




ORIGINAL ARTICLE

Development of a hypoglycaemia risk score to identify high-risk individuals with advanced type 2 diabetes in DEVOTE

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Abstract

Aims: The ability to differentiate patient populations with type 2 diabetes at high risk of severe hypoglycaemia could impact clinical decision making. The aim of this study was to develop a risk score, using patient characteristics, that could differentiate between populations with higher and lower 2-year risk of severe hypoglycaemia among individuals at increased risk of cardiovascular disease.

Materials and methods: Two models were developed for the risk score based on data from the DEVOTE cardiovascular outcomes trials. The first, a data-driven machine-learning model, used stepwise regression with bidirectional elimination to identify risk factors for severe hypoglycaemia. The second, a risk score based on known clinical risk factors accessible in clinical practice identified from the data-driven model, included: insulin treatment regimen; diabetes duration; sex; age; and glycated haemoglobin, all at baseline. Both the data-driven model and simple risk score were evaluated for discrimination, calibration and generalizability using data from DEVOTE, and were validated against the external LEADER cardiovascular outcomes trial dataset.

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Results: Both the data-driven model and the simple risk score discriminated between patients at higher and lower hypoglycaemia risk, and performed similarly well based on the time-dependent area under the curve index (0.63 and 0.66, respectively) over a 2-year time horizon.

Conclusions: Both the data-driven model and the simple hypoglycaemia risk score were able to discriminate between patients at higher and lower risk of severe hypoglycaemia, the latter doing so using easily accessible clinical data. The implementation of such a tool (<http://www.hyporiskscore.com/>) may facilitate improved recognition of, and education about, severe hypoglycaemia risk, potentially improving patient care.

KEYWORDS

risk score, severe hypoglycaemia, type 2 diabetes

1 | INTRODUCTION

Optimizing the treatment of type 2 diabetes (T2D) can be complex; published data demonstrate that, despite the availability of improved therapies and new technologies for the treatment and management of diabetes, glucose levels remain far from recommended targets.^{1,2} Fear of hypoglycaemia may be a barrier to insulin treatment initiation and intensification and thus achievement of glycaemic targets. Hypoglycaemic events, both symptomatic and severe, have been shown to be frequent, underestimated^{3–6} and associated with adverse consequences, including impaired quality of life, cognitive impairment, and cardiac morbidity and mortality.^{7–18} Practical tools to identify those at high risk of hypoglycaemia may support clinicians in improving patient awareness and education, thereby potentially reducing the risk of hypoglycaemia and improving patient care.

The use of risk scores in the management of other medical conditions has shown the potential of such tools to provide important clinical benefits; risk scores are commonly used for patients with cardiovascular disease (CVD) or malignancies, to tailor therapies based on guidelines, for example.^{19,20} This demonstrates that risk scores can drive individualized treatment, value-based reimbursement and even patient engagement, through self-calculation of their own scores with widely available online tools. As such, hypoglycaemia risk-scoring tools, with the potential to offer similar benefits, would be of considerable clinical utility in the management of T2D.

It has previously been demonstrated that a range of patient characteristics can predict the risk of severe hypoglycaemia, morbidity and mortality,^{3,21–24} and these have been used to develop hypoglycaemia risk scores.^{25,26} These scores include patient characteristics that are not easily accessible in clinical records; for example, they may rely on a history of severe hypoglycaemia or abnormal scores using a hypoglycaemia awareness scale as key predictors, thereby limiting their applicability.^{25,26}

We used data from DEVOTE,^{27,28} a cardiovascular outcomes trial of patients with T2D, the majority with advanced T2D requiring insulin treatment, to develop a hypoglycaemia risk score. The aim of this analysis was to develop a simple risk score with sufficient accuracy to differentiate patients according to their risk of severe hypoglycaemia. We

anticipate that this practical tool could be of use to all clinicians treating patients with diabetes, including endocrinologists, and could be of particular value to general internists, primary care providers and their teams.

