Article:
Rosenstock, J., Bajaj, H.S., Lingvay, I. et al. (2024) Clinical perspectives on the frequency of hypoglycemia in treat-to-target randomized controlled trials comparing basal insulin analogs in type 2 diabetes: a narrative review. BMJ Open Diabetes Research & Care, 12. e003930. ISSN: 2052-4897

https://doi.org/10.1136/bmjdrc-2023-003930

BMJ Open Diabetes Research & Care

Clinical perspectives on the frequency of hypoglycemia in treat-to-target randomized controlled trials comparing basal insulin analogs in type 2 diabetes: a narrative review

Julio Rosenstock [1], Harpreet S Bajaj,[2] Ildiko Lingvay [3], Simon R Heller [4]

To cite: Rosenstock J, Bajaj HS, Lingvay I, *et al*. Clinical perspectives on the frequency of hypoglycemia in treat-to-target randomized controlled trials comparing basal insulin analogs in type 2 diabetes: a narrative review. *BMJ Open Diab Res Care* 2024;**12**:e003930. doi:10.1136/bmjdrc-2023-003930

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjdrc-2023-003930).

Received 21 November 2023
Accepted 26 April 2024

For numbered affiliations see end of article.

Correspondence to
Dr Julio Rosenstock; juliorosenstock@dallasdiabetes.com

ABSTRACT

The objective of this review was to comprehensively present and summarize trends in reported rates of hypoglycemia with one or two times per day basal insulin analogs in individuals with type 2 diabetes to help address and contextualize the emerging theoretical concern of increased hypoglycemic risk with once-weekly basal insulins.

Hypoglycemia data were extracted from treat-to-target randomized clinical trials conducted during 2000–2022. Published articles were identified on PubMed or within the US Food and Drug Administration submission documents. Overall, 57 articles were identified: 44 assessed hypoglycemic outcomes in participants receiving basal-only therapy (33 in insulin-naive participants; 11 in insulin-experienced participants), 4 in a mixed population (insulin-naive and insulin-experienced participants) and 9 in participants receiving basal-bolus therapy. For the analysis, emphasis was placed on level 2 (blood glucose <3.0 mmol/L (<54 mg/dL)) and level 3 (or severe) hypoglycemia.

Overall, event rates for level 2 or level 3 hypoglycemia across most studies ranged from 0.06 to 7.10 events/person-year of exposure (PYE) for participants receiving a basal-only insulin regimen; the rate for basal-bolus regimens ranged from 2.4 to 13.6 events/PYE. Rates were generally lower with second-generation basal insulins (insulin degludec or insulin glargine U300) than with neutral protamine Hagedorn insulin or first-generation basal insulins (insulin detemir or insulin glargine U100). Subgroup categorization by sulfonylurea usage, end-of-treatment insulin dose or glycated hemoglobin reduction did not show consistent trends on overall hypoglycemia rates. Hypoglycemia rates reported so far for once-weekly basal insulins are consistent with or lower than those reported for daily-administered basal insulin analogs.

INTRODUCTION

As recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) 2022 consensus on the management of hyperglycemia,[1] basal insulin has been replaced by injectable incretin-related therapy as the first-line injectable therapy for type 2 diabetes (T2D) insufficiently controlled by combinations of oral glucose-lowering agents. However, many individuals with T2D may still eventually require basal insulin as beta-cell function declines over time or if insufficiently controlled by injectable incretin-related therapy.[2]

Hypoglycemia is a common adverse event associated with insulin therapy, and hypoglycemia risk increases with intensive glycemic control and duration of T2D.[3] Optimizing T2D management with insulin therapy is therefore a balancing act between achieving optimal glycemic control while minimising hypoglycemia risk, irrespective of the insulin formulation used in clinical practice. Overall hypoglycemia may be considered as any episode with blood glucose (BG) <3.9 mmol/L (<70 mg/dL) irrespective of time of day. 'Level 1' hypoglycemia consists of BG values between 3.0 and 3.9 mmol/L (54–70 mg/dL), which are regarded as 'alerts' to take action but do not have regulatory implications.[4 5] Clinicians and regulators consider 'level 2' (or 'clinically significant') hypoglycemia, defined as a BG value <3.0 mmol/L (<54 mg/dL), and 'level 3' (or 'severe') hypoglycemia, defined as an episode causing sufficient cognitive impairment to require assistance from another person, to be most relevant when evaluating treatment.[4 6] Both level 2 and level 3 hypoglycemia have substantial clinical impacts, increasing mortality and morbidity[7 8] while also reducing quality of life[9] and exerting indirect effects via increased healthcare resource utilization (ie, hospital admissions), increased workplace absenteeism and reduced productivity.[10] Recent real-world analyses in the USA show

alarmingly high rates of level 3 or severe hypoglycemia, supporting the urgent need for hypoglycemia-mitigating interventions.[11]

Over the past three decades, there have been major improvements in the pharmacokinetic (PK) and pharmacodynamic (PD) properties of basal insulins, starting with first-generation basal insulin analogs (ie, insulin detemir (detemir) and insulin glargine U100 (glargine U100)), generating more predictable, longer-acting soluble formulations with flatter PK and PD profiles among insulin analogs, resulting in reduced hypoglycemia risk compared with neutral protamine Hagedorn (NPH) insulin.[12–14]

The 'Treat-To-Target' Study published in 2003, comparing glargine U100 with NPH insulin, led to a paradigm shift in the accepted standard of care regarding insulin therapy for T2D.[15] This trial established the concept of gradually increasing the insulin dose to attain a predefined fasting glucose target or until unacceptable hypoglycemia occurs. This 'treat-to-target' approach would thus enable glycated hemoglobin (HbA1c) parity between comparators, and in turn allow for differentiation based on other outcomes of interest (eg, hypoglycemia). This study reduced hypoglycemia risk using basal insulin analogs that showed a more predictable PK/PD; this enabled systematic insulin titrations resulting in fewer hypoglycemic episodes, particularly at night.[16] Subsequent development of second-generation insulin analogs with an even longer duration of action, flatter insulin PK/PD profiles, and lower insulin peak:trough ratios (ie, more constant circulating insulin levels), such as insulin degludec (degludec) U100 and U200, and insulin glargine U300 (glargine U300), further reduced hypoglycemia risk compared with glargine U100.[17–19]

Despite these developments, hypoglycemia remains a fundamental challenge of basal insulin therapy. Fear of hypoglycemia, delays in treatment initiation partly due to the injection barrier, titration inertia and a lack of concordance are perhaps the main barriers to the effective use of insulin therapy in patients with T2D.[20 21] To help overcome clinical inertia and to reduce the injection burden with daily basal insulin, two once-weekly basal insulins have been developed and are in late-stage clinical trials: insulin icodec (icodec) and basal insulin Fc efsitora alfa (efsitora). The efficacy of icodec and efsitora was demonstrated in phase 1 and phase 2 randomized clinical trials (RCTs),[22–28] and further confirmed for icodec in the phase 3a ONWARDS program in insulin-naive individuals newly initiating insulin, individuals treated with basal insulin alone or individuals already established on basal-bolus insulin regimens.[29–34]

Given the protracted duration of action of once-weekly insulin, physicians may have a theoretical concern regarding the risk of hypoglycemia.[35] Contextualizing the risk of hypoglycemia observed with once-weekly insulin in RCTs requires a clear and up-to-date understanding of the risk of hypoglycemia seen with currently available once-daily or two times per day basal analogs. However, owing to heterogeneity in trial designs, hypoglycemia definitions, titration interventions and study populations, it is difficult to compare hypoglycemia outcomes between RCTs in a formal meta-analysis. Therefore, the aim of this narrative review was twofold: (1) to define the hypoglycemia risk with current one or two times per day basal insulin analogs; and (2) to use these data to help contextualize emerging once-weekly basal insulin hypoglycemia data. Here, we comprehensively summarize mean hypoglycemia rates from treat-to-target trials of daily basal insulins in T2D conducted over the past 22 years (2000–2022), with reference to the differences between studies. Importantly, given the narrative nature of this review, no comparative statistical analyses were possible.

METHODS: TRIAL IDENTIFICATION AND DATA EXTRACTION

Published articles were identified in Ovid MEDLINE and Embase via targeted searches using the search strings shown in online supplemental table 1. The US Food and Drug Administration (FDA) submission documents for glargine U100,[36] detemir,[37] degludec[38] and glargine U300[39] were also used to source additional studies. Only English articles were included.

Treat-to-target RCTs (sample size >30 participants/arm) assessing daily basal insulins (detemir, glargine U100, degludec and glargine U300) in adults (≥18 years of age) with T2D conducted between January 1, 2000 and December 30, 2022 and reporting BG-confirmed hypoglycemia were eligible for inclusion. RCTs assessing premix insulin or fixed-dose basal insulin/glucagon-like peptide-1 receptor agonist (GLP-1 RA) combinations without a basal-only insulin arm were not eligible. Data from phase 3a RCTs assessing icodec were added during development, as the publications became available.[30–33 40]

The primary outcomes of interest were the mean event rates/person-year of clinically relevant 'level 2' hypoglycemia (BG value <3.1 mmol/L (55 mg/dL) or <3.0 mmol/L (54 mg/dL)), severe 'level 3' hypoglycemia, overall hypoglycemia (any BG value <3.9 mmol/L (70 mg/dL) irrespective of time of day) and nocturnal hypoglycemia; these definitions were selected to provide the greatest data inclusivity, given the changes in hypoglycemia definitions over time. Prior to 2017 and the position statement by the International Hypoglycaemia Study Group,[5] the glucose threshold for 'level 2' hypoglycemia was applied arbitrarily across studies; hence, both <3.1 mmol/L (55 mg/dL) and <3.0 mmol/L (54 mg/dL) thresholds have been accounted for in the analysis. Hypoglycemia rates are presented as events/person-year of exposure (PYE) reported for the defined study treatment period. Continuous glucose monitoring (CGM)-based time below range (TBR), defined as proportion of time spent with sensor glucose levels below target range (<3.9 mmol/L (<70 mg/dL)), was also captured; however, trials reporting CGM-based

hypoglycemia without also providing BG-confirmed values were excluded. Study design and participant baseline characteristics (body mass index (BMI), HbA1c, age and diabetes duration), in addition to changes in HbA1c from baseline to end of treatment (EOT), were also captured. Sulfonylurea usage and continuation (yes/no) after trial randomization was also extracted. As access to the raw data was not possible, and to avoid any inadvertent introduction of errors, all data reported here employ the format and number of decimal places used in the original publication.

OVERVIEW OF TREAT-TO-TARGET DAILY BASAL INSULIN TRIALS IN PEOPLE WITH T2D (2000–2022)

Overview of trials

Overall, 57 treat-to-target RCTs were identified: 39 via the targeted literature search, 13 from the FDA submission documents (NPH insulin (n=4),[41–44] glargine U100 (n=6),[41–43 45–47] detemir (n=4),[44 48–50] degludec (n=4),[46 51–53] and glargine U300 (n=1)[45]) and 5 phase 3a icodec publications that were added as they became available.[30–33 40]

Of these 57 RCTs, 44 assessed outcomes in individuals receiving basal-only therapy (33 in insulin-naive participants; 11 in insulin-experienced participants), 4 in a mixed population of insulin-naive and insulin-experienced participants and 9 in individuals receiving basal-bolus therapy.

