Diabetes and Heart Failure

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12.1 The Bidirectional Link Between Diabetes and Heart Failure

Coronary artery disease (CAD) and heart failure (HF) are major complications of diabetes mellitus (DM) [1], and type 2 diabetes mellitus (T2DM) and HF are common comorbidities [1, 2]. Unfortunately, HF has been described as an "often neglected complication of diabetes" [3, p. 3]; however, it is essential to consider its significance, as it has been included among the most serious complications of DM [1]. Further, a bidirectional link between diabetes and HF has been identified [3].

Diabetes has been identified as a risk factor for HF, and HF is also a risk factor for diabetes [2]. Diabetes is associated with at least a doubling in the risk of cardiovascular (CV) disease [4]. Historically, CV risk in diabetes has been considered primarily related to atherosclerotic disease [4], but heart failure is now considered the most common and morbid cardiovascular complication of T2DM [4, 5]. Thus, providers should consider the potential for DM in those with HF, as well as HF for those with DM. The incidence of DM has been found to be substantially higher for those with HF than the general population, and there is a two- to fourfold increased risk of HF in individuals with DM compared with those without DM [2].

Both HF and DM have complex pathophysiology, and there is an interplay between many mechanisms of these diseases [3]. Diabetes can contribute to structural and functional changes in the myocardium that lead to the development and progression of HF [3]. Diabetes-associated HF is highly complex, with "multiple mechanisms and consequent manifestations" evident at systemic, cardiac, and cellular/molecular levels and predispose the heart to myocardial dysfunction, including impaired cardiac relaxation, compliance, and contractility [1, p. 340].

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Some processes that have been linked with diabetes-associated HF pathology include hyperglycemia; hyperinsulinemia [1–3]; insulin resistance; inflammation, oxidative stress [1–3, 5]; alterations in the renin-angiotensin-aldosterone system (RAAS); advanced glycation end products (AGEs); and autonomic, endothelial, and mitochondrial dysfunctions [1–3].

In addition to T2DM being a risk factor for the development of HF, there is also risk for adverse outcomes for those with established disease [2]. Patients with HF and DM are known to have worse clinical outcomes than patients with HF without DM, including increased risk of hospitalization, readmission, and mortality, as well as worse health-related quality of life [2]. A scientific statement by the American Heart Association/Heart Failure Society of America (AHA/HFSA) [2] highlighted, "Identifying and implementing optimal treatment strategies for patients living with DM and HF is critical to improving outcomes in this high-risk population" (p. e294). Fortunately, there have been new developments in pharmacotherapy for T2DM, with certain drugs demonstrating significant benefits for cardiovascular disease and HF.

12.2 Management of Type 2 Diabetes Mellitus

The prevalence of diabetes in the general population is significant—according to the Centers for Disease Control (CDC) 2020 statistics report, 37.3 million people have diabetes, with T2DM being the most common type and accounting for 90–95% of diagnosed cases [6]. Options for the treatment of T2DM are evolving, and there is enhanced understanding of complex pathophysiology, specific roles of drugs, and patient-specific factors [7–9].

12.2.1 Evidence-Based Recommendations

There are many valuable resources to help providers stay abreast of growing medication options for the treatment of T2DM (Table 12.1), such as the American Diabetes Association's (ADA) Standards of Medical Care in Diabetes, which offers routinely updated, evidence-based recommendations [10], and the American

Table 12.1 Examples of evidence-based resources for management of diabetes mellitus

American Diabetes Association Standards of Medical Care in Diabetes	Available online: https://diabetesjournals.org/care (also available as free mobile application)
AACE/ACE Diabetes Management Algorithm	Available online: https://pro.aace.com/disease-state-resources/diabetes
Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement from the American Heart Association and the Heart Failure Society of America	Available online: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000691

Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), which published a clinical practice guideline and updated consensus statement and algorithm for management of T2DM [11, 12]. Both the ADA and AACE/ACE highlighted the importance of clinical judgment, considering benefits and risks, and individualizing therapy [10, 11]. A writing group of experts associated with the AHA and HFSA stated, "Although there are separate, dedicated guidelines for the management of DM and HF as isolated conditions, there is insufficient guidance on caring for patients with both DM and HF" [2, p. e294]. Thus, this group collaborated to publish a scientific statement that reviewed and summarized pertinent information for clinicians, including clinical considerations regarding pharmacologic options for the management of T2DM for those with HF [2].

12.2.2 Individualized Therapy

There is not one "best" medication for T2DM that will uniformly and optimally work for all patients—each drug has risks and benefits that must be weighed in the context of individual factors and preferences. What may be best for one person may not be a good fit for another. There are a variety of pharmacologic options, with differences in mechanisms of action, anticipated efficacy/degree of hemoglobin A1c lowering, administration requirements, adverse effect profiles, safety data, and costs.

A variety of factors are considered when choosing the best medication option for an individual; several are outlined in Fig. 12.1. When individualizing therapy, several key components of medication profiles can be considered, including mechanism of action, anticipated efficacy, contraindications, cautions, adverse effect profile (such as hypoglycemia risk and weight effects), cost (which may vary or change), and additional benefits of therapy (such as CV benefits). The ADA's Standards of Medical Care also highlighted consideration of patient burden [10]. A patient and provider can partner to determine the best therapy decisions for the individual and incorporate the patient's preferences and priorities. For example, cost may be most important for one patient, while avoidance of weight gain may be priority for another. Further, the optimal therapy for a patient can change over time, so it is prudent to continually review individual factors and other information (such

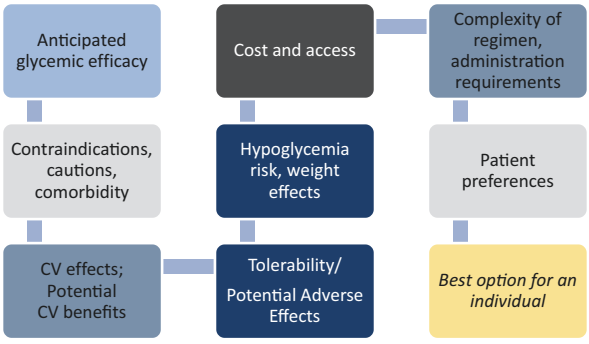

Fig. 12.1 Some key considerations when choosing a medication for type 2 diabetes

as available therapy options, current research and recommendations, cost, health parameters and comorbidities, etc.) to determine if changes are needed.

