REPORT

A Retrospective Real-World Study of Dapagliflozin Versus Other Oral Antidiabetic Drugs Added to Metformin in Patients with Type 2 Diabetes

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Type 2 diabetes (T2D) affected approximately 30.3 million (9.4%) people in the United States in 2015, according to the CDC.[1] The estimated cost of diabetes in the United States exceeded $245 billion in 2012, including $176 billion in direct medical costs.[1] The goals of treatment in T2D are to achieve glycemic control (glycated hemoglobin [A1C] level <7% [53 mmol/mol]) and minimize the risks of macrovascular and microvascular complications. Poor glycemic control is associated with a variety of microvascular complications (eg, neuropathy, retinopathy, and renal disease) and macrovascular complications (eg, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease).[2] As T2D progresses, attaining and maintaining glycemic control become increasingly challenging, the risk of cardiovascular comorbidities increases, and weight gain is common.

Current standard treatment for T2D involves the subsequent addition of new therapies as needed for maintenance of glycemic control. Metformin is the recommended first-line pharmacological treatment; other antidiabetic treatments (eg, sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 [DPP-4] inhibitor, sodium-glucose cotransporter-2 [SGLT2] inhibitor) are added when metformin is not sufficient.[3,4] According to the American Association of Clinical Endocrinologists, A1C reduction, change in body weight, change in blood pressure, and risk of hypoglycemia are factors to consider when choosing an appropriate agent.[5]

Dapagliflozin is an oral, once-daily therapy that was approved by the FDA in January 2014 for use as monotherapy or in combination with other antidiabetic therapies.[6,7] It is an SGLT2 inhibitor, which alters the regulation of glucose reabsorption within the kidneys to increase renal glucose excretion, thus reducing plasma glucose levels.[8]

Dapagliflozin has been shown in clinical trials to be an effective treatment in lowering blood glucose in patients with T2D as monotherapy[9] and in combination with other oral antidiabetic drugs (OADs).[6,7,10] Results from multiple clinical trials (dapagliflozin + metformin vs glipizide + metformin; dapagliflozin + saxagliptin + metformin vs dapagliflozin + metformin vs saxagliptin + metformin) showed that dapagliflozin offered better A1C control, with the additional benefits of weight loss and reduction in systolic blood pressure,

ABSTRACT

Objectives: The efficacy of dapagliflozin as add-on therapy to metformin has been assessed in randomized trials. However, its effectiveness has not been assessed in a US real-world setting.

Methods: Electronic medical record (EMR) data were used to compare clinical outcomes among patients with type 2 diabetes (T2D) treated with dapagliflozin and metformin with or without other oral antidiabetic drugs (D + M ± OAD), versus metformin with at least 1 other OAD (M + OAD). Adult patients with T2D on these regimens from January 01, 2014, to February 28, 2015, were identified in a US EMR database, with the date of first prescription for dapagliflozin (D + M ± OAD) or other OAD (M + OAD) as the index date. Patients were observed for 12 months before the index date (baseline) and 12 months afterward (ie, follow-up). Patients in the M + OAD group were propensity score matched 1:1 to those in the D + M ± OAD group. Outcomes included change in glycated hemoglobin (A1C) level, weight, and systolic and diastolic blood pressures (SBP/DBP) from baseline to follow-up.

Results: A total of 1093 patients receiving M + OAD were matched to 1093 patients receiving D + M ± OAD. Compared with those given M + OAD, patients given D + M ± OAD had a greater reduction in A1C level (mean, −1.0% vs −0.7%; P <.01), greater weight loss (−1.8 kg vs −0.7 kg, P <.01), and greater change in SBP (−3.6 mm Hg vs −0.1 mm Hg, P <.01) and DBP (−2.0 mm Hg vs −0.6 mm Hg, P <.01) from baseline to follow-up.

Conclusions: In current US clinical practice, patients receiving D + M ± OAD had greater reductions in important clinical outcomes of T2D—A1C level, weight loss, and blood pressure—versus patients receiving M + OAD. This study supports the use of dapagliflozin as add-on therapy to metformin with or without other OADs for patients with T2D.

