Cardiovascular risk in patients with type 2 diabetes: A systematic review of prediction models

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ARTICLE INFO

ABSTRACT

Aims: To identify all cardiovascular disease risk prediction models developed in patients with type 2 diabetes or in the general population with diabetes as a covariate updating previous studies, describing model performance and analysing both their risk of bias and their applicability

Methods: A systematic search for predictive models of cardiovascular risk was performed in PubMed. The CHARMS and PROBAST guidelines for data extraction and for the assessment of risk of bias and applicability were followed. Google Scholar citations of the selected articles were reviewed to identify studies that conducted external validations.

Results: The titles of 10,556 references were extracted to ultimately identify 19 studies with models developed in a population with diabetes and 46 studies in the general population. Within models developed in a population with diabetes, only six were classified as having a low risk of bias, 17 had a favourable assessment of applicability, 11 reported complete model information, and also 11 were externally validated.

Conclusions: There exists an overabundance of cardiovascular risk prediction models applicable to patients with diabetes, but many have a high risk of bias due to methodological shortcomings and independent validations are scarce. We recommend following the existing guidelines to facilitate their applicability.

Contents

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1.   Introduction

Type 2 diabetes is one of the most prevalent chronic diseases in the world [1], and cardiovascular disease (CVD) is one of the major complications of patients with diabetes, with a twofold increased risk compared with the general population [2]. Prevention of cardiovascular disease is a key issue, and evaluation and stratification of the cardiovascular risk of patients with diabetes is needed to establish and personalize treatments and maximize the benefit of those treatments. CVD risk prediction models are the main tool for risk estimation and stratification, and they have increasingly been included in clinical guidelines [3,4]. Over the last few years, many cardiovascular risk models have been developed in different locations, and consequently, several systematic reviews of prediction model studies, both in the general population [5,6] and in people with type 2 diabetes, have also been published in recent years [7,8].

Risk prediction models need to fulfil strict conditions that go beyond usual methodological requirements to be useful as valid decision support tools in clinical practice. However, according to the aforementioned reviews and despite the overabundance of CVD risk prediction models, many of them fail to meet key quality criteria [8], such as being methodologically correct, being appropriately presented, being externally validated and having impact studies that assess the effect of using them in clinical practice [5]. The issues of poor reporting and low development quality in prediction model development studies have been addressed in recent years with the publication of different guidelines and checklists: the TRIPOD statement for transparent reporting of a multivariable prediction model [9], CHARMS checklist for critical appraisal and data extraction for systematic reviews [10] and PROBAST tool for the assessment of risk of bias and applicability [11].

This study was intended to identify all cardiovascular disease risk prediction models developed in patients with type 2 diabetes or in the general population with diabetes as a covariate, updating the study conducted by Van Dieren et al. [7], describing model performance and analysing both their risk of bias and their applicability, and assessing whether they have gone under external validation or whether their implementation has been assessed in the case of models developed in patients with type 2 diabetes.

2.   Methods

2.1.   *Search strategy*

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [12]. To identify prediction model development studies, a search was performed in PubMed covering the period April 1, 2011, to June 18, 2021. This search was conducted on two different moments. The first search took place on April 2018 in the previous PubMed version and was applied to the period April 1, 2011 to April 6, 2018. The search terms included were exactly those used in Van Dieren et al. [7]. The second search was conducted on June 2021 in the new PubMed version and was applied to the period April 6, 2018 to June 18, 2021. The search strategy used for this second search had to be adapted, since the previous search was not reproducible in this new PubMed version. The terms selection process for this second search was conducted trying to maintaining both precision and recall. The entire process is detailed in Additional file 1. In addition, known reviews and

lists of references of selected articles were tracked to find other records.

2.2. Inclusion criteria

Models were included if 1) they were developed in patients with type 2 diabetes or if they included diabetes as a predictor, and 2) the outcome was CVD or any subtype as coronary heart disease (CHD), heart failure (HF) or stroke. Exclusion criteria were: models not applicable to patients with type 2 diabetes, models derived for populations with specific diseases, models with outcomes different from CVD or subtypes of CVD, non-original articles, commentaries or reviews, studies that analysed the added prediction value of a predictor without formal validation, those that were not prediction studies, and those that were only validation or impact studies.

2.3. Data extraction, analysis and reporting

All records were divided into two sets, and each set was reviewed independently by two groups of reviewers, AG/JL and IT/BI/ME. Each group analysed one set of records and the selected records were merged. The screening was performed in three phases: first, only titles were analysed; second, abstracts of the selected titles were considered; and finally, full texts of the selected abstract were read. Discrepancies were resolved by consensus. A unified chart of exclusion criteria was applied in the title, abstract and full-text screening steps.