Both basal-only and basal-bolus regimens were administered with or without non-insulin glucose-lowering agents including GLP-1 RAs and/or sulfonylureas.

Hypoglycemia data collection and definitions

Across studies, hypoglycemia data were collected using self-measured blood glucose (SMBG) measurements (n=50), CGM devices (n=1) or a combination of both (n=1) (online supplemental tables 2 and 3). SMBG measurements were used to measure overall and nocturnal hypoglycemia rates, while CGM was used to measure TBR. Overall and nocturnal hypoglycemia definitions for the included trials are shown in online supplemental table 4. Most trials used definitions of BG-confirmed <3.1 mmol/L (<55 mg/dL), severe hypoglycemia or BG-confirmed <3.1 mmol/L (<55 mg/dL) or severe hypoglycemia or BG-confirmed values of <3.0 mmol/L (<54 mg/dL), which were grouped together for the purpose of this analysis.

Trial characteristics

A summary of concomitant sulfonylurea usage, trial duration, baseline characteristics, SMBG titration targets, EOT insulin dose and changes in HbA1c across all studies is presented in table 1. Additional details on an individual study basis are presented in online supplemental tables 2 and 3. Most trials were phase 3 (three were phase 4) and multicenter; two single-center studies were included (online supplemental table 2). Trial duration was ≤16 weeks for 4 studies, 22–28 weeks for the majority of studies (n=34), 36–41 weeks for 4 studies, 52–54 weeks for 10 studies, and ≥64 weeks for 5 studies. Ten of the trials reported a non-inferiority statistical framework (online supplemental table 2). Generally, the mean ranges for baseline age and duration of diabetes for insulin-experienced individuals in the basal-only (54.7–62.9 years and 13.0–15.6 years, respectively) and basal-bolus trials (56.5–62.1 years and 12.4–16.4 years, respectively) were higher than those for insulin-naive individuals receiving basal-only insulin therapy (52.9–64.0 years and 6.4–11.6 years, respectively). Across each set of studies per insulin type, the range in HbA1c reduction was improved with successive generations of insulin (table 1). All included studies employed treat-to-target protocols based on glucose targets, except one study that used both glucose and HbA1c (<7.0%) targets (online supplemental table 2).[54]

Summary of overall and nocturnal hypoglycemia event rates

Overall and nocturnal hypoglycemia event rates (events/PYE) across studies are summarized in table 1. Itemized outcomes, including incidence rates and number of participants reporting hypoglycemia, for each individual trial are shown in online supplemental tables 5 and 6. Generally, there were wide variations in rates of overall hypoglycemia and nocturnal hypoglycemia across RCTs (table 1).

Across basal-only trials in insulin-naive individuals, overall BG-confirmed hypoglycemia rates (any BG threshold <3.9 mmol/L (<70 mg/dL) at any time of day (level 1 or two hypoglycemia)) ranged from 0.06 to 8.5 events/PYE[41 45 48–50 55–58] for NPH insulin, detemir, glargine U100, glargine U300, and degludec with a general trend for lower rates (events/PYE) with successive generations of insulin (table 1). Severe hypoglycemia (level 3) rates across these basal insulins were low and ranged from 0.0 to 0.14 events/PYE. Nocturnal hypoglycemia rates (insufficient information to group by level) ranged from 0.03 to 1.3 events/PYE, with a trend for lower rates with second-generation analogs than with first-generation analogs (table 1).

For basal-only trials in insulin-experienced individuals, reported overall BG-confirmed hypoglycemia rates (any BG threshold <3.9 mmol/L (<70 mg/dL)) ranged from 0.28 to 8.11 events/PYE for glargine U100, glargine U300, and degludec (table 1). For these basal insulins, severe (or level 3) hypoglycemia rates ranged from 0.0 to 0.09 events/PYE, while nocturnal hypoglycemia rates ranged from 0.11 to 2.3 events/PYE. Studies with NPH or detemir in this group were either not conducted or did not report hypoglycemia rates (table 1).

For the basal-bolus trials, reported overall BG-confirmed hypoglycemia rates were substantially higher (any

Table 1 Summary of trials and hypoglycemia rates per insulin type for treat-to-target basal-only and basal-bolus insulin T2D trials

Insulin type	Trial duration, weeks	Number of randomized participants*	Baseline characteristics				SU usage at BL, yes/no	Fasting SMBG titration target, mmol/L	EOT insulin dose, U/day	HbA1c reduction from BL, %	Overall BG-confirmed hypoglycemia		Nocturnal hypoglycemia	
			Age, years	HbA1c, %	BMI, kg/m^2	T2D duration, years					Incidence, %	Rates, events/ PYE†	Incidence, %	Rates, events/ PYE
Basal-only insulin trials (insulin-naive individuals with T2D), N=34														
NPH insulin, n=2 [41 50]	24	232–238	60.4–62	8.5–9.1	28.9–29.0	9.3–9.8	Yes: n=2	≤5.6–6.0	37–45	–0.84, –1.9	Overall: 64–80 Severe: 2.6	Overall: NR/7.14 Severe: 0.08–0.12	0.4–47	Overall: NR/1.77 Severe: 0.01
Glargine U100, n=26 [33 41 45 46 52 54–57 64 67 70–8433 41 45 46 52 54–66 70–76]	12–104	20–1978	52.9–63.8	7.5–9.4	23.5–35.6	6.4–11.6	Yes: n=15/26 No: n=9/26 NR: n=2/26	3.9–7.2	15.7–62.0	–0.4, –2.76	Overall: 4.4–79.8 Severe: 0.5–7.2	Overall: 0.33–8.5 NR: n=11/25 Severe: 0.0–0.14 NR: n=10/25	3.4–59.8	Overall: 0.045–2.43 NR: n=15/25
Detemir, n=6 [48–50 55–57]	24–52	162–565	56.8–61.3	7.6–9.1	28.9–34.9	8.0–11.0	Yes: n=3/6 No: n=3/6	>3.9–6.0	39.5–65.6 NR:2/6	–0.48, –1.8	Overall: 9.2–64 Severe: 2	Overall: 0.23–3.67 NR: n=1/6 Severe: 0–0.01 NR: n=1/6	26–33	Overall: 0.7–1.1 NR: n=3/6
Degludec, n=6 [32 46 51 52 67 68]	26–52	111–773	55.7–59.4	7.6–8.5	26.5–33.4	7.5–9.7	Yes: 0/5 No: 5/5	3.9–7.2	27–62	–0.93, –1.4	Overall: 17.3–23.1 Severe: 0.3–0.4	Overall: 0.09–1.6 Severe: 0.0–0.01 NR: n=3/5	1.7–13.8	Overall: 0.03–0.25
Glargine U300, n=3 [45 56 58]	26–52	175–1651	58.2–64.0	8.5–9.1	30.3–33.9	10.1–11.6	Yes: n=2/3 No: n=1/3	4.4–7.2	29.41–59.4	–1.4, –1.6	Overall: 9.9–46.2 Severe: NR: 3/3	Overall: 0.24–6.41 Severe: 0.02 NR: n=2/3	3.9–17.9	Overall: 0.1–1.31
Icodec, n=3 [32–34]	26–78	294–542	58–59.1	8.5–9.0	29.9–32.6	10.5–11.9	No: n=1 Yes: n=2	4.4–7.2	29–32	–1.35, –1.68	Overall: NR Severe: NR	Overall: 2.34–3.02 Severe: 0.00–0.01	NR	NR
Basal-only insulin trials (insulin-experienced individuals with T2D), n=10														
NPH insulin, n=1 [42]	28	259	59.2	8.5	30.4	14.1	No: 1/1	4.4–7.8	~50	–0.59	Overall: 66.8 Severe: 2.3	Overall: NR Severe: NR	40.2	Overall: NR
Glargine U100, n=7 [42 65 66 85 86 99 100]	26–65	120–498	56.7–62.9	7.6–8.6	4.8–34.8	11.4–15.6	Yes: 3/7 No: 4/7	3.9–7.8	20.6–83 NR: 3/7	–0.3, –1.0	Overall: 11.3–79.3 Severe: 0.4–3.9	Overall: 0.28–8.11 NR: n=3/7 Severe: 0.02–0.09 NR: n=3/7	11.6–41.6	Overall: 0.884–2.30 NR: n=3/7
Degludec, n=5 [30 47 69 85 86]	22–65	151–720	54.7–62.9	7.6–8.9	27.4–33.4	11.5–16.9	No: 2/4 Yes: 1/4 NR: 1/4	3.9–7.2	35–83	–0.5, –1.0	Overall: 4.6–54.9 Severe: 0.9–2.2	Overall: 0.483–5.66 Severe: 0.00–0.01 NR: n=1/4	4.6–27.3	Overall: 0.107–1.7
Glargine U300, n=2 [65 100]	26–52	121–404	57.9–61.1	8.0–8.3	25.7–34.8	13.0–14.0	Yes: 1/2 No: 1/2	4.4–5.6	25.1–91	–0.3, –0.6	Overall: 0.6–71.5 Severe: 1.0	Overall: 6.76 Severe: 0.03	8.2–30.5	Overall: 2.3