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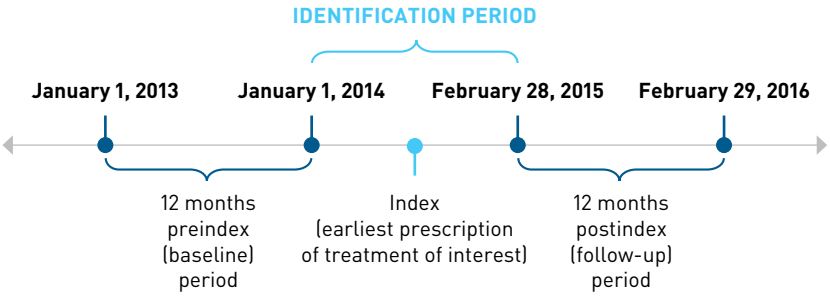
For author information and disclosures, see end of text.

when added to metformin (with or without another OAD), compared with another OAD.[11,12]

To confirm that patients experience the benefits of dapagliflozin seen in clinical trials, observational data can be used to replicate the results. Clinical effectiveness studies of dapagliflozin using European data have shown that dapagliflozin reduced A1C level, weight, and blood pressure at 6 months after initiation, and that these changes were comparable to the results for dapagliflozin clinical trials.[13] Furthermore, dapagliflozin was associated with A1C improvement and weight loss benefit when added to a glucagon-like peptide-1 receptor agonist.[14] However, there are no similar studies published in the United States. To compare results from clinical trials with real-world evidence in the United States, this retrospective cohort study used electronic medical record (EMR) data to compare A1C reduction, weight change, and change in blood pressure among patients with T2D treated with dapagliflozin plus metformin combination therapy, with or without other OADs (D + M ± OAD group), versus metformin in combination with at least 1 other OAD (M + OAD group).

FIGURE. Study Diagram



Methods

Data Source

The IQVIA EMR (formerly GE Centricity) database, a large, centralized, EMR-based data source, was used for this study. The EMR database includes patients with commercial insurance, Medicaid, and Medicare. As of November 2015, the EMR files contained data on more than 30 million active patients. Patient-level variables included demographic information, clinical characteristics (eg, weight and blood pressure), *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (*ICD-9-CM* or *ICD-10-CM*)–based medical diagnoses, patient complaints, diagnostic tests/results, procedures, insurance information (commercial, Medicare, etc), and prescription details. Information from specialty healthcare providers (eg, endocrinologists) and laboratory test orders/results were also available. The data were organized by practice and provide a longitudinal medical record for each patient.

Comparisons of the EMR database patient population with the general population of the United States on demographics (US Census), healthcare utilization (National Ambulatory Medical Care Survey), and disease prevalence (National Health and Nutrition Examination Survey) demonstrate that these patients with EMRs were similar to the US population receiving healthcare.[15,16]

Patient Selection

The study population was selected from adult patients who initiated at least 1 prescription order for treatment of interest (dapagliflozin or other non-metformin OAD) between January 1, 2014, and February 28, 2015 (ie, the selection period). A patient's index date was defined as the date of the earliest prescription of a treatment of interest (**Figure**). Patients were required to have a 12-month preindex (baseline) period and were followed for 12 months. All patients were required to have at least 1 record (eg, any office visit, any medical encounter) in the EMR before the 12-month baseline period and 1 record after the 12-month follow-up period to ensure that each patient was continuous in the EMR system for the entire study period.

All patients were required to have evidence of a T2D diagnosis (*ICD-9-CM* codes 250.x0 or 250.x2, or *ICD-10-CM* codes E11.xx) at any time before the index date. Patients were also required to have baseline A1C value of at least 7%. In addition, patients were required to not have any evidence of SGLT2 inhibitor use (other than dapagliflozin), type 1 diabetes, gestational diabetes, or pregnancy during the baseline or follow-up periods.

Study Cohorts and Follow-up

Patients meeting the selection criteria were stratified into 2 cohorts: patients treated with dapagliflozin and metformin, with or without other OADs (D + M ± OAD) versus patients treated with metformin and at least 1 other OAD (M + OAD). For the D + M ± OAD cohort, the index date was the date of the first dapagliflozin prescription. Patients were required to have a prescription for metformin within 30 days from the index date (this included patients who were taking metformin previously and continued their metformin treatment, or patients with an initial prescription for metformin). Patients in this cohort could receive dapagliflozin + metformin dual therapy or dapagliflozin + metformin + 1 or more OADs.

