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Prognostic models for cardiovascular and kidney outcomes in people with type 2 diabetes: living systematic review and meta-analysis of observational studies

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ABSTRACT

OBJECTIVE To summarise available evidence regarding the performance metrics of validated prognostic models on cardiovascular and kidney outcomes in adults with type 2 diabetes mellitus.

DESIGN Living systematic review and meta-analysis of observational studies.

DATA SOURCES Medline, Embase, Central, and the Cochrane Database of Systematic Reviews from 1 January 2020 to 17 January 2024.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Studies validating prognostic models that predicted all cause and cardiovascular mortality, admission to hospital for heart failure, kidney failure, myocardial infarction, or ischaemic stroke in adults with type 2 diabetes mellitus, including people with established cardiovascular disease or chronic kidney disease, or both. Risk models evaluating composite outcomes were not eligible.

DATA SYNTHESIS For each model and outcome, using a random effects model, the reported discrimination measures were pooled, reported as c statistics. Furthermore, when available, calibration plots were reconstructed and interpreted narratively. The Prediction Model Risk of Bias Assessment (PROBAST) tool was used to assess the risk of bias of each analysed study cohort and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to evaluate our certainty in the evidence.

RESULTS 6529 publications were identified, of which 35 studies reporting on 13 models were included, all of which were developed for general populations with type 2 diabetes but no established cardiovascular disease or chronic kidney disease. Among the identified models, the Risk Equations for Complications of Type 2 Diabetes (RECODe) and the UK Prospective Diabetes Study Outcomes Model 2 (UKPDS-OM2) evaluated all outcomes except for admission to hospital for heart failure. Relative to a threshold c statistic of 0.7, RECODe had an acceptable discrimination for cardiovascular mortality (0.79, high certainty), probably has an acceptable discrimination for myocardial infarction (0.72, moderate certainty) and stroke (0.71, moderate certainty), and may have an acceptable discrimination for kidney failure (0.76, low certainty). High certainty evidence suggests that UKPDS-OM2 has unacceptable discrimination for myocardial infarction (0.64) and stroke (0.65). RECODe showed acceptable calibration for cardiovascular mortality (high certainty), myocardial infarction (high certainty), and kidney failure (moderate certainty) but had unacceptable calibration for stroke (moderate certainty). UKPDS-OM2 showed acceptable calibration for cardiovascular mortality (moderate certainty), stroke (moderate certainty), and kidney failure (low certainty), but may have unacceptable calibration for myocardial infarction (moderate certainty).

CONCLUSION 13 unique models were identified that evaluated cardiovascular and kidney outcomes in patients with type 2 diabetes. Two models, RECODe and UKPDS-OM2, evaluated all outcomes except for admission to hospital for heart failure. Of all the appraised prognostic models, RECODe had acceptable discrimination and calibration in validation studies for most outcomes; although, additional studies directly comparing models are needed.

STUDY REGISTRATION NUMBER PROSPERO, CRD42023423075.

READERS' NOTE This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several risk prediction models incorporating multiple risk factors have been developed and validated for people with type 2 diabetes mellitus

⇒ Risk stratification of key patient groups, through the use of risk prediction models, is a core component in the development of clinical practice guidelines

WHAT THIS STUDY ADDS

⇒ Although several prediction models for cardiovascular and kidney outcomes in people with type 2 diabetes have been validated, only two models, the Risk Equations for Complications of Type 2 Diabetes (RECODe) and the UK Prospective Diabetes Study Outcomes Model 2 (UKPDS-OM2), assessed most of the patient important outcomes

⇒ RECODe had acceptable discrimination and calibration in validation studies for most outcomes, and UKPDS-OM2 had variable discrimination and calibration across outcomes

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ When risk stratifying their patients with type 2 diabetes, clinicians should consider patients' individual anticipated risk of cardiovascular and kidney related outcomes using validated risk prediction models

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from the date of original publication. This version is the original article.

Introduction

Type 2 diabetes mellitus affects approximately 537 million adults worldwide, and this number is projected to rise to 643 million by 2030, and 783 million by 2045.[1] Diabetes related healthcare expenditures represent a significant economic burden, costing US$966 billion annually worldwide.[1] In 2021, diabetes was the cause of 6.7 million deaths globally, accounting for 12.2% of all deaths in individuals aged 20-79 years old.[1] Furthermore, individuals living with diabetes have high rates of comorbidity, with approximately 32% of people also having cardiovascular disease and 27% having chronic kidney disease.[2–4]

However, substantial variation exists in prognoses across patients living with type 2 diabetes mellitus; factors such as age, sex, glycaemic control, obesity, and pre-existing cardiovascular and kidney diseases affect an individuals' risk of future cardiovascular and kidney outcomes. To account for the impact of these variables, many risk prediction models incorporating multiple risk factors have been developed and validated for people with type 2 diabetes mellitus.[5–7] These models show great promise: clinicians can use them to prognosticate patients and in clinical decision making, or they can be used by researchers and policy makers to better understand the risk of events across different groups of patients. However, these prognostic models need to yield valid and reliable risk estimates to inform decision making.

