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Effectiveness of dapagliflozin versus comparators on renal endpoints in the real world: A multicentre retrospective study

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Aim: To evaluate the changes in renal endpoints in type 2 diabetes patients treated with dapagliflozin versus other glucose-lowering medications in routine clinical practice.

Materials and Methods: DARWIN-T2D was a retrospective study conducted at 46 outpatient diabetes clinics in Italy. An automated software collected data on 17 285 patients who received dapagliflozin, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, or gliclazide, 6751 of whom had a follow-up visit. We analysed changes in albumin excretion rate (AER) and estimated glomerular filtration rate (eGFR).

Results: Patients who received dapagliflozin ($n = 473$) were younger, more obese, and had a poorer glucose control than those who received a comparator ($n = 2973$). After ~6 months, median (interquartile range) AER declined by 37%, from 19.5 (7.5–78.2) to 13.2 (6.5–45.0) mg/g ($P < 0.0001$) in the dapagliflozin group and did not change in the comparator group. After adjusting for confounders, therapy with dapagliflozin versus comparators was associated with an AER reduction of 26.4 ± 13.1 mg/g ($P = 0.045$), and eGFR (mL/min/1.73 m^2) diminished by 1.1 ± 0.5 ($P = 0.049$) in the dapagliflozin group and by 0.6 ± 9.1 ($P = 0.002$) in the comparator group ($P = 0.35$ between groups). No patient treated with dapagliflozin versus four patients treated with comparators experienced a doubling of serum creatinine.

Conclusions: The antiproteinuric effect of dapagliflozin is confirmed here for the first time by real-world data. Despite a mild decline in eGFR, there was no evidence of clinically relevant worsening in renal function.

KEYWORDS

antidiabetic drug, dapagliflozin, database research, diabetic nephropathy, type 2 diabetes

1 | INTRODUCTION

The effects of glucose-lowering medications (GLM) on cardiovascular and renal outcomes have become a major issue influencing therapeutic choices for type 2 diabetes (T2D).[1] Regulatory agencies require that, in addition to lowering blood glucose, diabetes medications have a safe cardiovascular profile. During the last 3 years, a few new GLM have proved capable of protecting patients with T2D and high cardiovascular risk from major adverse cardiovascular events (MACE). Among these, the sodium-glucose co-transporter 2 inhibitors (SGLT2i) empagliflozin and canagliflozin,[2,3] as well as the glucagon-like peptide-1 receptor agonists (GLP-1RA) liraglutide and semaglutide[4,5] reduced the risk of MACE (cardiovascular death, non-fatal myocardial infarction or stroke). Strikingly, these drugs also showed evidence of renal protection, by reducing albuminuria and/or slowing the progression of chronic kidney disease (CKD).[2,4,6,7]

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In phase III randomized controlled trials (RCTs), treatment with SGLT2i reduced albumin excretion rate (AER),[8] and slowed the decline in estimated glomerular filtration rate (eGFR) over time.[9] The mechanisms mediating such effects likely result from modulation of the tubular-glomerular feedback[8] and are independent from background therapy with angiotensin converting enzyme (ACE) inhibitors.[10]

CKD is highly prevalent in T2D and is a strong accelerator of cardiovascular risk.[11] In the longitudinal Italian Renal Insufficiency and Cardiovascular Events (RIACE) study, higher AER and lower eGFR, even in the normal range, identified individuals with increased mortality.[12] Other observational studies and meta-analyses show that an excess cardiovascular morbidity and mortality is linked to impaired renal function.[13,14] Therefore, it has been hypothesized that kidney protection contributes to cardiovascular protection in patients treated with SGLT2i.[15,16]

However, data from RCTs may suffer from a limited external transferability and their findings need to be reproduced in clinical practice.[17] So-called "real-world studies" use data accumulated during routine clinical practice to challenge results obtained in RCTs, address broader patient populations, and find predictors of clinical response.[18] In the present study, we retrospectively analysed the effectiveness of the SGLT2i dapagliflozin on renal endpoints (AER and eGFR) in an Italian clinical care setting.

