

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

A. Kautzky-Willer¹, L. Kosi¹, J. Lin² & R. Mihaljevic³

¹Division of Endocrinology and Metabolism, Gender Medicine Unit, Medical University of Vienna, Vienna, Austria

²Novosys Health, Flemington, NJ, USA

³Scientific Affairs, Diabetes, Sanofi, Vienna, Austria

Aims: To determine the impact of gender on glycaemic control and hypoglycaemia in insulin-naïve patients with type 2 diabetes (T2DM).

Methods: Data were pooled from six randomized clinical trials of insulin glargine or NPH insulin in insulin-naïve, inadequately controlled patients. Female [$n = 1251$; mean glycated haemoglobin (HbA1c) level 8.99%, age 56.91 years, diabetes duration 9.84 years] and male patients ($n = 1349$; mean HbA1c 8.9%, age 57.47 years, diabetes duration 10.13 years) were started on and treated with insulin glargine or NPH insulin for 24–36 weeks. HbA1c and fasting blood glucose levels, percent achieving HbA1c target of <7% and insulin dose change were recorded.

Results: For both men and women, HbA1c levels were significantly reduced over time ($p < 0.001$); a significantly greater HbA1c reduction was observed in men than in women (-1.36 vs. -1.22 ; $p = 0.002$). Significantly fewer women achieved target HbA1c of <7% ($p < 0.001$). At the study end, women had a significantly higher insulin dose/kg than men (0.47 vs. 0.42 U/kg; $p < 0.001$). The incidence rates of severe and severe nocturnal hypoglycaemia were significantly higher in women (3.28% vs. 1.85%; $p < 0.05$ and 2.24% vs. 0.59%; $p < 0.001$, respectively). Women were more likely to experience severe hypoglycaemia [odds ratio (OR) 1.80; 95% confidence interval (CI) 1.08, 3.00; $p = 0.02$] and severe nocturnal hypoglycaemia (OR: 3.80; 95% CI 1.72, 8.42; $p = 0.001$).

Conclusions: These observations confirm studies that found a smaller improvement in HbA1c and greater hypoglycaemia in women during insulin treatment. Physicians should be aware of the need to determine and closely monitor dosing, particularly in women, to optimize the balance between glycaemic control and hypoglycaemia risk.

Keywords: gender, hypoglycaemia, insulin glargine, NPH insulin, type 2 diabetes

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Introduction

Marked gender differences in glucose control have been observed in several studies, and these differences may influence treatment in women with type 2 diabetes (T2DM). When compared with men, women with normal glucose tolerance have been found to be more insulin-sensitive and have better β -cell function; however, greater postmenopausal metabolic deterioration has been observed [1,2]. Gender-related differences have been measured using oral glucose tolerance testing, showing that in prediabetic states, women have higher rates of impaired glucose tolerance, whereas the rates of impaired fasting glucose are higher in men [3,4]. The causes of these differences in glucose control are not clearly understood, although gender-related differences in body fat distribution

and hormones, as well as slower glucose absorption in women, may contribute to the observed gender dimorphism [5,6].

Although gender is not a direct risk factor for developing T2DM, gender differences in glucose regulation and hypoglycaemia incidence have been observed. One *post hoc* analysis of six pooled clinical trials observed a gender difference in postprandial glucose (PPG) levels in patients with T2DM treated with insulin [7]. In the analysis, women had lower PPG levels than men after both lunch and dinner, and further weight gain was also significantly greater in women in this study. The risk of developing hypoglycaemia also seems to be greater in insulin-treated women with T2DM [8], although this has not always been observed [7]. Studies indicate that hypoglycaemia may be related to increased mortality in those who cannot reach their metabolic goals; furthermore, hypoglycaemia is associated with reduced quality of life and productivity, increased patient anxiety and higher healthcare costs [9]. As a result, the detection of gender-based differences in glycaemic control and hypoglycaemic events is an important consideration when selecting an appropriate management plan for T2DM.

The present analysis examines pooled, patient-level data from six multisite, randomized clinical trials with similar

Correspondence to: Prof. Alexandra Kautzky-Willer, Division of Endocrinology and Metabolism, Gender Medicine Unit, Medical University of Vienna, Spitalgasse 23, Vienna A-1090, Austria.
E-mail: Alexandra.kautzky-willer@meduniwien.ac.at

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Table 1. Pooled clinical trials: study characteristics.