In the selected articles, population size, number of events and details of the developed model were extracted, including type of statistical model, identification of predictors and selection method (if available), and internal validation results, following the CHARMS guidelines for systematic reviews of prediction modelling studies [10] and the TRIPOD guidelines for reporting prediction models [9].The risk of bias (ROB) and applicability of individual studies were evaluated with the Prediction Model Risk Of Bias Assessment Tool (PROBAST) [11]. This tool evaluates four domains, namely participants, predictors, outcome and analysis, using 20 signalling questions and classifies models as having high, low or unclear risk of bias and as high, low or unclear concern regarding applicability.

2.4. External validation studies

An additional search was performed to identify all studies that carried out an external validation of the identified models. Citations to the identified models were individually searched in Google Scholar, and after screening titles, abstracts and full text, validation studies were selected and summarized.

3. Results

The study selection process is described in Fig. 1. A total of 10,556 records were extracted from the search and screened based on their title. Of them, 688 were screened during the abstract review, 119 full texts were assessed for eligibility, and 65 studies were included in the review, including three studies added from reference search. Of the included studies, 19 were developed in patients with type 2 diabetes, whereas 46 were developed in the general population and included diabetes as a covariate.

3.1. Models developed in populations with diabetes

3.1.1. Design, population, follow-up
The results of the 19 models developed in patients with type 2 diabetes are given in Table 1.[13–31] Fourteen of them used observational cohort data, four used registry data and the latter used clinical trial data. Eight were developed in the European population, six in the Asian population, three in the North American population and the other two in the Oceanian population. The majority of models were developed in populations with prevalent diabetes; only two were developed in populations with incident diabetes. Sixteen studies included a lower bound for age in their inclusion criteria; most ranged between 18 and 40 years old, and ten included an upper bound for age, which ranged between 64 and 84 years old. Follow-up time varied among the studies, ranging from a median of 2 –15 years.

3.1.2. CVD outcomes and predictors
Outcome definitions varied substantially among the models. Fifteen out of the 19 studies reported using International Classification of Disease ICD (9 or 10) codes. Fifteen referred to a general CVD outcome and the last four to a specific subtype of CVD: two to stroke [18,23], one to cerebrovascular disease [21] and one to heart failure [26]. Among those referred to general CVD, three were very restrictive and included only CVD death [13,14,30], five included only fatal and nonfatal acute myocardial infarction (AMI), stroke or CVD death [16,20,22,25,29], and the last seven were inclusive and accounted for a variety of fatal and nonfatal events [15,17,19,24,27,28,31], one of which included even peripheral arterial disease (PAD) [27].

The median number of included predictors was 12, ranging from 6 to 91. Age (as time indicator in one model) and sex (as a predictor in 15 models and as a stratification variable in the last four) were presented in all studies and smoking status, cholesterol (HDL, LDL, total or total to HDL ratio), blood pressure (total, SBP or DBP) and HbA1c or fasting plasma glucose were presented in more than 75% of the studies. Body Mass Index (BMI) and diabetes duration were presented in 11 (57.9%) models, and other less common predictors were glucose lowering medication, presented in eight (42.1%) models and atrial fibrillation, which was presented in seven (36.8%) of the models.

3.1.3. Sample size, type of model, predicted horizon and presentation
The number of participants was presented in all studies, and all except one also reported the number of events. The total population in derivation cohorts ranged from 777 to 907,992 participants, and observed events ranged from 164 to 54,365. The most common predicted horizons were five years (9 studies) and ten years (6 studies), with the shortest predicted horizon being one year and the longest that of the model

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┌─────────────────────────────┐        ┌─────────────────────────────┐
│ Records identified through  │        │ Records excluded (n = 9868) │
│ PubMed searching, screened  │───────▶│                             │
│ on title (n = 10556)        │        │                             │
└─────────────────────────────┘        └─────────────────────────────┘
              │
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┌─────────────────────────────┐        ┌─────────────────────────────────────────┐
│ Records screened on abstract│        │ Records excluded (n = 569)              │
│ (n = 688)                   │───────▶│ 131  non-applicable to diabetes         │
│                             │        │      population                         │
└─────────────────────────────┘        │ 31   non original articles              │
                                       │ 23   review articles                    │
                                       │ 116  outcome not CVD                     │
                                       │ 118  added predictive value of a marker  │
                                       │      without formal validation          │
                                       │ 109  etiologic or intervention study,    │
                                       │      not predictive                     │
                                       │ 40   validation study                   │
                                       │ 1    impact study                       │
                                       └─────────────────────────────────────────┘
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┌─────────────────────────────┐        ┌─────────────────────────────────────────┐
│ Full-text articles assessed │        │ Full-text articles excluded (n = 57)    │
│ for eligibility (n = 119)   │───────▶│ 25  non-applicable to diabetes          │
│                             │        │     population                          │
└─────────────────────────────┘        │ 1   non original articles               │
                                       │ 8   outcome not CVD                      │
                                       │ 17  added predictive value of a marker   │
                                       │     without formal validation           │
                                       │ 5   etiologic or intervention study,     │
                                       │     not predictive                      │
                                       │ 1   validation study                    │
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┌─────────────────────────────┐        ┌─────────────────────────────────────────┐
│ Studies included in         │◀───────│ Studies included from other sources     │
│ qualitative synthesis       │        │ (reference search) (n = 3)              │
│ (n = 65)                    │        │                                         │
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Fig. 1 – Flow chart of systematic review of studies providing cardiovascular risk prediction models that can be applied to individuals with type 2 diabetes.

