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Title:
Incidence and severity of hypoglycaemia in type 2 diabetes by treatment regimen: a UK multi-site 12-month prospective observational study

Short Running Title:
Hypoglycaemia prospective study

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ABSTRACT (246 words)

Aims:

To determine the incidence and severity of self-reported hypoglycaemia in a primary care population with type 2 diabetes. The study also aimed to compare incidence by treatment regimen.

Materials and methods:

A prospective observational study in 17 centres throughout the UK. Recruitment was based on treatment regimen (metformin, sulfonylurea, insulin or incretin-based therapy). Participants were asked to keep a blood glucose diary and self-report hypoglycaemia episodes (non-severe (self-treated) and severe (requiring external help), over a 12-month period.

Results:

325 participants were enrolled, of whom 274 (84%) returned ≥1 monthly diary. Overall, 39% reported experiencing hypoglycaemia; 32% recorded ≥1 symptomatic episode, 36% ≥1 non-severe and 7% ≥1 severe. By treatment, incidence (events per person/year) for any hypoglycaemia type was 4.39 for insulin, 2.34 sulfonylurea, 0.76 metformin and 0.56 incretin-based. Compared to metformin, risk of non-severe hypoglycaemia was around three times higher for participants on sulfonylureas and over five times higher for those on insulin (IRR 3.02 [1.76- 5.18], $p<0.001$, and IRR 5.96 [3.48-10.2], $p<0.001$, respectively). For severe episodes, the incidence for sulfonylurea (0.09) was similar to metformin (0.07) and incretin-based (0.07); for insulin the risk remained almost five times higher than metformin (incidence 0.32; IRR 4.55 [1.28-16.20], $p=0.019$).

Conclusions:

Hypoglycaemia represents a substantial burden for people with type 2 diabetes. Sulfonylureas and insulin are both associated with a risk of reported non-severe hypoglycaemia, but only insulin with severe episodes. This suggests the importance of the continued use of sulfonylureas in appropriate patients with type 2 diabetes.

Trial registration:

NCT02666521, CLINICALTRIALS.GOV

INTRODUCTION

Good glycaemic control is a major goal of diabetes management and is associated with fewer diabetes-related complications [1-4]. Hypoglycaemia remains a common and potentially hazardous complication of treatment, and is the principal limiting factor preventing individuals from achieving optimal glycaemic control through intensive treatment [5].

Although Type 2 diabetes (T2DM) comprises most cases of diabetes [6], the overall incidence of hypoglycaemia and associated risk factors in people with T2DM have not been documented as exhaustively as in Type 1 diabetes (T1DM). Previous studies in T2DM have often had methodological limitations. A large meta-analysis containing over 530,000 individuals with T2DM estimated an annual incidence of 0.8 severe and 19 non-severe episodes per-person-year (PPY) [7]. However, these estimates may be inaccurate as hypoglycaemia was often variably defined, and many retrospective or cross-sectional studies are subject to poor recall and under-estimate the frequency. More recently, a prospective study involving 23,627 people with T1DM and T2DM from 24 countries similarly reported hypoglycaemia incidence at 19.3 events PPY for T2DM [8]. Although examining a large cohort, the period of follow up was short (4 weeks). The UK Hypoglycaemia Group Study prospectively studied hypoglycaemia incidence over 12 months. However, this study, which was conducted more than a decade ago, recruited individuals with good glycaemic control from specialist centres, and may not be representative of the wider

population with T2DM [9]. Since it was conducted, newer anti-hyperglycaemic drugs with a lower risk of hypoglycaemia have been introduced [10, 11]. Additionally, more patients are managed in generalist settings, as models for diabetes care have become primary care-centred [12], and glycaemic thresholds for reporting hypoglycaemia have been updated [13, 14]. A prospective study was therefore warranted that included newer therapies for diabetes and conducted in people who were managed exclusively within primary care.

Of mutual importance is the consideration of factors associated with hypoglycaemia development which influence an individual's risk. A study which identified hypoglycaemia rates within routine clinical practice would identify individuals who may be at greater risk and help in determining personalised glycaemic targets.

The present study aimed to prospectively examine rates of hypoglycaemia in a general population with T2DM managed in primary care. Specific objectives included: 1) to determine the incidence and severity of self-reported hypoglycaemia, over a 12-month period; 2) to compare hypoglycaemia episodes by treatment regimen; and 3) to explore associated predictors.

MATERIALS AND METHODS

This prospective observational study was conducted in UK primary care settings between July 2012 and August 2016. Participants were recruited via volunteer general practices.

Eligibility included: 1) T2DM, diagnosed ≥6 months; 2) receiving one of the following treatment regimens, i) metformin alone, ii) sulfonylurea-based iii) insulin-based, or iv) incretin-based therapy (dipeptidyl peptidase-4 (DPP-4) inhibitor or glucagon-like peptide-1 receptor agonists (GLP-1RA). (Further inclusion/exclusion criteria and full methods, see Supplementary Appendix S1)

Practice staff collected key study data at baseline (and 12-months). Participants prospectively self-recorded data on: 1) capillary blood glucose (≥3 readings/week) using a blood glucose meter and test strips (Accu-Chek, Roche Diabetes Care Ltd, UK) and entered details in a monthly diary; and 2) hypoglycaemia episodes (date, time, symptom intensity, blood glucose, remedial treatment/action taken) immediately after the event using a study-specific form.

