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Dapagliflozin acutely improves kidney function in type 2 diabetes mellitus. The PRECARE study

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ABSTRACT

Dapagliflozin has been demonstrated to improve glycemic control, blood pressure, and body weight in type 2 diabetes mellitus (T2D); indeed, it can also reduce the risk of progression to renal failure, of hospitalization for heart failure and of cardiovascular death. We aim to investigate the acute effect of Dapagliflozin on kidney function in the common clinical practice in T2D. This is a study including 1402 patients with T2D recruited from 11 centers in Lombardia, Italy, who were evaluated at baseline and after 6 months of treatment with Dapagliflozin 10 mg per day. The primary outcome of the study was the change in HbA1c, while the secondary outcomes were modification of weight, BMI, systolic and diastolic pressure, creatinine, eGFR and albuminuria status. After 24 weeks of treatment with Dapagliflozin, a reduction in Hb1Ac was observed ($-0.6 \pm 1.8\%$) as well as in BMI (-1.5 ± 5.2 kg/m^2). Statistically significant changes were also found for systolic and diastolic blood pressure, cholesterol and triglycerides. Interestingly, a statistically significant acute improvement of kidney function was evident. Our analyses confirm the beneficial effects of dapagliflozin after 6 months of therapy, with improvements of glycemic and lipid profiles, blood pressure, BMI. Finally, an acute positive effect on albuminuria and KIDGO classes was observed during a 6 months treatment with dapagliflozin in patients with T2D.

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1. Introduction

Type 2 diabetes mellitus (T2D) is a chronic and progressive metabolic disorder whose etiology is characterized by insulin resistance and a relative deficiency of insulin secretion with a progressive decline in β-cell function [1,2]. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a class of drugs that reduces glucose reabsorption in the proximal convoluted tubule of the kidney, thereby enhancing urinary glucose excretion [3,4]. SGLT2 inhibitors have been shown to have important extra-glycemic effects, in particular inducing blood pressure reduction, weight loss and improving cardio-renal outcomes in T2D [5–8]. Several studies demonstrated that SGLT2 inhibitors can reduce rates of death, cardiovascular events and hospitalization due to hearth failure among patients with T2D [9–12]. Furthermore, the impact on kidney function of this class of drugs has been demonstrated in large cardiovascular outcome trials, with empagliflozin, canagliflozin, and dapagliflozin slowing the rate of decline of eGFR and reducing albuminuria [13–15]. Dapagliflozin is a selective inhibitor of the SGLT2, approved as therapy in T2DM both in combination with other oral antidiabetic agents, glucagon-like peptide 1 (GLP1) receptor agonists or insulin, and as monotherapy [16,17]. Numerous studies have confirmed the efficacy of dapagliflozin in achieving improved glycemic control, weight loss and lower blood pressure [18–20]. Recent studies have also shown that the potential of dapagliflozin extends far beyond its hypoglycemic effect, being able to reduce the risk of renal failure, hospitalization for heart failure (HHF), major adverse cardiovascular event (MACE), cardiovascular death (CVD) and death from all causes. Indeed, in the DAPA-CKD multicenter trial, dapagliflozin reduced albuminuria by an average of 30% within the first two weeks and progression of renal disease by 36% in all patients; this study demonstrated that among patients with chronic kidney disease, regardless of the presence or absence of T2D, the risk of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo [21]. The DECLARE-TIMI58 clarified the role of dapagliflozin in cardiovascular diseases: the study demonstrated a reduction in one of the dual primary composite outcomes of CVD/HHF (hazard ratio 0.83, 95% CI 0.73–0.95), driven by a reduction in HHF, and also met the prespecified criterion for noninferiority, but did not achieve statistically significant superiority with respect to the second dual primary outcome of MACE (HR 0.93, 95% CI 0.84–1.03); moreover, the renal-specific outcome was significantly reduced with dapagliflozin (HR 0.53, 95% CI 0.43–0.66). Interestingly, the results of this study not only confirm the efficacy of SGLT2 inhibitors in patients with T2D and established cardiovascular disease, but for the first time they have been shown to reduce the risk of death from a cardiovascular event or heart failure even in patients with DM2 and high cardiovascular risk in primary prevention [9]. The aim of this study is to evaluate the acute benefits of dapagliflozin on renal outcomes in patients with T2D, in the real clinical practice.

