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Title Page

Title: Association of hypoglycaemia and cardiac arrhythmia risk in patients with diabetes mellitus: A systematic review and meta-analysis

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Appendices: Supplementary Material: 1. Search Strategy adapted for use within Medline 2. Quality Assessment of Included Studies 3. Funnel plot for QTc interval length

Abstract

Summary

Aims

Hypoglycaemia is associated with increased cardiovascular risk amongst individuals with diabetes mellitus. It has been hypothesised that hypoglycaemia may trigger autonomic changes leading to increased cardiac arrhythmia risk. We conducted a systematic review and meta-analysis to explore this association.

Materials and Methods

Ovid Medline, Embase, Scopus, Web of Science and Cochrane were searched from inception to October 10, 2017. We included studies of adults with diabetes (Type 1 or Type 2) which compared acute electrocardiogram (ECG) changes during episodes of hypoglycaemia and euglycaemia.

Results

Our search returned 4625 citations, from which 20 studies met our predefined inclusion criteria. Sixteen studies were included in our descriptive analysis and 15 in our meta-analysis. Overall hypoglycaemia was associated with a reduction in heart rate variability and an increase in arrhythmia occurrence. QTc interval length was more significantly prolonged during hypoglycaemia compared to euglycaemia (pooled mean difference (95% confidence intervals) (0.64 (0.27-1.01), $p=0.001$). Subgroup analysis based on diabetes type showed that QTc prolongation occurred in individuals with Type 1 and Type 2 diabetes however the change between euglycaemia only reached statistical significance amongst individuals with Type 1 diabetes.

Conclusion

Our findings suggest that hypoglycaemia results in ECG alterations associated with increased cardiac arrhythmia risk which is associated with increased cardiovascular events and mortality. More clinical studies are needed to determine the cardiac risks of hypoglycaemia in people with diabetes especially in Type 2 diabetes.

Introduction

The global prevalence of diabetes is increasing with estimates suggesting over 415 million adults are living with the condition, of which over 90% have Type 2 (T2DM).^[1] Despite increasing awareness of the detrimental effects that poor diabetes control can exert, the incidence of secondary complications continues to rise.^[2, 3] Cardiovascular disease (CVD), is the most prevalent cause of morbidity and mortality among this population^[4] and a plethora of research has been conducted to explore the underlying pathophysiological mechanisms. Whilst convincing evidence demonstrates adverse effects of hyperglycaemia on CVD development, meta-analyses of large clinical trials suggest that hypoglycaemia may also contribute to poor CVD outcomes.^[4, 5] What remains unknown is whether hypoglycaemia serves as a marker of vulnerability to cardiovascular events or whether it triggers a direct causal effect.

In 1991, Tattersall and Gill^[6] described a series of cases of sudden, unexplained, nocturnal deaths amongst young people with type 1 diabetes (T1DM). Asymptomatic patients who had gone to sleep at night were later found dead in undisturbed beds. Circumstantial evidence suggests that nocturnal hypoglycaemia may be to blame for this, subsequently described as the ‘dead in bed syndrome’. Whilst the results of a recent meta-analysis report that intensive glucose lowering is associated with significant reductions in non-fatal myocardial infarction (MI) risk,^[7] individually, three large scale clinical trials have shown no benefit, with one study demonstrating a detrimental effect on overall cardiovascular outcomes.^[8-10] Although subjectively measured, intensive management was associated with a significant increase in hypoglycaemia frequency and severity.

Whilst hypoglycaemia is common, particularly amongst individuals with T1DM, sudden deaths are rare,^[11, 12] which suggests the interplay of several contributing factors which, under certain conditions, results in the development of adverse cardiac events. As many episodes of hypoglycaemia are unrecognised, the exact mechanism underpinning this relationship has not been clearly established. It has been hypothesised that hypoglycaemia may trigger acute electrocardiographic (ECG) changes which increase an individual’s vulnerability to arrhythmic events, leading to adverse outcomes such as sudden cardiac death.^[13, 14] By being

able to identify the underlying mechanisms, clinicians may be able to identify individuals most at risk and can therefore modify and personalise management in high risk individuals and improve patient outcomes.

