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DIABETES AND CARDIOVASCULAR DISEASE (N WONG, SECTION EDITOR)

Mechanisms and Evidence for Heart Failure Benefits from SGLT2 Inhibitors

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Abstract

Purpose of Review To review the clinical trial data and underlying mechanistic principles in support of the robust cardiovascular (CV) benefits, in particular, heart failure (HF) outcomes association with sodium-glucose co-transporter-2 (SGLT2) inhibitors.

Recent Findings Several large CV outcome trials in patients with type 2 diabetes mellitus (T2DM) and with either established atherosclerotic CV disease (ASCVD) or at high risk for ASCVD reveal that SGLT2 inhibitors cause reductions in CV and HF endpoints. The reduction in ASCVD appears to be confined to those with established ASCVD on the order of ≈ 14%, as does the mortality benefit—all-cause and CV-related. However, hospitalization for HF are reduced by ≈ 33% and occur regardless of baseline patient characteristics. The unprecedented HF outcomes are theorized to occur via several possible mechanisms and include optimization of conventional ASCVD risk factors, improvement in hemodynamics, prevention of cardiac and renal remodeling, inhibition of hormone dysregulation, use of more efficient metabolic substrates, ion channel inhibition, anti-inflammatory effects, and anti-oxidant effects.

Summary Recent evidence has unveiled the irrefutable data that SGLT2 inhibitors reduce CV events in patients with T2DM, with a profound effect on reductions in hospitalization for HF. Though several mechanisms conveying this benefit are suggested, most are based in limited data requiring further validation. Nonetheless, the arrival of SGLT2 inhibitors has ushered in a new era of CV risk reductions therapies.

Keywords Cardiovascular disease · Heart failure · Pharmacotherapy · Clinical trials

Introduction

Cardiovascular (CV) death is the leading cause of death among patients with diabetes. Although the atherothrombotic a.k.a. macrovascular complications of diabetes are well appreciated, heart failure (HF) is one of the most common and serious complications experienced by ≈ 20–40% of patients with diabetes, leading to frequent hospitalizations and decreased quality of life. Therefore, there exists a need to focus on the development and appraisal of therapies lowering CV risk in patients with diabetes, with a special emphasis on HF pathophysiology [1].

Recent multi-societal guidelines recommend the preferred use of sodium-glucose co-transporter-2 (SGLT2) inhibitors, a.k.a. gliflozins, in patients with type 2 diabetes mellitus (T2DM) who are at increased atherosclerotic cardiovascular disease (ASCVD) risk, in particular when they have HF and proteinuria [2–5]. This recommendation is based on the results of several cardiovascular outcome trials (CVOT), which demonstrated CV benefits in particular affecting outcomes related to HF [6•, 7•, 8•, 9].

While gliflozins are a new class of medications, they have been derived from the glycoside phlorizin isolated in 1835 from apple tree bark [10]. Phlorizin has been subsequently described to cause glucosuria and polyuria [11] and was used in early animal experiments to recreate wasting and weight loss observed in untreated diabetes [12].

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SGLT2 inhibitors currently approved by the Food and Drug Administration (FDA) include empagliflozin (Jardiance®), canagliflozin (Invokana®), dapagliflozin (Farxiga®), and ertugliflozin (Steglatro™)—see Table 1 for a comparison among the various agents. Three more gliflozins approved for clinical use outside of the USA include ipragliflozin (Suglat®), luseogliflozin (Lusefi®), and tofogliflozin (Apleway®, Deberza®). Sotagliflozin (Zynquista™) is a dual SGLT2/SGLT1 inhibitor currently in clinical trials.

While empagliflozin seems to have the strongest evidence, it is believed that reported benefits are a class effect and therefore observed differences in outcomes depend on clinical trial design and subsequent patient population studied. A recent meta-analysis of the three CVOT which included almost 35,000 patients (60.2% with established ASCVD) did show that SGLT2 inhibitors reduced major adverse cardiovascular events (MACE) by 11% (95% confidence interval [CI], 0.83–0.96, $p = 0.0014$), with statistically significant benefit seen only in patients with ASCVD (14% relative risk reduction [RRR], 95% CI, 0.80–0.93, $p < 0.001$). Moreover, SGLT2 inhibitors reduced the risk of CV death or HF hospitalization by 23% (95% CI, 0.71–0.84, $p < 0{\cdot}0001$) regardless of pre-existing ASCVD or HF. The risk of progression of renal disease has also been reduced by 45% (95% CI, 0.48–0.64, $p < 0.0001$) regardless of the ASCVD status [13].

The results of this meta-analysis contrast with data from a large observational study CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors), which demonstrated benefit in reduction of CV events also in patients without pre-existing ASCVD. This study included over 300,000 of patients, with only 13% of them having pre-existing ASCVD. Initiation of an SGLT2 inhibitor was associated with 44% lower risk of death in patients with and without ASCVD (95% CI, 0.44–0.70, $p < 0.001$ and 0.50–0.63, $p < 0.001$ respectively) as well as 28% (95% CI, 0.63–0.82, $p < 0.001$) lower risk of HF for patients with ASCVD and 39% (95% CI, 0.48–0.78, $p < 0.001$) lower risk of HF for patients without ASCVD [14].

This review will analyze the available CVOT evidence, followed by a thorough evaluation of potential mechanisms mediating the beneficial effects of SGLT2 inhibitors and their effect on HF development and progression (Fig. 1).

