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REVIEW

# The Pleiotropic Effects of Sodium–Glucose Cotransporter-2 Inhibitors: Beyond the Glycemic Benefit

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## ABSTRACT

Type 2 diabetes (T2D) is associated with an increased risk of macro- and microvascular complications, including cardiovascular disease (CVD), heart failure (HF), and chronic kidney disease (CKD). Of the currently available glucose-lowering therapies, sodium–glucose cotransporter-2 inhibitors (SGLT-2is) are the only class to target the pathophysiologic increase in renal glucose reabsorption in patients with T2D. In CV outcomes trials of SGLT-2is in patients with T2D and established CVD or varying levels of CV risk, empagliflozin, canagliflozin, and dapagliflozin were associated with significant improvements in the risk of composite CV and renal outcomes compared with placebo that extended beyond their glycemic effects. Real-world observational studies have also reported improvements in CV outcomes with SGLT-2is compared with other glucose-lowering therapy in routine clinical practice. This review describes the pleiotropic effects of SGLT-2is and discusses the potential mechanisms for these effects as well as how they potentially provide benefits beyond glycemic control in patients with T2D. These favorable nonglycemic effects indicate that SGLT-2is may be of particular benefit in patients with diabetic complications, such as CVD, HF, or CKD. Ongoing large randomized trials in specific patient populations, including those with CVD, HF, or CKD (with or without T2D), may help to confirm the benefits of SGLT-2is in these patients and further elucidate the potential mechanisms of their pleiotropic effects.
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**Keywords:** Cardiovascular disease; Chronic kidney disease; Pleiotropic effects; Sodium–glucose cotransporter-2 inhibitors; Type 2 diabetes

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## INTRODUCTION

Type 2 diabetes (T2D) is a progressive disease characterized by impaired insulin secretion and/or increasing insulin resistance, resulting in chronic hyperglycemia [1]. In patients with T2D, chronic hyperglycemia often leads to macrovascular (cardiovascular disease [CVD]) and microvascular (nephropathy, retinopathy, and neuropathy) complications, which are associated with an increased risk of morbidity

and mortality [2]. In addition, T2D is associated with worsened health-related quality of life and increased healthcare costs [3–6].

Current glucose-lowering therapy options target one or more of the eight metabolic and endocrine defects (the ominous octet) underlying the pathophysiology of T2D (Fig. 1) [7, 8]. These defects include decreased pancreatic insulin secretion, decreased incretin effect, increased glucagon secretion, increased hepatic glucose production, decreased glucose uptake, increased lipolysis, increased renal glucose reabsorption, and neurotransmitter dysfunction [7, 8].

The kidneys perform an essential role in glucose homeostasis, with renal glucose reabsorption predominantly (~ 80%–90%) mediated by sodium–glucose cotransporter-2 (SGLT-2) in the proximal tubule [9, 10]. In healthy individuals without T2D, the maximum renal glucose reabsorptive capacity exceeds the amount of glucose filtered at the glomerulus, and all of the filtered glucose is reabsorbed into the plasma circulation to maintain normal plasma glucose levels [9]. In patients with T2D, increased SGLT-2 expression and activity in the proximal tubule lead to abnormally high renal glucose reabsorption, which contributes to persistent hyperglycemia (Fig. 2) [10–12].

SGLT-2 inhibitors (SGLT-2is) reduce plasma glucose levels in patients with T2D by decreasing the renal glucose reabsorptive capacity in the proximal tubule by up to 50% of the filtered glucose load, thereby promoting urinary excretion of glucose (Fig. 2) [12, 13]. In contrast to other classes of glucose-lowering therapy, SGLT-2is are the only class to specifically target the

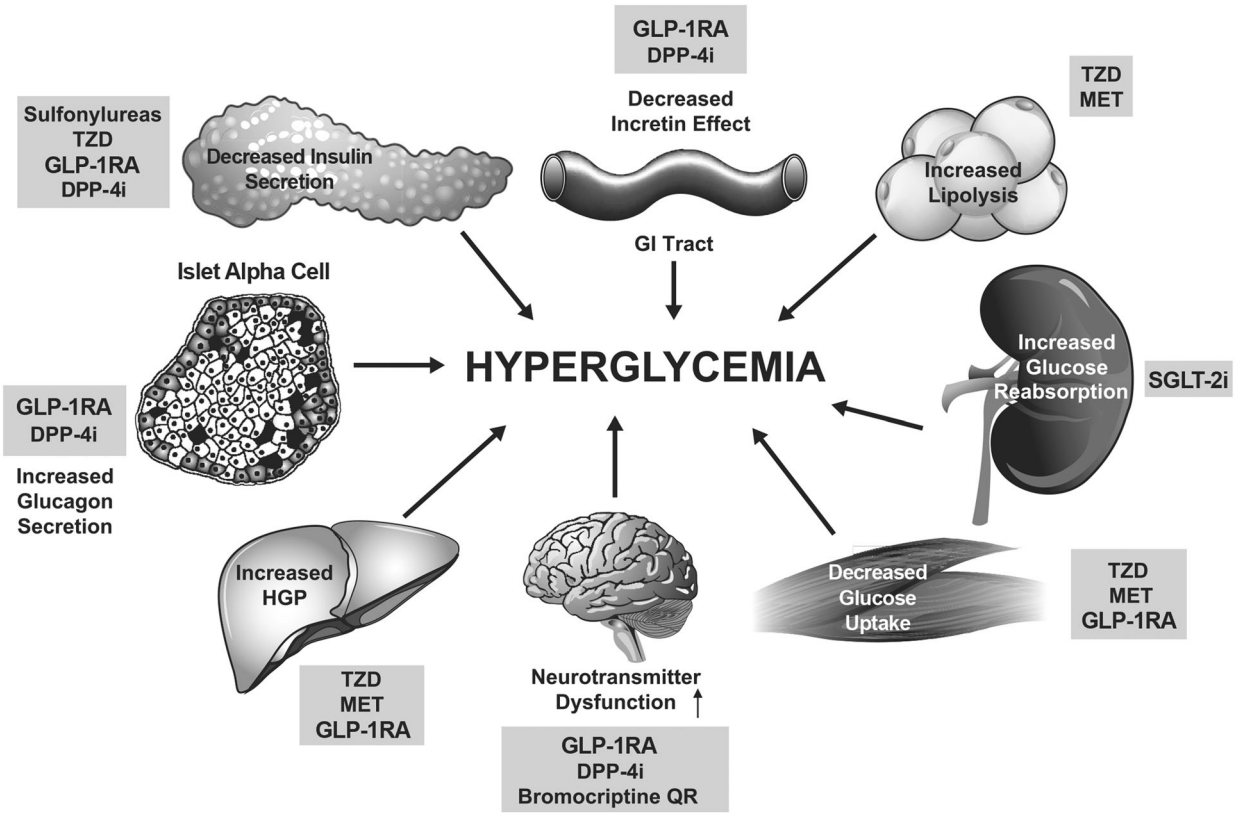


**Fig. 1** The ominous octet. Mechanisms and site of action of glucose-lowering medications based on pathophysiologic disturbances in type 2 diabetes [7]. Reproduced with permission from Thrasher et al. 2017 [8]. *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GI* gastrointestinal, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *HGP* hepatic glucose production, *MET* metformin, *QR* quick release, *SGLT-2i* sodium–glucose cotransporter-2 inhibitor, *TZD* thiazolidinedione

