Optimizing Management of Type 2 Diabetes and Its Complications in Patients With Heart Failure

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Diabetes is an independent risk factor for heart failure (HF), with current trends indicating that nearly half of patients with type 2 diabetes will develop this complication. The presence of diabetes also worsens the prognosis of those with HF; people with both conditions have nearly double the mortality rate of those with HF who do not have diabetes (1–3). Additional risk factors for the development of HF in people with diabetes include increasing age, longer duration of disease, insulin use, ischemic heart disease, peripheral artery disease, nephropathy, poor glycemic management, hypertension, obesity, and higher levels of N-terminal pro b-type natriuretic peptide (2,4,5). Recently, HF, including diabetic cardiomyopathy, has become a more well-recognized complication of diabetes, with a prevalence rivaling that of established cardiovascular disease (CVD). Clinical interest in the management of type 2 diabetes in the presence of HF has grown with the publication of cardiovascular outcomes trials (CVOTs) for sodium–glucose cotransporter 2 (SGLT2) inhibitors demonstrating HF-related benefits and other trials showing heightened risk with the use of certain other antihyperglycemic therapies.

To understand the interrelatedness of diabetes and HF, it is important to understand the pathophysiology of HF in people with diabetes. Structural heart disease via cardiac ischemia and infarction, also known as ischemic cardiomyopathy, is a documented complication of hyperglycemia. Yet, ischemic events are not a requirement for the development of HF in people with diabetes. The presence of systolic or diastolic dysfunction in people with diabetes, in the absence of common causes such as coronary artery disease, hypertension, or valvular heart disease, is termed "diabetic cardiomyopathy" (5). The development of diabetic cardiomyopathy is multifactorial, with insulin resistance, changes in cellular metabolism, and hyperglycemia-induced advanced glycation end products triggering a cascade of deleterious effects that contribute to hypertrophy, fibrosis, autonomic dysfunction, and ultimately impaired ventricular contraction and relaxation (Figure 1) (5–10). These mechanisms lead to the development of HF and should be taken into consideration when selecting pharmacologic therapy for type 2 diabetes.

Recent guidelines for the management of type 2 diabetes focus on patients' comorbidities to determine the most appropriate add-on therapy. In its *Standards of Medical Care in Diabetes—2020,* the American Diabetes Association (ADA) stratifies specific comorbidities that include atherosclerotic CVD, chronic kidney disease (CKD), and HF (11). Metformin, in conjunction with lifestyle modifications that improve glycemic management, continues to be the preferred first-line therapy for the management of type 2 diabetes regardless of comorbidities. For patients with HF, SGLT2 inhibitors demonstrate the strongest evidence for clinical benefit related to HF morbidity and mortality and are recommended regardless of the patient's baseline A1C. A glucagon-like peptide 1 (GLP-1) receptor agonist with established cardiovascular benefit can be considered in this population if SGLT2 inhibitor use is contraindicated or not tolerated or can be added to SGLT2 inhibitor therapy, if needed. Other agents with demonstrated cardiovascular safety may be considered if additional or alternative therapy is needed to further reduce the patient's A1C. These include select dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e., sitagliptin and linagliptin), select basal insulins (i.e., degludec and glargine 100 units/mL), and sulfonylureas with a lower risk of hypoglycemia (i.e., glipizide and glimepiride).

This review describes the co-management of diabetes and HF, provides a review of the preferred medication classes for the treatment of people with both of these diseases, and discusses recent clinical trial data for newer antihyperglycemic agents. It also offers practical considerations for clinicians who treat people with both diabetes

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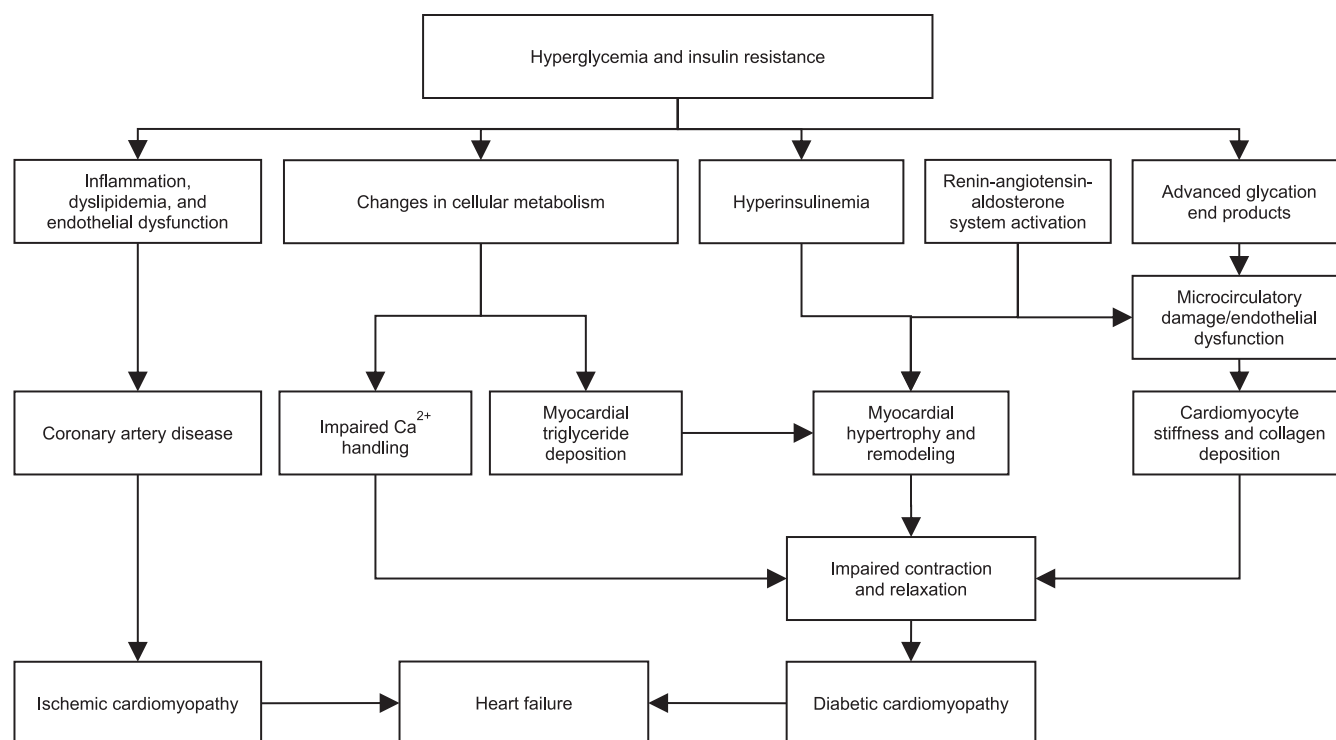**Corresponding author:** Christie A. Schumacher, cschum@midwestern.edu

