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Original article

Glycaemic control and hypoglycaemia risk with insulin glargine 300 U/mL versus glargine 100 U/mL: A patient-level meta-analysis examining older and younger adults with type 2 diabetes

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ABSTRACT

Aim. – Older people with type 2 diabetes (T2DM) are at an increased risk of hypoglycaemia and its consequences. However, efficacy and safety data for basal insulin therapy are limited in these individuals. This patient-level meta-analysis assessed the treatment effects of insulin glargine 300 U/mL (Gla-300) versus glargine 100 U/mL (Gla-100) in people with T2DM ≥ 65 years old.
Methods. – Data were pooled for patients randomised to receive Gla-300 or Gla-100 in the Phase 3a, treat-to-target EDITION 1, 2 and 3 trials. Glycaemic efficacy, hypoglycaemia, changes in body weight and insulin dosage and adverse events were examined over 6 months' treatment with Gla-300 versus Gla-100 for participants aged ≥ 65 and < 65 years.
Results. – Of 2496 participants randomised, 662 were ≥ 65 years (Gla-300, *n* = 329; Gla-100, *n* = 333). Glycaemic control was comparable for Gla-300 and Gla-100 in participants ≥ 65 years (LS mean [95% CI] difference in HbA_{1c} change from baseline to month 6: 0.00 [−0.14 to 0.15] %; 0.00 [−1.53 to 1.64] mmol/mol) and < 65 years (0.00 [−0.09 to 0.08] %; 0.00 [−0.98 to 0.87] mmol/mol). Fewer participants receiving Gla-300 versus Gla-100 experienced nocturnal confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia (relative risk: ≥ 65 years: 0.70 [0.57 to 0.85]; < 65 years: 0.77 [0.68 to 0.87]). Annualised rates of nocturnal confirmed or severe hypoglycaemia were lower with Gla-300 than Gla-100 for both age groups.
Conclusion. – Gla-300 was associated with a reduced risk of nocturnal hypoglycaemia versus Gla-100, accompanied by comparable glycaemic improvement, for people aged ≥ 65 and < 65 years with T2DM.

Introduction

Type 2 diabetes (T2DM) represents a substantial health burden in older adults. In 2017, an estimated 123 million people aged 65–99 years had diabetes, and this number is expected to increase to 438 million by 2045 [1]. Older adults with T2DM are at an increased risk of hypoglycaemic events [2] versus younger adults, and have poor hypoglycaemia-related outcomes [2–4]

Abbreviations: FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; LS, least-squares; mITT, modified intention-to-treat; NNT, number needed to treat; SMPG, self-monitored plasma glucose; T2DM, type 2 diabetes; TEAEs, treatment emergent adverse events.

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(e.g. increased mortality and emergency department visits/hospitalisation) [5], resulting in significant costs and burden on healthcare resources [6].

Older adults with diabetes have the highest rates of comorbidities, including lower limb amputation, myocardial infarction, visual impairments and end-stage renal disease [2]. Age- and diabetes-related comorbidities such as neuropathy, impaired renal function, cognitive defects and frailty contribute to an increased hypoglycaemia risk with older age [2,7,8]. In addition, older adults have reduced awareness of hypoglycaemia versus younger individuals [9,10], which may reflect their increased risk of severe hypoglycaemia. Hypoglycaemia can have severe consequences in older individuals including falls, deterioration in general health, cognitive impairment and hospital admissions [11,12].

The management of diabetes in older individuals may be complicated by heterogeneity in health status, comorbidities, polypharmacy and increased hypoglycaemia rates [11,13–17]. Reflecting these complexities, and the higher risk of hypoglycaemia and its consequences in older individuals, the American Diabetes Association (ADA) recommends less stringent glycaemic targets of < 7.5% and < 8.5% (< 58 and < 69 mmol/mol) in older adults versus younger adults [14]. In healthy individuals with few comorbidities, good cognitive and functional status and a longer life expectancy, the recommended glycaemic target is < 7.5% (< 58 mmol/mol), but no lower than 7.0% (53 mmol/mol). The most relaxed target (< 8.5% [< 69 mmol/mol]) is recommended for older individuals with complex health needs and poor health, in whom limited life expectancy makes the benefit of glycaemic control less certain [14].

Despite a globally ageing population and the greater complexity in treating diabetes in older people, there is a surprising lack of evidence supporting diabetes therapy in this population [18]. In the phase 3a EDITION program [19–24], insulin glargine 300 U/mL (Gla-300) demonstrated a similar level of glycaemic control with less hypoglycaemia over 6 months versus insulin glargine 100 U/mL (Gla100) in participants with T2DM 18–87 years of age [25]. The aim of this trial-level post hoc exploratory analysis was to compare the efficacy and safety of Gla-300 and Gla-100 in a patient-level meta-analysis in older people (aged ≥65 years) with T2DM in the EDITION 1, 2 and 3 studies. Trial-level post hoc analyses will help to address the paucity of available information by pooling available data across comparable studies to evaluate effects in this important age group. Further potential benefits or risks of diabetes therapies in older populations can be determined by comparisons with younger adults < 65 years old, as this population is well characterised in clinical trials; such a comparison has been performed herein.