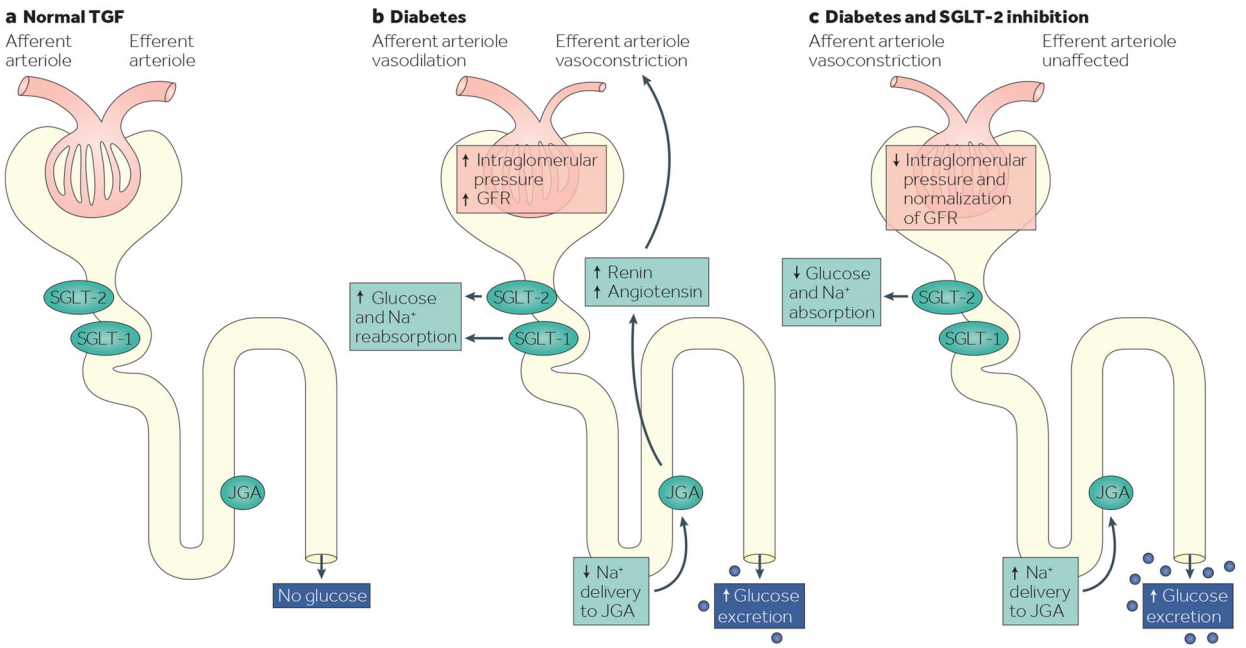


**Fig. 2** Glucose homeostasis in the kidney (**a**) in individuals without diabetes, in whom all of the filtered glucose is reabsorbed (along with $Na^+$) by SGLT-2 and SGLT-1 and TGF is maintained; **b** in patients with T2D, in whom the glucose reabsorption is increased by SGLT-2 and SGLT-1; **c** in patients with T2D receiving SGLT-2is, in whom reabsorption of glucose and $Na^+$ is decreased and urinary glucose excretion is increased. Reproduced with permission from DeFronzo et al. 2017 [12]. *GFR* glomerular filtration rate, *JGA* juxtaglomerular apparatus, *$Na^+$* sodium, *SGLT* sodium–glucose cotransporter, *SGLT-2is* SGLT-2 inhibitors, *T2D* type 2 diabetes, *TGF* tubuloglomerular feedback

renal pathophysiologic defect of T2D [8]. Because this mechanism of action is independent of insulin and does not affect the metabolic regulation of glucose, SGLT-2is are associated with a low risk of hypoglycemia [13, 14]. SGLT-2is also remain effective in the presence of progressive loss of beta-cell function or insulin resistance and may act synergistically when used in combination with other glucose-lowering therapies [14].

In CV outcomes trials (CVOTs) of SGLT-2is, reductions in the risk of various composite CV and renal end points compared with placebo were observed with empagliflozin in patients with T2D and established CVD [15, 16] and with canagliflozin [17] and dapagliflozin [18] in patients with T2D and established CVD or varying levels of CV risk. These findings led to revisions in the treatment strategy for T2D, with clinical associations recommending the inclusion of SGLT-2is in patients with established CVD, heart failure (HF), or chronic kidney disease (CKD) [19–21].

This review describes the pleiotropic effects of SGLT-2is and discusses the potential mechanisms for these effects as well as how they may provide additional benefits beyond glycemic control in patients with T2D.

## SEARCH STRATEGY

A literature search of PubMed was conducted on February 13, 2019, for English-language publications using the following search terms: (SGLT2 inhibitors OR SGLT-2 inhibitors OR SGLT-2is OR SGLT2is OR sodium–glucose cotransporter 2 inhibitors OR sodium–glucose cotransporter-2 inhibitors OR empagliflozin OR canagliflozin OR dapagliflozin OR ertugliflozin) AND (type 2 diabetes mellitus OR type 2 diabetes OR T2D OR non-insulin dependent diabetes) AND (nonglycemic effects OR nonglycaemic effects OR non-glycemic effects

OR non-glycaemic effects OR pleiotropic effects). Additional literature was identified by review of bibliographies from the reference data set. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## CARDIOVASCULAR EFFECTS OF SGLT-2 INHIBITORS

### Randomized Clinical Trials

In clinical studies of patients with T2D, SGLT-2is provided effective reductions in glycated hemoglobin and fasting blood glucose and were associated with improvements in several CV risk factors, including decreases in body weight, blood pressure (BP), waist circumference, and triglycerides, and an increase in high-density lipoprotein (HDL) cholesterol [22–24]. However, slight increases in low-density lipoprotein (LDL) cholesterol levels have also been observed with SGLT-2is [15, 17].

In CVOTs of empagliflozin (EMPA-REG OUTCOME) and canagliflozin (CANVAS), the risk of the three-point major adverse CV event composite outcome [3-point MACE; defined as CV death, nonfatal myocardial infarction (MI), or nonfatal stroke] was significantly reduced by 14% versus placebo in patients with T2D and established CVD in EMPA-REG OUTCOME [15] or in patients with T2D and established CVD or multiple CVD risk factors in CANVAS [17] (Table 1). These trials also demonstrated a significant reduction in the risk of hospitalization for HF with empagliflozin (by 35%) and with canagliflozin (by 33%) versus placebo [15, 17, 25, 26].

Although absolute numbers of patients with established CVD were similar across the three CVOTs, the DECLARE-TIMI 58 study of dapagliflozin included a larger proportion of patients with multiple CV risk factors without established CVD (~ 60%) and a smaller proportion of patients with established CVD than the other two SGLT-2i trials (~ 40%; vs. > 99% in EMPA-REG OUTCOME and ~ 66% in CANVAS [15, 17]), representing a population at an earlier stage of CVD risk [18, 27]. In DECLARE-TIMI 58, dapagliflozin showed noninferiority to placebo in the risk of three-point MACE [18], with a greater risk reduction in patients with a prior MI versus those without (16% vs. 0%) [28], and dapagliflozin significantly reduced the risk of the composite outcome of CV death or hospitalization for HF by 17% versus placebo (Table 1), primarily resulting from a lower rate of hospitalization for HF [18]. A subanalysis showed that dapagliflozin reduced the risk of CV death or hospitalization for HF to a greater extent in patients with a history of HF with reduced ejection fraction (HFrEF) than in those without HFrEF, defined as HF without known reduced EF or without history of HF (38% vs. 12%) [29].