We conducted a systematic review and meta-analysis of clinical human studies exploring both experimentally induced, or spontaneous clinical hypoglycaemia identified through continuous glucose monitoring (CGM), to evaluate the acute effects of hypoglycaemia contributing to cardiac arrhythmia (CA) risk in adults with T1DM and T2DM. We particularly sought to compare differences in QTc (QT corrected for heart rate) interval duration between euglycaemic and hypoglycaemic periods however changes in heart rate variability (HRV) and arrhythmia incidence were also compared.

Materials and Methods

This systematic review and meta-analysis has been registered on PROSPERO (No. CRD42017059460) and was conducted in accordance with the PRISMA^[15] and MOOSE guidelines.^[16] In consultation with a clinical librarian we searched Ovid Medline (Epub ahead of print, in process and other non-indexed citations) 1946, Ovid Embase 1974, Scopus 1966, Web of Science 1970, and Cochrane Central Register of Controlled Trials from inception to October 09, 2017. We searched for “diabetes mellitus” (T1DM and T2DM), “hypoglycaemia” and “cardiac arrhythmias” using a combination of Medical Subject Headings, keywords and synonyms with English and American spellings. An example search strategy modified for Ovid Medline can be found in Supplement 1. We hand searched the reference lists and forward citations of included articles and contacted authors of conference abstracts.

Two investigators (CF and SS) independently screened titles and abstracts and examined full texts of potentially eligible articles using pre-specified inclusion criteria. Discrepancies were resolved through discussion. We included comparative observational (hypoglycaemia identified through CGM and ECG changes through ambulatory Holter monitoring) and experimental (induced hypoglycaemia) studies in which glycaemic and cardiac monitoring were performed simultaneously; that were conducted among adult patients (≥ 18 years) with T1DM or T2DM, and which compared acute cardiac changes in QTc, HRV and any CAs between episodes of

hypoglycaemia and euglycaemia. We included articles published in any language. We excluded case studies and studies that retrospectively reviewed hospital records due to lack of generalisability of their findings and/or poor data quality.

Data collection

Data extraction using an original extraction form, developed alongside a medical statistician (DHB), were performed by one reviewer (CF) and checked by one of two others (SS or SC). Where available, we recorded study characteristics (authors, year of publication, study design, duration and sample size); participant characteristics (mean age, percentage male, diabetes type and mean diabetes duration); exposure (glycaemia definitions) and outcome measures (QTc, HRV, CAs). Where studies also included participants without diabetes, only data relating to participants with diabetes were extracted. Where possible data relating to T1DM and T2DM were extracted separately. We contacted study authors where insufficient data were available within the publication.

We assessed quality by adapting the criteria suggested by the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional studies^[17] and the Cochrane Collaboration Risk of Bias Tool.^[18] Quality was evaluated based on study design, participant selection, exposure assessment, outcome assessment and adjustment for potential cofounders. Publication and selective reporting bias was assessed by the symmetry of the funnel plot.

Statistical analysis

For QTc interval duration, we calculated standardised means using formulae described previously,^[19] and pooled standardised mean differences (SMD) were estimated using random-effects meta-analysis to account for heterogeneity in study designs and population characteristics. We calculated heterogeneity using the I^2 statistic and publication bias was assessed using the Egger test. $I^2 < 25\%$, $25-75\%$ and $> 75\%$ was considered low, moderate and high heterogeneity respectively.^[20]

Studies calculated QTc using a variety of different formulae, with some studies calculating and comparing two or more. Bazett's formula (QTb)^[21] was most widely adopted, therefore where available, QTb data were used within the meta-analysis. Where QTb was unavailable, subject specific (n=2),^[22] or unknown formulae (n=1),^[23] were used.

For experimental studies providing data at different time points during the hyperinsulinemic clamps, to ensure consistency, we extracted data from the last time point. One study,^[24] compared outcomes between euglycaemia, hypoglycaemia with glibenclamide and hypoglycaemia without glibenclamide, to promote standardisation, data from the hypoglycaemia without glibenclamide group were used in the analysis.

