Real-World Assessment of Efficacy and Safety Parameters for Dapagliflozin in Management of Type 2 Diabetes Mellitus: REWARD Study

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Keywords

Dapagliflozin · Sodium-glucose cotransporter type 2 · Sodium-glucose cotransporter type 2 inhibitors · Diabetes mellitus · Type 2 diabetes mellitus · Type 2 diabetes

Abstract

Introduction: While ample evidence on improved glycemic control, weight reduction, and lowered blood pressure (BP) with sodium-glucose cotransporter type 2 inhibitors (SGLT2is) exists, real-world data on the potential benefit of SGLT2i on the diabetic population in the Middle East are lacking. The aim of our study was to describe the glycemic control, changes in body weight, body mass index (BMI), lipid profile, and BPs in patients receiving dapagliflozin with other antidiabetic medication. **Methods:** The REWARD study was a multicenter, post-authorization, prospective, open-label, noninterventional, real-world, cohort study. We enrolled 511 adult, type 2 diabetes mellitus patients on antidiabetic medications. These patients were started on dapagliflozin

and followed up for 1 year to assess changes in their clinical and laboratory outcomes. **Results:** The mean HbA1c decreased significantly from $8.5 \pm 1.6\%$ at baseline to $7.6 \pm 1.3\%$ after 12 months (p value <0.001), with an absolute change of 0.9%. Of the study population, 41.6% of patients reached an HbA1c level less than 7% (53 mmol/mol). The systolic pressure improved (mean change = -1.9 mm Hg, p value = 0.003), yet no change in the diastolic pressure was observed. Both body weight and BMI significantly decreased by 0.7 kg and 0.2 kg/m^2 , respectively (p value <0.001). About 84.5% of patients were on antidiabetic agents, while 57.4% were on antihypertensives. Approximately 83.6% of adverse events were mild. A total of 90 hypoglycemic episodes were reported; none were severe. **Conclusion:** In a real-world setting, dapagliflozin in combination with other antidiabetic medications exhibited significant improvement in glycemic control, weight, BMI, and systolic BP. Additionally, it demonstrated a well-tolerated safety profile.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, either due to defective insulin action, insulin secretion, or both [1]. According to the International Diabetes Federation (IDF), the global prevalence rate of diabetes is 9.3% and is among the top 10 leading causes of death worldwide. Without sufficient intervention to address this pandemic, the prevalence rate is predicted to reach 10.2% by 2030 and 10.9% by 2045. The IDF also reported a national prevalence rate of 15.4% among the adult population of the United Arab Emirates (UAE) and 22% in Kuwait [2].

Type 2 diabetes mellitus (T2DM), which accounts for approximately 90% of all diabetes cases, mainly involves abnormal hepatic glucose metabolism, insulin resistance, and increased glucose reabsorption by the kidneys, among others, leading to hyperglycemia [1, 3, 4]. The prevalence of T2DM has increased dramatically over the last few decades and is considered one of the major healthcare challenges worldwide [5]. Analysis from the UAE showed that less than 40% of diabetes patients reached the desired glycemic controls [6]. While, in a study conducted in Kuwait, an approximate 25% of T2DM patients exhibited adequate glycemic control [7]. Therefore, there is a great need to explore the means of improving glycemic control through novel approaches.

Recent advances in understanding diabetes led to the development of sodium-glucose cotransporter type 2 (SGLT2) inhibitors (SGLT2is). SGLT2is were found to lower glucose levels by partially blocking the reabsorption of glucose from the kidneys back to the bloodstream. SGLT2is lead to an increase in the amount of glucose passing in the urine, hence improving diabetes control [8, 9]. These agents have an important role, especially in the management of T2DM patients with established atherosclerotic cardiovascular disease (CVD), heart failure, or chronic kidney disease, as per the recent guidelines of the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE), released in 2020 [10, 11]. Furthermore, the AACE has placed the SGLT2i at number 3 in the hierarchy for diabetes monotherapy, after metformin and GLP1a [11]. Dapagliflozin is a potent, highly selective, and reversible SGLT2i administered orally. The safety, tolerability, pharmacokinetics, and pharmacodynamics of the drug were evaluated in many clinical studies [12].

While ample evidence on improved glycemic control, weight reduction, and lowered blood pressure (BP) with

SGLT2is exists, real-world data on the potential benefit of SGLT2is on the diabetic population in the Middle East are lacking. This is particularly important with the recent forecasts indicating an increase in the use of the SGLT2i in the Middle East, which is attributed mainly to empagliflozin and dapagliflozin [13]. The aim of our study was to describe the clinical outcomes of T2DM patients in the UAE and Kuwait, treated with dapagliflozin for a period of 1 year, in a real-world study. Primarily, we measured the change in HbA1c levels from baseline as a parameter of blood glucose control over the 1-year period. Secondly, we aimed to describe the changes in total body weight, total cholesterol, LDL-C, non-HDL-C, and triglycerides, as well as systolic and diastolic BPs, from baseline.

