Use and effectiveness of dapagliflozin in routine clinical practice. An Italian multicenter retrospective study

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Abstract

In randomized controlled trials (RCTs), SGLT-2 inhibitors (SGLT2i) showed glycaemic and extra-glycaemic benefits. The DARWIN-T2D (DApagliflozin Real World evIdeNce in Type 2 Diabetes) was a multicenter retrospective study designed to evaluate baseline characteristics of patients

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receiving dapagliflozin versus selected comparators (DPP-4 inhibitors, gliclazide, or GLP-1 receptor agonists), and drug effectiveness in routine clinical practice. From a population of 281,217 patients, the analysis included 17,285 initiating dapagliflozin or comparator glucose lowering medications (GLM), 6751 of whom had a follow-up examination. At baseline, patients starting dapagliflozin were younger, had a longer disease duration, higher HbA1c, and a more complex history of previous GLM use, but the clinical profile of patients receiving dapagliflozin was changing during the study period. Dapagliflozin reduced HbA1c by 0.7%, body weight by 2.7 kg, and systolic blood pressure by 3.0 mm Hg. Effects of comparator GLM were also within the expected range based on RCTs. This real-world study demonstrates an initial channelling of dapagliflozin to difficult-to-treat patients. Nonetheless, dapagliflozin provided significant benefits on glucose control, body weight, and blood pressure that were in line with findings from RCTs.

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Introduction

Sodium glucose co-transporter-2 inhibitors (SGLT2i) exert a variety of favourable glycaemic and extra-glycaemic effects [1]: in phase III randomized controlled trials (RCTs), SGLT2i lowered HbA1c by about 0.5-0.7%, body weight by 2-3 kg, and blood pressure by 3-4 mm Hg in patients with type 2 diabetes (T2D) [2, 3]. Although RCTs deliver the best evidence for clinical decision, they suffer from limited external transferability [4]. Real-world retrospective studies using routinely accumulated clinical data are gathering a revamped interest for their ability to collect large representative datasets in a relatively short time. These studies are subjected to channelling bias (or confounding by indication) [5], especially for newly marketed drugs [6], which can be addressed using strategies of propensity score matching (PSM) [7]. When a sufficient overlap between patient groups exists [8], PSM can generate quasi-experimental comparisons that make retrospective studies closer to RCTs. For instance, two RCTs indicate that SGLT2i improve cardiovascular outcomes in patients with T2D and high risk for or established cardiovascular disease [9, 10] and two retrospective studies on administrative databases have confirmed such finding in broader T2D patient populations [11, 12].

The DARWIN-T2D was a multicenter Italian retrospective study designed to evaluate use and effectiveness of dapagliflozin, the first-in-class SGLT2i in Italy, compared to other glucose lowering medications (GLM) in routine clinical practice [13]. We herein present data on baseline clinical characteristics with their temporal trends, along with an initial assessment of effectiveness.

Materials and Methods

We have previously published a detailed description of the design of this study [13] and an expanded Method section can be found in the Supplementary Appendix. Briefly, DARWIN-T2D was a multicentre nationwide retrospective study designed to evaluate the baseline clinical characteristics and the change in glycaemic and extra-glycaemic effectiveness parameters in patients initiated on dapagliflozin versus patients initiated on DPP4 inhibitors (DPP4i), gliclazide, or GLP-1 receptor agonists (GLP-1RA), in Italian diabetes outpatient clinics. The study flowchart is shown in Figure S1. An automated software retrospectively extracted data from the same electronic chart system at all Centres.

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Statistical analysis

Continuous variables were presented as mean±standard deviation, whereas categorical variables were expressed as percentage. Normality was checked using the Kolmogorov-Smirnov test and non-normal variables were log-transformed. Comparison between two groups was performed using the two-tail unpaired Student's t test or chi square test. Adjusting for multiple testing was performed using the Benjamini-Hochberg procedure. The two-tail paired Student's t test was used to compare data collected at follow-up with those collected at baseline. Statistical significance level was set at $p<0.05$.

