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ORIGINAL ARTICLE

Add-on therapy with dapagliflozin in routine outpatient care of type 2 diabetes patients from Turkey: a retrospective cohort study on HbA1c, body weight, and blood pressure outcomes

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Abstract

Background The efficacy of dapagliflozin has been less extensively studied in the real-life context, limiting the comparability of observational real-world evidence with results from dapagliflozin clinical trials. This study aimed to evaluate HbA1c, blood pressure (BP), and weight outcomes in dapagliflozin-treated patients with type 2 diabetes (T2D) treated in a real-world setting.

Methods A total of 1683 T2D patients (mean (SD) age: 54.6 years (9.1), 56.6% were females) initiating dapagliflozin were included in this multicenter retrospective observational cohort study. Data on patient demographics, comorbidities, duration of diabetes, and concomitant antidiabetic treatment were recorded. Change in glycated hemoglobin (HbA1c), body weight, body mass index (BMI), and BP levels with dapagliflozin treatment and dapagliflozin discontinuation rates were evaluated based on baseline, 3rd-month, and 6th-month data.

Results At the end of 6-month dapagliflozin treatment (discontinued in 4.3% of patients), HbA1c levels were ≤7% in 30.1% of patients, BP was ≤140/90 mmHg in 95.9% of patients, and >5% weight loss was evident in 38.0% of patients. Less than 5-year diabetes duration was associated with significantly higher rate of achieving HbA1c ≤7% ($p = 0.032$), BP ≤140/90 mmHg ($p = 0.001$), and BP ≤130/80 mmHg ($p < 0.001$) targets at the 6th month ($p = 0.032$) as compared with longer diabetes duration.

Conclusion In conclusion, this nationwide observational study in T2D patients treated with dapagliflozin in Turkey provided real-life evidence on significant and clinically meaningful reductions in HbA1c, body weight, and BP within 6-month therapy.

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Keywords Type 2 diabetes · Dapagliflozin · Second-line therapy · Glycemic control · Body weight · Blood pressure

Introduction

In accordance with the global estimates on rapidly increasing prevalence of the diabetes worldwide [1], type 2 diabetes (T2D) remains a serious health issue in Turkey with an average prevalence of 13.7% (over 6.5 million people) as reported in the Turkish Diabetes Hypertension Obesity and Endocrine Disease Prevalence Study (TURDEP-II) [2].

Owing to a causal link between dysglycemia, diabetes-related complications, and premature deaths, achievement of optimal glycemic control is considered to be of critical importance in T2D management [1, 3–6]. According to current guidelines, standard treatment for T2D involves the use of metformin, in conjunction with lifestyle changes, as first-line glucose-lowering therapy, and treatment intensification in case of failure to achieve glycemic control [7]. For patients with clinical cardiovascular disease, treatment intensification is recommended to be based on addition of a sodium–glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit [7].

SGLT2 inhibitors comprise a novel class of antidiabetic agents with unique insulin-independent mode of action in lowering blood glucose levels (i.e., blocking the reabsorption of filtered glucose in the kidneys) which also enable their combination with other glucose-lowering agents with different mechanistic pathways [8–13].

Dapagliflozin is a highly selective SGLT2 inhibitor approved by the FDA in January 2014 for use as monotherapy or in combination with other antidiabetic therapies in adult patients [8, 14, 15]. Dapagliflozin (Forziga®, also known as Forxiga® or Farxiga®) is the first SGLT-2 inhibitor approved in Turkey in 2015 and reimbursed as restricted to internal medicine and endocrinology prescriptions since July 2016 [16].

The efficacy of dapagliflozin on reduction of HbA1c, body weight, body fat, and blood pressure (BP) as monotherapy [17] or in combination with other oral antidiabetic drugs (OADs) has been shown in numerous randomized controlled trials (RCTs) [10, 14, 15, 18–25]. However, the efficacy of dapagliflozin has been less extensively studied in the real-life context, limiting the comparability of observational real-world evidence with results from dapagliflozin clinical trials [11–13, 26–29].

Scientific societies and health care professionals have repeatedly expressed the need to collect and publish real-world evidence on SGLT-2 inhibitor use across the country [13, 29, 30], whereas to our knowledge, no studies to date investigated the outcomes related to dapagliflozin treatment in patients with T2D in Turkey.

Hence, this retrospective cohort study, providing data on SGLT-2 inhibitors for the first time in Turkish patients, was designed to investigate add-on therapy with dapagliflozin in routine outpatient care of T2D patients from Turkey in terms of patient profile and HbA1c, weight, body mass index (BMI), and BP outcomes in relation to clinical variables and concomitant antidiabetic medications in a real-life clinical setting.

Methods

Study population

A total of 1683 T2D patients initiating dapagliflozin were included in this multicenter retrospective observational cohort study (ClinicalTrials.gov Identifier: NCT03407196) conducted over three visits (baseline, 3rd month, and 6th month) between July 2016 and August 2017 across 79 internal medicine and endocrinology clinics from Turkey.

T2D patients who received first prescription for dapagliflozin between July 2016 and August 2017, aged ≥18 and ≤75 years, and registered in that center for at least 6 months prior to index date (the date of the first prescription for dapagliflozin in patient medical records) were included in the study. Presence of type 1 diabetes, gestational diabetes, EGFR < 30 ml/min, and another interventional clinical trial participation between index date and enrollment date were the exclusion criteria of the study. The selection of sites and investigators was made in accordance with the national situation regarding dapagliflozin prescription (reimbursement, public or private insurance) and the proportion of the different types of centers (internal medicine, endocrinology clinics, different types of hospitals, geographical distribution) and investigators (different types of specialists) involved in dapagliflozin-treated T2D patient management to achieve representativeness of dapagliflozin-treated T2D patients across Turkey.

The study was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice, and the local regulations for clinical research.

Study parameters

Data on patient demographics (age, gender), smoking status, type of outpatient clinic, comorbidities, duration of diabetes, microvascular complications, and concomitant antidiabetic treatment including oral antidiabetic drugs (OADs) and injectable drugs including insulin, glucagon-like peptide-1 receptor agonists (GLP1RA) or insulin + GLP1RA were recorded in

each patient. Change in HbA1c, body weight, BMI, and systolic and diastolic BP levels, rates of HbA1c target achievement under dapagliflozin treatment, and dapagliflozin discontinuation rates were evaluated based on baseline, 3rd-month, and 6th-month data and analyzed with respect to diabetes duration and concomitant antidiabetic regimen.

Persistence to dapagliflozin was evaluated based on the time from initial prescription to end of period covered by the final prescription in patient records. A patient was considered to have discontinued treatment if there was a period of greater than 30 days without coverage following the period covered by the final prescription.