2 | MATERIALS AND METHODS

2.1 | DEVOTE trial design

To develop the risk score, data from DEVOTE (ClinicalTrials.gov number NCT01959529) were used. DEVOTE was a treat-to-target, randomized, double-blind, active basal insulin comparator, cardiovascular outcomes trial designed to continue until at least 633 major adverse cardiovascular events (MACE) had accrued.^{27,28} Full details and the protocol are available in the primary publication.^{27,28} Patients were eligible for inclusion if they were treated with at least one oral or injectable antidiabetic medication, and had either a glycated haemoglobin (HbA1c) concentration ≥ 53 mmol/mol ($\geq 7\%$), or an HbA1c concentration < 53 mmol/mol ($< 7\%$) while receiving ≥ 20 units of basal insulin per day.²⁸ Included patients had T2D, and were either aged ≥ 50 years with ≥ 1 cardiovascular or kidney condition, or were aged ≥ 60 years with ≥ 1 cardiovascular risk factor.²⁸ Overall, 7637 patients with T2D at high risk of CVD were randomized 1:1 to receive either insulin degludec (degludec) or insulin glargine 100 units/mL (glargine U100) once daily, both in identical vials.²⁸ Basal insulin doses were adjusted weekly using a titration algorithm based on self-measured blood glucose (SMBG) values, with the aim of achieving SMBG 4.0 to 5.0 mmol/L (71–90 mg/dL) for most patients.²⁸ A less intensive titration algorithm was also available, based on clinical characteristics. DEVOTE was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guideline.^{29,30}

The primary endpoint in DEVOTE was defined as the time from randomization to the first occurrence of major adverse cardiovascular events (MACE) (a composite of death from cardiovascular causes,

non-fatal myocardial infarction or non-fatal stroke).²⁸ Severe hypoglycaemia was the secondary confirmatory endpoint and was defined in accordance with the 2013 American Diabetes Association (ADA) criteria as an episode requiring the assistance of another person to actively administer carbohydrate or glucagon or to take other corrective action.³¹ Both endpoints were externally confirmed by an independent event-adjudication committee.²⁷

2.2 | DEVOTE key results

Overall, 83.9% of the trial population were receiving insulin treatment at baseline. In the degludec and glargine U100 arms, respectively, 29.3% and 29.1% were treated with sulphonylureas at baseline.²⁸ Over the trial period, the rate of severe hypoglycaemia was 3.70 events per 100 patient-years of exposure in the degludec arm, with 280 events in 187 patients; in the glargine U100 arm there were 6.25 events per 100 patient-years of exposure, with 472 events in 252 patients.²⁸ Among patients receiving degludec, 1.2% experienced >1 severe hypoglycaemic episode, compared with 2.2% of those receiving glargine U100.

2.3 | LEADER trial design

In order to separate the training and validation of the risk score, the risk score was validated using data from the LEADER cardiovascular outcomes trial.³² LEADER was a randomized, double-blind, placebo-controlled, cardiovascular outcomes trial.³² Patients with T2D at high risk of cardiovascular events ($n = 9340$) were randomized 1:1 to receive either liraglutide (1.8 mg or the maximum tolerated dose) or placebo once daily in addition to standard of care.³² Patients included in LEADER had T2D with HbA1c ≥ 53 mmol/mol ($\geq 7\%$), and were eligible if they had not previously received antidiabetic medication; patients were also eligible if they had received any combination of one or more oral antidiabetic medications and/or insulin therapy, excluding previous treatment with glucagon-like peptide-1 receptor agonists, dipeptidyl-peptidase-4 inhibitors, pramlintide and/or rapid-acting insulin.³² The primary endpoint in LEADER was the first occurrence of a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.³² As in DEVOTE, severe hypoglycaemia was defined in accordance with the 2013 ADA criteria.³¹

2.4 | LEADER key results

In the liraglutide and placebo arms, respectively, 43.7% and 45.6% of patients were using insulin at baseline and 28.8% and 43.2%, respectively, used insulin during the trial period.³² Similarly, 50.8% and 50.6% of patients in the liraglutide and placebo arms, respectively, were receiving sulphonylureas at baseline and, in total, 7.5% and 10.8%, respectively, received them during the trial.³² In a *post hoc*

analysis, rates of severe hypoglycaemia over the trial period were 0.5, 2.1 and 0.9 events per 100 patient-years of observation in those not treated with insulin, those treated with insulin at baseline and those initiated on insulin during the trial, respectively, with 433 total events in 267 patients over the whole study population.¹⁸ This included 114 patients (2.4%) in the liraglutide arm, and 153 (3.3%) in the placebo arm.¹⁸