Subgroup analyses were carried out based on diabetes type (Type 1; Type 2) and study design (experimental; observational), and meta-regression based on participant age (continuous, years), gender (continuous, % male), diabetes duration (continuous, years) and HbA1c (continuous, mean %).

We performed sensitivity analyses by first excluding two studies which identified their data as non-normally distributed and which were included in the meta-analysis by estimating the mean from the median and the standard deviation from the range.^[19] Second, despite QTb being the most commonly used formula for QTc, data have suggested it is not optimal.^[25, 26] A sensitivity analysis favouring QT corrected by Frederica's formula, the second most commonly reported method, was undertaken. The following heart rate correction formulae were combined in this analysis; Frederica (n=5), Bazett (n=6), subject specific (n=3) and unknown (n=1). Finally, we systematically excluded one study at a time from the analysis and assessed any change in pooled effect size.

All analyses were performed in Stata V14.1 (StataCorp), using the METAN, METAREG and METANINF commands. Results were reported with 95% confidence intervals (CI); $p < 0.05$ was considered statistically significant.

We used descriptive data synthesis to summarise findings relating to HRV and CA to account for the heterogeneity of study designs and outcome measures reported.

Results

Our initial search yielded 4625 citations, of which 67 full texts were assessed for eligibility (Figure 1). After examination, 24 publications from 21 studies were considered eligible.^[22-24, 27-47] Duplicate publications of three studies were identified.^[29-32, 34, 36] As the articles reported different study outcomes both were included in the review; however they were acknowledged as a single study which will henceforth be referenced by the original publication. During data extraction a further article had to be excluded;^[47] despite meeting the inclusion criteria, insufficient data were included in the publication to be involved in the analysis. A failed attempt at contact with the author meant the relevant data could not be obtained. This left 23 publications of 20 studies meeting the predefined inclusion criteria. Fifteen studies contained comparable outcome data for meta-analysis. Screening of references lists and forward citations did not identify any additional results.

Studies were conducted between 1992 and 2017; 17 were undertaken in Europe, two in Australia and one in the United States. Total participant numbers were 357 (T1DM=241, T2DM=116) with a range of 6-37 per study. Typically studies recruited more men (n=205) than women (n=132) (not reported=20), and the mean age of participants was 45 years (range 18-77) (T1DM (38 years, range 18-67) T2DM (61years, range 37-77). Eight studies were of observational design, reporting outcomes amongst participants with T1DM (n=5),^[23, 29, 35, 37, 45] T2DM (n=2),^[22, 44] or both (n=1).^[38] The remaining 12 studies involved experimentally induced hypoglycaemia in participants with T1DM (n=6),^[28, 31, 33, 36, 40, 42] T2DM (n=5),^[24, 27, 39, 41, 46] or both (n=1).^[43] The definition of hypoglycaemia varied across studies. The majority of observational studies defined hypoglycaemia as interstitial glucose values <3.5 mmol/L (n=7 out of 8; 88%), with a valid episode defined as a period of $\geq$ 20 minutes (5 out of 8; 63%). The definition of hypoglycaemia was more varied among experimental studies, ranging from 2.0- <4.0 mmol/L. To minimise the contaminative effects of hypoglycaemia, six out of eight observational studies did not compare the ECG traces of consequent hypoglycaemic to euglycaemic periods and instead used isolated episodes (time/duration matched period on a different day n=3; excluded $\geq$ 30 minutes following hypo n=2; duration matched period before hypoglycaemic event n=1). Amongst the experimental studies, comparisons were made between hypoglycaemic and euglycaemic conditions conducted on different days (n=5) or where analyses of euglycaemic conditions were obtained prior to hypoglycaemic conditions. QTc, HRV and CA occurrence were reported in 17 (observational n=7, experimental n=10), seven (observational n=4, experimental

n=3) and seven (observational n=6, experimental n=1) studies respectively. The characteristics of included studies appear in Table 1.

Seventeen studies reported outcome data for QTc. As two of these studies reported mean change between the conditions as opposed to absolute mean values, random effects meta-analysis was only possible on 15 studies.^[22-24, 28, 29, 31, 33, 35, 36, 38-40, 43-45] The two studies excluded from the meta-analysis,^[27, 42] reported a significant increase in QTc length during hypoglycaemia ($p<0.05$).

