Circulation

AHA SCIENTIFIC STATEMENT

Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease

A Scientific Statement From the American Heart Association

ABSTRACT: Chronic kidney disease (CKD) with type 2 diabetes (T2D) is a major public health problem, resulting in significant cardiovascular and kidney adverse outcomes worldwide. Despite the widespread use of standard-of-care therapies for CKD with T2D over the past few decades, rates of progression to end-stage kidney disease remain high with no beneficial impact on its accompanying burden of cardiovascular disease. The advent of the newer classes of antihyperglycemic agents, including SGLT2 (sodium glucose cotransporter 2) inhibitors and GLP-1 (glucagon-like peptide-1) receptor agonists, has changed the landscape of therapeutic options for patients with CKD with T2D, with demonstration of significant reductions in cardiovascular adverse events and progression to end-stage kidney disease. Several potential mechanisms exist through which these beneficial effects are achieved in both drug classes, which may be independent of their antihyperglycemic effects. This scientific statement summarizes the current literature on the cardiorenal protective effects with SGLT2 inhibitors and GLP-1 receptor agonists in patients with CKD and T2D. It reviews potential mechanistic pathways that may drive these benefits and summarizes the literature on adverse effects in patients with CKD and T2D at risk for or with established cardiovascular disease. Last, it provides practical guidance on a proposed collaborative care model bridging cardiologists, nephrologists, endocrinologists, and primary care physicians to facilitate the prompt and appropriate integration of these therapeutic classes in the management of patients with T2D and CKD.

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Chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) represents a major public health problem and accounts for most patients with end-stage kidney disease (ESKD) in the United States and worldwide.[1] Despite current standard-of-care therapies, a disproportionately high burden of cardiovascular disease (CVD) and ESKD exists in this population, accounting for high morbidity, mortality, and healthcare resource use and poor health-related quality of life. Lifestyle modification, optimization of glycemic and blood pressure control, statins, and the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have been the cornerstone of treatment for patients with CKD and T2D for several decades; however, substantial residual disease burden of CVD and ESKD remains even in optimally managed patients.[2] In this backdrop, the newer classes of antidiabetic agents, including SGLT2 (sodium glucose cotransporter 2) inhibitors (SGLT2is) and GLP-1 (glucagon-like peptide-1) receptor agonists (GLP-1 RAs), have demonstrated significant reductions in cardiovascular and kidney adverse outcomes in patients with T2D and CKD.[3] They represent a paradigm shift in the antihyperglycemic therapeutic algorithm for optimization of cardiovascular and kidney outcomes in these patients.

This scientific statement summarizes the current evidence for the cardiorenal protective effects of SGLT2is and GLP-1 RAs, with emphasis on outcomes in patients with CKD (not on dialysis) with T2D. It also reviews the relevant mechanisms that may explain both the salutary effects of these drug classes and adverse events. Finally, it provides a practical clinical decision-making algorithm, prescribing information, and a proposed collaborative practice model for cardiologists, nephrologists, diabetologists, and internists to facilitate the prompt and appropriate incorporation of these drug classes into the treatment algorithm of patients with T2D and CKD.

METHODOLOGY

The need for a comprehensive overview of the cardiovascular and kidney benefits of SGLT2is and GLP-1 RAs in patients with nondialytic CKD and T2D was identified by the Council on the Kidney in Cardiovascular Disease of the American Heart Association. A writing group was commissioned to review the current literature and to develop an expert-based consensus summary on this topic. Members of the writing group were chosen for their expertise in diabetes, heart failure, kidney disease, and cardiometabolic disease. The writing group held a series of teleconferences and web-based communications from August 2019 to January 2020. A manuscript outline was developed on the initial conference call, with individual section reviews being assigned to authors on the basis of their expertise. All authors had continuous access to the working document to provide input, and each section editor provided critical review and revisions.

The writing group used MEDLINE (1966–present) and the Cochrane Central Register of Controlled Trials as the primary sources for the literature search, which was limited to human subjects and the English language. Related article searches were conducted in MEDLINE to find additional relevant articles. Key relevant search words, Medical Subject Heading descriptors and abbreviations used in this document are available in Supplementary Table A. Supplementary Table B displays the definitions of CVD and its components, as well as the kidney end points used in the major trials involving SGLT2is and GLP-1 RAs that are referenced throughout this document. In addition, writing group members recommended articles outside the scope of the formal searches. Finally, findings from conference proceedings, medical textbooks, and relevant online data sources were also reviewed. Given the rapid reporting of new trial data in this field, the writing group limited the summary of available evidence to an a priori–specified time point of March 31, 2020, as pertaining to the scope of this document. Alternate avenues via the American Heart Association's learning platform will be explored to refresh the current evidence summarized in this statement, as new data are available.

CONFLICT OF INTEREST

The American Heart Association has a strict conflict-of-interest policy for the development of scientific statements. Each writing group member declared all relevant current conflicts, and >50% of the writing group were free of relevant conflicts. The chair did not have any relevant industry-related conflicts related to this activity. The writing group members updated an electronic file of conflict-of-interest disclosures from the beginning of the work until the article was published, and each member reported any new relevant conflicts at the beginning of each teleconference. No new relationships with the industry were accrued during the writing process timeline. Readers are referred to the writing group disclosures table and details on individual conflict-of-interest reporting.

CARDIOVASCULAR AND KIDNEY OUTCOME TRIALS WITH SGLT2i

In 2008, the US Food and Drug Administration (FDA) offered guidance to the industry, mandating dedicated cardiovascular outcomes trials for novel antihyperglycemic medications to exclude excess risk for nonfatal myocardial infarction (MI), nonfatal stroke, or cardiovascular death.[4] Currently, 4 SGLT2is are approved by the FDA for glycemic control: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Three

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Table 1. Baseline Study and Patient Characteristics With the Cardiovascular Outcomes Trials of SGLT2is

	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58	CREDENCE	DAPA-HF	VERTIS-CV*
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin	Ertugliflo z
n	7020	10 142	17 160	4401	4744	8238
Study dose, mg	25, 10	300, 100	10	100	10	5, 15
Duration of T2D, mean±SD or median (IQR), y	≥10 (4011 [57% had T2D >10 y])	13.5±7.8	11 (6–16)	15.8±8.6	NA; only 42% had T2D	12.9±8.3
Median follow-up, y	3.1	2.4	4.2	2.62	1.52	3.5
Statin use (baseline), n (%)	5403 (77)	7599 (75)	12 868 (75)	3036 (69)	…	6705 (81)
ACE inhibitor/ARB, n (%)	5666 (81)	8116 (80)	13 950 (81)	4395 (100)	3968 (84)	6705 (81)
MRA, n (%)	441 (6)	…	…	…	3370 (71)	675 (8.2)
ARNi, n (%)	…	…	…	…	508 (11)	
Metformin, n (%)	5193 (74)	7825 (77)	14 068 (82)	2545 (58)	1016 (51)	6285 (76)
Entry eGFR (lower limit), mL·min^{-1}·1.73 m^{-2}	30	30	60	30	30	30
eGFR threshold/criteria for drug discontinuation	If eligibility criteria are violated (GFR <30 mL·min^{-1}·1.73 m^{-2})	eGFR <15 mL·min^{-1}·1.73 m^{-2}	CrCl <30 mL/min	Initiation of dialysis or kidney transplantation	No specific GFR cutoff for drug discontinuation	eGFR <15 mL·min^{-1}·1.73 m^{-2}
Baseline UACR, n (%)						
≥300 mg/g	769 (11)	760 (8)	1169 (7)	3874 (88)		75 (9)
>300 mg/g	2012 (29)	2266 (23)	4029 (24)	496 (11)		2486 (30)
Baseline established CVD, n (%)	6964 (99)	7324 (72)	6974 (41)	2220 (50)	4744 (100)	8236 (99)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor blocker/neprilysin inhibitors; CANVAS, Canagliflozin Cardiovascular Assessment Study Program; CrCl, creatine clearance; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; CVD, cardiovascular disease; DAPA-HF, Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; GFR, glomerular filtration rate; IQR, interquartile range; MRA, mineralocorticoid receptor blocker; NA, not applicable; SGLTA2i, sodium glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; and VERTIS-CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

*VERTIS-CV is ongoing.

SGLT2is (canagliflozin, empagliflozin, dapagliflozin) have been studied in 5 completed cardiovascular or kidney disease outcomes randomized controlled trials (RCTs) at this time. On the basis of the initially unexpected cardiovascular and kidney benefits identified in these trial programs, the FDA issued additional labels for their use for reduction of cardiovascular events (cardiovascular death for empagliflozin,[5] prevention of hospitalization for heart failure [HF] for dapagliflozin,[6] and the treatment of CKD with T2D, cardiovascular death, major adverse cardiovascular events, and HF hospitalizations in patients with CKD and T2D [each as an individual component] for canagliflozin[7,8]). The key cardiovascular benefits, baseline differences in kidney function, and cardiovascular effects across estimated glomerular filtration rates (eGFR)/albuminuria strata from these RCTs are summarized in this section. Hazard ratios (HRs), 95% CIs, and *P* values are listed for key findings.

