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Predicting the risk of stroke among patients with type 2 diabetes: a systematic review and meta-analysis of C-statistics

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ABSTRACT

Objective Stroke is a major cause of disability and death worldwide. People with diabetes are at an increased risk for stroke compared with people without diabetes. This study systematically reviews the literature on available stroke prediction models specifically developed or validated in patients with diabetes and assesses their predictive performance through meta-analysis.

Design Systematic review and meta-analysis.

Data sources A detailed search was performed in MEDLINE, PubMed and EMBASE (from inception to 22 April 2019) to identify studies describing stroke prediction models.

Eligibility criteria All studies that developed stroke prediction models in populations with diabetes were included.

Data extraction and synthesis Two reviewers independently identified eligible articles and extracted data. Random effects meta-analysis was used to obtain a pooled C-statistic.

Results Our search retrieved 26202 relevant papers and finally yielded 38 stroke prediction models, of which 34 were specifically developed for patients with diabetes and 4 were developed in general populations but validated in patients with diabetes. Among the models developed in those with diabetes, 9 reported their outcome as stroke, 23 reported their outcome as composite cardiovascular disease (CVD) where stroke was a component of the outcome and 2 did not report stroke initially as their outcome but later were validated for stroke as the outcome in other studies. C-statistics varied from 0.60 to 0.92 with a median C-statistic of 0.71 (for stroke as the outcome) and 0.70 (for stroke as part of a composite CVD outcome). Seventeen models were externally validated in diabetes populations with a pooled C-statistic of 0.68.

Conclusions Overall, the performance of these diabetes-specific stroke prediction models was not satisfactory. Research is needed to identify and incorporate new risk factors into the model to improve models’ predictive ability and further external validation of the existing models in diverse population to improve generalisability.

INTRODUCTION

Stroke, also known as a cerebrovascular accident, is the third leading cause of disability and accounted for over 6 million deaths worldwide in 2015.12 Diabetes mellitus, characterised by chronic hyperglycaemia due to an absolute or relative deficiency in insulin, is a major risk factor for stroke. People with diabetes are at a twofold to fivefold increased risk for stroke compared with people without diabetes.2–7 Large clinical trials performed in people with diabetes supports the need for targeted cardiovascular risk reduction strategies to prevent the onset, recurrence and progression of acute stroke.8

Risk prediction models are statistical tools to estimate the probability that an individual with specific risk factors (eg, diabetes mellitus) will develop a future condition, such as stroke, within a certain time period (eg, 5 years).2 Such tools for the estimation of stroke risk are frequently used to assist in decisions about clinical management for both individuals and populations. Accurate risk prediction models of stroke is thus necessary to provide patients with accurate information on the expected benefit from a therapy or intervention. The importance of well-performing prediction models is increasingly being recognised and health researchers continue to develop parsimonious risk prediction models under different scenarios.

Strengths and limitations of this study

- The breadth of the comprehensive systematic literature search is a strength of this study.
- To our knowledge, this is the first study where a meta-analysis and study quality assessment was performed on stroke prediction models in patients with diabetes.
- We were only able to use C-statistics to compare the model performance, which might be insensitive to identify differences in models’ ability to accurately risk-stratify patients into clinically meaningful risk groups.

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to meet this demand. Model performance statistics, such as C-statistic or AUC (area under the receiver operating characteristic curve) are indicators frequently used to identify models with the best predictive ability. These metrics can be compared and assessed through a formal systematic review and meta-analysis. Performing a systematic review and meta-analysis can also provide a comprehensive quantitative summary of the predictive ability of these models and evaluate their predictive performance within the available literature.

Risk factors for stroke include lifestyle-related factors, predisposing medical conditions, specific genetic diseases, as well as sociodemographic factors. Over the past decade, a number of prediction models (or risk scores) have been developed incorporating these risk factors to predict a person’s risk of developing stroke. Prediction of stroke is important for a number of reasons: to detect or screen high-risk subjects to prevent developing stroke through early interventions, to facilitate patient–doctor communication based on more objective information and to help patients to make an informed choice regarding their treatment. While multiple stroke prediction models have been proposed in patients with diabetes, little is known about which is the most accurate one. There has also been a lack of consistency in estimating risk across these different models. With this in mind, we aimed to systematically identify all prediction models for stroke that have been applied to patients with diabetes. We characterised the study populations in which these models were derived and validated. We also assessed the predictive performance and generalisability of these stroke prediction models so that the selection of models for clinical implementation can be informed.

METHODS

Data sources and searches

Similar to previously employed methodology, we searched MEDLINE, EMBASE and PubMed (from database inception to 22 April 2019) for studies predicting the risk of stroke among patients with diabetes. We also searched the reference lists of all identified relevant publications. The search strategy focused on three key elements: diabetes, risk prediction with specific names of known risk scores and stroke. Only studies published in English were considered. The detailed search strategy is given in online supplemental table S1.

Study selection

Eligible articles were identified by two reviewers independently using a two-step process. First, an initial screen of titles and abstracts was performed. Abstracts were retained if they reported data from an original study and reported on the development and/or validation of a stroke risk prediction model for patients with type 2 diabetes. We defined a stroke risk prediction model as one combining two or more independent variables to obtain estimates of the predicted risk for developing stroke. We considered any clinical-based or laboratory-based definition of stroke. Selected abstracts were further screened based on a full-text review. We used broad inclusion criteria to provide an extensive systematic review of the topic. There were no restrictions on study design (eg, cohort study, case–control study), geographic region or age ranges. Studies that developed prediction models for stroke in populations with type 2 diabetes and in the general population were included; however, models that were developed in the general population but did not validate their model in a type 2 diabetes population or models developed on a type 1 diabetes population were excluded. A study was included if the outcome of the prediction model was any type of stroke or stroke that was part of a composite cardiovascular disease (CVD) outcome, but excluded if the outcome was any other cardiovascular conditions (eg, coronary heart disease (CHD), coronary artery disease (CAD), heart failure). We excluded studies that did not predict stroke. Studies on recurrent stroke or other vascular conditions (eg, patients with hypertension) were also excluded. Studies that focused only on the added predictive value of new risk factors to an existing prediction model without reporting the performance of the existing model were excluded. Studies on score-based tools, such as risk charts were also excluded. Agreement between reviewers at the full-text stage was quantified using the kappa statistic. Any disagreement between reviewers was solved through consensus.

Data extraction

Data were extracted from the finally selected studies using a standardised form by two reviewers. Information collected from each study included, outcome of the prediction model, location where the model was developed, predictors included in the model, age and gender of the study participants, number of events, duration of follow-up, modelling method used, measures of discrimination and calibration of the prediction model and the external validation of the prediction model. For the external validation studies, a different data extraction sheet was used. The collected information included specifics of the validation population, number of events, type of outcome, statistical tests and measures of discrimination, and calibration of the prediction model. Study quality was assessed using the CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) Checklist. The following items were evaluated for each study: Was inclusion/exclusion criteria for study participants specified? Was there non-biased selection of study participants? Did the authors discuss or consider missing values/information? Was there blinded assessment of the outcome? Was duration of follow-up adequate? Were modelling assumptions satisfied? Was the model externally validated? And was the potential clinical utility of the model discussed in light of study limitations?
Data analysis

The selection process for this systematic review and meta-analysis is summarised using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. Discrimination is defined as any assessment of the ability of the model to differentiate between subjects who will develop stroke from those who will not. The discrimination of a prediction model is often assessed using the concordance or C-statistic (also known as AUC). Calibration is defined as any report of the agreement between predicted probabilities and observed probabilities. Calibration is assessed using goodness-of-fit tests (e.g., Hosmer-Lemeshow test), calibration slopes, tabular or graphical comparisons of predicted versus observed values within groupings of predicted risk or calibration plots. In studies that only provided a C-statistic but no measure of its variance, the SE and 95% CI of the AUC (C-statistic) was calculated using the formula:

\[
\text{SE} (\text{AUC}) = \sqrt{\frac{\text{AUC}(1-\text{AUC}) \cdot [N_1-1] \cdot [\text{AUC}(2-\text{AUC}) - \text{AUC}^2] + [N_2-1] \cdot [2\text{AUC}^2/(1+\text{AUC}) - \text{AUC}^2]}{N_1 \times N_2}}
\]

where \(N_1\) = the number of patients with stroke and \(N_2\) = the number of patients without stroke and the upper 95% CI = AUC + [1.96 × SE (AUC)] and lower 95% CI = AUC − [1.96 × SE (AUC)].

The summary statistic from the individual studies was the C-statistic or AUC. We grouped studies based on the outcome of the risk prediction models developed in diabetes populations, whether stroke was the primary outcome of the model or stroke was a part of composite CVD outcome. Random effects meta-analysis was used to obtain the pooled weighted average C-statistic with 95% CIs for common groups of models using the DerSimonian and Laird method. Heterogeneity was assessed using the Cochran Q and the I² statistic and was explored using meta-regression and stratified analyses according to model outcomes. Small study effects were examined using funnel plots and Begg’s test. The analyses were performed using Stata version 13.1 (Stata, College Station, Texas, USA) using the metan, metareg, metabias and metafunnel commands.