2 | METHODS

2.1 | Study design and aims

The DApagliflozin Real World evIdeNce in Type 2 Diabetes (DARWIN-T2D) was a retrospective multicentre study performed at 46 diabetic specialist outpatient clinics in Italy. Details of the rationale and design of the study have been published previously.[19] Briefly, the study aimed to describe the baseline clinical characteristics of patients who received a new prescription of dapagliflozin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, a long-acting GLP-1RA (liraglutide or once-weekly exenatide), or gliclazide in Italian routine clinical practice, and to retrospectively evaluate the change in effectiveness parameters at the first available follow-up after 3-12 months. An automatic software program extracted data from the same electronic chart system at all centres. The following data were collected: demographics, anthropometrics, diabetes duration, blood pressure, smoking status, fasting plasma glucose, HbA1c, lipid profile, liver enzymes, AER, eGFR (CKD-EPI), history of complications, concomitant and previous GLM. AER values reported in charts as mg/l or mg/min (normal value 0-20) were multiplied by 1.5 to convert to mg/g creatinine or mg/24 h equivalent (normal value 0-30), assuming a standard urinary volume of 1500 mL.

The primary results of the study have been published previously[20]: although dapagliflozin was initially channelled to difficult-to-treat patients, it provided significant benefits with regard to the control of glucose, body weight, and blood pressure that were in line with findings from RCTs. Owing to the massive channelling bias, it was not possible to perform a propensity score matched comparison between the groups of patients who initiated dapagliflozin and those who initiated comparators.

In the present sub-analysis of the DARWIN-T2D study, we aimed to evaluate the effects of dapagliflozin on renal endpoints (the change from baseline in AER and eGFR) and to compare them with the effects of other GLM (combined GLP-1RA, DPP-4 inhibitors, or gliclazide).

2.2 | Patient selection

Because the primary study aim was to describe the baseline clinical characteristics of patients who received dapagliflozin in clinical practice, the follow-up visit was available for only a fraction of patients. We anticipated that data on AER and eGFR would only be available at both visits for some of the patients with a follow-up visit because the guidelines do not necessarily recommend checking renal function at short intervals in all patients. We thus identified patients for whom AER was available at both visits, those for whom eGFR was available at both visits, and those for whom both AER and eGFR were available at both visits. We calculated the change in AER and eGFR as the difference from baseline to follow-up. We also calculated the changes in HbA1c, body weight and blood pressure in the subgroup of patients with available data for AER and/or eGFR at both visits.

2.3 | Statistical analysis

Normality of continuous variables was tested with the Kolmogorov-Smirnov test. Non-normal variables were log-transformed before statistical analysis. Normal variables are presented as mean ± standard deviation, whereas non-normal variables are given as median (interquartile range [IQR]). Categorical variables are summarized using percentages. Differences between the two groups of patients who received dapagliflozin or comparator GLM were analysed using the unpaired Student's t test for continuous variables or the chi-squared test for categorical variables. Owing to the large number of comparisons, the Bonferroni correction was used to adjust for alpha inflation because of multiple testing. Significance of the change from baseline in AER and eGFR was tested using the paired Student's t test or, if necessary, the Wilcoxon rank test. We also calculated the percentage of patients in the various categories of AER (normo-, micro-, macro-albuminuria) at baseline and at follow-up. The significance of moving along AER categories was tested using the Wilcoxon rank test. A multiple regression analysis was used to adjust the effects of dapagliflozin versus those of comparator GLM on renal endpoints. Covariates were selected as those being significantly different between the two groups after Bonferroni correction. Variables with missing data were handled with a multiple imputation (MI) procedure using the Monte Carlo Markov Chain (MCMC) method and $n = 20$ imputations. The Pearson's r coefficient was used to test linear correlations between the change in AER (log-transformed) or eGFR and clinical characteristics, as well as the change in other effectiveness variables. In addition, to detect clinical response patterns, we used random forests (RF) and partial least squares (PLS) algorithms with change in AER (log-transformed) as the dependent variable (see the File S1 for this article for further details). The statistical significance level was set at 0.05. SPSS ver. 23 and R ver. 3.5.0 were used.

3 | RESULTS

3.1 | Characteristics of study patients

Of the 2484 patients identified at baseline and who started dapagliflozin, 830 had an available follow-up visit during the observation period. Of these, 497 (60.0%) had at least one renal endpoint available both at the baseline and follow-up visits; n = 273 patients had valid AER data at both visits, n = 393 patients had valid eGFR values at both visits, and n = 169 patients had both endpoints available at both visits. Of the 14 801 patients in the comparator group who were evaluated at baseline, 5921 had a follow-up visit and 2973 (50.2%) had AER and/or eGFR available at both visits (n = 2277 for eGFR, n = 1380 for AER, n = 684 for both) (Figure 1).

