Short Communication

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DAPA-RWE: a retrospective multicenter study comparing dapagliflozin and sitagliptin in patients with Type 2 diabetes treated under routine clinical practice in Spain

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Background: Weight reduction and glycemic control are key goals during Type 2 diabetes management. However, there are few country-specific, real-world data on cotransporter 2 inhibitors. **Materials & methods:** DAPA-RWE was a retrospective, multicenter study comparing the efficacy of dapagliflozin versus sitagliptin in Type 2 diabetes patients in Spain. **Results:** The study population comprised 1046 patients (594 with dapagliflozin, 452 with sitagliptin). Age was 61.8 ± 10.0 and 66.2 ± 11.4 years and glycosylated hemoglobin (HbA1c) 8.9 and 8.8%, respectively. The main end point (reduction in weight and HbA1c) was reached by 24.4 and 56.1% of patients, respectively; $p < 0.05$. This was confirmed with a propensity score matching analysis balanced for obesity-related variables at baseline. **Conclusion:** DAPA-RWE confirmed dapagliflozin to be more effective than sitagliptin in reducing HbA1c and weight.

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Keywords: dapagliflozin • HbA1c • obesity • real-world evidence • sitagliptin • Type 2 diabetes • weight reduction

Glycemic control is essential if we are to reduce the morbidity and long-term mortality of patients with Type 2 diabetes (T2D) [1]. Consequently, optimal therapeutic management is of paramount importance. Oral metformin, a first-line T2D drug, loses antihyperglycemic efficacy over time, thus necessitating intensification of treatment [2].

A loss of antihyperglycemic efficacy, which can appear rapidly after the first year of treatment, has also been reported with sulfonylureas. In addition, both sulfonylureas and insulins are related to weight gain and the appearance of hypoglycemia, which harms the patient, negatively impacts adherence to treatment [3] and thus worsens glycemic control [4]. Moreover, approximately 50% of T2D patients are obese, more than 80% are hypertensive [5] and almost 40% have inadequate metabolic control [6]. These characteristics highlight the difficulty and complications associated with treatment of T2D.

Real-world studies are critical if we are to understand the clinical factors that influence the safety and effectiveness of treatments, as they include patient groups generally excluded from randomized controlled trials because of comorbidities and other criteria. A comparison between the number of hypoglycemic episodes of insulin-treated

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patients in randomized clinical trials and real-life studies found a greater number of events in routine clinical practice [7], thus highlighting the need for real-world data on glycemic control in T2D patients.

Dapagliflozin (FORXIGA™) is a reversible sodium–glucose cotransporter 2 inhibitor (SGLT2i) that reduces hyperglycemia by inhibiting the reabsorption of glucose in the kidney and promoting the excretion of glucose in urine through an insulin-independent mechanism of action [8]. Dapagliflozin is approved in the European Union for the treatment of insufficiently controlled T2D, either when metformin is contraindicated or in combination with other glucose-lowering treatment. Although there are several publications on the clinical development of dapagliflozin, including data at 4 years and studies on experience in clinical practice from several countries [9,10], information on its use in Spain is lacking.

Sitagliptin is an alternative oral antihyperglycemic agent that is frequently prescribed in Spain. This DPP4i acts by preventing degradation of incretins, which are intestinal hormones involved in the regulation of glucose. Inhibition of DPP-4 increases the active forms of GLP-1 and GIP, leading to glucose-dependent increased insulin secretion and reduced glucagon levels.

The DAPA-RWE study aimed to assess the efficacy and safety of oral antihyperglycemic drugs as used in the routine clinical treatment of T2D patients in Spain. The main objective of this retrospective, multicenter and observational study was to compare the real-world efficacy of dapagliflozin with that of sitagliptin, measured as a composite end point comprising reduced glycosylated hemoglobin (HbA1c) and weight at 6 months of treatment.

Materials & methods

Study design & patients

DAPA-RWE was an observational, retrospective, multicenter study performed on patients with T2D under conditions of usual clinical practice to compare the effectiveness and safety profile of dapagliflozin with that of sitagliptin.