FIGURE 1 Proposed pathophysiology for HF in people with diabetes (5–10).

and HF. For a more extensive review of all of the drugs used for the treatment of type 2 diabetes, readers are referred to the ADA's Standards of Care (11).

Antihyperglycemic Therapy in People With Type 2 Diabetes and HF

The following noninsulin therapies are highlighted in the ADA's Standards of Care as options for the management of type 2 diabetes in people with HF. Below, we discuss hypothesized mechanisms of benefit or harm in people with HF and review relevant recent clinical trial data.

Metformin

Metformin is the preferred initial therapy in the management of patients with type 2 diabetes, including those with HF, because it is affordable, efficacious, and generally well tolerated (11). Metformin exerts its blood glucose–lowering effects by decreasing hepatic glucose production and intestinal absorption of glucose and increasing peripheral glucose uptake and utilization, thereby improving insulin sensitivity.

Despite initial concerns of lactic acidosis, metformin is considered safe in patients with stable HF and can safely be used in patients with an estimated glomerular filtration rate >30 mL/min/1.73 m^2 (12,13). A systematic review of nine cohort studies involving nearly 34,000 patients

demonstrated that patients with concomitant diabetes and HF who were receiving metformin had a 31% lower risk of all-cause mortality (14). A recent population-based retrospective cohort study further supported this finding, demonstrating a lower risk of hospitalization for HF (HHF) in patients treated with metformin when compared with those who have never been treated with metformin, with an overall risk reduction of 65% in the unmatched cohort and 43% in the matched cohort (15). These two studies and others have demonstrated the cost-effectiveness and safety of metformin in patients with diabetes and HF (14–16).

Caution should be used if there is a decline in cardiac output and subsequent decrease in renal perfusion from acute decompensated HF because the risk of lactic acidosis is greatest in hypoxic states. Metformin should be held or discontinued in such situations and can be reinitiated if patients' renal function recovers and they are hemodynamically stable.

SGLT2 Inhibitors

The significant reduction in HHF seen with SGLT2 inhibitors in clinical trials has established them as second-line therapy after metformin for patients with established atherosclerotic CVD, and they should be considered before a GLP-1 receptor agonist with cardiovascular benefit in patients with CKD or HF independent of baseline

TABLE 1 Summary of SGLT2 Inhibitor CVOTs in Patients With Type 2 Diabetes (17–19)

	EMPA-REG Outcome (Empagliflozin)	CANVAS Program (Canagliflozin)	DECLARE-TIMI 58 (Dapagliflozin)
Study size, *n*	7,020	10,142	17,160
Median follow-up, years	3.1	2.4	4.2
Patient population	A1C 7.0–9.0% without therapy or 7.0–10.0% on therapy; established CVD	A1C 7.0–10.5%; age ≥50 years with at least two CVD risk factors or age ≥30 years with a history of symptomatic CVD	A1C 6.5–12.0%; men age ≥55 years and women age ≥60 years with at least one CVD risk factor or established CVD
Primary end point(s), HR (95% CI)	3-point MACE*: 0.86 (0.74–0.99)	3-point MACE*: 0.86 (0.75–0.97)	3-point MACE*: 0.93 (0.84–1.03); cardiovascular death + HHF: 0.83 (0.73–0.95)
HF-related secondary end point, HR (95% CI)	HHF: 0.65 (0.50–0.85)	HHF: 0.67 (0.52–0.87)	HHF: 0.73 (0.61–0.88)

*3-point MACE included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events; EMPA-REG Outcome, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio.

A1C or individualized A1C target (11). SGLT2 inhibitors promote glucose homeostasis through an insulin-independent mechanism at the proximal tubule of the kidney. SGLT2 facilitates ~90% of renal glucose reabsorption, thereby increasing urinary glucose excretion and ultimately lowering blood glucose levels. In addition, inhibition of SGLT2 increases the fractional excretion of sodium, resulting in a moderate diuretic effect.

