Efficacy of Dapagliflozin in Southern Europe Across the Spectrum of Characteristics of Type 2 Diabetes: An International Real-World Analysis

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Purpose: To extend a prior real-world analysis (DARWIN-T2D) of patients with type 2 diabetes initiating dapagliflozin in Italy, Greece, and Spain by evaluating changes in glycemic and extra-glycemic endpoints after initiation of dapagliflozin.

Patients and Methods: The association among demographic/clinical characteristics and the change in glycemic and extraglycemic effectiveness endpoints during the observation period was assayed using a mixed effects model.

Results: A total of 1438 (860 males; 59.8%) patients were evaluated; patients were followed for a mean of 5.6 months. At baseline, 93.4% and 61.9% of patients were on concomitant metformin and insulin, respectively. A significant mean decrease in HbA1c from 8.7% to 7.5% was observed. The mixed model used also revealed several associations between different glycemic and laboratory parameters and patient characteristics at baseline; insulin use was significantly associated with lower HbA1c. Patients with BMI ≥30 kg/m² experienced greater weight loss than those with BMI <30 kg/m². A consistent glucose-lowering effect of dapagliflozin was seen in all subgroups of patients, including those with stage 2 renal impairment and cardiovascular disease.

Conclusion: The present analysis confirms the efficacy of dapagliflozin in diversified real-world settings with broadly similar effects on HbA1c across countries and baseline characteristics.

Keywords: type 2 diabetes, dapagliflozin, real-life, glycemic control

Introduction

Type 2 diabetes (T2D) is estimated to affect more than 400 million individuals worldwide, with a massive burden due to chronic comorbidities, reduced quality of life, and shortened survival.1 In addition, about 10% of global healthcare expenditure is due to diabetes.1

SGLT2 inhibitors (SGLT2i) are a class of glucose-lowering agents that block resorption of glucose in the kidney to improve glucose homeostasis.2 In addition to lowering HbA1c with a low risk of hypoglycemia, SGLT2i are associated with weight loss, blood pressure control, and favorable cardiovascular (CV) and renal effects.3 According to ADA-EASD recommendations, therapeutic choices should be driven by the presence or absence of atherosclerotic CVD, heart failure or renal disease, which are conditions that favor the use of SGLT2i or GLP-1 receptor agonists.4 The availability of these agents led to change from the primary objective of glucose control without hypoglycemia and weight gain to include cardiovascular and renal protection whenever warranted.5 Expert consensus considers that in patients with established cardiorenal disease or at high cardiorenal risk, SGLT-2i and/or GLP-1RAs should be used routinely.6

For dapagliflozin, renal and CV benefits were demonstrated in DECLARE–TIMI 58, a large trial conducted in >17,000 patients with or at risk for atherosclerotic cardiovascular disease.7 Dapagliflozin was noninferior to placebo considering the...
primary safety outcome of major adverse cardiac events (MACE) and was associated with a significantly lower rate of cardiovascular death or hospitalization for heart failure (second co-primary outcome), with additional findings of a lower rate of adverse renal events. Several real-world studies have been carried out with dapagliflozin and other SGLT2 inhibitors.8–11 Overall, results of these studies confirm the favorable CV outcomes and lower event rates of hospitalization for both heart failure and CV mortality.8–11 The DARWIN-T2D (DApagliflozin Real World evideNce in Type 2 Diabetes) study was a multicenter retrospective analysis in Italy that evaluated patients receiving dapagliflozin and its efficacy in daily practice.12 Confirming data from randomized clinical trials, dapagliflozin was associated with a decrease in HbA\textsubscript{1c} of 0.7%, weight loss of 2.7 kg and significant improvement in albuminuria.13 Real-world studies help to understand the efficacy of a drug outside the rigid trial setting in which some groups of patients may be under-represented or excluded. Differences may also be reflected in primary vs specialist care, as well as reimbursement policies.14 This was shown in a recent real-world analysis of the clinical characteristics of patients with type 2 diabetes initiating dapagliflozin in Italy, Greece, and Spain,14 reporting that dapagliflozin was initiated at different stages of diabetes according to the country and prescribing setting. Herein, we extended the prior analysis in the same cohort of patients by evaluating changes in glycemic and extra-glycemic endpoints after initiation of dapagliflozin.

