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How much is too much? Outcomes in patients using high-dose insulin glargine

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Disclosures
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SUMMARY

Background and objectives: Many patients with type 2 diabetes mellitus (T2DM) do not achieve glycaemic control targets on basal insulin regimens. This analysis investigated characteristics, clinical outcomes and impact of concomitant oral antidiabetes drugs (OADs) in patients with T2DM treated with high-dose insulin glargine. **Methods:** Patient-level data were pooled from 15 randomised, treat-to-target trials in patients with T2DM treated with insulin glargine ± OADs for ≥ 24 weeks. Data were stratified according to whether patients exceeded three insulin dose cut-off levels (> 0.5, > 0.7 and > 1.0 IU/kg). End-points included glycated haemoglobin A1c (A1C), fasting plasma glucose, body weight, and overall, nocturnal and severe hypoglycaemia. **Results:** Data from 2837 insulin-naïve patients were analysed. Patients with insulin titrated beyond the three doses investigated had significantly higher baseline A1C levels and were younger, with shorter diabetes duration than those at/below cut-offs ($p < 0.05$ for all cut-offs); they also had greater weight gain ($p < 0.001$ for the > 0.5 and > 0.7 IU/kg cut-offs) than those who did not exceed the cut-offs, regardless of concomitant OAD. Patients on concomitant metformin alone had higher insulin doses at Week 24, but achieved greater reductions in A1C, less weight gain and lower hypoglycaemia rates than patients on a concomitant sulfonylurea or metformin plus a sulfonylurea, regardless of whether cut-offs were exceeded. **Conclusion:** In patients with T2DM, increasing basal insulin doses above 0.5 IU/kg may not improve glycaemic control; treatment strategies targeting postprandial glucose control should be considered for such patients.

What's known
A large proportion of patients with type 2 diabetes mellitus do not achieve the glycated haemoglobin A1c (A1C) goals of < 7.0% recommended in current guidelines. This may be attributed to clinical inertia in initiating insulin earlier and the failure to intensify diabetes treatment appropriately when the A1C goal of < 7.0% is not achieved.

What's new
This analysis highlights that continued upward titration of basal insulin glargine to doses > 0.5, > 0.7 and even > 1.0 IU/kg does not appear to result in further improvements in glycaemic control but, for those patients needing higher doses, is associated with increased weight gain and also an increased risk of hypoglycaemia once the dose cut-off is exceeded. Intensification of treatment to control residual postprandial hyperglycaemia should be considered for patients whose diabetes is inadequately controlled with high-dose insulin glargine plus oral antidiabetes drugs.

Introduction

The joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) notes that, because of disease progression, many patients with type 2 diabetes mellitus (T2DM) ultimately require insulin therapy, either alone or in combination with other oral antidiabetes drugs (OADs), to maintain glycaemic control (1). Guidance from the ADA/EASD and also the American Association of Clinical Endocrinologists suggests that insulin should be initiated as a single daily injection of basal insulin at a dose of 0.1–0.2 IU/kg of body weight although higher doses (e.g. 0.2–0.4 IU/kg) are appropriate for patients who are severely hyperglycaemic (1,2). The ADA/EASD position statement also alerts practitioners to consider the need for additional mealtime insulin or consider a glucagon-like peptide 1 (GLP-1) receptor agonist trial to reduce postprandial hyperglycaemia once the daily insulin dose exceeds 0.5 IU/kg and particularly as it approaches 1.0 IU/kg (1).

Recent cross-sectional data from the National Health and Nutrition Examination Surveys (NHANES) suggest that the proportion of patients who achieve a glycated haemoglobin A1c (A1C) goal of < 7.0% has increased over the last decade, though only 52.5% of the NHANES participants in the 2007–2010 survey period met the A1C target of < 7.0% (3). This may be attributed to clinical inertia, defined as failure to intensify diabetes treatment appropriately when the A1C goal of < 7.0% is not achieved – which affects about one-third of patients with T2DM, including 26.1% of patients on insulin monotherapy and 21.4% of patients receiving insulin plus OADs (4). Clinical inertia is often a consequence of the discrepancy between evidence-based

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practice and real-world clinical decision-making and has been identified at several stages in the course of diabetes management (5,6).

Clinical decision-making in the setting of basal insulin treatment would be aided by an improved understanding of the clinical impact of high basal insulin doses in the absence of further intensification in patients with T2DM. The aim of this pooled patient-level analysis of data from 15 randomised controlled trials was to investigate the characteristics of, and clinical outcomes in, patients who received insulin glargine doses exceeding 0.5 IU/kg – the dose at which the ADA/EASD position statement suggests that intensification of insulin therapy with prandial therapy should be considered. The impact of the OAD regimen used concomitantly with insulin glargine was also evaluated.

Methods

Study and patient selection

The source for this analysis was a database of 63 insulin glargine clinical trials conducted by Sanofi and its predecessor companies between 1997 and 2007. To be eligible for inclusion in the analysis, studies were required to have been phase 3 (or higher), prospective, randomised, controlled, treat-to-target trials; conducted in insulin-naïve adult patients with T2DM treated with insulin glargine once daily in combination with OADs for ≥ 24 weeks; and have utilised protocol-driven titration algorithms to target fasting plasma glucose (FPG) levels < 100 mg/dl. A total of 15 eligible studies were identified (Table S1) (7–21).