A plethora of randomised controlled trials have also shown benefits of several novel antidiabetic treatments, including sodium glucose cotransporter-2 inhibitors (SGLT2-i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and non-steroidal mineralocorticoid receptor antagonists, in reducing the risk of cardiovascular and kidney outcomes in adults with diabetes, with weight loss as another outcome of global interest.[8] A continued flow of new randomised controlled trials as well as new medications, combined with the rising prevalence of diabetes worldwide, prompted an update to a previous clinical practice guideline (*BMJ* Rapid Recommendations) on antidiabetic treatments, to become a living guideline.[2]

Furthermore to that living clinical practice guideline, the panel confirmed that individuals living with diabetes with various levels of risk (eg, high *v* low) for cardiovascular and kidney outcomes experience different absolute magnitudes of benefit. These variations warrant potentially different recommendations depending on risk strata. As for the first version of the guideline, the panel identified the need to determine the most trustworthy and best performing prognostic models assessing individual outcomes to obtain the most credible baseline risks to inform the development of recommendations. Therefore, to inform the living guideline—as well as other guidelines—on drugs for type 2 diabetes mellitus, we conducted this living systematic review and meta-analysis to identify, critically appraise, and summarise the available evidence regarding the performance of validated prognostic models on cardiovascular and kidney outcomes in people with type 2 diabetes mellitus (box 1).

BOX 1 | : LINKED ARTICLES IN THIS BMJ RAPID RECOMMENDATION CLUSTER

Practice article: Agarwal A, Mustafa R, Manja V, et al. Cardiovascular, kidney-related, and weight loss effects of therapeutics for type 2 diabetes: a living clinical practice guideline. *BMJ* 2025;390:e082071. doi:10.1136/bmj-2024-082071

Research article: Nong K, Jeppesen BT, Shi Q, et al. Medications for adults with type 2 diabetes: a living systematic review and network meta-analysis. *BMJ* 2025;390:e083039. doi:10.1136/bmj-2024-083039

Methods

This living systematic review and meta-analysis follows Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidance and established guidance on prognostic model reviews.[9 10 11] We report our systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[12] and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist[13] (see online supplemental appendix 1 for the completed MOOSE checklist). We prospectively registered our protocol on PROSPERO (CRD42023423075).

Search strategy and selection criteria

A previous systematic review and meta-analysis of prognostic models in adults with type 2 diabetes mellitus identified 15 observational studies reporting on seven risk models, of which one showed adequate calibration and discrimination.[14] We updated this systematic review and meta-analysis and transitioned to a living evidence model. Electronic database searches using Medline, Embase, Central, and the Cochrane Database of Systematic Reviews were conducted; this iteration incorporates a search update from 1 January 2020 to 17 January 2024 (see online supplemental appendix 2 for search strategies). Relevant search terms included "diabetes mellitus", "cardiovascular", "MACE", "kidney failure", "mortality", and "admission" as well as search terms for clinical prediction

guides ("prognosis", "diagnosed", "cohort", and "predictor"). We included observational studies and post-hoc analyses of randomised controlled trials that enroled ambulatory adults (≥18 years) with type 2 diabetes mellitus (with or without established cardiovascular disease or chronic kidney disease) and assessed prognostic models with at least two predictors. Specifically, we included validation (internal and external) studies that assessed the performance of models for all cause mortality, cardiovascular mortality, admission to hospital for heart failure, kidney failure, myocardial infarction or stroke, and reported model discrimination or calibration measures. Studies validating prognostic models used to predict composite outcomes were not eligible for inclusion; for example, studies evaluating the SCORE2-Diabetes model[15] evaluated a composite outcome of cardiovascular disease events including cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke, making them ineligible for inclusion. Furthermore, we restricted our included studies to those reporting prognostic models validated in three or more cohorts. To identify additional studies, we searched the reference lists of included studies and consulted clinical experts and methodologists participating on the guideline panel for the linked living *BMJ* Rapid Recommendation on medications for type 2 diabetes mellitus.

