Primary Care Diabetes 17 (2023) 379–385

Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: www.journals.elsevier.com/primary-care-diabetes

Response to insulin glargine 100 U/mL treatment in newly-defined subgroups of type 2 diabetes: *Post hoc* pooled analysis of insulin-naïve participants from nine randomised clinical trials

Wolfgang Landgraf [a,*], Gregory Bigot [b], Brian M. Frier [c], Geremia B. Bolli [d], David R. Owens [e]

[a] *Sanofi, Berlin, Germany*
[b] *Ividata Life Sciences, Levallois-Perret, France*
[c] *The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK*
[d] *University of Perugia School of Medicine, Department of Medicine, Section of Endocrinology and Metabolism, Perugia, Italy*
[e] *Swansea University, Diabetes Research Group Cymru, College of Medicine, Swansea, UK*

ARTICLE INFO

Keywords:
Clustering
C-peptide
Type 2 diabetes
Randomised clinical trial
Insulin glargine

ABSTRACT

Aims: To assess insulin glargine 100 U/mL (IGlar-100) treatment outcomes according to newly-defined subgroups of type 2 diabetes mellitus (T2DM).
Methods: Insulin-naïve T2DM participants (n = 2684) from nine randomised clinical trials initiating IGlar-100 were pooled and assigned to subgroups *"Mild Age-Related Diabetes (MARD)"*, *"Mild Obesity Diabetes (MOD)"*, *"Severe Insulin Resistant Diabetes (SIRD)"*, and *"Severe Insulin Deficient Diabetes (SIDD)"*, according to age at onset of diabetes, baseline HbA1c, BMI, and fasting C-peptide using sex-specific nearest centroid approach. HbA1c, FPG, hypoglycemia, insulin dose, and body weight were analysed at baseline and 24 weeks.
Results: Subgroup distribution was MARD 15.3 % (n = 411), MOD 39.8 % (n = 1067), SIRD 10.5 % (n = 283), SIDD 34.4 % (n = 923). From baseline HbA1c 8.0–9.6% adjusted least square mean reductions after 24 weeks were similar between subgroups (1.4–1.5 %). SIDD was less likely to achieve HbA1c < 7.0 % (OR: 0.40 [0.29, 0.55]) than MARD. While the final IGlar-100 dose (0.36 U/kg) in MARD was lower than in other subgroups (0.46–0.50 U/kg), it had the highest hypoglycemia risk. SIRD had lowest hypoglycemia risk and SIDD exhibited greatest body weight gain.
Conclusions: IGlar-100 lowered hyperglycemia similarly in all T2DM subgroups, but level of glycemic control, insulin dose, and hypoglycemia risk differed between subgroups.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a heterogenous disease with considerable variation in clinical presentation, disease progression, and development of complications [1–3]. Therefore, different approaches, including k-means clustering of clinical variables, have been employed to subclassify diabetes. Recently, five subgroups have been described from real world populations [4–12] and replicated in diabetes populations from randomised clinical trials [13–19]. These newly-defined subgroups categorised as *"Mild Age-Related Diabetes (MARD)"*, *"Mild Obesity-related Diabetes (MOD)"*, *"Severe Insulin-Resistant Diabetes (SIRD")*, *"Severe Insulin-Deficient Diabetes (SIDD),* and *"Severe Autoimmune Diabetes (SAID)"* differ significantly in age at onset of diabetes, residual ß-cell function, presence of obesity/insulin resistance, glycemic status, and risk of development of diabetes-related microvascular complications.

At present, data describing responses to glucose-lowering therapies in these newly-defined diabetes subgroups are sparse. Retrospective analyses suggest that the SIRD subgroup responds better to thiazolidinediones [5], although contradictory results were observed in the EDICT and Qatar studies [17]. A good response to sulfonylureas has been reported for the MARD subgroup, which is represented by many older people [5]. The SIDD subgroup, in which insulin deficiency is most advanced, appears to derive the greatest benefit from the use of basal insulin compared of standard-of-care therapy, as was shown in the ORIGIN trial with insulin glargine 100 U/mL (IGlar-100) [17,18]. The diabetes subgroups also vary considerably in ß-cell function as expressed by differing fasting C-peptide (FCP) levels [4,19], which has been shown

* Correspondence to: Sanofi, General Medicines, Medical Department Diabetes Franchise, C/o Oskar Helene Park 33, 14195 Berlin, Germany.
E-mail address: wolfgang.landgraf@sanofi.com (W. Landgraf).

https://doi.org/10.1016/j.pcd.2023.04.010
Received 17 January 2023; Received in revised form 13 April 2023; Accepted 29 April 2023
Available online 2 May 2023