Three CVOTs evaluating SGLT2 inhibitors have demonstrated significant reductions in the risk for HHF in patients with type 2 diabetes (35% with empagliflozin, 33% with canagliflozin, and 27% with dapagliflozin) (Table 1) (17–19). These results were consistent regardless of whether patients had a history of HF or established CVD at baseline, and they have been further confirmed in real-world analyses (20–22). In the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, dapagliflozin was shown to decrease both the risk for worsening HF and death from cardiovascular causes in patients with HF with and without diabetes (23). These results appear to be independent of blood glucose, body weight, and blood pressure reductions, a finding that has led investigators to propose potential mechanisms for cardiac benefit. The three most commonly discussed proposed mechanisms are *1)* the diuretic hypothesis, *2)* the "thrifty substrate" hypothesis, and *3)* the sodium hypothesis (24,25).

The diuretic hypothesis is derived from the natriuretic and osmotic effect of inhibition of glucose-coupled sodium reabsorption in the proximal tubule. The increase in sodium excretion drives plasma volume contraction, which may hemodynamically reduce the preload and ventricle filling pressure, leading to a decrease in myocardial oxygen demand, myocardial stretch, and ventricular wall tension (25). In addition, the increase in osmotic diuresis has been shown to decrease both systolic and diastolic blood pressure, which may be the result of persistent volume depletion. Clinical data regarding the diuretic effect are controversial because the plasma volume contraction has been shown to level off at ~12 weeks of treatment (26). In addition, diuretics have not demonstrated morbidity and mortality benefit in patients with HF, leading researchers to believe the benefit extends beyond natriuresis (27).

The thrifty substrate hypothesis is derived from the observation that SGLT2 inhibitors produce an increase in mean plasma ketone levels, notably β-hydroxybutyrate (BHB) (28). The lower glucose levels from SGLT2 inhibitors decrease the insulin response leading to lipolysis and ketogenesis, and it has been suggested that SGLT2 inhibitors directly stimulate glucagon secretion from pancreatic α-cells, which in turn stimulates hepatic ketogenesis. Research has suggested that BHB is a "super fuel" that is used preferentially by cardiomyocytes over fatty acids and glucose and is more energy efficient, improving cardiac contractility. BHB oxidation increases cardiac efficiency and decreases oxygen consumption compared with fatty acids and glucose, leading to a cardioprotective state. In addition, BHB has been shown to have antioxidative, anti-inflammatory, and antiarrhythmic properties, which may also provide cardiac benefit (24,25,29).

The sodium hypothesis is related to the direct effects of SGLT2 inhibitors on cardiac ion homeostasis. Failing

cardiac myocytes demonstrate an increase in activity of the sarcolemmal sodium-hydrogen exchanger, leading to an efflux of calcium from the mitochondria, which further results in a decline in cellular function and a decrease in antioxidant capacity (25). SGLT2 inhibitors may directly bind to the sodium-hydrogen exchanger, decreasing their activity in myocardial cells, leading to a decrease in intracellular sodium, an influx in calcium, and restored myocardial calcium handling. This process is thought to improve mitochondrial energetics, prevent oxidative stress, and subsequently decrease the incidence of ventricular arrhythmias and sudden cardiac death. More detail regarding these hypotheses can be found in a recent publication by Bertero et al. (25).

Despite the cardioprotective benefits demonstrated by SGLT2 inhibitors in recent clinical trials, some precautions exist for their use. Genitourinary tract infections are of concern after initial premarketing studies showed an increased risk; however, real-world data recently demonstrated that the risk may not be as high as previously described (30). Patients should be counseled on good hygiene on initiation of therapy to reduce the risk of this undesirable side effect.

Although SGLT2 inhibitors increase the production of ketones, which may be a mechanism for their cardiovascular benefit, this increase may result in the accumulation of ketones, and patients may experience the rare side effect of euglycemic diabetic ketoacidosis (euDKA). It would be prudent to alert patients to possible precipitating factors for euDKA such as dehydration, discontinued or reduced insulin doses, surgery, and infections (28). Patients should also be educated on possible symptoms of euDKA such as abdominal pain, shortness of breath, fatigue, nausea, and vomiting and should seek immediate medical attention if they experience these symptoms.

The effects of SGLT2 inhibitors on systemic and renal hemodynamics have raised concerns regarding their safety with concomitant use of diuretics or renin-angiotensin-aldosterone system (RAAS) inhibitors, given their duplicative ability to reduce intravascular volume and intraglomerular pressure. The U.S. Food and Drug Administration (FDA) has strengthened its warning about the risk for acute kidney injury with SGLT2 inhibitors in combination with diuretics and RAAS inhibitors; however, these agents all play a valuable role in the management of patients with HF (31).

To reduce the risk of acute kidney injury, caution should be used when starting or increasing the dose of an SGLT2 inhibitor at the same time as an RAAS inhibitor to minimize hemodynamic changes at the kidney.

Additionally, clinicians should reevaluate the need for traditional diuretic therapies, specifically thiazide diuretics, given their mechanism for sodium-wasting at the distal convoluted tubule. Clinical judgement should be used when determining whether to decrease the dose of a loop diuretic when initiating an SGLT2 inhibitor, taking into consideration kidney function, functional class, and volume status.

Another clinical concern may be the risk for hyperkalemia with concomitant use of ACE inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin (ARN) inhibitors, or aldosterone antagonists as guideline-directed medical therapy for HF (32,33). Despite initial concerns for hyperkalemia from the increased sodium load to the distal tubule, subsequent studies have shown that these agents pose no higher risk for this adverse effect compared with placebo and that these medications can be used together safely (34,35).