End-points and statistical analyses

Three insulin glargine dose cut-offs were investigated: > 0.5, > 0.7 and > 1.0 IU/kg. Baseline characteristics and end-point variables were pooled for all patients who were randomised and received ≥ 1 dose of insulin glargine and summarised for patients maintaining insulin glargine doses ≤ 0.5, 0.7 and 1.0 IU/kg throughout the 24-week treatment period or exceeding the insulin glargine dose cut-offs at some point during the treatment period.

End-point variables included A1C, FPG, body weight, and overall, nocturnal and severe hypoglycaemic event rates during the entire treatment period, and prior to and after exceeding high-dose insulin glargine cut-offs.

The definitions of hypoglycaemia were as follows. Overall hypoglycaemia was defined as a plasma glucose (PG) level of < 70 or < 56 mg/dl (including events requiring third-party assistance). Nocturnal hypoglycaemia was defined as a PG level < 70 or < 56 mg/dl occurring between 0:01 am and 5:59 pm. Severe hypoglycaemia was defined as hypoglycaemic events that required third-party assistance to treat.

A1C was analysed and adjusted using an analysis of covariance (ANCOVA) model that included age, gender, duration of diabetes, FPG and weight at baseline; using exceeding the high-dose cut-off and pool as fixed factors; and using the baseline A1C as the covariate. FPG was also analysed and adjusted using an ANCOVA model that included age, duration of diabetes, weight, A1C and starting insulin dose; using exceeding the high-dose cut-off and pool as fixed factors; and using the baseline FPG as the covariate. The analysis of A1C at end-point < 7.0% was limited to patients with a baseline A1C ≥ 7.0%. Body weight was analysed by an ANCOVA model and adjusted by age, gender, A1C, FPG and starting insulin dose; using exceeding the high-dose cut-off and pool as fixed factors; and using the baseline weight as the covariate.

Hypoglycaemia event rates were analysed using a generalised linear model that included age, gender, duration of diabetes, baseline body mass index (BMI), baseline FPG and starting insulin glargine dose as variables with exceeding the high-dose cut-off and pool as fixed factors.

Results

Patient demographics and baseline characteristics

Overall, the analysis included data from 2837 patients with a mean age of 52.8–59.0 years and a duration of diabetes ranging from 7.6 to 9.5 years depending on dose cut-off group; mean baseline A1C ranged from 8.6% to 9.2% and mean baseline FPG levels ranged from 183.2 to 227.4 mg/dl (Table 1). During 24 weeks of treatment across the 15 studies, 1075, 453 and 111 patients exceeded the insulin glargine dose cut-offs of > 0.5, > 0.7 and > 1.0 IU/kg, respectively. Compared with patients who did not exceed the insulin glargine dose cut-offs, those exceeding insulin glargine dose cut-offs were younger, more likely to be women, with a shorter duration of T2DM, greater body weight and BMI, and higher baseline A1C and FPG levels and starting insulin glargine dose (Table 1). Patients receiving metformin only during the treatment period were more likely to exceed insulin glargine dose cut-offs than those receiving a sulfonylurea alone or metformin plus a sulfonylurea ($p < 0.001$ in both cases, for all cut-off levels) (Table 1). Patient baseline characteristics according to the concomitant OAD they received insulin glargine are presented in Table S2.

Table 1 Patient baseline demographics and clinical characteristics by insulin glargine dose cut-off

Characteristic	Dose cut-off					
	≤ 0.5 IU/kg (*n* = 1762)	> 0.5 IU/kg (*n* = 1075)	≤ 0.7 IU/kg (*n* = 2384)	> 0.7 IU/kg (*n* = 453)	≤ 1.0 IU/kg (*n* = 2726)	> 1.0 IU/kg (*n* = 111)
Age (years)	59.0 (9.9)*	55.6 (9.4)	58.3 (9.8)*	54.6 (9.5)	57.9 (9.8)*	52.8 (8.3)
Men, *n* (%)	1004 (57.0)*	522 (48.6)	1311 (55.0)*	215 (47.6)	1473 (54.1)	53 (47.7)
Duration of diabetes (years)	9.5 (6.6)*	8.2 (5.9)	9.2 (6.4)*	8.1 (5.9)	9.1 (6.4)*	7.6 (4.6)
Weight (kg)	85.6 (17.8)*	88.2 (19.2)	86.1 (18.0)*	89.2 (20.2)	86.5 (18.3)	89.8 (20.7)
BMI (kg/m^2)	30.1 (5.2)*	31.5 (5.5)	30.4 (5.3)*	31.9 (5.5)	30.5 (5.3)*	32.2 (5.5)
A1C (%)	8.6 (1.0)*	9.0 (1.1)	8.7 (1.0)*	9.2 (1.1)	8.8 (1.1)*	9.2 (1.0)
FPG (mg/dl)	183.2 (51.5)*	216.1 (57.4)	190.8 (54.5)*	221.7 (57.6)	194.4 (55.8)*	227.4 (55.5)
Initial insulin glargine dose at randomisation (IU/kg)	0.15 (0.06)*	0.18 (0.10)	0.15 (0.07)*	0.19 (0.12)	0.16 (0.08)	0.18 (0.10)
Concomitant OAD use during the treatment period, *n* (%)						
Metformin	323 (18.3)	311 (28.9)	483 (20.3)	151 (33.3)	594 (21.8)	40 (36.0)
Sulfonylurea	567 (32.2)	339 (31.5)	778 (32.6)	128 (28.3)	879 (32.2)	27 (24.3)
Metformin plus sulfonylurea	872 (49.5)	425 (39.5)	1123 (47.1)	174 (38.4)	1253 (46.0)	44 (39.6)

A1C, glycated haemoglobin A1c; BMI, body mass index; FPG, fasting plasma glucose; OAD, oral antidiabetes drug. All values represent the mean (SD) unless stated otherwise. *p < 0.05 for not exceeding cut-off compared with exceeding cut-off.