presented in Berkelmans et al. [19] which allows for lifetime prediction. All studies used survival models except one, which used a logistic model; Cox proportional hazard models in 15 cases, Fine-Gray competing risks model in two cases and Weibull parametric models in one. Eleven studies reported complete information, coefficient estimates (hazard ratios or beta coefficients) and baseline hazards to allow individual estimation. In the remaining studies, four presented risk charts and four presented information that was insufficient to obtain individual risk estimations.

3.1.4.   Performance and external validation studies

All studies presented a validation study; ten of them (52.6%) only performed internal validation, one of them (5.3%) presented only external validation, and eight studies presented both. Among those with internal validations, discrimination was reported in all of them, and the c-statistic values ranged from 0.640 to 0.996. Ten of the internal validations used the split-sample method, four used the apparent validation method, and other four used cross validation or bootstrap. Calibration was assessed in 16 (84.2%) of the models, with 13 of them presenting at least calibration plots, and three studies computing only Hosmer-Lemeshow or Gronnesby and Borgan goodness-of-fit statistics.

Nine of the studies (47.4%) validated the prediction model through evaluation in an external cohort. In addition, five independent studies [32–36] externally validated three of the 19 models developed in population with type 2 diabetes [28,29,31] (see Table A2.1 in Additional file 2). Overall, 11 (57.8%) of the 19 models have been externally validated. Calibration was assessed in all external studies using calibration plots and computing calibration slope in four of them. Discrimination in external cohorts showed a high degree of variation in the c-statistic values, ranging from 0.54 to 0.78. For the model developed in Hippisley-Cox and Coupland [26], the external c-statistic value was slightly higher than that of the internal cohort (women 0.783 and men 0.769 vs women 0.770 and men 0.764). For the model developed in Mukamal et al. [29], the external validations performed in Read et al. [32] and Dziopa et al. [36] showed similar results to those presented in the development study, but that conducted in Van der Leeuw et al. [33] showed worse results in two of the three cohorts used (see Additional file 2). Calibration, as shown in the calibration plots, was good in the external validations presented along with the derivation models [25,26,29], but external validations presented in independent studies reported poor calibration when applying models directly [32,33,36], a problem that did not always completely disappear with simple recalibration techniques, such as adjusting

Table 1 – Cardiovascular prediction models developed in patients with diabetes.

