



Safety and Effectiveness of Concomitant iGlarLixi and SGLT-2i Use in People with T2D During Ramadan Fasting: A SoliRam Study Sub-analysis

Mohamed Hassanein · Rachid Malek · Saud Al Sifri · Rakesh Kumar Sahay · Mehmet Akif Buyukbese · Khier Djaballah · Lydie Melas-Melt · Inass Shaltout

Received: June 21, 2024 / Accepted: August 14, 2024 / Published online: September 9, 2024
© The Author(s) 2024

ABSTRACT

Introduction: The aim of this work was to assess the safety and effectiveness of concomitant iGlarLixi and sodium-glucose co-transporter-2 inhibitors (SGLT-2i) use in adults with type 2 diabetes (T2D) who fasted during Ramadan.

Methods: Of the 420 eligible participants from the SoliRam study, 174 were using SGLT-2i in addition to iGlarLixi and 246 were not using SGLT-2i, referred to as SGLT-2i user and

non-user, respectively. The primary endpoint was the proportion of participants experiencing ≥ 1 severe and/or symptomatic documented (< 70 mg/dl [< 3.9 mmol/l]) hypoglycemia.

Results: More than 50% of participants in both groups were male. The mean weight, glycated hemoglobin (HbA1c), and fasting plasma glucose (FPG) were similar in both groups. Approximately half of participants in the SGLT-2i-user group and ~25% participants in the SGLT-2i-non-user group were on two oral anti-hyperglycemic drugs (OADs), whereas ~20% in the SGLT-2i-user group and ~1% of participants in the SGLT-2i-non-user group were on three OADs in addition to iGlarLixi. Around 35% and 55% of participants in the SGLT-2i-user and SGLT-2i-non-user groups, respectively, were taking concurrent sulphonylureas. About 97% of participants in both groups were able to fast for ≥ 25 days. The incidence of primary

Prior presentation: Data of this analysis were partly presented at the 12th Annual Meeting of the Diabetes and Ramadan (DAR) International Alliance Conference. Dubai, UAE. 13–14 Jan 2024.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13300-024-01642-2>.

M. Hassanein (✉)
Mohamed Bin Rashid University and Dubai
Hospital, Dubai, United Arab Emirates
e-mail: mhassanein148@hotmail.com

R. Malek
CHU Mohamed Saadna Abdennour, Setif, Algeria

S. Al Sifri
Al Hada Military Hospital, Taif, Saudi Arabia

R. K. Sahay
Osmania Medical College, Hyderabad, Telangana,
India

M. A. Buyukbese
Private Practice, Gaziantep, Turkey

K. Djaballah
Sanofi, Paris, France

L. Melas-Melt
IVIDATA Life Sciences, Levallois-Perret, France

I. Shaltout
Cairo University, Cairo, Egypt

endpoint was low in both groups; SGLT-2i user: 0.6%, 4.2%, and 0.6% and SGLT-2i-non-user: 1.3%, 0.9% and 0% during pre-Ramadan, Ramadan, and post-Ramadan period, respectively. The incidence of severe and/or symptomatic documented (<54 mg/dl [<3.0 mmol/l]) hypoglycemia events was also low throughout the study, including during Ramadan. No severe hypoglycemia occurred during Ramadan in either group. Improvements in HbA1c and FPG, with a small reduction in weight, were observed from pre- to post-Ramadan in both groups. No serious adverse event was reported in either group.

Conclusions: Concomitant iGlarLixi and SGLT-2i therapy with or without other OADs was demonstrated to be safe in adults with T2D during Ramadan fast, with a low risk of hypoglycemia and improvements in glycemic outcomes.

Keywords: Fasting; iGlarLixi; Ramadan; SGLT-2i; Hypoglycemia; Type 2 diabetes

Therefore, this current sub-analysis study was conducted to assess safety and effectiveness of concomitant use of iGlarLixi and SGLT-2i in people with T2D during Ramadan fasting.

What was learned from the study?

The incidence of ≥ 1 severe and/or symptomatic documented hypoglycemia (<70 mg/dl [<3.9 mmol/l] and <54 mg/dl [<3.0 mmol/l]) was low in both groups throughout the study. No incidence of severe hypoglycemia was reported during Ramadan in either group.

Improvements in glycated hemoglobin and fasting plasma glucose, along with a small reduction in weight, were observed from pre- to post-Ramadan in both groups.

Few incidences of adverse event were observed in both groups, with no serious adverse event reported in either group.

Key Summary Points

Why carry out this study?

SoliRam, a prospective, real-world, observational study demonstrated that iGlarLixi, a fixed-ratio combination of basal insulin (BI) glargine 100 U/m and glucagon-like peptide-1 receptor agonist (GLP-1RA) lixisenatide, was safe and effective in people with type 2 diabetes (T2D) during Ramadan fasting.

An increasing number of people with T2D who are taking a combination of BI and GLP-1RA for glycemic control will require sodium-glucose co-transporter-2 inhibitors (SGLT-2i) for cardiovascular or renal protection.

In the SoliRam study, over 40% of participants were taking concomitant iGlarLixi and SGLT-2i, with or without other oral anti-hyperglycemic drugs. This highlights the importance of assessing the safety and effectiveness of this combination during Ramadan fast.

INTRODUCTION

People with diabetes are at high risk of cardiovascular (CV) and kidney diseases, contributing to most of the diabetes-related morbidity and mortality [1, 2]. Owing to the established safety and efficacy of sodium-glucose co-transporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) in type 2 diabetes (T2D) along with additional cardio- and renoprotective benefits, the guidelines (American Diabetes Association [ADA]/European Association of Diabetes [EASD] and American Association of Clinical Endocrinology [AACE]) recommend treatment intensification with SGLT-2i and GLP-1RA in people with T2D who are sub-optimally controlled by oral anti-hyperglycemic drugs (OADs) and have an established CV or kidney disease or risk factors [3, 4]. People who are already taking SGLT-2i or GLP-1RA and require further glycemic control, intensification with basal insulin (BI) is recommended, either by adding BI separately to the existing therapy or switching, for those receiving a GLP-1RA, from their previous therapy to

a fixed-ratio combination (FRC) of BI and GLP-1RA [3]. FRCs simplify the complexity of insulin therapy and reduce injection burden/frequency, with no increase in the risk of hypoglycemia and weight gain compared with BI, which indicates that FRCs are a more effective treatment approach [5, 6].

iGlarLixi is an FRC of BI glargine 100 U/ml and GLP-1RA lixisenatide. Randomized controlled trials have shown that iGlarLixi is an effective and well-tolerated treatment advancement approach in people with T2D previously sub-optimally controlled by either OADs alone or combined with BI or GLP-1RA [7–10]. In a post hoc exploratory analysis of the LixiLan-G study and real-world evidence from the US Optum-Humedica database, concomitant iGlarLixi and SGLT-2i therapy was shown as safe and effective, showing similar robust glycemic outcomes and low hypoglycemia rates as reported by people receiving iGlarLixi alone [11].