Glycaemic control

Adjusted mean A1C at Week 24 was 7.28%, 7.34% and 7.51% in those patients exceeding the 0.5, 0.7 and 1.0 IU/kg dose cut-offs, respectively. This was significantly higher than in those patients at or below the cut-offs: 7.16%, 7.18% and 7.20%, respectively (all p < 0.05).

The change in A1C from baseline to Week 24 was smaller for patients who exceeded each of the specified dose cut-offs (Figure 1A). A similar pattern was observed when the A1C data were analysed according to the concomitant OAD received. Those patients who received metformin only during the treatment period (Figure 1B) appeared to have the largest change in A1C from baseline to Week 24, followed by those treated with metformin plus a sulfonylurea (Figure 1D), irrespective of having reached the cut-off or not. Those patients receiving a sulfonylurea alone appeared to have the smallest change in A1C from baseline to Week 24 (Figure 1C).

At the dose cut-off of > 1.0 IU/kg, significantly fewer patients who exceeded the cut-off achieved an A1C < 7.0% at 24 weeks compared with patients not exceeding the dose cut-off (33.0% vs. 45.8%, respectively; p = 0.0205). Fewer patients exceeding the dose cut-off of > 1.0 IU/kg achieved an A1C < 7.0% at 24 weeks without experiencing a hypoglycaemic event compared with patients not exceeding the dose cut-off. These differences were statistically significant for nocturnal hypoglycaemia with PG < 70 mg/dl (25.5% vs. 36.1%, respectively; p = 0.0377) and severe hypoglycaemia, (32.1% vs. 44.8%, respectively; p = 0.0212). When split according to concomitant OAD, the percentage of patients who achieved their A1C target was numerically lower in the patients who exceeded the 1.0 IU/kg cut-off in all OAD subgroups.

Compared with patients exceeding the dose cut-offs, adjusted mean FPG levels at Week 24 were lower for patients at or below the dose cut-offs (Figure 2A). At Week 24, adjusted FPG levels in patients not exceeding and exceeding dose cut-offs, respectively, were 116.6 vs. 120.7 mg/dl for 0.5 IU/kg (p = 0.0104); 117.6 vs. 121.1 mg/dl for 0.7 IU/kg (p = 0.0919); and 117.6 vs. 132.0 mg/dl for 1.0 IU/kg (p = 0.0002). Similar patterns were observed when the FPG data were analysed according to concomitant OAD use during the treatment period (Figure 2B–D). The difference in FPG levels at Week 24 in those patients who exceeded compared with those at or below the 1.0 IU/kg cut-off was most marked in those receiving concomitant metformin (p = 0.0026) or metformin plus a sulfonylurea (p = 0.0062). However, the adjusted mean FPG levels at Week 24 were within or approaching the < 130 mg/dl target specified by the ADA/EASD (1) in all groups regardless of dose cut-off or concomitant OAD. The highest adjusted mean Week-24 FPG level was 136.04 mg/dl, observed in patients receiving concomitant metformin plus a sulfonylurea exceeding the 1.0 IU/kg dose cut-off.

Insulin dose

As would be expected, the change in weight-adjusted insulin dose from baseline (starting insulin dose) to

