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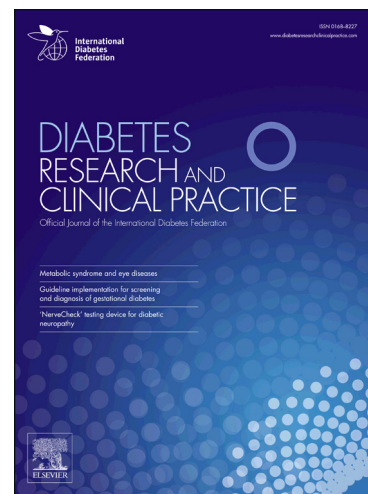
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Continuous Glucose Monitoring Detected Hypoglycaemia in the Treating to Target in
Type 2 Diabetes Trial (4-T)

Short running title: CGM hypoglycaemia in the 4-T trial

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Abstract

Aims: Hypoglycaemia is a significant risk in insulin treated type 2 diabetes and has been associated with future risk of cardiovascular events. We compared the frequency of low-glucose events using continuous glucose monitoring (CGM) with that of self-reported hypoglycemic events at the end of the first and third years of the Treating to Target in Type 2 Diabetes Trial (4-T), which compared biphasic, prandial and basal insulin regimens added to sulfonylurea and metformin.

Methods: CGM using a Medtronic Gold system was performed in a subgroup of 4-T participants. CGM detected low-glucose events were defined at thresholds of ≤ 3.0 (CGM3.0) and ≤ 2.2 (CGM2.2) mmol/l.

Results: Of the 110 participants, 106 and 70 had CGM analysable data at the end of years 1 and 3 respectively. In both years, the frequency of CGM detected low glucose events was several fold higher than that of self-reported hypoglycaemia (symptoms with blood glucose less than 3.1 mmol/l [<56 mg/dl]). At the end of the first year, CGM3.0 and CGM2.2 mean (95%CI) event frequencies, expressed at events per participant per year, were 120 (85, 155) and 41 (21, 61) compared with 17 (8, 29) self-reported events during CGM, each $p=0.001$. The disparity at the end of the third year was similar.

Conclusions: These data demonstrate the likely under-reporting of hypoglycaemia and of potential hypoglycaemia unawareness in clinical trials. The clinical implications of these findings need to be explored further. (ISRCTN No ISRCTN51125379)

(Abstract word count: 233)

Keywords : type 2 diabetes, clinical trials, insulin therapy, hypoglycaemia, continuous glucose monitoring.

1 Introduction

Hypoglycaemia occurs less often in people with type 2 diabetes than type 1 diabetes but remains a clinically significant problem. In addition to personal inconvenience and interruption of normal activities it can limit achievable HbA1c control and the ability to drive. It has direct effects on cardiac electrophysiology [1] and severe hypoglycaemia has been associated with cardiac morbidity and mortality in recent large scale clinical trials [2-4]. 4-T was a randomised comparison of three different regimens of insulin initiation and maintenance when added to maximally tolerated metformin and sulfonylurea therapy, targeting an HbA1c $\leq 6.5\%$ (48 mmol/mol) [5, 6]. A single biphasic, prandial or basal insulin formulation was allocated at randomisation [6], which was intensified at the end of the first year by the addition of a second insulin formulation for patients not reaching target [5]. Self-reported rates of hypoglycaemia, with and without concomitant capillary glucose measurements were collected throughout the course of the study.

In a 4-T sub-study a subset of patients underwent Continuous 72 hour Glucose Monitoring (CGM) at the end of the first and the third years. This sub-study examined the rates of CGM low-glucose events and compared them with self-reported hypoglycaemia.

2 Materials and methods

2.1 Patient Recruitment: 4-T recruited 708 patients from 1st November 2004 to 31st July 2006. It included men and women aged 18 years or older with type 2 diabetes for at least 12 months who had previously not been treated with insulin. All patients at baseline had suboptimal glycemic control with HbA1c 7.0 to 10.0% (53 to

86 mmol/mol), on maximally tolerated doses of metformin and a sulfonylurea for at least 4 months, and had a Body Mass Index (BMI) of 40 Kg/m² or less. Full exclusion criteria have been described previously [6]. The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent to the main trial and to the CGM sub-study. Recruitment of patients able and willing to join the CGM sub-study occurred during the first year of the main trial. The first year of the 4-T study assessed the effect of adding a single insulin formulation, so, for the purpose of the current analysis, those patients requiring glycaemic rescue with a second insulin formulation before the end of year one were not included. From year two onwards, a second insulin formulation was added if the target HbA_{1c} of less than 6.5% (<48mmol/mol) was not achieved.