CARDIOVASCULAR OUTCOMES WITH THE SGLT2i TRIALS

The EMPA-REG OUTCOME RCT (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose)[9], the CANVAS Program (Canagliflozin Cardiovascular Assessment Study),[10] and the DECLARE-TIMI 58 RCT (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial 58)[11] have reported the cardiovascular benefits of empagliflozin, canagliflozin, and dapagliflozin, respectively, in patients with T2D and varying baseline CVD risk profiles. The CREDENCE RCT (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) was a kidney disease and cardiovascular outcomes trial that reported significant cardiorenal benefits with canagliflozin in patients with CKD; it was stopped early because it met the prespecified efficacy

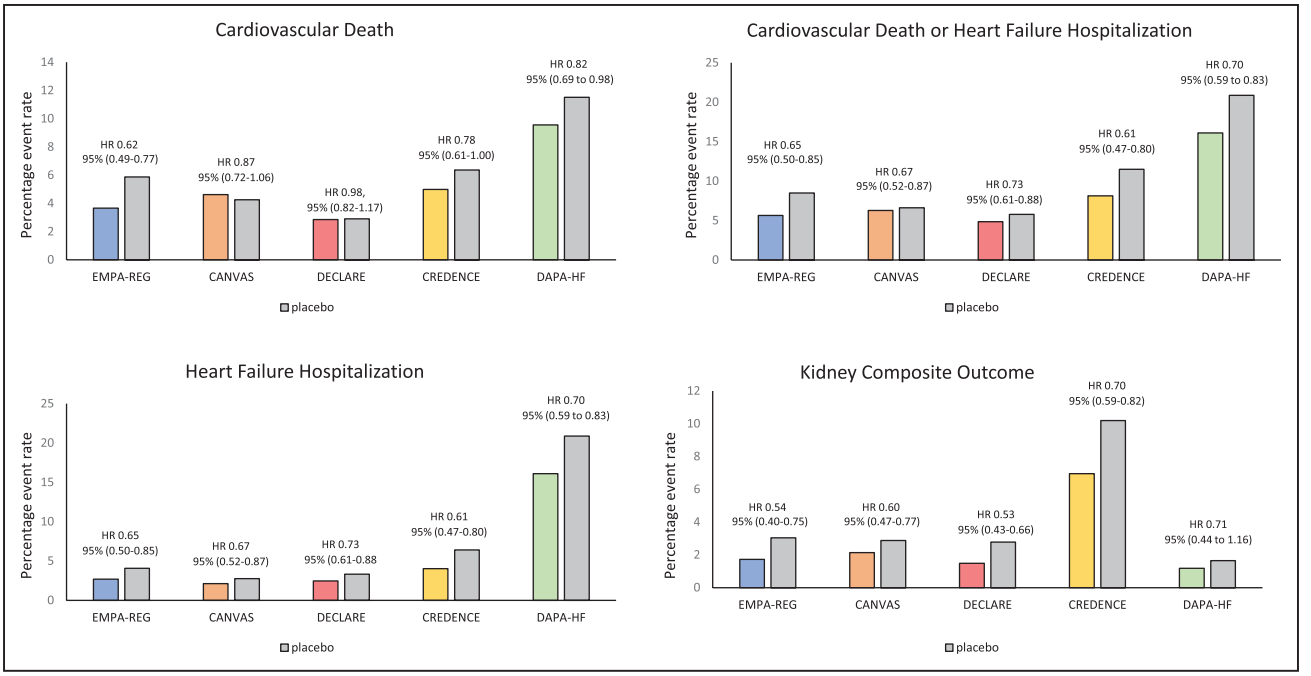

Figure 1. Hazard ratios (HRs) for key cardiovascular and kidney outcomes in cardiovascular outcomes trials with the SGLT2 (sodium glucose cotransporter 2) inhibitors .

CANVAS indicates Canagliflozin Cardiovascular Assessment Study Program; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-HF, Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; and HR, hazard ratio.

criteria for premature cessation.[12] The DAPA-HF RCT (Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction) compared dapagliflozin with placebo in patients with HF with reduced ejection fraction (HFrEF) with and without T2D.[13] Table 1 summarizes the baseline characteristics and medication use and duration in the SGLT2i RCTs. Figure 1 depicts the HRs for key cardiovascular and kidney disease outcomes across the SGLT2i RCTs.

BASELINE DIFFERENCES IN KIDNEY FUNCTION WITH THE SGLT2i TRIALS

The RCTs for SGLT2is are characterized by varying levels of baseline kidney function and definitions for eGFR measurement and albumin-to-creatinine ratio (UACR), which influence the differences in reductions in rates of cardiovascular and kidney disease events in these trials (Table 2). The CREDENCE trial had the lowest mean baseline eGFR (56.2 mL·min^{-1}·1.73 m^{-2}) compared with DECLARE-TIMI 58, CANVAS, and EMPA-REG OUTCOME (85.2, 76.5, and 74 mL·min^{-1}·1.73 m^{-2}, respectively). CREDENCE also had the highest levels of albuminuria (median UACR, 927 mg/g) compared with the median UACR of 12.3 and 13.1 mg/g for CANVAS and DECLARE-TIMI 58, respectively. In EMPA-REG OUTCOME, the distribution of values was as follows: 59.4% with UACR <30, 28.6% with UACR >30 to 300, and 11.0% with UACR >300 mg/g. Thus, the CREDENCE population had the highest baseline kidney disease risk across the SGLT2i RCTs, and DECLARE-TIMI 58 had the lowest according to the eGFR and UACR, resulting in CREDENCE having the highest absolute occurrence of kidney disease events among the cardiovascular outcomes trials (in both the active treatment and placebo arms) and DECLARE-TIMI 58 having the lowest.[14] The importance of CKD as an established risk factor for CVD is highlighted with the highest cardiovascular event rate being reported in CREDENCE despite only a 50.4% baseline established CVD rate (compared with 99.4% in EMPA-REG OUTCOME).[15] Thus, the heterogeneity in inclusion criteria for eGFR/albuminuria and their population central tendency must be considered in the evaluation of the effects on cardiovascular risk reduction of these trials.

CARDIOVASCULAR OUTCOMES WITH THE SGLT2i ACROSS STRATA OF GLOMERULAR FILTRATION RATE AND ALBUMINURIA

Microalbuminuria and eGFR are the 2 key parameters measured to accurately define and stage CKD, and both independently influence CVD risk. This section discusses available data on post hoc analyses of cardiovascular

Table 2. Baseline eGFR ranges and UACRs in Cardiovascular and Kidney Outcome Trials (Reported and Ongoing) With SGLT2is

eGFR Categories, mL·min^{-1}·1.73 m^{-2}		UACR Categories, mg/g		
		<30, Normal-Mild Increase (A1)	30–300, Moderate Increase (A2)	>300, Severe Increase (A3)
≥90, Normal	G1	DECLARE TIMI-58 CANVAS EMPA-REG OUTCOME VERTIS-CV	DECLARE TIMI-58 CANVAS EMPA-REG OUTCOME VERTIS-CV	
60–89, Mild reduction	G2	DECLARE TIMI-58 CANVAS EMPA-REG OUTCOME VERTIS-CV	DECLARE TIMI-58 CANVAS EMPA-REG OUTCOME DAPA-CKD EMPA-KIDNEY VERTIS-CV	CREDENCE DAPA-CKD EMPA-KIDNEY VERTIS-CV
45–59, Mild-moderate reduction	G3a	DECLARE TIMI- 58 CANVAS EMPA-REG OUTCOME VERTIS-CV	DAPA-CKD EMPA-KIDNEY VERTIS-CV	CREDENCE DAPA-CKD EMPA-KIDNEY VERTIS-CV
30–44, Moderate-severe reduction	G3b	EMPA-KIDNEY VERTIS-CV	DAPA-CKD EMPA-KIDNEY VERTIS-CV	CREDENCE DAPA-CKD EMPA-KIDNEY VERTIS-CV
15–29, Severe reduction	G4	EMPA-KIDNEY	DAPA-CKD EMPA-KIDNEY	DAPA-CKD EMPA-KIDNEY
<15, Kidney failure	G5			

CANVAS indicates Canagliflozin Cardiovascular Assessment Study Program; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, Study of Heart and Kidney Protection With Empagliflozin; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; SGLT2i, sodium glucose cotransporter 2 inhibitor; UACR, urine microalbumin to creatinine ratio; and VERTIS-CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

outcomes from key RCTs of the SGLT2is across strata for eGFR and microalbuminuria. Neuen et al[16] reported a post hoc analysis of the primary outcome in the CANVAS trial by eGFR. In the 20.1% of participants with an eGFR<60 mL·min^{-1}·1.73 m^{-2}, 71.6% of whom had a history of CVD, the effect of canagliflozin on the primary outcome (HR, 0.70 [95% CI, 0.55–0.90]) was similar to the effect in those with preserved kidney function (HR, 0.92 [95% CI, 0.79–1.07]). Relative effects on most cardiovascular and kidney disease outcomes were similar across eGFR subgroups. When stratified by baseline albuminuria (2266 participants [22.3%] with moderately increased albuminuria [UACR, 30–300 mg/g] and 760 [7.5%] with severely increased albuminuria [UACR >300 mg/g]), another analysis of CANVAS showed that cardiovascular outcomes were mostly consistent across albuminuria levels but with increased risks for amputation across albuminuria subgroups (heterogeneity P=0.66).[17] In an analysis of CREDENCE (a trial with a substantial representation of patients with moderate to severe CKD and macroalbuminuria), in an assessment of the effect of canagliflozin on primary and secondary CVD prevention, canagliflozin reduced the risk of major cardiovascular events overall (HR, 0.80 [95% CI, 0.67–0.95]), with consistent reductions in both the primary (HR, 0.68 [95% CI, 0.49–0.94]) and secondary (HR, 0.85 [95% CI, 0.69–1.06]) prevention groups (defined by baseline risk or presence of atherosclerotic CVD [ASCVD]). Effects were also similar for the components of the composite, including cardiovascular death (HR, 0.78 [95% CI, 0.61–1.00]), nonfatal MI (HR, 0.81 [95% CI, 0.59–1.10]), and nonfatal stroke (HR, 0.80 [95% CI, 0.56–1.15]).[18] Another subgroup analysis of the CREDENCE trial in patients with an initial eGFR <30 mL·min^{-1}·1.73 m^{-2} at randomization also reported trends toward reduced risk for ESKD (HR, 0.67 [95% CI, 0.35–1.27]) and doubling of serum creatinine (HR, 0.72 [95% CI, 0.34–1.54]).[19]

In an analysis of cardiovascular outcomes in the EMPA-REG OUTCOME trial in subjects with an eGFR <60 mL·min^{-1}·1.73 m^{-2} and UACR >300 mg/g at baseline, empagliflozin compared with placebo reduced the risk of cardiovascular death by 29% (HR, 0.71 [95% CI, 0.52–0.98]), all-cause mortality by 24% (HR, 0.76 [95% CI, 0.59–0.99]), hospitalization for HF by 39% (HR, 0.61 [95% CI, 0.42–0.87]), and risk of all-cause hospitalization by 19% (HR, 0.81 [95% CI, 0.72–0.92]). Effects of empagliflozin on these outcomes were consistent across categories of eGFR and UACR at baseline and across the 2 doses studied. The adverse event profile of empagliflozin in patients with eGFR <60 mL·min^{-1}·1.73 m^{-2} was consistent with the overall trial population.[20] The cardiorenal benefits of empagliflozin in EMPA-REG OUTCOME

extended to participants with eGFR <60 mL·min^{-1}·1.73 m^{-2} and UACR <30 mg/g, highlighting the benefits with SGLT2is regardless of baseline albuminuria.[21] This observation is highly pertinent with the increasing recognition of the nonalbuminuric phenotype of CKD with T2D, wherein the clinical evidence for cardiovascular and kidney benefits in this population is less studied compared with that in patients with albuminuria.