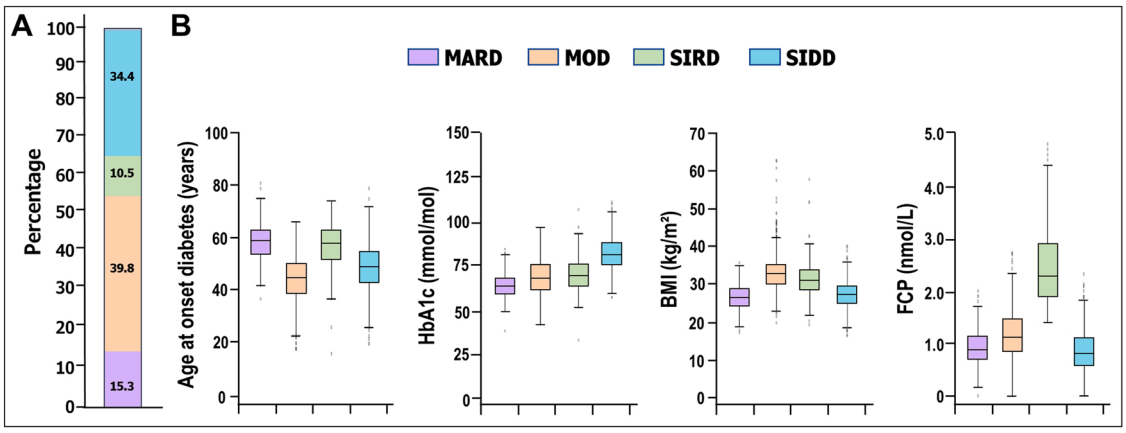

Fig. 1. Distribution of IGlar-100-treated participants (%) into newly-defined T2DM diabetes subgroups in pooled RCTs (A) and distribution of the variables at study entry used for classification of participants (B). MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIRD, severe insulin-resistant diabetes; SIDD, severe insulin-deficient diabetes; FCP, fasting C-peptide; BMI, body mass index. Boxes are the median, and 25th and 75th percentiles; whiskers represent the most extreme value less than or equal to 1.5 times the interquartile range. Values outside the whiskers are outliers.

to determine the insulin dose and hypoglycemia risk in people with T2DM treated with basal insulin IGlar-100 [20].

The aim of the present pooled analysis was to investigate responses to basal IGlar-100 treatment in insulin-naive T2DM participants from randomised clinical trials (RCTs) who were assigned *post hoc* to the T2DM subgroups [19]. Treatment outcomes at 24 weeks were assessed in the T2DM subgroups, comprising those uncontrolled on oral anti-hyperglycemic drugs (OADs) and subsequently exposed to basal IGlar-100.

2. Methods

2.1. RCT population and assignment to T2DM subgroups

Out of an original population of more than 12,000 T2DM participants from 14 RCTs [19] a subset of 9 RCTs [21–29] (Table S1, Supplementary data) was selected for this *post hoc* analysis. IGlar-100 was studied as the investigational medicinal product and compared with other glucose-lowering medications at 12 and 24 weeks. A total of 2687 participants, treated with IGlar-100, were identified and have been reassigned to the newly-defined diabetes subgroups as previously described in detail [4,13,19] and briefly summarised in Table S2. Only three participants were classified to the SAID (T1DM) subgroup and excluded from this analysis (Fig. S1). A sex-specific nearest centroid approach was used to assign remaining T2DM participants (n = 2684) into one of the four other subgroups. Variables that included age at onset of known diabetes, HbA1c, BMI and FCP at baseline were scaled and centred for each participant who was then assigned to one of the four T2DM subgroups to which they were most similar, estimated as the smallest Euclidean distance to subgroup centroids derived from ANDIS coordinates [4]. All participants had originally been enrolled solely according to clinical parameters and inclusion criteria across studies (Table S1).

2.2. Outcomes

All clinical outcomes (HbA1c, fasting plasma glucose, glycemic outcome achievement, insulin dose, hypoglycemia, body weight) were assessed at baseline and over the 24-weeks study period after the introduction and titration of IGlar-100, administered once-daily. Hypoglycemia was determined according to the international consensus on definition as adopted by ADA/EASD [30] using a confirmed plasma glucose (PG) value of ≤ 3.9 or < 3.0 mmol/L (≤70 or <54 mg/dL). Nocturnal hypoglycemia was defined as the time period between 0.00 AM and 5.59 AM and severe hypoglycemia events were defined as those requiring external assistance for recovery.

2.3. Statistical analysis

Baseline variables and clinical outcomes are presented descriptively up to 24 weeks using mean (SD), median (range), or proportion (%). Treatment outcomes were compared further using MARD as the reference subgroup comprising mainly of older individuals with relatively good glycemic control and no other clinical characteristics except few microangiopathies [31,32]. Quantitative outcomes were analysed using a mixed model with repeated measures (MMRM) and an unstructured covariance matrix, including fixed categorical covariates of study, study visits, diabetes subgroups, and diabetes subgroups-by-visit interaction as well as continuous covariates of baseline value and baseline value-by-visit interaction. Least-squares (LS) means change from baseline, corresponding standard errors (SE) and 95 % confidence intervals (CI) were provided. Categorical outcomes were analysed using a logistic regression model with fixed categorical covariates of study and diabetes subgroups providing odds ratios and corresponding 95 % CI. Count data were analysed using an over-dispersed Poisson regression model with a log-link function, logarithm of 24-week on-treatment period duration as an offset variable and fixed categorical covariates of study and diabetes subgroups providing rate ratios and corresponding 95 % CI. Dunnett's test for *post hoc* pairwise multiple comparisons was applied with MARD subgroup as reference. All models were adjusted for age, sex, race/-ethnicity, and diabetes duration at study entry. P-values are displayed for descriptive purpose only. Mapping and pooling of databases were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

3. Results

3.1. Distribution and characteristics of T2DM subgroups

The pooled IGlar-100 study population (n = 2684) comprised of the newly-defined T2DM subgroups MARD (15.3 %; n = 411), MOD (39.8 %; n = 1067), SIRD (10.5 %; n = 283), and SIDD (34.4 %; n = 923) (Fig. 1A). Distribution of the variables used for subgroup classification are shown in Fig. 1B with baseline characteristics and demographics summarised in Table 1. Median age at onset of diabetes was lowest in MOD (45 years) and highest in MARD (59 years), with median known diabetes duration ranging from 6 years (SIRD) to 9 years (SIDD). SIDD and MARD subgroups had the lowest (27 kg/m^2) and MOD the highest

Table 1
Demographics and characteristics of IGlar-100-treated study participants according to newly-defined T2DM subgroups.

