Descriptive Regional Subanalysis of a Real-World Study in Patients with Type 2 Diabetes Treated with Gliclazide MR During Fasting: DIA-RAMADAN

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ABSTRACT

Introduction: To analyse the safety and effectiveness of gliclazide modified release (MR) in adults with type 2 diabetes mellitus participating in Ramadan from three geographically and culturally different regions of the world included in the DIA-RAMADAN study.

Methods: DIA-RAMADAN was a real-world, observational, international, non-comparative study. The global study population was divided into three regional subgroups, with data gathered at inclusion 6–8 weeks prior to Ramadan (V0), during Ramadan (4.5 weeks) and 4–6 weeks after Ramadan (V1). Primary endpoint was the proportion of patients reporting ≥ 1 symptomatic hypoglycaemic events

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(HE), which were collected using a patient diary along with other adverse events.

Results: Patient numbers from the three regions were $n = 564$ (46.5%; Indian sub-continent), $n = 354$ (29.1%; Middle East) and $n = 296$ (24.4%; South-East Asia). Patient baseline characteristics, demographics, fasting habits and antidiabetic treatments varied between regions. There were similar proportions of symptomatic HE between regions, with no severe HE. Significant weight reductions were observed in all regions following Ramadan, along with reductions in HbA$_{1c}$ and fasting plasma glucose.

Conclusion: These real-world study data indicate that gliclazide MR is safe and effective for management of type 2 diabetes during Ramadan in all three regions studied as part of DIA-RAMADAN.

Trial Registration: Clinicaltrials.gov identifier NCT04132934.

Infographic:

Keywords: Diabetes mellitus; Fasting; Gliclazide; Ramadan; Type 2

DIGITAL FEATURES

This article is published with digital features, including a summary slide and infographic, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14453745.

INTRODUCTION

The number of patients with diabetes mellitus is predicted to grow over the next 25 years, with a global increase of up to 51% by 2045 [1]. Type 2 diabetes is the most common form of the disease, representing about 90% of cases [1].

Ramadan is one of the five pillars of Islam and involves a period of fasting (including abstention from food and fluid intake) from dawn to dusk throughout the ninth lunar month of the Islamic calendar. Although some patients with chronic diseases are amongst the groups that may be exempt from fasting, many people with diabetes still choose to fast as they consider it important to their health and well-being [2]. This can result in several risks for these people, including hypoglycaemia and hyperglycaemia due to reduced dosing of antidiabetic medication [3]. Other factors to consider include disrupted sleep patterns, meal timings and the type of food consumed while breaking fast [4].

The large global Muslim population means that it is important to understand how best to manage diabetes during Ramadan [5]. Based on this, the International Diabetes Federation (IDF) and Diabetes and Ramadan (DAR) International Alliance have published guidelines for management of diabetes during Ramadan [4].

Sulphonylureas are a group of antidiabetic medications that act by increasing insulin secretion by pancreatic beta cells [6]. This class of drugs has previously been associated with an increased risk of hypoglycaemia during fasting; however, more recent second-generation sulphonylureas are considered safe to use during fasting [6–10]. Gliclazide is a sulphonylurea that is available in both immediate release (IR) and modified release (MR) forms [11]. The MR formulation results in progressive release of the drug based on a once-daily dosing regimen, with evidence of a lower risk of hypoglycaemia compared with the sulphonylurea glimepiride [11, 12]. Both forms have previously been associated with a low instance of hypoglycaemia during the Ramadan fast versus other sulphonylureas [7, 10]. Recently published Ramadan guidelines consider people with type 2 diabetes treated with newer sulphonylureas, including gliclazide MR, as being at low risk of hypoglycaemic events during Ramadan fasting [13].

The DIA-RAMADAN study was an international, real-world, prospective observational study conducted in clinical centres from nine Asian and Middle Eastern countries, carried out to investigate the effectiveness and safety of gliclazide MR in people with type 2 diabetes mellitus who are fasting during Ramadan [14]. Patients were assessed at two study visits, one before and one after Ramadan. Glycaemic control was well maintained by the patients in this study, with a small decline in weight observed. Only 2.2% of patients reported one or more symptomatic hypoglycaemic events (HEs), and no severe HEs were reported.

In this descriptive subanalysis of DIA-RAMADAN, we present individual results from the three regions studied: the Indian subcontinent (India/Pakistan/Bangladesh), Middle East (Egypt/Kuwait/United Arab Emirates/Saudi Arabia) and South-East Asia (Indonesia/Malaysia), including baseline characteristics, safety and effectiveness (i.e. maintenance of glycaemic control) data. These regions of the world are culturally different, with different nutritional habits. Their location also results in different hours of fasting during Ramadan and means that weather conditions will vary between the regions. The aim of this study is therefore to examine whether the positive results observed in the DIA-RAMADAN study are relevant to each of these different subregions. Moreover, this subanalysis will add to the currently sparse data about Ramadan fasting in the three areas studied.