2. Research design and methods

PRECARE study is an observational, multicenter study, aimed at investigating the therapeutic efficacy at 6 months (February 27, 2021 - December 31, 2021) of a treatment with Dapagliflozin 10 mg 1 tablet per day in patients with T2D from 11 Diabetes Centers in Lombardia, Italy. The participant centers were: Sacco and Fatebenefratelli (Milan) (coordinating centers), Monzino Hospital (Milan), IRCC Ca' Granda Policlinico (Milan), San Paolo Hospital (Milan), San Carlo Hospital (Milan), Multimedica Sesto San Giovanni Hospital, Papa Giovanni Hospital (Bergamo), San Matteo Hospital (Vigevano), San Giuliano Milanese Hospital, Spedali Civili Hospital (Brescia). The inclusion criteria were: (a) age > 18 years old, diagnosis of T2D, according to ADA indications for at least 3 months [4] stable therapy for at least 3 months with oral hypoglycemic agents or insulin and Dapagliflozin. Patients with the following characteristics were excluded from the study: (b) mental incapacity, unavailability or language barriers that preclude adequate understanding or cooperation; diagnosis of type 1 diabetes mellitus, MODY (maturity-onset diabetes of the young), LADA (latent autoimmune diabetes in adults), gestational diabetes mellitus, secondary diabetes mellitus or any other hyperglycemic state other than T2D; (c) women who were pregnant or breastfeeding, or women planning to become pregnant; (d) previous participation in the study or participation in another clinical study on T2D that includes any clinical intervention or administration of an investigational drug within 3 months prior to enrollment in the study. The following data were collected at the baseline visit and after 6 months of treatment: duration of the disease, weight, height, BMI, waist circumference, eGFR (according to CKD-EPI), heart rate, blood pressure, glycated hemoglobin (HbA1c), fasting blood sugar, total cholesterol, HDL cholesterol, triglycerides, calculated LDL cholesterol, creatinine, urinary albumin to creatinine ratio (ACR) (mg/g), presence of diabetic retinopathy, positive anamnesis of ischemic heart disease, heart failure, cerebral vascular disease (TIA, stroke), peripheral vascular disease, TSA vascular disease, PRE-visit hypoglycemic therapy. In the follow-up visit some additional data were collected, including side effects and drug suspension. The primary outcome measure was the change in HbA1c from baseline to 6 months of follow-up. The secondary outcome measures were changes in fasting glycemia, body weight, BMI, systolic and diastolic pressure, heart rate, creatinine, eGFR and albuminuria. Normoalbuminuria is defined with an ACR < 30 mg/g or with an albumin excretion rate (AER) < 30 mg/24 h, microalbuminuria with an ACR between 30 and 299 mg/g or with an AER of 30–299 mg/24 h, and macroalbuminuria with ACR> 300 mg/g or AER> 300 mg/24 h. All data collected on patients have been entered in electronic printouts and analyzed using the GraphPad Prism statistical software (version 8). In cases of drop-out, only the data available up to the time of drop-out have be considered for the analysis. No source data verification has been performed. For all the variables considered in the study, the normality of the distribution has been evaluated by means of the Kolmogorov-Smirnov test. Continuous variables have been described by standard deviation of the mean, while categorical ones have been described by frequency expressed in %. The longitudinal variations have been statistically evaluated using the student's t-test as regards the normally distributed variables, while the Wilcoxon signed-rank test has been used for those not normally distributed. Levels of significance has been considered for p values < 0.05. Multivariable logistic regression was used to model the relationships between co-factors and the albuminuria/proteinuria measured at the follow-up (Stata version 12; StataCorp). Data collection and analysis were approved by the Institutional Review Board (Protocol ID 2022002; Luigi Sacco Hospital, University of Milan). The trial is registered in Trialgov.com (NCT0518946).

3. Results

3.1. Characteristics of patients

We analyzed the data from a total number of 1402 patients (480 M, 922 F), with 1073 of which were re-evaluated at 6 months, being 367 (36.5%) females and 692 (64.5%) males. Our study population had a mean age of 65.8 ± 10.1 years and a median duration of diabetes of 8.2 ± 7.4 years. Median HbA1c at the start of the study for the whole group was 7.7 ± 1.2% and median BMI 29.8 ± 4.9 kg/m^2. Complete baseline characteristics are shown in Table 1. Regarding the BMI, 18.5% of the population was normal weight, 41.4% overweight (BMI between 25 and 29 kg/m^2), 35.0% had grade I-II obesity (BMI between 30 and 40 kg/m^2), 5.1% grade III obesity (BMI> 40 kg/m^2). Baseline data of major vascular events, including stroke, myocardial infarction and obliterating arterial disease of the lower limbs, showed that 48.2% of patients had a positive history for them; of these, 25.9% of subjects had a single event, 17.5% two events, and 1.9% three or more events. Patients who had a

Table 1
Baseline characteristics of the group of patients with T2D.

Parameter	Value
Age (mean)	65.8 ± 10.1 yrs
Gender	F 34.3% (480)
	M 65.7% (922)
Ethnicity	Cau 91.0% (1263)
	As 3.0% (44)
	Af 3.0% (45)
	Lat 3.0% (32)
Smokers	Yes 15.0% (208)
	No 60.0% (841)
	Ex 25.0% (353)
Hypertension	Yes 80.0% (1120)
	No 20.0% (282)
Dyslipidemics	Yes 76.0% (1060)
	No 24.0% (342)
T2D duration	8.2 ± 7.4 yrs
BMI	29.8 ± 4.9 kg/m2

Abbreviations. Yrs: years; F: female, M: male; Cau: Caucasian, As: Asiatic, Af: African, Lat: lLatin; BMI: body mass index.

