

Consensus Statement

Type 2 Diabetes Mellitus and Heart Failure, A Scientific Statement From the American Heart Association and Heart Failure Society of America[☆]

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ABSTRACT

Type 2 diabetes mellitus is a risk factor for incident heart failure and increases the risk of morbidity and mortality in patients with established disease. Secular trends in the prevalence of diabetes mellitus and heart failure forecast a growing burden of disease and underscore the need for effective therapeutic strategies. Recent clinical trials have demonstrated the shared pathophysiology between diabetes mellitus and heart failure, the synergistic effect of managing both conditions, and the potential for diabetes mellitus therapies to modulate the risk of heart failure outcomes. This scientific statement on diabetes mellitus and heart failure summarizes the epidemiology, pathophysiology, and impact of diabetes mellitus and its control on outcomes in heart failure; reviews the approach to pharmacological therapy and lifestyle modification in patients with diabetes mellitus and heart failure; highlights the value of multidisciplinary interventions to improve clinical outcomes in this population; and outlines priorities for future research. (*J Cardiac Fail* 2019;25:584–619)

Key Words: AHA Scientific Statement, Diabetes mellitus, type 2, Drug therapy, Heart failure, Lifestyle, Risk factors.

More than 29 million adults in the United States have type 2 diabetes mellitus (DM),¹ whereas 6.5 million have heart failure (HF),² and both conditions are expected to continue to increase in prevalence over time. Although DM and HF are each individually associated with considerable morbidity and mortality, they often occur together, which further worsens adverse patient outcomes, quality of life, and costs of care. Identifying and implementing optimal treatment strategies for patients living with DM and HF is critical to improving outcomes in this high-risk population. Although there are separate, dedicated guidelines for the management of DM and HF as isolated conditions,^{3–8} there

is insufficient guidance on caring for patients with both DM and HF. Such guidance is necessitated by the shared pathophysiology of the 2 conditions, the potentially intersecting and discordant treatment approaches, and their synergistic effects on patient health. Furthermore, recent data from DM cardiovascular outcomes trials have underscored that HF is a critical outcome in patients with DM and suggest that glucose-lowering medications may influence the risk of HF development and progression. The purpose of this American Heart Association/Heart Failure Society of America joint scientific statement is to summarize current understanding of the epidemiology, pathophysiology, and outcomes of patients with type 2 DM and HF. In addition, it provides a review of contemporary data on the efficacy and safety of pharmacological and lifestyle management options in patients with DM at risk for HF and those with established disease. This document is not intended to replace or update the 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America heart failure guideline update.⁷

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This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update.

See page 605 for disclosure information.

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Epidemiology of DM and HF

Epidemic of DM and HF

The prevalence of type 2 DM has increased by 30% globally in the past decade, with the number affected increasing from 333 million in 2005 to 435 million in 2015.⁹ As of 2015, 30.3 million Americans (9.4% of the US population) had DM.¹ HF affects at least 26 million people worldwide and is increasing in prevalence.¹⁰ In the United States, an estimated 6.5 million adults have HF.²

DM and HF often occur concomitantly, and each disease independently increases the risk for the other. In HF cohorts, including both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), the prevalence of DM ranges from 10% to 47%.^{11–15} The prevalence of DM is higher in patients hospitalized with HF, with some reports of >40%.¹⁶ In patients with DM, the prevalence of HF is between 9% and 22%, which is 4 times higher than the general population,¹⁷ and the prevalence is even higher in patients with DM who are ≥60 years old.^{18–20}

DM as a Risk Factor for HF

Observational studies have consistently demonstrated a 2- to 4-fold increased risk of HF in individuals with DM

compared with those without DM (Table 1). In the Framingham Heart Study, DM was associated with a nearly 2-fold increase in the risk of incident HF in men and a 4-fold increase in women, even after adjustment for other cardiovascular risk factors.²¹ In patients with known coronary artery disease (CAD) in the Heart and Soul Study, DM was also associated with a higher adjusted risk of incident HF (hazard ratio [HR], 3.34 [95% CI, 1.65–6.76]).²³ The risk of HF associated with DM might be even higher in younger adults¹⁷ and women.²¹ DM is also an important predictor of the development of symptomatic HF in patients with asymptomatic left ventricular (LV) systolic dysfunction.¹² Furthermore, poor glycemic control is associated with greater risk for the development of HF; for each 1% increase in hemoglobin A1c (HbA1c), the risk of incident HF increases by 8% to 36%.^{23,26–28} The risk of incident HF among patients with DM increases with older age, CAD, peripheral arterial disease, nephropathy, retinopathy, longer duration of DM, obesity, hypertension, and higher NT-proBNP (N-terminal pro-B-type natriuretic peptide).^{17,18,29,30}

The risk of HF is increased even with milder abnormalities in glucose regulation. In a prospective cohort study of 18 084 people without DM at high risk for cardiovascular disease, a 1-mmol/L higher fasting plasma glucose was associated with a 1.23-fold increased risk of HF

Table 1. Incidence of HF in Individuals With and Without DM in Selected US Observational Studies.

Study	Cohort	N	Follow-Up, y	Incidence of HF	Adjusted Risk of HF With vs Without DM	Population-Attributable Fraction
Framingham ²¹ (study sample included ages 45–74 y)	45–74 y	5209	Up to 20	Age-adjusted rates (person-years): DM (men): 7.6/1000 No DM (men): 3.5/1000 DM (women): 11.4/1000 No DM (women): 2.2/1000	RR (men): 1.82 RR (women): 3.75	Men: 7.7% Women: 18.0%
Cardiovascular Health Study ²²	>65 y	5888	Mean 5.5	Rates (person-years): DM (men): 44.6/1000 No DM (men): 22.9/1000 DM (women): 32.5/1000 No DM (women): 12.1/1000	RR: 1.74 (95% CI, 1.38–2.19)	8.3%
Heart and Soul Study ²³	Stable CAD	839	Mean 4.1	Rates (person-years): DM: 36.6/1000 No DM: 17.9/1000	HR, 3.34 (95% CI, 1.65–6.76)	...
MESA ²⁴	4–84 y	6814	Median 4	...	HR, 1.99 (95% CI, 1.08–3.68)	DM-attributable risk: 19 per 1000
NHANES ²⁵	25–74 y	13 643	Mean 19	Cumulative incidence at age 85 y: DM (men): 65.5% No DM (men): 36.9% DM (women): 61.8% No DM (women): 28.9%	RR, 1.85 (95% CI, 1.51–2.28) Similar in men and women	...
Retrospective cohort of Kaiser Permanente Northwest Database ¹⁷		8231 +DM, 8845 no DM	Up to 6	Rates (person-years): DM: 30.9/1000 No DM: 12.4/1000 Rate ratio, 2.5 (95% CI, 2.3–2.7)	...	...

CAD indicates coronary artery disease; DM, diabetes mellitus; ellipses (...), not reported; HF, heart failure; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; and RR, relative risk.

hospitalization (95% CI, 1.03–1.47).³¹ The ARIC study (Atherosclerosis Risk in Communities) similarly demonstrated a progressively increasing risk of incident HF hospitalization with a rising HbA1c among participants without DM or HF.³² Smaller studies further linked insulin resistance to an increased risk of incident HF³³ and the development of LV systolic and diastolic dysfunction.^{34,35}

Subclinical Cardiac Abnormalities in Patients With DM

Patients with DM without symptomatic HF nevertheless often have subclinical abnormalities of cardiac structure and function corresponding to American College of Cardiology/American Heart Association stage B HF.⁸ These changes include LV systolic dysfunction; DM-associated increases in LV mass, relative wall thickness, and left atrial size; diastolic dysfunction; and an increase in extracellular volume fraction.^{36–43} The presence of each of these abnormalities is associated with increased risk of symptomatic HF and death.^{40,41}

HF as a Risk Factor for DM

Metabolic impairment is intrinsic to HF pathophysiology, and insulin resistance is present in up to 60% of patients with HF.⁴⁴ Among nondiabetic patients with HF enrolled in the CHARM Program (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)⁴⁵ and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure),⁴⁶ the incidence of DM was 28 and 21 per 1000 person-years, respectively, which is substantially higher than adults of similar age in the general population (9.4–10.9 per 1000 person-years for

adults 45 and older).⁴⁷ The predictors of incident DM among patients with HF include elevated body mass index and waist circumference, history of smoking, elevated glucose or HbA1c, higher systolic blood pressure, longer duration of HF, diuretic therapy, and higher New York Heart Association functional class.^{45,46,48,49}

Pathophysiology of DM and HF

DM can contribute to the development of structural heart disease and HF via systemic, myocardial, and cellular mechanisms. A recent state-of-the-art review provides a detailed account of the underlying mechanisms of DM-associated HF.⁵⁰

DM commonly causes structural heart disease and HF via myocardial ischemia/infarction.⁵¹ Hyperglycemia and hyperinsulinemia accelerate atherosclerosis via vascular smooth muscle cell proliferation and inflammation (Figure 1). DM is also associated with more atherogenic dyslipidemia, in which low-density lipoprotein cholesterol particles are more atherogenic, and with endothelial dysfunction, which promotes leukocyte and platelet adhesion, thrombosis, inflammation, and coronary plaque ulceration.

DM can also cause myocardial disease in the absence of major epicardial CAD. The term diabetic cardiomyopathy was first introduced in 1972 by Rubler et al,⁵² who found postmortem evidence of cardiomegaly in the absence of major CAD in 4 individuals with DM. Diabetic cardiomyopathy is defined as the presence of diastolic or systolic dysfunction in a patient with DM without other obvious causes for cardiomyopathy, such as CAD, hypertension, or valvular heart disease.

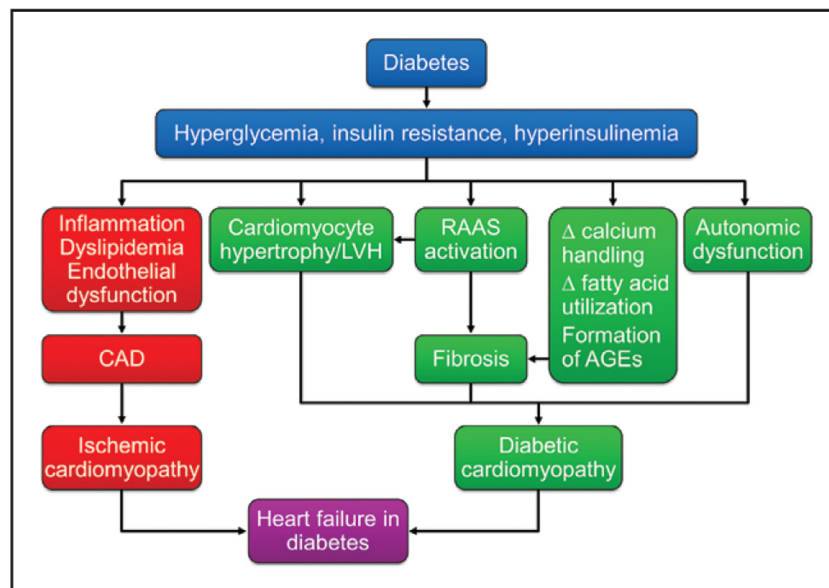


Fig. 1. Pathophysiology of heart failure in diabetes mellitus.

The hyperglycemia, insulin resistance, and hyperinsulinemia that often accompany diabetes mellitus trigger a cascade of deleterious effects that contribute to the development of heart failure in diabetes mellitus. AGEs indicates advanced glycation end products; CAD, coronary artery disease; LVH, left ventricular hypertrophy; and RAAS, renin-angiotensin-aldosterone system.

Imaging studies have shown that LV hypertrophy, thought to be caused by insulin resistance and hyperinsulinemia, is an important characteristic of the diabetic heart.⁵³ LV hypertrophy causes diastolic dysfunction, which is an early functional manifestation of diabetic cardiomyopathy and is present in 40% to 75% of patients with DM.⁵⁴ Hyperglycemia results in the formation of advanced glycation end products; advanced glycation end products cause cross-links in collagen molecules, leading to increased fibrosis with increased myocardial stiffness and impaired cardiac relaxation.⁵⁵ Maladaptive calcium homeostasis and endoplasmic reticular stress may also play a role in cardiomyocyte fibrosis and diastolic dysfunction.⁵⁶ Finally, hyperglycemia contributes to activation of the local renin–angiotensin–aldosterone system (RAAS), which leads to overproduction of angiotensin II and aldosterone, which induces cardiac hypertrophy and fibrosis and exacerbates diastolic dysfunction.⁵⁷

The diabetic heart is energy starved because of impaired glucose utilization and accordingly relies more heavily on free fatty acid utilization.⁵⁸ Excessively high fatty acid oxidation rates contribute to the abnormalities in energy metabolism and cardiac dysfunction that are observed in diabetic cardiomyopathy. Elevated levels of free fatty acids cause lipid accumulation in cardiomyocytes and lipotoxicity, which manifests as contractile dysfunction and eventual cardiomyocyte apoptosis. Cardiac magnetic resonance imaging studies have demonstrated that insulin resistance and DM are associated with a significant increase in cardiac lipid content.⁵⁹ In addition, an increase in mitochondrial reactive oxygen species production could explain metabolic substrate dysregulation, inflammation, increased apoptosis, and impaired calcium handling.⁵⁰ Recent human studies further linked mitochondrial dysfunction with cardiac abnormalities such as cardiac hypertrophy and fibrosis.^{60,61} Analysis of myocardial tissue obtained from patients with DM at the time of elective heart surgery revealed a higher apoptosis rate.⁶² Finally, DM and obesity may overlap in up to one-third of patients with HFpEF, and recent data suggest that this may be a distinct pathophysiological subgroup with increased plasma volume, greater LV and right ventricular remodeling, and worse exercise-induced hemodynamics.⁶³

Impact of DM on HF Outcomes

Patients with HF and DM have worse clinical outcomes than patients with HF without DM. In population-based studies, concomitant DM increases the risk of death in both hospitalized and ambulatory patients with HF.^{11,64–66} Multivariable HF risk models (eg, the MAGGIC [Meta-analysis Global Group in Chronic Heart Failure] risk score⁶⁷) frequently highlight DM as an independent risk factor for death.⁶⁸ Outcomes other than mortality in patients with HF are also adversely affected by DM. Risk of hospitalization is up to 50% higher in patients with DM than in those without DM.^{69–71} Hospital readmission is modestly increased in patients with DM.⁷² Finally, patients with DM and HF have worse health-related quality of life than patients with HF alone.^{73,74}

In community-based HF cohorts, presence of DM carries adverse risk of death and hospitalization for patients with HFrEF and HFpEF.⁷⁵ In the CHARM trial, DM was associated with a greater relative risk of cardiovascular death or HF hospitalization in patients with HFpEF (HR, 2.0 [95% CI, 1.70–2.36]) than in those with HFrEF (HR, 1.60 [95% CI, 1.44–1.77]; interaction $P=0.0009$), but for all-cause mortality, the risk conferred by DM was similar in both HFpEF and HFrEF.⁷⁶ In the I-PRESERVE trial (Irbesartan in Heart Failure With Preserved Ejection Fraction), over a median follow-up of 4.1 years, cardiovascular death or HF hospitalization occurred in 34% of patients with DM and HFpEF versus 22% of HFpEF patients without DM (adjusted HR, 1.75), and all-cause mortality was 28% and 19%, respectively (adjusted HR, 1.59).⁷⁷ A recent network analysis showed that biomarker profiles specific for HFrEF are related to cellular proliferation and metabolism, whereas those specific for HFpEF are related to inflammation and extracellular matrix reorganization.⁷⁸ How these pathophysiological differences might translate into different outcomes in patients with DM and HFpEF versus HFrEF remains to be determined.

Management of DM in HF

In this section, we will first review glycemic goals in patient with DM and HF. We will then provide a thorough discussion of the available glucose-lowering medications for patients with DM and their potential impact on cardiovascular and HF outcomes.

Glycemic Goals in Patients With DM and HF

Intensive treatment to achieve low HbA1c targets in type 2 DM reduces the long-term risk of microvascular events (retinopathy, nephropathy, and peripheral neuropathy).^{79–85} Although intensive glycemic control does not appear to reduce the risk of all-cause mortality, cardiovascular mortality, or stroke, it may reduce the risk of nonfatal myocardial infarction (MI).⁸⁶ Although hyperglycemia with or without DM is associated with increased risk of developing HF,^{23,26–28} available data suggest that intensive glycemic control in patients with established DM does not reduce the risk.⁸⁷ The UKPDS (UK Prospective Diabetes Study),⁸⁴ ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation),⁸³ ACCORD (Action to Control Cardiovascular Risk in Diabetes),⁸⁸ and VADT (Veterans Affairs Diabetes Trial)⁸¹ studies reported on HF as a secondary end point and found no difference in event rates between the intensive (mean HbA1c 6.4%–7.0%) and standard (mean HbA1c 7.3%–8.4%) treatment arms. Long-term follow-up of VADT reported no difference in the risk of new or worsening HF.⁸⁹ A meta-analysis of 8 randomized controlled trials (RCTs) that included 37 229 patients found no significant difference in the risk of HF between intensive glycemic control and standard treatment arms (odds ratio, 1.20 [95% CI, 0.96–1.48]).⁸⁷

More recent RCTs have focused on the cardiovascular safety of glucose-lowering drugs (as mandated by the US Food and Drug Administration [FDA]) rather than the potential benefits of lower HbA1c targets or more intensive therapies. These trials focused on the conventional 3-point major adverse cardiovascular event end point (cardiovascular death, MI, or stroke) but sometimes included HF as a secondary end point (see Choice of Glucose-Lowering Pharmacotherapy in Patients With DM at High Risk for HF or With Established HF). Although participants in the investigational drug arms of these trials achieved net HbA1c reductions between 0.3% and 0.6% compared with the comparator arms, any observed cardiovascular or HF benefits did not correlate with the degree of HbA1c reduction and were thus largely independent of glycemic control.^{90–98}

Observational studies suggest that moderate glycemic control may be optimal for patients with DM and HF. Although studies consistently demonstrated a progressive increase in the risk of incident HF or HF hospitalization with rising HbA1c,^{27,99–103} this was most apparent when HbA1c levels exceeded 8%,¹⁰⁰ 9%,^{101,102} or even 10%.¹⁰⁴ Indeed, some studies identified higher HF event rates when HbA1c levels fell below 6%.^{100,104} The association between HbA1c and mortality among patients with HF is consistently U shaped, with the lowest mortality in patients with HbA1c 7% to 8%.^{105–108}

Current DM management guidelines vary in the precise glycemic targets or ranges recommended, but most agree on HbA1c thresholds $\leq 7.0\%$ for the majority of adults with DM and no significant comorbidities or DM complications who are not experiencing severe hypoglycemia.^{3–6} Older patients, particularly those with established microvascular or macrovascular complications or extensive comorbid conditions, are advised to target higher HbA1c levels, up to 8% to 8.5%, depending on the guideline. Patients with short life

expectancy, advanced microvascular or macrovascular complications, or any end-stage comorbidity are advised to treat to minimize symptomatic hyperglycemia and hypoglycemia, corresponding to HbA1c 8% to 9%.^{3–6}

Clinical Considerations. Optimal glycemic targets for patients with DM and HF should be individualized to reflect comorbidity burden, including the severity of HF, and to balance the benefits likely to be achieved by lowering HbA1c with the potential risks. Potential harms of intensive treatment include hypoglycemia, polypharmacy, treatment burden, and high costs of care. The benefits of glucose-lowering therapy should also be considered within a broader context of the patient's life expectancy, because there is nearly a 10-year lag period to demonstrable benefit of more intensive glycemic control.^{82,89} Moreover, treatment decisions need to consider potential benefits and harms of individual glucose-lowering medications (discussed in Choice of Glucose-Lowering Pharmacotherapy in Patients With DM at High Risk for HF or With Established HF).

