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RESEARCH ARTICLE

Comparative effectiveness of dapagliflozin vs DPP-4 inhibitors on a composite endpoint of HbA1c, body weight and blood pressure reduction in the real world

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Abstract

Background: Treatment of type 2 diabetes (T2D) should aim at preventing or delaying complications through the control of glycaemia and cardiovascular risk factors. We herein compared the SGLT-2 inhibitor dapagliflozin vs DPP-4 inhibitors (DPP-4i) on a composite endpoint of glycaemic and extraglycaemic effectiveness.

Methods: This was a multicentre, retrospective real-world study conducted at 56 outpatient clinics in Italy. We collected data on patients newly started on dapagliflozin or DPP-4i in 2015-2017. The primary endpoint was the proportion of patients attaining a simultaneous reduction of HbA1c ≥0.5%, body weight ≥2 kg, systolic blood pressure (SBP) ≥2 mmHg. Confounding by indication was addressed by propensity score matching (PSM) or multivariable adjustment (MVA).

Results: Patients initiating dapagliflozin (n = 2091) or DPP-4i (n = 2144) differed for most clinical characteristics. After PSM, two well-balanced groups of 1149 patients each were compared. The primary endpoint was reached in a greater proportion of patients who received dapagliflozin (17.6%) compared to DPP-4i (11.7%), with a relative risk of 1.50 (1.21-1.86; $P < .001$). Similar results were obtained in the as-treated and intention-to-treat datasets or using MVA in place of PSM. The beneficial effect of dapagliflozin was mainly due to its greater effectiveness on body weight and, to a lesser extent, on SBP. The change in HbA1c did not differ between groups.

Conclusions: T2D patients initiating the SGLT2i dapagliflozin had a greater probability of attaining a composite endpoint of clinically relevant reductions in HbA1c, body weight and SBP, compared to similar patients initiating a DPP-4i in the same period and healthcare setting.

KEYWORDS
glycaemia, obesity, observational, pharmacoepidemiology, sodium glucose cotransporter-2

1 | INTRODUCTION

According to international recommendations, therapeutic management of type 2 diabetes (T2D) should pursue multiple benefits that reduce the rate of chronic complications. This can be achieved

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preferentially with some classes of glucose lowering medications (GLM).[1] Sodium-glucose co-transporter-2 inhibitors (SGLT2i) lower glucose levels by increasing urinary glucose excretion. Glycosuria results in a significant reduction of body weight and, along with natriuresis, improves blood pressure.[2] Owing to these multiple benefits, SGLT2i are ideal second-line agents for the management of T2D patients,[3] who have high prevalence of obesity and hypertension. Cardiovascular outcome trials (CVOTs) have consistently shown that SGLT2i can reduce the rate of major adverse cardiovascular events (MACE), cardiovascular death and hospitalization for heart failure (HHF) compared to placebo across a range of baseline cardiovascular risk.[4-6] Additionally, SGLT2i have shown prominent capacity for protection against adverse renal outcomes in T2D.[7] While inducing all these benefits, glycosuria is responsible for the most common adverse event (AE) of SGLT2i, namely genital tract infections.[8] Some serious, but very rare, AEs have been reported during therapy with SGLT2i: diabetic ketoacidosis, acute kidney injury, bone fractures, amputations and Fournier's gangrene.[8-10] Thus, despite their wide range of benefits, SGLT2i are underutilized in clinical practice, in favour of other second-line oral agents devoid of cardio-renal protective effects but perceived to be safer, such as dipeptidyl peptidase-4 inhibitors (DPP-4i). DPP-4i have become popular because of their recognized safety profile,[11] despite four large CVOTs showed a neutral effects on hard cardiovascular and renal outcomes.[12]

In phase III randomized controlled trials (RCTs), add-on therapy with SGLT2i yielded similar or greater improvement of HbA1c than DPP-4i,[13, 14] and greater improvements in body weight and systolic blood pressure (SBP).[14, 15] However, only a few studies evaluated the simultaneous attainment of multiple risk factor goals. In a post-hoc trial analysis, more dapagliflozin-treated than saxagliptin-treated patients achieved the composite endpoint of HbA1c reduction ≥0.5%, weight loss ≥2 kg, SBP reduction ≥2 mmHg.[16] Similar results have been obtained with canagliflozin compared to sitagliptin.[17]

It is important to understand whether the multiple benefits observed in RCTs apply to clinical practice. Differences in patient characteristics, adherence and motivation, as well as resource availability and follow-up schedules make clinical practice much different from the RCT setting.[18, 19] Thus, regulatory agencies increasingly value real-world data to complement RCT findings and extend them to wider populations of T2D patients.[20-22]

We herein devised and conducted a multicentre retrospective study to compare effectiveness of the SGLT2i dapagliflozin vs DPP-4i when added to ongoing therapies in patients with T2D, on a composite outcome of simultaneous improvement in HbA1c, body weight and SBP.