Primary outcomes included the frequency of non-severe (self-treated) hypoglycaemia episodes: 1) proportion of participants who experienced ≥1 episode during the follow-up period (on which the sample size was calculated); and 2) incidence of self-reported hypoglycaemia episodes. Secondary outcomes included

the frequency of: severe (requiring external help), symptomatic and nocturnal hypoglycaemia.

Sample size

The UK Prospective Diabetes Study reported that 6.3% of participants experienced ≥1 non-severe hypoglycaemia event during follow up [15]. The UK Hypoglycaemia Study Group showed that 39% of participants taking sulfonylureas and 64% for insulin, experienced ≥1 hypoglycaemia event within 12-months of follow up [9]. Based on the findings of the LEAD trial, it was anticipated that around 10% of people taking a GLP-1RA would report hypoglycaemia within the last year [16]. Incidence in those taking DDP-4 inhibitors was likely to be significantly lower than those taking GLP-1RA's [17]. Therefore, a conservative estimate of 10% was used for the incretin group. Our original sample size (total n= 422) was based on an assessment of these differences. Recruitment of 140 participants to both the sulfonylurea and the insulin groups, 62 taking metformin alone and 80 on incretin-based therapies, would give 80% power to detect these differences, accounting for a potential 50% loss through drop out or switching treatment.

Statistical methods

The overall proportion of participants having ≥1 episode of hypoglycaemia (any/symptomatic/severe/non-severe/nocturnal) and the proportion by treatment group were calculated, based on participants who returned ≥1 diary. Incidence of

hypoglycaemia (PPY) was also calculated; follow-up time was calculated using diaries, based on the number of weeks participants were contributing data to the study. Negative binomial regression was used to calculate the incidence rate with robust SEs and specifying a log-transformed exposure time offset term. Logistic regression was used to assess the association between hypoglycaemia and key variables: age, sex, ethnicity, diabetes duration, hypoglycaemia awareness score, body mass index, estimated glomerular filtration rate (eGFR), HbA1c and cardiovascular disease.

Sensitivity analyses were conducted, excluding participants who changed treatment group during the study period. Hypoglycaemia experience in participants who were more or less engaged with the study (contributed ≥ or < the mean number of weeks of diary data) and by frequency of blood glucose monitoring (recorded ≥ or < the mean number of measurements/week), were also explored. Stata version 14 (StataCorp) was used to conduct all analyses. Statistical significance related to $p<0.05$ and 95% confidence intervals (CI) are presented.

RESULTS

Recruitment and follow-up

From 23 general practices that initially volunteered and received training in study procedures, 17 practices recruited participants (Scotland n=1, Wales n=2, England n=14). Subsequently, 325 eligible participants were enrolled into the study (Supplementary Figure S1), (median per practice, n=19, range 5–54). At baseline, recruitment according to treatment regimen was metformin alone n=75, sulfonylurea-based n=107, insulin-based n=93, and incretin-based n=50 (GLP-1RA, n=14; DPP-4 inhibitors, n=36).

A total of 306 participants (94%) completed 12 months in the study. Self-recording of blood glucose and hypoglycaemia events was variable but 84% (n=274) of participants returned ≥1 monthly diary, over 60% ≥6 months of diary data and over 30% returned all 12 months (Supplementary Figure S1); mean number of weeks 37.0 (SD±16.95). Follow-up data were collected for most participants (self-completion questionnaire n= 239; key medical record data n=303).

Further details on anti-hyperglycaemic drugs prescribed (single/dual therapy combinations) within each treatment group are outlined in Supplementary Table S1.

Demographic and biomedical characteristics

Table 1 provides participant characteristics (mean age 62.6 (SD±12.0) years; 91% of white ethnicity; 61% male). Overall, 62% of participants had no previous experience of severe hypoglycaemia and 45% for insulin. For non-severe, this varied from 17% (insulin) to 60% (incretin-based), who had never experienced hypoglycaemia.

Frequency of hypoglycaemia

In the 12-months of follow-up, overall 39.2% (95%CI 33.4–45.0) of participants experienced ≥1 hypoglycaemia episode. Of these, 92% experienced ≥1 non-severe episode, 17% ≥1 severe and 53% ≥1 nocturnal episode. According to baseline treatment, the proportion for insulin was 56.4% (45.2–67.0), sulfonylurea 51.6% (41.4–61.8), metformin 18.8% (10.9–30.3) and incretin-based 9.8% (3.6–23.6), (Table 2). All episodes were reported as symptomatic for metformin and incretin-based therapies. The majority were symptomatic for sulfonylurea (~70%) and insulin (~80%). For non-severe episodes, overall, 35.8% experienced ≥1, approximately half of people on insulin (51.3%) and sulfonylurea (48.4%) had ≥1, with substantially lower rates for metformin (17.2%) and incretin-based (7.3%). For severe, overall, 6.6% experienced ≥1 episode, with 11.5% for insulin and around 4% for other agents. Nocturnal episodes were experienced by 41.0% for insulin but fewer for other groups (sulfonylurea 19.8%, metformin 7.8%, incretin-based 4.9%).