2.2 Continuous glucose monitoring: CGM was performed at the end of years one and three. A blinded CGM device, Medtronic Gold CGM System (CGMS) was fitted, with the sensor inserted under the skin of the abdomen and connected to the monitor. Glucose measurements were acquired every 10 seconds with an average of the signal recorded every 5 minutes [7, 8]. After a one-hour initiation period during which the sensor was calibrated, the participant wore the CGMS for a period of approximately 72 hours. The minimum glucose concentration recordable by the sensor was 2.2 mmol/l. During each 24-hour period, sensor glucose data was calibrated to four or more capillary plasma equivalent glucose values measured and entered by the subject. CGMS measurements provide estimates of plasma glucose concentrations, modulated by time lags between plasma and interstitial fluid in non-steady state conditions. All participants kept a daily record of meals and self-reported hypoglycemic events. CGMS values and patient diary data were uploaded and analysed by the Diabetes Trials Unit.

2.3 The principal outcome measure was the frequency and duration of biochemical hypoglycaemia during the 72 hour CGM measurement period, with separate analyses of daytime and night-time readings.

2.3.1. As part of the main trial protocol, participants recorded hypoglycemic episodes in their study diary which was transcribed by the study nurse at each visit. Hypoglycaemia in the main trial was categorized as grade 1 if a patient had symptoms with a self-measured capillary glucose level less than 3.1 mmol/L (56 mg/dL), grade 2 (minor) if the patient had symptoms with a self-measured capillary glucose level of <56 mg/dL, or grade 3 (major) if third party assistance was required [6]. In this paper the term 'self-reported hypoglycaemia' includes only events confirmed by capillary glucose, *i.e.* grade 2 and grade 3 but not grade 1 episodes. The proportion of participants with self-reported hypoglycaemia, and the hypoglycaemia rates *per patient per year* were calculated during CGM at years one and three, for comparison with the corresponding CGM low-glucose events during these periods.

2.3.2 CGM traces were examined electronically and visually to exclude electrical dropouts and periods of calibration instability. As CGMS monitors glucose concentrations in the subcutaneous interstitial fluid, the term 'CGM low-glucose event' is used in preference to 'hypoglycaemia'. CGM low-glucose event.

Thresholds have been defined variously in different studies. For this sub-study the two thresholds used were (i) CGM3.0, which was pre-specified in the analysis plan to match the main trial definition of self-reported symptomatic hypoglycaemia and defined as a period starting with at least two consecutive measurements (10 min) ≤ 3.0 mmol/L and ending with four consecutive measurements (20 min) > 3.0 mmol/L, and (ii) CGM2.2, starting with four consecutive measurements (20 min) ≤ 2.2 mmol/L

and ending with four consecutive measurements (20 min) >2.2 mmol/L, as defined by the UK Hypoglycaemia Study Group [9], and supported by evaluations of reproducibility and accuracy in free-living and hyperinsulinaemic clamp circumstances [10]. Low-glucose events were characterised as daytime (6:00 am to 10:59 pm inclusive) or nocturnal (11:00 pm to 5:59 am inclusive). The number of events *per* participant and the total duration of CGM low-glucose events was standardised using the actual duration of the analysable CGM trace and expressed as hours of hypoglycaemia *per* 24-hours and as events *per* participant *per* year.