history of myocardial infarction were 227 (21.2%), 118 of lower limb vasculopathy (11.0%), and 46 of stroke (4.3%). More than one third of patients (33.4%) had heart failure, of which 16.8% in New York Hearth Association (NYHA) class I, 11.6% in NYHA class II, the 4.3% in NYHA III class, and only 0.6% in NYHA IV class. 60.2% of patients had detectable albuminuria, classified as micro- or macroalbuminuria. More than half of patients had some degree of chronic kidney disease (CKD), with 46.5% of the total in stage 2 (GFR-EPI between 60 and 90), 12.4% had stage 3a (GFR between 45 and 60), 3,0% in stage 3b (GFR between 30 and 45). Subdividing the subjects according to the KDIGO classification, the patients were distributed as follows: 316 patients were in the Group 1, including subjects at low risk (GFR> 60 ml/min/1.73 m2 and ACR <30 mg / g); 315 in the Group 2, including patients at moderate risk (GFR> 60 ml/min/1.73 m2 and ACR 30–300 mg/g or GFR 45–59 ml/min/1.73 m2 and ACR <30 mg / g); 145 in the Group 3, including subjects at high risk and very high risk (GFR> 60 ml /min/1.73 m2 and ACR> 300 mg/g or GFR 45–59 ml/ min/1.73 m2 and ACR 30–300 mg/g or GFR 30–45 ml/min/1.73 m2 and ACR <30 mg/g or GFR 45–59 ml/ min/1.73 m2 and ACR> 300 mg/g). Regarding the stratification of cardiovascular risk, the ESC/EASD classification was used based on the presence of established atherosclerotic disease, organ damage (proteinuria, eGFR <30 ml/min/1.73 m^2, left ventricular hypertrophy, retinopathy) or major cardiovascular risk factors (age, smoking, obesity, hypertension, dyslipidemia). The stratification provides for the subdivision of people with DM into three groups: very high risk (10-year event risk> 10%), high risk (between 5% and 10%) and moderate risk (<5%). Among our patients 18.1% were in moderate risk, 60.0% in high risk and 18.9% in very high risk. In summary, our population was at high renal and cardiovascular risk.

3.2. Follow up

A reduction of Hb1Ac from 7.7 ± 1.2–7.1 ± 0.8% (Delta −0.6%, Fig. 1) was observed after 6 months of therapy with dapagliflozin, with 83.7% of patients being responders to therapy (n = 901). BMI reduced from 29.8 ± 4.9–28.3 ± 5.5 mg/m^2 (Delta −1.5 mg/m^2). A statistically significant change was also observed for other extra glycemic cardio-

