Effects of age, gender, and body mass index on efficacy and hypoglycaemia outcomes across treat-to-target trials with insulin glargine 100 U/ml added to oral antidiabetes agents in type 2 diabetes

D. Owens[1], G. Bolli[2], B. Charbonnel[3], T. Haak[4], W. Landgraf[5], F. Porcellati[2], L. Traylor[6] & A. Kautzky-Willer[7]

[1]Diabetes Research Group, Institute of Life Sciences, College of Medicine, Swansea University, Swansea[2]Department of Medicine, University of Perugia School of Medicine, Perugia, Italy

[3]University of Nantes, Nantes, France

[4]Diabetes Center Mergentheim, Bad Mergentheim, Germany

[5]Sanofi, Frankfurt, Germany

[6]Sanofi US, Inc., Bridgewater, NJ, USA

[7]Department of Endocrinology & Diabetes, Gender Medicine, Medical University of Vienna, Vienna, Austria

Short running title: Outcomes across treat-to-target trials with Gla-100

Abstract: 250 words

Main text: 3,215

Figures: 6

Tables: 4

References: 27

Abstract

Aims: Analyse effects of patient characteristics and different OAD use on standardised clinical outcomes in type 2 diabetes patients initiating insulin glargine 100 U/ml (Gla-100).

Materials and Methods: Patient-level data were analysed from 16 randomised, treat-to-target clinical trials that added Gla-100 to existing metformin (MET), sulfonylurea (SU), or metformin plus sulfonylurea (MET+SU) in insulin-naïve patients inadequately controlled on oral therapy and followed for ≥24 weeks. Change in glycated haemoglobin A1c (HbA1c) from baseline to Week 24, other glycaemic endpoints, and incidence of hypoglycaemia (overall, nocturnal, and severe) were analysed by age (<65 vs. ≥65 years), gender (male vs. female), body mass index (BMI; <25 vs. ≥25 to <30 vs. >30 kg/m^2), and concomitant OAD (MET vs. SU vs. MET+SU).

Results: At baseline, overall population (N=3.188) had a mean age of 57.7 years, BMI 30.5 kg/m^2, HbA1c 8.7%, fasting plasma glucose 192 mg/dl, 52.7% were male. Younger and older patients had similar HbA1c reductions with Gla-100 and similar risk of hypoglycaemia. Females and patients with BMI <25 kg/m^2 were less likely to achieve HbA1c targets and more likely to experience hypoglycaemia, regardless of concomitant OAD. Adding Gla-100 to SU therapy (alone or combination with MET) increased hypoglycaemia risk across all analyses.

Conclusions: Our data suggest that T2DM female patients and normal-weight patients treated with Gla-100 and metformin ±sulfonylurea are less likely to achieve glycaemic targets and therefore, may require more clinical attention. Addition of Gla-100 to SU regimens may increase hypoglycaemia risk irrespective of age, gender or BMI.

Introduction

The number of people with diabetes has grown almost fourfold in recent decades to an estimated 422 million in 2014 [1], due largely to type 2 diabetes (T2D), which is characterised by progressive insulin resistance, insulin deficiency, and defects in beta cell function [2]. Owing to the progressive nature of T2D, patients who are treated initially with oral antidiabetes drugs (OADs) may need to initiate basal insulin to maintain overall glucose control and minimise risk of developing diabetes-related complications [3,4].

Present guidelines recommend intensification of therapy in patients inadequately controlled with current treatments, proposing basal insulin as one of the suitable options. [3,4] Yet the presence of different patient characteristics, types of studies, types of combination therapies, and definitions for hypoglycaemia—to name just a few confounding factors—may confuse the issue. Further, the position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on the management of hyperglycaemia in T2D emphasises the importance of tailoring therapy for adult patients with T2D [3,4], and states that patient factors such as age, gender, and body mass index (BMI) should be taken into account when making treatment decisions. The guidelines state that special care is required in prescribing and monitoring pharmacological treatment in older adults [3,4]. Separately, previous studies have suggested that females with T2D are less likely to reach glycaemic targets and have a higher risk of hypoglycaemia with insulin therapy compared with males, suggesting that gender may play a role when tailoring therapy for individual patients [5,6]. Previous studies also have suggested that BMI may affect the glycated haemoglobin A1c (HbA1c) level achieved and hypoglycaemia risk in patients with T2D [7,8]. Clear guidance is needed to help physicians weigh patient characteristics when initiating basal insulin.

The objective of this study was to analyse patient-level data comparing standardised clinical outcomes in insulin-naïve patients with T2D adding insulin glargine 100 U/ml (Gla-100) to existing OADs according to these important variables- age, gender, BMI category, and type of concomitant OAD use.

Methods

Study selection

To be eligible for inclusion in this analysis, studies had to be prospective, randomised, controlled treat-to-target trials (target fasting plasma glucose [FPG] level ≤100 mg/dl) with a duration of ≥24 weeks for which safety population patient-level data were available for analysis. This last criterion therefore limited studies to those published by Sanofi. All the Sanofi-sponsored studies fulfilling the inclusion criteria were included in the analysis. Inclusion criteria were: Treat-to-target with protocol driven titration and an FPG target of <100 mg/dL, study duration >=24 weeks, T2D patients with glargine in combination with SU, Met or SU+Met, collection of sufficient hypoglycaemia data. No imputation was used, only data was included captured within the visit window. Patients were insulin-naive adults with T2D, adding Gla-100 to their current oral therapy. No data was used from patients requiring bolus insulin. Only bedtime glargine regimes were used for calculations. A total of 16 studies fulfilled all of the inclusion criteria (Supplementary Table 1) [9–24].

Endpoints

Efficacy endpoints evaluated included change in HbA1c level from baseline to Week 24, percentage of patients achieving HbA1c <7.0% at Week 24, and change in FPG from baseline to Week 24. Other endpoints included the percentage of patients achieving HbA1c <7.0% without overall, nocturnal, or severe hypoglycaemia; insulin dose; and weight change from baseline. Hypoglycaemia was defined as overall (with plasma glucose [PG] <70 mg/dl or requiring third-party assistance); nocturnal (events

occurring between 0:01 AM and 5:59 AM with PG <70 mg/dl); severe (events requiring third-party assistance); and nocturnal severe (events occurring between 0:01 AM and 5:59 AM requiring third-party assistance).

Statistical analyses

Standardised patient-level data were pooled from the identified studies. Baseline and Week 24 patient characteristics were reported using descriptive statistics. The effects of demographic and baseline characteristics such as younger vs. older age (<65 vs. ≥65 years), gender (male vs. female), BMI category (normal [<25 kg/m^2], overweight [≥25 to <30 kg/m^2], and obese [≥30 kg/m^2]), duration of diabetes, HbA1c, FPG, starting insulin dose (IU/kg), and concomitant OAD received (metformin [MET], a sulfonylurea [SU], or MET+SU) were examined using analysis of covariance (ANCOVA) models for HbA1c, FPG, and weight change from baseline. Logistic regression (PROC GENMOD, binomial distribution, logit link) was used for the percentage of patients reaching HbA1c <7.0% or FPG ≤100 mg/dl at endpoint. Adjusted hypoglycaemia incidence (percentage of patients with ≥1 event) was derived using logistic regression (PROC GENMOD, binomial distribution, logit link), and adjusted event rates (events/patient-year) were derived using negative binomial regression (PROC GENMOD, negative binomial distribution, log link); data were adjusted for age, gender, duration of diabetes, BMI, baseline HbA1c, baseline FPG, baseline insulin dose, and concomitant OAD. The corresponding baseline value was also included in the models for efficacy variables. All models also included OAD groups and study.

