Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People With Type 1 and Type 2 Diabetes: A Cohort Study

Kamlesh Khunti,[1,2] Melanie Davies,[1,2] Azeem Majeed,[3] Brian Larsen Thorsted,[4] Michael Lyng Wolden,[4] and Sanjoy K. Paul[5]

Diabetes Care 2015;38:316–322 | DOI: 10.2337/dc14-0920

OBJECTIVE

Hypoglycemia has been associated with an increased risk of cardiovascular (CV) events and all-cause mortality. This study assessed whether, in a nationally representative population, there is an association between hypoglycemia, the risk of CV events, and all-cause mortality among insulin-treated people with type 1 diabetes or type 2 diabetes.

RESEARCH DESIGN AND METHODS

This retrospective cohort study used data from the Clinical Practice Research Datalink database and included all insulin-treated patients (≥30 years of age) with a diagnosis of diabetes.

RESULTS

In patients who experienced hypoglycemia, hazard ratios (HRs) for CV events in people with type 1 diabetes were 1.51 (95% CI 0.83, 2.75; *P* = ns) and 1.61 (1.17, 2.22), respectively, for those with and without a history of CV disease (CVD) before the index date. In people with type 2 diabetes, the HRs for patients with and without a history of CVD were 1.60 (1.21, 2.12) and 1.49 (1.23, 1.82), respectively. For all-cause mortality, HRs in people with type 1 diabetes were 1.98 (1.25, 3.17), and 2.03 (1.66, 2.47), respectively, for those with and without a history of CVD. Among people with type 2 diabetes, HRs were 1.74 (1.39, 2.18) and 2.48 (2.21, 2.79), respectively, for those with and without a history of CVD. The median time (interquartile range) from first hypoglycemia event to first CV event was 1.5 years (0.5, 3.5 years) and 1.5 years (0.5, 3.0 years), respectively, for people with type 1 and type 2 diabetes.

CONCLUSIONS

Hypoglycemia is associated with an increased risk of CV events and all-cause mortality in insulin-treated patients with diabetes. The relationship between hypoglycemia and CV outcomes and mortality exists over a long period.

Hypoglycemia is associated with a number of blood glucose–lowering therapies, but is a particular problem for patients receiving insulin therapy. As the most effective method of lowering blood glucose levels, insulin therapy is an essential element of treatment for people with type 1 diabetes and longer-duration type 2 diabetes. However, hypoglycemia is a major obstacle to achieving optimal glycemic control (1–4).

[1]*Leicester Diabetes Centre, University of Leicester, Leicester, U.K.*
[2]*Leicester Clinical Trials Unit, University of Leicester, Leicester, U.K.*
[3]*Department of Primary Care and Public Health, Imperial College London, London, U.K.*
[4]*Novo Nordisk A/S, Bagsværd, Denmark*
[5]*Clinical Trials and Biostatistics Unit, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia*

Corresponding author: Kamlesh Khunti, kk22@leicester.ac.uk.

Received 11 April 2014 and accepted 6 November 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0920/-/DC1.

K.K. and S.K.P. contributed equally to this study.

A large prospective study by the UK Hypoglycaemia Study Group (5) demonstrated that severe hypoglycemia is a common problem in people with insulin-treated type 2 diabetes and that the incidence increases with the duration of insulin therapy. The acute effects of hypoglycemia are well documented, yet the relationship between hypoglycemia and long-term cardiovascular (CV) risk has been harder to elucidate, largely because of the complex nature of diabetes and the presence of comorbidities.

Large-scale diabetes outcomes trials (2,4,6–8) have presented conflicting results regarding the impact of intensive blood glucose–lowering therapy on mortality and CV risk. Notwithstanding, there is a growing consensus that hypoglycemia is a risk factor for CV events, particularly among high-risk patients (6,8–10).

