In fact, for every 1% increase in the A1c above 7.5%, there is a 15% increase in the risk of HF. Moreover, the United Kingdom Prospective Diabetes Study showed that a 1% decrease in A1c results in a significantly reduced risk of microvascular and other CV complications such as HF (16%), myocardial infarction (MI) (-14%), and stroke (-12%). These data make it clear that, while lowering the blood glucose level is important, lowering CV risk is also a key treatment goal in people with T2DM.

When it comes to reducing CV events, the focus has typically been on MI and stroke, yet, in people with T2DM, HF is the most common CV complication. People with T2DM have more than twice the risk of HF than individuals without T2DM, and up to 40% of people with HF have DM. The risk of death in people with DM has been shown to be nearly 9 times higher for those with HF compared to those without HF. Risk factors for HF and DM overlap and include obesity, hypertension, sleep apnea, advanced age, dyslipidemia, anemia, coronary heart disease, and chronic kidney disease.

When it comes to reducing CV events, the focus has typically been on MI and stroke, yet, in people with T2DM, HF is the most common CV complication. People with T2DM have more than twice the risk of HF than individuals without T2DM, and up to 40% of people with HF have DM. The risk of death in people with DM has been shown to be nearly 9 times higher for those with HF compared to those without HF. Risk factors for HF and DM overlap and include obesity, hypertension, sleep apnea, advanced age, dyslipidemia, anemia, coronary heart disease, and chronic kidney disease.

HF is a common initial presentation of CV disease in T2DM, yet is undiagnosed in one-quarter of people with T2DM.

Not surprisingly, HF in people with T2DM often results in hospitalization, with increasing mortality with repeated hospitalization. Of people hospitalized for acute HF, those with DM have a worse outcome (composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation) than those without DM. In people with HF with preserved ejection fraction (HFpEF), ie, ejection fraction >40% (also called diastolic HF), people with DM have significantly worse exercise capacity than those without DM. Moreover, in people with DM vs without DM, those with HFpEF have a significantly higher risk of CV death or HF hospitalization compared with those with HF with reduced ejection fraction (HFrEF), ie, ejection fraction ≤40% (also called systolic HF) (FIGURE).
Among people with HFpEF, those with vs without DM have a more severe disease phenotype, more extensive comorbidities (obesity, hypertension, renal dysfunction, pulmonary disease, vascular disease), greater left ventricular hypertrophy, and higher circulating markers of vasoconstriction, oxidative stress, inflammation, and fibrosis.

INITIAL EVALUATION
Patients who present with dyspnea, fatigue, fluid retention, or other signs or symptoms suggesting HF should initially be evaluated by a thorough history and physical examination to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF. Initial diagnostic testing should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, blood glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone. B-type natriuretic peptide (BNP) or N-terminal proBNP is useful. In addition to a 12-lead electrocardiogram, a chest X-ray should be done to assess heart size and pulmonary congestion and to rule out other diseases that may be the cause of the patient’s symptoms. A 2-dimensional echocardiogram with Doppler is the most useful diagnostic test and should be performed to assess ventricular function, size, wall thickness, wall motion, and valve function. Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients with known coronary artery disease and no angina.

FDA 2008 GUIDANCE
In 2008, the US Food and Drug Administration (FDA) issued its guidance Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, which required pharmaceutical sponsors to demonstrate that a new antihyperglycemic therapy for T2DM is not associated with an unacceptable increase in CV risk compared to placebo as part of standard care. The guidance established requirements for assessing CV risk by conducting a randomized, double-blind, parallel, placebo-controlled, multicenter clinical trial. The trial is to assess CV risk using a composite of CV death, nonfatal MI, and nonfatal stroke, so-called major adverse CV events (MACE).

CARDIOVASCULAR OUTCOME TRIALS
The 2008 FDA guidance applies to all new antidiabetic therapies to treat T2DM and thus, includes dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), glucagon-like peptide-1 receptor agonists (GLP-1R agonists) except exenatide twice-daily, and sodium glucose cotransporter-2 inhibitors (SGLT-2 inhibitors).

