# DAPAGLIFLOZIN: FOR THE TREATMENT OF TYPE-2 DIABETES.

[1]Pratik Laxman Wagh, [2]Ruchika Sheshrao Vahadane, [3]Dr. S.B. Bhawar.

[1]Student, [2]Student, [3]Professor.

PHARMACY

Pravara Rural College Of Pharmacy, Pravaranagar.

**Abstract**

Dapagliflozin ( Forxiga®) is a globally recognized treatment for type 2 diabetes, known for its high potency, reversibility, and selectivity as a sodium-glucose cotransporter-2 inhibitor. Dapagliflozin, taken orally once daily, is approved in the EU for use as monotherapy (in patients intolerant of metformin) and as an add-on combination therapy (with other glucose-lowering agents, including insulin) for T2D when diet and exercise alone are insufficient for adequate glycemic control. Dapagliflozin, whether used alone or in combination with other

Antihyperglycemic agents, demonstrated effective glycemic control and led to reductions in body weight and blood pressure in a wide range of patients, as evidenced by numerous meticulously conducted clinical studies and their extensions. Dapagliflozin decreased the occurrence of cardiovascular (CV) death or hospitalization for heart failure (HHF), showed no negative impact on major adverse CV events (MACE), and potentially slowed the progression of renal disease compared to a placebo in individuals with confirmed atherosclerotic CV disease (CVD) or multiple CVD risk factors. Dapagliflozin was generally well received, exhibiting a minimal risk of hypoglycemia. While diabetic ketoacidosis (DKA), though infrequent, genital infections were more prevalent with dapagliflozin compared to the placebo. Due to its antihyperglycemic, cardioprotective, and potentially reno protective attributes, along with a generally well-tolerated profile, dapagliflozin emerges as a significant choice for treating a Adiverse range of patients, irrespective of their cardiovascular history.

**Keywords:** Dapagliflozin, Type 2 diabetes, cardiovascular disease, Adverse event.

**Introduction**

Sodium glucose cotransporter-2 (SGLT2) inhibitors represent a recent category of antihyperglycemic agents used in treating type 2 diabetes [1-3]. These agents inhibit the highcapacity glucose transporter SGLT2 in the proximal convoluted tubule, leading to a reduction in glucose reabsorption in the kidneys. This, in turn, facilitates the excretion of glucose in the urine and results in a decrease in glucose levels, independent of insulin action [1, 2]. The distinctive way SGLT2 inhibitor's function complements other classes of AHAs, enabling their combination with insulin and other AHAs in therapy. Dapagliflozin (Forxiga®), an approved SGLT2 inhibitor for treating T2D globally, including in the EU and USA, has been thoroughly reviewed for its pharmacological properties and clinical use in adults with T2D in previous publications in Drugs [4, 5]. This EU-oriented article highlights recent trials, notably the DECLARE-TIMI 58 cardiovascular outcomes trial involving patients with type 2 diabetes (T2D), with or without established cardiovascular disease (CVD). Additionally, dapagliflozin is offered in fixed-dose combinations such as dapagliflozin/metformin (Xigduo®) and dapagliflozin/saxagliptin (Qtern®) tablets.

**Pharmacological Properties**

Dapagliflozin, with an inhibitory constant of 0.55 nmol/L, is a significantly potent and reversible SGLT2 inhibitor. It exhibits over 1400 times greater selectivity for SGLT2 compared to SGLT1, the primary transporter involved in glucose absorption in the gut [6, 7]. Dapagliflozin enhanced glucose excretion in urine and demonstrated improvements in both fasting (FPG) and postprandial plasma glucose levels among patients with T2D [8]. Dapagliflozin led to consistent urinary glucose excretion (glucuresis) from the initial dose, persisting throughout the 24-hour dosing interval and maintaining this effect throughout the therapy [7, 8]. Glucuresis triggered by dapagliflozin in individuals with type 2 diabetes was linked to a decrease in calories and a slight decline in body weight, accompanied by mild osmotic diuresis and temporary natriuresis [7, 9, 10]. The reduction in body weight with SGLT2 inhibitors appears to be lower than what would be expected based solely on the calorie loss from glucuresis. This discrepancy could be attributed to compensatory mechanisms, such as an elevated energy intake [11]. Dapagliflozin also demonstrated a slight reduction in blood pressure, possibly attributed to its diuretic/natriuretic properties, leading to a decrease in circulating volume [10]. Section 3 summarizes the impact of dapagliflozin on glycemic parameters, body weight, and blood pressure in extensive clinical trials involving patients with type 2 diabetes.

Dapagliflozin is quickly absorbed upon oral administration, typically achieving peak plasma concentrations within 2 hours in a fasted state [7]. After administering a 10 mg dose, dapagliflozin exhibits a 78% absolute oral bioavailability. Its mean steady-state volume of distribution is 118 L, with approximately 91% of the drug bound to proteins. The pharmacokinetics of dapagliflozin remain largely unaffected by food. UGT1A9, an enzyme in the liver and kidneys, predominantly metabolizes dapagliflozin to its major inactive metabolite, 3-O-glucuronide. Notably, the various metabolites, including the major ones, do not contribute significantly to the

glucose-lowering effects of dapagliflozin. Dapagliflozin and its metabolites are primarily excreted in the urine, with 75% of the dose recovered in the urine (less than 2% as unchanged parent drug) and 21% in the feces (approximately 15% as unchanged parent drug). Following a single dose of 10 mg dapagliflozin in healthy subjects, the mean plasma terminal elimination half-life is 12.9 h [7].

**Therapeutic Efficacy of Dapagliflozin Glycaemic and Other Outcomes**

As previously evaluated in the Drugs journal [4, 5], a variety of randomized, double-blind, multicenter, phase 3 trials involving dapagliflozin, both as monotherapy and in combination therapy, have consistently shown its effectiveness in enhancing glycemic control. These trials have also demonstrated its ability to reduce body weight and blood pressure across a diverse range of patients with type 2 diabetes, including those with initially elevated HbA1c levels (≥ 9%) [12]. And the elderly population (those aged 65 years and older) [13]. Findings from recent trials, encompassing diverse groups like individuals with stage 3A chronic kidney disease (CKD) [14], High blood pressure as referenced in sources [15, 16]. The details of cardiovascular diseases (CVD) [17, 18]. In a phase 3 study involving 182 patients insufficiently controlled with metformin, the addition of dapagliflozin resulted in a significant reduction in body weight. This reduction was primarily attributed to a decrease in fat mass compared to the placebo, with fat mass contributing to around two-thirds of the total weight loss [19]. At week 24, patients supplemented with dapagliflozin 10 mg once daily exhibited significantly reduced total body weight (primary endpoint; difference from placebo -2.1 kg; baseline ≈ 92 kg; $p < 0.0001$), diminished waist circumference (-1.5 cm; baseline ≈ 105 cm; $p = 0.0143$), and lower fat mass measured by dual X-ray absorptiometry (DXA) (-1.5 kg; baseline ≈ 33 kg; $p = 0.0001$) compared to those receiving placebo. The decrease in body weight, evident in the early weeks of dapagliflozin treatment, continued gradually and had not reached a plateau by week 24. This weight change corresponded with daily spot urinary glucose levels, indicating an initial rapid increase followed by stable levels, supporting the DXA findings that the loss in body weight and fat mass with dapagliflozin primarily resulted from caloric loss through glucosuria. Nonetheless, the swift initial decline in body weight in dapagliflozin recipients may be partly attributed to fluid loss [19].

