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ORIGINAL ARTICLE

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Risk of severe hypoglycaemia and its impact in type 2 diabetes in DEVOTE

Simon Heller MD[1] | Ildiko Lingvay MD[2] | Steven P. Marso MD[3] | Athena Philis-Tsimikas MD[4] | Thomas R. Pieber MD[5] | Neil R. Poulter FMedSci[6] | Richard E. Pratley MD[7] | Elise Hachmann-Nielsen MD[8] | Kajsa Kvist PhD[8] | Martin Lange MD[8] | Alan C. Moses MD[8,9*] | Marie Trock Andresen MD[8] | John B. Buse MD[10] | DEVOTE Study Group

[1]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

[2]Department of Internal Medicine and Department of Population and Data Sciences, University of Texas Southwestern Medical Center, Dallas, Texas

[3]HCA Midwest Health Heart and Vascular Institute, Overland Park, Kansas

[4]Scripps Whittier Diabetes Institute, San Diego, California

[5]Department of Internal Medicine, Medical University of Graz, Graz, Austria

[6]Imperial Clinical Trials Unit, National Heart and Lung Institute, Imperial College London, London, UK

[7]AdventHealth Translational Research Institute, Orlando, Florida

[8]Novo Nordisk A/S, Søborg, Denmark

[9]Independent consultant, Novo Nordisk A/S, Portsmouth, New Hampshire

[10]University of North Carolina School of Medicine, Chapel Hill, North Carolina

Correspondence
Simon Heller, MD, Department of Oncology and Metabolism, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK.
Email: s.heller@sheffield.ac.uk

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Abstract

Aims: To undertake a post-hoc analysis, utilizing a hypoglycaemia risk score based on DEVOTE trial data, to investigate if a high risk of severe hypoglycaemia was associated with an increased risk of cardiovascular events, and whether reduced rates of severe hypoglycaemia in patients identified as having the highest risk affected the risk of cardiovascular outcomes.

Materials and Methods: The DEVOTE population was divided into quartiles according to patients' individual hypoglycaemia risk scores. For each quartile, the observed incidence and rate of severe hypoglycaemia, major adverse cardiovascular event (MACE) and all-cause mortality were determined to investigate whether those with the highest risk of hypoglycaemia were also at the greatest risk of MACE and all-cause mortality. In addition, treatment differences within each risk quartile [insulin degludec (degludec) vs. insulin glargine 100 units/mL (glargine U100)] in terms of severe hypoglycaemia, MACE and all-cause mortality were investigated.

Results: Patients with the highest risk scores had the highest rates of severe hypoglycaemia, MACE and all-cause mortality. Treatment ratios between degludec and glargine U100 in the highest risk quartile were 95% confidence interval (CI) 0.56 (0.39; 0.80) (severe hypoglycaemia), 95% CI 0.76 (0.58; 0.99) (MACE) and 95% CI 0.77 (0.55; 1.07) (all-cause mortality).

Conclusions: The risk score demonstrated that a high risk of severe hypoglycaemia was associated with a high incidence of MACE and all-cause mortality and that, in this high-risk group, those treated with degludec had a lower incidence of MACE. These observations support the hypothesis that hypoglycaemia is a risk factor for cardiovascular events.

*Affiliation at the time of the trial.

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KEYWORDS
all-cause mortality, MACE, severe hypoglycaemia, type 2 diabetes

1 | INTRODUCTION

Hypoglycaemia is one of the main barriers preventing optimal glycaemic control in insulin-treated patients with diabetes.[1] Although hypoglycaemia, at all levels, is associated with a range of adverse events, severe hypoglycaemia in particular has been linked to an increased risk of major adverse cardiovascular events (MACE) and all-cause mortality in patients with type 2 diabetes (T2D).[1–10] Whether the association is causal or whether hypoglycaemia identifies vulnerable individuals that would probably suffer adverse outcomes is still debated. One factor favouring a causal link between hypoglycaemia and MACE is the number of plausible mechanisms whereby hypoglycaemia could lead to adverse cardiovascular consequences. These include changes in the electrocardiogram (T-wave inversions; ST segment depressions; QTc prolongation), cardiac arrhythmias, sympathoadrenal activation, changes in blood coagulation and prolonged low-grade inflammation with impaired endothelial function lasting weeks after a hypoglycaemic event.[11–15] Regardless of whether hypoglycaemia is a risk factor or a risk marker, it is important to avoid hypoglycaemic episodes and their detrimental effects on patients.[16]