Materials and Methods

This study complied with the ethical principles of the Declaration of Helsinki, ICH-GCP, and the applicable legislation on non-interventional studies (NISs), as well as the laws and regulations and any applicable guidelines of the UAE and Kuwait, where the study was conducted. The final protocol of this NIS was approved in writing by the Ethics Committee of all participating centers. Written informed consent was obtained from all patients prior to enrollment.

The final protocol of the study (ClinicalTrials.gov identifier: NCT02805361) was approved in writing by the Ethics Committee. The study's protocol gained the ethical approval of the Ethics Committee of the Ministry of Health and Population in the UAE (ref No. MOHP/REC-2017/17 dated January 29, 2017), the Dubai Health Authority in the UAE (ref No. DSREC-07/2016_06 dated September 07, 2016, and ref No. DRSEC-02/2017_14 dated March 23, 2017), the Medical Military Service in the UAE (ref 2016-1 dated January 09, 2016), and the Dasman Diabetes Institute in Kuwait (ref No. RA/189/2016 dated July 28, 2016, and RA/190/2016 dated July 28, 2016).

Study Design

REWARD (NCT02805361) is a multicenter, post-authorization, prospective, open-label, noninterventional, real-life, observational, cohort study. The study was conducted at 11 sites in the UAE and Kuwait, over a period of 1 year. Patients' enrollment started on the September 7, 2016, and ended on the April 29, 2017. Patients were recruited from 9 centers in the UAE (Dubai Diabetes Center, NMC Specialty Hospital Abu Dhabi, Zayed Military Hospital, Aster Medical Center, Prime Medical Center, Belhoul Specialty Hospital, Rashid Hospital, NMC Hospital Al Nahda, and Thumbay Hospital) and 1 center in Kuwait (Dasman Diabetes Institute). The number of recruited patients from each center is present in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000519871).

We collected anonymized data on patients' demographics, disease profile, concomitant medications, and outcomes. The demographic and disease information collected included patients' age,

gender, renal function, and baseline measurements of HbA1c, weight, body mass index (BMI), and BP. All recorded clinical measurements were taken from routine data, and when baseline measurements were unavailable for HbA1c, weight, or BP, the most recent available measurement within the preceding 3 months was used. Additionally, patients' compliance with the medication and treatment interruptions were recorded in each visit as stated by patients.

Population

A total of 511 T2DM patients were initially enrolled in the study at baseline and signed an informed consent form; however, 1 patient was ineligible and was excluded. The 510 patients were selected from a total of 11 centers across the UAE and Kuwait.

Inclusion Criteria

- Male and female participants aged 18 years and older, who were diagnosed with T2DM.
- Patients treated with dapagliflozin (as per routine care and in compliance with the locally approved prescribing information) for >4 weeks and <24 weeks prior to the recruitment date.
- Patients with creatinine clearance >60 mL/min or an eGFR >60 mL/min/1.73 m².
- Patients who provided written informed consent.

Exclusion Criteria

- Patients with contraindications to dapagliflozin, as per the locally approved prescribing information.
- Patients participating in another clinical trial.
- Patients with clinically significant renal, hepatic, hematological, oncological, endocrine, psychiatric, or rheumatic disease.
- Patients who had a disease with a life expectancy less than 1 year.
- Medical claims with a diagnosis (or procedure, where appropriate) indicative of pregnancy or childbirth at baseline.

Study Medication

Due to the observational nature of this study, the assignment of a patient to a particular therapeutic strategy was not decided in advance by a protocol but rather fell within current practice. Dapagliflozin is an SGLT2-selective inhibitor administered orally, once daily (morning or evening) with no regards to meals. The administered dose was 10 mg daily.

Study Outcomes

Primary Efficacy Variable

The primary efficacy variable was measured as the mean change in HbA1c from the mean baseline to the 12th month.

Secondary Efficacy Variables

Secondary efficacy variables included the measurement of the mean changes in total body weight, total cholesterol, LDL-C, non-HDL-C, triglycerides, as well as systolic and diastolic BPs from the mean baseline values to the 12th month.

Safety Variables

The frequency and incidence of the reported adverse events (AEs) during the 12-month period of the study were measured. Patients were asked to report if they experienced any AE or adverse drug reactions. This mainly encompassed hypoglycemic episodes,

volume depletion-related AEs (hypotension, syncope, and dehydration), genital infections, and urinary tract infections (UTIs).

Statistical Analysis

Sample Size

The sample size calculation took the safety endpoints as a base for calculations, which yielded a larger sample size than that of the efficacy outcomes. Calculations done for the study were based on the number of patients who experienced at least 1 AE from 10 mg dapagliflozin in a phase III trial [14]. The incidence noticed was 59% with 5% precision. We adjusted for 10% missing data and a 15% dropout rate since the sample size is large, and missing covariates and dropouts were expected.

