13</sup> ( $n = 72\,215$ ). 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-centre 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.<sup>12</sup> 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 are 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 1 June 2008 with risk factors recorded nearest to this date, including during the prior 2 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 30–85 years were included. The definition of Type 2 diabetes diagnosis in all data sources can be found in [Supplementary material online, Table S1](#).

### 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),<sup>14</sup> 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 > 30 mg/mmol for severe albuminuria<sup>15</sup>), body mass index ( $\text{kg/m}^2$ ), 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,<sup>10</sup> therefore interactions with baseline age for all predictors were added. To assess the association of continuous predictors with outcome variables, a 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 non-fatal myocardial infarction, non-fatal 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 (see [Supplementary material, Table S2](#)), 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 the outcome (function A) and another for non-CVD mortality as the 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 material online, 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, the lifetime risk of CVD and non-CVD mortality was estimated. This was done by adapting previously validated lifetable methods.<sup>16</sup> 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. The 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 online](#).

## Geographical recalibration

The DIAL2 model was systematically recalibrated to the European risk regions defined in the 2021 ESC Cardiovascular Prevention Guidelines (see [Supplementary material online, Figure S2](#)), using similar methods as were used for recalibration of SCORE2 and SCORE2-OP.<sup>17,18</sup> 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 material online, 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 regions and from the

Swedish NDR data for moderate-risk regions. Annual CVD and non-CVD mortality rates were extracted from WHO global burden of disease database.<sup>19</sup> Previously published SCORE2 multipliers were used to convert WHO CVD mortality rates of the total population to the incidence of fatal and non-fatal CVD in people not having established CVD, including both apparently healthy people and people with diabetes.<sup>17</sup> Secondly, the incidence of fatal and non-fatal CVD in people not having established CVD was converted to the 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.<sup>20,21</sup> 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 NCDRisk risk factors collaboration. HRs for diabetes on CVD and non-CVD mortality were obtained from SCORE2<sup>17</sup> and SCORE2-OP<sup>18</sup> (see [Supplementary material online, Figure S3](#)).

## Model validation

Discrimination was quantified using Harrell's C-statistic corrected for competing risks.<sup>22</sup> 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<sup>23</sup> and TRIPOD.<sup>24</sup>

## 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.<sup>25</sup> This process is described in detail in [Supplementary material online, 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 an HR of 0.80 per 10 mmHg SBP reduction<sup>26</sup> or the effect of LDL reduction with an HR of 0.78 per 1 mmol/L.<sup>27</sup> 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, TX, USA).