2 | METHODS

2.1 | Study design

The DARWIN-FUP (DApagliflozin Real World evIdeNce in Type 2 Diabetes Follow-UP) was a multicentre retrospective no-profit study conducted at 56 diabetes specialist outpatient clinics in Italy. Qualified centres were well distributed among Italian regions being therefore representative of the country's outpatient clinics. The study was approved by the Ethical Committee of the coordinating centre (University Hospital of Padova, prot. no. 4356/AO/17) and by all participating centres. The study used anonymous data and, based on National and International regulations, a waiver was applied to the requirement for patients' informed consent. The protocol is registered in ClinicalTrials.gov (NCT04304430) and represents an evolution of the former DARWIN-T2D study,[23] except that an entirely new set of data was collected from a greater number of clinics. The study was promoted by the Italian Diabetes Society, which recruited centres using the same electronic medical record (EMR) system (MyStar Connect/Smart Digital Clinic, Meteda Srl, San Benedetto del Tronto, Italy). Such EMR is a digital chart optimized for the care of patients with diabetes and it records data on demographics, anthropometrics, blood exams, therapies and complications, but is not linked with administrative claims.

2.2 | Cohort identification

We included data of all patients aged 18-80 years, with T2D since at least 1 year (as recorded in the chart), who initiated dapagliflozin 10 mg or a full-dose DPP-4i (sitagliptin, vildagliptin, saxagliptin or alogliptin) at participating centres between 13th March 2015 and 31st December 2017. To avoid induction of prescription, enrolment of centres and data extraction were performed after 31st December 2017. Patients were included only if concomitantly treated with metformin and/or insulin because, at the time the study was conducted, SGLT2i were not reimbursed in combination with other GLM in Italy. Patients were excluded if they had a diagnosis of other forms of diabetes, had used any DPP-4i or SGLT2i in the past, or had an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, because this could selectively impact efficacy of dapagliflozin undermining the comparison with DPP-4i.[24] We also excluded patients initiating linagliptin, because, among DPP-4i, linagliptin has been used preferentially in patients with or at risk for chronic kidney disease (CKD).

For the present study, which refers to the pre-specified analysis plan, we retained only patients with a follow-up visit between 3 and 12 months after baseline and with complete information on HbA1c, SBP and body weight at baseline and follow-up visit.

2.3 | Data collection

A dedicated software interrogated the chart and retrospectively extracted anonymous study data for all patients. The index date (baseline) was set as the date when patients received for the first time new prescription of dapagliflozin or DPP-4i without being treated with such drugs in the past. The following baseline variables were collected within 30 days before index date: age, sex, diabetes duration, body weight, body mass index (BMI) waist circumference, systolic and

diastolic blood pressure, heart rate; laboratory exams (fasting plasma glucose, HbA1c, total cholesterol, HDL cholesterol, calculated LDL cholesterol, triglycerides, liver enzymes, serum creatinine for the calculation of eGFR using the CKD-EPI equation, urinary albumin excretion rate (UAER) in mg/g of urinary creatinine or equivalent). Retinopathy was classified according to the Early Treatment of Diabetic Retinopathy study (ETDRS) and macular oedema was coded separately; peripheral neuropathy was defined based on symptoms recorded in the Michigan Neuropathy Screening Instrument (MNSI) eventually confirmed by nerve conduction velocity, whereas autonomic neuropathy was defined based on cardiac autonomic tests; nephropathy was defined only as the presence of a UAER of 30 mg/g or greater because all patients had eGFR ≥60 mL/min/1.73 m^2; cerebral and peripheral atherosclerosis was defined as the presence of narrowing plaques of the carotid or leg arteries, respectively; ICD-9 codes were used to define a history of ischemic stroke / transient ischemic attack (TIA) (433-436), myocardial infarction (410-414), heart failure (428); left ventricular hypertrophy, carotid, peripheral or coronary revascularization were coded separately; coronary heart disease (CHD) was defined as a past history of angina or myocardial infarction or coronary revascularization. Established cardiovascular disease (CVD) was defined as a history of stroke or myocardial infarction or any site revascularization. Microangiopathy was defined as the presence of retinopathy/maculopathy, nephropathy or neuropathy. Macroangiopathy was defined as established CVD, or cerebral, coronary or peripheral atherosclerosis, even if asymptomatic. We finally collected data on ongoing and prior GLM and on therapies for the control of concomitant risk factors. The number of GLM classes that the patients used before initiating DPP-4i or dapagliflozin was recorded as an indicator of disease stage. We then identified the last available visit 3-12 months after baseline and collected updated information on the variables needed to define endpoints (HbA1c, SBP, body weight) and ongoing medications.

2.4 | Objectives and endpoints

The primary objective of the study was to compare the proportion of patients achieving the following composite endpoint between the two groups: simultaneous reduction of HbA1c ≥0.5% and reduction of body weight ≥2 kg and reduction of SBP ≥2 mmHg. The main secondary objective was to compare the proportion of patients achieving any simultaneous reduction of HbA1c, body weight and SBP.

In case the primary endpoint was met, the study was planned to explore which component(s) of the composite endpoints (primary and secondary) was/were responsible for the difference between the two groups, by evaluating the average changes in the variables that define individual components of the composite endpoint and the proportion of patients meeting individual components of the composite endpoint.

The pre-specified primary analyses followed an "intention-to-treat" (ITT) approach. The ITT dataset included all patients who were prescribed for the first time with a DPP-4i or dapagliflozin irrespectively of whether they continued to be prescribed such treatment at follow-up. This dataset included patients who stopped drugs before follow-up visit and those for whom the prescription of the drugs was not confirmed at follow-up. Reasons for stopping were not available. We also performed an analysis in the "as-treated" (AT) dataset, which included all patients for whom the prescription of DPP-4i or dapagliflozin was confirmed at the follow-up visit, although information on drug refills rates were not available to evaluate adherence.