Table 1 Comparison of available SGLT2 inhibitors and their effect on heart failure

Approved	Empagliflozin (Jardiance®) 2014	Canagliflozin (Invokana®) 2013	Dapagliflozin (Farxiga®) 2014	Ertugliflozin (Steglatro™) 2017
Dosing (oral, daily)	10 mg Max 25 mg	100 mg Max 300 mg	5 mg Max 10 mg	5 mg Max 15 mg
Renal dose adjustment	eGFR < 45 ml/min: NR eGFR < 30 ml/min: CI	eGFR < 45 ml/min: NR eGFR < 30 ml/min: CI	eGFR < 60 ml/min: NR eGFR < 30 ml/min: CI	eGFR < 60 ml/min: NR eGFR < 30 ml/min: CI
SGLT2: SGLT1 selectivity	2500-fold	250-fold	1200-fold	2000-fold
Half-life (hrs)	10–11	10–13	5–12	17
CYP metabolism	None	Minor via CYP3A4	Minor via various CYPs	Minimal via CYP3A4
Excretion	54% urine 41% feces	50% feces 33% urine	75% urine 21% feces	41% urine 50% feces
CV indication	Yes	Yes	No	No
CV outcomes trial	EMPA-REG	CANVAS, CREDENCE	DECLARE-TIMI 58	VERTIS-CV
% patients with established ASCVD	100%	66% (CANVAS) 50% (CREDENCE)	40%	100%
History of HF (%)	10.1	14.4 (CANVAS)	10	N/A
Composite CV outcome[a]	14% reduction	14% reduction (CANVAS) 20% reduction (CREDENCE)	No effect	N/A
CV death	38% reduction	No effect (CANVAS, CREDENCE)	No effect	N/A
HF hospitalization	35% reduction	33% reduction (CANVAS) 39% reduction (CREDENCE)	27% reduction	N/A
All-cause death	32% reduction	No effect (CANVAS, CREDENCE)	No effect	N/A
Composite renal outcome[b]	N/A	30% reduction	24% reduction	N/A

CI contraindicated; *CV* cardiovascular; *CYP* cytochrome P450; *eGFR* estimated glomerular filtration rate; hrs = hours; *Max* maximum; *N/A* not available; *NR* Not recommended; *SGLT* sodium-glucose transporter;

[a] Composite CV outcome = MI, stroke, and CV death

[b] Composite renal outcome = end-stage kidney disease, doubling of serum creatinine level, or death from renal or CV causes

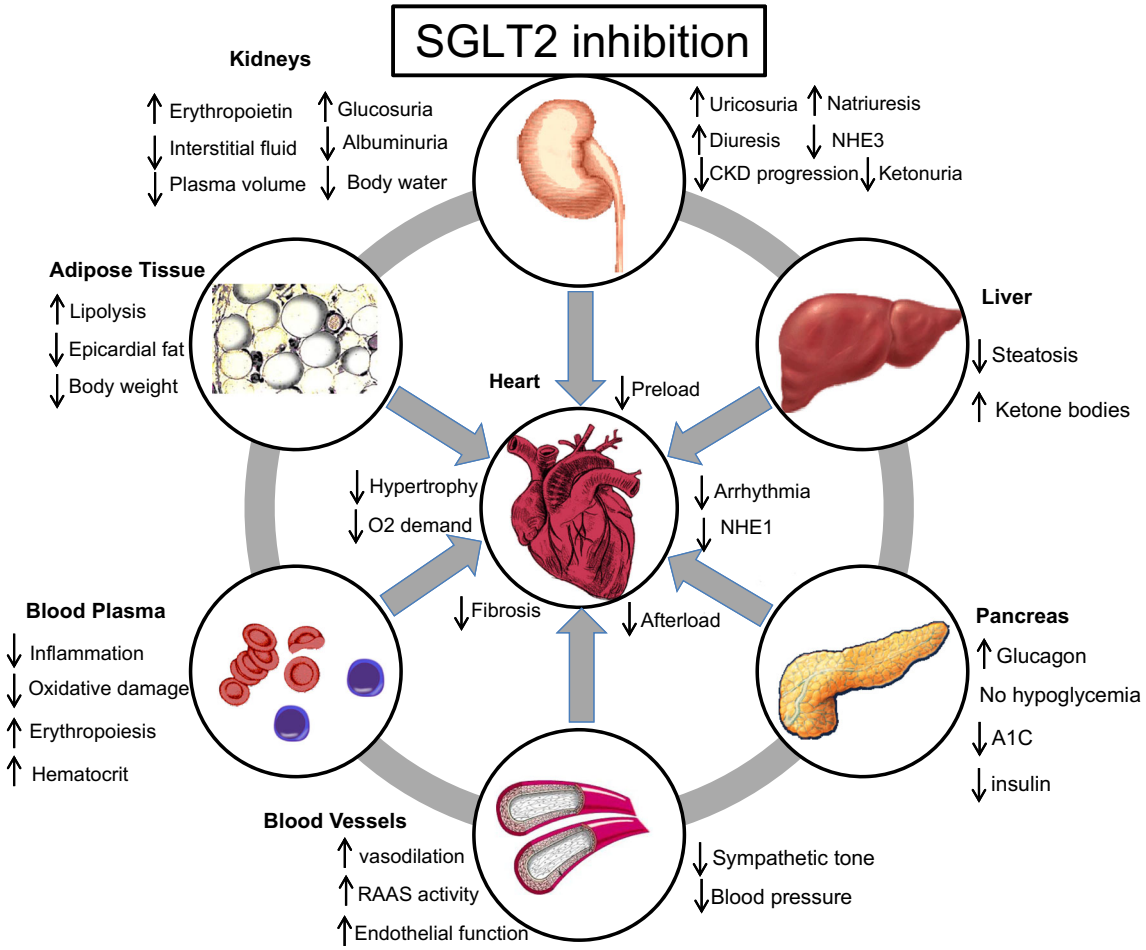

Fig. 1 A schematic representation of the different mechanisms implicated in the cardiovascular benefits of SGLT2 inhibitors

Clinical Trial Evidence

In older trials using agents such as sulfonylureas and insulin, intensive diabetic control (glycosylated hemoglobin [HbA1C] < 7%) versus more relaxed control (HbA1C < 9%) was associated with increased mortality and adverse events related to hypoglycemia without improvement of CV events [15]. A signal of CV harm has been associated with the use of sulfonylureas either alone or in addition to metformin [16, 17]. Furthermore, other antidiabetic therapies have shown negative outcomes in patients with established cardiovascular disease (CVD), especially those with HF. Both thiazolidinediones (TZDs) and dipeptidyl peptidase 4 (DPP4) inhibitors have been associated with an increased risk of HF in T2DM [18, 19]. In 2008, these concerns prompted the FDA to issue a guidance for the development of any new antidiabetic therapies that focused specifically on CV safety [20]. This requirement led to the unexpected discovery of CV benefits of SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA's). It therefore appears that not all diabetic medications are created equal: it matters more how a reduction in HbA1C is achieved rather than the levels of HbA1C itself. However, many patients are still treated with older diabetic medications. The time has come to implement a paradigm shift, switching from use of antiquated therapies towards novel agents with improved CV safety and efficacy [21].