In a subgroup analysis of DECLARE-TIMI 58, the rates of major adverse cardiovascular events did not differ according to eGFR groups >60 or <60 mL·min^{-1}·1.73 m^{-2}; however, the rates of the composite for cardiovascular death or hospitalization for HF favored dapagliflozin compared with placebo in patients with eGFR of 60 to 90 mL·min^{-1}·1.73 m^{-2} (HR, 0.79 [95% CI, 0.66–0.95]) and in the 189 patients with eGFR <60 mL·min^{-1}·1.73 m^{-2} (HR, 0.78 [95% CI, 0.55–1.09]) compared with those with an eGFR >90 mL·min^{-1}·1.73 m^{-2} (HR, 0.96 [95% CI, 0.77–1.19]).[11] Finally, 2 separate meta-analyses showed consistent cardiorenal benefits with SGLT2is in patients with an eGFR <60 mL·min^{-1}·1.73 m^{-2}.[22,23] Supplementary Table C shows the cardiorenal benefits with SGLT2is across eGFR strata.

Given the robust data in support of the overall cardiovascular benefits with the use of SGLT2is, these drugs have received broad endorsement across professional society guidelines and position statements, including as part of initial therapy for T2D in those at high CVD and CKD risk.[24–27] This writing group endorses high-priority consideration for the use of SGLT2is that have proven cardiovascular benefits in RCTs in patients with T2D with established or high risk for CVD or CKD. It also recognizes that the overall cardiovascular benefits with these agents appear to be consistent with a class effect on the basis of the summary of current available evidence. In subjects with T2D and CKD, the cardiovascular benefits reported with the secondary outcomes in CREDENCE and subgroup analyses of the other cardiovascular outcomes trials by eGFR and UACR align with the cardiovascular benefits reported in the general population with T2D and for primary prevention of CVD. The risks and benefits of initiation of an SGLT2i in patients with advanced CKD (eGFR <30 mL·min^{-1}·1.73 m^{-2}) are unclear, and initiation is not currently recommended. Canagliflozin, however, can be maintained in the eGFR range of <30 mL·min^{-1}·1.73 m^{-2} when initiated in higher eGFR ranges and until the point of dialysis initiation or kidney transplantation, as per the CREDENCE trial study protocol.

KIDNEY PROTECTIVE EFFECTS WITH THE SGLT2i TRIALS

The first dedicated kidney end point SGLT2i RCT to report, CREDENCE, randomized 4401 patients with T2D with an eGFR of 30 to 90 mL·min^{-1}·1.73 m^{-2} and macroalbuminuria (median follow-up, 2.6 years) with nearly 100% renin-angiotensin-aldosterone system inhibitor use to canagliflozin versus placebo.[12] The primary outcome of a composite of doubling of serum creatinine from baseline (sustained for at least 30 days), ESKD (defined as dialysis, kidney transplantation, or sustained eGFR <15 mL·min^{-1}·1.73 m^{-2}), or kidney disease or cardiovascular death occurred in 11.1% of canagliflozin-treated participants compared with 15.4% of those receiving placebo (HR, 0.70 [95% CI, 0.59–0.82]; *P*=0.00001). The hazard of the kidney disease composite end point of ESKD, doubling of the serum creatinine, or death resulting from kidney disease was lower by 34% (HR, 0.66 [95% CI, 0.53–0.81]), and the risk of ESKD was lower by 32% (HR, 0.68 [95% CI, 0.54–0.86]). Given the putative effects of SGLT2is on tubuloglomerular feedback and intraglomerular pressures, the initial drop in eGFR followed by a significant reduction in the slope of eGFR over time is consistent with a reduction in glomerular hypertension, analogous to the effects of renin-angiotensin-aldosterone system inhibitors.[28] Similar effects of canagliflozin on kidney disease outcomes were noted in CANVAS, in which 20.1% of participants had an eGFR <60 mL·min^{-1}·1.73 m^{-2} at baseline.[10] Canagliflozin significantly decreased the prespecified kidney disease composite of a 40% reduction in eGFR, the need for kidney replacement therapy, or death resulting from kidney disease (HR, 0.60 [95% CI, 0.47–0.77]), which was consistent in participants with and without CKD and across eGFR subgroups. In a recent prespecified analysis of CANVAS, canagliflozin was associated with a reduction in doubling of serum creatinine, ESKD, and kidney disease death (HR, 0.53 [95% CI, 0.33–0.84]).[29] These effects were consistent in subgroup analyses. In the EMPA-REG OUTCOME trial, incident or worsening nephropathy (prespecified secondary outcome) occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 (18.8%) in the placebo group (HR, 0.61 [95% CI, 0.53–0.70]).[30] A relative risk reduction of 44% in doubling of the serum creatinine level and a 55% lower relative risk in the initiation of kidney replacement therapy in the empagliflozin group were also reported. There was no significant difference in the rate of incident albuminuria by randomized group, but the absolute rates were low.

In a separate analysis of UACR data from EMPA-REG OUTCOME, patients treated with empagliflozin were more likely to experience a sustained improvement from microalbuminuria to normoalbuminuria (HR, 1.43 [95% CI, 1.22–1.67]) or from macroalbuminuria to microalbuminuria or normoalbuminuria (HR, 1.82 [95% CI, 1.40–2.37]) and less likely to experience a sustained deterioration from normoalbuminuria to microalbuminuria or macroalbuminuria (HR 0.84 [95% CI, 0.74–0.95]).[31] In an analysis of EMPA-REG OUTCOME by baseline HF status, the incidence of kidney outcome

Table 3. Key Cardiovascular and Kidney Outcomes Reported in Cardiovascular Outcomes Trials With SGTL2is

Outcomes	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI-58	CREDENCE	DAPA-HF
Cardiovascular death, nonfatal MI, or nonfatal stroke, HR (95% CI)	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.80 (0.67–0.95)	…
Cardiovascular death, HR (95% CI)	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.82 (0.69–0.98)
Nonfatal MI, HR (95% CI)	0.87 (0.70–1.09)	0.85 (0.69–1.05)	0.89 (0.77–1.01)	…	…
Nonfatal stroke, HR (95% CI)	1.24 (0.92–1.67)	0.90 (0.71–1.15)	1.01 (0.84–1.21)	…	…
Hospitalization for HF, HR (95% CI)	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	0.70 (0.59–0.83)
Cardiovascular death or hospitalization for HF, HR (95% CI)	0.66 (0.55–0.79)	0.78 (0.67–0.91)	0.83 (0.73–0.95)	0.69 (0.57–0.83)	0.75 (0.65–0.85)
All-cause mortality, HR (95% CI)	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.83–1.04)	0.83 (0.68–1.02)	0.83 (0.71–0.97)
Progression of albuminuria definition	Progression to macroalbuminuria	New-onset micro/macroalbuminuria or microalbuminuria to macroalbuminuria or with an ACR value increase of ≥30% from baseline	New-onset micro/macroalbuminuria or microalbuminuria to macroalbuminuria		…
Progression of albuminuria, HR (95% CI)	0.62 (0.54–0.72)	0.73 (0.67–0.79)	0.73 (0.67–0.79)	…	…
Kidney composite outcome definition	Doubling of serum creatinine, initiation of kidney replacement therapy, or death caused by kidney disease	40% Decrease in eGFR, death resulting from kidney disease, or kidney replacement therapy requirement	40% Decrease in eGFR, ESKD, or death caused by kidney disease	ESKD, doubling of serum creatinine, death caused by kidney disease	Sustained decline in the eGFR of ≥50%, ESKD, dialysis, or kidney transplantation
Kidney composite outcome, HR (95% CI)	0.54 (0.40–0.75)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	0.70 (0.59–0.82)	0.71 (0.44–1.16)

ACR indicates albumin-to-creatinine ratio; CANVAS, Canagliflozin Cardiovascular Assessment Study Program; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-HF, Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

events was numerically higher in patients with HF than in those without HF.[32] In the HF group, empagliflozin reduced the risk of incident or worsening nephropathy or cardiovascular death by 43% (HR, 0.57 [95% CI, 0.42–0.77]) and progression to macroalbuminuria by 50% (HR, 0.50 [95% CI, 0.33–0.75]). This observation shows promise for the stabilization of kidney function in a patients with HF, and future data from ongoing dedicated HF outcome trials should shed more light on kidney disease outcomes.[33]

Finally, in a meta-analysis of RCTs of SGLT2is that reported effects on adverse kidney outcomes in people with T2D and included 38 723 participants, the SGLT2i class substantially reduced the risk of dialysis, transplantation, or death resulting from kidney disease (HR, 0.67 [95% CI, 0.52–0.86]; *P*=0.0019) and ESKD (HR, 0.65 [95% CI, 0.53–0.81]).[34] A benefit was demonstrated for all eGFR subgroups, including for participants with a baseline eGFR of 30 to 45 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, which was consistent across studies regardless of baseline albuminuria. This meta-analysis also identified that SGLT2is protect against future episodes of acute kidney injury (AKI). Further data on the kidney-protective effects of SGLT2is as a class are awaited from the ongoing EMPA-KIDNEY (Study of Heart and Kidney Protection With Empagliflozin; URL: ClinicalTrials.gov. Unique identifier: NCT03594110); DAPA-CKD (Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; URL: ClinicalTrials.gov. Unique identifier: NCT03036150), which was terminated early because of demonstration of meaningful benefit in patients with and without T2D in CKD; and SCORED (Effect of Sotagliflozin on

Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; URL: ClinicalTrials.gov. Unique identifier: NCT03315143). Of note, sotagliflozin (yet to be approved by the FDA at the time of writing of this statement) is a first-in-class dual sodium glucose cotransporter 1 and SGLT2 compound that targets sodium glucose cotransporter 1 in addition to SGLT2. Table 3 summarizes key cardiovascular and kidney disease outcomes in the 5 RCTs with SGLT2is.