Incidence of any hypoglycaemia (PPY) ranged from 4.39 for insulin, 2.34 sulfonylurea, 0.76 metformin and 0.56 incretin-based, (Table 3). In comparison to

metformin, the incidence rate ratio was significantly higher for both sulfonylurea (IRR 3.09 [95%CI 1.83–5.21], p<0.001) and insulin (5.79 [3.44–9.74], p<0.001). The trend was similar for symptomatic episodes; the risk with blood glucose level ≥3.0 to ≤3.9mmol/L was around six times higher for participants on sulfonylurea and approximately nine times higher for insulin, IRR 6.29 (2.79–14.16; p<0.001) and 9.16 (4.08–20.50; p<0.001), respectively. For serious hypoglycaemia (blood glucose <3.0mmol/L), comparison was not possible as no episodes were experienced by participants on metformin. The risk of nocturnal episodes was substantially higher for both sulfonylurea and insulin in comparison to metformin, IRR 2.67 (1.13–6.28; p=0.025) and 7.48 (3.29–17.0; p<0.001), respectively. For non-severe episodes the trend remained similar, sulfonylurea IRR 3.02 (1.76–5.18; p<0.001) and insulin 5.96 (3.48–10.2; p<0.001). For severe episodes the incidence was similar for metformin, incretin-based and sulfonylurea (PPY, 0.07, 0.07 and 0.09, respectively); in comparison, the rate for insulin was significantly higher (IR 0.32 [95%CI 0.19–0.53]; IRR 4.55 [95%CI 1.28–16.2], p=0.019), (Table 3).

Sensitivity analyses, excluding participants who changed treatment group from baseline (~20%), suggested that hypoglycaemia frequency remained broadly similar (Supplementary Table S2 and S3). Compared to metformin (IR 0.69), the incidence (95%CI) of symptomatic hypoglycaemia (all) became significantly lower for incretin-based (IR 0.24 [0.09–0.61]; IRR 0.34 [0.12–0.99], p=0.049), although the number involved was very small (n= 3). Comparison of participants who contributed ≥ or <

the mean (37 weeks) of diary data, found risk of nocturnal hypoglycaemia was slightly higher for participants who were less engaged (IRR 0.35 [0.22–0.58], p<0.001), but there were no significant differences for risk of severe, non-severe and symptomatic episodes (data not shown); both groups had a similar history of previous hypoglycaemia (severe and non-severe), at recruitment. Taking into account the frequency of blood glucose self-monitoring (≥ or < the mean (5.3) number of measurements/week recorded in diaries), risk of non-symptomatic hypoglycaemia was slightly higher for participants who measured more frequently (IRR 0.17 [0.06-0.47], p=0.001). There were no differences for symptomatic episodes (data not shown).

Factors associated with hypoglycaemia episodes

Diabetes duration was found to be significantly associated with a small (4–5%) increased risk of any, non-severe or symptomatic episodes, unadjusted. After adjusting for treatment group, age and ethnicity, only symptomatic episodes remained associated (OR 1.05 [95%CI 1.01–1.10]), (Figure 1, Supplementary Table S4, S5 and S6). Older adults aged ≥65 years were around 50% less likely to have any, non-severe or symptomatic episodes, compared to those <65 years; OR 0.45 (0.24–0.84), 0.50 (0.27–0.94) and 0.44 (0.24–0.83), respectively, adjusted for treatment group, ethnicity and diabetes duration. Hypoglycaemia awareness score was associated with a small (15%) lower risk of non-severe and symptomatic episodes, but no associations were seen following multi-variate adjustment.

Participants of non-white ethnicity were around 70% less likely to have any (OR 0.26 [0.08–0.82]) hypoglycaemia episodes compared to those of white ethnicity (adjusted for treatment group, age and diabetes duration), and non-severe reached borderline significance (OR 0.33 [0.10–1.04]), (Figure 1), Supplementary Table S4 and S6. No significant associations were found with any factors for severe hypoglycaemia, (Supplementary Table S7). Unfortunately, ethnicity could not be explored as a risk factor in these additional analyses as no severe episodes were recorded for non-white participants, (Supplementary Table S8).

DISCUSSION

In the present study, incidence rates (PPY) for non-severe hypoglycaemia ranged from 3.84 for insulin and 1.94 for sulfonylurea, to 0.64 and 0.49 for metformin and incretin-based therapy, respectively. For severe episodes, surprisingly the incidence for those treated with sulfonylureas (0.09) was very similar to metformin and incretin-based, but the incidence was significantly higher with insulin (0.32), which was to be expected.

The rates observed in our study indicate that hypoglycaemia episodes continue to represent a substantial burden for people with T2DM and were comparable to those reported in previous studies.