For the M + OAD cohort, patients were required to have a metformin prescription and at least 1 other OAD (ie, non-metformin) order on the same day or after the metformin order. The index date was defined as the date of the first prescription for another OAD. Patients were required to receive metformin within 30 days of the index date. Patients were required not to have any prescription for an SGLT2

TABLE 1. Patient Demographics Among Patients With T2D Receiving D + M ± OAD Versus M + OAD at Baseline

Characteristic	D + M ± OAD N = 1093	M + OAD N = 1093	*P*
Age (years), mean ± SD	56.2 ± 10.8	56.6 ± 11.9	.49
Sex, n (%)			.80
Female	496 (45.4)	490 (44.8)	
Male	597 (54.6)	603 (55.2)	
Race, n (%)			.97
White	860 (78.7)	856 (78.3)	
Black	112 (10.3)	122 (11.2)	
Asian	22 (2.01)	23 (2.1)	
Other[a]	20 (1.9)	19 (1.8)	
Unknown	79 (7.2)	73 (6.7)	
Region, n (%)[b]			.91
Midwest	178 (16.3)	170 (15.6)	
Northeast	161 (14.7)	157 (14.4)	
South	671 (61.4)	687 (62.9)	
West	83 (7.6)	79 (7.2)	
Provider type, n (%)			.48
Primary care	601 (55.0)	581 (53.2)	
Endocrinologist	177 (16.2)	203 (18.6)	
Other[c]	150 (13.7)	154 (14.1)	
Unknown	165 (15.1)	155 (14.2)	

Data source: IQVIA electronic medical record data from January 1, 2013, to February 29, 2016.
D indicates dapagliflozin; M, metformin; OAD, oral antidiabetic drug; T2D, type 2 diabetes.
[a]Other includes Indian (Native American) and Native Hawaiian/Other Pacific Islander.
[b]Follows US Census regions: Northeast = New England, Mid-Atlantic states; Midwest = East North Central, West North Central states; South = South Atlantic, East South Central, West South Central states; West = Mountain, Pacific states.
[c]Other provider type included physician assistants, nurse practitioners, and nurse specialists.

inhibitor during the entire study period. This cohort consisted of patients only on oral therapies (metformin + 1 OAD dual therapy or metformin + 2 or more OADs, with no metformin monotherapy).

Study Measures

Baseline measures included patient demographics (eg, age, sex, race, geographic region, and provider type), clinical characteristics (eg, weight, baseline body mass index [BMI], baseline A1C level, baseline systolic blood pressure [SBP] and diastolic blood pressure [DBP]), clinical comorbidities, preindex antidiabetic therapy, and use of other concomitant medications (eg, antihypertensive agents, angiotensin-converting-enzyme [ACE] inhibitors, and angiotensin receptor blockers [ARBs]). For clinical comorbidities, adapted Charlson comorbidities, and other comorbidities of interest (eg, hypertension and hyperlipidemia) were reported, consistent with other literature.[17] Baseline A1C levels and SBP and DBP measurements were based on the most recent laboratory measures during the 12-month baseline period.

The primary outcome measure was the change in A1C level from baseline to 12-month follow-up, and it was calculated as the difference between follow-up and baseline measurements. A1C level at 12-month follow-up was based on the latest A1C measurements between 180 and 365 days after the index. If multiple measurements existed, the latest value within the 180- to 365-day window was used. Secondary outcome measures included changes in weight and SBP and DBP readings between follow-up and baseline measurements, using the same definition as A1C level for follow-up measures (ie, 180-365 days post index).

Additional measures included the duration of index treatment, which was defined as the number of days on the index treatment. Treatment with gaps of less than 90 days was considered continuous treatment. A gap of greater than 90 days resulted in the patient being discontinued on treatment, consistent with published literature.[18] Other measures such as A1C level at follow-up, weight and blood pressure at follow-up, and the presence of hypoglycemic events were also examined.