Empagliflozin has been evaluated in the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose), where 7020 patients with T2DM and known ASCVD were followed for a median of 3.1 years. In this high-risk, secondary prevention population, empagliflozin lowered the primary composite outcome of myocardial infarction (MI), stroke, and CV death by 14% (95% CI, 0.74–0.99; $p < 0.001$), CV death by 38% (95% CI, 0.49–0.77; $p < 0.001$), death from any cause by 32% (95% CI, 0.57–0.82, $p < 0.001$), and reduced HF hospitalizations by 35% (95% CI, 0.50 – 0.85; $p = 0.002$) [6•]. The unexpected but highly significant results prompted the development of several additional trials to evaluate the effect of empagliflozin on outcomes in patients with HF with both reduced and preserved ejection fraction (Table 2).

Canagliflozin was originally evaluated in the CANVAS program (Canagliflozin Cardiovascular Assessment Study)

Table 2 Ongoing outcome clinical trials of SGLT2 inhibitors in patients with heart failure

Trial name[a]	NCT number	Primary outcome	Sample size	Duration	Estimated completion date
Empagliflozin					
EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction)	NCT03057977	Composite of CV death or HHF	2850	3.2 years	6/2020
EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction)	NCT03057951	Composite of CV death or HHF	5250	3.2 years	10/2020
ELSI (Analysing the Effect of Empagliflozin on Reduction of Tissue Sodium Content in Patients With Chronic Heart Failure)	NCT03128528	Skin sodium content	84	14 weeks	12/2019
Empire HF (Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction)	NCT03198585	NT-proBNP	189	90 days	10/2019
EMPA-RESPONSE (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure)	NCT03200860	Dyspnea, diuretic resistance, length of stay, NT-proBNP	80	4 days	2/2020
EMPA-VISION (Mechanistic Cardiac Magnetic Resonance Study to Investigate the Effects of Empagliflozin Treatment on Cardiac Physiology and Metabolism in Patients With Heart Failure)	NCT03332212	PCr/ATP ratio	86	12 weeks	10/2019
EMPERIAL-reduced (Effect of 12 Weeks Treatment of Once Daily EMPagliflozin 10 mg Compared With Placebo on ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Reduced Ejection Fraction)	NCT03448419	Distance on 6 min walk test	300	12 weeks	12/2019
EMPERIAL-preserved (Effect of 12 Weeks Treatment of Once Daily EMPagliflozin 10 mg Compared With Placebo on ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Preserved Ejection Fraction)	NCT03448406	6MWD	300	12 weeks	12/2019
EMPA-TROPISM (Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity?)	NCT03485222	LV end systolic volume	80	6 months	12/2020
EmDia (Effects of Empagliflozin on Left Ventricular Diastolic Function Compared to Usual Care in Type 2 Diabetics)	NCT02932436	E/E′ ratio	158	12 weeks	6/2019
EMBRACE-HF (Empagliflozin Impact on Hemodynamics in Patients With Diabetes and Heart Failure)	NCT03030222	Pulmonary artery diastolic pressure	60	12 weeks	9/2019
ERA-HF[b] (Empagliflozin Versus Placebo on the Rate of Arrhythmic Events in Heart Failure Patients)	NCT03271879	Premature ventricular complex burden	128	8 weeks	6/2020
EMPA[b] (Empagliflozin in Heart Failure: Diuretic and Cardio-Renal Effects)	NCT03027960	Urine sodium output	50	36 days	6/2022
EMPA Acute Heart Failure (Effect of Empagliflozin on Cardiac Output in Patients with Acute Heart Failure)	NCT03554200	Cardiac output	56	30 days	5/2020
SUGAR (Studies of Empagliflozin and Its Cardiovascular, Renal, and Metabolic Effects in Patients with Diabetes Mellitus and Heart Failure)	NCT03485092	LVESVI, LV global strain	130	40 weeks	2/2020
(Effects of Empagliflozin on Exercise Capacity and Left Ventricular Diastolic Function in Patients With Heart Failure With Preserved Ejection Fraction and Type-2 Diabetes Mellitus)[c]	NCT03753087	6MWD	100	24 weeks	5/2020
RECEDE-CHF (SGLT2 Inhibition in Combination With Diuretics in Heart Failure)	NCT03226457	Urine output	34	6 weeks	12/2019
(SGLT2 inhibition in diabetes and heart failure)[d]	NCT02862067	Peak VO2, VE/VOC2	18	4 weeks	Completed, awaiting results
(Treatment of diabetes in patients with systolic heart failure)	NCT02920918	Aerobic exercise capacity, ventilator efficiency	36	12 weeks	Completed, awaiting results
Dapagliflozin					

Table 2 (continued)

Trial name[a]	NCT number	Primary outcome	Sample size	Duration	Estimated completion date
DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure With Reduced Ejection Fraction)	NCT03036124	Composite of CV death, HHF, or urgent HF visit	4744	3 years	7/2019
DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure)	NCT03619213	Composite of CV death, HHF, or urgent HF visit	4700	2.8 years	6/2021
DETERMINE-reduced (Dapagliflozin Effect on Exercise Capacity Using a 6-min Walk Test in Patients With Heart Failure With Reduced Ejection Fraction)	NCT03877237	6MWD	300	16 weeks	1/2020
DETERMINE-preserved (Dapagliflozin Effect on Exercise Capacity Using a 6-min Walk Test in Patients With Heart Failure With Preserved Ejection Fraction)	NCT03877224	6MWD	400	16 weeks	2/2020
(Effect of Dapagliflozin Plus Low Dose Pioglitazone on Hospitalization Rate in Patients With HF and HFpEF)	NCT03794518	HHF	648	3 years	9/2021
PRESERVED-HF (Effects of Dapagliflozin on Biomarkers, Symptoms, and Functional Status in Patients with PRESERVED Ejection Fraction Heart Failure)	NCT03030235	NT-proBNP	320	12 weeks	9/2019
DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients with Heart Failure	NCT02653482	NT-proBNP	263	12 weeks	6/2019
DAPA-LVH (Does Dapagliflozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes?)	NCT02956811	LV mass	64	52 weeks	3/2019
REFORM (Safety and Effectiveness of SGLT-2 Inhibitors in Patients With Heart Failure and Diabetes)	NCT02397421	LV end systolic, and diastolic volumes	56	1 year	Completed, awaiting results
Ertugliflozin					
ERADICATE-HF (ERtugliflozin triAl in DIabetes With Preserved or Reduced ejeCtion FrAcTion mEchanistic Evaluation in Heart Failure)	NCT03416270	FENa	36	12 weeks	3/2021
ERTU-GLS (Effect of Ertugliflozin on Cardiac Function in Diabetes)	NCT03717194	LV global strain	120	24 weeks	10/2020
Sotagliflozin					
SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure)	NCT03521934	Composite of CV death or HHF	4000	2.7 years	1/2021
(Safety, tolerability and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure)	NCT03292653	AEs, plasma volume, hemoconcentration	81	14 days	11/2020

