Cardiorenal Outcomes in Type 2 Diabetes

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LEARNING OBJECTIVES

1. Distinguish the cardiovascular (CV) risk-benefit of individual DPP-4 (dipeptidyl peptidase-4) inhibitors.
2. Evaluate the cardiorenal risk-benefit of incretin mimetics and SGLT-2 (sodium-dependent glucose cotransporter-2) inhibitors.
3. Using guidelines and primary literature, develop a patient-specific plan on the basis of CV and renal history and risk factors.

ABBREVIATIONS IN THIS CHAPTER

ACS	Acute coronary syndrome
AKI	Acute kidney injury
ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome trial
DKD	Diabetic kidney disease
DPP-4	Dipeptidyl peptidase-4
ESRD	End-stage renal disease
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
HHF	Hospitalization for heart failure
MACE	Major adverse cardiovascular events
RAS	Renin-angiotensin system
SGLT-2	Sodium-dependent glucose cotransporter-2
T2DM	Type 2 diabetes
UACR	Urine albumin/creatinine ratio

Table of other common abbreviations.

INTRODUCTION

The prevalence of diabetes in the United States has continued to increase over the past 20 years. In 2018, it was estimated that over 34 million adults in the United States had diabetes, with rates as high as 26.8% in adults 65 and older (CDC 2020). Micro- and macrovascular complications contribute significantly to the morbidity, mortality, and costs associated with diabetes management. Heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD), which manifests as coronary artery disease, ischemic stroke, and peripheral arterial disease, tend to be more severe and to occur at an earlier age in patients with type 2 diabetes (T2DM) than in patients without diabetes. Despite decreasing cardiovascular (CV) event rates, ASCVD remains the leading cause of death and disability among patients with diabetes (ADA 2018; Low-Wang 2016).

Kidney disease, a major risk factor for ASCVD, affects around 37% of patients with diabetes and significantly affects morbidity and mortality. Diabetes is currently the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESRD), accounting for 38.5% of cases (CDC 2020). The presence of kidney disease in patients with diabetes increases the risk of mortality by 23.4% (CDC 2020; Afkarian 2013).

Several studies have shown that intensive glycemic control prevents microvascular complications, especially retinopathy and nephropathy; however, the effects on CV events and mortality have not been consistent, with some studies showing increased mortality (Duckworth 2009; ACCORD 2008; ADVANCE 2008; UKPDS 1998a, 1998b; DCCT 1993). In one study, intensive blood glucose control with metformin in overweight patients with T2DM significantly reduced diabetes-related end points and all-cause mortality compared with standard and intensive treatment with a sulphonylurea or insulin. Metformin also significantly reduced diabetes-related death,

myocardial infarction (MI), and composite macrovascular complications compared with standard treatment (UKPDS 1998b). Although these data suggest CV risk reduction, it is unclear whether intensive A1C control or metformin is responsible for the benefit. However, given these data together with the relative safety and efficacy of metformin, it became the first-line treatment for diabetes for decades (ADA 2020; Buse 2020; Garber 2020). A more recent meta-analysis showed that although metformin lowered all-cause mortality, CV death, MI, and peripheral vascular disease, no statistical difference occurred (Griffin 2017). Without randomized controlled trials designed to evaluate CV safety, debate arose regarding the CV safety of diabetes medications, specifically rosiglitazone.

Because of the uncertainty of CV effects, the FDA in 2008 issued a guidance document requiring all newly approved therapies to show CV safety in clinical trials. This mandate resulted in many cardiovascular outcome trials (CVOTs), not only for medications within the dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 receptor agonist (GLP-1 RA), and sodium-dependent glucose cotransporter-2 (SGLT-2) inhibitor classes, but also some for bromocriptine, acarbose, and insulin. With few exceptions, medications did not increase CV events, and many reduced CV risk. Citing these trends, the FDA in 2020 withdrew this guidance and published a draft guidance document. This document outlines the continued need to accurately assess the long-term safety of diabetes medications and sets parameters for the amount of patient exposure and types of patients to be included in the safety data set. If approved, safety data will need to include at least 1500 patients exposed for 1 year, 500 patients exposed for 2 years, and at least 4000 patient-years of exposure in phase III clinical trials. Safety data will also require phase III trials to include at least 500 patients with stage 3 or 4 CKD, 600 patients with established CV disease (CVD), and 600 patients older than 65 who were exposed to the medication (FDA 2020).

Over the past several years, major guidelines related to diabetes management have shifted from a standard algorithm to a patient-centered, individualized approach. Guidelines continue to recommend metformin as first-line therapy and consider effects on glycemic control, risk of hypoglycemia, effect on weight, adverse effects, and cost for adjunctive treatment selection. Since the publication of several cardiorenal outcome trials, the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the European Association for the Study of Diabetes (EASD) have added the presence of ASCVD, HF, or CKD to their treatment algorithms (ADA guidelines, AACE/ACE guidelines, ADA/EASD guidelines). Furthermore, the American College of Cardiology (ACC) released an expert consensus decision pathway on novel therapies for CV risk reduction in patients with T2DM that summarizes data from CVOTs and provides recommendations for diabetes management (Das 2020). Despite potential CV risk reduction data with pioglitazone, bromocriptine, and acarbose, these agents are not as highly recommended because of adverse effects, moderate glucose effects, and cost. Given the robust data with incretin mimetics and SGLT-2 inhibitors, this chapter outlines the data for cardiorenal outcomes for these classes and reviews the most current recommendations from major guiding documents.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the risk factors and pathophysiology of T2DM
- Consequences associated with T2DM, including micro- and macrovascular complications
- Drug knowledge of oral and parenteral pharmacologic agents used to treat T2DM and prevent associated complications
- Clinical staging of CKD and AKI

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Diabetes Association. Pharmacology approaches to glycemic treatment: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020;43:S98-S110.
- Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2020 executive summary. Endocr Pract 2020;26:107-39.
- KDOQI. Clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850-86.

CV OUTCOMES

Incretin Mimetic Therapies

Two incretin-based therapeutic classes, GLP-1 RAs and DPP-4 inhibitors, are currently available. The CVOTs with individual agents vary in study design, patient population, and results. The primary outcomes evaluated in most trials are 3-point major adverse CV events (MACE); a composite of CV death, nonfatal MI, or stroke; and 4-point or expanded MACE, which is 3-point MACE plus hospitalization for unstable angina. Table 1 and Table 2 summarize the CVOTs evaluating incretin therapies.

Table 1. Summary of CVOTs Evaluating DPP-4 Inhibitors

Trial	Agent	Study Population	n	Median Trial Duration	Outcomes (95% CI)
TECOS (Green 2015)	Sitagliptin 50–100 mg daily (based on eGFR)	Age ≥ 50 (mean 65) A1C: 6.5%–8.0% (mean 7.2%) Established CVD Mean duration of T2DM: 11.6 yr	14,735	3 yr	4-pt MACE (CV death, nonfatal MI or stroke, hospitalization for UA) HR: 0.98 (0.89–1.11)
EXAMINE (White 2013)	Alogliptin 6.25–25 mg daily (based on eGFR)	Median age: 61 A1C: 6.5%–11.0% (mean 8.0%) ACS within 15–90 days Median duration of T2DM: 7.2 yr	5380	18 mo	3-pt MACE (CV death, nonfatal MI or stroke) HR: 0.96 (one-sided < 1.17); p=0.32
SAVOR-TIMI 53 (Scirica 2013)	Saxagliptin 2.5–5 mg daily (based on eGFR)	Mean age: 65.1 A1C: 6.5%–12.0% (mean 8.0%) Age ≥ 40 and established CVD (78.4%) or Age ≥ 55 and several CV risk factors Median duration of T2DM: 10.3 yr	16,492	2.1 yr	3-pt MACE HR: 1.0 (0.89–1.12) HHF HR: 1.27 (1.07–1.51)
CARMELINA (Rosenstock 2019a)	Linagliptin 5 mg daily	Mean age: 66.1 A1C: 6.5%–10.0% (mean 7.8%) High CV risk (established CVD 57%) or High renal risk (kidney disease 74%) Mean duration of T2DM: 15 yr	6991	2.2 yr	3-pt MACE HR: 1.02 (0.89–1.17)
CAROLINA (Rosenstock 2019b)	Linagliptin 5 mg vs. glimepiride 1–4 mg daily	Mean age: 64 A1C: 6.5%–8.5% (mean 7.2%) Established CVD (42%) or high CV risk Median duration of T2DM: 6.3 yr	6042	6.3 yr	3-pt MACE HR: 0.98 (0.84–1.14)

ACS = acute coronary syndrome; CV = cardiovascular; CVD = cardiovascular disease; CVOT = cardiovascular outcome trial; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; HHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events; pt = point; T2DM = type 2 diabetes; UA = unstable angina.

Information from: Green JB, Angelyn Bethel M, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232-42; Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA 2019a;321:69-79; Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019b;322:1155-66; Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26; White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.

DPP-4 Inhibitors

The DPP-4 inhibitor class has lesser effect on glycemic control than other classes of diabetes medications, with mean reductions in A1C of 0.6%–1.1% in trials and reductions in fasting blood glucose of 13–28 mg/dL (Aroda 2012). Effects on other CV risk factors, including body weight, blood pressure, and lipid concentrations, have been neutral or modest (Ussher 2014; Aroda 2012; Karagiannis 2012).

Two CVOTs with DPP-4 inhibitors included exclusively patients with established CVD. The TECOS trial evaluated sitagliptin in patients 50 and older with T2DM and a history of CVD. The primary outcome of 4-point MACE and secondary outcome of 3-point MACE met the criteria for noninferiority, but not superiority, compared with placebo (Green 2015).