Study (treatment duration)	Treatment arms	Treatments	Primary analysis
Fritsche et al. [11] 24 weeks 4001 Study	NPH (n = 232) Glargine, AM (n = 236) Glargine, PM (n = 227)	<u>Pre-study:</u> OADs only <u>Study:</u> 3 mg glimepiride once daily for 4 weeks, then added Glargine or NPH, once daily	Δ in HbA1c from baseline to study end Frequency of patients experiencing hypoglycaemic episodes
Pan et al. [12] 24 weeks LEAD/4012 Study	NPH (n = 223) Glargine (n = 220)	<u>Pre-study:</u> OADs only <u>Study:</u> 3 mg glimepiride once daily for 4 weeks, then added Glargine or NPH, once daily	Demonstrate non-inferiority of baseline to study end Δ in HbA1c between glargine and NPH
Kawamori et al. [15] 28 weeks 3102 Study	NPH (n = 168) Glargine (n = 167)	<u>Pre-study:</u> Sulphonylurea + α -glucosidase inhibitor and/or biguanide <u>Study:</u> Glargine or NPH, once daily, added to previous treatment	Δ in HbA1c from start of treatment to completion of treatment
Riddle et al. [13] 24 weeks Treat-to-target/4002 Study	NPH (n = 389) Glargine (n = 367)	<u>Pre-study:</u> OADs only <u>Study:</u> Glargine or NPH, once daily, added to previous OAD regimen	Percentage of subjects achieving HbA1c $\leq 7\%$ without an instance of symptomatic nocturnal hypoglycaemia and/or severe hypoglycaemia
Eliaschewitz et al. [10] 24 weeks HOE901/4013 LA Study	NPH (n = 250) Glargine (n = 231)	<u>Pre-study:</u> OADs only <u>Study:</u> 4 mg glimepiride for 4 weeks, then added Glargine or NPH, once daily	Δ in HbA1c from baseline to the end of the study
Yki-Jarvinen et al. [14] 36 weeks LANMET/6001 Study	NPH (n = 49) Glargine (n = 61)	<u>Pre-study:</u> Sulphonylurea + metformin or metformin alone <u>Study:</u> Glargine or NPH, once daily, added to current metformin dosage (sulphonylurea discontinued where used)	Δ in HbA1c from baseline to study end

OAD, oral antidiabetic drug.

research methodologies. The aim of the data analysis was to determine the impact of gender on glycaemic control and the incidence of hypoglycaemia in patients with T2DM treated with insulin.

Materials and Methods

Study Population and Patient Selection

Patients with T2DM from intent-to-treat populations were pooled from six multinational, multicentre, randomized, open-label clinical trials with similar study designs and research methodologies, where individual patient-level data were available [10–15]. The trials compared the efficacy and safety of insulin glargine with NPH insulin in previously insulin-naïve patients, and the study characteristics are contained in Table 1 [10–15].

Patients with T2DM were enrolled in their respective study if they were inadequately controlled on one or two oral antidiabetic drugs (OADs; sulphonylureas, metformin, pioglitazone or rosiglitazone) for ≥ 6 months and were insulin-naïve. Patients included within the pooled analysis were aged 20–80 years, and had a body mass index (BMI) of 20–40 kg/m² and glycated haemoglobin (HbA1c) levels of 7.5–12%. Patients were excluded if they were nightshift workers, pregnant or breast feeding, had a history of ketoacidosis or alcohol or drug abuse, were treated with insulin or any investigational drugs within the previous 3 months or had any clinically

relevant somatic or mental disease. All trials were conducted in accordance with the Declaration of Helsinki and approved by the Independent Ethics Committee or Institutional Review Board of each centre or site. Before participating in any study-related procedure, all patients provided written informed consent.

Study Designs

Across all six studies, the primary goal was to assess the efficacy and safety of insulin glargine compared with NPH insulin in patients with T2DM. Patients were started on either insulin glargine or NPH insulin and treated daily for 24–36 weeks, depending on the study. In addition, patients either continued to adhere to their previous OAD therapy, or 3–4 mg of glimepiride was substituted for the previous OAD. No additional diabetes treatments (e.g. rapid-acting insulins) were permitted. Across the studies, there was some variation in the insulin starting dose and dose titration method used. Three of the studies calculated the initial insulin dose as a function of each patient's fasting blood glucose (FBG) level; however, in the other three, patients were started on the same preset dose. Across all studies, dose was titrated to achieve a target FBG level, which ranged from 4.4 to ≤ 5.5 mmol/l. In three studies, a predefined regimen was used to titrate dose. In the remaining studies, titration was at the discretion of the investigator, or a function of the patient's condition or laboratory/metre measurements.