Given the lack of HF-specific data to guide HbA1c goals in patients with DM and HF, we suggest a target range of HbA1c 7% to 8% for most patients with HF (Figure 2), consistent with DM clinical practice guidelines for patients with DM and serious comorbidities. For patients with advanced, stage D HF not pursuing mechanical circulatory support or transplantation, less stringent goals may be appropriate.

Choice of Glucose-Lowering Pharmacotherapy in Patients With DM at High Risk for HF or With Established HF

Available data to guide the clinical use of glucose-lowering medications are reviewed in this section by medication class. Potential considerations for use of glucose-lowering medications, including route of administration, cost, hypoglycemia

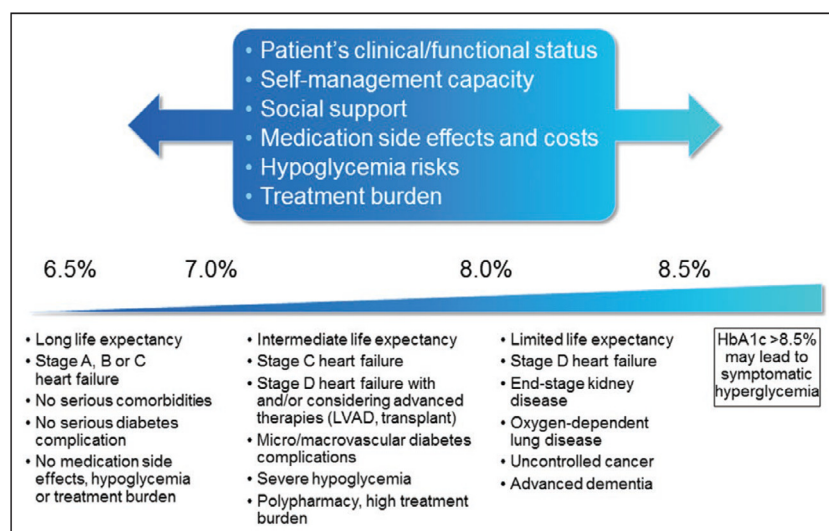


Fig. 2. Hemoglobin A1c (HbA1c) goals in patients with diabetes mellitus and heart failure.

The HbA1c goal should be individualized in patients with heart failure and diabetes mellitus based on the patient's clinical/functional status (life expectancy, comorbidities, presence of complications of diabetes mellitus), history of hypoglycemia, self-management capacity and support system, and overall treatment burden. LVAD indicates left ventricular assist device.

risk, use in chronic kidney disease (CKD), contraindications, and adverse effects, are summarized in Table 2. The associations of glucose-lowering medications with cardiovascular outcomes in the cardiovascular outcomes trials are shown in Table 3 and Figure 3. In Table 4, clinical vignettes are used to demonstrate the application of these data to guide glucose-lowering medication choice in patients with DM.

Metformin. Metformin is currently recommended as the preferred initial pharmacotherapy in patients with type 2 DM in the absence of contraindications.¹¹¹ Metformin is effective, safe, and generally well tolerated. Although metformin was previously contraindicated in HF because of concerns regarding the rare risk of lactic acidosis, multiple observational studies suggest a survival benefit.^{112–116} In a meta-analysis of 9 cohort studies of nearly 34 000 patients, metformin was associated with reduced mortality (pooled adjusted risk estimate, 0.80 [95% CI, 0.74–0.87]) and a small reduction in all-cause hospitalization (pooled adjusted risk estimate, 0.93 [95% CI, 0.89–0.98]) in patients with HF compared with control subjects.¹¹⁷ In a large, propensity-matched observational study, initiation of metformin was associated with lower risk of HF hospitalization than sulfonylurea drugs.¹¹⁸ Whether this reflects potential benefits of metformin or an adverse effect of sulfonylurea drugs is unknown. Small, randomized clinical trials (not powered to examine cardiovascular outcomes), including a subset of the UKPDS, also demonstrated metformin-associated reductions in macrovascular events, including MI and all-cause mortality.^{85,119} In light of these findings, the FDA removed HF as a contraindication to metformin use in 2006.

Clinical Considerations. It is reasonable to use metformin in patients with DM at risk of or with established HF. Metformin should be discontinued in patients presenting with acute conditions associated with lactic acidosis, such as cardiogenic or distributive shock (Table 2).

Sulfonylurea Drugs. Limited data exist regarding the use of sulfonylurea therapy and the development of HF in individuals with DM. In the UKPDS, intensive glycemic control with sulfonylurea drugs or insulin in patients with newly diagnosed DM was not associated with increased rates of HF compared with conventional diet-based therapy.⁸⁴ In the BARI-2D trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes) of patients with DM and CAD, treatment with sulfonylurea drugs, insulin, or both was associated with a similar risk of HF as a strategy of metformin, thiazolidinedione drugs (TZDs), or both.¹²⁰ In the ADVANCE trial, no difference in HF hospitalization was observed in patients randomized to standard glucose control (with no sulfonylurea drugs) or intensive glucose control with the use of glimepiride (plus other medications).⁸³ Contrary to these limited prospective trials, several observational studies have suggested that sulfonylurea therapy may be associated with increased risk of HF events compared with metformin^{118,121,122} or newer agents,^{123,124} although not all studies have yielded consistent findings.¹²⁵

Despite the common use of sulfonylurea drugs in patients with HF, there are no RCTs examining their effect on clinical outcomes. In an observational study of Medicare beneficiaries with DM discharged after an HF hospitalization, there was no association between sulfonylurea use and subsequent mortality.¹²⁶ In observational studies of patients with DM and HF, sulfonylurea therapy was associated with greater risk of death than metformin.^{113,114,127}

Clinical Considerations. On the basis of the available data, use of other agents, such as metformin and SGLT-2 (sodium glucose cotransporter type 2) inhibitors (see SGLT2 Inhibitors), is preferable to use of sulfonylurea drugs in patients at high risk for HF and those with established HF. The ongoing CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; URL: ClinicalTrials.gov. Unique identifier: NCT01243424) will offer the best evidence to date on the cardiovascular safety of sulfonylurea drugs, including effects on hospitalization for HF.

Insulin. Many patients with DM require insulin as monotherapy or in combination with other glycemic agents to achieve adequate glycemic control. The only RCT to specifically assess the cardiovascular safety of insulin was the ORIGIN trial (Outcome Reduction With Initial Glargine Intervention),¹²⁸ which randomized 12 537 individuals with pre-DM or DM to insulin glargine or standard care and found no difference in any cardiovascular outcomes, including hospitalization for HF.^{128,129} Other trials of DM treatment strategies that have included insulin, such as UKPDS⁸⁴ and BARI-2D,¹²⁰ have not demonstrated increased rates of HF with insulin.

In contrast, observational studies suggested an increase in HF with insulin therapy.^{17,130,131} Most^{71,77,131–133} but not all¹²⁶ observational studies and subgroup analyses of clinical trials have demonstrated that insulin use is associated with greater risk of death in patients with DM and HF. Despite attempts to statistically adjust for differences between insulin users and nonusers, residual confounding is possible.

Clinical Considerations. Insulin is sometimes required to achieve adequate glycemic control in individuals with DM and HF. Insulin use is associated with weight gain and risk of hypoglycemia and should be used with caution and close monitoring. Other agents, such as metformin and SGLT-2 inhibitors, are preferred if adequate glycemic control can be achieved without insulin (Table 4).

Thiazolidinedione Drugs. RCTs have demonstrated that TZDs are associated with increased rates of HF hospitalization in patients without HF at baseline. In the PROactive trial (Prospective Pioglitazone Clinical Trial in Macrovascular Events), which included 5238 individuals with macrovascular disease, pioglitazone was associated with a reduced risk of cardiovascular death, MI, or stroke but an increased risk of HF events compared with placebo.¹³⁴ Similarly, in the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of

Table 2. Considerations for Use of Glucose-Lowering Medications.

Class/Medication	Oral/SC	Cost	Hypoglycemia	Impact on Weight	Adjustment With CKD	FDA Black Box Warnings and Other Considerations
Biguanides	Oral	Low	No	Neutral, potential weight loss	Contraindicated with eGFR <30	FDA Black Box Warning: Lactic acidosis rare but can result in death, hypothermia, hypotension, and resistant bradyarrhythmias. Risk factors include renal impairment, concomitant use of certain drugs (eg, carbonic anhydrase inhibitors), age ≥ 65 y, having a radiologic study with contrast, surgery and other procedures, hypoxic states (eg, acute HF), excessive alcohol intake, and hepatic impairment. Discontinue immediately if lactic acidosis is suspected; prompt hemodialysis is recommended.
Metformin					Do not affect progression of kidney disease	Common side effects: nausea, diarrhea, potential for vitamin B12 deficiency with prolonged use Cardiovascular side effects: chest discomfort, palpitations
Sulfonylureas (2nd generation)	Oral	Low	Yes	Weight gain	Glyburide not recommended; glipizide and glimepiride can be used with caution	Common side effects: dizziness/ nervousness
Glipizide Glimepiride Glyburide					Do not affect progression of kidney disease	Cardiovascular side effects: may increase cardiovascular mortality,* syncope
Thiazolidinediones	Oral	Low	No	Weight gain	Generally not recommended in CKD because of potential for fluid retention	FDA Black Box Warning: Thiazolidinediones, including rosiglitazone, may cause or exacerbate HF; closely monitor for signs and symptoms of HF, particularly after initiation or dose increases. If HF develops, treat accordingly and consider dose reduction or discontinuation. Not recommended for use in any patient with symptomatic HF.
Rosiglitazone Pioglitazone					Do not affect progression of kidney disease	Common side effects: fluid retention, bladder cancer (pioglitazone), increased LDL cholesterol (rosiglitazone), bone fractures
Insulin	SC	Human: low	Yes	Weight gain	Can use at any eGFR but may require lower doses and frequent monitoring with worsening renal function	Common side effects: weight gain
Human insulins: regular, NPH Analog insulins: Rapid-acting: aspart, lispro, glulisine, inhaled		Analog: high			Do not affect progression of kidney disease	Cardiovascular side effects: fluid retention

(continued)

Table 2 (Continued)

Class/Medication	Oral/SC	Cost	Hypoglycemia	Impact on Weight	Adjustment With CKD	FDA Black Box Warnings and Other Considerations
Long-acting: glargine, detemir, degludec Premixed insulins GLP-1 receptor agonists	SC	High	No	Weight loss	Exenatide: not recommended if eGFR <30	FDA Black Box Warning: GLP-1 receptor agonists can increase the risk of thyroid C-cell tumors. They are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2.
Liraglutide					Lixisenatide: caution with eGFR <30	Common side effects: nausea, diarrhea, cholelithiasis
Lixisenatide					Others can be used with dose adjustment	Cardiovascular side effects: increased heart rate
Semaglutide					Use caution with renal impairment; acute renal failure and worsening of chronic renal failure have been reported	
Exenatide Albiglutide Dulaglutide					Liraglutide: may slow progression of kidney disease	
DPP-4 inhibitors	Oral	High	No	Neutral	Can be used in renal impairment, but dose adjustment required	Common side effects: joint pain, acute pancreatitis have been reported
Saxagliptin						Cardiovascular side effects: Saxagliptin has been associated with increased risk of HF hospitalization. Use DPP-4 inhibitors with caution in patients at risk for HF (eg, history of HF or renal impairment) and monitor for signs and symptoms of HF during therapy; consider discontinuation if HF develops. Peripheral edema is common.
Sitagliptin Alogliptin Linagliptin						
SGLT-2 inhibitors	Oral	High	No	Weight loss	Contraindicated with eGFR <30 [†]	FDA Black Box Warning: Canagliflozin has been associated with lower-limb amputations, most frequently of the toe and mid-foot, in patients with type 2 DM who have established CVD or are at risk for CVD.
Empagliflozin					Canagliflozin not recommended if eGFR <45 [†]	Common side effects: bone fractures (canagliflozin), genital mycotic infections, ketoacidosis
Canagliflozin					Dapagliflozin not recommended if eGFR <60 [†]	Cardiovascular side effects: hypotension, [‡] elevated LDL cholesterol, volume depletion

(continued)

Table 2 (Continued)

Class/Medication	Oral/SC	Cost	Hypoglycemia	Impact on Weight	Adjustment With CKD	FDA Black Box Warnings and Other Considerations
Dapagliflozin						Canagliflozin and empagliflozin may slow progression of kidney disease

CKD indicates chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate (in mL·min⁻¹·1.73 m⁻²); FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide-1; HF, heart failure; LDL, low-density lipoprotein cholesterol; NPH, neutral protamine Hagedorn; SC, subcutaneous; and SGLT-2, sodium glucose cotransporter type 2.

*Data to support this association are limited, and several studies, including a large prospective trial (UKPDS [UK Prospective Diabetes Study]), have not supported an association.

[†]Recommendation to not use with low eGFR is because of attenuated glycemic efficacy.

[‡]Caused by intravascular volume depletion.

Glycaemia in Diabetes) of 4447 patients with DM without HF,¹³⁵ the risk of HF hospitalization or death approximately doubled with rosiglitazone compared with sulfonylurea plus metformin.^{135,136} Meta-analyses of randomized trials confirmed an increased risk of HF events with rosiglitazone or pioglitazone in individuals with DM.^{137–139}

The association of TZDs with increased HF risk has also been demonstrated in patients with DM and HFrEF. Both rosiglitazone and pioglitazone are associated with fluid retention and HF events.^{140,141} Despite this, no reduction in ejection fraction (EF) was observed with TZD use,^{140,142} which suggests that the predominant mechanism for

Table 3. Impact of Glucose-Lowering Medications on Cardiovascular End Points in Cardiovascular Outcomes Trials.

Medication Trial (Year)	Population	N	Median % HF	Follow-Up, y	Primary Outcome	Impact on Primary Cardiovascular End Point	Impact on HF Hospitalization
GLP-1 agonists							
Lixisenatide - ELIXA (2015) ⁹³	Recent ACS	6068	22	2.1	Cardiovascular death, MI, UA, stroke	No difference in risk (HR, 1.02 [95% CI, 0.89–1.17])	No difference in risk (HR, 0.96 [95% CI, 0.75–1.23])
Liraglutide - LEADER (2016) ⁹¹	CVD or high risk	9340	14	3.8	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.87 [95% CI, 0.78–0.97])	No difference in risk (HR, 0.87 [95% CI, 0.73–1.05])
Semaglutide - SUSTAIN-6 (2017) ⁹²	CVD or high risk	3297	24	2.1	Cardiovascular death, MI stroke	Decreased risk (HR, 0.74 [95% CI, 0.58–0.95])	No difference in risk (HR, 1.11 [95% CI, 0.77–1.61])
Exenatide - EXSCEL (2017) ¹⁰⁹	+/– CVD	14 752	16	3.2	Cardiovascular death, MI, stroke	No significant difference* (HR, 0.91 [95% CI, 0.83–1.00])	No difference in risk (HR, 0.94 [95% CI, 0.78–1.13])
DPP-4 inhibitors							
Saxagliptin - SAVOR TIMI-53 (2014) ^{30,97}	CVD or high risk	16 492	13	2.1	Cardiovascular death, MI, stroke	No difference in risk (HR, 1.00 [95% CI, 0.89–1.12])	Increased risk of HF (HR, 1.27 [95% CI, 1.07–1.51])
Alogliptin - EXAMINE (2013) ⁹⁸	Recent ACS	5380	28	1.5	Cardiovascular death, MI, stroke	No difference in risk (HR, 0.96; P<0.001 for noninferiority)	No difference in risk (HR, 1.19 [95% CI, 0.90–1.58])
Sitagliptin - TECOS (2016) ^{95,110}	CVD	14 724	18	3.0	Cardiovascular death, MI, UA, stroke	No difference in risk (HR, 0.98 [95% CI, 0.88–1.09])	No difference in risk (HR, 1.00 [95% CI, 0.83–1.20])
SGLT-2 inhibitors							
Empagliflozin - EMPA-REG OUTCOME (2015) ⁹⁰	CVD	7020	10	3.1	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.86 [95% CI, 0.74–0.99])	Decreased risk (HR, 0.65 [95% CI, 0.50–0.85])
Canagliflozin - CANVAS Program (2017) ⁹⁴	High cardiovascular risk	10 142	14	3.6	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.86 [95% CI, 0.75–0.97])	Decreased risk (HR, 0.67 [95% CI, 0.52–0.87])

ACS indicates acute coronary syndrome; CANVAS, Canagliflozin Cardiovascular Assessment Study; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME, BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP-1, glucagon-like peptide-1; HF, heart failure; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; SAVOR TIMI-53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53; SGLT-2, sodium glucose cotransporter type 2; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin; and UA, unstable angina.

*In EXSCEL, the difference in the primary composite end point did not reach statistical significance (P=0.06). However, there was a significant reduction in all-cause mortality with exenatide (HR, 0.86 [95% CI, 0.77–0.97]).

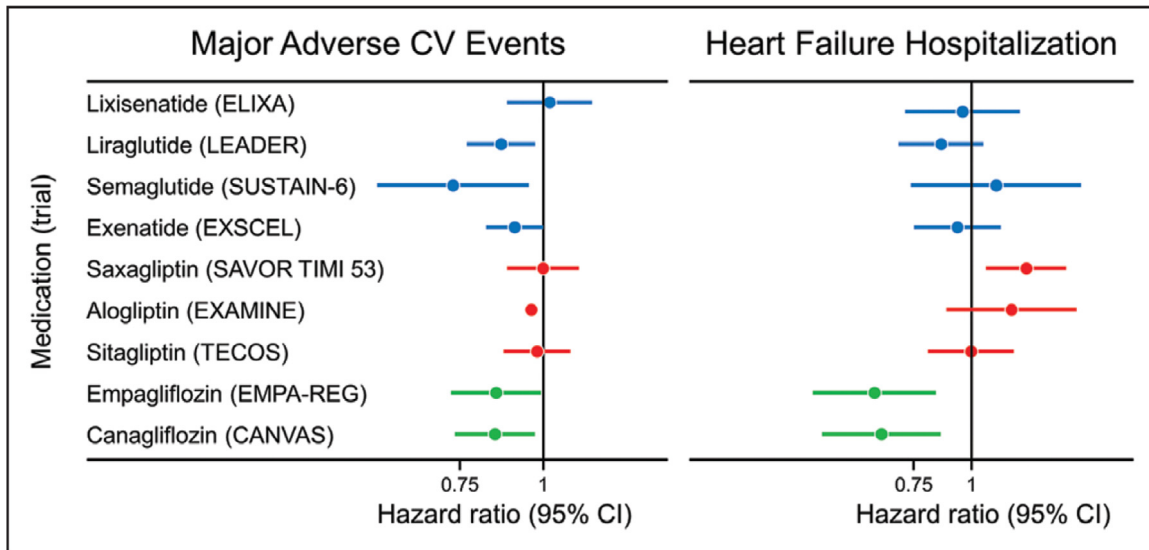


Fig. 3. Associations of glycemic medications with risks of cardiovascular events and heart failure hospitalization.