For insulin, the prevalence we observed is broadly similar to that found for T2DM by previous prospective studies, including the large global HAT study [8] and the UK Hypoglycaemia Study [9]. In contrast, generally the overall incidence of hypoglycaemia observed in the present study for insulin (4.39 PPY) is substantially lower than previous estimates for Northern Europe/Canada (18.1) [8] and the UK (16.36) [18]. However, our study provided a much longer duration of prospective follow-up (12-months) with a mean of 37 (SD±17) weeks of diary data, compared to the one month diary data collected in the other studies [8, 18]. Furthermore, for severe events the rates we observed were similar to those found previously by Donnelly et al (0.35 PPY) [18].

For sulfonylureas, the hypoglycaemia rates observed (48% experienced ≥1 non-severe; 4% experienced ≥1 severe; incidence 0.09 PPY) were similar to those reported by the UK Hypoglycaemia Study Group (39% ≥1 non-severe episode; 7% ≥1 severe; incidence 0.1 PPY), based on prospective data captured over 9-10 months [9]. However, the UK Hypoglycaemia Group Study was conducted >10 years ago, and studied people with diabetes who were managed in secondary care specialist centres. Although, a similar rate of severe hypoglycaemia (0.08 PPY) for secretagogues (including sulfonylurea) was reported by the more recent Italian Hypos-1 study, estimated from participant re-call over the previous 4 weeks [19].

Metformin and incretin-based therapies are generally associated with a very low risk of hypoglycaemia [15, 20]. The rates of non-severe and severe episodes we observed were low but higher than anticipated, particularly for severe episodes (0.07 PPY for both metformin and incretin-based). Unfortunately, in the present study, we were unable to account for participant level factors, such as reduced dietary intake/fasting, increased physical activity/exercise or alcohol consumption, which may have contributed to hypoglycaemia risk. We also need to acknowledge the subjective nature of self-recording hypoglycaemia episodes and the reliance on individuals to record episodes in event diaries, which may have introduced bias. Severe episodes were based on the need for third party assistance (not blood glucose level). However, this required both participant reporting of the need for

assistance and third party confirmation. Cases of severe hypoglycaemia in people on metformin (monotherapy) have previously been reported in the literature [21-24]. Furthermore, for non-severe hypoglycaemia, a recent model-based meta-analysis of trial data suggests a small increased risk for both metformin (RR~2.0) and GLP1-RAs (RR up to 3.1), compared to placebo [25].

In our study, older adults aged ≥65 years were ~50% less likely to have experienced most types of hypoglycaemia (with the exception of severe), compared to those aged <65. Previous studies have demonstrated a modestly lower risk of any (IRR 0.99) [8] and symptomatic (IRR 0.98) episodes [19], for each additional year of age. Perceived symptoms of hypoglycaemia differ in older people [26], and may lead to under recognition/reporting [27]. In our study, no difference in hypoglycaemia awareness score was observed at recruitment, but previous history of severe hypoglycaemia (≥1 episode/year) was higher in older ≥65 years compared to younger participants, (20.5% vs 10.2%, respectively, p=0.018). No difference was observed for non-severe episodes.

The association between diabetes duration and a small but higher risk of hypoglycaemia that was observed in our study is consistent with the report from the Hypos-1 study [19], of OR 1.10 and RR 1.02, respectively, for symptomatic episodes. However, in contrast to the Hypos-1 study, no association was found for the above factors with severe episodes. Data to allow comparison with ethnic

differences we found are scarce. However, lower rates of severe hypoglycaemia have previously been observed for people of Asian and of Latino extraction compared to white ethnicity [28], and a higher risk for people identified as African American/Black compared to white ethnicity [28, 29].

The role of renal impairment on the risk of hypoglycaemia has previously been highlighted, particularly for patients on sulfonylurea and insulin based treatment regimens [30]. In our study, renal insufficiency was not shown to be a predictor of hypoglycaemia, including after adjustment for treatment group. However, the number of participants who had moderate/severe renal impairment (eGFR <60ml/min) at baseline was low.

Considerable variation was observed in the number of times people chose to measure their blood glucose routinely (participants were asked to perform ≥3/week, and some did considerably more). However, when collating data, this could be used as an indicator of being actively engaged in the study. Therefore, for analysis purposes, if a participant was poorly engaged and did not return a hypoglycaemia recording form we could take account of this, rather than assume that hypoglycaemia was not experienced during a particular week/period. A further strength is the availability of blood glucose readings for most reported episodes, enabling both alert level (≤3.9mmol/L (70mg/dL)) and serious, clinically important

hypoglycaemia (<3.0mmol/L (54mg/dL)) to be identified, as proposed for more transparent reporting in clinical studies [13].

Unfortunately, despite a robust recruitment approach, we did not reach our planned study sample size. This will have limited our ability to detect significant differences between treatment classes. At practice level, despite originally aiming to involve more general practices, some practices which had shown an interest and received training to participate did not take part in the study. Implications regarding staff changes, staff availability and a lack of approval to conduct the study in certain localities (because of perceived prescribing implications for meters and test strips following study cessation) led to difficulties in practice recruitment. At participant level, the number enrolled fell short of target. This was primarily as a result of changes in prescribing guidance/practices (to include a wider choice of add-on therapies/intensification options) over the study duration [31], and the combination of treatment regimens allowed for study eligibility, which caused difficulties in recruitment of certain treatment groups, particularly those on incretin-based therapy. A further limitation is that it was not possible to include SGLT-2 inhibitors as a treatment class, as they were not licensed for use in the UK until after the study had commenced.