**Materials and Methods**

The same cohort of patients studied in our previous report was followed and investigated herein.14 In that study, 3135 patients with T2D and who were initiating dapagliflozin in Italy (n = 2484), Spain (n = 564) and Greece (n = 87) were assessed.

The DARWIN-T2D study was approved by the local ethical committee at all participating centers detailed in Table S1. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Recruitment in Italy, Spain, and Greece**

Recruitment criteria have been previously described in detail and are briefly summarized below. For Italy, data from the DARWIN-T2D was used.15 Patients (age 18–80 years, diagnosis of T2D at least 1 year earlier) and initiating dapagliflozin 10 mg as add-on to metformin and/or insulin in Italy from March 2015 until the end of 2016 were enrolled. In Spain, therapy with dapagliflozin could have been started 6 months before inclusion, and enrolled patients 18–75 years with T2D and on stable therapy with glucose-lowering agents. In Greece, data from patients enrolled in real-world studies was used. To be enrolled, the following was required: signed informed consent form, age at least 18 years, and diagnosis of T2D. In Spain and Greece, SGLT2i could be prescribed by primary care physicians, while in Italy at the time of the study only diabetologists were allowed to prescribe SGLT2i.

**Study Objectives and Endpoints**

The main objectives of this study were: i) to evaluate the effectiveness in glycemic and extra-glycemic endpoints in patients who received dapagliflozin in a multinational real-world cohort; ii) to determine if there were any baseline characteristics associated with differential changes in effectiveness endpoints during follow-up. Follow-up data from each country were analyzed individually and compared to investigate differences between countries, and the pooled population was also assessed.

Common definitions of clinical variables were standardized. In particular, chronic kidney disease (CKD) was considered as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m\textsuperscript{2}, while a cut-off of 90 mL/min/1.73 m\textsuperscript{2} was used in further analyses. CV disease (CVD) was defined as history of myocardial infarction, angina, stroke, transient ischemic attack, peripheral arterial disease, or revascularization of any arterial site. Age, body mass index (BMI), eGFR, and duration of diabetes were categorized using 65 years, 30 kg/m\textsuperscript{2}, 90 mL/min/1.73 m\textsuperscript{2} and 10 years as cut-offs, respectively. The datasets used in this study did not contain information on drug safety and adverse events.

**Statistical Analysis**

Continuous variables are presented as means with standard deviations (SD) and categorical variables as number of subjects and percentage values. The clinical and demographic baseline differences in country groups were tested by the ANOVA or Pearson’s Chi-square test (Fisher’s Exact where appropriate) for continuous and categorical variables, respectively. To properly account for dependency of measurements from the same patient, endpoint data were analyzed by the mixed-effect (ME) model. In particular, the patient variability was inserted as random effect in all ME models and the linear and binomial ME models were applied to continuous and categorical endpoint, respectively. The association among demographic/clinical characteristics and the change in
glycemic and extraglycemic effectiveness endpoints during the entire observation period was assayed using the ME model. Moreover, to test whether the changes in HbA1c and body weight from baseline were different in subgroups of patients defined by baseline characteristics, a sensitivity analysis was performed in the entire study cohort by the interaction test in the ME model.

The Likelihood Ratio test was used as the test of statistical significance and the estimated p-values were adjusted for multiple comparisons by the Holm correction method. Differences, with a p value <0.05, were selected as significant, and data were acquired and analyzed with R v4.1.1 software.

**Results**

**Baseline Characteristics**

A total of 1438 (860 males; 59.8%) patients were included in the analysis. The demographic and clinical characteristics of the study participants are summarized in Table 1. Briefly, the mean age, BMI, duration of diabetes and HbA1c was 60.6 years, 33.3 kg/m², 12.4 years and 8.7%, respectively; patients were followed for a mean of 5.6 months. Overall, 93.4% of patients were on concomitant metformin, and 61.9% of patients were on concomitant insulin therapy as baseline.