Moreover, there was a significantly higher percentage of patients experiencing a reduction in body weight of ≥ 5% among those treated with dapagliflozin compared to those on placebo (31% vs. 4%; $p < 0.0001$) [19]. Additionally, a sub study involving 80 patients revealed through magnetic resonance imaging that dapagliflozin led to reductions in both visceral and subcutaneous adipose tissues compared to the placebo recipients (difference from placebo −258 and −185 $cm^3$, respectively; both nominal $p < 0.05$) [19]. The decreases in body weight, fat mass, and waist circumference observed with the addition of dapagliflozin compared to a placebo at week 24 were sustained throughout 102 weeks of therapy [20].

**Patients with Hypertension**

Dapagliflozin, taken at a daily dose of 10 mg, demonstrated a decrease in systolic blood pressure (SBP) and enhanced glycemic management in two phase 3 trials involving individuals with insufficiently controlled type 2 diabetes (T2D) and hypertension, even when already receiving antihypertensive treatment, specifically angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy alone [15]. Alternatively, consider combining it with another antihypertensive medication [16]. In both studies, dapagliflozin demonstrated significantly lower mean SBP and HbA1c compared to the placebo at week 12, meeting the first and second coprimary endpoints, respectively. An analysis conducted after the study indicated that dapagliflozin led to a more significant reduction in systolic blood pressure (SBP) among patients using a β blocker or a calcium-channel blocker as an additional antihypertensive drug compared to those using a thiazide diuretic [16].

**Patients with Cardiovascular Disease**

Dapagliflozin, taken at a daily dose of 10 mg, demonstrated enhanced glycemic control and decreased body weight and systolic blood pressure in two phase 3 trials involving patients with insufficiently controlled Type 2 Diabetes (HbA1c 7–10.5%) and pre-existing cardiovascular disease and hypertension [17, 18]. At the 24-week mark in both studies, the reduction in HbA1c was significantly more pronounced when adding dapagliflozin compared to adding a placebo. Additionally, a higher percentage of patients in the dapagliflozin group achieved a 3-item response compared to the placebo group, as indicated by the coprimary endpoints [17, 18]. The benefits of dapagliflozin remained consistent through week 52 in the extension studies [17, 18]. In both studies, a notably higher percentage of patients in the dapagliflozin groups, compared to the placebo groups ($p < 0.005$), reached the target HbA1c of < 7% at week 24 (19% vs. 13% [17]; 16% vs. 8% [18]). Maintaining the between-group distinctions at week 52 (19% vs. 10% [17]; 15% vs. 5% [18]). The effectiveness of dapagliflozin remained consistent throughout an extended 52-week period, totaling 104 weeks of therapy, as indicated by a post hoc pooled analysis of the two studies [21]. In an analysis combining five phase 2–3 clinical trials lasting up to 52 weeks, patients with type 2 diabetes (T2D) and a history of heart failure experienced meaningful reductions in HbA1c (adjusted mean change −0.55% from baseline; baseline 8.2%), body weight (−2.7 kg; baseline ≈ 97 kg), and systolic blood pressure (−2.1 mmHg; baseline ≈ 134 mmHg) when treated with dapagliflozin 10 mg either as monotherapy or added to other AHA regimens (n = 171) compared to placebo/active comparator (n = 149) [22].

**Patients with Renal Impairment**

An analysis conducted after a phase 2/3 study indicated potential treatment advantages for dapagliflozin in individuals with stage 3A chronic kidney disease (eGFR ≥ 45 and < 60 mL/min 1.73 $m^2$) [14]. with findings supported by the randomized, double-blind, multinational, phase 3 DERIVE study [23]. In the DERIVE study, individuals with insufficiently controlled type 2 diabetes (HbA1c 7–11%) and a BMI of 18–45 $kg/m^2$, receiving other antihyperglycemic agents while having stage 3A chronic kidney disease, were randomly assigned to either dapagliflozin 10 mg once daily (n = 159) or placebo (n = 161) for 24 weeks. Results at week 24 showed that dapagliflozin significantly reduced HbA1c (primary endpoint; placebo-adjusted mean change

−0.34; baseline ≈ 8.2%), FPG (−0.9 mmol/L; baseline ≈ 10 mmol/L), body weight (−1.3 kg; baseline ≈ 90 kg), and SBP (−3.1 mmHg; baseline ≈ 135 mmHg) compared to placebo ($p = 0.05$) [23]. A phase 3 study (CompoSIT-R) involving patients with inadequate control on metformin ± sulfonylurea (HbA1c 7–9.5%) and mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m2)

demonstrated that adding sitagliptin 100 mg once daily (n = 307) was noninferior (primary hypothesis) and superior to dapagliflozin 10 once daily (n = 306) in enhancing glycaemic control [HbA1c least squares (LS) mean change from baseline − 0.51 vs. − 0.36%; baseline ≈ 7.8% p = 0.006] [24].

**Cardiovascular and Renal Outcomes**

The DECLARE-TIMI 58 trial, a randomized, double-blind phase 3 study, evaluated the impact of dapagliflozin on cardiovascular and renal outcomes in individuals aged 40 years or older with type 2 diabetes (HbA1c ≥ 6.5 to < 12%) and either established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD [25]. Patients needed to have a creatinine clearance (CLCR) of ≥ 60 mL/min. Those with multiple risk factors included men aged ≥ 55 years or women aged ≥ 60 years with at least one traditional risk factor, such as hypertension, dyslipidemia (i.e., low-density lipoprotein level > 130 mg/dL or use of lipid-lowering therapies), or tobacco use [25].

The research was initially structured to evaluate the impact of dapagliflozin on the main safety measure of major adverse cardiovascular events (MACE) [25, 26]. Nevertheless, considering the results obtained from the EMPA-REG OUTCOME trial involving empagliflozin [27]. During the implementation of DECLARE-TIMI 58, the study design was adjusted to incorporate dual primary efficacy outcomes: major adverse cardiovascular events (MACE) and the composite of cardiovascular death and hospitalization for heart failure (CV death/HHF) [25, 26]. Initially, the 17,160 randomized patients had an average age of 64 years, with 41% having established atherosclerotic cardiovascular disease (ASCVD), encompassing coronary artery disease (33% of patients) and heart failure (10%) [25]. The average duration of diabetes was around 11 years, with a mean HbA1c of 8.3% and a mean estimated glomerular filtration rate (eGFR) of 85 mL/min/1.73 m² (45% with an eGFR of 60–90 and 7% with < 60 mL/min/1.73 m²). Participants were randomly assigned to receive either dapagliflozin 10 mg once daily or a placebo, in addition to other antihyperglycemic agents (AHAs), with the choice of other AHAs left to the treating physician's discretion. The study had a median follow-up duration of 4.2 years (69,547 patient-years) [25].