DEVOTE was a treat-to-target, randomized, double-blind, active-comparator, cardiovascular outcomes trial designed to investigate the cardiovascular safety of insulin degludec (degludec) compared with insulin glargine 100 units/mL (glargine U100) in patients with T2D.[17,18] DEVOTE demonstrated that degludec was non-inferior to glargine U100 in terms of a three-point MACE, including cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, and was superior with regard to hypoglycaemia risk, with lower rates of both severe and nocturnal severe hypoglycaemia at equivalent glycaemic control.[17,18]

We utilized data from DEVOTE to develop a simple hypoglycaemia risk score with sufficient accuracy to identify patients at increased risk of experiencing severe hypoglycaemia, as well as differentiate between those at high and low risk (as described in our companion manuscript).[19] The aim of the current study was to undertake a post-hoc analysis utilizing the hypoglycaemia risk score to investigate if a high risk of severe hypoglycaemia was associated with an increased risk of cardiovascular events. Furthermore, we investigated whether a reduction in severe hypoglycaemia in patients identified as having the highest risk impacts upon the risk of cardiovascular outcomes.

2 | MATERIALS AND METHODS

DEVOTE (ClinicalTrials.gov number NCT01959529) was a treat-to-target, randomized, double-blind, active basal insulin comparator, cardiovascular outcomes trial designed to continue until at least 633 MACE had accrued.[17,18] DEVOTE was conducted in accordance with the Declaration of Helsinki principles and ICH Good Clinical Practice guidelines.[20,21] Patients with T2D at high risk of cardiovascular events (n = 7637) were randomized 1:1 to receive either degludec or glargine U100 once daily, both in identical vials.

The primary endpoint in DEVOTE was defined as the time from randomization to the first occurrence of MACE (a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke). Severe hypoglycaemia was defined in accordance with the American Diabetes Association criteria as an episode requiring the assistance of another person to administer carbohydrate or glucagon or to take other corrective actions actively, and was the secondary confirmatory endpoint.[22]

The hypoglycaemia risk score, the development and validation of which is described in our companion manuscript, was used to divide the patient population into quartiles according to the patient's risk score and arbitrarily named 'moderate', 'moderately high', 'high' and 'very high'. Factors that increased the risk of hypoglycaemia were insulin treatment regimen, diabetes duration, female gender, age and glycated haemoglobin (HbA1c). These quartiles were deliberately not described as low risk, given that the trial population was mostly receiving insulin therapy. For each risk quartile, the observed incidence and rate of severe hypoglycaemia, MACE and all-cause mortality were determined to investigate whether those with the highest risk of hypoglycaemia were also at the greatest risk of MACE or all-cause mortality. This analysis was also repeated using the LEADER trial population.[23]

The prespecified primary models used to compare the randomized treatment arms in DEVOTE (a Cox proportional hazard model and a negative binomial model) were used to investigate treatment differences within each risk quartile (degludec vs. glargine U100) in terms of severe hypoglycaemia, MACE and all-cause mortality.

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

3 | RESULTS

The baseline characteristics across the risk quartiles are summarized in Table 1. Notably, all quartiles had a comparable proportion of patients with established cardiovascular disease. Glucose-lowering efficacy was similar across the quartiles, with reductions in HbA1c of 1.0% (very high-risk quartile), 0.9% (high-risk quartile), 0.9% (moderately high-risk quartile) and 0.7% (moderate risk quartile) (Table S1; see Supporting Information). Patients in the very high-risk quartile had the highest HbA1c levels at both baseline (8.6%) and at the end of the trial (7.6%).