Results

Baseline clinical characteristics

The study collected data from 46 Italian Diabetes Specialist Outpatient Clinics, for a total background population 281,217 T2D patients. For the purpose of the present analysis, we extracted detailed information on 17,285 patients who initiated dapagliflozin (n=2484), a DPP-4i (n=6594: sitagliptin 57.2%; alogliptin 19.7%; vildagliptin 19.6%; saxagliptin 3.5%), gliclazide (n=5960) or a long-acting GLP-1RA (n=2247: liraglutide 73.3%; exenatide extended release 26.7%) between March15th 2015 and December 31th 2016.

Baseline clinical characteristics of patients in the 4 groups are shown in Table S1. Significant differences among groups were detected for most variables: patients initiated on dapagliflozin were younger, had longer diabetes duration and higher fasting plasma glucose, HbA1c, and blood pressure than patients in the other 3 groups and were more obese than patients initiated on DPP-4i or gliclazide, but less than patients initiated on a GLP-1RA. The baseline lipid profile was slightly but significantly worse in the dapagliflozin versus the DPP-4i and gliclazide groups, but not when compared to the GLP-1RA group. The frequency of microangiopathy at baseline was higher in patients initiated on dapagliflozin than in the other 3 groups, whereas the frequency of macroangiopathy was lower in the dapagliflozin than in the DPP-4i and gliclazide groups.

Metformin and insulin use were more common in the dapagliflozin group than in the other 3 groups, at the time of prescription of the new drugs and in the previous prescription. More than half of patients receiving dapagliflozin were insulin-treated, about half of whom were on basal-bolus insulin. The historical therapeutic regimen was also more complex in the dapagliflozin than in other

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groups. All concomitant cardiovascular medications were less frequent among dapagliflozin users than in control groups.

Heterogeneity arising from the Center effect, geographical location, and temporal trends are described in the Online Appendix (Table S2-3; Figures S2-3).

Analyses of effectiveness

Changes in glycaemic and extraglycaemic effectiveness parameters were calculated for patients having a follow-up visit 3-12 months after baseline and still being on drug. Of the 17,285 patients evaluated at baseline, n=6751 (39.1%) had a follow-up visit: n=830 (33.4%) for dapagliflozin, n=2999 (45.5%) for DPP-4i, n=2111 (35.4%) for gliclazide, and n=811 (36.1%) for GLP-1RA (Table 1 and Figure 1).

Patients initiated on dapagliflozin, after an average 168 days (5.5 months), showed significant improvements in fasting plasma glucose (-28.2 mg/dl), HbA1c (-0.7%), body weight (-2.7 kg), systolic blood pressure (-3.0 mm Hg), diastolic blood pressure (-1.3 mm Hg), total cholesterol (-3.5 mg/dl), HDL cholesterol (+1.6 mg/dl), and triglycerides (-15.9 mg/dl), with no change in LDL cholesterol. For patients initiating dapagliflozin on a background of insulin therapy, HbA1c significantly declined by 0.8% (from 9.1% to 8.3%) and body weight significantly declined by 2.2 kg (from 93.2 to 91.0 kg).

Patients initiated on a DPP-4i, after an average 185 days (6.1 months), showed significant improvements in fasting plasma glucose (-11.5 mg/dl), HbA1c (-0.6%), body weight (-0.5 kg), total cholesterol (-5.4 mg/dl), triglycerides (-8.1 mg/dl) and LDL cholesterol (-4.2 mg/dl).

Patients initiated on gliclazide, after an average 185 days (6.1 months) showed significant improvements in fasting plasma glucose (-14.8 mg/dl), HbA1c (-0.6%), total cholesterol (-8.0 mg/dl), triglycerides (-12.9 mg/dl), and LDL cholesterol (-5.5 mg/dl).

Patients initiated on a GLP-1RA, after an average 169 days (5.6 months), showed significant improvements in fasting plasma glucose (-17.2 mg/dl), HbA1c (-0.6%), body weight (-2.4 kg), total cholesterol (-11.6 mg/dl), and LDL cholesterol (-10.1 mg/dl).

The percentage of patients meeting the composite endpoint of simultaneous HbA1c and body weight reduction was 56.9% for dapagliflozin, 40.5% for DPP-4i, 28.7% for gliclazide, and 56.2% for GLP-1RA (Figure S4). The corresponding percentages for the combined endpoint of simultaneous HbA1c, body weight and SBP reductions were 31.5%, 18.2%, 12.3%, and 29.7%, respectively.