The study was conducted at 22 Spanish sites in accordance with the ICH Good Clinical Practice guidelines and with the approval of the respective Research Ethics Committees. Eligible patients were 18 years or older with stable T2D managed with regular therapy based on antihyperglycemic agents, including either dapagliflozin or sitagliptin. Treatment with dapagliflozin or sitagliptin had started at least 6 months before inclusion. To be included and evaluable, the following information had to be available at baseline: gender, age, date of diagnosis of T2D, weight, height, systolic and diastolic blood pressure, BMI, concomitant medication, fasting blood glucose, HbA1c and estimated glomerular filtration rate (eGFR). Moreover, the patient had to attend a follow-up visit (6 ± 3 months). Patients with Type 1 diabetes or gestational diabetes were excluded.

Study outcomes

The main objective of the study was to compare the effectiveness of dapagliflozin with that of sitagliptin, measured as a composite end point comprising reduced HbA1c and weight at 6 months of treatment under conditions of usual clinical practice. Weight was considered to have been reduced if the patient lost $\geq$1.5 kg, and HbA1c was reduced if it fell by $\geq$0.5%.

The secondary objectives were assessment of the use of SGLT2i/DPP4i (in mono-, double or triple therapy), measurement of the incidence and severity of hypoglycemia, measurement of the incidence of urinary and genital infections and evaluation of differences in patient characteristics at the beginning and end of treatment (6 months $\pm$ 3 months).

Patients were retrospectively evaluated at initiation of treatment (baseline), 6 months ($\pm$3 months) of treatment and, if applicable and available, every 6 months ($\pm$2 months) of treatment thereafter. Evaluable patients were those with complete data at the start of treatment (baseline) and at 6 months of treatment ($\pm$3 months).

Statistical analysis

The primary outcome was the percentage of patients who achieved a change of $\geq$0.5% in HbA1c and $\geq$1.5 kg in bodyweight after 6 months of treatment. The study aimed to demonstrate that dapagliflozin was superior to sitagliptin in achieving this composite end point. Assuming that 60% of dapagliflozin-treated patients and 50% of sitagliptin-treated patients achieved the primary outcome, 407 evaluable patients per cohort were required to reject (with 80 and 5% 2-sided significance levels) the null hypothesis that the effectiveness of dapagliflozin and sitagliptin was the same. Since 25% of patients were expected to be nonevaluable, 509 patients per cohort were required, thus giving a total of 1018 patients.

Table 1. Baseline characteristics of evaluable patients per treatment cohort.[†,‡]

Outcome	Sitagliptin (n = 452)	Dapagliflozin (n = 594)
Gender – male	57.6%	56.6%
Arterial hypertension	64.3%	69.4%
Dyslipidemia	70.3%	75.6%
Obesity (BMI>30)	**39.03%**	**71.6%**
Chronic kidney disease[§]	**27.3%**	**19.8%**
Secondary CV prevention	24.6%	21.7%
Ischemic heart disease	14.9%	14.5%
Cerebrovascular disease	6.9%	5.1%
Peripheral arterial disease	7.8%	6.2%
Chronic heart failure	5.1%	3.7%
Nonalcoholic fatty liver disease	**5.2%**	**10.4%**
PDR	13.6%	13.1%

[†]Data presented as % of patients.
[‡]Statistically significant differences are marked in bold.
[§]Chronic kidney disease is defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2.
CV: Cardiovascular; PDR: Proliferative diabetic retinopathy.

In order to reduce bias due to covariates, a matching analysis of multiple covariates was performed to identify confounding factors. A propensity score was calculated using logistic regression. The covariates selected for the propensity score model were those found to be statistically and potentially clinically significant.

Categorical variables were presented as frequency (absolute, relative) and continuous variables as summary statistics (mean, standard deviation).

The statistical analyzes were performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., NY, USA).