There are many potential adverse effects of various T2DM drugs; two that are commonly highlighted are hypoglycemia and weight gain. Prevention of hypoglycemia is important for all, but there are additional cautions about potential detrimental effects for older adults and those with cardiovascular disease [10]. In fact, severe hypoglycemia is recognized as a predictor of macrovascular events, adverse clinical outcomes, and mortality in patients with T2DM [13]. Other potential adverse effects of various diabetes drugs include gastrointestinal symptoms, fluid retention, vitamin B12 deficiency, fracture, diabetic ketoacidosis (DKA), genitourinary infections, and joint pain. Some potential adverse effects of various therapies are included in the sections on drug classes below, as well as in Table 12.2.

Efficacy, affordability, weight effects, hypoglycemia risk, and ease of use are among factors that are commonly considered when selecting drug therapy for T2DM. Insulin is considered the most potent antihyperglycemic agent, but there are also other non-insulin options that can have robust glucose-lowering effects [11]. Non-insulin therapies with the greatest anticipated HbA_{1c} reductions include glucagon-like peptide 1 receptor agonists (GLP-1 RA), metformin, sulfonylureas, and thiazolidinediones (TZDs) [14, 15]. If cost is the determining factor, some drugs are expected to have lower costs, such as metformin, sulfonylureas, and pioglitazone [15]. When weight loss is primary, a GLP-1 RA or sodium–glucose cotransporter 2 inhibitors (SGLT-2i) may be preferred [14]. The hypoglycemia risks associated with insulin and sulfonylureas can be significant, but several other classes have lower hypoglycemia risks (Table 12.2).

Some drugs for T2DM may also offer benefits for other conditions, such as HF, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and diabetic kidney disease (DKD) [10]. For example, SGLT2 inhibitors and GLP-1 RA have been highlighted for demonstrated benefits for those with ASCVD [10]. Certain SGLT-2 inhibitors have shown benefits for HF (such as empagliflozin, dapagliflozin, canagliflozin), and these drugs also demonstrated reduced chronic kidney disease (CKD) progression in cardiovascular outcomes trials (CVOTs) [10]. Many options are administered orally, whereas some are injected (most GLP-1 RAs and insulins), and one inhaled rapid-acting insulin is available at the time of writing.

12.2.3 Cardiovascular Safety

There has been an increased focus on cardiovascular safety of diabetes therapies in recent years. In addition, standards of trial design and evaluation have evolved [28], which presents both benefits and challenges. First, it is important to be aware of an important event that significantly impacted our understanding of cardiovascular effects of drugs for T2DM. Prior to 2008, there was a lack of robust research evaluating long-term cardiovascular outcomes with therapies for DM; however, in 2008, the FDA issued guidance for industry to perform CVOTs for all new medications for T2DM. This paved the way for “dramatic growth in clinical investigations

Table 12.2 Some considerations for select pharmacologic therapies for type 2 diabetes mellitus [2, 8, 10, 11, 14–27]

Class	Examples	Anticipated efficacy/average HbA1c reduction	Hypoglycemia risk	Potential weight effects	Anticipated cost (may vary or change)	Other select considerations
Biguanide	Metformin Metformin ER	Higher ~1.0–1.5%	Neutral	Mild loss (~2 pounds) or neutral	Lower	Endo/Renal: consider factors that could increase risk for lactic acidosis; carefully review cautions for renal insufficiency [17], such as caution if <45 mL/min/1.73 m^2, avoid eGFR <30 mL/min/1.73 m^2 GI: diarrhea, nausea, vomiting, abdominal pain Hematologic: B12 deficiency [10, 11] CV: potential ASCVD benefit [10]; VA-IMPACT study is expected to provide more information regarding its CV safety [28] HF: considered a reasonable option for T2DM in those with stable HF and appropriate renal function [2, 10], considered to have neutral effects on HF [10, 11], ADA recommended avoiding in hospitalized patients with HF [10], avoid for those with unstable or acute heart failure or shock [29]

(continued)

Table 12.2 (continued)

Class	Examples	Anticipated efficacy/average HbA1c reduction	Hypoglycemia risk	Potential weight effects	Anticipated cost (may vary or change)	Other select considerations
SGLT-2 inhibitor	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Intermediate ~0.5–1%	Neutral	Loss (~1.5–7.7 pounds)	Higher	Endo: FDA warning—DKA [18, 30]; not FDA-approved for use in T1DM [18, 26, 30] GU: genitourinary infections [22], genital mycotic infections [11], serious urinary tract infections [18] Renal: risk of volume depletion, see drug labels for renal considerations [10]; some have demonstrated benefits in CKD [10]; drugs in this class are expected to have limited efficacy in patients with an eGFR <45 mL/min/1.73 m^2 due to their mechanism of action [11] MS: risk of bone fracture (canagliflozin) [10, 24] noted in CANVAS Program but not CREDENCE trial [25] CV: risk of hypotension [10], some have demonstrated ASCVD benefits [10]; empagliflozin and canagliflozin have indications for CV event risk reduction [26] HF: some have HF indications (such as dapagliflozin and empagliflozin) [26]; some SGLT2i have shown demonstrated benefits in HF in CVOTs (such as empagliflozin, dapagliflozin, canagliflozin) [10]; an SGLT2i, such as dapagliflozin or empagliflozin, was recommended by the ACC's 2021 expert consensus decision pathway for those with HFrEF (EF ≤40%) with or without T2DM and NYHA class II–IV HF [27]; the 2022 AHA/ACC/HFSA HF guideline added SGLT2i as a component of GDMT and recommended SGLT2i for patients with symptomatic chronic HFrEF to reduce hospitalization for HF and CV mortality, irrespective of the presence of T2DM [22]