2.5 | Hypoglycaemia risk score development

Two models were developed to differentiate patients according to their risk of severe hypoglycaemia. The first, a more complex and objective model, used a data-driven approach to identify risk factors for severe hypoglycaemia. The second was a simpler hypoglycaemia risk score, with risk factors selected based on clinical knowledge and parameters that would be easily assessable in clinical practice. The endpoint used to develop the model was the first occurrence of an in-trial, event adjudication committee-confirmed severe hypoglycaemic episode, defined according to the 2013 ADA criteria.³¹

2.5.1 | Data-driven model

The data-driven model determined individual risk estimates via step-wise regression with bidirectional elimination, using all baseline information (including baseline demographics, characteristics and treatments) available for patients in DEVOTE.^{27,28} This was used to include or exclude risk factors based on inclusion and exclusion P values of <0.1 in a Cox proportional hazard model. To establish the sensitivity of the identified risk factors, random-forest selection based on recursive partitioning, k -fold cross-selection, bootstrap selection and simple backward selection were also employed and gave the same overall result. The 10 risk factors at baseline for severe hypoglycaemia, in decreasing order of impact, identified by the data-driven model were insulin treatment regimen, baseline estimated glomerular filtration rate (eGFR), previous stroke, diabetes duration, sex, baseline LDL:HDL ratio, baseline HbA1c, diastolic blood pressure, hepatic impairment and smoking status (Table 1).

Factors associated with a greater risk of hypoglycaemia included: basal-bolus insulin treatment; previous stroke; increasing diabetes duration or baseline HbA1c; and the presence of hepatic impairment (Table 1). Decreasing baseline eGFR, LDL:HDL ratio, or diastolic blood pressure were all associated with a lower risk of hypoglycaemia, as was being insulin-naïve, male or a previous/never smoker (Table 1).

2.5.2 | Hypoglycaemia risk score

The hypoglycaemia risk score was developed based on clinical knowledge and selection of parameters that would be easily assessable in clinical practice, and therefore not require detailed clinical information or extensive laboratory measurements. The basis of the

TABLE 1 Identified predictors and model coefficients for severe hypoglycaemia in the data-driven and hypoglycaemia risk score models

Data-driven model							Hypoglycaemia risk score model						
Predictor	Estimate	SE of the estimate	HR	SE of the HR	Z-score	P	Predictor	Estimate	SE of the estimate	HR	SE of the HR	Z-score	P
1. Insulin treatment regimen ^a							1. Insulin treatment regimen ^a						
Insulin-naïve	-0.046624	0.17450	0.95	0.17	-0.28	.783	Insulin-naïve	-0.075453	0.17415	0.92	0.17	-0.47	.638
Basal-bolus	0.5004728	0.11119	1.65	0.11	4.49	<.001	Basal-bolus	0.5520181	0.11096	1.74	0.11	4.97	<.001
2. eGFR at baseline	-0.511858	0.13373	0.60	0.13	-3.83	<.001	2. Diabetes duration	0.0195860	0.00530	1.02	0.01	3.58	<.001
3. Previous stroke (yes)	0.4715405	0.11451	1.60	0.11	4.13	<.001	3. Sex (male)	-0.344977	0.09731	0.70	0.10	-3.62	<.001
4. Diabetes duration	0.0163985	0.00535	1.02	0.01	3.06	.002	4. Age	0.0167213	0.00686	1.02	0.01	2.43	.015
5. Sex (male)	-0.330072	0.10168	0.72	0.10	-3.25	.001	5. HbA1c at baseline	0.0498281	0.02955	1.05	0.03	1.69	.091
6. LDL:HDL ratio at baseline	-0.142023	0.05701	0.87	0.06	-2.48	.013							
7. HbA1c at baseline	0.0657269	0.02945	1.07	0.03	2.22	.026							
8. Diastolic blood pressure	-0.009104	0.00481	0.99	0.00	-1.09	.002							
9. Hepatic impairment (yes)	0.3913658	0.22859	1.48	0.23	1.70	.089							
10. Smoking status													
Previous smoker	-0.204106	0.15887	0.81	0.16	-1.29	.195							
Never smoker	-0.334850	0.16033	0.71	0.16	-2.10	.036							

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; SE, standard error.