Statistical Methods

This analysis is descriptive in nature; no hypotheses were formulated or tested. Efficacy endpoints, including HbA1c, weight, BP, and serum lipids, were analyzed descriptively by time points. Change and percent change from baseline were reported. Descriptive statistics were used to represent demographics and baseline covariates for different patients recruited by each center. Continuous variables were presented by the mean and standard deviation (SD), while frequency was used for categorical data. The mean change from baseline to month 12 in the primary and secondary continuous variables was studied using a paired *t*-test. Point estimates and 95% CI were calculated for the mean change from baseline. Two-way repeated-measures ANOVA was used to test for interaction between time and groups (by gender, age categories [<50 and ≥50 years], and BMI [<25, <30, and ≥30]). Greenhouse-Geisser *p* values were used in all tests for interaction to correct for any possible violations of sphericity assumption. All analyses were done using IBM-SPSS (version 22, Armonk, NY, USA).

Results

Patients' Disposition

A total of 511 patients with T2DM were enrolled in the study, 1 of whom was excluded for not meeting the eligibility criteria; the patient was taking pioglitazone. Additionally, about 32 patients had less than 2 available measurements.

Baseline Characteristics

The majority of the study population were from the UAE (*n* = 479; 93.9%) and were males (*n* = 355; 69.6%). About half of the enrolled patients (*n* = 263; 51.6%) were Middle Eastern. The mean age in both the UAE and Kuwait was 50 years ± 10.9 and 58 years ± 9.4, respectively. The mean height of the population was 165.2 cm ± 9.2, and the mean weight was 81.4 kg ± 15.5. Additionally, more than 80% of the population from both countries was either overweight or obese. A total of 425 patients (83.5%) had HbA1c ≥ 7% at the time of study's enrollment (Table 1).

Table 1. Baseline characteristics of the included patients (*N* = 510)

Variables	Patients	
Age (mean [SD], range), years	50.5 (10.9)	19–84.5
Age group, <i>n</i> (%)		
<50 years	249 (48.8)	
50+ years	261 (51.2)	
Gender, <i>n</i> (%)		
Female	155 (30.4)	
Male	355 (69.6)	
Country, <i>n</i> (%)		
KWT	31 (6.1)	
UAE	479 (93.9)	
Race, <i>n</i> (%)		
Asian	238 (46.7)	
Black	7 (1.4)	
Hispanic	2 (0.4)	
Middle Eastern	263 (51.6)	
Medical history, <i>n</i> (%)		
Dyslipidemia	401 (83.8)	
Hypertension	207 (43.2)	
Microalbuminuria	35 (7.3)	
Diabetic neuropathy	26 (5.4)	
Diabetic retinopathy	28 (5.8)	
Hypothyroidism	25 (5.2)	
Obesity	23 (4.8)	
Myocardial ischemia	12 (2.5)	
Arteriosclerosis	14 (2.9)	
Erectile dysfunction	8 (1.7)	
Goiter	11 (2.3)	
HbA1c, <i>n</i> (%)		
Controlled (<7%)	84 (16.5)	
Uncontrolled (≥7%)	425 (83.5)	
Vital signs (mean [SD], range)		
Sitting systolic BP, mm/Hg	129 (14)	81–181
Sitting diastolic BP, mm/Hg	74.7 (10.8)	40–109
Sitting heart rate (beats, <i>n</i>)	81.3 (10.8)	56–116
Laboratory (mean [SD], range)		
eGFR, mL/min/1.73 m ²	101.6 (19.7)	60–207
HbA1c, %	8.5 (1.6)	5.8–14
Total cholesterol, mg/dL	170.6 (46.2)	72–38
LDL, mg/dL	101.7 (40)	15–230
HDL, mg/dL	45.1 (14.1)	21–174
Triglycerides, mg/dL	157.2 (161.2)	33–2782

The mean systolic and diastolic BP was 129 mm Hg ± 14 and 74.7 mm Hg ± 10.8, respectively. The mean HbA1c at baseline was 8.5% ± 1.6, showing that most patients were inadequately controlled. Total cholesterol, LDL, HDL, and triglycerides were also measured at baseline and had values of 170.6 ± 46.2 mg/dL, 101.7 ± 40 mg/dL, 45.1 ± 14.1 mg/dL, and 157.2 ± 161.2 mg/dL, respectively. The eGFR was also calculated in all patients, with a mean value of 101.6 mL/min/1.73 m² (SD: 19.7) (Table 1).

Dyslipidemia was the most common medical condition in our study, encountered in 83.8% (*n* = 401) of the study population, followed by hypertension in 43.2% (*n* = 207). A total of 297 patients (62.1%) had CVDs and 273 patients (57.2%) had endocrine disorders; the endocrine disorders were mainly thyroid disorders (mostly hypothyroidism and goiter). These conditions remained in 99.7% of the cases by the end of the study. Other medical conditions were also reported, with a percentage ranging from 1.9% to 7.1% (Table 1).