Dapagliflozin demonstrated a significant reduction in the incidence of cardiovascular death and hospitalization for heart failure compared to the placebo. However, there was no significant difference between the groups in the rate of major adverse cardiovascular events (MACE), as assessed after confirming the noninferiority of dapagliflozin and placebo for the primary safety outcome of MACE (Table 1) [25]. As MACE did not significantly decrease with dapagliflozin compared to placebo, the analyses of secondary and additional endpoints (Table 1) were purely exploratory. The observed reduction in the composite endpoint of CV death and hospitalization for heart failure (HHF) with dapagliflozin recipients was primarily attributed to a lower rate of HHF compared to the placebo group, while the rate of CV death was generally comparable between the two groups (Table 1). Sensitivity analyses of the primary efficacy endpoints confirmed the results from the initial analysis of outcomes [25].

The findings indicate that dapagliflozin decreases the probability of renal disease progression, evident in lower occurrences of renal composite and additional renal composite outcomes among dapagliflozin recipients compared to those receiving a placebo. [25]. Dapagliflozin, in comparison to a placebo, demonstrated a significant decrease in the risk of sustained decline in eGFR by ≥ 40% to < 60 mL/min per 1.73 m2 (hazard ratio 0.54; 95% CI 0.43–0.67; p < 0.0001), end-stage renal disease (ESRD; HR 0.31; 95% CI 0.13–0.79; p = 0.013), and renal death or ESRD (HR 0.41; 95% CI 0.20–0.82; p = 0.012) for individual renal outcomes [28]. The decline from the baseline in eGFR showed a significant difference (p < 0.0001) favoring dapagliflozin over placebo at 6 months. However, this gap had disappeared by 2 years, and at 3- and 4-years post-randomization, the decrease with dapagliflozin remained significantly lower than that with placebo (p < 0.0001) [28].

The incidence rates of overall mortality, myocardial infarction (MI), ischemic stroke, and noncardiovascular (CV) mortality showed comparable patterns in both groups. Dapagliflozin demonstrated improvements in CV risk factors, notably a consistently lower HbA1c level compared to the placebo group throughout the trial (average LS mean absolute difference between groups 0.42%; 95% CI 0.40–0.45) [25]. Dapagliflozin exhibited lower body weight (LS mean difference between groups 1.8 kg; 95% CI 1.7–2.0), systolic blood pressure (SBP; 2.7 mmHg; 95% CI 2.4–3.0), and diastolic blood pressure (DBP; 0.7 mmHg; 95% CI 0.6– 0.9) compared to the placebo throughout the trial [25].

**Subgroup Analyses**

In subgroup analyses, the effectiveness of dapagliflozin in preventing cardiovascular death and hospitalization for heart failure remained consistent, irrespective of patients' history of cardiovascular disease (ASCVD), history of heart failure, or baseline estimated glomerular filtration rate (eGFR) categories (≥ 90, 60 to < 90, or < 60 mL/min/1.73 m²). No significant interactions were observed across these subgroups [25]. There was no significant difference in the rate of MACE between dapagliflozin and placebo recipients in any subgroup, including those with ASCVD (HR 0.90; 95% CI 0.79–1.02) or multiple risk factors (HR 1.01; 95% CI 0.86– 1.20). The beneficial effect of dapagliflozin on slowing the progression of renal disease was observed regardless of the baseline history of CVD, HF, or CKD (all p interactions nonsignificant) [25].

A predefined subgroup analysis indicated significant clinical advantages with dapagliflozin among high-risk patients with Type 2 Diabetes and previous myocardial infarction (median time since the last event was 5.4 years), showing robust outcomes for both major adverse cardiovascular events (MACE) and the composite of cardiovascular death/heart failure hospitalization [29]. Dapagliflozin demonstrated a significant 16% reduction in Major Adverse Cardiovascular Events (MACE) with a hazard ratio (HR) of 0.84 (95% CI 0.72–0.99; p = 0.04) in patients with prior myocardial infarction (MI) (n = 3584). However, no such reduction was observed in those without prior MI (n = 6771; HR 1.00; 95% CI 0.88–1.13) or in those without prior MI but with established atherosclerotic cardiovascular disease (ASCVD) (n = 3390; HR 0.98; 95% CI 0.81–1.19). The decreased MACE rate in prior MI patients primarily stemmed from a lower recurrence of MI (HR 0.78; 95% CI 0.63–0.95), yielding an absolute risk reduction (ARR) of 2.6% and a number needed to treat (NNT) over 4 years of 39. Notably, the benefit of dapagliflozin in terms of MACE seemed more pronounced in patients closer to their last acute event, with the greatest benefit observed in those with a recent MI (> 12 to 24 months). In contrast to MACE, a consistent treatment benefit (HR < 1) for cardiovascular death/heart failure (CV death/HHF) was

evident across all subgroups, including patients with prior MI (HR 0.81; 95% CI 0.65–1.00, p = 0.046), those without prior MI (HR 0.85; 95% CI 0.72–1.00), and those without prior MI but with ASCVD (HR 0.87; 95% CI 0.68–1.12). The corresponding ARR over 4 years was 1.9% (NNT 53), 1.0%, and 0.5%, respectively [29].

Another predetermined subgroup analysis evaluated the effectiveness of dapagliflozin in individuals with Type 2 Diabetes (T2D) and Heart Failure (HF) characterized by reduced ejection fraction (HFrEF, EF < 45%; n = 671) and in those without HFrEF. This latter group included patients with HF without known reduced EF (n = 1316) and patients without HF (n = 15,173) [30]. Dapagliflozin demonstrated a more pronounced decrease in cardiovascular death and hospitalization for heart failure (CV death/HHF) in patients with heart failure with reduced ejection fraction (HFrEF) (HR vs. placebo 0.62; 95% CI 0.45–0.86) compared to those without HFrEF (HR vs. placebo 0.88, 95% CI 0.76–1.02) (interaction p-value 0.046). This difference primarily resulted from a reduction in CV death in HFrEF patients (HR vs. placebo 0.55; 95% CI 0.34–0.90, p = 0.02) compared to those without known HFrEF (HR vs. placebo 1.08; 95% CI 0.89–1.31). Additionally, all-cause death was significantly reduced with dapagliflozin in HFrEF patients (HR 0.59; 95% CI 0.40–0.88, p = 0.01), but not in those without known HFrEF (HR 0.97; 95% CI 0.86–1.10) (interaction p-value 0.016). The number needed to treat (NNT) over 4 years for CV death/HHF, CV death, and all-cause death in HFrEF patients was 11, 19, and 16, respectively. Notably, dapagliflozin reduced hospitalization for heart failure (HHF) regardless of baseline ejection fraction (EF), with comparable reductions in HFrEF patients (HR 0.64; 95% CI