METHODS

Details of the study design have previously been published [14]. Key methodological details are presented below.

Study Design

In brief, DIA-RAMADAN was a real-world, observational, non-comparative, international study including adult patients with type 2 diabetes and controlled or suboptimally controlled glycosylated haemoglobin (HbA$_{1c}$) (< 9%), who had already been undergoing treatment with breakable gliclazide MR 60 mg tablets for $\geq$ 90 days prior to study start, and not requiring insulin treatment.

Two patient visits were planned as per IDF-DAR Ramadan guidelines [4]: the first (V0) 6–8 weeks prior to Ramadan and the second (V1) 4–6 weeks following Ramadan. As previously detailed, the following information was gathered during V0: informed patient consent; patient demographics, lifestyle habits, physical activity levels, IDF-DAR risk classification and medical history. Study eligibility was assessed and a physical examination carried out. Advice was given regarding gliclazide intake during Ramadan; according to IDF-DAR guidelines, gliclazide MR should be administered during iftar (sunset meal). Patients used a diary to record any treatment changes, details of hypoglycaemic symptoms and adverse events.

At the second visit (V1), routine investigations were carried out, including glycaemic profile and laboratory values. Details regarding treatment adherence and nutritional habits during Ramadan (including adherence to fasting) were collected.

Inclusion Criteria

Inclusion and exclusion criteria have previously been presented in detail elsewhere [14]; in brief, adult patients with type 2 diabetes and controlled or sub-optimally controlled HbA$_{1c}$ (< 9%) who were already receiving gliclazide MR 60 mg for at least 90 days prior to the start of the study and did not require insulin treatment were included. The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the following independent ethics committees or institutional review boards: Conscience Independent Ethics Committee (India, IRB00010059), Drug Regulatory Authority of Pakistan (F.No.03-01/2019-DD(PS)), Bangladesh Medical Research Council (BMRC/NREC/2016-2019/933(1-3)), Independent ethics Committees (Sains IRB00010568, Kebangsaan, not available and Malaya, MREC ID No. 2017528-5276) (Malaysia), Dubai Scientific Research Ethics Committee (UAE, DSREC-12/2018_14)), Dasman Institute Ethics Committee (Kuwait, RA/054/2019), Institutional Review Board King Fahad Medical City (Saudi Arabia, IRB00010471, FWA00018774), Ministry of Health (Egypt, not available) and Badan Pengawas Obat dan Makanan (Indonesia, BPOM128/NKT/III/2019). All patients provided informed written consent to participate in the study. The trial was registered on ClinicalTrials.gov (NCT04132934).

Study Treatments

Patients were treated with gliclazide MR 60 mg oral tablets for $\geq$ 90 days prior to the start of the study. Before Ramadan, gliclazide MR was taken at breakfast according to the Summary of Product Characteristics [15]. During Ramadan, physicians advised their patients to take their gliclazide MR following iftar. Any dose adjustments were at the investigator's discretion and based on routine practice and any relevant local guidelines. Treatment adherence was calculated as follows: (sum of number of intakes during Ramadan/sum of number of intakes to be taken during Ramadan) $\times$ 100 [14]. Due to the real-world setting of the study, concomitant treatments were permitted at the investigator's discretion and new treatments were initiated if deemed beneficial for the patient, and not contra-indicated for use with gliclazide MR.

Study Endpoints

The primary endpoint of the study was the proportion of patients with ≥ 1 symptomatic HE (either suggestive or confirmed by a measured glucose concentration ≤ 3.9 mmol/l [16]. Secondary endpoints included change of HbA_{1c}, FPG and weight between V0 and V1 as well as the proportion of patients with ≥ 1 confirmed HE (asymptomatic or symptomatic). The proportion of patients with ≥ 1 HE of any type and ≥ 1 severe HE were also examined.

HEs were defined in this study according to the following criteria: confirmed asymptomatic HE—absence of typical hypoglycaemia symptoms (e.g. sweating, pallor, tremor, intense hunger, pounding heart, visual disturbance, drowsiness, weakness, dizziness, difficulty in concentrating, difficulty in speaking or writing, incoordination, unexplained behaviour or mood change, confusion, nausea or headache) but with a measured glucose concentration ≤ 70 mg/dl (≤ 3.9 mmol/l); confirmed symptomatic HE—presence of typical symptoms of hypoglycaemia and a measured glucose concentration ≤ 72 mg/dl (≤ 4 mmol/l); suggestive HE—presence of typical hypoglycaemic symptoms without a measured glucose concentration or a measurement of > 72 mg/dl (> 4 mmol/l); severe hypoglycaemia—symptoms of severe cognitive impairment and requiring third-party assistance for recovery.