GLP-1 receptor agonist	Albiglutide Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Higher ~1–2%	Neutral	Loss (~2.2–8.8 pounds)	Higher	General: administration considerations—many are injected with a pen-delivery device Endocrine: Black box warning, avoid personal/family history of MTC or history of MEN2 [11] GI: nausea, vomiting; see cautions regarding pancreatitis and gastroparesis Renal: possible benefits in CKD are being examined, see drug labels for renal considerations [10] CV: may reduce the risk of major adverse cardiovascular events and mortality in the general population of patients with T2DM [2]; some have demonstrated ASCVD benefits, such as liraglutide, semaglutide, dulaglutide [10] HF: ADA categorized HF effects as neutral [10]; role in HF has been described as unclear [5], AHA/HFSA highlighted studies indicating potential for worse outcomes for patients with established HFrEF and recent decompensation [2]
DPP-4 inhibitor	Alogliptin Linagliptin Saxagliptin Sitagliptin	Intermediate ~0.5–1%	Neutral	Neutral	Higher	GI: see cautions regarding pancreatitis MS: FDA warning joint pain [19] CV: ADA noted ASCVD effects as neutral [10] HF: FDA warnings regarding potential increased HF risk with saxagliptin [2, 10, 20] and alogliptin [11, 21]; the 2022 AHA/ACC/HFSA HF guideline recommended avoiding saxagliptin and alogliptin in patients with HF [22]
Sulfonylurea	Glimepiride Glipizide Glyburide	Higher ~1–1.5%	Higher	Gain (~4.6–5.7 pounds)	Lower	CV/HF: considered to have neutral ASCVD and HF effects (second generation) [10]; CAROLINA trial expected to provide more evidence on cardiovascular safety, including effects on hospitalization for HF [2]

(continued)

Table 12.2 (continued)

Class	Examples	Anticipated efficacy/average HbA1c reduction	Hypoglycemia risk	Potential weight effects	Anticipated cost (may vary or change)	Other select considerations
TZD	Pioglitazone Rosiglitazone	Higher ~1–1.5%	Neutral	Gain (~5–6 pounds)	Lower (pioglitazone)	GU: FDA warning to avoid pioglitazone with active bladder cancer, and carefully consider caution and potential risks in those with a history [31] MS: fracture risk CV: potential ASCVD benefit with pioglitazone [11] HF: edema; black box warning regarding HF; avoid with symptomatic HF; contraindicated in NYHA Class III-IV HF [26]
Insulin	Multiple options—long, rapid, short, intermediate-acting; premixed	High	High	Gain (~2–6 pounds more than other agents) [11]	Variable	General: administration and training requirements Resp: pulmonary considerations for inhaled insulin [10] CV: considered neutral for ASCVD [10, 11] HF: potential for fluid retention [2], ADA categorized HF effects as neutral [10]

focusing on cardiovascular effects of drugs" for T2DM, and significant progress has been made as large numbers of patients (hundreds of thousands) have been included in CVOTs for newer T2DM agents with follow-up over multiple years [5, p. S13]. However, randomized controlled trials on older medications, such as insulin, sulfonylureas, and metformin, have been described as limited [5], and it can be challenging to compare cardiovascular profiles of older and newer drugs for T2DM [28].

T2DM medications have shown different cardiovascular effects, including benefits, risks, and neutral cardiovascular impact. The ADA Standards of Medical Care-2021 published a helpful table summarizing several current cardiovascular safety considerations for drug classes [10]. Additionally, our understanding of the safety of some DM medications for those with HF has evolved over time. For example, HF was previously a contraindication to metformin use due to concerns about the risk of lactic acidosis, but, in 2006, the FDA removed the warning, and several studies have suggested a survival benefit with metformin [2]. A meta-analysis revealed metformin was associated with reduced mortality and a small reduction in all-cause hospitalization in patients with HF when compared to those in the control group [2]. It is important to note that metformin should not be used for patients with unstable or acute heart failure or shock [29], and the ADA Standards of Care-2021 recommended avoiding in hospitalized patients with heart failure [10]. An ongoing trial that is due to conclude in mid-2024, the Investigation of Metformin in Prediabetes on Atherosclerotic Cardiovascular OuTcomes (VA-IMPACT), is expected to provide more information regarding the cardiovascular safety of metformin [28].

There have also been some questions and concerns over the years about the cardiovascular safety of sulfonylureas. The ADA Standards of Medical Care-2021 noted that sulfonylureas may increase cardiovascular mortality, but the document expounds that data to support this association are limited [10]. In addition, the ADA's T2DM treatment algorithm noted: (1) if a sulfonylurea is needed for a patient with ASCVD or indicators of high risk, a later generation sulfonylurea should be chosen to lower risk of hypoglycemia, and (2) glimepiride has shown similar CV safety to DPP4 inhibitors [10]. The AHA/HFSA 2019 scientific statement recommended considering an SGLT-2i or metformin before a sulfonylurea [2]. The CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes) is expected to offer important evidence on the cardiovascular safety of sulfonylurea drugs, including effects on hospitalization for HF [2].

There are warnings about use in HF for TZDs (pioglitazone and rosiglitazone) and some DPP4 inhibitors (saxagliptin and alogliptin) [2, 10, 11]. Though there is a potential ASCVD benefit for pioglitazone, there is increased risk in HF with TZDs [10], and drugs in this class should be avoided in symptomatic heart failure [2, 10, 29] and are contraindicated in New York Heart Association (NYHA) class III and IV heart failure [29]. The ADA Standards of Medical Care-2021 concluded that overall DPP-4 inhibitors are expected to have neutral ASCVD effects [10], but there are cautions about HF risks with some, such as saxagliptin [10] and alogliptin [11], as noted in Table 12.2 and discussed in the DPP-4 inhibitor section below. Potential

adverse effects of T2DM medications are also discussed in another chapter in this text: "Medications to Avoid when Treating Heart Failure."