Baseline characteristic	Pooled (n = 2.684)	MARD (n = 411)	MOD (n = 1.067)	SIRD (n = 283)	SIDD (n = 923)
Age (years), median (range)	59 (19–87)	67 (47–84)	54 (24–81)	65 (19–87)	59 (26–85)
Age at onset of diabetes (years), median (range)	50 (11–81)	59 (37–81)	45 (11–66)	57 (16–74)	49 (20–79)
Known diabetes duration (years), median (range)	8 (0–50)	7.0 (0–23)	8.0 (1–43)	6.0 (1–29)	9.0 (0–50)
• <5 years, N (%)	633 (23.6)	104 (25.3)	242 (22.7)	104 (36.7)	183 (19.8)
• 5–10 years, N (%)	1027 (38.3)	182 (44.3)	401 (37.6)	117 (41.3)	327 (35.4)
• ≥10 years, N (%)	1024 (38.2)	125 (30.4)	424 (39.7)	62 (21.9)	413 (44.7)
Men, N (%)	1447 (54)	241 (59)	523 (49)	133 (47)	550 (60)
Caucasian (White), N (%)	2282 (85)	379 (92)	888 (83)	263 (93)	752 (82)
Body weight (kg), mean (SD)	84.8 (17.6)	75.8 (12.7)	94.0 (18.3)	88.7 (16.1)	77.0 (13.0)
BMI (kg/m^2), mean (SD)	30.0 (5.0)	26.6 (3.1)	33.2 (4.8)	31.3 (4.5)	27.4 (3.5)
eGFR (mL/min/1.73 m^2), mean (SD)	85.7 (18.3)	78.9 (14.5)	90.9 (17.6)	75.3 (17.9)	85.7 (18.3)
• eGFR <60 mL/min/1.73 m^2), N (%)	239 (9.5)	46 (12.3)	47 (4.6)	58 (22.2)	88 (10.3)
Creatinine (μmol/L), mean (SD)	78.3 (19.2)	80.7 (15.9)	74.9 (18.5)	84.6 (19.6)	79.3 (20.5)
Diabetic retinopathy, N (%)	354 (13.2)	46 (11.2)	126 (11.8)	26 (9.2)	156 (16.9)
Diabetic nephropathy, N (%)	215 (8.0)	35 (8.5)	91 (8.5)	29 (10.2)	60 (6.5)
Diabetic neuropathy, N (%)	689 (25.7)	115 (28.0)	277 (26.0)	93 (32.9)	204 (22.1)
HbA1c (%), mean (SD)	8.83 (1.0)	8.03 (0.58)	8.50 (0.86)	8.62 (0.86)	9.62 (0.80)
HbA1c (mmol/mol), mean (SD)	73.0 (10.3)	64.3 (6.3)	69.4 (9.4)	70.7 (9.4)	81.6 (8.7)
FPG (mmol/L), mean (SD)	11.0 (3.0)	9.7 (2.4)	10.6 (2.8)	10.4 (2.6)	12.1 (3.3)
FPG (mg/dL), mean (SD)	196 (54)	175 (43)	189 (50)	187 (47)	218 (59)
Fasting C-peptide (nmol/L), mean (SD)	1.18 (0.79)	0.93 (0.35)	1.18 (0.43)	2.65 (1.41)	0.85 (0.38)
• ≤0.4 nmol/L, N (%)	161 (6.0)	27 (6.6)	23 (2.2)	0 (0)	111 (12.0)
• 0.4–1.2 nmol/L, N (%)	1546 (57.6)	300 (73.0)	583 (54.6)	0 (0)	663 (71.8)
• 1.2–2.0 nmol/L, N (%)	745 (27.8)	84 (20.4)	420 (39.4)	97 (34.3)	144 (15.6)
• >2.0 nmol/L, N (%)	232 (8.6)	0 (0)	41 (3.8)	186 (65.7)	5 (0.5)
Total cholesterol (mmol/L), mean (SD)	5.2 (1.2)	5.0 (1.2)	5.1 (1.2)	5.2 (1.0)	5.3 (1.3)
LDL cholesterol (mmol/L), mean (SD)	3.0 (1.0)	3.0 (1.0)	2.9 (1.0)	2.9 (0.9)	3.1 (1.0)
HDL cholesterol (mmol/L), mean (SD)	1.2 (0.3)	1.3 (0.5)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)
Triglycerides (mmol/L), mean (SD)	2.4 (2.2)	1.9 (1.0)	2.7 (2.3)	2.9 (1.9)	2.3 (2.3)
Triglycerides/HDL cholesterol ratio, mean (SD)	2.4 (2.5)	1.6 (1.4)	2.6 (2.8)	3.1 (2.8)	2.1 (2.1)
Metformin use, N (%)	2069 (77)	279 (68)	885 (83)	178 (63)	727 (79)
Sulfonylurea use, N (%)	2377 (89)	380 (93)	894 (84)	269 (95)	834 (90)
Thiazolidinedione use, N (%)	335 (13)	40 (10)	172 (16)	18 (6)	105 (11)
Lipid-lowering therapy, N (%)	669 (25)	92 (23)	276 (26)	84 (30)	217 (24)

MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIRD, severe insulin-resistant diabetes; SIDD, severe insulin-deficient diabetes; FCP, fasting C-peptide; eGFR, estimated glomerular filtration rate.

(33 kg/m^2) mean BMI. Interestingly, only 12 % of individuals classified as SIDD had FCP levels ≤ 0.4 nmol/L, whereas the majority (72 %) were between > 0.4 and 1.2 nmol/L. In contrast and as expected, all individuals in the SIRD subgroup had FCP levels > 1.2 nmol/L. HbA1c at baseline ranged from 8.0 % (64 mmol/mol) in MARD to 9.6 % (82 mmol/mol) in SIDD with the lowest mean FPG values in MARD (175 mg/dL; 9.7 mmol/L) and highest mean values in SIDD (218 mg/dL; 12.1 mmol/L) (Table 1).