SoliRam, a multicenter, real-world observational study, demonstrated safety and effectiveness of iGlarLixi in people with T2D before, during and after Ramadan [12]. About 85% of the SoliRam study participants were using concomitant OADs, of which 41.2% were on SGLT-2i [12]. To date, no studies investigating the concomitant use of iGlarLixi and SGLT-2i during Ramadan or fasting conditions have been published. Therefore, a sub-analysis of the SoliRam study was conducted, the first ever analysis to explore this combination during Ramadan fast. The objective of this sub-analysis was to assess the safety and effectiveness of concomitant iGlarLixi and SGLT-2i use, with or without other OADs, in adults with T2D who fasted during Ramadan in the SoliRam study. The results of this analysis would contribute to establishing an evidence base for the concurrent use of iGlarLixi and SGLT-2i in individuals with T2D planning to fast.

METHODS

Study Design and Participants

Detailed SoliRam study design and methods have been previously published [12]. Briefly, SoliRam was a prospective, real-world, observational study conducted across nine countries in adults (≥ 18 years of age) with T2D treated with iGlarLixi for ≥ 3 months at study entry. The study spanned for 3–5 months; pre-Ramadan (1–3 months prior to Ramadan), Ramadan (1 month) and post-Ramadan (1 month). Participants who were willing to fast for ≥ 15 days during Ramadan, measure self-monitored plasma glucose (SMPG) and maintain records were included in the study. Data were collected from the self-maintained diary provided at study entry, where participants recorded their blood glucose values, iGlarLixi doses, any episodes of symptomatic hypoglycemia, and details on fasting (including reasons for not fasting). Detailed inclusion and exclusion criteria were described earlier [12]. All participants provided their written informed consent. This study was conducted in accordance with the Declaration of Helsinki of 1964 and all subsequent amendments. The study protocol was approved by the local institutional review board/independent ethics committee of the country of each participating investigator (Supplementary Table S1), and regulatory submissions were performed in accordance with the local data protection guidelines.

Study Endpoints

The primary endpoint was the proportion of participants experiencing ≥ 1 severe and/or symptomatic documented (< 70 mg/dl [< 3.9 mmol/l]) hypoglycemia during pre-Ramadan (last month), Ramadan, and post-Ramadan periods and the overall study duration. The secondary hypoglycemia endpoints included the incidence of severe and/or symptomatic documented (< 54 mg/dl [< 3.0 mmol/l]) hypoglycemia and the incidence and event rate of hypoglycemia according to the time of day during Ramadan (any time between Suhur and Iftar and between Iftar and Suhur).

Other secondary endpoints included the mean change in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting SMPG and weight from pre- to post-Ramadan, and the mean change in iGlarLixi doses from pre-Ramadan to Ramadan and to post-Ramadan. Safety endpoints included adverse events (AEs), including serious AEs and AEs of special interest.

Statistical Analyses

The number and percentage of participants reporting the primary endpoint during each period were presented with 95% confidence interval (CI), computed based on the Clopper–Pearson method. The primary endpoint was analyzed on eligible population defined as all participants included in the study who met the inclusion and exclusion criteria.

The categorical secondary endpoints were analyzed the same way as the primary endpoint in eligible population. For continuous effectiveness endpoints, descriptive statistics were provided for the mean change in evaluable population. The evaluable population consisted of all participants with glycemic endpoint data available for both pre-Ramadan and post-Ramadan periods. An analysis of AEs was performed in included population (all participants who provided signed informed consent forms).

RESULTS

This SoliRam sub-analysis included all 420 eligible participants involved in the overall study. Of the 420 eligible participants, 174 participants were using SGLT-2i in addition to iGlarLixi and 246 participants were not using SGLT-2i, henceforth, referred to as SGLT-2i user and non-user, respectively.

Baseline Demographics and Participant Characteristics

More than 50% of participants were males in both groups (Table 1). The mean age of participants in SGLT-2i-user group (55 years) was lower than that in SGLT-2i-non-user group (58 years) and more participants in SGLT-2i-non-user

group were aged ≥ 65 years (Table 1). The mean weight, duration of diabetes, HbA1c, and FPG were similar in both groups. Any complications and/or comorbidities were higher in SGLT-2i-non-user group, whereas the use of OADs was higher in SGLT-2i-user group (Table 1).

Fasting During Ramadan

Around 97% of the participants in both groups were able to fast for ≥ 25 days. Most participants in SGLT-2i-user (93.6%) and SGLT-2i-non-user (66.7%) groups considered their personal decision as motivation for fasting. Other reasons for fasting included improving health (SGLT-2i user, 2.3% and SGLT-2i-non-user, 1.3%), coping with family and community (SGLT-2i user, 0.6% and SGLT-2i-non-user, 2.5%), enhancing self-discipline (SGLT-2i user, 1.7% and SGLT-2i-non-user, 3.4%) and other (SGLT-2i user, 1.7% and SGLT-2i-non-user, 26.2%). Meanwhile, 16 (9.3%) and 15 (6.3%) participants in SGLT-2i-user and SGLT-2i-non-user groups, respectively, broke their fast. The main reasons for breaking the fast were traveling (SGLT-2i user, $n=4$ and SGLT-2i-non-user, $n=6$), pre-existing conditions (SGLT-2i user, $n=1$ and SGLT-2i-non-user, $n=6$), AEs (SGLT-2i user, $n=4$ and SGLT-2i-non-user, $n=0$), hypoglycemia (SGLT-2i user, $n=3$ and SGLT-2i-non-user, $n=1$) or menses (SGLT-2i user, $n=4$ and SGLT-2i-non-user, $n=2$). More than 60% of the participants received diabetes education specific to Ramadan either by educational programs or face-to-face sessions or website/self-education (Supplementary Table S2).