Cardiovascular safety
CV outcome trials conducted in accord with the FDA guidance have been completed for 13 medications (TABLE 1). All trials involved people with established CV disease (2nd prevention), while some also included patients at high CV risk (1st prevention). These and other differences in study design and patient population preclude direct comparison of these trials. All
have provided reassurance that the specific DPP-4 inhibitors, GLP-1R agonists, and SGLT-2 inhibitors investigated cause no increased risk in CV safety compared to placebo as part of standard care.24-36

**Cardiovascular benefit**

The FDA guidance also provided standards whereby an antidiabetic medication could demonstrate superiority to placebo as part of standard care. Some of the antidiabetic medications have demonstrated superiority to placebo, thereby reducing CV risk (TABLE 1).28,29,31,33-36 These are the GLP-1R agonists albiglutide, dulaglutide, liraglutide, and semaglutide, and the SGLT-2 inhibitors canagliflozin, dapagliflozin, and empagliflozin. These results have contributed to updated recommendations in the 2019 American Diabetes Standards of Care and the 2019 American Association of Clinical Endocrinologists/American College of Endocrinology type 2 diabetes algorithm, as well as in the 2019 American College of Cardiology/American Heart Association primary prevention of CV disease guideline, to consider the use of antidiabetic medications with a CV benefit in appropriate patients earlier in the treatment algorithm.16,38 Such patients include those with established atherosclerotic CV disease, HF, or chronic kidney disease.1 Differences among these medications with respect to their effects on CV events provide an opportunity to go beyond reducing CV risk to also selecting individualized therapy based on patient medical history, such as HF.

**Hospitalization for heart failure**

Of the 13 medications that have completed a CV outcome trial, empagliflozin has been reported to significantly reduce HF hospitalization (0.94 vs 1.45 events/100 patient-years; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.50-0.85; \( P= .002 \)) (TABLE 2).28,29,31,33-36 In EMPA-REG OUTCOME, the significant reduction in HF hospitalization with empagliflozin was independent of history of prior MI and/or stroke and did not differ between women and men.39-41

Other SGLT-2 inhibitors also reduce HF hospitalization. In the DECLARE-TIMI 58 trial comparing dapagliflozin with placebo, dapagliflozin significantly reduced the composite endpoint of CV death or HF hospitalization (HR, 0.83; 95% CI, 0.73-0.95; \( P= .005 \)).\(^{35}\) This reduction was due to a lower rate of HF hospitalization in the dapagliflozin group (HR, 0.73; 95% CI, 0.61-0.88) as there was no difference between the groups in the rate of CV death (HR, 0.98; 95% CI, 0.82-

---

**TABLE 1** Cardiovascular outcome trials of antidiabetic medications for type 2 diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>CV outcome trial(s)</th>
<th>Use/prevention</th>
<th>CV safety*</th>
<th>CV benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dipeptidyl peptidase-4 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin(^{24})</td>
<td>EXAMINE</td>
<td>2°</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Linagliptin(^{25})</td>
<td>CARMELINA</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin(^{26})</td>
<td>SAVOR-TIMI 53</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin(^{27})</td>
<td>TECOS</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Glucagon-like peptide-1 receptor agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide(^{28})</td>
<td>HARMONY</td>
<td>2°</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dulaglutide(^{29})</td>
<td>REWIND</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Exenatide once-weekly(^{30})</td>
<td>EXSCEL</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Liraglutide(^{31})</td>
<td>LEADER</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lixisenatide(^{32})</td>
<td>ELIXA</td>
<td>2°</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Semaglutide(^{33})</td>
<td>SUSTAIN 6</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Sodium glucose cotransporter-2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin(^{34})</td>
<td>CANVAS, CANVAS-R, CREDENCE</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dapagliflozin(^{35})</td>
<td>DECLARE-TIMI 58</td>
<td>1° &amp; 2°</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Empagliflozin(^{36})</td>
<td>EMPA-REG OUTCOME</td>
<td>2°</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>VERTIS CV</td>
<td>2°</td>
<td></td>
<td>NC</td>
</tr>
</tbody>
</table>

**Abbreviations:** CV, cardiovascular; MI, myocardial infarction; NC, not completed.

*Non-inferior to placebo as part of standard care for the composite endpoint of CV death, non-fatal MI, and non-fatal stroke.

1*, primary prevention (ie, person who has not suffered a cardiac event) 2*, secondary prevention (ie, person who has suffered a cardiac event).
The significant reduction in the composite of CV death or HF hospitalization with dapagliflozin was consistent across several subgroups, including patients with established atherosclerotic CV disease, as well as history of HF at baseline. Additional analysis showed that dapagliflozin reduced HF hospitalization both in those with and in those without HFrEF, whereas it reduced CV death only in those with HFrEF but not in those without HFrEF. With respect to canagliflozin, combined analysis of CANVAS and CANVAS-R showed a similar benefit in the MACE endpoint for patients with HFrEF and HFpEF. Canagliflozin significantly lowered the risk of HF hospitalization (HR, 0.67; 95% CI, 0.52-0.87). The reduction in HF hospitalization with canagliflozin vs placebo was significantly greater in those with a history of HF (HR 0.51, 95% CI 0.33-0.78), but not in those with no history of HF (HR,0.79; 95% CI, 0.57-1.09). Further analysis of the CANVAS program showed that canagliflozin also significantly reduced the composite of fatal HF or HF hospitalization (HR, 0.70; 95% CI, 0.55-0.89).