## 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 the 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

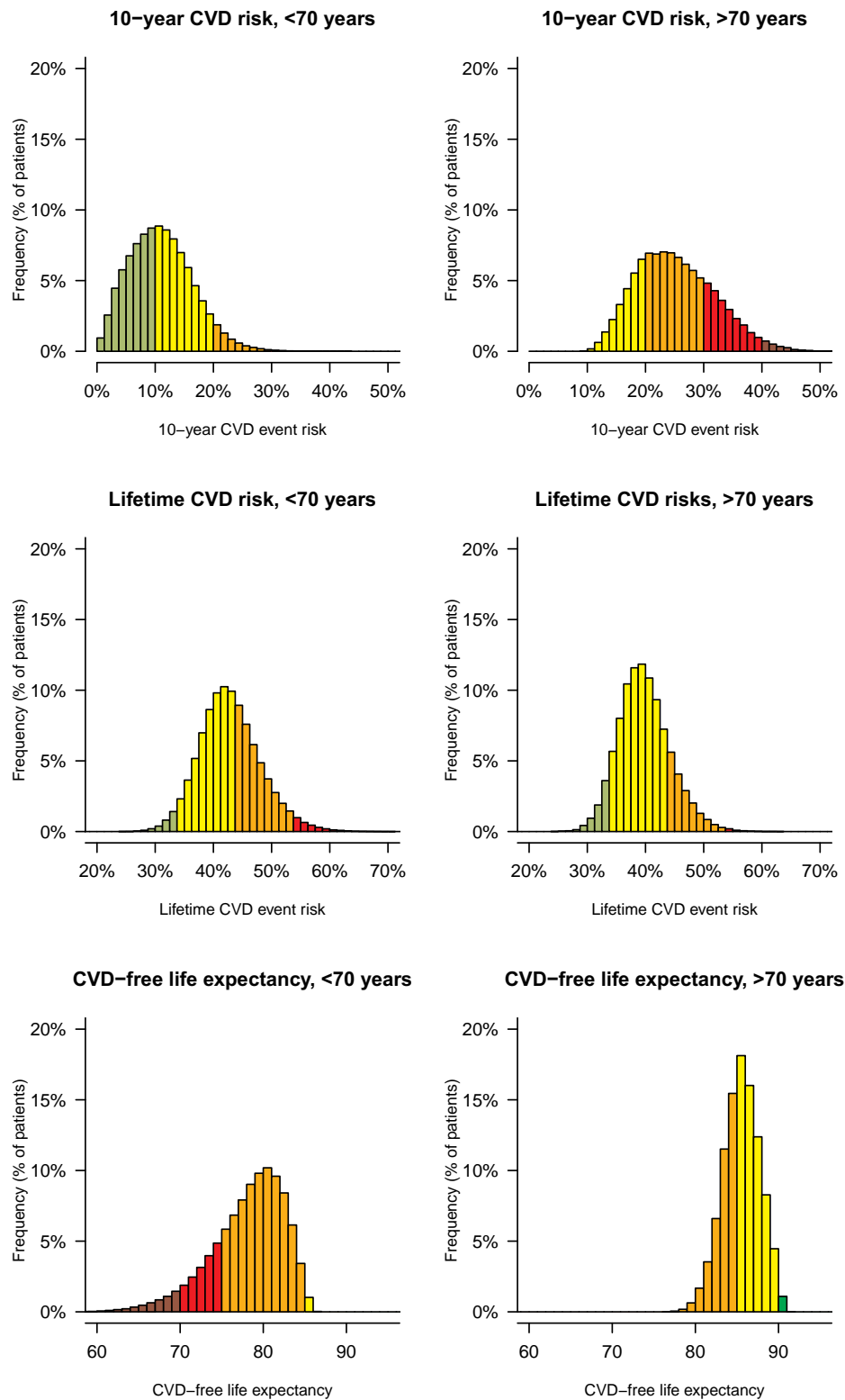
The Swedish NDR cohort used for derivation comprised 467 856 people with Type 2 diabetes and without established CVD. The mean age at baseline was 63 years and 55% were male. The median age at Type 2 diabetes diagnosis was 58 years [interquartile range (IQR) 50–67 years]. Baseline characteristics are 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 (see [Supplementary material online, Table S6](#)). All parameters necessary for individual predictions are listed in the [Supplementary material online: coefficients for individual predictions for both the core and extended model are shown in \[Supplementary material online, Table S3\]\(#\), and shown graphically across different ages in](#)

**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/m <sup>2</sup> )	31 ± 6	30 ± 5
eGFR (mL/min/1.73m <sup>2</sup> )	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). 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 > 30 mg/mmol for severe albuminuria.

eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; T2D, Type 2 diabetes.



**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.



**Table 2** Baseline characteristics of the external validation cohorts

	CPRD (n = 75 215)	SCID (n = 143 042)
Age (years)	63 ± 12	63 ± 13
Male sex	39 708 (53%)	75 797 (53%)
Current smoking	11 999 (21%)	27 383 (19%)
Insulin use		44 303 (31%)
Age at T2D onset	57 (49–66)	58 (49–66)
Antihypertensive medication use		78 744 (55%)
Lipid-lowering medication use		70 007 (49%)
Antiplatelet medication use		48 714 (34%)
Systolic blood pressure (mmHg)	136 ± 16	136 ± 16
Diastolic blood pressure (mmHg)		87 ± 6
Body mass index (kg/m <sup>2</sup> )		33 ± 7
eGFR (mL/min/1.73m <sup>2</sup> )	75 (61–90)	80 (67–98)
Moderate albuminuria		26 319 (18%)
Severe albuminuria		3 969 (3%)
HbA1c (mmol/mol)	59 ± 17	58 ± 17
Triglycerides (mmol/L)		2.3 ± 1.3
Total cholesterol (mmol/L)	4.4 ± 1.1	4.4 ± 1.1
HDL-c (mmol/L)	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). Albuminuria was defined as a urine-albumin/creatinine ratio of 3–30 mg/mmol for moderate albuminuria and urine-albumin/creatinine ratio >30 mg/mmol for severe albuminuria. eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol, LDL-c, low-density lipoprotein cholesterol, T2D, Type 2 diabetes.

Supplementary material online, Figure S4. The age-specific baseline hazards are provided in Supplementary material online, Table S4. The smoothed baseline hazards are shown in Supplementary material online, Figure S5.

## 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 (see Supplementary material online, Figure S6) and the rates for recalibrating non-CVD mortality (see Supplementary material online, Figure S7). The rescaling factors derived for geographical recalibration are provided in Supplementary material online, Table S5. 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).

## Validation of the model

After recalibration, the DIAL2 model was validated in the data from CPRD, in SCID (both low-risk regions), and the Swedish NDR (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 7286 CVD events and 5236 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.