Study selection and data extraction

Pairs of calibrated reviewers (DGR, DS, SD, DG, and JZXC) independently assessed titles and abstracts of identified citations as well as full texts of articles that were deemed potentially eligible using Covidence (Veritas Health Innovation, Melbourne, Australia). Pairs of reviewers (DGR, DS, SD, DG, and JZXC) independently extracted data using prepiloted, structured Excel forms. Reviewers resolved conflicts through discussion or, if necessary, through adjudication by a third reviewer (FF). Reviewers collected information related to the data source, time frame of recruitment, duration of patient follow-up, characteristics of the validation cohorts (eg, age, sex, body mass index, comorbidities, laboratory values, etc), details of the prognostic model assessed (eg, predictors included, and definition and measurement of the outcome) and measures of model performance (model discrimination (ie, c statistics or areas under the curve) and calibration (ie, calibration plots)). When studies do not report relevant data in corresponding tabular or narrative formats, we use WebPlotDigitizer v4.7 (Pacifica, CA, USA) to extract values from figures and graphs. If one or more publications reported on the validation of the same model using the same cohort, we included the publication with the largest analytical sample size.

Risk of bias assessment

Pairs of reviewers (DGR, DS, SD, DG, and JZXC) independently used the Prediction Model Risk of Bias Assessment Tool (PROBAST) to assess the risk of bias of the individual cohorts at the outcome level.[16] Disagreements were resolved through discussion between reviewers or, if necessary, adjudication by a third reviewer (FF). PROBAST considers four domains: participants, predictors, outcomes, and analysis. Domains were rated as low, high, or unclear risk of bias. We categorised a study as having an overall high risk of bias if reviewers judged one or more domains to be at high risk of bias, or two or more to be at an unclear risk of bias, otherwise, the study was classified as having a low risk of bias.

Data synthesis and subgroup analyses

STATA SE (v18) was used to perform all analyses. We considered a two sided P value of 0.05 or less statistically significant. Using the "metan" function,[17] we pooled estimates and 95% confidence intervals (CIs) of discrimination statistics (eg, c statistics) for prognostic models validated in three or more cohorts, using restricted maximum likelihood random effects models with Hartung-Knapp-Sidik-Jonkman corrections.[10 11] We followed guidance from Debray et al and colleagues to estimate the standard error for discrimination statistics for studies in which the authors did not report the 95% CI.[10]

Extracted data from all calibration plots assessing the same model on the same outcome were re-plotted and calibration was assessed through visual inspection of these reconstructed plots, considering people at low and high risk. We did not use statistical measures (eg, observed to expected ratios or Hosmer-Lemeshow χ^2 tests) to assess model calibration, as these measures were not optimal when calculated for the entire cohort without regard to varying risk categories.[18 19] For example, observed to expected ratios may suggest perfect model calibration (ratio=1.0) if in half of the patients (who may be high risk) the model underestimates the true risk and in the other half (who may be low risk) the model overestimates the true risk. In a meta-analysis of observed to expected ratios where half the studies reported a ratio of less than 1.0 and the other half reported more than 1.0, the pooled ratio may incorrectly suggest perfect calibration (observed to expected ratio=1.0).[18] Likewise, Hosmer-Lemeshow χ^2 tests have several drawbacks, including low statistical power and a lack of information regarding the type or extent of miscalibration.[19]

We assessed heterogeneity through visual inspection of the individual point estimates and their 95% CIs. To explore the observed heterogeneity, we conducted prespecified subgroup analyses to evaluate the effect of high versus low risk of bias on

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model performance and relied on studies at low risk of bias if a significant difference was observed.

Certainty of the evidence

In order to assess the credibility of the risk prediction models, we evaluated the certainty of the evidence using GRADE.[18 20] We rated certainty in relation to an acceptable discrimination threshold informed by clinician intuition. We selected a threshold of 0.7 to represent clinician intuition, based on a previous systematic review of studies evaluating discrimination of clinicians in disease areas similar to diabetes.[21] GRADE rates certainty drawn on the performance of prognostic models, starting as high for a body of evidence informed by observational studies. Certainty may be decreased due to issues related to risk of bias, imprecision, inconsistency, indirectness, and publication bias. When appropriate, we assessed publication bias through visual inspection of funnel plots.