In the EXAMINE trial, patients with a recent acute coronary syndrome (ACS) were randomized to receive alogliptin or placebo. The primary end point of 3-point MACE and secondary end point of 3-point MACE plus urgent revascularization as a result of unstable angina reached noninferiority, but not superiority, compared with placebo (White 2013). A prespecified subgroup analysis showed that CV death and hospitalization for HF (HHF) were similar among all groups regardless of baseline characteristics, except in patients who did not have HF at baseline, who experienced a significantly increased rate of HHF (2.2% vs. 1.3%; p=0.026) (Zannad 2015). Although the absolute risk increase was small and represented a small subset of the total trial population, a warning for patients at risk of HF was added to the FDA labeling for alogliptin.

Table 2. Summary of CVOTs Evaluating GLP-1 RAs

Trial	Agent	Study Population	n	Median Trial Duration	Outcomes (95% CI)
Harmony Outcomes (Hernandez 2018)	Albiglutide 30–50 mcg weekly	Age ≥ 40 (mean 64.1) A1C > 7.0% (mean 8.7%) Established CVD Mean duration of T2DM: 14.1 yr	9463	1.6 yr	3-pt MACE (CV death, nonfatal MI or stroke) HR: 0.78 (0.68–0.90) Expanded MACE (3-pt MACE + revascularization for UA) HR: 0.78 (0.69–0.90) Fatal or nonfatal MI: 0.75 (0.61–0.90)
ELIXA (Pfeffer 2015)	Lixisenatide 10–20 mcg daily	Age ≥ 30 (mean 60) A1C: 5.5%–11.0% (mean ACS within 180 days) Mean duration of T2DM: 9.4 yr	6068	25 mo	4-pt MACE (3-pt MACE + hospitalization for UA) HR: 1.02 (0.89–1.17)
LEADER (Marso 2016b)	Liraglutide 1.8 mg daily	Mean age: 64.2 A1C > 7% (mean 8.0%) Age ≥ 50 and established CVD, CKD, or HF (81.3%) or Age ≥ 60 and 1 CV risk factor Mean duration of T2DM: 12.8 yr	9340	3.8 yr	3-pt MACE HR: 0.87 (0.78–0.97) CV death HR: 0.78 (0.66–0.93) All-cause mortality HR: 0.85 (0.74–0.97)
SUSTAIN-6 (Marso 2016a)	SC semaglutide 0.5–1.0 mg weekly	Mean age: 64.7 A1C > 7% (mean 8.7%) Age ≥ 50 and established CVD, CKD, or HF (83.0%) or Age ≥ 60 and 1 CV risk factor Median duration of T2DM: 13.9 yr	3297	109 wk	3-pt MACE HR: 0.75 (0.58–0.95) Nonfatal stroke HR: 0.61 (0.39–0.99)
PIONEER-6 (Husain 2019)	Oral semaglutide 14 mg daily	Mean age: 66 A1C > 7% (mean 8.2%) Age ≥ 50 and established CVD, CKD, or HF (84.7%) or Age ≥ 60 and 1 CV risk factor Median duration of T2DM: 14.9 yr	3183	15.9 mo	3-pt MACE HR: 0.79 (0.57–1.11) CV death HR: 0.49 (0.27–0.92) All-cause mortality HR: 0.51 (0.31–0.84)
REWIND (Gerstein 2019)	Dulaglutide 1.5 mg weekly	Age ≥ 50 (mean 66.2) A1C < 9.6% (mean 7.2%) Age ≥ 50 with vascular disease or Age ≥ 55 with MI; coronary, carotid, or peripheral artery stenosis; LVH, eGFR < 60 mL/min/1.73 m^2 or Age ≥ 60 plus 2 risk factors Median duration of T2DM: 9.5 yr	9901	5.4 yr	3-pt MACE HR: 0.88 (0.79–0.99) Nonfatal stroke HR: 0.76 (0.61–0.95)
EXSCEL (Holman 2017)	Exenatide ER 2 mg weekly	Mean age: 62 A1C 6.5%–10.0% (median 8.0%) Established ASCVD (73.1%) or high CV risk Median duration of T2DM: 12 yr	14,752	3.2 yr	3-pt MACE HR: 0.91 (0.83–1.0) All-cause mortality HR: 0.86 (0.77–0.97)

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; ER = extended release; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; LVH = left ventricular hypertrophy; SC = subcutaneous(ly).

Information from: Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. Lancet 2019;394:121-30; Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomized placebo-controlled trial. Lancet 2018;392:1519-29; Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228-39; Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841-51; Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016a;375:1834-44; Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016b;3756:311-22; Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57.

The CVOTs evaluating saxagliptin and linagliptin included patients with CVD or patients at high risk of CVD. The SAVOR-TIMI 53 trial evaluated saxagliptin in patients with CVD or several risk factors, defined as age 55 for men and age 60 for women plus dyslipidemia, hypertension, or active smoking. Again, although 3- and 4-point MACE, HF, or coronary revascularization met the criteria for noninferiority, superiority was not met. Furthermore, SAVOR-TIMI 53 again showed an increased risk of HHF compared with placebo (3.5 vs. 2.8%; p=0.007) (Scirica 2013). In a subanalysis, patients at highest risk of HHF had a history of HF, an eGFR of less than 60 mL/minute/1.73 m^2, or an elevated N-terminal proBNP (Scirica 2014). As a result, saxagliptin also has a warning related to the risk of HF. The CVOT program for linagliptin contains two trials, CARMELINA and CAROLINA, which have the most distinctive designs. One trial includes patients with high CV and renal risk, and the other contains a single active comparator group. In CARMELINA, high CV risk was defined as a history of coronary artery disease, stroke, or peripheral vascular disease but also included micro- or macroalbuminuria. High renal risk was defined as an eGFR of 45–75 mL/minute/1.73 m^2 and a urine albumin/creatinine ratio (UACR) greater than 200 mg/g or an eGFR of 15–45 mL/minute/1.73 m^2, regardless of UACR. There were no significant differences in 3-point MACE, 4-point MACE, or HHF compared with placebo (Rosenstock 2019a). The CAROLINA included patients at high CV risk, which was defined as established ASCVD, the presence of two or more risk factors (T2DM for more than 10 years, systolic blood pressure [SBP] greater than 140 mm Hg, current smoker, LDL 135 mg/dL or greater on antihypertensives or lipid-lowering therapies), age 70 and older, or the presence of microvascular disease (eGFR 30–59 mL/minute/1.73 m^2, UACR 30 mg/g or greater, or proliferative retinopathy). Despite earlier trials suggesting sulfonylureas increase the risk of CV events, there were no significant differences in any CV outcomes, including 3-point MACE, 4-point MACE, CV death, or HHF, between linagliptin and glimepiride (Rosenstock 2019b).

Overall, CVOTs show the CV safety of DPP-4 inhibitors compared with placebo and sulfonylureas, at least with respect to 3- and 4-point MACE. However, there is evidence that HHF was increased with alogliptin in patients shortly after ACS and with saxagliptin in patients at high CV risk, so caution should be used in these populations. The DPP-4 inhibitors are safe and effective therapy for glucose control but do not reduce CV risk.

GLP-1 Receptor Agonists

The GLP-1 RAs as a class have greater effects on A1C than the DPP-4 inhibitors as well as beneficial effects on blood pressure, weight, and lipids. In studies, reductions in A1C were 0.5%–1.9%, with greater effects with semaglutide, followed by liraglutide and dulaglutide and then exenatide immediate release (IR) and ER and lixisenatide (Lyseng-Williamson 2019; Aroda 2018). Short-acting agents (lixisenatide and exenatide IR) have greater effects on postprandial blood glucose, whereas longer-acting agents (liraglutide, exenatide ER, and semaglutide) have greater effects on fasting blood glucose (Lyseng-Williamson 2019; Aroda 2018). All GLP-1 RAs have produced a significant weight loss of 1–3 kg compared with placebo. However, semaglutide has resulted in weight loss of up to 6.4 kg (Lyseng-Williamson 2019; Aroda 2018). Effects on blood pressure and lipids are less dramatic and somewhat inconsistent in clinical trials. In the CVOT programs with GLP-1 RAs, SBP was lowered by 1.2–2.6 mm Hg, whereas diastolic BP (DBP) was increased by 0–0.6 mm Hg. Although LDL, TG, and HDL were modestly improved with all medications, the clinical impact is likely insignificant (Gerstein 2019a; Husain 2019; Hernandez 2018; Holman 2017; Marso 2016a, 2016b).

In the CVOT programs, all GLP-1 RAs met noninferiority for CV safety, and some reduced CV events. Differences in inclusion criteria, baseline characteristics, and study durations may account for variations in outcomes. The CV safety of albiglutide was evaluated in the Harmony Outcomes trial, which exclusively enrolled patients with established ASCVD, defined as coronary, cerebrovascular, or peripheral arterial disease. The primary outcome of 3-point MACE, driven by a 25% reduction in MI, was significantly reduced with albiglutide (HR 0.78; p=0.0006) (Hernandez 2018). The benefit occurred relatively early, but this was a very high-risk patient population. Of note, albiglutide was withdrawn from the market in 2018 because of a lack of sales. The ELIXA trial evaluating lixisenatide included patients with a recent ACS. Lixisenatide showed CV safety but did not meet superiority for any of the CV outcomes, including 3-point MACE, 4-point MACE, or HHF (Pfeffer 2015).