Changes in Anti-hyperglycemic Therapy

iGlarLixi Treatment

At the study initiation visit, 67.2% and 73.6% participants in SGLT-2i-user and SGLT-2i-non-user groups, respectively, used an iGlarLixi 10–40 pen (insulin glargine 100 units/ml + lixisenatide 50 $\mu\text{g/ml}$) and 32.8% and 26.4% participants in SGLT-2i-user and SGLT-2i-non-user groups, respectively, used an iGlarLixi 30–60 pen (insulin glargine 100 units/ml + lixisenatide 33 $\mu\text{g/ml}$).

Table 1 Baseline demographics and clinical characteristics

Characteristics	SGLT-2i user (<i>n</i> = 174)	SGLT-2i-non-user (<i>n</i> = 246)	Total (<i>N</i> = 420)
Age (years)	55.2 ± 9.6	58.4 ± 9.8	57.1 ± 9.8
≥ 65 years, <i>n</i> (%)	33 (19.0)	68 (27.7)	101 (24.0)
Male, <i>n</i> (%)	98 (56.3)	134 (54.5)	232 (55.2)
Weight (kg)	87.9 ± 16.2	85.5 ± 14.0	86.5 ± 14.9
BMI (kg/m ²)	31.3 ± 5.4	30.7 ± 5.3	30.9 ± 5.3
Duration of diabetes (years)	11.4 ± 6.3	12.6 ± 6.4	12.1 ± 6.4
≥ 10 years, <i>n</i> (%)	96 (55.2)	150 (61.0)	246 (58.6)
HbA1c (%) ^a	8.2 ± 1.3	8.2 ± 1.0	8.2 ± 1.2
FPG (mg/dl) ^b	141.1 ± 49.9	138.9 ± 26.3	139.8 ± 37.5
Duration of iGlarLixi treatment (months) ^{c,d}	7.2 ± 4.6	5.5 ± 3.7	6.2 ± 4.2
iGlarLixi started in insulin-naïve participants, <i>n</i> (%) ^c	55 (32.2)	119 (48.8)	174 (41.9)
iGlarLixi started after prior insulin therapy, <i>n</i> (%) ^c	116 (67.8)	125 (51.2)	241 (58.1)
Any complication and/or comorbidities, <i>n</i> (%)	100 (57.5)	163 (66.3)	263 (62.6)
Diabetic neuropathy	69 (39.7)	144 (58.5)	213 (50.7)
Diabetic retinopathy	22 (12.6)	71 (28.9)	93 (22.1)
Renal function impairment	34 (19.5)	81 (32.9)	115 (27.4)
Coronary heart disease	13 (7.5)	20 (8.1)	33 (7.9)
Myocardial infarction	3 (1.7)	7 (2.8)	10 (2.4)
Heart failure	6 (3.4)	4 (1.6)	10 (2.4)
Any anti-diabetic non-insulin medication, <i>n</i> (%)	174 (100)	186 (75.6)	360 (85.7)
Biguanides	150 (86.2)	85 (34.6)	235 (56.0)
Sulphonylureas	55 (31.6)	134 (54.5)	189 (45.0)
SGLT-2i	174 (100)	0	174 (41.4)
Thiazolidinedione	9 (5.2)	9 (3.7)	18 (4.3)
Glinides	3 (1.7)	4 (1.6)	7 (1.7)
DPP-4i	1 (0.6)	0	1 (0.2)

Data presented as mean ± SD unless otherwise noted

The analysis included eligible population, defined as all participants included in the study who met the inclusion criteria and did not meet exclusion criteria

BMI body mass index, *DDP-4i* dipeptidyl peptidase-4 inhibitor, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *SD* standard deviation, *SGLT-2i* sodium-glucose co-transporter-2 inhibitor

^aData at pre-Ramadan; SGLT-2i user, *n* = 135; SGLT-2i-non-user, *n* = 208; and total, *N* = 343

^bData at pre-Ramadan; SGLT-2i user, *n* = 133; SGLT-2i-non-user, *n* = 201; and total, *N* = 334

^cUp to signing of informed consent form

^dSGLT-2i user, *n* = 173; SGLT-2i-non-user, *n* = 243; and total, *N* = 416

^eSGLT-2i user, *n* = 171; SGLT-2i-non-user, *n* = 244; and total, *N* = 415

During pre-Ramadan period, 45.1%, 32.9%, and 22.0% of participants in SGLT-2i-user group and 39.2%, 38.8%, and 22.0% of participants in SGLT-2i-non-user group administered iGlarLixi at breakfast, lunch, and dinner, respectively. During Ramadan, as aligned with the recommendations, most participants in SGLT-2i-user (93.0%) and SGLT-2i-non-user (85.7%) groups injected iGlarLixi in the evening at Iftar, remaining 7% participants in SGLT-2i-user group and 13.9% in SGLT-2i-non-user group injected iGlarLixi in the morning (prior to Suhur).

In SGLT-2i-user group, the mean $\pm$ standard deviation (SD) iGlarLixi daily dose was 27.8 ± 11.6 , 26.7 ± 10.8 and 27.8 ± 11.9 dose steps during pre-Ramadan, Ramadan, and post-Ramadan periods, respectively; iGlarLixi daily dose increased by 0.1 ± 3.4 dose steps from pre- to post-Ramadan. In SGLT-2i-non-user group, the mean $\pm$ SD iGlarLixi daily dose was 24.3 ± 10.3 , 23.5 ± 9.0 , and 24.4 ± 9.9 dose steps during pre-Ramadan, Ramadan and post-Ramadan periods, respectively; iGlarLixi daily dose increased by 0.4 ± 3.3 dose steps from pre- to post-Ramadan.

The iGlarLixi interruption was reported for 3 days in SGLT-2i-user and 5 days in SGLT-2i-non-user groups; reasons for iGlarLixi interruption were hypoglycemia (SGLT-2i user, $n=1$ and SGLT-2i-non-user, $n=0$), pre-existing conditions (SGLT-2i user, $n=0$ and SGLT-2i-non-user, $n=2$), AEs (SGLT-2i user, $n=1$ and SGLT-2i-non-user, $n=0$) and other (SGLT-2i user, $n=1$ and SGLT-2i-non-user, $n=3$).