Patient and public involvement

There was no direct patient or public involvement in this review.

RESULTS

The search retrieved 21,797 citations (after duplicate removal) with an additional 63 potentially relevant papers retrieved from our grey literature search. After title and abstract screening, 262 studies were selected for full-text screening. After examining the full-text papers, 56 studies remained (reasons for exclusion stated

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**Figure 1**  PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram for systematic review of studies presenting stroke prediction models developed or validated in individuals with diabetes.
in figure 1), describing 38 models predicting stroke in patients with diabetes. Agreement between reviewers on the final articles eligible for inclusion in the systematic review was good (κ=0.83). Of these 38 models, 34 were specifically developed in patients with diabetes and 4 were developed in the general population but later externally validated in patients with diabetes. Among the models developed in patients with diabetes, nine models reported their outcome as stroke and presented a corresponding performance measure (C-statistic) for the models. Twenty-three models reported their outcome as a composite CVD outcome where stroke was one of the components and presented the model’s performance measure (C-statistic) for the composite CVD outcome. Among the models developed in the general population, one model reported its outcome as stroke and three models reported a composite CVD outcome, which included stroke. Of these 38 prediction models, 17 were validated by 33 studies (some studies validated more than one model in the same study), of which 10 models had multiple validations, 7 models had a single validation and 21 models were not validated. Among the models with multiple validations, eight models were developed in a diabetes population (validated by 31 studies) and two were developed in the general population (validated by four studies). United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine for Stroke by Kothari et al21 was the most validated risk score (validated by 12 studies). Figure 1, describes the systematic selection process of studies presenting a stroke prediction model applicable to patients with diabetes.

Predicting the risk of stroke within models developed in populations with diabetes

Table 1 describes the study characteristics of the nine risk prediction models developed in diabetes populations and presented a corresponding performance measure. The number of participants ranged from 1748 to 26 140 in the model development. The outcome of most models was stroke regardless of type. Duration of follow-up (total/median/mean) ranged from 501 days to 10.5 years with six models having ≥5 years of follow-up (defined as long duration) and three models with <5 years of follow-up. Most of the prediction models were developed using Cox proportional hazards modelling techniques. The number of predictors included in the prediction models ranged from 4 to 29 with an average of 11 predictors per model. Several predictors were common to multiple models including age, sex, duration of diagnosed diabetes, systolic blood pressure and haemoglobin A1c (HbA1c). Only two models were externally validated after their development and four of them had never been validated in an external population. Calibration of the prediction model was reported by six studies (most commonly using the Hosmer-Lemeshow test). Discrimination was assessed using the C-statistic (or AUC) and reported by six models with values ranging from 0.64 to 0.80. The median C-statistic of the models was 0.71 with a large amount of unexplained heterogeneity in the discriminative performance of these models (I²=94.6%; Cochran Q-statistic p<0.001; figure 2). Stratifying pooled results by sample size (small vs large, p=0.19), follow-up time (short vs long, p=0.60), variables included in the model (few vs many, p=0.24) and geographic location (Asia vs others, p=0.60) did not explain the observed heterogeneity in the discriminative performance of these models. The discriminative ability of the model by Kiadaliri et al22 was highest (C-statistic=0.80). The funnel plot and Begg’s test (p=0.999) suggested the absence of small study effects, with no correlation between studies of smaller cohorts reporting higher C-statistics (online supplemental figure S1).

A set of nine criteria was used to assess the quality of the studies and was summarised in table 2. All the studies specified inclusion/exclusion criteria. Non-biased selection of study participants was clear in all studies except the study by Palmer et al.23 Handling of missing values was reported in four (44%) studies, modelling assumptions was satisfied by two studies and model external validation was performed in two studies. Stevens et al was the only study to mention whether the outcome was assessed without knowledge of the candidate predictors.24 Duration of follow-up was long (≥5 years) in six models (67%). The clinical utility of the models was discussed in six (67%) studies and almost all studies reported their study limitations.

Predicting risk of stroke (as part of a composite CVD outcome) in populations with diabetes

We identified 23 models developed in diabetes populations that reported their outcome as a composite of CVD. A summary of the characteristics of these prediction models is described in table 3. The number of participants considered in the model development ranged from 132 to 1 816 19 with an average age of >50 years. Duration of follow-up (mean, median, maximum) ranged from 11 months to 11.8 years with 14 models with ≥5 years and nine models with <5 years of follow-up. The number of predictors included in prediction models ranged from 4 to 18 with an average of 11 predictors per model. The most common predictors included in the models were age, sex, systolic blood pressure and HbA1c, smoking and high-density lipoprotein-cholesterol. Four models were externally validated after its development and 17 of them had never been validated in an external population. Calibration of the prediction models was reported by 13 studies while discrimination reported by almost all studies with C-statistics ranging from 0.60 to 0.92. The median C-statistic of the models was 0.70 with a large amount of unexplained heterogeneity in the discriminative performance of these models (I²=93.7%; Cochran Q-statistic p<0.001; figure 3). Sample size (small vs large, p=0.46), models’ external validation (externally validated vs not externally validated, p=0.71), variables included in the model (few vs many, p=0.21) and geographic location (Europe vs others, p=0.08) were not identified as significant sources of heterogeneity in the discriminative...
Table 1  Characteristics of prediction models when outcome and corresponding performance measure (C-statistic) were reported for stroke

| Study | Location | Outcome | No of Predictors | Age | Gender | Events (n)/total participants (n) | Duration of follow-up | Modelling method | Calibration | Discrimination (with CI) | External Validation |
|-------|----------|---------|------------------|-----|--------|----------------------------------|----------------------|------------------|-------------|--------------------------|-------------------|
| Yang et al[8] | Hong Kong, China | Stroke (stroke or deaths from stroke), haemorrhagic stroke and ischaemic stroke | 4 (age, A1C, spot urine ACR and history of CHD) | Median age 57 years | Both male and female | 372/7209 | Median follow-up 5.37 years | Cox proportional hazard model | The Life Table Method, Adequate calibration, value NR. | Adjusted: AUROC=0.776 (considering follow-up time and censoring); unadjusted AUROC=0.749 (0.716 to 0.782) | No |
| Kothari et al[11] | UK | Stroke (defined as a neurological deficit with symptoms or signs lasting 1 month or more) | 7 (duration of diabetes, age, sex, smoking, systolic blood pressure, total cholesterol to high-density lipoprotein cholesterol ratio and presence of atrial fibrillation) | 25 to 65 years | Both male and female | 188/4549 | Median follow-up 10.5 years | Maximum likelihood estimation using the Newton-Raphson method | NR | NR | Yes |
| Wells et al[17] | USA | CHD, heart failure, stroke, mortality | 29 (different variables for different models) | 18 years of age or older | Both male and female | Stroke: 1088/26140 | | Competing risks regression model | Calibration plot (predicted risk against actual risk): less-well calibration (stroke and mortality) | C-statistic=0.6881 (stroke) | No |
| Stevens et al, UKPDS 66[14] | UK | MI case fatality and stroke case fatality | 5 (sex, Hba1c, SBP, previous stroke, white cell count for Stroke model) | Between 25 and 65 years | Both male and female | Stroke: 234/5102 | Median follow-up of 7 years | Stepwise selection algorithm | HL test: p=0.248 (Stroke model) | NR | No |
| Tanaka et al, Risk Engine[18] | Japan | CHD, stroke, non-cardiovascular mortality, overt nephropathy and progression of retinopathy | 11 (sex, age, Hba1c, years after diagnosis, BMI, non-HDL cholesterol, ACR, atrial fibrillation, current smoker and leisure-time physical activity) | 40-84 years | Both male and female | Stroke: 89/1748 | Median follow-up of 7.2 years | Cox regression model | HL test: p=0.12 (Stroke model) | C-statistic=0.636 (0.564 to 0.708) (Stroke model) | No |
| Palmer et al, (IRS)[23] | Scotland | Fatal or non-fatal stroke | 5 genotypes (IL-6 GG/GC, MCP-1 GG, ICAM-1 EE, sel·E RR and MMP-3 5A5A) | Mean age 64.5±11.7 years | Both male and female | 108/2182 | Mean follow-up of 6.2±1.1 years | Cox regression model | HL χ² statistic: 11.22 (p=0.19) (first stroke); 8.09 (p=0.03) (second stroke) | C-statistic=0.80 (0.78 to 0.82) (first stroke); C-statistic=0.74 (0.71 to 0.77) (second stroke) | No |
| Kiadaliri et al[22] | Sweden | First and second events of: AMI, heart failure, non-acute ischaemic heart disease and stroke | 12 (age, TC/HDL, diabetes duration, Hba1c, BMI, SBP and diastolic BP, history of events before diagnosis, LDL cholesterol, albuminuria, smoking status, BMI and gender) | Male: mean age, 55.36±9.28 years; Female: mean age, 57.15±9.55 years | Both male and female | 993/21 775 (first stroke); 314/21 775 (second stroke) | 82232 person-years for first stroke and 4127 person-years for second stroke | Weibull proportional hazard model | HL χ² statistic: 11.22 (p=0.19) (first stroke); 8.09 (p=0.03) (second stroke) | C-statistic=0.80 (0.78 to 0.82) (first stroke); C-statistic=0.74 (0.71 to 0.77) (second stroke) | No |