All other CVOTs were conducted in patients with either established ASCVD or at high CV risk; however, these definitions varied by trial. The CVOTs evaluating liraglutide, subcutaneous semaglutide, and oral semaglutide included similar patient populations who were 50 and older with at least one CV condition (congenital heart disease, CVD, peripheral vascular disease, CKD stage 3 or greater, or HF New York Heart Association class II or III) or who were 60 and older with one additional risk factor (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or ankle-brachial index less than 0.9). The primary outcome of 3-point MACE was significantly reduced with liraglutide compared with placebo (13.0% vs. 14.9%; HR 0.87; p=0.01). This result was primarily driven by a reduction in CV death, which was the only component of the composite that was significantly reduced. Subgroup analyses showed that benefit was greatest in patients with an eGFR of less than 60 mL/minute/1.73 m^2 and in those with established CVD (Marso 2016b).

The SUSTAIN-6 and PIONEER-6 trials evaluated subcutaneous and oral semaglutide, respectively. In SUSTAIN-6, 83% of patients had established CVD, according to the trial

definition. If CKD is removed as a criterion, 58.8% of patients had CVD. The primary outcome of 3-point MACE was significantly reduced by 26% (p<0.001), with nonfatal stroke being the only individual component that was significantly reduced (1.6% vs. 2.7%; HR 0.61; p=0.04). No difference occurred in treatment effect in subgroup analyses. Diabetic retinopathy complications increased compared with placebo (3 vs. 1.8%; HR 1.76; p=0.02). The difference occurred early in the trial and was thought to be related to rapid glucose lowering (Marso 2016a). Of patients experiencing complications, 83.5% had preexisting retinopathy, which led to the exclusion of patients with retinopathy in PIONEER-6. As opposed to SUSTAIN-6, PIONEER-6 was an event-driven trial that resulted in a shorter follow-up period. The primary outcome, 3-point MACE, was reduced by 21% for oral semaglutide, which met the criteria for noninferiority, but not superiority. The extended composite outcome, which included 3-point MACE plus hospitalization for unstable angina or HF, also met the terms for noninferiority, but not superiority. When exploring individual components of the composite outcome, CV death was significantly reduced with oral semaglutide compared with placebo (0.9% vs. 1.9%; HR 0.49; CI, 0.27–0.92). All-cause mortality also occurred in fewer patients receiving oral semaglutide (1.4% vs. 2.8%; HR 0.51; CI, 0.31–0.84). Of note, because the primary outcomes did not meet statistical significance for superiority, they are considered exploratory (Husain 2019). The difference in outcomes of these trials is of interest because all other parameters, including glycemic control and weight loss, have been similar between the two formulations. The PIONEER-6 was shorter in duration, which may account for the decreased effect, even though there were sufficient events to grant adequate power. Given the results of LEADER, SUSTAIN-6, and PIONEER-6, liraglutide and subcutaneous semaglutide, but not oral semaglutide, were granted an indication for reducing MACE for patients with established CVD.

Dulaglutide was evaluated in the REWIND trial, which used inclusion criteria on the basis of CV risk stratified by age. Of all the CVOTs conducted in the GLP-1 RA class, REWIND had the fewest patients with established CVD at baseline and the longest study duration. Patients also had a lower mean A1C and shorter duration of diabetes. After a 5.4-year follow-up, 3-point MACE was significantly reduced with dulaglutide by 12% (p=0.026). This was driven by a significant reduction in nonfatal stroke, which was reduced by 24% (p=0.017). Results were consistent across all subgroups, including those with or without established CVD. Other individual components as well as all-cause mortality and HHF were similar between dulaglutide and placebo (Gerstein 2019a). Dulaglutide is now approved for reducing MACE in patients with established CVD and those at high CV risk.

Finally, the EXCSEL trial evaluating exenatide ER included 70% of patients who had previous CV events. Median follow-up was 3.2 years; however, the median time of exposure to study drug was only 2.4 years, and the median percentage of time patients received the study medication was 75%. The primary outcome of 3-point MACE met the criteria for noninferiority, but not superiority (HR 0.91; p=0.06). The risk of all-cause mortality was lower with exenatide but cannot be considered statistically significant because of the hierarchical testing model. No other CV outcomes were significant (Holman 2017).

Mechanism of CV Risk Reduction

Given the evidence of CV efficacy, the benefits of GLP-1 RAs outweigh the risks for most patient populations, especially those with a history, or at high risk, of CVD. The GLP-1 RAs are thought to exert CV protective effects through improved endothelial function, vasodilation, and improved blood flow. Additional effects thought to improve CV outcomes are reduced fatty acid use; reduced body weight, blood pressure, and lipids; and natriuresis, resulting in decreased blood volume. These effects are more pronounced with GLP-1 RAs than with DPP-4 inhibitors, which likely explains the differences in CV outcomes in clinical trials (Scheen 2018; Ussher 2014).

SGLT-2 Inhibitors

Effects on CV Risk Factors and CV Outcomes

The SGLT-2 inhibitors improve several CV risk factors, including A1C, fasting blood glucose, weight, and HDL. As a class, the SGLT-2 inhibitors lower A1C by a mean of 0.6%–0.9%, with canagliflozin having a greater effect than empagliflozin or dapagliflozin (Zaccardi 2016). In studies, fasting blood glucose was significantly reduced by a mean of 19.8–36 mg/dL compared with placebo (Zaccardi 2016). The SGLT-2 inhibitors lowered SBP and DBP by 2.5–5 mm Hg and 1.5–2 mm Hg, respectively (Mazidi 2017; Zaccardi 2016). Weight loss, though statistically significant, is somewhat lower than with GLP-1 RAs, at 1–2.8 kg (Mazidi 2017; Zaccardi 2016). Compared with other agents, especially those known to cause weight gain like sulfonylureas and insulin, weight loss with the SGLT-2 inhibitors was as high as 4.4 kg (Zaccardi 2016). The SGLT-2 inhibitors have produced not only increases in HDL, but also modest increases in LDL (Mazidi 2017; Zaccardi 2016).

Table 3 summarizes the CVOTs evaluating empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin: the EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and VERTIS CV trials, respectively (Cannon 2020; Wiviott 2019; Neal 2017; Zinman 2015). The EMPA-REG OUTCOME and VERTIS CV trials included only patients with established ASCVD, whereas CANVAS and DECLARE-TIMI 58 included patients with established ASCVD or with several risk factors for ASCVD, which was defined differently in the two trials (Cannon 2020; Wiviott 2019; Neal 2017; Zinman 2015). The CANVAS defined high risk as 50 and older with two additional risk factors, including duration of diabetes of at least 10 years, SBP greater than 140 mm Hg while receiving antihypertensive treatment, smoking, micro- or macroalbuminuria, or HDL less than 38.7 mg/dL

Table 3. Summary of CVOTs Evaluating SGLT-2 Inhibitors

Trial	Agent	Study Population	n	Median Trial Duration	Outcomes (95% CI)
EMPA-REG OUTCOME (Zinman 2015)	Empagliflozin 10–25 mg daily	Mean age: 63 A1C 7%–10% (mean 8.0%) Established CVD	7020	3.1 yr	3-pt MACE (CV death, nonfatal MI or stroke) HR: 0.86 (0.74–0.99) 4-pt MACE (3-pt MACE + hospitalization for UA) HR: 0.89 (0.78–1.01) CV death HR: 0.62 (0.49–0.77) All-cause mortality HR: 0.68 (0.57–0.82) HHF HR: 0.65 (0.5–0.85)
CANVAS (Neal 2017)	Canagliflozin 100–300 mg daily	Mean age: 63.3 A1C: 7.0%–10.5% (mean 8.2%) Age ≥ 30 with established CVD (65.6%) or Age ≥ 50 with ≥ 2 CV risk factors Mean duration of T2DM: 13.5 yr	10,142	126 wk	3-pt MACE HR: 0.86 (0.75–0.97) All-cause mortality HR: 0.87 (0.74–1.01) CV death HR: 0.87 (0.72–1.06)
DECLARE-TIMI 58 (Wiviott 2019)	Dapagliflozin 10 mg daily	Mean age: 64 A1C 6.5%–10% (mean 8.3%) Age ≥ 40 with established CVD (40.5%) or Men ≥ 55 or women ≥ 60 with ≥ 1 additional CV risk factor Mean duration of T2DM: 11 yr	17,160	4.2 yr	3-pt MACE HR: 0.93 (0.84–1.03) CV death or HHF HR: 0.83 (0.73–0.95) HHF HR: 0.73 (0.61–0.88)
VERTIS CV (Cannon 2020)	Ertugliflozin 5–15 mg daily	Mean age: 64.4 A1C 7.0%–10.5% (mean 8.2%) Mean duration of T2DM: 13 yr Established ASCVD	8246	3.0 yr	3-pt MACE HR: 0.97 (0.85–1.11) CV death or HHF HR: 0.88 (0.75–1.03) HHF HR: 0.70 (0.54–0.9)

SGLT-2 = sodium-dependent glucose cotransporter-2.

Information from: Neal B, Perkovic B, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57; Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57; Zinman B, Wanner C, Lachin HM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28; Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425-35.

(Neal 2017). High risk in DECLARE-TIMI 58 was considered men older than 55 or women older than 60 with one or more risk factors, including hypertension, dyslipidemia (LDL greater than 130 mg/dL or use of lipid-lowering therapy), or tobacco use (Wiviott 2019). The EMPA-REG OUTCOME and VERTIS CV trials included the highest percentage of patients with established ASCVD, whereas the DECLARE-TIMI 58 had the lowest (Cannon 2020; Wiviott 2019; Neal 2017; Zinman 2015). This is important when interpreting results, especially with respect to primary versus secondary prevention.