2.5 | Statistical analysis

Continuous variables are presented as mean and SD if normally distribution or as median and interquartile range, whereas categorical variables are presented as percentages. The comparison of baseline characteristics between the two groups was performed using Student's *t* test for continuous variables and the χ^2 test for categorical variables. Non-normal variables were log-transformed before analysis. To evaluate the balance between groups, we assessed *P*-values and the standardized mean difference (SMD). Good balance was achieved when the difference was not statistically significant and SMD was ≤0.1. Intra-group variation in endpoint variables between baseline and end of follow-up was analysed using paired 2-tail Student's *t* test.

To control the confounding by indication (channelling bias), we used two different approaches as depicted in Figure 1. In the primary analysis, we performed a propensity score matching (PSM), where patients in the dapaglifozin group were matched 1:1 with patients in the DPP-4i group. Propensity scores (PS) were calculated from the following baseline covariates: age, sex, duration of diabetes, baseline body weight, systolic and diastolic blood pressure, HbA1c, fasting

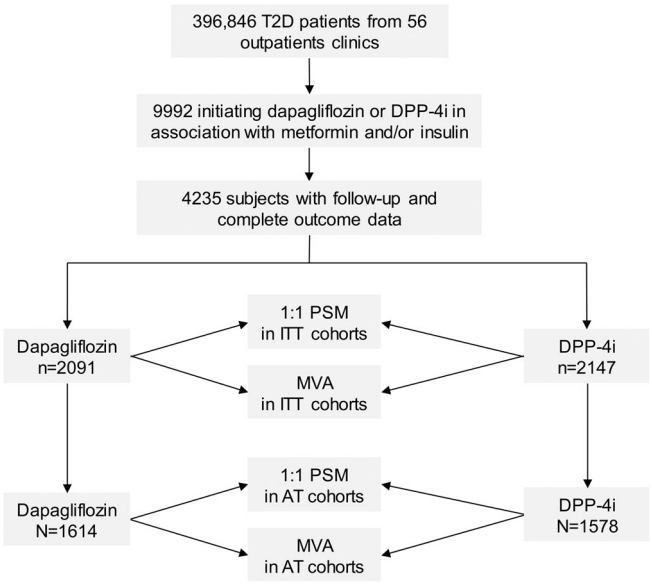

FIGURE 1 Study flowchart. T2D, type 2 diabetes. DPP-4i, dipeptidyl peptidase-4 inhibitors. AT, as treated; ITT, intention to treat; MVA, multivariable analysis; PSM, propensity score matching

plasma glucose, total and HDL cholesterol, triglycerides, eGFR, micro- or macro-albuminuria, diabetic retinopathy, diabetic macular oedema, microangiopathy, macroangiopathy, carotid atherosclerosis, carotid revascularization, history of stroke/TIA, coronary revascularization, ischemic heart disease (IHD), coronary heart disease (CHD), history of heart failure, left ventricular hypertrophy (LVH), use of other GLM (metformin and insulin), and other medications (angiotensin converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, anti-platelet therapies, beta-blockers, diuretics, lipid lowering therapies). To reduce bias arising from immortal time and time lag, we also included in PS models the number of GLM classes used by the patients before starting DPP-4i or dapagliflozin and the calendar year of index date. PSM were performed with nearest neighbour without replacement, with a calliper of 0.20 SD of the distribution of the logit PS. In matched cohorts, a direct between-group comparison of the outcome was allowed when there was no residual imbalance (SMD ≤0.1 and $P \geq .05$ for all variables). Thus, the percentage of patients meeting the primary and secondary endpoints were compared with log-binomial regression model without any further adjustment.

As an alternative approach to reduce bias and to confirm results obtained in matched cohorts, we performed sensitivity analyses in the entire dataset by means of multivariable adjusted (MVA) linear or log-binomial regression models (or, whenever the latter failed to converge, using Poisson regression model with robust error variances). These MVA analyses were adjusted for all clinical characteristics used to compute PS, as listed above.

For both PSM and MVA, full datasets of baseline variables were needed to compute PS or to be entered in the regression models. Therefore, missing data were handled with multiple imputation (MI). MI was performed as previously described.[25] Briefly a fully conditional specification (FCS) algorithm[26] was used to obtain 10 imputed datasets and including only covariates with less than 50% of missing values. Outcome variables were not imputed. Outcome analysis after PSM and MVA was performed on each imputed dataset and pooled estimated treatment difference (ETD) are presented.[27] For PSM, matched cohorts from each of the 10 imputed datasets slightly varied in their composition and size because the 10 imputed datasets were different and independent. The average of the 10 imputed dataset is presented. Relative risk (RR) with 95% confidence interval (C.I.) was calculated for binomial outcomes. A 2-tail *P*-value <.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (TS1M4), graphs were produced with GraphPad Prism ver. 8.