Results

The study population comprised 1056 patients with Type 2 diabetes. Patients were included from March 2018 to June 2018 and 1046 were considered evaluable. Treatment was with sitagliptin in 452 patients and dapagliflozin in 594. Mean age was 61.8 (±10.0) years in the dapagliflozin cohort and 66.2 (±11.4) years in the sitagliptin cohort.

The baseline characteristics were generally well-balanced between the sitagliptin and dapagliflozin cohorts (Table 1). No statistically significant differences were observed between the cohorts in terms of gender, hypertension, dyslipidemia, retinopathy or ischemic heart disease. Similarly, no differences were observed in HbA1c (8.9 dapagliflozin vs 8.8% sitagliptin). However, statistically significant differences were observed between the cohorts in terms of obesity, with a higher percentage of obese patients in the dapagliflozin cohort (71.6 vs 39%) and the highest baseline weight in the dapagliflozin cohort (92.0 vs 80.4 kg). The comorbidities chronic kidney disease and nonalcoholic fatty liver disease were also unbalanced, with chronic kidney disease being more frequent in the sitagliptin cohort and nonalcoholic fatty liver disease more frequent in the dapagliflozin cohort.

The clinical characteristics were generally wellbalanced between the sitagliptin and dapagliflozin cohort with respect to disease duration, HbA1c and blood pressure (Table 2). However, statistically significant differences were observed for age, data related to obesity (waist circumference, BMI, weight, low-density lipoprotein cholesterol, triglycerides) and eGFR values. Patients in the sitagliptin cohort were older, less obese and had lower eGFR values than patients in the dapagliflozin cohort.

Exposure to sitagliptin/dapagliflozin and other antihyperglycemic treatments was similar between the cohorts. Data on the type of antihyperglycemic treatments received before initiation of treatment with sitagliptin or dapagliflozin are shown in Table 2. Almost half of the patients had received insulin analogues (45.5 and 42.4%, respectively, in the sitagliptin and dapagliflozin cohorts), most patients had received metformin (88.9 and 86%, respectively) and approximately 25% had previously received sulfonylurea/repaglinide.

The main objective of the study was to evaluate the effectiveness and safety of the use of dapagliflozin versus sitagliptin based on a composite goal of reducing HbA1c and weight at 6 months of treatment under conditions of usual clinical practice. Weight reduction and HbA1c reduction were defined as a reduction of at least 1.5 kg and of at least 0.5%, respectively. The composite end point was reached by 56.1 and 24.4% of patients in the

Table 2. Baseline clinical characteristics of evaluable patients per treatment cohort.[†,‡]

Outcome	Sitagliptin	Dapagliflozin	Statistical significance[‡]
Age (years)	**66.2 ± 11.4**	**61.8 ± 10.0**	¶
Disease duration (years)	14.0 ± 9.4	13.1 ± 7.8	NS
HbA1c (%)	8.8 % ± 5.8	8.9 % ± 7.2	NS
FPG (mg/dl)	170.3 ± 60.9	173.9 ± 62.8	NS
Weight (kg)	**80.4 ± 16.7**	**92.0 ± 17.5**	¶
Waist circumference (cm)	**99.7 ± 17.6**	**106.9 ± 18.1**	¶
BMI (kg/m^2)	**29.9 ± 5.6**	**33.8 ± 5.8**	¶
SBP (mmHg)	140.5 ± 17.8	140.3 ± 18.0	NS
DBP (mmHg)	79.1 ± 10.7	80.5 ± 11.2	NS
eGFR (mg/dl)[§]	**77.2 ± 24.7**	**82.7 ± 24.8**	¶
LDL (mg/dl)	**102.5 ± 36**	**95.7 ± 33**	¶
HDL (mg/dl)	46.9 ± 15	44.3 ± 14	NS
Triglycerides (mg/dl)	**160.9 ± 99**	**187.9 ± 149**	¶
Uric acid (mg/dl)	5.2 ± 1.6	5.5 ± 4.4	NS
Hematocrit (%)	41.5 ± 6.5	42.8 ± 5.3	NS
Prior treatment:			
Metformin	88.9%	86%	NS
Sulfonylurea/repaglinide	25.3%	27.8%	NS
Pioglitazone	3.8%	3.9%	NS
DPP4	**0%**	**17.2%**	¶
SGLT2 inhibitor	**4.4%**	**0%**	¶
Glucagon-like peptide-1	13.7%	16.8%	NS
Insulin analogues	45.5%	42.4 %	NS