We did meta-analysis on 15 studies for changes in QTc duration, five reported a significant increase ($p<0.05$); nine a non-significant ($p>0.05$) increase; and one showed QTc duration to significantly ($p<0.05$) decrease with hypoglycaemia. Pooled SMD (95% CI) of the 15 studies showed that hypoglycaemia was associated with significant QTc prolongation when compared to euglycaemia 0.64 (0.27-1.01), $p=0.001$.

We report significant, moderate heterogeneity between studies ($I^2=63.9$, $p<0.001$). To examine possible sources of heterogeneity, we carried out sub-group analyses according to study design and diabetes type. Analysis according to study design showed experimental hypoglycaemia to have a greater effect on QTc prolongation (0.88 (0.51-1.24), $p<0.001$) than spontaneous clinical episodes reported in observational studies (0.24 (-0.45-0.93), $p>0.05$) (Figure 2). When experimental studies were further subdivided depending on whether they consisted of one (baseline euglycaemia followed by a hypoglycaemic clamp or a sequential euglycaemic to hypoglycaemic clamp) or two (separate euglycaemic and hypoglycaemic conditions) experimental arms, the pooled SMD for those with two arms was greater (1.06 (0.29-1.82) $p=0.007$) than those with one (0.74 (0.37-1.12) $p<0.001$). When analyses were undertaken based on diabetes type (Figure 3), the pooled SMD for QTc for T1DM was 0.54 (0.10-0.99) $p=0.017$, and 0.55 (-0.18-1.28) $p>0.05$ for T2DM. The pooled SMD for studies including both T1DM and T2DM was 1.31 (0.02- 2.60) $p=0.001$. Additionally we conducted meta-regression with the following study level covariates as the explanatory variable: participant age, gender, diabetes duration, and HbA1c. No variables were shown to be statistically significant ($p>0.05$; Table 2).

When sensitivity analysis were performed, limiting the results to those containing only normally distributed data, a similar, albeit slightly attenuated, effect size was observed (0.52 (0.15-0.90), $p=0.006$). Combining mean

QTC calculated by alternative formula resulted in minimal difference to the observed effect size (0.61 (0.23-0.98), $p=0.001$). Systematic exclusion of each individual study from the meta-analyses did not result in any changes to effect size. The only observation of note was that removal of the study by Koivikko 2017^[35] led to a reduction in the width of the CI.

Apart from one obvious outlier, the funnel plot (Figure 4, Supplement 3), and Egger's test showed no obvious publication bias ($p=0.098$) for studies comparing QTC duration during euglycaemic and hypoglycaemic periods.

Within the descriptive analysis, seven studies reported eight different components of HRV, five reported average values over the entire recording period,^[27, 31, 37, 40, 46] however two^[22, 45] separated outcomes into average nocturnal and daytime periods. In total 46 components of HRV were reported, however inclusion varied across studies- time domain methods included: standard deviation of normal to normal RR interval (SDNN) ($n=6$), root mean square of successive differences (RMSSD) ($n=5$), proportion of the number of NN intervals which differ by more than 50ms divided by the number of NN intervals (pNN50) ($n=1$) and frequency domain methods included: low-frequency power (LF: ms^2 , $\ln \text{ms}^2$, $\log \text{ms}^2$ or nu ($n=13$)), high-frequency power (HF: ms^2 , $\ln \text{ms}^2$, $\log \text{ms}^2$ or nu ($n=10$)), very-low-frequency power (VLF: ms^2 ($n=3$)), LF:HF (nu ($n=5$)) and total-power (TP: ms^2 or $\ln \text{ms}^2$ ($n=3$)). Of the seven studies, five^[22, 31, 37, 45, 46] reported that hypoglycaemia triggered a significant reduction in at least one component of HRV. Of the 26 components of HRV reported in the five studies providing average values over the entire recording period, nine components significantly decreased during hypoglycaemia ($p<0.05$). Whilst 13 of the remaining 17 components suggested a trend towards decreased HRV, the change was not significant ($p>0.05$). The two studies which separated outcomes into nocturnal and daytime periods reported ten components of HRV under each condition. During nocturnal periods, hypoglycaemia did not trigger any significant effects on HRV; however, during the day, hypoglycaemia triggered significant reductions in TP^[22], Log HF^[22] and Log LF^[22, 45].