In the ADVANCE, ACCORD, and VADT trials, severe hypoglycemia was significantly higher in the intensive glucose-lowering arms compared with the standard arms, as follows: ACCORD 16.2% vs. 5.1% (6); VADT 21.2% vs. 9.9% (9); and ADVANCE 2.7% vs. 1.5% (7). All these trials recruited participants who were at high risk for CV disease (CVD). The much lower risk for severe hypoglycemia in ADVANCE may be due to the fact that the patients in that trial had a shorter duration of diabetes, by 2–3 years, and lower HbA_{1c} level at study entry, despite very little use of insulin at baseline (11). A substudy from the treat-to-target ADVANCE trial investigated the impact of severe hypoglycemia (defined as requiring third-party assistance) on long-term CV risk and found that it was associated with a significant increase in the adjusted risk of major macrovascular events (hazard ratio [HR] 2.88 [95% CI 2.01, 4.12]), major microvascular events (1.81 [1.19, 2.74]), death from CV cause (2.68 [1.72, 4.19]), and death from any cause (2.69 [1.97, 3.67]) (12). A recent systematic review (13) collated data from cohort studies to evaluate the association between severe hypoglycemia and CV events in patients with type 2 diabetes. The study, which screened 34,443 citations (excluding studies from short-term hospital settings), reported a twofold increased risk of CV events among patients who experienced severe hypoglycemia (rate ratio 2.05 [95% CI 1.74, 2.42]) (13). Interestingly, the bias analysis suggested that comorbidity alone could not explain this association.

In patients with type 1 diabetes, the DCCT study (14) did not show any significant association between more frequent severe hypoglycemia and increased CV mortality among patients in the intensive treatment group. The Epidemiology of Diabetes Interventions and Complications (EDIC) study showed a reduction in CVD during follow-up; however, the risk of CV events among the people who experienced severe hypoglycemia was not reported, and this issue has scarcely been explored in clinical and epidemiological studies. The EURODIAB Prospective Complications Study (15) of 2,181 patients with type 1 diabetes, who were observed for 7 years, reported no association of baseline hypoglycemia with the risk of CVD. However, a retrospective analysis (16) of a large cohort of patients with type 1 diabetes on continuous subcutaneous insulin infusion pointed to a higher prevalence of CVD in patients with a history of repeated episodes of hypoglycemia. Further exploration of any potential relationship between severe hypoglycemia and CV events is vitally important because the large number of patients requiring insulin therapy means that even a small increase in risk could have major clinical and public health implications. In addition, a link between hypoglycemia and CV risk would be of particular consequence for those insulin-treated patients who require treatment intensification, especially when they have pre-existing CVDs or elevated CV risk factors. The current study explored whether there is an association between severe hypoglycemia and CV risk and mortality in a contemporary, real-world setting of people with type 1 or type 2 diabetes who were treated with insulin. In addition, we wanted to quantify the risk separately for those with and without pre-existing CVD.

RESEARCH DESIGN AND METHODS

Study Design and Selection Criteria

This retrospective cohort study used data from the Clinical Practice Research Datalink (CPRD) database and included all insulin-treated patients (≥30 years of age) with a diagnosis of diabetes (Read/OXMIS code C10+) in the period between 1 January 2001 and 31 December 2007. The CPRD holds anonymized, longitudinal, primary care records of ~5% of the population registered with a general practice in the U.K. and is widely used for epidemiological research. Patients registered with general practices participating in the database represent a population that is similar to, and therefore representative of, that of the U.K. (http://www.cprd.com/). Participating practices follow an agreed protocol for the collection of demographic, clinical, laboratory, and prescription data, and regularly submit anonymized records to the database. The patient-level primary care records in the CPRD are now linked to Hospital Episode Statistics (HES) data. The HES database contains details of all hospital admissions, outpatient appointments, and emergency attendances at National Health Service hospitals in England (not Northern Ireland, Scotland, or Wales). Only the subset of people in the CPRD from England who were eligible for linkage to HES was included in our study. All recordings of hypoglycemia in the HES database were severe (defined as requiring hospital admission), whereas those in the CPRD may be severe or nonsevere. Data on hypoglycemia recorded in CPRD plus HES and CPRD alone were analyzed. The CPRD-alone analysis excluded HES recordings of hypoglycemia: both analyses were performed in the same cohort of patients. CPRD plus HES data yield estimates for all recordings of hypoglycemia, both in general practice and on admission to hospital, whereas CPRD alone is more representative of those events reported only in general practice.