Descriptive statistics of demographic and clinical characteristics in each country at baseline are reported in Table S2. The mean BMI, weight, and HbA1c at baseline were similar among countries. Small but significant differences were observed between countries for duration of diabetes, age, height, systolic blood pressure, and low-density lipoprotein (LDL) cholesterol (p-value for all <0.05). Significant differences among countries were also seen in glucose-lowering therapy, concomitant therapies, and

**Table 1 Demographic and Clinical Characteristics of Study Participants at Baseline (N = 1438)**

| Characteristic | N   | Overall        |
|----------------|-----|----------------|
| Follow-up time, months | 1438 | 5.6 (1.51)     |
| Duration, years | 1410 | 12.4 (8.34)    |
| Duration ≥ 10 years | 813  | 60.6 (9.66)    |
| Gender, male    | 1438 | 524 (36.44%)   |
| Age, years      | 1438 | 524 (36.44%)   |
| Age ≥ 65 years  | 524  | 92.4 (18.26)   |
| Weight, kg      | 1377 | 166.5 (9.59)   |
| Height, cm      | 1389 | 33.3 (5.87)    |
| BMI, kg/m²      | 1348 | 933 (64.88%)   |
| BMI ≥ 30 kg/m²  | 1348 | 933 (64.88%)   |
| Waist, cm       | 427  | 110.2 (14.02)  |
| SBP, mm Hg      | 1119 | 138.9 (17.9)   |
| DBP, mm Hg      | 1116 | 80.5 (10.64)   |
| FPG, mg/dl      | 1269 | 173.4 (57.86)  |
| HbA1c, mmol/mol | 1364 | 71.2 (52.91)   |
| HbA1c, %        | 8.7  | 8.7 (4.84)     |
| TC, mg/dl       | 1095 | 176.2 (41.18)  |
| TC, mmol/l      | 1022 | 45.0 (13.72)   |
| HDL, mg/dl      | 1022 | 1.2 (0.35)     |
| TG, mg/dl       | 1090 | 176.8 (134.69) |
| TG, mmol/l      | 968  | 2 (1.52)       |
| LDL, mg/dl      | 968  | 96.8 (33.69)   |
| LDL, mmol/l     | 968  | 2.5 (0.87)     |
| sGOT, U/l       | 828  | 26 (15.88)     |
| sGPT, U/l       | 915  | 32.4 (20.4)    |
| Creatinine, mg/dl | 1082 | 0.8 (0.28)     |
| eGFR, mL/min/1.73 m² | 1041 | 85.7 (20.66)   |

(Continued)
comorbidities (p-value <0.05). In particular, in Italy 426 (54.6%) patients received concomitant insulin, while none were receiving other glucose-lowering medications, as required by reimbursement criteria. In Greece, few patients were receiving concomitant insulin therapy (N = 3; 5.2%) compared to Italy (54.4%) and Spain (100%). Significant differences were also evident in other therapies in addition to glucose-lowering agents. Significant differences were also observed for the proportion of patients with cardiovascular complications, notably peripheral artery disease (11.1%, 6.6%, and 0% in Italy, Spain, and Greece, respectively).

Effectiveness Endpoints
Glycemic and laboratory data at baseline and follow-up for the entire population are shown in Table 2. Significant mean decreases in HbA1c from 8.7% to 7.5% and in FPG from 173.8 mg/dl to 139.6 mg/dl were observed (p-value <0.0001). Significant decreases in weight, SBP, DBP, TC, TG, and LDLc were also apparent at follow-up. A small but significant increase was seen for HDL

| Characteristic                        | N     | Overall |
|--------------------------------------|-------|---------|
| eGFR ≥90 mL/min/m²                   | 502   | (34.91%)|
| Metf. N (%)                          | 1403  | (93.44%)|
| Insulin. N (%)                       | 1077  | (61.93%)|
| SU or repaglinide. N (%)             | 994   | (15.9%) |
| GLP-1RA. N (%)                       | 932   | (10.41%)|
| Pioglitazone. N (%)                  | 861   | (2.9%)  |
| Acarbose. N (%)                      | 840   | (0.12%) |
| ACEi / ARBs. N (%)                   | 1042  | (77.54%)|
| Beta-blockers. N (%)                 | 800   | (36.88%)|
| CCB. N (%)                           | 749   | (25.63%)|
| Statin. N (%)                        | 912   | (70.18%)|
| Fibrates/omega-3 fatty acids. N (%)  | 786   | (22.26%)|
| APA. N (%)                           | 840   | (51.31%)|
| Retino. N (%)                        | 1177  | (18.52%)|
| Stroke. N (%)                        | 1402  | (3.14%) |
| AMI. N (%)                           | 1251  | (11.59%)|
| HF. N (%)                            | 1253  | (2.95%) |
| PAD. N (%)                           | 954   | (7.76%) |
| CVD. N (%)                           | 426   | (32.86%)|

Note: Results are expressed as mean with standard deviation or as number of subjects with percentage.