3.2. Glycemic responses to IGlar-100 therapy in T2DM subgroups

The observed mean HbA1c and FPG at baseline, 12 and 24 weeks and change from baseline to 24 weeks with IGlar-100 therapy are illustrated in Fig. 2 A+B and summarised in Table S3. The adjusted reductions in LS means from baseline to week 24 in HbA1c ranged from − 1.4 % to − 1.5 % (−16 mmol/mol) and from − 62 to − 73 mg/dL (−3.5 to −6.1 mmol/L) in FPG indicating no difference between MOD, SIRD and SIDD versus MARD (Table S3).

In the MARD subgroup, which presented with the lowest baseline HbA1c and FPG, 55 % of participants achieved the target HbA1c level of < 7.0 % (<53 mmol/mol) and 41 % the target FPG < 100 mg/dL (<5.6 mmol/L) at week 24 (Fig. 3). In contrast, only 29 % of participants achieved the target HbA1c in the SIDD subgroup (adjusted OR vs. MARD: 0.40; 95 % CI: 0.29–0.55) (Table S3). The SIRD and MOD subgroups had numerically the lowest proportions achieving target FPG (27 % and 31 %, respectively).

3.3. IGlar-100 dose in T2DM subgroups

The observed mean starting doses of IGlar-100 ranged from 0.16 to 0.21 U/kg/day reaching 0.36, 0.46, 0.47 and 0.50 U/kg/day at 24 weeks in MARD, SIDD, SIRD and MOD, respectively, with the lowest dose increment of 0.18 U/kg/day observed in the MARD subgroup at week 24 (Fig. 2C).

Adjusted LS means changes in IGlar-100 dose from baseline to week 24 were 0.21 U/kg/day for MARD and 0.28–0.31 U/kg/day for the other subgroups with greater increments of dose between 0.08 and 0.10 U/kg/day versus MARD (p < 0.001) (Table S4).

3.4. Hypoglycemia with IGlar-100 therapy in T2DM subgroups

Cumulative incidences of severe, anytime (24-hours), and nocturnal hypoglycemia over 24 weeks across T2DM subgroups are shown in Fig. 4, with hypoglycemia event rates provided in Table S5**.** The cumulative incidence and event rate of severe hypoglycemia was generally low at 2.4 % (0.11 events/person-year), ranging from 1.4 % (0.07 events/person-year) in the SIRD subgroup to 3.0 % (0.11 events/person-year) in the MOD subgroup, with no difference across subgroups.

The MOD and SIRD subgroups, both representing the more obese and insulin-resistant T2DM participants, had a lower hypoglycemia risk compared to MARD, which had the highest cumulative incidence of hypoglycemia. The SIDD subgroup showed a risk comparable to MARD (Fig. 4). Notably, participants in the SIRD subgroup experienced the least anytime level 1 (adjusted OR: 0.41; 95 % CI: 0.28–0.61) and level 2 (adjusted OR: 0.37; 95 % CI: 0.23–0.61) episodes of hypoglycemia compared to MARD. Similar results were observed for SIRD with regard to nocturnal hypoglycemia.