MECHANISMS OF CARDIORENAL PROTECTION WITH SGLT2i

Several mechanisms have been proposed to explain the early separation of the Kaplan-Meier curves for primary and secondary outcomes in the SGLT2i cardiovascular outcomes trials well ahead of any expected cardiovascular or kidney disease benefit potentially incurred from the lowering of glucose, blood pressure, or body weight.[35,36] No single pathway has proved to be conclusive, and multiple pathways may be operative in concert with SGLT2is in cardiovascular and kidney disease protection.[37] Some of these mechanisms include the activation of tubuloglomerular feedback with its resultant reduction in intraglomerular pressure, diuresis, lower blood pressures, weight loss, reductions in uric acid, and higher red cell mass. These mechanisms are discussed briefly in this section.

Improved blood pressure and volume control with the diuretic effects of the SGLT2is play a role in the HF-specific benefits with SGLT2is. The DAPA-HF trial reported only a modest reduction in diuretic use with dapagliflozin added to standard diuretic regimens in HFrEF. A recent study in 42 healthy subjects randomized to dapagliflozin or bumetanide, coupled with a mathematical model illustrating that electrolyte free water clearance results in greater reduction in interstitial volume than blood volume, showed that osmotic diuresis with dapagliflozin produces a 2-fold greater reduction in interstitial compared with blood volume, whereas the relevant reduction with bumetanide was 0.8-fold.[38] The authors suggested that this SGLT-2i may selectively reduce interstitial volume without large concurrent reductions in blood volume.

Decreased blood flow to the kidney and relative medullary hypoxia also may contribute to increase erythropoietin production and increase red blood cell mass, which may improve cardiac oxygen delivery with higher hemoglobin levels. SGLT-2is prevent glucose entry into these cells, limiting glucotoxicity and potentially leading to an inflammatory response and downregulation of the expression of the cardioprotective factor Klotho. Other indirect effects of SGLT2is include modest weight loss and lowering of serum uric acid levels.[39]

In an analysis of the CREDENCE trial by eGFR strata with hemoglobin A_{1c} as a time-varying covariate, despite no reduction in hemoglobin A_{1c} in the lowest eGFR group, risk reduction for the primary end point did not differ by screening eGFR (HR, 0.75, 0.52, and 0.82 for eGFR of 30–45, 45–60, and 60–90 mL·min^{-1}·1.73 m^{-2}). Risk reduction with canagliflozin after adjustment for time-averaged hemoglobin A_{1c} was similar to the primary results, suggesting that the kidney-protective benefits with canagliflozin are independent of glycemic control and therefore may be linked to the nonglycemic pathways of SGLT2i action.[40]

SGLT2 inhibition is a particularly appealing molecular approach to treat T2D and CKD. SGLT2 expression increases in the setting of type 1 diabetes or T2D.[41] SGLT2i increases the delivery of sodium, along with glucose and chloride (accompanying sodium), to the macula densa, where increased solute uptake activates the tubuloglomerular feedback pathway to promote afferent arteriole vasoconstriction, with a resultant decrease in intraglomerular pressure.[42,43] A detailed schema of the putative mechanisms of cardiorenal protection with the SGLT2i is provided in Figure 2.[41,44–46] van Bommel et al[47] compared the kidney hemodynamic effects of dapagliflozin with gliclazide in 44 subjects with T2D on metformin. Dapagliflozin reduced measured glomerular filtration rate by 5, 10, and 12 mL·min^{-1}·1.73 m^{-2} in consecutive phases of measurement and reduced the filtration fraction without increasing kidney vascular resistance. This observation raises the possibility of a reduction in measured glomerular filtration rate and filtration fraction with the SGLT2is being mediated by postglomerular vasodilation akin to the renin-angiotensin-aldosterone system inhibitors. This is an area for future studies for clarification.

The SGLT2is also may have effects apart from tubuloglomerular feedback. In the pancreas, SGLT2 inhibition leads to increased glucagon secretion, which may contribute to a higher availability of ketones. However, it is uncertain whether increased substrate availability of ketones in turn leads to their preferential use by cardiomyocytes or key cell types in the kidney over fatty acids.[48] Finally, off-target inhibitory effects on sodium-hydrogen exchanger (NHE) family by direct binding of SGLT2i to NHE channels have been reported; cardiac NHE1 and renal NHE3 have been proposed to directly protect cardiomyocytes and to promote the kidney effects described above, respectively.[49] The beneficial effects reported with SGLT2is in HFrEF (including in nondiabetics in DAPA-HF) expand the scope of use of this medication class as primary agents in the risk reduction and treatment of HFrEF, outside diabetes status. Trials looking at the effects of SGLT2is with HF with preserved ejection fraction have not reported at the time of writing of this manuscript.

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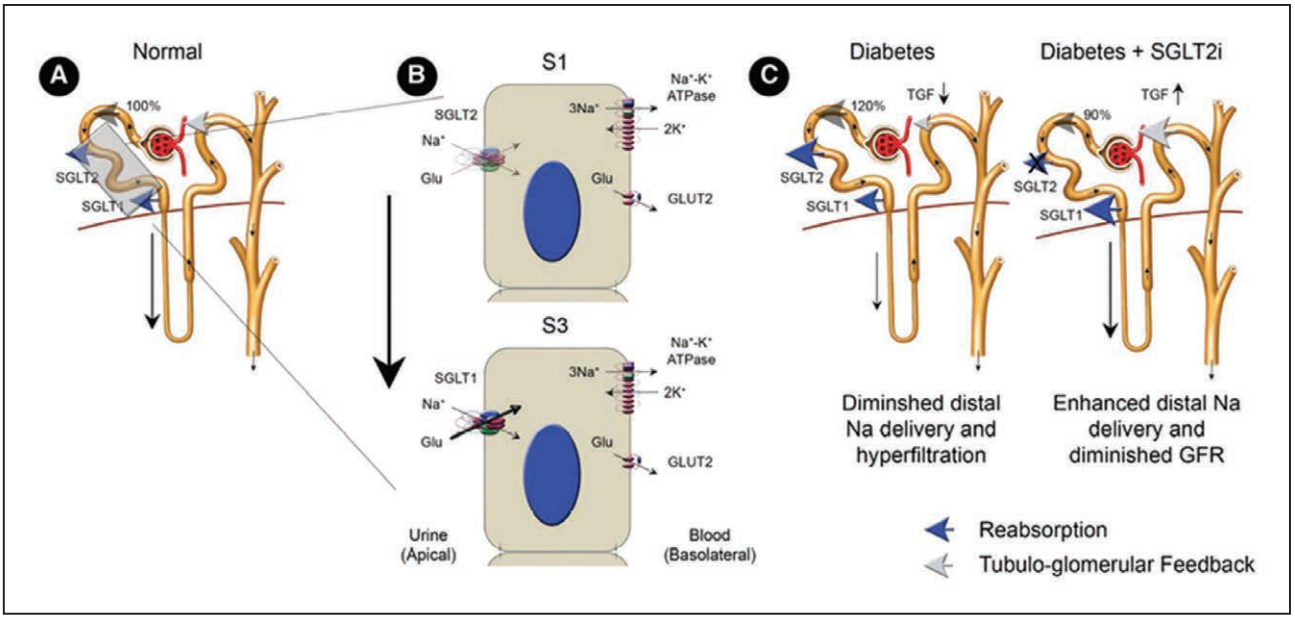


Figure 2. Mechanism of action of the SGLT (sodium glucose cotransporter) 2 inhibitors (SGLT2is)
A, SGLT2 reabsorbs 97% of filtered glucose and a related transporter, SGLT1, reabsorbs the remaining 3% of filtered glucose.[44] **B**, Glucose (Glu) is reabsorbed via SGLT2 and SGLT1 from the urinary lumen at the apical membrane in the S1 and S3 segments of the proximal tubule, respectively. Glucose is then reabsorbed into the circulation via glucose transporter 2 or related transporters. With pharmacological or genetic inhibition of SGLT2, glucose reabsorption via SGLT1 compensates in part. Thus, with treatment with SGLT2is, for example, empagliflozin, canagliflozin, or dapagliflozin, glucosuria is present but not as predicted by the tonic reabsorption of glucose via SGLT2 under normal conditions.[45] **C**, SGLT2is may reduce the progression of kidney disease via enhanced tubuloglomerular feedback (TGF). Diabetes via multiple mechanisms, including hyperglycemia, increases SGLT2-mediated glucose reabsorption.[46] This diminishes distal sodium (Na) delivery to the macula densa, which leads to afferent arteriole vasodilation and increased glomerular filtration rate (GFR), or hyperfiltration. With SGLT2 inhibition, sodium and glucose reabsorption are inhibited, leading to enhanced distal delivery of sodium to the macula densa, enhanced TGF, and reduction of GFR.[41,46] Sites of reabsorption are shown in blue; sites of TGF are shown in gray.