Continued
| Study          | Location          | Outcome                          | No of Predictors                                                                 | Age                | Gender               | Events (n)/total participants (n) | Duration of follow-up | Modelling method                  | Calibration | Discrimination (with CI)         | External Validation |
|---------------|-------------------|----------------------------------|----------------------------------------------------------------------------------|--------------------|----------------------|-----------------------------------|-----------------------|----------------------------------|-------------|-------------------------------|---------------------|
| Li et al<sup>18</sup> | Taiwan            | Ischaemic stroke                 | 14 (age, gender, smoking habit, duration of type 2 diabetes, blood pressure, HbA1c level, total cholesterol to HDL ratio, creatinine, fasting plasma glucose variation, arterial embolism and thrombosis, diabetes retinopathy, hypoglycaemia, antidiabetes medication use and cardiovascular medication) | 30-84 years        | Both male and female | 2091 (derivation set), 1076 (validation set)/18 750 (derivation set), 9374 (validation set) | Mean follow-up of 8 years | Cox proportional hazard regression model | NR          | AUROC=0.72 (3 years); AUROC=0.71 (5 years); AUROC=0.68 (8 years) | No                   |
| Basu et al<sup>18</sup> | USA and Canada    | Microvascular: nephropathy, retinopathy, neuropathy; Cardiovascular: composite of atherosclerotic cardiovascular disease (first fatal or non-fatal MI or stroke), fatal or non-fatal MI, fatal or non-fatal stroke, congestive heart failure, or death from any cardiovascular cause | 14 (Age, sex, ethnicity, smoking, SBP, history of CVD, blood pressure-lowering drugs use, statin use, anticoagulants use, HbA1c, total cholesterol, HDL cholesterol, serum creatinine, urine ACR) | 40-79 years        | Both male and female | 197 (stroke)/9635 Median follow-up of 4.7 years | C-statistic for stroke=0.70 (0.66 to 0.74) (internal validation); C-statistic for stroke=0.67 (0.63 to 0.71) (external validation) | Cox proportional hazard models | Calibration slope=1.16, $\chi^2=7.4$, p value=0.38 (internal validation); calibration slope=0.99, $\chi^2=8.2$, p value=0.22 (external validation) | Yes                  |

ACR, albumin-to-creatinine ratio; AMI, acute myocardial infarction; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; Hb, haemoglobin; HbA1c, haemoglobin A1C; IRIS, inflammatory risk score; J, The JDCS-U-EDF; LDL, low-density lipoprotein; MI, myocardial infarction; NR, not reported; RECODE, Risk Equations for Complications of Type 2 Diabetes; SBP, systolic blood pressure; TC, total cholesterol; UKPDS, United Kingdom Prospective Diabetes Study.
C-statistics for stroke prediction models for diabetes patients
(Stroke is the outcome of the prediction models)

| Study ID | C-statistic (95% CI) |
|----------|----------------------|
| Yang et al. (2007) | 0.76 (0.75, 0.80) |
| Wells et al. (2013) | 0.69 (0.67, 0.71) |
| Tanaka et al. (2013) | 0.64 (0.56, 0.71) |
| Kiadalar et al. (2013) | 0.80 (0.78, 0.82) |
| Basu et al. (2017) | 0.70 (0.66, 0.74) |
| Li et al. (3-years) (2018) | 0.72 (0.71, 0.73) |
| Li et al. (5-years) (2018) | 0.71 (0.70, 0.72) |
| Li et al. (8-years) (2018) | 0.66 (0.67, 0.69) |

Figure 2  Forest plot of C-statistics, with 95% CIs of risk prediction models when outcome was reported for stroke.

The discriminative ability of the model by Ofstad et al was highest (C-statistic=0.92) when novel risk markers were added to their standard model. The funnel plot and Begg’s test (p=0.24) suggested the absence of small study effects, with no correlation between studies of smaller cohorts reporting higher C-statistics (online supplemental figure S2). Only four models were developed using logistic regression models while others were developed mostly using Cox proportional hazards models.

The study quality for this group of models is summarised in table 4. Similar to the models developed in diabetic populations that look at the outcome of stroke specifically, we found that study quality was similar.

Validation studies of stroke prediction models developed in populations with and without diabetes

Seventeen risk prediction models for stroke (developed both in patients with diabetes and in general populations) were validated in diabetes populations by 33 studies (table 5). Among the 17 validated models, 14 of them were externally validated in independent cohorts and 3 of them were internally validated in a test sample or separate data set from the same cohort. Three studies validated more than one risk model in the same cohort. Models with multiple validations (two or more) and reported C-statistics are provided in figure 4. Models that had only been validated once were excluded from meta-analysis. In addition, only those studies that provided enough information to estimate the variance of the provided C-statistic for meta-analysis were considered for analysis.

UKPDS Risk Engine for Stroke by Kothari et al was the most frequently externally validated model with a total of 12 studies reporting its performance in different diabetes cohorts. In 12 external validation studies, a total of 126323 patients were included with considerable variations in sample sizes across the different studies. The pooled C-statistic for the model by Kothari et al was 0.72
| Study                | Location          | Outcome                                                                 | No of predictors | Age            | Gender          | Duration of follow-up (N) | Modelling Method          | Calibration                  | Discrimination (with CI) | External Validation |
|----------------------|-------------------|--------------------------------------------------------------------------|------------------|----------------|-----------------|--------------------------|----------------------------|------------------------------|--------------------------|---------------------|
| Brownrigg et al      | England           | CVD events (non-fatal MI, coronary revascularisation, congestive cardiac failure, transient ischaemic attack and stroke) | 6 (age, sBP, smoking status, LDL-C and HDL-C and peripheral neuropathy) | Mean age of 63.8 years | Both male and female | 399/13043 Total 2.5 years | Probability weighted Cox regression | $\chi^2=121.2$, p<0.001 | C-statistic=0.661 (0.636 to 0.686) (with PN) | No                  |
| Khalili et al        | Iran              | CVD events (definite MI, probable MI, unstable angina, angiographic-proven CHD, stroke, death from CVD) | 4 (BMI, waist circumference, WHR, and waist-to-height ratio) | Mean age 55.7 years (male), 52.7 years (female) | Both male and female | 188/1010 Median follow-up 8.4 years | Cox proportional hazard model | NR                        | C-statistic=0.64 (0.58 to 0.70) (for diabetic men with WHR, model 2) and C-statistic=0.70 (0.65 to 0.75) (for diabetic women with WHR, model 2) | No                  |
| Cederholm et al      | Sweden            | Fatal or non-fatal CVD (CHD or stroke, whichever came first)              | 9 (A1C, age at the onset of diabetes, diabetes duration, sex, BMI, smoking, sBP, antihypertensive drugs and lipid-reducing drugs) | Mean age 18–70 years | Both male and female | 1482/11 646 Mean follow-up 5.64 years | Cox regression model | HL test: $\chi^2=4.29$ (p=0.03) and the ratio of observed to predicted survival rates=0.999. Excellent calibration | C-statistic=0.70 | No                  |
| Davis et al          | Australia         | CVD (hospitalisation for/with MI or stroke, and death from cardiac or cerebrovascular causes or sudden death) | 7 (age, sex, prior CVD, ln (urinary albumin : creatinine ratio), lnHbA1C, ln(HDL-C), Southern European ethnic background and aboriginality) | Mean age 64.1 (38.7–83.7) years | Both male and female | 185/1240 Mean follow-up 4.5 years | Cox proportional hazards model | HL$^2$ test, p=0.74 | AUC=0.80, p<0.001 | Yes                  |
| Kengne et al         | 20 Countries      | CVD (fatal or non-fatal MI or stroke or CV death)                         | 10 (age at diagnosis, known duration of diabetes, sex, pulse pressure, treated hypertension, atrial fibrillation, retinopathy, HbA1c, log of urinary albumin/creatinine ratio and non-HDL-C at baseline) | Mean age 65.8 (6.3) years | Both male and female | 473/1688 4.5 years | Cox regression model | HL test: p=0.76 (ADVANCE cohort) AUC=0.702 (0.676 to 0.728) (ADVANCE cohort) | Yes                  |
| Ofstad et al         | Norway            | Death or first CV event (MI, stroke or hospitalisation for unstable angina pectoris) | 11 (age, gender, known CVD, dBP, microalbuminuria, serum levels of HDL-C and creatinine), novel risk markers: (IL-6, log Activin A, E/E', Em, pathol recovery loop) | Mean age 58.5±10.0 (SD) years | Both male and female | 36/132 8.6±2.1 years | Cox proportional hazard model | NR                        | C-statistic: STD model: 0.794; STD + IL-6 model: 0.913; STD + log Activin A model: 0.859; STD + IL-6 + log Activin A model: 0.923; STD + E/E' + pathol recovery loop model: 0.891 | No                  |
| Looker et al         | Five cohorts from Europe | CVD (acute CHD or an ischaemic stroke) | 14 (age, sex, smoking, sBP and dBP, LDL-C, HDL-C, triacylglycerol, diabetes duration, HbA1C, BMI, height, (eGFR, cohort and current medication (including antihypertensive agents, aspirin, lipid-lowering agents and insulin therapy)). +6 Biomarkers (NT-proBNP, apoCIII hsTnT IL-6 sRAGE IL-15) | Mean age 68.4 years (controls) and 68.8 years (cases) | Both male and female | 1123/2310 Median follow-up 3.2 years for cases and 6.5 years for controls | Forward selection using logistic regression | NR                        | AUROC=0.72 (full clinical covariate set plus forward selection biomarkers) | No                  |