Materials and methods

Study design and participants

EDITION 1, 2 and 3 (ClinicalTrials.gov: NCT01499082, NCT01499095, and NCT01676220, respectively) were multicentre, randomised, open-label, two-arm, parallel-group, phase 3a studies in people with T2DM [19–24]. The studies comprised a 6-month main treatment phase and a 6-month safety extension period. In EDITION 1, participants had established (≥ 1 year) basal and mealtime insulin therapy with or without metformin [20], EDITION 2 participants had at least 6 months' prior basal insulin treatment in combination with other oral anti-hyperglycaemic agents [22], and in EDITION 3, participants were insulin naïve but used other anti-hyperglycaemic agents prior to screening [23]. The key inclusion criteria of the EDITION studies were: 1) participants aged ≥ 18 years with T2DM, 2) HbA_{1c} ≥ 7.0 to ≤ 10.0% (≥ 53 to ≤86 mmol/mol; EDITION 1 and EDITION 2) or ≥ 7.0 to ≤ 11.0% (≥ 53 to ≤ 97 mmol/mol; EDITION 3), and 3) basal insulin ≥ 42 U/day (EDITION 1 and EDITION 2 only). Eligible participants were randomised (1:1) to once-daily evening injections of Gla-300 or Gla-100, titrated to a fasting self-monitored plasma glucose (SMPG) target of 4.4–5.6 mmol/L (80–100 mg/dL). Appropriate ethics committees approved the study protocols and the studies were conducted according to Good Clinical Practice and the Declaration of Helsinki. All participants provided written, informed consent.

Outcomes

The EDITION 1, 2 and 3 studies had similar endpoints, which supported the approach of a patient-level meta-analysis of the combined data. Efficacy endpoints were examined in the modified intention-to-treat (mITT) population, defined as all randomised participants who received at least one dose of study drug and had both a baseline and ≥ 1 post-baseline assessment. These included: change from baseline to month 6 (and 12) in HbA_{1c}, percentage of participants achieving HbA_{1c} targets (HbA_{1c} < 7.0% [< 53 mmol/mol], HbA_{1c} < 7.5% [< 58 mmol/mol] or HbA_{1c} reduction ≥ 0.5% [≥ 5.5 mmol/mol]) and the composite endpoint of percentage of participants achieving HbA_{1c} targets without confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia.

Safety endpoints were analysed according to the treatment received and using the safety population, which included all participants randomised and exposed to ≥ 1 dose of study drug. These included percentage of participants with ≥ 1 hypoglycaemic event (classified based on ADA definitions [26]; confirmed and severe events were combined for the main hypoglycaemia endpoint) and events per participant-year during the night (00:00–05:59 h; protocol definition) or at any time of day (24 h); number needed to treat (NNT) with Gla-300 versus Gla100 to avoid one participant experiencing a confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe nocturnal hypoglycaemic event; and change from baseline to month 6 (and 12) in basal insulin dose and body weight.

This post hoc analysis presents data for the 6-month on-treatment period, where both insulins were administered and titrated according to protocol. Analyses of the 6-month safety extension period (12-month data) are also presented.

Patient-level meta-analysis and statistics

This analysis included EDITION 1, 2 and 3 participants ≥ 65 and < 65 years old. This cut-off was chosen as it reflects the definition of older adults used in key treatment guidelines [1,14,27]. Analysis of change in HbA_{1c} was conducted using a mixed model for repeated measurements. For hypoglycaemic events, analysis of rate ratio was based on an over dispersed Poisson regression model adjusted on HbA_{1c} strata using treatment period as offset. Analysis of relative risk was based on a Cochran–Mantel–Haenszel method stratified by screening HbA_{1c} (< 8.0 and ≥ 8.0% [< 64 and ≥64 mmol/mol]) and study. Body weight was assessed based on an analysis of covariance model, with age group and age group-by-treatment interaction as fixed effects. Insulin dose and adverse events were analysed descriptively.

Results

Study population

Of the 2496 participants included in this analysis, 1247 and 1249 were randomised to receive Gla-300 and

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Table 1
Baseline characteristics for participants ≥ 65 years old (randomised population).

	EDITION 1 (BB)		EDITION 2 (BOT)		EDITION 3 (BOT naïve)		Patient-level meta-analysis	
	Gla-300 (*n* = 127)	Gla-100 (*n* = 119)	Gla-300 (*n* = 87)	Gla-100 (*n* = 103)	Gla-300 (*n* = 115)	Gla-100 (*n* = 111)	Gla-300 (*n* = 329)	Gla-100 (*n* = 333)
Age, years (SD)	69.1 (3.7)	69.6 (4.0)	69.2 (3.7)	70.0 (3.7)	70.0 (4.3)	69.7 (4.7)	69.4 (3.9)	69.8 (4.2)
Aged ≥ 75 years, *n* (%)	13 (10.2)	14 (11.8)	7 (8.0)	15 (14.6)	17 (14.8)	19 (17.1)	37 (11.2)	48 (14.4)
Gender (male), *n* (%)	77 (60.6)	70 (58.8)	43 (49.4)	48 (46.6)	70 (60.9)	66 (59.5)	190 (57.8)	184 (55.3)
BMI, kg/m^2 (SD)	35.2 (5.9)	36.1 (5.6)	33.5 (5.9)	33.3 (4.5)	31.7 (6.2)	32.0 (6.5)	33.5 (6.2)	33.9 (5.9)
eGFR, mL/min/1.73 m^2 (SD)	65.9 (16.9)	63.5 (19.4)	69.2 (17.9)	68.9 (18.2)	67.7 (17.4)	72.5 (18.4)	67.4 (17.3)	68.2 (19.0)
History of cardiovascular disorder, *n* (%)	56 (44.1)	63 (52.9)	31 (35.6)	50 (48.5)	38 (33.0)	22 (19.8)	125 (38.0)	135 (40.5)
Ischaemic coronary artery disorders	21 (16.5)	28 (23.5)	11 (12.6)	18 (17.5)	18 (15.7)	6 (5.4)	50 (15.2)	52 (15.6)
Coronary artery disorders	26 (20.5)	28 (23.5)	12 (13.8)	19 (18.4)	11 (9.6)	11 (9.9)	49 (14.9)	58 (17.4)
Heart failure	6 (4.7)	9 (7.6)	7 (8.0)	4 (3.9)	6 (5.2)	2 (1.8)	19 (5.8)	15 (4.5)
Duration of diabetes, years (SD)	18.6 (7.6)	19.6 (8.1)	15.6 (8.7)	14.9 (8.2)	12.8 (7.1)	12.7 (7.6)	15.8 (8.1)	15.9 (8.4)
Duration of prior basal insulin treatment, years (SD)[a]	7.7 (5.5)	7.8 (5.9)	4.1 (4.4)	4.8 (3.5)	–	–	6.2 (5.4)	6.4 (5.1)
Previous basal insulin daily dose, U/kg (SD)[a]	0.64 (0.21)	0.65 (0.22)	0.65 (0.20)	0.67 (0.23)	–	–	0.65 (0.20)	0.66 (0.22)
HbA_{1c}, % (SD)	8.02 (0.75)	7.96 (0.73)	8.16 (0.82)	8.10 (0.73)	8.36 (0.95)	8.34 (1.03)	8.17 (0.85)	8.13 (0.85)