Furthermore, CANVAS, DECLARE-TIMI 58, and VERTIS CV all had changes in trial design after patient enrollment, which affected statistical analysis. The CANVAS trial was initiated before FDA approval and was designed to establish CV safety. After approval of canagliflozin in 2013, a second study, CANVAS-R, with a similar trial design but aimed at evaluating renal outcomes, was initiated. Data from the two trials were compiled to evaluate CV, renal, and safety outcomes (Neal 2017). In addition, because the EMPA-REG OUTCOME showed primary improvements in CV death and HHF, the primary outcome in DECLARE-TIMI 58 was changed from MACE alone to include two primary outcomes: MACE and CV death or HHF. As a result, the α level was reduced to 0.023 for each outcome. If either was met, the other could be reevaluated at an α level of 0.046 (Wiviott 2019). The VERTIS CV increased sample size and included superiority of CV and renal outcomes in addition to noninferiority (Cannon 2020).

The EMPA-REG OUTCOME and CANVAS both resulted in a significant 14% relative risk reduction in the primary end point of MACE (Neal 2017; Zinman 2015). Empagliflozin also

significantly reduced the risk of CV death by 38%, all-cause death by 32%, and HHF by 15% compared with placebo, with no significant differences in nonfatal MI or stroke (Zinman 2015). Canagliflozin significantly reduced all-cause mortality. Because this was the first of the secondary outcomes in a hierarchical testing model, no other CV outcomes were assessed (Neal 2017). In DECLARE-TIMI 58, dapagliflozin met noninferiority, but not superiority, for reducing MACE. However, the second primary outcome of CV death or HHF was reduced by 17% (p=0.005). This outcome was primarily driven by a 27% reduction in HHF because CV death did not differ between groups (Wiviott 2019). Because DECLARE-TIMI 58 included fewer patients with ASCVD, the effect on CV death may be greater in secondary prevention, whereas the reduction in HHF may be more widely applicable, given that this benefit occurred in both patients with and without HF at baseline. Of note, a meta-analysis of these three trials showed significant reductions of 14% in MACE, 15% in MI, and 20% in CV death with SGLT-2 inhibitors but only in patients with established ASCVD (Zelniker 2019). The VERTIS CV trial evaluating ertugliflozin included exclusively patients with established ASCVD and showed noninferiority to placebo for 3-point MACE. However, the only outcome to show superiority was a 30% reduction in HHF (Cannon 2020).

Two real-world cohort studies, CVD-REAL and CVD-REAL 2, compared the CV effects of SGLT-2 inhibitors as a class with other antihyperglycemic agents on the basis of claims data, medical records, and national registries. Although the studies included any SGLT-2 inhibitor, CVD-REAL included patients receiving primarily canagliflozin (53%) and dapagliflozin (42%), whereas CVD-REAL 2 included patients receiving primarily dapagliflozin (75%) and empagliflozin (9%). At baseline, 13%–26% of patients had CVD, which was lower than in randomized clinical trials. Both studies showed significant reductions in both HHF and all-cause death. Furthermore, CVD-REAL 2 showed a 19% reduction in MI and 32% reduction in stroke, which was not significant in randomized trials. These studies help confirm the CV benefit of SGLT-2 inhibitors, suggest a class effect, and indicate that they are superior to other treatment options (Kosiborod 2018, 2017). New indications on the basis of CVOT data include reduction in CV death in adults with T2DM and established CVD for empagliflozin, reduction in MACE in adults with T2DM and established CVD for canagliflozin, and reduction in HHF in adults with T2DM and established CVD or several risk factors for dapagliflozin.

Several studies have been aimed at further elucidating the use of SGLT-2 inhibitors in HF. Two large randomized clinical trials, DAPA-HF and EMPEROR-Reduced, evaluated dapagliflozin and empagliflozin, respectively, in patients with heart failure with reduced ejection (HFrEF) receiving guideline-directed therapy. At baseline, 42%–50% of enrolled patients had a diagnosis of diabetes. The primary end point, a composite of worsening of HF or CV death, was significantly decreased by 25% in both trials with a 30% reduction in HHF. Of interest, dapagliflozin significantly reduced CV death by 18%, whereas empagliflozin did not differ from placebo. Results were similar regardless of diabetes status (Packer 2020; McMurray 2019). On the basis of the DAPA-HF study, dapagliflozin was approved to reduce the risk of CV death and HHF in adults with HFrEF. The EMPRISE study is a claims-based, cohort trial comparing DPP-4 inhibitors and SGLT-2 inhibitors using real-world data from three major databases. The first interim analysis only compared empagliflozin with sitagliptin but reported a 50% reduction in HHF with empagliflozin 10 mg and 25 mg daily. The percentages of patients with CVD and HF at baseline were 25% and 5%, respectively, again suggesting the HF benefit is preventive. The remaining 5-year analyses will compare HF outcomes with any SGLT-2 inhibitor with those of any DPP-4 inhibitor (Patorno 2019).

Although several trials have shown the CV benefit of SGLT-2 inhibitors, especially as related to HHF, a significant adverse effect occurred in one CVOT. The CANVAS trial showed more lower-limb amputations with canagliflozin than with placebo (6.3 vs. 3.4 events/1000 patient-years; p<0.001). Of note, the absolute risk increase was small, and most increases were in patients with peripheral arterial disease, previous amputation, or neuropathy (Neal 2017). Because no other studies to date have indicated this same risk of amputation, the black box warning was removed; however, canagliflozin still carries a general warning. With careful patient selection, appropriate monitoring, and patient counseling, the SGLT-2 class can safely be prescribed for CV benefit or HHF reduction.

Mechanism for CV Risk Reduction

Despite the improvements in A1C, blood pressure, and weight, the mechanism of CV benefit of this class is thought to be more than simply improvement in CV risk factors. There are several proposed mechanisms by which SGLT-2 inhibitors improve HF-related outcomes. First, natriuresis with SGLT-2 inhibitors occurs in the proximal tubule, which leads to sustained osmotic diuresis, which in turn decreases fluid overload associated with HF. Decreases in blood pressure may also reduce filling pressures and afterload, lessening the demand on the heart. Furthermore, decreases in blood pressure associated with SGLT-2 inhibitors generally do not result in a reflex activation of the sympathetic nervous system, which could result in progression or worsening of HF. Other theories suggest that SGLT-2 inhibitors reduce ventricular remodeling, promote ketone use and metabolism flexibility, and reduce uric acid concentrations, all of which improve cardiac function over time (Verma 2019, 2018; Yuliya 2017).

RENAL OUTCOMES

Diabetic kidney disease (DKD) is defined as an eGFR less than 90 mL/minute/1.73 m^2 or the presence of albuminuria (UACR of 30 mg/g or more) (ADA 2020; Gerstein 2019a). Risk factors for developing DKD include increasing concentrations

of albumin in the urine, the presence of macroalbuminuria, declining eGFR, increasing blood pressure, retinopathy, elevated lipid and/or uric acid concentrations, and a family history of hypertension, macrovascular disease, or DKD (KDOQI 2012). In addition to optimizing glycemic control, renin-angiotensin system (RAS) blockade—including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs)—is the preferred therapy for preventing DKD in patients with diabetes with albuminuria or hypertension (KDOQI 2012). This has been the only recommended pharmacotherapy for 18 years; however, there are some limitations of use, including a history of cough or angioedema, hyperkalemia, renal artery stenosis, or acute renal insufficiency (Perkovic 2019). In addition, RAS blockade may not be as effective in the black population, and some patients may not be reaching optimal or target doses (KDOQI 2012). Of note, even with maximized pharmacotherapy, the risk of developing DKD in patients with diabetes remains.

SGLT-2 Inhibitors

Because the SGLT-2 inhibitor class primarily works to lower glucose through renal mechanisms, glycemic efficacy wanes as eGFR decreases. As a result, early clinical trials targeted populations with limited DKD, and product labels included threshold limitations for use with eGFRs lower than 45 or 60 mL/minute/1.73 m^2. In addition to efficacy concerns below this range, more information was needed to establish renal safety with SGLT-2 inhibitors because they promote diuresis, thereby posing a risk of acute kidney injury (AKI). To date, six randomized clinical controlled trials have been published with primary or secondary renal outcomes (Table 4) (Cannon 2020; Heerspink 2020; Perkovic 2019; Wiviott 2019; Neal 2017; Zinman 2015).

The CREDENCE and DAPA-CKD trials were designed with primary renal composite outcomes. Both studies were terminated early because of apparent efficacy in the treatment arms (Heerspink 2020; Perkovic 2019).

The CREDENCE trial compared canagliflozin 100 mg daily with placebo in patients with diabetes with albuminuric CKD. Patients receiving canagliflozin had a 30% relative risk reduction in the primary composite outcome of SCr doubling, ESRD, or renal or CV death. The results were driven by a 40% reduction in the doubling of SCr and a 32% decrease in the development of ESRD. Important secondary outcomes that met statistical significance were a 20% decrease in a composite of CV death, MI, or stroke and a 39% decrease in HHF. Patients with eGFR values less than 60 mL/minute/1.73 m^2 and UACR concentrations greater than 1000 mg/g experienced the most benefit from therapy. Although hazard ratios were lower in the treatment group, no statistical significance occurred for CV death or death from any cause (Perkovic 2019).

The DAPA-CKD included patients with and without a diagnosis of T2DM (67.5% and 32.5%, respectively) who had an eGFR of 25–75 mL/minute/1.73 m^2 and albuminuria (200–5000 mg/g). There was a 39% relative reduction in the primary composite outcome of decrease in eGFR by 50% or more, development of ESRD, CV death, or renal death in those receiving dapagliflozin 10 mg daily. Although no statistically significant differences in death from renal or CV causes were appreciated, all-cause mortality was 31% lower in the treatment arm (p=0.004). Subgroup analyses indicated consistent benefits in those with an eGFR above and below 45 mL/minute/1.73 m^2 and a UACR above and below 1000 mg/g (Heerspink 2020).