For the extended model, the C-statistic for predicting CVD events was 0.705 (0.695–0.714) in the SCID (see Supplementary material online, Table S6). 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 (see Supplementary material online, Figure S8). In older individuals, predictions were adequate in Swedish NDR but underestimated in CPRD. In SCID, the 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 (see Supplementary material online, Figure S9).

## 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. Figure 3(A) additionally has an HbA1c of 75 mmol/mol, diagnosis of Type 2 diabetes 10 years prior to the current age and, an eGFR of 70 mL/min/1.73 m<sup>2</sup>. Figure 3(B) has an HbA1c of 50 mmol/mol, newly diagnosed Type 2 diabetes, and an eGFR of 70 mL/min/1.73 m<sup>2</sup>.

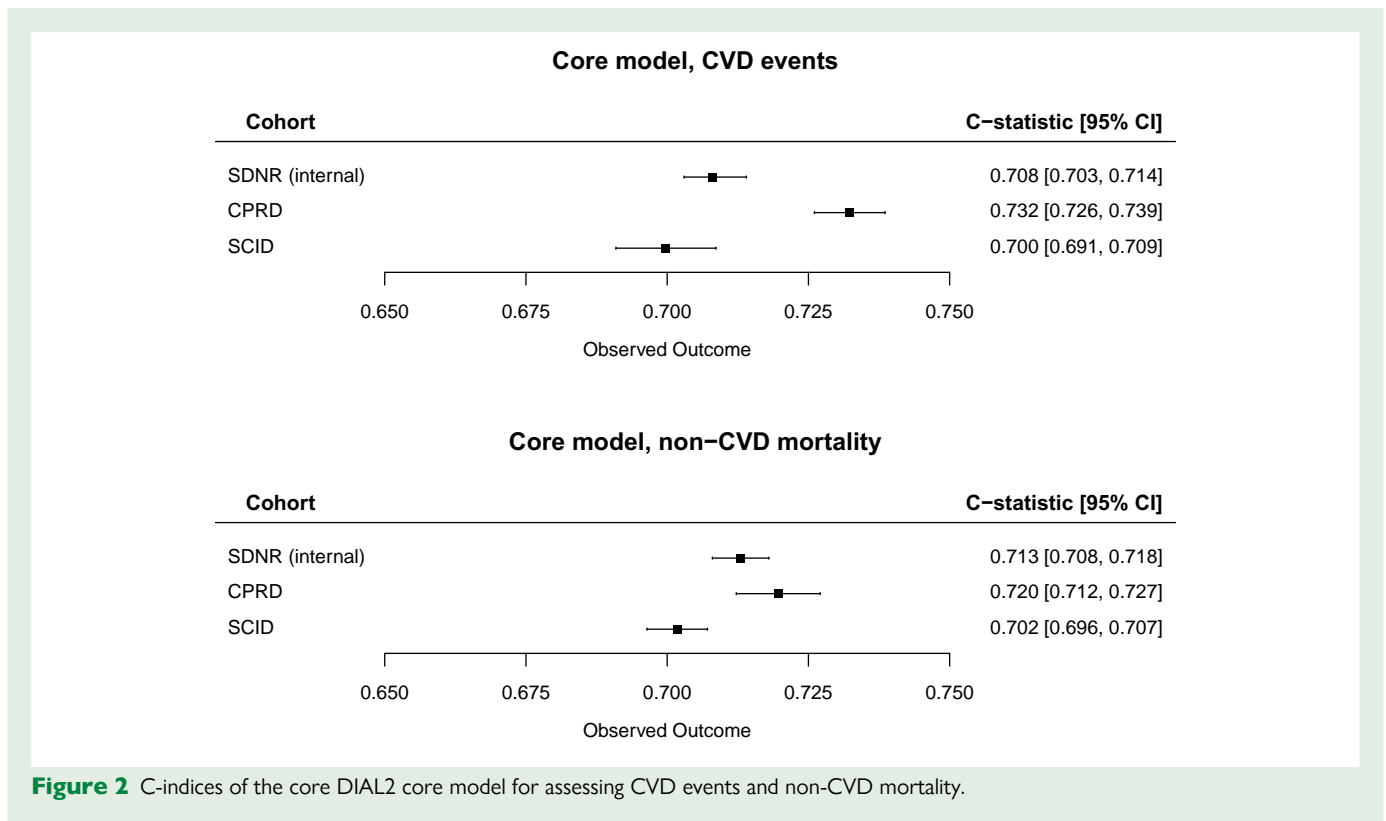
## Sensitivity analyses

The discriminative performance of the core model was comparable among those on lipid-lowering therapy and those not on lipid-lowering therapy (see Supplementary material online, Table S7). 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 (see Supplementary material online, Table S8).