The last follow-up date was set on 31 December 2010. The index date for patients was the start of insulin treatment (identified by the second insulin prescription) after 1 January 2001. Data on hypoglycemic episodes were obtained from the HES via ICD-10 codes (E16.0, E16.1, and E16.2). Patients with a record (one or more episode) of severe hypoglycemia before the initiation of insulin therapy were excluded from the analysis. Patients were classified as exposed from the time of the first hypoglycemic episode or were otherwise considered to be unexposed, thus avoiding immortal time bias. Separate cohorts for people with type 1 and type 2 diabetes were created. Patients were classified into diabetes groups following the Royal College of General

Practitioners guidelines (17), as follows: classification into diabetes type relies on a combination of Read codes, therapy, and age at diagnosis (18). Measurements of HbA_{1c} and BMI were recorded in a window extending to 3 months on either side of the index date. Patients with no data on HbA_{1c} levels, smoking, and/or BMI were categorized separately to be able to characterize these groups.

CV event was defined as a composite of myocardial infarction, stroke, or CV death (cause of death obtained through linkage to Office for National Statistics mortality data). The numbers of CV events were counted for each exposure group, and were only considered as happening in exposed risk time if patients had experienced a hypoglycemic episode before the CV event, thus retaining the time relationship between exposure and outcome. Patients with a registered code for any CV event in the HES or CPRD, which took place before the index date, were classified in a group with a history of CVD. (Read/OXMIS codes for diabetes, hypoglycemia, CV events, and smoking are provided in Supplementary Table 1.)

Statistical Analysis

Basic statistics on the study population were presented as *n* (%), mean ± SD, or median (interquartile range [IQR]), as appropriate.

The rates of events were calculated as the number of events per 1,000 person-years along with the 95% CI using a standard life table analysis technique. For all patients, the exposure time started from the initiation of insulin treatment. To evaluate the risk of events associated with hypoglycemia, the "time to event" for those who experienced at least one hypoglycemic event was calculated from the time of the first episode of hypoglycemia. Stratified univariate and multivariate Cox regression models were fitted to estimate the risk of vascular events and mortality associated with hypoglycemia, with practice-level deprivation score (derived from the Index of Multiple Deprivation [19]) as the stratification factor. The covariates with complete data in the multivariate models were as follows: age on index date, sex, smoking status, geographical region, history of CV events before index date, use of oral antidiabetic medications, Charlson comorbidity index (20), BMI, and HbA_{1c} level on the index date. A sensitivity regression analysis was performed including only persons with known values in all covariates.

This protocol (13_027RMn) was approved by the Independent Scientific Advisory Committee.

RESULTS

Patient Demographics and Baseline Characteristics

The primary data set included a total of 265,868 individuals who had received a diagnosis of diabetes. After exclusion criteria were applied for the combined CPRD plus HES population, 3,260 patients with type 1 diabetes and 10,422 patients with type 2 diabetes were included in the regression analyses. (The results of the exclusion criteria are presented in Supplementary Table 2.) The baseline characteristics of people with type 1 and type 2 diabetes are shown in Table 1. Missing values for HbA_{1c} level, BMI, and smoking status did not affect the direction of the estimates. The number of patients in the type 1 and type 2 diabetes cohorts with data for blood pressure (systolic and diastolic) was 2,555 and 8,087, respectively, and for lipid parameters the number of patients in each diabetes cohort ranged between 805 and 1,800, and 2,636 and 5,569, respectively.