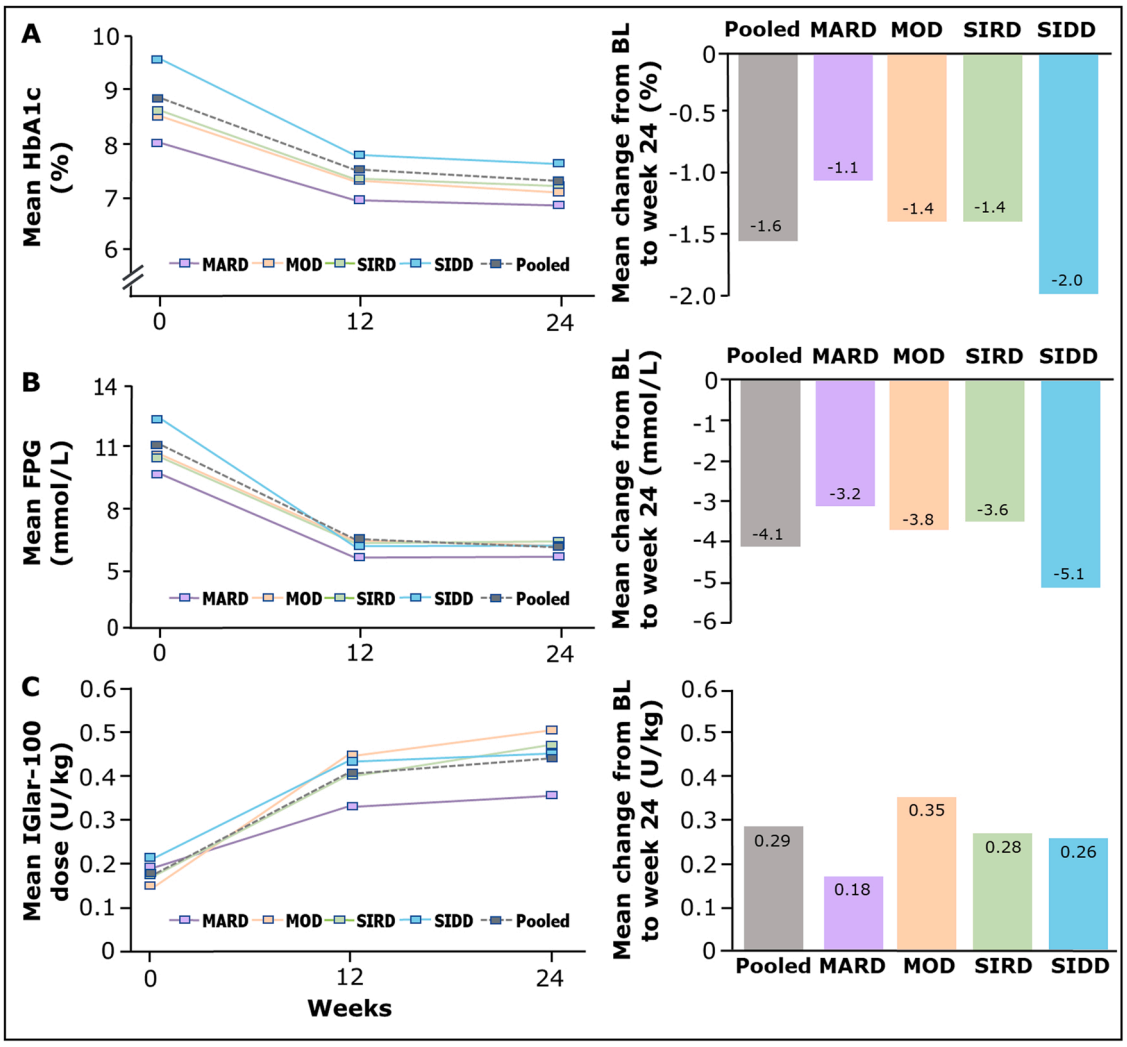

Fig. 2. Observed mean HbA1c (A), fasting plasma glucose (B) and IGlar-100 dose (C) over 24 weeks, and change from baseline to week 24 in IGlar-100-treated participants classified to newly-defined T2DM subgroups. MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIRD, severe insulin-resistant diabetes; SIDD, severe insulin-deficient diabetes; FPG, fasting plasma glucose; IGlar-100, insulin glargine 100 U/mL; BL, baseline.

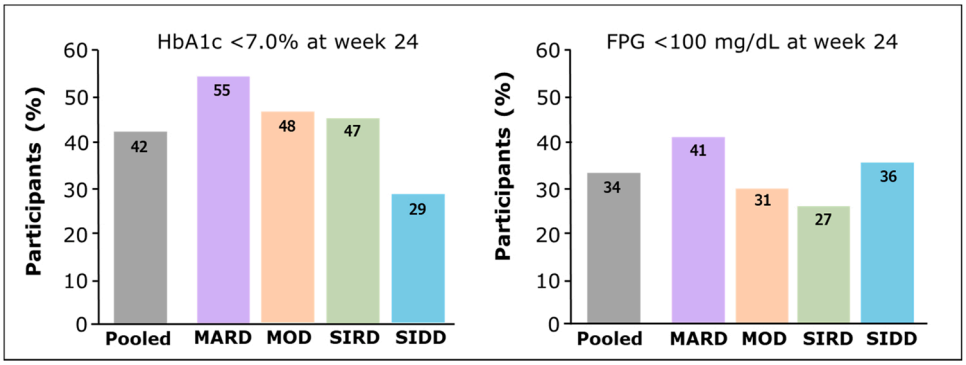

Fig. 3. Achievements of HbA1c and FPG targets at 24 weeks in IGlar-100-treated participants classified to newly-defined T2DM subgroups. MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIRD, severe insulin-resistant diabetes; SIDD, severe insulin-deficient diabetes.

3.5. Body weight with IGlar-100 therapy across T2DM subgroups

Mean body weight at baseline and 24 weeks was lowest in participants assigned to MARD and SIDD subgroups (Table S6). Mean body weight increased in all T2DM subgroups by 24 weeks and the adjusted LS means change was greatest in the leaner SIDD subgroup (+2.8 kg) and least in the overweight/obese SIRD subgroup (+1.6 kg). Compared to MARD the effect of IGlar-100 therapy on body weight was greatest in SIDD (+1.0 kg) ($p < 0.001$).

4. Discussion

This *post hoc* pooled analysis is the first to report responses to basal IGlar-100 treatment in newly-defined type 2 diabetes subgroups that were