Living model of evidence synthesis

To iteratively incorporate new evidence regarding performance metrics of prognostic models and newly available prognostic models for adults with type 2 diabetes mellitus, we commit to a living systematic review model. The systematic review is planned for updates if practice changing evidence is made available. Our dynamically updated systematic review will directly inform the linked living *BMJ* Rapid Recommendation on medications for type 2 diabetes mellitus, planned for update every six months, and other international practice guideline development endeavours addressing type 2 diabetes mellitus management. We will collaborate with members of the linked living guideline to monitor for practice changing evidence and to determine whether an update is warranted. The search strategy and core team of methodologists informing the development and conduct of the living systematic review will remain consistent and convene on at least an annual basis to review the scope and methods of the review and to determine if and when the living review should be retired. We aim to publish major updates of this review on prognostic models in a scientific journal with minor or more frequent updates available through the living guideline as published in the open access authoring and publication platform MAGICapp.[22]

Patient and public involvement

Patient partners participated as part of the living *BMJ* Rapid Recommendation guideline panel informing the scope and prioritised clinical outcomes for this living review. This study had no public participation. On publication, the study findings will be disseminated to related patients and the public as linked evidence for the paralleled *BMJ* Rapid Recommendation (https://www.bmj.com/rapid-recommendations) on the use of antidiabetic treatments in people with type 2 diabetes mellitus.

Results

The systematic search yielded 6529 unique citations and 224 potentially relevant full texts. Ultimately, 35 studies were eligible by reporting on the internal or external validation of 13 prognostic models across 52 validation cohorts (figure 1).[23–57] Three models predicted all cause mortality, four predicted cardiovascular mortality, four predicted kidney failure, two predicted myocardial infarction, three predicted stroke, and five predicted admission to hospital for heart failure. Two identified models, RECODe and UKPDS-OM2, evaluated all outcomes except for admission to hospital for heart failure. All studies reported the validation of prognostic models in people with type 2 diabetes mellitus with the presence of various risk factors for the development of cardiovascular and kidney outcomes; none reported validation of models specifically for patients with established cardiovascular disease and/or chronic kidney disease on our outcomes of interest.

Characteristics of synthesised studies

The cohorts included a median of 4329 patients (range 125-94 946). The median of mean ages was 61.4 years (range of means 50.9-70.7), median of mean HbA_{1c} was 7.4% (range of means 6.1% to 8.7%) and a median of 54% of participants were male (range 0-100%). Among the cohorts enrolling participants from a single country, the most common countries were the United States (n=9), Italy (n=8), and China (n=7) (Online supplemental appendix 3).

Risk of bias of individual studies

Online supplemental appendix 4 presents the risk of bias assessments for each validation cohort and respective outcome across the 35 synthesised studies, leading to 119 separate risk of bias assessments. We found 47 assessments to be at a low risk of bias, and 72 to be at a high risk of bias. Common study limitations included inappropriate methods for handling missing data (eg, complete case analysis and use of a separate category to capture missing data), an inadequate number of events observed, and use of administrative databases and codes from International Classification of Diseases (ICD) 9th edition for identifying outcomes, which may face high rates of missing data and poor specificity.

All cause mortality

Three models predicted all cause mortality in people with type 2 diabetes mellitus: estimation of mortality risk in type 2 diabetic patients (ENFORCE), risk equations for complications of type 2 diabetes (RECODe), and UK prospective diabetes study outcomes model (UKPDS-OM)-2 (table 1; online supplemental appendix 5). Compared with a threshold c statistic