Continued
| Study                   | Location  | Outcome                              | No of predictors                                                                 | Events (n/total participants (N))                      | Duration of follow-up | Modelling Method               | Calibration                        | Discrimination (with CI) | External Validation |
|------------------------|-----------|--------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------|------------------------|--------------------------------|-----------------------------------|------------------------|----------------------|
| Mukamal et al          | USA       | MI, stroke, CV death                 | 7 in basic model (Age, smoking, sBP, total cholesterol, HDL-C, creatinine and the use of glucose-lowering agents) | Mean age 72.6 years for female and 73.0 years for male | 265/782                | Cox proportional hazard model | Basic model: HL p=0.25; basic model+CRP; HL p=0.87; Basic Model +CRP + ABI, internal carotid wall thickness, ECG left ventricular hypertrophy: HL p=0.65 | Yes                    |
| Paynter et al          | USA       | MI, ischaemic stroke, coronary revascularisation or CV death | 8 in different models (age, sBP, total cholesterol, HDL-C, smoking, CRP, parental history of premature MI and HbA1c) | Median age 55 years for female and 67.8 years for male | 125/685 (women); 170/563 (men) | Cox proportional hazards model | C-statistic=0.64 | No                     |
| Price et al            | Scotland  | All CV events (fatal and non-fatal MI, angina, fatal IHD, fatal and non-fatal stroke and TIA) | 18 (age, sex, baseline CVD status, duration, diabetes treatment, lipid-lowering drugs, BP-lowering drugs, smoking status, BMI, sBP, dBP, HbA1c, HDL-C, total cholesterol, eGFR, microalbuminuria and social status «NT-proBNP» (model D) | Median follow-up 10.2 years (women); median follow-up 11.8 years (men) | Cox proportional hazards model | C-statistic=0.692 (ATP III) and=0.697 (RRS) for women; C-statistic of model with HbA1c=0.692 (ATP III) and=0.605 (RRS) for men. | No | No                     |
| Selby et al            | USA       | Macrovascular and microvascular complications (MI, other ischaemic heart disease, congestive heart failure, cerebrovascular accident, etc) | 16 (outpatient diagnoses, inpatient events, age, antihypertensives, serum creatinine, diabetes treatment, mean HbA1c, albuminuria, primary care visits, outpatient diagnoses of obesity, outpatient ID diagnoses, mean total cholesterol, self-report of neuropathy, education, type of diabetes, sex) | Mean age of 60.8 years | 1997/28 838 | Logistic regression model | AUC=0.64 (full model) | No | No                     |
| Zethelius et al        | Sweden    | Fatal/non-fatal CVD (the composite of CHD or stroke) | 12 (onset age of diabetes, diabetes duration, total-cholesterol-to-HDL-C ratio, HbA1c, sBP, BMI, males sex, smoker, microalbuminuria, macroalbuminuria, atrial fibrillation, previous CVD) | 30–74 years | 2488/24 288 | Cox proportional hazard model | Modified HL $\chi^2$ statistic=0.13 (p=0.3) | C-statistic=0.71 | No                     |
| Alrawahi et al         | Oman      | First fatal or non-fatal CHD, stroke, or PAD | 7 (age, diabetes duration, HbA1c, total cholesterol, albuminuria, hypertension, BMI) | Mean follow-up of 4.8 years | 192/2039 | Cox regression model | NR | No                     |
| Study          | Location   | Outcome                                                                 | No of predictors                                                                 | Age                  | Gender                  | Duration of follow-up | Modelling Method                  | Calibration                        | Discrimination (with CI)                                                                 | External Validation |
|---------------|------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------|-------------------------|------------------------|-----------------------------------|-------------------------------------|-----------------------------------------------------------------------------------------|---------------------|
| Zarkogianni et al<sup>56</sup> | Greece     | Fatal or non-fatal CVD: stroke and CHD                                  | 16 (age, diabetes duration, BMI, glycosylated haemoglobin, pulse pressure, fasting glucose, total cholesterol, triglycerides, HDL-C, smoking habit, sex, hypertension, lipid-lowering therapy, aspirin, insulin therapy, parental history of diabetes) | 58.56±10.70 years   | Both male and female   | 5-year follow-up         | Machine learning: HWNNs and SOMs | Brier score: 0.08±0.01 (HWNN-based ensemble 4); 0.07±0.01 (SOM-based ensemble 4); 0.007±0.02 (hybrid ensemble) | AUC=0.6764±0.1509 (HWNN-based ensemble 4); AUC=0.7054±0.1372 (SOM-based ensemble 4); AUC=0.7148±0.1573 (hybrid ensemble) | No |
| Price et al<sup>57</sup>  | Scotland   | Fatal or non-fatal MI or stroke, angina, fatal IHD, TIA, coronary intervention | 13 (age, sex, smoking, atrial fibrillation, CKD, arthritis, hypertension, BMI, SBP, total HDL-C, social status, baseline CVD status, lipid-lowering medication) in basic model + (ABI, hs-cTnT, GGT, proBNP, g) in full model | 60–75 years          | Both male and female   | 8 years                 | Binary logistic regression   | C-statistic=0.722 (0.681 to 0.763) (basic model), C-statistic=0.74 (0.699 to 0.781) (full model) | No |
| Wan et al<sup>58</sup>   | China      | IHD, MI, coronary death and sudden death, heart failure, fatal and non-fatal stroke | 13 (age, eGFR, total cholesterol/HDL-C ratio, urine ACR, smoker, duration of diabetes mellitus, sBP, HbA1c, anti-hypertensive drugs used, DBP, BMI, insulin used, anti-glucose oral drugs used) | 18–79 years          | Both male and female   | Median follow-up of 5 years | Cox proportional hazard regression | Calibration plots: good calibration | Harrell’s C-statistic Male: 0.705 (0.693 to 0.718) (model 1), 0.689 (0.678 to 0.701) (model 2); Female: 0.719 (0.707 to 0.731) (model 1) 0.708 (0.696 to 0.719) (model 2) | No |
| Young et al<sup>59</sup> | USA        | MACE: non-fatal MI, non-fatal stroke and CVD-related death; MACE-plus: any MACE, hospitalisation for unstable angina, or hospitalisation for congestive heart failure; CVD-related death | 12 (age, gender, type of insurance, race, region, diabetes-related hospitalisations, prior CVD diagnoses, chronic pulmonary disease, use of antithyroidotropic drugs, use of antihypergammaglobulin, drugs, HbA1c, urine ACR) | 50 years or older    | Both male and female   | Median duration of the at-risk period: 12 months (primary prevention population) and 11 months (secondary prevention population) | Logistic regression | NR                              | C-statistic=0.70 (MACE); C-statistic=0.72 (MACE-plus); C-statistic=0.77 (CVD-related death) | No |
| van der Leevu et al<sup>60</sup> | The Netherlands | Major CV events (MI, stroke and vascular death) | 12 (age at diabetes diagnosis, duration of diagnosed diabetes, sex, smoking, HbA1c, sBP, total cholesterol/HDL-C ratio, previous CV event, urinary ACR or eGFR) in base model + NT-proBNP, osteopontin, and MMP-3 in multimarker model | Mean age 59±10 years (SMART), 59±7 (EPIC-NL) | Both male and female | Median follow-up 9.2 years in SMART and 11.3 years in EPIC-NL | Cox proportional hazard model | Calibration plots | Base model: C-statistic=0.70 (0.67 to 0.74) (SMART), C-statistic=0.69 (0.64 to 0.74) (EPIC-NL); Multimarker model: C-statistic=0.73 (0.68 to 0.79) (SMART), C-statistic=0.72 (0.64 to 0.77) (EPIC-NL) | No |