Non-insulin Anti-hyperglycemic Treatments

All participants in SGLT-2i-user ($n=174$) and 75.6% ($n=186$) of participants in SGLT-2i-non-user groups were taking OADs in addition to iGlarLixi. In SGLT-2i-user group, 80 (46.0%) and 34 (19.5%) participants were on 2 and ≥ 3 OADs, respectively, whereas in the SGLT-2i-non-user group, 63 (25.6%) and 2 (0.8%) participants were taking 2 and ≥ 3 OADs, respectively (Table 2). The most commonly used OADs in the SGLT-2i-user group were sulphonylureas (31.6%), biguanides (86.2%) and SGLT-2i (100%). In the SGLT-2i-non-user group, the most frequently used OADs were biguanides (34.6%) and sulphonylureas (54.5%). There was no substantial

Table 2 Number of concomitant OADs taken during the overall study period, pre-Ramadan, Ramadan, and post-Ramadan period

Number of OADs	SGLT-2i user ($n=174$)	SGLT-2i-non-user ($n=246$)	Total ($N=420$)
Overall study period			
0	0	60 (24.4)	60 (14.3)
1	59 (33.9)	121 (49.2)	180 (42.9)
2	80 (46.0)	63 (25.6)	143 (34.0)
3	33 (19.0)	2 (0.8)	35 (8.3)
4	2 (1.1)	0	2 (0.5)
Pre-Ramadan period			
0	1 (0.6)	60 (24.4)	61 (14.5)
1	59 (33.9)	121 (49.2)	180 (42.9)
2	80 (46.0)	63 (25.6)	143 (34.0)
3	32 (18.4)	2 (0.8)	34 (8.1)
4	2 (1.1)	0	2 (0.5)
Ramadan period			
0	4 (2.3)	64 (26.0)	68 (16.2)
1	60 (34.5)	119 (48.4)	179 (42.6)
2	76 (43.7)	61 (24.8)	137 (32.6)
3	33 (19.0)	2 (0.8)	35 (8.3)
4	1 (0.6)	0	1 (0.2)
Post-Ramadan period			
0	10 (5.7)	65 (26.4)	75 (17.9)
1	56 (32.2)	122 (49.6)	178 (42.4)
2	74 (42.5)	57 (23.2)	131 (31.2)
3	33 (19.0)	2 (0.8)	35 (8.3)
4	1 (0.6)	0	1 (0.2)

Data presented as number of participants (%)

The analysis included eligible population, defined as all participants included in the study who met the inclusion criteria and did not meet exclusion criteria

OAD oral anti-hyperglycemic drug, SGLT-2i sodium-glucose co-transporter-2 inhibitor

change in the proportion of participants taking OADs from pre-Ramadan to Ramadan in both groups (Supplementary Table S3).

Hypoglycemia

Primary Endpoint

The incidence of severe and/or symptomatic documented (<70 mg/dl [<3.9 mmol/l]) hypoglycemia events was low throughout the study for both groups. During the last month pre-Ramadan, Ramadan and first month post-Ramadan, 0.6%, 4.2%, and 0.6% participants in SGLT-2i-user and 1.3%, 0.9%, and 0% participants in SGLT-2i-non-user groups, respectively, experienced severe and/or symptomatic documented (<70 mg/dl [<3.9 mmol/l]) hypoglycemia (Fig. 1A).

Secondary Hypoglycemia Endpoints

The incidence of severe and/or symptomatic documented (<54 mg/dl [<3.0 mmol/l]) hypoglycemia events was also extremely low throughout the study for both groups, including Ramadan (Fig. 1B). Events of severe and/or symptomatic documented hypoglycemia (<70 mg/dl [<3.9 mmol/l] or <54 mg/dl [<3.0 mmol/l]) during Ramadan were reported more frequently during fasting hours (between Suhur and Iftar) than during non-fasting hours (Supplementary Fig. 1A and 1B). Only one severe hypoglycemia event was reported during the whole study period, which occurred in SGLT-2i-user group during pre-Ramadan period.

Change in Glycemic Endpoints (HbA1c, FPG, and SMPG)

A mean $\pm$ SD reduction in HbA1c was observed from pre- to post-Ramadan in both SGLT-2i-user ($0.69 \pm 1.20\%$) and SGLT-2i-non-user groups ($0.78 \pm 0.92\%$) (Fig. 2A). The proportion of participants with HbA1c $<7\%$ increased from pre- to post-Ramadan in both groups (SGLT-2i user, 16.3% to 39.3% and SGLT-2i-non-user, 6.7% to 35.1%). A mean $\pm$ SD reduction of 16.0 ± 40.4 mg/dl and 19.8 ± 26.6 mg/dl was observed in FPG

from pre- to post-Ramadan in SGLT-2i-user and SGLT-2i-non-user groups, respectively (Fig. 2B). Fasting SMPG also reduced from pre- to post-Ramadan in both groups; 5.4 ± 26.9 mg/dl in SGLT-2i-user and 13.5 ± 25.0 mg/dl in SGLT-2i-non-user groups (Fig. 2C).

Change in Weight

A mean $\pm$ SD reduction of 0.52 ± 2.50 kg and 1.31 ± 2.04 kg was observed in weight from pre- to post-Ramadan period in SGLT-2i user and SGLT-2i-non-user groups, respectively (Fig. 2D).

Adverse Events

A total of 14 (7.9%) participants in SGLT-2i-user and six (2.4%) participants in SGLT-2i-non-user groups experienced at least one AE throughout the study period. Of these, five (2.9%) participants in SGLT-2i-user and one (0.4%) participant in SGLT-2i-non-user groups experienced at least one AE during Ramadan (Table 3). There were no AEs leading to permanent treatment discontinuation in SGLT-2i-user group, whereas one (0.4%) participant in the SGLT-2i-non-user group had such an event during the whole study period. No serious AEs, treatment-related AEs, and AEs leading to death were reported in either of the treatment groups throughout the study period.

DISCUSSION

In this sub-analysis of the real-world SoliRam study [12], concomitant iGlarLixi and SGLT-2i therapy with or without other OADs, was well tolerated in people with T2D who observed fast during Ramadan, alongside improvement in glycemic parameters and a small reduction in weight. Most participants (97%) were able to fast for ≥ 25 days during Ramadan without increasing the risk of hypoglycemia, which was consistent with the findings in the overall SoliRam population as well as in other previously published Ramadan studies [DAR-MENA study and DAR global survey 2020] [13, 14].