During follow-up, 573 patients (18%) with type 1 diabetes and 1,463 patients (14%) with type 2 diabetes experienced hypoglycemia. The proportions of patients experiencing CV events or death were broadly similar both in patients with type 1 diabetes and type 2 diabetes (Table 2). The median duration of follow-up among patients with type 1 diabetes was 5.0 years, while for patients with type 2 diabetes it was 4.8 years. The incidence rates (per 1,000 person-years) of CV outcomes among patients with a history of CVD were 3.5-fold and 2.8-fold higher, respectively, in the type 1 and type 2 diabetes cohorts, compared with those patients without a history of CVD. Death rates were twofold higher in both cohorts for patients with a history of CVD (Table 3).

Hypoglycemia and CV Risk

During follow-up, patients who experienced hypoglycemia were at a greater risk of CV events. Unadjusted and covariate-adjusted CV risk HRs for exposed patients with type 1 and type 2 diabetes are presented in Table 3. Among patients without a history of CVD, patients who experienced at least one episode of hypoglycemia had a 92% and 50% significantly increased risk, respectively, of composite CV events in type 1 and type 2 diabetes cohorts (CPRD plus HES population, Table 3). Hypoglycemia was also significantly associated with the increased risk of CV events among patients with a history of CVD in the type 2 diabetes cohort. It is important to mention here that the adjusted and unadjusted risk estimates associated with hypoglycemia were similar in the CPRD plus HES data, separately for the two cohorts of patients with type 1 and type 2 diabetes. The assumption of proportional hazards was not violated in the Cox regression analyses.

Hypoglycemia and All-Cause Mortality

In the type 1 diabetes cohort, hypoglycemia was associated with an approximately

Table 1—Characteristics of the cohorts of patients with type 1 and type 2 diabetes

	Type 1 diabetes (*n* = 3,260)	Type 2 diabetes (*n* = 10,422)
Age at index (years), mean ± SD	60 ± 15	63 ± 13
Men, *n* (%)	1,828 (56)	5,819 (56)
BMI at index (kg/m^2)	29.93 ± 6.35 (*n* = 1,327)	29.88 ± 6.44 (*n* = 5,977)
HbA_{1c} level at index (% [mmol/mol])	8.69 ± 1.9 [71.5 ± 20.8] (*n* = 1,939)	8.89 ± 1.89 [73.7 ± 20.6] (*n* = 6,712)
History of CVD prior to initiation of insulin, *n* (%)	367 (11)	1,477 (14)
Smoking status at index, *n* (%)		
Current smoker	299 (9.17)	852 (8.18)
Previous smoker	474 (14.54)	1,683 (16.15)
Charlson comorbidity score	1.83 ± 1.23	2.03 ± 1.41
Practice-level deprivation score*	2.26 ± 1.32	2.21 ± 1.35

Data are mean ± SD, unless otherwise indicated. *Practice-level deprivation score was derived from the Index of Multiple Deprivation (19).

Table 2—Numbers of patients experiencing at least one episode of hypoglycemia, CV event, or death during follow-up

	Type 1 diabetes	Type 2 diabetes
Number of individuals experiencing hypoglycemic episodes during follow-up	573 (17.6)	1,463 (14.0)
MI	137 (4.2)	527 (5.1)
Stroke	103 (3.2)	380 (3.6)
CV death	23 (0.7)	60 (0.6)
Composite CV event (MI/stroke/CV death)	263 (8.1)	972 (9.3)
All-cause mortality	754 (23.1)	2,394 (23.0)
Duration of follow-up, median (IQR)	5.0 (2.9, 7.5)	4.8 (2.7, 6.9)

Data are *n* (%), unless otherwise indicated. MI, myocardial infarction.