6MWD 6-min walk distance, *AEs* adverse events, *ATP* adenosine triphosphate, *CV* cardiovascular, *E/E' ratio* ratio between early mitral inflow velocity and mitral annular early diastolic velocity, *FENA* proximal sodium reabsorption, *HHF* hospitalization for heart failure, *LV* left ventricle, *LVESVI* left ventricular end systolic volume index, *NCT* national clinical trial, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *PCr* phosphocreatine, *VO2* carbon dioxide production, *VE* minute ventilation, *VO2* peak oxygen consumption

[a] Randomized, double-blinded, placebo-controlled trials unless otherwise indicated

[b] Crossover randomized trial

[c] Open label, randomized trial

[d] Prospective, observational trial

followed by a second trial called CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy and Clinical Evaluation). The CANVAS program consisted of two combined trials, which enrolled 10,142 diabetic patients with high CV risk for a median of 3.6 years. Similarly to empagliflozin, canagliflozin lowered the primary composite outcome of MI, stroke, and CV death by 14% (95% CI, 0.75–0.97; $P < 0.001$) and reduced HF hospitalizations by 33% (95% CI, 0.52–0.87, $p < 0.001$). However, despite trending towards benefit, canagliflozin did not significantly reduce overall or CV mortality, what can be attributed to trial design with only 66% of trial participants having preexisting ASCVD [7•]. A secondary CANVAS analysis has demonstrated nephroprotective effects of canagliflozin, prompting the development of CREDENCE, which has randomized 4401 patients with T2DM and proteinuric chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) between 30 and 90 mL/min/1.73m^2 to receive canagliflozin or placebo [9]. Only 50.4% of CREDENCE participants had pre-existing ASCVD. This trial was stopped early with a median follow up of 2.62 years due to observed overwhelming benefits of therapy. The primary composite outcome of end-stage kidney disease, doubling of serum creatinine level, or death from renal or CV causes was reduced by 30% (95% CI, 0.59–0.82; $P = 0.00001$). The prespecified secondary outcome of MI, stroke, and CV death was reduced by 20% (95% CI, 0.67–0.95; $P = 0.01$), while hospitalization for HF was reduced by 39% (95% CI, 0.47–0.80; $P < 0.001$). Other secondary outcomes including CV death and death from any cause were trending towards reduction but did not reach statistical significance likely from the early termination of the trial [9]. In contrast to CANVAS, in CREDENCE, there was no evidence of increased risk of amputations or fractures. The observed differences between CANVAS and CREDENCE could be attributed to different study populations, different trial designs, and possibly due to random variation [9, 22].

Dapagliflozin was evaluated in the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial which enrolled 17,160 T2DM patients either with established ASCVD (40.5%) or at high risk of ASCVD for a median of 4.2 years. In contrast to both empagliflozin and canagliflozin, dapagliflozin did not result in a lower rate of the primary composite outcome of MI, stroke, and CV death compared to placebo, nor lower rates of CV death or overall mortality [8•]. However, dapagliflozin did reduce the co-primary endpoint consisting of the composite CV death or hospitalizations for HF by 17% (95% CI, 0.73–0.95; $P = 0.005$). Dapagliflozin also decreased hospitalization for HF by 27% (95% CI, 0.61–0.88, $p < 0.001$) and renal outcomes by 24% (95% CI, 0.67–0.87, $p < 0.001$). The failure to hit the primary endpoint can be attributed to a relatively low proportion of patients with pre-existing ASCVD (40.4% in DECLARE-TIMI 58 vs 66% in CANVAS vs 100% in EMPA-REG-OUTCOME) as well as a more restrictive exclusion of patients according to creatinine clearance in DECLARE-TIMI 58 (patients with a creatinine clearance < 60 ml per minute were excluded). In other SGLT2 trials, patients with CKD appeared to have greater benefits from therapy than those with normal eGFR; therefore, excluding these patients may have limited a mortality benefit.

Ertugliflozin will be evaluated in the VERTIS-CV trial (eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes trial), which enrolled 8246 participants ≥ 40 years old with T2DM (HbA1c 7.0–10.5%) all of whom had established ASCVD. The results are expected to be available by September 2019 [23]. Finally, the SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk trial) will investigate the effect of sotagliflozin and is expected to enroll 10,500 participants with results expected by March 2022 [24]. Many other clinical trials exploring benefits of SGLT2 inhibitors in different patient groups are under way, as listed in Table 2.

The CVD-REAL study compared the rates of HF hospitalization and total mortality among new users of SGLT2 inhibitors versus other glucose-lowering drugs based on data from over 300,000 patients obtained from medical claims, primary care records, hospital records, and national registries from several countries [14]. Fifty-three percent of patients used canagliflozin, 42% used dapagliflozin, while only 5% empagliflozin. There was an overall 39% lower risk of HF hospitalization (95% CI, 0.51–0.73; $P < 0.001$), 51% reduction in total death (95% CI, 0.41–0.57; $P < 0.001$), and 46% reduction in the composite of HF hospitalization or death (95% CI, 0.48–0.60; $P < 0.001$). In contrast to previously discussed CVOT of SGLT2 inhibitors, the majority of patients (87%) in CVD-REAL did not have prior ASCVD. As discussed before, reduction of CV events was also demonstrated in patients without pre-existing ASCVD. The CVD-REAL results suggest a possible class effect, at least in terms of HF hospitalization and total mortality.