Table 3  Continued
| Study | Location | Outcome | No of predictors | Age | Gender | Duration of follow-up | Modelling Method | Calibration | Discrimination (with CI) | External Validation |
|-------|----------|---------|-----------------|-----|--------|----------------------|-----------------|------------|------------------------|------------------|
| Alshehry et al (41) | 20 countries from Asia, Australasia, Europe and North America | Non-fatal MI, non-fatal stroke, and CV death | 14 (age, sex, BMI, SBP, glycocaehaemoglobin, LDL-C, eGFR, diabetes duration, CRP, history of macrovascular disease, history of heart failure, use of antihypertensive medication, use of antiplatelet medication, exercise) in base model + 7 lipid species | Mean age 67 years | Both male and female | Median follow-up of 5 years | Weighted Cox regression | NR | Base model: C-statistic=0.68 (0.678 to 0.682); base model + 7 lipid species: C-statistic=0.70 (0.698 to 0.702) | No |
| Woodward et al (30) | The AD-ON Risk Score (42) | 20 countries from Asia, Australasia, Europe and North America | Non-fatal MI, non-fatal stroke or death from any CV cause, renal death or requirement for renal replacement therapy or renal transplantation | Mean age of 65.8 years | Both male and female | Median follow-up of 9.9 years | Cox regression model | Calibration plots and HL test (p=0.13). Excellent calibration | C-statistic=0.668 (0.651 to 0.685) | No |
| Paninello et al (43) | USA | Incident CHD, stroke, heart failure, CKD, lower extremity amputation or peripheral vascular bypass | 18 (age, sex, race, education, smoking status, alcohol consumption, physical activity, family history of CVD, glucose-lowering medication use, antihypertensive medication use, cholesterol-lowering medication use, recent onset of diabetes, BMI, LDL-C, HbA1C, triglycerides, sBP, HbA1C) + 12 biomarkers | Mean age of 58.1 years | Both male and female | Median follow-up of 10 years | Fine and Gray model | Calibration plots: well calibrated | C-statistic=0.667 (0.64 to 0.70) (model 1); C-statistic=0.683 (0.65 to 0.71) (model 2); C-statistic=0.694 (0.66 to 0.72) (model 3); C-statistic=0.716 (0.69 to 0.74) (model 4) | No |
| Colombo et al (44) | UK and Ireland | Acute CHD (MI, unstable angina, revascularisation or acute CHD death), fatal or non-fatal stroke | 8 (age, sex, SBP, total cholesterol, LDL-C, smoking status, apoCIII and NT-proBNP) | Mean age of 62.9 years | Both male and female | Maximum follow-up of 5 years | Cox proportional hazard model | NR | AUROC=0.661 (0.615 to 0.706) (Framingham covariates alone); AUROC=0.745 (0.701 to 0.789) (full model with additional biomarkers) | No |
| Elley et al (NZ DCS) (45) | New Zealand | Fatal or non-fatal CVD event (ischaemic heart disease, cerebrovascular accident/transient ischaemic attack, PAD) | 9 (age at diagnosis, diabetes duration, sex, SBP, smoking status, total cholesterol: HDL ratio, ethnicity, glycated HbA1C, urine ACR) | Median age of 59 years | Both male and female | Median follow-up of 3.9 years | Cox proportional hazards regression models | Calibration plot AUROC=0.68 (0.67 to 0.70) (CVD) | Yes |

ABI, ankle-brachial index; AD-ON, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation—Observational ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; apoCIII, Apolipoprotein C-III; ATP, Adult Treatment Panel; AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; CRP, C reactive protein; CV, cardiovascular; CVD, cardiovascular disease; dFFP, diastolic blood pressure; eGFR, estimated glomerular filtration rate eGFR-NL, European Prospective Investigation into Cancer and Nutrition Netherlands; GGT, gamma-glutamyl transferase; HbA1C, haemoglobin A1C; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; IL-6, interleukin 6; IHD, ischaemic heart disease; Lp(a), lipoprotein (a); LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; MMP-3, matrix metalloproteinase-3; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NZ DCS, New Zealand Diabetes Cohort Study; PAD, peripheral artery disease; PH, peripheral neuropathy; RPR, Rapid Plasma Reagin; sBP, systolic blood pressure; SMART, second manifestations of arterial disease; SOMs, self-organising maps; STD, standard; TIA, transient ischaemic attack; VAF, wrist-to-hip ratio.
C-statistics for stroke prediction models for diabetes patients

(Stroke is a part of a composite cardiovascular disease outcome)

| Study ID | C-statistic (95% CI) |
|----------|----------------------|
| Selby et al. (2001) | 0.64 (0.63, 0.65) |
| Cushman et al. (2008) | 0.70 (0.69, 0.72) |
| Davis et al. (2010) | 0.69 (0.76, 0.84) |
| Elly et al. NZDGS Score (2010) | 0.68 (0.67, 0.70) |
| Kengne et al. (2011) | 0.70 (0.65, 0.73) |
| Paynter et al. (Men) (2011) | 0.60 (0.56, 0.65) |
| Paynter et al. (Women) (2011) | 0.69 (0.64, 0.75) |
| Zihlout et al. (2011) | 0.70 (0.70, 0.72) |
| Kholi et al. (Men) (2012) | 0.64 (0.56, 0.70) |
| Kholi et al. (Women) (2012) | 0.70 (0.85, 0.75) |
| Ohtani et al. (2013) | 0.79 (0.70, 0.89) |
| Mukamal et al. (2013) | 0.64 (0.60, 0.68) |
| Browning et al. (2014) | 0.68 (0.64, 0.69) |
| Price et al. (2014) | 0.75 (0.69, 0.81) |
| Looker et al. (2015) | 0.72 (0.70, 0.74) |
| van der Lee et al. (Base Model SMART) (2016) | 0.70 (0.67, 0.74) |
| van der Lee et al. (Base Model EPIC-NL) (2016) | 0.69 (0.64, 0.74) |
| van der Lee et al. (Multimarker model SMART) (2016) | 0.73 (0.68, 0.79) |
| van der Lee et al. (Multimarker Model EPIC-NL) (2016) | 0.72 (0.64, 0.77) |
| Alshohry et al. (Base Model) (2016) | 0.68 (0.64, 0.68) |
| Alshohry et al. (Bone Model + 7 lipid species) (2016) | 0.70 (0.70, 0.70) |
| Woodward et al. The AD-ON Risk Score (2016) | 0.67 (0.65, 0.69) |
| Pavlinco et al. Model 1 (2016) | 0.67 (0.64, 0.70) |
| Pavlinco et al. Model 2 (2016) | 0.68 (0.65, 0.71) |
| Pavlinco et al. Model 3 (2016) | 0.69 (0.66, 0.72) |
| Pavlinco et al. Model 4 (2016) | 0.72 (0.69, 0.74) |
| Price et al. (Basic Model) (2017) | 0.72 (0.68, 0.76) |
| Price et al. (Full Model) (2017) | 0.74 (0.70, 0.78) |
| Wan et al. Model 1 (2017) | 0.70 (0.69, 0.72) |
| Wan et al. Model 2 (2017) | 0.68 (0.68, 0.70) |
| Wan et al. Model 1 Female (2017) | 0.72 (0.71, 0.73) |
| Wan et al. Model 2 Female (2017) | 0.70 (0.70, 0.72) |
| Zarkogianni et al. (HVN based ensemble 4) (2018) | 0.68 (0.66, 0.69) |
| Zarkogianni et al. (SM-based ensemble 4) (2018) | 0.71 (0.69, 0.73) |
| Young et al. MACE (2018) | 0.71 (0.70, 0.73) |
| Young et al. MACE-pilot (2018) | 0.72 (0.72, 0.72) |
| Coleman et al. Model with Framingham covariates alone (2018) | 0.68 (0.62, 0.71) |
| Coleman et al. Full Model (2018) | 0.75 (0.70, 0.79) |

Figure 3  Forest plot of C-statistics, with 95% CIs of risk prediction models when stroke was reported as part of a composite cardiovascular disease outcome. AD-ON, Action in Diabetes and Vascular Disease:Preterax and Diamicron Modified Release Controlled Evaluation—Observational; EPIC-NL, European Prospective Investigation into Cancer and Nutrition—Netherlands; HWWNs, hybrid wavelet neural networks; MACE, major adverse cardiovascular event; NZDCS, New Zealand Diabetes Cohort Study; SMART, second manifestations of arterial disease; SOMs, self-organising maps.