Adverse Events

For all reported adverse events (AEs), possible relationship to the study drug, severity of the reported AE and outcome were assessed by the patient's physician. Details regarding reporting of AEs and definition of serious AEs are reported elsewhere [14]. MedDRA version 19.0 was used to code AEs.

Statistical Analysis

Paired Student's T test was used to analyse differences in HbA_{1c} and FPG between V0 and V1. A ranked sign test was used to analyse the change in weight between V0 and V1. The threshold for statistical significance was defined as $P = 0.05$.

Analyses were carried out using SAS software version 9.4 or higher (SAS Institute, Cary, NC, USA).

RESULTS

Patient Demographics and Baseline Characteristics

A total of 1214 patients were recruited across 9 countries. Patients were divided into subgroups based on three regions—Indian sub-continent (India/Pakistan/Bangladesh; $n = 564$, 46.5% global study population), Middle East (Egypt/Kuwait/United Arab Emirates/Saudi Arabia; $n = 354$, 29.1%) and South-East Asia (Indonesia/Malaysia; $n = 296$, 24.4%). Details of the number of patients contributed by each country within regions are included as Supplementary Material.

Patient baseline characteristics and demographics are shown in Table 1. Patients from the Indian sub-continent were generally younger; 42.7% patients in this subgroup were 50 years or younger compared with 33.6% in the Middle East and 16.2% in South-East Asia. Patients in South-East Asia had a lower bodyweight compared with the other two regions. The mean gliclazide MR dose was higher in the Middle East, and more patients from the Middle East were treated with 90 mg and 120 mg doses of gliclazide MR. A higher proportion of patients in South-East Asia had arterial hypertension (47.6%) vs. the Indian sub-continent (38.7%) and the Middle East (21.5%). Diabetic complications were generally similar among the subgroups, although diabetic neuropathy was more frequently encountered in the Middle East. A greater proportion of patients in South-East Asia were in the lowest IDF-DAR risk category.

Treatment adherence to gliclazide MR during Ramadan was high for each subgroup (Indian sub-continent: 99.4%; Middle East: 99.9%; South-East Asia: 99.1%).

In the overall population, the most common combination partners for gliclazide MR were metformin (27%), dipeptidyl peptidase 4 (DPP4)

Table 1 Baseline characteristics

Characteristic	Indian sub-continent (*n* = 564)	Middle East (*n* = 354)	South-East Asia (*n* = 296)	Global (*n* = 1214)
Mean age (SD), years	51.8 (10.8)	54.4 (10.3)	58.0 (8.7)	54.1 (10.5)
Age groups, *n* (%)				
< 50 years	241 (42.7)	119 (33.6)	48 (16.2)	408 (33.6)
≥ 50 and ≤ 65 years	264 (46.8)	180 (51.0)	193 (65.2)	637 (52.5)
> 65 years	59 (10.5)	55 (15.5)	55 (18.6)	169 (14.0)
Female, *n* (%)	253 (44.9)	153 (43.2)	143 (48.3)	549 (45.2)
Mean disease duration (SD), years	5.5 (6.2)	5.5 (5.2)	5.3 (4.9)	5.4 (5.7)
BMI (SD), kg/m^2	28.5 (4.0)	30.1 (4.2)	26.7 (4.1)	28.4 (4.3)
Weight (SD), kg	75.6 (12.6)	84.4 (13.9)	69.4 (12.8)	76.5 (14.1)
Mean HbA$_{1c}$ (SD), %	7.4 (0.9)	7.7 (0.9)	7.4 (0.9)	7.5 (0.9)
Mean FPG, mg/dl	141.3 (45.5)	144.0 (34.1)	135.6 (40.5)	140.3 (41.1)
Mean dose of gliclazide MR (SD), mg	69.8 (24.9)	84.0 (28.6)	69.9 (24.8)	74.0 (26.8)
Dose groups for gliclazide MR, *n* (%)				
30 mg	33 (5.9)	12 (3.4)	16 (5.4)	61 (5.0)
60 mg	413 (73.2)	167 (47.2)	218 (73.6)	798 (65.7)
90 mg	19 (3.4)	55 (15.5)	10 (3.4)	84 (7.0)
120 mg	99 (17.6)	120 (33.9)	52 (17.6)	271 (22.3)
Established cardiovascular disease, *n* (%)	14 (2.5)	38 (10.7)	25 (8.4)	77 (6.3)
Arterial hypertension, *n* (%)	218 (38.7)	76 (21.5)	141 (47.6)	435 (35.8)
Dyslipidaemia, *n* (%)	152 (27.0)	53 (15.0)	145 (49.0)	350 (28.8)
Diabetic nephropathy, *n* (%)	2 (0.4)	4 (1.1)	3 (1.0)	3 (1.0)
Diabetic retinopathy, *n* (%)	3 (0.5)	2 (0.6)	4 (1.4)	9 (0.7)
Diabetic neuropathy, *n* (%)	34 (6.0)	42 (11.9)	9 (3.0)	85 (7.0)
Cardiovascular drugs, *n* (%)				
Statin or ezetimibe	193 (34.2)	66 (18.6)	154 (52.0)	413 (34.0)
ACEI or ARB	85 (15.1)	28 (7.9)	66 (22.3)	179 (14.7)
Beta-blocker	38 (6.7)	53 (15)	30 (10.0)	121 (10.0)
Antiplatelet agents	55 (9.8)	22 (6.2)	33 (11.0)	110 (9.1)
Calcium channel blockers	41 (7.3)	5 (1.4)	64 (21.6)	110 (9.1)
Diuretics	22 (3.9)	7 (2.0)	13 (4.4)	42 (3.5)

