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Effectiveness and safety of dapagliflozin in real-life patients: data from the DAPA-RWE Spanish multicentre study

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Abstract

Background: This study aims to evaluate dapagliflozin in patients with type 2 diabetes (T2D) in clinical practice in Spain.

Methods: This is a retrospective study including adults with T2D under stable antidiabetic therapy, with either dapagliflozin or sitagliptin ≥6 months, before inclusion. Data about the effectiveness and safety of dapagliflozin are presented.

Results: A total of 594 patients (61.8±9.9 years, 21.7% cardiovascular disease) were included. After 6 months, HbA1c, weight, blood pressure, urine albumin-to-creatinine ratio and uric acid significantly decreased (1.63%, 2.88 kg, 4.82/2.70 mmHg, −17.38 mg/g and −0.30 mg/dL, respectively), whereas glomerular filtration rate and haematocrit significantly increased (3.72 mL/min/1.73 m^2 and 1.8%, respectively). No cases of hypoglycaemia, diabetic ketoacidosis, Fournier gangrene, fractures or amputations were reported.

Conclusion: Thus, dapagliflozin provides a comprehensive cardiometabolic protection in patients with T2D.

Keywords: clinical practice, dapagliflozin, diabetes, HbA1c, weight.

Citation

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Introduction

It has been estimated that the current prevalence of diabetes is around 10% of the adult population but this number will increase in the following years because of the higher life expectancy and unhealthy lifestyles, including obesity and sedentarism.[1,2] In Spain, the estimated incidence of diabetes adjusted for sex and age is of 11.6 cases per 1000 person-years and that of known diabetes is of 3.7 cases per 1000 person-years.[3] Type 2 diabetes (T2D) increases the risk of both microvascular (renal disease, neuropathy and retinopathy) and macrovascular complications (ischaemic heart disease, heart failure, stroke and peripheral arterial disease).[4]

A comprehensive approach in the management of patients with T2D that includes not only the achievement of glycosylated haemoglobin (HbA1c) goals but also the control of other cardiovascular risk factors, such as blood pressure, hyperlipidaemia or obesity, as well as the use of antihyperglycaemic drugs with proven cardiovascular benefits (i.e. some sodium-glucose cotransporter 2 (SGLT2) inhibitors or some glucagon-like peptide 1 receptor (GLP1R) agonists) is required to reduce the risk of diabetes-associated complications.[5,6]

Metformin is considered as a first-line therapy for T2D. However, a loss of its antihyperglycaemic efficacy over time requiring an intensification of the treatment has been

reported.[7] This observation has also been reported with other antihyperglycaemic drugs such as sulfonylureas.[8,9] In addition, a high number of patients with T2D do not attain the recommended glycaemic targets despite conventional treatments.[10,11] Moreover, traditional antihyperglycaemic drugs (i.e. sulfonylureas or insulin) have been associated with side effects, including weight gain and hypoglycaemia, that may have a negative impact on therapeutic adherence and glycaemic control, leading to worse outcomes.[6,12]

Dapagliflozin is an SGLT2 inhibitor that reduces hyperglycaemia by inhibiting the reabsorption of glucose in the kidney and promoting the excretion of glucose in the urine through an insulin-independent mechanism of action.[13] The DECLARE-TIMI 58 trial demonstrated that, amongst patients with T2D with or at risk of cardiovascular disease, compared with placebo, the addition of dapagliflozin was associated not only with a significant decrease in HbA1c, weight and blood pressure but, more importantly, with a reduction of the combined endpoint of cardiovascular death or hospitalization for heart failure, mainly driven by a decrease in heart failure hospitalizations.[14] Real-life studies are necessary to ascertain whether the results of clinical trials can be translated into clinical practice.[15] Despite some studies analysing the role of dapagliflozin in the management of patients with T2D in routine practice, data from Spain are lacking.[16–19]

The DAPA-RWE study is an observational, retrospective and multicentre study performed with the aim of evaluating the effectiveness and safety of dapagliflozin compared with sitagliptin in patients with T2D in routine clinical practice in Spain.[20] In this study, the effectiveness and safety of dapagliflozin were analysed.