Clinical characteristics of the two groups are compared in Table 1: variables that remained significantly different after Bonferroni correction were age, BMI, diastolic blood pressure, fasting plasma glucose, baseline HbA1c, triglycerides, concomitant use of metformin, insulin, and diuretics, and prevalence of microangiopathy. Extended data are available in Table S1 (see the File S1 for this article).

To evaluate selection bias, we compared the 3470 patients with and the 3281 patients without follow-up data for renal endpoints: variables with a standardized difference > 0.1 (indicating imbalance) were age, diabetes duration, LDL cholesterol and statin use, baseline eGFR, and microangiopathy (Table S2).

3.2 | Change in renal endpoints during therapy with dapagliflozin versus comparators

The change in AER was examined in 273 patients who received dapagliflozin and in 1380 patients who received a comparator (Table 2). During therapy with dapagliflozin, median (IQR) AER declined from 19.5 (7.5-78.2) to 13.2 (6.5-45.0) mg/g ($P < 0.0001$), equivalent to a 37% reduction (Figure 2A). The average $\pm$ SEM AER change was -39.3 ± 14.8 mg/g. Significant decreases in AER occurred only in patients with micro- or macroalbuminuria, but not in patients with normoalbuminuria at baseline (Figure 2B,D).

In patients who received a comparator, overall AER did not change significantly from baseline to follow-up (average $\pm$ SEM change -5.9 ± 4.1 mg/g; $P = 0.156$), although it declined in those with baseline macroalbuminuria. The change in AER was significantly greater during therapy with dapagliflozin than with comparators, especially for patients with micro/macroalbuminuria at baseline (Table 2). During therapy with dapagliflozin, AER declined significantly both in patients with and in those without ongoing therapy with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs), while AER did not change significantly in the comparator group, irrespective of therapy with ACEi/ARBs. The change from baseline in AER in patients on ACEi/ARBs was significantly greater during therapy with dapagliflozin than comparators. Dapagliflozin reduced AER irrespectively of baseline eGFR (< or > 90 mL/min/1.73 m^2) and significantly more than comparators in patients with eGFR <90 mL/min/1.73 m^2 (Table 2).
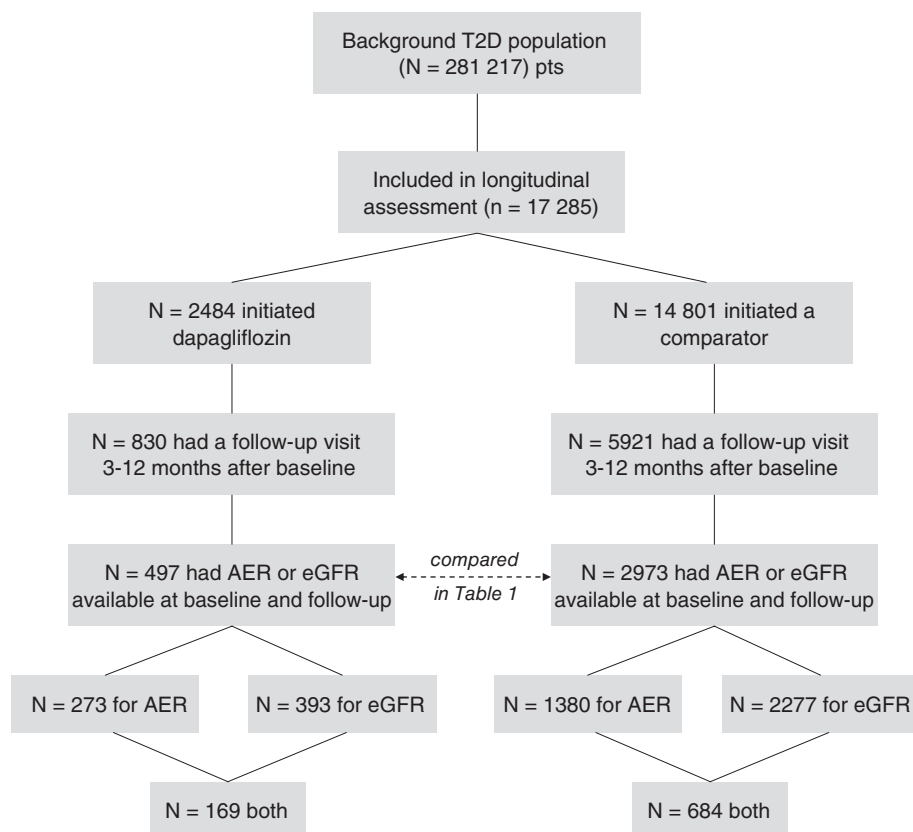