Certain SGLT-2 inhibitors and GLP-1 RAs have been highlighted for their cardiovascular benefits. The ADA Standards of Medical Care-2021 highlighted that "There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in patients with type 2 diabetes treated with an SGLT-2 inhibitor (empagliflozin, canagliflozin, dapagliflozin) or GLP-1 RA (liraglutide, semaglutide, dulaglutide)" [10, p. S118]. At this time, canagliflozin, dapagliflozin, and empagliflozin have shown reduction in HF in CVOTs, with dapagliflozin and empagliflozin having primary heart failure outcome data [10]. An SGLT-2i or GLP-1 RA with demonstrated CV benefit is recommended as part of the treatment regimen for patients with T2DM and established ASCVD or indicators of high ASCVD risk—with consideration of patient-specific factors and independent of HbA_{1c} and metformin use [10]. The AHA/HFSA [2] scientific statement highlighted the finding that some drugs in the GLP-1 RA class "may reduce the risk of major adverse cardiovascular events and mortality in the general population of patients with DM" (p. e304). However, the current role of GLP-1 RAs among patients with heart failure has been described as unclear [5], and the AHA/HFSA [2] highlighted two small randomized control trials that suggested there is potential for worse outcomes for patients with established HFrEF and recent decompensation.

SGLT-2 inhibitors have been highlighted as a treatment option that should be considered for patients with T2DM and established HF with reduced ejection fraction (HFrEF), as well as those at high risk of HFrEF, due to their beneficial effects and potential to reduce hospitalizations [2, 4]. There may be more to learn regarding the potential mechanisms by which SGLT-2 inhibitors might reduce HF-associated risk, and research is ongoing [2]. Mechanisms that might explain the reduction in HF events (beyond glucose-lowering or diuresis) include reductions in oxidative stress, improvement in endothelial function, and anti-inflammatory effects [2]. The important role of SGLT2 inhibitors in HF is discussed further in a following section. Though type 1 diabetes mellitus (T1DM) is not as common as T2DM, there are many important cardiovascular considerations with T1DM; however, at this time, comorbid HF and T1DM has not been as extensively explored as in patients with T2DM, and further clinical investigation has been recommended [4].

12.2.4 T2DM and Kidney Disease

Some T2DM drugs may have beneficial effects for patients with CKD and DKD, but the degree of renal impairment is a critical factor that must be considered before initiating therapy, as some drugs may require dose adjustments or may need to be avoided at certain levels of renal function. The ADA [10] Standards of Medical Care-2021 recommended that "SGLT2 inhibitors and GLP-1 RAs should be considered for patients with type 2 diabetes and CKD who require another drug added to metformin to attain target A1C or cannot use or tolerate metformin" (p. S155). An SGLT-2i with evidence of reducing progression of disease may have benefits for

some with T2DM and CKD or DKD and albuminuria [10]. The ADA Standards of Medical Care-2021 highlighted that canagliflozin, empagliflozin, and dapagliflozin reduced CKD progression in CVOTs, with canagliflozin and dapagliflozin having primary renal outcome data [10]. Because of their mechanism of action, SGLT2 inhibitors are expected to have limited efficacy in patients with an eGFR <45 mL/min/1.73 m^2 [11]. Cautious use of a GLP-1 RA may be considered for some patients with T2DM and CKD, as drugs in this class may slow CKD progression, and in cardiovascular outcomes trials, some GLP-1 RAs revealed beneficial effects on indices of CKD (liraglutide, semaglutide, and dulaglutide) [10]. It is important to appropriately select and dose drugs for patients with kidney disease. A provider may consult a prescribing reference, nephrologist, or pharmacist when needed for more details or individualized recommendations. The ADA [10] Standards of Medical Care-2021 included a table that summarizes some important renal dosing/drug use considerations for many therapies for T2DM.

12.2.5 Special Considerations for Treatment of DM in Patients with HF

12.2.5.1 Individualized Glycemic Goals

There are some variations among recommendations for glycemic goals in DM. The ADA [10] Standards of Medical Care-2021 stated an HbA_{1c} level of less than 7.0%, pre-prandial glucose of 80–130 mg/dL, and peak post-prandial glucose less than 180 mg/dL (without significant hypoglycemia) are appropriate for many nonpregnant adults with DM, with a caveat that "more or less stringent glycemic goals may be appropriate for individual patients" (p. S79). Further, glycemic goals may need to be adjusted over time, as medical status and circumstances change for a patient. A less stringent HbA_{1c} goal may be considered when the harms of treatment are greater than the benefits [10]. Some factors that may prompt less stringent glycemic targets include increased risks with hypoglycemia, long-standing disease duration, limited life expectancy, severe comorbidity, severe vascular complications, limited resources and support system, and patient preference for less burdensome therapy [8, 10].

The AHA/HFSA [2] scientific statement suggested a target range of HbA_{1c} 7–8% for most patients with HF, while also acknowledging there is currently a lack of HF-specific data to guide HbA_{1c} goals in patients with DM and HF. The statement adds that "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 HbA_{1c} levels 8–9%" [2, p. e298]. The recommendation expounds that for patients with advanced, stage D HF who are not pursuing mechanical circulatory support or transplantation, less stringent HbA_{1c} goals may be appropriate [2]. The AHA/HFSA statement highlighted that "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 HbA_{1c} with the potential

risks. Potential harms of intensive treatment include hypoglycemia, polypharmacy, treatment burden, and high costs of care. Moreover, treatment decisions need to consider potential benefits and harms of individual glucose-lowering medications" [2, p. e298].

The AHA/HFSA [2] scientific statement noted:

- A meta-analysis of 8 randomized controlled trials (RCTs) that included over 35,000 patients found no significant difference in the risk of HF between intensive glycemic control and standard treatments [2].
- Observational studies suggest that moderate glycemic control may be optimal for patients with DM and HF, with the lowest mortality in patients with HbA_{1c} 7–8% [2].
- Some studies identified higher HF event rates when HbA_{1c} levels fell below 6% [2].