BB: basal bolus; BMI: body mass index; BOT: basal-supported oral therapy; eGFR: estimated glomerular filtration rate; SD: standard deviation.
[a] Participants in EDITION 3 were insulin naïve and were therefore excluded from the calculations of the means for these parameters.

Gla-100, respectively (Figure S1; see supplementary material associated with this article on line). The randomised population included 329 and 333 participants ≥ 65-year-old who received Gla-300 and Gla-100, respectively. The mITT population included 1239 and 1235 participants receiving Gla-300 and Gla-100, respectively, of whom 326 and 329, respectively were ≥ 65 years 65 years old.

Baseline characteristics

Baseline characteristics from the individual and pooled study populations are shown in Table 1 (participants ≥ 65 years old) and Table S1 (see supplementary material associated with this article on line) (participants < 65 years old). Baseline characteristics were comparable across the trials with some minor differences: participants in EDITION 1 had somewhat higher BMI and duration of diabetes compared with the other EDITION trials; participants in EDITION 3 had the lowest BMI and duration of diabetes [25]. Overall, the percentage of participants with prior history of cardiovascular disorder was higher for older participants (~40%) than younger participants (~25%). The percentages of participants ≥65 years old with prior coronary artery disorder differed slightly between the studies, with the highest percentage being observed in EDITION 1 (~20%) and the lowest in EDITION 3 (~10%); similar between-study differences were observed for the younger group. A total of 37 participants (11.2%) in the Gla-300 group and 48 participants (14.4%) in the Gla-100 group were aged ≥ 75 years. The number of participants ≥ 75 years old was lowest in EDITION 2 and highest in EDITION 3.

Glycaemic control

Mean HbA_{1c} at month 6 was 7.19% (55.1 mmol/mol) in both treatment groups for participants ≥ 65 years old (SD: 0.90% [9.8 mmol/mol] for Gla-300 and 0.88% [9.6 mmol/mol] for Gla-100) (Fig. 1a). The least-squares (LS) mean decrease in HbA_{1c} from baseline to month 6 was −1.02% (−11.1 mmol/mol; standard error [SE]: 0.05% [0.6 mmol/mol]) for both treatment groups. The LS mean difference was 0.00% (0.0 mmol/mol; 95% confidence interval [CI]: −0.14 to 0.15% [−1.53 to 1.64 mmol/mol]). Similar results were seen in participants < 65 years old: LS mean change from baseline to month 6 was −1.02% (−11.1 mmol/mol) for Gla-300 versus −1.01% (−11.0 mmol/mol) for Gla-100 (SE: 0.03% [0.3 mmol/mol] for both treatment groups). The LS mean difference for participants < 65 years old was −0.00% (−0.00 mmol/mol; 95% CI: −0.09 to 0.08% [−0.98 to 0.87 mmol/mol]). Slight differences were observed in baseline HbA_{1c} between the older and younger age groups (Fig. 1a). More than half of participants achieved HbA_{1c} < 7.5% (< 58 mmol/mol) at 6 months with Gla-300 and Gla-100, in both the older (56.7% and 54.4%, respectively) and younger age groups (53.2% and 52.3%, respectively).

Mean fasting plasma glucose (FPG) at month 6 in participants ≥ 65 years old was similar for both treatment groups (Gla-300: 6.57 mmol/L [118 mg/dL]; Gla-100: 6.49 mmol/L [117 mg/dL]) with the greatest change in FPG occurring within the first 12 weeks (Gla-300: −2.56 mmol/L [−46.1 mg/dL]; Gla-100: −2.22 mmol/L [−39.9 mg/dL]) (Fig. 1b). Similar results were observed for the younger participants (Fig. 1b).

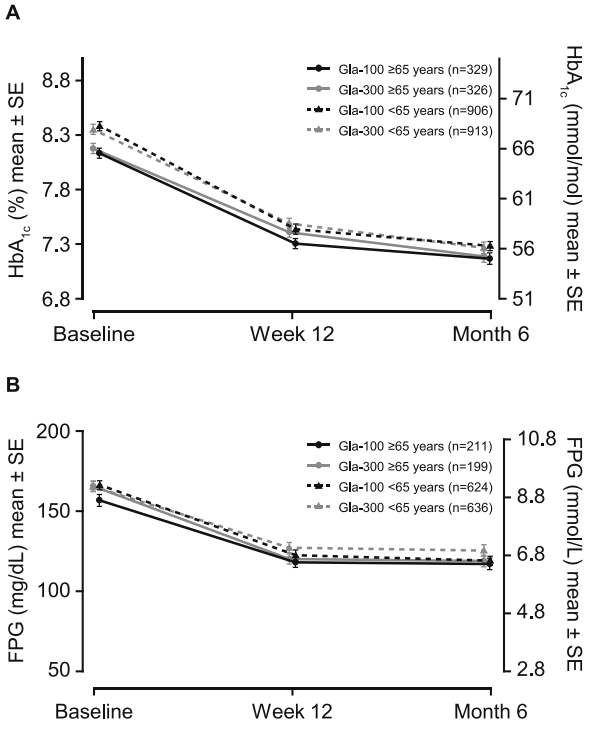

Fig. 1. A. HbA_{1c} and B. FPG by study visit for pooled patient-level data from EDITION 1, 2 and 3 (mITT population). mITT, modified intention-to-treat.