[†]Data presented as mean (± standard deviation).
[‡]Statistically significant differences are marked in bold (t-test for comparing means).
[§]The eGFR was calculated using the CKD-EPI method.
¶% relative frequency.
CKD: Chronic kidney disease; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NS: Not significant; SBP: Systolic blood pressure; SGLT2: Sodium-glucose cotransporter 2.

Table 3. Reduction in weight and HbA1c after 6 months of treatment.[†]

Outcome	Sitagliptin	n	Dapagliflozin	n	Dapa-Sita[‡]
Weight reduction[§]	30.8%	428	64.7%	567	33.9%
HbA1c reduction[¶]	79.3%	430	82.3%	566	3%
Weight + HbA1c reduction	24.4%	427	56.1%	565	31.7%
Weight reduction total	-0.61 kg (80.56 → 79.95 kg)	428	-2.88 kg (92.05 → 89.17 kg)	567	
HbA1c reduction total	-1,43% (8.79% to 7.36%)	430	-1,63% (8.91% to 7.28%)	566	

[†]Statistically significant differences are marked in bold.
[‡]'Dapa-Sita' was calculated as follows: % in dapagliflozin cohort – % in sitagliptin cohort.
[§]Weight reduction was defined as a reduction of ≥1.5 kg after 6 months of treatment.
[¶]HbA1c reduction was defined as a reduction of ≥0.5% after 6 months of treatment.
HbA1c: Glycosylated hemoglobin.

dapagliflozin cohort and sitagliptin cohort, respectively (Figure 1). The difference between the cohorts (31.7%) was statistically significant. Thus, the DAPA-RWE study met its primary objective of showing that at least 10% more patients reached the composite variable of reduction in weight and HbA1c in the dapagliflozin cohort than in the sitagliptin cohort.

Compared with the sitagliptin cohort, more patients in the dapagliflozin cohort achieved a weight reduction of ≥1.5 kg (64.7 vs 30.8%; Figure 1), as well as a reduction in HbA1c (82.3 vs 79.3%; Figure 1), although the difference in HbA1c was not statistically significant (Table 3).