The overall incidence of hypoglycemia was low in both groups, consistent with a previously

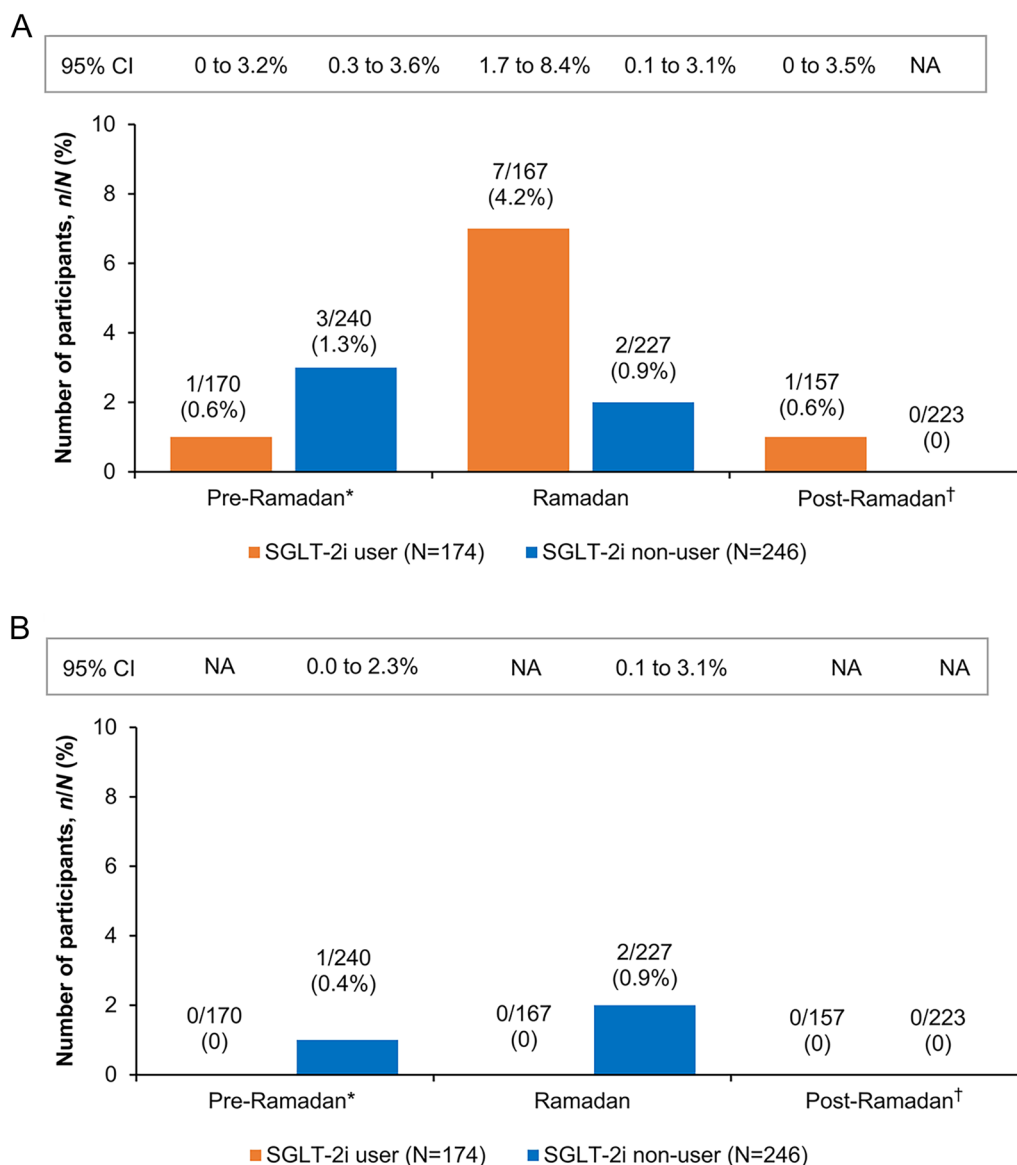


Fig. 1 Proportion of participants with severe and/or symptomatic documented hypoglycemia: **A** < 70 mg/dl (< 3.9 mmol/l) and **B** < 54 mg/dl (< 3.0 mmol/l). *Last month of pre-Ramadan. †First month of post-Ramadan. The analysis included eligible population, defined as all

participants included in the study who met the inclusion criteria and did not meet exclusion criteria. *CI* confidence interval, *n* number of participants reporting hypoglycemia event, *N* total number of participants, *NA* not applicable, *SGLT-2i* sodium-glucose co-transporter-2 inhibitor

published post hoc analysis, which reported a similar and low incidence of hypoglycemia in people with T2D receiving either iGlarLixi alone or iGlarLixi+SGLT-2i in addition to one or more OADs [11]. A recent post hoc analysis of three non-Ramadan trials (LixiLan-G, SoliMix, and LixiLan ONE CAN), conducted among a diverse

population with varying treatment backgrounds, also showed no increase in hypoglycemia with concomitant use of iGlarLixi and SGLT-2i and demonstrated comparable efficacy and tolerability to iGlarLixi use without SGLT-2i [15]. The pharmacodynamic effects of SGLT-2i are independent of insulin, which could be attributable