Results

Patients

Overall, 3188 patients from 16 studies were included in this analysis. Patient demographics and clinical characteristics are summarised here (full data of the subgroups are in Supplementary Table 2). In the overall population, 52.7% were male, mean age was 57.7 years, and T2D duration was 9.0 years. Mean weight at baseline was 86.0 kg, and mean BMI was 30.5 kg/m^2. Mean HbA1c at baseline was 8.7% and FPG 192.1 mg/dl. Gla-100 was added to MET in 644 patients, to SU in 920 patients, and to MET+SU in 1624 patients.

With regards to age at baseline (Supplementary Table 2A), 75.6% of patients were aged <65 years and 24.4% were aged ≥65 years. Younger patients had shorter mean duration of T2D, higher weight and BMI, and slightly higher HbA1c and FPG than older patients. The mean starting dose of Gla-100 was similar in both age groups.

Mean age, duration of T2D, and HbA1c were the same for males and females (Supplementary Table 2B**)**. Mean FPG was slightly higher among males than females. The mean starting dose of Gla-100 was similar in both genders.

Of patients with BMI data available at baseline (n=3187), (Supplementary Table 2C), BMI category was normal in 11.5%, overweight in 38.1%, and obese in 50.4% patients. Patients with a lower BMI had a longer duration of T2D. Baseline HbA1c levels were similar across all BMI categories, and FPG was highest in overweight patients; normal and obese patients had remarkably similar FPG. Initial Gla-100 dose was highest among normal and lowest among obese patients.

Efficacy

All analyses compared baseline with results at 24 weeks. In addition, separate analyses looked at patients by age, gender, and BMI regardless of the type of OAD used, and by age, gender, and BMI stratified by the type of OAD used.

In the overall study population, mean HbA1c decreased from 8.74% at baseline to 7.19% at Week 24. Age ($p=0.003$), male gender ($p<0.001$), and baseline FPG ($p=0.008$) were negatively related to HbA1c at endpoint. Baseline HbA1c ($p<0.001$), diabetes duration ($p<0.001$), and treatment with SU only (vs. MET) ($p=0.007$) were positively related to HbA1c at endpoint. Overall, 45.6% of patients reached the target HbA1c of <7.0%.

FPG decreased from 191.7 to 118.1 mg/dl. Age ($p<0.001$) and insulin starting dose ($p=0.001$) were negatively related to FPG at Week 24, and baseline BMI ($p=0.002$), use of SU only ($p<0.001$), or MET+SU ($p=0.002$) (vs. MET) were positively related to endpoint FPG. Overall, 34.7% of patients achieved the target FPG of ≤100 mg/dl.

Summary of patients by age revealed that younger patients had a slightly greater mean reduction in HbA1c compared with older patients regardless of concomitant OAD (Figure 1A), whereas age had little impact on mean reductions in FPG at Week 24 (Figure 1B). Mean reductions in FPG for patients using SU only or MET+SU did not differ by age. However, among patients using MET only, younger patients had greater mean reductions in FPG than those aged ≥65 years (Figure 1B). The proportion of patients in varying groups reaching HbA1c <7% are depicted in Supplementary Table 3.

Summarised by gender, mean reductions in HbA1c from baseline to Week 24 were lower in females than in males (Figure 2A). Mean FPG at Week 24 was similar in males and females, regardless of concomitant OAD (Figure 2B). When summarised by concomitant OAD, females had slightly smaller reductions in HbA1c than men, except for patients using SU only (Figure 2A).

Summary of patients by BMI category revealed that mean changes in HbA1c from baseline to Week 24 were similar across BMI categories and according to concomitant OAD use. However, a smaller percentage of patients in the normal BMI category achieved HbA1c <7.0% at Week 24 versus the overweight and obese categories; this pattern also was seen regardless of the concomitant OAD used (Supplementary Figure). Mean changes in FPG from baseline to Week 24 differed according to BMI category, with larger reductions observed in patients in the normal category versus the overweight and obese categories; consequently, FPG levels at Week 24 were lower in patients in the normal category

and higher in patients in the overweight and obese categories (109.3 vs. 116.6 vs. 121.2 mg/dl, respectively).

Hypoglycaemia

Age had little effect on the incidence (Figure 3A) and event rates (Figure 3B) of overall, nocturnal, and severe hypoglycaemia, which were comparable in younger and older patients. Age ($p=0.02$), baseline BMI ($p<0.001$), and HbA1c ($p=0.003$) were negatively associated, and duration of disease ($p=0.004$), insulin starting dose ($p<0.001$), SU only ($p=0.002$), and ME+SU ($p=0.001$) (vs. MET) were positively associated with overall hypoglycaemia incidence. Age ($p=0.023$), gender (male vs. female) ($p=0.012$), baseline BMI ($p<0.001$) and baseline HbA1c ($p=0.002$) were negatively associated, and duration of diabetes ($p=0.009$), insulin starting dose ($p<0.001$), SU only ($p<0.001$), and MET+SU ($p<0.001$) (vs. MET) were positively associated with the event rate of overall hypoglycaemia.

Overall hypoglycaemia incidence was similar in both age groups, regardless of concomitant OAD. The incidence of nocturnal hypoglycaemia was higher in older patients using SU only and in younger patients using MET+SU. The incidence of severe hypoglycaemia was mostly similar between younger and older patients regardless of OAD group, except that the incidence was higher among younger patients using MET only. The event rate for overall and nocturnal hypoglycaemia was highest among patients using MET+SU, regardless of age, followed by patients using SU only, with a slightly higher rate in older patients versus younger patients

When summarised by gender, the incidence and event rates of overall and nocturnal severe hypoglycaemia and the event rates of overall, nocturnal, and nocturnal severe hypoglycaemia were significantly higher in females than males (Figure 4). This pattern generally was repeated when analysed

by concomitant OAD. In all cases, the incidence of hypoglycaemia was at least slightly higher in females than in males. The difference was most pronounced among patients using SU only.

In the summary of patients by BMI category, the hypoglycaemia incidence and event rates were highest in patients in the normal BMI category, irrespective of the concomitant OAD used (Figure 5). When analysed by concomitant OAD, overall hypoglycaemia incidence was highest in patients taking MET+SU regardless of BMI category; hypoglycaemia incidence in the patients in the normal BMI category taking MET only or SU only were similar to one another, but in each case higher than in patients in the overweight and obese BMI categories. Of note, the incidence of overall hypoglycaemia among patients in the obese BMI category was higher in those taking SU only (33.43%) than those taking MET only (27.20%). Overall hypoglycaemia event rates were higher in patients in the normal BMI category taking SU only (9.67 events/patient-year) or MET+SU (10.03 events/patient-year) versus MET only (6.16 events/patient-year). For patients in the overweight and obese BMI categories, hypoglycaemia event rates were highest in patients taking MET+SU, followed by patients taking SU only, and lowest in patients taking MET only.