Table 1 continued

Characteristic	Indian sub-continent (n = 564)	Middle East (n = 354)	South-East Asia (n = 296)	Global (n = 1214)
Number of antidiabetic drugs, %				
1	42.0	47.0	31.0	41.0
2	25.0	20.0	51.0	30.0
≥ 3	33.0	33.0	18.0	29.0
Working status, %				
Active full-time worker	37.2	35.0	30.4	35.0
Active part-time worker	9.9	13.0	13.9	12.0
Non-active worker	20.0	18.4	7.4	17.0
Student	0.5	0	0	0.2
Retired	7.8	22.0	28.4	17
Other	24.5	6.8	19.9	18.2
Physical activity, %				
Sedentary	36.9	31.6	36.1	35.0
Moderate	56.6	52.5	55.4	55.0
Intermediate	6.2	9.3	7.4	7.4
Intensive	0.4	1.1	1.0	1.6
IDF-DAR risk category				
Category 1: very high	0.2	13	0	3.9
Category 2: high	16.8	15.8	1.4	12.8
Category 3: moderate/low	83.0	65.8	98.6	81.8
Patients advised not to fast, %	24.3	38.1	8.4	24.5

ACEI angiotensin-converting enzyme 1 inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *FPG* fasting plasma glucose, *HbA$_{1c}$* glycosylated haemoglobin, *IDF-DAR* International Diabetes Federation-Diabetes and Ramadan, *MR* modified release, *SD* standard deviation

inhibitors (16%) and sodium glucose cotransporter-2 (SGLT2) inhibitors (10%) [14]. Fewer patients in South-East Asia had received three or more antidiabetic treatments (18%) versus the Middle East and the Indian sub-continent (both 33%). The proportions of patients receiving combinations of antidiabetic medications for each region are shown in Fig. 1.

Overall, 82% of patients received a maximum of two antidiabetic treatments in South-East Asia versus 67% in patients from both the Middle East and Indian sub-continent. South-East Asia included the highest proportion of patients treated with gliclazide MR + metformin (42.9%). In the Indian sub-continent, a greater percentage of patients were treated with gliclazide MR + DPP4 inhibitors and gliclazide MR + SGLT2 inhibitors with or without other treatments (22.3% and 11.5%, respectively) compared with other regions (South-East Asia 8.1% and 4.7%, respectively; Middle East 13.6% and 4.2%, respectively). The highest instance of
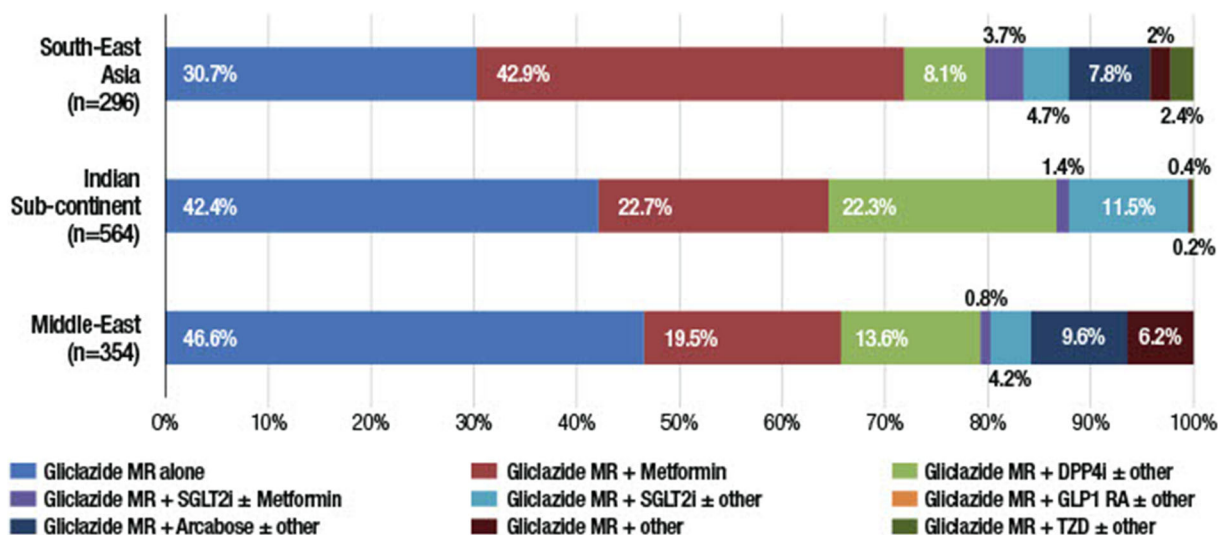
Fig. 1 Antidiabetic treatments in the three regions. *DPP4i* dipeptidyl peptidase 4 inhibitor, *GLP1 RA* glucagon-like peptide 1 receptor agonist, *SGLT-2i* sodium glucose cotransporter 2 inhibitor, *MR* modified release, *TZD* thiazolidinedione

