Glucagon-Like Peptide 1 Receptor Agonists. Cardiovascular effects of the glucagon-like peptide 1 receptor agonists (GLP-1RA) that may mediate HF risk include reduced RAAS activity, reduced oxidative stress, decreased BP, improved endothelial function, weight loss, and reduced triglyceride and LDL cholesterol levels. There are also some potential negative effects of the class including increased sympathetic nervous system activity and direct sinoatrial node simulation, with a resulting increase in heart rate (146).

Several cardiovascular outcomes trials have evaluated the cardiovascular safety of GLP-1RA. In patients with T2D and established ASCVD enrolled in the Harmony Outcomes trial, treatment with the GLP-1RA albiglutide was shown to reduce the risk of incident HF hospitalizations compared with placebo; however, this medication is no longer available (147). In outcomes trials of patients with T2D and high cardiovascular risk, treatment with liraglutide (148), exenatide (149), semaglutide (150,151), lixisenatide (152), and dulaglutide (153) did not significantly alter rates of HF hospitalization compared with placebo. Only small trials of GLP-1RA treatment in patients with established HF have been completed, with results not suggestive of an outcomes benefit (151,152). In addition, in a recent analysis from Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (148), no significant difference was found in risk of HF hospitalization with liraglutide versus placebo in individuals with or without HF at baseline (154). These data suggest that GLP-1RA may be used in patients with HF but not with the goal of improving HF outcomes.

Thus, despite the lack of conclusive evidence of direct HF risk reduction with GLP-1RA to date, their indirect beneficial effects on weight and BP reduction, and reduced hypoglycemia risk, and impact on atherothrombotic disease are important considerations in selecting the best therapeutic strategies for individuals with T2D with or without prevalent HF.

Metformin. Metformin remains the most widely used of oral medications for T2D (1,155). Metformin improves insulin sensitivity, is typically weight neutral or may induce weight loss, effectively prevents diabetes development, and is affordable given its low costs (156).

Although historically metformin was contraindicated in individuals with HF, a meta-analysis of nine cohort studies of nearly 34,000 individuals suggested that metformin was associated with a 20% reduced mortality risk and a smaller but significant reduction in all-cause hospitalization in individuals with HF compared with control subjects (2,157). In another large, propensity-matched observational study, initiation of metformin was associated with lower risk of HF hospitalization than sulfonylurea drugs (4,158). However, no randomized controlled trials of metformin relative to HF risk have been performed, making these results hypothesis generating at best. Metformin should be discontinued in individuals presenting with acute conditions associated with lactic acidosis, such as cardiogenic or distributive shock.

While metformin is still considered first-line therapy for many individuals and is preferred to sulfonylureas as discussed below, current treatment recommendations are to favor SGLT2i and GLP-1RA in those with HF or atherothrombotic disease (7,159).

Sulfonylureas. Sulfonylureas, including glyburide, glipizide, and glimepiride, continue to be widely used oral medications for T2D (160,161) but, given their mechanism of action, promote weight gain and fluid retention (161), with a perennial uncertainty about cardiovascular safety.

The evidence regarding use of sulfonylureas and development of HF in individuals with T2D is quite limited. However, in contrast to the safety and possible benefits of metformin, several observational studies have suggested that sulfonylurea therapy may be associated with increased risk of HF events compared with metformin or with other agents (2). Evidence from a large retrospective cohort, with data combined from the National Veterans Health Administration, Medicare, Medicaid, and the National Death Index, that included 24,685 metformin users and 24,805 sulfonylurea users with reduced kidney function (median age 70 years, estimated glomerular filtration rate 55.8 mL/min/1.73 m^2) showed significantly fewer HF hospitalizations per 1,000 person-years for metformin compared with sulfonylurea users (155). In addition, in a most recent comparative effectiveness study with analysis of data from 128,293 participants with T2D in the U.S. Department of Veterans Affairs, of whom 23,870 received an SGLT2i and 104,423 received a sulfonylurea, it was reported that SGLT2i treatment was associated with a reduced risk of all-cause mortality compared with sulfonylureas (162). These studies provide real-world data that might help further guide the choice of antihyperglycemic therapy.

Insulin. In the treatment of T2D, insulin is often initiated when there is a need to intensify glycemic management, particularly in specific settings such as more advanced stages of CKD when other agents cannot be used. Recently, several studies have investigated the relationship between insulin use and development of adverse cardiac outcomes including HF. In Outcome Reduction With Initial Glargine Intervention (ORIGIN Trial), individuals with T2D were randomized to insulin glargine versus standard of care, with no increase found in the occurrence of hospitalization for HF associated with insulin glargine use (163). In the Degludec Cardiovascular Outcomes Trial (DEVOTE) there was no difference in HF events in patients with T2D with high risk for CVD randomized to insulin glargine or insulin degludec (164).

Although insulin remains available to optimize diabetes management in general, it should be used judiciously in individuals with HF given its effects in inducing fluid retention, weight gain, and hypoglycemia, each of which can negatively affect HF outcomes and management.

Dipeptidyl Peptidase 4 Inhibitors. Dipeptidyl peptidase 4 (DPP-4) inhibitors have been evaluated in several cardiovascular outcomes trials, and their impact on HF (165,166) has been mixed. In Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), those who were randomized to saxagliptin were more likely to be hospitalized for HF within the first year of treatment relative to those on placebo (167). In EXAMINE, individuals with T2D and cardiovascular disease who were randomized to alogliptin did not have an increased risk of