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For each group, we estimated the expected improvement in cardiovascular risk using the UKPDS risk engine [14]. Patients initiated on dapagliflozin showed the most consistent and significant reduction in the estimated 10-year risk of CHD, fatal CHD, stroke, and fatal stroke (Table S4).

Results of PSM are described in the Supplementary Appendix. Common support between the dapagliflozin and comparator groups was very low (Figure S5) and the conditions for comparing matched cohorts were precarious (Figure S6). Therefore, outcome analysis after PSM was not performed.

Discussion

DARWIN-T2D was a large retrospective study using clinical data routinely accumulated in electronic charts, involving 17,285 patients, of whom 6751 had a follow-up examination. The comparison of baseline characteristics revealed statistically significant and clinically meaningful differences in most variables between patients who started dapagliflozin and those who started a comparator. This was expected from an individualized therapy approach, but the HbA1c divide among groups was striking. A baseline HbA1c value of 8.7% reflects that dapagliflozin was being preferentially used in patients with moderately to severely uncontrolled diabetes. The reason for this channelling is likely twofold. First, incretin-based therapies were reimbursed by the Italian Healthcare System only if initiated in patients with an HbA1c between 7.5% and 9.0%, whereas such limitation was not imposed to SGLT2i. Dapagliflozin was reimbursed only in association with metformin and/or insulin (including the basal-bolus regimen), whereas incretin-based therapies could be reimbursed with multiple combinations of GLM but not with basal-bolus insulin, and gliclazide had no reimbursement limitations. These different criteria were responsible for enriching insulin therapy among patients initiating dapagliflozin. The high baseline HbA1c and the more frequent use of previous GLM suggests that many patients initiating dapagliflozin were poor responders to other GLM classes. Second, newly marketed drugs are initially tested on the most difficult-to-treat patients, whereas the peculiar characteristics of patients initiating a new drug are expected to mitigate over time when the new drug becomes more established. A time-trend analysis showed that the overall differences in clinical characteristics at the time patients initiated dapagliflozin versus other treatments were tapering over time, indicating that dapagliflozin was being progressively used in less severe cases.

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The analysis of effectiveness was based on 6751 patients still on drug at follow-up, about 6 months after baseline. The within-group analysis in the total cohort showed improvements in HbA1c (-0.7%), FPG (-28.2 mg/dl), body weight (-2.7 kg), and systolic blood pressure (-3.0 mm Hg) after initiation of dapagliflozin that were consistent with findings from phase III RCTs [2, 3]. A benefit on lipid profile was also observed, confirming the increase in HDL cholesterol and reduction of triglycerides seen in RCTs [15], but with no significant increase in LDL cholesterol. Among patients initiating dapagliflozin on a background of insulin therapy, HbA1c and body weight declined more than in the corresponding RCTs [16]. Effectiveness in patients initiated on DPP4i, gliclazide, or a GLP-1RA also was also well within the range expected from RCTs [17]. Cardiovascular risk estimated using the UKPDS risk engine [14], improved with all treatments, but only dapagliflozin therapy was associated with a significant reduction in the projected risk of all the four endpoints, because of simultaneous improvements in glucose, body weight, blood pressure, and lipids.

Between-group comparisons of effectiveness were hampered by massive differences in baseline clinical characteristics, that could not be overcome by PSM. Further analyses will be performed on the DARWIN-T2D database and its follow-up extension to provide more information on comparative effectiveness.

This study suffers from all the limitations inherent to its retrospective nature, including patient heterogeneity, risk of inverse causality, concerns on data quality and missingness. Importantly, the DARWIN-T2D database is not yet linked with administrative registries and data on hard cardiovascular endpoints are not available. Major strengths of DARWIN-T2D include the large sample size with nationwide distribution, the extensive patient characterization and, above all, the automatic data extraction from the same electronic chart, which granted uniform data coding and limited reporting errors.