^aPatients in DEVOTE were classified into three groups based on insulin usage: insulin-naïve (not on insulin at baseline); basal-only; and basal-bolus (including pre-mixed or bolus-only). Basal-only classification was not identified as a predictor of hypoglycaemia and does not affect the risk score.

The estimates refer to a 1-unit change for each predictor. For continuous variables, the estimate is associated with the increasing value of the predictor.

Grey boxes highlight where the same predictors were included in the data-driven model and the hypoglycaemia risk score model.

All baseline information (including baseline demographics, characteristics and treatments) collected during the trial were investigated using the data-driven model. Only the top 10 predictors identified by the data-driven model were selected and refined for use in the hypoglycaemia risk score model. For a full list of baseline information collected during the trial please refer to Marso et al. *Am Heart J.* 2016;179:175-183 and Marso et al. *N Engl J Med.* 2017;377:723-732.

hypoglycaemia risk score was derived from the 10 risk factors identified by the data-driven model. To provide an objective basis for their selection among the other identified variables, the association between the risk factors and hypoglycaemia had to be supported by the literature, as well as the data-driven model. On this basis, four of the risk factors detailed above were chosen: insulin treatment regimen,^{33,34} diabetes duration,^{22,34} sex,^{33,34} and HbA1c³³ at baseline (Table 1). In addition, age, which was not amongst the 10 risk factors identified by the data-driven model, was added; this variable had previously been identified as a predictor of severe hypoglycaemia and is an easily available metric in routine clinical practice compared with the other baseline data collected in DEVOTE.²²

2.6 | Validation methods

2.6.1 | Internal validation

To ensure that the data-driven model and the hypoglycaemia risk score could identify patients at risk of severe hypoglycaemia, both were validated by assessing calibration, discrimination and generalizability, and compared with each other. Calibration was assessed graphically with histograms by visual comparison of the predicted and observed risk of severe hypoglycaemia in DEVOTE within deciles of hypoglycaemia risk. In addition, to assess potential overfitting, the predicted and observed risks of severe hypoglycaemia were compared in bootstrapped versions of DEVOTE data.

Generalizability and discrimination were assessed internally by applying the data-driven model and hypoglycaemia risk score to bootstrapped replicates of the DEVOTE data and then applying Harrel's c-index, the Brier score and optimization of the time-dependent area under the curve (AUC) index.^{35,36} It should be noted that optimization of the AUC index has previously been demonstrated to be superior compared with the other methods.³⁶

2.6.2 | External validation

The data-driven model and the hypoglycaemia risk score were validated externally by determining the risk scores in the LEADER trial population³² to examine whether the scores could accurately differentiate patients' risk in an external population for severe hypoglycaemia. Discrimination was assessed graphically with histograms in LEADER within deciles of hypoglycaemia risk.

3 | RESULTS

3.1 | Internal validation: Data-driven model and hypoglycaemia risk score

Internal validation of the data-driven model and the hypoglycaemia risk score, using actual DEVOTE data and a 10 000 bootstrapped version of the DEVOTE data, confirmed sufficient calibration and discrimination abilities of both, and that the data were not overfitted