The risks of major adverse cardiovascular events (left) and heart failure hospitalization (right) in the cardiovascular outcomes trials are shown. Trials of GLP-1 (glucagon-like peptide 1) receptor agonists are shown in blue, DPP-4 (dipeptidyl peptidase-4) inhibitors in red, and SGLT-2 (sodium glucose cotransporter type 2) inhibitors in green. The EXAMINE trial (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) was powered for noninferiority of cardiovascular events, with only a hazard ratio and 99% upper-limit CI reported. CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CV, cardiovascular; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SAVOR TIMI-53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; and TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

increased HF events may be volume expansion caused by increased renal sodium reabsorption.¹⁴³ Observational data have also demonstrated increased risk of HF hospitalization with TZDs.¹²⁶

Clinical Considerations. TZDs are not recommended in patients with established HF^{144,145} and may increase the risk of HF events in individuals with DM without HF.

GLP-1 Receptor Agonists. GLP-1 (glucagon-like peptide-1) receptor agonists stimulate glucose-dependent insulin release with a low risk of hypoglycemia. Important secondary effects include a decrease in appetite and food intake, which leads to weight loss of 2 to 4 kg, and improved lipid levels, with decreased triglyceride levels and increased high-density lipoprotein levels. Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide are FDA approved for the treatment of type 2 DM (Table 2). GLP-1 receptor agonists are administered subcutaneously and can be given alone or in addition to other glucose-lowering agents, including insulin.

In large-scale postmarketing cardiovascular outcomes trials required by the FDA to demonstrate the cardiovascular safety of glucose-lowering medications, GLP-1 receptor agonists have shown mostly beneficial effects on cardiovascular outcomes but no effect on HF hospitalization (Table 3; Figure 3). In the ELIXA RCT (Evaluation of Lixisenatide in Acute Coronary Syndrome),⁹³ lixisenatide, a short-acting and less potent GLP-1 agonist (up to 20 μ g/d), did not alter

the rate of major cardiovascular events compared with placebo in patients with recent acute coronary syndrome. However, in the LEADER study (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), liraglutide, a more potent and longer-acting GLP-1 agonist (up to 1.8 mg/d),⁹¹ decreased the risk of cardiovascular death, MI, or stroke by 13%, as well as cardiovascular death and all-cause death, in patients at high risk for or with established cardiovascular disease. Although SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) was not powered to demonstrate cardiovascular superiority, semaglutide (0.5 or 1.0 mg/wk) decreased the rate of cardiovascular death, MI, or stroke by 26% compared with placebo.⁹² In the EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering), the risk of major cardiovascular events was numerically lower with exenatide (2 mg) versus placebo, although this difference did not reach statistical significance.⁹⁶ Across all 4 trials, there was no difference in the risk of HF hospitalization in patients randomized to GLP-1 agonists compared with placebo. Notably, the baseline prevalence of HF in these studies ranged from 14.0% in LEADER to 23.6% in SUSTAIN-6. Because limited data characterizing the type of HF were provided, differential effects of medication by EF are unknown.

Despite no impact on HF hospitalization risk observed in the cardiovascular outcomes trials, results of animal and

human studies suggested that GLP-1 receptor agonists may be beneficial in patients with established HF. In dogs with dilated cardiomyopathy, an infusion of recombinant GLP-1 improved LV contractility and cardiac output and decreased LV filling pressure and systemic vascular resistance.¹⁴⁶ In a mouse model of diabetic cardiomyopathy, administration of a selective GLP-1 agonist reduced LV hypertrophy, attenuated oxidative stress, and improved survival.¹⁴⁷ Nikolaidis et al¹⁴⁸ administered a 72-hour infusion of GLP-1 to 10 patients with acute MI and LV dysfunction and demonstrated improvement in regional and global LV function. In an open-label study, Sokos et al¹⁴⁹ infused GLP-1 for 5 weeks in 12 patients with New York Heart Association functional class III to IV HF. GLP-1 agonists increased EF, exercise capacity, and quality of life. More recently, Nathanson et al¹⁵⁰ studied the hemodynamic effects of exenatide in patients with DM and HFrEF. Compared with placebo, exenatide increased cardiac index and decreased pulmonary capillary wedge pressure; however, there were also concerns about increased heart rate because of its direct effect on the sinus node.

Against this background, Margulies et al¹⁵¹ sought to determine whether a GLP-1 receptor agonist could improve clinical stability after hospitalization for acute HF. The FIGHT study (Functional Impact of GLP-1 for Heart Failure Treatment) randomized 300 patients with chronic HFrEF and recent HF hospitalization to liraglutide (1.8 mg/d) or placebo for 6 months. Compared with placebo, liraglutide had no effect on posthospitalization clinical stability and tended to increase the risk of HF readmission (41% versus 34%; HR, 1.30 [95% CI, 0.89–1.88]). Similar disappointing results with liraglutide were reported in an RCT from Denmark.¹⁵² In 241 patients with stable HFrEF with or without DM, liraglutide (1.8 mg/d) had no effect on LV function at 24 weeks and was associated with an increase in heart rate and more serious cardiac events. Lastly, a 12-week study of albiglutide, a novel long-acting GLP-1 agonist, in stable patients with HFrEF demonstrated no significant effect on LVEF, submaximal exercise capacity, or quality of life.¹⁵³ As expected, both liraglutide and albiglutide resulted in a 1 to 2 kg weight loss.

Other cardiovascular and off-target effects of GLP-1 agonists may explain the variable results in patients with cardiovascular risk and those with HF.¹⁵⁴ GLP-1 agonists increase heart rate by 3 to 10 beats/min while lowering systolic blood pressure by 2 to 3 mm Hg.¹⁵⁵ The latter effect could be caused in part by improved endothelium-dependent vasodilation.¹⁵⁶ Preclinical and clinical data also suggest that GLP-1 agonists can improve renal function by enhancing natriuresis and reducing albuminuria and can decrease systemic inflammation and platelet aggregation. In addition to cost and the need for parenteral administration, adverse effects of GLP-1 agonists that have slowed their uptake in clinical practice include delayed gastric emptying leading to nausea, vomiting, and possible increase in the risk of cholelithiasis (Table 2).

Clinical Considerations. GLP-1 receptor agonists may reduce the risk of major adverse cardiovascular events and mortality in the general population of patients with DM. GLP-1 receptor agonists have had no impact on the risk of HF hospitalization in large RCTs, which suggests they are safe to use but not beneficial in preventing HF in patients at risk for HF. In patients with established HFrEF and recent decompensation, GLP-1 receptor agonists should be used with caution, given no evidence of benefit and a trend toward worse outcomes in 2 small RCTs. There are no data to guide their use in HFpEF.

Dipeptidyl Peptidase-4 Inhibitors. DPP-4 (dipeptidyl peptidase-4) is an enzyme involved in the rapid degradation of GLP-1, and thus, the effects of the incretin system could be enhanced by DPP-4 inhibition.¹⁵⁷ Alogliptin, linagliptin, saxagliptin, and sitagliptin are FDA approved for the treatment of type 2 DM (Table 2). These oral medications are included in practice guidelines as a second-line option after metformin.¹⁵⁸

Several DPP-4 inhibitors have been evaluated in large-scale cardiovascular outcomes trials (Table 3; Figure 3). In SAVOR TIMI-53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53), the risk of cardiovascular events was similar with saxagliptin compared with placebo in patients with DM at high risk for cardiovascular events; however, there was a surprising 27% relative increase in the risk of HF hospitalization.³⁰ In the EXAMINE trial (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care), alogliptin had no effect on the risk of cardiovascular events compared with placebo in patients with DM and recent acute coronary syndrome.⁹⁸ In contrast to SAVOR TIMI-53, no significant difference in the risk of HF hospitalization was observed. Finally, the TECOS trial (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) demonstrated no impact of the DPP-4 inhibitor sitagliptin on risk of cardiovascular events or HF hospitalization.¹¹⁰ Two meta-analyses evaluating the risk of HF hospitalization with DPP-4 inhibition showed no statistically significant increase in risk compared with placebo (relative risk, 1.118 [95% CI, 0.997–1.254]; $P = 0.06$ ¹⁵⁹ and HR, 1.13 [95% CI, 1.00–1.28]¹⁶⁰). However, in a recent network meta-analysis of 236 trials, the risk of HF was higher with DPP-4 inhibitors than with either GLP-1 receptor agonists (HR, 1.22 [95% CI, 1.05–1.42]) or SGLT-2 inhibitors (HR, 1.81 [95% CI 1.50–2.18]).¹⁶⁰

Importantly, only a small minority of patients enrolled in the SAVOR TIMI-53, EXAMINE, and TECOS trials had established HF. The VIVID trial (Vildagliptin in Ventricular Dysfunction Diabetes) of vildagliptin, another DPP-4 inhibitor, was a mechanistic study that specifically enrolled patients with DM and reduced EF. The primary end point, a change in EF from baseline to 52 weeks, showed no difference between vildagliptin and placebo; however, LV diastolic and systolic volumes were both significantly higher in patients treated with vildagliptin.¹⁶¹ Somewhat reassuringly, a real-world observational study of nearly 1.5 million

patients across several countries compared incretin-based therapies, both GLP-1 receptor agonists and DPP-4 inhibitors, to other glucose-lowering drugs, using claims data to evaluate HF outcomes.¹⁶² There was no increase in HF hospitalization with either GLP-1 receptor agonists or DPP-4 inhibitors compared with other glucose-lowering therapies.

Additional data are still needed to determine whether there is, in fact, a higher risk of HF with DPP-4 inhibitors in individuals with DM. Some additional information could come from the CARMELINA trial (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; URL: ClinicalTrials.gov. Unique identifier: NCT01897532), which compares linagliptin versus placebo in ≈ 7000 patients. In addition, the currently ongoing MEASURE-HF trial (Mechanistic Evaluation of Glucose-lowering Strategies in Patients With Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT02917031), which is evaluating the effects of saxagliptin, sitagliptin, or placebo in patients with DM and HFrEF, will provide additional mechanistic data via detailed evaluation of LV size and function using cardiac magnetic resonance.

Clinical Considerations. There is no evidence that DPP-4 inhibitors provide cardiovascular benefit. In patients with DM at high cardiovascular risk, some DPP-4 inhibitors could increase the risk of hospitalization for HF. The effects in patients with established HF have not been well studied, with some potentially concerning signals in mechanistic trials. On the basis of these data, the risk-benefit balance for most DPP-4 inhibitors does not justify their use in patients with established HF or those at high risk for HF.

SGLT-2 Inhibitors. SGLT-2 inhibitors lower glucose via an insulin-independent mode of action through increased urinary excretion of glucose.¹⁶³ In addition to glucose excretion, SGLT-2 inhibitors increase fractional excretion of sodium and have modest diuretic and natriuretic effects. Canagliflozin, dapagliflozin, and empagliflozin are FDA approved for the treatment of type 2 DM (Table 2).

The EMPA-REG OUTCOME trial (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) randomized patients with DM and cardiovascular disease to 10 or 25 mg of empagliflozin versus placebo (Table 3; Figure 3).⁹⁰ Patients treated with empagliflozin experienced a 14% relative decrease in the risk of major cardiovascular events compared with placebo; this was primarily driven by a 38% reduction in cardiovascular death.⁹⁰ Although the trial enrolled primarily patients with DM and atherosclerotic cardiovascular disease ($\approx 10\%$ of patients had HF at baseline), there was also a 35% reduction in HF hospitalizations, an effect that was observed within weeks of randomization. This lower risk of acute HF was consistent between those with and without a history of HF.¹⁶⁴

The CANVAS Program was a combination of the original canagliflozin cardiovascular safety trial (CANVAS

[Canagliflozin Cardiovascular Assessment Study]) and a separate CANVAS-R trial (CANVAS-Renal) designed to examine cardiovascular safety. Patients with established cardiovascular disease (65%) or at high risk for cardiovascular events (35%) who were treated with canagliflozin experienced a 14% reduction in the risk of major cardiovascular events and a 33% relative reduction in the risk of HF hospitalization compared with placebo.⁹⁴ Additional analyses suggested the morbidity and mortality benefits might be greater in patients with a prior history of HF.¹⁶⁵ A large, international observational study (CVD-REAL [Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors]) combined registry data across 6 countries and evaluated $>300\,000$ patients with DM, 87% of whom did not have cardiovascular disease at baseline.¹⁶⁶ After propensity matching, initiation of SGLT-2 inhibitors versus other glucose-lowering agents was associated with a 39% relative decrease in the risk of HF hospitalization, which suggests that HF benefits observed in clinical trials might extend to a broader population of patients with DM seen in clinical practice.¹⁶⁶ In the subsequent multinational CVD-REAL2 study, which used a similar approach but included patients from 6 other countries, SGLT-2 inhibitors were associated with a 49% lower risk of death and 36% lower risk of HF hospitalization.¹⁶⁷

The potential mechanisms by which SGLT-2 inhibitors might reduce HF-associated risk remain unclear and are the subject of ongoing investigation.¹⁶⁸ In fact, mechanisms beyond glucose lowering or diuresis might explain the reduction in HF events.¹⁶³ Provocative animal studies of SGLT-2 inhibitors show reductions in oxidative stress, improvement in endothelial function and neurohormonal modulation, and anti-inflammatory effects.^{163,169} Most recently, it has been postulated that reduction in plasma volume without neurohormonal activation,^{170,171} or possibly a change in metabolic fuel sources away from glucose oxidation to free fatty acid and ketone bodies, could play a role in improving myocardial efficiency.¹⁷² Supporting a pleiotropic effect of SGLT-2 inhibitors is a recent randomized controlled study in older patients with DM, in which canagliflozin attenuated a rise in serum NT-proBNP and high-sensitivity troponin I at 26, 52, and 104 weeks.¹⁷³

Potential benefits of SGLT-2 inhibitors in patients with established HF are being investigated in several large outcomes trials. The EMPEROR-PRESERVED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; URL: ClinicalTrials.gov. Unique identifier: NCT03057951) and EMPEROR-REDUCED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; URL: ClinicalTrials.gov. Unique identifier: NCT03057977) trials will evaluate the effects of empagliflozin versus placebo on clinical outcomes in HFpEF and HFrEF, respectively, whereas DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart

Table 4. Patient Case Examples.

Clinical Presentation	Choice of Glucose-Lowering Medication	
	Best Options	Avoid/Contraindicated
Case #1: 68-year-old woman at high risk for HF with DM, hypertension, hyperlipidemia, and coronary artery disease. Creatinine 1.1 mg/dL, eGFR 55 mL·min ⁻¹ ·1.73 m ⁻²	Metformin SGLT-2 inhibitor: may decrease risks of cardiovascular events and HF hospitalization GLP-1 receptor agonist: may decrease risk of cardiovascular events	TZDs may increase the risk of HF DPP-4 inhibitors, sulfonylureas, insulin should be considered only if unable to achieve adequate glycemic control with alternative options
Case #2: 78-year-old man with DM, recently diagnosed stage C HFrEF caused by non-ischemic cardiomyopathy (EF 30%). Creatinine 1.0 mg/dL, eGFR 77 mL·min ⁻¹ ·1.73 m ⁻²	Metformin SGLT-2 inhibitor: may decrease risk of HF hospitalization	TZDs are contraindicated in HF Avoid DPP-4 inhibitors, because some may increase the risk of HF hospitalization (no increased HF signal with sitagliptin) Avoid GLP-1 receptor agonists if recent HF decompensation Sulfonylureas and insulin should be considered only if unable to achieve adequate glycemic control with alternative options
Case #3: 59-year-old man with DM and recently diagnosed stage C HFpEF (EF 60%). Creatinine 1.1 mg/dL, eGFR 71 mL·min ⁻¹ ·1.73 m ⁻²	Metformin SGLT-2 inhibitor: may decrease risk of HF hospitalization	TZDs are contraindicated in HF Avoid DPP-4 inhibitors, because some may increase the risk of HF hospitalization (no increased HF signal with sitagliptin)
Case #4: 72-year-old woman with DM, stage C HFrEF caused by ischemic cardiomyopathy (EF 35%). Creatinine 2.0 mg/dL, eGFR 25 mL·min ⁻¹ ·1.73 m ⁻²	Insulin	TZDs are contraindicated in HF Metformin should not be used with eGFR <30 mL·min ⁻¹ ·1.73 m ⁻² Trials of SGLT-2 inhibitors at eGFR as low as 20 mL·min ⁻¹ ·1.73 m ⁻² ongoing, but for now, should not use if eGFR <30 mL·min ⁻¹ ·1.73 m ⁻² Other options (sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists if no recent HF decompensation) could be considered, but use with caution; may require dose adjustment

DM indicates diabetes mellitus; DPP-4, dipeptidyl peptidase-4; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT-2, sodium glucose cotransporter type 2; and TZDs, thiazolidinedione drugs.

Failure; URL: ClinicalTrials.gov. Unique identifier: NCT03036124), will evaluate the effects of dapagliflozin versus placebo on outcomes in 4500 patients with HFrEF, the complementary DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT03619213) will evaluate dapagliflozin versus placebo in HFpEF, and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT03521934) will evaluate the effects of sotagliflozin (a combined SGLT-1 and SGLT-2 inhibitor) in patients with worsening heart failure and EF <50%. The first 3 trials include patients with and without DM, thus specifically evaluating the potential role of SGLT-2 inhibition as a treatment for HF in patients without DM. In addition, the DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure; URL: ClinicalTrials.gov. Unique identifier: NCT02653482), PRESERVED-HF (Dapagliflozin in Preserved Ejection Fraction Heart Failure; Unique identifier: NCT03030235), and EMBRACE-HF (Empagliflozin Impact on Hemodynamics in Patients With Heart Failure; Unique identifier: NCT03030222) trials are evaluating

the potential mechanisms of SGLT-2 inhibitors in patients with established HFrEF and HFpEF.

Clinical Considerations. SGLT-2 inhibitors are the first class of glucose-lowering agents demonstrated to reduce the risk of HF hospitalization in patients with DM. Combined with significant reductions in cardiovascular and all-cause mortality seen with empagliflozin, it is reasonable to consider SGLT-2 inhibitor use as part of a prevention strategy in patients with DM at high risk for HF. Because secondary analyses of the cardiovascular outcomes trials have suggested that SGLT-2 inhibitors reduce the risk of HF hospitalization in patients with and without HF at baseline, SGLT-2 inhibitors are also a good glucose-lowering medication choice in patients with established HF and DM. Although this class appears promising for treatment of established HF in patients without DM, recommending their use in this patient group would be premature until appropriately powered trials are completed. Cardiovascular benefits of SGLT-2 inhibitors should be balanced with their potential risks, including genital candidiasis and other, rare potential complications, such as euglycemic diabetic ketoacidosis, lower-limb amputation, and fractures (the latter 2 complications only observed with canagliflozin to date; Table 2).

Management of HF in DM

In this section, we will first summarize existing data comparing the effectiveness of HF therapies in patients with and without DM from RCTs. Next, we will discuss the safe use of HF medications in patients with CKD. Finally, we will review the impact of HF medications on glycemic control.