Results of the LEADER and SUSTAIN-6 trials showed liraglutide and semaglutide, respectively, did not significantly reduce the rate of HF hospitalization compared with placebo (TABLE 2). The HF effects of the GLP-1R agonists albiglutide and liraglutide have been investigated in randomized, placebo-controlled trials. Albiglutide provided no detectable effect on cardiac function or myocardial glucose use, although there

<table>
<thead>
<tr>
<th>Glucagon-like peptide-1 receptor agonists</th>
<th>Rate of heart failure hospitalization/100 patient-years</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.83</td>
<td>0.89</td>
<td>0.93</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1.2</td>
<td>1.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>1.76</td>
<td>1.61</td>
<td>1.11</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence intervals; NR, not reported.

Other evidence suggesting improved cardiac function with dapagliflozin includes significant reductions in the left atrial volume index and left ventricular mass index, as well as a significant reduction in B-type natriuretic peptide in patients whose level was ≥100 pg/mL at baseline. With respect to canagliflozin, another trial showed that it delays the rise in N-terminal-proB-type natriuretic peptide and high-sensitivity troponin I in 666 older adults with T2DM over 2 years.

The HF effects of the GLP-1R agonists albiglutide and liraglutide have been investigated in randomized, placebo-controlled trials. Albiglutide provided no detectable effect on cardiac function or myocardial glucose use, although there

1.17). The significant reduction in the composite of CV death or HF hospitalization with dapagliflozin was consistent across several subgroups, including patients with established atherosclerotic CV disease, as well as history of HF at baseline. Additional analysis showed that dapagliflozin reduced HF hospitalization both in those with and in those without HFrEF, whereas it reduced CV death only in those with HFrEF but not in those without HFrEF. With respect to canagliflozin, combined analysis of CANVAS and CANVAS-R showed a similar benefit in the MACE endpoint for patients with HFrEF and HFpEF. Canagliflozin significantly lowered the risk of HF hospitalization (HR, 0.67; 95% CI, 0.52-0.87). The reduction in HF hospitalization with canagliflozin vs placebo was significantly greater in those with a history of HF (HR 0.51, 95% CI 0.33-0.78), but not in those with no history of HF (HR,0.79; 95% CI, 0.57-1.09). Further analysis of the CANVAS program showed that canagliflozin also significantly reduced the composite of fatal HF or HF hospitalization (HR, 0.70; 95% CI, 0.55-0.89).

Results of the LEADER and SUSTAIN-6 trials showed liraglutide and semaglutide, respectively, did not significantly reduce the rate of HF hospitalization compared with placebo (TABLE 2). The HF effects of the GLP-1R agonists albiglutide and liraglutide have been investigated in randomized, placebo-controlled trials. Albiglutide provided no detectable effect on cardiac function or myocardial glucose use, although there

**TABLE 2** Effect on heart failure hospitalization of antidiabetic medications for type 2 diabetes mellitus shown to reduce cardiovascular risk

<table>
<thead>
<tr>
<th>Rate of heart failure hospitalization/100 patient-years</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon-like peptide-1 receptor agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.83</td>
<td>0.89</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>1.76</td>
<td>1.61</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence intervals; NR, not reported.

1.17). The significant reduction in the composite of CV death or HF hospitalization with dapagliflozin was consistent across several subgroups, including patients with established atherosclerotic CV disease, as well as history of HF at baseline. Additional analysis showed that dapagliflozin reduced HF hospitalization both in those with and in those without HFrEF, whereas it reduced CV death only in those with HFrEF but not in those without HFrEF. With respect to canagliflozin, combined analysis of CANVAS and CANVAS-R showed a similar benefit in the MACE endpoint for patients with HFrEF and HFpEF. Canagliflozin significantly lowered the risk of HF hospitalization (HR, 0.67; 95% CI, 0.52-0.87). The reduction in HF hospitalization with canagliflozin vs placebo was significantly greater in those with a history of HF (HR 0.51, 95% CI 0.33-0.78), but not in those with no history of HF (HR,0.79; 95% CI, 0.57-1.09). Further analysis of the CANVAS program showed that canagliflozin also significantly reduced the composite of fatal HF or HF hospitalization (HR, 0.70; 95% CI, 0.55-0.89).