Medication and Concomitant Medications

A total of 480 patients (94.1%) were taking dapagliflozin at a dose of 10 mg once daily, while 30 (5.9%) were taking the 5 mg dose once daily. All patients were taking dapagliflozin during the 4–24 weeks prior to enrollment in this study. About 24.5% of patients (*n* = 125) were on dapagliflozin for 4 weeks prior to enrollment, while 20 weeks was the maximum number of weeks a patient was receiving the drug prior to their first visit. Besides, 509 (99.6%) of the patients reported taking other antidiabetic drugs. The most commonly administered drugs are shown in Figure 1. Three patients reported stopping dapagliflozin and shifting to canagliflozin. The first patient shifted to canagliflozin due to a decrease in the eGFR level to 59 mL/min/1.73 m², and the second was due to the development of a numbness sensation, while the reason was unknown in the third patient. A total of 29 patients stopped their treatment over the course of the study, while 3 patients interrupted their treatment. The details of the patients who stopped their treatment over the course of the study are present in online supplementary Table 2.

The vast majority of patients reported taking concomitant medications, mainly for the management of dyslipidemias and cardiovascular comorbidities, especially hypertension. The most common concomitant medication in the study population was atorvastatin, taken by 263 patients (55.9%) followed by rosuvastatin, taken by 108 patients (17.6%). Perindopril (13.5%) and amlodipine (12.2%) were the most common antihypertensive medications taken by patients with hypertension in this study.

Efficacy Outcomes

Primary Efficacy Outcomes

Study results show that the mean HbA1c ±SD decreased significantly from 8.5 ± 1.6% at baseline to 7.6 ± 1.3% after 12 months (*p* value <0.001), with an absolute change of 0.9% (95% CI 0.73–1.03). HbA1c changes were

Fig. 1. Patients receiving other antidiabetic medications ($n = 509$).

Table 2. HbA1c values difference between baseline and the last observation in all cases and in relation to gender, age, and BMI ($N = 469$)

	Before			After			Mean difference	95% CI for the difference	p value
	mean %, mmol/mol	std. deviation	95% CI	mean %, mmol/mol	std. deviation	95% CI			
Total	8.48 (69)	1.62 (18)	[8.35–8.64]	7.60 (60)	1.25 (14)	7.71–7.48	0.88	0.73–1.03	
p values	<0.001a								
Gender									
Female	8.54 (70)	1.79 (20)	[8.37–8.7]	7.90 (63)	1.43 (15)	7.77–8.03	0.64	0.34–0.94	<0.001
Male	8.46 (69)	1.54 (17)	8.32–8.59	7.48 (58)	1.15 (12)	7.37–7.58	0.98	0.81–1.15	<0.001
p values	<0.001a 0.002b 0.83c								
Age									
<50 years	8.64 (71)	1.70 (19)	[8.48–8.78]	7.51 (59)	1.29 (14)	7.39–7.62	1.12	0.89–1.35	<0.001
50+ years	8.33 (68)	1.53 (17)	[8.19–8.46]	7.68 (60)	1.21 (13)	7.57–7.78	0.65	0.46–0.83	<0.001
p values	<0.001a 0.147b 0.039c								
BMI, kg/m ²									
Normal (<25)	8.75 (72)	1.75 (20)	8.59–8.9	7.66 (60)	1.26 (14)	7.54–7.77	1.09	0.69–1.48	<0.001
Overweight (<30)	8.39 (68)	1.58 (18)	8.24–8.53	7.46 (58)	1.00 (11)	7.37–7.55	0.92	0.71–1.14	<0.001
Obese (30+)	8.50 (69)	1.61 (18)	8.35–8.64	7.74 (61)	1.48 (16)	7.6–7.87	0.77	0.53–1.00	<0.001
p values	<0.001a 0.088 b 0.205c								

Pa, test change with time across the variable; Pb, test difference between the groups at endpoint; Pc, test the interaction using two-way repeated-measures ANOVA between groups and time. The number of cases with missing HbA1c: 9 cases.

significantly affected by gender, where male patients had a greater decrease in their HbA1c values than females (Table 2). In our study, 41.6% of the patients reached a glycemic control of less than 7%, while 16.4% of patients

had HbA1c levels of less than 6.5% by the end of the study. We also assessed the glycemic control in patients with uncontrolled diabetes at baseline (HbA1c level above 7%). Results showed that 34.6% of uncontrolled patients

Fig. 2. Percentage of patients achieving the targeted glycemic control ($N = 469$).

Table 3. Secondary outcomes difference between baseline and the last observation in all cases ($N = 478$)