Methods

This was an observational and retrospective study performed in 22 Spanish centres. Patients aged 18 years or older, with T2D under stable therapy with antihyperglycaemic agents, including either dapagliflozin or sitagliptin at least 6 months before inclusion and with a follow-up visit (6±3 months), were included in the study. Patients with type 1 diabetes or with gestational diabetes were excluded. The study was approved by the Research Ethics Committees of the university hospitals Virgen Macarena and Virgen del Rocio from Seville, Spain, and endorsed by all the participating centres. All patients provided written informed consent before any data were collected.

Patients were retrospectively evaluated at three time points: at the start of treatment (baseline), at 6 months (±3 months) of treatment and, if applicable and available, every 6 months (±2 months) of treatment. Evaluable patients included those with complete data at start of treatment (baseline) and at 6 months of treatment (±3 months).

The following variables were recorded at baseline: biodemographic data (age, sex, duration of diabetes), physical examination (weight, waist circumference, body mass index (BMI), blood pressure), cardiovascular risk factors (hyperlipidaemia, obesity, hypertension), vascular disease (ischaemic heart disease, peripheral artery disease, cerebrovascular disease, heart failure), other conditions (chronic kidney disease (CKD), diabetic proliferative retinopathy, non-alcoholic fatty liver disease) and blood and urine analysis (HbA1c, fasting plasma glucose, estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio, complete lipid profile, uric acid and haematocrit). Obesity was defined as a BMI of ≥30 kg/m^2 and CKD as an eGFR of <60 mL/min/1.73 m^2 (calculated by the CKD-EPI method). Hyperlipidaemia was defined as any of the following: total cholesterol >200 mg/dL, LDL cholesterol >100 mg/dL, triglycerides >150 mg/dL or receiving lipid-lowering drugs. In addition, previous antihyperglycaemic treatments were also recorded.

The evolution of the following variables after 6 months of treatment with dapagliflozin *versus* baseline was analysed: HbA1c, fasting plasma glucose, weight, waist circumference, systolic blood pressure, diastolic blood pressure, eGFR, urine albumin-to-creatinine ratio, LDL cholesterol, HDL cholesterol, triglycerides, uric acid, and haematocrit. Moreover, weight and HbA1c reduction, defined as a decrease of at least 1.5 kg and 0.5%, respectively, and the composite goal of reducing HbA1c (≥0.5%) and weight (≥1.5 kg) at 6 months of treatment were also analysed.

The occurrence of side effects, including hypoglycaemia, urinary and genital infections, diabetic ketoacidosis, Fournier gangrene, fractures and amputations, during the study period was evaluated.

Statistical analysis

Categorical variables were presented in frequency (absolute, relative) tables and continuous variables with summary statistics (mean, standard deviation). The evolution of quantitative variables was analysed with the paired Student *t*-test. A level of statistical significance of 0.05 was applied in all the statistical tests. Statistical analyses were performed with the statistical package SPSS® version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 1056 patients with T2D were included in the study from March 2018 to June 2018, 1046 being considered evaluable (452 patients treated with sitagliptin and 594 with dapagliflozin). As a result, the 594 patients treated with dapagliflozin 10 mg daily were analysed in this study.

Baseline clinical characteristics are shown in Table 1. Mean age was 61.8±9.9 years, 56.6% were men and mean BMI was 33.8±5.7 kg/m^2. Cardiovascular risk factors were frequent, with hyperlipidaemia (75.6%), obesity (71.6%) and hypertension (69.4%) being the most common; 21.7% of patients had previous cardiovascular disease, particularly chronic ischaemic heart disease (19.8%). At baseline, the mean HbA1c was

Table 1. Baseline characteristics of evaluable patients treated with dapagliflozin.