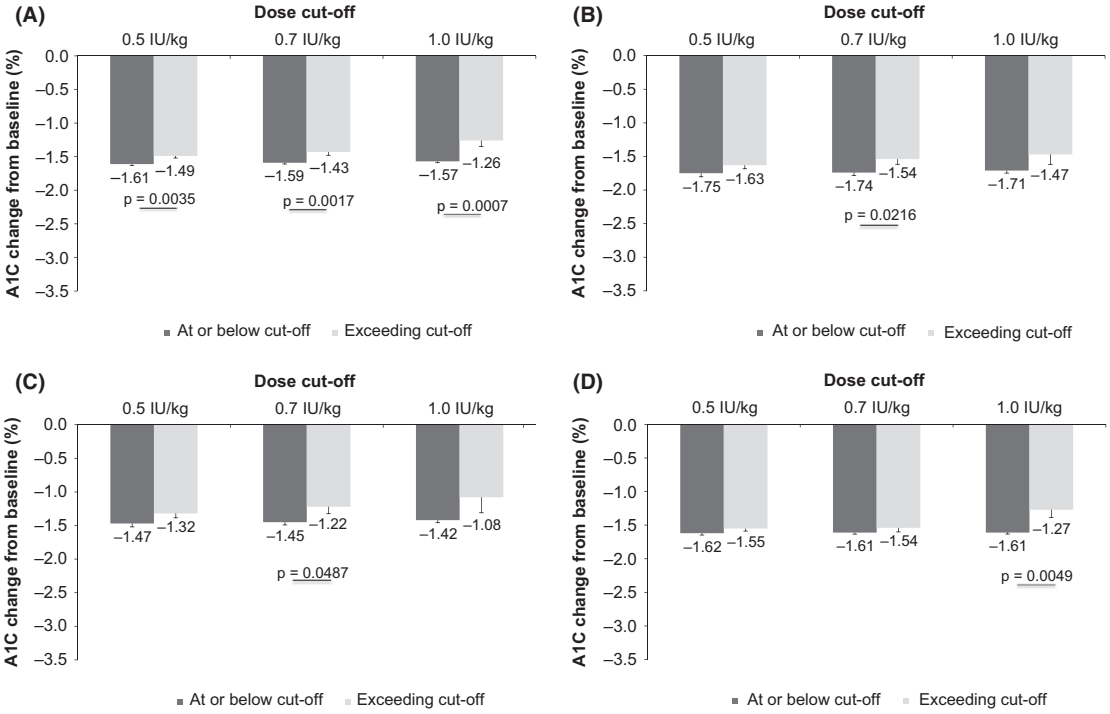

Figure 1 Adjusted mean A1C change from baseline to Week 24 in (A) the overall population, (B) patients with concomitant metformin use, (C) patients with concomitant sulfonylurea use and (D) patients with concomitant metformin plus sulfonylurea use. A1C, glycated haemoglobin A1c. All values represent the mean (SE)

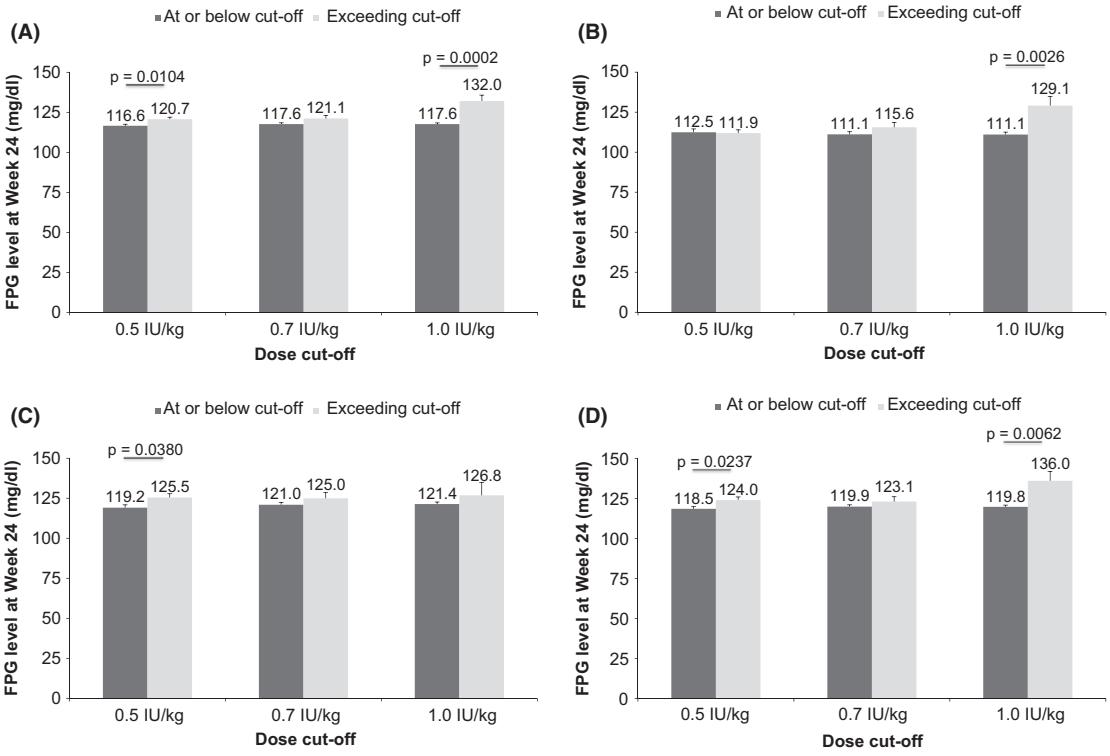

Figure 2 Adjusted mean FPG at Week 24 in (A) the overall population, (B) patients with concomitant metformin use, (C) patients with concomitant sulfonylurea use and (D) patients with concomitant metformin plus sulfonylurea use. FPG, fasting plasma glucose. All values represent the mean (SE)

Week 24 was greater in patients who exceeded the dose cut-offs compared with those at or below the dose cut-offs (0.51 vs. 0.15 IU/kg for the > 0.5 IU/kg dose cut-off; 0.70 vs. 0.21 IU/kg for the > 0.7 IU/kg dose cut-off; and 0.99 vs. 0.26 IU/kg for the > 1.0 IU/kg dose cut-off; Table 2). Patients who received metformin only or metformin plus a sulfonylurea appeared to reach higher insulin doses at Week 24 than patients receiving sulfonylurea only (Table 2).

Starting insulin doses were similar in those patients receiving metformin only or metformin plus a sulfonylurea during the treatment period regardless of whether the patient went on to exceed dose cut-offs. However, baseline dose requirements were numerically larger in patients receiving sulfonylurea only who subsequently exceeded the dose cut-offs compared with those patients who remained at or below the dose cut-offs (0.25 vs. 0.17 IU/kg for the > 0.5 IU/kg cut-off; 0.28 vs. 0.19 for the > 0.7 IU/kg cut-off; and 0.25 vs. 0.20 IU/kg for the > 1.0 IU/kg cut-off). This difference was not seen in the other OAD subgroups.