	Before			After			Paired difference		<i>p</i> value
	mean	std. deviation	95% CI	mean	std. deviation	95% CI	mean difference	95% CI for the difference	
SBP, mm Hg	129.2	14.1	127.93–130.46	127.3	13.3	126.1–128.49	1.86	0.63–3.1	0.003
DBP, mm Hg	74.6	10.9	73.62–75.75	74.6	10.0	73.7–75.49	–0.05	–0.93 to 0.838	0.912
Pulse, per min	81.3	11.0	80.3–82.28	80.3	10.6	79.34–81.25	1.08	0.17–2	0.02
Weight, kg	81.7	15.5	80.31–83.09	81.0	15.8	79.58–82.41	0.79	0.46–1.11	<0.001
BMI, kg/m ²	29.9	5.4	29.4–30.38	29.7	5.5	29.2–30.19	0.28	0.17–0.4	<0.001
eGFR, mL/min/1.73 m ²	101.4	19.6	99.64–103.15	99.3	17.0	97.77–100.82	2.07	0.56–3.58	0.007
Total cholesterol, mg/dL	169.4	46.3	165.24–173.55	162.8	40.9	159.12–166.47	6.64	2.014–11.28	0.005
LDL, mg/dL	101.5	40.2	97.89–105.1	94.7	37.0	91.37–98.02	6.8	2.74–11.01	0.001
HDL, mg/dL	44.7	13.8	43.46–45.93	47.0	15.2	45.63–48.36	–2.27	(–3.8) to (–0.69)	0.005
Triglyceride, mg/dL	102.5	33–2782	99.51–105.48	126.5	31–672	123.65–129.34	10.2	–5.4 to 25.82	0.641

reached HbA1c levels of less than 7%, while 11.7% reached HbA1c levels of less than 6.5% by the end of the study (shown in Fig. 2).

Secondary Efficacy Outcomes

Our patients generally showed a significant decrease of -1.9 mm Hg in systolic BP (p value = 0.003). On the contrary, there was no change in the mean diastolic BP (p value = 0.912). Regarding patients' pulse, there was a slight decrease of -1 pulse/min in the mean heart rate by the end of the study (p value = 0.02). BMI decreased sig-

nificantly (p value <0.001) from baseline (29.9) to the end of the study (29.7). Regarding weight, there was a significant change in weight with time (p value <0.001). Furthermore, we observed a significant change in the eGFR in our study (p value = 0.007) with an average change of 0.94% (Table 3). Besides, we observed a significant decrease in the mean cholesterol (p value = 0.005), LDL (p value = 0.001), and HDL (p value = 0.005) levels. On the other hand, there was no significant change in the mean value of triglycerides over time (p value = 0.641; Table 3).

We explored the impact of age, gender, and BMI on the secondary outcomes of the included patients. Gender had a significant impact on the change in the systolic BP by time (p value = 0.047) and patients' pulse (p value 0.048) only. On the other hand, patients older than 50 years had significantly less change in the eGFR than patients younger than 50 years (p value = 0.012). Last, the baseline BMI had no significant associations with the changes in any of the secondary outcomes.

Safety Outcomes

A total of 117 (83.57%) patients reported experiencing mild AEs, 19 (13.57%) reported moderate AEs, and only 4 (2.86%) reported serious events, including one transurethral prostatectomy/hematuria, one dysuria, and 2 UTIs. Out of the 4 severe AEs, 2 required hospitalization, and the other 2 were considered medically significant. It was found that only 28.6% of the AEs were related to the study drug. Out of all the reported AEs, 88.6% fully recovered, 4.3% had improving conditions, and 7.1% had conditions that remained till the end of the study. A total of 90 hypoglycemic episodes were reported in 62 patients throughout the study, none of which were considered severe in nature; 81 mild (15.9%) and 9 moderate (1.2%). About 79 hypoglycemic episodes occurred in patients taking insulin, sulfonylurea derivatives, or both. Furthermore, 10 patients (1.96%) reported having UTIs; 9 were reported as UTIs, and 1 was reported as a fungal urogenital infection. Three patients (0.59%) reported genital infections, 2 of which reported having a genital infection and 1 reported having increased vaginal secretions. Additionally, 1 patient (0.2%) reported having volume depletion-related AEs in the form of dehydration. The female-to-male ratio was 4:1 for UTIs and 2:1 for genital infections. No episodes of diabetic ketoacidosis (DKA) or amputation were recorded.

Discussion/Conclusion

In our study, we primarily aimed to evaluate the change in HbA1c levels from baseline in adult patients with pre-existing T2DM, receiving dapagliflozin, over a 1-year period. Secondly, the changes from baseline in total body weight, BMI, and systolic and diastolic BPs were described. Additionally, we observed the frequency and incidence of hypoglycemic episodes, volume depletion, genital infections, and UTIs as reported AEs during the 12-month period of the study.

Dapagliflozin can be used as monotherapy or in combination with other oral hypoglycemic agents and insulin at any stage of T2DM. In this observational NIS, T2DM patients were exposed to dapagliflozin (10 mg) for 1 year and had received it 4–24 weeks prior to enrollment. Patients showed significant improvement in their glycemic control (HbA1c), with a mean change of -0.9% (10 mmol/mol). Fadini et al. [15] reported similar results from the Italian observational study DARWIN-T2D; in >17,000 patients on dapagliflozin, there was a significant improvement in HbA1c levels (-0.7% [8 mmol/mol]) after an average of 5.5 months of treatment. Additionally, a more recent study assessed the effectiveness of dapagliflozin on T2DM patients and found that the administration of dapagliflozin as add-on therapy in combination with standard diabetic treatments decreased HbA1c levels significantly by 0.8% (9 mmol/mol) after 6 months and by 1.5% (16 mmol/mol) after 12 months [16]. Moreover, a randomized phase III trial conducted on treatment-naïve Asian patients with T2DM demonstrated a -1.04% (11 mmol/mol) and 1.11% (12 mmol/mol) mean reduction in their HbA1c level after 24 weeks of treatment with 5 mg and 10 mg dapagliflozin, respectively [17].