The study aimed to include a general population with T2DM to reflect real world practice. However, despite broad inclusion criteria, potential for selection bias still

exists. By excluding people treated solely in secondary care, whose needs are more complex, people with more problematical hypoglycaemia could be absent from the study population. Conversely, people with previous hypoglycaemia problems may have been more willing to volunteer for the study. Anticipated health benefits and better care are known to motivate people to participate in research [32, 33].

Because of the limited number of hypoglycaemia events recorded (overall, n=107 experienced ≥1 episode, and the numbers were much less in some categories), this may have limited the power to compare treatment groups. Particularly, between those were you would expect to see a small difference in hypoglycaemia rates, and for incretin-based therapies where the numbers recruited were small. Furthermore, we were unable to explore possible differences in hypoglycaemia rates between specific anti-hyperglycaemic therapies (or dosing regimens) within each treatment class. This is something that future studies and analyses may want to consider.

In the present study, the observed lower incidence of severe hypoglycaemia for participants prescribed sulfonylureas compared to those on insulin is in agreement with findings from previous observational studies, and adds support to the continued importance of sulfonylureas as a possible therapy choice in T2DM, for certain patients, especially in low-income and middle-income countries [34]. However, the incidence of non-severe episodes still represents a significant burden, given the potential impact on an individual's daily activities and wellbeing [35, 36], the

economic consequences of reduced work productivity and increased treatment costs [37], and the associated increased risk of severe events [38]. Risk prediction of hypoglycaemia is an important area for both research and clinical practice. Future research should consider further identification of potential risk factors, including ethnicity, to help individualise therapy choices to give a lower risk of hypoglycaemia.

Conclusion

The present study contributes to the contemporary evidence for rates of hypoglycaemia for patients with T2DM treated in primary care and the substantial burden of hypoglycaemia in T2DM. For appropriate patients, sulfonylurea's continue to be an important treatment option. Further consideration of factors associated with hypoglycaemia could help identify "at risk" groups and inform ways to individualise therapy choices and glycaemic targets.

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Author contributions:

KK was the Chief Investigator for the study and conceived the idea for the study, contributed methodological and practical advice to all components of the research programme, commented on drafts of the manuscript and approved the final version, and is guarantor of the overall content.

AJD was the lead researcher for the study and was responsible for its design and conduct and drafted and revised the manuscript.

RCF was the project manager for the study and contributed to drafting and revising the manuscript.

LJG designed the statistical analysis plan, analysed the quantitative results and oversaw their reporting and interpretation and contributed to drafting and revising the manuscript.

GW conducted the statistical analysis under the supervision of LJG and reviewed the final manuscript.

SRH contributed methodological advice for the research programme and reviewed the final manuscript.

BMF contributed methodological advice for the research programme and reviewed the final manuscript.

MJD contributed methodological and practical advice for the research programme and reviewed the final manuscript.

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Conflicts of interest:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

KK has acted as a consultant and speaker for Amgen, AstraZeneca, Bayer, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Lilly, Servier and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from AstraZeneca, 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 AstraZeneca, Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk.

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SRH has served on scientific advisory boards and provided consultancy for which his institution has received remuneration from Lilly, Novo Nordisk, Takeda, Boeringher Ingelheim, UN-EEG and Zealand; has served as a speaker for which he received remuneration from AstraZeneca, Lilly, Novo Nordisk and Takeda.

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The study was conducted in accordance with the approvals granted by the East Midlands Leicester Research Ethics Committee (reference: 11/EM/0228).

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LEGEND TO FIGURES

Figure 1: Risk factors for hypoglycaemia (any type of episode)