ADVERSE EVENTS AND RISK/BENEFIT PROFILE WITH SGLT2i

The adverse events with the use of SGLT2is are summarized in Supplementary Table D. Several pertain to the mechanisms of action of these drugs, including glycosuria, induction of mild ketosis, and putative effects on the NHE pathway.[49] An increased risk of genital mycotic infections is the most common adverse event attributable to SGLT2is. Advice given for daily hygienic measures such as rinsing the genital area after voiding and before bedtime significantly lessened the risk for genital mycotic infections (6 of 125 versus 51 of 125; P=0.015) and improved compliance with SGLT2i treatment over a 3-year period.[50] Urinary tract infections also have been reported with SGLT2is, but the risk of urinary tract infections has not been higher compared with placebo in clinical trials. A propensity score–matched analysis from 2 large claims databases showed no increased risk for severe and nonsevere urinary tract infections in patients being initiated on SGLT2is versus GLP-1 RAs or DPP-4 (dipeptidyl peptidase-4) inhibitors.[51] Case reports linking Fournier gangrene with the use SGLT2is prompted a US FDA warning in August 2018.[52] A claims-based analysis showed a slightly higher (but not statistically significant) risk of Fournier gangrene of ≈1 case per 10 000 men treated with SGLT2is compared with men treated with other antihyperglycemic agents.[53] Nevertheless, given the morbidity with necrotizing fasciitis, a careful discussion of the possibility of serious genital soft tissue infections is important for patients initiated on an SGLT2i.

Euglycemic diabetic ketoacidosis (DKA) is another rare but serious complication reported with SGLT2is.[54] Patients with signs or symptoms of ketoacidosis such as nausea, vomiting, and abdominal pain should be instructed to discontinue SGLT2is even in the presence of normal or modest elevations in blood sugar and seek immediate medical attention. In general, rates of DKA are low in T2D; therefore, the absolute risk of DKA attributable to SGLT2is is also low. Rates of DKA are much higher in type 1 diabetes, and this is the major barrier in extending SGLT2is to this population. Anticipatory guidance to holding SGLT2i dosing during periods of low oral intake or before elective surgeries may limit this adverse effect.

Canagliflozin has been associated with an increased risk of amputation in the CANVAS trial, prompting an FDA drug safety communication to this effect.[10,55] In a secondary analysis of CANVAS, the excess risk was found across all examined categories, and the proportional risks of amputation associated with canagliflozin were consistent across different subsets of amputation defined on the basis of site,

severity, and pathogenesis.[56] Of note, the CREDENCE trial did not report any increased risk of amputation with canagliflozin. A protocol amendment during the trial required all investigators to conduct foot examinations and to temporarily interrupt therapy during active conditions that may increase risk of amputations, which may have reduced amputation rates or the effects of canagliflozin on amputations. A post hoc analysis of EMPA-REG OUTCOME did not show a difference in the incidence of lower limb amputations between treatment groups but was limited by retrospective identification of these adverse events.[55] In addition, no increase in lower limb amputation incidence between groups was observed in an analysis of participants with peripheral artery disease in EMPA-REG OUTCOME.[57] Currently, it is unknown whether amputation risk is causally related to canagliflozin or extends to other drugs in this class. Given the significant morbidity with lower extremity amputations, potential risks should be discussed with patients, and frequent foot care along with self-examination should be promoted. Therapy should be stopped in patients with active ulceration or foot lesions, as was done in the CREDENCE trial.

There is a theoretical concern that SGLT2is could increase risk of AKI through volume depletion or reduction of intraglomerular pressure. The initial decrease in eGFR when SGLT2is are initiated is consistent with these hemodynamic effects. This concern prompted an FDA warning for AKI for canagliflozin and dapagliflozin. However, a lower risk for AKI was observed in clinical trials, including a meta-analysis that demonstrated a consistently reduced risk of AKI across studies (HR, 0.75 [95% CI, 0.66–0.85]; $P<0.0001$). The DAPA-HF trial also showed reductions in adjudicated AKI rates with the use of dapagliflozin in subjects with HFrEF. A recent propensity-matched cohort analysis did not show an elevated risk for AKI with the use of the SGLT2is according to electronic health record data from 2 major healthcare systems.[58] The expected decline in eGFR with a reduction in intraglomerular pressure must be distinguished from intrinsic AKI to avoid inappropriate cessation of these agents. To this end, the use of biomarkers of tubular injury may help to distinguish hemodynamic causes of fluctuations in eGFR from true AKI.[3]

CARDIOVASCULAR BENEFITS WITH THE GLP-1 AGONISTS

GLP-1, an insulinotropic hormone secreted in the gut after food intake, mediates the effect of 2 classes of glucose-lowering medications: GLP-1 RAs and DPP-4 inhibitors.[59] There are currently 7 FDA-approved and marketed GLP-1 RAs for the treatment of T2D. Liraglutide and injectable semaglutide received additional cardiovascular-specific labels for major adverse cardiovascular event risk reduction in 2017 and 2020, respectively. In the LEADER trial (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes), 9340 patients with T2D and high cardiovascular risk were randomized to liraglutide versus placebo.[60] The primary composite outcome in the time-to-event analysis of first occurrence of death resulting from cardiovascular causes, nonfatal MI, or nonfatal stroke occurred in significantly fewer patients in the liraglutide group than in the placebo group (HR, 0.87 [95% CI, 0.78–0.97]). Patients with CKD (eGFR <60 mL·min^{-1}·1.73 m^{-2}) appeared to derive greater benefit (HR, 0.69 [95% CI, 0.57–0.85]) than patients with eGFR >60 mL·min^{-1}·1.73 m^{-2} (HR, 0.94 [95% CI, 0.83–1.07]) from liraglutide treatment. This difference may have been driven in part by the higher ASCVD event rate in patients with lower eGFR. SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) showed that semaglutide significantly reduced the primary composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke (HR, 0.74 [95% CI, 0.58–0.95]).[61] These beneficial effects were driven mostly by a significant (39%) reduction in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal MI, with no significant difference in the rate of cardiovascular death. However, treatment with semaglutide increased the risk of retinopathy (HR, 1.76 [95% CI, 1.11–2.78]). Mann et al[62] reported a significant reduction with liraglutide in the prespecified secondary kidney disease outcome of the composite of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine, ESKD, or death resulting from kidney disease in the LEADER trial (HR, 0.78 [95% CI, 0.67–0.92]). This outcome was driven largely by a reduction in new-onset macroalbuminuria.

The EXSCEL trial (Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes) randomized 14 752 patients with T2D with or without prior cardiovascular disease to weekly exenatide or placebo with a median follow-up of 3.2 years.[63] A primary composite outcome event occurred in 839 of 7356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR, 0.91 [95% CI, 0.83–1.00]), with the intention-to-treat analysis indicating that exenatide administered once weekly was noninferior to placebo with respect to safety, but superiority was not demonstrated. In the ELIXA trial (Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome), the only GLP-1 RA trial conducted in a post–acute coronary syndrome setting, the addition of lixisenatide to usual care did not significantly alter

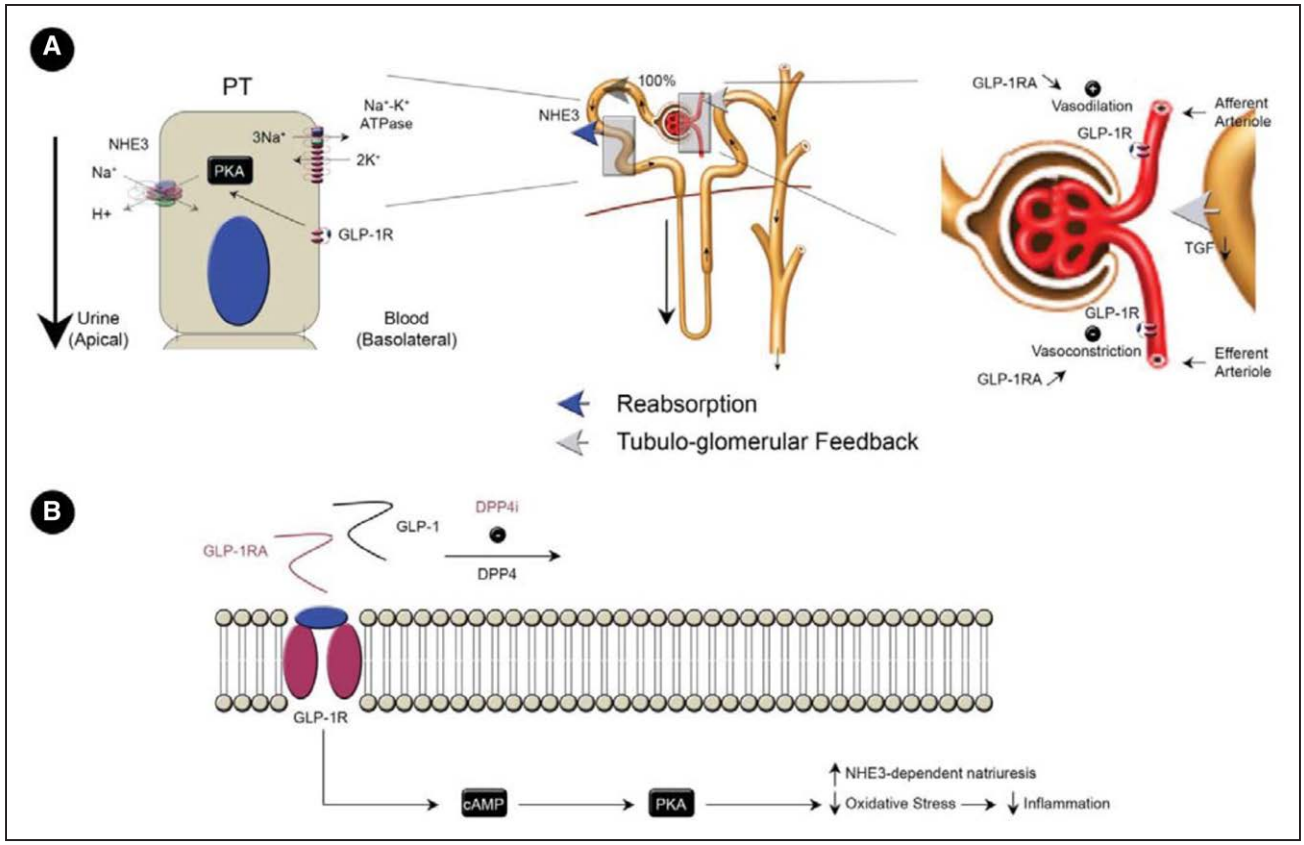


Figure 3. Mechanisms of action of glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs).
Sites of action for GLP-1 RAs or DPP-4 (dipeptidyl peptidase) inhibitors are less well characterized than those for SGLT2is, but several putative intrarenal effects are proposed on the basis of preclinical data. **A**, Two primary sites of action are proposed: proximal tubular (PT) epithelial cells and arterioles. Within the PT (**left** inset), direct agonism of the GLP-1 receptor (GLP-1R) by GLP-1 RAs can antagonize NHE3 (sodium-hydrogen exchanger 3) at the apical membrane of PT epithelial cells.[71–73] This can activate tubuloglomerular feedback (TGF) to reduce the progression of kidney disease. At the glomerulus (**right** inset), the therapeutic effects of GLP-1 RAs are mixed. GLP-1 RAs promote vasodilation of the afferent arteriole[74,75] in healthy, but not diabetic, individuals.[75–77] Relief of vasoconstriction of efferent arterioles is also proposed.[78] **B**, GLP-1 RAs and DPP-4 inhibitors act directly via stimulation of the GLP-1R or indirectly via reduction in GLP-1 proteolysis. These drugs have been shown to reduce NHE3-mediated sodium reabsorption and oxidative stress via cAMP- and PKA (protein kinase A)–mediated pathways.[79] The latter mechanism may reduce renal inflammation as a distinct, hemodynamic-independent benefit of these classes of drugs. Sites of reabsorption are shown in blue; sites of TGF are shown in gray.