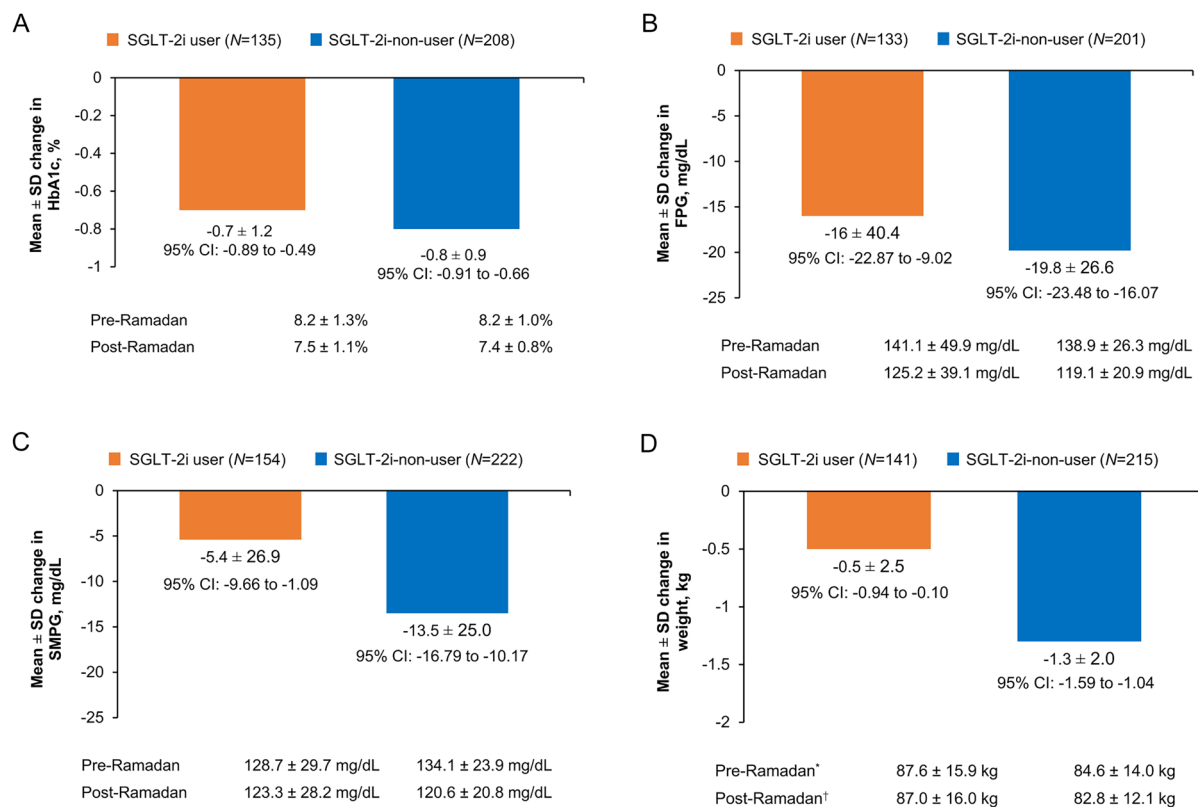


Fig. 2 Change in **A** HbA1c (%), **B** FPG (mg/dl), **C** SMPG (mg/dl), and **D** weight (kg) from the pre-Ramadan to the post-Ramadan period. *SGLT-2i user, $n = 171$ and SGLT-2i-non-user, $n = 245$. †SGLT-2i user, $n = 141$ and SGLT-2i-non-user, $n = 215$. The analysis included the evaluable population, defined as all participants who had gly-

cemic endpoint for both pre-Ramadan and post-Ramadan periods (HbA1c, FPG, and fasting SMPG). *CI* confidence interval, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *SMPG* self-monitoring of plasma glucose, *SD* standard deviation, *SGLT-2i* sodium-glucose co-transporter-2 inhibitor

to the low risk of hypoglycemia observed in this analysis [16]. In the current sub-analysis, no severe hypoglycemia occurred during Ramadan in any of the treatment groups, reassuring the safety of concomitant iGlarLixi and SGLT-2i therapy during Ramadan fasting. Importantly, most incidences of hypoglycemia during Ramadan, occurred during fasting hours, which is understandable considering the fasting status in people treated with multiple anti-hyperglycemic agents. Daytime hypoglycemia is easier to manage, contrary to nocturnal hypoglycemia that occurs during non-fasting hours (night) and can have a greater impact on overall health and work productivity and may also increase the risk of CV events, particularly, during the night [17, 18].

As recommended by the guidelines, participants in the present study administered iGlarLixi with their major meal of the day, either at Iftar or prior to Suhur. Further, the overall incidence of hypoglycemia was low in both the groups irrespective of injection timing. A previously published pooled analysis from the REALI study concluded that iGlarLixi was safe for people with inadequately controlled T2D who were using OADs with or without BI, regardless of the timing of injection [19]. However, additional analyses are warranted to establish impact of injection timing and incidence of hypoglycemia during the Ramadan period.

In this study, a higher proportion of participants in the SGLT-2i-user group were treated with ≥ 3 concomitant OADs than those in the

Table 3 Incidence of AEs

Adverse events, <i>n</i> (%)	SGLT-2i user		SGLT-2i-non-user	
	Overall study period (<i>n</i> = 177)	During Ramadan (<i>n</i> = 172)	Overall study period (<i>n</i> = 251)	During Ramadan (<i>n</i> = 237)
Any AE	14 (7.9)	5 (2.9)	6 (2.4)	1 (0.4)
Infections and infestations	5 (2.8)	2 (1.2)	0	0
COVID-19	2 (1.1)	1 (0.6)	0	0
Gingivitis	1 (0.6)	–	0	–
Nasopharyngitis	1 (0.6)	–	0	–
Pharyngitis	1 (0.6)	1 (0.6)	0	0
Rhinitis	1 (0.6)	–	0	–
Metabolism and nutrition disorders	3 (1.7)	1 (0.6)	3 (1.2)	0
Worsening of diabetes	1 (0.6)	1 (0.6)	2 (0.8)	0
Hyperglycemia	1 (0.6)	–	1 (0.4)	–
Vitamin D deficiency	1 (0.6)	–	0	–
Nervous system disorders	1 (0.6)	1 (0.6)	2 (0.8)	1 (0.4)
Headache	1 (0.6)	1 (0.6)	2 (0.8)	1 (0.4)
Gastrointestinal disorders	3 (1.7)	1 (0.6)	1 (0.4)	0
Gastritis	1 (0.6)	1 (0.6)	0	0
Toothache	1 (0.6)	–	0	–
Vomiting	1 (0.6)	–	0	–
Nausea	0	–	1 (0.4)	–

The analysis was conducted on the included population, defined as all participants who had signed the informed consent

A participant can be counted in several categories

AE adverse event, *COVID-19* coronavirus disease 2019, *SGLT-2i*, sodium-glucose co-transporter-2 inhibitor

SGLT-2i-non-user group. Studies report an increased risk of hypoglycemia as the number of concurrent medications increases [10, 20]. The PROFAST study, conducted in people with T2D taking multiple (≥ 3) anti-hyperglycemic medications during Ramadan, reported a higher incidence of hypoglycemia (16.3%), particularly in those who received both insulin and sulphonylureas [21]. Further analysis showed that the risk of hypoglycemia was higher in participants who were on ≥ 4 OADs than those receiving ≥ 3 OADs (odds ratio [OR]: 3.43, 95% CI: 1.42–8.42;

$p < 0.007$). However, no severe hypoglycemia was reported [21]. On the contrary, in current sub-analysis, the risk of hypoglycemia remained low despite participants being treated with multiple OADs. These results align with the real-world DIA-RAMADAN study, conducted in people with T2D fasting during Ramadan and treated concomitantly with gliclazide modified-release and other OADs [22]. Although about 30% of participants in the DIA-RAMADAN study were receiving ≥ 3 OADs, the incidences of hypoglycemia reported throughout the study duration were

low (pre-Ramadan: 0.2%; Ramadan: 2.2% and post-Ramadan: 0.3%). Notably, participants in the DIA-RAMADAN study were not taking insulin therapy, which could be a probable reason for the low hypoglycemia in this study [22].