GLP-1 Receptor Agonists

The ADA Standards of Care recommends an SGLT2 inhibitor after metformin for patients with type 2 diabetes and comorbid HF (11). A GLP-1 receptor agonist with proven cardiovascular benefit is preferred in this population if SGLT2 inhibitor use is contraindicated or is not tolerated by the patient or can be added to SGLT2 inhibitor therapy if further blood glucose lowering is needed. GLP-1 receptor agonists decrease glucagon secretion, increase glucose-dependent insulin secretion, delay gastric emptying, decrease food intake, and preserve β-cell function.

Seven CVOTs have been published investigating the cardiovascular safety of GLP-1 receptor agonists, including oral semaglutide (Table 2). Like other CVOTs, these trials included a primary composite outcome of major adverse cardiovascular events (MACE), which most often included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (36–42). All agents demonstrated at least noninferiority compared with placebo regarding the composite MACE outcome, and four agents (albiglutide, dulaglutide, liraglutide, and semaglutide) demonstrated a reduction in cardiovascular events (37,38,40–42).

Each of the CVOTs with GLP-1 receptor agonists included HHF as a secondary or exploratory outcome. There was no significant difference compared with placebo for any agent with regard to HHF, indicating that these agents are likely safe in patients with HF (36–42). In addition, a subanalysis of patients enrolled in the HARMONY Outcomes (A Long Term, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Effect of

TABLE 2 Summary of GLP-1 Receptor Agonist CVOTs in Patients With Type 2 Diabetes (36–42)

	ELIXA (Lixisenatide)	LEADER (Liraglutide)	SUSTAIN-6 (Semaglutide)	EXSCEL (Exenatide ER)	HARMONY Outcomes (Albiglutide)	REWIND (Dulaglutide)	PIONEER-6 (Oral Semaglutide)
Study size, *n*	6,068	9,340	3,297	14,752	9,463	9,901	3,183
Median follow-up, years	2.1	3.8	2.1	3.2	1.6	5.4	1.3
Patient population	A1C 5.5–11.0%; age ≥30 years with ACS within 180 days of screening	A1C ≥7.0%; age ≥60 years with at least one CVD risk factor or age ≥50 years with established CVD, CKD stage ≥3, or chronic heart failure (NYHA class II or III)	A1C ≥7.0%; age ≥60 years with at least one CVD risk factor, or age ≥50 years with established CVD, CKD stage ≥3, or chronic heart failure (NYHA class II or III)	A1C 6.5–10.0%; no specifications for established CVD or CVD risk factors; per investigators, "designed so that 70% of patients had a history of a CV event"	A1C ≥7.0%; age ≥40 years with established coronary artery disease, cerebrovascular disease, or peripheral arterial disease	A1C ≤9.5%; age ≥60 years with at least two CVD risk factors or age ≥55 years with subclinical vascular or renal disease or age ≥50 years with established CVD	A1C ≥7.0%; age ≥60 years with at least one CVD risk factor or age ≥50 years with established CVD, CKD stage ≥3, or chronic heart failure (NYHA class II or III)
Primary end point(s),* HR (95% CI)	4-point MACE: 1.02 (0.89–1.17)	3-point MACE: 0.87 (0.78–0.97)	3-point MACE: 0.74 (0.58–0.95)	3-point MACE: 0.91 (0.83–1.00)	3-point MACE: 0.78 (0.68–0.90)	3-point MACE: 0.88 (0.79–0.99)	3-point MACE: 0.79 (0.57–1.11)
HF-related secondary end points, HR (95% CI)	HHF: 0.96 (0.75–1.23)	HHF: 0.87 (0.73–1.05)	HHF: 1.11 (0.77–1.61)	HHF: 0.94 (0.78–1.13)	Cardiovascular death + HHF: 0.85 (0.70–1.04)	HHF: 0.93 (0.77–1.12)	HHF: 0.86 (0.48–1.55)

*3-point MACE included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; 4-point MACE also included hospitalization for unstable angina. ACS, acute coronary syndrome; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; ER, extended release; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PIONEER-6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Patients With Type 2 Diabetes Mellitus) trial demonstrated that patients with a history of HF were less likely to experience the primary composite outcome compared with those with no such history when treated with the commercially unavailable albiglutide (40).

Liraglutide has also been evaluated for its impact on clinical stability in high-risk patients within the first 180 days after an admission for HF (43). Approximately 60% of the 300 patients enrolled in the study had a history of type 2 diabetes, 63% had New York Heart Association (NYHA) Class III HF, and liraglutide was titrated to the maximum dose of 1.8 mg per day. There was no difference in clinical stability based on death, hospitalization, and N-terminal pro b-type natriuretic peptide levels. An additional trial evaluating the use of liraglutide in patients with chronic HF with and without diabetes found that liraglutide did not affect left ventricular function; however, it was associated with an increase in heart rate and adverse cardiovascular events, warranting further evaluation of GLP-1 receptor agonists in this population (44).

Weight loss is an additional potential benefit of GLP-1 receptor agonist use in patients with HF. Obesity has been considered a risk factor for developing HF and type 2 diabetes, and strategies to safely reduce weight are encouraged as part of the management plan for both conditions (5,32). Dulaglutide, liraglutide, and semaglutide have demonstrated the strongest cardiovascular benefit in their CVOTs, and although they have shown no

impact on the risk of HHF, their overall efficacy and weight loss benefit may still provide benefit to patients with both diabetes and HF (37,38,41). These agents should be considered after metformin and an SGLT2 inhibitor in patients with type 2 diabetes and HF as long no contraindications are present.