Almost all study participants in CREDENCE and DAPA-CKD were on background RAS blockade, which shows the clinical importance of the findings. Benefits from therapy occurred despite only modest differences in glucose, weight, and blood pressure results between groups. After the release of CREDENCE, major guidelines for diabetes management were updated to recommend canagliflozin for patients with DKD (AACE/ACE 2020; ADA 2020). The results of DAPA-CKD will support the use of dapagliflozin in this population as well (Heerspink 2020).

The EMPA-REG, CANVAS/CANVAS-R, DECLARE-TIMI 58, and VERTIS CV trials were designed as CVOTs but included secondary or exploratory renal outcomes (Cannon 2020; Wiviott 2019; Neal 2017; Zinman 2015). In the 2017 CANVAS program, canagliflozin doses at 100 mg and 300 mg were compared with placebo. The studies evaluated patients with an average eGFR of 76 mL/minute/1.73 m^2 with varying degrees of albuminuria at baseline. There was a decrease in progression of albuminuria (HR 0.73; 0.67–0.79) compared with placebo. This effect was greater in the CANVAS-R study, but both studies within the program had a statistically significant decrease compared with placebo. In addition, canagliflozin performed better in the composite outcome of a sustained 40% reduction in eGFR, the need for renal replacement therapy, or renal death (HR 0.60; 0.47–0.77). There was no difference in the degree of therapy impact on this outcome between the two program trials. Rates of AKI and hyperkalemia did not differ between treatment groups (Neal 2017).

Secondary outcomes of the EMPA-REG OUTCOME trial have been evaluated in post hoc subgroup analyses to garner more information about the renal outcomes of empagliflozin (Wanner 2018, 2016). Patients had established ASCVD at baseline and an eGFR as low as 30 mL/minute/1.73 m^2. Those taking empagliflozin 10 mg or 25 mg daily had a 39% decrease in incident or worsening nephropathy and a 46% decrease in the composite of SCr doubling, initiation of renal replacement therapy, or renal death. Renal safety was also better in the empagliflozin group, with a lower incidence of both acute renal failure and AKI (Zinman 2015).

Renal outcomes of dapagliflozin 10 mg daily were also evaluated in the DECLARE-TIMI 58 study and subsequently reported in 2019 (Mosenzon 2019). The study included fewer patients with established CVD (40.6%) at baseline than the

Table 4. Effects of SGLT-2 Inhibitors on Renal Outcomes in Placebo-Controlled Trials

Trial	Agent	Study Population	n	Median Trial Duration	Outcomes (95% CI)
CREDENCE (Perkovic 2019)	Canagliflozin 100 mg daily	Mean age: 63 34% female eGFR 56.2 mL/min/1.73 m^2 (30 to < 90) UACR > 300–5000 mg/g A1C 8.3% (6.5%–12.0%) > 99% on RAS blockers 50% with established CVD 96.8% with HTN	4401	2.62 yr	ESRD, doubling of SCr, or renal or CV death, HR 0.70 (0.59–0.82), p=0.00001[a] ESRD, doubling of SCr, or renal death, HR 0.66 (0.53–0.81), p<0.001 ESRD, HR 0.68 (0.54–0.86), p=0.002 RRT, kidney transplantation, or renal death, HR 0.72 (0.54–0.97) CV death, HR 0.78 (0.61–1.00), p=0.05 All-cause death, HR 0.83 (0.68–1.02) Safety: AKI, HR 0.85 (0.64–1.13)
CANVAS program (Neal 2017)	Canagliflozin 100 or 300 mg daily	Mean age: 63.3 36% female eGFR 76.7 mL/min/ 1.73 m^2 (≥ 30 mL/min/1.73 m^2) UACR (mg/g) • < 30 (70%) • 30–300 (23%) • > 300 (7%) A1C 8.2% (7.0%–10.5%) 80% on RAS blockers 59% (CANVAS) and 71% (CANVAS-R) with established CVD 90% with HTN	10,142 (4330 CANVAS, 5812 CANVAS-R)	126.1 wk (295.9 wk CANVAS, 108.0 wk CANVAS-R)	40% reduction in eGFR, RRT, or renal death, HR 0.60 (0.47–0.77) Progression of albuminuria, HR 0.73 (0.67–0.79) Safety: AKI, 3.0 per 1000 patient-yr in canagliflozin group vs. 4.1 per 1000 patient-yr in placebo group, p=0.33 Renal-related adverse drug events, including AKI, 19.7 events per 1000 patient-yr in canagliflozin group vs. 17.4 events per 1000 patient-yr in placebo group, p=0.32
DAPA-CKD (Heerspink 2020)	Dapagliflozin 10 mg daily	Mean age: 62 33% female eGFR 43.1 mL/min/ 1.73 m^2 UACR 949 mg/g 67.5% with T2DM 98% on RAS blockade 37.4% with established CVD	4304	2.4 yr	Decline in eGFR ≥ 50%, ESRD, death from renal or CV causes, HR 0.61 (0.51–0.72), p<0.001[a] Decline in eGFR ≥ 50%, ESRD, or death from renal causes, HR 0.56 (0.45–0.68), p<0.001 Death from CV causes or HHF, HR 0.71 (0.55–0.92), p=0.009 Death from any cause, HR 0.69 (0.53–0.88), p=0.004 Safety: Renal-related adverse events were similar between groups, p=0.07

Table 4. Effects of SGLT-2 Inhibitors on Renal Outcomes in Placebo-Controlled Trials (*continued*)

Trial	Agent	Study Population	n	Median Trial Duration	Outcomes (95% CI)
DECLARE-TIMI 58 (Mosenzon 2019; Wiviott 2019)	Dapagliflozin 10 mg daily	Mean age: 64 36% female eGFR 85 mL/min/1.73 m^2 (CrCl ≥ 60) UACR (mg/g) • < 30 (70.9,[b] 69.5,[c] 55.6[d]%) • 30–300 (23.5,[b] 23.2,[c] 30.9[d]%) • > 300 (5.6,[b] 7.3,[c] 13.5[d]%) A1C 8.1%–8.5% (6.5%–12.0%) 81.3% on RAS blockers 39.1,[b] 40.6,[c] 50.8[d]% with established CVD Baseline HTN rate unknown	17,160	4.2 yr	40% decline in eGFR to < 60 mL/min/1.73 m^2, ESRD, or death from renal or CV causes, HR 0.76 (0.67–0.87), p<0.0001 40% decline in eGFR to < 60 mL/min/1.73 m^2, ESRD, or death from renal causes, HR 0.53 (0.43–0.66) p<0.0001 ESRD, HR 0.31 (0.13–0.79), p=0.013 40% decline in eGFR, HR 0.54 (0.43–0.67), p<0.0001 Renal death, HR 0.60 (0.22–1.65), p=0.32 Safety: AKI, 0.8% in dapagliflozin group vs. 1.2% in placebo group
EMPA-REG OUTCOMES (Wanner 2016; Zinman 2015)	Empagliflozin 10 or 25 mg daily	Mean age: 63 30% female eGFR (mL/min/1.73 m^2) • 30 to < 60 (26%) • 60 to < 90 (52%) • ≥ 90 (22%) UACR (mg/g) • < 30 (60%) • 30–300 (29%) • > 300 (11%) A1C 8.1% (7%–10%) 81% on RAS blockers > 99% with established CVD	7020	2.6 yr	Incident or worsening nephropathy, HR 0.61 (0.53–0.70), p<0.001 Doubling of SCr, initiation of RRT, or death from renal disease, HR 0.54 (0.40–0.75), p<0.001 Progression to macroalbuminuria, HR 0.62 (0.54–0.72), p<0.001 RRT, HR 0.45 (0.21–0.97), p=0.04 Safety: Acute renal failure, 5.2% in empagliflozin group vs. 6.6% in placebo group, p<0.01 AKI, 1.0% in empagliflozin group vs. 1.6% in placebo group, p<0.05
VERTIS CV (Cannon 2020)	Ertugliflozin 5–15 mg daily	Mean age: 64.4 30% female eGFR 76 mL/min/1.73 m^2 A1C 8.2% (7.0%–10.5%) Established ASCVD	8246	3.0 yr	Death from renal causes, RRT, or doubling of SCr, HR 0.81 (0.63–1.04) Safety: Acute renal insufficiency was similar between groups

[a]Primary outcome. All other outcomes were secondary or exploratory.
[b]Group with eGFR ≥ 90 mL/min/1.73 m^2.
[c]Group with eGFR 60 to < 90 mL/min/1.73 m^2.
[d]Group with eGFR < 60 mL/min/1.73 m^2.
AKI = acute kidney injury; ESRD = end-stage renal disease; HTN = hypertension; RAS = renin-angiotensin system; RRT = renal replacement therapy; UACR = urine albumin/creatinine ratio (mg/g).
Information from: Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425-35; Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46; Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol 2019;7:606-17; Neal B, Perkovic B, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57; Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306; Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323-34; Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.

EMPA-REG study or CANVAS program. Despite enrolling a group with a lower cardiorenal disease burden, benefits of therapy occurred in renal composite outcomes. These benefits were driven by decreased progression to ESRD and less decline in eGFR with treatment compared with placebo. Development of AKI did not differ between the groups (Mosenzon 2019; Wiviott 2019).

The VERTIS CV, which included a secondary renal composite outcome, including death from renal causes, renal replacement therapy, or doubling of SCr, found no statistically significant benefit with ertugliflozin. Investigators hypothesize that an increase in secondary preventive therapies leading to their study or slight pharmacologic differences in SGLT receptor selectivity contributed to the difference in outcomes in this trial compared with those previously published (Cannon 2020).