gliclazide MR monotherapy was observed in the Middle East (46.6%).

Fasting and Nutritional Habits During Ramadan

All three regions had similar numbers of fasted days during Ramadan (Table 2). The mean fasted hours per day was highest in the Middle East (15.8 h) and lowest in South East Asia (13.7 h). In terms of meal type, the increase in carbohydrate intake was highest in South-East Asia, whereas the increase in fat intake was highest in patients from the Indian sub-continent. Rates of breaking fast were highest in the Indian sub-continent and lowest in South-East Asia; however, rates of breaking fast on > 3 consecutive days were similarly low between subgroups.

The number of meals consumed per day decreased from nearly three meals per day outside Ramadan to slightly more than two per day during Ramadan in all three regions (Table 2). The number of snacks also reduced to less than one per day in all three regions.

Safety Outcomes

The proportion of patients reporting at least one symptomatic hypoglycaemic event during Ramadan was generally low overall, with similar rates in all three regions (Table 3). Importantly, there were no severe hypoglycaemia events, and no gliclazide MR-related adverse events were noted in any of the three regions. A significant weight reduction was observed following Ramadan in all regions (Fig. 2a), with the greatest decrease observed in the Middle East (84.4 vs. 83.8 kg, $P < 0.001$).

Changes in HbA$_{1c}$ and FPG

Mean HbA$_{1c}$ decreased significantly in all three regions at V1 following Ramadan (Fig. 2b). The Indian subcontinent exhibited the greatest decrease between V0 and V1 (7.4 vs. 7.0%, respectively, $P < 0.001$). Patients from this region also had the youngest population and a high proportion of patients (33%) taking at least three antidiabetic medications, as described in Table 1. Mean FPG also decreased in all regions following Ramadan (Fig. 2c), although this change was not significant in South-East Asia (135.6 vs. 131.6 mg/dl, $P = 0.096$).

Table 2 Fasting and dietary changes during Ramadan

Characteristic	Indian sub-continent (n = 564)	Middle East (n = 354)	South-East Asia (n = 296)	Global (n = 1214)
Days fasted during Ramadan, mean (SD)	28 (3.9)	29.6 (1.8)	29.1 (3.8)	28.7 (3.5)
Hours/day fasted during Ramadan, mean (SD)	14.7 (1.6)	15.8 (1.1)	13.7 (0.9)	14.7 (1.5)
Patients who broke fast during Ramadan, n (%)	312 (55.3)	143 (40.4)	39 (13.2)	494 (40.7)
Patients who broke fast for more than 3 consecutive days, n (%)	34 (6.0)	11 (3.1)	17 (5.7)	62 (5.1)
Dietary changes during Ramadan				
More carbohydrate, %	15.2	12.0	21.6	15.9
More proteins, %	15.4	14.4	7.1	13.1
More fat, %	20.0	6.0	9.8	13.4
Other change, %	0.7	0.3	13.1	3.6
Average numbers of meals consumed per day (SD)				
Outside Ramadan	2.7 (0.5)	2.8 (0.4)	2.8 (0.5)	2.8 (0.5)
During Ramadan	2.3 (0.5)	2.2 (0.4)	2.0 (0.4)	2.2 (0.4)
Average numbers of snacks consumed per day (SD)				
Outside Ramadan	1.5 (0.9)	1.0 (0.8)	1.3 (1.0)	1.3 (0.9)
During Ramadan	0.7 (0.8)	0.9 (0.7)	1.0 (0.7)	0.8 (0.8)

SD standard deviation

Table 3 Proportion of patients with at least one hypoglycaemia event during Ramadan