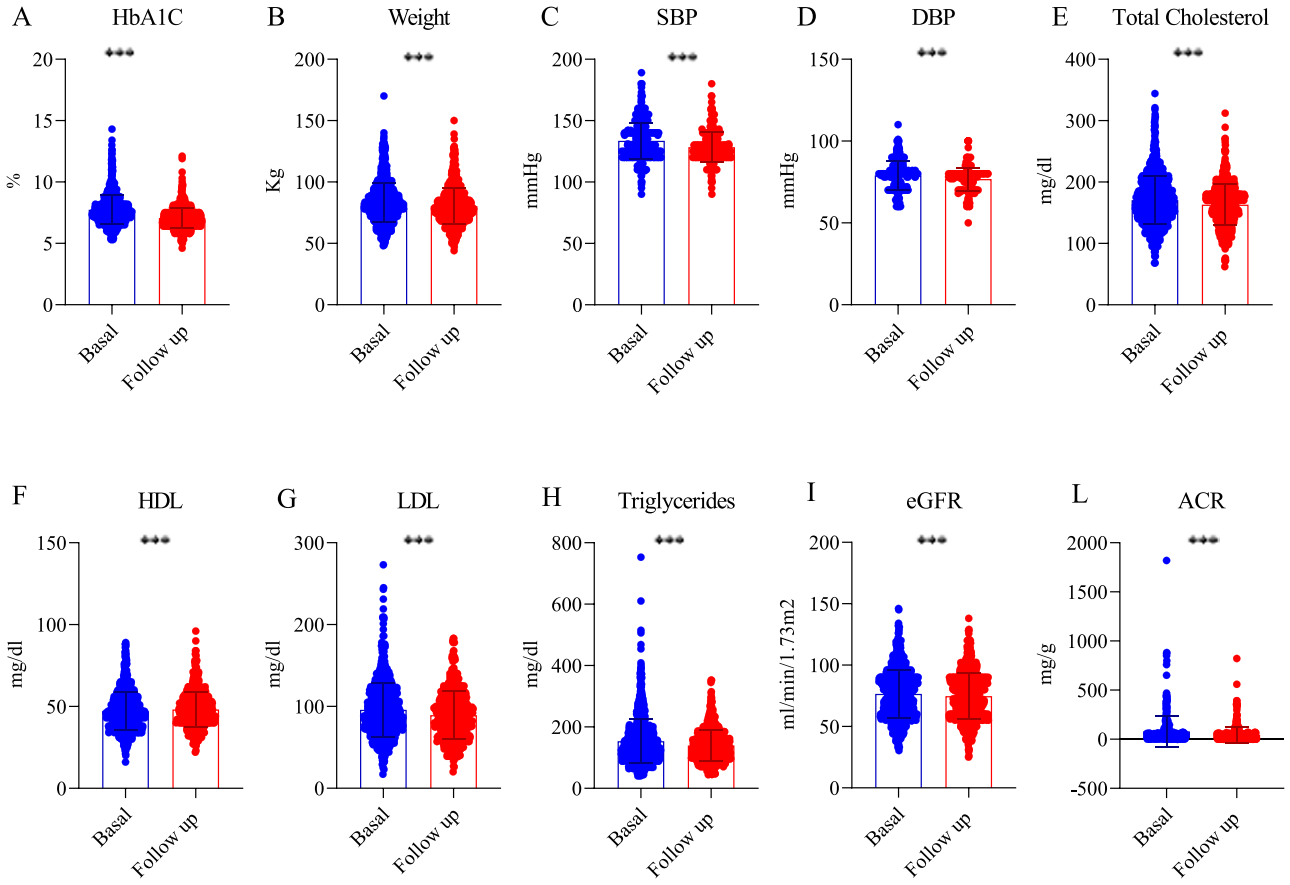

Fig. 1. Graphic representation of the modification of the main parameters analyzed at follow-up. Abbreviations. Hb1Ac: glycated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; eGFR: estimated glomerular filtration rate; ACR: albumin/creatinine ratio. Data are reported as mean ± SD. P < 0.05*; P < 0.01**; P < 0.001***; NS non statistically significant.

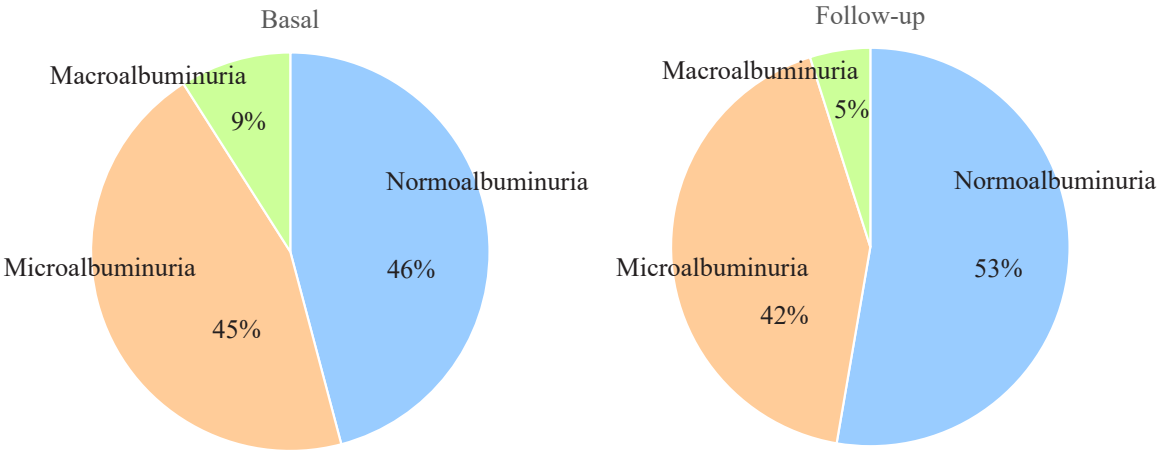

Fig. 2. Class changes of albuminuria at 24 weeks of treatment.