In a meta-analysis evaluating the various renal outcomes from EMPA-REG, CANVAS/CANVAS-R, DECLARE-TIMI 58, and CREDENCE, the results indicated a consistent benefit with all renal outcomes when using SGLT-2 inhibitors compared with placebo. Benefits were consistent throughout all four trials, observed at any eGFR value down to less than 30 mL/minute/1.73 m^2, with all baseline UACRs, and regardless of concurrent use of angiotensin-converting enzyme inhibitors or ARBs. In addition, despite concerns about the diuretic effects posing a risk of development or worsening of AKI, there was a 25% decrease in the relative risk of AKI with SGLT-2 inhibitor use (Neuen 2019).

Several ongoing clinical trials are evaluating the renal effects of SGLT-2 inhibitors in those with hepatorenal disease or ESRD, for use in combination with other agents, and compared with other agents. In particular, it will be useful to evaluate the long-term impact on albuminuria and major renal outcomes when using the likely combinations of SGLT-2 inhibitors and incretin mimetics with background therapy of metformin and RAS blockade.

Mechanism for Renal Outcomes

In the CREDENCE trial, reductions in the renal primary composite outcome occurred despite modest differences in glucose control, blood pressure, and weight between the treatment and placebo groups. This suggests that although improvements in these measures will help with renal benefits, canagliflozin's renal effects can also be attributed to glucose-independent mechanisms, specifically intraglomerular pressure reduction (Perkovic 2019). In addition, in nondiabetic CKD models, SGLT-2 inhibitors reduced oxidative stress, fibrosis formation, inflammation, tubular senescence, and glomerular damage (Vergara 2019).

Incretin Mimetics

The pharmacologic impact of GLP-1 RAs on renal health and outcomes remains uncertain. Renal outcomes were evaluated with the use of dulaglutide, liraglutide, subcutaneous semaglutide, and lixisenatide as secondary or exploratory outcomes in four randomized placebo-controlled trials (Gerstein 2019b; Muskiet 2018; Marso 2016a, 2016b). Although there were statistically significant improvements in composite outcomes, these were all driven primarily by improvements in measures of albuminuria. No differences were identified in need for renal replacement therapy, development of ESRD, need for transplantation, doubling of SCr, renal death, or other individual components.

The REWIND, ELIXA, and SUSTAIN-6 trials all reported renal safety profiles for dulaglutide, lixisenatide, and subcutaneous semaglutide similar to placebo. The LEADER publications did not provide information for renal safety outcomes. In addition, although there are no trials with renal outcomes data for exenatide, use should be avoided when the CrCl is less than 30 mL/minute for the short-acting product and when the eGFR is less than 45 mL/minute/1.73 m^2 for the long-acting product. Although rare, there have been published postmarketing reports of AKI or worsening of CKD with the use of the GLP-1 RAs, sometimes resulting in the need for renal replacement therapy.

The TECOS and SAVOR-TIMI 53 CVOTs evaluated secondary renal outcomes in sitagliptin and saxagliptin, respectively. Both studies showed statistically significant decreases in albuminuria with therapy. However, the sitagliptin arm in TECOS had a slight reduction in eGFR compared with placebo early in the trial, which was maintained throughout by an average of 4 mL/minute/1.73 m^2 ($p<0.001$) (Mosenzon 2019; Cornel 2016). The impact of linagliptin was evaluated in a 2013 retrospective pooled analysis of four phase III clinical trials. The investigators evaluated UACR among the 217 participants who had albuminuria on RAS blockade. Over 24 weeks, linagliptin treatment decreased UACR by 28% compared with placebo (Groop 2013). However, in the subsequent small prospective clinical trial MARLINA-T2D, which evaluated linagliptin in patients with early stages of DKD, there was no significant decrease in UACR over the same period. Although MARLINA-T2D was a prospective trial evaluating primary renal outcomes, it was notably shorter and included fewer patients than TECOS and SAVOR-TIMI 53. In addition, both linagliptin trials only included patients treated with RAS blockade, whereas in TECOS and SAVOR-TIMI 53, only 73%–80% of the patients were treated with these agents (Groop 2017).

Overall, the renal data for GLP-1 RAs and DPP-4 inhibitors are largely hypothesis generating (Table 5). The main benefit throughout the studies was improved measures of albuminuria. There are limitations with using albuminuria as the sole marker of beneficial renal effects because there are patients with DKD and reduced eGFR without elevated urinary albumin concentrations. To draw conclusions about the clinical importance of the GLP-1 RAs decreasing albuminuria, longer-term trials with primary renal outcomes will be necessary.

Table 5. Effects of GLP-1 RAs on Renal Outcomes in Placebo-Controlled Trials

Trial	Agent	Study Population	n	Median Trial Duration	Outcomes (95% CI)
REWIND (Gerstein 2019a, 2019b)	Dulaglutide 1.5 mg weekly	Mean age: 66.2 46.3% female eGFR 76.9 mL/min/1.73 m^2 (≥ 15 mL/min/1.73 m^2) UACR—Mean 16.28 mg/g • < 30 (65%) • 30–300 (27%) • > 300 (8%) A1C 7.2% (≤ 9.5%) 81.5% on RAS blockers 31.5% with established CVD 93.2% with HTN	9901	5.4 yr	First occurrence to new macroalbuminuria, 30% decline in eGFR, or RRT, HR 0.85 (0.77–0.93), p=0.0004 New macroalbuminuria, HR 0.77 (0.68–0.87), p<0.0001 Sustained 30% eGFR decline, HR 0.89 (0.78–1.01), p=0.066 RRT, HR 0.75 (0.39–1.44), p=0.39 Safety: Serious renal adverse event, HR 0.90 (0.67–1.20), p=0.46
ELIXA (Muskiet 2018; Pfeffer 2015)	Lixisenatide 10–20 mcg daily	Mean age: 60 30.7% female A1C 7.6% (5.5%–11%) eGFR—76 mL/min/1.73 m^2 (≥ 30 mL/min/1.73 m^2) • 23.3% eGFR ≥ 90 • 53.3% eGFR 60 to < 90 • 23.1% eGFR 30 to < 60 • 0.1% eGFR 15 to < 30 • UACR (mg/g) • < 30 (74%) • 30–300 (19%) • > 300 (7%) 85% on RAS blockers 100% with established CVD (all had a recent acute coronary event per trial design) 76.4% with HTN	6068	108 wk	Change in albuminuria: • 1.69% in patients with normoalbuminuria at baseline, p=0.7398 • 21.10% in patients with microalbuminuria at baseline, p=0.0502 • 39.18% in patients with macroalbuminuria at baseline, p=0.0070 New-onset macroalbuminuria, HR 0.815 (0.665–0.999), p=0.0491 Safety: Renal adverse events 1.6% in both groups
LEADER (Mann 2018; Marso 2016a)	Liraglutide 1.8 mg daily or maximally tolerated dose (median dose reached 1.78 mg)	Mean age: 64.3 35.7% female eGFR 80 mL/min/1.73 m^2 (≥ 15 mL/min/1.73 m^2) A1C 8.7% (≥ 7%) 11.3% with micro- or macroalbuminuria 83.8% on RAS blockers 81.4% with established CVD Baseline HTN rate unknown	9340	3.8 yr	Nephropathy (new-onset macroalbuminuria or doubling of SCr and eGFR ≤ 45 mL/min/1.73 m^2, RRT, or death from renal causes) or retinopathy, HR 0.84 (0.73–0.97), p=0.02 Nephropathy (new-onset macroalbuminuria or doubling of SCr and eGFR ≤ 45 mL/min/1.73 m^2, RRT, or death from renal causes), HR 0.78 (0.67–0.92), p=0.003 New-onset macroalbuminuria, HR 0.74 (0.60–0.91), p=0.004 Rate of eGFR decline was slightly slower in the liraglutide group at 36 mo, HR 1.02 (1.00–1.03) Doubling of SCr, HR 0.89 (0.67–1.19), p=0.49 RRT, HR 0.87 (0.61–1.24), p=0.44 Death from renal causes, HR 1.59 (0.52–4.87), p=0.41

(*continued*)

Table 5. Effects of GLP-1 RAs on Renal Outcomes in Placebo-Controlled Trials (*continued*)

Trial	Agent	Study Population	n	Median Trial Duration	Outcomes (95% CI)
SUSTAIN-6 (Marso 2016b)	Semaglutide SC injection 0.5 mg or 1.0 mg weekly	Mean age: 64.6 39.3% female A1C 8.7% (≥ 7%) eGFR (mL/min/1.73 m^2)—Overall mean unknown • 30% eGFR ≥ 90 • 41.5% eGFR 60 to < 90 • 25.2% eGFR 30 to < 60 • 2.9% eGFR 15 to < 30 • 0.4% eGFR < 15 UACR—Baseline unknown, patients with micro- or macroalbuminuria could enter the trial 83.5% on RAS blockers 83.0% with established CVD 92.8% with HTN	3297	2.1 yr	New or worsening nephropathy (macroalbuminuria, doubling of SCr, eGFR < 45 mL/min/1.73 m^2, or RRT), HR 0.64 (0.46–0.88), p=0.005 Macroalbuminuria, HR 0.54 (0.37–0.77), p=0.001 Doubling of SCr and eGFR mL/min/1.73 m^2 45, HR 1.28 (0.64–2.58), p=0.48 RRT, HR 0.91 (0.40–2.07), p=0.83 <u>Safety:</u> Acute renal failure • Semaglutide 0.5 mg weekly (5.1%) • Semaglutide 1.0 mg weekly (2.8%) • Placebo (4.2%)

Information from: Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. Lancet 2019a;394:121-30; Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomized, placebo-controlled trial. Lancet 2019b;394:131-8; Mann JFE, Fonseca V, Mosenzon O, et al. Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. Circulation 2018;138:2908-18; Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016a;3756:311-22; Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016b;375:1834-44; Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomized placebo-controlled trial. Lancet Diabetes Endocrinol 2018;6:859-69; Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57.