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). Chi-square (χ^2) test and Mantel-Haenszel test were used for the comparison of categorical data, while numerical data were analyzed using Students' *t* test and one-way ANOVA and post hoc Tukey test. Change over time was evaluated by paired Students' *t* test. Data were expressed as "mean (standard deviation (SD))", minimum-maximum, percent (%), and 95% confidence interval (CI) where appropriate. $p < 0.05$ was considered statistically significant.

Results

Baseline demographic and clinical characteristics (*n* = 1683)

Overall, mean (SD) patient age was 54.6 years (9.1; 73.3% aged 45–64 years), 56.6% of patients were females, and average diabetes duration was 8.7 years. Neuropathy was the most common microvascular complication (31.1%), while hypertension (57.3%) and hyperlipidemia (55.4%) were the two most common comorbidities (Table 1).

Antidiabetic treatments during the study period

Dapagliflozin was discontinued in 26 (2.2%) and 72 (4.3) patients in the 3rd and 6th months of study, respectively. Concomitant antidiabetics at baseline, 3rd-month, and 6th-month visits involved OAD in 52.2%, 50.2%, and 52.8% of patients, and OAD ± injectable drug in 47.8%, 49.7%, and 46.3% of patients, respectively. Most commonly prescribed OADs were metformin (88.1%, 86.0%, and 86.7%, respectively) and DPP4i (51.8%, 52.0%, and 52.3%, respectively). At baseline, 3rd-month, and 6th-month visits, respectively, insulin (overall: 36.6%, 38.5%, and 35.4%) was the most commonly used injectable drug, while most of the insulin-

Table 1 Baseline demographic and clinical characteristics (*n* = 1683)

Age (year)	
Mean (SD)	54.6 (9.1)
Median (min-max)	54.2 (20.1–83.4)
<45, *n* (%)	209 (12.6)
45–64, *n* (%)	1212 (73.3)
≥65, *n* (%)	233 (14.1)
Gender (*n* (%))	
Female	952 (56.6)
Male	731 (43.4)
Clinic (*n* (%))	
Endocrinology	861 (51.2)
Internal medicine	780 (46.3)
Nephrology	42 (2.5)
Duration of diabetes (years)	
Mean (SD)	8.7 (5.9)
Median (min-max)	7.0 (1.0–34.0)
≤5 years (*n* (%))	465 (36.1)
5.1–10 years (*n* (%))	447 (34.7)
10.1–15 years (*n* (%))	206 (16.0)
>15 years (*n* (%))	170 (13.2)
Missing	395
Smoking status (*n* (%))	
Non-smoker	1195 (77.6)
Active smoker	231 (15.0)
Former smoker	113 (7.3)
Missing	144
Comorbidities (*n* (%))	
Hypertension	928 (57.3)
Hyperlipidemia	878 (55.4)
Myocardial infarction	132 (9.0)
Depression	121 (8.4)
Unstable angina	81 (5.7)
Heart failure	54 (3.7)
Arrhythmia	45 (3.1)
Peripheral artery disease	28 (2.0)
Cancer	20 (1.4)
Stroke	20 (1.4)
Microvascular complications (*n* (%))	
Neuropathy	444 (31.1)
Retinopathy	190 (14.0)
Nephropathy	140 (10.0)
HbA1c level (%)	
≤7%	162 (10.0)
≤7.5%	321 (20.0)
Blood pressure (mmHg)	
≤140/90	1000 (80.8)
≤130/80	661 (53.4)

treated patients were receiving basal insulin (33.0%, 34.3%, and 31.6%, respectively) (Table 2).

HbA1c, body weight, and BP outcome and treatment dose under dapagliflozin treatment

A significant decrease in HbA1c levels was noted from 9.0% (SD 1.8, 75 mmol/mol) at baseline to 8.0% (SD 1.3, 64 mmol/mol) in the 3rd month (mean difference −0.95%) and to 7.8% (SD 1.4, 62 mmol/mol) in the 6th month (mean difference −1.22%) of treatment ($p < 0.001$ for each) (Table 3).

A significant decrease in BMI levels was noted from 32.6 kg/m^2 (6.1) at baseline to 31.5 kg/m^2 (18.0) in the 3rd month (mean difference −0.93 kg/m^2) and to 31.0 kg/m^2 (17.6) in the 6th month (mean difference −1.42 kg/m^2) of treatment ($p < 0.001$ for each) (Table 3).

A significant decrease in body weight was noted from 89.2 kg (16.2) at baseline to 86.3 kg (15.2) kg in the 3rd month (mean difference −2.49) and to 85.1 kg (15.3) in the 6th month (mean difference −3.83) of treatment ($p < 0.001$ for each) (Table 3).

A significant decrease in systolic BP was noted from 131.9 mmHg (15.0) at baseline to 126.1 mmHg (11.9) in the 3rd month (mean difference −6.68) and to 124.1 mmHg (11.3) in the 6th month (mean difference −7.78) of treatment ($p < 0.001$ for each). A significant decrease in diastolic BP was noted from 81.2 mmHg (9.4) at baseline to 77.6 mmHg (7.8) in the 3rd month (mean difference −4.16) and to 76.8 mmHg (7.7) in the 6th month (mean difference −4.29) of treatment ($p < 0.001$ for each) (Table 3).

A significant reduction from baseline insulin dose (31.2 U/day (14.5)) was noted that involved total (mean −3.39

Table 2 Antidiabetic treatments during the study period

	Baseline (n = 1683)	3rd month (n = 1618)	6th month (n = 1683)
Dapagliflozin treatment (n (%))			
Yes	1683 (100.0)	1142 (97.8)	1596 (94.8)
Discontinued	0 (0.0)	26 (2.2)	72 (4.3)
Antidiabetic regimen (n (%))			
OAD only	878 (52.2)	586 (50.2)	888 (52.8)
OAD ± injectable drug	805 (47.8)	580 (49.7)	780 (46.3)
Injectable drug only	0 (0.0)	2 (0.2)	6 (0.4)
Type of OAD (n (%))			
Metformin	1482 (88.1)	1004 (86.0)	1459 (86.7)
DPP4i	872 (51.8)	607 (52.0)	880 (52.3)
Sulphonylurea	556 (33.0)	340 (29.1)	500 (29.7)
Thiazolidinedione	207 (12.3)	145 (12.4)	195 (11.6)
Glinide	114 (6.8)	85 (7.3)	110 (6.5)
Alpha glucosidase inhibitor	42 (2.5)	20 (1.7)	27 (1.6)
Type of injectable therapy (n (%))			
None	878 (52.2)	586 (50.2)	897 (53.3)
Insulin	616 (36.6)	450 (38.5)	596 (35.4)
GLP1A	109 (6.5)	90 (7.7)	126 (7.5)
Insulin + GLP1A	80 (4.8)	42 (3.6)	64 (3.8)
Type of insulin therapy (n (%))			
None	987 (58.6)	676 (57.9)	1023 (60.8)
Basal insulin	555 (33.0)	401 (34.3)	532 (31.6)
Bolus insulin	283 (16.8)	188 (16.1)	249 (14.8)
Mixed insulin	135 (8.0)	84 (7.2)	118 (7.0)
Insulin dose (mean (SD))	56.1 (37.8)	51.6 (36.0)	51.3 (35.3)
Bolus insulin	50.4 (25.4)	48.4 (26.7)	48.3 (24.7)
Basal insulin	31.2 (14.5)	29.8 (13.9)	28.9 (13.1)
Mixed insulin	55.5 (26.3)	51.8 (23.0)	54.4 (28.0)