Efficacy

In five of the studies, the primary efficacy outcome was change in HbA1c level from baseline to study end. In the sixth study, the primary outcome was the percentage of patients achieving HbA1c $\leq 7.0\%$ without an instance of symptomatic nocturnal and/or severe hypoglycaemia. Secondary efficacy outcomes included HbA1c and FBG levels, percent achieving an HbA1c efficacy target of $<7\%$ and change in insulin dose.

Hypoglycaemia

Hypoglycaemia was defined as symptomatic or asymptomatic and confirmed with blood or plasma glucose levels that ranged from <4.2 to <4.0 mmol/l, depending upon the trial. Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia that required the assistance of another person, or was followed by prompt recovery after oral carbohydrate, intravenous glucose or glucagons and confirmed with blood or plasma levels that ranged from <3.1 to <2.8 mmol/l, depending on the trial. Nocturnal hypoglycaemia was defined as hypoglycaemia that occurred while the patient was asleep, after an evening insulin injection and before rising in the morning. Additional adverse events were also recorded within all pooled studies.

Statistical Analyses

All outcome measures were analysed according to gender, and then further by BMI group (determined as the median population BMI of 28 kg/m^2). Descriptive univariate statistics were used to measure and describe safety and efficacy outcomes. Student's *t*-tests and chi-squared tests were used to compare continuous and categorical variables, respectively. Additionally a meta-analytical approach with a random-effects model was used to analyse the summary endpoint measurements, including HbA1c change and likelihoods of severe hypoglycaemia and severe nocturnal hypoglycaemia. Furthermore, multivariable generalized linear regressions were used to evaluate the impact of gender on HbA1c change from baseline to study end and likelihoods of severe hypoglycaemia and severe nocturnal hypoglycaemia after controlling for key covariates that may potentially influence the outcomes. Such covariates included insulin type, age, baseline BMI, duration of diabetes, baseline HbA1c, baseline insulin dose and metformin and sulphonylurea usage. Meta-analytical analyses were carried out in Review Manager (RevMAN version 5.1, Copenhagen: Cochrane Collaboration). Other statistical analyses were carried out in SAS 9.3. A *p* value of 0.05 was taken to indicate statistical significance.

Results

Baseline Characteristics

A total of 2600 patients comprised the pooled study population (women, $n = 1251$; men, $n = 1349$) (Table 2). A comparison of baseline demographics showed no significant effect of gender for the characteristics of age, disease duration, glargine/NPH use, insulin dose, HbA1c levels or FBG levels, but there were

Table 2. Baseline characteristics.

	Women (n = 1251)	Men (n = 1349)	<i>p</i> *
Age, years	56.909 (9.390)	57.469 (8.988)	0.120
Age groups, n (%)			
<35 years	16 (1.3)	17 (1.3)	—
35 to <45 years	112 (9.0)	89 (6.6)	
45 to <55 years	396 (31.7)	420 (31.1)	
55 to <65 years	457 (36.5)	517 (38.3)	
65 to <75 years	248 (19.8)	294 (21.8)	
≥ 75 years	22 (1.8)	12 (0.9)	
Weight, kg	72.550 (17.182)	84.474 (19.328)	<0.001
BMI, kg/m^2	28.663 (5.342)	28.047 (4.876)	0.002
T2DM duration, years	9.837 (6.163)	10.128 (6.245)	0.233
HbA1c, %			
Overall	8.993 (1.005)	8.919 (0.975)	0.054
BMI $\leq 28 \text{ kg/m}^2$	9.100 (1.011)	8.986 (0.953)	0.033
BMI $> 28 \text{ kg/m}^2$	8.890 (0.989)	8.837 (0.995)	0.344
FBG, mmol/L			
Overall	11.275 (3.115)	11.026 (2.978)	0.062
BMI $\leq 28 \text{ kg/m}^2$	11.610 (3.219)	11.226 (3.035)	0.024
BMI $> 28 \text{ kg/m}^2$	10.902 (2.973)	10.786 (2.892)	0.484
Insulin dose, U			
Overall	13.841 (8.141)	13.557 (8.140)	0.375
BMI $\leq 28 \text{ kg/m}^2$	12.792 (6.346)	12.394 (6.514)	0.258
BMI $> 28 \text{ kg/m}^2$	14.855 (9.458)	14.962 (9.568)	0.843
Insulin dose, U/kg			
Overall	0.199 (0.117)	0.166 (0.098)	<0.001
BMI $\leq 28 \text{ kg/m}^2$	0.216 (0.107)	0.175 (0.091)	<0.001
BMI $> 28 \text{ kg/m}^2$	0.182 (0.124)	0.154 (0.104)	<0.001

All values are mean \pm standard deviation, unless otherwise specified. BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; T2DM, type 2 diabetes.

