Response to Insulin Glargine 100 U/Ml Treatment in Newly Identified Type 2 Diabetes Subgroups: Post Hoc Pooled Analysis of Patients in Nine Randomised Clinical Trials Who Have Never Taken Insulin

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Abstract

Aims: To examine the outcomes of the treatment with insulin glargine 100 U/mL (IGlar-100) in newly identified subgroups of type 2 diabetes mellitus (T2DM).

Methods: Participants with insulin-nave T2DM (n = 2684) from nine randomised clinical trials that started IGlar-100 were pooled and put into subgroups called "Mild Age-Related Diabetes (MARD)," "Mild Obesity Diabetes (MOD)," "Severe Insulin Resistant Diabetes (SIRD)," and "Severe Insulin Deficient Diabetes (SIDD)" based on their age at diagnosis, HbA1c, FPG, hypoglycemia, insulin portion, and body weight were examined at standard and 24 weeks.

Results: MARD 15.3 percent (n = 411), MOD 39.8 percent (n = 1067), SIRD 10.5 percent (n = 283), and SIDD 34.4 percent (n = 923). After 24 weeks, the subgroups' adjusted least square mean reductions in HbA1c from baseline (8.0–9.6%) were comparable (1.4–1.5%). SIDD was more averse to accomplish HbA1c < 7.0 % (OR: 0.40 [0.29, 0.55]) as opposed to MARD. While the last IGlar-100 portion (0.36 U/kg) in MARD was lower than in different subgroups (0.46-0.50 U/kg), it had the most noteworthy hypoglycemia risk. SIRD had least hypoglycemia risk and SIDD showed most prominent body weight gain.

Conclusion: IGlar-100 brought down hyperglycemia likewise in all T2DM subgroups, yet level of glycemic control, insulin portion, and hypoglycemia risk varied between subgroups.

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

Introduction

Type 2 diabetes mellitus (T2DM) is a diverse condition with a wide range of clinical manifestations, disease progression, and complications. To subclassify diabetes, various methods, such as k-means clustering of clinical variables, have been used. As of late, five subgroups have been depicted from genuine populaces and recreated in diabetes populaces from randomized clinical preliminaries [1]. These recently characterized subgroups ordered as "Gentle Age-Related Diabetes (MARD)", "Gentle Weight related Diabetes (MOD)", "Extreme Insulin-Safe Diabetes (SIRD"), "Serious Insulin-Lacking Diabetes (SIDD), and "Extreme Immune system Diabetes (SAID)" contrast fundamentally in age at beginning of diabetes, leftover ß-cell capability, presence of corpulence/insulin opposition, glycemic status, and hazard of improvement of diabetes-related microvascular difficulties [2].

These newly identified diabetes subgroups' responses to glucose-lowering therapies are currently poorly documented. Although contradictory results were observed in the EDICT and Qatar studies, retrospective analyses suggest that the SIRD subgroup responds better to thiazolidinediones. A decent reaction to sulfonylureas has been accounted for the MARD subgroup, which is addressed by numerous more established individuals. The SIDD subgroup, where insulin lack is generally exceptional, seems to get the best advantage from the utilization of basal insulin thought about of standard-of-care treatment, as was displayed in the Beginning preliminary with insulin glargine 100 U/mL (IGlar-100). In people with T2DM who are being treated with basal insulin IGlar-100, it has been demonstrated that the insulin dose and the risk of hypoglycemia are determined by the ß-cell function differences among the diabetes subgroups.

The present pooled analysis sought to determine how insulin-naive T2DM participants from randomised clinical trials (RCTs) who were assigned post hoc to the T2DM subgroups responded to basal IGlar-100 treatment. Treatment results at 24 weeks were surveyed in the T2DM subgroups, containing those uncontrolled on oral antihyperglycemic drugs (OADs) and thusly presented to basal IGlar-100 [3].

Methods

RCT population and assignment to T2DM subgroups

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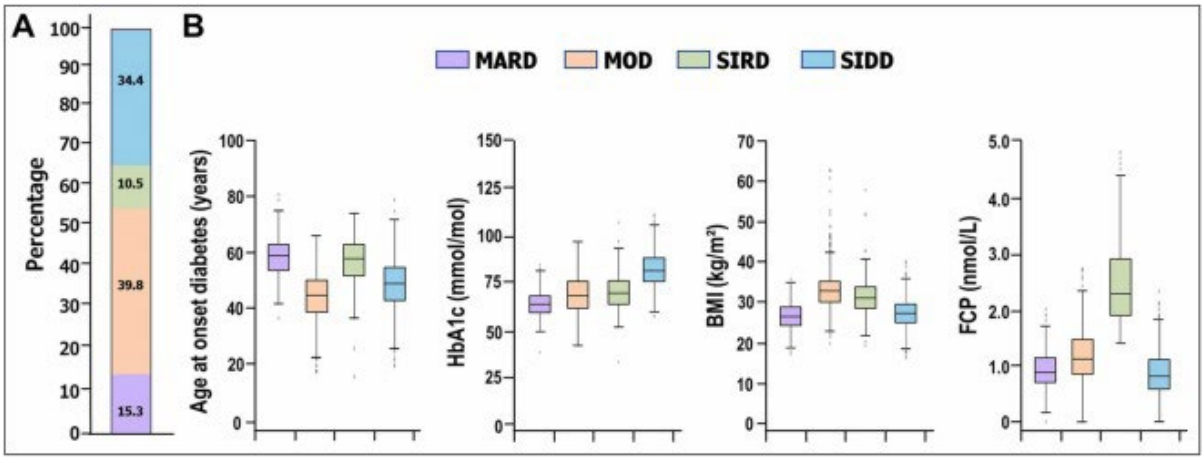

Figure 1: Distribution of IGlar-100-treated participants (%) into newly-defined T2DM diabetes subgroups in pooled RCTs (A) and distribution of the variables at study entry used for classification of participants (B). MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SIRD, severe insulin-resistant 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.