DPP4i, dipeptidyl peptidase-4 inhibitor; *OAD*, oral antidiabetic drug; *CI*, confidence inteirval; *LB*, lower bound; *UB*, upper bound

Table 3 HbA1c, body weight, and BP outcome and treatment dose under dapagliflozin treatment

	Baseline	3rd month	6th month	*p* value
HbA1c (%)				
n	1603	926	1455	**<0.001**
Mean (SD)	9.0 (1.8)	8.0 (1.3)	7.8 (1.4)	
Change, mean (SD; 95% CI UB, LB)	From baseline	−0.95 (1.39;0.86,1.05)	−1.22 (1.55; 1.14, 1.30)	
	From 3rd month	–	−0.37 (0.90; 0.31, 0.43)	
BMI (kg/m^2)				
n	1249	851	1186	**<0.001**
Mean (SD)	32.6(6.1)	31.5 (18.0)	31.0 (17.6)	
Change, mean (SD; 95% CI UB, LB)	From baseline	−0.93 (0.84, 1.03)	−1.42 (1.3, 1.5)	
	From 3rd month	–	−0.61 (0.5, 0.7)	
Body weight (kg)				
n	1273	866	1215	**<0.001**
Mean (SD)	89.2 (16.2)	86.3 (15.2)	85.1 (15.3)	
Change, mean (SD; 95% CI UB, LB)	From baseline	−2.49 (3.15; 2.28, 2.70)	−3.83 (4.20; 3.53, 4.13)	
	From 3rd month	–	−1.67 (5.29; 1.39, 1.95)	
Systolic BP (mmHg)				
n	1238	826	1166	**<0.001**
Mean (SD)	131.9 (15.0)	126.1 (11.9)	124.1 (11.3)	
Change, mean (SD; 95% CI UB, LB)	From baseline	−6.68 (5.93, 7.43)	−7.78 (7.08, 8.47)	
	From 3rd month	–	−2.18 (1.63, 2.73)	
Diastolic BP (mmHg)				
n	1238	826	1166	**<0.001**
Mean (SD)	81.2 (9.4)	77.6 (7.8)	76.8 (7.7)	
Change, mean (SD; 95% CI UB, LB)	From baseline	−4.16 (3.60, 4.73)	−4.29 (3.80, 4.78)	
	From 3rd month	–	−0.90 (0.45, 1.34)	
Insulin dose (U/day)				
Total				
n	616	476	621	
Mean (SD)	56.1 (37.8)	51.6 (36.0)	51.3 (35.3)	**<0.001**
Change from baseline, mean (SD; 95% CI UB, LB)		−3.39 (1.75, 5.03)	−4.68 (3.11, 6.25)	
Bolus				
n	283	178	229	
Mean (SD)	50.4 (25.4)	48.4 (26.7)	48.3 (24.7)	0.107[a]
Change from baseline, mean (SD; 95% CI UB, LB)		−1.74 (−0.38, 3.85)	−2.41 (0.47, 4.36)	**0.015**[b]
Basal				
n	555	383	488	
Mean (SD)	31.2 (14.5)	29.8 (13.9)	28.9 (13.1)	**0.007**[a]
Change from baseline, mean (SD; 95% CI UB, LB)		−1.17 (0.32, 2.03)	−2.04 (1.13, 2.95)	**<0.001**[b]
Mixed				
n	135	74	104	
Mean (SD)	55.5 (26.3)	51.8 (23.0)	54.4 (28.0)	0.234[a]
Change from baseline, mean (SD; 95% CI UB, LB)		−1.11 (−0.73, 2.95)	−0.75 (−1.39, 2.89)	0.488[b]
Number of OADs				
n	1683	1168	1683	
Mean (SD)	2.93 (0.87)	2.86 (0.88)	2.82 (0.93)	**<0.001**
Change from baseline, mean (SD; 95% CI UB, LB)		−0.07 (0.04, 0.10)	−0.11 (0.08, 0.14)	

CI, confidence interval; *LB*, lower bound; *UB*, upper bound; *BP*, blood pressure

Values in bold indicate statistical significance ($p < 0.05$)

[a] Paired Student's *t* test baseline vs. 3rd month

[b] Paired Student's *t* test baseline vs. 6th month

U/day, $p < 0.001$) and basal (mean −1.17 U/day, $p = 0.007$) insulin doses at the 3rd month and total (mean −4.68 U/day, $p < 0.001$), bolus (mean −2.41 U/day, $p = 0.015$), and basal (mean −2.04 U/day, $p < 0.001$) insulin doses at 6th-month visits. Similarly, a significant reduction was noted in the number of OADs from baseline value (mean (SD) 2.93 (0.87) at the 3rd-month (mean −0.007, $p < 0.001$) and 6th-month (mean −0.11, $p < 0.001$) visits (Table 3).

HbA1c levels during study period according to diabetes duration and concomitant regimens

No significant difference was noted in mean (SD) HbA1c levels at baseline, 3rd month, and 6th month, as well as in change from baseline at follow-up visits with respect to diabetes duration (Table 4).

HbA1c levels were significantly higher in patients with OAD ± injectable drug vs. OAD treatment at baseline (mean 9.3% (SD 1.8, 78 mmol/mol) vs. 8.8% (SD 1.7, 73 mmol/mol), $p = 0.001$), 3rd month (mean 8.2% (SD 1.3, 66 mmol/mol) vs. 7.8% (SD 1.3, 62 mmol/mol), $p < 0.001$), and 6th month (mean 8.1% (SD 1.4, 65 mmol/mol) vs. 7.6% (SD 1.3, 60 mmol/mol), $p < 0.001$) visits along with similar difference from baseline HbA1c levels during follow-up visits between the two treatment groups (Table 4).