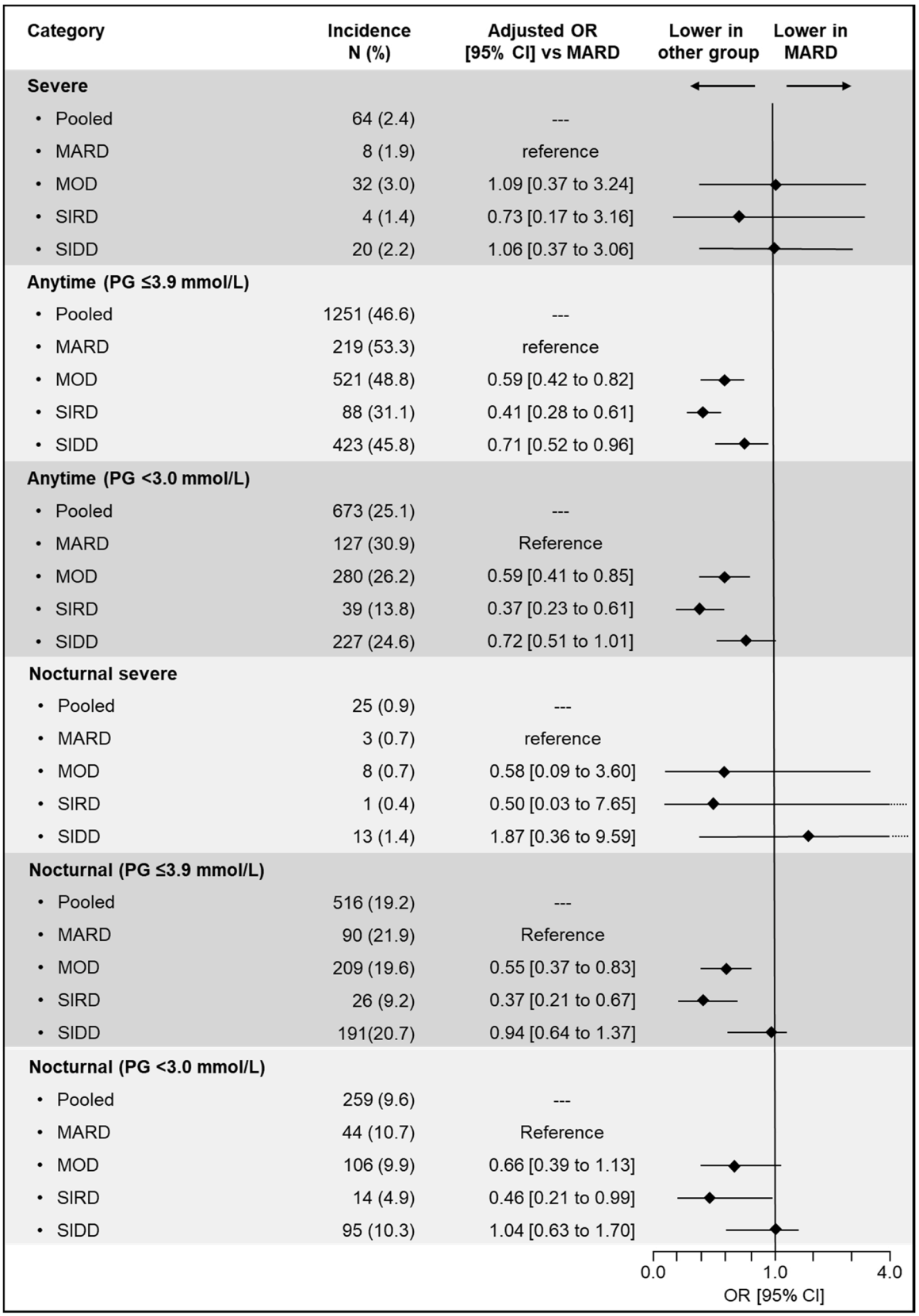

Fig. 4. Cumulative hypoglycemia incidences over 24 weeks in IGlar-100-treated participants classified to newly-defined T2DM subgroups. MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIRD, severe insulin-resistant diabetes; SIDD, severe insulin-deficient diabetes; OR, odds ratio; CI, confidence interval.

derived by classification of more than 2600 insulin-naïve T2DM participants enrolled in clinical trials. Classification into the subgroups MARD, MOD, SIRD and SIDD indicates the broad heterogeneity of T2DM engaged in RCT populations by different outcomes in glucose control, insulin dose requirements, and hypoglycemia risk after the initiation of basal insulin.

The present findings suggest that in general, basal insulin treatment has similar glucose lowering effects (HbA1c, FPG) in all T2DM subgroups, with the proportion achieving target HbA1c levels at 24 weeks predominantly determined by the initial/baseline degree of hyperglycemia. The SIDD subgroup from the pooled RCTs with high baseline HbA1c and FPG levels as described previously in real-world cohorts [4] emerged as the group with the poorest control when treated with basal insulin alone. This finding may be explained by the greater insulin deficiency of the SIDD subgroup, resulting in higher HbA1c, FPG and persistently raised postprandial glucose levels, that were treated with OADs only for many years prior to study entry, which could not be sufficiently corrected with basal IGlar-100 alone during 24 weeks in the RCTs. Therefore, in future, enrolment of individuals with SIDD having advanced T2DM should be avoided for RCTs that investigate the sole use of a basal insulin regimen [19]. A further observation that has been revealed by this subgroup analysis, is that SIDD individuals appear to be concealed when the total population in RCTs is analysed and they are often undetected in real-life in the wider diabetes population. Therefore, subclassification of T2DM into diabetes subgroups in routine clinical practice can identify those individuals (SIDD) who need both timely basal and prandial insulinisation.

In contrast, the MARD subgroup, that is characterised by mild-age related diabetes and shorter diabetes duration, responds very effectively to treatment with basal IGlar-100 alone. In this subgroup the mean HbA1c was lower at 24 weeks (6.9 %; 50 mmol/mol) with lower insulin titration and final insulin dose than in the other subgroups. However, despite receiving the lowest mean insulin dose, more people in the MARD subgroup experienced hypoglycemia. A low FCP level is acknowledged to be a strong predictive biomarker of hypoglycemia risk when initiating IGlar-100 treatment [20]. This might explain why individuals in the SIRD subgroup experienced the lowest hypoglycemia risk in comparison to the other subgroups, because all had FCP levels $>$ 1.20 nmol/L. The broad similarity in some of the hypoglycemia categories found in MARD, SIDD and MOD subgroups could be a consequence of the distribution of people that was based on their FCP values in each subgroup being very similar (Table 1). Therefore, the individual FCP value appears to be more indicative of hypoglycemia risk. The measurement of FCP values together with glycemic parameters and BMI as the main characteristics of these T2DM subgroups will also assist clinical decision-making to implement a personalised and optimal treatment strategy for those individuals.

This *post hoc* outcome analysis according to newly-defined T2D subgroups has some limitations. As full access to patient-level data was available only for this clinical database comprised of nine RCTs, the findings of this analysis are restricted to these study participants. Most of the RCTs involved did not conduct GADA testing, and therefore the few anticipated participants with T1DM or LADA were not excluded. It should also be noted that T2DM subgroups have been determined retrospectively and the study-defined IGlar-100 regimen was not targeted to the different needs of the heterogeneous diabetes subgroups. *A priori,* knowledge of the T2DM subgroup before initiating basal insulin may therefore influence the outcomes in different subgroups.