0.43–0.95) and those without known HFrEF (HR 0.76; 95% CI 0.62–0.92) (interaction p-value 0.45) [30]

**Real-World Studies**

Multiple extensive real-world investigations (involving a minimum of 1900 participants) have affirmed the effectiveness of dapagliflozin in individuals with type 2 diabetes [31–36]. Dapagliflozin, along with other AHAs, demonstrated improved efficacy outcomes for a duration ranging from 12 weeks to over 12–24 months. This improvement was observed in parameters such as HbA1c, body weight, and SBP in database studies conducted in the UK [31] and USA [32], as well as in a Korean post marketing study [33]. A study in India is currently being planned, involving multiple centers and adopting an observational approach [34]. In a study analyzing clinical data from a Canadian registry, patients with T2D (for over 6 months) who were treated with dapagliflozin (n = 1850), a dipeptidyl peptidase-4 inhibitor (DPP-4i; n = 1341), or a sulfonylurea (n = 579) demonstrated significantly higher rates of HbA1c reduction of ≥ 0.5%, any weight loss, and SBP reduction of ≥ 5.0 mmHg when receiving dapagliflozin compared to those receiving a DPP-4i or a sulfonylurea (composite primary endpoint; 26% vs. 21% and 15%; p < 0.05) [35]. In a separate investigation, the DARWIN-T2D Italian retrospective study revealed that administering dapagliflozin (830 participants) or a glucagonlike peptide-1 receptor agonist (GLP-1RA; 811 participants) led to significant reductions (p < 0.05) in HbA1c, body weight, and SBP [36]. In comparison, treatment using a DPP-4 inhibitor (n = 2999) significantly (p < 0.05) reduced two out of three parameters—HbA1c and body weight. Gliclazide, a sulfonylurea (n = 2111), significantly (p < 0.05) lowered only HbA1c. The reduction from baseline in HbA1c was generally similar across all four treatment groups (change from baseline −0.7, −0.6, −0.6, and −0.6%). However, treatment with dapagliflozin or a GLP-

1RA showed numerically greater improvements in body weight (change from baseline −2.7 and −2.4 vs. −0.5 and −0.1 kg) and SBP (−3.0 and −1.4 vs. −0.7 and +0.1 mmHg) compared to treatment with a DPP-4 inhibitor or gliclazide [36].

The effectiveness of dapagliflozin in reducing cardiovascular events in DECLARE-TIMI 58 was affirmed by real-world findings from the CVD-REAL Nordic study. This study utilized data from national registries in Denmark, Norway, and Sweden, focusing on individuals with type 2 diabetes who were prescribed antihyperglycemic agents between 2012 and 2015 [37].

Dapagliflozin, with a study involving 10,227 patients, demonstrated a significant reduction in the risk of Major Adverse Cardiovascular Events (MACE), Heart Failure Hospitalization (HHF), and all-cause death compared to DPP-4 inhibitors (n = 30,681) over an average follow-up period of 0.95 years (HR 0.79, 95% CI 0.67–0.94 for MACE; HR 0.62, 95% CI 0.50–0.77 for HHF; HR

0.59, 95% CI 0.49–0.72 for all-cause death) [37].

**Tolerability of Dapagliflozin**

Dapagliflozin at a dosage of 10 mg, whether used as a standalone treatment or in combination with other antihyperglycemic agents, demonstrated favorable tolerability in individuals with Type 2 Diabetes. This observation is based on a compilation of data from 13 to 30 clinical trials spanning 24 to 208 weeks, involving both placebo and active comparator controls [38]. In a combined analysis of 13 placebo-controlled trials lasting 12–24 weeks, 60% (1416/2360) of dapagliflozin recipients experienced treatment-emergent adverse events (AEs), compared to 56% (1279/2295) of those on placebo. Discontinuation due to these events occurred in 4% of patients in each group. The most common treatment-emergent AEs with dapagliflozin included nasopharyngitis (5% vs. 6% with placebo), diarrhea (3% vs. 4%), headache (3% vs. 4%), upper respiratory tract infections (3% vs. 4%), urinary tract infections (UTIs; 4% vs. 3%), and back pain (4% vs. 2%). Serious adverse events (SAEs) happened in 5% of patients in both groups, leading to treatment discontinuation in 0.7% of dapagliflozin recipients and 1% of placebo recipients. Deaths were rare in both groups (0.3% and 0.2%, respectively) [38]. In the

DECLARE-TIMI 58 trial, a higher percentage of participants receiving dapagliflozin, compared to those on placebo, withdrew from the trial regimen due to adverse events (8% vs. 7%; p = 0.01). However, significantly fewer dapagliflozin recipients experienced serious adverse events compared to placebo (34% vs. 36%; p < 0.001) in a safety population of 8574 and 8569 in the respective groups [25]. The most frequent serious adverse events, with an incidence greater than 2%, included unstable angina (2.8% vs. 2.8%) and acute myocardial infarction (2.7% vs. 2.3%) [25].

**Adverse Events of Special Interest**

Hypoglycemia occurred in 14% of those receiving dapagliflozin and 12% of individuals in the placebo group in the combined analysis of 13 studies [38]. The dapagliflozin group experienced three significant hypoglycemic events, while the placebo group had two. Most incidents occurred in patients using insulin as background therapy. A patient receiving dapagliflozin alongside insulin and

metformin discontinued therapy due to one such event [38]. In DECLARE-TIMI 58, there were significantly fewer major hypoglycemic events in dapagliflozin recipients compared to those receiving a placebo (0.7% vs. 1.0%; p = 0.02) [25].

Dapagliflozin showed a higher incidence of genital infections compared to the placebo in a combined analysis of 13 studies (5.5% vs. 0.6%). Notably, these infections occurred at least twice as frequently in women than in men in both treatment groups [38]. The genital infections observed were predominantly mild to moderate in severity, with treatment discontinuation necessary for only 0.2% of patients in the dapagliflozin group and none in the placebo group [38]. In this analysis, UTIs were observed in 5% of individuals receiving dapagliflozin and 4% of those receiving a placebo, with a nearly fivefold higher occurrence in women compared to men across treatment groups. The majority of UTIs were mild or moderate in severity, exhibited typical characteristics seen in T2D patients, were not kidney infections, and did not lead to therapy discontinuation (UTI-related discontinuation rate ≤ 0.2% in both groups). Most patients with genital infections or UTIs in both treatment groups responded well to initial antimicrobial therapy, requiring no additional treatment [38]. The DECLARE-TIMI 58 results confirmed the pooled analysis, indicating a higher occurrence of genital infections with dapagliflozin compared to placebo (0.9% vs. 0.1%, p < 0.001). However, there was no significant difference between the groups in the incidence of urinary tract infections (1.5% vs. 1.6%) [25]. Serious adverse events related to genital infections were uncommon in both treatment cohorts within the DECLARETIMI 58 study, with two occurrences in each group. Fournier's gangrene, a perineal necrotizing fasciitis, was documented in one individual receiving dapagliflozin and five individuals receiving a placebo [25]. Due to the rare yet serious risk of this potentially life-threatening event, patients should be cautioned to seek medical attention if they encounter symptoms. If Fournier's gangrene is suspected, discontinuation of dapagliflozin and immediate treatment are recommended [7].