3 | RESULTS

3.1 | Patient characteristics

The study collected data from 56 outpatient clinics, serving a total of 396 846 T2D patients, estimated to represent 21% of the total T2D population attending Italian diabetes clinics. From 9992 patients who started a new therapy with dapagliflozin or DPP-4i in the period of interest, we included 4235 subjects with available baseline and follow-up data for HbA1c, SBP, and body weight, of whom 2144 initiated DPP-4i and 2091 initiated dapagliflozin (Figure 1). Prior to matching, most clinical characteristics were significantly different between the two groups (Table 1). Patients who initiated dapagliflozin as compared to those who initiated DPP-4i were younger, yet with a longer duration of diabetes, worst glycaemic, lipid and blood pressure profile and higher prevalence of microangiopathy. Dapagliflozin was prescribed more often than DPP-4i as third line of treatment and with concomitant use of insulin. After the 1:1 PSM, 1149 patients were selected from the dapagliflozin and DPP-4i groups. In the matched cohorts, all baseline clinical characteristics were well balanced between groups (all $P > .10$ and SMD > 0.10; Table 1 and Figure S1). Patients were on average 63 years old, with a known diabetes duration of 11 years, a BMI of 31 kg/m^2 and a baseline HbA1c of 8.1%. The vast majority of patients were receiving metformin and 42% of patients were also on insulin. Prevalence of micro- and macroangiopathy was 29% and 32%, respectively. About two thirds of patients were on statins and renin-angiotensin blockers.

3.2 | Effectiveness in unmatched cohorts

After a median follow-up time of 7.2 months (IQR 6.2-9.9), the primary endpoint was reached in 14.4% of the patients included in the study (611/4235): 9.4% in the DPP-4i group (202/2144) and 19.6% in the dapagliflozin group (409/2091). As shown in Table 2, HbA1c declined by 0.5 ± 1.0% in the DPP-4i group and by 0.8 ± 1.4% in the dapagliflozin group; body weight declined by 0.8 ± 3.6 kg in the DPP-4i group and by 2.8 ± 4.9 kg in the dapagliflozin group; SBP declined by −1.3 ± 18.6 mmHg in the DPP-4i group and by −3.7 ± 18.8 mmHg in the dapagliflozin group.

3.3 | Comparative effectiveness in matched cohorts

After PSM, 1149 patients in each group were compared. The median follow-up time was 7.3 (IQR 6.2-9.9) months in the DPP-4i group and 7.1 (IQR 6.2-9.9) months in the dapagliflozin group ($P = .77$). The primary endpoint was reached in a greater proportion of patients who received dapagliflozin compared to those who received DPP-4i (17.6% vs 11.7%), with a RR of 1.50 (95% C.I. 1.21-1.86; $P < .001$; Figure 2). Such difference was mainly driven by the greater proportion of patients attaining a reduction of 2 kg or more in body weight in the dapagliflozin group (60.1% vs 37.7%; RR 1.59; 95% C.I. 1.44-1.76; $P < .001$). Conversely, there was no significant between-group difference in the proportion of patients attaining a 0.5% or greater reduction in HbA1c (51.4% vs 55.6%; RR 0.92; 95% C.I. 0.85-1.01; $P = .067$) and a 2 mmHg or greater reduction in SBP (47.5% vs 45.0%; RR 1.06; 95% C.I. 0.95-1.17; $P = .305$).

TABLE 1 Clinical characteristics of study patients in the intention-to-treat dataset