Mechanism for Renal Outcomes

Potential mechanistic theories of renal benefit with GLP-1 RAs include effects that are both direct (promotion of natriuresis and decrease in glomerular hyperfiltration) and indirect (glucose improvements, weight lowering, blood pressure, and lipid impact) (Muskiet 2019).

DISCUSSION ON PLACE IN THERAPY/ TREATMENT ALGORITHMS

Given the results of the CVOTs, renal outcome trials, and subgroup analyses, several guidance documents have recommended individualizing therapy on the basis of CV history, CV risk factors, and the presence of renal disease and risk factors (Table 6). In general, metformin continues to be first-line therapy for all patients without contraindications or intolerances. The GLP-1 RAs and SGLT-2 inhibitors are considered second-line options in both the AACE/ACE 2020 consensus statement and the ADA 2020 standards of care, with AACE/ACE recommending them above other classes (ADA 2020; Garber 2020).

For patients with high-risk or established ASCVD, the AACE/ACE, ADA, and ACC guidelines recommend GLP-1 RAs or SGLT-2 inhibitors with proven efficacy regardless of glucose control, which may result in patients starting these agents when their A1C is at goal or in place of metformin. Medications with proven efficacy for ASCVD and high risk of ASCVD include liraglutide, subcutaneous semaglutide, albiglutide, dulaglutide, empagliflozin, and canagliflozin (ADA 2020; Das 2020; Garber 2020). In general, SGLT-2 inhibitors are preferred in patients with HF, specifically with those with HFrEF. All SGLT-2 inhibitors decrease HHF, with dapagliflozin and empagliflozin having data in HF for patients without diabetes (ADA 2020; Das 2020; Garber 2020; Packer 2020). For patients with CKD and a sufficient eGFR, SGLT-2 inhibitors are preferred. Use of canagliflozin and dapagliflozin is supported by primary outcomes data, and empagliflozin has shown benefit in secondary analyses (Heerspink 2020; Perkovic 2019; Wanner 2016; Zinman 2015). Again, these agents can be initiated regardless of A1C or glycemic control.

Patient Care Scenario

A 63-year-old man with a history of T2DM for 10 years, hypertension for 12 years, HFrEF, and CKD presents to your clinic for diabetes management. Pertinent medications include metformin ER 1000 mg daily, saxagliptin 2.5 mg daily, amlodipine 10 mg daily, lisinopril 40 mg daily, carvedilol 12.5 mg twice daily, aspirin 81 mg daily, furosemide 20 mg as needed, and rosuvastatin 20 mg daily. Findings today include blood pressure 138/78 mm Hg, A1C 8.1%, eGFR 42 mL/minute/1.73 m^2, UACR 332 mg/g, and left ventricular ejection fraction 40%. The patient denies hypoglycemia but reports an increased need for furosemide because of lower-extremity edema. Which one of the following medication changes would be best to recommend for this patient?

A. Discontinue metformin and initiate dapagliflozin 10 mg daily.
B. Discontinue saxagliptin and initiate canagliflozin 100 mg daily.
C. Add empagliflozin 10 mg daily.
D. Discontinue saxagliptin and initiate semaglutide subcutaneously 0.25 mg weekly.

ANSWER

Answer B is correct. When evaluating the patient's current therapy, the safety of metformin may be of concern because the patient has CKD; however, new dosing guidance allows for maintenance of therapy for an eGFR greater than 30 mL/minute/1.73 m^2 with a maximum dose of 1000 mg daily. Therefore, metformin need not be discontinued at this time. Saxagliptin, conversely, has been shown in clinical trials to increase the risk of HHF. This risk was greatest in patients with a history of HF and an eGFR less than 60 mL/minute/1.73 m^2. Given this patient's reduced ejection fraction and increased furosemide use, it is likely prudent to discontinue saxagliptin at this time.

In general, SGLT-2 inhibitors have more data than GLP-1 RAs on improving outcomes in HF and CKD. Dapagliflozin has significant data in HF but has not been studied in patients with an eGFR less than 45 mL/minute/1.75 m^2; hence, it may not be appropriate for this patient. Canagliflozin and empagliflozin reduce the progression of kidney disease, and canagliflozin has a specific indication and dosing for patients with a UACR greater than 300 mg/g.

1. Scirica BM, Braunwald E, Raz I, et al. HF, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579-88.
2. Neal B, Perkovic B, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
3. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.

Table 6. Summary of Major Guideline Recommendations

Patient Population	ADA 2020	AACE/ACE 2020	ACC/AHA 2020
General diabetes management	First line: Metformin Second line: GLP-1 RA, SGLT-2, DPP-4 inh, TZD, SU (depending on compelling needs)	Strongest recommendation: Metformin, GLP-1 RA, SGLT-2 Other options: DPP-4 inh, TZD, SU, AGI	N/A
High-risk or established ASCVD	GLP-1 RA or SGLT-2[a]	GLP-1 RA or SGLT-2[a]	GLP-1 RA or SGLT-2[a]
HFrEF	First line: SGLT-2[a] Second line: GLP-1 RA	GLP-1 RA or SGLT-2[a]	SGLT-2[a]
CKD (stage 3 or with albuminuria)	First line: SGLT-2[a] Second line: GLP-1 RA	GLP-1 RA or SGLT-2[a]	First line: SGLT-2 with proven benefit[a] Second line: GLP-1 RA

[a]Regardless of baseline A1C or glycemic control.

AGI = α-Glucosidase inhibitor; DPP-4 inh = dipeptidyl peptidase-4 inhibitor; HFrEF = heart failure with reduced ejection fraction; N/A = not applicable; SU = sulfonylurea; TZD = thiazolidinedione.

Information from: American Diabetes Association (ADA). Pharmacology approaches to glycemic treatment: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020;43:S98-S110; Das SR, Everett BM, Birtcher KK, et al. 2020 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes. JACC 2020;76:1117-45; Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2020 executive summary. Endocr Pract 2020;26:107-39.

Practice Points

Key updates in cardiorenal outcomes in T2DM include the following:

- **Diabetes is associated with many cardiorenal complications, which may be affected by antihyperglycemic treatment strategies. The FDA previously required that newer diabetes medications prove CV safety, which led to the identification of many medications that reduce cardiorenal outcomes.**
- **Various guidelines stress the importance of using a patient-specific approach and recommend specific therapies for patients with ASCVD, HF, and CKD.**
- **DPP-4 inhibitors have relative CV safety but no benefit with respect to MACE; however, saxagliptin and alogliptin increase the risk of HHF. The risk of HHF is increased in patients with a history of HF and CKD.**
- **All GLP-1 RAs have consistently reduced 3-point MACE except for exenatide, oral semaglutide, and lixisenatide. This was most prominent in patients with established CVD.**
- **Empagliflozin and canagliflozin have also reduced MACE in patients with established CVD and those at high risk of CVD. All SGLT-2 inhibitors have decreased the risk of HHF.**
- **SGLT-2 inhibitors decrease the progression of albuminuria, decrease the progression to ESRD, and slow the decline of eGFR compared with placebo. Canagliflozin is currently preferred because of the benefits observed as primary outcomes in the CREDENCE trial. In addition, SGLT-2 inhibitors exert a protective effect against AKI.**
- **Clinicians should expect an initial decline in eGFR when initiating SGLT-2 inhibitors for renal benefits.**
- **GLP-1 RAs decrease the incidence and progression of albuminuria in patients with T2DM at various levels of baseline kidney function.**
- **DPP-4 inhibitors may decrease UACR and appear safe with respect to renal outcomes. All agents except for linagliptin require renal dose adjustment in those with CKD to avoid accumulation.**

Overall, guidelines have focused on providing patient-specific, evidence-based care for patients with T2DM to reduce the risk of CV and renal complications. Although some clinical trial outcomes have been consistent across agents in a certain class (progression of CKD with SGLT-2 inhibitors), others have varied (MACE reduction or HHF), and many outcomes are based on secondary objectives or subgroup analyses. It is still unclear whether variations in outcomes are related to trial design, study population, or effects of the medications. When determining therapy, the trial populations and primary outcome data should be considered. Further trials are required to elucidate what level of CV or renal risk indicates use of these agents and the role of early combination therapy with agents proven to have cardiorenal benefits.

CONCLUSION

Recent cardiorenal outcome trials, specifically with GLP-1 RAs and SGLT-2 inhibitors, have led to a major shift in the management of diabetes, CV risk, and nephropathy. Some GLP-1 RAs have reduced MACE in patients with established ASCVD and high CV risk in clinical trials. The SGLT-2 inhibitors have reduced HHF and progression of renal disease, and some agents have reduced MACE and CV death. According to these data, the role of these classes was expanded to a second-line option for diabetes management after metformin and as first-line or add-on therapy regardless of glycemic control for certain patient populations, including patients with ASCVD, HFrEF, and nephropathy. Further research may continue to elucidate the role of these agents outside diabetes.

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Self-Assessment Questions

1. A 65-year-old man presents to your clinic for diabetes management. He also has hypertension (HTN) and dyslipidemia. He smokes 1 pack/day. The patient previously managed his diabetes with diet and exercise together with metformin, but his A1C recently increased to 8.5%. He is adamantly against injections. Which one of the following oral agents is best to recommend to reduce this patient's risk of major adverse cardiovascular events (MACE)?

   A. Semaglutide
   B. Sitagliptin
   C. Canagliflozin
   D. Dapagliflozin

Questions 2 and 3 pertain to the following case.

A.J., a 48-year-old man, presents to your cardiovascular (CV) risk reduction clinic. He was hospitalized 3 months ago for his first MI. At that time, A.J. was given a diagnosis of diabetes on the basis of an A1C of 9.5% and was initiated on metformin and alogliptin. His A1C today is 6.8%. His blood pressure is 126/64 mm Hg and heart rate is 63 beats/minute. A.J. is very concerned about heart disease because his father died of an MI at age 50.