the rate of major cardiovascular events or other serious adverse events.[64] In the REWIND trial (Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes), the primary outcome of the first occurrence of the composite cardiovascular end point of nonfatal MI, nonfatal stroke, or cardiovascular death occurred at an incidence rate of 2.4 per 100 person-years in the dulaglutide group and 2.7 per 100 person-years in the placebo group (HR, 0.88 [95% CI, 0.79–0.99]). All-cause mortality did not differ between groups.[65] Although cardiovascular superiority was also demonstrated with albiglutide in HARMONY Outcomes (Effects of Albiglutide on Major Cardiovascular Events in Patients With Type 2 Diabetes Mellitus), this therapy has since been withdrawn from the global market. Given the cardiovascular benefits with this drug class, the 2019 European Society of Cardiology guidelines on diabetes, prediabetes, and CVD have assigned a Class 1A indication for the use of the GLP-1 RAs in patients with T2D and established ASCVD or at high/very high cardiovascular risk (target-organ damage or multiple risk factors). Liraglutide also carries a Class 1B indication for reducing risk of death in patients with T2D and CVD or at high risk for CVD.[24] GLP-1 RAs are endorsed by the 2020 American Diabetes Association Standards of Medical Care in Diabetes as therapies in patients with T2D who are at high risk for or with established ASCVD.[2] The PIONEER-6 trial (Oral Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes) demonstrated noninferiority with the oral formulation of semaglutide with respect to the primary composite outcome for major adverse cardiovascular events, as well as risk reductions for individual components,[66] and has received an FDA indication for improvement in glycemic control in patients with T2D.[67] Oral semaglutide is undergoing further specific cardiovascular outcome testing in the SOUL trial (A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes; URL: ClinicalTrials.gov. Unique identifier: NCT03914326).

Table 4. Baseline eGFRs and UACRs in Cardiovascular and Kidney Outcome Trials With GLP-1 RAs

		UACR Categories, mg/g		
		<30, Normal-Mild Increase	30–300, Moderate Increase	>300, Severe Increase
eGFR Categories, mL·min^{-1}·1.73 m^{-2}		A1	A2	A3
≥90, Normal	G1	ELIXA LEADER SUSTAIN-6 EXSCEL REWIND	LEADER SUSTAIN-6 EXSCEL REWIND	
60–89, Mild reduction	G2	ELIXA LEADER SUSTAIN-6 EXSCEL REWIND	LEADER SUSTAIN-6 EXSCEL REWIND	FLOW
45–59, Mild-moderate reduction	G3a	ELIXA LEADER SUSTAIN-6 EXSCEL AWARD-7	LEADER SUSTAIN-6 EXSCEL AWARD-7 FLOW	AWARD-7 FLOW
30–44, Moderate-severe reduction	G3b	LEADER SUSTAIN-6 EXSCEL AWARD-7	LEADER SUSTAIN-6 EXSCEL AWARD-7 FLOW	AWARD-7 FLOW
15–29, Severe reduction	G4	AWARD-7	AWARD-7 FLOW	AWARD-7 FLOW
<15, Kidney failure	G5			

AWARD-7 indicates Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes and Moderate to Severe CKD; eGFR, estimated glomerular filtration rate; ELIXA, Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome; EXSCEL, Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes; FLOW, Semaglutide Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LEADER, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes; REWIND, Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; and UACR, urine microalbumin-to-creatinine ratio.

GLP-1 RAs AND KIDNEY DISEASE OUTCOMES

The AWARD-7 trial (Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes and CKD) was the first RCT to examine the efficacy of GLP-1 RAs (dulaglutide) in moderate to severe CKD.[68] The mean eGFR in this trial was 38 mL·min^{-1}·1.73 m^{-2}, with the 1-year average decline in eGFR being –3.3 mL·min^{-1}·1.73 m^{-2} in the insulin group versus –0.7 mL·min^{-1}·1.73 m^{-2} in the dulaglutide group. Among AWARD-7 patients with macroalbuminuria (UACR >300 mg/g) at high risk for progression of kidney disease, attenuation of mean eGFR decline was maintained: –5.5 mL·min^{-1}·1.73 m^{-2} in the insulin glargine group compared with –0.7 and 0.5 mL·min^{-1}·1.73 m^{-2} in the dulaglutide 0.75 and 1.5 mg groups, respectively. Notably, fewer patients in the higher-dose dulaglutide group reached the composite end point of ESKD or >40% eGFR decline compared with the insulin glargine group (5.2% versus 10.8%; *P*=0.038). In an analysis of AWARD-7 participants by albuminuria status, the majority of events occurred in patients with macroalbuminuria (with similar eGFR between treatment groups within albuminuria subgroups), and the risk for the composite end point was reduced by approximately half for higher-dose dulaglutide at 1.5 mg weekly compared with daily insulin glargine.[69] Notably, the risk of hypoglycemia was also reduced by more than half, even when dulaglutide was used with short-acting premeal insulin, in the participants with moderate to severe CKD in AWARD-7.

In the LEADER and SUSTAIN-6 trials, treatment with liraglutide or semaglutide compared with placebo resulted in fewer patients experiencing a composite cardiovascular outcome and decreased risk of CKD development and progression, benefits driven mainly by the reduction in onset of macroalbuminuria. A prespecified secondary kidney disease composite outcome in LEADER occurred in fewer participants in the liraglutide group than in the placebo group (HR, 0.78 [95% CI, 0.67–0.92]; *P*=0.003).[62] This result was driven primarily by the new onset of macroalbuminuria, which occurred in fewer participants in the liraglutide group than in the placebo group (HR, 0.74 [95% CI, 0.60–0.91]; *P*=0.004). The rates of kidney adverse events were similar in the liraglutide group and the placebo group (15.1 and 16.5 events per 1000 patient-years), including the rate of AKI (7.1 and 6.2 events per 1000 patient-years,