[1] Model adjusted for treatment group at baseline

[2] Model adjusted for treatment group, age, ethnic group, diabetes duration

MAIN TABLES

Table 1: Key characteristics of participants

Characteristics	All n = 325	Metformin n = 75	Sulfonylurea n = 107	Insulin n = 93	Incretin-based n = 50	**P-value***
Demographic						
Age (years)	62.6 (± 11.95)	59.3 (13.27)	63.3 (11.07)	65.4 (11.66)	60.4(10.92)	0.005
Aged ≥65	158 (48.6)	33 (44.0)	53 (49.5)	55 (59.1)	17 (34.7)	0.035
Sex, Male, n (%)	198 (60.9)	46 (61.3)	67 (62.6)	56 (60.2)	29 (58.0)	0.954
Ethnicity, n (%)						
White	294 (90.5)	70 (93.3)	92 (86.0)	88 (94.6)	44 (88.0)	0.410
Asian	22 (6.8)	4 (5.3)	10 (9.4)	3 (3.2)	5 (10.0)	
Black	5 (1.5)	0	3 (2.8)	2 (2.2)	0	
Mixed	4 (1.2)	1 (1.3)	2 (1.9)	0	1 (2.0)	
Biomedical Measurements						
BMI (kg/m^2)	31.7 (± 6.37)	31.30 (± 6.18)	31.54 (± 6.14)	30.88 (± 6.22)	34.13 (± 6.95)	0.028
Systolic BP (mmHg)	129.8 (± 13.36)	130.65 (± 12.29)	130.43 (± 14.29)	130.42 (± 14.04)	126.26(±11.13)	0.236
HDL Cholesterol (mmol/l)	1.21 (± 0.42)	1.23 (± 0.38)	1.20 (± 0.49)	1.26 (± 0.42)	1.10 (± 0.25)	0.238
LDL Cholesterol (mmol/l)	2.03 (± 0.76)	1.92 (± 0.61)	2.03 (± 0.70)	2.18 (± 0.87)	1.91 (± 0.81)	0.167
HbA1c (mmol/mol) - baseline (%)	56.5(±10.72); 7.3(±0.98)	52.0(±10.38); 6.9(±0.95)	55.5(±9.42); 7.2(±0.86)	61.0(±11.3); 7.7(±1.03)	56.6(±9.80); 7.3(±0.90)	<0.001
< 58 mmol/mol, n (%)	183 (56.3)	56 (74.7)	66 (61.7)	33 (35.5)	28 (56.0)	<0.001
< 53 mmol/mol, n (%)	130 (40.0)	45 (60.0)	47 (43.9)	20 (21.5)	18 (36.0)	<0.001
< 48 mmol/mol, n (%)	78 (24.0)	31 (41.3)	23 (21.5)	14 (15.1)	10 (20.0)	0.327
HbA1c (mmol/mol) – 12 months (%)	56.2(±13.56); 7.3(±1.24)	49.6(±10.48); 6.7(±0.96)	54.7(±11.89); 7.2 (±1.09)	62.4(±14.32); 7.9 (±1.31)	57.3(±14.69); 7.4 (±1.34)	<0.001
< 58 mmol/mol, n (%)	189 (58.2)	60 (80.0)	68 (63.6)	32 (34.4)	29 (58.0)	0.144
< 53 mmol/mol, n (%)	143 (44.0)	49 (65.3)	49 (45.8)	23 (24.7)	22 (44.0)	0.117
< 48 mmol/mol, n (%)	103 (31.7)	39 (52.0)	34 (31.8)	15 (16.1)	15 (30.0)	0.089
eGFR ≥ 90 ml/min	95 (29.2)	16 (24.2)	35 (33.7)	25 (27.8)	19 (39.6)	0.003
60-89 ml/min	171 (52.6)	46 (69.7)	59 (56.7)	41 (45.6)	25 (52.1)	
30-59 ml/min	40 (12.3)	4 (6.1)	10 (9.6)	22 (24.4)	4 (8.3)	
≤ 29 ml/min	2 (0.6)	0	0	2 (2.22)	0	
Medical history						
Duration of diagnosed diabetes (years, IQR)	8 (4-12)	4 (2-7)	8 (4-11)	13 (8-18)	6.5 (3-10)	<0.001

Co-morbidities, n (%)						
Stroke	15 (4.6)	1 (1.3)	6 (5.6)	6 (6.5)	2 (4.0)	0.419
Coronary heart disease (IHD, MI, angioplasty, angina)	60 (18.5)	13 (17.3)	17 (15.9)	21 (22.6)	9 (18.0)	0.662
Peripheral arterial disease (or leg angioplasty)	4 (1.2)	1 (1.3)	1 (0.9)	2 (2.2)	0	0.716
Retinopathy	34 (10.5)	4 (5.3)	6 (5.6)	21 (22.6)	3 (6.0)	<0.001
Smoking status: current, n (%)	44 (13.5)	5 (6. 7)	18 (17.0)	18 (20.0)	3 (6.1)	0.024
Alcohol intake, n (%)						
Never	96 (29.5)	21 (28.0)	31 (31.10	29 (33.7)	15 (31.3)	0.650
Occasionally	128 (39.4)	28 (37.3)	46 (44.7)	35 (40.7)	19 (39.6)	
Weekly	88 (27.1)	26 (34.7)	26 (25.2)	22 (25.6)	14 (29.2)	
Current medication, n (%)						
Aspirin	107 (33.2)	20 (26.7)	34 (31.8)	36 (38.7)	17 (36.2)	0.392
Lipid lowering	270 (83.1)	61 (81.3)	88 (82.2)	78 (83.9)	43 (86.0)	0.641
Anti-hypertensive	245 (75.4)	53 (70.7)	82 (76.6)	71 (76.3)	39 (78.0)	0.748
Thyroid medication	29 (9.0)	6 (8.0)	6 (5.6)	12 (12.9)	5 (10.4)	0.327
Anti-obesity	4 (1.2)	0	2 (1.8)	0	2 (4.1)	0.127
Steroids	30 (9.3)	5 (6.7)	8 (7.5)	12 (12.9)	5 (10.4)	0.467
Previous severe hypoglycaemia, n (%)						
never	200 (61.5)	60 (80.0)	63 (58.9)	42 (45.2)	35 (70.0)	0.001
Previous non-severe hypoglycaemia, n						
never	123 (37.8)	40 (53.3)	37 (34.6)	16 (17.2)	30 (60.0)	<0.001
Hypo awareness score (1-7)**; mean (±SD)	3.15 (2.16)	4.43 (2.22)	3.00 (2.05)	2.57 (1.04)	3.25 (2.27)	<0.001
median (IQR)	2.5 [1-5]	5 [3-7]	2 [1-5]	2 [1-4]	2.5 [1-5]	<0.001
Score ≥ 4	77 (40.5)	24 (64.9)	26 (40.6)	18 (26.1)	9 (45.0)	0.002
Score < 4	113 (59.5)	13 (35.1)	38 (59.4)	51 (73.9)	11 (55.0)	

Data given as mean (±SD) for continuous outcomes, unless otherwise stated, and n (%) for categorical.