As expected, the hypoglycaemia risk score predicted a patient's risk of severe hypoglycaemia; this was evident by comparing the rates of hypoglycaemia across the risk quartiles, demonstrating that, as the risk score increased, so did the rates of hypoglycaemia (Figures 1A and 2A). In addition, the hypoglycaemia risk score was able to differentiate the patient population into different quartiles of hypoglycaemia risk.

TABLE 1 Baseline characteristics by quartiles

	Moderate (n = 1887)	Moderately high (n = 1887)	High (n = 1887)	Very high (n = 1887)
Age (years)	61.8 ± 6.4	64.6 ± 7.3	65.3 ± 7.0	68.1 ± 7.3
Female/male	179 (9.5)/ 1708 (90.5)	779 (41.3)/ 1108 (58.7)	648 (34.3)/ 1239 (65.7)	1215 (64.4)/ 672 (35.6)
Duration of diabetes (years)	10.1 ± 5.3	14.7 ± 7.2	17.3 ± 7.4	23.5 ± 9.3
Smoking status				
Current	283 (15.0)	233 (12.3)	187 (9.9)	139 (7.4)
Previous	883 (46.8)	784 (41.5)	859 (45.5)	790 (41.9)
Never	721 (38.2)	870 (46.1)	841 (44.6)	958 (50.8)
Renal status				
Normal renal function (eGFR ≥90 mL/min/1.73 m^2 per CKD-EPI)	522 (27.7)	409 (21.7)	335 (17.8)	213 (11.3)
Mild renal impairment (eGFR 60-89 mL/min/1.73 m^2 per CKD-EPI)	848 (44.9)	809 (42.9)	767 (40.6)	677 (35.9)
Moderate renal impairment (eGFR 30–59 mL/min/1.73 m^2 per CKD-EPI)	476 (25.2)	619 (32.8)	708 (37.5)	889 (47.1)
Severe renal impairment (eGFR <30 mL/min/1.73 m^2 per CKD-EPI)	29 (1.5)	38 (2.0)	58 (3.1)	89 (4.7)
Hepatic impairment	24 (1.3)	40 (2.1)	64 (3.4)	68 (3.6)
Insulin naive	678 (35.9)	405 (21.5)	119 (6.3)	12 (0.6)
Trial eligibility stratum				
Age ≥50 years and established cardiovascular or chronic kidney disease	1633 (86.5)	1548 (82.0)	1610 (85.3)	1644 (87.1)
Age ≥60 years and risk factors for cardiovascular disease	248 (13.1)	334 (17.7)	272 (14.4)	239 (12.7)
Body weight (kg) (lb)	98.5 ± 22.8 (217.2 ± 50.3)	93.7 ± 22.0 (206.5 ± 48.5)	97.7 ± 24.6 (215.4 ± 54.2)	94.6 ± 21.6 (208.7 ± 47.6)
BMI (kg/m^2)	32.9 ± 6.5	33.1 ± 6.7	33.8 ± 7.0	34.6 ± 7.0
Systolic blood pressure (mmHg)	135.0 ± 17.0	135.2 ± 18.1	135.8 ± 18.7	136.2 ± 18.1
Diastolic blood pressure (mmHg)	78.4 ± 9.9	77.0 ± 10.1	75.6 ± 10.3	73.7 ± 10.6
Pulse (beats/min)	73.6 ± 11.5	73.4 ± 11.1	73.0 ± 11.1	72.3 ± 11.5
HbA1c (%) (mmol/mol)	8.1 ± 1.5 (65.5 ± 16.4)	8.4 ± 1.6 (68.5 ± 17.5)	8.5 ± 1.7 (69.5 ± 18.8)	8.6 ± 1.7 (71.0 ± 18.9)
Fasting plasma glucose (mmol/L) (mg/dL)	9.2 ± 3.6 (166.0 ± 64.0)	9.4 ± 3.8 (169.9 ± 67.6)	9.7 ± 4.0 (174.7 ± 71.3)	9.8 ± 4.3 (176.2 ± 77.8)
eGFR (mL/min/1.73 m^2) based on CKD-EPI	74.4 ± 20.7	69.7 ± 21.0	66.5 ± 21.6	61.1 ± 20.6
Total cholesterol (mmol/L) (mg/dL)	4.2 ± 1.2 (161.2 ± 44.6)	4.3 ± 1.3 (167.5 ± 49.5)	4.2 ± 1.2 (163.5 ± 46.3)	4.4 ± 1.2 (168.2 ± 47.7)
LDL cholesterol (mmol/L) (mg/dL)	2.2 ± 0.9 (83.6 ± 35.2)	2.3 ± 1.0 (87.4 ± 37.5)	2.2 ± 0.9 (84.3 ± 35.9)	2.2 ± 1.0 (86.5 ± 37.2)
HDL cholesterol (mmol/L) (mg/dL)	1.1 ± 0.3 (41.5 ± 11.9)	1.2 ± 0.3 (44.5 ± 12.2)	1.1 ± 0.3 (43.8 ± 12.4)	1.2 ± 0.4 (47.7 ± 14.0)
Triglycerides (mmol/L) (mg/dL)	2.1 ± 1.7 (190.6 ± 152.8)	2.1 ± 1.9 (186.1 ± 171.3)	2.1 ± 1.6 (184.9 ± 140.7)	2.0 ± 2.0 (178.9 ± 174.5)