Body weight

Compared with patients at or below dose cut-offs, weight gain from baseline to Week 24 was larger for patients who exceeded dose cut-offs (Figure 3A). A similar pattern was observed when the data were split according to the concomitant OAD received by the patient. Patients receiving metformin only during the treatment period appeared to gain less weight than those patients receiving a sulfonylurea only or metformin plus a sulfonylurea (Figure 3B–D).

Hypoglycaemia

During the entire treatment period, overall and nocturnal hypoglycaemia event rates were consistently significantly lower in patients exceeding dose cut-offs compared with those at or below dose cut-offs ($p < 0.05$ for all cut-off level comparisons, Table 3). These differences appear to have been driven by significantly increased overall hypoglycaemia rates in the subgroup of patients with concomitant sulfonylurea use with or without metformin who did not exceed the insulin dose cut-offs compared with those who exceeded cut-offs ($p < 0.05$ for all cut-off level comparisons; Table 3). In patients who received concomitant metformin alone, hypoglycaemia rates were numerically lower than those observed in patients using concomitant sulfonylurea or metformin plus sulfonylurea; and in this OAD subgroup, there was no significant difference in hypoglycaemia rate in patients at or below the dose cut-offs compared with those exceeding the dose cut-offs (Table 3).

In patients who exceeded the dose cut-offs, the overall and nocturnal hypoglycaemia event rates prior to exceeding the dose cut-off were lower than after exceeding the cut-off at all three cut-off levels (Figure 4). Overall, nocturnal and severe hypogly-

Table 2 Weight-adjusted insulin dose at baseline (starting insulin dose) and Week 24, and change from baseline to Week 24, stratified by concomitant OAD use

	Dose cut-off					
Insulin dose (IU/kg)	**≤ 0.5**	**> 0.5**	**≤ 0.7**	**> 0.7**	**≤ 1.0**	**> 1.0**
Overall population	*n* = 1762	*n* = 1075	*n* = 2384	*n* = 453	*n* = 2726	*n* = 111
Baseline	0.15 (0.06)	0.18 (0.10)	0.15 (0.07)	0.19 (0.12)	0.16 (0.08)	0.18 (0.10)
Week 24	0.29 (0.11)	0.69 (0.23)	0.36 (0.16)	0.88 (0.22)	0.41 (0.21)	1.17 (0.23)
Change from baseline to Week 24	0.15 (0.11)	0.51 (0.25)	0.21 (0.16)	0.70 (0.27)	0.26 (0.21)	0.99 (0.26)
Concomitant metformin use	*n* = 323	*n* = 311	*n* = 483	*n* = 151	*n* = 594	*n* = 40
Baseline	0.16 (0.05)	0.17 (0.05)	0.16 (0.05)	0.16 (0.05)	0.16 (0.05)	0.17 (0.05)
Week 24	0.31 (0.10)	0.71 (0.24)	0.39 (0.15)	0.89 (0.23)	0.47 (0.22)	1.16 (0.24)
Change from baseline to Week 24	0.15 (0.11)	0.55 (0.26)	0.23 (0.15)	0.73 (0.24)	0.30 (0.22)	0.99 (0.25)
Concomitant sulfonylurea use	*n* = 567	*n* = 339	*n* = 778	*n* = 128	*n* = 879	*n* = 27
Baseline	0.17 (0.08)	0.25 (0.15)	0.19 (0.10)	0.28 (0.18)	0.20 (0.12)	0.25 (0.16)
Week 24	0.29 (0.11)	0.67 (0.20)	0.36 (0.16)	0.86 (0.19)	0.41 (0.21)	1.11 (0.20)
Change from baseline to Week 24	0.12 (0.11)	0.42 (0.25)	0.18 (0.15)	0.57 (0.30)	0.21 (0.20)	0.86 (0.29)
Concomitant metformin plus sulfonylurea use	*n* = 872	*n* = 425	*n* = 1123	*n* = 174	*n* = 1253	*n* = 44
Baseline	0.13 (0.04)	0.13 (0.04)	0.13 (0.04)	0.14 (0.04)	0.13 (0.04)	0.14 (0.05)
Week 24	0.29 (0.11)	0.69 (0.23)	0.35 (0.15)	0.90 (0.23)	0.39 (0.20)	1.21 (0.23)
Change from Baseline to Week 24	0.16 (0.12)	0.56 (0.24)	0.22 (0.16)	0.76 (0.23)	0.26 (0.20)	1.06 (0.22)

OAD, oral antidiabetes drug. All values represent the mean (SD).