Body weight during study period according to diabetes duration and concomitant treatments

Diabetes duration of 10.1 to 15 years was associated with highest body weight values at baseline ($p = 0.011$), 3rd-month ($p = 0.031$), and 6th-month ($p = 0.006$) visits as compared with shorter diabetes duration or diabetes for >15 years, while no significant change was noted in change from baseline at follow-up visits with respect to diabetes duration (Table 4).

Body weight was significantly higher in patients with OAD ± injectable treatment vs. OAD treatment at baseline (92.0 kg (16.8) vs. 86.1 kg (15.8), $p < 0.001$) and remained higher in OAD ± injectable treatment group at follow-up visits ($p < 0.001$ for each), despite significantly larger difference from baseline in this group as compared with OAD treatment at both 3rd-month (−2.79 kg (−3.09, −2.49) vs. −2.14 kg (−2.43, −1.85), $p = 0.002$) and 6th-month (−4.34 kg (−4.73, −3.95) vs. −3.30 kg (−3.75, −2.85), $p < 0.001$) visits (Table 4).

BP during study period according to diabetes duration and concomitant regimens

No significant difference was noted in baseline systolic BP levels with respect to diabetes duration, while less than 5-year diabetes duration was associated with significantly lower systolic BP levels at both 3rd-month and 6th-month visits ($p < 0.001$ for each). No significant difference was noted in diastolic BP levels with respect to diabetes duration at baseline or during follow-up visits (Table 5).

No significant difference was noted in systolic and diastolic BP levels with respect to concomitant treatments or HbA1c levels at baseline or during follow-up visits (Table 5).

Target HbA1c, body weight, and BP achievement rates with respect to diabetes duration and concomitant regimens

Rate of target HbA1c (≤7%) achievement increased from 10.0% at baseline to 21.7% and 30.1% at the 3rd- and 6th-month visits, respectively (Tables 1 and 6). Rate of target HbA1c (≤7.5%) achievement increased from 20.0% at baseline to 38.0% and 49.3% at the 3rd- and 6th-month visits, respectively (Tables 1 and 6).

An increase was noted in rate of patients with target BP levels of ≤140/90 mmHg and ≤130/80 mmHg from baseline (80.8% and 53.4%, respectively) to 3rd month (92.4% and 70.7%, respectively) and 6th month (95.9% and 77.3%, respectively) (Tables 1 and 6).

The >5% weight loss target was achieved by 17.5% and 38.0% of patients at 3rd-month and 6th-month visits, respectively (Table 6).

At baseline, HbA1c levels were similar (mean (SD) 9.1% (1.8) vs. 9.0% (1.7), $p = 0.293$), whereas body weight was significantly lower (86.0 kg (15.8) vs. 93.1 kg (15.9), $p = 0.000$) and systolic BP (132.8 mmHg (15.5) vs. 130.7 mmHg (14.4), $p = 0.012$) and diastolic BP (132.8 mmHg (15.5) vs. 130.7 mmHg (14.4), $p = 0.012$) levels were significantly higher in females vs. males. After 6-month of dapagliflozin treatment, higher rate of target HbA1c achievement was noted in male vs. female patients (55.5 vs. 44.6%, $p = 0.000$), along with no significant difference in target BP and body weight achievement rates under dapagliflozin therapy according to gender (Table 6). Less than 5-year diabetes duration was associated with significantly higher rate of achieving HbA1c ≤7% ($p = 0.032$), BP ≤140/90 mmHg ($p = 0.001$), and BP ≤130/80 mmHg ($p < 0.001$) targets at the 6th month ($p = 0.032$) as compared with longer diabetes duration. Diabetes duration had no significant impact on target weight loss achievement (Table 6).

Concomitant OAD therapy vs. OAD ± injectable therapy was associated with significantly higher achievement rates for HbA1c ≤7% (26.3 vs. 17.3%, $p = 0.001$ at 3rd month; 45.6 vs. 30.8% at 6th month, $p < 0.001$) and HbA1c ≤7.5% (37.1 vs. 22.8% at 3rd month; 56.9 vs. 41.4% at 6th month, $p < 0.001$ for each) targets during follow-up visits (Table 6).

OAD ± injectable therapy vs. OAD therapy was associated with higher achievement rate of >5% weight loss target (20.2

Table 4 Change in HbA1c levels and body weight during follow-up with respect to diabetes duration and concomitant regimen study variables