FIGURE 1 Study flowchart. T2D, type 2 diabetes; AER, albumin excretion rate; eGFR, estimated glomerular filtration rate

TABLE 1 Comparison of baseline characteristics between the two groups

	Dapagliflozin (n = 497)		Comparators (n = 2973)		
	% Available	Value	% Available	Value	P
Age, y	100.0	60.5 ± 9.3	100.0	67.3 ± 9.0	<0.001[a]
Sex: Male, %	100.0	61.0	100.0	59.8	0.625
Current smoking, %	22.3	23.4	22.3	20.1	0.426
Diabetes duration, y	100.0	12.5 ± 8.4	99.9	11.6 ± 7.8	0.012
BMI, kg/m^2	93.2	32.8 ± 5.8	91.3	29.9 ± 5.3	<0.001[a]
SBP, mm Hg	73.8	139.6 ± 18.3	78.3	137.8 ± 18.7	0.087
DBP, mm Hg	73.6	81.2 ± 10.3	78.2	78.7 ± 9.0	<0.001[a]
FPG, mg/dL	92.8	173.9 ± 52.3	91.2	157.1 ± 38.3	<0.001[a]
HbA1c, %	99.0	8.6 ± 1.3	98.8	7.9 ± 1.0	<0.001[a]
Total cholesterol, mg/dL	79.5	174.4 ± 40.6	79.3	170.1 ± 37.2	0.038
HDL cholesterol, mg/dL	77.9	46.5 ± 13.5	76.8	48.0 ± 13.5	0.035
Triglycerides, mg/dL	79.9	166.3 ± 133.3	78.1	147.0 ± 90.3	<0.001[a]
LDL cholesterol, mg/dL	73.4	95.8 ± 32.1	75.0	92.9 ± 31.3	0.104
SGOT, U/L	48.1	25.9 ± 20.1	48.6	23.0 ± 12.8	0.003
SGPT, U/L	53.1	33.0 ± 20.2	49.7	27.3 ± 17.6	<0.001[a]
eGFR, ml/min/1.73 m^2	83.1	87.8 ± 16.4	82.5	79.5 ± 18.7	<0.001[a]
AER, mg/g	63.2	104.9 ± 342.7	58.6	76.2 ± 261.3	0.089
Associated GLM					
Insulin	99.8	55.4	100.0	15.2	<0.001[a]
Metformin	99.8	99.2	100.0	79.7	<0.001[a]
Other medications					
Antiplatelet	87.3	48.6	86.7	54.6	0.022
Statin	87.3	65.0	98.4	59.2	0.023
ACEi/ARBs	87.3	72.6	86.7	71.3	0.577
CCB	87.3	25.1	98.4	20.1	0.016
Betablockers	87.3	31.6	98.4	26.7	0.032
Diuretics	87.3	9.7	86.7	23.2	<0.001[a]
Complications					
Microangiopathy	100.0	41.9	93.2	32.6	<0.001[a]
Macroangiopathy	86.5	32.8	83.3	36.8	0.115

Data are expressed as mean ± standard deviation, or as % where appropriate. Per cent of available data is reported for all variables.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AER, albumin excretion rate; ARBs, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GLM, glucose-lowering medications; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.
[a] Statistically significant after Bonferroni correction.

After adjusting for baseline differences between the two groups with a multiple regression analysis, therapy with dapagliflozin remained associated with a significantly greater reduction in AER than therapy with comparators (−26.4 ± 13.1 mg/g; P = 0.045) (Table 3).