*Comparison between genders.

significant gender effects for body weight, BMI and insulin dose/kg – characteristics associated with body composition. Although there was no impact of gender on the overall baseline HbA1c and FBG levels, the baseline levels for these measures of glycaemic control were both found to be significantly higher in women within the BMI $\leq 28 \text{ kg/m}^2$ cohort. Although the women weighed significantly less than the men, BMI and insulin dose/kg at baseline were significantly higher. A comparison of sulphonylurea treatment before insulin initiation across gender showed no significant difference (women, 23.2%; men, 24.3%; $p = 0.50$).

Efficacy

Insulin treatment significantly reduced HbA1c levels from baseline in male and female patients (both $p < 0.001$ vs. baseline); however, the overall comparison between genders showed that HbA1c levels at the end of the study were significantly lower in men ($p < 0.001$; Table 3). The significant differences between gender were also observed across both BMI cohorts (BMI $\leq 28 \text{ kg/m}^2$, $p < 0.001$; BMI $> 28 \text{ kg/m}^2$; $p = 0.002$). Furthermore, significantly more men achieved the target HbA1c level of $<7\%$ (33% of men vs. 26.5% of women; $p < 0.001$) and this effect of gender was also observed in both BMI cohorts (BMI $\leq 28 \text{ kg/m}^2$, $p = 0.002$; BMI $> 28 \text{ kg/m}^2$, $p = 0.007$;

Table 3. Measurements at end of study.

Measure at study end	Women (n = 1251)	Men (n = 1349)	p*
HbA1c, %			
Overall	7.775 (1.230)	7.558 (1.175)	<0.001
BMI ≤28 kg/m ²	8.000 (1.246)	7.722 (1.170)	<0.001
BMI >28 kg/m ²	7.558 (1.176)	7.359 (1.151)	0.002
% patients with HbA1c <7%			
Overall	26.54	32.99	0.001
BMI ≤28 kg/m ²	19.02	26.15	0.002
BMI >28 kg/m ²	33.81	41.24	0.007
FBG, mmol/L			
Overall	6.886 (1.914)	7.087 (1.964)	0.009
BMI ≤28 kg/m ²	6.877 (2.080)	7.066 (1.994)	0.091
BMI >28 kg/m ²	6.895 (1.739)	7.112 (1.927)	0.038
Weight change, kg			
Overall	+2.933 (3.241)	+3.154 (3.497)	0.098
BMI ≤28 kg/m ²	+2.824 (2.929)	+2.954 (2.892)	0.418
BMI >28 kg/m ²	+3.038 (3.515)	+3.397 (4.103)	0.099
Insulin dose, U			
Overall	34.333 (22.435)	36.813 (27.441)	0.012
BMI ≤28 kg/m ²	26.021 (17.558)	25.245 (17.435)	0.417
BMI >28 kg/m ²	42.371 (23.688)	50.786 (30.649)	<0.001
Insulin dose, U/kg			
Overall	0.466 (0.272)	0.418 (0.268)	0.001
BMI ≤28 kg/m ²	0.434 (0.277)	0.347 (0.225)	<0.001
BMI >28 kg/m ²	0.498 (0.263)	0.503 (0.289)	0.715

All values are mean ± standard deviation, unless otherwise specified. BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated haemoglobin. *Comparison between genders.

Table 3). Weight change from baseline to study end did not differ between men and women, either overall or among the BMI groups. Insulin treatment was also associated with a reduction in FBG levels from baseline in both men and women. In contrast to the HbA1c observations, however, reduction in FBG levels at endpoint was significantly greater in women (p = 0.009; Table 3). Comparisons of the impact of gender within the BMI cohorts found a significant effect only in the higher BMI cohort (p = 0.04).