In total, seven studies assessed CA occurrence.^[22, 23, 31, 35, 41, 44, 45] Of these, one reported no incidence,^[35] and two reported the occurrence of ventricular premature beats (VPB) across both glycaemic conditions.^[31, 41] In one study,^[41] an episode of bradycardia was also reported in one patient; however, this occurred during euglycaemia

(BG 4.4mmol/l) although the patient reported experiencing hypoglycaemia symptoms. One study reported occurrence of VPB, sinus bradycardia, or atrial premature beats (APB) in seven out of 13 hypoglycaemic episodes, with no alterations observed during euglycaemia.^[23] Two studies reported incident rate ratios (IRR) of the following arrhythmias; bradycardia, APB, VPB, complex VPB (bigeminy, trigeminy, couplets, Salvos and ventricular tachycardia) and total VPB during nocturnal and daytime periods.^[22, 45] Under nocturnal hypoglycaemic conditions, significant increases in IRR of bradycardia were reported in both studies. Hypoglycaemia triggered an eight fold increase in the study involving T2DM participants (8.42(1.40-51.0) $p=0.02$) and a six fold increase in the study involving T1DM participants (6.44 (6.26-6.63), $p<0.001$). In addition, the T2DM study reported significant increases in AEB (3.98 (1.10-14.40), $p=0.04$) and VPBs (3.06 (2.11-4.44), $p<0.01$). Under daytime conditions there were significant increases in VPB in the T2DM study (1.31 (1.10-15.7), $p<0.01$), however whilst the T1DM study displayed a significant increase in rates of AEB (2.29 (1.19-4.39), $p=0.013$) rates of bradycardia significantly decreased during the day (0.02 (0.002-0.26) $p=0.002$). The final study reported IRR of VPB and supra-VPB. Although not statistically significant, IRR were (1.58 (0.2-15) and (1.33 (0.54-1.79) respectively. Additionally one case of atrial fibrillation and one case of non-sustained ventricular tachycardia were observed, but these were unrelated to hypoglycaemia.

Most studies received an average quality rating, typically scoring poorly over lack of specified inclusion/exclusion criteria for participant eligibility, sample size justification and blinding of outcome analyst. A breakdown of study quality is presented in Supplement 2.

Discussion

To our knowledge, this is the first systematic review and meta-analysis to explore the acute effects of hypoglycaemia on CA risk. Studies of experimental and observational design were considered so that trial and real world evidence could be compared.

Our findings suggest that hypoglycaemia triggers a significant increase in QTc and a reduction in HRV, both of which have been identified as risk markers of mortality and sudden cardiac death in people with diabetes.^[48, 49]

Few studies looked at arrhythmia incidence directly; however our findings suggest that occurrence increased with hypoglycaemia, particularly under nocturnal conditions, thus supporting the notion that hypoglycaemia may be to blame for the dead in bed syndrome in susceptible individuals.

Previous, large scale prospective studies have shown disconcerting cardiovascular outcomes with intensive management of people with T2DM (target glyated haemoglobin level $<6.0\%$) which may be attributable to hypoglycaemia.^[8-10] Whilst findings from the Action to Control Cardiovascular risk in Diabetes (ACCORD) trial showed rates of non-fatal MI were lower in the group receiving intensive management, mortality rates were increased amongst this group with increased mortality attributed to fatal MI, arrhythmias and congestive heart failure leading to early trial termination.^[8] Despite these findings, and identification of a possible association between hypoglycaemia and CVD, evidence of a direct causal link is lacking.^[5, 8, 50] This review builds upon previous research by identifying potential mechanisms by which hypoglycaemia may be associated with cardiovascular morbidity and mortality.