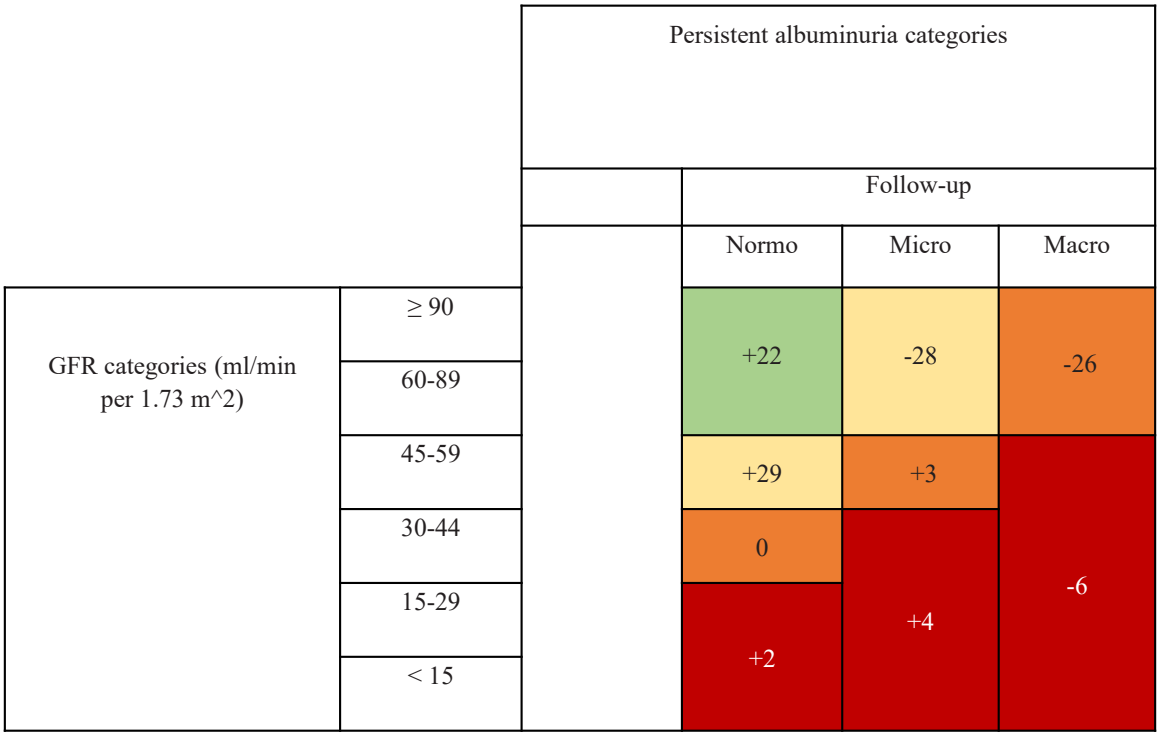

Fig. 3. Delta variation for each KDIGO renal impairment class at follow up. Abbreviations. GFR: glomerular filtration rate; Normo: normoalbuminuria; Micro: microalbuminuria; Macro: macroalbuminuria. Legend. low risk moderately increased risk high risk very high risk.

vascular risk factors. Systolic blood pressure decreased from 133.5 ± 14.6–128.8 ± 11.9 mmHg (Delta −4.7 mmHg), diastolic blood pressure decreased from 79.0 ± 8.5–76.9 ± 7.0 (Delta −2.1 mmHg). As for the lipid profile, a statistically significant change was found for total cholesterol, LDL and triglycerides, which respectively decreased on average by 7.3 mg/dl, 6.6 mg/dl and 14.0 mg/dl respectively; HDL cholesterol, on the other hand, increased significantly by 1 mg/dl (Fig. 1). Moreover, we observed a statistically significant reduction in albuminuria with dapagliflozin. The ACR decreased from a mean value of 79.4 ± 160.3 at baseline to 45.6 ± 79.6 mg/g after 6 months. A small reduction in GFR was also observed, going from a mean of 76.5 ± 19.2–74.8 ± 18.5 ml/min/1.73 m2 at 6 months. The percentage of patients with normoalbuminuria increased from 46.0% to 53.0%, together with an important reduction of macroalbuminuria (from 9.0% to 5.0%, Fig. 2). No age effect was observed since dapagliflozin was similarly effective in reducing albuminuria levels in all age groups. A modification of the KDIGO risk classes was also observed: at follow-up the patients in Group 1 went from 316 to 338, in Group 2 from 315 to 316 and in Group 3 from 145 to 122 (Fig. 3). At 6 months, the percentage of very high/high-risk patients decreased from 19.0% to 17.0%, with a statistically significant reduction in the overall class of risk. The reduction in albuminuria was positively correlated with the reduction in total cholesterol

Table 2
Clinical and biochemical changes after 6 months of follow-up.

Parameter	Baseline mean ± SD	Follow-up mean ± SD	Mean reduction	P value
HbA1c (%)	7.7 ± 1.2	7.1 ± 0.8	-0.6	p < 0.0001
FPG (mg/dl)	155 ± 44	132 ± 26	-23	p < 0.0001
Weight (kg)	83.2 ± 16.1	80.4 ± 15.0	-2.8	p < 0.0001
BMI (kg/m2)	29.8 ± 4.9	28.3 ± 5.5	-1.5	p < 0.0001
SBP (mmHg)	133.5 ± 14.5	128.5 ± 11.9	-5.0	p < 0.0001
DBP (mmHg)	79.0 ± 8.5	76.9 ± 7.0	-2.1	p < 0.0001
Total Cholesterol (mg/dl)	170.5 ± 39.2	163.2 ± 33.2	-7.3	p < 0.0001
HDL (mg/dl)	47.2 ± 11.6	48.2 ± 10.1	+1.0	P < 0.0001
LDL (mg/dl)	96.0 ± 33.0	89.4 ± 29.0	-6.6	p < 0.0001
Triglycerides (mg/dl)	153.4 ± 72.0	139.4 ± 50.9	-14.0	p < 0.0001
eGFR (ml/min/1.73 m2)	76.5 ± 19.2	74.8 ± 18.5	-1.7	p < 0.0001
ACR (mg/g)	79.4 ± 160,3	45.6 ± 79.6	-34.4	p < 0.0001
Albuminuria (mg/l)	61.6 ± 117.2	36.5 ± 60.5	-25.1	p < 0.0001
AER (mg/24 h)	144.0 ± 295.2	127.0 ± 287.7	-17.0	p < 0.0001

Abbreviations. Hb1Ac: glycated hemoglobin; FPG: fasting plasmatic glucose; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; eGFR: estimated glomerular filtration rate; ACR: albumin/creatinine ratio; AER: albumin excretion rate.

(p 0.01), and inversely related in eGFR reduction (p 0.004) and duration of diabetes ($p < 0.001$). The presence of a simultaneous improvement of two or more cardiovascular risk factors was also analyzed. An improvement in blood pressure was observed in 48% of patients. The percentage of patients receiving rapid insulin decreased from 18.7% to 14.4%, basal insulin from 36.5% to 34.8%, sulfonylurea from 15.1% to 3% and glinides from 2.3% to 0.4%. All the main changes found at follow up are summarized in Table 2.