5. Conclusions

The present analysis of more than 2.600 insulin-naïve study participants, who were retrospectively classified to the newly proposed subgroups of T2DM, i.e., MARD, MOD, SIRD and SIDD, has shown that initiation of IGlar-100 therapy leads to comparable HbA1c and FPG reductions after 24 weeks across these subgroups. The lowest hypoglycemia risk was observed in participants with severe insulin resistance (SIRD). An important clinical observation of the present analysis is that the MARD subgroup representing an early stage of T2DM showed the greatest metabolic benefit from basal insulin therapy alone by achieving the lowest mean HbA1c levels at 24 weeks with lower daily insulin doses compared to the MOD, SIRD, and SIDD subgroups. However, the hypoglycemia risk was highest in this subgroup. In contrast, participants assigned to SIDD having the highest level of hyperglycemia prior to the initiation of basal insulin, were least likely to achieve HbA1c $<$ 7.0 % with IGlar-100 alone despite a higher (compared to MARD) or similar final insulin dose compared to the MOD and SIRD subgroups. Suboptimal glycemic control observed with IGlar-100 therapy in MOD, SIRD, and SIDD subgroups may reflect the composite of higher baseline levels of hyperglycemia versus MARD, sub-optimal basal insulin titration, and in the case of the SIDD subgroup, by not addressing the postprandial hyperglycemia with the administration of prandial insulin supplementation.

The present findings, therefore, reinforce the need for an individualised approach to glucose-lowering therapy in people with T2DM. The determination and knowledge of diabetes subgroups at diagnosis may assist clinicians to make a better selection of the most effective glucose-lowering therapy for people with T2DM, while also alerting clinicians to those at greatest vulnerability to hypoglycemia. This personalised approach may assist the management of people with T2DM inadequately controlled by non-insulin therapies by ensuring the provision of both a timely intervention with basal insulin and adequate titration/intensification of insulin whilst avoiding hypoglycemia.

Future prospective clinical studies are warranted to further investigate the responses to different classes of glucose-lowering therapies according to the proposed new subclassification of T2DM to support the concept of evidence-based personalised diabetes management as part of diabetes treatment guidelines [33].

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The underlying diabetes RCTs were funded by Sanofi.

CRediT authorship contribution statement

Wolfgang Landgraf: Conceptualization, Data curation, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Gregory Bigot:** Conceptualization, Formal analysis, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **Brian M. Frier:** Validation, Writing – original draft, Writing – review & editing. **Geremia B. Bolli:** Validation, Writing – original draft, Writing – review & editing. **David R. Owens**: Validation, Writing – original draft, Writing – review & editing. All authors take responsibility for the accuracy and integrity of the data presented in this manuscript.

Declaration of Competing Interest

W.L. is an employee of Sanofi, Germany, and Sanofi shareholder. G. B. is an IVIDATA employee, contracted to Sanofi. B.M.F. has served on advisory panels for Eli Lilly and Zucara Therapeutics, and on the speakers' bureau for Eli Lilly, Novo Nordisk, Sanofi, and Abbott. G.B.B. is a consultant for Eli Lilly and Sanofi; has received research support from Sanofi; and is on the speakers' bureau for Eli Lilly, Menarini, and Sanofi. D.R.O. has received honoraria for lecturing and consulting from Boehringer Ingelheim, Eli Lilly, Roche Diagnostics, Sanofi, and Takeda.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pcd.2023.04.010.