Results of the LEADER and SUSTAIN-6 trials showed liraglutide and semaglutide, respectively, did not significantly reduce the rate of HF hospitalization compared with placebo (TABLE 2). The HF effects of the GLP-1R agonists albiglutide and liraglutide have been investigated in randomized, placebo-controlled trials. Albiglutide provided no detectable effect on cardiac function or myocardial glucose use, although there

The HF effects of the GLP-1R agonists albiglutide and liraglutide have been investigated in randomized, placebo-controlled trials. Albiglutide provided no detectable effect on cardiac function or myocardial glucose use, although there
was a modest increase in peak oxygen consumption over 12 weeks in patients with stable HFpEF.46

Several trials involving liraglutide have been conducted, providing conflicting results. One trial involving 32 patients with T2DM and New York Heart Association class II/III HF or left ventricular ejection fraction (LVEF) ≤45% showed significant improvement in LVEF and other measures of cardiac function in patients treated with liraglutide for 52 weeks.47 In contrast, another trial involving 241 patients (30% with T2DM, 60% with ischemic heart disease) with stable chronic HF (LVEF ≤45%) on optimal HF treatment showed liraglutide had no effect on left ventricular systolic function.48 Moreover, liraglutide was associated with serious cardiac events (notably atrial fibrillation, ventricular tachycardia, and acute coronary syndrome) in 10% of patients. These events were not assessed in the CV outcome trial for liraglutide and merit further investigation. Another trial of patients (N=300) with or without DM recently hospitalized with HF showed the use of liraglutide for 6 months following discharge resulted in a similar percentage of patients who experienced death or HF rehospitalization as placebo.49 In addition, the changes from baseline in LVEF, as well as left ventricular end-diastolic and -systolic volume index were similar in the 2 groups.

IMPLICATIONS FOR PRIMARY CARE

Reducing CV risk is the key treatment objective for patients with DM. To reduce the risk of HF in patients with T2DM, several steps can be taken: (1) early recognition of HF and people at increased risk of HF; (2) optimize glycemic control; and (3) utilize and optimize medications shown to reduce HF risk, including selected medications for T2DM.

Available evidence from CV outcome trials shows that 13 of the 15 DPP-4 inhibitors, GLP-1R agonists, and SGLT-2 inhibitors currently available do not pose an increased risk of major adverse cardiovascular events. Moreover, 4 of the GLP-1R agonists (albiglutide, dulaglutide, liraglutide, semaglutide) and 3 of the SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) are superior to placebo and significantly reduce CV risk. Of these seven medications, canagliflozin, dapagliflozin, and empagliflozin significantly reduce the occurrence of HF hospitalization. Albiglutide, liraglutide, and semaglutide provide no detectable benefit on measures of HF. Beyond individualizing treatment based on factors such as hypoglycemia and body weight, impact on CV events is now an important consideration.

CASE SCENARIO (CONT’D)

Following complete evaluation, the 62-year-old male patient was diagnosed with HFpEF. In addition to starting guideline-recommended therapy for HFpEF (diuretic, angiotensin receptor blocker),50 the decision is made to discontinue the sulfonylurea (due to increasing A1c and frequent hypoglycemia) and replace with a medication shown to reduce HF hospitalization. The American Diabetes Association prefers the use of an SGLT-2 inhibitor with evidence of reducing HF, noting that empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF-related events in a CV outcome trial.1 If an SGLT-2 inhibitor is not tolerated or is contraindicated, a GLP-1R agonist with proven CV benefit is recommended.1

REFERENCES

1. American Diabetes Association. Standards of Medical Care in Diabetes—2019. Dia-
abetes Care. 2019;42(Suppl 1):S1-S103.
3. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure:
ican Association of Clinical Endocrinologists and American College of Endocrinol-
ogy on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Execu-
7. Fidey RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovas-
cular disease, renal replacement, and death in the United States Medicare popula-
8. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary vascular disease, renal replacement, and death in the United States Medicare popula-
12. Nichols GA, Hiller TA, Erbey JR, Brown JR. Congestive heart failure in type 2 diabe-
14. Timmermans I, Denollet J, Pedersen SS, Meine M, Versteeg H. Patient-report-
17. Cavender MA, Steg PG, Smith SC, Jr., et al. Impact of diabetes mellitus on hospi-
19. van den Berge JC, Constantinescu AA, Boiten HJ, van Domburg RT, Deckers JW, Alkerhuizen KM. Short- and long-term prognosis of patients with acute heart fail-
20. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the manage-
ment of heart failure: a report of the American College of Cardiology Foundation/