DPP-4 Inhibitors

The ADA recommends using a DPP-4 inhibitor, with the exception of saxagliptin, as an alternative to an SGLT2 inhibitor or GLP-1 receptor agonist or as additional antihyperglycemic therapy after an SGLT2 inhibitor, given their neutral effect on MACE. Conversely, a combined statement from the American Heart Association and the Heart Failure Society of America noted the lack of patients with HF at baseline in the DPP-4 inhibitor CVOTs and acknowledged concerning signals with DPP-4 inhibitors in mechanistic trials (5). The statement concluded that the risk-benefit profile for most DPP-4 inhibitors does not justify their use in patients with type 2 diabetes and comorbid HF or those at risk for HF. DPP-4 inhibitors act by inhibiting the degradation of endogenous GLP-1 and therefore modestly increasing the effects of the incretin system to augment pancreatic insulin secretion.

The four CVOTs evaluating DPP-4 inhibitors established that these agents are noninferior compared with placebo for the FDA-mandated primary MACE outcome (Table 3) (45–49). Despite demonstrating safety with regard to the MACE end point, there was an unexpected 27% relative increase in the risk of HHF with the use of saxagliptin in the

TABLE 3 Summary of DPP-4 Inhibitor CVOTs in Patients With Type 2 Diabetes (45–49)

	SAVOR-TIMI 53 (Saxagliptin)	EXAMINE (Alogliptin)	TECOS (Sitagliptin)	CARMELINA (Linagliptin)
Study size, n	16,492	5,380	14,671	6,979
Median follow-up, years	2.1	1.5	3.0	2.2
Patient population	A1C 6.5–12.0%; men age ≥55 years and women age ≥60 years with at least one CVD risk factor or men and women age ≥40 years with established CVD	A1C 6.5–11.0%; hospitalization for ACS within 15–90 days of randomization	A1C 6.5–8.0%; age ≥50 years with established CVD	A1C 6.5–10.0%; age >18 years with high risk of cardiovascular events
Primary end point,* HR (95% CI)	3-point MACE: 1.00 (0.89–1.12)	3-point MACE: 0.96 (≤1.16)	4-point MACE: 0.98 (0.88–1.09)	3-point MACE: 1.02 (0.89–1.17)
HF-related secondary end points, HR (95% CI)	HHF: 1.27 (1.07–1.51)	HHF: 1.19 (0.90–1.58)†; HHF for patients with no history of HF at baseline: 1.76 (1.07–2.90)†	HHF: 1.00 (0.83–1.20)	HHF: 0.90 (0.74–1.08)

*3-point MACE included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; 4-point MACE also included hospitalization for unstable angina. †Based on a post hoc analysis from the EXAMINE trial. ACS, acute coronary syndrome; HR, hazard ratio.

SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction) trial (45). The EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) trial evaluating alogliptin did not initially measure rates of HHF; however, a post hoc analysis identified a 76% relative risk increase for HHF in patients with recent acute coronary syndrome and no history of HF at baseline, which constituted the majority of the study population (46,49). In contrast, TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) and CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) evaluating sitagliptin and linagliptin, respectively, demonstrated no increased risk of HHF with these agents compared with placebo (47,48). Signals for increased HHF seen with saxagliptin and alogliptin prompted the FDA to issue a safety alert, mandate that warnings be included in the labeling for these agents, specifically for patients who already have CVD or CKD, and recommend their discontinuation in patients who develop HF (50).

Since then, two meta-analyses evaluating DPP-4 inhibition compared with placebo showed no statistically significant increase in risk for HHF; however, one meta-analysis evaluated 236 trials and found a 22 and 81% increase in relative risk for HHF with these agents when compared with GLP-1 receptor agonists and SGLT2 inhibitors, respectively (51,52). Additional meta-analyses have demonstrated a 13–24% increase in HF-related end points with the use of all DPP-4 inhibitors, with no significant heterogeneity among drugs within the class (53–55).

The proposed mechanism for increased risk of HHF in patients with diabetes is partially derived from the effect of DPP-4 inhibition on plasma concentrations of stromal cell–derived factor 1 (SDF-1) (56). DPP-4 is responsible for the degradation of several substrates, including SDF-1, which has been linked to cardiac fibrosis, central nervous system activation with subsequent increases in myocardial cyclic adenosine monophosphate (AMP), and distal tubular natriuresis. Endogenous GLP-1 is also associated with an increase in cyclic AMP in cardiomyocytes; however, unlike the GLP-1 receptor agonists, DPP-4 inhibitors are not associated with a clinically significant chronotropic effect.

These proposed deleterious effects of DPP-4 inhibitors may be attenuated by a natriuretic effect, which would offset cardiac loading conditions; however, because the DPP-4 inhibitors exert their natriuretic effect through potentiation of SDF-1 at the distal tubule, they do not exhibit a natriuretic effect significant enough to reduce cardiac filling pressures. This process is in contrast to the SGLT2 inhibitors and GLP-1 receptor agonists, which are proposed to exert their natriuretic effect at the proximal tubule, the major site of sodium reabsorption, and therefore may assist in decreasing cardiac filling pressures.

In light of these postulated mechanisms for the increased HHF risk in patients using DPP-4 inhibitors, further research is required to confirm their safety in patients with HF. Although the initial signal for increased risk for HHF was isolated to saxagliptin with potential concern with the use of alogliptin, the proposed mechanisms for this increased risk and inconsistent findings from multiple meta-analyses may be enough evidence to give pause to using this drug class in patients at high risk for or with established HF (45,46,49).