	Before PSM					After 1:1 PSM*			
	Avail (%)	DPP-4i N = 2144	Dapagliflozin N = 2091	SMD	*P*	DPP-4i N = 1149	Dapagliflozin N = 1149	SMD	*P*
Age, years	100%	65.5 ± 9.7	61.1 ± 9.0	0.47	<.01	63.2 ± 10.2	62.6 ± 8.5	0.06	.22
Sex male, n (%)	100%	1264 (59.0%)	1284 (61.4%)	−0.05	.10	710 (61.8%)	705 (61.4%)	0.01	.84
Diabetes duration, years	100%	10.9 ± 7.8	12.2 ± 8.0	−0.16	<.01	11.2 ± 8.1	11.4 ± 8.0	−0.03	.59
Risk factors									
Weight, kg	100%	79.3 ± 16.0	91.8 ± 18.2	−0.73	<.01	84.9 ± 16.5	85.8 ± 15.6	−0.06	.19
BMI, kg/m^2	98%	28.8 ± 5.1	32.7 ± 5.8	−0.72	<.01	30.5 ± 5.3	30.8 ± 4.9	−0.06	.17
SBP, mm Hg	100%	136.7 ± 18.6	140.5 ± 18.7	−0.20	<.01	138.3 ± 19.3	138.3 ± 18.1	0.00	.99
DBP, mm Hg	100%	77.9 ± 9.1	80.2 ± 10.1	−0.24	<.01	78.9 ± 9.1	79.0 ± 9.7	−0.01	.79
Laboratory exams									
FPG, mg/dL	93%	153.9 ± 39.6	176.0 ± 58.0	−0.44	<.01	160.1 ± 42.4	161.9 ± 48.3	−0.04	.44
HbA1c, %	100%	7.8 ± 0.9	8.6 ± 1.5	−0.70	<.01	8.0 ± 1.0	8.1 ± 1.2	−0.09	.06
Total cholesterol, mg/dL	78%	169.0 ± 37.4	174.7 ± 38.3	−0.15	<.01	171.7 ± 38.4	172.6 ± 36.5	−0.01	.75
HDL cholesterol, mg/dL	76%	49.1 ± 13.4	45.8 ± 12.7	0.26	<.01	47.3 ± 12.6	47.1 ± 13.1	0.03	.53
Triglycerides, mg/dL	78%	136.8 ± 72.2	169.5 ± 127.1	−0.32	<.01	148.8 ± 79.0	153.0 ± 91.8	−0.03	.51
LDL cholesterol, mg/dL	74%	92.4 ± 31.5	95.7 ± 32.5	−0.10	<.01	94.3 ± 32.2	95.1 ± 31.1	−0.03	.62
eGFR, ml/min/1.73 m^2	100%	86.4 ± 13.4	90.0 ± 13.9	−0.26	<.01	88.2 ± 13.9	88.6 ± 13.5	−0.03	.47
AER, mg/24 hours	44%	74.9 ± 319.1	99.1 ± 330.3	−0.07	.11	94.6 ± 387.4	79.7 ± 297.9	0.04	.51
Complications									
CKD III stage, n (%)	100%	0 (0.0%)	0 (0.0%)	na	na	0 (0.0%)	0 (0.0%)	na	na
Nephropathy, n (%)	100%	230 (10.7%)	340 (16.3%)	−0.16	<.01	149 (13.0%)	151 (13.1%)	−0.01	.92
Retinopathy, n (%)	81%	186 (10.8%)	325 (18.8%)	−0.22	<.01	126 (13.9%)	135 (14.6%)	−0.02	.62
Any Neuropathy, n (%)	81%	34 (2.0%)	63 (3.7%)	−0.10	<.01	25 (2.7%)	26 (2.8%)	−0.01	.53
DME, n (%)	38%	205 (25.7%)	233 (28.5%)	−0.06	<.01	112 (27.6%)	111 (25.4%)	0.05	.90
Carotid ather, n (%)	55%	417 (34.7%)	367 (32.7%)	0.06	.31	210 (33.5%)	213 (35.6%)	0.00	.94
Carotid revasc, n (%)	55%	5 (0.4%)	1 (0.1%)	0.02	.12	2 (0.4%)	1 (0.1%)	0.01	.85
Stroke/TIA, n (%)	55%	81 (6.7%)	84 (7.5%)	−0.03	.48	37 (5.9%)	42 (7.0%)	−0.01	.80
Prior MI, n (%)	83%	96 (5.5%)	85 (4.8%)	0.02	.35	45 (4.9%)	46 (4.7%)	0.00	.95
Coronary revasc, n (%)	83%	147 (8.4%)	107 (6.0%)	0.08	.01	62 (6.8%)	63 (6.4%)	0.00	.94
CHD, n (%)	83%	213 (12.2%)	183 (10.3%)	0.04	.08	93 (10.2%)	102 (10.5%)	−0.02	.70
Heart Failure. n (%)	83%	36 (2.1%)	38 (2.1%)	−0.01	.86	18 (2.0%)	21 (2.1%)	−0.01	.81
LVH, n (%)	83%	125 (7.2%)	124 (7.0%)	0.01	.85	54 (5.9%)	58 (6.0%)	0.00	.97
PAD, n (%)	41%	122 (14.4%)	115 (12.9%)	0.05	.35	62 (14.6%)	63 (13.0%)	0.06	.41
LE revasc., n (%)	41%	20 (2.4%)	21 (2.4%)	0.00	.99	10 (2.4%)	14 (2.9%)	−0.03	.69
Microangiopathy, n (%)	100%	538 (25.1%)	741 (35.4%)	−0.23	<.01	332 (28.9%)	339 (29.5%)	−0.01	.80
Macroangiopathy, n (%)	87%	642 (34.9%)	574 (31.0%)	0.07	.01	314 (32.4%)	325 (32.2%)	0.00	.93

(Continues)

TABLE 1 (Continued)

	Before PSM					After 1:1 PSM*			
	Avail (%)	DPP-4i N = 2144	Dapagliflozin N = 2091	SMD	*P*	DPP-4i N = 1149	Dapagliflozin N = 1149	SMD	*P*
Established CVD, n (%)	87%	331 (18.0%)	288 (15.6%)	0.05	.05	149 (15.4%)	157 (15.5%)	−0.02	.75
Diabetes medications[a]									
Insulin, n (%)	100%	616 (28.7%)	1204 (57.6%)	−0.61	<.01	464 (40.4%)	505 (44.0%)	−0.07	.11
Metformin, n (%)	100%	2056 (95.9%)	1864 (89.1%)	0.26	<.01	1080 (94.0%)	1071 (93.2%)	0.03	.46
Prev. line of treatment[b]	80%	1.6 ± 0.9	2.1 ± 1.2	−0.42	<.01	1.7 ± 0.9	1.8 ± 1.1	−0.05	.29
Other medications									
Statin, n (%)	87%	1240 (67.5%)	1218 (65.7%)	0.04	.24	640 (66.1%)	667 (65.6%)	0.00	.97
ACEi/ARB, n (%)	87%	1193 (64.9%)	1294 (69.8%)	−0.10	<.01	649 (67.0%)	672 (66.1%)	0.01	.82
CCB, n (%)	87%	414 (22.5%)	427 (23.0%)	−0.01	.73	215 (22.2%)	225 (22.1%)	−0.01	.89
Beta-blockers, n (%)	87%	599 (32.6%)	551 (29.7%)	0.05	.06	301 (31.1%)	304 (29.9%)	0.01	.87
Diuretics, n (%)	87%	625 (34.0%)	645 (34.8%)	−0.01	.63	318 (32.8%)	342 (33.6%)	−0.02	.72
APT, n (%)	87%	867 (47.2%)	802 (43.2%)	0.07	.02	424 (43.7%)	438 (43.1%)	0.00	.99
Follow-up (months)	100%	7.9 ± 2.3	8.0 ± 2.3	0.00	.88	7.9 ± 2.3	8.0 ± 2.3	−0.01	.77

Note: The two groups were compared after propensity score matching (PSM). In addition to *P*-values, standardized mean differences (SMD) are shown. Only observed data are presented. *For matched cohorts, the baseline and SMD values are the means across the 10 imputed dataset.