twofold increased risk of all-cause mortality for both patient groups with and without the history of CVD (Table 3, CPRD plus HES data). In the type 2 diabetes cohort, after adjusting for the effects of possible confounding factors, hypoglycemia was associated with HRs of 94% (95% CI 1.52, 2.47) and 139% (2.13, 2.67), respectively, increased mortality risk among patients with and without history of CVD. The significant association of hypoglycemia with the increased mortality risk was also observed in the CPRD group (with the exception of an insignificant 53% increased risk among patients with a history of CVD in the type 1 diabetes cohort). Among patients with type 2 diabetes, those prescribed metformin had approximately half the risk of death compared with patients receiving sulphonylureas, both in patients with a history of CVD (HR 0.49 [95% CI 0.28, 0.87]) and in those without such a history (0.54 [0.42, 0.72]; $P < 0.05$). There was no difference in HR for CV events between metformin-treated and sulphonylurea-treated patients (data not shown). The assumption of proportional hazards was not violated in the Cox regression analyses.

Time From Hypoglycemia to First CV Event or Death

The median time (from CPRD plus HES data) from the first episode of hypoglycemia to the first CV event in patients with type 1 diabetes was 1.5 years (IQR 0.5, 3.5 years) (*n* = 38 patients with hypoglycemia who experienced at least one CV event). Among patients with type 2 diabetes, the median time from the first episode of hypoglycemia to the first CV event was 1.5 years (IQR 0.5, 3.0 years) (*n* = 97 patients with hypoglycemia experienced at least one CV event). The median time (from CPRD plus HES data) from the first episode of hypoglycemia to death in patients with type 1 diabetes was 1.1 years (IQR 0.3, 2.3 years) (*n* = 169 patients who experienced at least one episode of hypoglycemia died). Among patients with type 2 diabetes, the median time from the first episode of hypoglycemia to death was 0.8 years (IQR 0.3, 2.3 years) (*n* = 493 patients who experienced at least one episode of hypoglycemia died).

CONCLUSIONS

The results of this retrospective cohort analysis demonstrate that, in a nationally representative contemporary population, hypoglycemia is associated with an increased risk of CV events and all-cause mortality in insulin-treated patients with type 1 and type 2 diabetes. These results confirm the findings of the ACCORD study in people with type 2 diabetes, and add to the evidence for a link between hypoglycemia and CV events in people with type 1 diabetes. Likewise, our analysis also reconfirms that the increased risk of CV events after a hypoglycemic episode persists over a period of months and years.

CVD remains the primary cause of death among insulin-treated people with diabetes (21,22). This is largely due to the effects of hyperglycemia and pre-existing comorbidities, but the

Table 3—Unadjusted incidence rates and 95% CIs of CV outcomes and all-cause mortality

		Population	Unadjusted incidence rates (per 1,000 person-years)	Unadjusted HR (CPRD plus HES)	Adjusted HR	
					CPRD plus HES	CPRD
Type 1 diabetes	CV events	History of CVD before index (*n* = 298, events = 54)	45.6 (33.4, 57.8)	1.44 (0.56, 3.69)	1.10 (0.40, 3.01)	0.81 (0.23, 2.84)
		No CVD before index (*n* = 2,962, events = 209)	13.3 (11.5, 15.1)	1.99* (1.38, 2.87)	1.92* (1.32, 2.79)	1.73† (1.13, 2.65)
	All-cause mortality	History of CVD before index (*n* = 298, deaths = 113)	85.0 (69.3, 100.7)	2.83* (1.74, 4.62)	1.95† (1.14, 3.35)	1.53 (0.80, 2.90)
		No CVD before index (*n* = 2,962, deaths = 641)	39.5 (36.4, 42.6)	2.69* (2.23, 3.24)	2.05* (1.69, 2.49)	1.62* (1.28, 2.05)
Type 2 diabetes	CV events	History of CVD before index (*n* = 1,261, events = 232)	45.3 (39.5, 51.2)	1.80† (1.17, 2.77)	1.70† (1.09, 2.64)	1.62 (0.98, 2.68)
		No CVD before index (*n* = 9,161, events = 740)	16.2 (15.1, 17.4)	1.73* (1.38, 2.18)	1.50* (1.19, 1.88)	1.31† (1.01, 1.71)
	All-cause mortality	History of CVD before index (*n* = 1,261, deaths = 510)	90.0 (82.2, 97.8)	2.58* (2.04, 3.27)	1.94* (1.52, 2.47)	1.76* (1.32, 2.34)
		No CVD before index (*n* = 9,161, deaths = 1,884)	39.7 (37.9, 41.5)	3.24* (2.90, 3.63)	2.39* (2.13, 2.67)	1.94* (1.70, 2.22)