Continued

Table 1 Continued

Insulin type	Trial duration, weeks	Number of randomized participants*	Baseline characteristics: Age, years	HbA1c, %	BMI, kg/m^2	T2D duration, years	SU usage at BL, yes/no	Fasting SMBG titration target, mmol/L	EOT insulin dose, U/day	HbA1c reduction from BL, %	Overall BG-confirmed hypoglycemia: Incidence, %	Overall BG-confirmed hypoglycemia: Rates, events/PYE†	Nocturnal hypoglycemia: Incidence, %	Nocturnal hypoglycemia: Rates, events/PYE
Icodec, n=1[30]	26	263	62.3	8.2	29.5	16.5	No	4.4–7.2	38	−0.9	Overall: 55 Severe: 0	Overall: 7.79 Severe: 0	23	0.93
Basal-only insulin trials (insulin-naïve and insulin-experienced individuals with T2D), n=4														
NPH insulin, n=1[43]	52 weeks	281	59.4	8.9	28.8	10.5	Yes	6.66	NR	−0.4	Overall: 41/43 Severe: 1.1	NR	24	NR
Glargine U100, n=4[17 43 64 101]	26–104 weeks	230–3819	56.7–65	8.4–9.0	29–33.6	10.2–16.2	Yes:3/4 No:1/4	3.9–5.6	49.7/49.8 NR: n=3	−0.5, −1.4	Overall: 33–69 Severe: 1.7–6.6	Overall: 3.5–23.4 NR: n=2 Severe: 0–0.0625 NR: n=2	1.9–46	0.014–7.9 NR: n=1
Degludec, n=2[17 101]	26–104 weeks	228–3818	56.2–64.9	8.4–8.5	29.3–33.6	10.3–16.6	Yes: n=3	3.9–5.0	NR: n=3	−1.1, −1.4	Overall: 44–51 Severe: 4.9	Overall: 3.6 NR: n=1 Severe: 0.037 NR: n=2	1.0–13	0.6 NR: n=2
Basal-bolus insulin trials,‡ n=9														
NPH insulin, n=2[44 102]	22–26	146–199	58.2–61.8	8.1–8.8	28.7–32.0	14.5–16.4	No: 2/2	5.0–7.0	NR: n=2/2	−0.6, −1.0	Overall: 1.5–65.3 Severe: 1.0	Overall: NR: n=2/2 Severe: NR: n=2/2	12.8–69.9	Overall: NR: n=2/2
Glargine U100, n=7[31 59–63 103]	26–52	141–403	56.5–61.0	8.1–8.5	25.0–36.6 NR: n=1	12.4–16.3	No:4/6 NR:1/6 NR:1/6	3.9–7.2	29–94 NR: n=1/5	−0.8, −1.4	Overall: 9.4–82 Severe: 2.3–5.7	Overall: 2.71–26.76 Severe: 0.00–0.24	16.1–59.7	Overall: 0.53–4.20
Detemir, n=2[44 102]	22–26	125–195	58.3–62.1	8.2–8.9	29.8–31.6	13.7–16.2	NR: n=2/2	5.0–7.0	NR: n=2/2	−0.6, −1.1	Overall: 4.7–38.7 Severe: 1.0	Overall: NR: n=2/2 Severe: NR: n=2/2	7.9–30.1	Overall: NR: n=2/2
Degludec, n=1[63]	52	744	59.2	8.3	32.3	13.6	NR	3.9–5.0	NR: n=1/1	−1.1	Overall: 81 Severe: 5	Overall: 11.09 Severe: 0.06	40	Overall: 1.39
Glargine U300, n=1[61]	26	404	60.1	8.1	36.6	15.6	No	4.4–5.6	103U	−0.8	Overall: 70.0 Severe: 5.0	Overall: 25.48 Severe: 0.27	12.1/35.9	Overall: 3.13
Icodec, n=1[31]	26	291	59.7	8.3	30.5	18	No	4.4–7.2	44	−1.2		Overall: 31.45 Severe: 0.04	NR	NR

Baseline characteristics are presented as ranges of mean values reported from each trial. Overall BG-confirmed hypoglycemia: any plasma glucose measurement <3.9 mmol/L (<70 mg/dL) irrespective of symptoms. Severe hypoglycemia: a hypoglycemic event requiring another person's assistance or a BG-confirmed value <2.0 mmol/L (<36 mg/dL). Nocturnal hypoglycemia: a hypoglycemic event occurring between 23:00 and 06:00 (inclusive), 0:01 and 05:59 (inclusive) or 00:00 and 06:00 (inclusive). Hypoglycemia rates and the proportion of participants reporting hypoglycemia by study are itemized in online supplemental tables 5 and 6.
*The number of participants randomized to the specified insulin.
†NR indicates studies that either did not report the given parameter or did not report it in the required units.
‡The bolus insulin type for four of the eight basal-bolus trials was insulin aspart[59 60 63 102]; for the other four studies, the bolus insulin type was not specified.
BG, blood glucose; BL, baseline; BMI, body mass index; degludec, insulin degludec; detemir, insulin detemir; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; HbA1c, glycated hemoglobin; N, total number of trials; n, number of trials; NPH, neutral protamine Hagedorn; NR, not reported; PYE, person-year of exposure; SMBG, self-measured blood glucose; SU, sulfonylurea; T2D, type 2 diabetes; U, units.

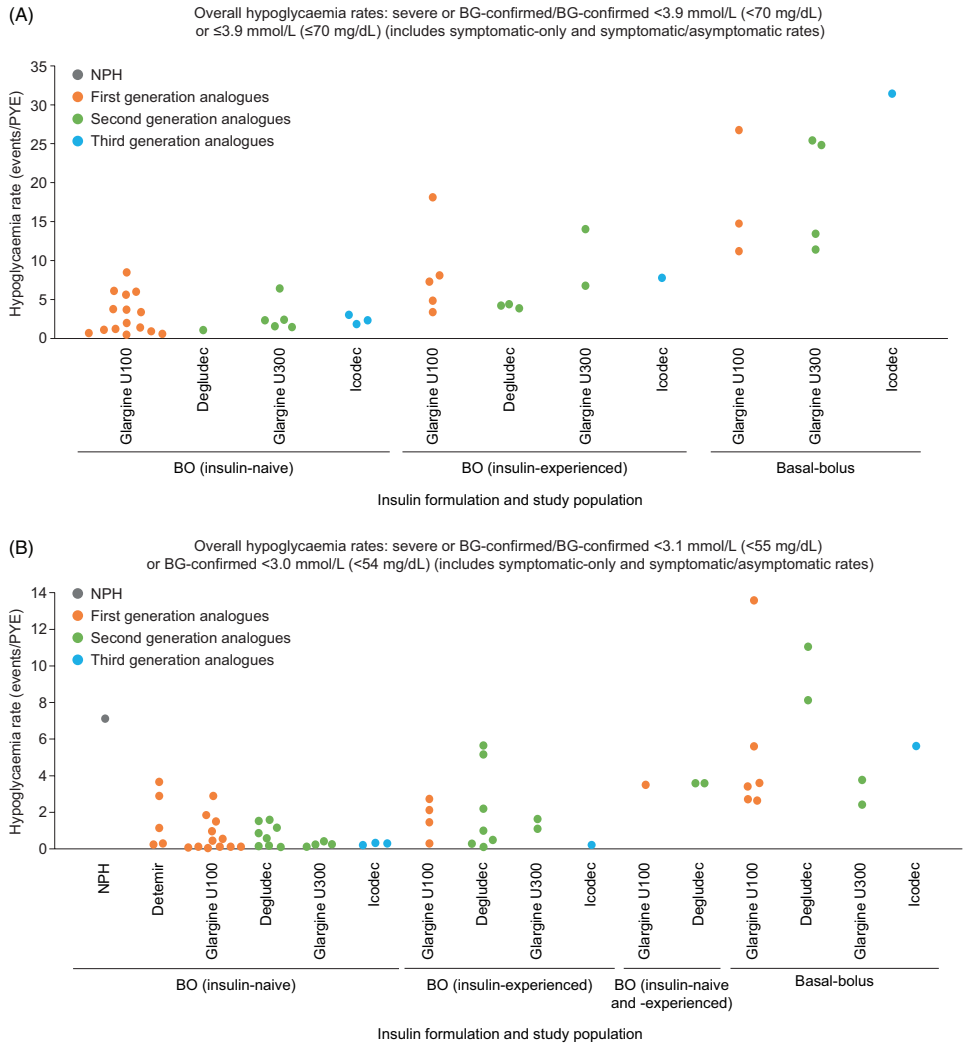

Figure 1 Overall hypoglycemia rates grouped according to hypoglycemia definitions (blood glucose thresholds: ≤3.9 mmol/L [≤70 mg/dL] [Panel A], <3.1 mmol/L [<55 mg/dL] or <3.0 mmol/L [<54 mg/dL] [Panel B]) used for treat-to-target basal-only (BO) and basal-bolus insulin T2D trials. Hypoglycemia rates are shown as events/PYE. Each data point represents a single trial. Six BO (insulin-naive) trials reported data for multiple basal insulins (Bolli *et al*[45]; Hermansen *et al*[50]; Meneghini *et al*[101]; Pan *et al*[46]; Rosenstock *et al*[57]; Zinman *et al*[67]); two BO (insulin-experienced) trials reported data for multiple basal insulins (Yki-Järvinen *et al*[65] and Wysham *et al*[85]). BG, blood glucose; degludec, insulin degludec; detemir, insulin detemir; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; NPH, neutral protamine Hagedorn insulin; PYE, person-year of exposure; T2D, type 2 diabetes.

BG threshold <3.9 mmol/L (<70 mg/dL)), ranging from 2.7 to 26.8 events/PYE for glargine U100, glargine U300, and degludec. Nocturnal hypoglycemia rates ranged from 0.3 to 4.2 events/PYE for glargine U100[59–63] and were 1.4 events/PYE for degludec.[63] Studies with NPH or detemir in this group were either not conducted or did not report hypoglycemia rates (table 1).

IMPACT OF STUDY FACTORS ON OVERALL HYPOGLYCEMIA RATES

To investigate the impact of hypoglycemia definition, overall hypoglycemia rates were grouped by respective study into two categories: (1) overall severe or BG-confirmed <3.9 mmol/L (<70 mg/dL) and (2) overall severe or BG-confirmed <3.1 mmol/L (<55 mg/dL) or <3.0 mmol/L (<54 mg/dL) (figure 1A,B). Hypoglycemia event rates were variable, with broader rate ranges observed among trials using a threshold of <3.9 mmol/L (<70 mg/dL; figure 1A)[45 54 56 58 61 64–66] than among those with BG <3.1 mmol/L (<55 mg/dL)[46–53 55 57 59 60 63 67–69] or <3.0 mmol/L (<54 mg/dL[17 24 45]; figure 1B). Hypoglycemia rates were generally higher for basal-bolus trials[60 61 63] than for basal-only trials in both insulin-naive[32–34 41 45 46 48–52 54–58 64 67 68 70–84] and insulin-experienced individuals,[47 53 65 66 69 79 85] whereas rates for mixed population trials tended to be in the middle (figure 1A,B). For overall severe or BG-confirmed <3.9 mmol/L (<70 mg/dL), hypoglycemia rates ranged from 0.7 to 8.5 events/PYE for basal-only (insulin-naive) trials (glargine U100, 0.7–8.5; glargine U300, 1.4–6.4),[45 54 56 58 64] from 3.36 to 18.14 events/PYE for basal-only (insulin-experienced) trials (glargine U100, 3.36–18.14; degludec, 4.22–3.39;

glargine U300, 6.76–14.01),[65 66] and from 11.24 to 26.76 events/PYE for the basal-bolus trial[61] (glargine U100, 11.24–26.76; glargine U300, 11.39–25.48; figure 1A). For overall severe or BG-confirmed <3.1 mmol/L (<55 mg/dL) or <3.0 mmol/L (<54 mg/dL), hypoglycemia rate ranges (events/PYE) were 0.06–7.14 for basal-only (insulin-naive) trials (NPH insulin 7.14; detemir 0.23–3.67; glargine U100, 0.06–2.9; glargine U300, 0.11–0.24; degludec, 0.09–1.6),[46 48–52 55 57 67 68 77 80 83 84] 0.28–5.66 for basal-only (insulin-experienced) trials (glargine U100, 0.28–2.75; glargine U300, 1.11–1.64; degludec, 0.28–5.66),[47 53 69 79 85] and 2.43–13.63 for basal-bolus trials (glargine U100, 2.56–13.63; glargine U300, 2.43–3.78; degludec, 11.09)[60 63] (figure 1B).