Reference	Cohort type	Location	Age range	Population/Events	Follow-up/Predicted Time	Predictors	Outcome	Model Type
Williams et al. 2021 [13]	Observational cohort	Canada	51–72	59180/ 6033	Mean 7.5 years/ 1–3–5 years	Age, heart failure, coronary artery disease, atrial fibrillation and cerebrovascular disease, blood urea nitrogen, A1C, albumin, Pre-existing T2D, Chloride, Red cell distribution width, sex, Alanine aminotransferase, Systolic blood pressure, Lymphocyte, Smoking status, Dementia, Valve disease, Hyperlipidemia, Glucose level, Heart rate, Implantable cardioverter-defibrillator, HDL cholesterol, Chest pain, Carbon dioxide, Edema, eGFR	Cardiovascular death	Cox
Liu et al. 2021 [14]	Observational Cohort	Taiwan	30–84	6461/560	8.7 years/3–5-10–15 years	Age, sex, education years, smoking, BMI, diabetes treatment, diabetes duration, FPG variation, HbA1c variation, SBP variation, triglycerides, peripheral neuropathy	Cardiovascular death	Cox
Pylypchuk et al. 2021 [15]	Observational Cohort	New Zealand	30–74	46652/ 4114	Median 5.2 years/ 5 years	Sex stratified; age; ethnicity; socioeconomic deprivation index; family history of cardiovascular disease; smoking status; SBP; TC-HDL ratio , atrial fibrillation, blood pressure lowering drugs, lipid lowering drugs, antithrombotic drugs, HbA1c, diabetes duration, ACR, eGFR, BMI oral hypoglycaemic drugs or insulin	Hospitalisations or deaths from ischaemic heart disease (including angina), ischaemic or haemorrhagic cerebrovascular events (including transient ischaemic attacks), peripheral vascular disease, congestive heart failure, or other ischaemic cardiovascular disease deaths.	Cox
Choi et.al. 2020 [16]	Register	Korea	greater than30	933/33	Mean 37.5 months	Age, sex, prior stroke, hypertension, diabetes duration, HbA1c, use of clopidogrel, abnormal ECG	Major adverse cardiac and cerebrovascular event (MACCE): cardiac death, nonfatal MI, or stroke.	Cox
Davis et.al 2020.[17]	Observational cohort	Australia	Not reported	1296/ 245	5 years follow up	Age, sex, heart rate, aboriginal Australian, HbA1c, diabetes duration, urinary albumin: creatinine ratio, eGFR , LVH, heart failure, history of CVD, and presence of PAD	Myocardial infarction, stroke, HF and CVD death.	Fine-Gray
Kim et. al. 2020 [18]	Observational Cohort	Korea	40–64	907992/24231	7.1 years / 5 years	Age, sex, smoking, regular exercise, BMI, CKD, CHD, diabetic duration, numbers of oral hypoglycemic agents or insulin, FBG,SBP, TC and atrial fibrillation.	Stroke	Cox
Quan et. al. 2019 [19]	Observational Cohort	Hong Kong	>=20	623294–610647/ 43215–54365	6.3 years/ 5 years	Age, sex, diabetes duration, smoking, BMI, SBP, DBP, HbA1c, LDL, atrial fibrillation, CKD, history of ischemic heart disease or cerebrovascular disease	Cerebrovascular disease/Ischemic Heart disease	Cox
Berkelmans et al. 2019 [20]	Register	Sweden	>=18	292024/21910	4.6–14.5/Lifetime risk age-range 30–95 years	Sex, smoking, SBP, BMI, HbA1c, eGFR, non HDL-c, albuminuria, diabetes duration, insulin treatment, previous history of CVD	Non-fatal myocardial infarction, non-fatal stroke, or vascular mortality	Fine-Gray
Yu et. al 2018 [21]	Observational Cohort	UK	No age bounds	4704/244	2 years/2 years	Age, sex, BMI, SBP, DBP, HbA1c, TC ,HDL, LDL	Cerebrovascular hospitalisation	Logistic
Nowak et. al. 2018 [22]	Observational Cohort	Sweden	55–65	834/136	6.4 years/5 years	Age, diabetes duration, TC/HDL, HbA1c, SBP, BMI, sex, smoking, microalbuminuria, atrial fibrillation, previous CVD + 80 proteins	Fatal or non-fatal myocardial infarction, fatal/non-fatal stroke	Cox gradient boosted machine
Li et al. 2018 [23]	Observational Cohort	China	30–84	18750/ 2091	10 years/.3–5-8 years	Age, sex, smoking, diabetes duration, BP, HbA1c, TC-HDL ratio, Abnormal creatinine., FPG-CV, Arterial embolism and thrombosis, retinopathy, Hypoglycemia, Anti-diabetes medication, cardiovascular medication	Ischemic stroke	Cox