Adverse events related to renal function were observed in 3% of individuals receiving dapagliflozin compared to 2% of those receiving a placebo in the combined analysis of 13 studies. These events were more prevalent in patients with a baseline estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m2 (19% vs. 1% in the dapagliflozin group) and in those aged 65 years and older compared to those younger than 65 years (8% vs. 2% in the dapagliflozin group) [38]. The most prevalent renal adverse events included a reduction in renal creatinine clearance (1.1% vs. 0.7%) and renal impairment (0.8% vs. 0.5%), predominantly of a transient and mild/moderate nature. These effects were not associated with significant abnormalities in renal function. Initial eGFR decline occurred with dapagliflozin but returned to baseline levels during treatment (mean change from baseline in the dapagliflozin group was -4.5 and -1.5 mL/min/1.73 m² at weeks 1 and 24, respectively) [38]. In DECLARE-TIMI 58, dapagliflozin demonstrated a significantly lower incidence of acute kidney injury compared to the placebo (1.5% vs. 2.0%; p = 0.002) [25].

In the combined analysis of 13 studies, adverse events related to volume depletion (such as hypotension, hypovolemia, and dehydration) were documented in 1.1% of individuals receiving dapagliflozin and 0.7% of those receiving a placebo. Notably, approximately half of these events in both groups occurred during the initial 8 weeks of therapy, with 19% and 18% of adverse events in their respective groups happening within the first 2 weeks [38]. Regardless of the assigned treatment group, patients using loop diuretics experienced a 2.5-fold higher incidence of volume depletion-related adverse events compared to those not using them. Additionally, individuals with an eGFR < 60 mL/min/1.73 m2 had approximately twofold higher incidence than those with eGFR ≥ 60 mL/min/1.73 m2. In the dapagliflozin group, patients aged ≥ 65 years also exhibited a twofold higher incidence of volume depletion-related adverse events than those aged < 65 years [38]. In DECLARE-TIMI 58, there was no significant distinction in symptoms of volume depletion between recipients of dapagliflozin and those receiving a placebo (2.5% vs.

2.4%) [25]. Patients taking loop diuretics are advised against using Dapagliflozin [7].

Dapagliflozin treatment showed modest elevations in parathyroid hormone levels, particularly in individuals with higher baseline parathyroid levels [7, 14, 39]. Dapagliflozin demonstrated no bone loss over a 2-year therapy period in patients with normal or mild renal impairment [7, 40]. Fractures occurred rarely in the combined analysis of 13 studies, with dapagliflozin and placebo showing a low incidence (0.3% vs. 0.7%) [38]. In DECLARE-TIMI 58, there was no significant difference in fracture rates between the two groups (5.3% vs. 5.1%) [25].

SGLT2 inhibitors, such as dapagliflozin, have been linked to infrequent occurrences of diabetic ketoacidosis (DKA), characterized by elevated blood glucose (> 250 mg/dL), anion gap acidosis, and heightened plasma ketones, with some cases being severe or fatal [7]. In an analysis combining data from 21 trials with placebo or active comparators, spanning up to 208 weeks and involving 5936 individuals in the dapagliflozin group and 3403 in the control group, dapagliflozin showed one serious adverse event (SAE) related to diabetic ketoacidosis (DKA), possibly due to insulin dose reduction. Additionally, two adverse events (AEs) of ketonuria and one AE of metabolic acidosis were observed with dapagliflozin, whereas no such events were reported in the control group. The estimated incidence of DKA alone was 0.02% (95% CI 0.004– 0.059), and for DKA/metabolic acidosis combined, it was 0.03% (95% CI 0.01–0.09) [38]. In the DECLARE-TIMI 58 trial, the incidence of diabetic ketoacidosis (DKA) was notably higher among those receiving dapagliflozin compared to placebo recipients (0.3% vs. 0.1%; p = 0.02) [25]. Before starting dapagliflozin, it's important to consider factors in the patient's medical history that could increase the risk of ketoacidosis [7]. Consider the possibility of diabetic ketoacidosis (DKA) if non-specific symptoms like nausea, vomiting, and anorexia manifest.

Discontinue treatment if DKA is confirmed. In cases of euglycemic DKA (DKA without high blood sugar), additional glucose may be necessary alongside standard DKA treatment, and dapagliflozin should be halted if DKA occurs [7].

In a pooled analysis of 21 studies, while the incidence rate ratio (IRR) for certain tumors (bladder IRR 5.2, breast 2.5, pancreatic 1.8) associated with dapagliflozin exceeded 1, and for others (e.g., blood and lymphatic 0.4, renal tract 0.4) it was below 1, the overall malignancy incidence rate did not significantly differ between the dapagliflozin and control groups (1.5% vs. 1.5%; IRR 1.03; 95% CI 0.7–1.5) [41]. In the DECLARE-TIMI 58 trial, individuals receiving dapagliflozin experienced a lower incidence of bladder cancer compared to those on a placebo (0.3% vs. 0.5%; p = 0.02). Additionally, there was no significant difference between the two groups in terms of breast cancer rates (0.4 % vs. 0.4%) [25].

Lower limb amputations were seldom reported in the pooled analysis of 30 studies, comparing dapagliflozin and control groups (0.1% vs. 0.2%) with a combined participant count of 9195 in the dapagliflozin group and 4629 in the control group, all lasting at least 12 weeks [38]. Both groups had a comparable time to amputation, and individuals undergoing amputation exhibited a notable prevalence of risk factors such as neuropathy, cardiovascular disease (CVD), dyslipidemia, and nephropathy [38]. There was no significant difference in amputation rates between dapagliflozin and placebo recipients in DECLARE-TIMI 58, with rates of 1.4% and 1.3%, respectively [25].