Table 5. Key Cardiorenal Outcomes With the Major GLP-1 RA Trials

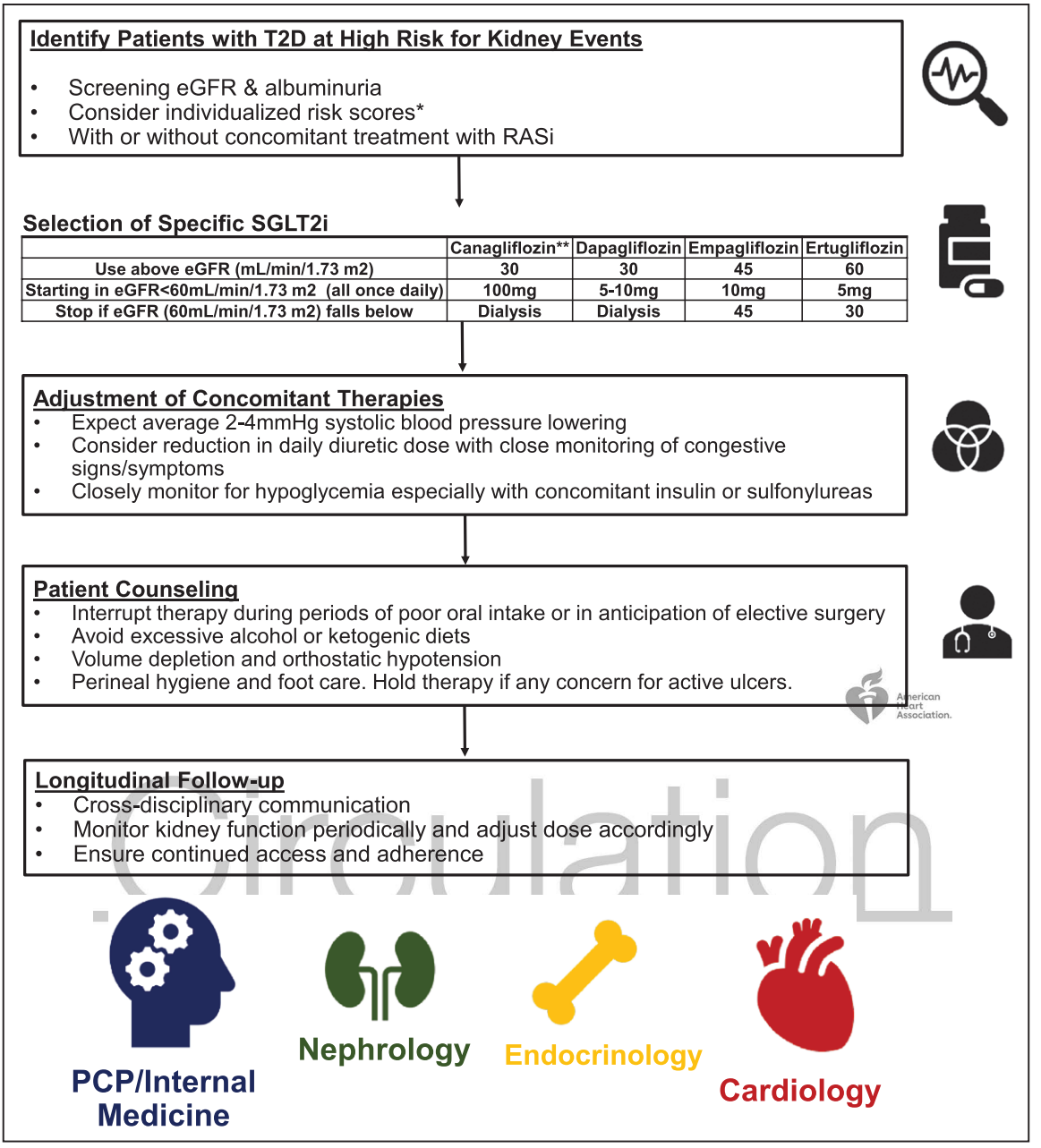
Outcomes	ELIXA	LEADER	SUSTAIN-6	EXSCEL	REWIND	HARMONY	PIONEER-6	AWARD-7
Cardiovascular death, nonfatal MI, or nonfatal stroke, HR (95% CI)	1.02 (0.89–1.17)	0.87 (0.78–0.97)	0.74 (0.58–0.95	0.91 (0.83–1.00)	0.88 (0.79–0.99)	0.78 (0.68–0.90)	0.79 (0.57–1.11)	
Cardiovascular death, HR (95% CI)	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.93 (0.73–1.19)	0.49 (0.27–0.92)	
Fatal or nonfatal MI, HR (95% CI)	1.03 (0 .87–1.22)	0.86 (0.73–1.00)	0.81 (0.57–1.16)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	0.75 (0.61–0.90)	1.04 (0.66– 1.66)	
Fatal or nonfatal stroke, HR (95% CI)	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.65 (0.41–1.03)	0.85 (0.70–1.03)	0.76 (0.62–0.94)	0.86 (0.66–1.14)	0.76 (0.37–1.56)	
Hospitalization for HF, HR (95% CI)	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.71 (0.53–0.94)	0.86 (0.48–1.55)	
All-cause mortality, HR (95% CI)	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.95 (0.79–1.16)	0.51 (0.31–0.84)	
Worsening kidney function, HR (95% CI)	1.16 (0.74–1.83)	0.89 (0.67–1.19)	1.28 (0.64–2.58)	0.88 (0.74–1.05)	0.70 (0.57–0.85)			0.45 (0.20–0.97); dose of 1.5 mg
Definition of worsening kidney function	Doubling of serum creatinine or ≥40% decline in eGFR	Doubling of serum creatinine or ≥40% decline in eGFR	Doubling of serum creatinine or ≥40% decline in eGFR	Doubling of serum creatinine or ≥40% decline in eGFR, ESKD, death caused by kidney disease	Doubling of serum creatinine or ≥40% decline in eGFR			40% eGFR decline or ESKD outcomes

AWARD-7 indicates Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes and Moderate to Severe CKD; eGFR, estimated glomerular filtration rate; ELIXA, Lixisenatide in Patients With Type 2 Diabetes and Acute Coronary Syndrome; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; EXSCEL, Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes; GLP-1 RA, glucagon like peptide-1 receptor agonist; LEADER, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes; HARMONY, Effects of Albiglutide on Major Cardiovascular Events in Patients With Type 2 Diabetes Mellitus; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PIONEER-6, Oral Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes; REWIND, Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes; and SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

respectively). Finally, in a meta-analysis of 7 GLP-1 RA RCTs involving >56 000 patients, treatment with GLP-1 RAs had overall beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with T2D.[70] The FLOW trial (Semaglutide Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease; URL: ClinicalTrials.gov. Unique identifier: NCT03819153) will be the first large RCT to report primary kidney outcomes in patients with T2D and CKD treated with semaglutide versus placebo and will target 3160 subjects. Figure 3 describes putative kidney-protective pathways that may be operative with the GLP-1 RAs.[71–79] Table 4 represents the baseline eGFRs and UACRs for cardiovascular and kidney disease outcomes trials with the GLP-1 RAs. Supplementary Table E summarizes baseline characteristics, and Table 5 describes the key cardiorenal outcomes with the major GLP-1 RA trials.

The cardiovascular and kidney disease benefits with GLP-1 RAs appear internally consistent across the drug class yet more heterogeneous compared with SGLT2is. These therapies fill an important gap with respect to the antihyperglycemic agents that can be used safely in patients with moderate to severe CKD or ESKD with T2D. The cardioprotective effects of GLP-1 RAs seem effective predominantly in reducing the burden of ASCVD, in contrast to the significant reduction with HF risk seen with SGLT2is. Given the lack of overlapping target outcomes, mechanisms of benefit, and side-effect profiles, there is potential for dual use of these agents to personalize CVD and CKD risk reduction. Current and future trials studying combinations of these agents will help to define such approaches. In this context, the DURATION 8 trial (Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy) reported that the coinitiation of exenatide and dapagliflozin improved various glycemic measures and cardiovascular risk factors in patients with T2D inadequately controlled by metformin monotherapy. The dual treatment regimen was well tolerated, with the safety profile along expected lines for this combination.[80]

AWARD-10 (Study of Dulaglutide in Participants With Type 2 Diabetes Mellitus) reported dulaglutide as add-on treatment to SGLT2i (with or without metformin), resulting in significant and clinically relevant improvements in glycemic control, with acceptable tolerability consistent with the established safety profile of dulaglutide.[81] The SUSTAIN-9 trial (Efficacy and Safety of Semaglutide Once-weekly Versus Placebo as Add-On to SGLT-2i in Subjects With Type 2 Diabetes



	Canagliflozin**	Dapagliflozin	Empagliflozin	Ertugliflozin
Use above eGFR (mL/min/1.73 m2)	30	30	45	60
Starting in eGFR<60mL/min/1.73 m2 (all once daily)	100mg	5-10mg	10mg	5mg
Stop if eGFR (60mL/min/1.73 m2) falls below	Dialysis	Dialysis	45	30

Figure 4. Multidisciplinary care model for identification of patients at high risk for adverse cardiovascular and kidney events with type 2 diabetes (T2D) and chronic kidney disease.
eGFR indicates estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitors; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

Mellitus) reported the feasibility of the combination of semaglutide with SGLT2 inhibition with favorable results for glycemic control and weight loss.[82] Future trials such as the EmpaSema trial (Renal Effects of Treatment With Empagliflozin Alone or in Combination With Semaglutide in Patients With Type 2 Diabetes and Albuminuria; URL: ClinicalTrials.gov. Unique identifier: NCT04061200) will report the effects of treatment with empagliflozin alone versus empagliflozin with semaglutide on kidney disease outcomes in patients with T2D and albuminuria.

MULTIDISCIPLINARY MODEL FOR INTEGRATION OF SGLT2i AND GLP-1 RAs IN CLINICAL PRACTICE

Scientific discovery and evidence supporting multiple clinical benefits of these 2 classes of antihyperglycemic agents have outpaced their effective implementation in clinical practice. Although GLP-1 RAs and SGTL2is received initial approval for glycemic control by the FDA in 2005 and 2013, respectively, their uptake has been modest,[83] especially among patients

at risk for CVD and CKD.[84,85] In a recent nationwide study of >1 million commercially insured and Medicare Advantage adult beneficiaries from 2013 to 2016, only 7% of patients with diabetes were treated with an SGLT2i.[86] Patients with CVD and CKD, older adults, Black patients, and those with noncommercial insurance were less likely to receive an SGLT2i.[86] These data highlight the need for efforts to reach patients at greatest risk for CVD and CKD progression for consideration of these agents.

Although SGLT2is and GLP-1 RAs are typically initiated by providers who treat T2D, mainly primary care physicians or endocrinologists, in current US practice,[87,88] moving toward integrated multispecialty care has distinct advantages. From a pragmatic perspective, there is currently limited access to the ≈8000 practicing endocrinologists in the United States, especially in certain states where the ratio of incident T2D cases to endocrinologists approaches 2000:1.[83] Beyond the number and distribution of clinicians, given their associated multimorbidity and clinical events, high-risk patients with T2D may more frequently encounter other medical specialists (including nephrologists and cardiologists), increasing opportunities to optimize therapeutic regimens. Hospitalization for acute cardiovascular care represents a unique setting in which therapies may be readdressed and allow a period of inpatient monitoring and the provision of anticipatory guidance and counseling in stabilized patients. Multidisciplinary care pathways may lessen uncertainties about the practicalities of prescription and facilitate early and longitudinal follow-up.