Unadjusted and adjusted HRs and 95% CIs for composite CV events and all-cause mortality in patients with type 1 and type 2 diabetes, separately for those with and without a history of CVD prior to the index date. *$P < 0.001$. †$P < 0.05$.

role of hypoglycemia in contributing to CV events or mortality, even if modest, is still important. Since the ACCORD and VADT results were published, attempts have been made to assess whether a relationship exists between hypoglycemia and CV risk or mortality, but only recently has a consensus begun to emerge suggesting that there is a link between the two (6,8,9).

Several potential mechanisms linking hypoglycemia and CV risk have been proposed, including QT prolongation, hemodynamic changes arising from catecholamine release, inflammation, and endothelial dysfunction (23–25). Although real, these effects are more likely to explain a transient increase in CV risk during the acute phase of hypoglycemia rather than the longer-term relationship observed in the current study. Our investigation has not attempted to make a causal link between these observations, but we have highlighted the importance of CV risk in patients who experienced hypoglycemia by showing that hypoglycemia is associated with very early CV events and mortality. Indeed, there are common characteristics among patients with diabetes who are at high risk of experiencing hypoglycemia or CV events, notably an increased duration of insulin treatment and age (5,26). The relationship between severe hypoglycemic events and CV outcomes may be due to a patient's health deteriorating much more at the time of their event than is the case for nonsevere hypoglycemic episodes. Conversely, our study, which includes both nonsevere and severe events, suggests that the relationship between hypoglycemia, and CV outcomes and all-cause mortality exists over a long period, and therefore possibly before any worsening of a patient's health. Patients with type 2 diabetes treated solely with oral hypoglycemic agents were not included in our analysis. This is because these patients typically have a shorter duration of diabetes and variable levels of clinical inertia (27)—confounders that would be difficult to adjust for. In our study, CV risk and all-cause mortality (not HR) were higher among patients with a history of CVD compared with those without. When interpreting HRs, we are looking at the association between hypoglycemia and CV risk/all-cause mortality. This association is often stronger in those patients without a history of CV, and hence the HR is often higher in this subgroup. Possible explanations are that the association between hypoglycemia and CV risk/all-cause mortality is masked in those patients who have previously experienced a CV event, or that hypoglycemia is not as strong a predictor in this case.

The current study has several limitations. First, as there is no randomization of patients in exposure groups in observational studies, it is important to correct for bias and confounding. Not all relevant confounding factors are captured in the CPRD database; thus, predicting causality was not possible. Under-reporting of hypoglycemia in the CPRD is another issue potentially affecting our analysis because patients may often self-manage an episode and not present to a physician. This may be compounded by the exclusion of non-HES–eligible patients. Furthermore, we expect that reported hypoglycemic events will be more severe than those not registered, but we do not have any data available to confirm this. Patients' second prescription of insulin was used as the index date to exclude erroneous registrations. Some patients may have started their insulin therapy in a hospital clinic and not received their insulin prescription from their general practitioner until later in the course of their illness.