(95% CI, 0.68 to 0.75), with high heterogeneity identified (I²=95%; Cochran Q statistic p<0.001). Stratification by sample size (small vs large, p=0.69), geographic location (Asia vs others, p=0.09) and stroke type (fatal vs non-fatal, p=0.07) did not explain the observed heterogeneity in the discriminative performance of this model. UKPDs Risk Engine by Stevens et al. was the second most externally validated model with five validation studies including 2826 patients. One study did not report the number of participants and none of the studies reported C-statistics. As a result, a pooled C-statistic and heterogeneity was not possible to assess for this model. The UKPDs Outcomes Model by Clarke et al. was externally validated by four studies including 65,056 patients. The pooled C-statistic was 0.66 (95% CI, 0.61 to 0.71) with high heterogeneity between studies (I²=84.5%; Cochran Q statistic p=0.002). Similar to the UKPDs Risk Engine for Stroke, stratification across select study characteristics did not explain the observed heterogeneity. The Framingham risk score by Anderson et al. was externally validated in two studies including 8574 patients. The pooled C-statistic was 0.58 (95% CI, 0.54 to 0.61) with non-significant heterogeneity between studies (I²=36.1%; Cochran Q statistic p=0.102). The Framingham risk score by D’Agostino et al. was externally validated in two studies including 7604 patients. One study (Ataoglu et al.) did not report the C-statistic for the model and one study (Kengne et al.) reported two C-statistic values, one for major events and one for any event. The pooled C-statistic for these two values was 0.58 (95% CI, 0.55 to 0.60). Models by Mukamal et al., Davis et al., Kengne et al. and Zethelius et al. were each externally validated by two studies with pooled C-statistics of 0.67 (95% CI, 0.67 to 0.68), 0.75 (95% CI, 0.58 to 0.92), 0.67 (95% CI, 0.65 to 0.69) and 0.69 (95% CI, 0.63 to 0.75), respectively. Observed heterogeneity was high in models by Davis et al. and Zethelius et al. while low in models by Mukamal et al. and Kengne et al. The model by Basu et al. was externally validated by two studies in three different population yielding a pooled C-statistic of 0.71 (95% CI, 0.67 to 0.76) with moderate heterogeneity between studies (I²=56.8%; Cochran Q statistic p=0.099). Separate models by D’Agostino et al. (Framingham Stroke Risk Score), Yang et al. (Hong Kong Diabetes Registry for Stroke), Kiadaliri et al., Stevens et al. (UKPDs 66), Hippisley-Cox et al. (Q Risk2), Elley et al. (New Zealand Diabetes Cohort Study) and Alrawahi et al. were each validated in one external or separate cohort with sample sizes ranging from 178 to 1,813,999 patients. For the studies that reported discrimination, C-statistics ranged from 0.67 to 0.79. In addition, calibration assessed by calibration plots and Hosmer-Lemeshow tests found good calibration in most studies.
Table 4  Study quality assessment of prediction models when stroke is reported as a part of composite CV outcome and performance measure (C-statistic) is presented for the composite CV outcome

| Study                      | Inclusion/exclusion criteria specified | Non-biased selection | Missing value/loss to follow-up considered | Modelling assumptions satisfied | Model external validation | Outcome assessed without knowledge of the candidate predictors (ie, blinded) | Duration of follow-up long enough | Potential clinical use of the model discussed | Study limitations discussed |
|----------------------------|---------------------------------------|-----------------------|-------------------------------------------|---------------------------------|---------------------------|------------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------------------|-----------------------------|
| Brownrigg et al.¹⁵         | Yes                                   | No                    | No                                        | No                              | No                        | Not clear                                                              | No                               | Yes                                                                      | Yes                         |
| Khalili et al.¹⁰           | Yes                                   | No                    | No                                        | Yes                             | No                        | Not clear                                                              | Yes                              | No                                                                      | Yes                         |
| Cederholm et al²¹          | Yes                                   | Not clear             | No                                        | Yes                             | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Davis et al³³              | No clear                              | Not clear             | No                                        | Yes                             | No                        | Not clear                                                              | No                               | No                                                                      | No                          |
| Kengne et al²⁴             | Yes                                   | Yes                   | No                                        | Yes                             | No                        | Not clear                                                              | No                               | Yes                                                                      | Yes                         |
| Ofstad et al²⁵             | Yes                                   | No clear              | Yes                                       | Yes                             | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Looker et al²²             | Yes                                   | Not clear             | Yes                                       | No                              | No                        | Not clear                                                              | No                               | Yes                                                                      | Yes                         |
| Mukamel et al²³            | Yes                                   | Yes                   | Yes                                       | Yes                             | Not clear                 | Yes                                                                    | No                               | Yes                                                                      | Yes                         |
| Paynter et al²³            | Yes                                   | Yes                   | No                                        | Yes                             | Not clear                 | Yes                                                                    | Yes                              | Yes                                                                      | Yes                         |
| Price et al²⁴              | Yes                                   | Not clear             | No                                        | No                              | No                        | Not clear                                                              | No                               | No                                                                      | Yes                         |
| Selby et al⁵⁵              | Yes                                   | Yes                   | Yes                                       | No                              | No                        | Not clear                                                              | No                               | Yes                                                                      | Yes                         |
| Zethelius et al²⁵          | Yes                                   | Not clear             | No                                        | Yes                             | No                        | Not clear                                                              | No                               | Yes                                                                      | Yes                         |
| Alrawahi et al⁴¹           | Yes                                   | Yes                   | No                                        | Yes                             | No                        | Not clear                                                              | No                               | Yes                                                                      | Yes                         |
| Zarkogianni et al²⁶        | No                                    | Not clear             | No                                        | Yes                             | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Price et al²⁷              | No clear                              | Yes                   | No                                        | No                              | No                        | Not clear                                                              | No                               | Yes                                                                      | Yes                         |
| Wan et al³⁴                | Yes                                   | Yes                   | Yes                                       | Yes                             | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Young et al³⁹              | Yes                                   | Not clear             | No                                        | Not clear                       | Yes                      | No                                                                    | Yes                              | Yes                                                                      | Yes                         |
| Van der Leeuw et al⁴⁰     | Yes                                   | No clear              | Yes                                       | Not clear                       | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Alshehry et al⁶¹           | Yes                                   | Yes                   | Not clear                                 | No                              | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Woodward et al. The AD-ON Risk Score⁶² | Yes                                   | Not clear             | Not clear                                 | No                              | Not clear                 | No                                                                    | Yes                              | Yes                                                                      | Yes                         |
| Parrinello et al³³         | Yes                                   | Yes                   | No                                        | Not clear                       | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Colombo et al⁴⁴            | Yes                                   | Yes                   | No                                        | Not clear                       | No                        | Not clear                                                              | Yes                              | Yes                                                                      | Yes                         |
| Elley et al. NZ DCS³⁰      | Yes                                   | Not clear             | Yes                                       | Yes                             | No                        | Not clear                                                              | No                               | Yes                                                                      | No                          |

AD-ON, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation-Observational; NZ DCS, New Zealand Diabetes Cohort Study.
Table 5  Characteristics of the validation studies of the stroke prediction models