A meta-analysis of data from these three CVOTs indicated that SGLT-2is reduced the overall risk of three-point MACE by 11% compared with placebo (Fig. 3) [30, 31]. This reduction in the risk of MACE was observed only in patients with atherosclerotic CVD, whereas patients with multiple CVD risk factors showed no treatment effect [30]. In this meta-analysis, SGLT-2is reduced the overall risk of the composite outcome of CV death or hospitalization for HF by 23% and hospitalization for HF by 31% compared with placebo. The hospitalization for HF outcome was similar among patients with atherosclerotic CVD and those with multiple CVD risk factors, with ~ 30% risk reduction in both subgroups.

### Real-World Observational Studies

Real-world studies have also indicated that SGLT-2is have beneficial CV effects in routine clinical practice that extend beyond those seen with other glucose-lowering therapy in patients with T2D (Table 2). The multinational CVD-REAL study showed improvements in CV outcomes, including reductions in the risk of hospitalization for HF (by 39%) and in the risk of hospitalization for HF or death (by 46%), with newly initiated SGLT-2i therapy (empagliflozin, canagliflozin, or dapagliflozin) compared with other glucose-lowering therapy (Table 2) [32–34]. This lower risk of hospitalization for HF

**Table 1** Summary of pleiotropic effects of SGLT-2is in randomized, placebo-controlled cardiovascular outcomes trials

| | EMPA-REG OUTCOME [15, 16] | CANVAS [17, 59] | DECLARE–TIMI 58 [18, 60, 61] |
|---|---|---|---|
| Study design | | | |
| Patient population | Age ≥ 18 years with T2D and established CVD ($n$ = 7020) | Age ≥ 30 years with T2D and established CVD or age ≥ 50 years with T2D and ≥ 2 CVD risk factors ($n$ = 10,142) | Age ≥ 40 years with T2D and established CVD or age ≥ 55 years (males) or ≥ 60 years (females) with T2D and ≥ 1 CVD risk factor (hypertension, dyslipidemia, or current smoker) ($n$ = 17,160) |
| Treatment | Empagliflozin (10 or 25 mg) or matched PBO once daily | Canagliflozin (100 or 300 mg) or matched PBO once daily | Dapagliflozin 10 mg or matched PBO once daily |
| Primary end point | Composite of CV death, nonfatal MI, or nonfatal stroke | Composite of CV death, nonfatal MI, or nonfatal stroke | Safety<br>CV death, MI, or ischemic stroke<br>Efficacy<br>(1) CV death, MI, or ischemic stroke<br>(2) CV death or hospitalization for HF |
| CV outcomes, SGLT-2i vs. PBO, rate per 1000 PY (HR [95% CI]) | | | |
| CV death, nonfatal MI, or nonfatal stroke | 37.4 vs. 43.9<br>(0.86 [0.74–0.99])<br>$P < 0.001$ for noninferiority<br>$P = 0.04$ for superiority | 26.9 vs. 31.5<br>(0.86 [0.75–0.97])<br>$P < 0.001$ for noninferiority<br>$P = 0.02$ for superiority | 22.6 vs. 24.2<br>(0.93 [0.84–1.03])<br>$P < 0.001$ for noninferiority<br>$P = 0.17$ for superiority |
| CV death or hospitalization for HF | 19.7 vs. 30.1<br>(0.66 [0.55–0.79])<br>$P < 0.001$ | 16.3 vs. 20.8<br>(0.78 [0.67–0.91]) | 12.2 vs. 14.7<br>(0.83 [0.73–0.95])<br>$P = 0.005$ |
| Hospitalization for HF | 9.4 vs. 14.5<br>(0.65 [0.50–0.85])<br>$P = 0.002$ | 5.5 vs. 8.7<br>(0.67 [0.52–0.87]) | 6.2 vs. 8.5<br>(0.73 [0.61–0.88]) |
| CV death | 12.4 vs. 20.2<br>(0.62 [0.49–0.77])<br>$P < 0.001$ | 11.6 vs. 12.8<br>(0.87 [0.72–1.06]) | 7.0 vs. 7.1<br>(0.98 [0.82–1.17]) |

**Table 1** continued

| | EMPA-REG OUTCOME [15, 16] | CANVAS [17, 59] | DECLARE–TIMI 58 [18, 60, 61] |
|---|---|---|---|
| Renal outcomes, SGLT-2i vs. PBO, rate per 1000 PY (HR [95% CI]) | | | |
| Composite renal outcomes | Incident or worsening nephropathy[a] or CV death<br>60.7 vs. 95.9<br>(0.61 [0.55–0.69])<br>$P < 0.001$ | 40% eGFR reduction, ESRD, or death from renal or CV causes<br>16.9 vs. 21.6<br>(0.77 [0.66–0.89]) | ≥ 40% decrease in eGFR to < 60 ml/min/1.73 $m^2$, new ESRD, or death from renal or CV causes<br>10.8 vs. 14.1<br>(0.76 [0.67–0.87]) |
| | Incident or worsening nephropathy[a]<br>47.8 vs. 76.0<br>(0.61 [0.53–0.70])<br>$P < 0.001$ | 40% eGFR reduction, ESRD, or death from renal causes<br>5.5 vs. 9.0<br>(0.60 [0.47–0.77]) | ≥ 40% decrease in eGFR to < 60 ml/min/1.73 $m^2$, new ESRD, or death from renal causes<br>3.7 vs. 7.0<br>(0.53 [0.43–0.66]) |
| Select additional renal outcomes | Progression to macroalbuminuria[b]<br>41.8 vs. 64.9<br>(0.62 [0.54–0.72])<br>$P < 0.001$ | Progression of albuminuria[c]<br>89.4 vs. 128.7<br>(0.73 [0.67–0.79]) | Progression of albuminuria[d]<br>(0.84 [0.79–0.89])[e] $P < 0.0001$ |
| | Doubling of sCr plus eGFR ≤ 45 ml/min/1.73 $m^2$<br>5.5 vs. 9.7<br>(0.56 [0.39–0.79])<br>$P < 0.001$ | 40% eGFR reduction<br>5.3 vs. 8.7<br>(0.60 [0.47–0.78]) | ≥ 40% decrease in eGFR to < 60 ml/min/1.73 $m^2$<br>(0.54 [0.43–0.67])[e]<br>$P < 0.0001$ |
| Other outcomes, SGLT-2i vs. PBO, mean difference (95% CI) | | | |
| Body weight, kg | Values NR | − 1.6 (− 1.7 to − 1.5) $P < 0.001$ | − 1.8 (− 2.0 to − 1.7)[f] |
| Systolic BP, mmHg | Values NR | − 3.9 (− 4.3 to − 3.6) $P < 0.001$ | − 2.7 (− 3.0 to − 2.4)[f] |
| Diastolic BP, mmHg | Values NR | − 1.4 (− 1.6 to − 1.2) $P < 0.001$ | − 0.7 (− 0.9 to − 0.6)[f] |
| HDL cholesterol, mmol/l | Values NR | + 0.05 (+ 0.05 to + 0.06) | NR |