According to AER categories, 12.8% of patients in the dapagliflozin group and 10.9% in the comparator group regressed to a lower AER class, whereas 4.4% in the dapagliflozin group and 8.3% in the comparator group progressed to a higher class, for a net improvement of 8.4% in the dapagliflozin group versus 2.6% in the comparator group (P < 0.001) (Figure S1).

The change in eGFR was analysed in 393 patients in the dapagliflozin group and 2277 patients in the comparator group. During therapy with dapagliflozin, mean ± SD eGFR declined from 87.5 ± 16.3 to 86.5 ± 17.8 mL/min/1.73 m^2 (P = 0.049), with a reduction of 1.1 mL/min/1.73 m^2. During therapy with a comparator, eGFR declined from 79.2 ± 18.8 to 78.6 ± 19.1 mL/min/1.73 m^2

(P = 0.002), equivalent to a reduction of 0.6 mL/min/1.73 m^2. The change from baseline in eGFR between the two groups was not significantly different (P = 0.35). No patient in the dapagliflozin group versus 4 patients in the comparator group exhibited a doubling of serum creatinine; no patient in the dapagliflozin group versus 11 patients in the comparator group exhibited a decline of >40% in eGFR (both not significantly different between groups).

3.3 | Overall effectiveness of dapagliflozin and comparators

Effectiveness of dapagliflozin and comparators on glucose control, blood pressure and body weight has already been described in the total cohort of patients with a follow-up examination.[20] In the present subgroups, HbA1c declined by 0.8 ± 1.2% in the dapagliflozin group (n = 490) and 0.6 ± 1.1% in the comparator group (n = 2899); body

TABLE 2 Change in AER in the various subgroups of patients

Subgroup	Dapagliflozin			Comparators		
	Baseline	Follow-up	Change	Baseline	Follow-up	Change
All patients, n	273	273	273	1380	1380	1380
Mean ± SEM	105.0 ± 20.3	65.8 ± 10.4[a]	−39.3 ± 14.8[b]	76.3 ± 6.6	70.4 ± 6.1	−5.9 ± 4.1
Median (IQR)	19.5 (7.5; 78.1)	13.2 (6.5; 45.0)[a]	−2.1 (−26.4; 2.3)[b]	14.9 (7.2; 41.3)	12.3 (7.0; 34.4)	−0.5 (−9.6; 4.3)
By baseline albuminuria						
Normoalbuminuria, n	164	164	164	951	951	951
Mean ± SEM	10.5 ± 0.6	13.3 ± 1.9	2.8 ± 1.8	10.6 ± 0.2	14.9 ± 1.1[a]	4.3 ± 1.1
Median (IQR)	8.4 (5.5; 15.2)	8.8 (4.8; 13.3)	0.0 (−3.0; 2.7)	8.9 (5.1; 15.3)	8.8 (4.9; 51.3)	0.0 (−3.0; 3.9)
Microalbuminuria, n	93	93	93	356	356	356
Mean ± SEM	108.6 ± 7.0	84.7 ± 14.1	−23.8 ± 13.6	90.6 ± 3.4	90.1 ± 7.8	−0.5 ± 6.9
Median (IQR)	90.0 (52.1; 143.9)	49.4 (21.6; 89.1)[a]	−35.3 (−75.9; −3.3)[b]	66.7 (42.0; 121.2)	43.5 (20.1; 93.4)	−17.7 (−46.7; 7.1)
Macroalbuminuria, n	16	16	16	73	73	73
Mean ± SEM	1054.0 ± 243.6	493.1 ± 107.2[a]	−560.9 ± 204.0[b]	861.5 ± 78.9	697.5 ± 76.4[a]	−164.0 ± 66.7
Median (IQR)	590.8 (480.2; 1228.5)	379.1 (172.4; 661.7)[a]	−265.4 (−786.0; −113.2)	630.6 (389.6; −1082.0)	519.0 (318.0; −858.0)[a]	−184.5 (−343.5; −95.0)
By ACEi/ARBs therapy						
No ACEi/ARBs, n	68	68	68	345	345	345
Mean ± SEM	44.5 ± 9.4	24.5 ± 4.3[a]	−20.1 ± 7.4	47.5 ± 10.1	32.7 ± 4.4	−14.7 ± 8.0
Median (IQR)	11.4 (6.5; 50.1)	10.8 (6.0; 27.0)[a]	−1.5 (−8.1; 2.0)	10.7 (6.8; 25.9)	10.5 (6.4; 23.0)	−0.5 (−6.0; 3.0)
ACEi/ARBs, n	179	179	179	872	872	872
Mean ± SEM	132.8 ± 30.2	83.5 ± 15.1[a]	−49.3 ± 22.4[b]	96.4 ± 9.6	93.2 ± 9.4	−3.2 ± 5.7
Median (IQR)	23.7 (8.5; 103.7)	15.8 (8.1; 66.8)[a]	−3.0 (−31.9; 3.0)[b]	16.9 (7.4; 56.5)	13.4 (7.1; 45.1)	−0.7 (−12.4; 4.6)
By baseline eGFR						
eGFR >90 mL/min/1.73 m², n	97	97	97	293	293	293
Mean ± SEM	136.5 ± 45.5	82.8 ± 23.8	−53.7 ± 33.6	58.5 ± 9.1	49.6 ± 8.8	−8.9 ± 8.0
Median (IQR)	19.0 (7.4; −75.0)	12.0 (7.5; −48.8)[a]	−2.1 (−27.0; −2.7)	15.2 (6.8; 47.3)	12.0 (6.0; 32.4)	−1.0 (−12.3; 4.5)
eGFR ≤90 mL/min/1.73 m², n	92	92	92	566	566	566
Mean ± SEM	115.6 ± 34.3	69.2 ± 15.0	−46.4 ± 25.6[b]	96.9 ± 12.5	94.2 ± 12.3	−2.8 ± 6.8
Median (IQR)	25.1 (8.1; −123.7)	18.5 (7.1; −70.1)[a]	−2.7 (−30.7; −2.0)[b]	15.8 (6.5; 48.9)	13.0 (6.0; 39.2)	−0.7 (−10.6; 4.6)