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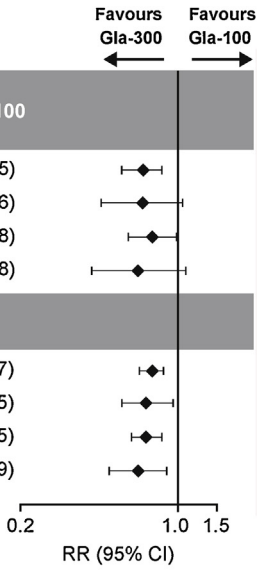
A Nocturnal hypoglycaemia (00:00–05:59 h)

Participants ≥65 years of age	Gla-300 N=327 n (%)	Gla-100 N=332 n (%)	Relative risk Gla-300 vs Gla-100 (95% CI)
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	104 (31.8)	149 (44.9)	0.70 (0.57 to 0.85)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	32 (9.8)	46 (13.9)	0.70 (0.46 to 1.06)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	81 (24.8)	105 (31.6)	0.77 (0.61 to 0.98)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	25 (7.6)	38 (11.4)	0.67 (0.42 to 1.08)
Participants <65 years of age	**Gla-300 N=915**	**Gla-100 N=914**	
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	268 (29.3)	347 (38.0)	0.77 (0.68 to 0.87)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	88 (9.6)	119 (13.0)	0.73 (0.57 to 0.95)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	209 (22.8)	283 (31.0)	0.73 (0.63 to 0.85)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	71 (7.8)	105 (11.5)	0.67 (0.50 to 0.89)



B Hypoglycaemia at any time of day (24 h)

Participants ≥65 years of age	Gla-300 N=327 n (%)	Gla-100 N=332 n (%)	Relative risk Gla-300 vs Gla-100 (95% CI)
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	234 (71.6)	257 (77.4)	0.93 (0.85 to 1.01)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	98 (30.0)	121 (36.4)	0.83 (0.67 to 1.02)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	168 (51.4)	191 (57.5)	0.89 (0.77 to 1.02)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	78 (23.9)	89 (26.8)	0.89 (0.69 to 1.15)
Participants <65 years of age	**Gla-300 N=915**	**Gla-100 N=914**	
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	580 (63.4)	640 (70.0)	0.90 (0.85 to 0.96)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	236 (25.8)	294 (32.2)	0.80 (0.70 to 0.92)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	448 (49.0)	512 (56.0)	0.87 (0.80 to 0.95)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	189 (20.7)	248 (27.1)	0.76 (0.65 to 0.89)

Pooled safety population

Fig. 2. Proportion (%) of participants experiencing ≥ 1 hypoglycaemic event over 6 months A. at night and B. at any time of day in pooled patient-level data from EDITION 1, 2 and 3 (safety population). CI: confidence interval; RR: relative risk (with regards to the percentage of participants experiencing ≥ 1 hypoglycaemic event) or rate ratio (with regards to annualised rates of hypoglycaemia).

Hypoglycaemia

The percentage of participants ≥ 65 years old experiencing ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event, or ≥ 1 documented symptomatic (≤ 3.9 mmol/L [≤ 70 mg/dL]) hypoglycaemic event, was lower with Gla-300 than Gla-100 at night (00:00–05:59 h) (Fig. 2). Although not significant, a consistent trend towards lower incidence of hypoglycaemia occurring at any time of day (24 h) was also seen. The percentage of participants < 65 years old experiencing either ≥ 1 confirmed or severe, or ≥ 1 documented symptomatic, hypoglycaemic event was lower with Gla-300 versus Gla-100 both at night and at any time of day, for both glycaemic thresholds examined (Fig. 2).

The annualised rates of nocturnal confirmed or severe hypoglycaemia, and documented symptomatic hypoglycaemia, were lower with Gla-300 than with Gla-100 at both glycaemic thresholds for participants ≥ 65 years old (Fig. 3). At any time of day (24 h), the annualised rates in participants ≥ 65 years old were comparable for both treatment groups, although, numerically lower with Gla-300 (Fig. 3). In participants < 65 years old, reduced annualised rates of nocturnal (00:00–05:59 h) hypoglycaemia with Gla-300 versus Gla-100 were also observed, although these were only significant for the higher glycaemic threshold (≤ 3.9 mmol/L [≤ 70 mg/dL]). At any time of day (24 h), significantly lower annualised rates of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia were observed (Fig. 3).