Summary of DM Subgroup Data From Pivotal HF Studies

RAAS and Angiotensin Receptor Neprilysin Inhibitors. A meta-analysis¹⁷⁴ of 6 angiotensin-converting enzyme (ACE) inhibitor trials (Table 5) demonstrated similar reductions in morbidity and mortality in patients with HF with or without DM. The pooled analysis of 2398 patients found a relative risk for death of 0.84 (95% CI, 0.70–1.00) in patients with DM versus 0.85 (95% CI, 0.78–0.92) in those without DM. The absolute reduction in mortality with ACE inhibitors in individuals with DM is substantial because of their baseline higher mortality risk. Similar results were seen in pivotal HF trials of angiotensin receptor blockers (ARBs), including CHARM, where the effect of candesartan in reducing cardiovascular morbidity and mortality was not modified by DM.⁷⁶ Moreover, a recent subgroup analysis of PARADIGM-HF (Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) demonstrated consistent treatment benefits with the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril-valsartan in patients with and without DM.¹⁸⁴ Finally, mineralocorticoid receptor antagonists (MRAs) have consistent benefits in HFrEF patients with and without DM.^{192,194}

β -Blockers. Most meta-analyses of β -blocker trials by DM status have demonstrated a consistent benefit in individuals with DM and HFrEF,^{174,207–209} although one suggested a comparatively greater benefit in individuals without DM.²¹⁰ The latter meta-analysis of 6 pivotal β -blocker studies, including 3230 patients with DM (25% of the cohort), showed that β -blockers significantly reduced mortality in individuals with (relative risk, 0.84 [95% CI, 0.73–0.91]) and without (relative risk, 0.72 [95% CI, 0.65–0.79]) DM,²¹⁰ although the magnitude of the reduction was greater in patients without DM ($P = 0.023$). Overall, the 3 FDA-indicated β -blockers for use in HFrEF (carvedilol,^{48,207} metoprolol succinate,^{189,209} and bisoprolol¹⁸⁶) have been shown to substantially reduce morbidity and mortality in individuals with DM.

Ivabradine. In the SHIFT trial (Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial), ivabradine significantly reduced the primary end point of cardiovascular death or HF hospitalization in patients with and without DM (interaction $P = 0.57$).¹⁹⁶ There was also a significant reduction in HF hospitalization in both groups.

Implantable Cardioverter-Defibrillator/Cardiac Resynchronization Therapy. In general, pivotal trials of both implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) found consistent benefits in patients with and without DM. For instance, MADIT-II

(Multicenter Automatic Defibrillator Implantation Trial II) demonstrated reduced mortality with ICD compared with conventional therapy in individuals with (HR, 0.61 [95% CI, 0.38–0.98]) and without (HR, 0.71 [95% CI, 0.49–1.05]) DM, without evidence of interaction.¹⁹⁸ However, in SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial),¹⁹⁹ the magnitude of ICD benefit appeared to be less in individuals with DM (HR, 0.95 [95% CI, 0.68–1.33]) than in those without (HR, 0.67 [95% CI, 0.50–0.90]), although DM was not a prespecified subgroup analysis. This is consistent with other data demonstrating that the relative benefit of ICDs may be attenuated with an increasing comorbidity burden.²¹¹ The overall benefit of CRT was also similar in patients with and without DM in COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure),²⁰¹ CARE-HF (Cardiac Resynchronization-Heart Failure),²⁰³ MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy),²⁰⁵ and RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial).²⁰⁶ Moreover, procedure-related complications and length of stay were similar in patients with and without DM.²⁰¹ Patients with DM and HbA1c <7.0% have better outcomes after CRT than do those with suboptimal glycemic control.²¹²

Clinical Considerations. Given the strength of the data regarding benefits of RAAS inhibitors, ARNIs, β -blockers, ivabradine, and ICDs/CRT in HFrEF regardless of DM status, these therapies should routinely be implemented in patients with DM and HFrEF who meet guideline indications.^{7,8}

Impact of HF Medications on Glycemic Control

RAAS Inhibitors and ARNIs. ACE inhibitors and ARBs may reduce the risk of new-onset DM in patients with HFrEF. Post hoc analyses of the SOLVD (Studies of Left Ventricular Dysfunction)²¹³ and CHARM²¹⁴ trials demonstrated a reduction in the incidence of DM among patients treated with enalapril and candesartan, respectively; however, there are limited data on their impact on glycemic control in patients with HF and preexisting DM. In the PARADIGM-HF trial, patients randomized to enalapril (rather than sacubitril-valsartan) experienced an average reduction in HbA1c of 0.16% in the first year on treatment.²¹⁵ However, there was no placebo arm for comparison, and patients receiving sacubitril-valsartan experienced even greater improvements in HbA1c (mean reduction of 0.26%).

Use of sacubitril-valsartan in patients with HFrEF enrolled in the PARADIGM-HF trial was associated with a 29% reduction in new insulin use compared with enalapril.²¹⁵ The observed improved glycemic control with sacubitril-valsartan compared with enalapril has physiological plausibility and could be attributable to the incremental effect of neprilysin inhibition. Neprilysin is known to stimulate lipolysis, increase lipid oxidation, and enhance muscle oxidative capacity. Inhibition of neprilysin by sacubitril could contribute to improved glycemic parameters.²¹⁶ In addition, because GLP-1 is degraded not only by DPP-4 but also by neprilysin, potentiation of GLP-1 receptor signaling could contribute to the glycemic-lowering actions of sacubitril-valsartan.²¹⁷

Table 5. DM Subgroup Data From Pivotal HF Trials.

Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	Treatment Effects by DM Status
ACE inhibitor CONSENSUS ¹⁷⁵ 1987	Enalapril	NYHA IV	253	22	From meta-analysis ¹⁷⁴ : mortality RR of 0.64 (95% CI, 0.46–0.88) in non-DM vs 1.06 (95% CI, 0.65–1.74) in DM
SAVE ¹⁷⁶ 1992	Captopril	Recent MI EF ≤40%	2231	22	No interaction by DM status (P=0.45) Benefit of captopril was similar among non-DM (HR, 0.80 [95% CI, 0.64–0.94]) and DM (HR, 0.83 [95% CI, 0.63–0.87]) ¹³²
SOLVD-Treatment ¹⁷⁷ 1991	Enalapril	No overt HF Chronic HF EF ≤35%	2569	26	From meta-analysis ¹⁷⁴ : mortality RR of 0.84 (95% CI, 0.74–0.95) in non-DM vs 1.01 (95% CI, 0.85–1.21) in DM
TRACE ¹⁷⁸ 1995	Trandolapril	NYHA IIIB-IV EF ≤25%	1749	14	Multivariable analysis ¹⁷⁹ : interaction analysis (P=0.3). Mortality RR of 0.82 (95% CI, 0.69–0.97) in non-DM vs 0.64 (95% CI, 0.45–0.91) in DM
ARB Val-HeFT ¹⁸⁰ 2001	Valsartan	NYHA class II–IV EF <40%	5010	25	Primary text: “Valsartan improved the composite outcome in those with and without diabetes” For overall trial, combined end-point mortality and morbidity, 3.3% ARR (28.8% vs 32.1%; RRR, 13%; P=0.009)
HEAAL ¹⁸¹ 2009	Losartan 150 mg vs 50 mg daily (target doses)	NYHA classes II–IV EF ≤40%	3846	31	No interaction by DM status (P=0.35) Death or HF admission: 0.87 (95% CI, 0.77–0.98) in non-DM vs HR 0.96 (95% CI, 0.82–1.12) in DM for 150 mg vs 50 mg
VALIANT ¹⁸² 2003	Valsartan vs valsartan plus captopril vs captopril	Intolerant of ACE inhibitors MI complicated by LVSD, HF, or both within past 10 d	14 703	23	A prespecified subgroup analysis found that patients with DM experienced similar treatment effects as patients without DM for death and cardiovascular death, reinfarction, or hospitalization for HF. Overall trial found no difference in mortality for valsartan vs captopril (HR, 1.00 [97.5% CI, 0.90–1.11]; P=0.98).
CHARM-Program 2008	Candesartan	Multiple trials: CHARM-Alternative, Added, and Preserved	7599	28	Summary paper from the CHARM Program ⁷⁶ : the effect of candesartan was not modified by DM status (P=0.09 test for interaction).
ARNI PARADIGM-HF ¹⁸³ 2014	Sacubitril- valsartan vs enalapril	NYHA II–IV EF ≤40%	8442	35	Primary paper: ARR of 4.7% in cardiovascular death or HF hospitalization with sacubitril/valsartan vs enalapril. Primary end-point interaction for DM subgroup not significant (P=0.40). The interaction P value for cardiovascular mortality was 0.05. Secondary paper: the benefit of sacubitril-valsartan was consistent across the range of HbA1c. ¹⁸⁴
β-Blocker CIBIS-II ¹⁸⁵ 1999	Bisoprolol	NYHA III–IV EF ≤35%	2647	12	Primary paper: Interaction P=0.48 for mortality benefit by DM status Secondary paper: RR of mortality was 0.66 (95% CI, 0.54–0.81) in

(continued)

Table 5 (Continued)

Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	Treatment Effects by DM Status
COPERNICUS ¹⁸⁷ 2001	Carvedilol	HF with EF $\leq 25\%$	2289	26	non-DM vs 0.81 (95% CI, 0.51–1.28) in DM ¹⁸⁶ Data from meta-analysis ¹⁷⁴ : Mortality RR of 0.67 (95% CI, 0.52–0.85) in non-DM vs 0.68 (95% CI, 0.47–1.00) in DM. RRR of 1.02 (95% CI, 0.65–1.61)
MERIT-HF ¹⁸⁸ 1999	Metoprolol succinate	NYHA IIIB-IV EF $\leq 25\%$	3991	25	Primary paper with DM subgroup predefined; similar mortality in DM and non-DM Data from meta-analysis ¹⁷⁴ : mortality RR of 0.62 (95% CI, 0.48–0.79) in non-DM vs 0.81 (95% CI, 0.57–1.15) in DM. RRR of 1.32 (95% CI, 0.86–2.02) Secondary paper: similar reductions for mortality and hospitalization in DM and non-DM ¹⁸⁹
MRA RALES ¹⁹⁰ 1999	Spironolactone	NYHA III–IV	1663	22	Not reported in primary paper; not one of the 6 prespecified subgroups of interest
EMPHASIS-HF ¹⁹¹ 2011	Eplerenone	EF $\leq 35\%$ NYHA II EF $\leq 35\%$	2737	32	No interaction by DM status Secondary paper: HR, 0.72 (95% CI, 0.58–0.88; $P=0.002$) in non-DM vs 0.54 (95% CI, 0.42–0.70; $P<0.0001$) in DM ¹⁹²
EPHESUS ¹⁹³ 2003	Eplerenone	Acute MI complicated by LVSD (EF $\leq 40\%$) and HF	6632	32	No interaction of DM status with mortality ($P=0.35$) Secondary paper: RRR for cardiovascular death or cardiovascular hospitalization of 17% in DM ($P=0.031$); greater ARR hospitalization in DM cohort (5.1%) than non-DM (3%) ¹⁹⁴
Ivabradine SHIFT ¹⁹⁵ 2010	Ivabradine	HF with LVEF $\leq 35\%$ in normal sinus rhythm with HR ≥ 70 bpm	6558	30	Secondary paper: ivabradine significantly reduced cardiovascular death or HF hospitalization in patients with and without DM (interaction $P=0.57$); HR, 0.84 (95% CI, 0.75–0.95) in non-DM vs 0.80 (95% CI, 0.68–0.94) in DM ¹⁹⁶ For HF hospitalization, HR 0.77 (95% CI, 0.67–0.89) in non-DM vs 0.71 (95% CI, 0.59–0.86) in DM. Interaction $P=0.53$
ICD/CRT MADIT-II ¹⁹⁷ 2002	ICD	Prior MI	1232	35	Primary paper indicated no differential effect of defibrillator therapy on survival according to DM status Secondary paper: reduction in death with ICD was similar in non-DM (HR, 0.71 [95% CI, 0.49–1.05]) and DM (HR, 0.61 [95% CI, 0.38–0.98]) ¹⁹⁸
SCD-HeFT ¹⁹⁹ 2005	ICD vs amiodarone vs placebo	NYHA II–III EF $\leq 35\%$	2521	30	DM was not a prespecified subgroup of interest Reduction in death with ICD in non-DM was 0.67 (97.5% CI, 0.50–0.90) vs 0.95 (97.5% CI, 0.68–1.33) in DM
COMPANION ²⁰⁰ 2004	CRT-P, CRT-D, or medical therapy	NYHA III–IV QRS ≥ 120 ms	1520	41	Secondary paper: CRT (pooled) had a consistent benefit in DM patients across the trial end points. ²⁰¹ With CRT, patients with DM had reduced all-cause mortality or all-cause hospitalization (HR, 0.77

(continued)

Table 5 (Continued)

Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	Treatment Effects by DM Status
CARE-HF ²⁰² 2005	CRT	NYHA III–IV	813	29	[95% CI, 0.62–0.97]), all-cause mortality or HF hospitalization (HR, 0.52 [95% CI, 0.40–0.69]), and all-cause mortality (HR, 0.67 [95% CI, 0.45–0.99]) compared with medical therapy. Secondary paper: DM did not influence the beneficial effect of CRT on any end point. ²⁰³ CRT reduced all-cause mortality and HF hospitalization with similar echocardiographic benefits in those with and without DM.
MADIT-CRT ²⁰⁴ 2009	CRT-D vs ICD alone	EF ≤35% QRS ≥120 ms LVEDD ≥30 mm NYHA I-II	1820	30	Secondary paper: CRT-D was associated with a significant reduction in risk of death or HF hospitalization ²⁰⁵ in both DM (HR, 0.56; P=0.001) and non-DM (HR, 0.67; P=0.003) patients (interaction P=0.44).
RAFT ²⁰⁶ 2010	CRT-D vs ICD alone	EF ≤30% QRS ≥130 ms NYHA II-III	1798	34	A prespecified DM interaction analysis was not significant (P=0.22).
		EF ≤30% Intrinsic QRS ≥120 ms or paced ≥200 ms			

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ARR, adjusted relative risk; CARE-HF, Cardiac Resynchronization-Heart Failure; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CRT, cardiac resynchronization therapy; CRT-D, CRT with defibrillator; CRT-P, CRT with pacemaker; DM, diabetes mellitus; EF, ejection fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHEUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HbA1c, hemoglobin A1c; HEAAL, Heart Failure Endpoint Evaluation of AII-Antagonist Losartan; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MADIT-II, Multicenter Automatic Defibrillator Implantation Trial II; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PARADIGM-HF, Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RALES, Randomized Aldactone Evaluation Study; RR, relative risk; RRR, relative risk reduction; SAVE, Survival and Ventricular Enlargement; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; SHIFT, Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation; Val-HeFT, Valsartan Heart Failure Trial; and VALIANT, Valsartan in Acute Myocardial Infarction Trial.

MRAs have been demonstrated to negatively impact some glycemic measures when used in patients without HF. A 2016 systematic review of 18 placebo-controlled trials found that spironolactone increased HbA1c by an average of 0.16% (95% CI, 0.02–0.30) but had no clear effect on fasting glucose or insulin levels.²¹⁸ In the EMPHASIS-HF trial, which randomized patients with HFrEF to eplerenone or placebo, eplerenone had no effect on the development of DM.⁴⁶ In a small comparative effectiveness study in HFrEF, HbA1c significantly increased in patients treated with spironolactone but not in those treated with eplerenone, a more selective MRA.²¹⁹ These limited data suggest that eplerenone might have a more favorable impact on glycemic control than spironolactone.

β -Blockers. Data in patients with and without HF suggest that β -blockers with α -blocking properties might have more favorable effects on glucose metabolism than those

without.^{48,220–223} In patients with DM and hypertension, but not HF, carvedilol was associated with improved insulin sensitivity and better glycemic control than metoprolol tartrate.²²⁰ In patients with HFrEF, carvedilol has been shown to decrease fasting insulin levels, reduce HbA1c, and reduce the incidence of DM.^{48,221,223} Similar improvements in glycemic parameters were not seen in patients with HFrEF treated with metoprolol tartrate or bisoprolol.^{48,223}

Ivabradine. There are no data on the impact of ivabradine on glycemic control in patients with HF. In patients with angina and DM, ivabradine was associated with a modest (mean 0.1%) decrease in HbA1c.²²⁴

Clinical Considerations. Overall, ACE inhibitors, ARBs, and ARNIs have favorable effects on the development of DM and glycemic control in patients with HFrEF and should be used according to guideline recommendations. Spironolactone may modestly worsen glycemic

control in patients with DM and HFrEF. Carvedilol might have more favorable effects on glycemic control than metoprolol succinate and bisoprolol and could be preferentially used in patients with HFrEF and DM with poor glycemic control.

Use of Glucose-Lowering and HF Medications in Patients With CKD

Use of Glucose-Lowering Medications With CKD. Despite the high prevalence of CKD among individuals with both DM and HF,²²⁵ there are limited data to guide the selection of optimal pharmacotherapy of DM in this group. Guidance for use of glycemic medications in patients with CKD is shown in Table 2. Metformin can be used safely and effectively in patients with an estimated glomerular filtration rate (eGFR) as low as 30 mL·min⁻¹·1.73 m⁻², albeit at reduced doses.²²⁶ The short-acting sulfonylurea agents (eg, glipizide, glimepiride) are considered safe in patients with eGFR <30 mL·min⁻¹·1.73 m⁻² but should be used cautiously at reduced doses because of their risk of hypoglycemia. Long-acting sulfonylurea agents (eg, glyburide) should not be used. Insulin can be used at any eGFR, but lower doses might be required with worsening renal function. Most GLP-1 agonists can be used with eGFR >15 mL·min⁻¹·1.73 m⁻² with no dose reduction, although there is limited evidence for liraglutide and dulaglutide at lower eGFR levels. DPP-4 inhibitors require dose reduction with lower eGFR levels. In EMPA-REG²²⁷ and CANVAS,⁹⁴ SGLT-2 inhibitors slowed progression of CKD and lowered rates of clinically significant renal events compared with placebo. Although current recommendations are that SGLT-2 inhibitors should not be used with eGFR <30 mL·min⁻¹·1.73 m⁻², ongoing trials (CANVAS [just stopped prematurely for efficacy], DAPA-CKD [Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; URL: ClinicalTrials.gov. Unique identifier: NCT03036150], EMPA-KIDNEY [Study of Heart and Kidney Protection With Empagliflozin; URL: ClinicalTrials.gov. Unique identifier: NCT03594110]) will provide more conclusive data on the effects of SGLT-2 inhibitors in patients with eGFR as low as 20 mL·min⁻¹·1.73 m⁻².

Clinical Considerations. As in those without CKD, metformin is reasonable first-line therapy in patients with HF and CKD, as long as eGFR exceeds 30 mL·min⁻¹·1.73 m⁻². Insulin is safe to use in patients with CKD and HF, although lower doses are required with impaired renal function. Other hypoglycemic agents can be considered, although dose adjustment might be needed in those with CKD, and the risk of adverse effects can be enhanced as renal function declines. Use of SGLT-2 inhibitors in patients with CKD seems promising given their HF benefit and potential for renal protection, but results of ongoing RCTs are needed to ensure they are safe to use at lower eGFR levels.

Use of HF Medications With CKD. Use of RAAS inhibitors to treat HF in patients with DM is frequently complicated by the presence of CKD,²²⁸ which can enhance the risk of adverse effects, including worsening renal function and hyperkalemia.²²⁹ Although the benefits of ACE inhibitors/ARBs, ARNIs, and MRAs generally appear to be similar in patients with and without CKD,^{183,190,230,231} most studies systematically excluded patients with moderate or severe CKD (stage 3B or worse), for whom the balance of benefit and risk is particularly uncertain. Although data from randomized trials of patients with DM, CKD, and microalbuminuria or macroalbuminuria suggest that use of RAAS inhibitors alone or in combination can slow progression of renal dysfunction,^{232,233} these data do not inform the effects in patients with HF, who were typically excluded from those studies.