Data listed are number [proportion (%)] or mean ± standard deviation. Percentage refers to the proportion of patients within each risk quartile. Hepatic impairment defined as having a score of >2 on a modified Child-Pugh criteria scale using only bilirubin and albumin values.

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

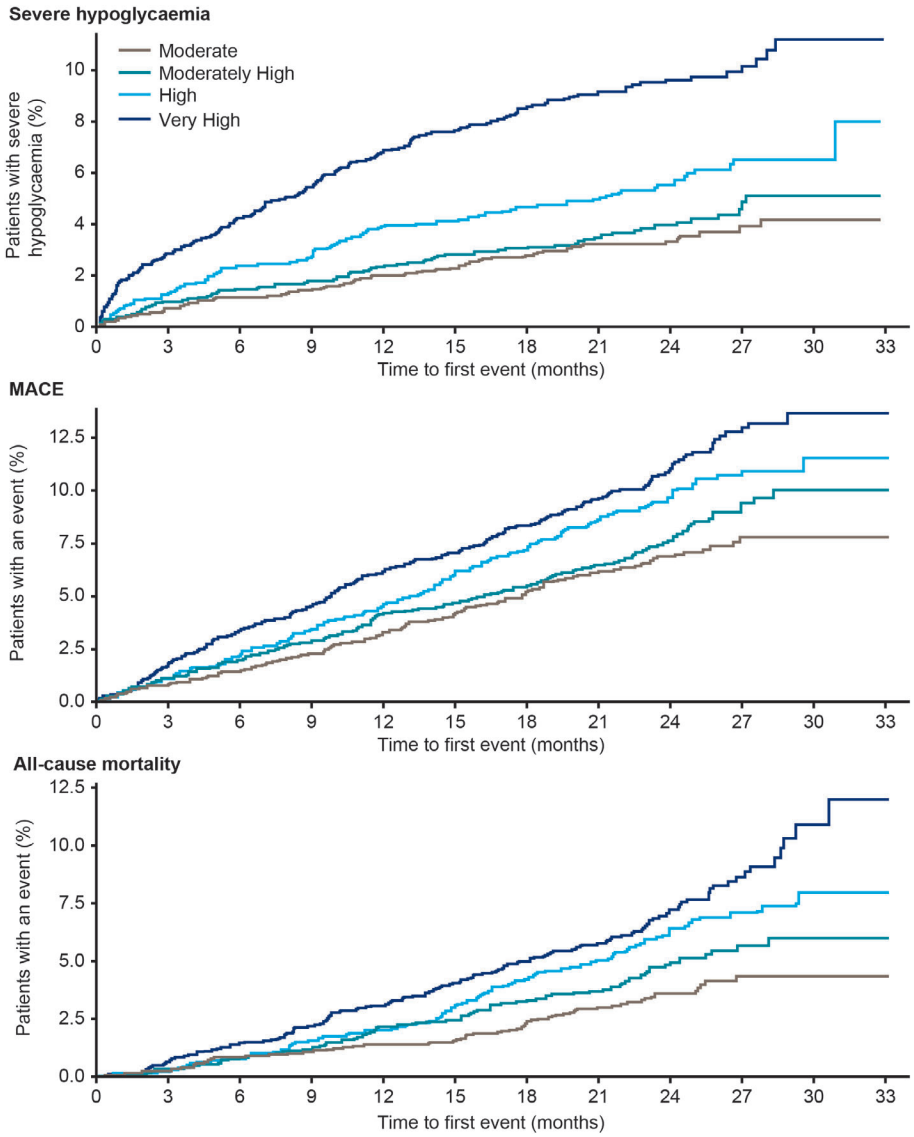

FIGURE 1 Risk of outcomes: A, severe hypoglycaemia, B, MACE and C, all-cause mortality by severe hypoglycaemia risk quartiles. MACE, major adverse cardiovascular events

Patients in the very high-risk quartile were also those with the highest observed incidence of MACE, as the incidence of MACE increased with each increasing risk quartile (Figures 1B and 2B). A similar trend was also observed for MACE and the individual MACE components when applied to the LEADER trial data (Figure S1; see Supporting Information).

Because of the size of the DEVOTE trial population and the fact that the hypoglycaemia risk score was based on baseline data, randomization was maintained. All baseline parameters were well balanced between the two arms in all four quartiles. This allowed for a fair treatment comparison within each quartile (Table S2; see Supporting Information). In all four quartiles, degludec was associated with risk ratios <1 for severe hypoglycaemia versus glargine U100, in line with the overall DEVOTE