	Baseline (n = 1683)			3rd month (n = 1618)					6th month (n = 1683)						
	n	Mean (SD)	p value	n	Mean (SD)	p value	Change from baseline		n	Mean (SD)	p value	Change from baseline		Change from 3rd month	
							Mean (95% CI LB, UB)	p value				Mean (95% CI LB, UB)	p value	Mean (95% CI LB, UB)	p value
HbA1c level (%)															
Diabetes duration															
≤5 years	457	9.0 (1.8)	0.336[a]	258	7.9 (1.3)	0.131[a]	−0.95 (−1.13, −0.77)	0.158[a]	417	7.7 (1.4)	0.336[a]	−1.36 (−1.52, −1.20)	0.078[a]	−0.41 (−0.53, −0.30)	0.233[a]
5.1–10 years	441	9.1 (1.7)		285	8.0 (1.3)		−1.02 (−1.16, −0.87)		410	7.9 (1.4)		−1.24 (−1.38, −1.10)		−0.32 (−0.42, −0.21)	
10.1–15 years	202	8.9 (1.6)		118	8.2 (1.3)		−0.69 (−0.93, −0.45)		195	7.8 (1.1)		−1.15 (−1.35, −0.94)		−0.45 (−0.61, −0.29)	
>15 years	164	8.9 (1.6)		112	8.0 (1.3)		−0.88 (−1.14, −0.63)		153	7.9 (1.3)		−1.01 (−1.23, −0.78)		−0.24 (−0.43, −0.05)	
Concomitant antidiabetics															
OADs	835	8.8 (1.7)	**<0.001**[b]	452	7.8 (1.3)	**<0.001**[b]	−0.91 (−1.04, −0.78)	0.347[a]	743	7.6 (1.3)	**<0.001**[b]	−1.22 (−1.33, −1.10)	0.997[b]	−0.41 (−0.50, −0.32)	0.232[b]
OAD ± injectable	768	9.3 (1.8)		474	8.2 (1.3)		−1.00 (−1.13, −0.87)		712	8.1 (1.4)		−1.22 (−1.33, −1.10)		−0.34 (−0.42, −0.25)	
Body weight (kg)															
Diabetes duration															
≤5 years	398	87.2 (15.8)	**0.011**[b]	266	84.4 (14.7)	**0.031**[b]	−2.27 (−2.64, −1.90)	0.683[b]	386	83.3 (15.0)	**0.006**[b]	−3.67 (−4.13, −3.21)	0.995[b]	−1.80 (−2.13, −1.47)	0.696[b]
5.1–10 years	403	89.8 (16.5)		277	87.1 (14.8)		−2.57 (−2.95, −2.19)		384	85.8 (15.4)		−3.63 (−4.29, −2.97)		−1.39 (−2.12, −0.66)	
10.1–15 years	188	91.5 (15.5)		122	88.5 (15.3)		−2.33 (−2.90, −1.76)		176	87.9 (14.2)		−3.73 (−4.37, −3.09)		−1.79 (−2.26, −1.31)	
>15 years	155	90.2 (16.4)		118	88.0 (16.2)		−2.27 (−2.88, −1.67)		146	85.8 (15.4)		−3.74 (−4.54, −2.95)		−1.69 (−2.35, −1.04)	
Concomitant antidiabetics															
OADs	622	86.1 (15.1)	**<0.001**[b]	405	84.1 (14.6)	**<0.001**[b]	−2.14 (−2.43, −1.85)	**0.002**[b]	591	82.7 (14.5)	**<0.001**[b]	−3.30 (−3.75, −2.85)	**<0.001**[b]	−1.40 (−1.90, −0.89)	0.073[b]
OAD ± injectable	651	92.0 (16.8)		461	88.2 (15.5)		−2.79 (−3.09, −2.49)		624	87.4 (15.7)		−4.34 (−4.73, −3.95)		−1.91 (−2.20, −1.62)	
HbA1c (%)															
>7%	1118	88.4 (15.9)	**<0.001**[b]	772	85.7 (14.7)	**<0.001**[b]	−2.41 (−2.63, −2.20)	0.109[a]	1077	84.6 (15.1)	**0.003**[b]	−3.65 (−3.97, −3.34)	**0.002**[b]	−1.55 (−1.85, −1.25)	**0.008**[b]
≤7%	126	94.7 (18.1)		81	92.7 (18.7)		−2.99 (−3.74, −2.24)		119	88.9 (16.2)		−5.26 (−6.29, −4.23)		−2.88 (−3.84, −1.92)	
>7.5%	991	88.2 (16.0)	**<0.001**[b]	675	85.5 (14.7)	**<0.001**[b]	−2.45 (−2.68, −2.22)	0.729	955	84.4 (15.0)	**0.002**[b]	−1.58 (−1.92, −1.25)	0.253	−3.68 (−4.02, −3.34)	0.096
≤7.5%	253	92.4 (16.9)		178	89.7 (16.8)		−2.54 (−3.02, −2.05)		241	87.7 (15.9)		−2.00 (−2.49, −1.50)		−4.32 (−4.95,-3.69)	

OAD, oral antidiabetic drug; *CI*, confidence interval; *LB*, lower bound; *UB*, upper bound

Values in bold indicate statistical significance ($p < 0.05$)

[a] One-way ANOVA–Tukey HSD test

[b] Student's t test

Table 5 Change in BP levels during follow-up with respect to diabetes duration and concomitant regimens

	Baseline (n = 1683)			3rd month (n = 1618)			6th month (n = 1683)		
	n	Mean (SD)	p value	n	Mean (SD)	p value	n	Mean (SD)	p value
Systolic BP (mmHg)									
Diabetes duration									
≤5 years	402	129.8 (15.0)	0.007[b]	263	123.7 (10.6)	**0.001**[b]	383	122.0 (9.9)	**<0.001**[b]
5.1–10 years	387	131.5 (14.4)		262	127.0 (12.3)		377	125.0 (12.4)	
10.1–15 years	179	132.8 (15.1)		114	126.0 (11.4)		161	125.6 (12.1)	
>15 years	147	134.3 (14.7)		112	128.3 (14.1)		136	125.7 (11.8)	
Concomitant antidiabetics									
OADs	609	131.7 (15.1)	0.724[a]	393	126.8 (12.4)	0.150[a]	577	124.1 (10.9)	0.877[a]
OAD ± injectable	629	132.0 (15.0)		433	125.6 (11.5)		589	124.0 (11.6)	
HbA1c (%)									
>7%	1098	131.9 (14.9)	0.755[a]	745	126.1 (11.8)	0.622[a]	1046	124.1 (11.3)	0.350[a]
≤7%	113	131.4 (17.1)		71	126.8 (13.1)		105	123.0 (10.0)	
>7.5%	974	132.2 (14.6)	0.093[a]	652	126.4 (11.8)	0.278[a]	932	124.2 (11.4)	0.237[a]
≤7.5%	237	130.4 (17.0)		164	125. (12.6)		219	123.2 (10.4)	
Diastolic BP (mmHg)									
Diabetes duration									
≤5 years	402	80.5 (9.3)	0.483[b]	263	77.2 (8.1)	0.717[b]	383	76.0 (7.5)	**0.026**[b]
5.1–10 years	387	81.1 (8.7)		262	78.0 (7.5)		377	77.2 (7.8)	
10.1–15 years	179	81.8 (9.4)		114	77.5 (7.4)		161	78.0 (8.0)	
>15 years	147	80.9 (10.8)		112	77.5 (8.2)		136	76.5 (7.8)	
Concomitant antidiabetics									
OADs	609	81.1 (9.5)	0.750[a]	393	77.8 (7.9)	0.328[a]	577	76.9 (7.6)	0.616[a]
OAD ± injectable	629	81.2 (9.3)		433	77.3 (7.7)		589	76.7 (7.7)	
HbA1c (%)									
>7%	1098	81.1 (9.3)	0.976[a]	745	77.5 (7.9)	0.208[a]	1046	76.7 (7.7)	0.889[a]
≤7%	113	81.2 (9.7)		71	78.7 (6.7)		105	76.6 (7.5)	
>7.5%	974	81.3 (9.3)	0.179[a]	652	77.7 (7.9)	0.422[a]	932	76.7 (7.8)	0.996[a]
≤7.5%	237	80.4 (9.6)		164	77.1 (7.2)		219	76.7 (7.2)	

[a] Student's t test

[b] Oneway ANOVA–Tukey HSD test

Values in bold indicate statistical significance ($p < 0.05$)

vs. 14.4%, p = 0.024) at the 3rd month visit, while type of concomitant regimen had no significant impact on target BP achievement during follow-up visits (Table 6).