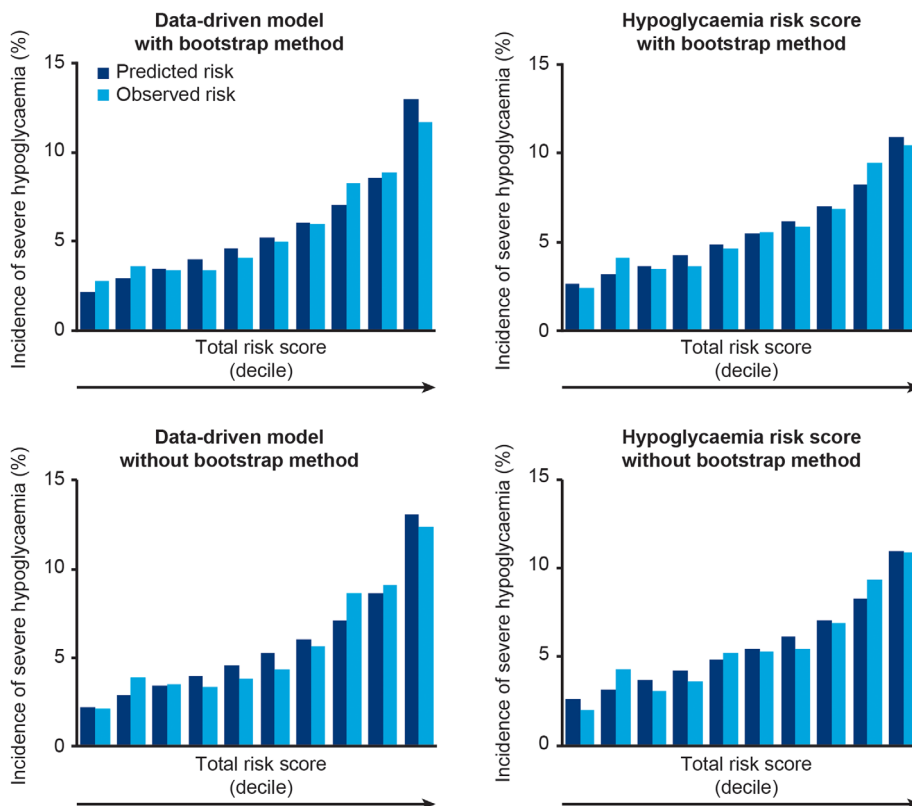


FIGURE 1 Internal validation of the data-driven model and hypoglycaemia risk score—observed vs. predicted probabilities to assess calibration and discrimination

(Figure 1). In addition, both the data-driven model and the hypoglycaemia risk score showed similar discrimination abilities when applying Harrel's c-index, the Brier score and optimization of the time-dependent AUC index.^{35,36} The time-dependent Harrel's c-index values for the data-driven model and the hypoglycaemia risk score were 0.63 and 0.65, respectively. The time-dependent Brier scores were 5.7 for both the data-driven model and the hypoglycaemia risk score model, and the time-dependent AUC index values were 0.63 and 0.66, respectively, supporting that, overall, the performance of both was similar.

3.2 | External validation: Data-driven model and hypoglycaemia risk score

Both the data-driven model and the hypoglycaemia risk score were also externally validated against the severe hypoglycaemia data from the LEADER trial (Figure 2). The histograms demonstrated that both were able to discriminate the LEADER patient population in terms of risk of severe hypoglycaemia.

3.3 | Hypoglycaemia risk score differentiation

As the performance for both the data-driven model and the hypoglycaemia risk score were similar, and given that it required significantly fewer predictors to calculate, the hypoglycaemia risk score was applied to the DEVOTE population and used to create risk score quartiles. These were arbitrarily named "Moderate," "Moderately high," "High" and "Very high," to reflect that this population was largely treated with insulin at baseline and was treated with insulin during the trial, and therefore was at the higher end of the hypoglycaemia risk spectrum.

4 | DISCUSSION

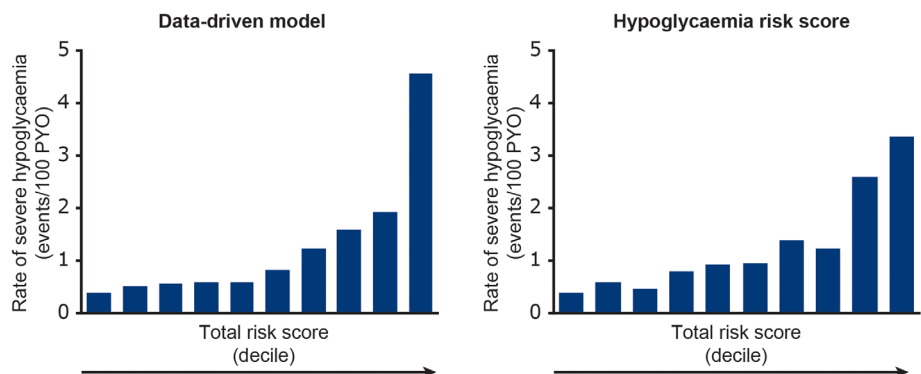
The hypoglycaemia risk score, developed from DEVOTE baseline data, was able to identify patients with T2D who were at high risk of severe hypoglycaemia, based on easily accessible parameters. As both the