The percentage of participants aged ≥ 65 years experiencing severe nocturnal (00:00–05:59 h) hypoglycaemic events was 1.5% (n = 5) with Gla-300 versus 1.2% (n = 4) with Gla-100 (rate ratio: [RR] 1.11 [95% CI: 0.40 to 3.08]). For participants aged < 65 years, 0.3% (n = 3) receiving Gla-300 versus 0.9% (n = 8) receiving Gla-100 experienced severe nocturnal hypoglycaemic events (RR: 0.50 [0.17, 1.46]). The percentage of participants aged ≥ 65 years experiencing severe anytime (24 h) hypoglycaemic events was 3.1% (n = 10) versus 4.2% (n = 14) for Gla-300 versus Gla-100, respectively (RR: 0.71 [0.33 to 1.49]). A total of 2.0% (n = 18) versus 2.1% (n = 19) of participants < 65-year-old who received Gla-300

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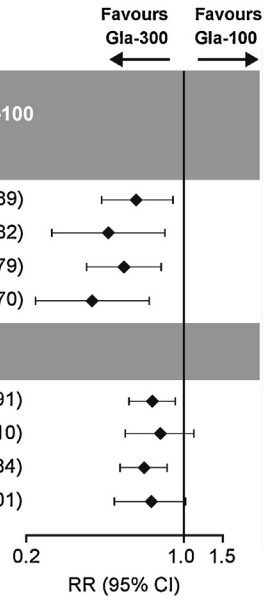
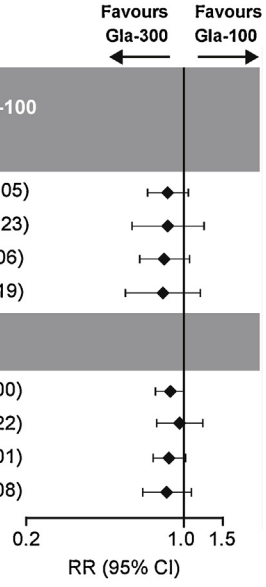
A Nocturnal hypoglycaemia (00:00–05:59 h)

Participants ≥65 years of age	Gla-300 N=327 n (events per participant-year)	Gla-100 N=332 n (events per participant-year)	Rate ratio Gla-300 vs Gla-100 (95% CI)
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	338 (2.2)	560 (3.6)	0.62 (0.43 to 0.89)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	50 (0.3)	110 (0.7)	0.46 (0.26 to 0.82)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	212 (1.4)	398 (2.6)	0.54 (0.37 to 0.79)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	37 (0.2)	97 (0.6)	0.39 (0.22 to 0.70)
Participants <65 years of age	**Gla-300 N=915**	**Gla-100 N=914**	
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	879 (2.1)	1231 (2.9)	0.72 (0.57 to 0.91)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	170 (0.4)	216 (0.5)	0.78 (0.55 to 1.10)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	556 (1.3)	837 (1.9)	0.66 (0.52 to 0.84)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	124 (0.3)	174 (0.4)	0.71 (0.49 to 1.01)



B Hypoglycaemia at any time of day (24 h)

Participants ≥65 years of age	Gla-300 N=327 n (events per participant-year)	Gla-100 N=332 n (events per participant-year)	Rate ratio Gla-300 vs Gla-100 (95% CI)
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	2733 (18.0)	3279 (21.3)	0.85 (0.69 to 1.05)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	321 (2.1)	379 (2.5)	0.85 (0.59 to 1.23)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	1269 (8.4)	1558 (10.1)	0.82 (0.64 to 1.06)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	211 (1.4)	262 (1.7)	0.81 (0.55 to 1.19)
Participants <65 years of age	**Gla-300 N=915**	**Gla-100 N=914**	
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe	6202 (14.2)	7094 (16.5)	0.87 (0.75 to 1.00)
Confirmed (<3.0 mmol/L [<54 mg/dL]) or severe	810 (1.9)	839 (2.0)	0.96 (0.76 to 1.22)
Documented symptomatic (≤3.9 mmol/L [≤70 mg/dL])	3120 (7.2)	3611 (8.4)	0.86 (0.73 to 1.01)
Documented symptomatic (<3.0 mmol/L [<54 mg/dL])	525 (1.2)	621 (1.4)	0.84 (0.66 to 1.08)



Pooled safety population

Fig. 3. Annualised rates of hypoglycaemia over 6 months A. at night and B. at any time of day in pooled patient-level data from EDITION 1, 2 and 3 (safety population). CI: confidence interval; RR: relative risk (with regards to the percentage of participants experiencing ≥ 1 hypoglycaemic event) or rate ratio (with regards to annualised rates of hypoglycaemia).

and Gla-100, respectively, experienced severe anytime hypoglycaemic events (RR: 0.95 [0.51, 1.77]).

The NNT for Gla-300 versus Gla100 to avoid one participant experiencing a confirmed (≤ 3.9 mmol/L [70 mg/dL]) or severe nocturnal hypoglycaemic event during a 6-month period was 8 for participants ≥ 65 years old and 12 for participants < 65 years old. For anytime confirmed (≤ 3.9 mmol/L [70 mg/dL]) or severe hypoglycaemic events, the NNT was 17 and 16 for older and younger adults, respectively.

Hypoglycaemia by time of day

The profile of hypoglycaemia risk by time of day during the 6-month treatment period was similar for both treatment groups and age groups. Smaller peaks of hypoglycaemia were observed around lunchtime (11:00–13:59 h), early evening (17:00–18:59 h), late evening (22:00–22:59 h), and the early hours (03:00–03:59 h; Fig. 4). The reduction in hypoglycaemia with Gla-300 compared with Gla-100 was greatest during the night and early morning.

Composite endpoint

The percentage of participants ≥ 65 years old reaching HbA_{1c} targets at month 6 without confirmed (both ≤ 3.9 mmol/L [≤ 70 mg/dL] and < 3.0 mmol/L [< 54 mg/dL]) or severe hypoglycaemia at night (00:00–05:59 h) or at any time of day (24 h), was consistently higher with Gla-300 than Gla-100 (Table 2). Statistically significant differences were seen for nocturnal confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia at all HbA_{1c} targets ($P < 0.05$; Table 2). The percentage of participants < 65 years old achieving HbA_{1c} targets (both < 7.0% 7.0% [< 54 mmol/mol] and < 7.5% [< 58 mmol/mol]) or achieving