The risk of hyperkalemia during treatment of HFrEF with ACE inhibitors/ARBs is dose dependent, amplified by both DM and CKD, and further increased by the addition of an MRA.^{234–236} The incidence of hyperkalemia (potassium level >5.5 mmol/L) among patients with DM and HFrEF assigned to enalapril in the ATMOSPHERE trial (Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure) was 11.8%, with rates of severe hyperkalemia (potassium level >6.0 mmol/L) approaching 4% over a median follow-up of 27 months.²³⁷ However, these rates in a clinical trial likely underestimate those in real-world clinical practice, where patient selection can be less restricted and laboratory surveillance less intensive.^{238–240} Dual RAAS inhibition with an ACE inhibitor and ARB or an ACE inhibitor and a plasma renin inhibitor in patients with DM is associated with even higher rates of hyperkalemia.^{234,241} The triple combination of an ACE inhibitor, ARB, and MRA is therefore discouraged.⁸ Data from PARADIGM-HF suggest that rates of hyperkalemia in patients with DM and HFrEF might be slightly lower with sacubitril-valsartan than with enalapril, particularly during concomitant treatment with an MRA.^{184,242}

Clinical Considerations. In patients with HFrEF, DM, and moderate CKD, it is reasonable to initiate an RAAS inhibitor at a low dose and titrate gradually to guideline-recommended doses with careful monitoring of renal function and serum potassium levels. Consideration should then be given to initiating an MRA in patients with eGFR >30 mL·min⁻¹·1.73 m⁻² and potassium ≤5.0 mmol/L after optimization of an ACE inhibitor/ARB/ARNI and β-blocker, while reducing or discontinuing potassium supplements. Patients should be educated to avoid over-the-counter potassium supplements and potassium-based salt substitutes, limit intake of high-potassium food and beverages, and avoid medications that may increase risk for hyperkalemia (such as nonsteroidal anti-inflammatory drugs).

Use of Glucose-Lowering and HF Medications With eGFR <30 mL·min⁻¹·1.73 m⁻². Management of DM and HF can be particularly challenging in patients with severely reduced renal function. In patients with eGFR <30 mL·min⁻¹·1.73 m⁻², insulin is safe to use but might require lower doses and frequent monitoring. Other selected agents,

including glimepiride, glipizide, DPP-4 inhibitors, and selected GLP-1 receptor agonists (Table 2) can be considered but should be used with caution and might require dose adjustment. Because major HF trials of ACE inhibitors and ARBs excluded patients with severe renal dysfunction, little is known about their safety in this population. The European Society of Cardiology guidelines recommend their use only if eGFR is $>30 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$,²⁴³ although the American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure suggests they should be used with caution in patients with creatinine $>3 \text{ mg/dL}$.⁸ If used in patients with advanced CKD, close monitoring of renal function and potassium is required. Data on safety and effectiveness of ARNIs in advanced CKD are limited because patients with $\text{eGFR} <30 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ were excluded from the PARADIGM-HF trial.¹⁸³ Recent data from the UK HARP-III trial (United Kingdom Heart and Renal Protection-III) suggest that sacubitril-valsartan and irbesartan have similar rates of adverse events in patients with eGFR as low as $20 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$.²⁴⁴ Hyperkalemia was common in patients treated with sacubitril-valsartan (32%) and irbesartan (24%), which underscores the importance of close monitoring of potassium if ACE inhibitors, ARBs, or ARNIs are used in patients with CKD. MRAs should not be initiated in patients with $\text{eGFR} <30 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$.

Collaborative Management of DM and HF

Complexity of Medical Regimen

Despite evidence-based therapies to improve glycemic control and, recently, cardiovascular outcomes, less is known about the translation and implementation of this clinical knowledge into practice. Patients with DM and HF can have extremely complex medical regimens. For example, glycemic control, an essential component of DM self-care, includes medication adherence, glucose monitoring, dietary modification, physical activity, weight and stress management, and individualized decision making.^{245,246} This is in addition to requisite HF self-care that includes all of the above plus restricted dietary sodium and fluid intake and symptom management.²⁴⁷ In a small, qualitative meta-analysis, patients with DM and HF reported lack of knowledge, skill, and efficacy in integrating multiple self-care behaviors, which led them to prioritize some over others (eg, glucose monitoring, but not daily weights).^{248,249} In a large, national survey of predominantly older adults, severe HF was associated with lower DM prioritization and self-care scores.²⁵⁰ These challenges to self-care across multiple conditions may be attributed to lack of integration of information received from multiple providers. Furthermore, as HF becomes more symptomatic, DM self-care is deemed a lesser priority and perhaps more difficult. Interventions are needed to integrate self-care behaviors across both DM and HF, including guidance from healthcare providers in setting priorities when capacity is limited.

Team-Based Care

The National Institutes of Health has called for definitive strategies that bridge the gap between clinical knowledge, optimized practice, and improved outcomes.^{251,252} The chronic care model collaborative addresses how to translate clinical research findings into real-world practice using a proactive, process-driven, team-based approach.²⁵³ An essential premise of the chronic care model is team-based care that typically includes physicians and advanced practice providers, nurses, pharmacists, dietitians, social workers, and community health workers (Figure 4).²⁵⁴ Central to team-based care is the recognition that approaches to chronic disease management require the development of individualized plans of care that consider patient preferences and effective coordination of care across all members of the healthcare team.^{255,256} According to the National Academy of Sciences, to improve outcomes for patients with chronic health conditions such as DM and HF, teams must consider the interpersonal, organizational, community, and societal factors that influence patient behavioral decision making.²⁵⁷ Although there is evidence that these factors influence clinical outcomes in people with HF and in those with DM,^{258,259} few studies have focused on individuals with both DM and HF. In one promising pilot study, an integrated HF-DM self-care intervention was effective in improving essential components of self-care, including HF knowledge and DM self-efficacy, with sustained effects on selected self-care behaviors.²⁶⁰ Additional multicenter studies that test the sustainability of results and examine clinical outcomes in this high-risk population are needed.

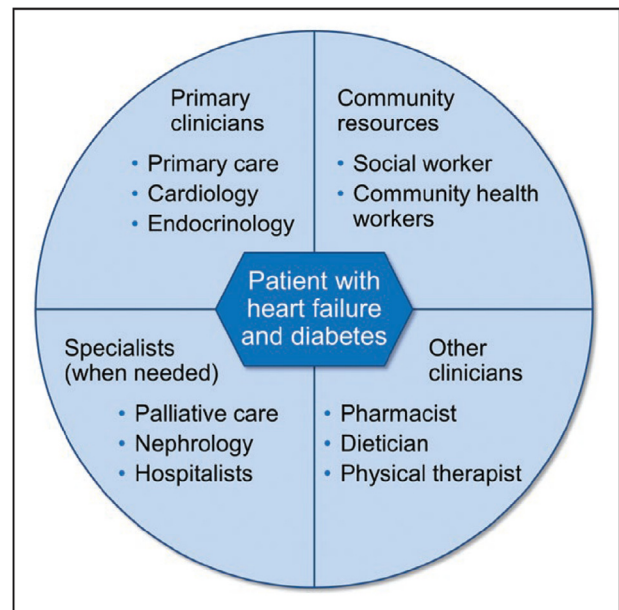


Fig. 4. Interdisciplinary team-based care in patients with heart failure and diabetes mellitus.

Team-based care should include primary clinicians, specialists, and community workers collaborating together to meet the needs of the patient. The ideal clinicians and community resources constituting the team may vary from patient to patient.

Lifestyle Management

Lifestyle management should be integral to the care of patients with DM and HF. DM is linked to obesity, inactivity, and poor dietary choices, which in turn are linked to cardiovascular diseases, including HF. Exercise can improve functional capacity for patients with DM and HF. In the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), 2331 individuals with HFrEF were randomized to exercise training or optimal medical care.²⁶¹ Patients with DM (32% of those enrolled) had more impaired functional status at baseline and were less adherent to exercise training. Despite this, patients with DM randomized to exercise had significant improvements in peak oxygen consumption ($\dot{V}O_2$) and 6-minute walk distance (both $P < 0.001$) compared with usual care, without safety concerns. Cardiac rehabilitation programs represent an excellent avenue to encourage exercise participation in patients with DM and HF. Referral is critical and represents a primary barrier to cardiac rehabilitation enrollment.²⁶²

Although unintentional weight loss is associated with poor prognosis in HF,^{263,264} limited data suggest that intentional weight loss can improve exercise capacity in obese patients with HF, including those with DM.^{265–267} Weight loss through calorie restriction, when combined with exercise, holds particular promise in patients with HFpEF. Using a 2×2 factorial design, a recent study randomized 100 obese patients (body mass index 38–40 kg/m²) with HFpEF and a high prevalence of DM to diet, exercise, both, or neither. Patients treated with either exercise or diet had improvements in peak, and the combination was additive.²⁶⁷ However, neither diet nor exercise had a significant effect on quality of life.

Clinical Considerations. Exercise is safe and beneficial in patients with HF and DM. Patients referred to cardiac rehabilitation should be counseled on the importance of adherence to training. In patients with HFpEF and obesity, many of whom also have DM, a combined diet and exercise program can improve functional capacity.

DM: Implications for Advanced HF Therapies

Approximately 18% of patients undergoing heart transplantation have DM.²⁶⁸ Analyses from the United Network of Organ Sharing database have demonstrated similar long-term survival in patients with uncomplicated DM compared with those without DM.²⁶⁸ However, DM associated with end-organ damage (other than nonproliferative retinopathy) is a relative contraindication to transplantation.²⁶⁹ Still, patients with diabetic nephropathy who are otherwise good candidates should be considered for combined heart and kidney transplantation, because survival is similar to heart transplantation alone.²⁷⁰ Before transplantation, patients should work with their clinicians to achieve a target HbA1c of $<7.5\%$.²⁶⁹ After transplantation, immunosuppressive agents, including corticosteroids and calcineurin inhibitors, can promote development of DM or worsen glycemic control among those with DM.²⁷¹ Management of DM after

heart transplantation is beyond the scope of this statement, but a helpful guideline was published previously.²⁷² Collaboration with an endocrinologist with experience in management of posttransplantation DM can be helpful.

Approximately 30% to 40% of patients undergoing placement of an LV assist device (LVAD) have DM.^{273,274} Most^{273,275–278} but not all²⁷⁴ studies have demonstrated worse post-LVAD outcomes in patients with DM, including higher risk of death,^{273,277} persistently poor quality of life,^{275,278} and thromboembolic events.^{273,276} Similar to heart transplantation, DM with end-organ damage is a relative contraindication to durable mechanical circulatory support.²⁷⁹ Consultation with an endocrinologist is recommended for patients with poorly controlled DM before LVAD implantation,²⁷⁹ although limited available data have found no association of pre-LVAD glycemic control (HbA1c level) with post-LVAD outcomes in patients without DM.^{273,274} Glycemic control often improves after LVAD placement, and patients may require fewer glucose-lowering medications.^{273,280–283} In a single-center study, HbA1c decreased from a mean of 7.4% before LVAD to 6.0% at 3 months and 6.3% at 1 year after LVAD implantation.²⁷³ Whether this benefit is attributable to reversal of the HF state, increased physical activity, improved self-care, or other factors remains to be determined.

Clinical Considerations

Endocrinology consultation is strongly advised for patients with end-stage HF, DM, and poor glycemic control undergoing evaluation for advanced HF therapies.

Future Directions and Unanswered Questions

There are many unanswered questions regarding the epidemiology, pathobiology, optimal pharmacotherapy, and co-disease management strategies for patients with DM and HF (Table 6). The epidemiology of both DM and HF may be changing because of modification of risk factors and introduction of novel therapies. Well-powered clinical trials and prospective population-based studies are needed to elucidate these changes. As with many complex diseases, genetic susceptibilities likely exist but will require large databases and powerful bioinformatics to uncover. The intensity of glycemic control may need to be tailored to the stage and severity of HF, with close monitoring for safety and efficacy of DM therapies. Likewise, more data are needed on the impact of old and new HF therapies on the incidence and progression of DM. Further research is needed to elucidate safe use of glycemic-lowering medications in patients with HF and renal dysfunction. Because both DM and HF are chronic diseases, integrated care that actively engages patients, family, and providers is key to optimizing both quality and quantity of life. Whether novel ambulatory or remote monitoring strategies can aid in this collateral benefit remains to be determined.

Table 6. Unanswered Questions Regarding the Intersection of DM and HF.

Is the epidemiology of DM and HF changing?
Development of HF in patients receiving new DM therapies (eg, SGLT-2 inhibitors)
Development of and risk factors for DM in patients on new HF therapies (eg, ARNI)
Is there a genetic susceptibility to DM in HF or HF in DM?
Is diabetic cardiomyopathy reversible? Which patients will have myocardial recovery vs remission?
What is the optimal method to identify patients with type 2 DM at highest risk for developing HF?
What are the optimal HbA1c targets for patients with stages B, C, and D HF?
Safety and efficacy of glucose-lowering medications:
Are sulfonylureas safe in patients with DM and increased cardiovascular risk (CAROLINA)?
What is the safety and efficacy of DPP-4 inhibitors in HFrEF (MEASURE-HF)?
Do SGLT-2 inhibitors reduce morbidity and mortality in HFrEF and HFpEF (EMPEROR, DAPA-HF, SOLOIST-WHF)?
What are the mechanistic benefits of SGLT-2 inhibition beyond diuresis?
What is the optimal glycemic-lowering medication regimen for patients with HF and advanced (stage 4–5) CKD (DAPA-CKD, EMPA-KIDNEY)?
Off-target effects of HF therapies:
What are the mechanisms by which ARNI improves glycemic control?
Should carvedilol be preferred over metoprolol succinate in patients with HF and DM?
Should eplerenone be preferred over spironolactone in patients with HF and DM?
Optimizing resources for care of patients with DM and HF:
What strategies should be implemented to help patients/families integrate self-care behaviors across DM and HF?
What are the optimal resources required in an ambulatory clinic?
What are the optimal interventions to be used after an acute HF hospitalization?
How can barriers to enrollment in cardiac rehabilitation be lowered?
What is the role of the HF specialist in choice and monitoring of DM therapies?
The future of remote monitoring beyond signs, symptoms, and blood glucose:
Are there biological sensors to manage both HF and DM?
What is the value added with remote monitoring for the patient, family, and provider?
What is the best way to integrate smartphones and social media in health promotion?

ARNI indicates angiotensin receptor neprilysin inhibitor; CAROLINA, Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; CKD, chronic kidney disease; DAPA-CKD, Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; EMPA-KIDNEY, Study of Heart and Kidney Protection With Empagliflozin; EMPEROR, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure; HbA1c, hemoglobin A1c; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MEASURE-HF, Mechanistic Evaluation of Glucose-Lowering Strategies in Patients With Heart Failure; SGLT-2, sodium glucose cotransporter type 2; and SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure.

Article Information

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Disclosures

Writing Group Disclosures

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Mikhail N. Kosiborod	Saint Luke's Mid America Heart Institute	AstraZeneca (research grant, other research support) [†] ; Boehringer Ingelheim (research grant) [†]	None	None	None	None	Amarin*; Amgen [†] ; Applied Therapeutics*; AstraZeneca [†] ; Bayer [†] ; Boehringer Ingelheim [†] ; Eisai [†] ; Glytec*; GlaxoSmithKline*; Intarcia*; Janssen [†] ; Merck (Diabetes) [†] ; Novartis*; Novo Nordisk [†] ; Sanofi [†]	None
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*Modest.

[†]Significant.

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References

- Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States. 2017. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>. Accessed November 26, 2017.
- Benjamin EJ, Virani SS, Callaway CW, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: a report from the American Heart Association [published correction appears in *Circulation*. 2018;137:e493]. *Circulation* 2018;137:e67–e492. <https://doi.org/10.1161/CIR.0000000000000558>.
- American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(suppl 1):S55–64.
- Conlin PR, Colburn J, Aron D, Pries RM, Tschanz MP, Pogach L. Synopsis of the 2017 U.S. Department of Veterans Affairs/U.S. Department of Defense clinical practice guideline: management of type 2 diabetes mellitus. *Ann Intern Med* 2017;167:655–63. <https://doi.org/10.7326/M17-1362>.
- Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA, Garber JR, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez GE. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2018 executive summary. *Endocr Pract* 2018;24:91–120. <https://doi.org/10.4158/CS-2017-0153>.
- NICE. Type 2 diabetes in adults: management. National Institute for Health and Care; Excellence website. Published December 2015. Updated May 2017 <https://www.nice.org.uk/guidance/ng28>. Accessed December 1, 2017.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a 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:e137–61. <https://doi.org/10.1161/CIR.0000000000000509>.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 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. *Circulation* 2013;128:e240–327. <https://doi.org/10.1161/CIR.0b013e31829e8776>.
- GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015 [published correction appears in *Lancet*. 2017;389:e1]. *Lancet* 2016;388:1545–602. [https://doi.org/10.1016/S0140-6736\(16\)31678-6](https://doi.org/10.1016/S0140-6736(16)31678-6).
- Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;3:7–11. <https://doi.org/10.15420/cfr.2016.25.2>.
- From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, Rodeheffer RJ, Roger VL. Diabetes in heart failure: prevalence and impact on outcome in the population. *Am J Med* 2006;119:591–9. <https://doi.org/10.1016/j.amjmed.2006.05.024>.
- Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) trials and registry. *Am J Cardiol* 1996;77:1017–20.
- Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Krowicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme: a survey on the quality of care among patients with heart failure in Europe, part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;24:442–63.
- Dei Cas A, Fonarow GC, Gheorghiade M, Butler J. Concomitant diabetes mellitus and heart failure. *Curr Probl Cardiol* 2015;40:7–43. <https://doi.org/10.1016/j.cpcardiol.2014.09.002>.
- Sandesara PB, O'Neal WT, Kelli HM, Samman-Tahhan A, Hammadah M, Quyyumi AA, Sperling LS. The prognostic significance of diabetes and microvascular complications in patients with heart failure with preserved ejection fraction. *Diabetes Care* 2018;41:150–5. <https://doi.org/10.2337/dc17-0755>.
- Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, Gheorghiade M, O'Connor CM, Sun JL, Yancy CW, Young JB, Fonarow GC. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) [published correction appears in *Am Heart J*. 2007;154:646]. *Am Heart J* 2007;154:277. <https://doi.org/10.1016/j.ahj.2007.05.001>. e1–277.e8.
- 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;27:1879–84.
- Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff Jr. DC. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699–703.
- Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE, Hoes AW. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 2012;55:2154–62. <https://doi.org/10.1007/s00125-012-2579-0>.
- Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, Sigurdsson G, Rydén L. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care* 2005;28:612–6.
- Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979;241:2035–8.

22. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;35:1628–37.
23. van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the Heart and Soul Study. *Diabetes Care* 2010;33:2084–9. <https://doi.org/10.2337/dc10-0286>.
24. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, Szklo M, Lima JA. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008;51:1775–83. <https://doi.org/10.1016/j.jacc.2007.12.048>.
25. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001;161:996–1002.
26. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;103:2668–73.
27. Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, Coresh J. HbA 1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia* 2008;51:2197–204. <https://doi.org/10.1007/s00125-008-1164-z>.
28. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
29. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Hulley SB, Grady D, Shlipak MG. Predictors of heart failure among women with coronary disease. *Circulation* 2004;110:1424–30. <https://doi.org/10.1161/01.CIR.0000141726.01302.83>.
30. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL, for the SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial [published correction appears in *Circulation*. 2015;132:e198]. *Circulation* 2014;130:1579–88. <https://doi.org/10.1161/CIRCULATIONAHA.114.010389>.
31. Held C, Gerstein HC, Yusuf S, Zhao F, Hilbrich L, Anderson C, Sleight P, Teo K, for the ONTARGET/TRANSCEND Investigators. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. *Circulation* 2007;115:1371–5. <https://doi.org/10.1161/CIRCULATIONAHA.106.661405>.
32. Matsushita K, Blecker S, Pazin-Filho A, Bertoni A, Chang PP, Coresh J, Selvin E. The association of hemoglobin A1c with incident heart failure among people without diabetes: the Atherosclerosis Risk in Communities study. *Diabetes* 2010;59:2020–6. <https://doi.org/10.2337/db10-0165>.
33. Ingelsson E, Sundström J, Arnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA* 2005;294:334–41. <https://doi.org/10.1001/jama.294.3.334>.
34. Arnlöv J, Lind L, Zethelius B, Andrén B, Hales CN, Vessby B, Lithell H. Several factors associated with the insulin resistance syndrome are predictors of left ventricular systolic dysfunction in a male population after 20 years of follow-up. *Am Heart J* 2001;142:720–4. <https://doi.org/10.1067/mhj.2001.116957>.
35. Arnlöv J, Lind L, Sundström J, Andrén B, Vessby B, Lithell H. Insulin resistance, dietary fat intake and blood pressure predict left ventricular diastolic function 20 years later. *Nutr Metab Cardiovasc Dis* 2005;15:242–9. <https://doi.org/10.1016/j.numecd.2004.10.002>.
36. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the Strong Heart Study. *Circulation* 2000;101:2271–6.
37. Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol* 2006;48:1548–51. <https://doi.org/10.1016/j.jacc.2006.07.033>.
38. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC, Devereux RB. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. *Circulation* 2001;103:102–7.
39. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003;107:448–54.
40. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction: a population-based study [published correction appears in *J Am Coll Cardiol*. 2010;56:1612]. *J Am Coll Cardiol* 2010;55:300–5. <https://doi.org/10.1016/j.jacc.2009.12.003>.
41. Swoboda PP, McDiarmid AK, Erhayiem B, Ripley DP, Dobson LE, Garg P, Musa TA, Witte KK, Kearney MT, Barth JH, Ajjan R, Greenwood JP, Plein S. Diabetes mellitus, microalbuminuria, and subclinical cardiac disease: identification and monitoring of individuals at risk of heart failure. *J Am Heart Assoc* 2017;6:e005539. <https://doi.org/10.1161/JAHA.117.005539>.
42. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003;108:977–82. <https://doi.org/10.1161/01.CIR.0000085166.44904.79>.
43. Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of “asymptomatic” left ventricular systolic dysfunction: implications for screening. *Ann Intern Med* 2003;138:907–16.
44. Paolillo S, Rengo G, Pellegrino T, Formisano R, Pagano G, Gargiulo P, Savarese G, Carotenuto R, Petraglia L, Rapacciuolo A, Perrino C, Piscitelli S, Attina E, Del Guercio L, Leosco D, Trimarco B, Cuocolo A, Perrone-Filardi P. Insulin resistance is associated with impaired cardiac sympathetic innervation in patients with heart failure. *Eur Heart J Cardiovasc Imaging* 2015;16:1148–53. <https://doi.org/10.1093/ehjci/jev061>.
45. Preiss D, Zetterstrand S, McMurray JJ, Ostergren J, Michelsson EL, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Gerstein HC, Sattar N. Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Investigators. Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Diabetes Care* 2009;32:915–20. <https://doi.org/10.2337/dc08-1709>.
46. Preiss D, van Veldhuisen DJ, Sattar N, Krum H, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, Zannad F, McMurray JJ. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients

- Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Eur J Heart Fail* 2012;14:909–15. <https://doi.org/10.1093/eurjhf/hfs067>.
47. Centers for Disease Control and Prevention. Incidence of Diagnosed Diabetes. <https://www.cdc.gov/diabetes/data/statistics-report/incidence-diabetes.html>. Accessed April 18, 2019.
 48. Torp-Pedersen C, Metra M, Charlesworth A, Spark P, Lukas MA, Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Remme WJ, Scherhag A, Investigators COMET. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007;93:968–73. <https://doi.org/10.1136/hrt.2006.092379>.
 49. Tenenbaum A, Motro M, Fisman EZ, Leor J, Freimark D, Boyko V, Mandelzweig L, Adler Y, Sherer Y, Behar S. Functional class in patients with heart failure is associated with the development of diabetes. *Am J Med* 2003;114:271–5.
 50. Marwick TH, Ritchie R, Shaw JE, Kaye D. Implications of underlying mechanisms for the recognition and management of diabetic cardiomyopathy. *J Am Coll Cardiol* 2018;71:339–51. <https://doi.org/10.1016/j.jacc.2017.11.019>.
 51. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, Gheorghiadu M, Fonarow GC. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail* 2015;3:136–45. <https://doi.org/10.1016/j.jchf.2014.08.004>.
 52. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972;30:595–602.
 53. Levell E, Mahmood M, Piechnik SK, Ariga R, Francis JM, Rodgers CT, Clarke WT, Sabharwal N, Schneider JE, Karimatos TD, Clarke K, Rider OJ, Neubauer S. Relationship between left ventricular structural and metabolic remodeling in type 2 diabetes. *Diabetes* 2016;65:44–52. <https://doi.org/10.2337/db15-0627>.
 54. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 2003;41:611–7.
 55. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. *Cardiovasc Res* 2004;63:582–92. <https://doi.org/10.1016/j.cardiores.2004.05.001>.
 56. Lebeche D, Davidoff AJ, Hajjar RJ. Interplay between impaired calcium regulation and insulin signaling abnormalities in diabetic cardiomyopathy. *Nat Clin Pract Cardiovasc Med* 2008;5:715–24. <https://doi.org/10.1038/ncpcardio.1347>.
 57. Waddingham MT, Edgley AJ, Tsuchimochi H, Kelly DJ, Shirai M, Pearson JT. Contractile apparatus dysfunction early in the pathophysiology of diabetic cardiomyopathy. *World J Diabetes* 2015;6:943–60. <https://doi.org/10.4239/wjd.v6.i7.943>.
 58. Fillmore N, Mori J, Lopaschuk GD. Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy. *Br J Pharmacol* 2014;171:2080–90. <https://doi.org/10.1111/bph.12475>.
 59. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS. Cardiac steatosis in diabetes mellitus: a ¹H-magnetic resonance spectroscopy study. *Circulation* 2007;116:1170–5. <https://doi.org/10.1161/CIRCULATIONAHA.106.645614>.
 60. Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ, Neuffer PD. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. *J Am Coll Cardiol* 2009;54:1891–8. <https://doi.org/10.1016/j.jacc.2009.07.031>.
 61. Montaigne D, Marechal X, Coisne A, Debry N, Modine T, Fayad G, Potelle C, El Arid JM, Mouton S, Sebt Y, Duez H, Preau S, Remy-Jouet I, Zerimech F, Koussa M, Richard V, Nevriere R, Edme JL, Lefebvre P, Staels B. Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circulation* 2014;130:554–64. <https://doi.org/10.1161/CIRCULATIONAHA.113.008476>.
 62. Chowdhry MF, Vohra HA, Galiñanes M. Diabetes increases apoptosis and necrosis in both ischemic and nonischemic human myocardium: role of caspases and poly-adenosine diphosphate-ribose polymerase. *J Thorac Cardiovasc Surg* 2007;134:124–31. <https://doi.org/10.1016/j.jtcvs.2006.12.059>. e1.
 63. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;136:6–19. <https://doi.org/10.1161/CIRCULATIONAHA.116.026807>.
 64. Dauriz M, Targher G, Laroche C, Temporelli PL, Ferrari R, Anker S, Coats A, Filippatos G, Crespo-Leiro M, Mebazaa A, Piepoli MF, Maggioni AP, Tavazzi L. for the ESC-HFA Heart Failure Long-Term Registry. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Diabetes Care* 2017;40:671–8. <https://doi.org/10.2337/dc16-2016>.
 65. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A. Prognostic implications of type 2 diabetes mellitus in ischemic and nonischemic heart failure. *J Am Coll Cardiol* 2016;68:1404–16. <https://doi.org/10.1016/j.jacc.2016.06.061>.
 66. Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, Drozd J, Ferrari R, Anker S, Coats A, Filippatos G, Crespo-Leiro MG, Mebazaa A, Piepoli MF, Maggioni AP, Tavazzi L. on behalf of the ESC-HFA HF Long-Term Registry Investigators. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;19:54–65. <https://doi.org/10.1002/ehfj.679>.
 67. MAGGIC heart failure risk calculator. <http://www.heartfailure-risk.org>. Accessed 18 April 2019.
 68. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. on behalf of the Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;34:1404–13. <https://doi.org/10.1093/eurheartj/ehs337>.
 69. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah N, Roger VL. Hospitalizations after heart failure diagnosis: a community perspective. *J Am Coll Cardiol* 2009;54:1695–702. <https://doi.org/10.1016/j.jacc.2009.08.019>.
 70. Chaudhry SI, McAvay G, Chen S, Whitson H, Newman AB, Krumholz HM, Gill TM. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the Cardiovascular Health Study. *J Am Coll Cardiol* 2013;61:635–42. <https://doi.org/10.1016/j.jacc.2012.11.027>.
 71. Lawson CA, Jones PW, Teece L, Dunbar SB, Seferovic PM, Khunti K, Mamas M, Kadam UT. Association between type 2 diabetes and all-cause hospitalization and mortality in the UK general heart failure population: stratification by diabetic

- glycemic control and medication intensification. *JACC Heart Fail* 2018;6:18–26. <https://doi.org/10.1016/j.jchf.2017.08.020>.
72. Arora S, Patel P, Lahewala S, Patel N, Patel NJ, Thakore K, Amin A, Tripathi B, Kumar V, Shah H, Shah M, Panaich S, Deshmukh A, Badheka A, Gidwani U, Gopalan R. Etiologies, trends, and predictors of 30-day readmission in patients with heart failure. *Am J Cardiol* 2017;119:760–9. <https://doi.org/10.1016/j.amjcard.2016.11.022>.
 73. Fotos NV, Giakoumidakis K, Kollia Z, Galanis P, Copanitsanou P, Pananoudaki E, Brokalaki H. Health-related quality of life of patients with severe heart failure: a cross-sectional multicentre study. *Scand J Caring Sci* 2013;27:686–94. <https://doi.org/10.1111/j.1471-6712.2012.01078.x>.
 74. Allen LA, Gheorghiade M, Reid KJ, Dunlay SM, Chan PS, Hauptman PJ, Zannad F, Konstam MA, Spertus JA. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. *Circ Cardiovasc Qual Outcomes* 2011;4:389–98. <https://doi.org/10.1161/CIRCOUTCOMES.110.958009>.
 75. Allen LA, Magid DJ, Gurwitz JH, Smith DH, Goldberg RJ, Saczynski J, Thorp ML, Hsu G, Sung SH, Go AS. Risk factors for adverse outcomes by left ventricular ejection fraction in a contemporary heart failure population. *Circ Heart Fail* 2013;6:635–46. <https://doi.org/10.1161/CIRCHEARTFAILURE.112.000180>.
 76. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ. for the CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377–85. <https://doi.org/10.1093/eurheartj/ehn153>.
 77. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie RS, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray JJ. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-PRESERVE Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). *Circulation* 2017;135:724–35. <https://doi.org/10.1161/CIRCULATIONAHA.116.024593>.
 78. Tromp J, Westenbrink BD, Ouwerkerk W, van Veldhuisen DJ, Samani NJ, Ponikowski P, Metra M, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Lang CC, Ng LL, Zannad F, Zwinderman AH, Hillege HL, van der Meer P, Voors AA. Identifying pathophysiological mechanisms in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2018;72:1081–90. <https://doi.org/10.1016/j.jacc.2018.06.050>.
 79. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, Arima H, Monaghan H, Joshi R, Colagiuri S, Cooper ME, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Lisheng L, Mancia G, Marre M, Matthews DR, Mogensen CE, Perkovic V, Poulter N, Rodgers A, Williams B, MacMahon S, Patel A, Woodward M. for the ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–406. <https://doi.org/10.1056/NEJMoa1407963>.
 80. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm Jr RH, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I. for the ACCORD Trial Group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial [published correction appears in *Lancet*. 2010;376:1466]. *Lancet* 2010;376:419–30. [https://doi.org/10.1016/S0140-6736\(10\)60576-4](https://doi.org/10.1016/S0140-6736(10)60576-4).
 81. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, Investigators VADT. Glucose control and vascular complications in veterans with type 2 diabetes [published correction appears in *N Engl J Med*. 2009;361:1028]. *N Engl J Med* 2009;360:129–39. <https://doi.org/10.1056/NEJMoa0808431>.
 82. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–89. <https://doi.org/10.1056/NEJMoa0806470>.
 83. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompont S, de Galan BE, Joshi R, Travert F. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–72. <https://doi.org/10.1056/NEJMoa0802987>.
 84. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999;354:602]. *Lancet* 1998;352:837–53.
 85. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in *Lancet*. 1998;352:1558]. *Lancet* 1998;352:854–65.
 86. Rodríguez-Gutiérrez R, Montori VM. Glycemic control for patients with type 2 diabetes mellitus: our evolving faith in the face of evidence. *Circ Cardiovasc Qual Outcomes* 2016;9:504–12. <https://doi.org/10.1161/CIRCOUTCOMES.116.002901>.
 87. Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, Gaita F, McMurray JJ. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. *Am Heart J* 2011;162:938–48. <https://doi.org/10.1016/j.ahj.2011.07.030>. e2.
 88. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–59. <https://doi.org/10.1056/NEJMoa0802743>.
 89. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, McCarren M, Duckworth WC, Emanuele NV. for the VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes [published correction appears in *N Engl J Med*. 2015;373:198]. *N Engl J Med* 2015;372:2197–206. <https://doi.org/10.1056/NEJMoa1414266>.
 90. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. for the EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28. <https://doi.org/10.1056/NEJMoa1504720>.
 91. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB. for the LEADER Steering Committee on behalf of the LEADER Trial Investigators. Liraglutide and

- cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–22. <https://doi.org/10.1056/NEJMoA1603827>.
92. Marso SP, Holst AG, Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2017;376:891–2. <https://doi.org/10.1056/NEJMc1615712>.
 93. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC, for the ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247–57. <https://doi.org/10.1056/NEJMoA1509225>.
 94. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondur N, Shaw W, Law G, Desai M, Matthews DR, for the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–57. <https://doi.org/10.1056/NEJMoA1611925>.
 95. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR, for the TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes [published correction appears in *N Engl J Med*. 2015;373:586]. *N Engl J Med* 2015;373:232–42. <https://doi.org/10.1056/NEJMoA1501352>.
 96. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Ohman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF, for the EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228–39. <https://doi.org/10.1056/NEJMoA1612917>.
 97. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I, for the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–26. <https://doi.org/10.1056/NEJMoA1307684>.
 98. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F, for the EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–35. <https://doi.org/10.1056/NEJMoA1305889>.
 99. Skrtic S, Cabrera C, Olsson M, Schnecke V, Lind M. Contemporary risk estimates of three HbA1c variables in relation to heart failure following diagnosis of type 2 diabetes. *Heart* 2017;103:353–8. <https://doi.org/10.1136/heartjnl-2016-309806>.
 100. Lind M, Olsson M, Rosengren A, Svensson AM, Bounias I, Gudbjörnsdóttir S. The relationship between glycaemic control and heart failure in 83,021 patients with type 2 diabetes. *Diabetologia* 2012;55:2946–53. <https://doi.org/10.1007/s00125-012-2681-3>.
 101. Blecker S, Park H, Katz SD. Association of HbA1c with hospitalization and mortality among patients with heart failure and diabetes. *BMC Cardiovasc Disord* 2016;16:99. <https://doi.org/10.1186/s12872-016-0275-6>.
 102. Kishimoto I, Makino H, Ohata Y, Tamanaha T, Tochiya M, Kada A, Ishihara M, Anzai T, Shimizu W, Yasuda S, Ogawa H. Hemoglobin A1c predicts heart failure hospitalization independent of baseline cardiac function or B-type natriuretic peptide level. *Diabetes Res Clin Pract* 2014;104:257–65. <https://doi.org/10.1016/j.diabres.2014.02.009>.
 103. Zhao W, Katzarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. HbA1c and heart failure risk among diabetic patients. *J Clin Endocrinol Metab* 2014;99:E263–7. <https://doi.org/10.1210/jc.2013-3325>.
 104. Parry HM, Deshmukh H, Levin D, Van Zuydam N, Elder DH, Morris AD, Struthers AD, Palmer CN, Doney AS, Lang CC. Both high and low HbA1c predict incident heart failure in type 2 diabetes mellitus. *Circ Heart Fail* 2015;8:236–42. <https://doi.org/10.1161/CIRCHEARTFAILURE.113.000920>.
 105. Elder DH, Singh JS, Levin D, Donnelly LA, Choy AM, George J, Struthers AD, Doney AS, Lang CC. Mean HbA1c and mortality in diabetic individuals with heart failure: a population cohort study. *Eur J Heart Fail* 2016;18:94–102. <https://doi.org/10.1002/ehf.455>.
 106. Selvin E, Rawlings AM, Lutsey PL, Maruthur N, Pankow JS, Steffes M, Coresh J. Fructosamine and glycated albumin and the risk of cardiovascular outcomes and death. *Circulation* 2015;132:269–77. <https://doi.org/10.1161/CIRCULATIONAHA.115.015415>.
 107. Aguilar D, Bozkurt B, Ramasubbu K, Deswal A. Relationship of hemoglobin A1c and mortality in heart failure patients with diabetes. *J Am Coll Cardiol* 2009;54:422–8. <https://doi.org/10.1016/j.jacc.2009.04.049>.
 108. Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 2006;151:91. <https://doi.org/10.1016/j.ahj.2005.10.008>.
 109. Holman RR, Bethel MA, Hernandez AF. Once-weekly exenatide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:2502. <https://doi.org/10.1056/NEJMc1714163>.
 110. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED, for the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study Group. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2016;1:126–35. <https://doi.org/10.1001/jamacardio.2016.0103>.
 111. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment [published correction appears in *Diabetes Care*. 2017;40:985]. *Diabetes Care* 2017;40(suppl 1):S64–74.
 112. 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;4:53–8. <https://doi.org/10.1161/CIRCHEARTFAILURE.110.952556>.
 113. Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jørgensen CH, Lange T, Abildstrøm SZ, Schramm TK, Vaag A, Køber L, Torp-Pedersen C, Gislason GH. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. *Diabetologia* 2010;53:2546–53. <https://doi.org/10.1007/s00125-010-1906-6>.
 114. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care* 2005;28:2345–51.
 115. Romero SP, Andrey JL, Garcia-Egido A, Escobar MA, Perez V, Corzo R, Garcia-Domiguez GJ, Gomez F. Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus: a propensity-matched study in the community. *Int J Cardiol* 2013;166:404–12. <https://doi.org/10.1016/j.ijcard.2011.10.141>.