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; APT, anti-platelet therapies; ARBs, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blockers; CHD, Coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DME, Diabetic Macular Edema; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GLM, glucose lowering medications; HDL, high density lipoprotein; LE revasc, lower extremities revascularization; LVH, left ventricular hypertrophy; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attack.

[a]The combination of SGLT-2 inhibitors were reimbursed only with concomitant metformin and/or insulin treatment.

[b]Number of classes of anti-diabetic drugs used by the patients before the initiation of DPP-4i or dapagliflozin.

Similar results were obtained for the main secondary endpoint, that is, the proportion of patients achieving simultaneously any reduction in HbA1c, body weight, and SBP (27.4% in the dapagliflozin group vs 21.1% in the DPP-4i group; RR 1.30; 95% C.I. 1.11-1.52; *P* = .001; Figure S2).

The change in HbA1c was superimposable (−0.6 ± 1.2%) in the two groups (*P* = .423). Body weight declined significantly more in the dapagliflozin group (ETD −1.64 ± 0.20 kg; *P* < .001), whereas the change in SBP was not significantly different (ETD −1.0 ± 0.9 mmHg; *P* = .271; Table 2).

The proportion of patients with persistent drug prescription at the follow-up visit was similar in the DPP-4i and dapagliflozin groups before (75.3% vs 75.5%; *P* = .888) and after PSM (74.2% vs 74.6%; *P* = .566). In the AT dataset, PSM yielded two groups of 819 patients with a good balance in all baseline characteristics (Table S1 and Figure S1). Results were very similar to those obtained in the ITT dataset (Figure 1 and Table 2): a greater proportion of patients in the dapagliflozin group reached the primary endpoint (RR 1.67; 95% C.I. 1.32-2.13; *P* < .001) and the main secondary endpoint (RR 1.43; 95% C.I. 1.20-1.69; *P* = .001). As expected, improvements in HbA1c, body weight and SBP tended to be greater in the AT than in the ITT analysis: reduction of HbA1c was still similar between groups, body weight declined more in the dapagliflozin group, and the difference in SBP was close to statistical significance in favour of dapagliflozin (*P* = .051).

3.4 | Effectiveness analysis with multivariable adjustment

MVA mostly confirmed results obtained in the PSM cohorts (Figure 1 and Table S2), with dapagliflozin being associated with a higher probability of reaching the primary endpoint (ITT: RR 1.60; 95% C.I. 1.33-1.92; AT: RR 1.74; 95% C.I. 1.41-2.14) and the main secondary endpoint (ITT: RR 1.30; 95% C.I. 1.11-1.52; AT: RR 1.34; 95% C.I. 1.18-1.52). MVA confirmed a 1.6 kg (ITT) and 1.9 kg (AT) greater reduction in body weight with dapagliflozin and revealed a greater reduction of HbA1c in the DPP-4i group by 0.1% (ITT and AT). In the AT dataset, reduction of SBP was significantly in favour of dapagliflozin by 1.8 mmHg.

TABLE 2 Analysis of secondary endpoints

	Outcome	DPP-4i				Dapagliflozin				ETD (SE)	*P*
Comparison		N	Baseline	Follow-up	Change	N	Baseline	Follow-up	Change		
ITT unmatched	HbA1c	2144	7.76 ± 0.95	7.26 ± 0.94	−0.50 ± 1.04*	2091	8.63 ± 1.49	7.78 ± 1.20	−0.84 ± 1.38*		
	Weight	2144	79.3 ± 16.0	78.5 ± 15.9	−0.8 ± 3.6*	2091	91.8 ± 18.2	89.0 ± 18.1	−2.8 ± 4.9*		
	SBP	2144	136.7 ± 18.6	135.5 ± 18.2	−1.3 ± 18.6*	2091	140.5 ± 18.7	136.8 ± 18.1	−3.7 ± 18.8*		
ITT matched	HbA1c	1149	8.01 ± 1.03	7.38 ± 1.00	−0.63 ± 1.17*	1149	8.11 ± 1.23	7.52 ± 1.08	−0.59 ± 1.18*	0.04 (0.05)	.423
	Weight	1149	84.9 ± 16.5	83.8 ± 16.3	−1.1 ± 3.8*	1149	85.8 ± 15.6	83.1 ± 15.8	−2.7 ± 5.0*	−1.64 (0.20)	<.0001
	SBP	1149	138.3 ± 19.3	136.3 ± 18.8	−2.0 ± 18.8*	1149	138.3 ± 18.1	135.3 ± 17.5	−3.0 ± 18.3*	−1.00 (0.90)	.271
AT unmatched	HbA1c	1614	7.77 ± 0.95	7.16 ± 0.85	−0.61 ± 0.99*	1578	8.68 ± 1.53	7.69 ± 1.15	−0.99 ± 1.39*		
	Weight	1614	78.7 ± 15.4	77.9 ± 15.2	−0.8 ± 3.4*	1578	91.9 ± 17.9	88.8 ± 17.9	−3.1 ± 4.9*		
	SBP	1614	136.7 ± 18.5	135.3 ± 18.0	−1.4 ± 18.5*	1578	140.4 ± 18.6	136.2 ± 17.8	−4.2 ± 18.6*		
AT matched	HbA1c	819	8.02 ± 1.05	7.25 ± 0.91	−0.77 ± 1.12*	819	8.12 ± 1.26	7.42 ± 1.03	−0.70 ± 1.20*	0.07 (0.07)	.290
	Weight	819	84.2 ± 15.9	83.2 ± 15.7	−1.1 ± 3.7*	819	85.2 ± 15.3	82.3 ± 15.5	−3.0 ± 5.4*	−1.90 (0.23)	<.0001
	SBP	819	138.1 ± 18.9	136.2 ± 18.6	−1.9 ± 18.6*	819	138.3 ± 18.4	134.5 ± 17.2	−3.8 ± 18.5*	−1.93 (0.99)	.051