Table 2 Glycemic and Laboratory Data in the Entire Population at Baseline and Follow-Up

| Characteristic | N     | Baseline | Follow-Up | Beta (95% CI) | p-value |
|----------------|-------|----------|-----------|---------------|---------|
| HbA1c, mmol/mol| 1341  | 71.5 (53.3) | 58.9 (13.2) | -12.5 (-15.38: -9.66) | <0.0001 |
| HbA1c, %       | 1346  | 8.7 (4.9) | 7.5 (1.2) | -1.2 (-1.41: -0.88) | <0.0001 |
| FPG, mg/dl     | 1186  | 173.8 (58.3) | 139.6 (42.6) | -34.2 (-37.51: -30.85) | <0.0001 |
| Weight, kg     | 1346  | 92.4 (18.3) | 89.6 (17.8) | -2.9 (-3.11: -2.63) | <0.0001 |
| SBP, mmHg      | 1047  | 138.7 (17.8) | 134.9 (16.3) | -3.8 (-4.79: -2.76) | <0.0001 |
| DBP, mmHg      | 1044  | 80.5 (10.6) | 78.6 (9.4) | -1.9 (-2.53: -1.28) | <0.0001 |
| TC, mg/dl      | 942   | 176.7 (42.0) | 170.0 (38.2) | -6.7 (-8.92: -4.42) | <0.0001 |
| HDL, mg/dl     | 849   | 45.0 (14.1) | 46.4 (12.9) | 1.4 (0.82: 1.94) | <0.0001 |
| TG, mg/dl      | 930   | 180.8 (142.6) | 159.2 (105.7) | -21.6 (-30.12: -13.03) | <0.0001 |
| LDLc, mg/dl    | 777   | 97.02 (33.8) | 93.0 (31.4) | -4.0 (-5.99: -1.98) | 0.0014 |
| eGFR, mL/min/m²| 918   | 84.77 (21.1) | 86.3 (17.9) | 1.6 (0.47: 2.65) | 0.0423 |

Notes: Baseline: mean with standard deviation at baseline; follow-up: mean with standard deviation at follow-up; Beta: beta coefficient of the mixed-effect model controlling for country effect; p-value: likelihood ratio, p-value adjusted with the Holm method.
cholesterol (1.4 mg; 95% CI 0.82 to 1.94; p-value <0.0001). Of note, there was a significant increase in eGFR from 84.8 mL/min/m² to 86.3 mL/min/m² (p-value=0.0423).

Descriptive statistics of glycemic and laboratory data in each country at baseline and follow-up are reported in Table S3. A significant HbA₁c decrease from baseline to follow-up of about 0.7%, 1.7%, and 1.1% was seen in Italy, Spain, and Greece, respectively (p-value <0.0001). Moreover, significant decreases in FPG, weight, TC, and LDLc from baseline were also observed at follow-up in each country (p-value <0.05). The changes in eGFR significantly differed only in Spain (from 82.6 mL/min/m² at baseline to 86.1 mL/min/m² at follow-up; p-value=0.0002).

Association Among Demographic/Clinical Characteristics and Glycemic and Laboratory Data Over Time

For each mixed effect model, one dependent variable (HbA₁c, FPG, weight, SBK, DBP, TC, HDL, TG, UAER, eGFR, or LDLc) was regressed on one independent variable (age, gender, BMI, HbA₁c, eGFR, duration, insulin, CVD, or HF), controlling for the country effect. Due to the multi-dimensional nature of the analysis, the results are presented by a heatmap where the color code identified significant associations (Figure 1). In detail, HbA₁c was significantly associated with insulin use (p-value <0.0001), while FPG was linked to both HbA₁c and insulin use (p-values <0.001 and 0.0008, respectively). Moreover, body weight was associated with age, gender, BMI, and duration of diabetes (p-values <0.0001, <0.0001, <0.0001, and 0.0003, respectively). A significant effect of age and BMI effect was estimated on SBP (p-values <0.0001 and 0.0026, respectively). Moreover, DBP was associated with age, BMI, and duration of diabetes (p-value <0.0001). A significant effect on age, gender, and diabetes duration was observed on TC (p-values: 0.0130, <0.0001, and 0.0130, respectively). Furthermore, a significant effect of age and