116. Shah DD, Fonarow GC, Horwich TB. Metformin therapy and outcomes in patients with advanced systolic heart failure and diabetes. *J Card Fail* 2010;16:200–6. <https://doi.org/10.1016/j.cardfail.2009.10.022>.
117. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, Vanderloo SE, McAlister FA. Comparative safety and effectiveness of metformin in patients with diabetes and heart failure: systematic review of observational studies involving 34000 patients. *Circ Heart Fail* 2013;6:395–402. <https://doi.org/10.1161/CIRCHEARTFAILURE.112.000162>.
118. Roumie CL, Min JY, D'Agostino McGowan L, Presley C, Grijalva CG, Hackstadt AJ, Hung AM, Greevy RA, Elasy T, Griffin MR. Comparative safety of sulfonylurea and metformin monotherapy on the risk of heart failure: a cohort study. *J Am Heart Assoc* 2017;6:e005379. <https://doi.org/10.1161/JAHA.116.005379>.
119. Khurana R, Malik IS. Metformin: safety in cardiac patients. *Heart* 2010;96:99–102. <https://doi.org/10.1136/hrt.2009.173773>.
120. The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503–15. <https://doi.org/10.1056/NEJMoa0805796>.
121. McAlister FA, Eurich DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. *Eur J Heart Fail* 2008;10:703–8. <https://doi.org/10.1016/j.ejheart.2008.05.013>.
122. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009;339:b4731. <https://doi.org/10.1136/bmj.b4731>.
123. Fadini GP, Avogaro A, Degli Esposti L, Russo P, Saragoni S, Buda S, Rosano G, Pecorelli S, Pani L. OsMed Health-DB Network. Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database. *Eur Heart J* 2015;36:2454–62. <https://doi.org/10.1093/eurheartj/ehv301>.
124. Kim YG, Yoon D, Park S, Han SJ, Kim DJ, Lee KW, Park RW, Kim HJ. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in patients with type 2 diabetes mellitus: a population-based cohort study. *Circ Heart Fail* 2017;10:e003957. <https://doi.org/10.1161/CIRCHEARTFAILURE.117.003957>.
125. Ou SM, Shih CJ, Chao PW, Chu H, Kuo SC, Lee YJ, Wang SJ, Yang CY, Lin CC, Chen TJ, Tarnag DC, Li SY, Chen YT. Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. *Ann Intern Med* 2015;163:663–72. <https://doi.org/10.7326/M15-0308>.
126. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 2005;111:583–90. <https://doi.org/10.1161/01.CIR.0000154542.13412.B1>.
127. Evans JM, Doney AS, AlZadjali MA, Ogston SA, Petrie JR, Morris AD, Struthers AD, Wong AK, Lang CC. Effect of metformin on mortality in patients with heart failure and type 2 diabetes mellitus. *Am J Cardiol* 2010;106:1006–10. <https://doi.org/10.1016/j.amjcard.2010.05.031>.
128. The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–28. <https://doi.org/10.1056/NEJMoa1203858>.
129. ORIGIN Trial Investigators. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). *Diabetes Care* 2016;39:709–16. <https://doi.org/10.2337/dc15-1676>.
130. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34.
131. Cooper LB, Mi X, Mentz RJ, Green JB, Anstrom KJ, Hernandez AF, Curtis LH. Management of newly treated diabetes in Medicare beneficiaries with and without heart failure. *Clin Cardiol* 2017;40:38–45. <https://doi.org/10.1002/clc.22603>.
132. Murcia AM, Hennekens CH, Lamas GA, Jiménez-Navarro M, Rouleau JL, Flaker GC, Goldman S, Skali H, Braunwald E, Pfeffer MA. Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. *Arch Intern Med* 2004;164:2273–9. <https://doi.org/10.1001/archinte.164.20.2273>.
133. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006;27:65–75. <https://doi.org/10.1093/eurheartj/ehi555>.
134. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; on behalf of the 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;366:1279–89. [https://doi.org/10.1016/S0140-6736\(05\)67528-9](https://doi.org/10.1016/S0140-6736(05)67528-9).
135. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; for the 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;373:2125–35. [https://doi.org/10.1016/S0140-6736\(09\)60953-3](https://doi.org/10.1016/S0140-6736(09)60953-3).
136. Komajda M, McMurray JJ, Beck-Nielsen H, Gomis R, Hanefeld M, Pocock SJ, Curtis PS, Jones NP, Home PD. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J* 2010;31:824–31. <https://doi.org/10.1093/eurheartj/ehp604>.
137. 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;11:115–28. <https://doi.org/10.2165/11587580-000000000-00000>.
138. 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;298:1180–8. <https://doi.org/10.1001/jama.298.10.1180>.
139. 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 randomized clinical trials. *Lancet* 2007;370:1129–36. [https://doi.org/10.1016/S0140-6736\(07\)61514-1](https://doi.org/10.1016/S0140-6736(07)61514-1).
140. Dargie HJ, Hildebrandt PR, Riegger GA, McMurray JJ, McMorn SO, Roberts JN, Zambanini A, Wilding JP. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart

- Association functional class I or II heart failure. *J Am Coll Cardiol* 2007;49:1696–704. <https://doi.org/10.1016/j.jacc.2006.10.077>.
141. Erdmann E, Charbonnel B, Wilcox RG, Skene AM, Massi-Benedetti M, Yates J, Tan M, Spanheimer R, Standl E, Dormandy JA. PROactive investigators. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease. *Diabetes Care* 2007;30:2773–8.
 142. Giles TD, Miller AB, Elkayam U, Bhattacharya M, Perez A. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail* 2008;14:445–52. <https://doi.org/10.1016/j.cardfail.2008.02.007>.
 143. Guan Y, Hao C, Cha DR, Rao R, Lu W, Kohan DE, Magnusson MA, Redha R, Zhang Y, Breyer MD. Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption. *Nat Med* 2005;11:861–6. <https://doi.org/10.1038/nm1278>.
 144. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, Jessup M, Kosiborod M, Pritchett AM, Ramasubbu K, Rosendorff C, Yancy C. on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing. Council on Hypertension. Council on Quality and Outcomes Research. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. *Circulation* 2016;134:e535–78. <https://doi.org/10.1161/CIR.0000000000000450>.
 145. Kaul S, Bolger AF, Herrington D, Giugliano RP, Eckel RH. Thiazolidinedione drugs and cardiovascular risks: a science advisory from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2010;121:1868–77. <https://doi.org/10.1161/CIR.0b013e3181d34114>.
 146. Nikolaidis LA, Elahi D, Hentosz T, Doverspike A, Huerbin R, Zourelas L, Stolarski C, Shen YT, Shannon RP. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. *Circulation* 2004;110:955–61. <https://doi.org/10.1161/01.CIR.0000139339.85840.DD>.
 147. Monji A, Mitsui T, Bando YK, Aoyama M, Shigeta T, Murohara T. Glucagon-like peptide-1 receptor activation reverses cardiac remodeling via normalizing cardiac steatosis and oxidative stress in type 2 diabetes. *Am J Physiol Heart Circ Physiol* 2013;305:H295–304. <https://doi.org/10.1152/ajpheart.00990.2012>.
 148. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, Shannon RP. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* 2004;109:962–5. <https://doi.org/10.1161/01.CIR.0000120505.91348.58>.
 149. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail* 2006;12:694–9. <https://doi.org/10.1016/j.cardfail.2006.08.211>.
 150. Nathanson D, Ullman B, Löfström U, Hedman A, Frick M, Sjöholm A, Nyström T. Effects of intravenous exenatide in type 2 diabetic patients with congestive heart failure: a double-blind, randomised controlled clinical trial of efficacy and safety. *Diabetologia* 2012;55:926–35. <https://doi.org/10.1007/s00125-011-2440-x>.
 151. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, McNulty SE, Anstrom KJ, Shah MR, Braunwald E, Cappola TP. for the 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;316:500–8. <https://doi.org/10.1001/jama.2016.10260>.
 152. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, Nilsson B, Möller JE, Hjort J, Rasmussen J, Boesgaard TW, Schou M, Videbaek L, Gustafsson I, Flyvbjerg A, Wiggers H, Tarnow L. 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. <https://doi.org/10.1002/ehf.657>.
 153. Lepore JJ, Olson E, Demopoulos L, Haws T, Fang Z, Barbour AM, Fossler M, Davila-Roman VG, Russell SD, Gropler RJ. Effects of the novel long-acting GLP-1 agonist, albiglutide, on cardiac function, cardiac metabolism, and exercise capacity in patients with chronic heart failure and reduced ejection fraction. *JACC Heart Fail* 2016;4:559–66. <https://doi.org/10.1016/j.jchf.2016.01.008>.
 154. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation* 2017;136:849–70. <https://doi.org/10.1161/CIRCULATIONAHA.117.028136>.
 155. Meier JJ, Rosenstock J, Hincelin-Méry A, Roy-Duval C, Delfolie A, Coester HV, Menge BA, Forst T, Kapitza C. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: a randomized, open-label trial. *Diabetes Care* 2015;38:1263–73. <https://doi.org/10.2337/dc14-1984>.
 156. Nandy D, Johnson C, Basu R, Joyner M, Brett J, Svendsen CB, Basu A. The effect of liraglutide on endothelial function in patients with type 2 diabetes. *Diab Vasc Dis Res* 2014;11:419–30. <https://doi.org/10.1177/1479164114547358>.
 157. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH₂-terminus in type II diabetic patients and in healthy subjects. *Diabetes* 1995;44:1126–31.
 158. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [published correction appears in *Diabetologia*. 2013;56:680]. *Diabetologia* 2012;55:1577–96. <https://doi.org/10.1007/s00125-012-2534-0>.
 159. 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;8:2450–8.
 160. Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, Meeran K. 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;319:1580–91. <https://doi.org/10.1001/jama.2018.3024>.

161. McMurray JJV, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, Lewsey JD, Krum H. VIVID Trial Committees and Investigators. Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial. *JACC Heart Fail* 2018;6:8–17. <https://doi.org/10.1016/j.jchf.2017.08.004>.
162. Filion KB, Azoulay L, Platt RW, Dahl M, Dormuth CR, Clemens KK, Hu N, Paterson JM, Targownik L, Turin TC, Udell JA, Ernst P. for the CNODES Investigators. A multicenter observational study of incretin-based drugs and heart failure. *N Engl J Med* 2016;374:1145–54. <https://doi.org/10.1056/NEJMoa1506115>.
163. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC, Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res* 2015;12:90–100. <https://doi.org/10.1177/1479164114559852>.
164. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. the EMPA-REG OUTCOME Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME. *Eur Heart J* 2016;37:1526–34. <https://doi.org/10.1093/eurheartj/ehv728>.
165. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B. Canagliflozin and heart failure in type 2 diabetes mellitus. *Circulation* 2018;138:458–68. <https://doi.org/10.1161/CIRCULATIONAHA.118.034222>.
166. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen M, Thuresson M. on behalf of the 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;136:249–59. <https://doi.org/10.1161/CIRCULATIONAHA.117.029190>.
167. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, Tangri N, Goh SY, Thuresson M, Chen H, Surmont F, Hammar N, Fenici P. 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;71:2628–39.
168. Husten L. CardioBrief: Specialty Rift Brewing Over Empagliflozin: Cardiologists Blame Endocrinologists' for Split FDA Panel Vote. MEDPAGE TODAY website. <http://www.medpagetoday.com/cardiology/cardiobrief/58907>. Accessed 18 April 2019.
169. Oelze M, Kröller-Schön S, Welsch P, Jansen T, Hausding M, Mikhed Y, Stamm P, Mader M, Zinius E, Agdauletova S, Gottschlich A, Steven S, Schulz E, Bottari SP, Mayoux E, Münzel T, Daiber A. The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity. *PLoS One* 2014;9:e112394. <https://doi.org/10.1371/journal.pone.0112394>.
170. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013;15:853–62. <https://doi.org/10.1111/dom.12127>.
171. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013;15:853–62. <https://doi.org/10.1111/dom.12127>.
172. 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;39:1115–22. <https://doi.org/10.2337/dc16-0542>.
173. Januzzi JL, Butler J, Jarolim P, Sattar N, Vijapurkar U, Desai M, Davies MJ. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol* 2017;70:704–12. <https://doi.org/10.1016/j.jacc.2017.06.016>.
174. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, Rhodes S, Barrett M, Fonarow GC, Greenberg B, Heidenreich PA, Knabel T, Konstam MA, Steimle A, Warner Stevenson L. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol* 2003;41:1529–38.
175. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429–35.
176. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown Jr EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669–77. <https://doi.org/10.1056/NEJM199209033271001>.
177. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
178. Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliassen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670–6. <https://doi.org/10.1056/NEJM199512213332503>.
179. Gustafsson I, Torp-Pedersen C, Køber L, Gustafsson F, Hildebrandt P. on behalf of the TRACE Study Group. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. *J Am Coll Cardiol* 1999;34:83–9.
180. Cohn JN, Tognoni G. for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–75. <https://doi.org/10.1056/NEJMoa010713>.
181. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez F, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA. for the HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial [published correction appears in *Lancet*. 2009;374:1888]. *Lancet* 2009;374:1840–8. [https://doi.org/10.1016/S0140-6736\(09\)61913-9](https://doi.org/10.1016/S0140-6736(09)61913-9).
182. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both [published correction appears in *N Engl J Med*. 2004;350:203]. *N Engl J Med* 2003;349:1893–906. <https://doi.org/10.1056/NEJMoa032292>.

183. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. for the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993–1004. <https://doi.org/10.1056/NEJMoa1409077>.
184. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M. for the PARADIGM-HF Investigators and Committees. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail* 2016;9:e002560. <https://doi.org/10.1161/CIRCHEARTFAILURE.115.002560>.
185. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
186. Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Eur J Heart Fail* 2001;3:469–79.
187. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. for the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–8. <https://doi.org/10.1056/NEJM200105313442201>.
188. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001–7.
189. Wedel H, Demets D, Deedwania P, Fagerberg B, Goldstein S, Gottlieb S, Hjalmarsen A, Kjekshus J, Waagstein F, Wikstrand J. on behalf of the MERIT-HF Study Group. Challenges of subgroup analyses in multinational clinical trials: experiences from the MERIT-HF trial. *Am Heart J* 2001;142:502–11. <https://doi.org/10.1067/mhj.2001.117600>.
190. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709–17. <https://doi.org/10.1056/NEJM199909023411001>.
191. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. for the EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11–21. <https://doi.org/10.1056/NEJMoa1009492>.
192. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, Pitt B. EMPHASIS-HF Investigators. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *J Am Coll Cardiol* 2013;62:1585–93. <https://doi.org/10.1016/j.jacc.2013.04.086>.
193. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction [published correction appears in *N Engl J Med*. 2003;348:2271]. *N Engl J Med* 2003;348:1309–21. <https://doi.org/10.1056/NEJMoa030207>.
194. O'Keefe JH, Abuissa H, Pitt B. Eplerenone improves prognosis in postmyocardial infarction diabetic patients with heart failure: results from EPHEUS. *Diabetes Obes Metab* 2008;10:492–7. <https://doi.org/10.1111/j.1463-1326.2007.00730.x>.
195. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study [published correction appears in *Lancet*. 2010;376:1988]. *Lancet* 2010;376:875–85. [https://doi.org/10.1016/S0140-6736\(10\)61198-1](https://doi.org/10.1016/S0140-6736(10)61198-1).
196. Komajda M, Tavazzi L, Francq BG, Böhm M, Borer JS, Ford I, Swedberg K. on behalf of the SHIFT Investigators. Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. *Eur J Heart Fail* 2015;17:1294–301. <https://doi.org/10.1002/ehf.347>.
197. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83. <https://doi.org/10.1056/NEJMoa013474>.
198. Wittenberg SM, Cook JR, Hall WJ, McNitt S, Zareba W, Moss AJ. Multicenter Automatic Defibrillator Implantation Trial. Comparison of efficacy of implanted cardioverter-defibrillator in patients with versus without diabetes mellitus. *Am J Cardiol* 2005;96:417–9. <https://doi.org/10.1016/j.amjcard.2005.03.090>.
199. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure [published correction appears in *N Engl J Med*. 2005;352:2146]. *N Engl J Med* 2005;352:225–37. <https://doi.org/10.1056/NEJMoa043399>.
200. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–50. <https://doi.org/10.1056/NEJMoa032423>.
201. Ghali JK, Boehmer J, Feldman AM, Saxon LA, Demarco T, Carson P, Yong P, Galle EG, Leigh J, Ecklund FL, Bristow MR. Influence of diabetes on cardiac resynchronization therapy with or without defibrillator in patients with advanced heart failure. *J Card Fail* 2007;13:769–73. <https://doi.org/10.1016/j.cardfail.2007.06.723>.
202. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. for the Cardiac Resynchronization—Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–49. <https://doi.org/10.1056/NEJMoa050496>.
203. Hoppe UC, Freemantle N, Cleland JG, Marijjanowski M, Erdmann E. Effect of cardiac resynchronization on morbidity and mortality of diabetic patients with severe heart failure. *Diabetes Care* 2007;30:722–4. <https://doi.org/10.2337/dc06-2035>.

204. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes 3rd NA, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. for the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329–38. <https://doi.org/10.1056/NEJMoa0906431>.
205. Martin DT, McNitt S, Nesto RW, Rutter MK, Moss AJ. Cardiac resynchronization therapy reduces the risk of cardiac events in patients with diabetes enrolled in the Multicenter Automatic Defibrillator Implantation Trial With cardiac resynchronization therapy (MADIT-CRT). *Circ Heart Fail* 2011;4:332–8. <https://doi.org/10.1161/CIRCHEARTFAILURE.110.959510>.
206. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. for the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363:2385–95. <https://doi.org/10.1056/NEJMoa1009540>.
207. Bell DS, Lukas MA, Holdbrook FK, Fowler MB. The effect of carvedilol on mortality risk in heart failure patients with diabetes: results of a meta-analysis. *Curr Med Res Opin* 2006;22:287–96. <https://doi.org/10.1185/030079906X80459>.
208. Wikstrand J, Wedel H, Ghali J, Deedwania P, Fagerberg B, Goldstein S, Gottlieb S, Hjalmarsen A, Kjekshus J, Waagstein F. How should subgroup analyses affect clinical practice? Insights from the Metoprolol Succinate Controlled-Release/Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Card Electrophysiol Rev* 2003;7:264–75. <https://doi.org/10.1023/B:CEPR.0000012438.04416.00>.
209. Deedwania PC, Giles TD, Klibaner M, Ghali JK, Herlitz J, Hildebrandt P, Kjekshus J, Spinar J, Vitovec J, Stanbrook H, Wikstrand J. MERIT-HF Study Group. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005;149:159–67. <https://doi.org/10.1016/j.ahj.2004.05.056>.
210. Haas SJ, Vos T, Gilbert RE, Krum H. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J* 2003;146:848–53. [https://doi.org/10.1016/S0002-8703\(03\)00403-4](https://doi.org/10.1016/S0002-8703(03)00403-4).
211. Steinberg BA, Al-Khatib SM, Edwards R, Han J, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LY, Sanders GD. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail* 2014;2:623–9. <https://doi.org/10.1016/j.jchf.2014.06.007>.
212. Shah RV, Altman RK, Park MY, Zilinski J, Leyton-Mange J, Orencole M, Picard MH, Barrett CD, Heist EK, Upadhyay G, Das R, Singh JP, Das S. Usefulness of hemoglobin A(1c) to predict outcome after cardiac resynchronization therapy in patients with diabetes mellitus and heart failure. *Am J Cardiol* 2012;110:683–8. <https://doi.org/10.1016/j.amjcard.2012.04.056>.
213. Vermees E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ventricular Dysfunction (SOLVD). *Circulation* 2003;107:1291–6.
214. Yusuf S, Ostergren JB, Gerstein HC, Pfeffer MA, Swedberg K, Granger CB, Olofsson B, Probstfield J, McMurray JV. on behalf of the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program Investigators. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure [published correction appears in *Circulation*. 2005;112:e292]. *Circulation* 2005;112:48–53. <https://doi.org/10.1161/CIRCULATIONAHA.104.528166>.
215. Seferovic JP, Claggett B, Seidemann SB, Seely EW, Packer M, Zile MR, Rouleau JL, Swedberg K, Lefkowitz M, Shi VC, Desai AS, McMurray JJV, Solomon SD. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2017;5:333–40. [https://doi.org/10.1016/S2213-8587\(17\)30087-6](https://doi.org/10.1016/S2213-8587(17)30087-6).
216. Langenickel TH, Dole WP. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discov Today Ther Strategies* 2012;9:e131–9.
217. Packer M. Augmentation of glucagon-like peptide-1 receptor signalling by neprilysin inhibition: potential implications for patients with heart failure. *Eur J Heart Fail* 2018;20:973–7. <https://doi.org/10.1002/ejhf.1185>.
218. Zhao JV, Xu L, Lin SL, Schooling CM. Spironolactone and glucose metabolism, a systematic review and meta-analysis of randomized controlled trials. *J Am Soc Hypertens* 2016;10:671–82. <https://doi.org/10.1016/j.jash.2016.05.013>.
219. Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M, Horie M. Effect of eplerenone versus spironolactone on cortisol and hemoglobin A_{1c} levels in patients with chronic heart failure. *Am Heart J* 2010;160:915–21. <https://doi.org/10.1016/j.ahj.2010.04.024>.
220. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright Jr JT, Oakes R, Lukas MA, Anderson KM, Bell DS. for the GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004;292:2227–36. <https://doi.org/10.1001/jama.292.18.2227>.
221. Ferrua S, Bobbio M, Catalano E, Grassi G, Massobrio N, Pinach S, Rossi C, Veglio M, Trevi GP. Does carvedilol impair insulin sensitivity in heart failure patients without diabetes? *J Card Fail* 2005;11:590–4. <https://doi.org/10.1016/j.cardfail.2005.06.431>.
222. Fonseca VA. Effects of beta-blockers on glucose and lipid metabolism. *Curr Med Res Opin* 2010;26:615–29. <https://doi.org/10.1185/03007990903533681>.
223. Wai B, Kearney LG, Hare DL, Ord M, Burrell LM, Srivastava PM. Beta blocker use in subjects with type 2 diabetes mellitus and systolic heart failure does not worsen glycaemic control. *Cardiovasc Diabetol* 2012;11:14. <https://doi.org/10.1186/1475-2840-11-14>.
224. Borer JS, Tardif JC. Efficacy of ivabradine, a selective I_f inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. *Am J Cardiol* 2010;105:29–35. <https://doi.org/10.1016/j.amjcard.2009.08.642>.
225. Patel PA, Liang L, Khazanie P, Hammill BG, Fonarow GC, Yancy CW, Bhatt DL, Curtis LH, Hernandez AF. Antihyperglycemic medication use among Medicare beneficiaries with heart failure, diabetes mellitus, and chronic kidney disease. *Circ Heart Fail* 2016;9:e002638. <https://doi.org/10.1161/CIRCHEARTFAILURE.115.002638>.
226. US Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding the use of the diabetes medicine metformin in certain patients with reduced

- kidney function. US Food and Drug Administration website. <https://www.fda.gov/drugs/drugsafety/ucm493244.htm>. Page last updated November 14, 2017. Accessed 8 November 2017.
227. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. for the EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–34. <https://doi.org/10.1056/NEJMoa1515920>.
 228. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 2007;13:422–30. <https://doi.org/10.1016/j.cardfail.2007.03.011>.
 229. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004;351:585–92. <https://doi.org/10.1056/NEJMra035279>.
 230. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation* 2009;120:1577–84. <https://doi.org/10.1161/CIRCULATIONAHA.109.853648>.
 231. Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, Rich MW, Pitt B, White M, Bakris GC, Fonarow GC, Ahmed A. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. *Int J Cardiol* 2013;167:151–6. <https://doi.org/10.1016/j.ijcard.2011.12.056>.
 232. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–9. <https://doi.org/10.1056/NEJMoa011161>.
 233. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. for the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–60. <https://doi.org/10.1056/NEJMoa011303>.
 234. Desai AS, Swedberg K, McMurray JJ, Granger CB, Yusuf S, Young JB, Dunlap ME, Solomon SD, Hainer JW, Olofsson B, Michelson EL, Pfeffer MA, Program Investigators CHARM. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. *J Am Coll Cardiol* 2007;50:1959–66. <https://doi.org/10.1016/j.jacc.2007.07.067>.
 235. Michel A, Martín-Pérez M, Ruigómez A, García Rodríguez LA. Risk factors for hyperkalemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. *Eur J Heart Fail* 2015;17:205–13. <https://doi.org/10.1002/ehf.226>.
 236. Sarwar CM, Papadimitriou L, Pitt B, Piña I, Zannad F, Anker SD, Gheorghiade M, Butler J. Hyperkalemia in heart failure. *J Am Coll Cardiol* 2016;68:1575–89. <https://doi.org/10.1016/j.jacc.2016.06.060>.
 237. Kristensen SL, Mogensen UM, Tarnesby G, Gimpelewicz CR, Ali MA, Shao Q, Chiang Y, Jhund PS, Abraham WT, Dickstein K, McMurray JJV, Køber L. Aliskiren alone or in combination with enalapril vs. enalapril among patients with chronic heart failure with and without diabetes: a subgroup analysis from the ATMOSPHERE trial. *Eur J Heart Fail* 2018;20:136–47. <https://doi.org/10.1002/ehf.896>.
 238. Abbas S, Ihle P, Harder S, Schubert I. Risk of hyperkalemia and combined use of spironolactone and long-term ACE inhibitor/angiotensin receptor blocker therapy in heart failure using real-life data: a population- and insurance-based cohort. *Pharmacoepidemiol Drug Saf* 2015;24:406–13. <https://doi.org/10.1002/pds.3748>.
 239. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;351:543–51. <https://doi.org/10.1056/NEJMoa040135>.
 240. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors: how much should we worry? *Arch Intern Med* 1998;158:26–32.
 241. McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM. for the ATMOSPHERE Committees Investigators. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med* 2016;374:1521–32. <https://doi.org/10.1056/NEJMoa1514859>.
 242. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Zile MR, Lefkowitz M, Shi V, Solomon SD. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF Trial. *JAMA Cardiol* 2017;2:79–85. <https://doi.org/10.1001/jamacardio.2016.4733>.
 243. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwiter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology [published correction appears in *Eur Heart J*. 2013;34:158]. *Eur Heart J* 2012;33:1787–847. <https://doi.org/10.1093/eurheartj/ehs104>.
 244. Haynes R, Judge PK, Staplin N, Herrington WG, Storey BC, Bethel A, Bowman L, Brunskill N, Cockwell P, Hill M, Kalra PA, McMurray JJV, Taal M, Wheeler DC, Landray MJ, Baigent C. Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease. *Circulation* 2018;138:1505–14. <https://doi.org/10.1161/CIRCULATIONAHA.118.034818>.
 245. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care* 2002;25:1159–71.
 246. Funnell MM, Brown TL, Childs BP, Haas LB, Hosey GM, Jensen B, Maryniuk M, Peyrot M, Piette JD, Reader D, Siminerio LM, Weinger K, Weiss MA. National standards for diabetes self-management education. *Diabetes Care* 2008;31 (suppl 1):S97–S104. <https://doi.org/10.2337/dc08-S097>.
 247. Riegel B, Moser DK, Anker SD, Appel LJ, Dunbar SB, Grady KL, Gurvitz MZ, Havranek EP, Lee CS, Lindenfeld J, Peterson PN, Pressler SJ, Schocken DD, Whellan DJ. on behalf of the American Heart Association Council on Cardiovascular Nursing. American Heart Association Council on Cardiovascular Nursing. American Heart Association Council on Clinical Cardiology. American Heart Association Council on Nutrition, Physical Activity, and Metabolism. American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research. State of the science: promoting self-care in persons with heart failure: a

- scientific statement from the American Heart Association. *Circulation* 2009;120:1141–63. <https://doi.org/10.1161/CIRCULATIONAHA.109.192628>.
248. Dickson VV, Buck H, Riegel B. A qualitative meta-analysis of heart failure self-care practices among individuals with multiple comorbid conditions. *J Card Fail* 2011;17:413–9. <https://doi.org/10.1016/j.cardfail.2010.11.011>.
 249. Dickson VV, Buck H, Riegel B. Multiple comorbid conditions challenge heart failure self-care by decreasing self-efficacy. *Nurs Res* 2013;62:2–9. <https://doi.org/10.1097/NNR.0b013e31827337b3>.
 250. Kerr EA, Heisler M, Krein SL, Kabeto M, Langa KM, Weir D, Piette JD. Beyond comorbidity counts: how do comorbidity type and severity influence diabetes patients' treatment priorities and self-management? *J Gen Intern Med* 2007;22:1635–40. <https://doi.org/10.1007/s11606-007-0313-2>.
 251. Sung NS, Crowley Jr WF, Genel M, Salber P, Sandy L, Sherwood LM, Johnson SB, Catanese V, Tilson H, Getz K, Larson EL, Scheinberg D, Reece EA, Slavkin H, Dobs A, Grebb J, Martinez RA, Korn A, Rimoin D. Central challenges facing the national clinical research enterprise. *JAMA* 2003;289:1278–87.
 252. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003;290:1624–32. <https://doi.org/10.1001/jama.290.12.1624>.
 253. Vargas RB, Mangione CM, Asch S, Keeseey J, Rosen M, Schonlau M, Keeler EB. Can a chronic care model collaborative reduce heart disease risk in patients with diabetes? *J Gen Intern Med* 2007;22:215–22. <https://doi.org/10.1007/s11606-006-0072-5>.
 254. Proia KK, Thota AB, Njie GJ, Finnie RK, Hopkins DP, Mukhtar Q, Pronk NP, Zeigler D, Kottke TE, Rask KJ, Lackland DT, Brooks JF, Braun LT, Cooksey T. Community Preventive Services Task Force. Team-based care and improved blood pressure control: a community guide systematic review. *Am J Prev Med* 2014;47:86–99. <https://doi.org/10.1016/j.amepre.2014.03.004>.
 255. Margolius D, Bodenheimer T. Transforming primary care: from past practice to the practice of the future. *Health Aff (Millwood)* 2010;29:779–84. <https://doi.org/10.1377/hlthaff.2010.0045>.
 256. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract* 1998;1:2–4.
 257. Eldredge LKB, Markham CM, Ruiter RA, Fernandez ME, Kok G, Parcel GS. *Planning Health Promotion Programs: An Intervention Mapping Approach*. 4th ed Hoboken, NJ: Jossey-Bass; 2016.
 258. Siabani S, Leeder SR, Davidson PM. Barriers and facilitators to self-care in chronic heart failure: a meta-synthesis of qualitative studies. *Springerplus* 2013;2:320. <https://doi.org/10.1186/2193-1801-2-320>.
 259. Dickson VV, McCarthy MM, Howe A, Schipper J, Katz SM. Sociocultural influences on heart failure self-care among an ethnic minority black population. *J Cardiovasc Nurs* 2013;28:111–8. <https://doi.org/10.1097/JCN.0b013e31823db328>.
 260. Dunbar SB, Butts B, Reilly CM, Gary RA, Higgins MK, Ferranti EP, Culler SD, Butler J. A pilot test of an integrated self-care intervention for persons with heart failure and concomitant diabetes. *Nurs Outlook* 2014;62:97–111. <https://doi.org/10.1016/j.outlook.2013.09.003>.
 261. Banks AZ, Mentz RJ, Stebbins A, Mikus CR, Schulte PJ, Fleg JL, Cooper LS, Leifer ES, Badenhop DT, Keteyian SJ, Piña IL, Kitzman DW, Fiuzat M, Whellan DJ, Kraus WE, O'Connor CM. Response to exercise training and outcomes in patients with heart failure and diabetes mellitus: insights from the HF-ACTION Trial. *J Card Fail* 2016;22:485–91. <https://doi.org/10.1016/j.cardfail.2015.12.007>.
 262. Dunlay SM, Witt BJ, Allison TG, Hayes SN, Weston SA, Koepsell E, Roger VL. Barriers to participation in cardiac rehabilitation. *Am Heart J* 2009;158:852–9. <https://doi.org/10.1016/j.ahj.2009.08.010>.
 263. Pocock SJ, McMurray JJ, Dobson J, Yusuf S, Granger CB, Michelson EL, Ostergren J, Pfeffer MA, Solomon SD, Anker SD, Swedberg KB. Weight loss and mortality risk in patients with chronic heart failure in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme. *Eur Heart J* 2008;29:2641–50. <https://doi.org/10.1093/eurheartj/ehn420>.
 264. Zamora E, Díez-López C, Lupón J, de Antonio M, Domingo M, Santesmases J, Troya MI, Díez-Quevedo C, Altimir S, Bayes-Genis A. Weight loss in obese patients with heart failure. *J Am Heart Assoc* 2016;5:e002468. <https://doi.org/10.1161/JAHA.115.002468>.
 265. Beck-da-Silva L, Higginson L, Fraser M, Williams K, Haddad H. Effect of Orlistat in obese patients with heart failure: a pilot study. *Congest Heart Fail* 2005;11:118–23.
 266. Mariotti R, Castrogiovanni F, Canale ML, Borelli G, Rondinini L. Weight loss and quality of life in chronic heart failure patients. *J Cardiovasc Med (Hagerstown)* 2008;9:576–80. <https://doi.org/10.2459/JCM.0b013e318282f2de13>.
 267. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2016;315:36–46. <https://doi.org/10.1001/jama.2015.17346>.
 268. Russo MJ, Chen JM, Hong KN, Stewart AS, Ascheim DD, Argenziano M, Mancini DM, Oz MC, Naka Y. the Columbia University Heart Transplant Outcomes Research Group. Survival after heart transplantation is not diminished among recipients with uncomplicated diabetes mellitus: an analysis of the United Network of Organ Sharing database. *Circulation* 2006;114:2280–7. <https://doi.org/10.1161/CIRCULATIONAHA.106.615708>.
 269. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA, Zuckermann A. on behalf of the International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases Council; International Society for Heart Lung Transplantation (ISHLT) Pediatric Transplantation Council; International Society for Heart Lung Transplantation (ISHLT) Heart Failure and Transplantation Council. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;35:1–23. <https://doi.org/10.1016/j.healun.2015.10.023>.
 270. Gill J, Shah T, Hristea I, Chavalitdhamrong D, Anastasi B, Takemoto SK, Bunnapradist S. Outcomes of simultaneous heart-kidney transplant in the US: a retrospective analysis using OPTN/UNOS data. *Am J Transplant* 2009;9:844–52. <https://doi.org/10.1111/j.1600-6143.2009.02588.x>.
 271. Ye X, Kuo HT, Sampaio MS, Jiang Y, Reddy P, Bunnapradist S. Risk factors for development of new-onset diabetes mellitus in adult heart transplant recipients. *Transplantation* 2010;89:1526–32. <https://doi.org/10.1097/TP.0b013e3181dd6bd9>.
 272. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernandez D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC. New-onset diabetes after transplantation: 2003 international consensus guidelines: proceedings of an international expert

- panel meeting: Barcelona, Spain, 19 February 2003. Transplantation 2003;75(suppl):SS3–SS24. <https://doi.org/10.1097/01.TP.0000069952.49242.3E>.
273. Asleh R, Briasoulis A, Schettle SD, Tchanchaleishvili V, Pereira NL, Edwards BS, Clavell AL, Maltais S, Joyce DL, Joyce LD, Daly RC, Kushwaha SS, Stulak JM. Impact of diabetes mellitus on outcomes in patients supported with left ventricular assist devices: a single institutional 9-year experience. *Circ Heart Fail* 2017;10:e004213. <https://doi.org/10.1161/CIRCHEARTFAILURE.117.004213>.
 274. Vest AR, Mistak SM, Hachamovitch R, Mountis MM, Moazami N, Young JB. Outcomes for patients with diabetes after continuous-flow left ventricular assist device implantation. *J Card Fail* 2016;22:789–96. <https://doi.org/10.1016/j.cardfail.2016.02.010>.
 275. Arnold SV, Jones PG, Allen LA, Cohen DJ, Fendler TJ, Holtz JE, Aggarwal S, Spertus JA. Frequency of poor outcome (death or poor quality of life) after left ventricular assist device for destination therapy: results from the INTERMACS Registry. *Circ Heart Fail* 2016;9:e002800. <https://doi.org/10.1161/CIRCHEARTFAILURE.115.002800>.
 276. Boyle AJ, Jorde UP, Sun B, Park SJ, Milano CA, Frazier OH, Sundareswaran KS, Farrar DJ, Russell SD. HeartMate II Clinical Investigators. Pre-operative risk factors of bleeding and stroke during left ventricular assist device support: an analysis of more than 900 HeartMate II outpatients. *J Am Coll Cardiol* 2014;63:880–8. <https://doi.org/10.1016/j.jacc.2013.08.1656>.
 277. Butler J, Howser R, Portner PM, Pierson 3rd RN. Diabetes and outcomes after left ventricular assist device placement. *J Card Fail* 2005;11:510–5. <https://doi.org/10.1016/j.cardfail.2005.05.003>.
 278. Kiernan MS, Sundareswaran KS, Pham DT, Kapur NK, Pereira NL, Strueber M, Farrar DJ, DeNofrio D, Rogers JG. Pre-operative determinants of quality of life and functional capacity response to left ventricular assist device therapy. *J Card Fail* 2016;22:797–805. <https://doi.org/10.1016/j.cardfail.2016.01.006>.
 279. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J. International Society for Heart and Lung Transplantation. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant* 2013;32:157–87. <https://doi.org/10.1016/j.healun.2012.09.013>.
 280. Choudhary N, Chen L, Kotyra L, Wittlin SD, Alexis JD. Improvement in glycemic control after left ventricular assist device implantation in advanced heart failure patients with diabetes mellitus. *ASAIO J* 2014;60:675–80. <https://doi.org/10.1097/MAT.0000000000000127>.
 281. Guglin M, Maguire K, Missimer T, Faber C, Caldeira C. Improvement in blood glucose control in patients with diabetes after implantation of left ventricular assist devices. *ASAIO J* 2014;60:290–3. <https://doi.org/10.1097/MAT.0000000000000064>.
 282. Yen DC, Watson MH, Burgess LD, Kuchibhatla M, Patel CB, Campbell KB, Vora AK. Positive impact of continuous-flow left ventricular assist device implantation on glycemic control in patients with type 2 diabetes mellitus and advanced chronic systolic heart failure. *Pharmacotherapy* 2016;36:1210–6. <https://doi.org/10.1002/phar.1853>.
 283. Uriel N, Naka Y, Colombo PC, Farr M, Pak SW, Cotarlan V, Albu JB, Gallagher D, Mancini D, Ginsberg HN, Jorde UP. Improved diabetic control in advanced heart failure patients treated with left ventricular assist devices. *Eur J Heart Fail* 2011;13:195–9. <https://doi.org/10.1093/eurjhf/hfq204>.