Note: For each comparison and outcome, we report the number of patients, the values (mean and SD) at baseline and follow-up, the change from baseline and the estimated treatment difference (ETD) with its standard error (SE), along with the respective *P*-values. For matched cohorts, the baseline, follow-up and changes values are the means across the 10 imputed datasets. The pooled ETD from the ten imputed dataset is presented.

Abbreviations: AT, as treated; FPG, fasting plasma glucose; ITT, intention to treat; SBP, systolic blood pressure.

*$P < .05$ vs baseline.

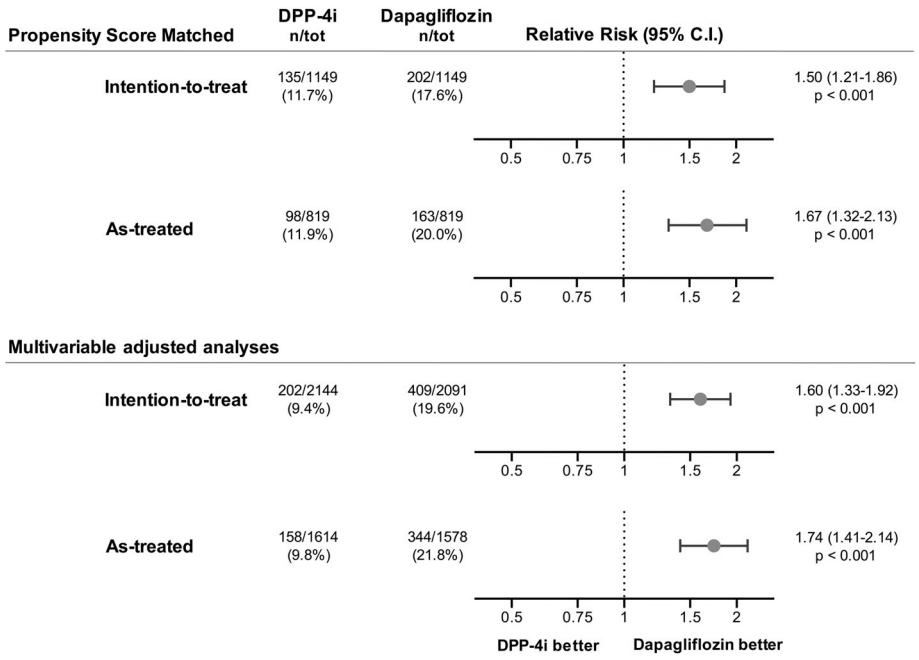

FIGURE 2 Analysis of the primary endpoint. Achievement of primary composite endpoint in the DPP-4i and dapagliflozin groups according to the primary analyses (propensity score matching [PSM] model in the intention-to-treat dataset) and in exploratory analyses (as-treated dataset and following multivariable analysis [MVA] models)

4 | DISCUSSION

In this multicentre, observational, real-world study, we found that T2D patients initiating the SGLT2i dapagliflozin on top of metformin and/or insulin had a 50%-70% relative greater probability of attaining a composite endpoint of clinically relevant simultaneous reductions in HbA1c, body weight and SBP, compared to similar patients initiating a DPP-4i in the same period and healthcare setting. These findings are in line with results obtained by RCTs[16] and extend them to the wider population of T2D patients seen in clinical practice. Since publication of the groundbreaking results of the STENO-2 trial,[28] multifactorial intervention has become a cornerstone for the prevention of chronic diabetic complications. Indeed, in large T2D populations, being at target for multiple risk factors is associated with better cardiovascular outcomes.[29, 30] The latest consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) emphasizes that treatment of T2D should aim at preventing or delaying complications through the control of glycaemia and cardiovascular risk factors.[31] The cardiovascular efficacy of intensive glucose control has been debated,[32, 33] whereas cardiovascular protection can be obtained with GLM that provide multiple extra-glycaemic benefits, such as SGLT2i and GLP-1 receptor agonists (GLP-1RA). In a recent analysis of the DARWIN study series, we found that the proportion of T2D patients attaining simultaneously a HbA1c reduction of 0.5% or greater, a body weight reduction of 2 kg or greater and a SBP reduction of 2 mmHg or greater was similar between dapagliflozin and GLP-1RA.[34] We now report, in a larger population of patients, the superiority of dapagliflozin vs DPP-4i on the same endpoint. This finding has important implications in the routine care of T2D because DPP-4i have become popular second-line GLM worldwide and in Italy,[35] despite they are devoid of solid cardio-renal protective effects.[36] We recognize that combination therapy with SGLT2i and DPP-4i or incretin-based therapies in general, which has recently become available in many countries, can provide an additional benefit on several clinical outcomes.[37]