Variable	Dapagliflozin (*n*=594)
Biodemographic data	
Age, years	61.8±9.9
Gender, male (%)	56.6
Duration of diabetes, years	13.1±7.8
Physical examination	
Body weight, kg	92.0±17.5
Waist circumference, cm	106.9±18.1
Body mass index, kg/m^2	33.8±5.7
Systolic blood pressure, mmHg	140.3±18.0
Diastolic blood pressure, mmHg	80.5±11.2
Cardiovascular risk factors	
Hyperlipidaemia (%)	75.6
Obesity (%)	71.6
Hypertension (%)	69.4
Vascular disease	
Secondary cardiovascular prevention	21.7
Ischaemic heart disease (%)	14.5
Peripheral arterial disease (%)	6.2
Cerebrovascular disease (%)	5.1
Chronic heart failure (%)	3.7
Other conditions	
Chronic kidney disease, eGFR <60 mL/min/1.73 m^2 (%)	19.8
Diabetic proliferative retinopathy (%)	13.1
Non-alcoholic fatty liver disease (%)	10.4
Blood and urine analysis	
HbA1c, %	8.9±3.2
Fasting plasma glucose, mg/dL	173.9±62.8
eGFR (CKD-EPI), mL/min/1.73 m^2	82.7±24.8
Urine albumin-to-creatinine ratio, mg/g	64.4±23.5
LDL cholesterol, mg/dL	95.7±33.0
HDL cholesterol, mg/dL	44.3±14.0
Triglycerides, mg/dL	187.9±149.0
Uric acid, mg/dL	5.5±4.4
Haematocrit, %	42.8±5.3

eGFR, estimated glomerular filtration rate.

8.9±3.2%, eGFR 82.7±24.8 mL/min/1.73 m^2 and LDL cholesterol 95.7±33.0 mg/dL. With regards to antihyperglycaemic treatments before starting treatment with dapagliflozin, 86.0% of patients were taking metformin, 42.4% insulin, 27.8% sulfonylureas/repaglinide and 17.2% dipeptidyl peptidase 4 (DPP4) inhibitors (Figure 1).

The evolution of different parameters during the 6-month period of treatment with dapagliflozin is shown in Table 2. During this period, HbA1c, weight, systolic/diastolic blood pressure, urine albumin-to-creatinine ratio, LDL cholesterol and uric acid significantly decreased from baseline (1.63%, 2.88 kg, 4.82/2.70 mmHg, –17.38 mg/g, –4.1 mg/dL and –0.30 mg/dL, respectively), whereas eGFR and haematocrit significantly increased (3.72 mL/min/1.73 m^2 and 1.8%, respectively).

After 6 months of treatment with dapagliflozin, 56.1% of patients reached the composite goal of a reduction in weight of ≥1.5 kg and in HbA1c of ≥0.5% (primary endpoint), 64.7% reached the goal of weight reduction ≥1.5 kg, and 82.3% reached the objective of HbA1c reduction ≥0.5% (Figure 2).

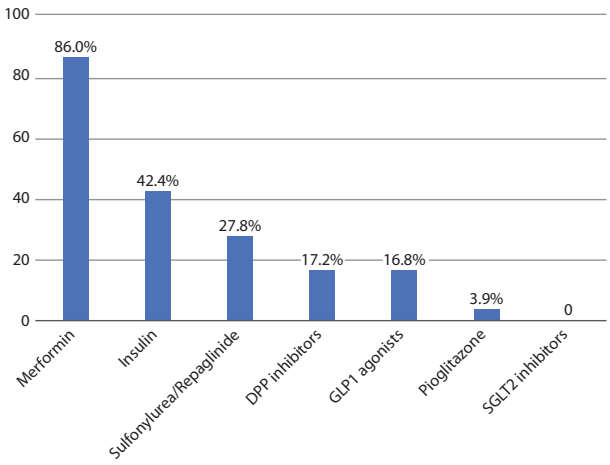
During the first 6 months of treatment with dapagliflozin, genital and urinary tract infections occurred in 5.7% and 2.2% of patients. No cases of hypoglycaemia, diabetic ketoacidosis, Fournier gangrene, fractures or amputations were reported.

Discussion

In this study, the effectiveness and safety of dapagliflozin were analysed in nearly 600 patients with T2D, showing a high capacity of dapagliflozin to reduce HbA1c, weight and blood pressure, and an improvement of renal function after 6 months of treatment in routine practice in Spain.

In our study, at baseline, mean age was 62 years, BMI 34 kg/m^2 and 22% of patients had previous cardiovascular disease. Mean HbA1c was 8.9%, and mean eGFR was 83 mL/min/1.73 m^2. With regards to the antihyperglycaemic treatments before starting treatment with dapagliflozin, 86% of patients were taking metformin and 42% insulin. These results are very similar to those found in the DECLARE-TIMI 58 trial, in which, amongst those patients treated with dapagliflozin, mean age was 64 years, BMI was 32 kg/m^2, and 41% of patients were on secondary

Figure 1. Previous antihyperglycaemic treatments.



DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; SGLT2, sodium-glucose cotransporter 2.

prevention. At baseline, mean HbA1c was 8.3% and eGFR was 85 mL/min/1.73 m^2. In addition, 82% of patients were taking metformin and 42% insulin.[14] These data suggest that the results of the DECLARE-TIMI 58 trial could be applied to clinical practice in Spain. In fact, different studies have shown that the clinical profile of patients attending daily clinical practice is more similar to those included in the DECLARE-TIMI 58 than to those in the EMPA-REG OUTCOME or CANVAS trials. Thus, whereas in EMPA-REG OUTCOME all patients had previous cardiovascular disease (secondary prevention), in CANVAS approximately two-thirds were secondary prevention and one-third were primary prevention patients and, in DECLARE–TIMI 58, 59% of patients had no previous cardiovascular disease.[14,21–24]

In our study, after 6 months of treatment with dapagliflozin, HbA1c and weight significantly decreased from baseline (by 1.6% and 2.9 kg, respectively). As a result, more than half of patients achieved the combined goal of a reduction in weight of ≥1.5 kg and in HbA1c of ≥0.5%. In the DECLARE-TIMI 58 trial, the mean absolute difference during the study between dapagliflozin and the control group regarding HbA1c and weight was 0.42% and 1.8 kg, respectively.[14] Other phase III clinical trials have reported sustained HbA1c and weight reductions of about 0.8% and 2.2–3.1 kg, respectively, with dapagliflozin.[25,26] The magnitude of our results was higher than that observed in clinical trials. Differences in the clinical profile of patients and changes in the treatment during follow-up could have had an impact on the results. However, in the multivariate analysis performed for the primary endpoint of the study comparing sitagliptin *versus* dapagliflozin, different cofactors were studies (i.e. BMI, antidiabetic treatment), and no impact on the results was found.[20] On the other hand, as, for inclusion, patients needed to be taking dapagliflozin for at least 6 months, this may overestimate the real efficacy and side effects could be underestimated, as responders to treatment could be selected. In routine practice, DARWIN-FUP was a retrospective study that compared the effectiveness of dapagliflozin *versus* DPP4 inhibitors on the cardiometabolic profile. The primary endpoint of attaining a simultaneous reduction of HbA1c ≥0.5%, body weight ≥2 kg and systolic blood pressure ≥2 mmHg was attained in 17.6% of patients taking dapagliflozin and in 11.7% of patients taking DPP4 inhibitors (RR 1.50, 95% CI: 1.21–1.86; $p<0.001$). In the intention to treat analysis, dapagliflozin significantly reduced HbA1c by 0.6% and body weight by 2.7 kg.[19] DARWIN-T2D was an Italian multicentre retrospective study that showed that dapagliflozin reduced HbA1c by 0.7% and weight by 2.7 kg.[16] All these data indicate that, in clinical practice, the effectiveness of dapagliflozin on glycaemic control and weight is consistent with clinical trials, including the Spanish population. Although in recent years glycaemic control has improved amongst patients with T2D,[27,28] there is much room for improvement.[29] In this context, the early addition of dapagliflozin may be very helpful to attain recommended targets as delaying the intensification of treatment may increase the risk of developing vascular complications.[30]

More than two-thirds of patients with T2D have hypertension. The coexistence of hypertension and T2D markedly increases the risk of developing microvascular complications as well as cardiovascular outcomes.[31] Although lifestyle interventions, together with antihypertensive treatment, are essential to reduce cardiovascular risk,[31] some antihyperglycaemic drugs could provide an additional benefit on attaining blood pressure goals. In our study, dapagliflozin significantly reduced systolic and diastolic blood pressure by about 4.8 and 2.7 mmHg, respectively, after only 6 months of treatment. In the DECLARE-TIMI 58 trial, the difference in the reduction in blood pressure between groups was 2.7 and 0.7 mmHg, respectively.[14] In other phase III clinical trials, this reduction ranged from 1.8 to 5.1 mmHg for systolic blood pressure and from 0.5 to 1.2 mmHg for diastolic blood pressure.[25,26] In the DARWIN-T2D study, dapagliflozin reduced systolic blood pressure by 3.0 mmHg.[16] In a recent clinical trial, dapagliflozin significantly reduced ambulatory brachial and central blood pressure levels and improved arterial stiffness parameters in patients with T2D.[32] Although all the studies consistently showed significant reductions in blood pressure values with dapagliflozin, the differences between them could be partially related with disparities in weight reduction.