Moreover, a large proportion of participants in this analysis were taking sulphonylureas, with 31.6% in SGLT-2i-user and 54.5% in SGLT-2i-non-user groups. The concomitant use of sulphonylureas with BI and SGLT-2i has been demonstrated to increase the risk of hypoglycemia and emergency room visits [23–25]. Guidelines recommend adjusting sulphonylureas dosage when initiating BI, particularly during Ramadan fasting [24]. Data from current sub-analysis are promising, considering study participants were able to fast safely, with low rates of hypoglycemia, despite taking sulphonylureas in addition to iGlarLixi with or without SGLT-2i. All sulphonylureas used in this study were second generation, explaining the low risk of hypoglycemia with concurrent sulphonylureas administration. There is a lack of studies comparing the concomitant use of FRCs of BI and GLP-1RA and SGLT-2i with other insulin-based intensified treatment, particularly during Ramadan. More studies are warranted to assess the safety and efficacy of concurrent use of FRCs of BI and GLP-1RA and SGLT-2i and to compare them with other regimens, generating evidence to guide physicians and people with T2D and helping them make an informed choice.

There were improvements in all glycemic parameters (HbA1c, FPG, and fasting SMPG) from the pre- to post-Ramadan period, with no major insulin-dose adjustment in both groups. There was no significant difference in the glycemic improvement across the groups, however, the decrease in weight was slightly higher in SGLT-2i-non-user group (1.3 kg) than that in SGLT-2i user group (0.5 kg).

Overall, the concomitant use of iGlarLixi and SGLT-2i was well tolerated throughout the study; only few AEs were reported. Instances of iGlarLixi use interruption were infrequent; interruptions due to hypoglycemia ($n=1$) and AE ($n=1$) were reported in SGLT-2i users. Given the recommended use of SGLT-2i therapy for people with T2D, particularly those at high-risk CV or kidney disease, the present analysis further supports the

safety and efficacy of advancing therapy with concomitant iGlarLixi and SGLT-2i therapy.

Furthermore, both iGlarLixi and SGLT-2i (except canagliflozin) share common features such as once-daily administration that can be decided based on individual's need, thereby offering treatment simplicity [26]. In summary, the ease of use, coupled with notable effectiveness and minimal risk of hypoglycemia, enhances the likelihood of adherence to this combined therapy.

A key strength of this study is its evidence-based prospective outcomes observed in a real-world setting, demonstrating the efficacy and safety of the concomitant use of iGlarLixi and SGLT-2i during the holy month of Ramadan in participants across multiple countries. Given that this is a sub-analysis of the SoliRam real-world study, inherent limitations associated with real-world data, such as missing information and potential unknown confounders and bias, may be present. Additionally, this sub-analysis was not planned in the protocol, which may have resulted in bias in terms of population selection and power in statistical analysis. Furthermore, the self-reporting of hypoglycemia events by participants, based on symptoms and SMPG, raises the possibility that the incidence of hypoglycemia may have been underreported.

CONCLUSIONS

In this sub-analysis of the SoliRam study, the concomitant iGlarLixi and SGLT-2i therapy, with or without other OADs, was demonstrated to be safe in adults with T2D during Ramadan fast, with a low risk of hypoglycemia along with improvements in glycemic outcomes. Notably, most participants in the iGlarLixi + SGLT-2i-user group, despite undergoing multiple therapeutic interventions, successfully observed the Ramadan fast without breaking. This underscores the robustness and adaptability of the iGlarLixi treatment regimen, highlighting its effectiveness in real-world scenarios.

ACKNOWLEDGEMENTS

The authors thank the participants, investigators, and staff who participated in data collection for the study. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Medical Writing, Editorial, and Other Assistance. Scientific writing and editorial support were provided by Daisy Masih, PhD, and Preeti Agarwal who are employees of Sanofi.

Author Contributions. Conceptualization and methodology: Mohamed Hassanein, Khier Djaballah, and Saud Al Sifri. Data collection and interpretation: Mohamed Hassanein, Rachid Malek, Saud Al Sifri, Rakesh Kumar Sahay, Mehmet Akif Buyukbese, and Inass Shaltout. Data analysis: Lydie Melas-Melt. Writing—review and editing: Mohamed Hassanein, Rachid Malek, Saud Al Sifri, Rakesh Kumar Sahay, Mehmet Akif Buyukbese, Khier Djaballah, Lydie Melas-Melt and Inass Shaltout.

Funding. The SoliRam study and the journal's Rapid Service Fee were funded by Sanofi.

Data Availability. Qualified researchers may request access to patient-level data and related documents [including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specification]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at <https://www.vivli.org>.

Declarations

Conflict of Interest. Mohamed Hassanein is an advisory board member for Sanofi, Boehringer Ingelheim and Novo Nordisk and

a speaker for Eli Lilly and Company, Janssen, LifeScan, Merck Sharp and Dohme, Novo Nordisk and Sanofi and has received lecturer/other fees from Sanofi, Novo Nordisk, Eli Lilly and Company, Merck Sharp and Dohme, Janssen and LifeScan. Rachid Malek has received speaker fees and advisory board honoraria from Novo Nordisk. Saud Al Sifri has acted as an adviser and speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, MSD, Novartis, Novo Nordisk and Sanofi. Rakesh Kumar Sahay is an advisory board member for Boehringer Ingelheim, Dr. Reddy's Laboratories, Eli Lilly and Company and Sanofi and a speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. Mehmet Akif Buyukbese has received speaker fees from Eli Lilly and Company and speaker/other fees from Novartis and Sanofi. Khier Djaballah is an employee of Sanofi and may hold shares/stocks in the company. Lydie Melas-Melt is an employee of IVIDATA Life Sciences. Inass Shaltout is a speaker and advisory board member for Sanofi, Novartis, MSD, AstraZeneca, Novo Nordisk, Eli Lilly and Company, Servier and Abbott.