12.3 Pharmacotherapy for T2DM

12.3.1 General Considerations

There are a variety of pharmacologic options for T2DM. In general, metformin has been recommended by the ADA [10] as an initial first-line pharmacologic therapy for T2DM if not contraindicated and tolerated. It is also recommended that a diabetes regimen be as simple as possible to promote adherence [11]. Compelling indications that prompt prioritization of certain drugs for patients with high risk or established ASCVD, HF, CKD, or DKD should also be considered, as discussed above.

12.3.2 Metformin

Metformin is the most prescribed oral diabetes medication in the United States and worldwide [32]. Much has been learned about this drug in the many years since its clinical discovery in the 1950s [33]. Its primary site of action appears to be the liver, decreasing hepatic glucose production [8, 33]. To a lesser extent, it also reduces intestinal glucose absorption [14, 34] and enhances glucose uptake in the peripheral tissues [33, 34], decreasing insulin resistance. In addition to a robust amount of long-term safety data, metformin has a number of other attributes that have contributed to recommendations as a first-line treatment option, including low cost, efficacy (average HbA_{1c} reduction of 1–1.5%) [15], low hypoglycemia risk, and potential weight loss [10, 11] (neutral weight effects or modest loss [10], such as approximately 2 pounds [16]).

Gastrointestinal (GI) adverse effects may occur, but this might be attenuated with certain strategies, such as gradual dose titration, food intake, or extended-release formulations [8]. Metformin has been associated with reversible vitamin B12 deficiency (particularly with long-term use [29]), which can cause anemia and peripheral neuropathy [10, 11]. Lactic acidosis is a rare, but severe and lethal, potential adverse

effect of metformin; some risk factors include unstable heart failure, hypoxic states (such as acute heart failure, acute myocardial infarction, shock), renal or hepatic impairment, excessive alcohol intake, surgery, and having a radiological study with contrast [29]. Patients 65 years of age and older are also at higher risk [29]. If lactic acidosis is suspected, it is recommended to immediately discontinue metformin and receive further evaluation and treatment in a hospital setting [2, 29]. Metformin is expected to have good antihyperglycemic efficacy, and a commonly considered dose range for many adults with T2DM is 1000–2000 mg/day [11], but it is important to note renal function and other factors may affect use of this drug and dosing.

The U.S. Food and Drug Administration (FDA) revised metformin safety information in 2016 to provide further guidance for mild or moderate renal impairment [17]. They recommended a shift in renal monitoring procedures from serum creatinine to estimated glomerular filtration rate (eGFR) in order to better estimate kidney function [17]. Because metformin therapy often lasts for many years, it is important to keep these cautions in mind and adjust therapy as needed if a pertinent change in health status develops.

Additional renal recommendations for metformin therapy include [17, 29]:

- Monitor eGFR at baseline and at least annually, more frequently for those with increased risk of renal impairment.
- Avoid metformin in patients with an eGFR below 30 mL/min/1.73 m^2.
- Initiating metformin is not recommended if the eGFR is 30–45 mL/min/1.73 m^2.
- If the eGFR falls to 30–45 mL/min/1.73 m^2 during therapy, assess the benefits and risks of continuing treatment. A dose reduction [11] and close monitoring have been suggested if metformin use is continued in this lower eGFR range [29].
- There are cautions with iodinated contrast procedures. It is recommended to discontinue metformin before these procedures in patients with eGFR 30–60 mL/min/1.73 m^2, history of heart failure, liver disease, or alcoholism, or those receiving intra-arterial iodinated contrast. Re-evaluate eGFR 48 h after the procedure and resume therapy if renal function is stable. Some potential benefits and risks to be considered with metformin are highlighted in Fig.12.2.

12.3.3 SGLT-2 Inhibitors

SGLT-2 inhibitors are oral glucose-lowering medications that block glucose reabsorption by the kidney, increasing glucosuria [10]. This class boasts several desirable effects, including weight loss (such as ~1.5–7.7 pounds) [14], mild blood pressure reduction, and low hypoglycemia risk [10, 11]. A moderate average HbA_{1c} reduction (such as ~0.5–1%) may be anticipated [15]. Some potential beneficial effects of SGLT-2i for ASCVD, HF, DKD, and CKD are outlined above.

Select potential adverse effects include volume depletion [10], hypotension, mycotic genital and other genitourinary infections, and slight increases in low-density lipoprotein cholesterol (LDL) levels [11]. Bone fracture risk has been linked with canagliflozin (see Table 12.2) [10], but the AACE/ACE 2020 algorithm described the SGLT2i class as having a neutral bone effect [11]. An increased risk

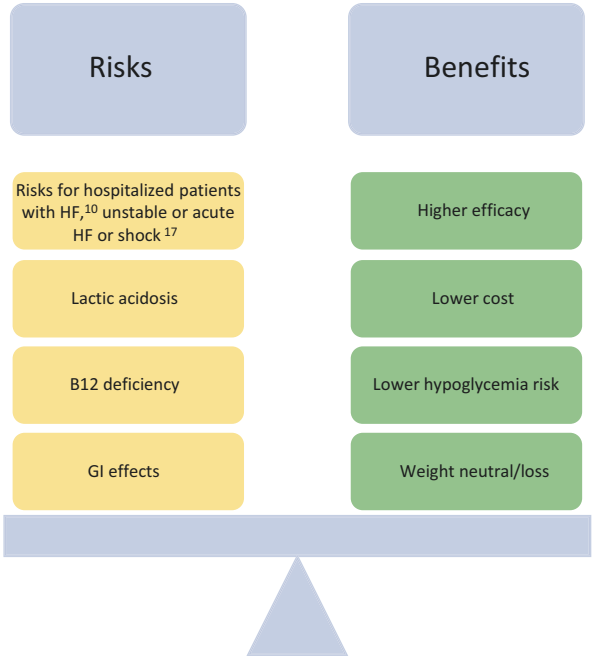

Fig. 12.2 Some potential benefits and risks for metformin [10] (individual factors and priorities can shift the weight for the final decision)

of necrotizing fasciitis of the perineum (Fournier's gangrene) has been identified as a rare but serious genital infection [10, 11].