**Table 1** continued

| | EMPA-REG OUTCOME [15, 16] | CANVAS [17, 59] | DECLARE–TIMI 58 [18, 60, 61] |
|---|---|---|---|
| LDL cholesterol, mmol/l | Values NR | + 0.12 (+ 0.09 to + 0.15) | NR |

[a] Defined as progression to macroalbuminuria (urine albumin-to-creatinine ratio > 300 mg/g), doubling of serum creatinine in addition to eGFR ≤ 45 ml/min/1.73 $m^2$, initiation of renal replacement therapy, or death from renal causes

[b] Defined as urine albumin-to-creatinine ratio > 300 mg/g

[c] Defined as > 30% increase in albuminuria plus a change from either normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria

[d] Progression from normoalbuminuria to microalbuminuria or macroalbuminuria

[e] Rate per 1000 PY not reported

[f] Least-squares mean difference

*BP* blood pressure, *CI* confidence interval, *CV* cardiovascular, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *HDL* high-density lipoprotein, *HF* heart failure, *HR* hazard ratio, *LDL* low-density lipoprotein, *MI* myocardial infarction, *NR* not reported, *PBO* placebo, *PY* patient-years, *SGLT-2i* sodium–glucose cotransporter-2 inhibitor, *T2D* type 2 diabetes

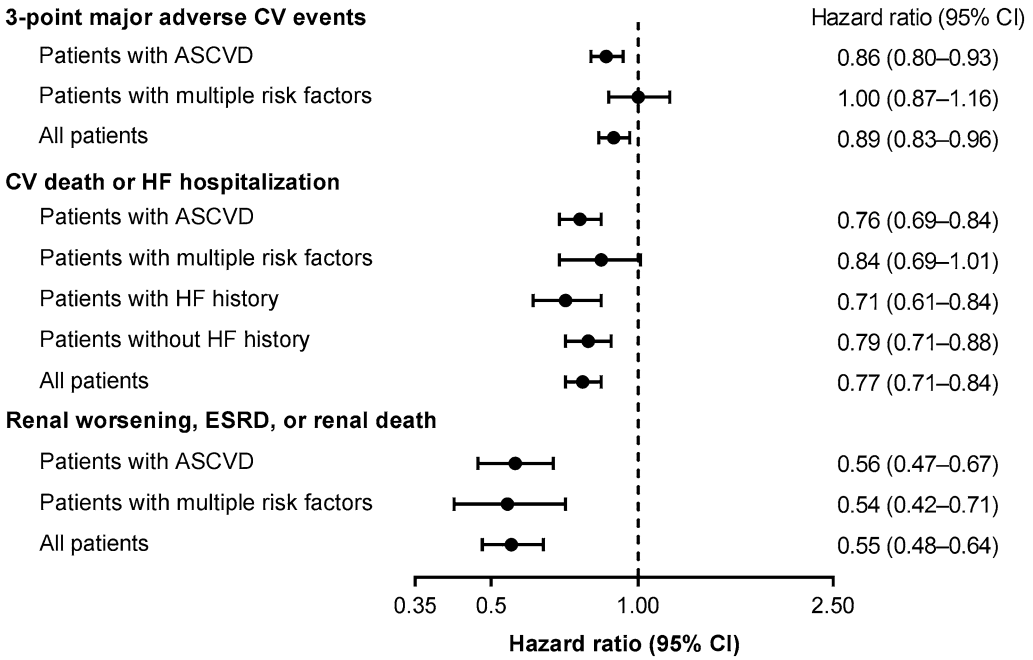


**Fig. 3** Summary of cardiovascular and renal outcomes with SGLT-2is as determined by a meta-analysis of the EMPA-REG OUTCOME, CANVAS, and DECLARE–TIMI 58 studies [30]. *ASCVD* atherosclerotic cardiovascular disease, *CI* confidence interval, *CV* cardiovascular, *ESRD* end-stage renal disease, *HF* heart failure, *SGLT-2i* sodium–glucose cotransporter-2 inhibitor

**Table 2** Summary of the pleiotropic effects of SGLT-2is in real-world studies of patients with T2D

| Study | No. of patients | Outcomes | HR (95% CI) | *P* value |
|---|---|---|---|---|
| CVD-REAL [32] | 309,056 | SGLT-2is vs. oGLT[a] | | |
| | | Hospitalization for HF | 0.61 (0.51–0.73) | < 0.001 |
| | | All-cause mortality | 0.49 (0.41–0.57) | < 0.001 |
| | | Hospitalization for HF or death | 0.54 (0.48–0.60) | < 0.001 |
| CVD-REAL (Nordic) [33, 34] | 91,320 | SGLT-2is vs. oGLT[a] | | |
| | | MACE | 0.78 (0.69–0.87) | < 0.0001 |
| | | Nonfatal MI | 0.87 (0.73–1.03) | 0.112 |
| | | Nonfatal stroke | 0.86 (0.72–1.04) | 0.965 |
| | | CV mortality | 0.53 (0.40–0.71) | < 0.0001 |
| | | Hospitalization for HF | 0.70 (0.61–0.81) | < 0.0001 |
| | | All-cause mortality | 0.51 (0.45–0.58) | < 0.0001 |
| | 40,908 | Dapagliflozin vs. DPP-4is | | |
| | | MACE | 0.79 (0.67–0.94) | 0.006 |
| | | Nonfatal MI | 0.91 (0.72–1.16) | 0.445 |
| | | Nonfatal stroke | 0.79 (0.61–1.03) | 0.086 |
| | | CV mortality | 0.76 (0.53–1.08) | 0.122 |
| | | Hospitalization for HF | 0.62 (0.50–0.77) | < 0.001 |
| | | All-cause mortality | 0.59 (0.49–0.72) | < 0.001 |
| CVD-REAL 2 [36] | 470,128 | SGLT-2i vs. oGLT[a] | | |
| | | MI | 0.81 (0.74–0.88) | < 0.001 |
| | | Stroke | 0.68 (0.55–0.84) | < 0.001 |
| | | Hospitalization for HF | 0.64 (0.50–0.82) | 0.001 |
| | | All-cause mortality | 0.51 (0.37–0.70) | < 0.001 |
| | | Hospitalization for HF or death | 0.60 (0.47–0.76) | < 0.001 |
| EMPRISE [41] | 32,886 | Empagliflozin vs. sitagliptin | | |
| | | Hospitalization for HF (specific)[b] | 0.50 (0.28–0.91) | < 0.001 |
| | | Hospitalization for HF (broad)[c] | 0.51 (0.39–0.68) | < 0.001 |
| | 35,102 | Empagliflozin vs. DPP-4is | | |
| | | Hospitalization for HF (specific)[b] | 0.49 (0.27–0.89) | 0.002 |
| | | Hospitalization for HF (broad)[c] | 0.56 (0.43–0.73) | < 0.001 |
| | 224,528 | SGLT-2is vs. DPP-4is | | |
| | | Hospitalization for HF (specific)[b] | 0.42 (0.35–0.50) | < 0.001 |
| | | Hospitalization for HF (broad)[c] | 0.70 (0.65–0.75) | < 0.001 |