2.4 Statistical Analysis: Baseline characteristics and hypoglycaemia data were calculated and compared for the biphasic, prandial and basal insulin regimens, in the participants in the CGM sub-study, and for those in the main trial not undergoing CGM. For unbiased calculation of self-reported and CGM events, traces were truncated to the maximum number of complete 24 hour periods monitored, to provide unbiased estimates for daytime vs. night time hypoglycaemia frequencies. Missing CGM glucose values were imputed by linear interpolation for interruptions in CGM traces lasting ≤ 80 minutes. There were 116 gaps in the 110 traces, 74% having a duration of 5 minutes only, and 97.4% having a duration of ≤ 30 minutes. In one trace a single interruption lasted 140 minutes, but as this constituted only 2.7% of all glucose values during that trace and there was minimal possibility of hypoglycaemia during this period given the glucose concentrations at the beginning and end of the interruption, this 4-day trace was included with interpolated values. The proportion of participants and the frequency of reported hypoglycaemia *per* patient during CGM were compared with self-reported hypoglycaemia data from the main trial during the year and the final 3 months of years 1 and 3. The frequency of hypoglycaemia *per* person mean (95% CI) was expressed as the number of events recorded *per* group

divided by the total number of participants in the group, *i.e.* including those who experienced no hypoglycaemia, and was expressed as the frequency *per year* equivalent. The duration of CGMS low-glucose events was calculated in those who experienced events. As the distributions of rates of hypoglycaemia and of total duration of hypoglycaemia *per 24-hours* were heavily zero weighted, the significance of paired and unpaired bivariate differences were obtained using Mann-Whitney or Wilcoxon's Signed Rank tests, and heterogeneity between the three insulin regimens using the Kruskal-Wallis tests. Ordinal logistic regression was used to identify variables associated with the occurrence of CGM events, with the number of events classified as 0, 1, 2 and >2 hypos *per person*. Covariates included HbA1c, standard deviation of CGM glucose values, BMI, gender, age and duration of diabetes. Statistical analyses were performed by J.C.L. using IBM SPSS version 22.

3 Results

3.1 Participant and CGM characteristics: Of the 708 participants from the 57 centres in the main trial, 110 were included in the CGM sub-study from the 332 participants in the 17 centres that had had prior CGM experience. Of these, 106 had analysable CGM traces at year one, 70 at year 3, and 67 at both time points. CGM participants had similar baseline characteristics and distribution of allocated insulin regimens compared with the non-CGM participants (Table 1). The mean (SD) duration of analysable CGM traces after truncation was mean (SE) 2.5 (0.1) hours *per 24-hour period* in year 1 and 2.3 (0.1) hours *per 24-hour period* in year 3.

3.2 Self-reported hypoglycemic episodes: There were no episodes of grade 3 hypoglycaemia during either of the continuous monitoring periods. At the end of year 1, numbers and proportions of participants self-reporting grade 2 hypoglycemic episodes during CGM differed significantly between treatment groups with the lowest

proportion being in the basal group. This was mirrored numerically by the proportions of participants with CGM low-glucose events, but this did not reach statistical significance. At the end of year 3, there were no significant differences between the three regimens for either self-reported reported hypoglycemic episodes or for CGM low-glucose events. Because of the overall low numbers of CGM low-glucose events, further analyses in this paper are reported for the three insulin regimens combined.

3.3 Characteristics of CGM low-glucose events: CGM low glucose events were evenly split between daytime and night-time: with daytime representing 55% and 68% of CGM3.0 events ($p=0.83$) and 52% and 65% of CGM2.2 events in years 1 and 3, respectively ($p=0.82$).

Among participants with low glucose events, the median (IQR) duration in minutes per day was 55 (32, 86) and 38 (28, 72) for CGM3.0 AND CGM2.2 in year 1, respectively, and 89 (35, 212) and 69 (33, 182) minutes per day in year 3. These did not differ between years or event type ($p=0.19$).

For both CGM low-glucose event thresholds at years 1 and 3, the frequency of low-glucose events *per person* was independently associated with lower HbA1c ($p=0.001$ to $p=0.025$) and higher standard deviation of CGM glucose ($p=0.008$ to $p=0.031$). There were no associations with baseline age, duration of diabetes, or BMI.

There was a marked disparity between the frequency of hypoglycaemic events reported by the non-CGM participants compared with CGM low glucose episodes identified in the CGM participants (approximately 20-fold and 7 fold lower compared with for CGM3.0 and CGM2.2 episodes, respectively (Table 3 and Figure 1). This

may in part be explained by a concatenation of sub-comparisons. Firstly, during years 1 and 3, CGM participants had a 1.5- to 2-fold lower frequency of self-reported episodes compared with non-CGM participants. Secondly, among CGM participants, fewer hypoglycaemic events were reported in the last 3 months of years 1 and 3 compared with those reported during CGM itself. However, during this period, there remain 7-fold and 2.5-fold differences for CGM3.0 and CGM2.2 episodes, respectively, between self-reported hypoglycaemia and low glucose episodes.