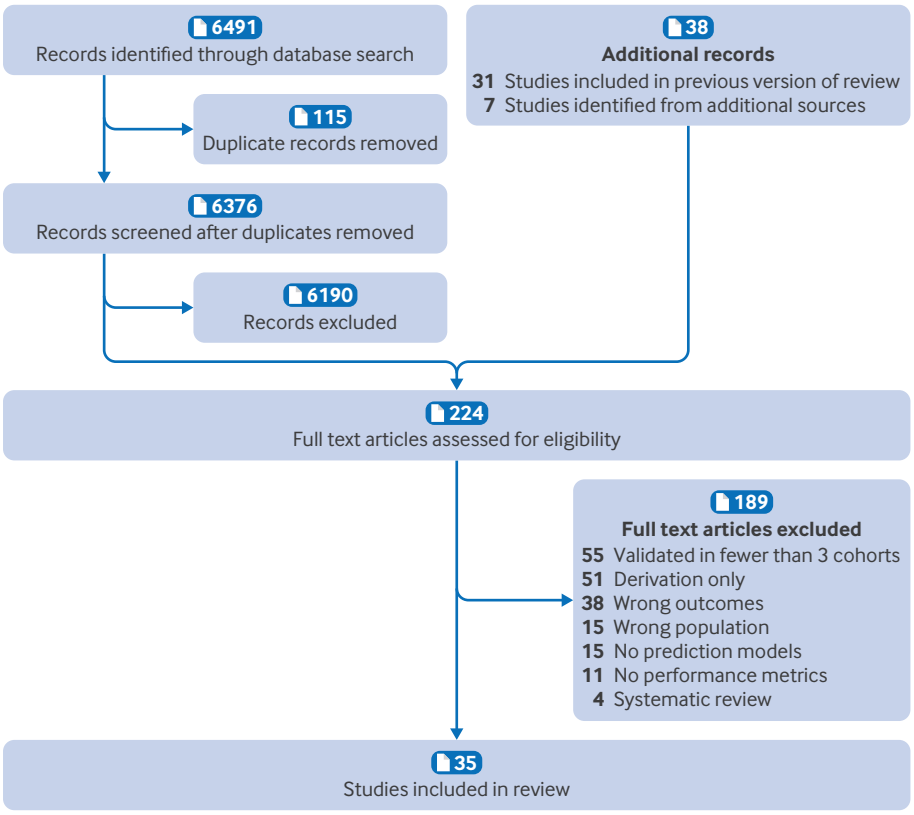

Figure 1 | PRISMA flowchart for study selection

of 0.7, high certainty evidence indicates that RECODe has acceptable discrimination for all cause mortality. Moderate certainty evidence suggests that ENFORCE and UKPDS-OM2 probably have acceptable discrimination.

With regards to model calibration, high certainty evidence showed that UKPDS-OM2 overestimates risk for all cause mortality. Moderate certainty evidence suggests that ENFORCE probably underestimates risk, and that RECODe probably has acceptable calibration (table 2; online supplemental appendix 6).

Cardiovascular mortality

Four models predicted cardiovascular mortality in people with type 2 diabetes mellitus: Framingham score (FHS), RECODe, systematic coronary risk evaluation (SCORE), and UKPDS-OM2 (table 1; online supplemental appendix 5). High certainty evidence indicates that RECODe has acceptable discrimination for cardiovascular mortality. FHS may have acceptable discrimination, and UKPDS-OM2 may have unacceptable discrimination (both low certainty). We are very uncertain about the discriminatory capability of SCORE (very low certainty).

High certainty evidence shows that RECODe has acceptable calibration. Moderate certainty evidence suggests that both SCORE and UKPDS-OM2 probably have acceptable calibration. No studies evaluated the calibration of FHS through calibration plots (table 2; online supplemental appendix 6).

Kidney failure

Four models predicted kidney failure in individuals with type 2 diabetes mellitus: ADVANCE (action in diabetes and vascular disease: preterax and diamicron MR controlled evaluation), the New Zealand model, RECODe, and UKPDS-OM2 (table 1; online supplemental appendix 5). Moderate certainty evidence indicates that ADVANCE and the New Zealand model probably have acceptable discrimination. RECODe may have acceptable discrimination, and UKPDS-OM2 may have unacceptable discrimination (low certainty).

Moderate certainty evidence suggests that ADVANCE and the New Zealand model probably underestimate the risk of kidney failure. RECODe probably has acceptable calibration (moderate certainty), while UKPDS-OM2 may have acceptable calibration for predicting kidney failure (low certainty) (table 2; online supplemental appendix 6).

Myocardial infarction

Two models predicted myocardial infarction in people with type 2 diabetes mellitus: RECODe and UKPDS-OM2. High certainty evidence indicates that UKPDS-OM2 has unacceptable discrimination for myocardial infarction. Meanwhile, RECODe probably has acceptable discrimination (moderate certainty) (table 1; online supplemental appendix 5).

High certainty evidence shows that RECODe has acceptable calibration for myocardial infarction,

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Table 1 | Summary of findings table for prediction model discrimination