**Table 2** continued

| Study | No. of patients | Outcomes | HR (95% CI) | *P* value |
|---|---|---|---|---|
| Gautam et al. [37] | 14,697 | SGLT-2is vs. DPP-4is | | |
| | | Hospitalization for HF | 0.68 (0.54–0.86) | 0.001 |
| Norhammar et al. [39] | 28,408 | Dapagliflozin vs. oGLT[a] | | |
| | | MACE | 0.90 (0.79–1.03) | 0.129 |
| | | MI | 0.91 (0.74–1.11) | 0.347 |
| | | Stroke | 1.06 (0.87–1.30) | 0.531 |
| | | CV mortality | 0.75 (0.57–0.97) | 0.003 |
| | | Hospitalization for HF | 0.79 (0.67–0.93) | 0.005 |
| | | Hospitalization for HF or CV mortality | 0.79 (0.69–0.92) | 0.002 |
| | | All-cause mortality | 0.63 (0.54–0.74) | < 0.001 |
| Patorno et al. [40] | 77,956 | Canagliflozin vs. DPP-4is | | |
| | | Hospitalization for HF | 0.70 (0.54–0.92) | NR |
| | | Composite CV end point[d] | 0.89 (0.68–1.17) | NR |
| | | Canagliflozin vs. GLP-1RAs | | |
| | | Hospitalization for HF | 0.61 (0.47–0.78) | NR |
| | | Composite CV end point[d] | 1.03 (0.79–1.35) | NR |
| | | Canagliflozin vs. SUs | | |
| | | Hospitalization for HF | 0.51 (0.38–0.67) | NR |
| | | Composite CV end point[d] | 0.86 (0.65–1.13) | NR |
| Kim et al. [38] | 118,958 | SGLT-2is vs. DPP-4is | | |
| | | Hospitalization for HF | 0.66 (0.58–0.75) | < 0.001 |

[a] Any oral or injectable glucose-lowering medication, including fixed-dose combinations, other than SGLT-2is
[b] Defined as an HF discharge diagnosis in the primary position
[c] Defined as an HF discharge diagnosis in any position
[d] Defined as hospitalization for acute MI, ischemic stroke, or hemorrhagic stroke
*CI* confidence interval, *CV* cardiovascular, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *HF* heart failure, *HR* hazard ratio, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *NR* not reported, *oGLT* other glucose-lowering therapy, *SGLT-2i* sodium–glucose cotransporter-2 inhibitor, *SU* sulfonylurea, *T2D* type 2 diabetes

or death was observed in patients regardless of CVD status at baseline [35]. A subanalysis (CVD-REAL Nordic) showed significant reductions in the risk of MACE (by 22%) and CV mortality (by 47%) with SGLT-2is versus other glucose-lowering therapy [33] and in the risk of MACE (by 21%) and hospitalization for HF (by 38%) with SGLT-2is versus dipeptidyl peptidase-4 inhibitors (DPP-4is) [34].

In the multinational CVD-REAL 2 study, the risk of hospitalization for HF, the composite outcome of hospitalization for HF or death, and

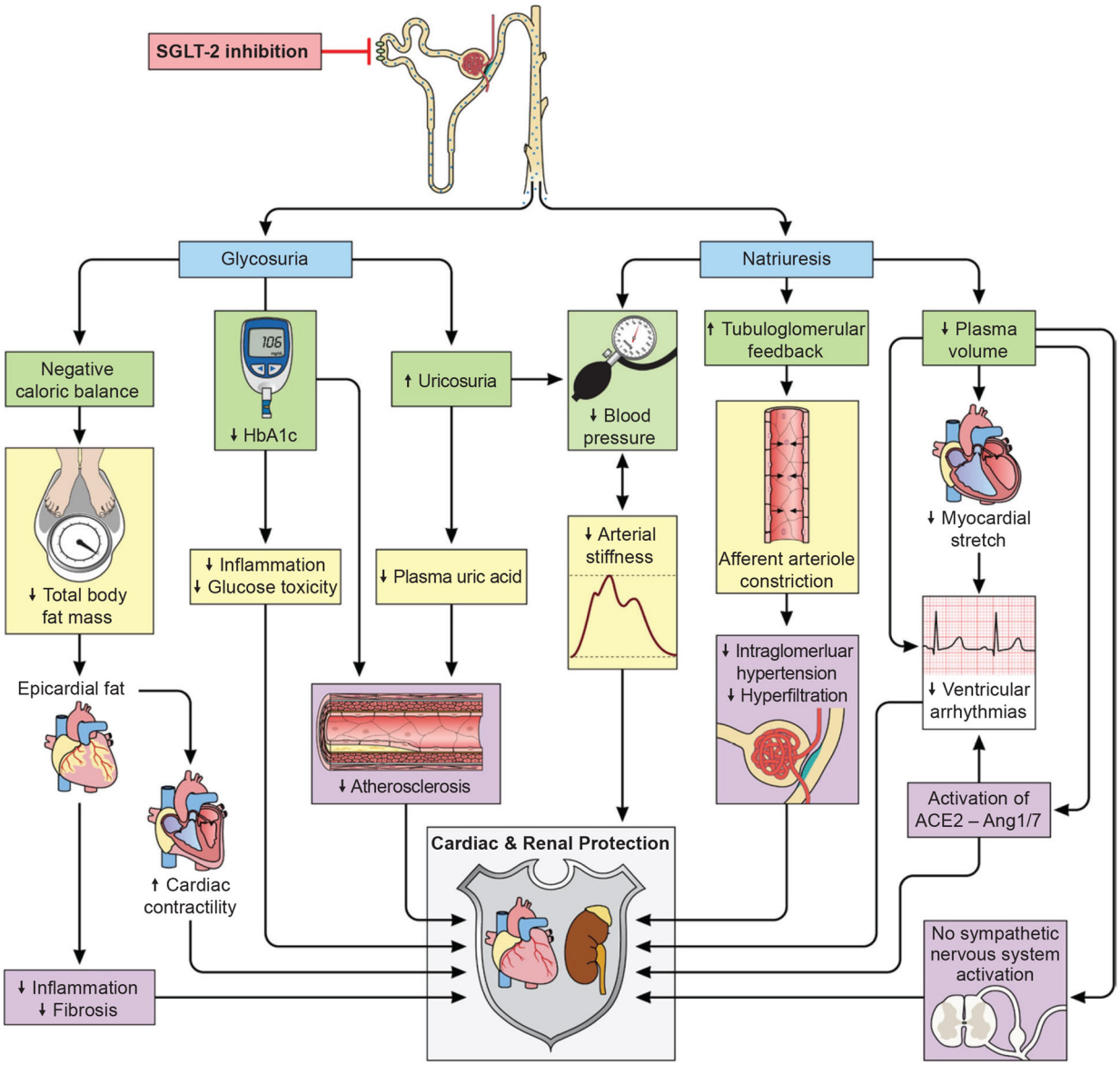


**Fig. 4** Potential mechanisms for pleiotropic effects of sodium–glucose cotransporter-2 inhibitors in patients with type 2 diabetes. Reproduced with permission from Heerspink et al. 2016 [42]. *ACE2* angiotensin-converting enzyme 2, *Ang1/7* angiotensin 1/7, *HbA1c* glycated hemoglobin, *SGLT-2* sodium–glucose cotransporter-2

MI was reduced with SGLT-2is to a similar extent to that seen in the CVD-REAL study compared with other glucose-lowering therapy (Table 2) [36]. In addition, the risk of stroke was reduced by 32%. Several retrospective studies have also demonstrated similar improvements in CV mortality and hospitalization for HF outcomes with SGLT-2i therapy (Table 2) [37–41].