data-driven model and the hypoglycaemia risk score were similar in terms of internal and external validation methods, we propose that the hypoglycaemia risk score should be used in preference to the data-driven model, both for differentiation of hypoglycaemia risk and for any future analyses, due to its simplicity and applicability to routine clinical practice. It is notable, however, that both methods produced similar results for hypoglycaemia risk differentiation. This could reflect the overlap in parameters between the two scores, and the possibility of correlation between the factors present in both scores and those used only in the data-driven model.

The hypoglycaemia risk score was digitized into a publicly available online tool (<http://www.hyporiskscore.com>) to allow translation into a clinical setting. The online risk score can be used by healthcare professionals (HCPs) and patients to differentiate between those at higher and lower risk of experiencing severe hypoglycaemia within 2 years, and to determine a patient's risk score quartile.³⁷ Although not recommended as a basis for diagnostic or management decisions, such a tool could form part of a holistic approach to minimizing hypoglycaemia by increasing recognition and awareness of a patient's risk level. This may contribute to improving HCP-patient dialogue and education, and in adopting strategies to mitigate hypoglycaemic risk.

The AUC indices reported here suggest that the value of both the data-driven model and hypoglycaemia risk scores may lie in the ability to differentiate between lower and higher risk populations, rather than in specific risk score predictions. There is no consensus on an absolute cut-off for an acceptable AUC in risk score development, and contextualization of the patient population and outcomes studied is important. Other groups have developed risk scores with similar objectives; the strength of this hypoglycaemia risk score is its simplicity and inclusion of easily accessible variables.^{23,25,26,38,39} Chow et al³⁸ developed a 5-year severe hypoglycaemia risk score for patients at high cardiovascular risk with T2D, based on Cox regression models of data from the ACCORD study investigating intensive glycaemic control. Their score attained a c-statistic of 0.782, but used a US/Canadian population only, and a 17-factor prediction model. Similarly, Misra-Hebert et al³⁹ also presented a severe hypoglycaemia prediction tool in US patients with T2D with previous non-severe hypoglycaemia; this score attained an AUC of 0.890, over a 3-month event horizon. The risk score was developed using electronic health record data in a Cox counting model process by Schroeder et al²⁵, as

FIGURE 2 External validation of the data-driven model and hypoglycaemia risk score against LEADER trial data to assess discrimination. PYO, patient-years of observation



6-month risk of severe hypoglycaemia was also an effective prediction tool in a US-specific population (c-statistic 0.81).

Our risk score was developed using a global population, over a 2-year event horizon, which may entail increased heterogeneity compared with previous analyses and may also contribute to differences in c-statistics. Equally, previous scores have frequently used more complex clinical data, such as urinary albumin:creatinine ratio,³⁸ numerous comorbidities³⁹ and history of hypoglycaemia³⁸ or severe hypoglycaemia.²⁵ The inclusion of fewer and more easily accessible risk factors in the hypoglycaemia risk score may limit the differentiation of patients compared with other risk scores that include a greater number of variables. However, it may also provide a tool that can be used more quickly and easily in clinical practice. In particular, this tool may be valuable for general clinicians or those working in primary care, for whom T2D represents a relatively small proportion of their workload, and who may have less clinical information available to them and shorter appointment lengths compared with specialist endocrinologists and diabetologists. Further research may also elucidate whether this simple risk differentiation tool could be used to facilitate patients to calculate their own individual risk score.