There was a concern about a link between SGLT-2 inhibitors and acute kidney injury (AKI) due to volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration [10]. Additionally, the FDA issued a warning about the risk of acute kidney injury with canagliflozin and dapagliflozin [35]. Several predisposing factors were identified, such as heart failure; decreased blood volume; chronic kidney insufficiency; and certain medications: diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs) [35]. However, the ADA Standards of Medical Care-2021 noted that the AKI risk of SGLT-2 inhibitors has been refuted in some randomized clinical outcome trials [10]. Further, the ADA [10] addressed the concern that SGLT2 inhibitors may promote AKI through volume depletion, particularly when combined with certain medications that reduce glomerular filtration, stating, "…this has not been found to be true in randomized clinical outcome trials of advanced kidney disease or high cardiovascular disease risk with normal kidney function" (p. S153). Monitoring renal function prior to initiation of an SGLTi and periodically thereafter is recommended [35]. Providers should weigh renal cautions in the context of individual factors when an SGLT2i is prescribed for a patient with HF; close clinic follow-up can be considered to assess volume status and monitor laboratory data as indicated.

There were also post-marketing reports of diabetic ketoacidosis (DKA) in patients with types 1 and 2 DM [18], and investigations are ongoing [11]. SGLT-2 inhibitor–associated DKA was found in 5% of 2500 patients with T1DM [11, 36]

(Of note, SGLT-2 inhibitors are not FDA-approved for use in T1DM [18, 30]), and in T2DM, the incidence rate ranged from 0.16 to 0.76 events per 1000 patient-years [10, 11, 37]. The majority of cases occurred in individuals with diabetes who were insulin deficient, including those with long-standing T2DM, T1DM, or latent autoimmune diabetes in adults (LADA) [30]. Metabolic stress was identified as a unifying theme among cases, with nearly all involving surgery, injury, acute illness, exercise, or severely reduced carbohydrate intake [30].

Some safety recommendations for SGLT-2 inhibitors to reduce the risk of ketoacidosis include:

- Avoid SGLT-2i in cases of severe illness, in patients with ketonemia or ketonuria, and during prolonged fasting and surgical procedures [10].
- SGLT-2 inhibitors should be stopped temporarily before scheduled surgeries (such as 3–4 days prior, depending on the drug) [10, 18]. For those undergoing emergency surgery or any severe stress event, the drug should be stopped immediately [30].
- SGLT-2 inhibitors should also be temporarily stopped prior to planned invasive procedures [30].
- Patients taking SGLT-2 inhibitors should avoid excess alcohol intake and very low carbohydrate/ketogenic diets [30].
- If a patient taking an SGLT-2 inhibitor presents with symptoms suggestive of DKA (such as abdominal pain, nausea, vomiting, fatigue, and dyspnea), a diagnosis of DKA should be considered and appropriate evaluation and treatment promptly initiated [30]. Some potential benefits and risks to be considered with SGLT-2 inhibitors are highlighted in Fig. 12.3.

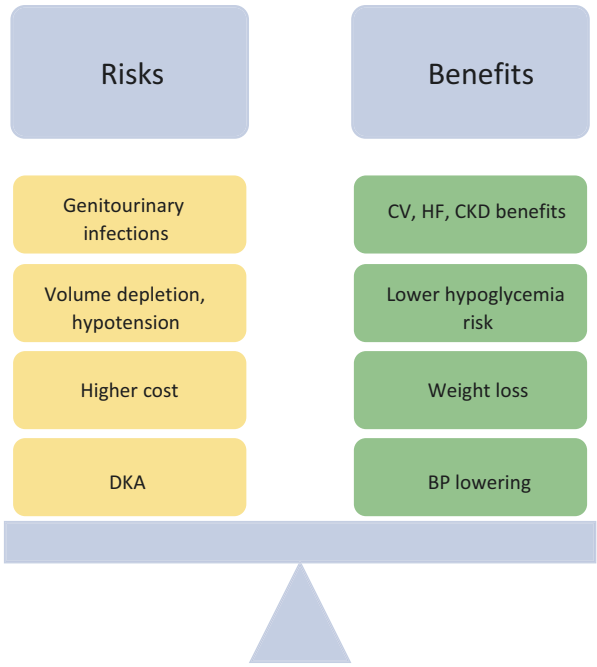

Fig. 12.3 Some potential benefits and risks for SGLT-2i [10] (individual factors and priorities can shift the weight for the final decision)

12.3.4 GLP-1 Receptor Agonists

The GLP-1 RA class continues to emerge as a valuable option for the treatment of T2DM due to its glycemic efficacy, weight loss, low hypoglycemia risk, and research highlighting cardiovascular benefits. Potential cardiovascular benefits and important considerations in ASCVD, HF, CKD, and DKD are discussed above [10]. This incretin-based therapy is expected to stimulate glucose-dependent release of insulin, decrease glucagon, delay gastric emptying, and suppress appetite [38]. Weight loss (such as about 2.2–8.8 pounds) [14] and average HbA_{1c} reduction of 1–2% may be anticipated [14, 15]. Many GLP-1 RAs are administered via subcutaneous injection, but at the time of writing, one drug in this class offers an oral option (semaglutide). GLP-1 RAs offer a variety of dosing options, such as once weekly, once daily, and twice daily.

Gastrointestinal adverse effects may occur, but these symptoms may be transient [39]. GLP-1 agonists have a black box warning to avoid use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or those with multiple endocrine neoplasia syndrome type 2 (MEN2) [11]. There are cautions for patients with a history of pancreatitis and gastroparesis [11]. Some potential benefits and risks to be considered with GLP-1 RAs are highlighted in Fig. 12.4.