* P-values are estimated using chi-square for categorical variables and one-way anova or Kruskal Wallis for continuous variables.

**Hypo awareness score (1 always aware to 7 never aware), a score of ≥4 implies impaired awareness.

BMI body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein;

Table 2: Experience of hypoglycaemia episodes (proportion having ≥1 episode)

Category and how identified	All (n=274) n (% ; 95% CI)	Metformin (n=64) n (% ; 95% CI)	Sulfonylurea (n=91) n (% ; 95% CI)	p-value	Insulin (n=78) n (% ; 95% CI)	p-value	Incretin-based (n=41) n (% ; 95% CI)	p-value
Any hypoglycaemia episode	107 (39.2; 33.4 to 45.0)	12 (18.8; 10.9 to 30.3)	47 (51.6; 41.4 to 61.8)	<0.001	44 (56.4; 45.2 to 67.0)	<0.001	4 (9.8; 3.6 to 23.6)	0.211
Symptomatic hypoglycaemia - all	87 (31.8; 26.5 to 37.5)	12 (18.8; 10.9 to 30.3)	34 (37.4; 28.0 to 47.8)	0.013	37 (47.4; 36.5 to 58.6)	<0.001	4 (9.8; 3.6 to 23.6)	0.211
Symptomatic - Blood glucose ≥3.0 to ≤3.9 mmol/L	63 (23.0; 18.4 to 28.4)	5 (7.8; 3.3 to 17.6)	25 (27.5; 19.2 to 37.6)	0.002	29 (37.2; 27.1 to 48.5)	<0.001	4 (9.8; 3.6 to 23.6)	0.729
Symptomatic - Blood glucose < 3.0 mmol/L	26 (9.5; 6.5 to 13.6)	0	6 (6.6; 3.0 to 14.0)	0.036	19 (24.4; 16.0 to 35.2)	<0.001	1 (2.4; 0.3 to 15.9)	0.209
Non-severe - No assistance required	98 (35.8; 30.3 to 41.7)	11 (17.2; 9.7 to 28.6)	44 (48.4; 38.2 to 58.6)	<0.001	40 (51.3; 40.2 to 62.2)	<0.001	3 (7.3; 2.3 to 20.7)	0.147

Severe - Assistance required	18 (6.6; 4.2 to 10.2)	3 (4.7;1.5 to 13.7)	4 (4.4; 1.6 to 11.2)	0.931	9 (11.5; 6.1 to 20.8)	0.144	2 (4.9; 1.2 to 17.9)	0.964
Nocturnal hypoglycaemia - all	57 (20.8; 16.4 to 26.1)	5 (7.8; 3.3 to 17.7)	18 (19.8; 12.8 to 29.3)	0.039	32 (41.0; 30.6 to 52.3)	<0.001	2 (4.9; 1.2 to 17.9)	0.556