Body weight and insulin dose

In the overall patient cohort, mean body weight increased from 85.9 kg to 87.8 kg. Age ($p<0.001$) and baseline BMI ($p=0.028$) were negatively associated, and baseline HbA1c ($p<0.001$), baseline FPG, and starting dose ($p<0.001$, each), SU only ($p<0.001$) and MET+SU ($p=0.006$) (vs. MET) were positively associated with weight at endpoint. The mean insulin dose increased from 0.16 to 0.43 IU/kg. Age and duration ($p<0.001$, each) and MET+SU ($p=0.001$ vs. MET) were negatively associated, and baseline BMI and FPG ($p<0.001$, each), baseline HbA1c ($p=0.002$) were positively associated with insulin dose at endpoint. (Supplementary Table 4)

Insulin dose increase was greater in younger patients compared with older patients. Mean (standard deviation [SD]) insulin dose increased by 0.30 (0.26) IU/kg from baseline to Week 24 in younger patients and by 0.18 (0.19) IU/kg in older patients. Analysis by concomitant OAD revealed that patients in either age group taking MET only had greater increases in insulin dose than those using SU only or MET+SU. Mean (SD) insulin dose increases were similar in males (0.27 [0.24] IU/kg) and females (0.28 [0.26] IU/kg). By concomitant OAD, insulin dose increases were highest for patients using MET only, regardless of gender, and lowest among those using SU only. Mean (SD) insulin dose requirements at Week 24 were higher among patients in the overweight (0.24 [0.22] IU/kg) and obese (0.32 [0.27] IU/kg) BMI categories compared with patients in the normal (0.16 [0.19] IU/kg) category.

Discussion

This was an analysis of pooled, standardised data from randomised, controlled treat-to-target trials with a duration of ≥24 weeks conducted in insulin-naïve adults with T2D who added Gla-100 to their current OAD therapy. The analysis used data from 16 different studies involving more than 3100 patients. The fact that Gla-100 is widely available and extensively used means that the findings of this analysis are of interest to a wide global audience. This analysis provides data on standardised clinical outcomes in patients initiating basal insulin therapy with Gla-100, taking into account the main confounders that have been present in clinical studies and presenting a more detailed picture with regard to age, gender, and BMI.

In the overall study population, certain trends were revealed: First, addition of Gla-100 to any OAD led to significant reductions in HbA1c and FPG, allowing 45.6% of patients to achieve a target HbA1c <7.0%. Second, baseline factors with a significant impact on HbA1c at endpoint were age, gender, and

baseline FPG, which had a negative association in the percentage of the specific group reaching HbA1c targets. Baseline HbA1c, diabetes duration, and treatment with SU only vs. MET only had a positive association in regards to reaching HbA1c targets. Third, although just over 40% of patients experienced some hypoglycaemia, severe hypoglycaemia occurred much less often in 1.99% of patients. Fourth, mean body weight increases with addition of Gla-100 were modest (<2 kg) in the overall cohort. Adding Gla-100 to MET only resulted in the highest percentage of patients achieving HbA1c <7.0%, mitigated weight increase, and was associated with a low incidence of hypoglycaemia.

In the summary by age, Gla-100 use in older patients with T2D resulted in clinical outcomes similar to those in younger patients, but at lower insulin doses and with less weight gain. Severe hypoglycaemia was rare in both age groups and was not increased in older patients. Patients at any age were most likely to achieve HbA1c <7.0% without hypoglycaemia when adding Gla-100 to background MET only.

The summary by gender revealed that female patients with T2D are less likely to reach glycaemic targets and have a higher risk of hypoglycaemia when adding basal insulin therapy to current OADs, particularly when adding Gla-100 to SU only or MET+SU. This finding supports previous data and suggests that women are more difficult to treat in terms of efficacy and safety compared with men, and that gender differences should be considered when tailoring treatment for individual patients [5,6]. The gender difference was consistent, possibly indicating a biological difference between males and females. Weight gain was low and similar for males and females, suggesting that weight gain is not an issue of particular concern when initiating Gla-100 in either gender. In both males and females, use of concomitant SU was associated with greater weight gain than use of concomitant MET alone.

The summary by BMI category revealed that overweight and obese patients are more likely to reach HbA1c targets with higher insulin doses and with less hypoglycaemia than normal-BMI patients. This finding is in line with previous findings that low BMI is a risk factor for hypoglycaemia [25]. Weight gain was lower in the overweight and obese BMI categories than in the normal BMI category, suggesting that weight gain is not an issue of particular concern among patients with a high BMI who are initiating insulin; weight gain is more likely to occur in patients with a normal BMI. In the subanalysis by BMI category and OAD use, patients across all BMI categories starting basal insulin on background SU had lower HbA1c reduction, were less likely to achieve HbA1c <7.0 %, and had greater rates of hypoglycaemia. Background OAD had an impact on weight gain across BMI categories and tended to be highest among patients adding insulin to SU.

What this study adds

Many patients with T2D require treatment with insulin at some point as disease progresses yet there is limited information available to assist clinicians in predicting response to basal insulin therapy. A PubMed search of "predictors of response" and "basal insulin therapy" and "gender or BMI or age or OAD" yielded only seven articles, three of which were unrelated to diabetes care. The other four studies were observational in design and did not examine the effect of background OAD therapy on insulin response [26-29] and two studies included treatment with multiple insulin types [26,28]. There is no other analysis of pooled patient-level data from clinical trials measuring response at the same time point, using the same insulin type.

Our results are broadly consistent with some, though not all, findings from other investigations. One study reported higher HbA1c among females after 1 to 4 years of insulin therapy [28] whereas in another, gender did not predict response to insulin therapy [26]. However, our analysis demonstrated that women were less likely to achieve HbA1c target and more likely to experience hypoglycaemia is

supported by the results of only two pooled analyses that examined only the effect of gender on glycaemic control and hypoglycaemia [5,6].

Consistent with our study, a survey of health care professionals (n = 1333) reported that lower BMI predicted worse glycemic control [8]. Conversely, two observational studies found that achieving glycemic goal was more likely in leaner patients [26,29] whilst another linked higher BMI to higher HbA1c [28].

Unlike our study findings, four investigations reported a significant effect of age on insulin response [8,26,28,29]. Older age was associated with achieving glycaemic target with basal insulin at 6 months [29] and at 12 months [26] whilst two studies reported an association between younger age and worse control [8,28].

Understanding hypoglycaemia

The association of hypoglycaemia with insulin use remains one of the most important issues in T2D management [30]. To enable informed decisions about therapy choices for their patients with T2D, it is important that clinicians understand how different patient factors and existing background medications affect the hypoglycaemia risk associated with the initiation of basal insulin [31].

Directions for Future Research

This analysis indicates that females compared with males patients, and those with normal BMI compared with overweight or obese individuals, were less likely to achieve HbA1c targets and more likely to develop hypoglycaemia when Gla-100 was added to background OAD therapy. Whether gender and body weight are associated with response to adding other basal insulin formulations, or other types of therapy, to background treatment including MET and/or SU is a question that needs to be addressed in future studies.

Strengths and Limitations

The number of patients included in this analysis, as well as inclusion of patients aged ≥65 years, can be considered a strength and lends validity to its conclusions. One of the other strengths of this analysis was that the definition of hypoglycaemia was defined consistently. Nonetheless, these patient data were drawn exclusively from clinical trial populations and, as such, were restricted to individuals who met the inclusion criteria for these studies. Additionally, we analysed only patients receiving concomitant MET, SU, or combined MET+SU, whereas today many patients with T2D receive treatment with other classes of oral agents or injected GLP-1 receptor agonists.