Prediction model	No. of cohorts	Sample size	C statistic (95% CI)	Certainty in the evidence	Plain language summary
All cause mortality (n=3)					
ENFORCE	5	7396	0.73 (0.68 to 0.79)	Moderate, due to serious imprecision	Probably has acceptable discrimination for all cause mortality
RECODe	12	155 332	0.75 (0.72 to 0.78)	High	Has acceptable discrimination for all cause mortality
UKPDS-OM2	7	160 791	0.74 (0.68 to 0.80)	Moderate, due to serious imprecision	Probably has acceptable discrimination for all cause mortality
Cardiovascular mortality (n=4)					
FHS	3	6711	0.72 (0.61 to 0.84)	Low, due to serious risk of bias and serious imprecision	May have acceptable discrimination for cardiovascular mortality
RECODe	5	103 067	0.79 (0.73 to 0.85)	High	Has acceptable discrimination for cardiovascular mortality
SCORE	3	5713	0.71 (0.53 to 0.90)	Very low, due to serious risk of bias and very serious imprecision	We are very uncertain of the discriminatory capability in predicting cardiovascular mortality
UKPDS-OM2	3	15 685	0.69 (0.63 to 0.76)	Low, due to serious risk of bias and serious imprecision	May have unacceptable discrimination for cardiovascular mortality
Kidney failure (n=4)					
ADVANCE	4	49 758	0.86 (0.83 to 0.89)	Moderate, due to serious risk of bias	Probably has acceptable discrimination for kidney failure
New Zealand model	3	24 022	0.88 (0.81 to 0.95)	Moderate, due to serious risk of bias	Probably has acceptable discrimination for kidney failure
RECODe	5	140 802	0.76 (0.62 to 0.90)	Low, due to serious risk of bias and serious imprecision	May have acceptable discrimination for kidney failure
UKPDS-OM2	6	142 966	0.68 (0.50 to 0.86)	Low, due to very serious imprecision	May have unacceptable discrimination for kidney failure
Myocardial infarction (n=2)					
RECODe	6	145 562	0.72 (0.70 to 0.75)	Moderate, due to serious imprecision	Probably has acceptable discrimination for myocardial infarction
UKPDS-OM2	13	190 322	0.64 (0.60 to 0.68)	High	Has unacceptable discrimination for myocardial infarction
Stroke (n=3)					
RECODe	5	103 067	0.71 (0.68 to 0.74)	Moderate, due to serious imprecision	Probably has acceptable discrimination for stroke
UKPDS-OM1	7	98 319	0.69 (0.61 to 0.77)	Moderate, due to serious imprecision	Probably has unacceptable discrimination for stroke
UKPDS-OM2	11	145 588	0.65 (0.61 to 0.69)	High	Has unacceptable discrimination for stroke
Admission to hospital for heart failure (n=5)					
DM-CURE	3	19 081	0.84 (0.74 to 0.93)	Moderate, due to serious risk of bias	Probably has acceptable discrimination for admission to hospital for heart failure
TRS-HFDM	5	35 632	0.75 (0.67 to 0.82)	Moderate, due to serious imprecision	Probably has acceptable discrimination for admission to hospital for heart failure
WATCH-DM (machine learning)	3	24 370	0.72 (0.52 to 0.91)	Low, due to serious risk of bias and serious imprecision	May have acceptable discrimination for admission to hospital for heart failure
WATCH-DM (regression)	3	24 370	0.71 (0.62 to 0.80)	Low, due to serious risk of bias and serious imprecision	May have acceptable discrimination for admission to hospital for heart failure
WATCH-DM (integer)	4	24 573	0.67 (0.57 to 0.77)	Low, due to serious risk of bias and serious imprecision	May have unacceptable discrimination for admission to hospital for heart failure

ADVANCE, action in diabetes and vascular disease: preterax and diamicron MR controlled evaluation ; CI, confidence interval; DM-CURE, socio-demographic variables, metabolic, diabetes-related complication factors, and health care utilization for risk evaluation; ENFORCE, estimation of mortality risk in type 2 diabetic patients; FHS, Framingham score; RECODe, risk equations for complications of type 2 diabetes; SCORE, systematic coronary risk evaluation; TRS-HFDM, thrombolysis in myocardial infarction risk score for heart failure in diabetes; UKPDS-OM, UK prospective diabetes study outcomes model.

and moderate certainty evidence suggests that UKPDS-OM2 probably overestimates risk (table 1; online supplemental appendix 6).

Stroke

Three models predicted stroke in individuals with type 2 diabetes mellitus: RECODe, UKPDS-OM1, and UKPDS-OM2. High certainty evidence indicates that UKPDS-OM2 has unacceptable discrimination for stroke. Moderate certainty evidence suggests that RECODe probably has acceptable discrimination and UKPDS-OM1 probably has unacceptable discrimination for stroke (table 1; online supplemental appendix 5).

Moderate certainty evidence suggests that RECODe probably overestimates the risk of stroke, and that both UKPDS-OM1 and UKPDS-OM2 probably have