## Potential Mechanisms of Cardiovascular Effects

The mechanisms underlying the beneficial CV effects of SGLT-2is in patients with T2D are not fully understood, but likely involve multiple contributing factors, including favorable effects on CV risk factors such as body weight, BP, and lipids (Fig. 4) [42]. One of the key mechanisms

**Table 3** Summary of ongoing outcomes trials of sodium–glucose cotransporter-2 inhibitors

| Study name (Clinical Trials.gov identifier) | Drug | Patient population |
|---|---|---|
| DAPA-CKD (NCT03036150) | Dapagliflozin | CKD |
| DAPA-HF (NCT03036124) | Dapagliflozin | HFrEF |
| DELIVER (NCT03619213) | Dapagliflozin | HFpEF |
| DETERMINE-reduced (NCT03877237) | Dapagliflozin | HFrEF |
| DETERMINE-preserved (NCT03877224) | Dapagliflozin | HFpEF |
| EMPA-KIDNEY (NCT03594110) | Empagliflozin | CKD |
| EMPEROR-Preserved (NCT03057951) | Empagliflozin | HFpEF |
| EMPEROR-Reduced (NCT03057977) | Empagliflozin | HFrEF |
| SCORED (NCT03315143) | Sotagliflozin | T2D, moderate renal impairment, CV risk |
| SOLOIST-WHF (NCT03521934) | Sotagliflozin | T2D after worsening HF |
| VERTIS-CV (NCT01986881) | Ertugliflozin | T2D and established ASCVD |

*ASCVD* atherosclerotic cardiovascular disease, *CKD* chronic kidney disease, *CV* cardiovascular, *HF* heart failure, *HFpEF* HF with preserved ejection fraction, *HFrEF* HF with reduced ejection fraction, *T2D* type 2 diabetes

for the observed CV benefits with SGLT-2is is believed to be improvement in ventricular loading through decreases in cardiac load [43]. Increased natriuresis and glucosuria, caused by inhibition of glucose and sodium renal reabsorption in the proximal tubule by SGLT-2is, lead to increased osmotic diuresis and reductions in preload, while reductions in BP (described later) and changes in vascular function are believed to decrease afterloading [43].

SGLT-2i therapy may increase cardiac efficiency through decreased cardiac load and increased oxygen delivery by hemoconcentration [44, 45]. SGLT-2is have been shown to reduce BP and improve markers of arterial stiffness, vascular resistance, and cardiac workload in patients with T2D [46–51]. Reductions in BP with SGLT-2is may play a role in their cardioprotective effects, although improvements in CV outcomes with empagliflozin versus placebo in EMPA-REG OUTCOME were observed earlier than is usually seen in studies of BP-lowering therapy [52].

SGLT-2i therapy may also improve cardiac efficiency by causing a systemic shift in fuel metabolism from glucose to fatty acid oxidation [43, 53, 54], while mild, persistent increases in blood ketone levels (which occur with SGLT-2i use) are believed to promote cardiac uptake and oxidization of ketone bodies, such as β-hydroxybutyrate, as an alternative fuel to fatty acids [44, 45].

Increased urinary glucose excretion with SGLT-2is potentially reduces cardiac glucotoxicity, consequently decreasing the risk of HF in patients with T2D and high CVD risk [55]. In addition, studies of animal models have suggested that SGLT-2is may act directly on cardiac tissues to reduce oxidative stress and inflammation [56, 57].

## Ongoing Studies of Cardiovascular Effects

Several randomized, placebo-controlled clinical studies are currently investigating CV outcomes with SGLT-2is (Table 3). CV and HF outcomes with empagliflozin and dapagliflozin are being assessed in patients with HF with preserved ejection fraction (HFpEF) and in those with HFrEF. Several studies are investigating long-term CV and renal outcomes with ertugliflozin or sotagliflozin (an SGLT-1 and SGLT-2

inhibitor) in patients with T2D and established CVD, CV risk, or HF [58].

Data from these studies may provide additional evidence of the beneficial CV effects of SGLT-2is in patients with CVD or HF (with or without T2D) and potentially address gaps in knowledge from the CVOTs of SGLT-2is.

## RENAL EFFECTS OF SGLT-2 INHIBITORS

### Randomized Clinical Trials

In CVOTs, SGLT-2is were associated with a significant reduction in the risk of kidney disease progression compared with placebo in patients with T2D and established CVD or varying levels of CV risk (Table 1) [16–18]. Empagliflozin reduced the risk of a composite renal outcome comprising macroalbuminuria, doubling of serum creatinine plus eGFR reduction, initiation of renal replacement therapy, or death from renal causes [16]. Canagliflozin and dapagliflozin each reduced the risk of composite renal outcomes comprising estimated glomerular filtration rate (eGFR) reduction, end-stage renal disease (ESRD), or death from renal causes [17, 18, 59]. EMPA-REG OUTCOME, CANVAS, and DECLARE–TIMI 58 also reported additional renal outcomes, including reductions in the risks of individual components of the composite outcomes, and analyses across prespecified patient subgroups [16, 17, 59–61].

In a meta-analysis of data from these three CVOTs, the overall risk of worsening of renal function, ESRD, or death from renal causes was reduced by 45% with SGLT-2is versus placebo (Fig. 3) [30, 31]. In this meta-analysis, similar renoprotective effects were found among patients with atherosclerotic CVD and those with multiple CVD risk factors [30]. In a meta-analysis of 25 randomized controlled trials of patients with T2D (with or without CKD), SGLT-2i therapy was associated with reduced risk of albuminuria progression (by 29%) and increased likelihood of regression of albuminuria (by 71%) compared with placebo [62]. This analysis also showed reductions in risk of the composite outcome of a sustained 40% reduction in eGFR, the need for renal replacement therapy, or death from renal causes (by 43%) and all-cause mortality (by 16%). The risk reductions for these outcomes were consistently observed regardless of baseline renal function, with no significant differences between different eGFR subgroups [62].

The CREDENCE trial investigated the effects of canagliflozin on renal failure and CV events in patients with T2D and established CKD (eGFR 30 to $< 90$ ml/min/1.73 $m^2$ and macroalbuminuria) and was stopped early after achievement of the primary end point, which consisted of a composite renal outcome, with renal events adjudicated. Canagliflozin was associated with a 30% reduction in the risk of the composite outcome of new ESRD, doubling of serum creatinine, or death from renal or CV causes compared with placebo [63].

In addition, the randomized, placebo-controlled DELIGHT trial assessed the effects of dapagliflozin or dapagliflozin + saxagliptin on albuminuria over 24 weeks in patients with T2D and moderate-to-severe CKD (urine albumin-to-creatinine ratio [UACR] of 30–3500 mg/g and eGFR of 25–75 ml/min/1.73 $m^2$) [64]. Both treatments reduced the UACR, with differences from placebo for the mean percentage change from baseline of − 21.0% ($P = 0.011$) in the dapagliflozin group and − 38.0% ($P < 0.0001$) in the dapagliflozin + saxagliptin group.