Statistical Analysis

Descriptive analyses of all study measures were performed across the cohorts. Categorical variables were summarized using frequencies and percentages, and continuous variables were summarized using means, SDs, medians, and interquartile ranges. The Wilcoxon rank sum test or *t* test, depending on the distribution of data, for continuous variables and χ^2 tests for categorical variables were performed to determine differences at baseline. Missing data were excluded from the analyses. All statistical analyses were conducted using SAS software (Version 9.4; SAS Institute; Cary, NC).

Patients receiving dapagliflozin were matched to the corresponding comparison patients by propensity score matching, using a 1:1 match ratio to control for confounding variables. For propensity score matching, a logistic regression model was developed including the following variables: patient age, sex, race, region, provider specialty, baseline BMI, baseline A1C level, baseline comorbidities, and baseline medication use. Patients in the comparison cohort were matched to patients given dapagliflozin based on their propensity score with caliper width equal to 0.2 of the SD of the logit for the dapagliflozin cohort.

A subpopulation analysis was conducted among patients with hypertension or who were taking ACE inhibitors or ARBs. Antihypertensive agents are frequently prescribed to patients with diabetes, and the American Diabetes Association guidelines recommend a treatment regimen that includes an ACE inhibitor or an ARB for patients with diabetes.[3] Dapagliflozin has been shown

to be effective in improving glycemic control and blood pressure in patients with T2D and hypertension in randomized trials.[19,20] Results from this subpopulation analysis will provide insight about the effectiveness of using real-world data.

Another subpopulation analysis was conducted among patients receiving dapagliflozin plus metformin dual therapy versus glipizide plus metformin dual therapy. Clinical trials have assessed these same treatments.[11,21,22]

Results

Study Population and Patient Demographics

The matched sample provided 1093 patients in the D + M ± OAD cohort and 1093 patients in the M + OAD cohort. Overall, the demographic characteristics for patients across the cohorts were similar (Table 1).

Clinical Characteristics and Baseline Comorbidities

The majority of baseline clinical characteristics were similar between the 2 treatment groups (Table 2). Mean baseline A1C level was 8.8% for both cohorts. Patients receiving D + M ± OAD had a significantly higher SBP (132 vs 130 mm Hg; $P = .02$) and DBP (79 vs 78 mm Hg; $P = .01$) compared with patients receiving M + OAD, but such differences were not clinically meaningful. The proportion of patients using each antidiabetic medication was similar across treatment groups, except those given D + M ± OAD had lower use of DPP-4 inhibitors (35% vs 42%; $P < .01$). The number of antidiabetic medication classes used during baseline was slightly lower in patients receiving D + M ± OAD (1.4 vs 1.6; $P < .01$) compared with those receiving M + OAD. Use of other medications during baseline was similar between the 2 cohorts.

Study Outcomes

Patients who received D + M ± OAD had a greater reduction in A1C levels during follow-up than those who received M + OAD (–1.0% vs –0.7%; $P < .01$). Patients taking D + M ± OAD had greater weight loss (–1.8 kg vs –0.7 kg; $P < .01$), SBP reduction (–3.6 mm Hg vs –0.1 mm Hg; $P < .01$),

TABLE 2. Clinical Characteristics Among Patients With T2D Receiving D + M ± OAD Versus M + OAD at Baseline