Discussion

Representing the first nationwide data on real-life dapagliflozin treatment in Turkish T2D patients, our findings revealed that first prescription for dapagliflozin in T2D patients was associated with significant decrease in HbA1c (−1.22% on average), BMI (−1.42 kg/m^2 on average), body weight (−3.83 kg on average), and systolic (−7.78 mmHg on average) and diastolic (−4.29 mmHg on average) BP levels from baseline to the 6th month of treatment. At the end of 6-month dapagliflozin treatment (discontinued in 4.3% of patients), HbA1c levels were ≤7% in 30.1% of patients, BP was ≤140/90 mmHg in 95.9% of patients, and >5% weight loss was evident in 38.0% of patients.

Results from past clinical trials showed that patients receiving dapagliflozin in combination with other glucose-lowering agents (OADs or insulin + OADs) had HbA1c reductions in the range of −0.4 to −1.2% [14, 15, 18, 20–24], weight loss reduction in the range of −0.69 to −3.2 kg at 1 year [14, 15, 18, 21–24], and a SBP reduction of −2.6 to 4.28 mmHg and a DBP reduction of −1.2 to 1.6 mmHg [20, 25, 31].

Observational data on the effects of dapagliflozin initiation among T2D patients in primary and secondary hospital care settings revealed reductions in HbA1c (0.89-1.16%), weight (1.8-4.6 kg) and BP (systolic 1.6-5.5 mmHg; diastolic 0.3-3.4 mmHg) after addition of dapagliflozin [13, 27, 28]. In addition, target HbA1c (≤7.0%) levels were noted in 27.0% of

Table 6 Target HbA1c, body weight, and BP achievement rates with respect to diabetes duration and concomitant regimens

	Patients with target HbA1c (*n* (%))						Patients with >5% weight loss				Patients with target BP (*n* (%))					
	3rd month			6th month			3rd month		6th month		3rd month			6th month		
	n	≤7%	≤7.5%	*n*	≤7%	≤7.5%	*n*	*n* (%)	*n*	*n* (%)	*n*	≤140/90	≤130/80	*n*	≤140/90	≤130/80
Overall	926	201 (21.7)	352 (38.0)	1455	438 (30.1)	718 (49.3)	864	151 (17.5)	1206	458 (38.0)	826	763 (92.4)	584 (70.7)	1166	1118 (95.9)	901 (77.3)
Gender																
Female	515	102 (19.8)	177 (34.4)	823	216 (26.2)	367 (44.6)	489	83 (17.0)	672	257 (38.2)	461	424 (92.0)	316 (68.5)	638	606 (95.0)	486 (76.2)
Male	411	99 (24.1)	175 (42.6)	632	222 (35.1)	351 (55.5)	375	68 (18.1)	534	201 (37.6)	365	339 (92.9)	268 (73.4)	528	512 (97.0)	415 (78.6)
p value[a]		0.116	**0.011**		**0.000**	**0.000**		0.656		0.830		0.627	0.126		0.089	0.326
Diabetes duration																
≤5 years	258	60 (23.3)	108 (41.9)	417	149 (35.7)	224 (53.7)	265	41 (15.5)	383	143 (37.3)	263	247 (93.9)	195 (74.1)	383	375 (97.9)	321 (83.8)
5.1–10 years	285	62 (21.8)	106 (37.2)	410	113 (27.6)	198 (48.3)	276	50 (18.1)	382	141 (36.9)	262	244 (93.1)	182 (69.5)	377	361 (95.8)	284 (75.3)
10.1–15 years	118	24 (20.3)	39 (33.1)	195	50 (25.6)	92 (47.2)	122	17 (13.9)	175	63 (36.0)	114	104 (91.2)	80 (70.2)	161	149 (92.5)	115 (71.4)
>15 years	112	25 (22.3)	46 (41.1)	153	45 (29.4)	74 (48.4)	118	17 (14.4)	146	47 (32.2)	112	101 (90.2)	72 (64.3)	136	126 (92.6)	98 (72.1)
p value[a]		0.699	0.495		**0.032**	0.136		0.648		0.339		0.159	0.068		**0.001**	**<0.001**
Antidiabetic regimen																
OAD	452	119 (26.3)	206 (45.6)	743	276 (37.1)	423 (56.9)	404	58 (14.4)	589	212 (36.0)	393	359 (91.3)	273 (69.5)	577	555 (96.2)	442 (76.6)
OAD ± injectable	474	82 (17.3)	146 (30.8)	712	162 (22.8)	295 (41.4)	460	93 (20.2)	617	246 (39.9)	433	404 (93.3)	311 (71.8)	589	563 (95.6)	459 (77.9)
p value[b]		**0.001**	**<0.001**		**<0.001**	**<0.001**		**0.024**		0.166		0.291	0.457		0.605	0.589

OAD, oral antidiabetic drug

Values in bold indicate statistical significance ($p < 0.05$)

[a] χ^2 test

[b] Mantel-Haenszel test

patients [27] alongside ≥1% reduction in HbA1c in 42% of patients, ≥5kg weight loss in 15% of patients [29], and reductions in body weight plus HbA1c in 67.7% of patients [11].

Our findings on clinical effectiveness of dapagliflozin in terms of overall change in HbA1c (- 1.2%) and body weight (3.8 kg) over 6-month treatment in daily clinical practice seem broadly consistent with previous dapagliflozin clinical trials [10, 14, 15, 18–25],

In our cohort, average HbA1c reductions obtained under dapagliflozin treatment were similar with respect to diabetes duration and body weight was significantly higher in patients with 10–15 years of diabetes duration at baseline and remained higher during follow-up visits, whereas systolic BP reduction during 6-month therapy was significantly higher in patients with less than 5 years of diabetes duration. However, less than 5-year diabetes duration was associated with significantly higher rate of achieving HbA1c ≤7%, BP ≤140/90 mmHg, and BP ≤130/80 mmHg targets at the 6th month of dapagliflozin treatment as compared with longer diabetes duration.

Notably, in a past study among 3774 T2D patients including either early (first intensification after metformin or sulfonylurea monotherapy, n = 951) or later (second- or higher-order intensification, n = 2823), users of dapagliflozin, shorter disease duration was reported among early users vs. later users along with baseline-adjusted mean reduction of 1.54% vs. 1.02% in HbA1c, 3.31% vs. 4.06% in weight and 2.50 mmHg vs. 2.84 mmHg in systolic BP after 6–12 months of treatment, respectively [32]. Authors noted early versus later dapagliflozin use to be associated with a greater likelihood of adjusted HbA1c reduction of ≥1% (OR: 1.68, 95% CI: 1.15–2.45) [32]. In this regard, improved HbA1c and BP control with dapagliflozin in our patients with <5-year diabetes duration seems to support the likelihood of improved glycemic and BP control with broader and earlier dapagliflozin use [32].