### Potential Mechanisms of Renal Effects

The mechanisms underlying improved renal outcomes with SGLT-2is are likely multifactorial and potentially associated with their direct hemodynamic and renovascular effects (Fig. 4) [2, 42]. Increased natriuresis leads to increased sodium levels at the macula densa, which results in activation of tubuloglomerular feedback and reductions in renal blood flow and glomerular hyperfiltration [2, 65]. Combined use of SGLT-2is with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may further reduce intraglomerular pressure [43]. Additive renal improvements with SGLT-2is and renin-aldosterone-angiotensin system inhibitors may result from

simultaneous blockade of sodium-hydrogen exchangers (NHE1 and NHE3) in the kidney [66]. Hyperglycemia, hyperinsulinemia, and adipokines stimulate NHE activity, which may contribute to glomerular hyperfiltration and other features of diabetic nephropathy. Furthermore, the NHE1 isoform is also expressed in the heart and vasculature and contributes to the pathophysiology of HF.

SGLT-2i—associated changes in renal hemodynamics lead to acute reductions in eGFR (that stabilize with long-term treatment) and albuminuria (that are sustained with longer treatment) and are not observed with other classes of glucose-lowering therapy [67]. SGLT-2is may also increase glucagon secretion, which may contribute to vasodilation, fasting-state natriuresis, protein-induced hyperfiltration, and nitrogen end-product excretion [2, 68].

### Ongoing Studies of Renal Effects

Two multicenter, randomized, double-blind, placebo-controlled outcomes trials are currently investigating the effects of dapagliflozin and empagliflozin on renal outcomes and CV mortality in patients with CKD (with or without T2D; Table 3). Two studies are investigating CV and renal outcomes with sotagliflozin in patients with T2D and worsening HF and in patients with T2D, moderate renal impairment, and CV risk. The results of these studies may help to establish SGLT-2is as effective therapy in patients with CKD (with or without T2D).

## BODY WEIGHT EFFECTS OF SGLT-2 INHIBITORS

In CVOTs of SGLT-2is, empagliflozin, canagliflozin, and dapagliflozin were associated with small reductions in body weight from baseline compared with placebo (Table 1) [15, 17, 18]. A meta-analysis of 43 randomized clinical trials with durations of 4–208 weeks also indicated that SGLT-2i therapy was associated with reductions in body weight, with a weighted mean (95% CI) difference of − 1.88 (− 2.11 to − 1.66) kg versus comparators across studies [22]. Given the favorable effects of SGLT-2is on body weight, they may be particularly beneficial in patients with T2D who are overweight or obese, especially when used in combination with other medications that increase satiety [69].

The reductions in body weight with SGLT-2is are believed to result from an increase in urinary glucose excretion [12]. SGLT-2is are associated with daily glucose losses of ~ 60–80 g or 240–320 calories [12], yet body weight reductions observed after 12–24 weeks of SGLT-2i therapy are typically in the 2- to 3-kg range [70–72]. Discrepancies between expected and observed weight loss may be accounted for by an increase in energy intake or compensatory mechanisms [73]. Although fluid loss may initially play a role in weight loss, overall reductions in body weight are believed to be mainly the result of fat loss [74–76].

## BLOOD PRESSURE EFFECTS OF SGLT-2 INHIBITORS

In CVOTs, SGLT-2is were associated with reductions in systolic and diastolic BP compared with placebo (Table 1) [15, 17, 18]. In a meta-analysis of 43 randomized clinical trials (4–208 weeks in duration), SGLT-2is were associated with reductions in systolic BP of − 2.46 mmHg (95% CI, − 2.86 to − 2.06 mmHg) and diastolic BP of − 1.46 mmHg (95% CI, − 1.82 to − 1.09 mmHg) versus comparators across studies [22].

Reductions in systolic BP and cardiac load may be caused by the diuretic effects of SGLT-2is through increased urinary excretion of glucose and sodium [55]. Increased natriuresis with SGLT-2is also leads to sustained reductions in intravascular volume, which likely contribute to the antihypertensive effects of SGLT-2is [77].

## OTHER EFFECTS OF SGLT-2 INHIBITORS, INCLUDING INSULIN SENSITIVITY, HDL CHOLESTEROL, HEPATIC FAT, HYPERURICEMIA, AND CARDIAC REMODELING

Reductions in glucotoxicity with SGLT-2is have been shown to result in improved insulin sensitivity and enhanced beta-cell function [54, 78, 79]. In patients with T2D, induction of glucosuria with dapagliflozin for 2 weeks significantly increased insulin-mediated glucose storage in skeletal muscle [78, 79] and significantly improved beta-cell function compared with placebo [78]. Similarly, empagliflozin was associated with improvements in insulin sensitivity and beta-cell function after a single dose, despite a decrease in insulin secretion and tissue glucose disposal, and an increase in endogenous glucose production [54].

SGLT-2is have been associated with improvements in HDL cholesterol in randomized trials [15, 17, 22, 80]. In CANVAS, canagliflozin was associated with higher levels of HDL cholesterol compared with placebo, and although LDL cholesterol also increased, the LDL-to-HDL cholesterol ratio remained unchanged (Table 1) [17]. Similarly, in EMPA-REG OUTCOME, empagliflozin was associated with small increases in both HDL cholesterol and LDL cholesterol compared with placebo [15]. In a 12-week randomized study of Japanese patients with T2D, there was a significant reduction in small, dense LDL cholesterol from baseline (− 19.9%; $P = 0.005$) and a significant increase in HDL cholesterol (+ 10.5%; $P < 0.001$) with dapagliflozin [80]. A meta-analysis of randomized trials (4–208 weeks in duration) indicated that HDL cholesterol was increased by 0.10 mmol/l (95% CI, 0.08–0.12 mmol/l) (3.89 mg/dl [95% CI 3.23–4.56 mg/dl]) with SGLT-2is versus comparators across studies [22].

SGLT-2is also have the potential to specifically reduce the accumulation of hepatic fat, particularly in patients with T2D and nonalcoholic fatty liver disease [81, 82]. Significantly greater reductions in hepatic fat were observed with empagliflozin plus standard glucose-lowering therapy than with standard therapy alone after 20 weeks (mean difference, − 4.0%; $P < 0.0001$) in patients with T2D and nonalcoholic fatty liver disease [81], and dapagliflozin resulted in a significant, placebo-corrected reduction in hepatic fat after 8 weeks (− 3.7%; $P < 0.01$) in obese patients with T2D [82].

Given that hyperuricemia is a contributing factor in the development of hypertension, CVD, and CKD, reduction in uric acid is another potential mechanism of CV and renal benefits with SGLT-2is [83]. Small reductions in uric acid were observed with empagliflozin in EMPA-REG OUTCOME [15]. A meta-analysis of 12 randomized clinical trials of 4–78 weeks' duration also indicated that empagliflozin significantly reduced serum uric acid levels, with differences from placebo of − 36.6 μmol/l with empagliflozin 10 mg and − 43.6 μmol/l with empagliflozin 25 mg (both $P < 0.001$) [83]. Reductions in serum uric acid have also been observed with dapagliflozin and canagliflozin [84–86].