![Figure 1](https://doi.org/10.2147/DMSO.S390075)

**Figure 1** Heatmap representing p-values calculated through a mixed effect model. In particular, each mixed effect model was constructed by regressing one dependent variable (HbA₁c, FPG, weight, SBK, DBP, TC, HDL, TG, UAER, eGFR, and LDLc) on one independent variable (age, gender, BMI, HbA₁c, eGFR, duration, insulin, CVD, and HF), controlling for the country effect. Bar color: p-values ranging from <0.0001 (light gray) to 0.9999 (dark gray) and NA values are reported as white boxes.
gender on HDL was found (p-value: 0.0286 and <0.0001, respectively). Finally, eGFR was associated with age, gender, HbA1c, duration of diabetes, CVD, and HF (p-values: <0.0001, <0.0001, 0.0002, <0.0001, 0.0199 and <0.0001, respectively), while a significant effect of age, HbA1c, and duration of diabetes on LDLc was seen (p-values: 0.0001, 0.0026 and 0.0008, respectively).

**Sensitivity Analysis by Baseline Clinical Characteristics**

We evaluated if, in the entire study cohort, the changes in HbA1c and body weight from baseline were different in subgroups of patients with different baseline characteristics. Notably, all subgroups of patients showed reductions in HbA1c and, as such, a non-responder phenotype was not identified (Figure 2A). The change in HbA1c from baseline was significantly different by country (p-value for interaction = 0.0024).

The changes in body weight from baseline were different in subgroups of patients defined by BMI, diabetes duration, and concomitant use of insulin (Figure 2B; p-value for interaction: <0.0001, 0.0064, and 0.0282, respectively). Beyond differences by country, patients with a BMI ≥30 kg/m² experienced greater weight decrease than those with a BMI <30 kg/m² [Beta (95% CI): −3.3 (−3.64: −3.00) versus −2.0 (−2.31: −1.67)]. Moreover, patients with a duration of diabetes <10 years experienced greater body weight reduction than those with a duration ≥10 years [Beta (95% CI): −3.3 (−3.66: −2.95) versus −2.49 (−2.81: −2.17)]. Finally, greater body weight reduction was observed in patients not using insulin compared to those with concomitant use of insulin [Beta (95% CI): −3.34 (−3.77: −2.91) versus −2.62 (−2.91: −2.33)].

**Discussion**

In the present real-world analysis of patients with type 2 diabetes in southern Europe, dapagliflozin was found to be effective in improving glycemic control (HbA1c and FPG), together with significant decreases in weight, blood pressure, and lipids. The changes in renal function were also encouraging but should thus be interpreted with caution because of the heterogeneity among countries, which has been noted in other studies.¹⁶ The decrease in HbA1c from 8.7% to 7.5% after a mean of 5.6 months is of particular note in this real-life analysis. Considering baseline characteristics and changes in HbA1c, only age ≥65 years showed a significant association. Expectedly, patients with BMI ≥30 kg/m² showed significantly more weight loss compared to those with lower BMI. The analysis also revealed several associations between different glycemic and laboratory parameters and patient characteristics at baseline, and insulin use was significantly associated with change in HbA1c.

The 1.2% decrease in HbA1c is broadly similar to the finding reported in other real-life analyses with canagliflozin, empagliflozin, and dapagliflozin. In a real-world analysis of patients initiating canagliflozin 300 mg or empagliflozin 25 mg, starting from baseline HbA1c values of 8.68% and 8.74, respectively, after 6 months HbA1c declined to 7.65% and 7.57%, respectively.¹⁷ The decrease in HbA1c we observe was greater than that seen with SGLT2 inhibitors in a real-world study of 1159 patients from Thailand, where mean HbA1c decreased by 0.7% at ≥3 months from a baseline value of 8.3%.¹⁸ However, the maximum reduction in HbA1c may not be apparent after 3 months of treatment. In a real-life analysis of patients in India being treated with dapagliflozin, starting from a baseline value of 9.1%, HbA1c values of 8.1% and 7.6% were seen at 3 and 6 months, respectively.¹⁹