A higher baseline HbA1c, shorter duration of diabetes, and male gender were reported to be independently associated with a greater HbA1c reduction in T2D patients who initiated dapagliflozin [27]. Our findings also revealed greater improvement in HbA1c levels in males vs. females, despite the similar baseline HbA1c values between males and females.

In accordance with higher baseline HbA1c levels in patients under concomitant OAD therapy, rates of achieving HbA1c ≤7% and ≤7.5 targets were significantly higher in this group as compared with OAD ± injectable therapy, while lower rates of achieving >5% weight loss were noted with concomitant OAD vs. with OAD ± injectable therapy. The increase in HbA1c target achievement in our OAD-treated patients at the end of 6-month dapagliflozin treatment supports the efficacy of dapagliflozin shown in patients with T2D inadequately controlled with metformin [18, 20, 33–35]. Notably, in accordance with the efficacy of add-on dapagliflozin in OAD-treated patients in terms of HbA1c levels, body weight and BP levels in our cohort, data from a retrospective real-world study of dapagliflozin vs. other OADs added to metformin in T2D patients revealed association of dapagliflozin + metformin with a greater reduction in HbA1c level (−1.0% vs. −0.7%), body weight (−1.8 kg vs. −0.7 kg), and SBP (−3.6 mmHg vs. −0.1 mmHg), and DBP (−2.0 mmHg vs. −0.6 mmHg) levels from baseline to 12-month follow-up [13].

Dapagliflozin was reported to be associated with placebo-subtracted changes from baseline in systolic BP of −3.6 to 4.28 mmHg [25, 31] and in diastolic BP of −1.2 mmHg in hypertensive patients, while systolic and diastolic BP reduction of −2.6 and −1.2 mmHg, respectively, in non-hypertensive patients with T2D [31]. The efficacy of dapagliflozin on BP reduction in hypertensive patients with T2D was also reported to be higher in those receiving a β-blocker or calcium-channel blocker agent [25].

Accordingly, the reductions obtained in BP with dapagliflozin in the present study (systolic 7.8 mmHg; diastolic 4.3 mmHg) seem consistent with rate (57.0%) of hypertension in the present cohort and support the likelihood of dapagliflozin treatment to optimize BP control in hypertensive T2D patients by providing a diuretic-like effect enhancing the efficacy of concomitant antihypertensive agents [25].

Data from DIVERSITY-CVR study in 340 patients with early-stage T2D on metformin alone or no glucose-lowering agents who were randomized to receive dapagliflozin or sitagliptin for 24 weeks revealed the superiority of dapagliflozin in terms of the achievement ratio of primary endpoint (HbA1c level maintenance < 7.0%, avoidance of hypoglycemia and ≥ 3.0% body weight loss from baseline) as well as in terms of several secondary endpoints that modulate cardiometabolic risk (reducing FPG, insulin, and uric acid, increasing HLD-c, and suppressing the increase in serum creatinine and the decrease in estimated GFR) [36].

Hence our findings support the preferable cardiometabolic effects of dapagliflozin with consistently reported efficacy at improving cardiometabolic risk factors in both randomized trials and large-scale real-life studies, suggesting that SGLT2 inhibitors might be more suitable than DPP-4 inhibitors for preventing cardiovascular events in patients with early-stage but inadequately controlled type 2 diabetes [30, 36–42]. Notably, the association of dapagliflozin therapy with improvement of several cardiometabolic indices and reduction in cardiovascular risk is considered to emphasize that approaches beyond glycemic control (such as body weight reduction) represent important strategies for reducing the risk of cardiovascular events and mortality in T2D patients [36, 43, 44].

Given the consideration of higher rate of HbA1c target achievement and greater reductions in body weight in patients treated with dapagliflozin beyond 6 months [28, 35], our

findings may indicate likelihood of a better efficacy of longer-term dapagliflozin treatment on HbA1c, body weight, and BP reduction in patients with higher baseline levels.

The major strength of this observational study is the inclusion from a database of 1683 T2D patients at 79 centers in Turkey. The large number of centers increases the likelihood that the study is representative of the overall T2D population and hence its generalizability. However, certain limitations to this study should be considered. First, missing or incorrect data, and the fact that data reflects everyday health care and were collected for non-research purposes is a limitation common to retrospective medical records database analyses. Therefore, clinical values are captured as part of routine clinical practice and there is considerable variation in the timing and completeness of measurements. Second, patient records report issued prescriptions only with no information available on whether the patient collected the prescription. Furthermore, prescriptions may not always include dosage information (not well recorded for insulin) which is needed for more accurate estimation of medication adherence/medication possession ratio. Third, first dapagliflozin prescription recorded in the participating centers may not be the patient's first ever as the patient could have initiated treatment outside of that clinic. Fourth, lack of data on control group values and adverse events such as hypoglycemia or renal dysfunction is another limitation which otherwise would extend the knowledge achieved in the current study. Fifth, this is a descriptive study with no comparative arm and any changes observed may not relate to the pharmaceutical intervention alongside likelihood of differences in data quality and accuracy between various hospitals. Therefore, future trials with larger sample size, adequate ethnicity representation, and long-term observation are necessary to confirm the generalizability of the study findings.

In conclusion, this first nationwide observational survey in T2D patients treated with dapagliflozin in Turkey provided real-life evidence on significant and clinically meaningful reductions in HbA1c, body weight, and BP after initiation of dapagliflozin. Association of 6-month dapagliflozin with higher rate of HbA1c target achievement when used as add-on therapy to OAD rather than to OAD ± injectable therapy, in relation to lower baseline HbA1c levels in the former group, and higher HbA1c and BP target achievement when used in patients with less than 5-year diabetes duration seem to emphasize the likelihood of improved glycemic and BP control with broader and earlier dapagliflozin use in T2D patients. Further prospective, longer-term longitudinal studies are warranted to identify appropriate indications and optimal combinations of dapagliflozin with other antidiabetic medications for optimal clinical efficacy of add-on dapagliflozin in T2D patients.

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Declarations

Ethics approval The study was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice, and the local regulations for clinical research.

Consent to participate This is a retrospective observational cohort study.

Consent for publication Permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Conflict of interest Ceren Yilmaz, M.D and Onur Utebay, M.D are Astra-Zeneca employees. Other authors declare that they have no conflict of interest.