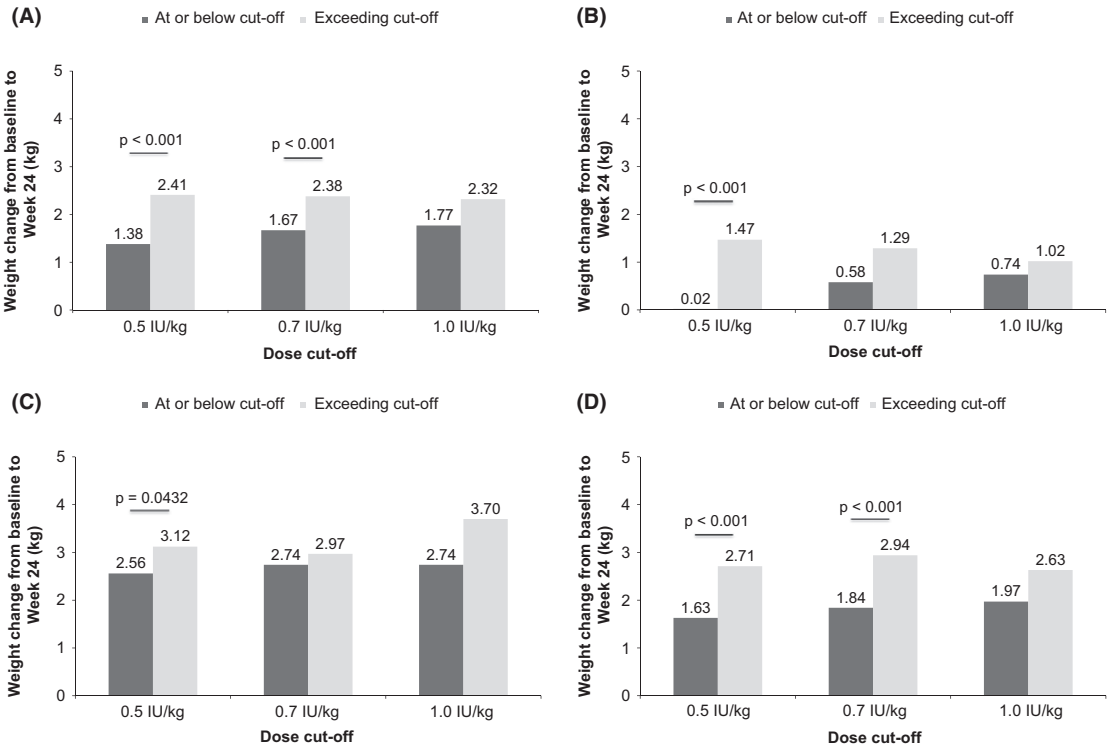

Figure 3 Adjusted mean weight change from baseline to Week 24 in (A) overall population, (B) patients with concomitant metformin use, (C) patients with concomitant sulfonylurea use and (D) patients with concomitant metformin plus sulfonylurea use

caemia event rates decreased as the dose cut-off level increased (Table 3, Figure 4).

Discussion

This analysis of pooled patient-level data from 2837 patients with T2DM suggests that, in certain patients, a low overall risk of hypoglycaemia permits continued titration of insulin glargine to doses exceeding 0.5 IU/kg. However, in the overall patient population, increasing the insulin dose beyond the dose cut-offs investigated in this analysis (> 0.5, > 0.7 and > 1.0 IU/kg) did not further improve glycaemic control in terms of A1C target achievement or mean FPG levels, and resulted in greater weight gain compared with patients titrated to insulin doses below the specified cut-off levels. Though overall and nocturnal hypoglycaemia event rates were consistently lower in patients exceeding dose cut-offs compared with those at or below dose cut-offs (perhaps permitting titration to higher doses), once a patient had exceeded the dose cut-off, there was a higher likelihood of hypoglycaemia.

The findings of this analysis also show that the concomitant OAD regimen with which insulin glargine is taken impacts efficacy, weight gain, hypoglycaemia rate and insulin glargine dose in patients with T2DM. This is supported by the results of a previous analysis based on the same clinical dataset (22) that previously reported that insulin in combination with a sulfonylurea is associated with fewer patients achieving target A1C levels, greater weight gain, and a greater risk of overall, daytime and nocturnal hypoglycaemia. Conversely, insulin glargine plus metformin alone was associated with improved clinical outcomes, despite higher insulin doses at the end of trial (22). Our analysis confirms and extends these findings, showing that greater reductions in A1C, less weight gain and lower hypoglycaemia rates were associated with concomitant use of metformin alone, despite a higher insulin dose at end-point and regardless of whether patients remained at or below or exceeded the dose cut-offs defined in this analysis.

Interestingly, we also identified that, in patients exceeding dose cut-offs, starting doses of insulin were higher in patients receiving concomitant sulfonylurea only compared with patients on concomitant metformin or metformin plus sulfonylurea. This could indicate that these patients were more insulin resistant at baseline and required more insulin during the course of observation, hence their subsequent titration of insulin dose beyond the cut-off levels, which resulted in greater weight gain and increased hypoglycaemia rates.

Table 3 Adjusted hypoglycaemia event rates (events per patient-year) during the entire treatment period in the overall population and according to concomitant OAD