Characteristic	Indian sub-continent (n = 564)	Middle East (n = 354)	South-East Asia (n = 296)	Global (n = 1214)
≥ 1 symptomatic hypoglycaemia event (confirmed or not), n (%)	10 (1.8)	8 (2.1)	9 (3.1)	27 (2.2)
≥ 1 confirmed hypoglycaemia event (symptomatic or not), n (%)	9 (1.6)	2 (0.6)	8 (2.7)	19 (1.6)
≥ 1 severe hypoglycaemia event, n	0	0	0	0

Symptomatic hypoglycaemia is defined as the presence of at least one of the following symptoms: sweating, pallor, tremor, intense hunger, pounding heart, visual disturbance, drowsiness, weakness, dizziness, difficulty in concentrating, difficulty in speaking or writing, incoordination, unexplained behaviour or mood change, confusion, nausea, headache; without (suggestive) or with (confirmed) a measurement of plasma glucose concentration ≤ 70 mg/dl (≤ 3.9 mmol/l). Confirmed hypoglycaemia is defined as the proportion of patients with ≥ 1 hypoglycaemia episode (symptomatic or not), confirmed with a measured plasma glucose concentration level ≤ 70 mg/dl (≤ 3.9 mmol/l). Severe hypoglycaemia is defined as reported severe cognitive impairment requiring third-party assistance for recovery
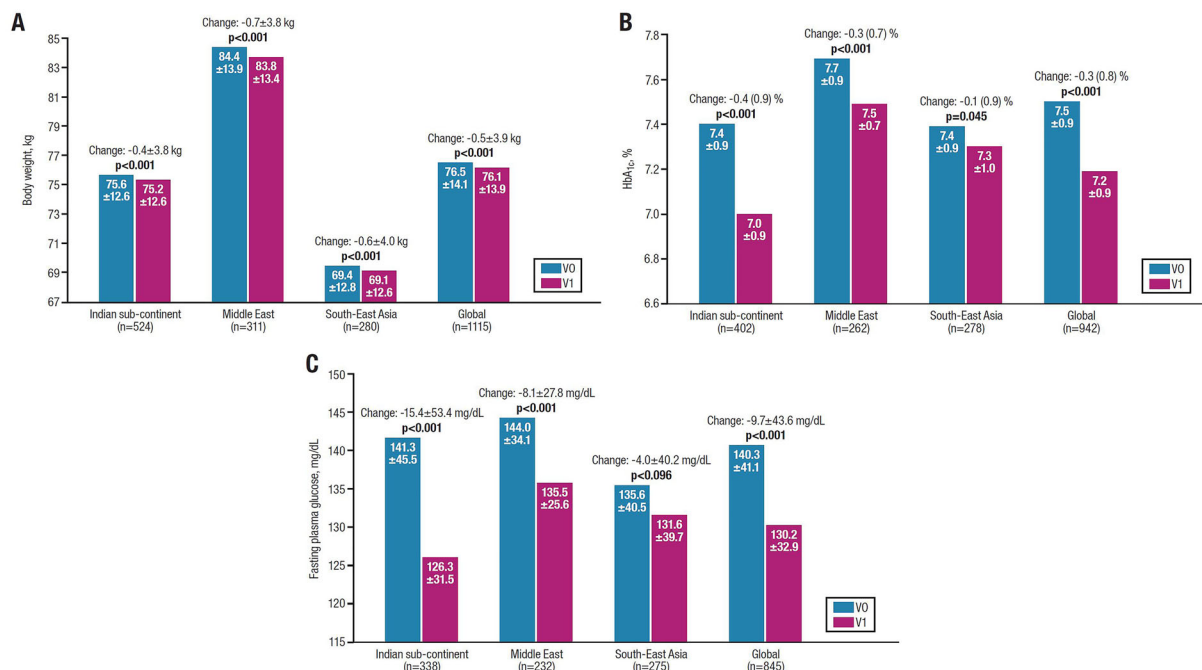
Fig. 2 a Change in weight between V0 and V1 (mean [kg] ± SD). Mean change was calculated based on patients with values available at V0 and V1. b Change in HbA_{1c} between V0 and V1 (mean [%] ± SD). Mean change was calculated based on patients with available data at V0 and V1. c Change in FPG between V0 and V1 (mean [mg/dl] ± SD). Mean change was calculated based on patients with values available at V0 and V1. P values were calculated with rank signed test (weight) and Student's t test (HbA1c and FPG). FPG fasting plasma glucose, HbA_{1c} glycosylated haemoglobin, SD standard deviation, V0/1 study visit 0/1

DISCUSSION

This sub-analysis of the DIA-RAMADAN study analysed the data from the constituent regions in the study—the Indian sub-continent, the Middle East and South-East Asia—representing the diverse cultural and nutritional habits of Muslims worldwide. Overall, the results show that gliclazide MR was safe for patients with type 2 diabetes fasting during Ramadan in the real-world setting. There were relatively few hypoglycaemic events in each region, and none were classed as severe. Effectiveness of gliclazide MR was also similar across regions, with reductions in HbA1c, FPG and bodyweight in all regions. These results are in line with the previously reported global analysis [14].