4 Discussion

4.1 This 4-T trial CGM sub-study focused on the relationships between CGM low-glucose events and self-reported hypoglycemic episodes at the end of the first and third years of the trial. At the end of both years, the proportion of CGM patients with self-reported hypoglycemic episodes and the frequency of CGM2.2 events mirrored those in the main trial. There were no significant baseline subject characteristics that were associated with the frequency of CGM detected events or self-reported episodes, though the frequency of the former was independently associated with a lower HbA1c and higher glucose variability during CGM.

4.2 The use of CGM monitoring in the context of a clinical trial adds considerably to the ability to assess hypoglycaemia and other aspects of glucose control not captured by average blood glucose control (HbA1c) and self-monitored blood glucose profiles [11]. In type 2 diabetes intervention trials this has been used for diet [12] oral [13] but particularly for insulin therapies [14-16]. While many have addressed the more general aspects of glucose variability and time within defined

ranges, few have focused specifically on hypoglycaemia [15, 17]. A recent ADA/EASD position statement recommended that in clinical trials the reporting of hypoglycaemia associated with commonly agreed blood glucose concentrations and it also recognised that symptom thresholds differ between different individuals [18]. Because of this variability, therefore, 'serious, clinically important hypoglycaemia' might be missed if blood glucose testing was limited to events prompted by symptoms. They stated that this could be done by either self monitoring, laboratory plasma glucose or continuous glucose monitoring. We believe that some form of continuous monitoring presents significant advantages over finger-prick testing, though the position statement did not suggest specific thresholds for interstitial glucose. Recent advances in continuous monitoring technology mean that routine non-invasive testing could now make this a practical and potentially affordable addition to large scale trials.

4.3 In the definition of low glucose or hypoglycaemia using CGM, there have been no generally agreed glucose threshold or temporal extent for episodes and many different ones have been used [9, 10, 15, 19-21] to suit different purposes. In this report we defined low glucose events in two ways. The CGM3.0 threshold was chosen to match the Grade 2 hypos as defined in the main study. The more stringent CGM2.2 threshold matched the 2007 UK Hypoglycaemia group paper [9] which was chosen to represent significant and sustained cognitive impairment.

4.4 The most striking finding of the present study was the markedly higher frequency of CGM3.0 and CGM2.2 low-glucose events compared with self-reported hypoglycemic episodes. A disparity between reported and CGM detected low glucose episodes has been noted in previous studies [9, 20-23], but we have taken the opportunity to examine this in detail. CGM low-glucose event frequency was 22

and 8 times higher during the final three months of year 1 than self-reported grade 2 hypoglycemic episodes in non-CGM participants, and 35 and 14 times higher during the final 3 months of year 3. These ratios are of importance, both to guide the methodology of the studies in this area and to emphasise the importance of further research on the clinical significance of low-glucose events in the treatment of type 2 diabetes. There appear to be several contributory reasons for the discrepancy. We were able to identify several contributory factors, but accounting for these still left an eight-fold difference between the frequency of CGM3.0 low-glucose events and self-reported hypoglycemic episodes during monitoring itself, and a three-fold difference for the more stringent CGM2.2 low-glucose events. In addition, between 67 and 80% of patients with CGM2.2 low-glucose events did not report any hypoglycemic episodes. In one third and two thirds of participants in years 1 and 3, respectively, the total duration of time spent in CGM2.2 events was over an hour per day. Both these observations raise the possibility of impaired hypoglycaemia awareness, with the attendant risks of severe hypoglycaemia, accidents and cardiovascular events [20, 24], and the association between hypoglycaemia with the cardiac mortality observed in recent large-scale treat-to-target trials [2-4].