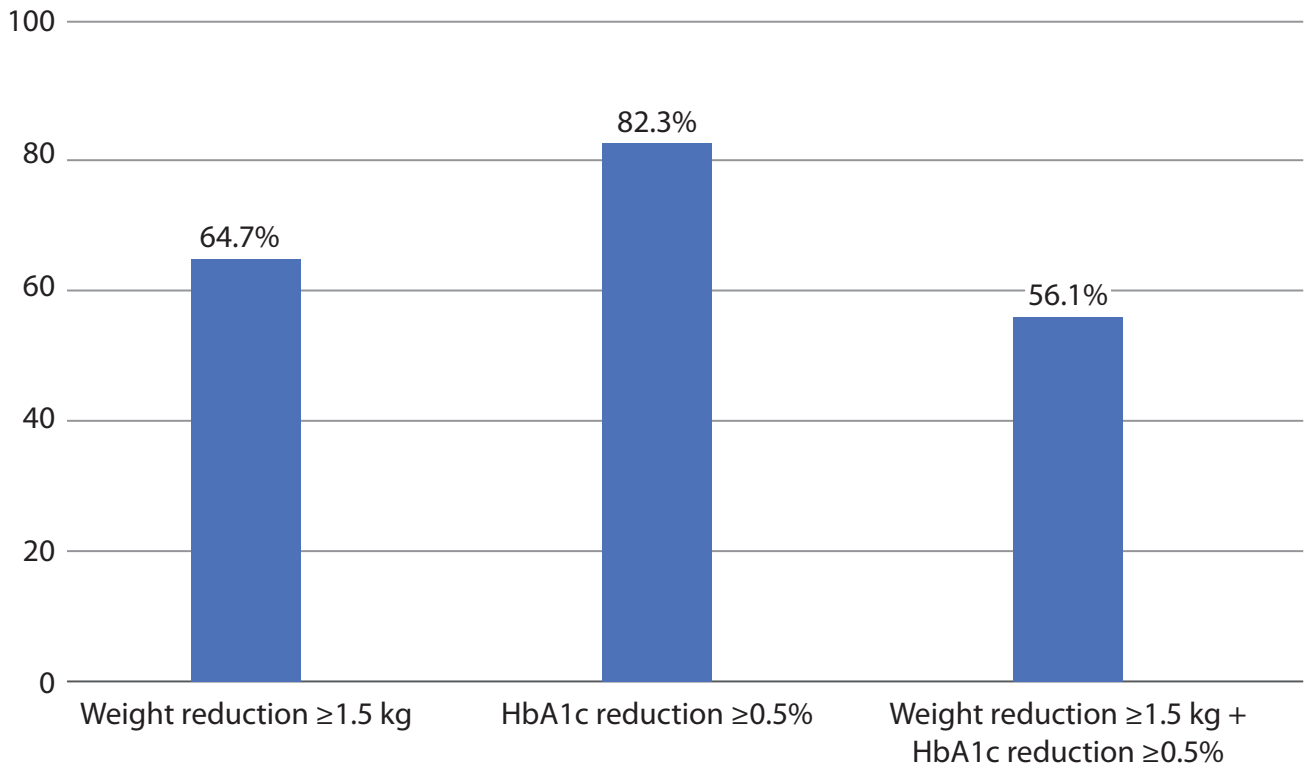
Elevated LDL cholesterol markedly increases the risk of atherosclerotic cardiovascular disease in T2D. Although the cornerstone to reduce this risk is the use of statins, some antihyperglycaemic drugs could also be useful to decrease LDL cholesterol levels.[33] In our study, after 6 months of treatment, dapagliflozin was associated with a small reduction in LDL cholesterol. Different meta-analyses have shown that treatment with SGLT2 inhibitors is associated with a reduction of LDL cholesterol of about 0.2–2.3 mg/dL.[34,35] In this context,

Table 2. Mean change of different variables after 6 months of treatment with dapagliflozin.