Whilst our meta-analysis identified that hypoglycaemia was associated with significant QTc prolongation, the strength of the association varied when results were stratified by study design and diabetes type. Experimental studies triggered a more profound increase in QTc prolongation. This may be due to differences in the glycaemic threshold used to define hypoglycaemia. Typically observational studies classified hypoglycaemia as interstitial glucose $<3.5\text{mmol/L}$, whereas experimental studies used $<3.0\text{mmol/L}$, a figure in line with current clinical definitions.^[51] Additionally, the influence of confounders amongst observational studies which lack controlled conditions should also be considered. In contrast, whilst the highly controlled and widely used hyperinsulinemic-euglycaemic clamp technique provides an ideal model for demonstrating mechanisms by which hypoglycaemia may increase arrhythmia risk, it does not deliver a true reflection of insulin and glucose dynamics and the sympathoadrenal responses during spontaneous clinical hypoglycaemia.^[28]

In relation to diabetes type, QTc prolongation occurred in individuals with T1DM and T2DM; however amongst those with T2DM the change between euglycaemia did not reach statistical significance. As far fewer studies have been conducted in T2DM, the ability to ascertain firm conclusions within this population is limited.

As previously mentioned, QT correction formula can also influence results with Bazett's, the most commonly adopted correction formula, over and under correcting at high and low heart rates respectively.^[25, 26] In addition, whilst the ECG is an easily accessible and established tool to assess cardiac rhythm and electrophysiological properties, it is acknowledged that accurate QT interval measurements can be challenging.^[52]

Our review was based on strict inclusion and exclusion criteria, and two authors independently reviewed and identified potentially eligible articles. Limitations of this review include the fact that the number of studies included in the meta-analysis was modest and their sample sizes were small. There was moderate heterogeneity across the studies, ranging from design and participant characteristics through to intervention and reported outcomes. These could be due to differing primary study objectives, with some studies focusing on more specific ECG alterations. At review level, the lack of comparable outcomes between studies meant further meta-analyses were not possible which led to less reliable descriptive data synthesis of HRV and arrhythmia incidence to be performed on some outcomes rather than a more robust meta-analysis. To minimise bias we reported and explained the results of each study in a structured and logical manner.

Despite the results of the funnel plot and Eggers tests suggesting no obvious publication bias, the possibility of bias remains. During study selection a number of potentially eligible conference abstracts were identified; however full texts could not be obtained. Elements of reporting bias were also acknowledged, as contact with numerous authors was required to obtain all relevant information. In some cases, contact failed preventing the study or certain outcome data being included in the analysis. During title and abstract screening, three titles of articles written in Spanish (n=2)^[53, 54] and German (n=1)^[55] and the abstract of a Russian article^[56] were identified as potentially eligible. As further detail could not be obtained in English we could not identify whether these studies met our inclusion criteria.

In summary, this review confirms that hypoglycaemia triggers acute ECG alterations in individuals with diabetes which may increase an individual's vulnerability to arrhythmic events leading to subsequent cardiovascular morbidity and mortality. These findings may explain detrimental cardiac outcomes in intensively controlled patients who are at greater risk of hypoglycaemia. Considerably less research exploring the

association between hypoglycaemia and CA risk has been conducted in T2DM. T2DM is strongly associated with ischaemic heart disease,^[57] particularly amongst individuals of advancing age and disease duration and previous research has reported increased frequency of ischaemia and chest pain during hypoglycaemia. This may be representative of cardioacceleration possibly suggesting that these individuals may be particularly susceptible. As T2DM is typically associated with an older population and its prevalence and comorbidities are increasing,^[1, 2] more research within this cohort is warranted. Studies of longer duration and greater participant numbers would help to support hypoglycaemia event capture and its subsequent impact upon arrhythmia risk. Additional studies which explore the impact of confounders e.g. exercise, ethnicity, rate of descent of blood glucose leading to hypoglycaemia and the impact of medications known to affect heart rate and rhythm e.g. beta-blockers and the extent to which they attenuate risk would further benefit our understanding. Of the 20 studies included in this review, 11 specified that individuals receiving medication known to affect cardiac rhythm were excluded, and a further eight made no reference. The initial study by Chow and colleagues,^[22] identified that two out of 25 participants were taking beta blockers; however, sensitivity analyses excluding these individuals was not associated with changes to arrhythmia risk. Further studies with larger comparative sample sizes are required to accurately explore the impact of such medications on risk.