4. Conclusions

In this observational multicenter study, Dapagliflozin improved glycemic profile, blood pressure, BMI and lipid profile. Interestingly, Dapagliflozin acutely improved renal function, with a reduction in albuminuria and an improvement in KIDGO classes. Trials of SGLT2 inhibitors have largely demonstrated glycemic and extra-glycemic benefits of this class of drugs irrespective of baseline cardiovascular risk [22]. As far as the primary outcome, the mean reduction in Hb1Ac observed was 0.7 ± 1.8% after 6 months of treatment with Dapagliflozin. This finding is in line with the literature on Dapagliflozin; indeed after 24 weeks of treatment glycated hemoglobin was reduced by 0.89% [16], with a higher decrease when Dapaglifozin was added to a pre-existing anti-diabetic therapy [17,18]. We confirmed a significant reduction in systolic, diastolic blood pressure and total cholesterol, triglyceride, HDL and LDL cholesterol, in line with several studies [23–25]. As regards the effect on blood pressure, our data seems in line with what is reported in the literature [26]. In our patient population, the reduction in systolic and diastolic blood pressure was respectively − 5.0 and − 2.1 mmHg, which is generally higher than those observed in literature, possibly because of a higher prevalence of hypertensive subjects in our cohort. The use of dapagliflozin leads to a substantial reduction in the use of hypoglycemic drugs, such as insulin and sulfonylureas, which represents an interesting clinical fact as these therapies expose the patient to hypoglycemia and induce weight gain. SGLT2 inhibitors have consistently demonstrated improvements in renal and cardiovascular outcomes [27–29], including both normalization of pre-existing albuminuria and reduction of conversion from normo- to micro or macroalbuminuria. Furthermore, SGLT2 inhibitors have been shown to slow the decline of eGFR and to induce a reduction of end-stage renal disease [13,30]. Our data suggests an acute improvement of kidney function following the use of SGLT2-I, with a particular benefit on albuminuria. Stratifying the patients by age, we observed that in both age groups Dapagliflozin is similarly effective in reducing albuminuria levels, therefore the effect of the drug would not seem to be influenced by the age and by the severity of the albuminuria. On the contrary, the levels of proteinuria at follow up were higher in patients who had experienced a greater reduction in GFR at 6 months, with a worsening of the risk class in these patients. The lipid profile also influenced the albuminuria data: an improvement in total cholesterolemia favors a greater reduction in albuminuria at 6 months, demonstrating that the correction of cardiovascular prevention factors also has an influence on the improvement of renal function. The fact that a longer duration of diabetes leads to a more unfavorable outcome on albuminuria underlines the importance of early intervention with drugs that can prevent worsening of renal function in these patients. As far as eGFR, dapagliflozin was reported to decrease eGFR in the first 2 weeks of treatment, with a subsequent slowing of the decline of renal function in patients with and without T2D. In the DAPA-CKD study, it was observed that an acute decline in renal function occurred at 2 weeks of treatment in the dapagliflozin group compared to placebo [31]. Interestingly, we observe a small reduction of eGFR (1.7 ml/min/1.73 m2) in our patient population. This is likely since the initial decline in GFR due to vasoconstriction of the afferent arteriole occurs earlier in the first weeks of treatment, whereas our analysis was conducted at 6 months, when the acute decrease in eGFR was eventually already resolved and the drug has already begun to exert its nephro-protective effect, slowing the progression of kidney disease. Of note, we also observed that after only 6 months of treatment a reduction in the renal risk class according to the KDIGO classification was evident, with a transition of patients from the very high/high risk classes to the moderate/low risk classes. This observation demonstrates that the reduction in the risk of chronic renal failure is significantly reduced by Dapagliflozin acutely in the first months of therapy. It is well demonstrated that the nephroprotective effect of Dapagliflozin extends beyond the glucose-lowering, weight-lowering and blood pressure-lowering effects that parallel the glycosuric action. A key mechanism of SGLT2 receptor inhibition is the action of Dapagliflozin on tubule-glomerular feedback, when sodium is sensed by the macula cells thus constricting afferent glomerular arterioles, thereby protecting glomeruli by reducing intraglomerular pressure. Among the effects of SGLT2 inhibition there is also the improvement of tubular oxygenation and metabolism and the reduction of renal inflammation and fibrosis [32]. This observational study confirmed that in clinical practice, the glycemic and extra-glycemic beneficial effects of Dapagliflozin occurred acutely after few months of therapy, with an improvement of the glycemic profile, blood pressure, BMI and lipidic profile. Particularly interesting was the result on renal function, which highlighted an already striking effect of this drug after 6 months of treatment on albuminuria, with a reduction in the severity class and in 4% of cases disappearance of proteinuria. In conclusion, the use of Dapagliflozin in the clinical practice leads to a reduction in nephro-cardiovascular risk in patients with type 2 diabetes.