Table 1 – continued

Reference	Cohort type	Location	Age range	Population/Events	Follow-up/Predicted Time	Predictors	Outcome	Model Type
Wan et al. 2017 [24]	Observational Cohort	China	18–79	91957	Median 5 years/ 5 years	Sex stratified. Age, smoking, diabetes duration, OHA, AntiHypertensive. Drug, Insulin drug , BMI, HbA1c, SBP, DBP, eGFR, TC/HDL ratio, urine ACR	CVD: ischemic heart disease, myocardial infarction, coronary deathand sudden death, heart failure and fatal and non-fatal stroke	Cox
Kaasenbrood et al. 2016 [25]	Clinical trial	UK	40–79	2725/164	Median 3.2 years/ 10 years	Age, sex, smoking, SBP, TC-HDL, history of CVD, FPG, statin-placebo	Nonfatal myocardial infarction, nonfatal ischemic or hemorrhagic stroke, cardiovascular death	Cox
Hippisley-Cox et al. 2015 [26]	Observational cohort	UK	25–84	437806/ 25480	15 years/ 10 years	Sex stratified. Age, TC/HDL, Smoking, Ethnicity, Diabetes Type, Atrial fibrillation, Previous CVD, Chronic renal disease	Heart failure	Cox
Piniés et al. 2014 [27]	Observational Cohort	Spain	>24	777/ 192	Median 10 years/ 10 years	Age, sex, NonHDL/HDL, SBP, HbA1c, smoking	CHD, stroke, PAD	Cox
Kiadaliri et al. 2013 [28]	Register	Sweden	>=18	21775/ 4547	5 years/ 5 years	Sex, age, SBP, DBP, TC/HDL, BMI, macroalbuminuria, microalbuminuria, smoking, previous disease history	AMI, HF, NAIHD, stroke, sudden death.	Weibull
Mukamal et al. 2013 [29]	Observational cohort	USA	>=65	782/ 265	10 years/ 10 years	Sex stratified. Age, former smoker, current smoker, SBP, TC, HDL, Creatinine, Insulin drug or OHA, Creatinine, C-reactive protein, Ankle-Brachial Index, Left ventricular hypertrophy, Internal carotid intima-media thickness	Myocardial infarction, stroke and cardiovascular death	Cox
McEwen et al. 2012 [30]	Observational cohort	USA	Not reported	5330/ 448	8 years/ 8 years	Age, sex, BMI, diabetes treatment, smoking, LDL, nephropathy, dyslipidemia, history of previous CVD, medication	Cardiovascular death	Cox
Zethelius et al. 2011 [31]	Register	Sweden	30–74	24288/2488	5 years/5 years	Age, diabetes duration, TC/HDL, HbA1c, SBP, BMI, sex, smoking, microalbuminuria, atrial fibrillation, previous CVD.	CHD, stroke	Cox

Reference	Model Presentation	Validation Discrimination c-statistic	Validation Calibration	Number of validations in independent studies
Williams et al 2021 [13]	Betas, HR,	Internal (apparent) 0.824, 0.819 (with 15 strongest predictors)	No	0
Liu et al. 2021 [14]	Betas and HR Risk score chart	Internal (split sample and bootstrap) 0.85, 0.83, 0.80, 0.79 Overall: 0.80 (0.78–0.82)	Hosmer Lemeshow, calibration plot, calibration in the large and calibration slope	0
Pylypchuk et al. 2021 [15]	Complete Equation in supplementary material (betas and baseline hazard)	Internal Apparent Women 0.73 (0.72–0.74) Men 0.69 (0.68–0.70) External Women 0.69 (0.67–0.70 Men 0.67 (0.66–0.68)	Calibration plot	0
Choi et.al.2020 [16]	Betas, HR and S0(10)	Internal (split sample) 0.708 (0.619–0.798) External 0.707 (0.655–0.750	Calibration plot and Hosmer Lemeshow test	0
Davis et.al 2020 [17]	Tree, HR	Internal (apparent) 0.82 (0.79–0.85) External: competing risk four-point MACE -C- 0.81 (0.74–0.89)	Calibration plot, Hosmer-Lemeshow test	0
Kim et. al. 2020 [18]	HR Risk score chart	Internal (split-sample) 0.703 (0.698–0.708)	Calibration plot	0
Quan et. al. 2019 [19]	Complete Equation in supplementary material (betas and baseline hazard)	Internal (bootstrap) M1:0.722 (0.720–0.725) M2: 0.700 (0.698–0.702) External: M1 0.695 (0.690–0.699) M2: 0.644 (0.640–0.647)	Calibration plot	0