The trials included in this analysis utilised different doses of MET and SU, and different regimens of Gla-100 administration (morning or bedtime). In some studies, patients received a thiazolidinedione or other anti-diabetes medications in addition to MET and/or SU (Supplementary Table 1). Patients in the trials reflected a diversity of populations, so that patient ethnicity and local clinical practice could have influenced results. Older adult participants recruited into the trials may have fewer comorbidities than those in clinical practice, including a lower incidence of cognitive dysfunction. Comorbidities and dementia may affect rates of hypoglycaemia in older adults [32,33]. Finally, our follow-up period in this analysis was limited to 24 weeks, and so could not account for differences in glycaemic control or hypoglycaemia that occurred in longer-term use of Gla-100 and OADs.

Conclusions

Taken together, the key message from these analyses is that when tailoring therapy for individual patients with T2D, women and patients within the normal BMI range are less likely to reach glycaemic targets and have a higher risk of hypoglycaemia when adding Gla-100 to current OAD therapy. Initiation of insulin therapy and ongoing management of these patients, therefore, should be carefully monitored. Age is less likely to be important, although factors for individual patients (e.g., polypharmacy,

comorbidity, and advanced age) should be taken into account. A patient's background OAD also is relevant, as use of concomitant SU was associated with more weight gain and hypoglycaemia, regardless of patient age, gender, or BMI, than use of concomitant MET. This suggests that physicians should consider discontinuing SU therapy when initiating Gla-100 regimen.

Acknowledgements

This study was funded by Sanofi. The authors received writing/editorial support in the preparation of this manuscript provided by Katherine Roberts, PhD, and Michael van der Veer, PhD, from Excerpta Medica, funded by Sanofi.

Conflicts of interest

D.O. has received honoraria for lectures and involvement in advisory boards from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Roche Diagnostics, Sanofi, Roche.G.B. is on speakers bureau of Sanofi, Eli Lilly and Company, Novartis. B.C. has received fees for consultancy, speaking, travel or accommodation from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Lilly, Merck Sharpe & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda.T.H. has received honoraria for consultation and invited lectures from Emperra, MSD, Roche, Boehringer Ingelheim, Sanofi, AstraZeneca. W.L. is an employee and stockholder of: Sanofi US, Inc. F.P. is on advisory panel, speakers bureau of Sanofi, Eli Lilly and Company, Bristol-Myers Squibb Company, Merck & Co., Inc. L.T.is an employee Sanofi US, Inc., Stockholder in Sanofi and spouse is an employee of Bristol-Myers Squibb.A.K-W. Has received honoraria for lectures from Boehringer Ingelheim, Lilly, Novo Nordisk, Novartis, AstraZeneca, Amgen.

References

1. World Health Organization. Global report on diabetes: Executive summary. 2016. Available from URL: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf. Accessed 25 June 2016.
2. American Diabetes Association. Standards of medical care in diabetes—2017. Diabetes Care 2017; 40(Suppl 1): S4-S5.
3. Inzucchi SE, Matthews DR, Bergenstal RM et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;**35**:1364–1379.
4. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;**38**:140–149.
5. McGill JB, Vlajnic A, Knutsen PG, Recklein C, Rimler M, Fisher SJ. Effect of gender on treatment outcomes in type 2 diabetes mellitus. Diabetes Res Clin Pract 2013;**102**:167–174.
6. Kautzky-Willer A, Kosi L, Lin J, Mihaljevic R. Gender-based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomized controlled trials. Diabetes Obes Metab 2015;**17**:533–540.
7. ORIGIN Trial Investigators. Predictors of nonsevere and severe hypoglycaemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. Diabetes Care 2015;**38**:22–28.

8. Nichols GA, Hillier TA, Javor K, Brown JB. Predictors of glycemic control in insulin-using adults with type 2 diabetes. Diabetes Care 2000;**23**:273–277.
9. Aschner P, Chan J, Owens DR et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. Lancet 2012;**379**:2262–2269.
10. Meneghini LF, Traylor L, Schwartz SL. Improved glycemic control with insulin glargine versus pioglitazone as add-on therapy to sulfonylurea or metformin in patients with uncontrolled type 2 diabetes mellitus. Endocr Pract 2010;**16**:588–599.
11. Hollander P, Sugimoto D, Vlajnic A, Kilo C. Combination therapy with insulin glargine plus metformin but not insulin glargine plus sulfonylurea provides similar glycemic control to triple oral combination therapy in patients with type 2 diabetes uncontrolled with dual oral agent therapy. J Diabetes Complications 2015;**29**:1266–1271.
12. Swinnen SG, Dain MP, Aronson R et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. Diabetes Care 2010;**33**:1176–1178.
13. Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) study. Diabet Med 2006;**23**:736–742.
14. Fritsche A, Schweitzer MA, Häring HU, 4001 Study Group. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in

patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med 2003;**138**:952–959.

15. Standl E, Maxeiner S, Raptis S, Karimi-Anderesi Z, Schweitzer MA, HOE901/4009 Study Group. Good glycemic control with flexibility in timing of basal insulin supply: a 24-week comparison of insulin glargine given once daily in the morning or at bedtime in combination with morning glimepiride. Diabetes Care 2005;**28**:419–420.
16. Eliaschewitz FG, Calvo C, Valbuena H et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. Arch Med Res 2006;**37**:495–501.
17. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;**26**:3080–3086.
18. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006;29:554–559.
19. HOE901_4021 [data on file]. ClinicalTrials.gov Identifier: NCT01336751.
20. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005;**28**:254–259.
21. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008;**371**:1073–1084.

22. Yki-Järvinen H, Juurinen L, Alvarsson M et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care 2007;**30**:1364–1369.
23. Blicklé JF, Hancu N, Piletic M et al. Insulin glargine provides greater improvements in glycaemic control vs. intensifying lifestyle management for people with type 2 diabetes treated with OADs and 7-8% A1c levels. The TULIP study. Diabetes Obes Metab 2009;11:379–386.
24. Home PD, Bolli GB, Mathieu C et al. Modulation of insulin dose titration using a hypoglycaemia–sensitive algorithm: insulin glargine versus neutral protamine Hagedorn insulin in insulin–naïve people with type 2 diabetes. Diabetes Obes Metab 2015;**17**:15–22.
25. Cariou B, Fontaine P, Eschwege E et al. Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: results from the DIALOG study. Diabetes Metab 2015;**41**:116–125.
26. Owen V, Seetho I, Idris I. Predictors of responders to insulin therapy at 1 year among adults with type 2 diabetes. Diabetes Obes Metab 2010;**12**::865–870.
27. Hanefeld M, Fleischmann H, Schiffhorst G, Bramlage P. Predictors of response to early basal insulin treatment in patients with type 2 diabetes—the EARLY experience. Diabetes Technol Ther 2014;**16**:241-246.
28. Balkou B, Calvi-Gries F, Freemantle N, et al. Predictors of HbA1c over 4 years in people with type 2 diabetes starting insulin therapies: the CREDIT study. Diabetes Res Clin Pract 2015;**108**:432-440.
29. Monami M, Ragghianti B, Zannoni S, et al. Identification of predictors of response to basal insulin and DPP4 inhibitors in patients with type 2 diabetes failing to other therapies. Acta Diabetol 2016;**53**:35-40.