Characteristic[a]	D + M ± OAD N = 1093	M + OAD N = 1093	*P*
BMI (kg/m²)	35.3 ± 7.6	35.3 ± 7.5	.74
A1C (%) category			.96
7.0-7.99	271 (24.8)	269 (24.6)	
8.0-8.99	274 (25.1)	285 (26.1)	
9.0+	269 (24.6)	264 (24.2)	
Unavailable	279 (25.5)	275 (25.2)	
A1C level (%)	8.8 ± 1.4	8.8 ± 1.4	.98
Systolic blood pressure (mm Hg)	131.9 ± 16.6	130.1 ± 16.4	.02
Diastolic blood pressure (mm Hg)	79.3 ± 10.0	78.1 ± 9.9	.01
Weight (kg)	103.0 ± 24.6	101.7 ± 24.6	.24
Other comorbidities			
Hypertension	103 (9.4)	105 (9.6)	.88
Hyperlipidemia	120 (11.0)	122 (11.2)	.89
Hypoglycemia	11 (1.0)	8 (0.7)	.49
Cardiovascular disease	50 (4.6)	61 (5.6)	.28
Renal impairment	38 (3.5)	57 (5.2)	.05
Adapted Charlson Comorbidity Index score[b]	0.3 ± 0.7	0.3 ± 0.8	.28
Patients receiving the following during the 12-month baseline period			
Alpha-glucosidase inhibitor	4 (0.4)	5 (0.5)	.74
Metformin	735 (67.3)	767 (70.2)	.14
DPP-4 inhibitor	377 (34.5)	453 (41.5)	<.01
Meglitinide	7 (0.6)	12 (1.1)	.25
Sulfonylurea	339 (31.0)	389 (35.6)	.02
TZD	54 (4.9)	58 (5.3)	.70
Insulin	22 (2.0)	31 (2.8)	.21
GLP-1 RA	34 (3.1)	46 (4.2)	.17
Number of antidiabetic medication classes used during the 12-month baseline	1.4 ± 1.0	1.6 ± 1.1	<.01
Other medication classes			
Antihypertensive agent	551 (50.4)	605 (55.4)	.02
ACE inhibitor	277 (25.3)	312 (28.6)	.09
ARB	134 (12.3)	150 (13.7)	.31
Antihyperlipidemic agent	453 (41.5)	504 (46.1)	.03

Data source: IQVIA electronic medical record data from January 1, 2013, to February 29, 2016.
A1C indicates glycated hemoglobin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; D, dapagliflozin; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; M, metformin; OAD, oral antidiabetic drug; T2D, type 2 diabetes; TZD, thiazolidinedione.
[a]Data are mean ± SD or n (%).
[b]Charlson Comorbidity Index score included hypertension, depression, warfarin use, and skin ulcers/cellulitis, in addition to the standard Charlson comorbidities. It did not include diabetes because all patients had diabetes in this study and the intent was to measure non–diabetes-related comorbidity.

TABLE 3. Outcomes Among Patients With T2D Receiving D + M ± OAD Versus M + OAD

Characteristic[a]	D + M ± OAD N = 1093	M + OAD N = 1093	*P*
Change in A1C level (%) from baseline to follow-up	−1.0 ± 1.6	−0.7 ± 1.5	<.01
Change in body weight (kg) from baseline to follow-up	−1.8 ± 4.0	−0.7 ± 5.6	<.01
Change in SBP (mm Hg) from baseline to follow-up	−3.6 ± 18.2	−0.1 ± 18.4	<.01
Change in DBP (mm Hg) from baseline to follow-up	−2.0 ± 11.2	−0.6 ± 10.4	<.01
Duration of treatment (days) during the follow-up period	349.2 ± 227.8	391.2 ± 301.8	<.01
A1C level (%) during the follow-up period	7.7±1.3	7.9±1.6	<.01
A1C category (%) during the follow-up period			
<6.5	95 (8.7)	93 (8.5)	<.01
6.5-6.99	131 (12.0)	108 (9.9)	
7.0-7.99	270 (24.7)	223 (20.4)	
8.0-8.99	141 (12.9)	114 (10.4)	
≥9.0	96 (8.8)	154 (14.1)	
Unavailable	360 (32.9)	401 (36.7)	
Patients with hypoglycemia during the follow-up period	7 (0.6)	14 (1.3)	.12

Data source: IQVIA electronic medical record data from January 1, 2013, to February 29, 2016.
A1C indicates glycated hemoglobin; D, dapagliflozin; DBP, diastolic blood pressure; M, metformin; OAD, oral antidiabetic drug; SBP, systolic blood pressure; T2D, type 2 diabetes.
[a]Data are mean ± SD or n (%).

and DBP reduction (−2.0 mm Hg vs −0.6 mm Hg; *P* <.01) than those taking M + OAD (**Table 3**).

Average treatment duration post index was similar for patients who received M + OAD (391.2 days) compared with those who received D + M ± OAD (349.2 days). At the 12-month follow-up, 20.7% of patients given D + M ± OAD and 18.4% of those given M + OAD had A1C levels less than 7%. Hypoglycemia affected 0.6% of patients who received D + M ± OAD and 1.3% of those who received M + OAD.