Beneficial effects of empagliflozin on prevention of HF-related hospitalization were also reported in the EMPIRSE (EMPagliflozin compaRative effectIveness and SafEty) study, which analyzed empagliflozin's effectiveness, safety, and healthcare utilization in routine care from August 2014 through September 2019 in 16,443 propensity matched patients identified from US insurance claims data (commercial and Medicare sources) [25]. Compared to sitagliptin, the initiation of empagliflozin decreased the risk of HF hospitalization by 50% (95% CI, 0.28–0.91, $p < 0.001$) over a mean follow-up of 5.3 months regardless of pre-existing ASCVD or empagliflozin dose.

A recent study compared the real-world effectiveness of SGLT2 inhibitors versus GLP-1 RA, another class of diabetic drugs with proven CV benefits. Compared to GLP-1 RA, the hazard ratio (HR) for the composite CV outcome (MI, stroke, mortality, and hospitalization for HF) was 1.10 (95% CI 0.95–1.26) for patients with ASCVD, and 1.23 (95% CI, 1.08–1.41) for patients without ASCVD. However, in the SGLT2 inhibitor group, there were significant reductions in HF hospitalizations when compared with GLP-1 RA, 33% (95% CI, 0.55–0.81) and 31% (95% CI, 0.51–0.92) for patients with and without ASCVD. Those benefits were offset by increased incidence of MI and stroke, especially in patients without preexisting ASCVD [26]. Those results reflect the effectiveness of GLP-1 RA on prevention of ischemic events in contrast to SGLT2 inhibitors, whose CV benefit is mediated principally through HF outcomes.

Mechanism of Action—Glucose Reduction

SGLT2 (encoded by *SGLT2*, also known as *SLC5A2*) is a sodium-glucose co-transporter located on the apical membrane of the renal proximal convoluted tubules (PCT). It accounts for more than 90% of glucose reabsorption in the kidney, the rest being mediated by SGLT1 (encoded by *SGLT1*, also known as *SLC5A1*) in the descending arm of the loop of Henle. The glucose concentration gradient between cytoplasm and plasma drives the passive transport of glucose through the basolateral membrane, towards the plasma, mediated by the glucose transporter 2 (GLUT2) [27].

In the absence of diabetes, glucosuria appears when blood glucose levels exceed 180 mg/dL. However, in those with diabetes, SLGT2 is paradoxically upregulated, leading to increased glucose reabsorption in the PCT and therefore shifting the threshold of glycosuria up to ≈ 220 mg/dL. SGLT2 activity requires energy provided by the sodium gradient created by the Na^+/K^+ ATPase located in the basolateral surface of PCT epithelial cells, in contrast to the passive transport of glucose from cytoplasm towards plasma via GLUT2 [28, 29].

The rationale for the development of SGLT2 inhibitors was provided by the benign phenotype of patients with SGLT2 loss-of-function mutations, a condition known as familial renal glucosuria [29]. Inhibition of SGLT2 causes glucosuria with glucose levels much lower than ≈ 220 mg/dL as long as they are above 40–80 mg/dL (depending on the SGLT2 inhibitor studied). As blood glucose levels drop, glucosuria caused by SGLT2 inhibitors decreases, preventing the occurrence of hypoglycemia. The degree of glycosuria is proportional to the starting levels of blood glucose. SGLT2 inhibitors display a modest efficacy in lowering plasma glucose levels, reducing HbA1C by ≈ 0.5–1%. Urinary glucose excretion requires at least moderately preserved renal function, thus SGLT2 inhibitors are contraindicated at eGFR < 30 ml/min/1.73m^2 [29, 30].

Mechanism of Action—Cardiovascular Protection

The revelation that inhibition of SGLT2 transporters translated into reductions in CV and renal events took the scientific community by surprise. The findings were borne out of chance discovery that stems back to the 2008 FDA mandate requiring all new antidiabetic medications to test for CV safety [20]. The intent was to prove the safety but instead, an entire medication class was unveiled with the capacity to reduce CV events, renal outcomes, and mortality across a wide spectrum of patient risk. The detection of CV benefit attributed to SGLT2 inhibitors was a monumental discovery and greatly added to the armamentarium against CVD—the question remained on how did these agents impart such a benefit?

SGLT2 inhibitors have a more robust and consistent effect on the prevention of HF and renal outcomes than on ASCVD. These observations fit with the mechanism of action of SGLT2 inhibitors on the heart, vasculature, and kidney. Second, although treatment with SGLT2 inhibitors appears to result in a moderate reduction in the risk of MACE solely in patients with established ASCVD, reductions in the risk of HF and renal outcomes occur regardless of patient characteristics [13].

Several theories have been postulated to describe the protective CV mechanisms imparted by SGLT2 inhibitors. The most obvious are improvements in conventional ASCVD risk factors; however, the magnitude of CV benefit is disproportionate to the modest improvements in these risk factors [31••, 32]. This suggests there are other mechanisms at play. The pathophysiology of diabetes causal in the development of CVD is complicated, involving hemodynamic changes, cardiac and renal remodeling mechanisms, hormone dysregulation, impaired energy utilization, ion channel alterations, and inflammatory, and oxidant upregulation [33••]. The subsequent sections will investigate the influence of modulating these factors to better understand the pathophysiology underpinning the vast CV benefit witnessed with SGLT2 inhibitors.