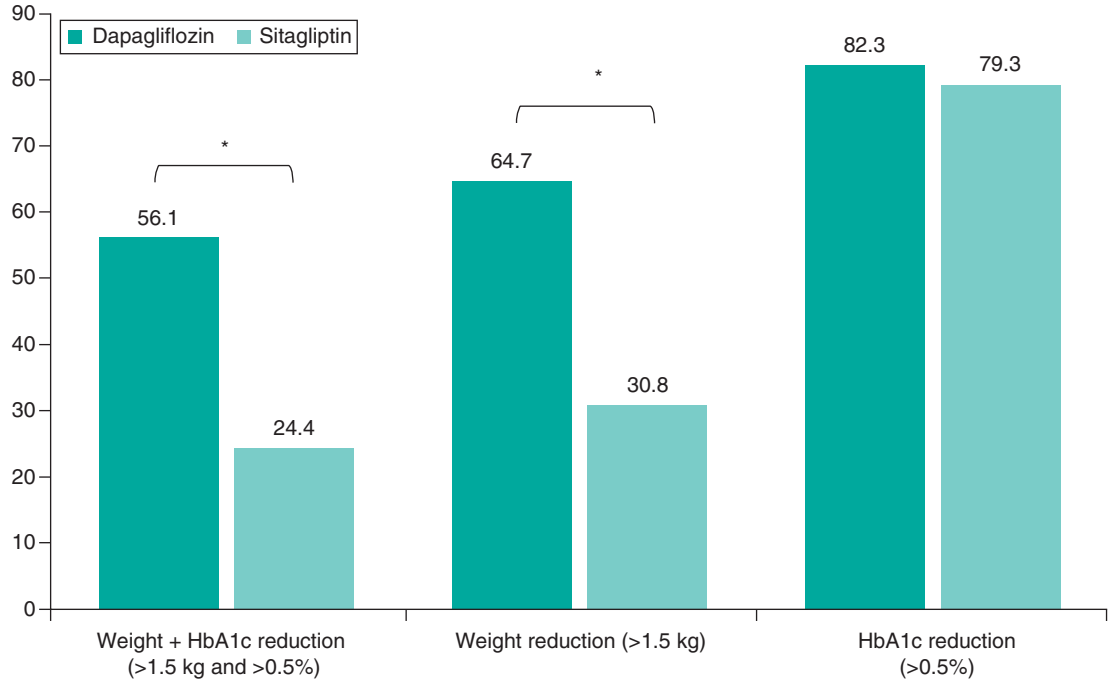

Figure 1. Primary end point (composite: reducing weight ≥1.5 kg and glycosylated hemoglobin [HbA1c] ≥0.5% at 6 months of treatment), weight reduction goal (≥1.5 kg) and HbA1c goal.
*Statistically significant.
HbA1c: Glycosylated hemoglobin.

Weight and HbA1c varied between baseline and the end of treatment. In the dapagliflozin cohort, weight fell from 92.05 to 89.17 kg (i.e., a decrease of 2.88 kg) and HbA1c fell from 8.91 to 7.28% (i.e., a decrease of 1.63 percentage points). Both differences were significant. Similarly, in the sitagliptin cohort, weight fell from 80.56 to 79.95 kg (i.e., a decrease of 0.61 kg) and HbA1c fell from 8.79 to 7.36% (i.e., a decrease of 1.43 percentage points). Both differences were significant.

The differences in weight, age, BMI, eGFR and waist circumference between the cohorts at baseline could be confounding factors, affecting the interpretation of the primary end point, in other words, a composite goal of reduced weight and HbA1c. In order to rule out the possibility that the difference in the primary outcome could be due to the presence of these differences, a propensity score matching analysis was performed. The aforementioned covariates (weight, age, BMI, eGFR and waist circumference at baseline) were entered into the propensity model. In the resulting 54 matched pairs, the composite end point was achieved by 53.7% of patients in the sitagliptin cohort and by 77.8% in the dapagliflozin cohort (Supplementary Table 1). The difference between the cohorts (24.1%) remained statistically significant, thus confirming the result obtained in the unbalanced population.

The incidence of genital and urinary tract infections during the first 6 months of treatment is shown in Supplementary Table 2. While genital and urinary tract infections were almost absent in the sitagliptin cohort (0 and 0.5%, respectively), 34 patients (6.6%) had genital infections and 13 patients (2.5%) had urinary tract infections in the dapagliflozin cohort. No hypoglycemia was reported during the study.

Discussion

The DAPA-RWE study retrospectively analyzed a large, representative population of 1046 T2D patients treated under conditions of routine clinical practice in Spain. The main objective of the study was to compare the effectiveness of the SGLT2i dapagliflozin with that of the DPP4i sitagliptin, based on a composite end point of ≥0.5% reduction in HbA1c and a 1.5-kg reduction in weight after 6 months of treatment. The compound variable was reached by 24.4 and 56.1% of patients, respectively, in the sitagliptin and dapagliflozin cohort. Thus, the DAPA-RWE study achieved its goal of demonstrating the superiority of dapagliflozin over sitagliptin. While it was anticipated that the difference between the cohorts would be around 10%, the observed difference was >30%. Notably, there was no statistically significant difference between the cohorts in terms of a 0.5% reduction in HbA1c.