In conclusion, during the first 21 months after marketing authorization approval in the Italian routine clinical practice, dapagliflozin was prescribed to the most difficult-to-treat patients, many of whom were poor responders to previous GLM and >50% were on insulin. A “launch effect” and differential reimbursement criteria were responsible for this massive channelling, but the scenario is progressively changing. Nonetheless, even in difficult-to-treat patients, effectiveness of dapagliflozin on glycaemic and extraglycaemic endpoints was comparable to results obtained in RCTs and >50% of patients experienced a simultaneous reduction in HbA1c and body weight.

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Table 1. Change in glycaemic and extra-glycaemic effectiveness parameters in the four groups. For each treatment group and for each variable, the number of patients with available data in both the baseline and follow-up (F-up) visit are reported. SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; HDL, high density lipoprotein cholesterol; TG, triglycerides; LDL, low density lipoprotein cholesterol.

	Dapagliflozin					**DPP-4 inhibitors**				
	n	**Baseline**	**Follow-up**	**Delta**	**p**	**n**	**Baseline**	**Follow-up**	**Delta**	**p**
Age, years	830	60.2±9.3				2999	67.2±9.1			
Sex male %	830	61.2				2999	59.3			
BMI, kg/mq	748	33.1±6.0				2644	29.1±4.9			
Duration, yrs	830	12.4±8.2				2999	11.0±7.7			
F-up, days	830	168.1±55.5				2999	185.7±49.0			
Weight, kg	735	92.8±19.0	90.1±18.8	-2.7±3.5	<0.001	2420	79.7±15.2	79.2±15.0	-0.5±3.1	<0.001
SBP, mm Hg	513	138.6±18.0	135.7±17.1	-3.0±17.7	<0.001	1702	136.3±18.0	135.6±17.7	-0.7±19.6	0.122
DBP, mm Hg	512	80.4±10.3	79.1±9.2	-1.3±9.9	0.004	1701	78.3±9.1	78.0±9.0	-0.3±10.3	0.293
FPG, mg/dl	616	174.7±53.3	146.6±45.0	-28.2±54.5	<0.001	2004	153.4±37.1	141.9±34.1	-11.5±39.9	<0.001
HbA1c, %	751	8.6±1.4	7.9±1.3	-0.7±1.2	<0.001	2531	7.8±0.9	7.1±0.9	-0.6±1.0	<0.001
TC, mg/dl	426	175.1±40.6	171.6±40.6	-3.5±34.7	0.039	1361	171.5±35.7	166.1±34.8	-5.4±29.8	<0.001
HDL, mg/dl	409	45.9±13.8	47.6±13.2	1.6±8.1	<0.001	1293	48.9±13.9	49.2±13.6	0.3±7.9	0.235
TG, mg/dl	420	171.0±134.1	155.0±113.4	-15.9±135.4	0.016	1325	142.2±84.3	134.1±72.3	-8.1±70.3	<0.001
LDL, mg/dl	387	95.3±32.8	93.3±33.4	-2.0±27.1	0.147	1238	94.4±31.0	90.2±30.3	-4.2±26.7	<0.001
	Gliclazide					**GLP-1RA**				
	n	**Baseline**	**Follow-up**	**Delta**	**p**	**n**	**Baseline**	**Follow-up**	**Delta**	**p**
Age, years	2111	67.5±9.2				811	61.7±9.1			
Sex male %	2111	59.0				811	54.1			
BMI, kg/mq	1851	29.8±5.1				736	35.2±5.7			
Duration, yrs	2111	11.7±7.5				811	10.0±7.1			
F-up, days	2111	185.4±59.4				811	168.8±52.3			
Weight, kg	1741	82.1±16.0	82.1±15.9	-0.1±3.2	0.393	685	97.9±17.9	95.5±18.0	-2.4±4.0	<0.001
SBP, mm Hg	1390	139.5±19.6	139.6±19.2	0.1±19.2	0.894	386	140.2±18.7	138.8±16.8	-1.4±18.6	0.138
DBP, mm Hg	1389	78.7±9.6	78.3±9.1	-0.3±10.0	0.206	386	80.7±9.6	81.0±9.7	0.3±10.7	0.556
FPG, mg/dl	1439	166.5±44.8	151.7±39.6	-14.8±49.6	<0.001	473	156.4±35.6	139.2±36.3	-17.2±40.9	<0.001
HbA1c, %	1710	8.1±1.2	7.5±1.1	-0.6±1.3	<0.001	688	7.8±0.8	7.1±0.9	-0.6±1.0	<0.001
TC, mg/dl	868	173.6±39.8	165.6±37.0	-8.0±31.3	<0.001	332	175.1±43.1	163.5±39.6	-11.6±35.8	<0.001
HDL, mg/dl	826	47.4±13.3	47.4±12.9	0.0±7.6	1.000	318	45.2±11.4	45.6±11.7	0.4±7.0	0.255
TG, mg/dl	843	155.1±104.7	142.2±78.3	-12.9±83.2	<0.001	336	174.0±112.5	165.0±102.8	-8.9±105.4	0.121
LDL, mg/dl	785	95.7±33.6	90.2±31.8	-5.5±26.4	<0.001	308	95.1±35.2	85.0±35.4	-10.1±32.3	<0.001