Baseline Characteristics

Several differences in baseline characteristics among the three regions were noted, and these may influence the slight differences in outcomes observed between the regions. Patients from the Indian sub-continent were generally younger with relatively low BMI (28 kg/m^2), with a high proportion (83%) being in the IDF-DAR moderate/low risk category. In addition, many patients (33%) were taking ≥ 3 antidiabetic medications. These factors could have contributed to the large decreases in HbA1c and FPG observed between V0 and V1 for patients from the Indian sub-continent.

Patients in the Middle East showed a higher BMI compared with the other two regions. This is in line with current understanding of obesity in the Middle East, where rates of obesity are high and increasing [17]. This finding is largely

due to urbanisation and changes in technology leading to a more sedentary lifestyle [17]. In particular, women face more barriers to physical activity, as men have more freedom to exercise and participate in recreational activities [17, 18]. In the present study, the finding that patients in the Middle East had the greatest reduction in bodyweight is likely linked to the initial high mean bodyweight of this subgroup. Despite having a lower BMI and bodyweight overall, patients in South-East Asia exhibited greater arterial hypertension and dyslipidaemia compared with the other two regions. This is in line with findings regarding the two constituent countries (Malaysia and Indonesia); arterial hypertension has a prevalence of 47.9% and 34.5%, respectively [19, 20], and the estimated prevalence of dyslipidaemia in Indonesian adults is 36% [21]. Patients from this region were less likely to be advised not to fast compared with the Indian sub-continent and Middle East, although this is likely due to the generally lower IDF-DAR risk category assigned to these patients.

Antidiabetic Treatments

A relatively high proportion of patients received gliclazide MR in combination with other antidiabetic treatments. Gliclazide MR monotherapy was most widely used in the Middle East region, whereas patients from the Indian sub-continent and South-East Asia tended to receive combinations of antidiabetic treatments. This is in agreement with published survey data indicating that sulphonylureas are commonly used as first-line therapies in the Middle East [22]. Additionally, the mean gliclazide MR dose used in the Middle East was higher than in the other subregions, and more patients in the Middle East were receiving higher gliclazide MR doses (90 mg and 120 mg) at baseline. Fewer patients from South-East Asia received a combination of three or more antidiabetic treatments. This finding may be reflected in the lower IDF-DAR risk category; this suggests that most patients had well-controlled type 2 diabetes in their physician's opinion, with a mono- or bi-therapy of antidiabetic treatment based on gliclazide MR.

Fasting and Nutritional Habits During Ramadan

Although many patients broke the fast at some point during Ramadan, particularly in the Indian sub-continent, the relatively low level of symptomatic hypoglycaemia events in all three subgroups suggests that very few of these breaks of fast were for reasons of hypoglycaemia. There are several non-medical reasons that Muslims may be exempted from the Ramadan fast, such as breast-feeding, pregnancy, menstruation or travel. Medical reasons may include dizziness, diarrhoea/vomiting, extreme dehydration and fatigue, as well as any other medical conditions [23]. There are limited data available reporting dietary changes during Ramadan. A recent meta-analysis compared nutritional data from four studies conducted in different regions [24]. Studies from the Greater Middle East region (Algeria and Tunisia) reported increased fat intake and decreased carbohydrate consumption during Ramadan [25, 26]. Studies from South-East Asian countries showed increased and decreased fat intake during Ramadan in Singapore and Indonesia, respectively [27, 28].

In the present study, patients from South-East Asia broke fast rarely compared with patients from the Middle East and the Indian sub-continent. However, the three subgroups did not differ greatly in the proportion of patients who broke fast for > 3 consecutive days. There are several possible explanations for why fewer overall breaks of fast and similar amounts of short breaks of fast (≤ 3 days duration) occurred in the South-East Asian group compared with the other subgroups. Patients from South-East Asian countries consumed more carbohydrates during Ramadan compared with the other two regions, resulting in less need to interrupt the fast because of higher glucose availability. Patients from the Indian subcontinent had a higher IDF risk overall and were more frequently advised not to fast compared with the other regions. The physicians managing these patients may have advised

breaking fast if necessary because of a greater risk of hypoglycaemia, although this would need to be clarified with further data.