**Cardiovascular Safety**

A predefined meta-analysis of cardiovascular events in 21 placebo/active comparator-controlled phase 2b/3 clinical studies lasting up to 208 weeks revealed that dapagliflozin treatment did not show an elevated cardiovascular risk in patients with type 2 diabetes. The analysis suggested a potential cardiovascular benefit, supported by hazard ratios (HRs) below 1 for cardiovascular outcomes [42]. In both the dapagliflozin and control groups, the event rate per 100 patient-years for major adverse cardiovascular events (MACE) plus unstable angina was 1.5 compared to 2.2 in the overall population (HR 0.79; 95% CI 0.58–1.1). This trend continued with rates of 2.9 versus 3.8 in patients with cardiovascular disease (CVD) (HR 0.81; 95% CI 0.56–1.16) and 4.2 versus 5.1 in elderly patients (aged ≥ 65 years) with CVD risk (HR 0.82; 95% CI 0.5–1.37). DECLARE-TIMI 58 confirmed dapagliflozin's cardiovascular safety in patients with type 2

diabetes at risk of atherosclerotic cardiovascular disease (ASCVD), demonstrating noninferiority compared to placebo for the primary composite safety outcome of MACE ($p < 0.001$ for noninferiority) and superiority for one of the dual composite efficacy outcomes (CV death/HHF). [25].

**Dosage and Administration**

Dapagliflozin is authorized for monotherapy (in individuals intolerant to metformin) and as an add-on combination therapy (with various glucose-lowering agents, including insulin) for patients with type 2 diabetes in the EU when diet and exercise alone are insufficient for proper glycemic control [7]. Take 10 mg of dapagliflozin once daily orally, with or without food. If used with insulin or insulin secretagogues, consider a lower dose to reduce the risk of hypoglycemia. Do not start dapagliflozin in patients with GFR < 60 mL/min, and discontinue if GFR persists < 45 mL/min. No dosage adjustment is needed based on renal function or in mild/moderate hepatic impairment. In severe hepatic impairment, initiate dapagliflozin at 5 mg/day, increasing to 10 mg/day if well-tolerated [7].

**The Role of Dapagliflozin in treating T2D**

The goal of managing Type 2 Diabetes treatment is to avoid complications and enhance the patient's quality of life [43]. The consensus guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) from 2018 [43]. And the guidelines established by the ADA in 2019 [44]. Offer a patient-oriented strategy to handle glycemic levels and cardiovascular risks in Type 2 Diabetes (T2D). Customize glycemic goals by considering potential risks such as hypoglycemia and weight gain, the patient's unique characteristics like comorbidities and frailty, as well as their preferences and aspirations [43]. Different types of AHAs (Alpha Hydroxy Acids) with varied mechanisms of action can be employed in treating Type 2 Diabetes (T2D). Metformin, unless unsuitable or not well-tolerated, along with holistic lifestyle adjustments encompassing bodyweight control and regular physical activity, stand as the initial treatment approach. Selecting additional AHAs should be tailored to individual patients, considering factors such as their medical history related to cardiovascular disease (CVD), body weight, risk of hypoglycemia, chronic kidney disease (CKD), treatment costs, and the patient's preferences (Source: [43]. Cardiovascular disease (CVD) stands as the primary contributor to mortality in Type 2 Diabetes (T2D), with approximately 80% of all deaths

attributed to heart attacks (MI) and strokes [45]. So, it's crucial that the AHA choice for enhancing glycemic control in patients with T2D doesn't worsen, and ideally enhances, cardiovascular risk factors while lowering cardiovascular illness and death [45].

SGLT2 inhibitors, a recently developed type of oral AHAs, lower blood glucose levels by boosting the excretion of glucose through urine [46]. Due to their mechanism of action that doesn't rely on insulin, SGLT2 inhibitors can be safely used alongside other AHAs, such as insulin, with minimal risk of causing hypoglycemia [46]. The currently approved SGLT2 inhibitors in the EU—dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin—are taken orally once a day. Dapagliflozin, specifically, stands out as a potent and highly selective SGLT2 inhibitor, as demonstrated, showing proven effectiveness and safety in patients with T2D, as highlighted. In meticulously designed phase 3–4 clinical trials, dapagliflozin's once-daily administration, either as a standalone treatment or in combination with other AHAs, effectively managed blood sugar levels, reduced body weight, and lowered blood pressure across a wide range of T2D patients, including those with hypertension and/or cardiovascular disease (as discussed in Section 3). Real-world studies further supported dapagliflozin's effectiveness in treating patients with T2D.

Moreover, in the extensive DECLARE-TIMI 58 cardiovascular outcomes trial involving high-risk CV patients, dapagliflozin demonstrated noninferiority regarding MACE. Importantly, it significantly reduced the incidence of cardiovascular death and hospitalization for heart failure compared to the placebo. This difference between the groups was mainly due to a notable decrease in the rate of hospitalization for heart failure among those treated with dapagliflozin. Dapagliflozin also decreased the chances of advancing renal disease, although the statistical significance of these results wasn't shown due to hierarchical testing. The positive effects of dapagliflozin on cardiovascular and kidney health remained consistent among various subgroups, indicating its beneficial treatment potential across a wide range of patients, irrespective of their history of ASCVD, HF, or CKD at the beginning of treatment. Another set of subgroup analyses indicated that dapagliflozin decreased both major adverse cardiovascular events (MACE) and cardiovascular death or hospitalization for heart failure (CV death/HHF) among high-risk patients with type 2 diabetes and a history of myocardial infarction (MI) [29]. In patients with HFrEF, the reduction in cardiovascular death and hospitalization for heart failure is notably greater compared to those without HFrEF, primarily due to a more significant decrease in cardiovascular death among HFrEF patients [30]. The ongoing Phase 3 DAPA-HF trial is investigating the effects of dapagliflozin in patients with confirmed HFrEF. Additionally, the Phase 3 DELIVER and Phase 4 PRESERVED-HF trials are examining the impact of dapagliflozin in

patients with preserved ejection fraction HF. Meanwhile, the Phase 3 DAPACKD trial aims to assess whether dapagliflozin delays the progression of kidney disease in patients with CKD.

Dapagliflozin was generally well received, showing a minimal risk of hypoglycemia and adverse events related to its drug class, such as volume depletion, lower limb amputations, acute kidney injury, and bladder cancer. In the DECLARE-TIMI 58 trial, dapagliflozin showed a higher frequency of DKA (rare) and genital infections (common), both related to drug class, compared to the placebo. Additionally, there was a single case of Fournier's gangrene reported in the dapagliflozin group and five cases in the placebo group .

Additionally, the EMPA-REG OUTCOME trial of empagliflozin demonstrated cardiovascular and renal benefits similar to those observed in the DECLARE-TIMI 58 trial for SGLT2 inhibitors [27]. "The CANVAS Program, which involves canagliflozin, was discussed in [47]."