Sustained glycemic control is the cornerstone of management of T2DM. The majority of patients in our study were not controlled on their previous regimens as the mean HbA1c value at the beginning of the study was 8.5% (69 mmol/mol). Enrolled patients had a wide range of HbA1c levels, affecting the mean value in the beginning and at the end of the study. Our study showed that a total of 41.6% of patients achieved a glycemic control target of an HbA1c level of less than 7% (53 mmol/mol) by the end of the study duration. The observational nature of this study had no prior influence on the HbA1c level of the study population. Accordingly, glycemic control results could be due to various factors including (1) the impact of adding dapagliflozin to other antidiabetic regimens, (2) better patient adherence to treatment regimens, and (3) tolerability of medications and the absence of disturbing AEs. Furthermore, the analysis showed that around 35% of patients with uncontrolled diabetes at baseline reached the target glycemic level by the end of this study. Bailey et al. [18] found that patients with uncontrolled diabetes improved by adding dapagliflozin to metformin. Their study showed that 40.6% of patients achieved glycemic control (HbA1c <7% [53 mmol/mol]) after 24 weeks of treatment.

In a study by Lambers et al. [19], investigators described a decrease in patients' systolic BP and weight. They attributed this decrease to the enhanced excretion

of sodium during the SGLT2 blockade. Similarly, our study also showed significant improvement in systolic pressure and pulse rates and a reduction in total body weight, with a significant difference between young and old age groups. Additionally, 2 phase III studies reported that dapagliflozin 10 mg once daily reduced systolic BP and improved glycemic control in patients with inadequately controlled T2DM and hypertension despite receiving antihypertensive therapy [20].

Renal function was also monitored in our study, showing a total decrease in the eGFR by a 0.94% median change from baseline. Additionally, we found that age had an impact on this change, where patients above the age of 50 years showed a difference in the change in the eGFR with time than those below the age of 50 years. Similarly, a review on dapagliflozin in T2DM reported that the renal outcomes of dapagliflozin relative to the placebo were associated with a substantial reduction in the sustained decline of the eGFR by $\geq 40\%$ to < 60 mL/min per 1.73 m^2 [20, 21]. Another observational study by McGurnaghan et al. [22] showed an initial drop in the eGFR ($-1.81 \text{ mL/min/1.73m}^2$; 95% CI, $-2.10, -1.52$) after 3 months from the study baseline and varied afterward. The relatively high mean eGFR value in the Kuwaiti population can be attributed to many factors such as the smaller sample size in relation to the Emirati population (31 vs. 479 patients) or the high mean age and the percentage of patients above 50 years of age in the Kuwaiti population (83.9%). It can also be related to the higher mean weight and BMI in the Kuwaiti population.

An interesting observation was the lipid profile status in our study population. There was a general improvement of the lipid profile of enrolled patients throughout the study, except for triglycerides. The total cholesterol, HDL-C, and LDL-C levels significantly improved with time in relation to gender, age, and BMI. The only difference observed was in the age groups, where a significant difference in all lipid parameters was shown, while there was a significant difference between males and females in the HDL parameter as well. A previous study observing the impact of once-daily dapagliflozin (10 mg) has shown a mean change in total cholesterol of 2.5%, HDL-C of 6%, low-density lipoprotein of 2.9%, and triglycerides of -2.7% compared to the placebo after 24 weeks of treatment [12].

Furthermore, a previous meta-analysis also showed a decrease in weight of about 1–2 kg with the use of dapagliflozin and up to 5 kg in combination with sulfonylurea derivatives [23]. The benefits with systolic BP, weight, BMI, and lipids shown in this study may suggest a favor-

able cardiovascular benefit of dapagliflozin. A randomized study conducted on Japanese patients to compare the efficacy of dapagliflozin versus sitagliptin showed that a body weight reduction of $\geq 3.0\%$ was significantly achieved with dapagliflozin. Moreover, dapagliflozin was superior to sitagliptin regarding cardiometabolic risks, specifically in increasing HDL-C and suppressing the increase in serum creatinine and the decrease in the eGFR. This suggested that the SGLT2i could be more suitable in preventing cardiovascular events in early stages [24]. Moreover, another study by Avgerinos et al. [25] stated that treatment with dapagliflozin decreased the composite outcome risks of cardiovascular death or hospitalization for heart failure as compared to the placebo among T2DM patients who had or were at risk of atherosclerotic CVD. Additionally, the CVD-REAL study conducted on more than 400,000 T2DM patients across 6 countries, 74% of whom did not have a history of established CVD, which supported the association of cardiovascular benefits with the use of dapagliflozin [26].