The similarity in short breaks of fast among the three regions may be associated with differences in demographic characteristics. For example, the South-East Asian subgroup was older and had a higher proportion of female patients. This has several potential consequences; first, the proportion of retired and non-active workers in South-East Asia was higher, so there may have been less opportunity for exercise-induced hypoglycaemia. The higher proportion of female patients may result in more frequent breaking of fast due to menstruation, and the presence of a higher proportion of older female patients may further contribute to this because of an increased proportion of menopausal patients.

Changes in dietary habits are highly variable between countries and regions and can be influenced by local customs or religious beliefs. It was not possible to analyse an association between patterns of meal intake at suhoor (pre-dawn meal) and iftar and hypoglycaemic events due to the overall low number of these events in this study; however, this would be an interesting analysis for future studies.

A previous study has noted that dietary habits during Ramadan fall into four categories: (1) Western-like (fast foods, salt, nuts, potatoes); (2) high cholesterol and sweet junk foods; (3) Mediterranean-like (vegetables, olive oil, dried fruit); (4) Ramadan-like (soups, legumes, whole grains) [29]. In general, the Mediterranean style diet was considered the healthiest option to maintain during Ramadan. It would be interesting to understand into which diet profile the three regions presented in this study fall.

Safety Outcomes

As expected from the primary analysis, there were no gliclazide MR-associated adverse events in this study and no severe hypoglycaemic events [14]. Additionally, the occurrence of symptomatic and confirmed hypoglycaemic events remained similarly low between all subgroups, with no group having a particularly high instance of these events. These data support results from other studies conducted in similar regions showing a low risk of hypoglycaemic events in patients treated with gliclazide MR during Ramadan [7, 9, 10]. All three regions also showed significant decreases in weight, with the greatest decrease observed in the Middle East; this is likely due to the high baseline weight in patients from this region. It is important to note that despite the patients receiving gliclazide MR (a sulphonylurea), there is still significant weight loss in this region during Ramadan; this is likely attributable to the Ramadan fast.

Changes in HbA$_{1c}$ and FPG

Improvements in HbA$_{1c}$ and FPG were observed in all three regions in this study, which is in line with the overall results [14]. It is important to note that the observed improvements may be due to the Ramadan fast itself rather than gliclazide MR treatment, as the present study lacks a control group with patients not receiving gliclazide MR. Similar decreases in HbA$_{1c}$ and FPG were reported in a meta-analysis of 28 observational studies that aimed to assess metabolic profile and hypoglycaemic events in patients with type 2 diabetes during Ramadan [24]. Another study found that patients from Bangladesh, Pakistan and India showed a mean reduction in HbA$_{1c}$ of 0.8% between pre- and post-Ramadan [30]. The STEADFAST study also reported that patients from the Middle East, Europe and Asia receiving gliclazide and metformin showed decreases in HbA$_{1c}$ and bodyweight when comparing pre- and post-Ramadan values [31]. In the South-East Asian population, FPG did not change significantly. As the numerical change was relatively small with large error margins ($- 4 \pm 40.2$ mg/dl), this suggests that the subgroup size of patients having a FPG value at V0 and V1 ($n = 275$) was too small to detect any effect. The change in FPG and HbA$_{1c}$ was largest amongst patients from the Indian sub-continent—this is an interesting observation given the increased proportion of dietary carbohydrate (15.2% more) consumed throughout Ramadan in this

region. However, it is important to note that the patients from this region were the youngest overall and a high proportion were receiving at least three antidiabetic agents, which may be associate with better glycaemic control overall. The results for HbA_{1c} and FPG are similar to those observed for newer oral antidiabetic agents (DPP4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists) during Ramadan presented in a recent meta-analysis [32].

Limitations

There are several limitations associated with this study, including those typically associated with observational and non-comparative study designs. There was no control group not receiving gliclazide MR, so it was not possible to conclude if any of the observed effects on body weight, HbA_{1c} or FPG were due to gliclazide MR treatment. The enrolled patients had already been receiving an established regimen of gliclazide MR for at least 90 days prior to inclusion, implying that the drug was well tolerated in this population. There is also the potential for under-reporting of adverse events and hypoglycaemic episodes due in part to patient self-reporting and recall bias [14]. Analyses of larger patient groups in each of the regions included in this study would potentially yield more robust conclusions, particularly for the South-East Asian region. In addition, the descriptive nature of the study could limit some of the comparisons discussed here.

CONCLUSIONS

The data from this study indicate that gliclazide MR is safe and effective in maintaining glycaemic control for patients with type 2 diabetes during Ramadan in all three regions studied as part of DIA-RAMADAN, despite cultural and geographical differences among these regions. As anticipated from the primary analysis, no severe hypoglycaemic events or gliclazide MR-related adverse events were observed in any of the regions during the study [14]. This sub-analysis provides additional real-world evidence to support the safety and tolerability of gliclazide MR in three diverse regions of the world where diabetes is a growing problem due to changing behaviour and dietary habits.

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Data Availability. The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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