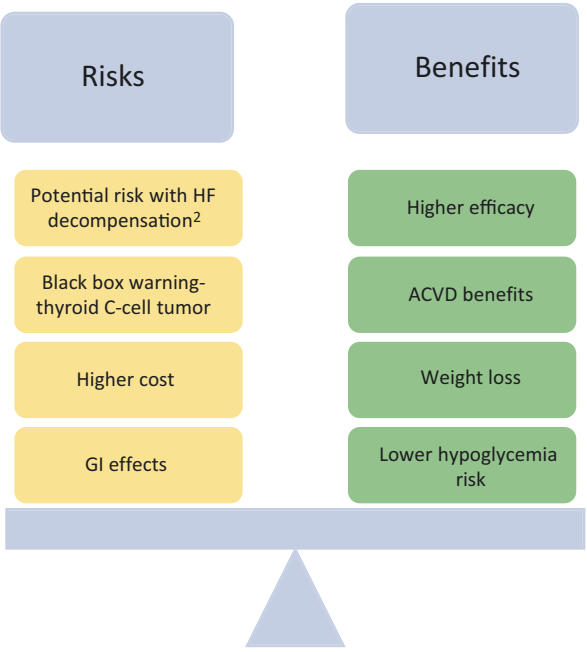

Fig. 12.4 Some potential benefits and risks for GLP-1 RA [10] (individual factors and priorities can shift the weight for the final decision)

12.3.5 DPP-4 Inhibitors

This oral incretin therapy stimulates glucose-dependent insulin secretion and suppresses glucagon [11]. DPP-4 inhibitors (DPP4i) are considered a weight neutral option that is expected to have intermediate HbA_{1c} reductions (average 0.5–1%) [15] and low hypoglycemia risk as monotherapy [10, 11]. In 2015, the FDA issued a safety alert regarding cases of severe joint pain associated with the use of DPP-4 inhibitors [19]. Providers also have been cautioned regarding use in patients with a history of pancreatitis [11].

Potential heart failure risks with some DPP-4 inhibitors have been identified [10, 11]. The increase in heart failure hospitalization with certain DPP-4 inhibitors has been described as an unexpected finding, and the reasons for discrepancies with regard to this risk unclear, but studies are ongoing [5]. There are warnings about possible increased risk of HF with saxagliptin [2, 10, 11, 20] and alogliptin [11, 21]. The FDA prescribing information for saxagliptin and alogliptin refers to findings in the SAVOR and EXAMINE trials, respectively, and contains warnings to consider the risks and benefits prior to initiating treatment in patients at risk for HF and consider discontinuation if HF develops [20, 21]. The 2022 guideline for the management of HF by the American Heart Association, American College of Cardiology, and Heart Failure Society of America (AHA/ACC/HFSA) highlighted increased risk of HF hospitalization associated with saxagliptin and alogliptin in patients with T2DM and high cardiovascular risk, and this guideline recommended these drugs be avoided in patients with HF [22]. The AHA/ACC/HFSA guideline stated it is unclear if risk of worsening HF is a class effect of DPP4i [22]. The AHA/HFSA scientific statement discussed concerning findings in some trials, and although they stated additional data is still needed, they recommended on the basis of current 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" [2, p. e305]. Some potential benefits and risks to be considered with DPP-4 inhibitors are highlighted in Fig. 12.5.

12.3.6 Sulfonylureas

Sulfonylureas are sometimes referred to as insulin secretagogues [11], as they lower glucose by stimulating insulin secretion from the pancreas [14]. Drugs in this class usually have lower costs [10], and an average HbA_{1c} reduction of ~1–1.5% may be anticipated [15]. Some primary disadvantages include hypoglycemia and weight gain [11] (an approximate 4.6–5.7 pounds increase has been noted) [16]. Additional cardiovascular considerations for sulfonylureas are discussed above. Some potential benefits and risks to be considered with sulfonylureas are highlighted in Fig. 12.6.

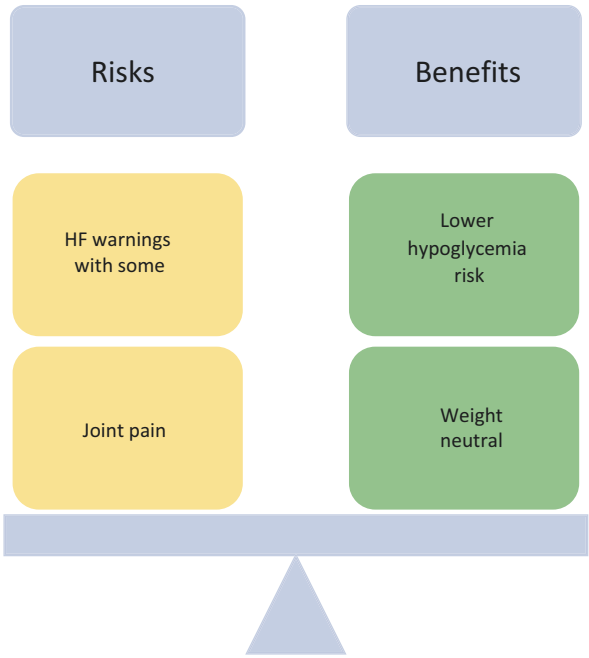

Fig. 12.5 Some potential benefits and risks for DPP-4i [10] (individual factors and priorities can shift the weight for the final decision)

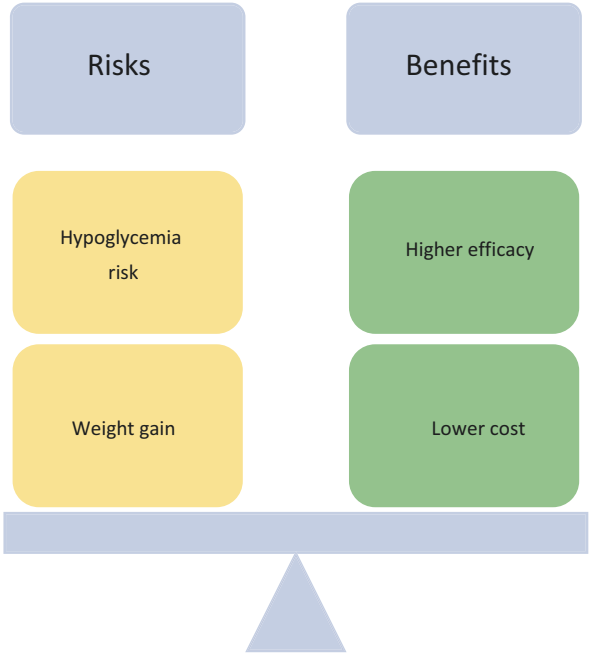

Fig. 12.6 Some potential benefits and risks for sulfonylureas [10] (individual factors and priorities can shift the weight for the final decision)