Innovative care approaches such as fully integrated multidisciplinary ambulatory centers are being considered nationally. Several practical steps may be undertaken to encourage safe and effective use of evidence-based antihyperglycemic therapies to lower CVD and CKD risks (Figure 4).[89]

1. Identification of at-risk patients. Given patterns of late referral to nephrologists, early identification of at-risk patients and potential candidates for therapy may be facilitated by other clinicians. Cross-disciplinary clinical practice guidelines and expert consensus documents now support the assessment of CVD and CKD risk status. Measurement of eGFR and albuminuria is encouraged in various care settings, including among hospitalized patients. Real-time, efficient estimation of ASCVD, HF, and CKD progression risks may be facilitated by the use of validated risk scores.[90,91]
2. Selection of therapy. Patients with established CKD may benefit from both SGLT2is and GLP-1 RAs compared with other antihyperglycemic classes, although data from ongoing dedicated kidney disease outcomes trials for both classes continue to evolve. Kidney disease benefits of SGLT2is appear durable even among patients already treated with renin-angiotensin system inhibitors. Given consistent class-wide effects, the choice of a specific SGLT2i or GLP-1 RA may be dictated by affordability, coverage, and formulary considerations. Given the dominant benefits noted for HF with SGLT2is and for ASCVD with GLP-1 RAs, the phenotype of CVD in patients with diabetes and CKD must be assessed on an individual basis, and drug choice should be tailored accordingly. At this time, because there is more experience with GLP-1 RAs in patients with severe CKD (stage 4 and 5 CKD, not on dialysis), a stratified approach may be considered wherein an SGLT2i may be used preferentially in earlier stages of CKD with a transition to GLP-1 RAs with advanced CKD given the safety and efficacy profile with the GLP-1 RAs in patients with eGFR <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. It must be noted that these suggestions are proposed in the context of currently available data and may evolve as data from ongoing kidney outcome RCTs with SGLT2is become available. Collaboration with advanced practice providers and clinical pharmacists may facilitate prescription access.
3. Adjustment of concomitant therapies and deprescribing. With the use of SGLT2is or GLP-1 RAs and other antihyperglycemic therapies in patients with T2D and CKD, careful attention must be paid to the risk of inducing hypoglycemia. There is insufficient knowledge at this time about how the widespread use of these agents will affect the risk of hypoglycemia. Patients on concomitant agents such as insulin and the sulfonylureas are at higher risk for hypoglycemia. It is reassuring, however, that the risk of hypoglycemia was actually reduced by half in the dulaglutide arm of AWARD-7, as described previously, even when administered with short-acting premeal insulin in participants with moderate to severe CKD. A recent post hoc analysis of EMPA-REG OUTCOME showed that hypoglycemia was associated with an elevated risk of HF and MI. However, empagliflozin did not increase the risk of hypoglycemia, and the cardiovascular benefits were not attenuated by the occurrence of hypoglycemia.[92] Research is needed to identify which patients are at greatest risk for hypoglycemia with the initiation of these drugs. Collaborative care with endocrinologists is an important consideration for insulin titration and concurrent use of other antihyperglycemic therapies. Furthermore, adjustment of antihypertensive therapies may be needed in patients with lower baseline blood pressure or those who

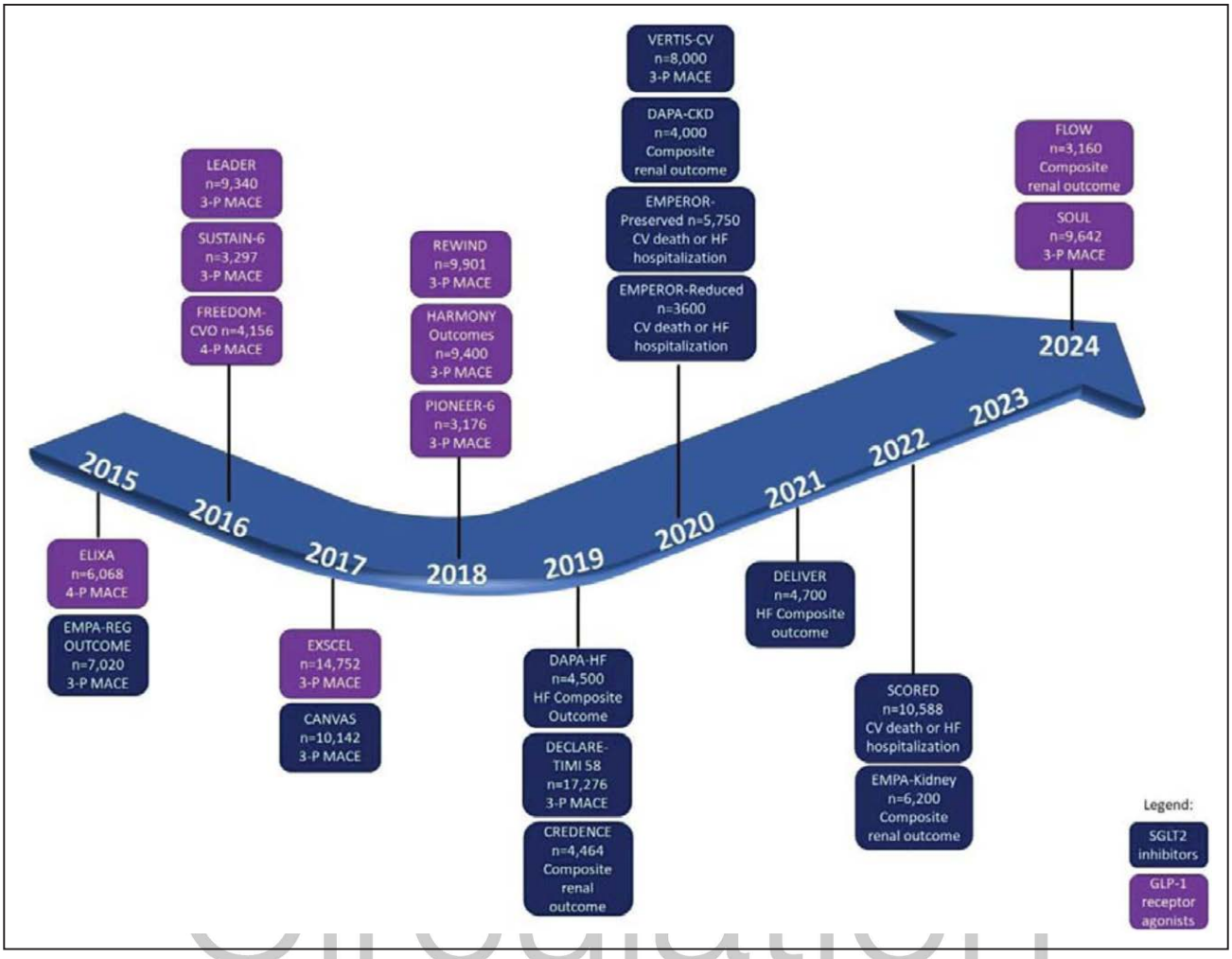


Figure 5. Timeline of key current and future randomized controlled trials involving sodium glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the cardiorenal space.

CANVAS indicates Canagliflozin Cardiovascular Assessment Study Program; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; CV, cardiovascular; DAPA-CKD, Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (trial has concluded early because of demonstration of efficacy); DAPA-HF, Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; ELIXA, Lixisenatide in Patients With Type 2 Diabetes and Acute Coronary Syndrome; EMPA-KIDNEY, Study of Heart and Kidney Protection With Empagliflozin; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; EXSCEL, Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes; FLOW, Semaglutide Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease; FREEDOM-CVO, Novel Drug-Device GLP-1 Receptor Agonist in Uncontrolled Type 2 Diabetes and Very High A1C; HARMONY Outcomes, Effects of Albiglutide on Major Cardiovascular Events in Patients With Type 2 Diabetes Mellitus; HF, heart failure; LEADER, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes; 3-P MACE, 3-point major adverse cardiovascular event; 4-P MACE, 4-point major adverse cardiovascular event; PIONEER-6, Oral Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes; REWIND, Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes; SCORED, Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOUL, A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; and VERTIS-CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

are frail given the modest blood pressure lowering by both SGLT2is and GLP-1 RAs. Background diuretic adjustments in patients being started on an SGLT2i should be individualized with close monitoring of body weight, symptoms, and blood pressure. Mild transient decreases in eGFR are anticipated, related to shifts in intraglomerular pressures on initiation of an SGLT2i, and should not prompt cessation of these drugs.

Finally, the burden of polypharmacy and its related impact on prescription adherence are significant in patients with T2D, CKD, and CVD. This may be a limiting factor when deciding on appropriate regimens that satisfy both the need for optimal glycemic control and cardiorenal end-organ benefit. Each office visit should be used as an opportunity to minimize polypharmacy and to deprescribe agents that have no

proven cardiorenal benefit. The polypill model has been proposed as a potential solution to this problem and has been effective in other models for CVD prevention.[93] There are no definitive data in support of this model in the cardiorenal metabolic space at this time, but this is certainly an area for future research.

4. Patient counseling. Patients should be counseled about the risks and presenting symptoms of euglycemic DKA with SGLT2is and should interrupt therapy during periods of inadequate oral intake, ketogenic diets, or upcoming planned procedure/surgery. Excessive alcohol should be avoided. Perineal hygiene and regular foot care should be encouraged. Precautions similar to the protocol amendment during the CREDENCE trial requiring universal foot examinations and temporary interruption of therapy during active conditions that may increase risk of amputations are necessary in real-world practice to reduce amputation risk. However, it is noteworthy that the FDA has since removed the black box warning of amputation risks related to canagliflozin due to the totality of emerging evidence supporting its safety.
5. Longitudinal follow-up. Clinical follow-up is needed to assess for treatment-attendant adverse events and to ensure treatment adherence. Close monitoring for hypoglycemia and ketoacidosis is important, especially in high-risk patients, as outlined previously.

As the broad health implications of T2D are recognized, multispecialty care models help to promote targeted and equitable integration of these evidence-based therapies in clinical care, especially with support from healthcare systems and payers.

CONCLUSIONS AND FUTURE DIRECTIONS

SGLT2is and GLP-1 RAs represent antihyperglycemic therapies shown to reduce CVD and CKD risks in patients with T2D. In addition, SGLT2is have shown benefit in patients with HFrEF independently of diabetes status, which opens up exciting possibilities for the use of these therapies in patients at risk for or with established cardiovascular or kidney disease without T2D. Several ongoing trials will report cardiovascular and kidney disease outcomes with these agents, including in patients with HF with preserved ejection fraction and those with CKD without T2D (Figure 5). Given the well-proven CVD and CKD benefits from these drug classes in RCTs, there is an urgent need to incorporate multidisciplinary care in the identification of high-risk patients who may benefit from these agents. Finally, legislative support should promote equitable access to these agents, especially for vulnerable and underrepresented patient populations who also carry the highest burden of CVD and CKD risk with T2D. Achieving these targets aligns closely with the innovative Advancing American Kidney Health Executive Order by the government of the United States as outlined by the US Department of Health and Human Services, particularly with the important goal of reducing the burden of ESKD by 25% by the year 2030. With multidisciplinary efforts from primary care physicians, cardiologists, nephrologists, endocrinologists, pharmacists, advanced practitioners, and other allied health professionals toward providing targeted therapies for CVD and CKD risk reduction in patients with T2D, there is opportunity to meaningfully reduce morbidity, mortality, and healthcare expenditures for this vulnerable patient population.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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*Modest.

†Significant.

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