Ethical Approval. All participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki of 1964 and all subsequent amendments. The study protocol was approved by the local institutional review board/independent ethics committee of the country of each participating investigator (Supplementary Table S1), and regulatory submissions were performed in accordance with the local data protection guidelines.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons

licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Rajbhandari J, Fernandez CJ, Agarwal M, Yeap BXY, Pappachan JM. Diabetic heart disease: a clinical update. *World J Diabetes*. 2021;12:383–406.
- Pelle MC, Provenzano M, Busutti M, et al. Update on diabetic nephropathy. *Life (Basel)*. 2022;12:1202.
- Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. 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.
- Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm–2023 update. *Endocr Pract*. 2023;29:305–40.
- Kwiendacz H, Nabrdalik K, Czupryniak L, et al. The wedding bells sound really good! iGlarLixi fixed-ratio combination in the treatment of type 2 diabetes: a narrative review. *Adv Ther*. 2023;40:3395–409.
- Jung HN, Cho YK, Min SH, et al. Free versus fixed-ratio combination of basal insulin and GLP-1 receptor agonists in type 2 diabetes uncontrolled with GLP-1 receptor agonists: a systematic review and indirect treatment comparison. *Front Endocrinol (Lausanne)*. 2022;13: 870722.
- Rosenstock J, Emral R, Sauque-Reyna L, et al. Advancing therapy in suboptimally controlled basal insulin–treated type 2 diabetes: clinical outcomes with iGlarLixi versus premix BIAsp 30 in the SoliMix randomized controlled trial. *Diabetes Care*. 2021;44:2361–70.
- Blonde L, Rosenstock J, Del Prato S, et al. Switching to iGlarLixi versus continuing daily or weekly GLP-1 RA in type 2 diabetes inadequately controlled by GLP-1 RA and oral antihyperglycemic therapy: the LixiLan-G randomized clinical trial. *Diabetes Care*. 2019;42:2108–16.
- Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. 2016;39:1972–80.
- Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. *Diabetes Care*. 2016;39:2026–35.
- Guja C, Giorgino F, Blonde L, et al. Concomitant iGlarLixi and sodium-glucose co-transporter-2 inhibitor therapy in adults with type 2 diabetes: LixiLan-G trial and real-world evidence results. *Diabetes Ther*. 2022;13:205–15.
- Hassanein M, Malek R, Shaltout I, et al. Real-world safety and effectiveness of iGlarLixi in people with type 2 diabetes who fast during Ramadan: the SoliRam observational study. *Diabetes Metab Syndr*. 2023;17: 102707.
- Hassanein M, Hussein Z, Shaltout I, et al. The DAR 2020 Global survey: Ramadan fasting during COVID-19 pandemic and the impact of older age on fasting among adults with type 2 diabetes. *Diabetes Res Clin Pract*. 2021;173: 108674.
- Hassanein M, Al Awadi FF, El Hadidy KES, et al. The characteristics and pattern of care for the type 2 diabetes mellitus population in the MENA region during Ramadan: an international prospective study (DAR-MENA T2DM). *Diabetes Res Clin Pract*. 2019;151:275–84.
- Giorgino F, Guja C, Aydın H, Lauand F, Melas-Melt L, Rosenstock J. Consistent glycaemic efficacy and safety of concomitant use of iGlarLixi and sodium-glucose co-transporter-2 inhibitor therapy for type 2 diabetes: a patient-level pooled analysis of three randomised clinical trials. *Diabetes Res Clin Pract*. 2024;209: 111604.
- Lajara R. Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists as complementary agents that address multi-organ defects in type 2 diabetes. *Postgrad Med*. 2019;131:555–65.
- Bureau AS, Guyomarch B, Gourdy P, et al. Nocturnal hypoglycemia is underdiagnosed in older people with insulin-treated type 2 diabetes: the HYPOAGE observational study. *J Am Geriatr Soc*. 2023;71:2107–19.

18. Andersen A, Jørgensen PG, Knop FK, Vilsbøll T. Hypoglycaemia and cardiac arrhythmias in diabetes. *Ther Adv Endocrinol Metab.* 2020;11:2042018820911803.
19. Haluzík M, Seufert J, Guja C, et al. Effectiveness and safety of iGlarLixi (insulin glargine 100 u/ml plus lixisenatide) in type 2 diabetes according to the timing of daily administration: data from the REALI pooled analysis. *Diabetes Ther.* 2023;14(4):639–52.
20. Naser AY, Wong ICK, Whittlesea C, et al. Use of multiple antidiabetic medications in patients with diabetes and its association with hypoglycaemic events: a case-crossover study in Jordan. *BMJ Open.* 2018;8: e024909.
21. Elhadd T, Dabbous Z, Bashir M, et al. Incidence of hypoglycaemia in patients with type-2 diabetes taking multiple glucose lowering therapies during Ramadan: the PROFAST Ramadan Study. *J Diabetes Metab Disord.* 2018;17:309–14.
22. Hassanein M, Al Sifri S, Shaikh S, et al. A real-world study in patients with type 2 diabetes mellitus treated with gliclazide modified-release during fasting: DIA-RAMADAN. *Diabetes Res Clin Pract.* 2020;163: 108154.
23. Filippas-Ntekouan S, Filippatos TD, Elisaf MS. SGLT2 inhibitors: are they safe? *Postgrad Med.* 2018;130:72–82.
24. Hassanein M, Afandi B, Yakoob Ahmedani M, et al. Diabetes and Ramadan: Practical guidelines 2021. *Diabetes Res Clin Pract.* 2022;185: 109185.
25. McCoy RG, Lipska KJ, Van Houten HK, Shah ND. Association of cumulative multimorbidity, glycaemic control, and medication use with hypoglycaemia-related emergency department visits and hospitalizations among adults with diabetes. *JAMA Netw Open.* 2020;3: e1919099.
26. Padda IS, Mahtani AU, Parmar M. Sodium-glucose transport protein 2 (SGLT2) inhibitors. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. <https://www.ncbi.nlm.nih.gov/books/NBK576405/> Accessed on 21 March 2024.