2. Which one of the following best evaluates the CV safety and efficacy of A.J.'s current therapy?

   A. Alogliptin has neutral effects on MACE outcomes in patients after acute coronary syndrome (ACS) but increases hospitalization for heart failure (HHF) in patients without a history of heart failure (HF).
   B. Alogliptin significantly decreases MACE in patients with established CV disease (CVD) and is best for his therapy because his A1C has reached goal.
   C. Other dipeptidyl peptidase-4 (DPP-4) inhibitors are superior with respect to reducing MACE and should be used in place of alogliptin to reduce HF risk.
   D. Classes in addition to DPP-4 inhibitors have significantly reduced MACE in patients immediately after ACS.

3. Assuming all other laboratory values are within normal limits, which one of the following is best to recommend to lower A.J.'s risk of CV events?

   A. Continue metformin and alogliptin, and repeat A1C in 3 months.
   B. Continue metformin and alogliptin, and initiate canagliflozin.
   C. Discontinue alogliptin, and initiate lixisenatide.
   D. Discontinue alogliptin, and initiate empagliflozin.

Questions 4 and 5 pertain to the following case.

H.D. is a 60-year-old woman with a medical history that includes diabetes, HTN, peripheral vascular disease, coronary artery disease, HF, dyslipidemia, and chronic kidney disease (CKD). Her home medications include metformin 500 mg twice daily, lisinopril 40 mg daily, metoprolol succinate 100 mg daily, furosemide 20 mg daily, aspirin 81 mg daily, and atorvastatin 80 mg daily. Her blood pressure today is 146/90 mm Hg with heart rate 72 beats/minute. Other pertinent findings include A1C 8.8%, eGFR 40 mL/minute/1.73 m^2, urine albumin/creatinine ratio (UACR) 356 mg/g, and left ventricular ejection fraction 35%.

4. Which one of the following best evaluates metformin use for H.D.?

   A. Metformin is contraindicated in patients with an eGFR less than 45 mL/minute/1.73 m^2 and should be discontinued because of the risk of lactic acidosis.
   B. Because the patient has been tolerating metformin, she may continue it as long as her eGFR is greater than 30 mL/minute/1.73 m^2 with a maximum dose of 1000 mg daily.
   C. Metformin is considered safe in patients with an eGFR greater than 30 mL/minute/1.73 m^2, and the dose should be increased to reach the A1C goal.
   D. Metformin can significantly worsen renal function and should therefore be discontinued in patients with an eGFR less than 45 mL/minute/1.73 m^2.

5. Which one of the following is best to recommend for H.D.?

   A. Discontinue metformin and initiate exenatide 2 mg weekly.
   B. Discontinue metformin and initiate dapagliflozin 5 mg daily.
   C. Add canagliflozin 100 mg daily.
   D. Add oral semaglutide 3 mg daily.

Questions 6–8 pertain to the following case.

M.H. is a 61-year-old man (BMI 34 kg/m^2) with a history of diabetes, HTN, and tobacco use. His home drug include ramipril 10 mg daily and metformin 1000 mg twice daily. M.H.'s vital signs include blood pressure 154/96 mm Hg and heart rate 76 beats/minute. Recent blood tests show A1C 7.8%, UACR 90 mg/g, TC 196 mg/dL, LDL 121 mg/dL, TG 156 mg/dL, HDL 42 mg/dL, SCr 1.0 mg/dL, and BUN 18 mg/dL.

6. M.H.'s prescriber is considering adding a sodium-dependent glucose cotransporter-2 (SGLT-2) inhibitor. Which one of the following CV risk factors is most likely to be worsened by adding this agent?

   A. Blood pressure
   B. Weight
   C. LDL
   D. A1C

7. Which one of the following is best to recommend for M.H. to reduce MACE and progression of nephropathy?

   A. Linagliptin 5 mg daily
   B. Liraglutide 0.6 mg daily
   C. Empagliflozin 10 mg daily
   D. Dapagliflozin 10 mg daily

8. The prescriber is considering using a glucagon-like peptide-1 receptor agonist (GLP-1 RA) for M.H. Which one of the following agents has the most evidence to support its use for MACE reduction for M.H.?

   A. Liraglutide
   B. Dulaglutide
   C. Exenatide ER
   D. Oral semaglutide

9. A 56-year-old woman has a medical history of diabetes, HTN, ischemic stroke, and dyslipidemia. Her home medications include metformin 1000 mg twice daily. Her HTN and dyslipidemia are well controlled. Her most recent A1C was 7.6%. Which one of the following is the best adjunctive therapy to recommend for this patient?

   A. Dapagliflozin
   B. Glipizide
   C. Sitagliptin
   D. Dulaglutide

10. A 64-year-old man with heart failure with reduced ejection fraction (HFrEF) is receiving guideline-directed medical therapy. His medical history includes MI, HTN, and dyslipidemia. The patient was recently initiated on dapagliflozin. Which one of the following best evaluates the CV benefits from dapagliflozin in this patient?

    A. Dapagliflozin reduces HHF in patients with and without diabetes and should be continued.
    B. Dapagliflozin reduces MACE in patients with established atherosclerotic cardiovascular disease (ASCVD) and should be continued.
    C. Dapagliflozin reduces HHF but only in patients with diabetes, so it should not be used.
    D. Dapagliflozin has not been shown to reduce MACE or HHF, so it should not be used.

Questions 11 and 12 pertain to the following case.

T.R., a 57-year-old man (BMI 30.3 kg/m^2) with a 6-year history of type 2 diabetes (T2DM), presents for diabetes management. His medical history also includes HTN, peripheral neuropathy, retinopathy, and dyslipidemia. T.R. takes metformin ER 2000 mg daily, vitamin B_{12} 500 mcg daily, gabapentin 300 mg three times daily, losartan 50 mg daily, atorvastatin 40 mg daily, and aspirin 81 mg daily. His blood pressure today is 138/78 mm Hg and heart rate is 78 beats/minute. Laboratory workup reveals A1C 7.4%, SCr 1.3 mg/dL, BUN 21 mg/dL with an eGFR of 53 mL/minute/1.73m^2 (stable), and UACR 975 mg/g.

11. Which one of the following is best to recommend as the next step for T.R.'s therapy?

    A. Add linagliptin 5 mg daily.
    B. Decrease metformin to 1000 mg daily.
    C. Add semaglutide 0.25 mg weekly.
    D. Add canagliflozin 100 mg daily.

12. Six months later, T.R. returns to the clinic for a follow-up. He was initiated on empagliflozin, which is titrated to 25 mg daily. He has been pleased with losing a few kilograms, which has motivated him to improve his lifestyle. T.R. is now part of a social media group that is participating in a cleanse program, in which he fasts and drinks only 1 juice per day. His laboratory results today are A1C 6.9%, SCr 1.5 mg/dL, BUN 34 mg/dL, and eGFR 47 mL/minute/1.73 m^2. Which one of the following is best to recommend for T.R.?

    A. Make no changes.
    B. Continue current medications and counsel on healthy diet and fluid intake.
    C. Discontinue empagliflozin.
    D. Discontinue metformin.

13. A 47-year-old woman has a medical history that includes diabetes (8 years) and longstanding uncontrolled HTN. She currently takes metformin 500 mg twice daily, sitagliptin 100 mg daily, amlodipine 10 mg daily, lisinopril/hydrochlorothiazide 40/12.5 mg daily at bedtime, and carvedilol 12.5 mg twice daily. The patient also has a 3-year history of stage 3b CKD. She has been working on her diet and exercise routine over the past several months. She would like to continue and has a goal of losing another 2–4.5 kg (5–10 lb) (BMI 31.1 kg/m^2). Her A1C is 6.4%, and her continuous glucose monitoring download indicates that she is in her target glucose range 86% of the time. Her blood pressure in the clinic has ranged 152/84 mm Hg to 168/88 mm Hg, with heart rate 68–72 beats/minute. Other laboratory values include eGFR 35 mL/minute/1.73 m^2. Which one of the following is best to recommend for this patient?

    A. Add dapagliflozin 10 mg daily.
    B. Discontinue sitagliptin and add canagliflozin 100 mg daily.
    C. Discontinue metformin.
    D. Add liraglutide 0.6 mg daily.

14. A 57-year-old patient with T2DM, HTN, HF, and CKD is initiated on dapagliflozin. According to clinical trials, which one of the following is this patient most likely to experience?

    A. Reduced MACE.
    B. Decreased HHF.
    C. Improved kidney function.
    D. Increased blood pressure.

15. A 63-year-old man (weight 103 kg [228 lb], BMI 37.2 kg/m^2) with a medical history that includes coronary artery bypass grafting 4 years ago, a transient ischemic attack 12 years ago, HTN, and arthritis. He was diagnosed with diabetes 1 year ago. The patient was unable to tolerate metformin. He currently takes semaglutide subcutaneously 1 mg weekly, losartan 100 mg daily, metoprolol succinate 50 mg daily, aspirin 81 mg daily, rosuvastatin 20 mg daily, and acetaminophen 650 mg every 6 hours as needed for arthritis pain. His blood pressure today is 132/68 mm Hg and heart rate is 58 beats/minute. Other pertinent objective findings include A1C 7.4 % (goal <7%), SCr 1.0 mg/dL, eGFR 82 mL/minute/1.73 m^2, UACR 395 mg/g, and ejection fraction 55%. Which one of the following is best to recommend for this patient?

    A. No changes are necessary.
    B. Continue current regimen; emphasize diet and exercise.
    C. Add canagliflozin 100 mg daily.
    D. Add dapagliflozin 5 mg daily.