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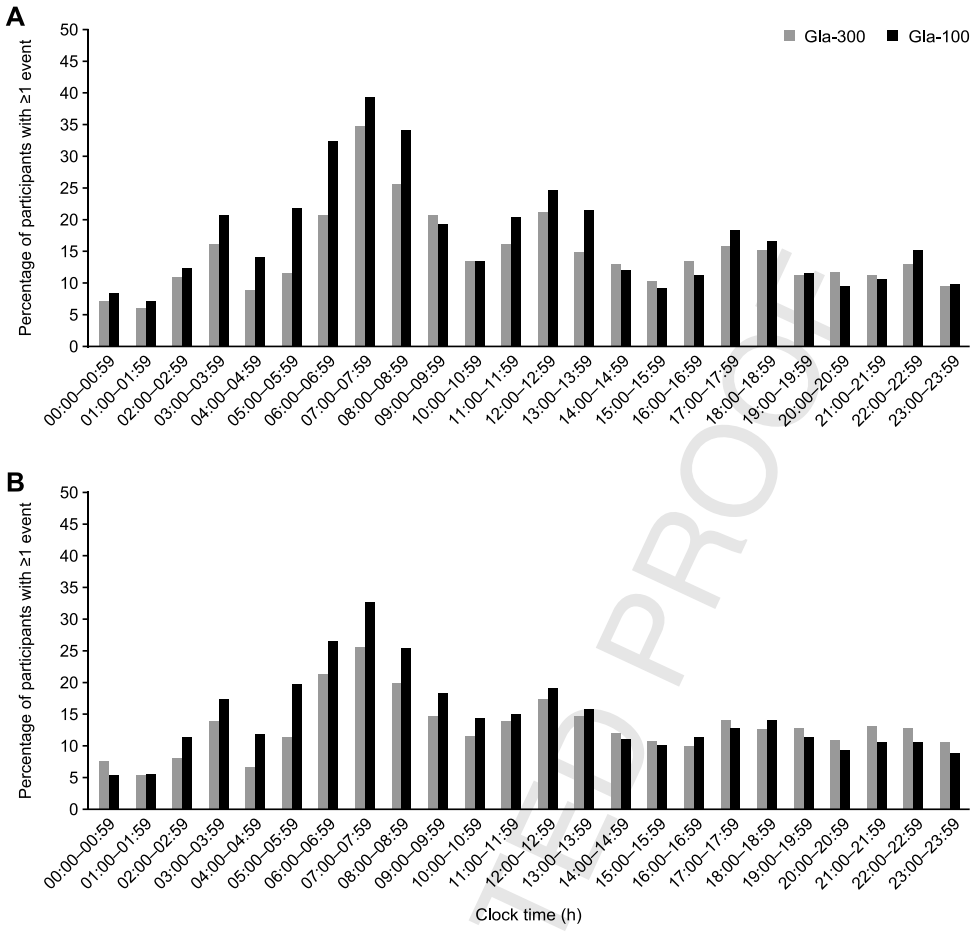

Fig. 4. Percentage of participants A. ≥ 65 years old and B. < 65 years old experiencing ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event during 6 months of treatment by time of the day in pooled patient-level data from EDITION 1, 2 and 3 (safety population).

a reduction of ≥ 0.5% (≥ 5.5 mmol/mol) without anytime (24 h) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia was significantly greater ($P < 0.05$) with Gla-300 than with Gla-100. Significantly greater percentages of participants < 65 years old receiving Gla-300 versus Gla-100 also achieved $HbA_{1c} < 7.5\%$ or a reduction of ≥ 0.5% ($P < 0.05$) without nocturnal (00:00–05:59 h) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia (Table 2).

Table 2
Percentages of participants ≥ 65 years old and <65 years old meeting composite hypoglycaemia endpoints in pooled patient-level 6-month data from EDITION 1, 2 and 3 (mITT population).

	Protocol-defined nocturnal hypoglycaemia (00:00–05:59 h)				Hypoglycaemia at any time (24 h)			
	% participants				% participants			
	Gla-300	Gla-100	RR (95% CI)	*P*-value	Gla-300	Gla-100	RR (95% CI)	*P*-value
Participants ≥ 65 years old	*n* = 326	*n* = 329			*n* = 326	*n* = 329		
Absence of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia and								
$HbA_{1c} < 7.0\%$	25.5	17.3	1.55 (1.16 to 2.07)	0.003	11.0	7.9	1.45 (0.90 to 2.33)	0.127
$HbA_{1c} < 7.5\%$	38.3	27.1	1.46 (1.17 to 1.82)	0.001	15.0	11.2	1.35 (0.91 to 2.01)	0.127
HbA_{1c} reduction from baseline ≥ 0.5%	42.3	31.9	1.31 (1.07 to 1.60)	0.007	16.6	12.8	1.28 (0.88 to 1.85)	0.192
Absence of confirmed (< 3.0 mmol/L [< 54 mg/dL]) or severe hypoglycaemia and								
$HbA_{1c} < 7.0\%$	34.7	28.6	1.25 (1.01 to 1.55)	0.044	27.6	21.3	1.33 (1.03 to 1.73)	0.031
$HbA_{1c} < 7.5\%$	51.5	45.3	1.15 (0.99 to 1.34)	0.071	39.9	33.1	1.22 (1.00 to 1.48)	0.048
HbA_{1c} reduction from baseline ≥ 0.5%	57.4	48.6	1.14 (0.99 to 1.32)	0.064	43.6	36.8	1.15 (0.96 to 1.37)	0.138
Participants < 65 years old	*n* = 913	*n* = 906			*n* = 913	*n* = 906		
Absence of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia and								
$HbA_{1c} < 7.0\%$	23.4	20.9	1.12 (0.95 to 1.33)	0.183	10.5	7.4	1.42 (1.06 to 1.90)	0.017
$HbA_{1c} < 7.5\%$	35.2	30.1	1.16 (1.02 to 1.32)	0.021	16.3	11.7	1.39 (1.11 to 1.74)	0.004
HbA_{1c} reduction from baseline ≥ 0.5%	43.2	37.2	1.17 (1.05 to 1.31)	0.005	21.0	15.5	1.37 (1.14 to 1.66)	0.001
Absence of confirmed (< 3.0 mmol/L [< 54 mg/dL]) or severe hypoglycaemia and:								
$HbA_{1c} < 7.0\%$	32.2	31.6	1.01 (0.89 to 1.15)	0.835	26.0	23.6	1.09 (0.94 to 1.28)	0.258
$HbA_{1c} < 7.5\%$	47.4	45.5	1.04 (0.94 to 1.14)	0.444	38.1	34.2	1.11 (0.99 to 1.25)	0.084
HbA_{1c} reduction from baseline ≥ 0.5%	56.6	54.5	1.05 (0.97 to 1.13)	0.263	45.5	41.7	1.10 (0.99 to 1.21)	0.072