Table 1 – continued

Reference	Model Presentation	Validation Discrimination c-statistic	Validation Calibration	Number of validations in independent studies
Berkelmans et. al 2019 [20]	Complete Equation in supplementary material (betas and baseline hazard)	Internal (split sample): External:	Calibration plot	0
Yu et. al 2018 [21]	Complete Equation (betas and intercept)	Internal (bootstrap): 0.9961 (0.9928–0.9995) External: 0.9853 (0.9756–0.9966)	Calibration plot, calibration slope	**0**
Nowak et. al. 2018 [22]	–	Internal (split sample): 0.825 (0.824, 0.827)	No	**0**
Li et al. 2018 [23]	Betas Supplementary scoring chart	Internal (split sample) Development sample: 0.72, 0.71, and 0.67 Validation sample: 0.72, 0.71, and 0.68	No	0
Wan et. al. 2017 [24]	Hazard ratio (HR) Risk score chart	Internal (split sample) Validation sample: M1 Male 0.705 Female 0.719 M2 Male 0.689 Female 0.708	Calibration plot	0
Kaasenbrood et al. 2016 [25]	Complete equation Betas and baseline hazard HR in suppl.	External cohorts: 0.64 and 0.68	Calibration plot, expected-observed risk ratio and Gronnesby and Borgan test.	0
Hippisley-Cox et. al. 2015 [26]	HR and spline graph Complete equation and calculator published	Internal (split sample): Validation sample: Women 0.770 Men 0.764 External cohort Women 0.783, Men 0.769	Calibration plot	0
Piniés et. al. 2014 [27]	Complete equation in supplementary material	Internal (cross-validation) 2–5- 10 years 0.75, 0.64, 0.63.	Hosmer-Lemeshow test	0
Kiadaliri et. al. 2013 [28]	Weibull complete equation reported	Internal (split-sample) Development sample: AMI 0.78 HF0.84 Stroke 0.80 NAIHD 0.76 Validation sample: AMI 0.79 HF 0.84 Stroke 0.79 NAIHD 0.75	Gronnesby and Borgan test	1
Mukamal et. al. 2013 [29]	HR	Internal (apparent) M1 0.64, M2 0.64, M3 0.68 External M1 0.65, M2 0.66, M3 0.68	Hosmer-Lemeshow test. Calibration plot	2
McEwen et. al. 2012 [30]	HR and complete equation published (for 8 years)	Internal (Cross-validation) 0.84	Hosmer-Lemeshow test	0
Zethelius et. Al. 2011 [31]	Complete equation	Internal (split sample) Development sample: 0.71 Validation sample: 0.72	Calibration plot, expected-observed risk ratio and Hosmer-Lemeshow test	2

BP = Blood pressure, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, TC = Total cholesterol, HDL = High density lipoprotein, LDL = Low density lipoprotein, FPG: Fasting plasma glucose, FPG-CV = Fasting plasma glucose coefficient of variation, eGFR = Estimated glomerular filtration rate, Hba1C = Glycated hemoglobin, BMI = Body mass index, OHA = Oral hypoglycaemic agents, ACR = Albumin to creatinine ratio, CVD = Cardiovascular disease, CHD = Coronary heart disease, PAD = Peripheral artery disease, AMI = acute myocardial infarction, HF = Heart Failure, NAIHD = non-acute ischaemic heart disease.

the intercept, requiring more advance recalibration techniques [32].

3.1.5. Risk of bias and applicability

The results of the risk of bias and applicability assessment based on PROBAST guidelines are presented in Table 2, and the detailed information by domain in Additional file 3. Low risk of bias was assigned to five studies, one was unclear and the rest (68%) were classified as having high risk of bias. By domain, all studies scored a low risk of bias in predictor and outcome assessments. In the participant domain, 16 (84.2%) scored a low risk of bias and one was rated as unclear risk of bias, remaining two as high risk of bias, whereas in the analysis domain one study was classified as unclear risk of bias and only five studies (26.3%) scored low risk of bias. The main reasons for this poor compliance with analysis requirements were dichotomization of variables, inadequate handling of missing data, selection of predictors based on univariate analysis and lack of accounting for optimism and overfitting. Regarding the domain 'concern for applicability', low concern was assigned to 17 (89.5%) studies, one was classified as having high concern of applicability because data were gathered from a clinical trial, and for the remaining study, there was not enough information to rate the participants item, so it was classified as unclear concern for applicability.

3.2. Models developed in the general population while using diabetes as a covariate

3.2.1. Design, population, follow-up

All 46 studies used observational cohort data (see Additional file 4 for the summary of the models developed and Additional file 5 for the list of references [S1-S46]). Seventeen models were developed in North American cohorts (15 in the US and two in Canada), and 15 were developed in different European countries: 13 in one country (Netherlands, France, Denmark, UK, Norway and Spain), one in two (UK and Finland) and the other in four (Italy, Belgium, Denmark, Norway). Eight models were developed in an Asian population (five in Japan, two in Korea and one in Iran), four were developed in Oceanian population and two in a set of worldwide cohorts. The median follow-up time ranged from 3.1 to 28 years, but most of the studies were between 10 and 15 years, with a median of 10 years.

3.2.2. Outcome and predictors

Outcome definitions and reporting varied among the studies. Eighteen models (39.1%) were developed with outcomes defined as an inclusive combination of fatal and nonfatal events, 20 models (43.5%) considered a more restrictive combination of events, such as CVD mortality events, stroke or CHD, seven models (15.2%) were developed with a specific outcome, such as sudden cardiac death, heart failure or peripheral arterial disease and in one study the outcome was not specified.

The median number of predictors was nine, ranging from four to 473. Sex appeared as covariate in 25 (54.3%) models, and in other five models, this variable was used for stratification purposes. A set of four common predictors (age, blood pressure indicators, smoking status and cholesterol indicators) was included in 28 (60.1%) of the models. Other common predictors were BMI (n = 13, 28.3%) and chronic kidney disease or urine parameters, such as albumin to creatinine ratio, microalumin, or estimated glomerular filtration rate (n = 14, 30.4%).