In terms of the predictors identified by this hypoglycaemia risk score, these are consistent with those identified by previous studies, including intensive glycaemic control, antecedent hypoglycaemia, renal impairment, cognitive dysfunction, age, duration of diabetes, insulin regimen and liver disease,^{3,21–23,40–42} thereby corroborating the design and applicability of the model to a wider population with T2D. It is interesting that age was not identified by the data-driven model as a top 10 factor affecting hypoglycaemia risk; this may be attributable, in part, to the narrower age range of the patient populations in these studies compared with previous analyses, given that they were selected for their high cardiovascular risk. Additionally, heterogeneity of patient characteristics between age groups in the study population was introduced by the differences in inclusion criteria based on age, with lower age cut-offs for patients with clinical CVD or chronic kidney disease compared with those with cardiovascular risk factors only.

Previous severe hypoglycaemia risk scores have shown high predictive power when based on direct measurement of SMBG or continuous glucose monitoring data; for example, the low blood glucose index developed by Kovatchev et al.⁴³ However, while these tools may offer improved risk prediction, their use in T2D is often not possible in routine clinical practice, where routine continuous glucose monitoring or frequent SMBG is uncommon, especially in primary care settings.

The present analysis has some limitations. While the number of patients included in DEVOTE was large, it was still smaller than a clinical practice dataset and is not fully representative of a real-world patient cohort. However, clinical practice and claims datasets are inadequate for effectively predicting the true risk of hypoglycaemia due to underreporting, missing data and selection bias when compared with clinical trial data.

The risk score presented here has been shown to be predictive in one external dataset different from the DEVOTE population (i.e.

LEADER), albeit a randomized controlled, cardiovascular outcomes trial. This supports generalizability across a patient population with T2D beyond that of DEVOTE, including patients less likely to be treated with insulin. However, both trials included patients with advanced diabetes at high risk of, or with established, CVD. In particular, DEVOTE used an aggressive treat-to-target insulin titration regimen, which may not be reflective of most patients in clinical practice. Therefore, the applicability and extrapolation to other diabetes populations, particularly to those at lower cardiovascular risk and/or lower risk of severe hypoglycaemia, is still uncertain. Nevertheless, the patient populations included in these studies are typical of many of those seen in clinical practice.

The factors that could be evaluated for inclusion within the hypoglycaemia risk score were also limited by data availability. Previous episodes of hypoglycaemia have been shown to be a risk factor for future episodes, and have been included within other risk scores.^{25,38,39} This information was not collected as a part of DEVOTE and could not be assessed for inclusion within the risk score. Not including this factor may have helped to develop a simple tool suitable for use in routine practice, where information on previous hypoglycaemia episodes is not always easily available. The relative infrequency of severe hypoglycaemic events in the DEVOTE population (3.70–6.25 events/100 patient-years²⁸) may have prevented more precise risk prediction in this study population.

Strengths of the risk score include derivation from a clinical trial dataset with broad, clinically relevant inclusion criteria and uniform measures, a high completion rate of 98%, few missing data and the external adjudication of severe hypoglycaemic events. In addition, the risk score was based on information available to most patients and HCPs and did not include a patient's history of severe hypoglycaemic events, which, in turn, allows the risk score to be applied to a broader patient population.

Lastly, in a companion paper, we apply the hypoglycaemia risk score to evaluate its prediction of cardiovascular events and explore the issue of causality of severe hypoglycaemia on cardiovascular events.⁴⁴ The observed risk of MACE, associated with an individual's 2-year risk quartile for severe hypoglycaemia, is also available through the risk score app published online.

In conclusion, we have developed and validated both a complex data-driven model and a practical hypoglycaemia risk score for the assessment of hypoglycaemia risk; the latter uses clinical characteristics readily available to patients and HCPs at the point of care and could therefore be used in routine clinical practice. The distribution and implementation of such a tool may aid in increasing awareness and recognition of populations at high risk of severe hypoglycaemia, and thereby facilitate improved education and holistic care.