Finally, QT interval per se is not an absolute arrhythmic risk marker although there are inherited and acquired long QT syndromes that predispose to lethal arrhythmias. The QT interval is a surrogate measurement of the averaged ventricular action potential duration (APD). More recently, it is recognised that it is the dynamic behaviour of the APD (and QT interval) to changes in heart rate, termed APD restitution, that is an important marker of arrhythmic risk.^[58] Electrical restitution can be measured on the ECG as prognostic risk markers in patients at risk of sudden cardiac death^[59] and has been shown to be an important mechanism underlying the autonomic modulation of ventricular fibrillation initiation.^[60] These properties are potentially important parameters to investigate in the association between hypoglycaemic effects on QT interval and arrhythmia risk.^[60] These properties are potentially important parameters to investigate in the association between hypoglycaemic effects on QT interval and arrhythmia risk.

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Legends to tables and figures

Table 1. Characteristics of studies included in the systematic review

Table 2. Meta-regression results showing the effect of study level variables on QTc

Figure 1. Study selection process

Figure 2. Standardised mean difference (SMD) in QTc interval length between hypoglycaemic and euglycaemic periods by study design

Figure 3. Standardised mean difference (SMD) in QTc interval length between hypoglycaemic and euglycaemic periods based on diabetes type

Table 1. Characteristics of studies included in the systematic review											
First Author Year	Country	Study design	Population	N (%Male)	Mean age (years)	Mean HbA1c (%)	Mean diabetes duration (years)	Study duration	Hypoglycaemia definition (mmol/L)	Euglycaemia definition	Outcomes reported (QTc formula reported)
Chow (2014) ^[22]	UK	Observational	T2DM	25 (52)	64	7.5	17	5 days	d3.5	e3.5 - <15.0	HRV QTc (s) Arrhythmias
Chow (2017) ^[27]	UK	Experimental ₁	T2DM	12 (75)	54	9.8	11	-	2.5	6.0	HRV QTc (b,n)
Christensen (2007) ^[29]	Denmark	Experimental ₂	T1DM	10 (60)	32	-	15	-	3	NR	QTc (b,f)
Christensen (2010) ^[31]	Denmark	Observational	T1DM	21 (38)	58	7.9	34	3 days	<3.5	5.0-10.0	HRV QTc (b,f,s,n) Arrhythmias
Christensen (2014) ^[28]	Denmark	Experimental ₃	T1DM	10 (100)	41	7.3	9	-	<4	>4.0	QTc (b,f)
Faerch (2015) ^[33]	Denmark	Experimental ₄	T1DM	9 (89)	56	7.8	30	-	2.5-2.7	5.0-6.0	QTc (b,f)
Gill (2009) ^[23]	UK	Observational	T1DM	25 (48)	36	8.3	13	2 days†	<3.5	>5.0	QTc (u) Arrhythmias
Koivikko (2005) ^[36]	Finland	Experimental ₁	T1DM	16 (44)	32	7.0	13	-	2.0-3.5	4.5-5.5	HRV‡ QTc (b,f,n)
Koivikko (2012) ^[37]	Finland	Observational	T1DM	37 (41)	28	8.0	13	3 nights	<3.5	>3.9	HRV
Koivikko (2017) ^[35]	Finland	Observational	T1DM	11 (36)	28	7.6	15	3 nights	<3.5	e5.0	QTc (b,n) Arrhythmias
Landstedt-Hallin (1999) ^[24]	Sweden	Experimental ₁	T2DM	13 (77)	57	7.6	9	-	2.5-3.0	5.0-6.0	QTc (b)
Lee (2004) ^[39]	UK	Experimental ₄	T1DM	28 (93)	36	9.2	36	-	2.5	5.0	QTc (b)
Lee (2016) ^[38]	Australia	Observational	Total T1DM	14 3	58	8.9	9	Up to 48 hours	d 3.9	>4.0	QTc (b)