Variable	Baseline	Mean change after 6 months	*p* value
Glycaemic parameters			
HbA1c, %	8.9±3.2	−1.63	<0.05
Fasting plasma glucose, mg/dL	173.9±62.8	−39.35	<0.05
Physical examination			
Weight, kg	92.0±17.5	−2.88	<0.05
Waist circumference, cm	106.9±18.1	−3.24	<0.05
Systolic blood pressure, mmHg	140.3±18.0	−4.82	<0.05
Diastolic blood pressure, mmHg	80.5±11.2	−2.70	<0.05
Renal parameters			
eGFR (CKD-EPI), mL/min/1,73 m^2	82.7±24.8	+3.72	<0.05
Urine albumin-to-creatinine ratio, mg/g	64.4±23.5	−17.38	<0.05
Lipid parameters			
LDL cholesterol, mg/dL	95.7±33.0	−4.1	<0.05
HDL cholesterol, mg/dL	44.3±14.0	+1.2	<0.05
Triglycerides, mg/dL	187.9±149.0	−24.4	<0.05
Other biochemical parameters			
Uric acid, mg/dL	5.5±4.4	−0.30	<0.05
Haematocrit, %	42.8±5.3	+1.8	<0.05

eGFR, estimated glomerular filtration rate.

Figure 2. Proportion of patients reaching weight reduction ≥1.5 kg, glycosylated haemoglobin (HbA1c) ≥0.5%, and the composite goal of reducing weight ≥1.5 kg and HbA1c ≥0.5% (primary endpoint) after 6 months of treatment with dapagliflozin.



although the reduction was modest, dapagliflozin could be beneficial to achieve better lipid control.

It has been reported that chronic hyperuricaemia is an independent risk factor for diabetic CKD and cardiovascular disease.[36,37] In our study, dapagliflozin significantly reduced uric acid by 0.3 mg/dL. This is in line with previous studies that have shown a reduction of uric acid with dapagliflozin up to 0.9 mg/dL.[25,26] On the other hand, as in our sample, other studies have shown an increase in haematocrit, likely not only due to the diuretic effects and haemoconcentration of dapagliflozin but also because of the suppression of hepcidin and the modulation of other iron regulatory proteins.[25,26,38]

Of note, after 6 months of treatment, dapagliflozin significantly reduced the urine albumin-to-creatinine ratio and improved eGFR. This sustained benefit has also been confirmed in clinical trials and meta-analyses.[25,26,39] In addition, the DECLARE-TIMI 58 trial demonstrated that dapagliflozin had a beneficial effect on renal events, with a significant reduction of 24% in the composite endpoint of ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, new end-stage renal disease, or death from renal or cardiovascular causes.[14] This positive effect has also been observed amongst patients with CKD (DAPA CKD trial) regardless of the presence or absence of diabetes.[40] On the other hand, although a decline in renal function has been observed with SGLT2-inhibitors during the first months of treatment,[14,40] it should be considered that, in our study, patients had been treated with dapagliflozin for at least 6 months before inclusion, and that data of renal function at baseline and after 6 months of follow-up were reported.

With regards to side effects, during the first 6 months of treatment with dapagliflozin, genital and urinary tract infections occurred in 5.7% and 2.2% of patients but no cases of hypoglycaemia, diabetic ketoacidosis, Fournier gangrene, fractures or amputations were reported. This good safety profile shown in our study is consistent with the incidence of side effects reported in all clinical trials with dapagliflozin, indicating that, in clinical practice, dapagliflozin can be safely used.[14,41–43]

This study has some limitations. As this was a retrospective study, no control group was available, reducing the generalizability of the results. However, this is the best design to ascertain the effectiveness and safety of a drug in clinical practice as no additional intervention was performed for inclusion in the study. As this was an observational and retrospective study, changes in antidiabetic treatment could have been performed, with a possible impact on the results. However, according to clinical practice, these changes would be small. Furthermore, concomitant treatment (i.e. antihypertensive drugs, lipid-lowering drugs) was not recorded. Finally, this was a multicentre study performed in Spain; although this could reduce the application of the results to other environments, the fact is that our results were consistent with those observed in clinical trials and real-life studies.

Conclusion

In clinical practice, after 6 months of treatment, dapagliflozin significantly decreases HbA1c, BMI, blood pressure, urine albumin-to-creatinine ratio, LDL cholesterol and uric acid, whereas eGFR and haematocrit significantly increase, with an excellent safety profile. Thus, dapagliflozin can be considered an excellent option for the comprehensive management of patients with T2D.

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