analysis, where the rate ratio was 95% confidence interval (CI) 0.60 (0.48; 0.76) (Figures 1A and 2A). The incidences of MACE and all-cause mortality increased with each increasing risk quartile overall and for both treatment arms, demonstrating that those patients with the highest risk of severe hypoglycaemia had the highest incidences of MACE and all-cause mortality (Figures 1B,C and 2B,C). In the very high-risk quartile, the rate ratio (degludec vs. glargine U100) with regard to severe hypoglycaemia was 95% CI 0.56 (0.39; 0.80). In this risk quartile, the estimated risk of experiencing MACE was lower with degludec versus glargine U100 [hazard ratio 95% CI 0.76 (0.58; 0.99)]. The effect of a reduced rate of severe hypoglycaemia on MACE with degludec as compared with glargine U100 diminished in the lower risk quartiles, where the rates of hypoglycaemic events were notably lower.

4 | DISCUSSION

By using the hypoglycaemia risk score, developed from DEVOTE baseline data, it was possible to identify patients with T2D who were at high risk of severe hypoglycaemia. With each increasing risk quartile, the incidences of severe hypoglycaemia, MACE and all-cause mortality increased. In addition, those patients identified as having the highest risk of severe hypoglycaemia appeared to have a higher incidence of MACE and all-cause mortality, which is consistent with other studies.[4–6,24]