30. DeVries H, Meneghini L, Barnett AH et al. A Patient-level Analysis of Efficacy and Hypoglycaemia Outcomes Across Treat-to-target Trials with Insulin Glargine Added to Oral Antidiabetes Agents in People with Type 2 Diabetes. Europ Endocrin, 2014;10(1):23–30.
31. Shafiee G, Mohajeri-Tehrani M, Pajouhi M et al. The importance of hypoglycemia in diabetic patients. Journal of Diabetes & Metab Dis 201211:17.
32. Prinz N, Stingl J, Dapp A, et al. High rate of hypoglycemia in 6770 type 2 diabetes patients with comorbid dementia: A multicentre cohort study on 215,932 patients from the German/Austrian diabetes registry. Diabetes Res Clin Pract 2016;**112**:73-81.
33. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med. 1997;**157**:1681-1686.

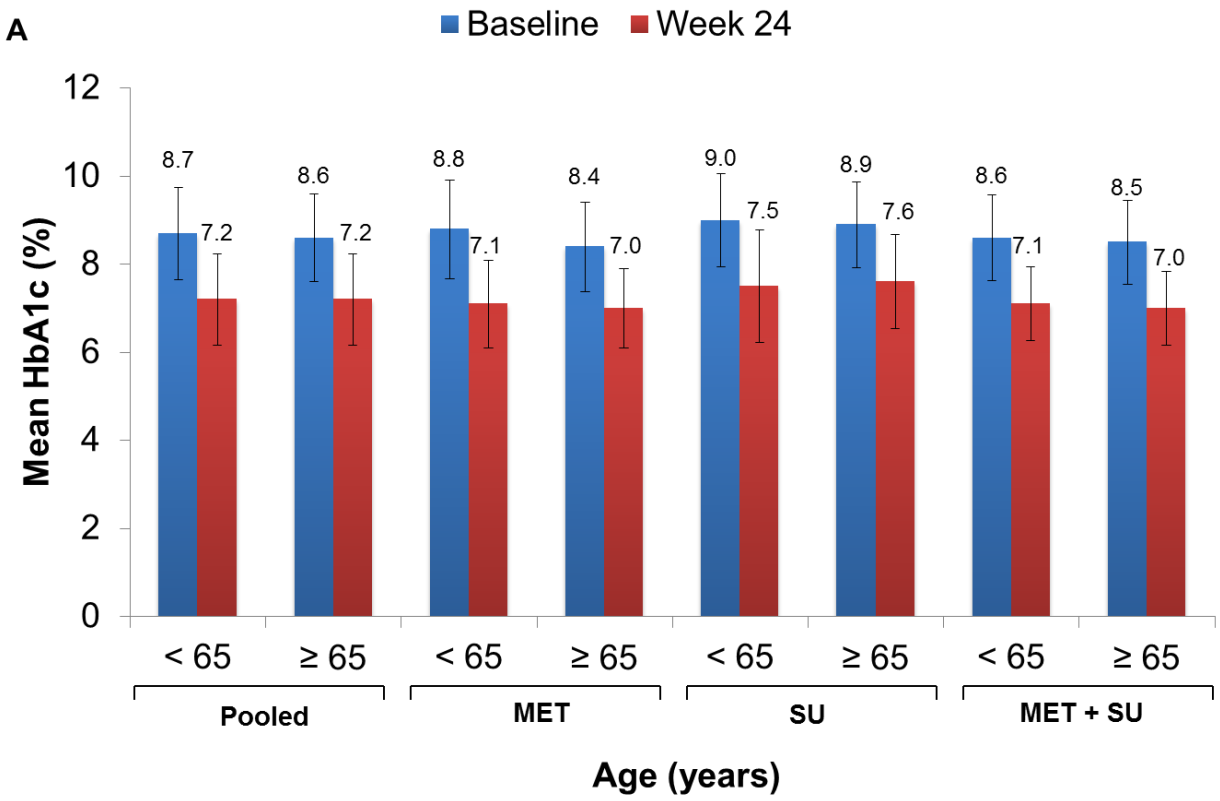
Supplementary Table 1. Summary of included studies.

Supplementary Table 2. Baseline patient demographic and clinical characteristics of patients in the subanalyses.

Supplementary Table 3. Percentage of patients achieving target HbA1c at 24 weeks.

Supplementary Table 4. Mean weight gain at 24 weeks.

Figure 1. Baseline and week 24 HbA1c **(A)** and FPG **(B)** levels, stratified by age. Data represent mean (standard deviation) and includes all patients with baseline and Week 24 data available. FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; MET, metformin; SU, sulfonylurea.