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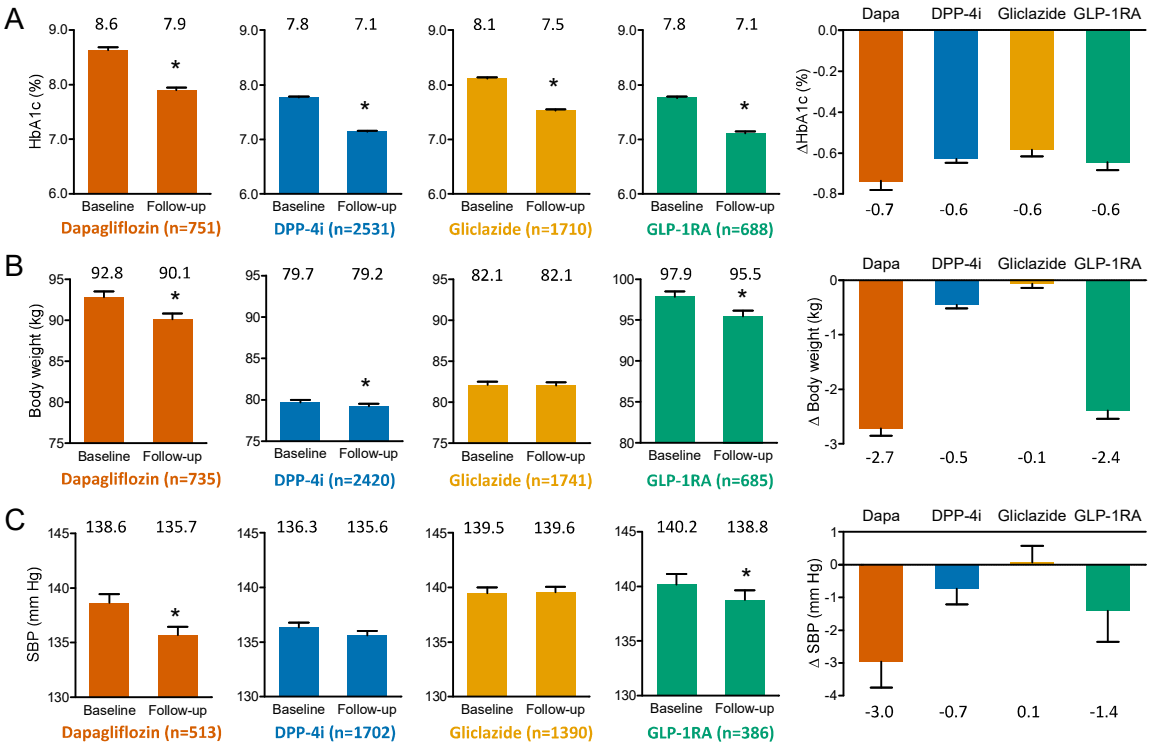
Figure 1. Within group analysis of effectiveness. For HbA1c (A), body weight (B) and systolic blood pressure (C), panels show baseline and follow-up values, along with changes from baseline (right panels). Numbers on top of columns indicate the corresponding values. Numbers between brackets indicates the number of available measures for each outcome. *p<0.05 versus baseline. SBP, systolic blood pressure.



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