Although variables like BMI, smoking status, and HbA_{1c} level at index are well captured with the introduction of the Quality and Outcomes Framework (QOF), they were not available for all patients during the 6-month window around the index date. It was not possible to accurately calculate the duration of diabetes in our analysis because patients may have received a diagnosis many years previously or in practices not included in the CPRD, but we believe that age is a good proxy for the duration of diabetes. Likewise, recordings of blood pressure and lipid levels in the CPRD are sparse, and were not incorporated in the main analysis. However, we do not believe that this invalidates the findings, as the measures would not independently alter the outcomes. Supporting our approach, a sensitivity analysis, carried out using the available lipid and blood pressure data in a subset of patients with known values for all covariates, did not change the size or direction of the estimates significantly (data not shown in the RESULTS section). Finally, our study only included patients with Read codes in C10+. We believe that this is a minor limitation as this study focuses on insulin-treated patients only, and the QOF has resulted in more standardized use of Read codes by general practitioners as correct coding of patients leads to a higher prevalence of diabetes, and hence to higher QOF payments for general practices.

This present study has several strengths. First, the sample size was large and was derived from the CPRD, which is representative of patients across the UK. As the UK has a health system with universal coverage, this means that no section of the population is excluded from the CPRD (28). Additionally, our study takes place within the QOF period, beginning in 2004. QOF has greatly improved the completeness and accuracy of the data recorded in the CPRD (29,30). The study assessed type 1 and type 2 diabetes together, comparing the effect of hypoglycemia on CV risk and all-cause mortality in both populations. The high quality and nationally representative nature of the data used in the present analysis affirms its validity, especially in comparison with smaller studies, or with those using less robust or less well-curated indexes; however, we acknowledge that the selection criteria applied to our cohort could potentially affect its representative quality, particularly among the type 2 diabetes cohort. Despite this limitation, we believe that the results of the type 2 diabetes cohort play an important role in informing the debate concerning the growing body of evidence associating severe hypoglycemia with CV risk. Second, our study took a robust approach to the analysis, adjusting for multiple covariates, including the practice-level deprivation and Charlson comorbidity scores. Unlike the ACCORD study, which only analyzed severe hypoglycemia, our study captures all hypoglycemia (CPRD) and severe hypoglycemia (HES). This provides a broader picture of the potential impact of hypoglycemia on CV risk. Moreover, a recently published analysis (31) of national health record services has suggested that general practices submitting data to the CPRD are likely to be better at recording disease

events compared with those practices not participating in the CPRD.

In conclusion, our study confirms a relationship between hypoglycemic events and an increased risk of CV outcomes and all-cause mortality in patients with both type 1 and type 2 diabetes. Furthermore, the association between these outcomes endures over a long period. The nature of our analysis precludes us from making a causal link; however, hypoglycemia has been proposed as a surrogate measure of greater disease burden and thus an indirect marker of CV risk (32). Based on the results of our analysis and previously published studies, we recommend that special attention should be paid to insulin-treated patients who experience a hypoglycemic event—especially those who are at elevated risk for CV events—and an effort should be made to reduce the incidence of future hypoglycemic events.

Acknowledgments. The authors thank Michael Soljak, PhD, Imperial College London, for his advice on analyzing smoking status in the current study.

Funding. This work was supported by both the East Midlands National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) and the NIHR CLAHRC for Northwest London; the Leicester–Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit; the Imperial NIHR Biomedical Research Centre; and the Imperial Centre for Patient Safety and Service Quality and received infrastructure support from Therapeutic Innovation Australia. The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the NIHR, the Biomedical Research Centre, or the Imperial Centre for Patient Safety and Service Quality.