Values of AER are reported both as mean ± SEM (with p values from paired Student's t test) and as median and IQR (with P values from Wilcoxon rank test). ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
[a] $P < 0.05$ versus baseline.
[b] $P < 0.05$ versus comparators.

weight decreased by 2.9 ± 3.5 kg in the dapagliflozin group (n = 456) and 0.6 ± 3.3 kg in the comparator group (n = 2631); systolic blood pressure declined by 3.3 ± 17.5 mm Hg in the dapagliflozin group (n = 336) and 0.2 ± 19.4 mm Hg in the comparator group (n = 1972).

Because there was no correlation between the changes in HbA1c and systolic blood pressure (SBP) (r = 0.04; P = 0.100), in an exploratory analysis we selected patients who experienced a below median response in HbA1c and an above median response in SBP: in 31 patients who received dapagliflozin, AER declined by 35%, from median (IQR) 23.7 (6.7; 137.3) to 16.9 (6.8; 80.4) (P = 0.09), while in 162 patients who received comparators, AER tended to increase by 23% (P = 0.13).

3.4 | Predictors of improvement in AER

To detect predictors of AER decline in patients who received dapagliflozin, we first analysed linear correlations: the change in AER was inversely related to change in eGFR (r = −0.17; P = 0.024; n = 169),

but not to the change in other efficacy variables (HbA1c, blood pressure and body weight). Thus, we used two complementary non-linear approaches: random forests and PLS (Table S3). Variables detected by RF were, in order of importance, HDL, LDL, diastolic blood pressure, triglycerides, total cholesterol, SBP and disease duration. According to PLS, only baseline AER, HbA1c and diastolic blood pressure had a significant impact.