Overall severe or BG-confirmed hypoglycemia rates <3.1 mmol/L (<55 mg/dL) or <3.0 mmol/L (<54 mg/dL) were grouped according to concomitant sulfonylurea usage (figure 2A), EOT basal insulin dose (figure 2B) and change from baseline to EOT in HbA1c (figure 2C). No trends were observed across these parameters. Similarly, achieving EOT HbA1c <7.0% vs ≥7.0% did not consistently lead to higher severe or BG-confirmed hypoglycemia rates (online supplemental figure 1).

EXPLORING TRENDS IN HYPOGLYCEMIA RATES ACROSS DIFFERENT STUDY POPULATIONS

Basal-only (insulin-naive) trials: BG-confirmed <3.9 mmol/L (<70 mg/dL) irrespective of symptoms

Only glargine U100 or U300 trials reported rates with BG-confirmed <3.9 mmol/L in insulin-naive individuals, with the largest range seen with glargine U100 (figure 1A). The highest rate was seen in Bolli *et al* with glargine U100; 8.5 events/PYE after 26 weeks with a corresponding reduction in HbA1c from baseline to EOT of −1.46% points (EOT insulin dose, 52 units (U)/day; titration target, 4.4–5.6 mmol/L (80–100 mg/dL)).[45] Conversely, the lowest rate was observed in Yang *et al* with glargine U100; 1.1 events/PYE after 24 weeks, substantially lower than that for the 26-week trial, and a corresponding HbA1c reduction of −1.45% points (EOT insulin dose, 19.5 U; titration target, ≤6.1 mmol/L (≤110 mg/dL)).[84] Moreover, in the 24-week trial, sulfonylurea usage was continued after randomization,[84] whereas sulfonylureas were discontinued in the 26-week trial.[45] In addition, mean T2D duration and baseline BMI in the 24-week trial (7.9 years and 25.6 kg/m^2)[64 84] were lower than in the 26-week trial (9.6 years and 33.2 kg/m^2)[45]; these differences may help account for the higher rates of overall hypoglycemia in the 26-week trial (figure 1A).[45]

Basal-only (insulin-naive) trials: BG-confirmed <3.1 mmol/L (<55 mg/dL) irrespective of symptoms

Five trials[48–50 55 57] reported these hypoglycemia rates for detemir (figure 1B), including a 26-week trial[48 48] and a 52-week trial,[49 49] both of which used a titration target of 4.1–6.0 mmol/L (74–108 mg/dL). In these trials, the hypoglycemia rates for detemir were 0.28 and 0.23 events/PYE, respectively (EOT insulin dose, 39.5 U/day and 42 U/day, respectively), with corresponding HbA1c reductions of only −0.5% point (baseline HbA1c: 7.6% in both). However, in Rosenstock *et al*[57] (52 weeks) and Hermansen *et al*[50] (24 weeks), overall hypoglycemia rates for detemir were higher (2.9 and 3.67 events/PYE, respectively; EOT insulin dose, not reported and 36.1 U/day, respectively; titration target: <6.0 mmol/L (<108 mg/dL)) than those reported in DeVries *et al* and Rosenstock *et al*[48 49]; however, corresponding HbA1c reductions were greater (−1.5% points (52-week trial[57]) and −1.8% points (24-week trial[50])), potentially explaining the higher hypoglycemia rates. The fifth trial, Meneghini *et al* (26 weeks), used a tighter titration target (>3.9–5.0 mmol/L); the reported rate was 1.15 events/PYE with a modest HbA1c reduction (−0.48% point).[55] In Rosenstock *et al* and Hermansen *et al*, sulfonylureas were continued after randomization,[50 57] but they were discontinued in DeVries *et al*, Rosenstock *et al* and Meneghini *et al*.[48 49 55] Across all five trials, there was some variation in diabetes duration (range: 8.0–9.6 years), but there was no trend with respect to hypoglycemia rates. These data suggest that a combination of concomitant sulfonylurea usage with detemir and greater HbA1c reductions may have contributed to the higher hypoglycemia rates (figure 1B).

Basal-only trials (insulin-experienced): severe or BG-confirmed <3.1 mmol/L (<55 mg/dL) irrespective of symptoms

Four trials reported overall hypoglycemia rates for degludec (figure 1B).[47 53 69 85] Sulfonylurea usage was generally discontinued after study randomization, although baseline use was reported for some studies.

Two 26-week trials, Pei *et al* and Mathieu *et al*,[53 69] with titration targets of 4.0–5.0 mmol/L (72–90 mg/dL), reported rates of 0.48 events/PYE[53 69] and 1.0 events/PYE, respectively, for degludec, with corresponding HbA1c reductions of −1.0% point and −0.7% point, respectively (baseline HbA1c: 9.0% and 7.7%, respectively). In Pei *et al*,[69] EOT basal insulin dose was 37 U/day and diabetes duration was 11.5 years. In Mathieu *et al*,[53] EOT basal insulin dose was not reported and diabetes duration was 12.9 years.

A 64-week trial[85] and a 22-week trial,[47] both with titration targets of 4.0–5.0 mmol/L (72–90 mg/dL), reported rates of overall hypoglycemia for degludec of 2.2 and 5.66 events/PYE, respectively, which were higher than those reported in Pei *et al* and Mathieu *et al*; there was a corresponding HbA1c reduction of −0.7% point in Bode *et al* (baseline: 8.2%)[47] and −0.49% point in Wysham *et al* (baseline: 7.6%).[85]

Compared with Pei *et al* and Mathieu *et al*,[53 69] diabetes duration and EOT insulin dose from Wysham *et al*[85] (14.1 years and 83 U/day, respectively) and Bode *et al*[47] (12.9 years and 76 U/day, respectively) were higher. No trends were seen regarding sulfonylurea usage.[47 53 69 85] These data suggest that greater EOT insulin dose and diabetes

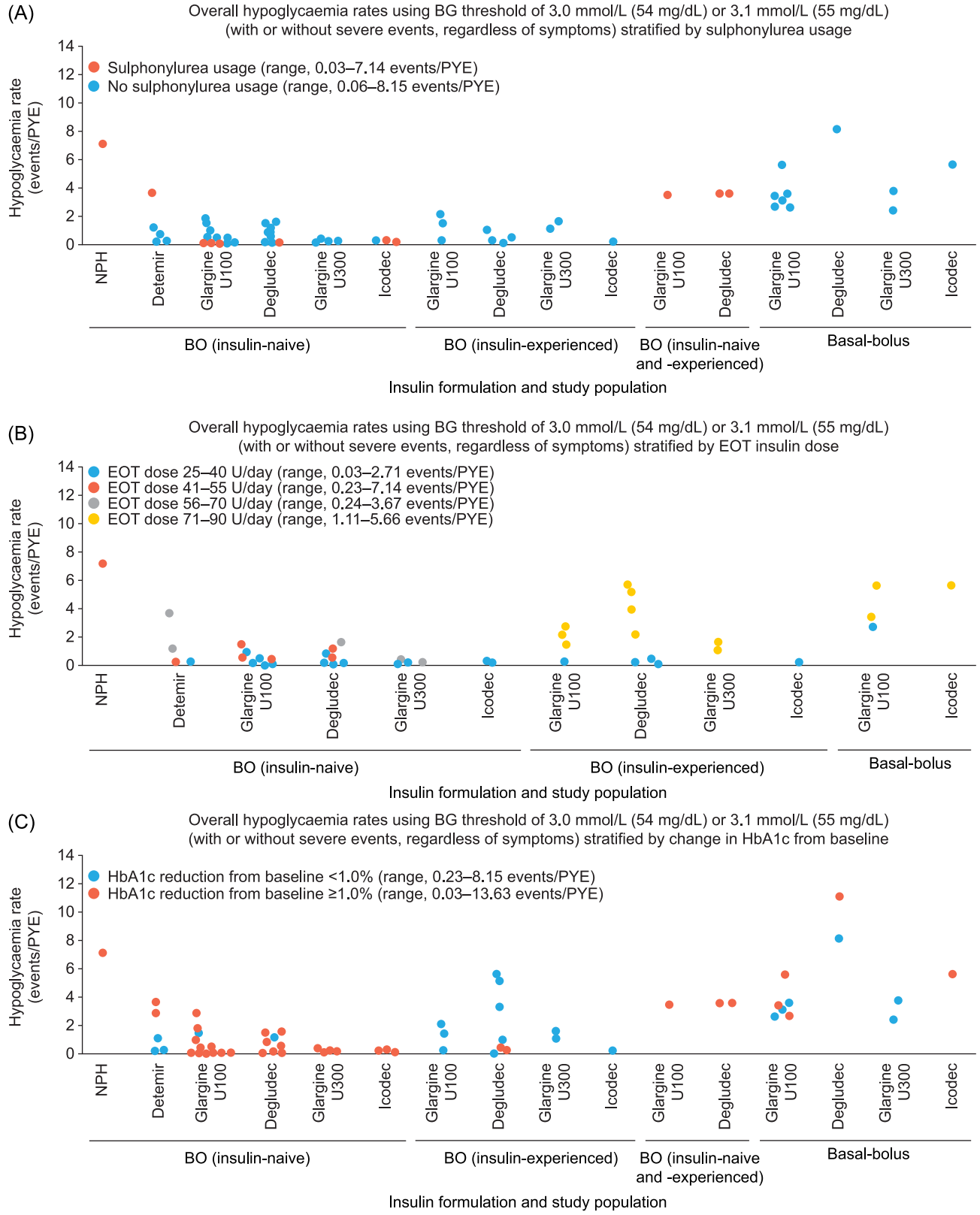

Figure 2 Overall hypoglycemia rates (overall severe or BG-confirmed/BG-confirmed value of <3.0 mmol/L (<54 mg/dL) or <3.1 mmol/L (<55 mg/dL)) grouped according to sulfonylurea usage (A), EOT basal insulin dose (B) and change from baseline to EOT in HbA1c (C). Hypoglycemia rates are shown as events/PYE. Each data point represents a single trial; some trials reported hypoglycemia rates for more than one basal insulin. Numbers of data points differ across panels because not all trials reported sulfonylurea usage or the insulin dose used. BG, blood glucose; BO, basal-only; degludec, insulin degludec; detemir, insulin detemir; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; HbA1c, glycated hemoglobin; NPH, neutral protamine Hagedorn; PYE, person-year of exposure.

duration may have contributed to higher hypoglycemia rates with degludec (figure 1B).