CI: confidence interval; mITT: modified intention-to-treat; RR: relative risk.

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Insulin dose

Mean daily average basal insulin dose increased in both treatment groups. At month 6, mean (SD) basal dose was: 0.80 (0.35) U/kg/day and 0.73 (0.32) U/kg/day for participants ≥ 65 years old with Gla-300 and Gla-100, respectively. Mean (SD) 6-month basal dose was 0.86 (0.37) U/kg/day and 0.77 (0.32) U/kg/day for participants < 65 years old with Gla-300 and Gla-100, respectively. The majority of the dose increases occurred within the first 12 weeks of treatment. At month 6, the dose of either insulin was greater in younger versus older participants (6–8%) (Figure S2; see supplementary material associated with this article on line).

Body weight

The LS mean (SE) change in body weight from baseline to month 6 was similar for Gla-300 (0.4 kg [0.19]) and Gla-100 (0.5 kg [0.19]) in participants ≥ 65 years old. The LS mean difference between treatment groups was −0.12 kg (95% CI: −0.64 to 0.40). For participants < 65 years old, the LS mean (SE) change in body weight was slightly higher with Gla-100 (0.9 kg [0.1]) than with Gla-300 (0.6 kg [0.1]). The LS mean difference between treatment groups for younger participants was −0.34 kg (95% CI: −0.65 to −0.03).

Adverse events

The percentage of participants experiencing treatment emergent adverse events (TEAEs) was similar for both insulins (58.4% versus 56.0% in participants ≥ 65 years of age and 56.9% versus 52.8% in participants < 65 years of age for Gla-300 and Gla-100, respectively). Incidence of serious TEAEs was 8.6% and 7.5% for Gla-300 and Gla-100, respectively, in participants ≥ 65 years of age and 4.0% for both treatment groups in the younger age group. Incidence of TEAEs leading to death or treatment discontinuation were low (< 2%) across both treatment groups and age groups (Table S2; see supplementary material associated with this article on line).

-month extension data (12 months time point)

The HbA_{1c} reductions achieved at 6 months were maintained at 12 months (Figure S3a; see supplementary material associated with this article on line). FPG remained stable following the reductions observed within the first 12 weeks of treatment (Figure S3b; see supplementary material associated with this article on line), and no differences in change in body weight or insulin dose were observed at month 12 compared with month 6 (data not shown). At 12 months, between 63% and 69% of participants experienced TEAEs across treatments and age groups. Serious TEAEs were experienced by 15–16% of participants aged ≥ 65 years and 8–9% of participants aged < 65 years (Table S2; see supplementary material associated with this article on line).

Discussion

The results of this post hoc patient-level meta-analysis demonstrate a lower risk of nocturnal hypoglycaemia with Gla-300 versus Gla-100 in participants ≥ 65 years old. This finding is consistent with results obtained for the younger participants aged < 65 years, with the results of the overall EDITION study program [19–25], and may be attributed to the more even steady-state profile and longer duration of action observed for Gla-300 versus Gla-100 [28]. The reduction in nocturnal annualised rates achieved with Gla-300 compared with Gla-100 appeared greater in participants ≥ 65 years old than in younger participants, with significantly lower rates observed with Gla-300 than Gla-100 for both glycaemic thresholds (≤ 3.9 mmol/L [≤ 70 mg/dL]) and < 3.0 mmol/L [< 54 mg/dL]).

This post hoc analysis focussed on data for the 6-month on-treatment period, where both insulins were administered and titrated according to protocol; such data may provide more meaningful comparisons between Gla-300 and Gla-100 than the 6-month safety extension period, where participants were required to maintain their own insulin treatments, with less frequent clinic visits. Nevertheless, at 12 months, the findings in the older participants were consistent with the 6-month results. The benefit in terms of nocturnal hypoglycaemia with Gla-300 versus Gla-100 was maintained and the HbA_{1c} reduction remained similar with both insulin treatments.

While the key objective in older people with T2DM should be to minimize hypoglycaemia, achieving appropriate glycaemic goals remains important. In the present analysis, HbA_{1c} outcomes were comparable with both Gla-300 and Gla-100 at 6 and 12 months, consistent with the overall EDITION program [19–25]. A greater percentage of participants ≥ 65 years old in the Gla-300 versus Gla-100 group achieved HbA_{1c} levels of < 7.0% (< 53 mmol/mol), or < 7.5% (< 58 mmol/mol), or HbA_{1c} reductions ≥ 0.5% [≥ 5.5 mmol/mol] without experiencing nocturnal confirmed or severe hypoglycaemia. A similar finding was observed for confirmed or severe hypoglycaemia at any time of day (24 h). In participants < 65 years of age, a greater percentage of participants achieved composite endpoints of HbA_{1c} target achievement without confirmed or severe hypoglycaemia at the ≤ 3.9 mmol/L (≤ 70 mg/dL) threshold with Gla-300 compared with Gla-100, but similar percentages of participants achieved composite endpoints at the lower glycaemic threshold (< 3.0 mmol/L (< 54 mg/dL). These data indicate that Gla-300 may be beneficial in older people by enabling them to achieve their individualised target HbA_{1c} levels, while reducing the risk of hypoglycaemia compared with Gla-100. This supposition is supported by the results from the DELIVER 3 real-world evidence programme which showed comparable glycaemic control with reduced incidence ($P < 0.0001$) and rates ($P = 0.0002$) of hypoglycaemia in people ≥ 65 years of age switching basal insulin to Gla-300 versus other basal insulins [29]. The daily insulin dose was higher with Gla-300 than Gla100, which was consistent with the findings from the overall EDITION program [19–25].