Change from baseline HbA1c and FBG were calculated and analysed overall and within each BMI cohort (Figures 1, 2). Consistent with men having significantly lower HbA1c levels at the end of the study, the change in HbA1c from baseline was found to be significantly greater in men overall (p = 0.002), as well as in both BMI cohorts (BMI ≤28 kg/m², p < 0.01; BMI >28 kg/m², p = 0.03; Figure 1). Consistent with women having significantly lower FBG levels at study end, change in FBG from baseline was also significantly greater in women overall (p < 0.001) as well as in both BMI cohorts (BMI ≤28 kg/m², p = 0.001; BMI >28 kg/m², p = 0.048; Figure 2).

Insulin Dose and Insulin Dose/kg

Insulin dose significantly increased from baseline in both women and men. At the end of the study, an overall comparison across gender showed that the mean daily insulin dose was significantly higher in men (p = 0.012). This difference was driven predominantly by men in the BMI >28 kg/m²

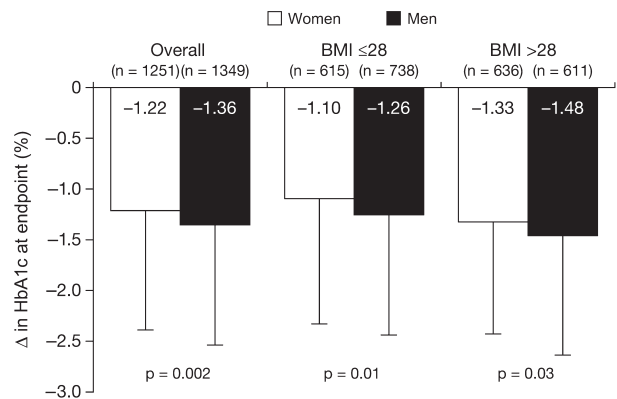


Figure 1. Change in glycated haemoglobin (HbA1c) by gender and body mass index (BMI) strata.

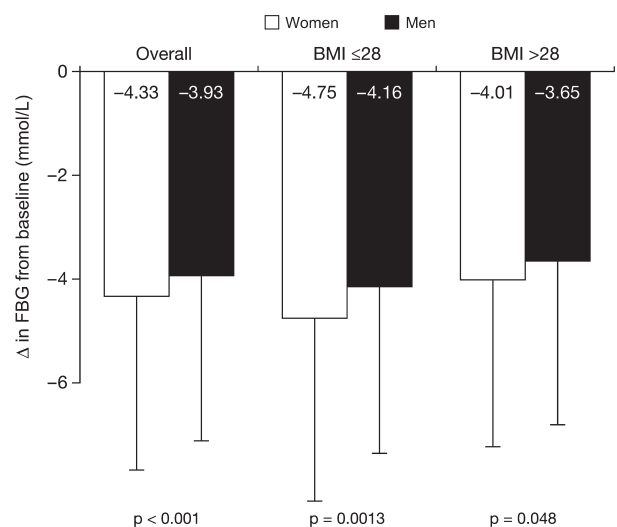


Figure 2. Change in fasting blood glucose (FBG) by gender and body mass index (BMI) strata.

cohort, as there was no difference between genders in the BMI ≤28 kg/m² cohort (Table 3). By contrast, insulin dose/kg was significantly higher in women overall (p < 0.001; Figure 3), primarily because of significantly higher values in the BMI ≤28 kg/m² cohort (p < 0.001; Table 3). Insulin dose/kg was also significantly higher in women at baseline (p < 0.001; Figure 3).

Hypoglycaemia

The comparison of the percentage of patients experiencing a hypoglycaemic episode showed that a significantly higher proportion of women overall (p = 0.02) experienced a hypoglycaemic episode; this was also observed for women in the BMI ≤28 kg/m² cohort (p = 0.02; Figure 4). Although a greater percentage of women in the BMI >28 kg/m² cohort experienced episodes of hypoglycaemia, the difference was not significant (p = 0.4). Similarly, a significantly higher percentage of women overall experienced episodes of nocturnal hypoglycaemia (p < 0.001), and this was also observed in the BMI

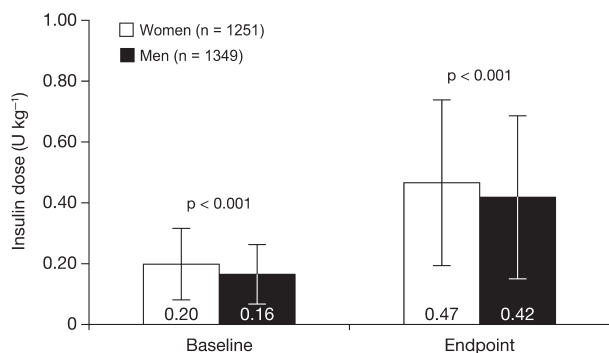


Figure 3. Baseline and study end insulin dose/kg by gender.