4.5 This study analysis is subject to several limitations. The participants represented a minority of those in the main trial and were recruited from centres with prior experience of CGM. However, their baseline characteristics were representative of non-participants. The limited duration of CGMS is always a problem with such studies, even those using more recent technologies. CGM, based on interstitial glucose measurements will be based on concentrations which are lower than plasma glucose levels in steady state conditions because of the metabolism of glucose by cells in subcutaneous tissue. However, as CGM

measurements are calibrated to plasma glucose, they do represent values normally used in clinical practice. While one of the earlier systems in use, CGMS Gold has reasonable accuracy (Clarke Error Grid 94-96% A+B zones [25]), but like all interstitial glucose monitors, in non-steady state conditions it is subject to lag, depending on the rate of glucose change [26]. While this presents difficulties for real-time CGM, it is less of a problem for a blinded evaluation of glucose control. Indeed, interstitial glucose may over-estimate plasma glucose [25, 27] and therefore underestimate the frequency of hypoglycaemia, meaning that our results may be a conservative estimate of the true picture. All CGM technologies are subject to technical difficulties including poor probe insertion, disconnection and electronic drop-out (loss of signal), but by careful visual examination of individual traces we were able to eliminate these artefacts. CGM offers an objective blinded source of information that is essential for the full evaluation of glycemic control.

4.6 In summary, 4-T was a robust, protocol driven three-year trial in patients adding insulin to oral therapy and the 4-T CGM sub-study addressed key question of objectively assessing hypoglycaemia of during treat to target trial designs. The choice of the appropriate glucose thresholds for the definition of relevant hypoglycaemia and their relevance to hypoglycaemic unawareness and clinical risk remain important and challenging areas for continued research. Our data emphasise the importance and frequency of hypoglycaemia in insulin treated type 2 diabetes as well as demonstrating inadequacies in the conventional methods of assessing it in clinical trials. Reported hypoglycemic episodes are likely to represent only the tip of the iceberg of clinically significant hypoglycaemia central to the evaluation of glucose lowering therapies.

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6 Declarations of interest

Dr Levy has acted on advisory boards for Lilly, Novo Nordisk and Novartis.

Professor Melanie Davies has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly. Professor Holman reports receiving grant support from Bayer, AstraZeneca, MSD and consulting fees from Amgen, Elcelyx, MSD, Novartis, Novo Nordisk.

No other potential conflict of interest relevant to this article was reported.

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9 Tables

9.1 Table 1: Characteristics of the CGM and non-CGM participants at baseline, year 1 and year 3

Baseline	CGM Cohort	Non-CGM Cohort	P-Value
Number of participants	110 (15.5%)	598 (84.4%)	
Male sex	71 (65%)	383 (64%)	0.92
Allocated insulin regimen (Biphasic / Prandial / Basal)	36 / 35 / 39 (33% / 32% / 35%)	199 / 204 / 195 (33% / 34% / 33%)	0.83
Age (years)	61.8 (61.6, 62.0)	61.0 (60.6, 61.5)	0.43 ^a
Duration Of Diabetes* (years)	8.9 (8.7, 9.1)	8.9 (8.4, 9.4)	0.72 ^b
BMI* (kg/m ²)	30.1 (29.9, 30.3)	29.2 (28.8, 29.7)	0.07 ^a
HbA1c at baseline (%)	8.5 (7.9, 9.0)	8.6 (8.1, 9.3)	0.08 ^b
HbA1c at baseline (mmol/mol)	69 (63, 75)	70.5 (65, 78)	
Year 1			
Number of participants (%)	107	554	
HbA1c Biphasic (%)	7.0 (6.6, 7.3)	7.2 (6.7, 7.9)	0.06 ^b
(mmol/mol)	53 (48, 56)	55 (50, 63)	
Prandial (%)	7.0 (6.5, 7.5)	7.1 (6.6, 7.6)	0.58 ^b
(mmol/mol)	53 (48, 59)	54 (49, 60)	
Basal (%)	7.5 (7.1, 7.8)	7.5 (6.9, 8.1)	0.87 ^b
(mmol/mol)	58 (54, 62)	58 (52, 65)	
Insulin Dose (Units/Kg)	0.55 (0.36, 0.74)	0.54 (0.36, 0.80)	0.83 ^b
Year 3			
Number of participants (%)	70	530	
HbA1c Biphasic (%)	7.0 (6.6, 7.5)	7.1 (6.5, 7.9)	0.55 ^b
(mmol/mol)	53 (49, 58)	54 (48, 63)	
Prandial (%)	6.7 (6.2, 7.4)	6.9 (6.4, 7.7)	0.11 ^b
(mmol/mol)	50 (44, 57)	52 (46, 60)	
Basal (%)	6.7 (6.4, 7.2)	6.9 (6.3, 8.0)	0.22 ^b
(mmol/mol)	50 (46, 55)	52 (45, 64)	
Insulin Dose (Units/Kg)	0.92 (0.54, 1.40)	0.85 (0.52, 1.43)	0.45 ^b