CRediT authorship contribution statement

Elisa Lazzaroni, Francesca D'Addio, Moufida Ben Nasr, Cristian Loretelli, analyzed data and wrote the paper. **Maria Elena Lunati, Laura Montefusco, Ida Pastore, Enrica Chebat, Vincenzo Cimino, Paola Silvia Morpurgo, Milena Muratori, Laura Plebani, Andrea Bolla, Antonio Rossi, Luciana Vallone, Alessandra Gandolfi, Camilla Tinari, Francesca D'Addio, Moufida Ben Nasr, Cristian Loretelli, Cristiana Scaranna, Rosalia Bellante, Roberto Manfrini, Fabrizio Muratori, Ivano Franzetti, Emanuela Orsi, Carmine Gazzaruso, Renata Ghelardi, Paolo Desenzani, Stefano Genovese, Angela Girelli, Franco Folli, Cesare Berra** enrolled patients in the study and collected data. **Maria Elena Lunati and Enrica Chebat** coordinated and designed research and edited the paper. **Paolo Fiorina** conceived the idea, designed the study, and wrote and edited the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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Author contributions

E.L., F.D., M.B.N. and C.L., analyzed data and wrote the paper; M.E. L., L.M., I.F.P., E.C., P.M., M.M, L.P., A.B., A.R., L.V., A.G., V.C., C.T., S. G., E.O., R.M., F.M., I.F., C.S., R.B., C.G., R.G., P.D., A.G., F.F. and C.B. enrolled patients in the study and collected data; E.L. and E.C. coordinated and designed research and edited the paper; P.F. conceived the idea, designed the study, and wrote and edited the paper.

Data availability

All requests for raw and analyzed data will be reviewed to verify if the request is subject to any intellectual property or confidentiality obligations. Any data and materials that can be shared will be released via a Material Transfer Agreement.