Dapagliflozin is generally well tolerated but is suggested to have an increased risk of genitourinary infections and UTIs [23]. UTIs mainly occurred in female patients, whereas only 1 patient reported having volume depletion. However, though hypoglycemia was not previously associated with dapagliflozin monotherapy or with dual therapy with metformin [27], it is associated with an increased risk of hypoglycemia when used with other hypoglycemic agents, such as insulin and sulfonylurea classes. Our study reported a total of 90 hypoglycemic episodes in 62 patients. Most of the reported episodes were mild in nature, and only 9 were moderate. Contrarily, the study by Ji et al. [17] reported that hypoglycemia was uncommon (0.8%) in patients receiving 10 mg dapagliflozin, whereas genital infections occurred in 4.5% of patients and UTIs in 5.3% of patients. Pooled data from 12 studies suggested UTI rates of 4.3% in study subjects treated with dapagliflozin 10 mg ($n = 1,193$) [28]. On the other hand, our study only reported 10 patients (1.96%) experiencing a UTI and 3 patients (0.59%) experiencing genital infections. Dapagliflozin was well tolerated in this study with only 4 patients with serious AEs, and only 2 of them required hospitalization. The majority of the reported AEs were mild (83%), while about 14% were moderate. Patients with reported AEs recovered from almost 90% of the AEs occurring in this study. This is consistent with all previous data that proved SGLT inhibitors to be well tolerated and with a low possibility of serious AEs [27].

The risk of DKA was a raised concern among diabetic patients on an SGLT2i. Some observational studies high-

lighted an increased risk of DKA among patients receiving an SGLT2i, yet the results were conflicting so far [29–31]. Other real-world studies reported no episodes in DKA among their patients receiving the SGLT2i [32]. In the present study, which continued for 12 months, we observed no incidence of DKA over the study's period.

We acknowledge that the present study has some limitations. The study may suffer from limited generalizability, especially regarding the Kuwaiti population, due to the relatively small sample size, which does not provide adequate representation of the T2DM population in the UAE and Kuwait. Additionally, some variables were based on self-reporting, which may lead to inaccurate collection of these variables. The treatment adherence might have been affected by the self-procurement of the study medication.

Conclusion

The findings of our real-world study “REWARD” suggest that dapagliflozin, in combination with other anti-diabetic agents, improved glycemic control, weight, BMI, and systolic BP. The well-tolerated safety profile was consistent with previous worldwide real-world settings. Combination of dapagliflozin with insulin or sulfonylurea derivatives was the main observed cause of hypoglycemia. However, our data should be interpreted cautiously given the lack of data regarding the impact of lifestyle changes on the glycemic control of the patients on dapagliflozin.

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Statement of Ethics

This study complied with the ethical principles of the Declaration of Helsinki, ICH-GCP, and the applicable legislation on NISs, as well as the laws and regulations and any applicable guidelines of the UAE and Kuwait, where the study was conducted. The final protocol of the study (ClinicalTrials.gov identifier: NCT02805361) was approved in writing by the Ethics Committee. The study's pro-

tocol gained the ethical approval of the ethic committee of the Ministry of Health and Population in the UAE (ref No. MOHP/REC-2017/17 dated January 29, 2017), the Dubai Health Authority in the UAE (ref No. DSREC-07/2016_06 dated September 07, 2016, and ref No. DRSEC-02/2017_14 dated March 23, 2017), the Medical Military Service in the UAE (Ref 2016-1 dated January 09, 2016), and the Dasman Diabetes Institute in Kuwait (ref No. RA/189/2016 dated July 28, 2016, and RA/190/2016 dated July 28, 2016). Written informed consent was obtained from all patients prior to enrollment.

Conflict of Interest Statement

A.H., D.D., J.N., Y.A., A.K., A.Bi., M.A., K.H., M.A., and R.A. have received personal fees from AstraZeneca as compensation for enrolling subjects in the REWARD study. Additionally, S.Q., M.A., and A.B. are AstraZeneca employees.

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Author Contributions

All the investigators contributed equally in building the concept of the manuscript during investigators/authors meeting, where the study data were interpreted by authors; moreover, they all revised the draft manuscript and approved the final version submitted to the journal, and they are all accountable for all aspects of this manuscript. In addition to that, Dr. Hassoun is the corresponding author.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as online supplementary information.

References

- 1 European Medicines Agency (EMA). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (draft guidance CPMP/EWP/1080/00 Rev. 2). *Diabetes Obes Metab*. 2018;44(January):1–24.
- 2 International Diabetes Federation. *IDF diabetes atlas ninth*. Dunia: IDF; 2019. p. 168.
- 3 Mayo Clinic (Mayo Foundation for Medical Education and Research). *Type 2 diabetes*; 2019.