[†] T-test, ^b Mann Whitney U test, Data are median (interquartile range)

9.2 Table 2. Proportion of CGM participants with reporting grade 2 or 3 hypoglycemic episodes and CGM low-glucose events

	Whole cohort	By insulin regimen			p value between regimens
		Biphasic	Prandial	Basal	
Year 1					
No. of participants	106	35 (33%)	33 (31%)	38 (36%)	
No. with self-reported grade 2 or 3 hypoglycemic episodes during CGM ^a	11 (10%)	6 (17%)	5 (15%)	0 (0%)	0.032
No. with CGM low-glucose events ≤ 3.0 mmol/l	45 (42%)	16 (46%)	16 (49%)	13 (34%)	0.37
No. with CGM low-glucose events ≤ 2.2 mmol/l	19 (18%)	9 (26%)	6 (18%)	4 (11%)	0.24
Year 3					
No. of participants	70	21 (30%)	24 (34%)	25 (36%)	
No. with self-reported grade 2 or 3 hypoglycemic episodes during CGM	8 (11%)	3 (14%)	2 (8%)	3 (3%)	0.82
No. with CGM low-glucose events ≤ 3.0 mmol/l	28 (40%)	8 (38%)	9 (38%)	11 (44%)	0.89
No. with CGM low-glucose events ≤ 2.2 mmol/l	14 (20%)	6 (29%)	2 (8%)	6 (24%)	0.12

^a Definition of 'during CGM': during the period of contiguous whole days on CGM; numbers represent number with event (% of relevant cohort)

9.3 Table 3. Frequency of reported hypoglycemic episodes in the CGM and non-CGM cohorts and low-glucose events in CGM cohort

		CGM participants	p value as specified	Non-CGM participants	p value (CGM vs. non-CGM)
Year 1					
No. of participants		106		599	-
Grade 2 or 3 hypoglycemic episodes reported in last 3 months	(1a)	12.2 (8.8, 15.5) 8 (0, 93)		5.9 (5.0, 6.9) 0 (0, 85)	0.001
Grade 2 or 3 hypoglycemic episodes reported during CGM	(1b)	17 (6, 29) 0 (0, 365)	0.001 vs. 1a	-	
CGM low-glucose events ≤ 3.0 mmol/l	(1c)	120 (85, 155) 0 (0, 913)	0.001 vs. 1b	-	-
CGM low-glucose events ≤ 2.2 mmol/l	(1d)	41 (21, 61) 0 (0, 487)	0.001 vs. 1c 0.033 vs. 1b	-	-
Year 3					
No. of participants		70		598	-
Grade 2 or 3 hypoglycemic episodes reported in last 3 months	(3a)	7.7 (4.8, 10.6) 4 (0, 57)		4.8 (4.0, 5.6) 0 (0, 81)	0.010
Grade 2 or 3 hypoglycemic episodes reported during CGM	(3b)	22 (6, 38) 0 (0, 365)	0.11 vs. 3b	-	
CGM low-glucose events ≤ 3.0 mmol/l	(3c)	163 (98, 228) 0 (0, 1217)	0.001 vs. 3c	-	-
CGM low-glucose events ≤ 2.2 mmol/l	(3d)	63 (24, 103) 0 (0, 852)	0.001 vs. 3c 0.038 vs. 3b	-	-

Frequency expressed as number per year: mean (95 CI%) and median (min, max)

Statistical significance for all comparisons was calculated using the Mann Whitney test