| Study name | No of Studies | Validation study | Location | Outcome | Age | Gender | Events (n)/Total participants (N) | Calibration | Discrimination (with CI) |
|------------|---------------|------------------|----------|---------|-----|--------|---------------------------------|-------------|-------------------------|
| Kothari et al, UKPDS Risk Engine for Stroke (UKPDS 60) | 12 | Kenge et al | 20 Countries (Australia, Asia, Europe, North America) | Major CHD, major CVD and major cerebrovascular event (death from cerebrovascular disease and non-fatal stroke) | Mean age 66 years for both males and females | Both male and female | 288/7502 | HL χ²=138.7 (p<0.0001) (major event); HL χ²=114.3 (p<0.0001) (any event) | AUC=0.62 (major event); AUC=0.61 (any event) |
| Davis et al | Australia | Fatal stroke, all stroke | Mean age of 62.2 years | Both male and female | 13 (fatal stroke), 23 (all stroke)/791 | HL χ²-test: p=0.06 (fatal stroke) and p=0.33 (all stroke), good calibration | AUC=0.88 (0.81 to 0.96) (fatal stroke); AUC=0.86 (0.78 to 0.93) (all stroke) |
| Jiao et al | Hong Kong | Stroke | Mean age 64.3 years (RAMP-DM) and 65.3 years (control) | Both male and female | Total CVD events n=10 (RAMP-DM) and n=13 (control group) | NR | NR |
| Yang et al | Hong Kong, China | Stroke | Median age 57 years | Both male and female | 182/3541 | NR | Unadjusted AUROC=0.588 (0.549 to 0.626) |
| Lahoz-Rallo et al | Spain | Cerebrovascular risk (stroke) | Mean age 65.5 years | Both male and female | Events (n) NR/n=1846 | NR | NR |
| Metcalf et al | New Zealand | Stroke | 35 to 74 years | Both male and female | Events (n) NR/n=423 | NR | NR |
| Tanaka et al | Japan | Stroke | 40 to 84 years | Both male and female | 89/1748 | HL test: (p=0.54) | C-statistic=0.638 (0.566 to 0.711) |
| Wells et al | USA | Stroke | 18 years of age or older | Both male and female | Events (n): stroke (1088)/total participants (N: stroke (26 140) | Risk underestimated when examining calibration in the large | C- statistic=0.752 |
| Bannister et al | UK | CHD, fatal CHD, stroke, fatal stroke | Mean age 60.3 years (male) and 62.6 years (female) | Both male and female | 6717/79 966 (stroke, 7037/79 966 (fatal stroke) | NR | C-statistic=0.73 (0.72 to 0.74) (stroke, female), C-statistic=0.71 (0.70 to 0.72) (Stroke, male), C-statistic=0.77 (0.74 to 0.80) (fatal stroke, female), C-statistic=0.78 (0.76 to 0.81) (fatal stroke, male) |
| Study name | No of Studies | Validation study | Location | Outcome | Age | Gender | Events (n) | Total participants (N) | Calibration | Discrimination (with CI) |
|------------|---------------|------------------|----------|---------|-----|--------|------------|------------------------|------------|------------------------|
| Wu et al\(^{29}\) | 70 | China | Stroke and CHD | 20 years and above | Both male and female | Events (n) NR/ n=1584 | NR | NR |
| Ipadeola et al\(^{71}\) | 71 | Nigeria | CHD and stroke | Mean age 60.5±9.89 years | Both male and female | Events (n) NR/340 | NR | NR |
| Clarke et al, UKPDS Outcomes Model\(^{27}\) | 4 | UK | MI/stroke/MI/heart failure/amputation/ blindness/renal failure/death from any cause | Mean age 62 years | Both male and female | Events (n) NR/ n=4031 | Calibration plots: overestimated | C-statistic=0.68 (0.65 to 0.71) (stroke) |
| McEwan et al\(^{72}\) | UK | CHF/MI/stroke/blindness/ESRD/amputation | Mean age 51.49 years (low risk) and 66.08 years (intermediate) | Both male and female | 723 (stroke)/54 169 (all in low-risk patient) | NR | ROC=0.62 (stroke) |
| Pagano et al\(^{74}\) | Italy | MI, other IHD, stroke, CHF and amputation (2000 survey) and mortality (1991 survey) | Mean age 57.9 years (1991 survey) and 57.4 years (2000 survey) | Both male and female | Events (n) NR/ n=2514 (2000 survey) and n=1443 (1991 survey) | NR | NR |
| Tao et al\(^{75}\) | UK, Denmark and the Netherlands | MI and stroke | 40–69 years (50–69 years in the Netherlands) | Both male and female | Events (n) NR/2899 | HL test: p=0.33 (Stroke) | AUROC=0.70 (0.64 to 0.77) (stroke) |
| Stevens et al, UKPDS Risk Engine (UKPDS 53)\(^{26}\) | 5 | India | CHD and stroke | Mean age 63.3 years | Both male and female | NR | NR | NR |
| Moazzam et al\(^{77}\) | Pakistan | CHD, fatal CHD, stroke, fatal stroke | 30–74 years | Both male and female | Events (n) NR/470 | NR | NR |
| Ezenwaka et al\(^{78}\) | Trinidad and Tobago | Absolute CHD and stroke | Mean age 63.1 years (male) and 59.5 years (female) | Both male and female | Events (n) NR/325 | NR | NR |
| Sun et al\(^{79}\) | China | CHD and stroke | 21–94 years (58.4±12.9 years) | Both male and female | Events (n) NR/863 (no of patients with CKD) | NR | NR |
| Pang et al\(^{80}\) | China | CHD and stroke | 21–90 years | Both male and female | Events (n) NR/1178 | NR | NR |

Continued
| Study name                                      | No of Studies | Validation study | Location                        | Outcome                                                                 | Age               | Gender                      | Events (n) / Total participants (N) | Calibration | Discrimination (with CI) |
|------------------------------------------------|---------------|------------------|---------------------------------|-------------------------------------------------------------------------|-------------------|-----------------------------|----------------------------------|-------------|--------------------------|
| Anderson et al., (Framingham Risk Score)     | 2             | Herder et al     | Germany                         | MI, stroke, cardiovascular death                                       | NR                | Both male and female        | 84/1072                          | Observed/expected events reported. | C-statistic=0.636                  |
|                                                                                             |                |                   |                                 |                                                                         |                   |                             |                                   | Good calibration <p <0.05 in all quintiles except quintile 4 |                     |
| Kengne et al,                                    |               | 20 countries     | Germany                         | MI, stroke, cardiovascular death                                       | NR                | Both male and female        | 288/7502                          | HL $\chi^2=42.7$ (p<0.0001) (major event); HL $\chi^2=149.0$ (p<0.0001) (any event) | AUC=0.568 (major event); AUC=0.555 (any event) |
| (Australasia, Asia, Europe, North America)      |                |                   |                                 |                                                                         |                   |                             |                                   | AUC=0.587 (major event); AUC=0.567 (any event) |                     |
| D’Agostino et al,                               | 2             | Ataoglu et al     | Turkey                          | Cardiovascular death, non-fatal MI, angina, ischaemic stroke           | NR                | Both male and female        | 66/102                           | NR                        | NR                       |
| (Framingham Risk Score)                        |                |                   |                                 |                                                                         |                   |                             |                                   |                                   |                     |
| Kengne et al,                                    |               | 20 countries     | Germany                         | Major CHD, major CVD and major cerebrovascular event (death from cerebrovascular disease and non-fatal stroke) | Mean age 66 years for both male and female | Both male and female | 288/7502                          | HL $\chi^2=19.9$ (p<0.0004) (major event); HL $\chi^2=32.7$ (p<0.0001) (any event) | AUC=0.587 (major event); AUC=0.567 (any event) |
| (Australasia, Asia, Europe, North America)      |                |                   |                                 |                                                                         |                   |                             |                                   | AUC=0.587 (major event); AUC=0.567 (any event) |                     |
| D’Agostino et al,                               | 1             | Costa et al      | Spain                           | Stroke                                                                  | 55–85 years       | Both male and female        | 9/178                            | NR                        | NR                       |
| (Framingham Stroke Risk)                      |                |                   |                                 |                                                                         |                   |                             |                                   |                                   |                     |
| Yang et al, (Hong Kong Diabetes Registry for Stroke) | 1           | Yang et al       | Hong Kong                       | Stroke                                                                  | Median age 57 years | Both male and female | 182/3541                          | The Life Table method, adequate calibration | Unadjusted AUROC=0.748 (0.716 to 0.782) and adjusted AUROC=0.776 |
|                                             |                |                   |                                 |                                                                         |                   |                             |                                   |                                   |                     |
| Mukamal et al,                                 | 2             | Mukamal et al    | USA                             | MI, stroke, cardiovascular death                                       | 45–84 years       | Both male and female        | 71/843                           | NR                        | Basic model: C - statistic=0.65; basic model+CRP: C-statistic=0.66; basic model+CRP + (ABI, internal carotid wall thickness, ECG left ventricular hypertrophy): C-statistic=0.68 |
|                                             |                |                   |                                 |                                                                         |                   |                             |                                   |                                   |                     |
| Read et al,                                    | 1             | Scotland         | Scotland                        | Hospital admission or death from MI, stroke, unstable angina, transient ischaemic attack, peripheral vascular disease, and coronary, carotid, or major amputation procedures | 30–89 years       | Both male and female        | 14 081/181 399 | Calibration plots: better calibration | C-statistic=0.674 (0.669 to 0.679) |
|                                             |                |                   |                                 |                                                                         |                   |                             |                                   |                                   |                     |
| Kadalirii et al,                               | 1             | Kadalirii et al  | Sweden                          | First and second events of: AMI, heart failure, non-acute IHD and stroke | Mean age 55.33 years (male) and 56.89 years (female) | Both male and female | NR/7259                          | HL $\chi^2$ statistic: 11.61 (p=0.17) (first stroke); 9.99 (p=0.27) (second stroke) | C-statistic=0.79 (0.76 to 0.82) (first stroke); C-statistic=0.70 (0.64 to 0.75) (second stroke) |
| Study name                  | No of Studies | Validation study | Location     | Outcome                                                                 | Age                                  | Gender                  | Events (n) /Total participants (N) | Calibration | Discrimination (with CI) |
|----------------------------|---------------|------------------|--------------|--------------------------------------------------------------------------|--------------------------------------|-------------------------|-----------------------------------|-------------|--------------------------|
| Davis et al, (Fremantle)   | 2             | Davis et al     | Australia    | CVD (hospitalisation for/with MI or stroke, and death from cardiac or cerebrovascular causes or sudden death) | Mean age 65.3 (35.9-89.0) years      | Both male and female     | 24/180                            | HLT, C-test, p=0.85; good calibration | AUC=0.84 (0.76 to 0.91); p<0.001 |
| Read et al                 | 3             | Scotland        |              | Hospital admission or death from MI, stroke, unstable angina, transient ischaemic attack, peripheral vascular disease, and coronary, carotid or major amputation procedures | 30-89 years                         | Both male and female     | 14 081/181 399                    | Calibration plots | C-statistic=0.665 (0.660 to 0.670) |
| Kangne et al, (ADVANCE)    | 2             | Kangne et al    | 16 countries | CVD (fatal or non-fatal MI or stroke or cardiovascular death)             | Mean age 64.4 (8.1) years            | Both male and female     | 183/1836                          | HLT; p=0.032; predicted/observed risk=0.82 | AUC=0.69 (0.646 to 0.724) |
| Read et al                 | 3             | Scotland        |              | Hospital admission or death from stroke, unstable angina, transient ischaemic attack, peripheral vascular disease, and coronary, carotid or major amputation procedures | 30-89 years                         | Both male and female     | 14 081/181 399                    | Calibration plots | C-statistic=0.666 (0.661 to 0.671) |
| Zethelius et al            | 2             | Zethelius et al | Sweden       | Fatal/non-fatal CVD (the composite of CHD or stroke)                      | Mean age 64.4 (8.1) years            | Both male and female     | 522/4906                          | Calibration slope=1.00, χ²=17.3, p value <0.001 (MESA); calibration slope=1.05, χ²=22.9, p value <0.001 (JHS) | C-statistic=0.670 (0.665 to 0.674) |
| Stevens et al, UKPDS 66    | 1             | Yao et al       | China        | CHD, stroke                                                              | Mean age 64.4 (8.1) years            | Both male and female     | Events (n) NR/1514                 | Calibration plots: better calibration | C-statistic=0.663 (0.658 to 0.668) |
| Hippisley-Cox et al, QRISK2 | 1             | Read et al      | Scotland     | Hospital admission or death from MI, stroke, unstable angina, transient ischaemic attack, peripheral vascular disease, and coronary, carotid or major amputation procedures | 30-89 years                         | Both male and female     | 14 081/181 399                    | Calibration plots | C-statistic=0.674 (0.669 to 0.679) |
| Elley et al, NZ DCS         | 2             | Read et al      | Scotland     | Hospital admission or death from MI, stroke, unstable angina, transient ischaemic attack, peripheral vascular disease, and coronary, carotid or major amputation procedures | 30-89 years                         | Both male and female     | 14 081/181 399                    | Calibration plots: better calibration | C-statistic=0.670 (0.665 to 0.674) |
| Basu et al, RECODE         | 2             | Basu et al      | USA          | Nephropathy (microalbuminuria, macroalbuminuria, renal failure, ESRD, reduction in glomerular filtration rate), moderate to severe diabetic retinopathy, fatal or non-fatal MI, fatal or non-fatal stroke, CHF and all-cause mortality | 35-84 years (MESA), 45-84 years (JHS) | Both male and female     | 89 stroke (MESA), 142 stroke (JHS) | Calibration slope=1.00, χ²=17.3, p value <0.001 (MESA); calibration slope=1.05, χ²=22.9, p value <0.001 (JHS) | C-statistic=0.75 for stroke (MESA), C-statistic=0.72 for stroke (JHS) |
Table 5 Continued