Basal-bolus trials: severe or BG-confirmed <3.9 mmol/L (<70 mg/dL) irrespective of symptoms

In a head-to-head trial of glargine U100 and glargine U300, both in combination with bolus insulin aspart,[61] severe or BG-confirmed hypoglycemia rates (6.8 and 25.5 events/PYE, respectively) were higher than that observed in basal-only trials in insulin-naive and insulin-experienced individuals receiving glargine U100[45 54 64–66] or glargine U300[45 56 58 65] (figure 1B). In the head-to-head basal-bolus trial (titration target, 4.4–5.6 mmol/L (80–100 mg/dL)), both glargine U100 and glargine U300 reduced HbA1c by −0.83% point from 8.15% at baseline (EOT daily basal insulin dose not reported), and diabetes duration was similar for both groups (16.1 years (glargine U100) vs 15.6 years (glargine U300)). It is likely that the higher hypoglycemia rates with basal-bolus than with basal-only regimens are attributed to the additional bolus insulin (figure 1B).[61]

Basal-only (insulin-naive) trial compared with basal-bolus trial: severe or BG-confirmed <3.1 mmol/L (<55 mg/dL) irrespective of symptoms

BEGIN ONCE LONG was a 52-week trial (titration target, 3.9–5.0 mmol/L (70–90 mg/dL)) of basal-only glargine U100 compared with basal-only degludec, while BEGIN BB T2 compared basal-bolus glargine U100 with basal-bolus degludec (both in combination with insulin aspart).[63 67] The rate of severe or BG-confirmed hypoglycemia was similar with basal-only glargine U100 and basal-only degludec (1.85 and 1.52 events/PYE, respectively), while the rate was statistically significantly lower with degludec than with glargine U100 in the basal-bolus comparison (11.1 vs 13.6 events/PYE; p=0.0359).[63 67] Corresponding HbA1c reductions of −1.2% and −1.3% points (baseline: 8.2% and 8.4%), respectively, were reported.[63 67] The higher hypoglycemia rates with basal-bolus than with basal-only regimens, despite similar glucose-lowering efficacy, can be attributed to the use of bolus insulin and longer diabetes duration (ie, disease progression) in the basal-bolus group (13.4 years vs 8.6 years) (figure 1B).[63 67]

For degludec, severe or BG-confirmed hypoglycemia rates were 1.5 and 11.1 events/PYE for insulin-naive (basal-only insulin) and insulin-experienced (basal-bolus insulin) individuals, respectively, with corresponding HbA1c reductions of −1.06% and −1.10% points (baseline: 8.2% and 8.3%).[63 67] Similarly, despite a small difference in glycemic efficacy, this suggests that the lower hypoglycemia rates may have been driven by the bolus insulin and longer diabetes duration (13.6 years (basal-bolus) vs 9.4 years (basal-only)).[63 67]

CGM-MEASURED HYPOGLYCEMIA: TBR

CGM-measured TBR data were only reported for two glargine U100 basal-only trials (figure 3)[71 86]: a head-to-head trial of glargine U100 versus degludec in insulin-experienced individuals,[86] and a glargine plus sulfonylurea (gliclazide) evaluation in insulin-naïve individuals.[71] Blinded CGM was used in both trials.

In the head-to-head trial,[86] the proportion of TBR was numerically lower with degludec than with glargine U100, despite an identical titration target of 3.9–5.0 mmol/L (70–90 mg/dL); both degludec and glargine U100 demonstrated similar HbA1c reductions from baseline (−0.5% vs −0.4% points, respectively; baseline: 7.6%) and comparable EOT insulin doses (56 vs 59 U/day). Overall, for glargine U100 and degludec, the proportion of TBR for level 1 hypoglycemia (sensor glucose 3.0–3.8 mmol/L (54–68 mg/dL); recommended target <4.0%) was 6.3% and 5.8%, while for level 2 hypoglycemia (sensor glucose <3.0 mmol/L (<54 mg/dL); recommended target <1.0%), it was 2.5% and 2.2%, respectively. The estimated mean treatment difference (degludec–glargine U100) in TBR for level 2 hypoglycemia was −0.24 (95% CI −0.79 to 0.31), which was not statistically significantly different.[86]

OVERALL HYPOGLYCEMIA RATES WITH ONCE-WEEKLY INSULIN

The efficacy and safety of once-weekly insulin in T2D were investigated in three phase 2 icodec studies,[22 23] five phase 3 icodec studies (ONWARDS 1–5)[29–33 40] and two phase 2 efsitora alfa studies.[27 28] In the icodec phase 3a studies, sulfonylureas were either discontinued or reduced by 50% at the investigator's discretion to mirror real-world conditions.[29–33 40] In ONWARDS 1 and ONWARDS 3, overall level 2 and 3 hypoglycemia rates (events/PYE) in basal-only insulin-naive individuals ranged from 0.19 to 0.31 for icodec, compared with 0.16 for glargine U100 and 0.15 for degludec (figures 1B and 2), with overall HbA1c reductions ranging from −1.3% to −1.6% points (baseline range: 8.4–8.6%), confirming statistical non-inferiority and superiority of icodec versus respective once-daily comparators.[32 33] In insulin-naive individuals, icodec plus a dosing guidance app was also compared against a pooled group of once-daily basal insulin analogs (degludec, glargine U100 or glargine U300) administered following real-world practice; overall combined level 2 or level 3 hypoglycemia rates (events/PYE) were 0.19 and 0.14, respectively, with corresponding HbA1c reductions of −1.68% and −1.31% points (baseline: 9.0% and 8.9%, respectively), confirming non-inferiority and superiority of icodec.[40] In basal-only insulin-experienced individuals, overall combined level 2 or level 3 hypoglycemia rates (events/PYE) were 0.7 for icodec and 0.3 for degludec (figures 1B and 2), but were not statistically significant, with corresponding HbA1c reductions of −0.93% and −0.71% points, respectively (baseline: 8.2% and 8.1%, respectively), confirming non-inferiority and superiority of icodec.[30] In individuals receiving basal-bolus therapy, the overall combined level 2 or level 3 hypoglycemia rates were similar for icodec+insulin aspart versus glargine U100+insulin aspart (5.6 events/PYE (both)) (figures 1B and 2), as were the corresponding HbA1c reductions

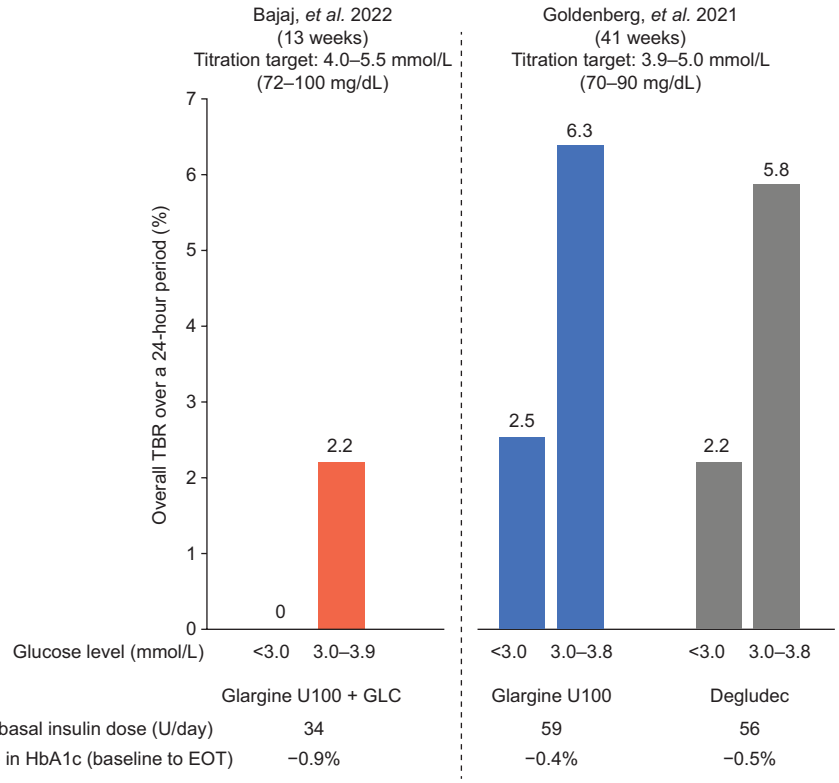

Figure 3 CGM-measured TBR (over a 24-hour period) for glargine U100 basal-only trials in insulin-naive individuals with T2D. Observed data are reported for Bajaj *et al*.[71] Estimated data are reported for Goldenberg *et al*.[86] In Bajaj *et al*, individuals wore blinded CGM devices during week 13. In Goldenberg *et al* (a 41-week crossover trial of glargine U100 vs degludec), after a 2-week screening period (week −4 to week −2) and a 2-week run-in period (week −2 to week 0), there were two consecutive 16-week treatment periods (weeks 0–16 and weeks 18–34), each followed by a 2-week maintenance period (weeks 16–18 and weeks 34–36); at the end of the second treatment period, there was a 1-week follow-up (weeks 36–37). The data shown in the figure are that collected during the two 2-week maintenance periods and were recorded by participants using a blinded CGM device. CGM, continuous glucose monitoring; degludec, insulin degludec; EOT, end of treatment; glargine U100, insulin glargine U100; GLC, gliclazide; HbA1c, glycated hemoglobin; T2D, type 2 diabetes; TBR, time below range; U, units.

(−1.16% and −1.18% points, respectively, both from 8.3% at baseline), confirming non-inferiority of icodec.[31]

Once-weekly efsitora alfa was compared with once-daily degludec as basal-only regimens in insulin-naive and insulin-experienced individuals using various titration targets in two phase 2 trials.[27 28] In insulin-naive individuals, the titration target for both treatments was 4.4–<5.6 mmol/L (80–100 mg/dL), while in insulin-experienced individuals, the two titration targets for efsitora were ≤7.8 mmol/L (≤140 mg/dL) (algorithm 1) and ≤6.7 mmol/L (≤120 mg/dL) (algorithm 2), and the titration target for degludec was ≤5.6 mmol/L (≤100 mg/dL).[27 28] In insulin-experienced individuals, baseline HbA1c was reduced after 32 weeks by −0.6% point for efsitora (both titration algorithms) and −0.7% point for degludec (baseline: 8.1% for both). The rate of level 1 hypoglycemia (<3.9 mmol/L (<70 mg/dL)) was statistically significantly lower with efsitora than with degludec (23.0 vs 30.5 events/PYE; p value not reported). For level 2 hypoglycemia (<3.0 mmol/L (<54 mg/dL)), there was no statistically significant difference between arms (2.2 vs 3.0 events/PYE; p value not reported).[28] The difference in level 1 hypoglycemia may be attributed to the more stringent titration target used for degludec than for efsitora, resulting in statistically significantly lower fasting blood glucose with degludec than with efsitora (change from baseline: −1.8 mmol/L (−32.7 mg/dL) vs −0.9 mmol/L (−17.0 mg/dL), respectively; p value not reported). In insulin-naive individuals, however, there was no statistically significant difference between efsitora and degludec using the same titration target in terms of level 1 (3.29 vs 2.77 events/PYE, respectively) or level 2 hypoglycemia (0.22 vs 0.15 events/PYE, respectively); reductions in HbA1c were −1.20% points and −1.26% points, respectively (baseline: ~8.0%).[27]

DISCUSSION

This narrative review comprehensively summarizes rates of hypoglycemia from T2D treat-to-target trials of one or two times per day administered basal insulins and provides relevant context for the event rates in the ongoing or completed once-weekly insulin trials, while considering the differences in trial design, hypoglycemia definitions, basal insulin type/dose, titration targets, data collection methods and HbA1c-lowering efficacy. Our narrative approach precludes definitive conclusions to be drawn regarding the relative efficacy and safety of basal

insulins as this can only be achieved using participant-level analyses of head-to-head RCT data.