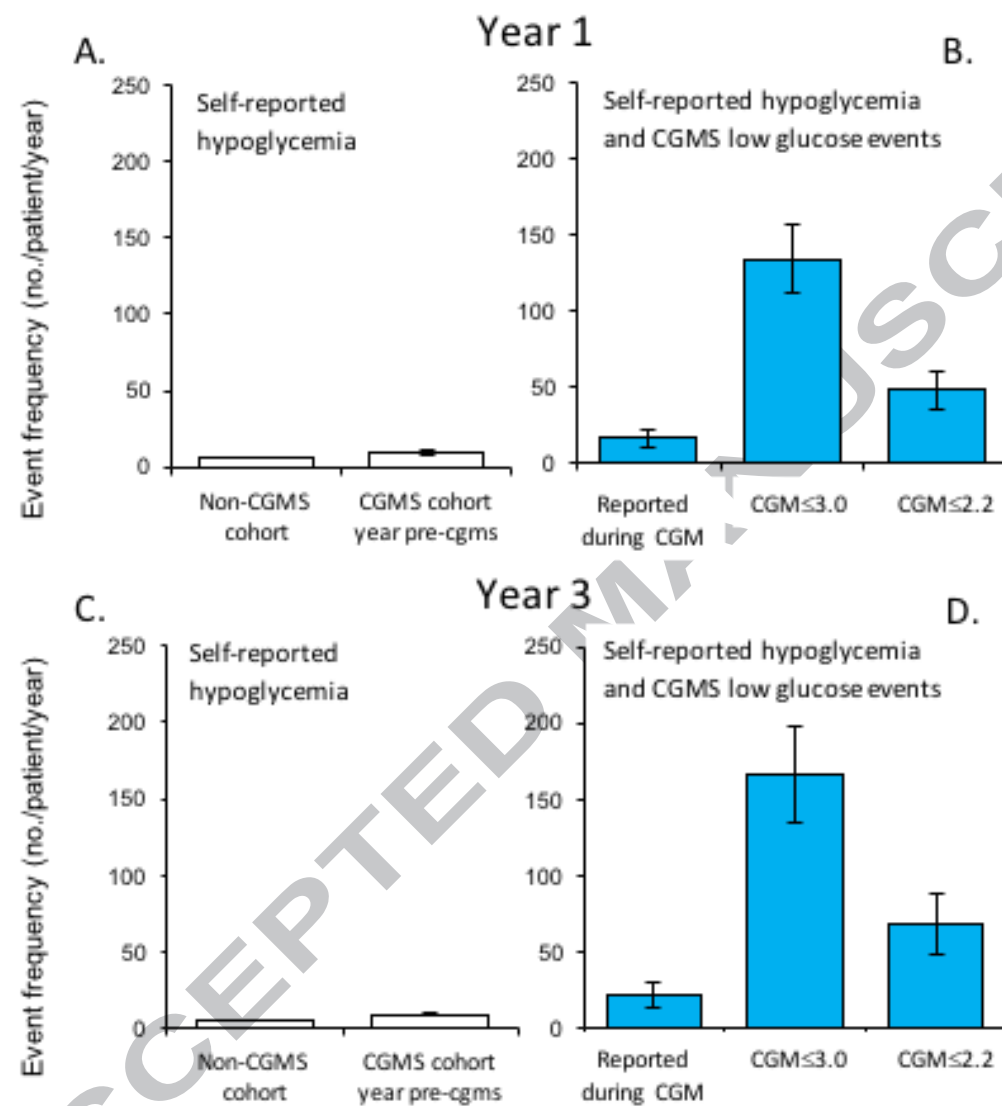
10 Figure Legend

Rates of reported hypoglycaemia and CGM low glucose events at years 1 and 3

Panel A: Year 1 self-reported hypoglycemic events in previous year in non-CGM and CGM cohorts; Panel B: Year 1 self-reported hypoglycaemia and CGM low-glucose events during CGM; Panel C: Year 3 self-reported hypoglycemic events in previous year in non-CGM and CGM cohorts; Panel D: Year 3 self-reported hypoglycaemia and CGM low-glucose events during CGM. Bars represent means, error bars, standard errors of the means. All data represent numbers per person per year.

11 Figures

Figure 1



Highlights

- Reported frequencies of self-reported hypoglycaemia in clinical trials may significantly underestimate interstitial hypoglycaemic events detected by continuous glucose monitoring.
- This highlights risk of minimising important adverse effects of glucose lowering therapies in the light of associations between hypoglycaemia and major cardiovascular events