Table 2 | Summary of findings table for prediction model calibration

Prediction model	No. of cohorts	Sample size	Certainty in the evidence	Plain language summary
All cause mortality (n=3)				
ENFORCE	2	2801	Moderate, due to serious risk of bias	Probably underestimates risk for all cause mortality
RECODe	8	66 525	Moderate, due to serious inconsistency	Probably has acceptable calibration for all cause mortality
UKPDS-OM2	6	146 222	High	Overestimates risk for all cause mortality
Cardiovascular mortality (n=4)				
FHS	—	—	—	No study assessed the calibration for cardiovascular mortality using a calibration curve
RECODe	4	17 696	High	Has acceptable calibration for cardiovascular mortality
SCORE	1	125	Moderate, due to serious risk of bias	Probably has acceptable calibration for cardiovascular mortality
UKPDS-OM2	1	456	Moderate, due to serious risk of bias	Probably has acceptable calibration for cardiovascular mortality
Kidney failure (n=4)				
ADVANCE	2	18 145	Moderate, due to serious risk of bias	Probably underestimates risk for kidney failure
New Zealand Model	3	24 022	Moderate, due to serious risk of bias	Probably underestimates risk for kidney failure
RECODe	1	42 495	Moderate, due to serious risk of bias	Probably has acceptable calibration for kidney failure
UKPDS-OM2	4	139 665	Low, due to very serious inconsistency	May have acceptable calibration for kidney failure
Myocardial infarction (n=2)				
RECODe	5	60 191	High	Has acceptable calibration for myocardial infarction
UKPDS-OM2	9	162 712	Moderate, due to serious inconsistency	Probably overestimates risk for myocardial infarction
Stroke (n=3)				
RECODe	4	17 696	Moderate, due to serious inconsistency	Probably overestimates risk for stroke
UKPDS-OM1	2	79 966	Moderate, due to serious risk of bias	Probably has acceptable calibration for stroke
UKPDS-OM2	8	120 217	Moderate, due to serious inconsistency	Probably has acceptable calibration for stroke
Admission to hospital for heart failure (n=5)				
DM-CURE	—	—	—	No study assessed the calibration for heart failure using a calibration curve
TRS-HFDM	3	22 275	High	Has acceptable calibration for heart failure
WATCH-DM (machine learning)	3	24 370	High	Has acceptable calibration for
WATCH-DM (regression)	3	24 370	High	Has acceptable calibration for heart failure
WATCH-DM (integer)	3	24 370	High	Has acceptable calibration for heart failure

DM-CURE, socio-demographic variables, metabolic, diabetes-related complication factors, and health care utilization for risk evaluation; ENFORCE, estimation of mortality risk in type 2 diabetic patients; FHS, Framingham score; RECODe, risk equations for complications of type 2 diabetes; SCORE, systematic coronary risk evaluation; TRS-HFDM, thrombolysis in myocardial infarction risk score for heart failure in diabetes; UKPDS-OM, UK prospective diabetes study outcomes model.

acceptable calibration (table 2; online supplemental appendix 6).

Admission to hospital with heart failure

Five models predicted admission to hospital with heart failure in people with type 2 diabetes mellitus: DM-CURE (socio-demographic variables, metabolic, diabetes-related complication factors, and health care utilization for risk evaluation), TRS-HFDM (thrombolysis in myocardial infarction risk score for heart failure in diabetes), and three WATCH-DM models (machine learning, regression, and integer based). Moderate certainty evidence suggests that DM-CURE and TRS-HFDM probably have acceptable discrimination for admission to hospital with heart failure. The machine learning and regression based WATCH-DM models may have acceptable discrimination, but the integer based WATCH-DM model may have unacceptable discrimination (all low certainty). No studies evaluated the calibration of DM-CURE using calibration plots. High certainty evidence showed that all other models for admission to hospital with heart failure had acceptable calibration.

Other analyses

We did not identify any significant effect modification on model discrimination (online supplemental appendix 7) or model calibration (online supplemental appendix 8) based on overall risk of bias.

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Similarly, we did not identify any evidence of publication bias (online supplemental appendix 9).

Discussion

Principle findings

This systematic review summarised the discrimination and calibration of prognostic models for adults with type 2 diabetes mellitus validated in three or more cohorts. We compared the discriminatory performance of each model to our best estimate of clinician intuition (c statistic=0.7) in predicting mortality (all cause and cardiovascular related), kidney failure, myocardial infarction, stroke, and admission to hospital with heart failure. Among the 13 identified prognostic models, RECODe has the most acceptable discriminatory performance and calibration across the evaluated outcomes; this finding aligns with a previous systematic review.[14]

Strengths and limitations

Strengths of this review include the use of rigorous and comprehensive methods for systematic reviews and meta-analyses of prognostic models[10 11] and the use of formal GRADE guidance to assess certainty of evidence for discrimination and calibration.[18 20] The GRADE approach allowed us to contextualise our findings in relation to the average discriminatory performance of clinicians, enabling our findings to have direct relevance to clinical practice. Furthermore, this updated review continues to be linked to a multidisciplinary *BMJ* Rapid Recommendation panel composed of clinical experts, methodologists, and patient partners. The panel has prespecified patient important outcomes of interest and has been consulted to ensure the comprehensiveness of our systematic literature search, ensuring that our review's findings are directly relevant to clinical practice.