The increase in eGFR we observed is of potential interest and was significantly associated with the history of HF, duration of diabetes, HbA1c, age and gender. However, this effect is likely driven by the cohort of patients from Spain, since changes in eGFR were not significant in the Italian or Greek cohorts. In a large, international, real-world study of >65,000 patients with type 2 diabetes, SGLT2i therapy was associated with reduced eGFR decline compared to other glucose-lowering drugs over at least 2 years of follow-up (difference of 1.53 mL/min per 1.73 m² per year).¹⁶ Small declines in renal function were observed in the Italian and Greek cohorts, but since there is no comparator group, no inference can be made about the rates of decline in renal function. Renal function is reported to decline by approximately 6.3 mL/min/1.73 m² per decade in healthy kidney donors.²⁰ In an observational study of patients with type 2 diabetes and nephropathy, the decline in eGFR was 5.2 mL/min/1.73 m² per year, but with high variability.²¹ In any case, further study of the decline in renal function during the real-world treatment with SGLT2 inhibitors is warranted.²² At present, it is important to underline that herein no significant differences in HbA1c or weight by eGFR category were seen. Moreover, a consistent glucose-lowering effect of dapagliflozin was seen in all subgroups of patients, including those with stage II CKD and CVD or those who were not obese.
Figure 2 Forest plots showing changes in HbA1c (A) and body weight (B) in subgroups of patients by baseline characteristics.
Among the limitations of the study, the differences in baseline characteristics of the cohorts and treatment settings in a pooled population should be noted, which may hinder the generalizability of the results. Moreover, the follow-up time is relatively short in a population of patients with type 2 diabetes. Although we included patients from three countries and we assume most of them were Caucasians, we had no data on ethnicity. This may be a limitation because SGLT2i in general, and dapagliflozin in particular, may be more effective in reducing HbA1c in Asian than in white people. It is therefore important to reinforce once more the concept of therapeutic individualization when assessing the benefits of glucose lowering medications. In addition, we acknowledge that we had no data on safety and adverse events (e.g., genitourinary tract infections, dehydration, hypoglycemia), which could provide a more complete representation of drug use and performance in routine clinical care. Lastly, the lack of a control cohort limits interpretation of the results. Indeed, some of the changes in glycemic and extraglycemic endpoints may have occurred independently from the initiation of dapagliflozin, being possibly due to spontaneous variations, changes in lifestyle or concomitant medications. Yet, exploring the comparative effectiveness of dapagliflozin versus other SGLT2i or other glucose lowering medications was outside the scope of the present study.

**Conclusion**

The present analysis confirms the effectiveness of dapagliflozin in diversified real-world settings in terms of decreased HbA1c and reduction in body weight. While significant, the decrease in blood pressure was clinically modest. Dapagliflozin may also have favorable effects on renal function, even if additional study with longer follow-up times and a control group is needed. Lastly, dapagliflozin was seen to have broadly similar effects on HbA1c across countries and baseline characteristics.

**Data Sharing Statement**

The data from this study are available from the corresponding author upon reasonable request.

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**References**

1. International Diabetes Foundation. Available from: [https://www.diabetesatlas.org/en/](https://www.diabetesatlas.org/en/). Accessed February 23, 2021.
2. Han S, Hagan DL, Taylor JR, et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. *Diabetes*. 2008;57(6):1723–1729. doi:10.2337/db07-1472
3. Bailey CJ, Day C. The future of new drugs for diabetes management. *Diabetes Res Clin Pract*. 2019;2019:155107785.
4. Davies MJ, D’Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669–2701. doi:10.2337/dc18-0035

5. Scheen AJ. Series: implications of the recent CVOTs in type 2 diabetes: impact on guidelines: the endocrinologist point of view. *Diabetes Res Clin Pract*. 2020;2020;159107726.