## 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



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

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 regions, 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 a competing risk, an asset that is crucial in preventing overestimation of risks and treatment benefits, especially in older individuals.<sup>22</sup> 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.<sup>28</sup> For individuals with such risks factors available in clinical practice, the extended model, therefore, allows for more accurate predictions.

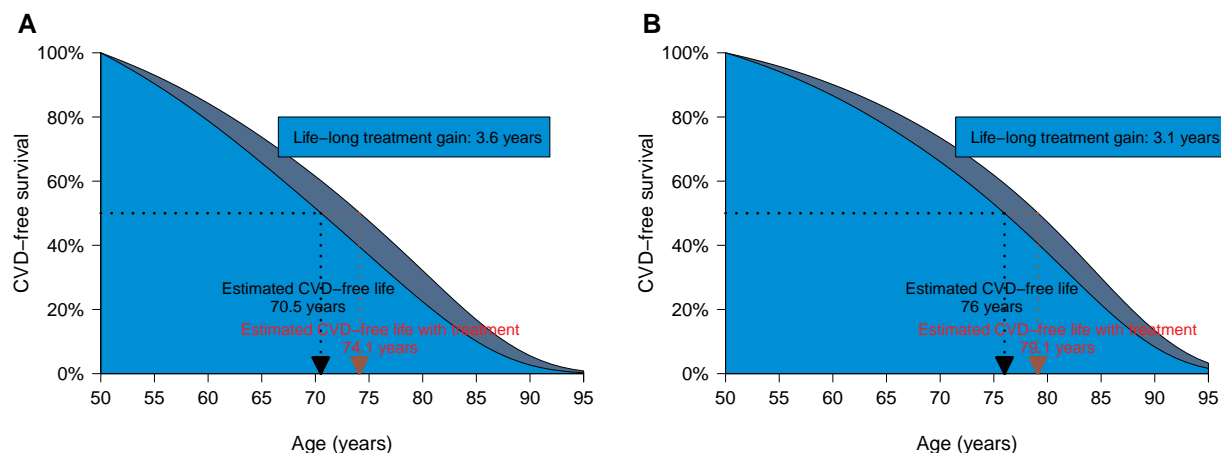
Furthermore, model derivation, recalibration, and validation were performed in large and contemporary cohorts, enhancing accuracy and generalizability to individuals with Type 2 diabetes without established CVD across different European countries, and minimizing the risk of model overfitting. The recalibrated 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

regions, 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.<sup>29</sup> 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. 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 the 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 benefits from long-term use of a preventive treatment may be substantial.<sup>30</sup> 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.<sup>3</sup>

The 2021 ESC prevention guidelines recommend a two-step approach as an individualized CVD prevention strategy for each individual



**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. 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). (A) an HbA1c of 75 mmol/mol, a diagnosis of Type 2 diabetes 10 years prior to the current age, and an eGFR of 70 mL/min/1.73 m<sup>2</sup>. (B) has an HbA1c of 50 mmol/mol, newly diagnosed Type 2 diabetes, and an eGFR of 70 mL/min/1.73 m<sup>2</sup>.

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.<sup>3</sup> 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 projecting 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.<sup>31</sup>

Several limitations of the current study merit consideration. First of all, validation was only performed for up to 10 years, since the cohort data did not have a longer follow-up. Although previous studies have shown the validity of lifetime predictions for up to 17 years,<sup>16</sup> predictors may change during the course of a lifetime and as long-term follow-up data become available, the model would 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.<sup>10,32</sup> Also, information on ethnicity, family history of pre-mature 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 of 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.

## Authors' contributions

H.B.Ø., S.H.J.H., J.A.N.D., F.L.J.V., L.P., S.K., C.P., Z.X., F.S., J.W.M., W.H., A.W., B.E., N.S., S.W., and E.D.A. contributed to the conception or design of the work. H.B.Ø., S.H.J.H., S.H.R., J.A.N.D., F.L.J.V., O.T., L.P., S.K., B.E., and S.W. contributed to the acquisition, analysis, or interpretation

of data for the work. H.B.Ø. and S.H.J.H. drafted the manuscript. J.A.N.D., F.L.J.V., S.H.J.H., O.T., L.P., S.K., C.P., Z.X., F.S., J.W.M., W.H., A.W., B.E., N.S., S.W., and E.D.A. critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

## Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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## Data Availability

The data from the local registries are not compliant with publishing individual data in an open-access institutional repository or as supporting information files with the published paper.

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