Potential limitations of this systematic review stem from current limitations of prognosis literature. Firstly, although the discriminatory performance of prognostic models can be quantitatively assessed by pooling the reported c statistics in each study, the methods used to assess the calibration of each model vary substantially. Given the limitations of statistical measures of calibration, including observed to expected ratios and Hosmer-Lemeshow χ^2 tests,[18 19] we only assessed calibration through the studies' reported calibration plots. This approach involved a visual assessment of reconstructed calibration plots, and a narrative summary of each model's calibration, resulting in the assessment of calibration being more subjective. Secondly, the included studies assessed model calibration among patients with relatively low cardiovascular risk, limiting assessment of model calibration across the full spectrum of risk including among those with established cardiovascular disease or chronic kidney disease. In the absence of credible risk prediction models for this large population with type 2 diabetes mellitus, the linked guideline had to use their clinical experience and perform pragmatic modelling to estimate risk for cardiovascular and kidney outcomes for people at moderate to high risk; patients who will benefit most from medications such as SGLT2-inhibitors and GLP1-RA (unpublished). Thirdly, we were unable to assess on the predictive model performance the influence of several potential sources of heterogeneity, including ascertainment of outcomes across studies, the time periods in which they were conducted and available antidiabetic treatments available during these periods, and diversities in healthcare systems and health outcomes across geographical regions. Fourthly, our review excluded prognostic models solely evaluating composite outcomes, such as major adverse cardiovascular events, as our linked guideline focused on individual cardiovascular and kidney outcomes. As a result, several robust risk prediction models for type 2 diabetes mellitus, such as SCORE2-Diabetes,[15] which may assist clinicians and patients with risk stratification in clinical practice, were not assessed in our review. Finally, our review assessed model performance relative to a threshold inferred by clinician intuition and did not directly compare performance between different models. Given the potential intransitivity between validation cohorts used to assess each model, future research is needed to directly compare promising models, such as those that predict multiple patient important outcomes (eg, RECODe, UKPDS-OM2), using the same validation cohort.

Implications for current practice and research

Models identified by our systematic review, such as RECODe, should help the development and updating of clinical practice guidelines, health technology assessments, and subsequently clinicians, patients, policy makers and payers in informing individual decision making. These models enable appropriate risk stratification for patients with type 2 diabetes mellitus, enable identification of risk stratified baseline risks (ie, likelihood of events occurring without treatment) across patient important outcomes, and facilitate estimation of risk stratified absolute effect estimates for treatments (applying the relative effects anticipated with treatments to baseline risks) and cost-effectiveness analyses. The models also allow clinicians and adults with type 2 diabetes mellitus to define a given individual's risk profile and individualised estimates of benefits or harms with treatment, facilitating evidence informed shared decision making. Additionally, previous clinical practice guidelines on the management of type 2 diabetes mellitus, including those from the American Diabetes Association[58] and the American Association of Clinical Endocrinology/American College of Endocrinology,[59] recommend the use of prognostic models developed and validated in

non-diabetic populations, such as the Pooled Cohort Equation and the FHS. Our findings may enable the adoption of diabetes specific prognostic models in the development of future clinical practice guidelines for diabetes management.

Our systematic review identified several areas for future research on prognostic models for adults with type 2 diabetes mellitus. Firstly, our review compared the discriminatory performance of identified prognostic models to a threshold informed by clinician intuition alone (c statistic=0.7).[21] In clinical practice, clinicians may use prognostic models in addition to other clinical factors to inform their risk estimation and decision making. One systematic review suggested that clinician intuition enhanced by prognostic models may be superior to clinician intuition alone.[21] Future research should investigate the usefulness of adding trustworthy prognostic models for diabetes, such as RECODe, to routine clinical practice. Secondly, most models had limited data assessing their calibration for patients at higher risk. Future research should focus on validating identified prognostic models in cohorts of adults at higher risk. Finally, our review was unable to assess the clinical usefulness of using risk stratification, by leveraging these prognostic models, to guide treatment of type 2 diabetes mellitus. Future research should evaluate the benefit of these identified prognostic models in clinical practice and their impact on patient important outcomes.

Conclusion

We identified 13 unique prognostic models evaluating cardiovascular and kidney outcomes in patients with type 2 diabetes mellitus, with no models explicitly reporting validation of patients with established cardiovascular disease or chronic kidney disease. We identified two models, RECODe and UKPDS-OM2, which evaluated all outcomes except for admission to hospital with heart failure. Of all the identified prognostic models, RECODe showed acceptable discrimination and calibration in validation studies for most outcomes.

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