In a real-world study in Italy, a patient cohort treated with dapagliflozin (n = 751) experienced a 0.7% reduction in HbA1c (±1.2; $p < 0.001$) after 6 months of treatment, while another cohort including several DDP4i (sitagliptin, alogliptin, vildagliptin and saxagliptin; n = 2531) experienced a 0.6% reduction (±1.0; $p < 0.001$) [9]. In the present cohort, the percentage of patients achieving a reduction of at least 0.5% in HbA1c with dapagliflozin was higher than with sitagliptin (82.3 vs 79.3%), although the difference was not statistically significant. However, the composite end point (reduction in weight + HbA1c), was reached by 24.4 and 56.1% of patients in the sitagliptin and dapagliflozin cohort, respectively. This finding was statistically significant.

As expected from an individualized therapy-based approach, the comparison of the baseline characteristics of both cohorts revealed statistically significant differences in clinically meaningful covariates such as weight, age, BMI, eGFR and waist circumference. The imbalance in baseline weight, BMI and waist circumference could be due to a greater decrease in weight loss demonstrated by SGLT2i during clinical development compared with sitagliptin However, this trend was probably observed during the first years on the market, as these baseline characteristics are no longer as relevant when deciding on the best treatment option. Similarly, a retrospective UK study of patients receiving second-line glucose-lowering therapies reported a higher baseline weight in patients who received an SGLT2i [10]. The authors suggested that this might be due to selection of this therapy for more obese patients owing to its established effects on weight, consistent with NICE guidelines. The correlation between baseline weight and weight loss could therefore partly account for the greater weight loss observed with dapagliflozin in the DAPA-RWE study. In order to rule out the possibility that the difference between the dapagliflozin and sitagliptin cohorts was due to the presence of these differences, we performed a propensity score matching analysis, which confirmed that a higher percentage of patients experienced weight loss in the dapagliflozin cohort than in the sitagliptin cohort.

The different types of prior antihyperglycemic treatments received were balanced between the sitagliptin and dapagliflozin cohorts, thus suggesting that the decision to treat a patient either with sitagliptin or with dapagliflozin was not made depending on the patient's prior treatments.

Urogenital infections have been described as adverse reactions of dapagliflozin. According to the summary of product characteristics, these infections are a common reaction, in other words, with a frequency of 1–10%. The incidence of genital and urinary tract infection in the present study was 6.6 and 2.5%, respectively, thus further supporting the external validity of the DAPA-RWE study.

The results of the Spanish DAPA-RWE study show that weight loss is greater in patients treated with dapagliflozin than in those treated with sitagliptin. Moreover, efficacy and safety data were in line with data reported elsewhere.

Conclusion

The DAPA-RWE study provides the first data on the use of dapagliflozin in clinical practice in Spain. The analysis demonstrates the greater effectiveness of dapagliflozin in reducing HbA1c and weight loss compared with sitagliptin and highlights its manageable tolerability and safety profile in a real-world setting in Spain. These findings confirm – and even exceed – the results for effectiveness reported in clinical trials. Furthermore, as T2D is frequently associated with obesity, selection of therapy might also be determined by its effect on weight.

Summary points

- There are few countryspecific, real-world data on the role of cotransporter 2 inhibitors in weight reduction and glycemic control in patients with Type 2 diabetes (T2D).
- DAPA-RWE was a retrospective, multicenter study comparing the efficacy of dapagliflozin versus sitagliptin in T2D patients in Spain.
- More than 1000 patients were included (594 with dapagliflozin, 452 with sitagliptin), mean age 61.8 ± 10.0 and 66.2 ± 11.4 years, HbA1c 8.9 and 8.8%, respectively.
- Dapagliflozin is more effective than sitagliptin at reducing HbA1c and weight in patients with T2D.
- As expected, although the incidence was low, more genital infections occurred in the dapagliflozin cohort.
- No hypoglycemia was reported during the study.
- The results of the DAPA-RWE study confirm – and even exceed – those reported in clinical trials, indicating that dapagliflozin is an excellent option for reducing weight and HbA1c in patients with T2D.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0264

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Ethical conduct of research

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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