Thiazolidinediones

Thiazolidinediones (TZDs) are generally not recommended in patients with HF because of their potential to cause fluid retention (11). These agents are selective agonists for the peroxisome proliferator–activated receptor-γ (PPAR-γ). Activation of PPAR-γ receptors increases the production of gene products responsible for glucose and lipid metabolism, thereby improving insulin sensitivity. PPAR-γ is found in the cells within the renal tubule, and therefore stimulation increases sodium reabsorption (57). Rosiglitazone was shown to increase the risk of HF causing hospitalization or death by twofold in the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) trial, and a 42-trial meta-analysis found that rosiglitazone increased the risk for cardiovascular death (58,59). The PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial demonstrated that pioglitazone was associated with a reduction in risk of MACE; however, pioglitazone was associated with an increase in the rate of HHF, and the incidence of edema was 26.4% compared with 15.1% in the placebo group (60,61). Additional trials cite a significant increase in edema and risk of HHF and related events with TZDs compared with other therapies used in the management of people with diabetes (62–65).

If TZDs are used in patients with NYHA Class I or II HF, it should be noted that these patients are more resistant to loop diuretics, and edema will resolve with discontinuation of TZD therapy. In addition, patients using these agents should be educated on careful monitoring for fluid

retention and daily weight monitoring. The increase in the risk of HHF and edema in people with diabetes and HF makes this class of medications an undesirable choice in this population, and drugs in this class should be avoided (11).

Sulfonylureas

The ADA supports sulfonylureas as a treatment option for patients with type 2 diabetes and HF who cannot afford an SGLT2 inhibitor, a GLP-1 receptor agonist, or a DPP-4 inhibitor. Drugs in this class stimulate insulin secretion from the pancreatic β-cells and have fallen out of favor because of their inability to reduce cardiovascular risk and concern about β-cell burnout. CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) evaluated the cardiovascular safety of the sulfonylurea glimepiride in comparison with the DPP-4 inhibitor linagliptin (66). The study found no difference between the two agents in the primary outcome, which was time to first occurrence of the composite MACE outcome. In addition, there was no difference in the risk of HHF between the two groups (3.7 vs. 3.1% with linagliptin and glimepiride, respectively). Although these agents do not confer any additional cardiovascular benefit, they also have not been shown to cause cardiovascular harm and remain a viable option for patients with type 2 diabetes and HF.

Other Considerations for the Co-Management of Type 2 Diabetes and HF

β-Blockers in Patients With HF and Diabetes

Historically, clinicians have been reluctant to use β-blockers in patients with diabetes because of concerns regarding hypoglycemia unawareness, worsening glycemic control, and insulin sensitivity. Because β-blockers are a first-line therapy along with ACE inhibitors, ARBs, and ARN inhibitors in patients with HF, their use is critical in patients with diabetes and concomitant HF.

Three mortality-reducing β-blockers are currently recommended for the treatment of patients with HF with reduced ejection fraction: carvedilol, metoprolol succinate, and bisoprolol (32). Metoprolol succinate and bisoprolol are β-1–selective agents and have been shown to significantly decrease insulin sensitivity in patients with hypertension, and many of the negative perceptions regarding β-blocker use are from clinical trials studying nonspecific first-generation β-blockers (e.g., propranolol) and second-generation β-1–selective agents (67).

Carvedilol, a nonselective third-generation β-blocker with additional vasodilatory activity produced by additional α-1 adrenergic receptor blockade, has been recommended as the preferred agent in the past for patients with diabetes who need additional blood pressure lowering (68). Beneficial effects were demonstrated in multiple studies comparing carvedilol to metoprolol, in which carvedilol increased insulin sensitivity compared with metoprolol and stabilized glycemic management (69,70). Unless patients have concomitant severe restrictive lung disease, a low baseline blood pressure, or another indication that would make carvedilol less favorable, carvedilol is the preferred β-blocker in patients with HF and diabetes.

Another concern with β-blocker use is the theoretical increased risk of masking common signs and symptoms of hypoglycemia, such as weakness, shakiness, and palpitations. In HF, the mortality-reducing benefits were found at the maximum doses of these agents, so the fear of hypoglycemia unawareness cannot deter clinicians from titrating to mortality-reducing doses. It is important for clinicians to counsel patients to look for signs such as sweating or agitation, which may not be affected by the antiadrenergic effects of β-blockers (32,67).

Fluid Restriction and Diuretic Management

Increasing fluid intake has been shown to have a beneficial effect on renal function in patients with or at risk for CKD, making it a desirable recommendation for patients with diabetes (71). In patients with HF and diabetes, a careful fluid intake balance must be maintained to ensure adequate hydration benefits on the kidney and prevent congestive symptoms of HF. Many clinicians continue to follow a tight fluid restriction recommendation in patients with HF, educating patients to consume no more than 1.5–2 L of liquid per day. However, recent HF guidelines have relinquished fluid restriction recommendations for all except those with stage D HF, especially in patients with hyponatremia. More general fluid restriction in all patients with HF regardless of symptoms or other considerations does not appear to result in significant benefit (32,72).

Patients should be counseled on signs and symptoms of fluid retention, such as edema, abdominal fullness, shortness of breath, paroxysmal nocturnal dyspnea, and orthopnea. Daily weight monitoring should be recommended, and patients should be instructed to contact their provider if they gain 2 lb or more in 1 day or 3–5 lb in 1 week.

Certain HF symptoms should be monitored more closely in patients taking GLP-1 receptor agonists because they have

the potential to cause weight loss and early satiety, especially upon initiation. These effects may mask weight gain from fluid overload and early satiety from fluid collection around the abdomen in patients with worsening HF. A more thorough examination for edema and heart and lung sounds may be required in patients with symptomatic HF who are started on GLP-1 receptor agonists.