Conventional Atherosclerotic Cardiovascular Risk Factors

Inhibition of SGLT2 establishes an improved metabolic patient profile, capable of inducing reductions in plasma glucose, blood pressure, body weight, and modifications to the lipid profile. The magnitude of improvement within these risk factors is modest: HbA1C reduced by ≈ 0.5–1%, systolic/diastolic blood pressure reduced by ≈ 4–6/1–2 mmHg (without raising heart rate), body weight reduced by ≈ 2–3 kg, and

no change/slight increase in low-density lipoprotein cholesterol (LDL-C) ≈ 1–2% (yet produce slight reductions in small dense LDL particles), slight increase in high-density lipoprotein cholesterol (HDL-C) ≈ 2%, and slight reduction in triglycerides ≈ 8–9% [31••, 32, 34–36]. Mechanisms for plasma glucose lowering are explained above. For blood pressure reduction, multiple factors are believed to be involved and include diuretic and natriuretic effects (preload), reduced arterial stiffness (afterload), improved endothelial function, and reduction in body weight [30, 37, 38]. Body weight reduction occurs via urinary glucose excretion of ≈ 60–80 g daily, translating into caloric loss of ≈ 240–320 kcal per day [39]. It has been postulated that the loss of adipose mass can be attributed to an energy loss as a compilation of increased glycosuria, lipolysis, fatty acid oxidation, ketogenesis, and glucagon exposure, as well as a reduction in insulin secretion [40]. Reduction in adiposity is of significant interest due to the interplay between obesity, diabetes, inflammation, and CVD. The mechanisms underlying lipid changes remains elusive but are hypothesized to be a combination of a shift in energy metabolism from glucose to fat oxidation, urinary excretion of calories, and a subsequent lipid mobilization as displayed by reduced subcutaneous and visceral adipose tissue [35]. Recently, an animal model demonstrated the increase in LDL-C was the result of reduced LDL-C plasma clearance and increased lipolysis of triglyceride-rich lipoproteins (TRL) such as very low-density lipoproteins (VLDL) via stimulation of lipoprotein lipase (LPL) [41]. Other lipid-lowering therapies that increase lipolysis of TRLs, such as fibrates and omega-3 fatty acids, have also been shown to increase LDL-C as a consequence of their metabolic pathway, with one agent, icosapent ethyl revealing substantial ASCVD reduction with a modest reduction in TRLs [42]. Though improvement in any one of the conventional risk factors is insufficient to explain the significant CV benefits, the cumulative effect of improvement in all seems more plausible. In opposition, the early CV benefits witnessed during the CVOTs are unlikely to be the result of changes in these parameters.

Diuresis/Natriuresis

By increasing glycosuria, and natriuresis, SGLT2 inhibitors act similarly to moderate diuretics, initially expelling on average an additional ~ 300 mL per day, returning to baseline after several weeks of therapy [31••]. The diuretic and natriuretic effects produce reductions in plasma volume, essential as sodium content is key to the prevention of fluid overload and HF exacerbation leading to hospitalization [43]. Dapagliflozin has shown to reduce skin sodium concentrations, which is important given data that correlates skin sodium to left ventricular (LV) mass and blood pressure, serving as a marker for volume expansion [44, 45]. Also, the reduction in plasma volume caused by SGLT2 inhibitors is thought to be superseded by the reduction in interstitial fluid, providing a better mechanism for reducing congestion without adversely affecting systemic perfusion [46]. Other diuretic and natriuretic influences include decreased ventricular filling pressures, myocardial stretch, and ventricular arrhythmias, the latter of which may help to explain the mortality benefit seen in the EMPA-REG OUTCOME trial [31••].

SGLT2 inhibitors display important differences compared to conventional diuretics (thiazides and loop). SGLT2 inhibitors induce their diuretic effect by reducing interstitial volume to a much greater extent than intravascular volume, whereas the opposite is true for conventional diuretics. This is of importance as HF patients are already intravascularly depleted, which is then compounded by the addition of conventional diuretics. This unique characteristic employed by SGLT2 inhibitors is thought to avoid the compensatory neurohormonal and sympathetic activation that plagues HF progression [33••]. Other salient features of this drug class include erythropoiesis (not present with conventional diuretics), uricosuria (conventional diuretics increase uric acid), and plasma electrolyte improvement (conventional diuretics cause electrolyte wasting increasing the risk for arrhythmias) [47–49].

Another potentially beneficial aspect relates to the uricosuria action induced by SGLT2 inhibition. These agents promote renal excretion of uric acid via glucose transporter 9 (GLUT9) within the PCT, reducing plasma uric acid by ≈ 10–15% [31••]. The resultant effect may also contribute to the CV protective effect as plasma uric acid levels are associated with CV complications including HF and renal disease [50–52].

Direct Myocardial Effects

Ventricular Remodeling

The hemodynamic response elicited from SGLT2 inhibitors creates a favorable environment to reduce cardiac hydrostatic pressure known to induce ventricular remodeling and hypertrophy. This was recently demonstrated in the EMPA-HEART Cardiolink-6 (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes) study which randomized 97 normotensive patients with T2DM and stable coronary artery disease but without HF, to empagliflozin 10 mg daily or placebo for 6 months and revealed a significant reduction in LV mass − 2.6 vs − 0.01 g/m^2, $p = 0.01$ [53]. There was also a 2.2% increase in LV ejection fraction noted in the empagliflozin arm. As LV mass is a strong predictor of CV events, these results lend themselves to consideration of salutary effects on LV remodeling as a contributor to the robust CV and HF benefits seen in the large CVOTs [53]. Reductions in both preload and afterload are believed to play a vital role in mitigating ventricular loading conditions through lowered cardiac workload and reduced oxygen consumption [33••, 37, 38].

In addition, cardiac fibrosis, which entails structural remodeling as a result of extracellular matrix (ECM) protein deposition by cardiac fibroblasts, culminating in ventricular noncompliance, is extensively implicated in the final steps of HF pathogenesis [33••]. Recent animal studies lend support to SGLT2 inhibitors ameliorating cardiac fibrosis by suppressing transforming growth factor β/Smad pathway, collagen synthesis, α-smooth muscle actin, connective tissue growth factor, ECM remodeling, and matrix metalloproteinase 2 [54, 55]. Another pathway leading to decreased cardiac fibrosis caused by chronic cardiac wall stress is associated with decreased sympathetic activity. SGLT2 inhibitors reduce renal afferent nervous activity and suppress associated central reflex mechanisms that contribute to generalized sympathetic activation. Chronic activation of sympathetic activity found in patients with T2DM plays an important role in the development of hypertension, HF, and other CV complications [56].