6. Consoli A, Czypriani L, Duarte R, et al. Positioning sulphonylureas in a modern treatment algorithm for patients with type 2 diabetes: expert opinion from a European consensus panel. *Diabetes Obes Metab*. 2020;22(10):1705–1713. doi:10.1111/dom.14102

7. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–357. doi:10.1056/NEJMoa1812389

8. Dalan R. Sodium-glucose cotransporter-2 inhibition in type 2 diabetes mellitus: a review of large-scale cardiovascular outcome studies and possible mechanisms of benefit. *Cardiol Rev*. 2018;26(6):312–320. doi:10.1097/CRD.0000000000000201

9. Norhammar A, Bodegard J, Nyström T, et al. Dapagliflozin and cardiovascular mortality and disease outcomes in a population with type 2 diabetes similar to that of the DECLARE-TIMI 58 trial: a nationwide observational study. *Diabetes Obes Metab*. 2019;21(5):1136–1145. doi:10.1111/dom.13627

10. Nyström T, Bodegard J, Nathanson D, et al. 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(6):831–841. doi:10.1111/dom.12889

11. Wittbrodt E, Chamberlain D, Arnold SV, et al. Eligibility of patients with type 2 diabetes for sodium-glucose co-transporter-2 inhibitor cardiovascular outcomes trials: an assessment using the Diabetes Collaborative Registry. *Diabetes Obes Metab*. 2019;21(8):1985–1989. doi:10.1111/dom.13738

12. Fadini GP, Zatti G, Consoli A, et al. Rationale and design of the DARWIN-T2D (DApagliflozin Real World evIdeNce in Type 2 Diabetes): a multicenter retrospective nationwide Italian study and crowdsourcing opportunity. *Natr Metab Cardiovasc Dis*. 2017;27(12):1089–1097. doi:10.1016/j.numecd.2017.08.001

13. Fadini GP, Solini A, Manca ML, et al. Effectiveness of dapagliflozin versus comparators on renal endpoints in the real world: a multicentre retrospective study. *Diabetes Obes Metab*. 2019;21(2):252–260. doi:10.1111/dom.13508

14. Fadini GP, Tentolouris N, Caballero Mateos I, et al. A multinational real-world study on the clinical characteristics of patients with type 2 diabetes initiating dapagliflozin in Southern Europe. *Diabetes Ther*. 2020;11(2):423–436. doi:10.1007/s13300-019-00744-6

15. Fadini GP, Sciannameo V, Franzetti I, et al. Similar effectiveness of dapagliflozin and GLP-1 receptor agonists concerning combined endpoints in routine clinical practice: a multicentre retrospective study. *Diabetes Obes Metab*. 2019;21(8):1886–1894. doi:10.1111/dom.13747

16. Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol*. 2020;8(1):27–35. doi:10.1016/S2213-8587(19)30384-5

17. Blonde L, Patel C, Wu B, et al. Real-world comparative effectiveness of canagliflozin versus empagliflozin and dapagliflozin in patients with type 2 diabetes in the United States. *Adv Ther*. 2021;38(1):594–606. doi:10.1007/s12325-020-01549-x

18. Srithrapradang C, Thewjitcharoen Y, Buranapin S, et al. Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors in Thai adults with type 2 diabetes mellitus: a real-world study. *Adv Ther*. 2020;36(10):1601–1610. doi:10.1080/03007995.2020.1808454

19. Viswanathan V, Singh KP. Use of dapagliflozin in the management of type 2 diabetes mellitus: a real-world evidence study in Indian patients (FOREFRONT). *Diabetes Technol Ther*. 2019;21(8):415–422. doi:10.1089/dia.2019.0052

20. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis*. 2016;23(1):19–28. doi:10.1053/j.ackd.2015.08.004

21. Rossing K, Christensen PK, Hovind P, et al. Progression of nephropathy in type 2 diabetic patients. *Kidney Int*. 2004;66(4):1596–1605. doi:10.1111/j.1523-1755.2004.00925.x

22. Fadini GP, Del Prato S, Avogaro A, et al. Challenges and opportunities in real-world evidence on the renal effects of sodium-glucose cotransporter-2 inhibitors. *Diabetes Obes Metab*. 2022;24(2):177–186. doi:10.1111/dom.14599

23. Chaturvedi N, Eastwood S. Prescribing by ethnicity: (im)precision medicine? *Diabetes Care*. 2020;43(8):1687–1689. doi:10.2337/dci20-0015