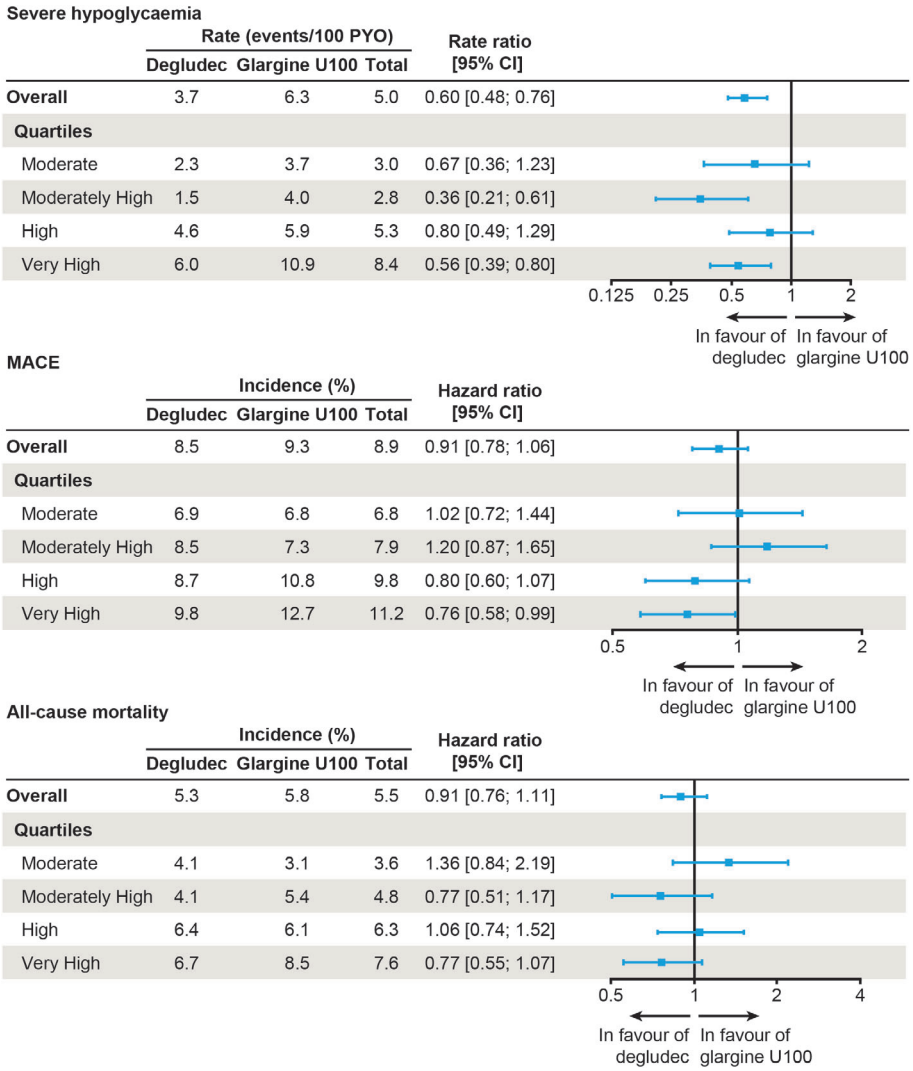

FIGURE 2 Risk of outcomes: A, severe hypoglycaemia, B, MACE and C, all-cause mortality with degludec vs. glargine U100 by severe hypoglycaemia risk quartiles. CI, confidence interval; glargine U100, insulin glargine 100 units/mL; MACE, major adverse cardiovascular events; PYO, patient-years of observation

In terms of the treatment arm comparisons, it is important to note that the significantly lower rate of severe hypoglycaemia seen with degludec compared with glargine U100 was reflected by a significantly lower rate of MACE in the highest risk quartile, where patients had the most events (both severe hypoglycaemia and MACE); albeit with a similar proportion of patients, compared with the other quartiles, aged ≥50 years with established cardiovascular or chronic kidney disease. These results did not appear to be confounded by the baseline information included in the risk score, as the patients' baseline characteristics across the four quartiles, including the reduction in HbA1c levels and previous history of cardiovascular disease, were similar between the risk quartiles, and therefore these factors do not confound the findings. The use of baseline information in the analysis protected randomization and therefore the baseline characteristics of patients allowed for the comparison of the treatment effect. In addition, comparing the two treatments within each quartile was equivalent to a standard subgroup comparison. The reduction in MACE in parallel with the reduction in severe hypoglycaemia with degludec versus glargine U100 supports but does not prove a causal link between these events. While not conclusive evidence of a causal relationship, the results from our study suggest that patients with high rates of hypoglycaemia are also the patients with high MACE and mortality incidences.