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CONFLICT OF INTEREST

S.H. has served on speaker panels for MSD, Eli Lilly, Takeda, Novo Nordisk and AstraZeneca, for which he has received remuneration. He has served on advisory panels or as a consultant for Zeeland, UNEEG Medical, Boehringer Ingelheim, Novo Nordisk, Eli Lilly and Takeda, for which his institution has received remuneration. I.L. received funds for research, consulting, editorial support and/or travel expenses from Novo Nordisk, Eli Lilly, Sanofi, AstraZeneca, Boehringer Ingelheim, Merck, Novartis, Intarcia, MannKind, TARGETPharma, GI Dynamics and Pfizer. S.P.M. has received personal fees from Abbott Vascular, Novo Nordisk, University of Oxford, AstraZeneca, Bristol-Myers Squibb, Asahi-Intec and Boehringer Ingelheim, and research support from Novo Nordisk. D.K.M. has led clinical trials for AstraZeneca, Boehringer Ingelheim, Eisai, Esperion, GlaxoSmithKline, Janssen, Lexicon, Merck & Co. Inc., Novo Nordisk and Sanofi Aventis, and has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Lilly, Merck & Co. Inc., Pfizer, Novo Nordisk, Metavant and Sanofi Aventis. A.P.T. has served on advisory panels for Eli Lilly and Co, Dexcom, Inc. and Voluntis, provided consultancy services for Novo Nordisk A/S and Sanofi US, and received research support from Merck & Co., Inc, Novo Nordisk A/S, Sanofi US, Eli Lilly and Co, AstraZeneca, Janssen Pharmaceuticals, Inc. and Genentech, Inc. A.P.T. did not receive any direct or indirect payment for these services. She is supported by grants from the US National Institutes of Health (R01DK112322, R18DK104250, R01NR015754 and 1UL1TR002550). T.R.P. has received research support from Novo Nordisk and AstraZeneca (paid directly to the Medical University of Graz), and personal fees as a consultant from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Novo Nordisk and Roche Diabetes Care. T.R.P. is also the Chief Scientific Officer of CBmed (Centre for Biomarker Research in Medicine), a public-funded biomarker research company. N.R.P. has received personal fees from Servier, Takeda, Novo Nordisk and AstraZeneca in relation to speakers' fees and advisory board activities (concerning diabetes mellitus), and research grants for his research group (relating to type 2 diabetes) from Diabetes UK, the UK National Institute for Health Research Efficacy and Mechanism Evaluation (NIHR EME), Julius Clinical and the British Heart Foundation. R.E.P.'s services were paid directly to AdventHealth, a non-profit organization. He reports speaker fees from Novo Nordisk, consulting fees from Novo Nordisk,

Merck, Pfizer, Sanofi, Scovia Pharmaceuticals Inc. and Sun Pharmaceuticals Inc., and grants from Hanmi Pharmaceutical Co., Janssen, Novo Nordisk, Poxel SA and Sanofi. K.K., M.L. and M.T.A. are full-time employees of, and hold stock in, Novo Nordisk A/S. E.H.N. is a full-time employee of Novo Nordisk A/S. A.C.M. was an employee of Novo Nordisk during the conduct of DEVOTE. He now serves as an independent consultant, including consulting for Novo Nordisk, and retains shares in Novo Nordisk A/S. J.B.B.'s contracted consulting fees and associated travel support are paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Eli Lilly, MannKind, NovaTarg, Novo Nordisk, Sanofi, Senseonics, vTv Therapeutics and Zafgen, and he receives grant support from Novo Nordisk, Sanofi, Tolerion and vTv Therapeutics. He is also a consultant to Cirius Therapeutics Inc, CSL Behring, Mellitus Health, Neurimmune AG, Pendulum Therapeutics and Stability Health. He holds stock/options in Mellitus Health, Pendulum Therapeutics, PhaseBio and Stability Health. He is supported by grants from the US National Institutes of Health (UL1TR002489, U01DK098246, UC4DK108612, U54DK118612, P30DK124723), the Patient-Centred Outcomes Research Institute and the American Diabetes Association.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the interpretation of data for the manuscript, drafted and critically revised the manuscript. All authors are responsible for the integrity of the work as a whole.

DATA AVAILABILITY STATEMENT

The datasets analysed during this study are available from the corresponding author on reasonable request.

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