Our data suggest that the greater probability of attaining the combined endpoint in dapagliflozin-treated vs DPP-4i-treated patients was largely dependent from the effect on body weight and, to a lesser extent, on SBP. On the other side, HbA1c improvement was similar in the two groups. In RCTs on patients uncontrolled with metformin, SGLT2i were reported to be more effective than[38] or non-inferior to[39, 40] DPP-4i in reducing HbA1c. In our study, patients in both groups had been treated with a median of two prior lines of GLM and more than 40% were on insulin. In addition, baseline HbA1c tended to be lower than in RCTs. Therefore, a direct comparison of glycaemic effect between our study and RCTs is confounded by the different disease stage and concomitant medications. A prior study conducted on a German primary care database of patients with T2D reported that initiation of dapagliflozin reduced HbA1c similar to basal insulin with the additional benefit of weight reduction.[41] Thus, the effects of dapagliflozin on body weight emerges as a major benefit of this therapy, which is expected to drive, at least in part, the cardiovascular protection observed in CVOTs.[42]

We wish to acknowledge that we herein considered only dapagliflozin, but similar results may apply to other molecules of the SGLT-2i class. Future real-world studies on effectiveness of empagliflozin, canagliflozin and ertugliflozin may confirm the findings we obtained with dapagliflozin.

The present study suffers from the typical limitations of observational research on comparative drug effectiveness. Analysis of the unmatched groups of patients initiating dapagliflozin or DPP-4i revealed large differences in most clinical characteristics, forming the basis of a strong confounding by indication. To reduce this channelling bias, we obtained two cohorts matched on propensity scores. This

approach simulates a pseudo-randomized condition, characterized by equal a posteriori probability of each subject being assigned to either treatment given baseline covariates. As an alternative strategy, we performed multivariable adjustment (MVA). While PSM restricts the cohorts being analysed, MVA avoids the exclusion of patients but assumes linearity between covariates and the outcome. Importantly, we obtained consistent results with these different methods, suggesting that known confounding was appropriately addressed. Yet, we cannot rule out residual confounding by unmeasured variables that could drive the outcome, such as socio-economic status, education, compliance, patient's and physician's attitudes. This is one reason why the level of evidence arising from observational comparative studies does not equate that of RCTs. Although the AT and ITT analyses produced very similar results, we had no information on drug refill rates to compute adherence, and persistence on treatment was defined based only on the refilled medical prescription. Additionally, no information was available on the reasons why about 25% of patients in each group discontinued treatment with dapagliflozin or DPP-4i and on eventual adverse events. Finally, although follow-up duration was similar to that of most phase III RCTs, it allows no conclusion on the long-term comparative effectiveness.

Notwithstanding these limitations, our real world study provides useful information on the multiple benefits experienced by T2D patients after initiating dapagliflozin as compared to DPP-4i in routine clinical practice. These findings complement results from RCTs and help the generation of a comprehensive set of evidence that can be useful for clinical decision-making.

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CONFLICT OF INTEREST

M.L.M. received lecture fees or grant support from Amryt Pharma and Servier. A.C. has consulting relationships with Astra Zeneca and Novo Nordisk; has participated in advisory panels for Abbot, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Novo-Nordisk, Sanofi-Aventis, Takeda; has received speaker fees from Abbot, Astra Zeneca, Boehringer Ingelheim, Bruno Farmaceutici, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Novo-Nordisk, Sanofi-Aventis, Takeda; has received research supporting grants from Astra Zeneca, Eli Lilly, Novo Nordisk. G.S. has received speaker/consulting honoraria from Novo Nordisk, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Sanofi, Amgen, Abbott, GlaxoSmithKline and Servier. F.P. has received honoraria for participating in advisory boards or speaking engagement from Eli Lilly, Novo Nordisk, Sanofi, MSD, AstraZeneca, Boheringer, GSK, Novartis, Menarini. A.A. received research grants, lecture or advisory board fees from Merck Sharp & Dome, AstraZeneca, Novartis, Boeringher-Ingelheim, Sanofi, Mediolanum, Janssen, Novo Nordisk, Lilly, Servier and Takeda. G.P.F. received lecture fees or grant support from Abbott, AstraZeneca, Boehringer, Lilly, Merck-Sharp-Dome, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier.

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Mario Luca Morieri analysed data and wrote the manuscript; Agostino Consoli, Giorgio Sesti, Francesco Purrello designed the study, provided supervision and revised the manuscript; Angelo Avogaro designed the study, collected data, provided support and wrote the manuscript; Gian Paolo Fadini designed the study, collected and analysed data, and wrote the manuscript. All authors approved the final version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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