p-value, metformin is the reference group

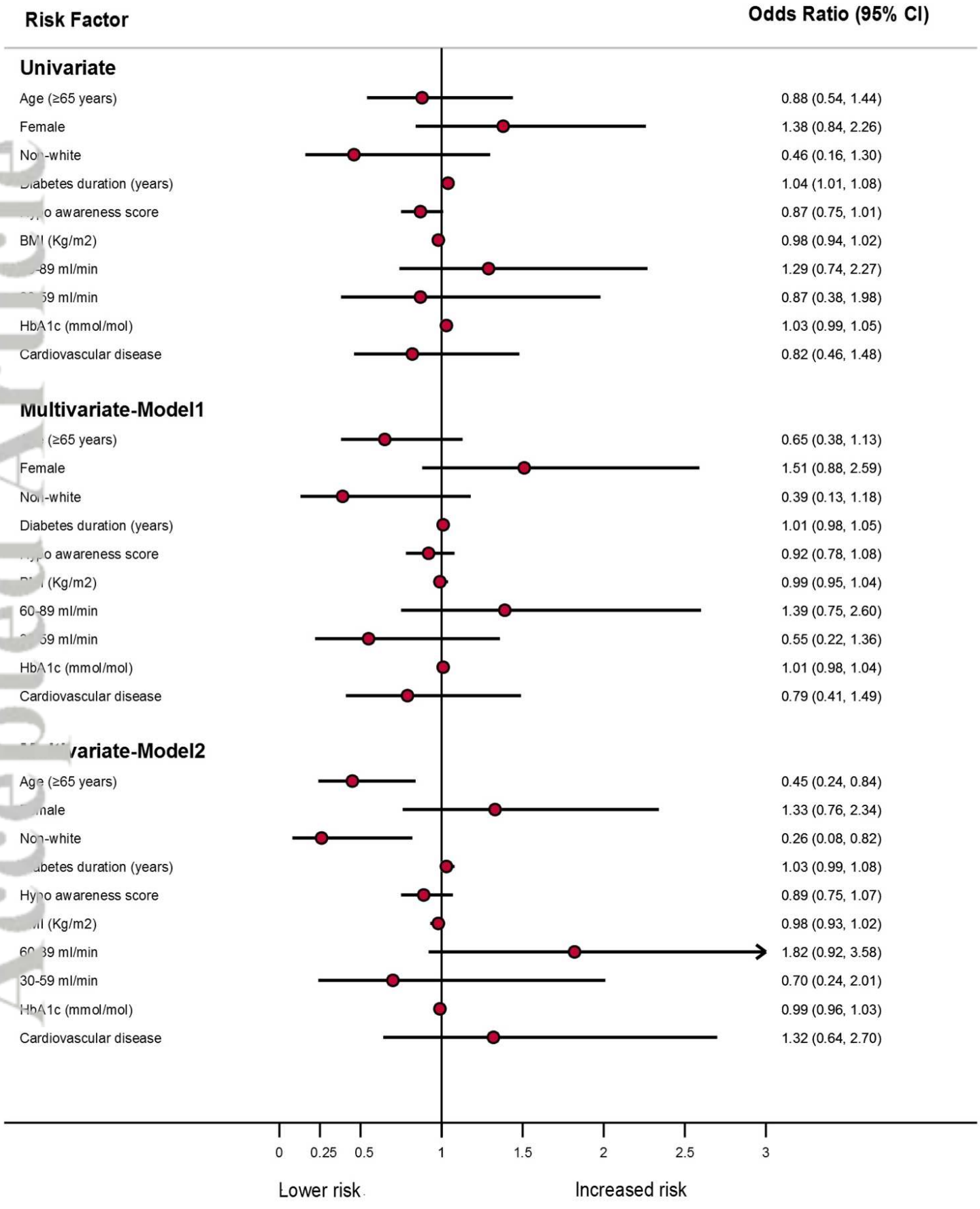
Table 3: Incidence of hypoglycaemia (per person-year by treatment group)

	All	Metformin	Sulfonylurea			Insulin			Incretin-based		
	IR (95% CI)	IR (95% CI)	IR (95% CI)	IRR (95% CI)	p-value	IR (95% CI)	IRR (95% CI)	p-value	IR (95% CI)	IRR (95% CI)	p-value
Any hypoglycaemia episode	2.26 (1.92 to 2.65)	0.76 (0.49 to 1.18)	2.34 (1.77 to 3.10)	3.09 (1.83 to 5.21)	<0.001	4.39 (3.33 to 5.78)	5.79 (3.44 to 9.74)	<0.001	0.56 (0.31 to 1.01)	0.74 (0.36 to 1.55)	0.427
Symptomatic hypoglycaemia - all	1.79 (1.51 to 2.11)	0.76 (0.49 to 1.18)	1.91 (1.43 to 2.54)	2.52 (1.48 to 4.26)	0.001	3.10 (2.35 to 4.09)	4.09 (2.43 to 6.89)	<0.001	0.48 (0.26 to 0.89)	0.64 (0.30 to 1.36)	0.245
Symptomatic - Blood glucose ≥3.0 to ≤3.9 mmol/L	0.92 (0.76 to 1.12)	0.18 (0.09 to 0.38)	1.14 (0.83 to 1.58)	6.29 (2.79 to 14.16)	<0.001	1.67 (1.22 to 2.28)	9.16 (4.08 to 20.5)	<0.001	0.14 (0.05 to 0.40)	0.79 (0.22 to 2.81)	0.711
Symptomatic - Blood glucose < 3.0 mmol/L	0.35 (0.26 to 0.46)	-	0.12 (0.06 to 0.26)	-		1.03 (0.72 to 1.47)	-		0.04 (0.00 to 0.26)	-	
Non-severe - No assistance	1.93 (1.63 to 2.27)	0.64 (0.41 to 1.02)	1.94 (1.46 to 2.59)	3.02 (1.76 to 5.18)	<0.001	3.84 (2.90 to 5.09)	5.96 (3.48 to 10.2)	<0.001	0.49 (0.26 to 0.90)	0.75 (0.35 to 1.63)	0.470
Severe - Assistance required	0.15 (0.11 to 0.23)	0.07 (0.02 to 0.23)	0.09 (0.04 to 0.22)	1.33 (0.32 to 5.59)	0.692	0.32 (0.19 to 0.53)	4.55 (1.28 to 16.2)	0.019	0.07 (0.02 to 0.30)	1.01 (0.16 to 6.36)	0.991
Nocturnal hypoglycaemia - all	0.59 (0.47 to 0.74)	0.18 (0.09 to 0.39)	0.49 (0.32 to 0.75)	2.67 (1.13 to 6.28)	0.025	1.37 (0.97 to 1.95)	7.48 (3.29 to 17.0)	<0.001	0.07 (0.02 to 0.29)	0.38 (0.08 to 1.89)	0.238

IR, Incidence Rate

IRR, Incidence Rate Ratio (metformin as a reference group)

MAIN FIGURES



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