4 | DISCUSSION

In this real-world study, T2D patients initiating dapagliflozin experienced a significant reduction in AER at the first follow-up visit, on average ~6 months after baseline. Remarkably, a similar effect was not observed with comparator GLM. While a mild and marginally significant decline in eGFR was observed during dapagliflozin use, there was no evidence of clinically meaningful impairment in renal function. These results are extremely consistent with findings from phase III
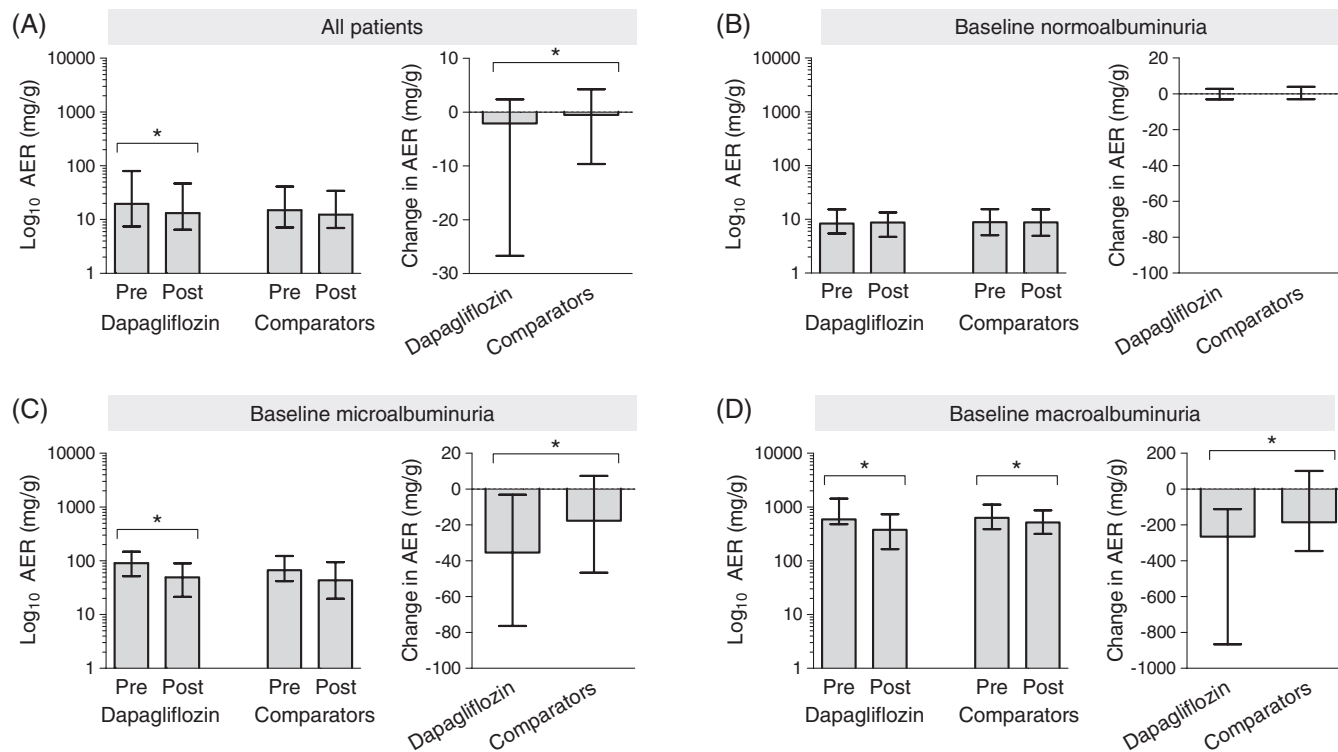
FIGURE 2 Change in AER during therapy with dapagliflozin or comparators. Values of AER at baseline (pre) and at follow-up (post), along with the change from baseline (right panel), are shown for A, all patients, B, patients with baseline normoalbuminuria, C, microalbuminuria or D, macroalbuminuria. Columns' height in histograms indicate median value, whereas bars indicate the interquartile range. *$P < 0.05$ for the indicated comparison

TABLE 3 Results of the multiple regression analysis

Variable	$B \pm SEM$	P
Dapagliflozin (vs. comparators)	-26.42 ± 13.14	0.045
Age, y	0.39 ± 0.57	0.497
BMI, kg/m^2	0.49 ± 0.86	0.564
Diastolic blood pressure, mm Hg	-0.36 ± 0.47	0.444
Fasting plasma glucose, mg/dL	-0.45 ± 0.18	<0.001
HbA1c, %	-4.14 ± 5.02	0.410
Triglycerides, mg/dL	0.02 ± 0.04	0.585
SGPT, U/L	0.12 ± 0.24	0.618
eGFR, mL/min/1.73 m^2	0.33 ± 0.29	0.251
Insulin use (yes vs. no)	-2.80 ± 11.4	0.806
Metformin use (yes vs. no)	24.50 ± 13.27	0.065
Diuretic use (yes vs. no)	-7.19 ± 11.16	0.520
Microangiopathy (yes vs. no)	-17.61 ± 8.80	0.045

Change in AER was the dependent variable, whereas covariates were selected as variables that remained different between the two groups after Bonferroni correction (see Table 1).