The percentage of participants aged ≥ 65 years who experienced TEAEs at 6 months (56–58%) was similar to the that reported from the meta-analysis of the overall EDITION population (54–57%) [25]. Treatment-emergent serious adverse events were slightly higher in the older participants (7.5–8.6%) than in the younger participants (4%) and the overall EDITION population (5%) [25].

The current analysis has a number of limitations. Primarily that this is a post hoc analysis, rather than a dedicated prospective trial in older individuals with diabetes. The EDITION trials were not statistically powered to determine efficacy and safety of Gla-300 versus Gla-100 in older adults. In addition, there was insufficient power to test the endpoints of the older participants against younger participants. The glucose target in the EDITION trials was 80–100 mg/dL (4.4–5.6 mmol/L), which is lower than recommended by guidelines for older individuals. Lastly, only limited number of participants aged ≥ 75 years were included in the EDITION trials, precluding conclusion for this demographic. A cut-off of ≥ 65 years was used to define older adults in the present study, in-line with key treatment guidelines [1,14,27]; however, there is discussion relating to the most appropriate cut-off to define older adults, with the United Nations proposing ≥ 60 years

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[30] and other guidelines suggesting ≥ 70 years [11]. In reality, older adults comprise a heterogeneous population and clinical decisions should be made based on factors such as functional status, comorbidities, frailty [14]. Notwithstanding these limitations, this analysis provides valuable information regarding the safety and efficacy of basal insulins in an older group of individuals who are often excluded from clinical trials. SENIOR (NCT02320721), is a dedicated randomised controlled trial investigating the safety and efficacy of basal insulins (Gla-300 versus Gla-100) in older adults (≥ 65 years of age), which may address many of the limitations of this post hoc analysis [31]. Furthermore, SENIOR was designed such that 20% of enrolled participants were ≥ 75 years of age, thereby enabling adequate power to detect statistical differences between treatments in this population [31].

In summary, it is important to recognise that balancing glycaemic treatment goals with safety in older people with diabetes, while maintaining a priority of limiting hypoglycaemia, is important. The results of this post hoc meta-analysis suggest that, compared with Gla-100, Gla-300 was associated with less nocturnal hypoglycaemia and comparable HbA_{1c} reduction in this vulnerable older age group, with similar results to those observed in participants < 65 years old. Given the increased burden of T2DM and its complications in older individuals, further studies focusing on therapeutic goals and outcomes in older people with T2DM will be important for defining the best treatment approaches for this growing patient population.

Author contributions

Sanofi was the sponsor of the EDITION 1, 2 and 3 studies, and was responsible for the design and coordination of the trials, monitoring clinical sites, and collecting and managing data. Claire Brulle-Wohlhueter and Ana Merino-Trigo developed the initial concept for this post hoc analysis. Gregory Bigot was responsible for the statistical analyses of these data. All authors contributed in interpreting the findings and writing, reviewing and editing the manuscript.

Clinical trial registration

NCT01499082, NCT01499095, NCT01676220 (ClinicalTrials.gov).

Disclosure of interest

Carlos Trescoli declares that he has no competing interest.
Jean-François Yale – Advisory panel: Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Janssen, Locemia, Medtronic, Merck, Novo Nordisk, Sanofi, Takeda; Research support: AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen, Locemia, Medtronic, Merck, Mylan, Sanofi; Speakers Bureau: Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Janssen, Locemia, Medtronic, Merck, Novo Nordisk, Sanofi, Takeda.
Vanita Aroda – Consultant: Sanofi, Novo Nordisk; Research support: Amylin, AstraZeneca, Boehringer Ingelheim, Eisai, Hanmi, Novo Nordisk, Sanofi, Takeda.
Bernard Charbonnel – Advisory Panel, Consultant and Speakers bureau: AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Takeda
Alan J Sinclair – Advisory board: Eli Lilly, Merck, Novartis, Pfizer, Sanofi; Speakers bureau: Eli Lilly, Merck, Novartis, Pfizer, Sanofi.
Avivit Cahn – Advisory board: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi; Speakers bureau: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi; Research support: AstraZeneca.
Gregory Bigot – Employee: IVIDATA (on behalf of Sanofi).
Ana Merino-Trigo – Employee: Sanofi; Stocks and shares: Sanofi.
Claire Brulle-Wohlhueter – Employee: Sanofi; Stocks and shares: Sanofi.
Geremia Bolli – Advisory panel: Sanofi; Consultant: Novartis; Speakers bureau: Eli Lilly.
Robert Ritzel – Consultant: AstraZeneca, Merck, Novo Nordisk, Sanofi, Servier; Speakers bureau: AstraZeneca, Boehringer Ingelheim; Eli Lilly, Merck, Novartis, Novo Nordisk, Sanofi.

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Appendix A. Supplementary material

Supplementary materials (Figures S1-S2-S3 and Tables S1-S2) associated with this article can be found at http://www.scincedirect.com, at doi:https://doi.org/10.1016/j.diabet.2018.10.002.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.diabet.2018.10.002.

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