Na^+/H^+ Exchanger Inhibition

The failing myocardium upregulates Na^+/H^+ exchanger (NHE) 1 resulting in increased intracellular sodium and calcium, inducing a pro-oxidant and pro-thrombotic state [43]. The increased NHE1 activity is suggested to be an early marker of cardiomyocyte injury, HF, and ultimately CV death [57, 58]. Though SGLT2 receptors are not explicitly expressed in cardiac tissue, SGLT2 inhibitors have been shown to inhibit NHE1 on cardiomyocytes by unknown mechanisms [59]. The pathophysiology of progressive HF has also been shown to upregulate NHE3 in the renal PCT, serving to mediate sodium reuptake and potentially responsible for resistance to diuretics and endogenous natriuretic peptides [60]. SGLT2 inhibitors also block the activity of NHE3, resulting in natriuresis and providing a possible mechanistic link for the cardiorenal protection displayed by this class of medications [60].

Epicardial Fat

Epicardial fat is adipose tissue located between the myocardium and visceral layer of the pericardium that possesses several local and systemic effects [61]. In diabetes, the ensuing insulin resistance increases lipolysis and subsequent fatty acid uptake and triglyceride storage into the myocardium, increasing the risk of epicardial fat accumulation [62]. Epicardial fat has been implicated in the development of cardiac fibrosis, reduced contractility, arrhythmias, and HF. Additionally, epicardial fat accumulation is suggested as a possible prognostic marker for survival within the HF population. Recently published studies of SGLT2 inhibitors demonstrated their ability to induce a reduction in epicardial fat and thus providing another possible mechanism for the beneficial CV and HF outcomes [63–65]. This theory is being further evaluated in an ongoing clinical study (NCT02235298).

Renal Effects

There exists an intricate relationship between cardiac and renal function such that dysfunction in one organ can often lead to dysfunction of the other. Adding to the complexity, diabetes creates a deleterious environment for both cardiac and renal function homeostasis. The resultant effect is a vicious and self-perpetuating cycle of diabetes, HF, and renal insufficiency. However, SGLT2 inhibitors are well positioned to dissolve this perilous triad [30]. The renal protection induced by SGLT2 inhibitors is not completely elucidated, yet are likely multifactorial, involving electrolyte, vascular, and hydrostatic alterations. Blockade of the SGLT2 receptor in the renal PCT increases natriuresis and volume contraction. This in turn reduces atrial natriuretic peptide causing vasoconstriction of the afferent renal arterioles. Simultaneously, the increased concentration of sodium within the tubular fluid is sensed by the macula densa which activates tubuloglomerular feedback by causing adenosine-mediated vasoconstriction of the afferent arteriole and inhibits the release of renin from the juxtaglomerular cells inducing vasodilation of the efferent arterioles. The combination of vasoconstriction of the afferent and vasodilation of the efferent arterioles reduce intraglomerular hydrostatic pressure and therefore confer long-term renal protection [30]. These effects culminate in substantial renoprotective outcomes such as reduction of nephropathy, progression to albuminuria, doubling of serum creatinine, and delay of initiation of renal replacement therapy. Preservation of renal function is of particular importance for patients with HF to avoid volume overload and diuretic resistance [43].

The natriuretic properties of SGLT2 inhibitors result in volume contraction and reduced arterial pressure as noted above, which activates systemic and local renin-angiotensin-aldosterone-system (RAAS) activity. However, the SGLT2 inhibitor activity is theorized to activate the non-classic RAAS pathways, type 2 angiotensin II receptor and Mas-receptor, not the type 1 angiotensin II receptor. Activation of type 1 angiotensin II receptor contributes to the pathogenesis of CVD (i.e., vasoconstriction, sodium retention, inflammation, oxidation, etc.), whereas activation of the type 2 angiotensin II receptor is associated with cardioprotective mechanisms (i.e., vasodilation, sodium excretion, anti-inflammatory, anti-hypertrophy, anti-arrhythmic, etc.) [66]. Studies have shown increased plasma levels of renin and RAAS mediators (i.e., aldosterone, angiotensin II) and urinary levels of angiotensinogen and angiotensin-converting enzyme in response to SGLT2 inhibitor administration [67, 68]. However, these effects were noted in type 1 diabetics and the former differed based on euglycemic compared to

hyperglycemic states. Thus, there appears to be contradictory effects of SGLT2 inhibition on renin and RAAS activity with natriuretic properties promoting renin release and inhibiting RAAS, and osmotic diuresis properties inhibiting renin release and stimulating RAAS. The interplay of these opposing effects and how they ultimately contribute to renal and systemic effects remains elusive.

Hemoconcentration/Erythropoiesis

In patients with diabetes, the renal PCT epithelial cells are overtaxed by excessive glucose reabsorption which requires increased ATP production through oxidative phosphorylation. The increased oxygen requirement causes tubulointerstitial hypoxia and impairs erythropoietin production by interstitial fibroblasts [69]. SGLT2 inhibitors, by way of inducing glycosuria, reduce the workload of the renal PCT and reverse the downstream consequences, resulting in erythropoiesis and improved oxygen delivery to tissues [70].

An analysis of the EMPA-REG OUTCOME trial showed that empagliflozin-induced increases in hematocrit and hemoglobin were the most important mediators of CV mortality reduction, accounting for ≈ 50% of the benefit [71]. This increase in hematocrit of ≈ 2–4% has been attributed to volume contraction and stimulation of erythropoiesis by SGLT2 inhibitors [70]. A hemodynamic benefit would lend support to the observed early Kaplan–Meier event curve separation for CV death and hospitalization for HF (≈ 3 months) in the major CVOTs.

Alternative Metabolic Requirements

In the failing heart, metabolic substrate utilization is impaired and an overreliance on fatty acid oxidation for energy generation may lead to an accumulation of free fatty acid intermediates that themselves may result in diastolic dysfunction [72]. SGLT2 inhibitors induce glucagon secretion from pancreatic α-cells and reduce insulin secretion leading to a shift in energy utilization from free fatty acids and glucose to ketone bodies (primarily β-hydroxybutyrate) [73]. Ketone production is increased not only from increased glucagon effect, but also a possible reduction in ketone renal excretion [33••]. Ketone bodies are readily taken up by myocardial tissue, providing an alternate energy source and one that is more efficiently converted to fuel for the heart (and kidney), requiring less ATP utilization. Thus, β-hydroxybutyrate has been termed a "superfuel" capable of reducing oxygen demand and improving cardiac and renal function [74, 75]. β-Hydroxybutyrate is also thought to carry anti-oxidant and anti-arrhythmic properties [76, 77]. In addition, the increase secretion of glucagon, which has positive inotropic and anti-arrhythmic effects, may contribute to improved cardiac efficiency and stability [78].