EMPA-REG OUTCOME specifically included individuals with ASCVD, whereas DECLARE-

TIMI 58 and the CANVAS Program comprised 41% and 65% of patients with confirmed ASCVD, respectively [25, 27, 47]. In all three CV results studies, SGLT2 inhibitors showed a

more dependable and substantial impact in preventing heart failure and renal outcomes compared to their effect on atherosclerotic CV events [25]. The variation might result from how SGLT2 inhibitors affect the kidneys and other factors, like natriuresis, lowering blood pressure, and enhancing endothelial function [25]. During the trials, SGLT2 inhibitors seemed to moderately lower the risk of MACE in individuals with ASCVD, yet this effect wasn't observed in patients with multiple risk factors [48]. However, unlike the findings in EMPA-REG OUTCOME, DECLARE-TIMI 58 did not show a significant reduction in the rates of cardiovascular death and all-cause death. This difference could potentially be attributed to variances in the drugs used or distinctions in the study designs [25].

The outcomes of a recent meta-analysis on the three CV outcome trials of SGLT2 inhibitors aligned with the conclusions drawn from the individual trials. They highlighted strong advantages in reducing HHF and slowing the progression of renal disease, along with moderate benefits regarding MACE, particularly among patients with ASCVD [48]. Several explanations have been suggested to account for the cardiovascular advantages associated with SGLT2 inhibitors. These include enhancements in ventricular loading conditions, improvements in cardiac metabolism and energy production, inhibition of myocardial Na+/H+ exchange, decrease in necrosis and cardiac fibrosis, along with changes in adipokines, cytokine production, and epicardial adipose tissue mass [49].

In various studies evaluating different AHAs for cardiovascular outcomes, liraglutide (LEADER) and semaglutide (SUSTAIN-6), which are GLP-1RAs, notably decreased the chances of MACE among individuals with T2D. However, exenatide (EXSCEL) and lixisenatide

(ELIXA) didn't show any cardiovascular benefit or harm in these trials [43, 50]. The cardiovascular outcome trials didn't show a notable impact of GLP-1RAs on hospitalization for heart failure (HHF) [43, 50]. The findings of a recent meta-analysis indicated that SGLT2 inhibitors showed a larger reduction in the risk of hospitalization for heart failure (HHF) compared to GLP-1RAs (SGLT2 inhibitors vs. GLP-1RAs: HR 0.71). However, there was no significant distinction observed between SGLT2 inhibitors and GLP-1RAs in reducing major adverse cardiovascular events (MACE) (GLP-1RAs vs. SGLT2 inhibitors: HR 1.02) [51]. In cardiovascular outcome trials evaluating DPP-4 inhibitors, sitagliptin (TECOS), saxagliptin (SAVOR-TIMI 53), and alogliptin (EXAMINE) showed cardiovascular safety without demonstrating any cardiovascular benefits. However, saxagliptin was linked to a 27% higher risk of hospitalization for heart failure compared to the placebo ($p = 0.007$) [43, 50]. Regarding renal outcomes, SGLT2 inhibitors notably decreased both albuminuria and the decline in eGFR, whereas GLP-1RAs were mainly linked to notable reductions in albuminuria without significant impact on eGFR. The impact of DPP-4is on renal outcomes remains uncertain and requires additional evaluation [52].

SGLT2 inhibitors have demonstrated cardiovascular advantages in extensive real-world investigations, such as the CVD-REAL study, which involved over 300,000 propensity scorematched Type 2 Diabetes patients from six countries: the USA, UK, Norway, Denmark, Sweden, and Germany [53]. Administration of an SGLT2 inhibitor was linked to a reduced likelihood of mortality (HR 0.49; $p < 0.001$) and hospitalization for heart failure (HR 0.61; $p < 0.001$) [53]. "There was a slightly reduced risk of myocardial infarction (MI) (HR 0.85; $p = 0.05$) and stroke (HR 0.83; $p = 0.02$) among patients newly starting treatment with an SGLT2 inhibitor. Among these patients, 53% received canagliflozin, 42% dapagliflozin, and 5% empagliflozin, while the remaining group received another anti-hyperglycemic agent (n = 154,528 patients in each group). Subgroup analysis indicated that SGLT2 inhibitors decreased the risk of heart failure (HF) irrespective of pre-existing cardiovascular disease, aligning with previous clinical cardiovascular outcome trials [54]." The cardioprotective benefits of SGLT2 inhibitors were observed in the CVD-REAL Nordic study involving Denmark, Norway, and Sweden, encompassing 40,908 participants [55]. and CVD-REAL 2 (Asia Pacific, the Middle East and North American regions; n = 235,064) [56]. Research demonstrated that starting an SGLT2 inhibitor was linked to a reduced risk of cardiovascular events, encompassing major adverse cardiovascular events (MACE) and hospitalization for heart failure (HHF), as well as decreased all-cause mortality.

The recent ADA/EASD consensus guidelines [43] highlight the advantages of SGLT2 inhibitors and GLP-1RAs in terms of CV benefits. and the ADA guidelines [44]. Here's a rephrased version: It's advisable to consider a patient's cardiovascular disease history early in their diabetes treatment. For those with established ASCVD who don't reach their HbA1c target with metformin (or can't tolerate it), adding an SGLT2 inhibitor or GLP-1RA with proven cardiovascular benefits is recommended. In cases of heart failure or chronic kidney disease, adding an SGLT2 inhibitor, known for reducing HF or CKD progression, is preferred. If still above target, intensifying treatment may involve adding another drug class with proven cardiovascular benefits, such as a GLP-1RA or SGLT2 inhibitor. Additionally, SGLT2 inhibitors can be considered for patients without ASCVD or CKD who need to minimize hypoglycemia or manage body weight [43,44].

**Conclusions**

Daily oral dapagliflozin enhances glycemic control, reduces body weight and blood pressure, and lowers the likelihood of cardiovascular death/heart failure hospitalization while potentially slowing the progression of renal disease. This makes it a valuable treatment choice for a wide range of patients, irrespective of their cardiovascular history.