Because SGLT-2i use is associated with improvements in glycemic control, insulin resistance, body weight, and BP, it is believed that these agents may also promote regression of left ventricular hypertrophy [87–89] and cardiac and arterial remodeling [48, 90]. Animal studies have indicated that SGLT-2is mitigate cardiac fibrosis and coronary artery remodeling [57, 91] and preserve cardiac function [92]. Furthermore, post hoc analyses of randomized clinical trials have shown favorable effects of empagliflozin on arterial stiffness, vascular resistance, and markers of cardiac load [46, 47]. In a preliminary analysis of data from the EMPA-HEART Cardiolink 6 trial, empagliflozin was associated with significantly greater reductions in left ventricular mass compared with placebo among patients with T2D and coronary artery disease [93].

## SAFETY CONSIDERATIONS FOR SGLT-2 INHIBITORS

SGLT-2is are generally well tolerated and have demonstrated a low risk of hypoglycemia in CVOTs [15, 17, 18]. An increased risk of some adverse events (AEs), such as genitourinary

infections, has been reported with SGLT-2is versus other glucose-lowering treatments or placebo [62, 94]. However, conflicting findings have been reported for urinary tract infections, with similar risks found among patients initiating SGLT-2is compared with those initiating DPP-4is or glucagon-like peptide-1 receptor agonists in a large cohort of patients seen in routine clinical practice [95]. In rare cases, some serious AEs, including diabetic ketoacidosis (DKA), acute kidney injury (AKI), lower extremity amputations, fractures, bladder cancer, and Fournier gangrene, have also been reported.

Cases of euglycemic DKA have been reported with SGLT-2i use, and awareness that DKA can occur in the absence of significant hyperglycemia is critical for recognition of this potentially serious AE [96]. All three CVOTs reported a low incidence of DKA [15, 17, 18]. However, a meta-analysis of the CVOTs found an increased risk of DKA with SGLT-2is versus placebo (hazard ratio [HR], 2.20 [95% CI, 1.25–3.87]; $P = 0.0060$), although the rate of DKA events in each CVOT was low (< 1 event per 1000 patient-years) [30]. Clinicians and patients should be aware that DKA is a possible complication of SGLT-2i therapy and should be able to recognize the symptoms of DKA, including nausea, vomiting, dyspnea, or malaise [96].

While postmarketing reports of AKI with SGLT-2is prompted the inclusion of a warning for AKI in the USA prescribing information for each drug [97–100], CVOTs of empagliflozin, canagliflozin, and dapagliflozin demonstrated no increase in the incidence of AKI versus placebo [15, 17, 18, 59]. In addition, a real-world study of patients with T2D showed SGLT-2is were associated with lower rates of hospitalization with AKI compared with DPP-4is [101]. Clinicians should consider factors that may predispose patients to AKI, including chronic renal insufficiency, hypovolemia, congestive HF, or concomitant medications (e.g., diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs) and discontinue SGLT-2i treatment in patients who develop AKI [97–100].

The risk of lower extremity amputation may differ among the SGLT-2 class. An increased risk of lower extremity amputation was observed with canagliflozin versus placebo (6.3 vs. 3.4 events per 1000 patient-years; HR, 1.97 [95% CI, 1.41–2.75]) in CANVAS [17]. However, in the CREDENCE trial, the risk of amputation with canagliflozin versus placebo was not significantly higher (12.3 vs. 11.2 events per 1000 patient-years; HR, 1.11 [95% CI, 0.79–1.56]) [63]. Furthermore, a real-world meta-analysis of four observational databases (OBSERVE-4D) found no increased risk of below-knee lower extremity amputation with canagliflozin versus non-SGLT-2i glucose-lowering medications (HR, 1.01 [95% CI, 0.93–1.10]) [102]. In contrast to CANVAS, empagliflozin and dapagliflozin showed no increase in the incidence of amputations in EMPA-REG OUTCOME or DECLARE–TIMI 58, respectively [18, 103]. A meta-analysis of the three CVOTs reported significant heterogeneity ($I^2 = 79.1\%$) for amputations; only CANVAS showed an increased risk for amputation with canagliflozin [30]. Across seven ertugliflozin phase 3 clinical trials, nontraumatic lower extremity amputations were observed among patients treated with ertugliflozin 5 mg ($n = 3$; 0.2% of patients), ertugliflozin 15 mg ($n = 8$; 0.5% of patients), and comparator ($n = 1$; 0.1% of patients) [100].

The risk of fractures also appears to vary among the SGLT-2i class. Canagliflozin was associated with an increased risk of fractures compared with placebo in CANVAS (15.4 vs. 11.9 events per 1000 patient-years; HR, 1.26 [95% CI, 1.04–1.52]) [17]. However, in the CREDENCE trial, no increased risk of fracture was observed with canagliflozin versus placebo (11.8 vs. 12.1 events per 1000 patient-years; HR, 0.98 [95% CI, 0.70–1.37]) [63]. Empagliflozin and dapagliflozin showed no increase in the risk of fractures in EMPA-REG OUTCOME or DECLARE–TIMI 58, respectively [15, 18]. Furthermore, dapagliflozin demonstrated no increase in the risk of treatment-emergent fractures in a population-based cohort study [104]. In a meta-analysis of the three CVOTs, significant heterogeneity ($I^2 = 78.2\%$) was found for fractures, with an increased risk of fracture observed only in CANVAS [30].

Postmarketing reports of Fournier gangrene associated with SGLT-2i use led to the inclusion of a warning for Fournier gangrene in the US prescribing information for each SGLT-2i [105]. Although cases of Fournier gangrene are rare, an analysis of the US Food and Drug Administration Adverse Event Reporting System and published case studies reported 55 cases of Fournier gangrene among patients treated with SGLT-2is in the 6 years since their approval compared with 19 cases associated with other glucose-lowering therapies over 35 years [106]. In DECLARE-TIMI 58, six cases of Fournier gangrene were reported, one with dapagliflozin treatment and five with placebo [18]. EMPA-REG OUTCOME and CANVAS did not report any cases of Fournier gangrene [15, 17]. Due to the substantial morbidity and mortality associated with Fournier gangrene, clinicians should be alert to recognizing the early signs and symptoms, including systemic symptoms (fatigue, fever, and malaise), local symptoms (tenderness, erythema, and swelling), and pain that seems disproportionate to findings on physical examination [106].

An imbalance in bladder cancers was observed in an analysis of the phase 2b/3 dapagliflozin trials, with a higher incidence of bladder cancer reported in patients receiving dapagliflozin versus those treated with a comparator (9 of 5936 patients vs. 1 of 3403 patients; incidence rate ratio, 5.17 [95% CI, 0.68–233.55]) [107]. Conversely, among $>17{,}000$ patients included in DECLARE-TIMI 58 over 4 years, a lower incidence of bladder cancer was observed with dapagliflozin versus placebo [18]. Likewise, no imbalance in bladder cancer rates was observed with empagliflozin or canagliflozin versus placebo in EMPA-REG OUTCOME or CANVAS, respectively [17, 108].

## CONCLUSIONS

As demonstrated in large randomized clinical trials and real-world observational studies, SGLT-2is have multiple nonglycemic effects in patients with T2D, including improvements in CV and renal outcomes and reductions in BP and body weight. These pleiotropic effects are beneficial for the prevention or reduction of macro- and microvascular complications and may be of particular benefit in patients with or at risk for complications of diabetes, such as CVD, HF, or CKD. Ongoing outcomes trials in specific patient populations may help to confirm the benefits of SGLT-2is for the prevention of CVD, HF, and CKD in patients with or without T2D and provide further insights into the potential mechanisms for these pleiotropic effects.

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