RCTs and confirm that dapagliflozin exerts beneficial effects on the kidney. Because renal protection can contribute to cardiovascular protection, we argue that these data lend support to the potential cardiovascular efficacy of dapagliflozin. While awaiting for results of the dedicated cardiovascular outcome trial,[21] registry studies indicate that dapagliflozin can protect from cardiovascular events similarly to other SGLT2i.[22]

In RCTs, dapagliflozin consistently reduced AER by 36-40%[8,9] irrespective of therapy with ACE inhibitors or ARBs.[10] In our study,

AER declined by 37% in patients taking, and by 45% in patients not taking ACEi/ARBs. The antiproteinuric effects of dapagliflozin are probably largely independent of glucose control, as patients who experienced a decline in SBP with no decline in HbA1c showed an AER reduction quantitatively similar to the entire cohort, while the same was not observed in patients taking other GLM. This observation is consistent with the supposed direct renal effect of SGLT2i via reactivation of the tubular-glomerular feedback.[23]

Owing to the non-randomized nature of the comparison between treatments, the analysis of AER response predictors was performed only in the dapagliflozin group. The change in eGFR emerged as the sole linear predictor, but it explained <3% of AER variation. Non-linear approaches identified blood pressure, lipid profile, HbA1c and disease duration as variables that impacted the ability of dapagliflozin to lower AER. While triglycerides have already been associated with diabetic nephropathy,[24-26] it is remarkable that cholesterol levels modulated the renal effects of SGLT2i.

In RCTs, dapagliflozin therapy was associated with an initial drop in eGFR, followed by eGFR stabilization, such that, after 2 years of treatment, eGFR was significantly higher than in placebo-treated patients.[27] The mild decline in eGFR we observe at ~6 months after initiation of dapagliflozin is consistent with RCTs and the change in eGFR during dapagliflozin was not significantly different than during therapy with comparators. Our data are also particularly reassuring on the risk that SGLT2i may acutely worsen renal function. Postmarketing pharmacovigilance has identified cases of acute kidney injury (AKI) in patients taking SGLT2i,[28,29] probably because of alterations of renal

haemodynamics.[30,31] On the contrary, an observational study comparing 377 SGLT2i users with 377 matched non-users did not find any association between SGLT2i and AKI.[32] In our survey, we found no case of doubling of serum creatinine among 393 patients initiated on dapagliflozin, also suggesting that dapagliflozin did not precipitate AKI over the ~6-month follow-up.

Interpretation of our results must take into consideration the study's limitations. First, AER was derived from a single measure and had to be converted from different units of measure. This is, however, commonly carried out in clinical practice and validated in epidemiological research.[33] Second, patients who received comparator GLM in the DARWIN-T2D trial were significantly different to those who received dapagliflozin. As already noted, because of the massive channelling of dapagliflozin to difficult-to-treat patients, a propensity score matching was inefficient and adjustment was performed using multiple regression. Thus, the degree of evidence that can be inferred from this observational study is not comparable to that of an RCT. Third, follow-up duration was short (~6 months), only allowing an analysis of acute changes in renal endpoints. While the effects of dapagliflozin on AER are expected to be rapid,[8] a longer observation will be needed to evaluate benefits over time and trends in eGFR. The fact that AER did not decline in the comparator group must also be interpreted in view of the short follow-up, because GLP-1RA and DPP-4 inhibitors may take longer to reduce AER.[34,35] Finally, the sample size was small: less than 60% of patients had AER and/or eGFR available at both visits. This was not surprising, because eGFR and AER are not routinely checked at short intervals in all patients, but it suggests that selection bias cannot be ruled out and generalizability should be considered with caution.

In summary, this is the first real-world study confirming that a short-term treatment with the SGLT2i dapagliflozin reduces albuminuria and does not cause a clinically meaningful worsening in renal function. Although longer and larger studies may be needed to establish whether these benefits persist over time in the real world, our study supports the validity and importance of registry interrogation to determine transferability of RCT data to the clinical setting.

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Composition of the DARWIN-T2D database

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Conflicts of interest

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SUPPORTING INFORMATION

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