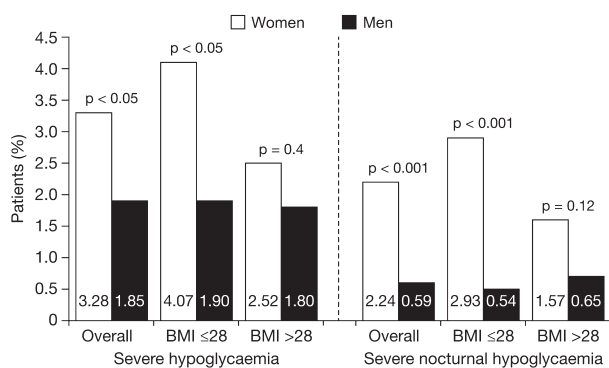


Figure 4. Incidence of severe hypoglycaemia and nocturnal hypoglycaemia by gender and body mass index (BMI).

≤28 kg/m² cohort (p < 0.001; Figure 4), but not in the BMI >28 kg/m² cohort (p = 0.12).

Meta-analytical Results

When the data were analysed using a meta-analytical approach, the Mantel-Haenszel Q statistic showed that there was no significant heterogeneity among the trials for HbA1c change (p = 0.81), severe hypoglycaemia (p = 0.87) or severe nocturnal hypoglycaemia (p = 0.56). Based on the results of the meta-analytical data analysis with a random-effects model, female gender versus male gender was associated with a smaller change in HbA1c [mean difference: 0.11%; 95% confidence interval (CI) 0.03, 0.20; p = 0.01] and a greater likelihood of having had severe nocturnal hypoglycaemia during trial periods [odds ratio (OR) 2.63; 95% CI 1.18, 5.85; p = 0.02]. There was a non-significant trend for women in comparison to men having had severe hypoglycaemia during trial periods (OR 1.54; CI 0.92, 2.57; p = 0.10).

Multivariable Regression Results

After controlling for key patient characteristics, including insulin type, age, baseline BMI, duration of diabetes, baseline HbA1c, baseline insulin dose and metformin and sulphonylurea usage, the results of the multivariable regression analyses showed that the mean change in HbA1c was lower for women than for men (difference: 0.20%; 95% CI 0.11, 0.28; p < 0.0001).

Women were also more likely than men to have had severe hypoglycaemia (OR 1.80; 95% CI 1.08, 3.00; p = 0.02) and severe nocturnal hypoglycaemia (OR 3.80, 95% CI 1.72, 8.42; p = 0.001) during the trial periods.

Discussion

The results from this patient-level pooled analysis showed a significant effect of gender on glycaemic control and safety, in addition to insulin dose. Previous research has established that women are more inclined to experience hypoglycaemia during insulin treatment [8,16]; but the impact of gender on glycaemic control, specifically HbA1c level, is less clear. In clinical trials, women with T2DM have significantly higher HbA1c levels and significantly fewer women than men achieve target HbA1c levels of <7 and <8% [17], but this finding was not observed in other research [18]. The results from the present study confirm the previous finding that women are at a higher risk of hypoglycaemia, but also that a gender-related distinction in efficacy/treatment response is observed.

Using three different approaches to data analysis, a univariate descriptive analysis, a meta-analytical approach and a multivariable generalized linear regression analysis, we found the results to be generally consistent with each other in terms of the direction of the findings. We note that the different approaches to estimating the overall gender difference have resulted in slightly different estimates. More sophisticated analyses might reconcile these small differences, but we believe the results are consistent and give strong confirmation that there is a statistically significant gender difference in reduction in HbA1c and severe nocturnal hypoglycaemia. The univariate analysis results were intended to be hypothesis-generating, and need to be further validated in future clinical studies.