Nevertheless, data indicate that, in treat-to-target RCTs, rates of hypoglycemia were generally lower with second-generation basal insulins (degludec and glargine U300) than with NPH insulin or first-generation basal insulin analogs (detemir and glargine U100) and, generally, most RCTs with basal insulin analogs reported an overall hypoglycemia rate (BG <70 mg/dL (<3.9 mmol/L) at any time of the day) of more than one event/PYE. Notably, those trials reporting lower hypoglycemic event rates had lower HbA1c reductions, well above the recommended target of <7.0%. As expected, owing to the more intensive insulin regimen, the use of mealtime bolus insulin and longer diabetes duration, hypoglycemia rates were higher in basal-bolus trials than in basal-only trials, particularly for previously insulin-naive individuals. However, the reported hypoglycemia rates were highly variable across trials, largely driven by heterogeneity in trial design, trial parameters (including eligible population), hypoglycemia definitions, glycemic control and hypoglycemia data collection methods, which can all directly impact the collection, reporting and analysis of hypoglycemia data. As these elements varied greatly across trials, it renders impossible any statistical comparison of hypoglycemia data across studies, yet holistically, these data can provide valuable clinical context when gauging hypoglycemic risk with weekly insulins relative to the ranges reported for widely used first-generation and second-generation daily basal insulin analogs.

Hypoglycemia risk is driven by a complex interplay of factors such as the use of concomitant sulfonylureas,[87] strictness of insulin titration regimens[88] and glucose-lowering efficacy, plus the strength of counter-regulatory responses which are impaired in many individuals with diabetes.[89] However, in this review, sulfonylurea usage, EOT insulin dose and the glucose-lowering efficacy of the insulins did not show consistent effects on overall hypoglycemia. Given the association between sulfonylurea usage and hypoglycemia, it was surprising that a clearer trend between the two was not seen; however, differences in other variables in the trial designs/methodologies may have had a confounding effect.

Concerns regarding greater frequency of hypoglycemia with once-weekly insulin use (icodec and efsitora) may be assuaged by contextualizing emerging once-weekly insulin data from SMBG and CGM analyses with observed hypoglycemia rates with first-generation and second-generation basal insulin analogs. Findings from this narrative review suggest that level 2 and level 3 hypoglycemia rates reported for icodec were below (in ONWARDS 1, 3, 2 and 5) or within (in ONWARDS 4) the rate ranges from basal-only (in insulin-naive and basal insulin-experienced) trials and basal-bolus insulin trials for daily-administered basal insulin analogs, respectively. Based on phase 2 data, level 2 hypoglycemia rates with efsitora were also lower than that observed with daily basal insulin analogs; however, as the phase 3 program will investigate a different titration algorithm and formulation, it remains to be seen whether these results will be replicated.

CGM is a relatively recent technological development, so for most trials included in the review, SMBG was the primary method for hypoglycemia data collection. Consequently, the detection of non-severe hypoglycemia relied on the identification of symptoms and/or self-reported BG readings, which may have underestimated actual values. The European Medicines Agency, EASD and ADA have recently recommended that CGM data be used in conjunction with participant-reported hypoglycemia outcomes as part of regulatory trials for the approval of drugs.[90 91] In RCTs, compared with SMBG, CGM systems have demonstrated greater sensitivity in detecting hypoglycemia,[91–93] and when used to inform titration decisions, have led to reduced proportions of TBR (<3.9 mmol/L (<70 mg/dL) and <3.0 mmol/L (<54 mg/dL)) and number of hypoglycemic events.[94 95] To date, CGM has been used in three once-weekly basal insulin studies (ONWARDS 1, 2 and 4)[30 31 33] but it was not used for titration or insulin dose adjustments as the CGM data were blinded; future use of open CGM with titration algorithms may help to further reduce the occurrence of hypoglycemia with once-weekly basal insulin. The further use of CGM in conjunction with SMBG-based data in future trials, such as those for once-weekly basal icodec and efsitora, will provide greater clinical context and may help to identify populations at risk of hypoglycemia, facilitating the movement of clinical practice into personalized diabetes management.

This narrative review thoroughly collected data from late-phase RCTs with diverse and large sample sizes over a 22-year period. Most studies were open label with an evaluation period less than 6 months, and only 10 studies implemented a non-inferiority statistical framework. To enable more robust evaluations, based on recent FDA guidance, future studies should include an efficacy evaluation period of 6–12 months, be blinded (if possible), and include non-inferiority or superiority statistical frameworks with defined estimands.[96–98] In addition, hypoglycemia definitions need to be standardized as much as possible. Nevertheless, the data collected here can be used to provide clinical perspective on the frequency of hypoglycemia event rates in ongoing and future clinical trials assessing the safety of basal insulin analogs. A meta-analysis was not conducted due to the considerable heterogeneity in trial protocols and hypoglycemia definitions. Accordingly, only observed trends were reported without the support of statistical rigor. Additionally, the hypoglycemia rates reported here may not directly apply to routine clinical practice as some populations with severe comorbidities may have been excluded, as is typical for RCTs. Trials may have also specifically excluded individuals prone to hypoglycemia, with prior severe hypoglycemia a common exclusion criterion. It was not possible to assess hypoglycemia rates by phase (ie, initial titration vs maintenance titration) as these were not consistently

reported across studies. Similarly, not all outcomes of interest were consistently reported across studies. Finally, given the emphasis on RCT data, the generalizability of our results to real-world clinical practice may be limited.

SUMMARY

Second-generation basal insulin analogs may reduce, but not eliminate, hypoglycemia risk. Hypoglycemia rates varied widely depending on the study population, study design, insulin titration targets, insulin dosages and diabetes duration. Overall, the frequency of event rates for level 2 and level 3 hypoglycemia in most treat-to-target RCTs testing basal insulin analogs as a basal-only insulin regimen ranged from 0.06 to 7.10 events/PYE; the hypoglycemia rate for basal-bolus regimens ranged from 2.4 to 13.6 events/PYE. These rate ranges may provide a useful reference when gaging hypoglycemia risk associated with once-weekly basal insulin analogs. Most notably, although more robust comparative data are needed, this review suggests that the hypoglycemia risk data reported so far on once-weekly basal insulins are consistent with or lower than those previously reported for daily insulin basal insulin analogs despite their longer duration of action.

Author affiliations
[1]Velocity Clinical Research at Medical City, Dallas, Texas, USA
[2]LMC Diabetes & Endocrinology, Brampton, Ontario, Canada
[3]Endocrinology Division, Department of Internal Medicine and Peter O'Donnell School of Public Health, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[4]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

Acknowledgements Medical writing support was provided by Samuel Bestall of Oxford PharmaGenesis, Oxford, UK, funded by Novo Nordisk.

Contributors JR contributed to the design, literature search, analysis of the extracted data, and to the writing, reviewing and editing of the manuscript. HSB contributed to the design, literature search, analysis of the extracted data, and to the writing, reviewing and editing of the manuscript. IL contributed to the design, literature search, analysis of the extracted data, and to the writing, reviewing and editing of the manuscript. SRH contributed to the design, literature search, analysis of the extracted data, and to the writing, reviewing and editing of the manuscript.

Funding This study was funded by Novo Nordisk (not applicable).

Competing interests JR has served on advisory panels for Applied Therapeutics, Biomea Fusion, Boehringer Ingelheim, Eli Lilly, Endogenex, Hanmi, Novo Nordisk, Oramed, Regor, Sanofi, Scholar Rock, Structure Therapeutics, Terns Pharmaceuticals and Zealand Pharma; and has received research support, consulting fees or honoraria from Applied Therapeutics, AstraZeneca, Biomea Fusion, Boehringer Ingelheim, Eli Lilly, Endogenex, Hanmi, Novo Nordisk, Oramed, Regor, Sanofi, Scholar Rock, Structure Therapeutics, Terns Pharmaceuticals and Zealand Pharma. HSB reports trial fees paid to his institution by Amgen, AstraZeneca, Boehringer Ingelheim, Ceapro, Eli Lilly, Gilead, Janssen, Kowa Pharmaceuticals, Madrigal Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, Ionis and Tricida. IL reports receiving grants, personal fees, or non-financial support from Sanofi, Lilly, Boehringer Ingelheim, Merck/Pfizer, Mylan, AstraZeneca, Johnson & Johnson, Intercept, Target Pharma, Zealand, Shionogi, Carmot, Structure, Bayer, Mediflix, WebMD, GI Dynamics, Intarcia Therapeutics, Mannkind, Novartis, Novo Nordisk, Structure Therapeutics and Valeritas. SRH reports consultancy with Eli Lilly, Zealand Pharma and Zucara Pharma; has participated in speaker panels for AstraZeneca, Medtronic and Novo Nordisk; and receives grant support from Dexcom.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

ORCID iDs
Julio Rosenstock http://orcid.org/0000-0001-8324-3275
Ildiko Lingvay http://orcid.org/0000-0001-7006-7401
Simon R Heller http://orcid.org/0000-0002-2425-9565

REFERENCES

1 Davies MJ, Aroda VR, Collins BS, *et al*. A consensus report by the American diabetes Association (ADA) and the European Association for the study of diabetes (EASD. *Diabetes Care* 2022;45:2753–86.
2 U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995;44:1249–58.
3 Tian J, Ohkuma T, Cooper M, *et al*. Effects of intensive Glycemic control on clinical outcomes among patients with type 2 diabetes with different levels of cardiovascular risk and hemoglobin A(1C) in the ADVANCE trial. *Diabetes Care* 2020;43:1293–9.
4 The United States Food and Drug Administration. Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products. FDA-2023-D-0625. 2023.
5 International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American diabetes Association and the European Association for the study of diabetes. *Diabetes Care* 2017;40:155–7.
6 ElSayed NA, Aleppo G, Aroda VR, *et al*. 6. Glycemic targets: standards of care in Diabetes-2023. *Diabetes Care* 2023;46:S97–110.
7 McCoy RG, Van Houten HK, Ziegenfuss JY, *et al*. Increased mortality of patients with diabetes reporting severe Hypoglycemia. *Diabetes Care* 2012;35:1897–901.
8 Zaccardi F, Ling S, Lawson C, *et al*. Severe Hypoglycaemia and absolute risk of cause-specific mortality in individuals with type 2 diabetes: a UK primary care observational study. *Diabetologia* 2020;63:2129–39.
9 Pawaskar M, Witt EA, Engel SS, *et al*. Severity of Hypoglycaemia and health-related quality of life, work productivity and Healthcare costs in patients with type 2 diabetes in Europe. *Endocrinol Diabetes Metab* 2018;1:e00011.
10 Aronson R, Galstyan G, Goldfracht M, *et al*. Direct and indirect health economic impact of Hypoglycaemia in a global population of patients with insulin-treated diabetes. *Diabetes Res Clin Pract* 2018;138:35–43.
11 Ratzki-Leewing A, Black JE, Kahkoska AR, *et al*. Severe (level 3) Hypoglycaemia occurrence in a real-world cohort of adults with type 1 or 2 diabetes mellitus (iNPHORM, United States). *Diabetes Obes Metab* 2023;25:3736–47.
12 Vague P, Selam J-L, Skeie S, *et al*. Insulin Detemir is associated with more predictable Glycemic control and reduced risk of Hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with Premeal insulin Aspart. *Diabetes Care* 2003;26:590–6.
13 Kølendorf K, Ross GP, Pavlic-Renar I, *et al*. Insulin Detemir LOWERS the risk of Hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in type 1 diabetes. *Diabet Med* 2006;23:729–35.