Management of Diabetes Complications in Patients With HF

Inappropriate management of the complications of diabetes in the setting of HF may have a detrimental effect on morbidity and mortality in this patient population, as well as increase the cost of care. For example, when considering pharmacologic options for the treatment of peripheral neuropathy resulting from long-standing hyperglycemia, clinicians should avoid the use of pregabalin. Although the manufacturer's labeling specifically notes that clinicians should use caution in the setting of NYHA class III or IV HF because of the risk for peripheral edema, there are case reports of acute decompensation with pregabalin in patients with stable, NYHA class I through III HF, which further support avoiding this agent in patients with diabetes and HF (73–75).

Furthermore, it is paramount to take measures to prevent acute infections or optimize therapy for inflammatory conditions that occur as a result of or in conjunction with suboptimal glycemic management to limit the use of glucocorticoids in this population. These therapies not only acutely worsen hyperglycemia, but also promote sodium and water retention to further increase the risk for HF exacerbation. The same can be said for the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The increased risk for volume expansion with NSAIDs' inherent ability to cause sodium and water retention is further compounded by their tendency to impair renal function in the presence of RAAS inhibitors and diuretics. As a result, NSAIDs may diminish the effects of diuretics used for maintaining euvolemia in patients with HF. It is imperative to be mindful of the use of these agents given their multimodal detrimental effects in patients with diabetes and HF.

The management of other comorbidities that commonly occur alongside diabetes and HF may require careful consideration of the risks versus benefits of certain therapies in this population, and publications exist to promote awareness of treatments to avoid in HF (76).

Future Directions and Conclusion

The management of diabetes in the setting of HF requires a comprehensive approach to optimize clinical outcomes for both conditions. Data from the published CVOTs provide some insight into the potential benefits of SGLT2 inhibitor therapy in patients with diabetes. The DAPA-HF trial, the anticipated Empagliflozin Outcome Trial in Patients with Chronic Heart Failure (EMPEROR)-Reduced, and additional follow-up studies examining their use in patients with HF with reduced ejection fraction regardless of diabetes status will provide more conclusive evidence (23,77). Additionally, multiple ongoing studies evaluating SGLT2 inhibitors will elucidate the role of these agents in patients with HF with preserved and midrange ejection fraction and may provide evidence that these therapies offer clinical benefits to this patient population (78,79).

The abundance of both cardiovascular safety and efficacy evidence for SGLT2 inhibitors make them a preferred choice for patients with HF regardless of glycemic control. Despite the aforementioned ongoing trials to establish the role of SGLT2 inhibitors in patients with HF, practitioners should not wait for the results of these studies to implement SGLT2 inhibitors and replicate their benefit in patients with diabetes and HF in clinical practice. In addition, it is equally imperative to ensure that patients do not receive medications, including those for diabetes and related complications, that may worsen or exacerbate HF. The optimal care of patients with diabetes and HF is an evolving area of clinical practice. Clinicians should be mindful of the interrelatedness of these comorbidities as they develop individualized management plans for their patients who have both conditions.

REFERENCES

1. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–34

2. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care 2004;27:1879–1884

3. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia 2019;62:1550–1560

4. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care 2004;27:699–703

5. Dunlay SM, Givertz MM, Aguilar D, et al.; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and the Heart Failure Society of America. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation 2019;140:e294–e324

6. Levelt E, Mahmod M, Piechnik SK, et al. Relationship between left ventricular structural and metabolic remodeling in type 2 diabetes. Diabetes 2016;65:44–52

7. Shimizu I, Minamino T, Toko H, et al. Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents. J Clin Invest 2010;120:1506–1514

8. Levelt E, Rodgers CT, Clarke WT, et al. Cardiac energetics, oxygenation, and perfusion during increased workload in patients with type 2 diabetes mellitus. Eur Heart J 2016;37:3461–3469

9. Falcão-Pires I, Hamdani N, Borbély A, et al. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. Circulation 2011;124:1151–1159

10. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. Cardiovasc Res 2004;63:582–592

11. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S98–S110

12. Aguilar D, Chan W, Bozkurt B, Ramasubbu K, Deswal A. Metformin use and mortality in ambulatory patients with diabetes and heart failure. Circ Heart Fail 2011;4:53–58

13. Andersson C, Olesen JB, Hansen PR, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia 2010;53:2546–2553

14. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail 2013;6:395–402

15. Tseng CH. Metformin use is associated with a lower risk of hospitalization for heart failure in patients with type 2 diabetes mellitus: a retrospective cohort analysis. J Am Heart Assoc 2019;8:e011640

16. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 2017;166:191–200

17. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

18. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657

19. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357

20. Kosiborod M, Cavender MA, Fu AZ, et al.; CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium–Glucose Cotransporter-2 Inhibitors). Circulation 2017;136:249–259

21. Kosiborod M, Lam CSP, Kohsaka S, et al.; CVD-REAL Investigators and Study Group. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol 2018;71:2628–2639

22. Patorno E, Pawar A, Franklin JM, et al. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. Circulation 2019;139:2822–2830

23. McMurray JJV, Solomon SD, Inzucchi SE, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008

24. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. Diabetes Care 2016;39:1115–1122

25. Bertero E, Prates Roma L, Ameri P, Maack C. Cardiac effects of SGLT2 inhibitors: the sodium hypothesis. Cardiovasc Res 2018;114:12–18