Efficacy in the present study was determined by analysing the treatment responses, HbA1c and FBG, and for both; baseline comparisons showed no effect of gender, except in the lighter BMI cohort, where these levels were significantly higher in women. After insulin treatment, the resulting gender-related distinction was characterized by a significantly lower reduction in HbA1c from baseline in women; this same group, however, experienced a significantly greater reduction in FBG levels. This is one of the first studies to observe a treatment response difference between HbA1c and FBG levels in women with T2DM. A pooled analysis of a differing set of nine randomized controlled studies (females, n = 1287; males, n = 1651) examined treatment outcomes with insulin glargine and numerous different diabetes interventions [19]. The present study reinforces the findings, as women were less likely to achieve glycaemic targets with insulin glargine and exhibited significantly greater reductions in FBG level, higher insulin doses and higher rates of hypoglycaemia [19].

A significant difference between men and women in terms of HbA1c activity and target HbA1c achievement was observed, and this difference was maintained regardless of BMI strata. Interestingly, women experienced a greater and significant reduction in FBG level, despite having significantly higher HbA1c levels at baseline; this significance was apparent only

in the higher BMI cohort. Statistical analysis of change in FBG from baseline showed a significant gender effect, which was maintained regardless of BMI group.

These results may point to the observation that in women PPG levels may exert a greater impact on metabolic control and cardiometabolic risk overall than in men, as indicated by previous research [20]. When treatment is intensified with basal insulin, basal hyperglycaemia still accounts for at least one third of hyperglycaemic exposure, and therefore, tight glycaemic control requires targeting both basal and PPG levels [21].

Glucose levels and kinetics—and thus, glucose control—depend on many variables, such as insulin sensitivity, insulin secretion, hepatic glucose production, gut glucose absorption and release of glucagon and incretins. In fact, many of these factors are inter-related [22]. Some of these variables were also shown to differ between men and women; the associations of insulin sensitivity and secretion with age and body weight within wide ranges also differ between genders [2]. As we could not measure these variables in this study, however, we can only speculate on the underlying mechanisms.

In subjects with normal glucose metabolism, women usually have higher insulin sensitivity, lower fasting glucose values and higher stimulated glucose concentrations at least 2 h after oral glucose loading during an oral glucose tolerance test; therefore, women more often have isolated impaired glucose tolerance, while men more often have isolated impaired fasting glucose [3]. Differences in gut glucose absorption, with prolonged gut absorption in women, may be attributed to different anthropometry and may contribute to more pronounced late postprandial hyperglycaemia in women [23].

In populations without diabetes, women also have lower HbA1c values in relation to fasting glucose values; however, when fasting glucose values exceed normal values, the HbA1c/gender differences become smaller or disappear [24]. Moreover, gender differences were shown in regard to HbA1c distribution within prediabetic states. It was suggested that differences in height, but not physiology of glucose regulation, could be responsible for differences in 2-h PPG levels, whereas gender differences in fasting glucose may be attributable to physiological differences involving both insulin sensitivity and β -cell function [22]. Gender differences in HbA1c could not be explained by differences in body composition. HbA1c may be influenced by many factors, including genetic factors, age, ethnicity and environment [25], and gender may also affect HbA1c variability. Overall there may be considerable differences between the correlation of individual average glucose and HbA1c levels.

In the present study at baseline, normal-weight to slightly overweight (BMI <28 kg/m²) women had higher FBG and HbA1c values compared with men, although there were no gender differences in glycaemic control in the overall groups. After insulin initiation, FBG levels dropped more markedly and were lower at the end of the investigation in women; however, they also had significantly higher rates of hypoglycaemia, although men were found to have better reduction in HbA1c level.

Typically, FBG is determined by endogenous glucose production and therefore mostly depends on the liver [26]. The product of hepatic glucose production and fasting insulin is

a surrogate of hepatic insulin resistance. It can be speculated that the normal-weight women having higher FBG and HbA1c values were not as well controlled, showing a higher degree of insulin resistance; that is, increased hepatic glucose production combined with inadequate insulin secretion. Both the insulin dose/kg and the reduction in FBG levels, however, were greater in this female subgroup, suggesting at least similar insulin sensitivity (although HbA1c reduction was lower in women irrespective of BMI group). The higher rate of nocturnal hypoglycaemia may further indicate that fewer efforts to reduce fasting glycaemia (e.g. increasing bedtime basal insulin and more focus on measurements and control of postprandial values) could have contributed to overall better metabolism with a lower risk of hypoglycaemia in lean women.