3.2.3. Sample size, type of model, predicted horizon and presentation

The number of participants was provided in all studies and the number of events in all but one. The median development cohort size was 22,199 (range 824–7,889,803), and the median number of events was 982 (range 76–640,804). Four studies were developed in cohorts of over a million people and more than 60,000 events. In contrast, 14 studies used cohorts of less than 10,000 people, and four of them were developed in cohorts with fewer than 200 events. All models used survival methods, except one that used logistic regression analysis, one that used the patient rule-induction method (PRIM) and two that fitted a set of machine learning methods. More precisely, Cox proportional hazard modelling was used in 35 models (76.1%), competing risk models were used in six (13.0%), and Weibull parametric modelling was used in one model (2.2%). The majority of models (52.2%) predicted 10-year risk, with a minimum of five-year risk and a maximum of 30-year risk, one model predicted lifetime-risk and in eight studies (17.4%) the prediction horizon was not specified.

3.2.4. Performance and external validation studies

Of the 46 studies included, 44 (95.7%) conducted internal or external validation using discrimination measures such as the c-statistic, whereas two did not report any discrimination measure. Apparent validation (24.4% of the internal validation studies), split sampling (26.8%), cross-validation (22.0%) and bootstrapping (26.8%) were the applied internal validation techniques. C-statistic values ranged from 0.65 to 0.91 in internal validation studies and from 0.63 to 0.88 in external validation studies. Calibration performance, presented in 40 studies (87.0%), was assessed with a goodness of fit test (Hosmer-Lemeshow, Nam–D'Agostino or Grønnesby–Borgan) in 21 (45.7%) studies, and calibration plots were presented in 30 (65.2%) of them.

A total of 15 out of the 46 models (32.6%) presented an external validation of the prediction model along with model development, and 12 studies were externally validated in independent studies [36, S47-S68] (see Table A2.2 in Additional file 2). Overall, 23 studies (50.0%) were validated in a different cohort than the cohort used for model development.

4. Discussion

This review shows all cardiovascular prediction models developed in patients with type 2 diabetes or in the general population with diabetes included as a covariate presented in recent years; the external validation and the risk of bias and concern of applicability were analyzed for the models developed in patients with diabetes. We found 65 prediction models applicable to patients with type 2 diabetes, 19 of them developed in a diabetes-specific population and the remain-

Table 2 – Risk of bias and applicability of models developed in patients with Type 2 Diabetes.

Study	Risk of Bias (ROB)				Concern of Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Williams et al. [13]	+	+	+	−	+	+	+	−	+
Liu et al. [14]	+	+	+	−	+	+	+	−	+
Pylypchuk et al. [15]	+	+	+	+	+	+	+	+	+
Choi et.al. [16]	+	+	+	−	+	+	+	−	+
Davis et.al. [17]	+	+	+	+	+	+	+	+	+
Kim et. al. [18]	−	+	+	−	+	+	+	−	+
Quan et al. [19]	+	+	+	+	+	+	+	+	+
Berkelmans et al. [20]	+	+	+	+	+	+	+	+	+
Yu et. al [21]	+	+	+	?	+	+	+	?	+
Nowak et. al. [22]	+	+	+	−	+	+	+	−	+
Li et al. [23]	+	+	+	−	+	+	+	−	+
Wan et al. [24]	+	+	+	−	+	+	+	−	+
Kaasenbrood et al. [25]	+	+	+	−	−	+	+	−	−
Hippisley-Cox et al. [26]	+	+	+	+	+	+	+	+	+
Piniés et al. [27]	?	+	+	−	?	+	+	−	?
Kiadaliri et al. [28]	−	+	+	−	+	+	+	−	+
Mukamal et al. [29]	+	+	+	−	+	+	+	−	+
McEwen et al. [30]	+	+	+	−	+	+	+	−	+
Zethelius et al. [31]	+	+	+	−	+	+	+	−	+

+: low ROB/low concern regarding applicability; −: high ROB/high concern regarding applicability; ?: unclear ROB/unclear concern regarding applicability.

ing 46 developed with diabetes specified as one of the covariates. These figures are higher than those obtained in the previous revision [7], which found 12 models developed in patients with type 2 diabetes and 33 in the general population using a similar search strategy and inclusion criteria as ours, even though the time window in our research was much smaller (a ten-year vs a 45-year time window). Our research confirms that the overabundance of CVD risk models detected in Damen et al. [5] still stands.