14 Rosenstock J, Dailey G, Massi-Benedetti M, *et al*. Reduced Hypoglycemia risk with insulin Glargine: A meta-analysis comparing insulin Glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;28:950–5.
15 Riddle MC, Rosenstock J, Gerich J, *et al*. The treat-to-target trial: randomized addition of Glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080–6.
16 Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, *et al*. Effect of insulin analogues on risk of severe Hypoglycaemia in patients with type 1 diabetes prone to recurrent severe Hypoglycaemia (Hypoana trial): a prospective, randomised, open-label, blinded-Endpoint crossover trial. *Lancet Diabetes Endocrinol* 2014;2:553–61.
17 Marso SP, McGuire DK, Zinman B, *et al*. Efficacy and safety of Degludec versus Glargine in type 2 diabetes. *N Engl J Med* 2017;377:723–32.
18 Vargas-Uricoechea H. Efficacy and safety of insulin Glargine 300 U/mL versus 100 U/mL in diabetes mellitus: A comprehensive review of the literature. *J Diabetes Res* 2018;2018:2052101.
19 Aye MM, Atkin SL. Patient safety and minimizing risk with insulin administration - role of insulin Degludec. *Drug Healthc Patient Saf* 2014;6:55–67.
20 Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. *Diabetes Obes Metab* 2018;20:488–96.
21 Polonsky WH, Fisher L, Guzman S, *et al*. Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. *Diabetes Care* 2005;28:2543–5.
22 Rosenstock J, Bajaj HS, Janež A, *et al*. Once-weekly insulin for type 2 diabetes without previous insulin treatment. *N Engl J Med* 2020;383:2107–16.
23 Bajaj HS, Bergenstal RM, Christoffersen A, *et al*. Switching to once-weekly insulin Icodec versus once-daily insulin Glargine U100 in type 2 diabetes inadequately controlled on daily basal insulin: A phase 2 randomized controlled trial. *Diabetes Care* 2021;44:1586–94.
24 Lingvay I, Buse JB, Franek E, *et al*. A randomized, open-label comparison of once-weekly insulin Icodec titration strategies versus once-daily insulin Glargine U100. *Diabetes Care* 2021;44:1595–603.
25 Kjeldsen TB, Hubálek F, Hjørringgaard CU, *et al*. Molecular engineering of insulin Icodec, the first Acylated insulin analog for once-weekly administration in humans. *J Med Chem* 2021;64:8942–50.
26 Moyers JS, Hansen RJ, Day JW, *et al*. Preclinical characterization of Ly3209590, a novel weekly basal insulin FC-fusion protein. *J Pharmacol Exp Ther* 2022;382:346–55.
27 Bue-Valleskey JM, Kazda CM, Ma C, *et al*. Once-weekly basal insulin FC demonstrated similar Glycemic control to once-daily insulin Degludec in insulin-naive patients with type 2 diabetes: A phase 2 randomized control trial. *Diabetes Care* 2023;46:1060–7.
28 Frias J, Chien J, Zhang Q, *et al*. Safety and efficacy of once-weekly basal insulin FC in people with type 2 diabetes previously treated with basal insulin: a Multicentre, open-label, randomised, phase 2 study. *Lancet Diabetes Endocrinol* 2023;11:158–68.
29 Philis-Tsimikas A, Bajaj HS, Begtrup K, *et al*. Rationale and design of the phase 3A development programme (ONWARDS 1-6 trials) investigating once-weekly insulin Icodec in diabetes. *Diabetes Obes Metab* 2023;25:331–41.
30 Philis-Tsimikas A, Asong M, Franek E, *et al*. Switching to once-weekly insulin Icodec versus once-daily insulin Degludec in basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3, randomised, open label, treat-to-target trial lancet diabetes Endocrinol. *Lancet Diabetes Endocrinol* 2023;11:414–25.
31 Mathieu C, Ásbjörnsdóttir B, Bajaj HS, *et al*. Switching to once-weekly insulin Icodec versus once-daily insulin Glargine U100 in basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3, randomised, open-label, treat-to-target, non-inferiority trial. *The Lancet* 2023;401:1929–40.
32 Lingvay I, Asong M, Desouza C, *et al*. Once-weekly insulin Icodec vs once-daily insulin Degludec in adults with insulin-naive type 2 diabetes: the ONWARDS 3 randomized clinical trial. *JAMA* 2023;330:228–37.
33 Rosenstock J, Bain SC, Gowda A, *et al*. Weekly Icodec versus daily Glargine U100 in type 2 diabetes without previous insulin. *N Engl J Med* 2023;389:297–308.
34 Bajaj HS, Aberle J, Davies M, *et al*. Once-weekly insulin Icodec with dosing guide App versus once-daily basal insulin analogues in insulin-naive type 2 diabetes (ONWARDS 5): a randomized trial. *Ann Intern Med* 2023;176:1476–85.
35 Rosenstock J, Del Prato S. Basal weekly Insulins: the way of the future. *Metabolism* 2022;126:S0026-0495(21)00224-9:154924:.
36 Sanofi-Aventis. Centre for Drug Evaluation and Research: LANTUS (application number: NDA 21-081/S-024). 2007.
37 Novo Nordisk. Centre for Drug Evaluation and Research: Levemir (application number: NDA 21536/S-033). 2013.
38 Novo Nordisk. Centre for Drug Evaluation and Research: Tresiba and Ryzodeg (application number: 203313Orig1S000/203314Orig1S000). 2015.
39 Sanofi-Aventis. Centre for Drug Evaluation and Research: Toujeo (application number: 206538Orig1S000). 2015.
40 Bajaj HS, Goldenberg RM. Insulin Icodec weekly: A basal insulin analogue for type 2 diabetes. *touchREV Endocrinol* 2023;19:4–6.
41 Fritsche A, Schweitzer MA, Häring H-U, *et al*. Glimepiride combined with morning insulin Glargine, bedtime neutral Protamine Hagedorn insulin, or bedtime insulin Glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med* 2003;138:952–9.
42 Rosenstock J, Schwartz SL, Clark CM Jr, *et al*. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin Glargine (HOE 901) and NPH insulin. *Diabetes Care* 2001;24:631–6.
43 Massi Benedetti M, Humburg E, Dressler A, *et al*. A one-year, randomised, Multicentre trial comparing insulin Glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. *Horm Metab Res* 2003;35:189–96.
44 Raslová K, Bogoev M, Raz I, *et al*. Insulin Detemir and insulin Aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract* 2004;66:193–201.
45 Bolli GB, Riddle MC, Bergenstal RM, *et al*. New insulin Glargine 300 U/ml compared with Glargine 100 U/ml in insulin-Naïve people with type 2 diabetes on oral glucose-lowering drugs. *Diabetes Obes Metab* 2015;17:386–94.
46 Pan C, Gross JL, Yang W, *et al*. A multinational, randomized, open-label, treat-to-target trial comparing insulin Degludec and insulin Glargine in insulin-Naïve patients with type 2 diabetes mellitus. *Drugs R D* 2016;16:239–49.
47 Bode B, Chaykin L, Sussman A, *et al*. Efficacy and safety of insulin Degludec 200 U/mL and insulin Degludec 100 U/mL in patients with type 2 diabetes (BEGIN: compare). *Endocr Pract* 2014;20:785–91.
48 DeVries JH, Bain SC, Rodbard HW, *et al*. Sequential intensification of metformin treatment in type 2 diabetes with Liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care* 2012;35:1446–54.
49 Rosenstock J, Rodbard HW, Bain SC, *et al*. One-year sustained Glycemic control and weight reduction in type 2 diabetes after addition of Liraglutide to metformin followed by insulin Detemir according to Hba1C target. J Diabetes Complications 2013;27:492–500.
50 Hermansen K, Davies M, Derezinski T, *et al*. A 26-week, randomized, parallel, treat-to-target trial comparing insulin Detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 2006;29:1269–74.
51 Aroda VR, Bailey TS, Cariou B, *et al*. Effect of adding insulin Degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and Liraglutide. *Diabetes Obes Metab* 2016;18:663–70.
52 Philis-Tsimikas A, Brod M, Niemeyer M, *et al*. Insulin Degludec once-daily in type 2 diabetes: simple or step-wise titration (BEGIN: once simple use). *Adv Ther* 2013;30:607–22.
53 Mathieu C, Rodbard HW, Cariou B, *et al*. A comparison of adding Liraglutide versus a single daily dose of insulin Aspart to insulin Degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab* 2014;16:636–44.
54 Davies MJ, Russell-Jones D, Selam J-L, *et al*. Basal insulin Peglispro versus insulin Glargine in insulin-Naïve type 2 diabetes: IMAGINE 2 randomized trial. *Diabetes Obes Metab* 2016;18:1055–64.
55 Meneghini L, Kesavadev J, Demissie M, *et al*. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin Detemir with insulin Glargine in patients with type 2 diabetes. *Diabetes Obes Metab* 2013;15:729–36.
56 Meneghini LF, Sullivan SD, Oster G, *et al*. A pragmatic randomized clinical trial of insulin Glargine 300 U/mL vs first-generation basal insulin analogues in insulin-Naïve adults with type 2 diabetes: 6-month outcomes of the ACHIEVE control study. *Diabetes Obes Metab* 2020;22:2004–12.
57 Rosenstock J, Davies M, Home PD, *et al*. A randomised, 52-week, treat-to-target trial comparing insulin Detemir with insulin Glargine