**References**


1. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus.Curr Opin Endocrinol Diabetes Obes. 2017;24(1):73–9.
2. Wilding J, Fernando K, Milne N, et al. SGLT2 inhibitors intype 2 diabetes management: key evidence and implications for clinical practice. Diabetes Ther. 2018;9(5):1757–73.
3. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs. 2015;75(1):33–59
4. Plosker GL. Dapagliflozin: a review of its use in type 2 diabetesmellitus. Drugs. 2012;72(17):2289–312.
5. Plosker GL. Dapagliflozin: a review of its use in patients withtype 2 diabetes. Drugs. 2014;74(18):2191–209.
6. Meng W, Ellsworth BA, Nirschl AA, et al. Discovery of dapa-gliflozin: a potent, selective renal sodium-dependent glucosecotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. J Med Chem. 2008;51(5):1145–9.
7. AstraZeneca. Forxiga (dapagliflozin): summary of product characteris-tics. 2019. https://www.ema.europa.eu/en. Accessed 4 Jun 2019.
8. Komoroski B, Vachharajani N, Feng Y, et al. Dapagliflozin, anovel, selective SGLT2 inhibitor, improved glycemic controlover 2 weeks in patients with type 2 diabetes mellitus. Clin Pharmacol Ther. 2009;85(5):513–9.
9. Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin inpatients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebocontrolled trial. Lancet. 2010;375(9733):2223–33.
10. Heerspink HJL, Kurlyandskaya R, Xu J, et al. Differentialeffects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. Diabetes. 2016;65(Suppl 1):A286.
11. Scheen AJ, Paquot N. Metabolic effects of SGLT-2 inhibitors beyond increased glucosuria: a review of the clinical evidence.Diabetes Metab. 2014;40(6 Suppl 1):S4–11.
12. Skolnik N, Bonnes H, Yeh H, et al. Dapagliflozin in the treat-ment of patients with type 2 diabetes presenting with high base-line A1C. Postgrad Med. 2016;128(4):356–63.
13. Fioretto P, Mansfield TA, Ptaszynska A, et al. Long-term safetyof dapagliflozin in older patients with type 2 diabetes mellitus: a pooled analysis of phase IIb/III studies. Drugs Aging.2016;33(7):511–22.
14. Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int. 2014;85(4):962–71.
15. Weber MA, Mansfield TA, Alessi F, et al. Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin-angiotensin system blockade. Blood Press. 2016;25(2):93–103.
16. Weber MA, Mansfield TA, Cain VA, et al. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol. 2016;4(3):211–20.
17. Leiter LA, Cefalu WT, de Bruin TW, et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, doubleblind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc. 2014;62(7):1252–62.
18. Cefalu WT, Leiter LA, de Bruin TWA, et al. Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Diabetes Care. 2015;38(7):1218–27.
19. Bolinder J, Ljunggren O, Kullberg J, 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(3):1020–31.
20. Bolinder J, Ljunggren O, Johansson L, 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(2):159–69.
21. Leiter LA, Cefalu WT, de Bruin TW, et al. Long-term mainte- nance of efficacy of dapagliflozin in patients with type 2 diabetes mellitus and cardiovascular disease. Diabetes Obes Metab. 2016;18(8):766–74.
22. Kosiborod M, Gause-Nilsson I, Xu J, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and concomitant heart failure. J Diabetes Complicat. 2017;31(7):1215–21.
23. Fioretto P, Del Prato S, Buse JB, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE study. Diabetes Obes Metab. 2018;20(11):2532–40.

24. Scott R, Morgan J, Zimmer Z, et al. A randomized clinical trial of the efficacy and safety of sitagliptin compared with dapagliflozin in patients with type 2 diabetes mellitus and mild renal insufficiency: the CompoSIT-R study. Diabetes Obes Metab. 2018;20(12):2876–84.

25. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2018;380(4):347–357.

26. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: participants' baseline characteristics. Diabetes Obes Metab. 2018;20(5):1102–10.

27. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.

28. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 2019. doi: https:// doi.org/10.1016/S2213-8587(19)30180-9.

29. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes and prior myocardial infarction: a sub-analysis from DECLARE TIMI-58 trial. Circulation. 2019;139(22):2516–27.

30. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139(22):2528–36.

31. Wilding J, Bailey C, Rigney U, et al. Dapagliflozin therapy for type 2 diabetes in primary care: effects on HbA1c, weight and blood pressure over two years follow-up [abstract no. P508]. Dia- bet Med. 2017;34(Suppl 1):189.

32. Huang H, Bell K, Gani R, et al. A retrospective real-world study of dapagliflozin vs. other oral antidiabetic therapies added to metformin in patients with type 2 diabetes (T2D) [abstract no.1233-P]. Diabetes. 2017;66(Suppl 1):A330

33. Han E, Kim A, Lee SJ, et al. Characteristics of dapagliflozin responders: a longitudinal, prospective, nationwide dapagliflozin surveillance study in Korea. Diabetes Ther. 2018;9(4):1689–701.

34. Viswanathan V, Singh KP. Usage of dapagliflozin, a sodium glucose co-transporter inhibitor, in the management of type-2 diabetes mellitus: a real world evidence study in Indian patients (FOREFRONT) [abstract no. PP50]. Int J Diabetes Dev Ctries. 2018;38(Suppl 2):S155.

35. Brown RE, Abitbol A, Aronson R. Real-world health outcomes of dapagliflozin vs. a DPP-4 inhibitor or a sulfonylurea in type 2 diabetes. Diabetes. 2017;66(Suppl. 1):A347.

36. Fadini GP, Zatti G, Baldi I, et al. Use and effectiveness of dapagliflozin in routine clinical practice: an Italian multicentre retrospective study. Diabetes Obes Metab. 2018;20(7):1781–6.

37. Persson F, Nystrom T, Jorgensen ME, 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(2):344–51.

38. Jabbour S, Seufert J, Scheen A, et al. Dapagliflozin in patients with type 2 diabetes mellitus: a pooled analysis of safety data from phase IIb/III clinical trials. Diabetes Obes Metab. 2018;20(3):620–8.

39. Bailey CJ, Morales Villegas EC, Woo V, et al. Efficacy and safety of dapagliflozin monotherapy in people with type 2 diabetes: a randomized double-blind placebo-controlled 102week trial. Diabet Med. 2015;32(4):531–41.

40. Ljunggren O, Bolinder J, Johansson L, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab. 2012;14(11):990–9.

41. Ptaszynska A, Cohen SM, Messing EM, et al. Assessing bladder cancer risk in type 2 diabetes clinical trials: the dapagliflozin drug development program as a 'case study'. Diabetes Ther. 2015;6(3):357–75.

42. Sonesson C, Johansson PA, Johnsson E, et al. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. Cardiovasc Diabetol. 2016;15:37.

43. 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):2669–701.

44. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2019 [web annotation]. Diabetes Care. 2019;42(Suppl 1):S90–102.

45. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J. 2015;36(34):2288–96.

46. Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits. Diabetologia. 2018;61(10):2118–25.

47. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.

48. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31–9.

49. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61(10):2108–17.

50. Bailey CJ, Marx N. Cardiovascular protection in type 2 diabetes: insights from recent outcome trials. Diabetes Obes Metab. 2019;21(1):3–14.

51. Hussein H, Zaccardi F, Khunti K, et al. Cardiovascular efficacy and safety of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a systematic review and network meta-analysis. Diabet Med. 2019;36(4):444–52.

52. Scheen AJ. Effects of glucose-lowering agents on surrogate end- points and hard clinical renal outcomes in patients with type 2 diabetes. Diabetes Metab. 2019;45(2):110–21.

53. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). Circulation. 2017;136(3):249–59.

54. Cavender MA, Norhammar A, Birkeland KI, et al. SGLT-2 inhibitors and cardiovascular risk: an analysis of CVD-REAL. J Am Coll Cardiol. 2018;71(22):2497–506.

55. Birkeland KI, Jorgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol. 2017;5(9):709–17.

56. Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol. 2018;71(23):2628–39.