All the studies were developed in Europe, North America, Asia and Oceania, and almost all of them were conducted in high-income countries. The absence of models for diabetes populations developed and validated in low- or middle-income countries is an obstacle to tailored risk estimation because socioeconomic status is an important factor for both cardiovascular disease and diabetes [37,38] and because outcome-predictor associations may differ between different ethnic groups [39]. Regarding outcome definitions, there was notable variability among studies. This is, in part, because studies with the same intended outcome used different codes and different intensities, with some including a wide range of CVD codes regardless of fatality, while others included only fatal cases or very specific codes.

Some heterogeneity in model discrimination performance was observed; some studies had c-statistic values below 0.70, others had values close to 0.90 and even one study reported a value of 0.996. The degree of heterogeneity was lower in studies developed in patients with type 2 diabetes than in models developed in the general population, as was already noted in Chowdhury et al. [8]. Most models derived for patients with type 2 diabetes presented only modest discrimination ability in internal and external validation analyses. Although the included studies generally claimed good calibration performance analysed in the derivation or external cohorts, independent studies that externally validated these cardiovascular prediction models reported suboptimal calibration performance even after simple model recalibration such as adjusting the intercept [32], which suggest that more advanced recalibration techniques are sometimes needed. This is a generalized problem, mainly caused by population differences not explained by predictor variables or methodological problems, such as statistical overfitting [40]. This confirms the need to externally validate the models in different cohorts to assess their adequacy in different populations and to improve the methodological quality of model development.

Regarding model development quality, according to our classification of studies following the PROBAST guidelines, only 26% of the studies developed from a population with diabetes showed a low risk of bias, with the remaining models failing to comply with the requirements regarding the statistical analysis. Several statistical procedures or techniques that have been shown to be nonoptimal, such as dichotomization of predictor variables [41], use of complete case data without multiple imputation [42], selection of predictors based on univariate analysis [43] and no correction for optimism and overfitting [44] are still common. These procedures could lead to model overfitting and poor performance of the models in external cohorts [44], questioning their applicability. The introduction of the PROBAST risk of bias and applicability tool could improve the methodological quality of the studies, correct these problems and generalize optimal techniques. In fact, recent studies show better methodological quality than older ones, with four of the five studies classified as low risk of bias published since 2019.

Eight out of 19 of the models developed in the diabetes population and 50.0% of those developed in the general population had not been validated in an external cohort in the time window assessed. This proportion is similar to that obtained in [8]; of the 13 studies analysed, seven had been externally validated. These results reflect that there is still a great lack of validation of these studies and confirm the importance of having multiple external validations in diverse populations with differing age ranges, ethnicities, sexes and cardiovascular risks, as stated in Beswick et al. [45].

The lack of validation studies was already pointed out in Damen et al. [5], who concluded that researchers dedicate more efforts to developing new models than to validating those that are most promising. In addition to this reality, the difficulty of easily reproducing the existing models could be another important reason for the lack of validation studies. Poor reporting of the derived model, without the estimated parameters or in the absence of a baseline hazard or with a baseline hazard referred to a different time horizon, makes it difficult or even impossible to apply the model. The variety and poor reporting of the outcome of interest is also a big pitfall for the reproducibility of the models. Presenting the ICD codes used in the outcome definition would make it easier to replicate the models in different cohorts. Further, it would be of interest to establish, by consensus, a reduced list of possible outcomes with a clear set of codes for assessing CVD risk, such as one to be used when the outcome of interest is hard CVD events and another to use when we want to focus on more broad CVD events. This simplification in the outcome definition is not expected to have a negative effect on health decision making because the model behaviour does not appear to be greatly affected by the specific outcome definition, and in contrast, it would be very helpful for reproduction of the models and facilitation of their comparability, which in turn would make the models much more applicable.

This review includes a comprehensive search with a detailed study selection procedure and extensive data extraction. Furthermore, this is the first global review of cardiovascular risk models that includes risk of bias and applicability assessment using the PROBAST tool. This study has also some limitations. First, the search was carried out on a single database. Second, we focused on identifying validation studies of the presented models, and we did not perform a comprehensive search of all published validation studies or for studies analysing the impact of applying a CVD prediction model in clinical practice.

5. Conclusion

This review shows that there is a great abundance of cardiovascular risk models applicable to patients with diabetes but identifies several important gaps among them: many

have a high risk of bias regarding methodological aspects, most are not validated, and many present barriers to their application, mainly because there is no complete specification of the parameters and because there is a high variability in the outcome definition. There exists a clear need to validate the existing prediction models applicable to patients with type 2 diabetes, providing modifications to adapt them to local features or to include new predictors that add significant value to the model performance. Validating these models, together with assessing the impact of implementing them on clinical and treatment decisions, should be priority issues ahead of developing more new models with different CVD codes and unknown parameter specifications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Funding

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