when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;51:408–16.
58 Bonadonna RC, Giaccari A, Buzzetti R, *et al*. Comparable efficacy with similarly low risk of Hypoglycaemia in Patient- vs physician-managed basal insulin initiation and titration in insulin-Naïve type 2 diabetic subjects: the Italian titration approach study. *Diabetes Metab Res Rev* 2020;36:e3304.
59 Onishi Y, Ono Y, Rabøl R, *et al*. Superior Glycaemic control with once-daily insulin Degludec/insulin Aspart versus insulin Glargine in Japanese adults with type 2 diabetes inadequately controlled with oral drugs: a randomized, controlled phase 3 trial. *Diabetes Obes Metab* 2013;15:826–32.
60 Philis-Tsimikas A, Astamirova K, Gupta Y, *et al*. Similar Glycaemic control with less nocturnal Hypoglycaemia in a 38-week trial comparing the Idegasp Co-formulation with insulin Glargine U100 and insulin Aspart in basal insulin-treated subjects with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2019;147:157–65.
61 Riddle MC, Bolli GB, Ziemen M, *et al*. New insulin Glargine 300 units/mL versus Glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and Hypoglycemia in a 6-month. *Diabetes Care* 2014;37:2755–62.
62 Jin Y, Sun X, Zhao X, *et al*. Adding Prandial insulin to basal insulin plus oral antidiabetic drugs in Chinese patients with poorly controlled type 2 diabetes mellitus: an open-label, single-arm study. *Diabetes Ther* 2017;8:611–21.
63 Garber AJ, King AB, Del Prato S, *et al*. Insulin Degludec, an ultra-Longacting basal insulin, versus insulin Glargine in basal-bolus treatment with mealtime insulin Aspart in type 2 diabetes (BEGIN basal-bolus type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012;379:1498–507.
64 Pollom RK, Ilag LL, Lacaya LB, *et al*. Lilly insulin Glargine versus Lantus(®) in insulin-Naïve and insulin-treated adults with type 2 diabetes: a randomized, controlled trial (ELEMENT 5). *Diabetes Ther* 2019;10:189–203.
65 Yki-Järvinen H, Bergenstal R, Ziemen M, *et al*. New insulin Glargine 300 units/mL versus Glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and Hypoglycemia in a 6-month. *Diabetes Care* 2014;37:3235–43.
66 Yuan X, Guo X, Zhang J, *et al*. Improved Glycaemic control and weight benefit with iGlarLixi versus insulin Glargine 100 U/mL in Chinese people with type 2 diabetes advancing their therapy from basal insulin plus oral Antihyperglycaemic drugs: results from the Lixilan-L-CN randomized controlled trial. *Diabetes Obes Metab* 2022;24:2182–91.
67 Zinman B, Philis-Tsimikas A, Cariou B, *et al*. Insulin Degludec versus insulin Glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN once long). *Diabetes Care* 2012;35:2464–71.
68 Wang W, Agner BFR, Luo B, *et al*. DUAL I China: improved Glycemic control with Ideglira versus its individual components in a randomized trial with Chinese participants with type 2 diabetes uncontrolled on oral antidiabetic drugs. *J Diabetes* 2022;14:401–13.
69 Pei Y, Agner BR, Luo B, *et al*. DUAL II China: superior Hba1C reductions and weight loss with insulin Degludec/Liraglutide (Ideglira) versus insulin Degludec in a randomized trial of Chinese people with type 2 diabetes inadequately controlled on basal insulin. *Diabetes Obes Metab* 2021;23:2687–96.
70 Ahmann A, Szeinbach SL, Gill J, *et al*. Comparing patient preferences and Healthcare provider recommendations with the pen versus vial-and-syringe insulin delivery in patients with type 2 diabetes. *Diabetes Technol Ther* 2014;16:76–83.
71 Bajaj HS, Chu L, Bansal N, *et al*. Randomized comparison of initiating the fixed-ratio combination of Iglarlixi or Biosimilar insulin Glargine together with Gliclazide in participants of South Asian origin with type 2 diabetes: VARIATION 2 SA trial. *Can J Diabetes* 2022;46:495–502.
72 Carlson AL, Mullen DM, Mazze R, *et al*. Evaluation of insulin Glargine and Exenatide alone and in combination: A randomized clinical trial with continuous glucose monitoring and ambulatory glucose profile analysis. *Endocr Pract* 2019;25:306–14.
73 Del Prato S, Kahn SE, Pavo I, *et al*. Tirzepatide versus insulin Glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, Multicentre, phase 3 trial. *Lancet* 2021;398:1811–24.
74 Diamant M, Van Gaal L, Stranks S, *et al*. Once weekly Exenatide compared with insulin Glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010;375:2234–43.
75 Feng W, Chen W, Jiang S, *et al*. Efficacy and safety of Ly2963016 insulin Glargine versus insulin Glargine (Lantus) in Chinese adults with type 2 diabetes: A phase III, randomized, open-label, controlled trial. *Diabetes Obes Metab* 2021;23:1786–94.
76 Hu X, Deng H, Zhang Y, *et al*. Efficacy and safety of a decision support intervention for basal insulin self-titration assisted by the nurse in outpatients with T2Dm: A randomized controlled trial. *Diabetes Metab Syndr Obes* 2021;14:1315–27.
77 Ji L, Wan H, Wen B, *et al*. Higher versus standard starting dose of insulin Glargine 100 U/mL in overweight or obese Chinese patients with type 2 diabetes: results of a Multicentre, open-label, randomized controlled trial (BEYOND VII). *Diabetes Obes Metab* 2020;22:838–46.
78 Kennedy L, Herman WH, Strange P, *et al*. Impact of active versus usual Algorithmic titration of basal insulin and point-of-care versus laboratory measurement of Hba1C on Glycemic control in patients with type 2 diabetes: the Glycemic optimization with Algorithms and LABS at point of care (GOAL A1C) trial. *Diabetes Care* 2006;29:1–8.
79 Kumar A, Franek E, Wise J, *et al*. Efficacy and safety of once-daily insulin Degludec/insulin Aspart versus insulin Glargine (U100) for 52 weeks in insulin-Naïve patients with type 2 diabetes: A randomized controlled trial. *PLoS ONE* 2016;11:e0163350.
80 Pan Q, Li Y, Wan H, *et al*. Efficacy and safety of a basal insulin + 2-3 oral Antihyperglycaemic drugs regimen versus a twice-daily Premixed insulin + metformin regimen after short-term intensive insulin therapy in individuals with type 2 diabetes: the Multicentre, open-label, randomized controlled BEYOND-V trial. *Diabetes Obes Metab* 2022;24:1957–66.
81 Vilsbøll T, Ekholm E, Johnsson E, *et al*. Dapagliflozin plus Saxagliptin add-on therapy compared with insulin in patients with type 2 diabetes poorly controlled by metformin with or without Sulfonylurea therapy: a randomized clinical trial. *Diabetes Care* 2019;42:1464–72.
82 Vilsbøll T, Ekholm E, Johnsson E, *et al*. Efficacy and safety of Dapagliflozin plus Saxagliptin versus insulin Glargine over 52 weeks as add-on to metformin with or without Sulphonylurea in patients with type 2 diabetes: A randomized, parallel-design, open-label, phase 3 trial. *Diabetes Obes Metab* 2020;22:957–68.
83 Yang W, Dong X, Li Q, *et al*. Efficacy and safety benefits of iGlarLixi versus insulin Glargine 100 U/mL or Lixisenatide in Asian Pacific people with Suboptimally controlled type 2 diabetes on oral agents: the Lixilan-O-AP randomized controlled trial. *Diabetes Obes Metab* 2022;24:1522–33.
84 Yang W, Ma J, Yuan G, *et al*. Determining the optimal fasting glucose target for patients with type 2 diabetes: results of the Multicentre, open-label, randomized-controlled FPG GOAL trial. *Diabetes Obes Metab* 2019;21:1973–7.
85 Wysham C, Bhargava A, Chaykin L, *et al*. Effect of insulin Degludec vs insulin Glargine U100 on Hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA* 2017;318:45–56.
86 Goldenberg RM, Aroda VR, Billings LK, *et al*. Effect of insulin Degludec versus insulin Glargine U100 on time in range: SWITCH PRO, a crossover study of basal insulin-treated adults with type 2 diabetes and risk factors for Hypoglycaemia. *Diabetes Obes Metab* 2021;23:2572–81.
87 Kolman KB, Freeman J, Howe CL. Hypoglycemia with insulin and Sulfonylureas. *Can Fam Physician* 2020;66:335.
88 Rubin DJ, Rybin D, Doros G, *et al*. Weight-based, insulin dose-related Hypoglycemia in hospitalized patients with diabetes. *Diabetes Care* 2011;34:1723–8.
89 Perlmuter LC, Flanagan BP, Shah PH, *et al*. Glycemic control and Hypoglycemia: is the loser the winner. *Diabetes Care* 2008;31:2072–6.
90 Danne T, Nimri R, Battelino T, *et al*. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017;40:1631–40.
91 Ratner RE. Hypoglycemia: new definitions and regulatory implications. *Diabetes Technol Ther* 2018;20:S250–3.
92 Chico A, Vidal-Ríos P, Subirà M, *et al*. The continuous glucose monitoring system is useful for detecting unrecognized Hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 2003;26:1153–7.
93 Henriksen MM, Andersen HU, Thorsteinsson B, *et al*. Hypoglycemic exposure and risk of asymptomatic Hypoglycemia in type 1 diabetes assessed by continuous glucose monitoring. *J Clin Endocrinol Metab* 2018;103:2329–35.
94 Beck RW, Riddlesworth T, Ruedy K, *et al*. Effect of continuous glucose monitoring on Glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 2017;317:371–8.

95 Heinemann L, Freckmann G, Ehrmann D, *et al*. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired Hypoglycaemia awareness or severe Hypoglycaemia treated with multiple daily insulin injections (Hypode): a Multicentre, randomised controlled trial. *Lancet* 2018;391:1367–77.
96 The United States Food and Drug Administration. Choice of control group and related issues in clinical trials. FDA-1999-D-1874. 2021.
97 The United States Food and Drug Administration. Statistical principles for clinical trials: Addendum: Estimands and sensitivity analysis in clinical trials. FDA-2017-D-6113. 2021.
98 The United States Food and Drug Agency. Diabetes mellitus. efficacy endpoints for clinical trials investigating antidiabetic drugs and biological products. FDA-2023-D-0625.
99 Kumar S, Jang HC, Demirağ NG, *et al*. Efficacy and safety of once-daily insulin Degludec/insulin Aspart compared with once-daily insulin Glargine in participants with type 2 diabetes: a randomized, treat-to-target study. *Diabet Med* 2017;34:180–8.
100 Terauchi Y, Koyama M, Cheng X, *et al*. Glycaemic control and Hypoglycaemia with insulin Glargine 300 U/mL compared with Glargine 100 U/mL in Japanese adults with type 2 diabetes using basal insulin plus oral anti-Hyperglycaemic drugs. *Diabetes Metab* 2017;43:446–52.
101 Meneghini L, Atkin SL, Gough SCL, *et al*. The efficacy and safety of insulin Degludec given in variable once-daily dosing intervals compared with insulin Glargine and insulin Degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care* 2013;36:858–64.
102 Fajardo Montañana C, Hernández Herrero C, Rivas Fernández M. Less weight gain and Hypoglycaemia with once-daily insulin Detemir than NPH insulin in intensification of insulin therapy in overweight type 2 diabetes patients: the PREDICTIVE BMI clinical trial. *Diabet Med* 2008;25:916–23.
103 Linjawi S, Lee B-W, Tabak Ö, *et al*. A 32-week randomized comparison of stepwise insulin intensification of Biphasic insulin Aspart (Biasp 30) versus basal–bolus therapy in insulin-Naïve patients with type 2 diabetes. *Diabetes Ther* 2018;9:1–11.