Results

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) (Figure 1A). Distribution of the variables used for subgroup classification are shown in (Figure 1B) with baseline characteristics and demographics summarised. 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/m²) and MOD the highest (33 kg/m²) 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[7]. 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) [8].

Glycemic responses to IGlar-100 therapy in T2DM subgroups

The observed mean HbA1c and FPG at baseline, 12 and 24 weeks, as well as the change from baseline to 24 weeks with IGlar-100 therapy, are depicted in (Figure 1). Glycemic responses to IGlar-100 therapy in T2DM subgroups 2 A+B and summed up in Table S3. From baseline to week 24, the adjusted reductions in LS means 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 that MOD, SIRD, and SIDD did not differ from MARD [9].

Body weight with IGlar-100 therapy across T2DM subgroups

The participants in the MARD and SIDD subgroups had the lowest mean body weight at baseline and 24 weeks. All T2DM subgroups experienced an increase in mean body weight by 24 weeks, with the leaner SIDD subgroup experiencing the greatest change (2.8 kg) and the overweight/obese SIRD subgroup experiencing the least change (1.6 kg). In SIDD, the effect of IGlar-100 therapy on body weight was greater (1.0 kg) than that of MARD (p 0.001) [10]. All clinical outcomes (HbA1c, fasting plasma glucose, glycemic outcome achievement, insulin dose, hypoglycemia, and body weight) were evaluated at baseline and throughout the 24-week study period following the introduction and titration of once-daily IGlar-100. Not entirely set in stone as per the worldwide agreement on definition as taken on by ADA/EASD utilizing an affirmed plasma glucose (PG) worth of ≤ 3.9 or < 3.0 mmol/L (≤70 or <54 mg/dL). The time period between 0.00 AM and 5.59 AM was considered to be nocturnal hypoglycemia, and severe hypoglycemia events were those that necessitated external assistance for recovery [11].

Discussion

This post hoc pooled analysis is the first to report responses to basal IGlar-100 treatment in newly defined type 2 diabetes subgroups derived from the classification of more than 2600 insulin-nave T2DM participants participating in clinical trials. Different outcomes in glucose control, insulin dose requirements, and hypoglycemia risk after the initiation of basal insulin indicate the broad heterogeneity of T2DM participants in RCT populations. Classification into the subgroups MARD, MOD, SIRD, and SIDD demonstrates this heterogeneity [12].

According to the present findings, basal insulin treatment has similar effects on glucose control (HbA1c, FPG) in all T2DM subgroups. The proportion of patients achieving target HbA1c levels at 24 weeks is largely determined by the degree of hyperglycemia at baseline. When treated with basal insulin alone, the SIDD subgroup from the pooled RCTs with high baseline HbA1c and FPG levels, as described previously in real-world cohorts [13], emerged as the group with the poorest control. This result may be due to the SIDD subgroup's greater insulin deficiency, which was treated with OADs only for a long time prior to study entry and could not be adequately corrected with basal IGlar-100 alone for 24 weeks in the RCTs. This led to higher HbA1c, FPG, and persistently elevated postprandial glucose levels. Therefore, RCTs that investigate the sole use of a basal insulin regimen should avoid enrolling SIDD patients with advanced T2DM in the future [15]. This subgroup analysis has also shown that SIDD patients appear to be hidden when the entire RCT population is analyzed, but they are frequently overlooked in the real-world diabetes population. Therefore, in routine clinical practice, subclassification of T2DM into diabetes subgroups can identify individuals (SIDD) who require prompt basal and prandial insulinization [16].

Conclusions

This study's retrospective classification of more than 2.600 insulin-nave study participants into the newly proposed subgroups of T2DM—MARD, MOD, SIRD, and SIDD—has revealed that initiating IGlar-100 therapy results in comparable reductions in HbA1c and FPG after 24 weeks across these subgroups. Participants with severe insulin resistance (SIRD) had the lowest risk of hypoglycemia. By achieving the lowest mean HbA1c levels at 24 weeks with lower daily insulin doses than the MOD, SIRD, and SIDD subgroups, the MARD subgroup, which represents an early stage of T2DM, demonstrated the greatest metabolic benefit from basal insulin therapy alone. This is an important clinical observation of the present analysis. However, this subgroup had the highest risk of hypoglycemia. Conversely, members relegated to SIDD having the most significant level of hyperglycemia before the inception of basal insulin, were to the least extent liable to accomplish HbA1c < 7.0 % with IGlar-100 alone notwithstanding a higher (contrasted with MARD) or comparative last insulin portion contrasted with the MOD and SIRD subgroups. The combination of higher baseline levels of hyperglycemia compared to MARD, suboptimal basal insulin titration, and, in the SIDD subgroup, the failure to address postprandial hyperglycemia with the administration of prandial insulin supplementation may account for the suboptimal glycemic control observed with IGlar-100 therapy in the MOD, SIRD, and SIDD subgroups.

Acknowledgement

None

Conflict of Interest

None

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