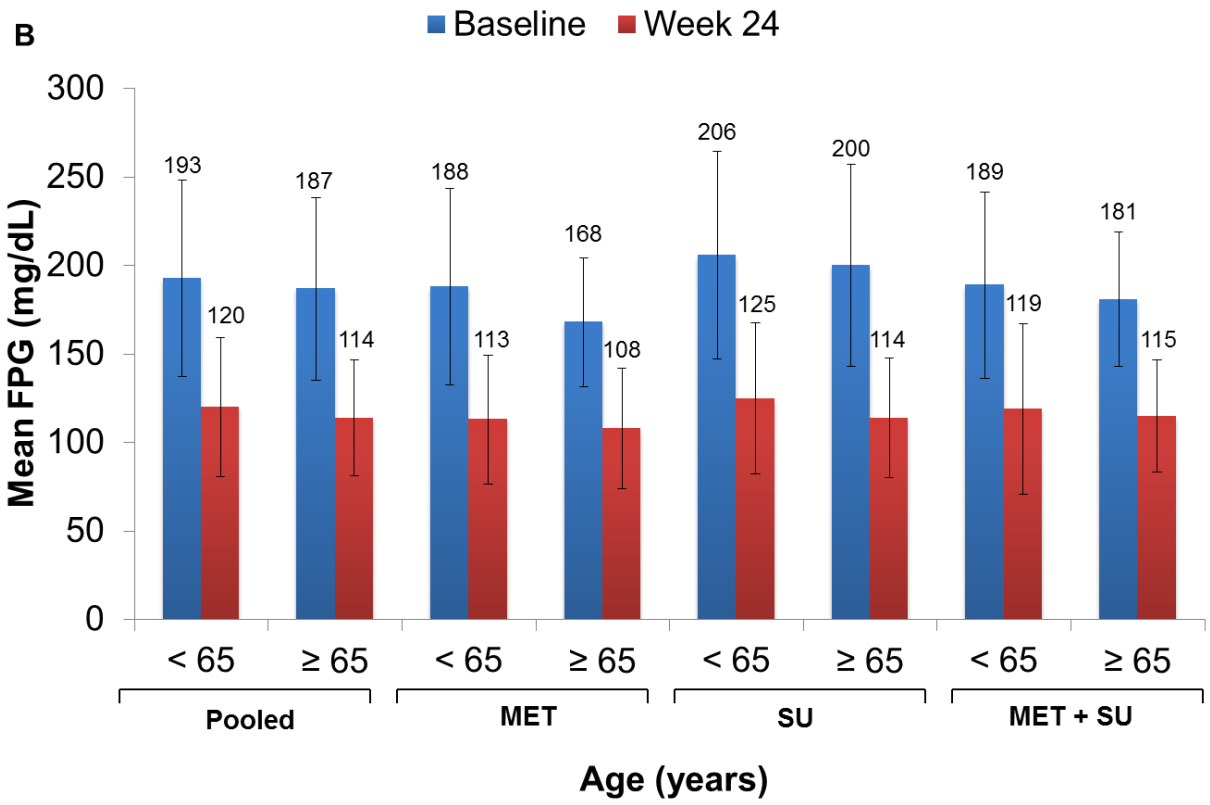
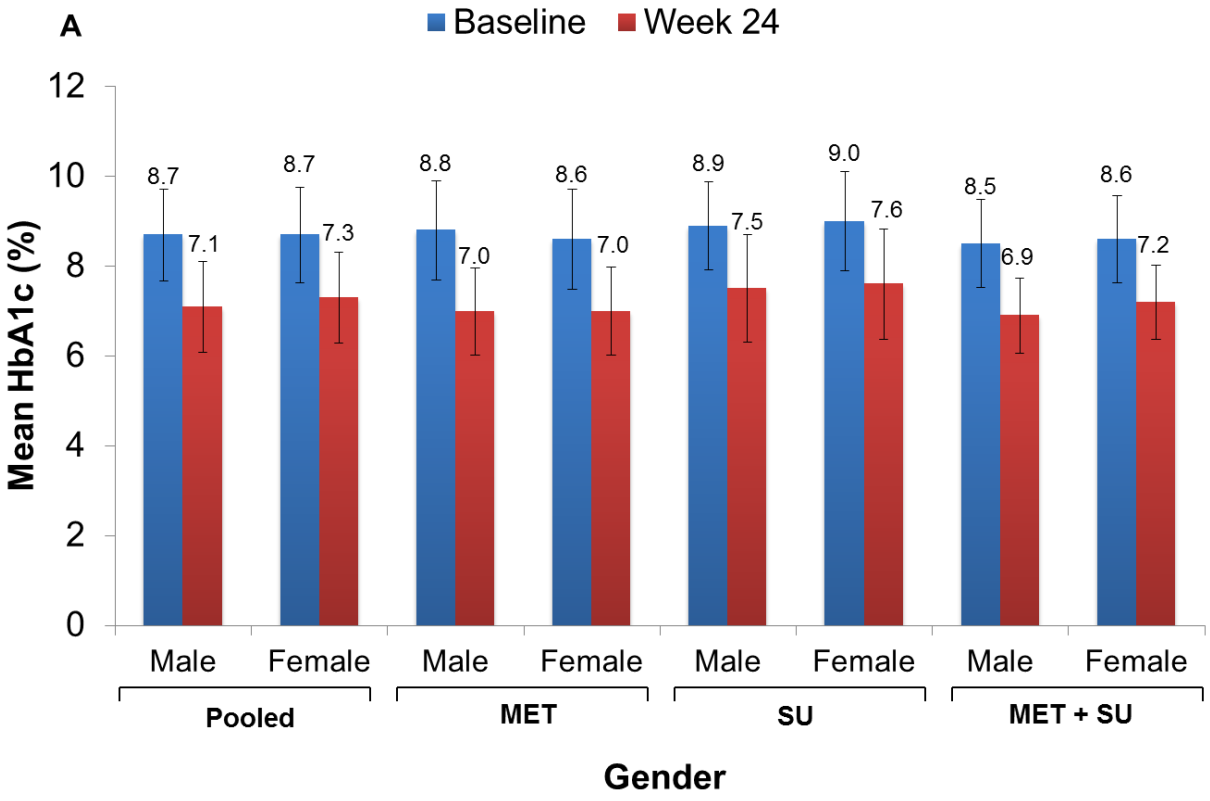

B
Baseline
Week 24
Mean FPG (mg/dL)
300
250
200
150
100
50
0
193
120
187
114
188
113
168
108
206
125
200
114
189
119
181
115
< 65
≥ 65
< 65
≥ 65
< 65
≥ 65
< 65
≥ 65
Pooled
MET
SU
MET + SU
Age (years)

Figure 2. Baseline and week 24 HbA1c **(A)** and FPG **(B)** levels, stratified by gender. Data represent mean (standard deviation) and includes all patients with baseline and Week 24 data available. FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; MET, metformin; SU, sulfonylurea.



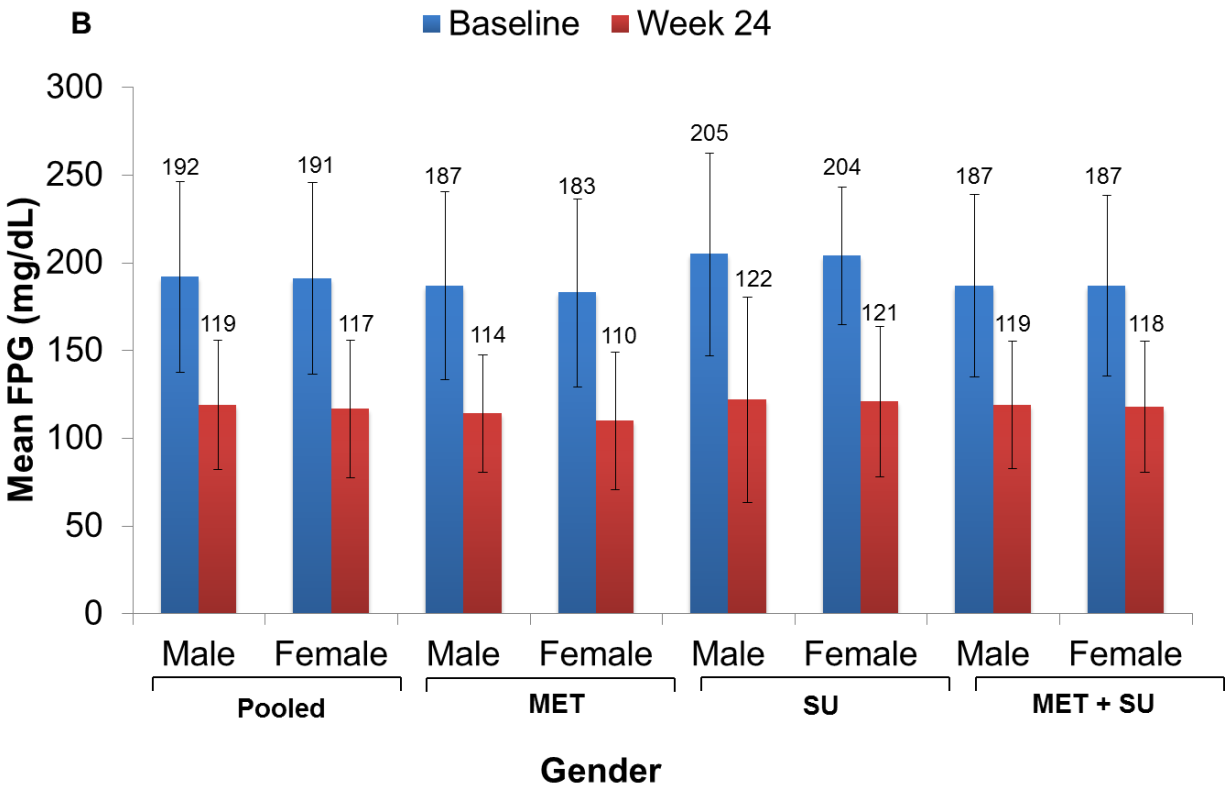

B
Baseline
Week 24
Mean FPG (mg/dL)
300
250
200
150
100
50
0
192
119
191
117
187
114
183
110
205
122
204
121
187
119
187
118
Male
Female
Male
Female
Male
Female
Male
Female
Pooled
MET
SU
MET + SU
Gender

Figure 3. Incidence **(A)** and event rates **(B)** of overall (PG <70 mg/dl), nocturnal (PG <70 mg/dl), and severe hypoglycaemia, stratified by age. Error bars represent standard error. PG, plasma glucose.