References

1. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019. http://www.diabetesatlas.org. Accessed 3 Feb 2020.
2. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, et al. TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 2013;28:169–80.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89.
4. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–72.
5. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–53.
6. Khunti K, Godec TR, Medina J, Garcia-Alvarez L, Hiller J, Gomes MB, et al. Patterns of glycaemic control in patients with type 2 diabetes mellitus initiating second-line therapy after metformin monotherapy: Retrospective data for 10 256 individuals from the United Kingdom and Germany. Diabetes Obes Metab. 2018;20:389–99.
7. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61:2461–98.
8. Jung CH, Jang JE, Park JY. A novel therapeutic agent for type 2 diabetes mellitus: SGLT2 inhibitor. Diabetes Metab J. 2014;38:261–73.
9. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther. 2014;8:1335–80.
10. Min KW, Ku BJ, Lee JH, Kim MS, Ahn KJ, Lee MK, et al. Addition of Ipragliflozin to metformin treatment in Korean patients with type 2 diabetes mellitus: subgroup analysis of a phase 3 trial. Diabetes Metab J. 2017;41:135–45.
11. Han E, Kim A, Lee SJ, Kim JY, Kim JH, Lee WJ, et al. Characteristics of dapagliflozin responders: A longitudinal, prospective, nationwide dapagliflozin surveillance study in Korea. Diabetes Ther. 2018;9:1689–701.
12. Chow W, Miyasato G, Kokkotos FK, Bailey RA, Buysman EK, Henk HJ. Real-world canagliflozin utilization: Glycemic control among patients with type 2 diabetes mellitus-A multi-database synthesis. Clin Ther. 2016;38:2071–82.
13. Huang H, Bell KF, Gani R, Tugwell CW, Eudicone JM, Krukas-Hampel MR. A retrospective real-world study of dapagliflozin versus other oral antidiabetic drugs added to metformin in patients with type 2 diabetes. Am J Manag Care. 2018;24:132–7.
14. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35:1473–8.
15. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011;13:928–38.
16. Forziga Turkey-Summary of Product Characteristics (SPC). 2016. https://www.astrazeneca.com/content/dam/az/Country-Sites/Turkey /Medicines/ Forziga-5-mg-KUB.pdf. Accessed 25 Dec 2019.
17. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010;33:2217–24.
18. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:2223–33.
19. Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014;16:159–69.
20. Nauck MA, Del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, doubleblind, active-controlled noninferiority trial. Diabetes Care. 2011;34:2015–22.
21. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, JWilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012;97:1020–31.
22. Matthaei S, Bowering K, Rohwedder K, Grohl A. Parikh S; Study 05 Group. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care. 2015;38:365–72.
23. Jabbour SA, Hardy E, Sugg J, Parikh S, Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37:740–50.
24. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, et al. Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med. 2012;156:405–15.
25. Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combinationantihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol. 2016;4:211–20.
26. Scheerer MF, Rist R, Proske O, Meng A, Kostev K. Changes in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy: a primary care database study. Diabetes Metab Syndr Obes. 2016;9:337–45.
27. Brown RE, Gupta N, Aronson R. Effect of dapagliflozin on glycemic control, weight, and blood pressure in patients with type 2 diabetes attending a specialist endocrinology practice in Canada: A retrospective cohort analysis. Diabetes Technol Ther. 2017;19:685–91.
28. Wilding J, Bailey C, Rigney U, Blak B, Beekman W, Emmas C. Glycated hemoglobin, body weight and blood pressure in type 2 diabetes patients initiating dapagliflozin treatment in primary care: A retrospective study. Diabetes Ther. 2016;7:695–711.
29. McGovern A, Dutta N, Munro N, Watters K, Feher M. Dapagliflozin: clinical practice compared with pre-registration trial data. Br J Diabetes Vasc Dis. 2014;14:138–43.
30. Nelson AJ, Navar AM. How Real-world Data Augments What We Know About SGLT-2 Inhibitors for Cardiovascular Risk Reduction. ACC Latest in Cardiology, Sep 09, 2020. https://www.acc.org/latest-in-cardiology/articles/2020/09/08/08/23/how-real-world-data-augments-what-we-know-about-sglt-2-inhibitors-for-cv-risk-reduction. Accessed 28 Oct 2020.

31. Sjöström CD, Johansson P, Ptaszynska A, List J, Johnsson E. Dapagliflozin lowers blood pressure in hypertensive and non-hypertensive patients with type 2 diabetes. Diab Vasc Dis Res. 2015;12:352–8.
32. Wilding JPH, Rigney U, Blak BT, Nolan ST, Fenici P, Medina J. Glycaemic, weight, and blood pressure changes associated with early versus later treatment intensification with dapagliflozin in United Kingdom primary care patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2019;155:107791.
33. Scorsone A, Saura G, Fleres M, Spano L, Aiello V, Brancato D, et al. Efficacy and renal safety of dapagliflozin in patients with type 2 diabetes mellitus also receiving metformin: A real-life experience. J Diabetes Res. 2018;2018:8501418.
34. Nyström T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes. Diabetes Obes Metab. 2017;19:831–41.
35. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013;11:43.
36. Fuchigami A, Shigiyama F, Kitazawa T, Okada Y, Ichijo T, Higa M, et al. Efficacy of dapagliflozin versus sitagliptin on cardiometabolic risk factors in Japanese patients with type 2 diabetes: a prospective, randomized study (DIVERSITY-CVR). Cardiovasc Diabetol. 2020;19:1.
37. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
38. Persson F, Nystrom T, Jorgensen ME, Carstensen B, Gulseth HL, Thuresson M, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: a multinational observational study. Diabetes Obes Metab. 2018;20:344–51.
39. Patorno E, Pawar A, Franklin JM, Najafzadeh M, Deruaz-Luyet A, Brodovicz KG, et al. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. Circulation. 2019;139:2822–30.
40. Schork A, Saynisch J, Vosseler A, Jaghutriz BA, Heyne N, Peter A, et al. Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: a prospective study using bioimpedance spectroscopy. Cardiovasc Diabetol. 2019;18:46.
41. Irace C, Casciaro F, Scavelli FB, Oliverio R, Cutruzzola A, Cortese C, et al. Empagliflozin influences blood viscosity and wall shear stress in subjects with type 2 diabetes mellitus compared with incretin-based therapy. Cardiovasc Diabetol. 2018;17:52.
42. Handelsman Y, Mathieu C, Del Prato S, Johnsson E, Kurlyandskaya R, Iqbal N, et al. Sustained 52-week efficacy and safety of triple therapy with dapagliflozin plus saxagliptin versus dual therapy with sitagliptin added to metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2018;21:883–92.
43. Rosenzweig JL, Bakris GL, Berglund LF, Hivert M-F, Horton ES, Kalyani RR, et al. Primary prevention of ASCVD and T2DM in patients at metabolic risk: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2019;104:3939–85.
44. Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCarren M, et al. Intensive glucose control in patients with type 2 diabetes-15-year follow-up. N Engl J Med. 2019;380:2215–24.

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