| Study name       | No of Studies | Validation study | Location | Outcome                                                                 | Age | Gender            | Events (n) / Total participants (N) | Calibration | Discrimination (with CI) |
|------------------|---------------|------------------|----------|-------------------------------------------------------------------------|-----|-------------------|-------------------------------------|-------------|-------------------------|
| Basu et al       | 36            | USA              |          | Microvascular: nephropathy, retinopathy, neuropathy; cardiovascular: composite of atherosclerotic CVD (first fatal or non-fatal MI or stroke), fatal or non-fatal MI, fatal or non-fatal stroke, CHF or death from any cardiovascular cause | Mean age of 58.9 years | Both male and female | 157/4760                                          | Calibration slope for stroke=0.99, χ²=8.2, p value=0.22 | C-statistic for stroke=0.67 (0.63 to 0.71) |
| Alrawahi et al   | 1             | Oman             |          | Fatal and non-fatal CHD, stroke and PAD                                 | Mean age 55.3±11.0 years (derivation sample) and 52.3±11.4 years (validation sample) | Both male and female | 126 (derivation sample), 52 (validation sample) / 1314 (derivation sample), 405 (validation sample) | HL χ² p value=0.15 (derivation sample) and HL χ² p value=0.06 (validation sample) | AUC=0.73 (0.69 to 0.77) (derivation sample); AUC=0.70 (0.59 to 0.75) (validation sample) |

ABI, ankle–brachial index; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; AMI, acute myocardial infarction; AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CRP, C reactive protein; CVD, cardiovascular disease; ESRD, end-stage renal disease; HL, Hosmer-Lemeshow; HLC, Hosmer-Lemeshow C-test; IHDS, Ischemic Heart Disease Study; MESA, Multiethnic Study of Atherosclerosis; MI, myocardial infarction; NR, not reported; NZ, DCs, New Zealand Diabetes Cohort Study; PVD, peripheral artery disease; PVO, predicted over observed; RAND-OM, Multidisciplinary Risk Assessment and Management Program for Patients with Diabetes Mellitus; RECODE, Risk Equations for Complications of Type 2 Diabetes; ROC, receiver operating characteristic; UKPDS, United Kingdom Prospective Diabetes Study.

**DISCUSSION**

This systematic review and meta-analysis provides an overview of all stroke prediction models that were specifically developed for, or validated in patients with diabetes to calculate future stroke risk. Therefore stroke prediction models were identified for patients with diabetes and only 22% of these prediction models had multiple validations. Ten stroke prediction models were developed in diabetes populations and the most reliable model was the UKPDS Risk Engine for Stroke. Four of the prediction models identified were originally developed in the general population but externally validated in diabetes populations. The most notable prediction model was the UKPDS Risk Engine for Stroke with 12 validation studies. Ten stroke prediction models were developed in diabetes populations and the most reliable model was the UKPDS Risk Engine for Stroke. Four of the prediction models identified were originally developed in the general population but externally validated in diabetes populations. The most notable prediction model was the UKPDS Risk Engine for Stroke with 12 validation studies. Ten stroke prediction models were developed in diabetes populations and the most reliable model was the UKPDS Risk Engine for Stroke.

The overall pooled C-statistic (0.7, 95% CI 0.67 to 0.72) for high heterogeneity between studies (I²=95.3%; Cochran Q statistic p<0.001). This observed difference in the two models makes sense as models that include stroke as part of a composite CVD outcome are expected to be different from models where stroke is the only outcome. A summary describing the characteristics of the studies where prediction models were developed in general populations but validated in patients with diabetes is presented in table 5.
composite CVD outcome. Further, the possible sources of heterogeneity are unexplained. Perhaps the difference in patient characteristics in the different cohorts could be a potential source of heterogeneity; however, geographic location, sample size, follow-up time, external validation and variables included in the models were not significant sources of heterogeneity in meta-regression.

The discrimination of the 17 models that were validated were generally comparable with those observed in the development cohorts. However, the performance of some models externally validated in multiple cohorts was heterogeneous and possible source for this heterogeneity remains unexplained. There was also variability in prediction model quality and the methodology used in developing them. Our study findings suggest that, from a large number of published models in patients with diabetes, very few well-validated models are available for stroke prediction. This is helpful to inform the determination of models for clinical uptake when risk stratification approaches for stroke are implemented.

No evidence of small-study effects was detected, in which smaller studies reported better discrimination of models for predicting stroke. Study quality assessment shows many of the models failed to meet some key criteria: consideration of missing values, modelling assumptions, model validation and blinded outcome assessment, which is a concern. Many studies lacked standard reporting. This, to some extend, may be due to lack of guidelines for standards of reporting for risk prediction studies during that time. Many authors reported different aspects of prediction models, and in varying ways created difficulty in collecting information. The publication of new guidelines such as Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) has been introduced and may help improve reporting standards in subsequent studies in this area.

In prior reviews examining risk prediction models in adults with diabetes (Chamnan et al, van Dieren et al, and Chowdhury et al), all components of cardiovascular disease such as CHD, stroke, CAD, myocardial infarction, heart failure were considered as outcomes of the prediction model. Our review adds to knowledge on predicting risk of stroke in persons with diabetes in the following ways: (1) We only considered models where the primary outcome of the model was stroke or when stroke was part of a composite CVD outcome and corresponding studies.
CONCLUSIONS

In conclusion, we have identified many models for predicting stroke in patients with diabetes and attempted to compare these models. Only a small number of models have undergone external validation and might provide generalisable predictions that would support their use in another clinical setting. It is difficult to choose one model over another as none of these models exhibited superior discriminative performance, and unfortunately, no single model appears to perform consistently well. It could be argued that risk prediction in patients with diabetes is not essential. Persons with diabetes are generally perceived to be at elevated risk of stroke and the current practice is to treat to common HbA1C, blood pressure and low-density lipoprotein targets based on diabetes status alone and not on calculated risk. This non-risk based approach may be leading to unnecessary overtreatment and the absence of high-quality validated risk prediction models which limits our ability to assess whether more targeted approaches are possible. Further research is warranted to identify new risk factors with high associated relative risk to improve the currently available prediction models.

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