- 4 Mintz ML. Role of the kidney in Type 2 diabetes and mechanism of action of sodium glucose cotransporter-2 inhibitors. *J Fam Pract*. 2016;65(12):supp_az_1216.
- 5 World Health Organization. *Diabetes facts sheet*; 2018.
- 6 Bashier A, Bin Hussain A, Abdelgadir E, Alawadi F, Sabbour H, Chilton R. Consensus recommendations for management of patients with type 2 diabetes mellitus and cardiovascular diseases. *Diabetol Metab Syndr*. 2019; 11(1):80–28.
- 7 Channanath AM, AlWotayan R, Alkandari H, Davidsson L, Tuomilehto J, Thanaraj TA. Glycaemic control in native Kuwaiti Arab patients with type 2 diabetes. *Prim Care Diabetes*. 2018 Dec;12(6):526–32.
- 8 Barutta F, Bernardi S, Gargiulo G, Durazzo M, Gruden G. SGLT2 inhibition to address the unmet needs in diabetic nephropathy. *Diabetes Metab Res Rev*. 2019;35(7):e3171–13.
- 9 Chao EC. SGLT-2 inhibitors: a new mechanism for glycemic control. *Clin Diabetes*. 2014 Jan;32(1):4–11.
- 10 Matthew CR. A. Standards of medical care in diabetes 2020 ADA. *Am Diabetes Assoc*. 2020;42(479):960–1010.
- 11 Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. *Endocr Pract*. 2020;26(1):107–39.
- 12 Electronic Medicines Compendium (EMC). *Forxiga 5 mg film-coated tablets: summary of product characteristics (SmPC)*; 2020.
- 13 Market Research Report. *Middle East and Africa sodium-dependent glucose co-transporter 2 (SGLT 2) market: growth, trends, and forecast (2019–2024)*. 2020. Available from: <https://www.mordorintelligence.com/industry-reports/middle-east-and-africa-sodium-dependent-glucose-cotransporter-2-inhibitors-market>.
- 14 Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in Type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010 Oct;33(10):2217–24.
- 15 Fadini GP, Zatti G, Consoli A, Bonora E, Sesti G, Avogaro A, et al. Rationale and design of the DARWIN-T2D (dapagliflozin real world evidence in type 2 diabetes). *Nutr Metab Cardiovasc Dis*. 2017 Dec;27(12):1089–97.
- 16 Al Adawi RM, Jassim Z, Elgaily D, Abdelaziz H, Sree B, Mohamed Ibrahim MI. Assessment of dapagliflozin effectiveness as add-on therapy for the treatment of type 2 diabetes mellitus in a Qatari population. *Sci Rep*. 2019 Dec;9(1):6864.
- 17 Ji L, Ma J, Li H, Mansfield TA, Tjoen CL, Iqbal N, et al. Dapagliflozin as monotherapy in drug-naïve asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. *Clin Ther*. 2014 Jan; 36(1):84–100.e9.
- 18 Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010 Jun;375(9733):2223–33.
- 19 Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab*. 2013 Sep;15(9):853–62.
- 20 Dhillon S. Dapagliflozin: a review in type 2 diabetes. *Drugs*. 2019 Jul;79(10):1135–46.
- 21 Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019 Aug;7(8):606–17.
- 22 McGurnaghan SJ, Brierley L, Caparrotta TM, McKeigue PM, Blackburn LAK, Wild SH, et al. The effect of dapagliflozin on glycaemic control and other cardiovascular disease risk factors in type 2 diabetes mellitus: a real-world observational study. *Diabetologia*. 2019 Apr;62(4):621–32.
- 23 Narendran P, Saeed M. Dapagliflozin for the treatment of type 2 diabetes: a review of the literature. *Drug Des Devel Ther*. 2014 Dec; 2493.
- 24 Fuchigami A, Shigiyama F, Kitazawa T, Okada Y, Ichijo T, Higa M, et al. Efficacy of dapagliflozin versus sitagliptin on cardiometabolic risk factors in Japanese patients with type 2 diabetes: a prospective, randomized study (DIVERSITY-CVR). *Cardiovasc Diabetol*. 2020 Dec;19(1):1.
- 25 Avgerinos I, Liakos A, Tsapas A, Bekiari E. Cardiovascular risk reduction in type 2 diabetes: therapeutic potential of dapagliflozin. *Diabetes Metab Syndr Obes*. 2019 Dec;12:2549–57.
- 26 Astrazeneca. *New data from landmark CVD-REAL study of patients with type-2 diabetes confirms CV benefits associated with SGLT-2 Inhibitors*; 2018.
- 27 Dandona P, Chaudhuri A. Sodium-glucose co-transporter 2 inhibitors for type 2 diabetes mellitus: An overview for the primary care physician. *Int J Clin Pract*. 2017 May;71(5): e12937.
- 28 Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. *J Diabetes Complications*. 2013 Sep; 27(5):473–8.
- 29 Fralick M, Schneeweiss S, Paterno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med*. 2017;376(23): 2300–2.
- 30 Wang Y, Desai M, Ryan PB, DeFalco FJ, Schuemie MJ, Stang PE, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes Res Clin Pract*. 2017;128:83–90.
- 31 Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ*. 2018;363:K4365.
- 32 Gorgojo-Martínez JJ, Serrano-Moreno C, Sanz-Velasco A, Feo-Ortega G, Almodóvar-Ruiz F. Real-world effectiveness and safety of dapagliflozin therapy added to a GLP1 receptor agonist in patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis*. 2017;27(2):129–37.