Another important metabolic difference is the lack of reliance on insulin for its glucose-lowering mechanism of action. The avoidance of insulin and the fact that urinary glucose excretion attenuates at lower plasma glucose levels both serve to substantially reduce the risk of hypoglycemia. This is an important distinction among antidiabetic agents as hypoglycemia has been associated with an increased CV risk [31••, 79].

Anti-Inflammatory/Anti-Oxidant Effects

Systemic inflammation, a consequence of diabetes and pathogenic in the development of atherosclerosis and ventricular remodeling, identifies another potential mechanistic link with SGLT2 inhibitors. Animal studies of SGLT2 inhibitors suggest modulation of inflammatory and oxidative mediators such as leptin, interleukins (IL) [IL-6, IL-10, IL-1β], nucleotide binding oligomerization domain-like receptor 3 (NLRP-3), caspase-1, tumor necrosis factor α (TNF-α), cyclooxygenase 2 (COX-2), cardiac macrophage infiltration, superoxide, nitrotyrosine, and signal transducer and activator of transcription 3 (STAT3) [80]. With the exception of dapagliflozin-induced high-sensitivity C-reactive protein (hsCRP) reduction in humans, most of these studies were conducted in vitro or in animals and evaluated effects in kidney tissue [81]. Less is known about these effects in the heart and warrants further investigation. A preliminary trial to evaluate the anti-oxidative effects of SGLT2 inhibitors is underway (NCT02890745).

SGLT1 Effect

In contrast to SGLT2 receptors which are almost exclusively located in the renal PCT, SGLT1 receptors are located in multiple tissues including intestine, heart, skeletal muscles, and kidney [31••]. The expression of SGLT1 was found to increase under both conditions of ischemic or diabetic cardiomyopathy [82]. Animal studies revealed that overexpression of the cardiac SGLT1 receptor produced myocardial hypertrophy, LV dysfunction, and cardiomyopathy that was reversible by SGLT1 suppression [83, 84]. Exposing cardiac fibroblasts to hyperglycemic states increased expression of matrix metalloproteinase-2, an enzyme involved in cardiac fibrosis, which was reversed by phlorizin (dual SGLT1 and SGLT2 inhibitor) but not by dapagliflozin (SGLT2 inhibitor) [85]. More recently, a Mendelian randomization study of missense variants in SGLT1 (essentially SGLT1 inhibitors) resulted in lower incidence of diabetes, initiation of diabetes therapies, death, and HF. Taken together, initial data looks promising for support of SGLT1 inhibition and reduction in HF pathogenesis [86]. Of the currently available SGLT2 inhibitors, canagliflozin displays the greatest SGLT1 inhibitor effect; however, its effect appears relegated to receptors in the small intestine, leaving the receptors in the heart and kidney unaffected at therapeutic doses [87]. The dual

SGLT2/SGLT1 inhibitor, sotagliflozin, is currently under phase III investigations and will shed light on the role of SGLT1 inhibition and CV outcomes (NCT03315143) [24].

The above stated theories in support of SGLT2 inhibitors and its role in modulating the pathophysiology of HF remain speculative for the moment and warrant additional investigation. Information provided from future mechanistic studies and clinical trial data will hopefully elucidate definitive mechanisms by which these agents impart their significant CV benefits.

Conclusion

The T2DM epidemic is on the rise with associated increases in morbidity and mortality, predominantly associated with CV complications, such as ASCVD events and HF. SGLT2 inhibitors are safe drugs, with very rare occurrence of serious side effects [88, 89]. As described above, they have substantial CV benefits in patients with and without established ASCVD regardless of their baseline HbA1C levels. In particular, through their unique mechanism of action, SGLT2 inhibitors significantly improve HF-related outcomes, decreasing the frequency of HF-related hospitalizations as well as CV-related death. Therefore, they are endorsed by the American College of Cardiology and American Diabetes Association for the treatment of T2DM with co-existing ASCVD [2–5]. The FDA has already granted empagliflozin the fast track designation for the reduction of risk for CV death and HF hospitalization in people with chronic HF. Other SGLT2 inhibitors are likely to follow. The theorized protective CV mechanisms induced by SGLT2 inhibitors are several fold and include optimization of ASCVD risk factors, improvement in hemodynamics, prevention of cardiac and renal remodeling, inhibiting hormone dysregulation, use of a more efficient metabolic substrate, NHE inhibition, anti-inflammatory effects, and anti-oxidant effects. The future of SGLT2 inhibitors and its role in preventing catastrophic CV events is bright. Moreover, dual SGLT1/SGLT2 inhibitors are theorized to be even more beneficial through additional effects. Aside from delineating the exact mechanism by which these medications exhibit their salutary effects, and investigating broader patient populations for use, the next significant hurdle entails improving patient access and affordability to these novel agents.

Addendum

A recent subanalysis of DECLARE-TIMI 58 has shown that dapagliflozin reduced HF hospitalizations both in those with HFrEF (HR, 0.64 [95% CI, 0.43–0.95]) and in those without HFrEF (HR, 0.76 [95% CI, 0.62–0.92]); however, it reduced CV death (HR, 0.55 [95% CI, 0.34–0.90]) and all-cause mortality (HR, 0.59 [95% CI, 0.40–0.88]) only in patients with HFrEF [90]. Moreover, dapagliflozin reduced the relative risk of MACE by 16% (15.2% versus 17.8%; hazard ratio [HR], 0.84; 95% CI, 0.72–0.99; P = 0.039) in patients with previous MI, whereas there was no effect in patients without previous MI including in patients with established ASCVD but no history of MI [91].

Compliance with Ethical Standards

Conflict of Interest Cezary Wojcik and Bruce A. Warden declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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