Subpopulation Analysis Results

The subpopulation analysis conducted among patients with hypertension or those taking ACE inhibitors or ARBs showed that the D + M ± OAD cohort (N = 421) had significantly greater reductions in A1C level (−1.2% vs −0.6%; *P* <.01), SBP (−4.6 mm Hg vs −1.1 mm Hg; *P* = .01), and DBP (−2.7 mm Hg vs −0.6 mm Hg; *P* <.01) compared with the M + OAD cohort (N = 469). Weight change was greater (−1.6 kg vs −0.9 kg) for the D +M ± OAD cohort, but did not reach statistical significance (*P* = .06).

The subpopulation analysis among patients receiving dapagliflozin + metformin dual therapy (N = 269) versus glipizide + metformin dual therapy (N = 269) showed that the dapagliflozin cohort had a significantly greater reduction in A1C level (−1.2% vs −0.7%; *P* = .03), significantly greater weight loss (−1.7 kg vs −0.5 kg; *P* = .02), and greater but not statistically significant reductions in SBP (−3.3 mm Hg vs −1.1 mm Hg; *P* = .3) and DBP (−1.9 mm Hg vs −1.3 mm Hg; *P* = .6).

Discussion

Results from this study showed that patients treated with dapagliflozin experienced significantly greater reductions in A1C level, weight, SBP, and DBP compared with patients treated with other OADs, when added to metformin. In addition, similar results were observed among the subpopulation of patients with hypertension or those taking ACE inhibitors or ARBs.

Results from clinical trials show that patients receiving dapagliflozin in combination with other OADs had A1C reductions in the range of −0.4% to −1.2% at 1 year.[6,7,22,23] Our study found that patients in the dapagliflozin cohort had a −1.0% reduction in A1C level at the 12-month follow-up, consistent with the clinical trial results.

Similarly, results from clinical trials demonstrated that patients receiving dapagliflozin in combination with other OADs had weight losses in the range of −0.69 kg to −3.2 kg at 1 year.[6,10,23] Our study showed that patients in the dapagliflozin cohort had a −1.8 kg weight loss at the 12-month follow-up, consistent with the clinical trial results.

Blood pressure results in our study are also consistent with those of published clinical trials. Dapagliflozin + metformin dual therapy resulted in an SBP reduction of −3.3 mm Hg and a DBP reduction of −1.9 mm Hg in our study. Patients who received the same treatment (ie, dapagliflozin + metformin dual therapy) in a 52-week clinical trial had an SBP reduction of −4.3 mm Hg and a DBP reduction of −1.6 mm Hg.[22]

Additionally, results from our study among the subpopulations of patients with hypertension or those taking ACE inhibitors or ARBs (eg, A1C reduction for dapagliflozin, −1.2%; weight loss, −1.0 kg; SBP reduction, −4.6 mm Hg, all at the 12-month follow-up) are also in line with the results from clinical trials (eg, A1C reduction for dapagliflozin, −0.6%; weight loss, −1.0 kg; SBP reduction, −10 mm Hg, all at the 12-week follow-up).[19,20]

Limitations

This study is subject to the limitations common to retrospective medical records database analyses, including possible missing data and incorrect data, and that the data were not collected solely for research purposes. In addition, the medication data used in the present study are based on prescription orders, not prescriptions filled by a patient. Clinical measures, including laboratory values and outcomes (eg, A1C level, weight, and blood pressure), were

defined over time windows rather than at specific points in time (eg, 180-365 days after index date), so that outcomes may not be exactly 12-month outcomes. There is a slight difference in treatment duration between the dapagliflozin cohort (349 days) and the comparison cohort (391 days). However, we do not expect this difference to have biased results given that a previous study demonstrated that a treatment effect occurred 2 months after treatment initiation and remained stable up to 2 years following initiation.[24] Finally, these findings may not be generalizable beyond the study sample (lack of Medicaid representation in the database, for example).

Conclusions

This observational study showed that patients in current clinical practice in the United States receiving dapagliflozin plus metformin, with or without other OADs, had greater reductions in A1C level, weight, and blood pressure when compared with patients receiving metformin in combination with at least 1 other OAD. The reductions were comparable with the results observed in dapagliflozin clinical trials. This study supports the use of dapagliflozin as add-on therapy to metformin ± other OADs for patients with T2D in real-world clinical practice. ■

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