			T2DM	(NR) 11 (NR)	63	8·5	21				
Limberg (2014) ^[40]	USA	Experimental ₂	T1DM	13 (54)	43	7·0	17	-	3·3	NR	HRV QTc (b)
Lindström (1992) ^[41]	Sweden	Experimental ₂	T2DM	6 (NR)	59	NR	13	-	<2·0	NR	Arrhythmias
Lipponen (2011) ^[42]	Finland	Experimental ₄	T1DM	13 (100)	45	NR	13	-	3·0	5·0-7·0	QTc (f)
Marques (1997) ^[43]	UK	Experimental ₁	Total T1DM T2DM	15 8 (88) 7 (100)	30 48	10·6 9·4	7 6	-	3·0	5·0	QTc (b)
Middleton (2017) ^[44]	Australia	Observational	T2DM	30 (60)	67	6·9	14	48 hours	<3·5	4·0-10·0	QTc (s) Arrhythmias
Novodvorsky (2017) ^[45]	UK	Observational	T1DM	37 (51)	34	8·1	19	96 hours	d3·5	5·0-10·0	HRV QTc (b) Arrhythmias
Soydan (2013) ^[46]	Germany	Experimental ₄	T2DM	12 (50)	56	6·5	3·6	-	3·3	5·0	HRV

†Only analysed nocturnal period 23:00-08:00; ‡Insufficient HRV data to include in analysis; Abbreviations; HbA1c - glycated haemoglobin, NR - Not Reported, HRV - Heart rate variability T1DM-Type 1 diabetes; T2DM- Type 2 diabetes; QTc formula: b - Bazett, f- Fridericia, s- subject specific, n- nomogram, u-unknown; Experimental₁ - Separate hypoglycaemic and euglycaemic clamps; Experimental₂ - Baseline euglycaemia and hypoglycaemic clamp; Experimental₃ - Separate conditions - Hypoglycaemia induced by bolus insulin - Euglycaemia through continuous insulin and glucose administration; Experimental₄ - Sequential euglycaemic-hypoglycaemic clamp

Table 2. Meta-regression results showing the effect of study level variables on QTc			
Explanatory variable	N studies	SMD (95% Confidence Intervals)	P-value
Mean age, years	15	-0.11 (-0.48-0.26)	0.54
% Male participants	13	0.01 (-0.26-0.27)	0.96
Mean diabetes duration, years	15	0.026 (-0.80-0.75)	0.94
Mean HbA1c, %	14	4.29 (-3.03-11.61)	0.225

Figure 1. Study selection process

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Contributions

CF developed the study protocol, carried out the scientific literature search, extracted and analysed data, quality assessed studies, interpreted the results, and drafted the report. SC contributed to the study protocol, extracted data, quality assessed studies, interpreted the results and contributed to the writing of the report. SS selected relevant papers, extracted data and contributed to the writing of the report. DHB analysed data, interpreted the results and contributed to the writing of the report. GAN, and MJD contributed to the writing of the report. KK had the concept of the study, contributed to the study protocol, interpreted the results and contributed to the writing of the report.

Declaration of Interests

CF has nothing to disclose. SC reports grants and personal fees from Janssen, grants and personal fees from Eli Lilly, grants and personal fees from Novo Nordisk, grants and personal fees from Astra Zeneca, grants and personal fees from Boehringer Ingelheim, outside the submitted work. SS has acted as a consultant and speaker for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim. He has received grants in support of implementation research from Janssen. He has served on advisory boards for, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim. DHB has nothing to disclose. GAN reports grants from Boston Scientific, grants and personal fees from St Jude Medical - Abbott, personal fees from Biosense Webster, outside the submitted work. MJD reports personal fees from Novo Nordisk, personal fees from Sanofi-Aventis, personal fees from Lilly, personal fees from Merck Sharp & Dohme, personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, personal fees from Janssen, personal fees from Servier, personal fees from Mitsubishi Tanabe Pharma Corporation, personal fees from Takeda Pharmaceuticals International Inc., grants from Novo Nordisk, grants from Sanofi-Aventis, grants from Lilly, grants from Boehringer Ingelheim, grants from Janssen, outside the submitted work. KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Servier and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. KK has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk.

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