References

[1] U.B. Pajvani, D. Accili, The new biology of diabetes, Diabetologia 58 (2015) 2459–2468.
[2] T. Tuomi, N. Santoro, S. Caprio, M. Cai, J. Weng, L. Groop, The many faces of diabetes: a disease with increasing heterogeneity, Lancet 383 (9922) (2014) 1084–1094.
[3] K. Faerch, A. Hulmán, T.P.J. Solomon, Heterogeneity of pre-diabetes and type 2 diabetes: implications for prediction, prevention, and treatment responsiveness, Curr. Diabetes Rev. 12 (1) (2016) 30–41.
[4] E. Ahlqvist, P. Storm, A. Käräjämäki, M. Martinell, M. Dorkhan, et al., Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables, Lancet Diabetes Endocrinol. 6 (2018) 361–369.
[5] J.M. Dennis, B.M. Shields, W.E. Henley, A.G. Jones, A.T. Hattersley, Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data, Lancet Diabetes Endocrinol. 7 (6) (2019) 442–451.
[6] O.P. Zaharia, K. Strassburger, A. Strom, G.J. Bönhof, Y. Karusheva, et al., Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study, Lancet Diabetes Endocrinol. 7 (9) (2019) 684–694.
[7] X. Zou, X. Zhou, Z. Zhu, L. Ji, Novel subgroups of patients with adult-onset diabetes in Chinese and US populations, Lancet Diabetes Endocrinol. 7 (1) (2019) 9–11.
[8] C. Herder, M. Roden, A novel diabetes typology: towards precision diabetology from pathogenesis to treatment, Diabetologia 65 (2022) 1770–1781.
[9] N. Safai, A. Ali, P. Rossing, M. Ridderstråle, Stratification of type 2 diabetes based on routine clinical markers, Diabetes Res Clin. Pract. 141 (2018) 275–283.
[10] R.C. Slieker, L.A. Donnelly, H. Fitipaldi, G.A. Bouland, et al., Replication and cross-validation of type 2 diabetes subtypes based on clinical variables: an IMI-RHAPSODY study, Diabetologia 64 (9) (2021) 1982–1989.
[11] R.B. Prasad, O. Asplund, R. Sharvari, S.R. Shukla, R. Wagh, et al., Subgroups of patients with young-onset type 2 diabetes in India reveal insulin deficiency as a major driver, Diabetologia 65 (1) (2022) 65–78.
[12] O. Fedotkina, O. Sulaieva, T. Ozgumus, L. Cherviakova, et al., Novel reclassification of adult diabetes is useful to distinguish stages of b-cell function linked to the risk of vascular complications: the DOLCE study from Northern Ukraine, Front. Genet. 12 (2021), 637945.
[13] M. Pigeyre, S. Hess, M.F. Gomez, O. Asplund, L. Groop, G. Paré, H. Gerstein, Validation of the classification for type 2 diabetes into five subgroups: a report from the ORIGIN trial, Diabetologia 65 (2022) 206–215.
[14] A.R. Kahkoska, M.S. Geybels, K.R. Klein, F.F. Kreiner, N. Marx, M.A. Nauck, R. E. Pratley, B.O. Wolthers, J.B. Buse, Validation of distinct type 2 diabetes clusters and their association with diabetes complications in the DEVOTE, LEADER and SUSTAIN-6 cardiovascular outcomes trials, Diabetes Obes. Metab. 22 (9) (2020) 1537–1547.
[15] A. Sharma, Y. Zheng, J.A. Ezekowitz, C.M. Westerhout, et al., Cluster analysis of cardiovascular phenotypes in patients with type 2 diabetes and established atherosclerotic cardiovascular disease: a potential approach to precision medicine, Diabetes Care 45 (1) (2022) 204–212.
[16] Y. Aoki, B. Hamrén, L.E. Clegg, C. Stahre, et al., Assessing reproducibility and utility of clustering of patients with type 2 diabetes and established CV disease (SAVOR -TIMI 53 trial), PLoS One 16 (11) (2021), e0259372.
[17] T. Abdul-Ghani, C. Puckett, O. Migahid, S. Abdelgani, et al., T2DM subgroups and response to glucose-lowering therapy: results from EDICT and Qatar study, Diabetes Obes. Metab. 24 (2022) 1810–1818.
[18] K.I. Birkeland, V. Grill, C. Wium, M.J. McQueen, et al., The association of basal insulin treatment versus standard care with outcomes in anti-GAD positive and negative subjects: a post-hoc analysis of the ORIGIN trial, Diabetes Obes. Metab. 21 (2) (2019) 429–433.
[19] W. Landgraf, G. Bigot, S. Hess, O. Asplund, et al., Distribution and characteristics of newly-defined subgroups of type 2 diabetes in randomised clinical trials: post hoc cluster assignment analysis of over 12,000 study participants, Diabetes Res Clin. Pract. 190 (2022), 110012.
[20] W. Landgraf, D.R. Owens, B.M. Frier, M. Zhang, G.B. Bolli, Fasting C-peptide, a biomarker for hypoglycaemia risk in insulin-naïve people with type 2 diabetes initiating basal insulin glargine 100 U/mL, Diabetes Obes. Metab. 22 (3) (2020) 315–323.
[21] A. Fritsche, M.A. Schweitzer, H.U. Häring, 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. 138 (12) (2003) 952–959.
[22] M.C. Riddle, J. Rosenstock, J. Gerich, The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients, Diabetes Care 26 (2003) 3080–3086.
[23] E. Standl, S. Maxeiner, S. Raptis, Once−daily insulin glargine administration in the morning compared to bedtime in combination with morning glimepiride in patients with type 2 diabetes: an assessment of treatment flexibility, Horm. Metab. Res 38 (2006) 172–177.
[24] F.G. Eliaschewitz, C. Calvo, H. Valbuena, et al., Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride, Arch. Med. Res. 37 (2006) 495–501.
[25] J. Rosenstock, D. Sugimoto, P. Strange, et al., Triple therapy in type 2 diabetes. Insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients, Diabetes Care 9 (2006) 554–559.
[26] P. Hollander, D. Sugimoto, A. Vlajnic, C. Kilo, Combination therapy with insulin glargine plus metformin but not insulin glargine plus sulfonylurea provides similar glycemic control to triple oral combination therapy in patients with type 2 diabetes uncontrolled with dual oral agent therapy, J. Diabetes Complicat. 29 (8) (2015) 1266–1271.
[27] H.U. Janka, G. Plewe, M.C. Riddle, et al., Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes, Diabetes Care 28 (2005) 254–259.
[28] R.G. Bretzel, U. Nuber, W. Landgraf, et al., Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial, Lancet 371 (2008) 1073–1084.
[29] S.G. Swinnen, M.-P. Dain, R. Aronson, M. Davies, et al., 24-Week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs, Diabetes Care 33 (2010) 1176–1178.
[30] 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 40 (2017) 155–157.
[31] H. Tanabe, H. Masuzaki, M. Shimabukuro, Novel strategies for glycaemic control and preventing diabetic complications applying the clustering-based classification of adult- onset diabetes mellitus: a perspective, Diabetes Res Clin. Pract. 180 (2021), 109067.
[32] S.B. Zaghlool, A. Halama, N. Stephan, V. Gudmundsdottir, et al., Metabolic and proteomic signatures of type 2 diabetes subtypes in an Arab population, Nat. Commun. 13 (2022) 7121, https://doi.org/10.1038/s41467-022-34754-z.
[33] M.J. Davies, V.R. Aroda, B.R. Collins, R.A. Gabbay, J. Green, et al., Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia 65 (2022) 1925–1966.