	Dose cut-off					
Insulin dose (IU/kg)	**≤ 0.5**	**> 0.5**	**≤ 0.7**	**> 0.7**	**≤ 1.0**	**> 1.0**
Overall population	*n* = 1762	*n* = 1075	*n* = 2384	*n* = 453	*n* = 2726	*n* = 111
PG < 70 mg/dl						
Overall hypoglycaemia	4.70 (0.24)*	3.40 (0.21)	4.49 (0.19)*	2.67 (0.26)	4.28 (0.17)*	1.87 (0.38)
Nocturnal hypoglycaemia	0.85 (0.07)*	0.60 (0.06)	0.82 (0.06)*	0.39 (0.06)	0.76 (0.05)*	0.34 (0.11)
PG < 56 mg/dl						
Overall hypoglycaemia	1.44 (0.09)*	1.06 (0.08)	1.40 (0.07)*	0.73 (0.09)	1.32 (0.07)*	0.45 (0.12)
Nocturnal hypoglycaemia	0.34 (0.04)*	0.22 (0.03)	0.33 (0.03)*	0.13 (0.03)	0.30 (0.03)*	0.08 (0.04)
Severe hypoglycaemia	0.09 (0.02)	0.07 (0.02)	0.09 (0.02)	0.04 (0.02)	0.08 (0.01)	0.02 (0.03)
Concomitant metformin use	*n* = 323	*n* = 311	*n* = 483	*n* = 151	*n* = 594	*n* = 40
PG < 70 mg/dl						
Overall hypoglycaemia	2.21 (0.28)	1.84 (0.24)	2.16 (0.22)	1.60 (0.31)	2.08 (0.19)	1.22 (0.45)
Nocturnal hypoglycaemia	0.49 (0.10)	0.37 (0.08)	0.46 (0.08)	0.32 (0.10)	0.43 (0.07)	0.32 (0.19)
PG < 56 mg/dl						
Overall hypoglycaemia	0.61 (0.10)	0.60 (0.10)	0.61 (0.08)	0.58 (0.14)	0.62 (0.08)	0.32 (0.16)
Nocturnal hypoglycaemia	0.17 (0.06)	0.12 (0.04)	0.17 (0.05)	0.08 (0.04)	0.15 (0.04)	0.08 (0.08)
Severe hypoglycaemia	0.03 (0.02)	0.05 (0.02)	0.04 (0.02)	0.05 (0.03)	0.04 (0.02)	0.03 (0.04)
Concomitant sulfonylurea use	*n* = 567	*n* = 339	*n* = 778	*n* = 128	*n* = 879	*n* = 27
PG < 70 mg/dl						
Overall hypoglycaemia	5.01 (0.47)*	3.30 (0.41)	4.69 (0.36)*	2.30 (0.46)	4.43 (0.32)*	1.48 (0.69)
Nocturnal hypoglycaemia	0.60 (0.09)	0.42 (0.08)	0.58 (0.07)*	0.21 (0.07)	0.54 (0.06)	0.25 (0.18)
PG < 56 mg/dl						
Overall hypoglycaemia	1.30 (0.15)*	0.87 (0.14)	1.26 (0.12)*	0.38 (0.10)	1.16 (0.10)*	0.24 (0.15)
Nocturnal hypoglycaemia	0.22 (0.04)	0.15 (0.04)	0.22 (0.04)*	0.05 (0.03)	0.20 (0.03)	0.00
Severe hypoglycaemia	0.10 (0.04)	0.05 (0.02)	0.09 (0.03)	0.01 (0.01)	0.08 (0.02)	0.06 (0.09)
Concomitant metformin plus sulfonylurea use	*n* = 872	*n* = 425	*n* = 1123	*n* = 174	*n* = 1253	*n* = 44
PG < 70 mg/dl						
Overall hypoglycaemia	7.95 (0.46)*	5.83 (0.50)	7.67 (0.39)*	4.53 (0.62)	7.40 (0.35)*	2.54 (0.71)
Nocturnal hypoglycaemia	1.72 (0.15)*	1.05 (0.14)	1.62 (0.13)*	0.69 (0.15)	1.53 (0.11)*	0.30 (0.15)
PG < 56 mg/dl						
Overall hypoglycaemia	3.02 (0.21)*	2.22 (0.23)	2.96 (0.17)*	1.50 (0.25)	2.82 (0.16)*	0.78 (0.29)
Nocturnal hypoglycaemia	0.76 (0.08)*	0.46 (0.08)	0.71 (0.07)*	0.32 (0.09)	0.67 (0.06)*	0.11 (0.08)
Severe hypoglycaemia	0.05 (0.02)	0.04 (0.02)	0.05 (0.02)	0.02 (0.02)	0.05 (0.01)	0.00

PG, plasma glucose. All values mean (SE). *$p < 0.05$ for not exceeding cut-off compared with exceeding cut-off.

Importantly, our analysis highlights that, regardless of the concomitant OAD received, increasing the insulin glargine dose beyond the cut-offs investigated did not improve glycaemic control but increased weight gain and also the risk of hypoglycaemia once the dose cut-off was exceeded. In such patients, prandial treatment may be required to control postprandial blood glucose excursions (1), which play an increasingly important role in the glycaemic control of T2DM patients as overall hyperglycaemia levels become more controlled (23,24). A previous study by Riddle et al. (24) has illustrated that, in patients treated with OADs with A1C levels above 7.0%, the relative contribution of basal hyperglycaemia dominates overall hyperglycaemic exposure. After intensification of therapy with basal insulin, postprandial hyperglycaemia becomes the more dominant contributor to overall hyperglycaemic exposure, underlining the importance of attending to postprandial hyperglycaemia and recognising the need for prandial therapy.