26. Sha S, Polidori D, Heise T, et al. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2014;16:1087–1095

27. Casu G, Merella P. Diuretic therapy in heart failure: current approaches. Eur Cardiol 2015;10:42–47

28. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38:1638–1642

29. Prattichizzo F, De Nigris V, Micheloni S, La Sala L, Ceriello A. Increases in circulating levels of ketone bodies and cardiovascular protection with SGLT2 inhibitors: is low-grade inflammation the neglected component? Diabetes Obes Metab 2018;20:2515–2522

30. Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections: a population-based cohort study. Ann Intern Med 2019;171:248–256

31. U.S. Food and Drug Administration. FDA drug safety communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-kidney-warnings-diabetes-medicines-canagliflozin. Accessed 19 January 2020

32. Yancy CW, Jessup M, Bozkurt B, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62: e147–e239

33. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137–e161

34. Wanner C, Lachin JM, Inzucchi SE, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation 2018;137: 119–129

35. Tang H, Zhang X, Zhang J, et al. Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials. Diabetologia 2016; 59:2546–2551

36. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257

37. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375:311–322

38. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844

39. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377: 1228–1239

40. Hernandez AF, Green JB, Janmohamed S, et al.; Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392: 1519–1529

41. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130

42. Husain M, Birkenfeld AL, Donsmark M, et al.; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841–851

43. Margulies KB, Hernandez AF, Redfield MM, et al.; NHLBI Heart Failure Clinical Research Network. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2016; 316:500–508

44. Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE): a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail 2017;19:69–77

45. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326

46. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335

47. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242

48. Rosenstock J, Perkovic V, Johansen OE, et al.; CARMELINA Investigators. 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 2019;321:69–79

49. Zannad F, Cannon CP, Cushman WC, et al.; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet 2015;385: 2067–2076

50. U.S. Food and Drug Administration. FDA drug safety communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Available from https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm. Accessed 19 January 2020

51. Kankanala SR, Syed R, Gong Q, Ren B, Rao X, Zhong J. Cardiovascular safety of dipeptidyl peptidase-4 inhibitors: recent evidence on heart failure. Am J Transl Res 2016;8: 2450–2458

52. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA 2018;319: 1580–1591

53. Verma S, Goldenberg RM, Bhatt DL, et al. Dipeptidyl peptidase-4 inhibitors and the risk of heart failure: a systematic review and meta-analysis. CMAJ Open 2017;5:E152–E177

54. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2014;24:689–697

55. Clifton P. Do dipeptidyl peptidase IV (DPP-IV) inhibitors cause heart failure? Clin Ther 2014;36:2072–2079

56. Packer M. Worsening heart failure during the use of DPP-4 inhibitors: pathophysiological mechanisms, clinical risks, and potential influence of concomitant antidiabetic medications. JACC Heart Fail 2018;6:445–451

57. Staels B. Fluid retention mediated by renal PPARgamma. Cell Metab 2005;2:77–78

58. Home PD, Pocock SJ, Beck-Nielsen H, et al.; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373: 2125–2135

59. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471

60. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366: 1279–1289

61. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR; PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf 2009;32:187–202

62. Berlie HD, Kalus JS, Jaber LA. Thiazolidinediones and the risk of edema: a meta-analysis. Diabetes Res Clin Pract 2007;76: 279–289

63. Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011;11:115–128

64. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298: 1180–1188

65. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 2007;370:1129–1136

66. Rosenstock J, Kahn SE, Johansen OE, et al.; CAROLINA Investigators. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322:1155–1166

67. McGill JB. Reexamining misconceptions about β-blockers in patients with diabetes. Clin Diabetes 2009;27:36–46

68. Torre JJ, Bloomgarden ZT, Dickey RA, et al.; AACE Hypertension Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of hypertension. Endocr Pract 2006;12:193–222

69. Jacob S, Rett K, Wicklmayr M, Agrawal B, Augustin HJ, Dietze GJ. Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. J Hypertens 1996;14:489–494

70. Bakris GL, Fonseca V, Katholi RE, et al.; GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 2004;292:2227–2236

71. Clark WF, Sontrop JM, Huang SH, Moist L, Bouby N, Bankir L. Hydration and chronic kidney disease progression: a critical review of the evidence. Am J Nephrol 2016;43:281–292

72. Travers B, O'Loughlin C, Murphy NF, et al. Fluid restriction in the management of decompensated heart failure: no impact on time to clinical stability. J Card Fail 2007;13:128–132

73. Lyrica (pregabalin) [package insert]. New York, NY, Pfizer, 2019

74. Fong T, Lee AJ. Pregabalin-associated heart failure decompensation in a patient with a history of stage I heart failure. Ann Pharmacother 2014;48:1077–1081

75. Page RL 2nd, Cantu M, Lindenfeld J, Hergott LJ, Lowes BD. Possible heart failure exacerbation associated with pregabalin: case discussion and literature review. J Cardiovasc Med (Hagerstown) 2008;9:922–925

76. Page RL 2nd, O'Bryant CL, Cheng D, et al.; American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. Circulation 2016;134:e32–e69

77. Boehringer Ingelheim. Empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced). Available from https://clinicaltrials.gov/ct2/show/NCT03057977. Accessed 19 January 2020

78. Boehringer Ingelheim. Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved). Available from https://clinicaltrials.gov/ct2/show/NCT03057951. Accessed 19 January 2020

79. AstraZeneca. Dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure (DELIVER). Available from https://clinicaltrials.gov/ct2/show/NCT03619213. Accessed 19 January 2020