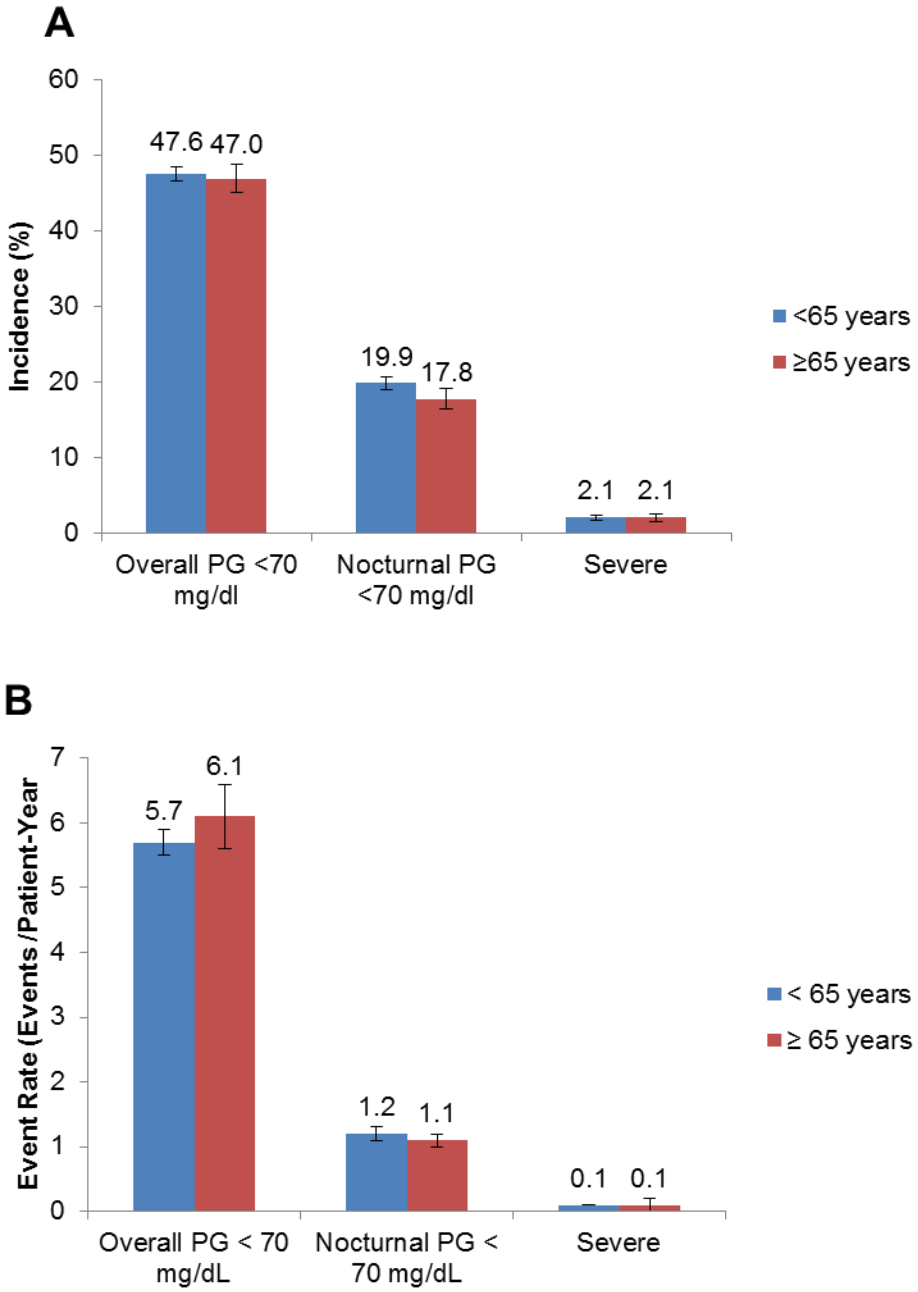
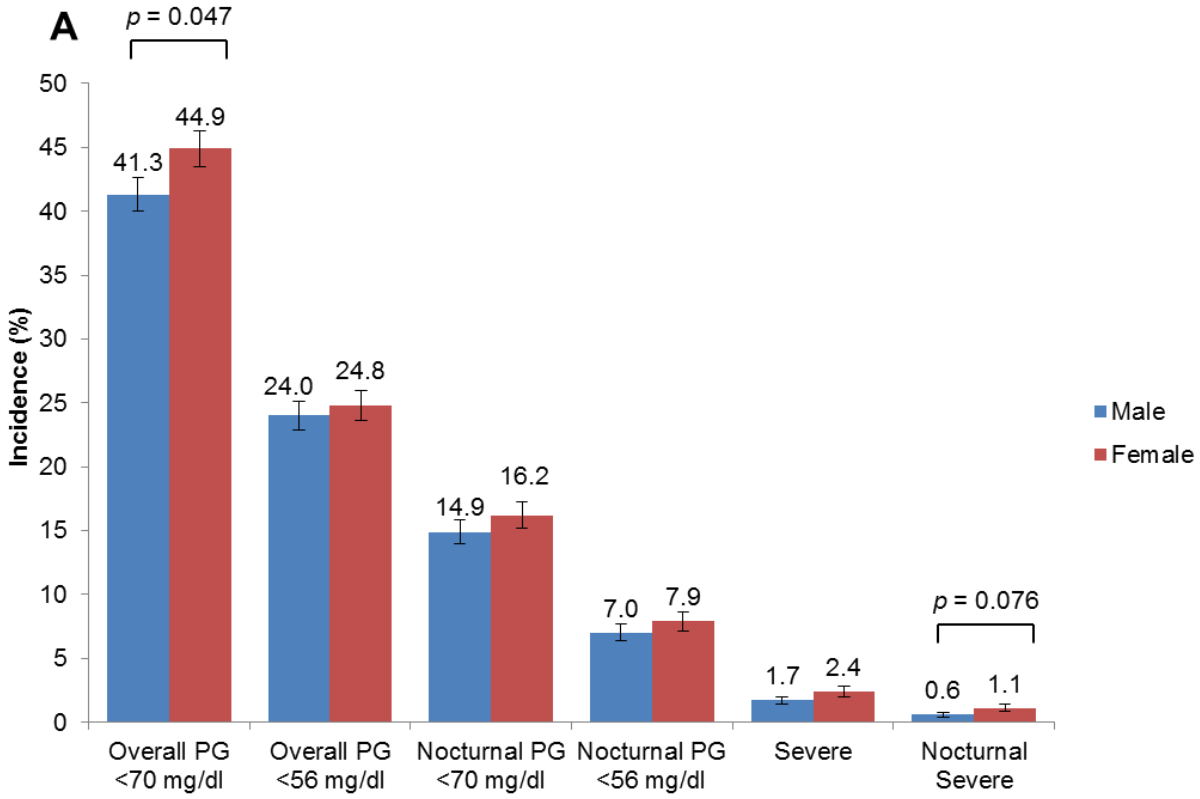


Figure 4. Incidence **(A)** and event rates **(B)** of overall, nocturnal and severe hypoglycaemia, stratified by gender. PG, plasma glucose.