In the absence of a specifically designed randomized controlled trial comparing high or low rates of severe hypoglycaemia and its relation to MACE, which is neither ethical nor feasible, a direct causal link between severe hypoglycaemia and adverse cardiovascular outcomes cannot be demonstrated. Interestingly, results from a post-hoc analysis of the LEADER trial have demonstrated a significantly higher risk of MACE, cardiovascular death and non-cardiovascular death following a severe hypoglycaemic event.[10] In addition, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial demonstrated that severe hypoglycaemia was associated with an increased risk of cardiovascular and all-cause death,[4] while a post-hoc analysis of the Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) trial indicated that severe hypoglycaemia was associated with higher risks of cardiovascular events and death.[5] However, a previous secondary analysis of DEVOTE demonstrated the lack of an association between MACE and a previous severe hypoglycaemic event, although a temporal association with all-cause mortality and cardiovascular death and a previous severe hypoglycaemic event was identified.[9] It should be noted that this previously reported DEVOTE analysis was limited by the small proportion of patients who experienced a severe

hypoglycaemic event before a MACE, making it difficult to establish a significant difference, although the point estimate was aligned with the above LEADER data.[9,10] Overall, based on our results, and those from other cardiovascular outcomes trials, we submit that it is most likely that MACE, in the context of severe hypoglycaemia, are related to both the underlying risk of MACE (vulnerability)[25] and to consequences of severe hypoglycaemia (causality).[26]

The analysis reported here has limitations. While DEVOTE included a large number of patients at high risk of cardiovascular events, these patients were selected for inclusion in a randomized trial setting and may therefore not be representative of a real-world patient cohort. In addition, DEVOTE only collected severe hypoglycaemic events, and therefore the contribution of non-severe events, which have also been shown to be associated with a higher risk of cardiovascular events, hospitalization and all-cause mortality, could not be assessed.[27,28] However, despite these limitations, we considered use of the DEVOTE cohort relevant to these issues as it represents a population in whom hypoglycaemia is of considerable concern.

Strengths of this analysis include use of a large, double-blind trial with a high retention rate, independent adjudication of cardiovascular and severe hypoglycaemic events, and use of a standard, robust definition of severe hypoglycaemia according to international guidelines.[22] To allow the translation of the hypoglycaemia risk score to the clinical setting, it was digitized into an online tool (http://www.hyporiskscore.com/). This tool provides patients and health care providers with both the level of risk of a patient experiencing a severe hypoglycaemic event within 2 years and the observed risk of MACE within the risk quartile.

In conclusion, we demonstrated that the risks of MACE and all-cause mortality appear to increase with the risk of severe hypoglycaemia, supporting the known relationship between hypoglycaemia and cardiovascular events. Furthermore, those patients with the highest hypoglycaemia risk had a lower incidence of MACE with degludec compared with glargine U100, in a patient population in whom degludec reduces the risk of hypoglycaemia. These observations support the hypothesis that hypoglycaemia is a risk factor for cardiovascular events.

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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.

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. DKM 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 1UL1 TR002550). 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 (Center 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 Florida Hospital, a non-profit organization. He has received consultancy and speaker fees from AstraZeneca, Takeda and Novo Nordisk, consultancy fees from Boehringer Ingelheim, GlaxoSmithKline, Hanmi Pharmaceutical Co. Ltd., Janssen Scientific Affairs LLC, Ligand Pharmaceuticals, Inc., Eli Lilly, Merck, Pfizer and Eisai, Inc., and research grants from Gilead Sciences, Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Inc., Eli Lilly, Merck, Sanofi US LLC and Takeda. 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, 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), the Patient-Centered Outcomes Research Institute and the American Diabetes Association. The trial sponsor was involved in the design of DEVOTE and this secondary analysis, the collection and analysis of data, and writing the clinical report. J.B.B. received support from The US National Institutes of Health (UL1TR002489). All authors interpreted the data and wrote the manuscript together with the sponsor's medical writing services team. The funders of the study had no role in the approval of the manuscript or the decision to submit for publication.

ORCID

Simon Heller https://orcid.org/0000-0002-2425-9565
Ildiko Lingvay https://orcid.org/0000-0001-7006-7401
Thomas R. Pieber https://orcid.org/0000-0003-3554-0405

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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