Treatment strategies that can be utilised to address postprandial hyperglycaemia in patients whose basal insulin has been optimally titrated include: rapid-acting prandial insulins (25–29); long- and short-acting prandial GLP-1 receptor agonists (30–34); dipeptidyl

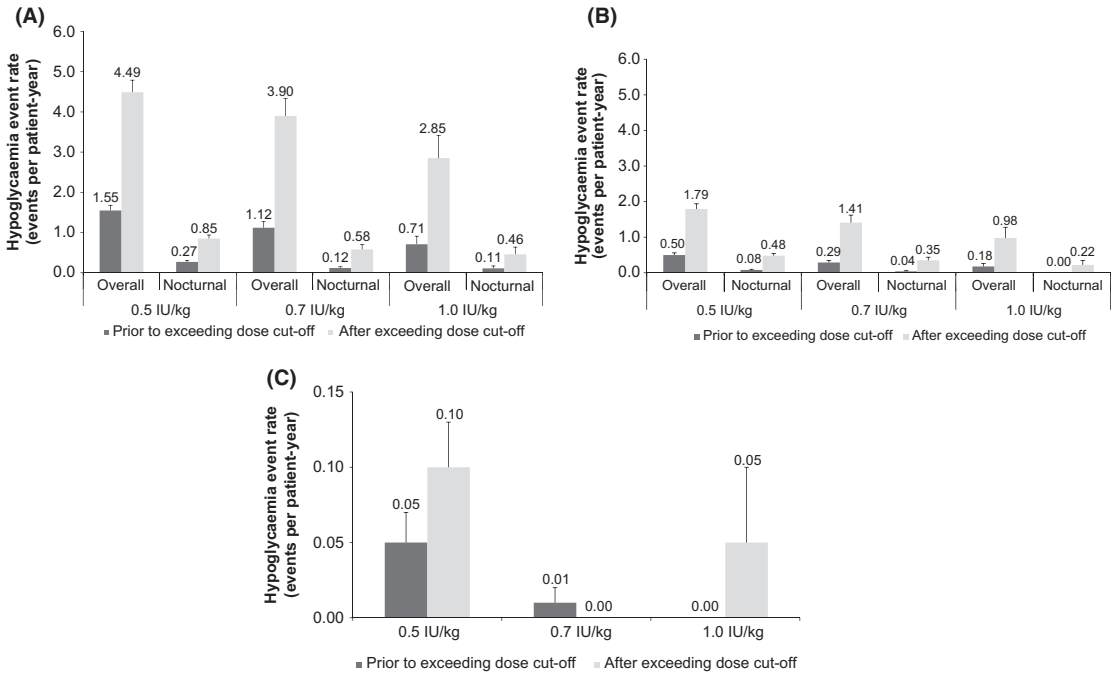

Figure 4 Adjusted mean hypoglycaemia event rates prior to and after exceeding dose cut-offs, with hypoglycaemia defined as: PG < 70 mg/dl (A); PG < 56 mg/dl (B); and severe hypoglycaemia (C). PG, plasma glucose. All values represent the mean (SE)

peptidase 4 inhibitors (35); and sodium glucose co-transporter type 2 inhibitors (36,37). However, to identify and optimally address postprandial hyperglycaemia, it is important to consider the need to examine pre- and postprandial self-monitored blood glucose (SMBG) profiles as well as mean FPG and A1C levels, and to work with patients to review SMBG patterns from their log books and glucose metre downloads. Using this approach in combination with prandial treatment intensification, an individualised treatment strategy can be developed to best suit the patient's lifestyle and mealtimes, as recommended by current management guidelines (1).

Our analysis has several limitations. First, it is limited by an unavoidable disparity in the number of patients who exceeded the 0.7 and 1.0 IU/kg dose cut-off levels compared with the number who did not exceed those cut-offs. This may have impacted the outcomes observed in the analysis, although a consistent trend was observed pre- and postcut-off, irrespective of cut-off level. Only three dose cut-off levels were investigated which makes it difficult to differentiate cause and effect. In addition, the sample sizes of some of the concomitant OAD subgroups investigated in this analysis were small, limiting the strength of the conclusions that can be drawn on the impact of the concomitant OAD regimen. Finally, it must be noted that the results presented here are representative only of clinical outcomes with insulin glargine, and caution must be applied when extrapolating these data to other basal insulin therapies.

In conclusion, continued upwards titration of basal insulin glargine to doses > 0.5, > 0.7 and even > 1.0 IU/kg does not appear to result in further improvements in glycaemic control but leads to increased weight gain and is associated with an increased risk of hypoglycaemia. Intensification of insulin glargine treatment to control residual postprandial hyperglycaemia, such as a prandial insulin or a GLP-1 receptor agonist, should be considered for such patients whose diabetes is inadequately controlled with high-dose insulin glargine plus OADs.

Author contributions

Reid: data analysis/interpretation; critical revision of article; final approval; accountable for accuracy and integrity. Gao: data analysis/interpretation; critical revision of article; final approval; accountable for accuracy and integrity. Gill: data analysis/interpretation; critical revision of article; final approval; accountable for accuracy and integrity. Stuhr: data analysis/interpretation; critical revision of article; final approval; accountable for accuracy and integrity. Traylor: data analysis/interpretation; critical

revision of article; final approval; accountable for accuracy and integrity. Vlajnic: concept/design; data analysis/interpretation; critical revision of article; final approval; accountable for accuracy and integrity. Rhinehart: data analysis/interpretation; critical revision of article; final approval; accountable for accuracy and integrity.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Eligible studies identified for inclusion.

Table S2. Patient baseline demographics and clinical characteristics by insulin glargine dose cut-off according to concomitant OAD.

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