B

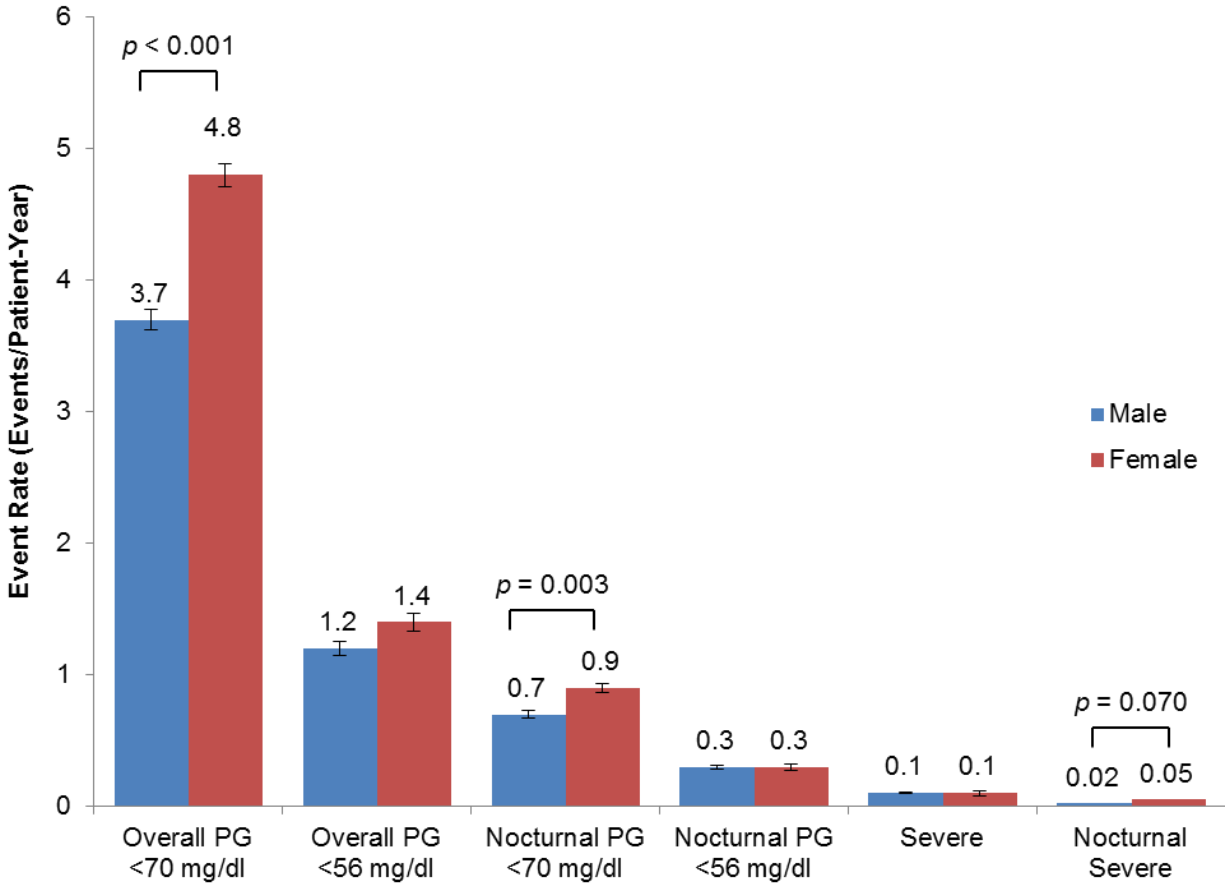
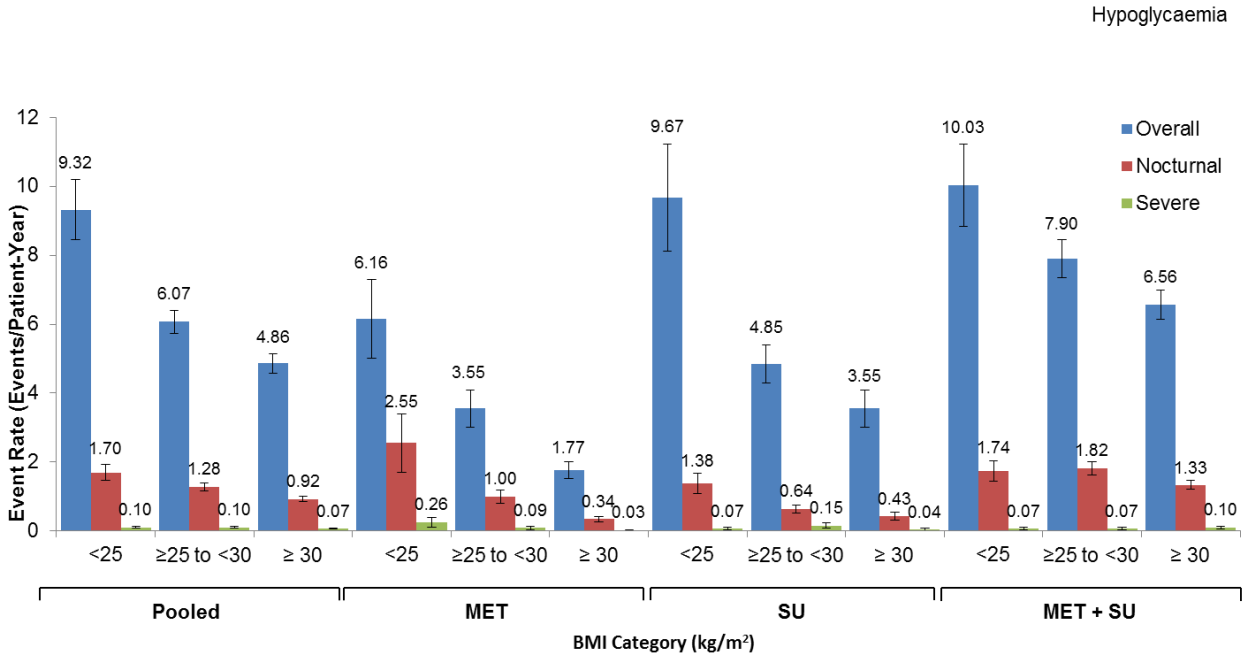

Event Rate (Events/Patient-Year)
6
5
4
3
2
1
0
p < 0.001
4.8
3.7
1.2
1.4
p = 0.003
0.7
0.9
0.3
0.3
0.1
0.1
p = 0.070
0.02
0.05
Male
Female
Overall PG <70 mg/dl
Overall PG <56 mg/dl
Nocturnal PG <70 mg/dl
Nocturnal PG <56 mg/dl
Severe
Nocturnal Severe

Figure 5. Hypoglycaemia event rates (overall and nocturnal with PG <70 mg/dl), by BMI category and OAD use. BMI, body mass index; MET, metformin; OAD, oral antidiabetes drug; SU, sulfonylurea.



Suppl Figure. Percentage of patients achieving HbA1c <7.0% at week 24, by BMI category and OAD use. BMI, body mass index; HbA1c, glycated haemoglobin; MET, metformin; OAD, oral antidiabetes drug; SU, sulfonylurea.