References

[1] R.A. DeFronzo, Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM, Diabetes 37 (6) (1988) 667–687.
[2] R.A. DeFronzo, Pathogenesis of type 2 diabetes mellitus, Med. Clin. N. Am. 88 (4) (2004) 787–835 (ix).
[3] V. Vallon, The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus, Annu. Rev. Med. 66 (2015) 255–270.
[4] A. Solini, V. Usuelli, P. Fiorina, The dark side of extracellular ATP in kidney diseases, J. Am. Soc. Nephrol. 26 (5) (2015) 1007–1016.
[5] A.J. Scheen, Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus, Drugs 75 (1) (2015) 33–59.
[6] D. Giugliano, M. Longo, P. Caruso, M.I. Maiorino, G. Bellastella, K. Esposito, Sodium-glucose co-transporter-2 inhibitors for the prevention of cardiorenal outcomes in type 2 diabetes: an updated meta-analysis, Diabetes Obes. Metab. 23 (7) (2021) 1672–1676.
[7] A.M. Vicari, M.V. Taglietti, F. Pellegatta, D. Spotti, M. Melandri, L. Galli, P. Ronchi, F. Folli, Deranged platelet calcium homeostasis in diabetic patients with end-stage renal failure. A possible link to increased cardiovascular mortality? Diabetes Care 19 (10) (1996) 1062–1066.
[8] P. Balakumar, U.K. Maung, G. Jagadeesh, Prevalence and prevention of cardiovascular disease and diabetes mellitus, Pharmacol. Res. 113 (Pt A) (2016) 600–609.
[9] S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M. G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D. K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P. A. Johansson, A.M. Langkilde, M.S. Sabatine, D.-T. Investigators, Dapagliflozin and cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 380 (4) (2019) 347–357.
[10] B. Neal, V. Perkovic, K.W. Mahaffey, D. de Zeeuw, G. Fulcher, N. Erondu, W. Shaw, G. Law, M. Desai, D.R. Matthews, C.P.C. Group, Canagliflozin and cardiovascular and renal events in type 2 diabetes, N. Engl. J. Med. 377 (7) (2017) 644–657.
[11] B. Zinman, C. Wanner, J.M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, M. Mattheus, T. Devins, O.E. Johansen, H.J. Woerle, U.C. Broedl, S.E. Inzucchi, E.-R. O. Investigators, Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med. 373 (22) (2015) 2117–2128.
[12] C.N. Koyani, I. Plastira, H. Sourij, S. Hallstrom, A. Schmidt, P.P. Rainer, H. Bugger, S. Frank, E. Malle, D. von Lewinski, Empagliflozin protects heart from inflammation and energy depletion via AMPK activation, Pharmacol. Res. 158 (2020), 104870.
[13] C. Wanner, S.E. Inzucchi, J.M. Lachin, D. Fitchett, M. von Eynatten, M. Mattheus, O.E. Johansen, H.J. Woerle, U.C. Broedl, B. Zinman, Investigators E-RO, Empagliflozin and progression of kidney disease in type 2 diabetes, N. Engl. J. Med. 375 (4) (2016) 323–334.
[14] C. Loretelli, F. Rocchio, F. D'Addio, M. Ben Nasr, E. Castillo-Leon, S. Dellepiane, A. Vergani, A. Abdelsalam, E. Assi, A. Maestroni, V. Usuelli, R. Bassi, I. Pastore, J. Yang, B. El Essawy, K.M. Elased, G.P. Fadini, E. Ippolito, A.J. Seelam, M. Pezzolesi, D. Corradi, G.V. Zuccotti, M. Gallieni, M. Allegretti, M.A. Niewczas, P. Fiorina, The IL-8-CXCR1/2 axis contributes to diabetic kidney disease, Metabolism 121 (2021), 154804.
[15] S. Dellepiane, M. Ben Nasr, E. Assi, V. Usuelli, T. Letizia, F. D'Addio, G.V. Zuccotti, P. Fiorina, Sodium glucose cotransporters inhibitors in type 1 diabetes, Pharmacol. Res. 133 (2018) 1–8.
[16] E. Ferrannini, S.J. Ramos, A. Salsali, W. Tang, J.F. List, 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 33 (10) (2010) 2217–2224.
[17] C.J. Bailey, J.L. Gross, A. Pieters, A. Bastien, J.F. List, Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial, Lancet 375 (9733) (2010) 2223–2233.
[18] J. Wilding, C. Bailey, U. Rigney, B. Blak, M. Kok, C. Emmas, Dapagliflozin therapy for type 2 diabetes in primary care: changes in HbA1c, weight and blood pressure over 2 years follow-up, Prim. Care Diabetes 11 (5) (2017) 437–444.
[19] E. Lazzaroni, M. Ben Nasr, C. Loretelli, I. Pastore, L. Plebani, M.E. Lunati, L. Vallone, A.M. Bolla, A. Rossi, L. Montefusco, E. Ippolito, C. Berra, F. D'Addio, G. V. Zuccotti, P. Fiorina, Anti-diabetic drugs and weight loss in patients with type 2 diabetes, Pharmacol. Res. 171 (2021), 105782.
[20] F. Folli, C.R. Kahn, H. Hansen, J.L. Bouchie, E.P. Feener, Angiotensin II inhibits insulin signaling in aortic smooth muscle cells at multiple levels. A potential role for serine phosphorylation in insulin/angiotensin II crosstalk, J. Clin. Investig. 100 (9) (1997) 2158–2169.
[21] N. Jongs, T. Greene, G.M. Chertow, J.J.V. McMurray, A.M. Langkilde, R. Correa-Rotter, P. Rossing, C.D. Sjostrom, B.V. Stefansson, R.D. Toto, D.C. Wheeler, H.J. L. Heerspink, D.-C.T. Committees, Investigators, Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial, Lancet Diabetes Endocrinol. 9 (11) (2021) 755–766.
[22] C. Berra, R. Manfrini, D. Regazzoli, M.G. Radaelli, O. Disoteo, C. Sommese, P. Fiorina, G. Ambrosio, F. Folli, Blood pressure control in type 2 diabetes mellitus with arterial hypertension. The important ancillary role of SGLT2-inhibitors and GLP1-receptor agonists, Pharmacol. Res. 160 (2020), 105052.
[23] Z. Szekeres, K. Toth, E. Szabados, The effects of SGLT2 inhibitors on lipid metabolism, Metabolites 11 (2) (2021).
[24] M. Calapkulu, S. Cander, O.O. Gul, C. Ersoy, Lipid profile in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data of six months retrospective lipid profile from single center, Diabetes Metab. Syndr. 13 (2) (2019) 1031–1034.
[25] S.A. Cha, Y.M. Park, J.S. Yun, T.S. Lim, K.H. Song, K.D. Yoo, Y.B. Ahn, S.H. Ko, A comparison of effects of DPP-4 inhibitor and SGLT2 inhibitor on lipid profile in patients with type 2 diabetes, Lipids Health Dis. 16 (1) (2017) 58.
[26] C.D. Sjostrom, P. Johansson, A. Ptaszynska, J. List, E. Johnsson, Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes, Diabetes Vasc. Dis. Res. 12 (5) (2015) 352–358.
[27] N. Sattar, D.K. McGuire, Pathways to cardiorenal complications in type 2 diabetes mellitus: a need to rethink, Circulation 138 (1) (2018) 7–9.
[28] M. Afkarian, M.C. Sachs, B. Kestenbaum, I.B. Hirsch, K.R. Tuttle, J. Himmelfarb, I. H. de Boer, Kidney disease and increased mortality risk in type 2 diabetes, J. Am. Soc. Nephrol. 24 (2) (2013) 302–308.
[29] B.M. Scirica, O. Mosenzon, D.L. Bhatt, J.A. Udell, P.G. Steg, D.K. McGuire, K. Im, E. Kanevsky, C. Stahre, M. Sjostrand, I. Raz, E. Braunwald, Cardiovascular outcomes according to urinary albumin and kidney disease in patients with type 2 diabetes at high cardiovascular risk: observations from the SAVOR-TIMI 53 trial, JAMA Cardiol. 3 (2) (2018) 155–163.
[30] V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, K.W. Mahaffey, C.T. Investigators, Canagliflozin and renal outcomes in type 2 diabetes and nephropathy, N. Engl. J. Med. 380 (24) (2019) 2295–2306.
[31] H.J.L. Heerspink, N. Jongs, G.M. Chertow, A.M. Langkilde, J.J.V. McMurray, R. Correa-Rotter, P. Rossing, C.D. Sjostrom, B.V. Stefansson, R.D. Toto, D. C. Wheeler, T. Greene, D.-C.T. Committees, Investigators, Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial, Lancet Diabetes Endocrinol. 9 (11) (2021) 743–754.
[32] C.J. Bailey, C. Day, S. Bellary, Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease, Curr. Diabetes Rep. 22 (1) (2022) 39–52.