Duality of Interest. Medical writing assistance and editorial/manuscript submission support was funded by Novo Nordisk. The authors thank Paul Tisdale, PhD, and Daria Renshaw at Watermeadow Medical, U.K., for medical writing assistance and editorial support, respectively (sponsored by Novo Nordisk). K.K. has acted as a consultant, advisory board member, and speaker for and has received research grants from Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Sanofi, Boehringer Ingelheim, and Roche. M.D. has acted as a consultant, advisory board member, and speaker for AstraZeneca, Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp & Dohme, and Boehringer Ingelheim and has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi, Eli Lilly, Pfizer, Merck Sharp & Dohme, and GlaxoSmithKline. B.L.T. and M.L.W. are employees and shareholders of Novo Nordisk A/S. S.K.P. has acted as a consultant and speaker for Novartis and Amylin Pharmaceuticals, LLC and has received grants in support of investigator and investigator-initiated clinical studies from Merck Sharp & Dohme, Novo Nordisk, Pfizer, Amylin Pharmaceuticals, Bristol-Myers Squibb, and Hospira. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. K.K. and S.K.P. contributed equally to the conception and design of the article, the analysis plan, and the data interpretation. M.D. contributed to data interpretation and the writing and revision of the article. A.M. contributed to hypothesis generation and to the drafting of the manuscript. B.L.T. contributed to the study design and data analysis and interpretation. M.L.W. contributed to the study design and data interpretation. K.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
3. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
5. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–1147
6. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
7. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
8. Abraira C, Duckworth W, McCarren M, et al.; VA Cooperative Study of Glycemic Control and Complications in Diabetes Mellitus Type 2. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. J Diabetes Complications 2003;17:314–322
9. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
10. Mellbin LG, Rydén L, Riddle MC, et al.; ORIGIN Trial Investigators. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J 2013;34:3137–3144
11. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34(Suppl. 2):S132–S137
12. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
13. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533
14. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46:271–286
15. Gruden G, Barutta F, Chaturvedi N, et al. Severe hypoglycemia and cardiovascular disease incidence in type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetes Care 2012;35:1598–1604
16. Giménez M, López JJ, Castell C, Conget I. Hypoglycaemia and cardiovascular disease in type 1 diabetes. Results from the Catalan National Public Health registry on insulin pump therapy. Diabetes Res Clin Pract 2012;96:e23–e25
17. Clinical Informatics Research Group. Diabetes codes [article online], 2014. Guildford, UK, Clinical Informatics Research Group. Available from http://www.clininf.eu/diabetescodes. Accessed 20 July 2014
18. de Lusignan S, Sadek N, Mulnier H, Tahir A, Russell-Jones D, Khunti K. Miscoding, misclassification and misdiagnosis of diabetes in primary care. Diabet Med 2012;29:181–189
19. Noble M, Wright G, Dibben C, et al. The English indices of deprivation 2004 (revised) [article online], 2004. London, UK, Office of the Deputy Prime Minister. Available from http://www.simonpoulter.co.uk/iod/iodpdf/odpm_urbpol_029534.pdf. Accessed 20 July 2014
20. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Fam Pract 2010;11:1
21. Laing SP, Swerdlow AJ, Slater SD, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 2003;46:760–765
22. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care 2006;29:798–804
23. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. Diabetes 2003;52:1469–1474
24. Sommerfield AJ, Wilkinson IB, Webb DJ, Frier BM. Vessel wall stiffness in type 1 diabetes and the central hemodynamic effects of acute hypoglycemia. Am J Physiol Endocrinol Metab 2007;293:E1274–E1279
25. Tsujimoto T, Yamamoto-Honda R, Kajio H, et al. Vital signs, QT prolongation, and newly diagnosed cardiovascular disease during severe hypoglycemia in type 1 and type 2 diabetic patients. Diabetes Care 2014;37:217–225
26. Donnelly LA, Morris AD, Frier BM, et al.; DARTS/MEMO Collaboration. Frequency and

predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. Diabet Med 2005;22:749–755
27. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013;36:3411–3417
28. Majeed A, Molokhia M. Primary care in the United Kingdom. J Ambul Care Manage 2008;31:198–200
29. Oluwatowoju I, Abu E, Wild SH, Byrne CD. Improvements in glycaemic control and cholesterol concentrations associated with the Quality and Outcomes Framework: a regional 2-year audit of diabetes care in the UK. Diabet Med 2010;27:354–359
30. Mathur R, Bhaskaran K, Chaturvedi N, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. J Public Health (Oxf). 8 December 2013 [Epub ahead of print]
31. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 2013;346:f2350
32. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 2012;35:1897–1901