Overweight/obese men had higher total insulin doses, reflecting greater weight and greater insulin resistance; therefore, they also had low hypoglycaemia rates. The fact that HbA1c was better and that more men achieved target HbA1c at the end of the observation may indicate that postprandial hyperglycaemia was less pronounced, basal hyperglycaemia predominated and the dose of bedtime insulin was appropriate/adequate.

Both postprandial and basal hyperglycaemia are components of glucose exposure. Postprandial glycaemia is the main contributor to overall glycaemia in patients with fairly well-controlled diabetes, whereas basal hyperglycaemia becomes the preponderant contributor in patients with poorly-controlled disease [27]. It is supposed, however, that in patients with lower HbA1c values (<7 – 7.5%), PPG peaks substantially contribute to overall glycaemia, whereas in patients with high glycaemia, fasting and preprandial glycaemia are predominant [27]. Interestingly, discordant results were observed in patients with HbA1c levels $<8\%$ if they were studied before or after initiation of basal insulin; although the relative contribution of postprandial glycaemia was $<25\%$ before insulin therapy, it increased to almost 60% after insulin treatment [27]. A 1% absolute impact of PPG on HbA1c was postulated. Interventional studies, however, proved the protective effect of lowering fasting glucose on development of vascular complications.

Even after initiation of basal insulin therapy, the contribution of basal hyperglycaemia accounted for 40–50% by use of 7-point self-measured glucose profiles [21]. Unfortunately, these studies did not analyse or report gender differences in the relative contribution of basal versus postprandial hyperglycaemia; however, they did report lower rates of hypoglycaemia after the addition of basal insulin versus other forms of intensification of therapy [21]. In addition to measuring FBG, random glucose measurements including postprandial state may be helpful to improve glycaemic control especially in women, particularly if there is a discrepancy between HbA1c and FBG levels. Continuous glucose monitoring systems in women may represent an important advancement in the management of both glycaemic control and hypoglycaemia, as use of these devices has improved control and safety [28]. This is especially important at night-time, when patients may have hypoglycaemic episodes of which they are not aware.

A gender effect on the counter-regulatory hormonal response that occurs during a hypoglycaemic event has been observed in women with and without diabetes [29] and, consistent with this, female gender (along with lower BMI) is associated with a higher risk of hypoglycaemia [8,16]. The present study confirms these observations, as we found that significantly more women experienced both severe hypoglycaemia and severe nocturnal hypoglycaemia, although this was not seen in the higher BMI cohort. This warrants particular emphasis, as patients with diabetes experiencing hypoglycaemia are at an increased risk of significant health complications (including higher rates of cardiovascular disease and risk of mortality), cognitive impairment and diminished quality of life. Furthermore, hypoglycaemia has a negative impact on productivity, treatment adherence and healthcare costs [9,30–33].

Hypoglycaemia is also correlated with higher weight-based insulin doses, regardless of which insulin type is used [34]. While dose titration protocols differed between studies (three based on FBG, three with common pre-set dose), the pooled patient data showed limited, if any, impact of patient weight as a notable contributory factor to weight-based insulin dose. Within the present study, the endpoint mean insulin dose was significantly higher in men overall, and particularly higher in the higher BMI cohort, although there was no difference across gender in the leaner cohort. When the patient's weight was taken into consideration, women overall and those in the leaner cohort were found to receive a higher insulin dose/kg, which was correlated with a difference in efficacy and a greater incidence of hypoglycaemia. These results are inconsistent with the observation from a previous study which found that the risk of hypoglycaemia increased only at a much higher dose, that of 0.6 U/kg and higher.

The results from the present study show that women and those with a lower BMI do not respond to treatment in the same way as men and those with higher BMI. There is a precedent for this, as marked gender differences have been observed with regard to insulin resistance [6]. Incidence of hypoglycaemia was also elevated in women and patients with low BMI. Achieving metabolic control to prevent diabetic complications is the treatment goal in T2DM. The results from this and other studies emphasize the need for treatment to be closely monitored and individualized, especially in women, to reflect this observed vulnerability.

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Conflict of Interest

A. K-W. and L. K. have no conflicts to disclose. J. L. is a consultant to Sanofi. R. M. is an employee of Sanofi.

A. K-W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. A. K-W. contributed to design, conduct, data collection

and analysis and writing of this manuscript. L. K. contributed to the data interpretation and writing of the manuscript. J. L. contributed to design, data collection, data analysis and writing of the manuscript. R. M. contributed to design, data interpretation and writing of the manuscript.

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