12.3.7 Thiazolidinediones

The TZDs have been found to directly reduce insulin resistance [11] and are expected to have relatively potent HbA_{1c} lowering properties (average 1–1.5% reduction) [15] and low risk of hypoglycemia [10, 11]. Pioglitazone is a lower-cost option [10] and may have some ASCVD benefits [11]. Some potential adverse effects include edema, increased bone fracture risk, and weight gain [10, 11] (an approximate 5.7 pounds increase has been noted) [16]. As discussed above, there are important HF risks with this class; the AHA/HFSA [2] scientific statement highlighted that a TZD is not recommended for patients with established HF and may increase the risk of HF in those with DM without HF. There were substantial safety cardiovascular concerns regarding rosiglitazone, but in 2013, the FDA removed rosiglitazone prescribing restrictions, and in 2015, the Risk Evaluation and Mitigation Strategy was eliminated [31, 40]. The FDA cautioned providers to carefully consider the risks and benefits before prescribing pioglitazone for individuals with a history of bladder cancer and avoid for those with active disease [23]. Some potential benefits and risks to be considered with TZDs are highlighted in Fig. 12.7.

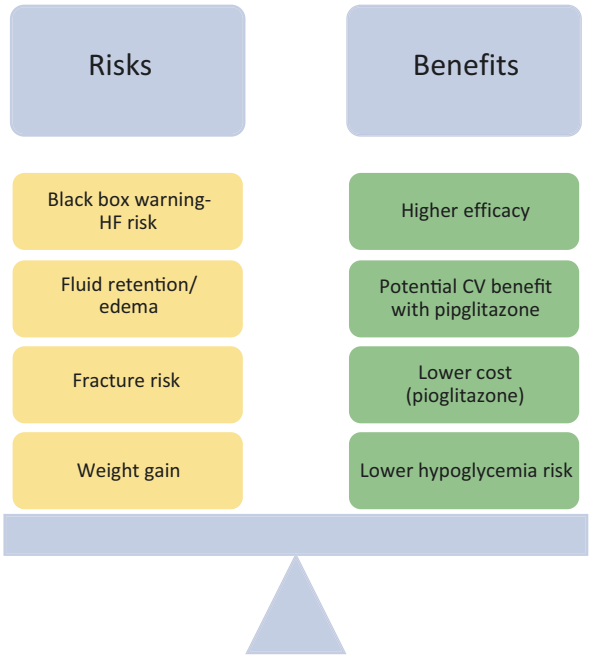

Fig. 12.7 Some potential benefits and risks for TZDs [10] (individual factors and priorities can shift the weight for the final decision)

12.3.8 Insulin

Evidence-based recommendations include insulin as an option for patients who are not achieving glycemic goals and those with severe hyperglycemia [10, 11]. Insulin is considered most potent among antihyperglycemic agents [11]. The AHA/HFSA [2] scientific statement discussed preference for other agents, such as metformin and SGLT-2i, if adequate glycemic control can be achieved without insulin. The ADA Standards of Medical Care-2021 [10] stated that a GLP-1 RA is "preferred to insulin" in T2DM when possible, and a basal insulin and GLP-1 RA can be a valuable combination (p. S113). However, there are times when insulin may be needed for certain patients with T2DM, such as for those experiencing weight loss, symptoms, and severe hyperglycemia, such as HbA_{1c} over 9–10% [5, 6] and high glucoses (>300 mg/dL) [10]. The ADA [10] Standards of Medical Care-2021 and AACE/ACE 2020 algorithm [11] both described ASCVD effects for insulin as neutral, and the ADA noted neutral HF effects. Insulin use has been associated with fluid retention [2], which is an important consideration for the patient with HF.

A variety of insulin products are available with various onsets, peaks, and duration of actions, and most are injected via a vial and syringe or insulin pen (there is one inhaled insulin option at the time of writing). There are long-acting, intermediate-acting, short-acting, and rapid-acting insulin options. Assorted types of premixed human and analog insulins (such as 70/30, 75/25, 50/50) are also available. Analog insulins are considered to offer more precise and physiologic pharmacokinetic properties (onset, peak, and duration of action) and less hypoglycemia than human insulin [11]. A basal insulin may be initially selected for some patients with T2DM. Administration of an insulin indicated for use at mealtime (such as rapid-acting insulin) for one or more meals may be considered when greater treatment intensity is indicated [11]. Insulin type and doses should be individualized and adjusted at regular intervals as needed [10].

Some potential disadvantages of insulin therapy are hypoglycemia, weight gain (described as about 2–6 pounds more than other agents) [11], and fluid retention [2]. Some patients with DM have a high degree of insulin resistance and may require high doses of insulin, and an endocrinology consult can be a very helpful resource and guide for those requiring complex insulin regimens. Some potential benefits and risks to be considered with insulin are highlighted in Fig. 12.8.

12.3.9 Combination Therapy

T2DM is progressive, and combination therapy comprised of medications with complementary actions is often necessary to address multiple pathophysiologic defects of T2DM [7] and meet glycemic goals [10, 11]. In general, the ADA [10] Standards of Medical Care-2021 recommended combining metformin with one of these six preferred treatment options: sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin; drug-specific effects and patient factors should guide drug selection. As noted in the ADA's T2DM algorithm, many diabetes medications are compatible in combination, but not all [10]. For example, combination of a

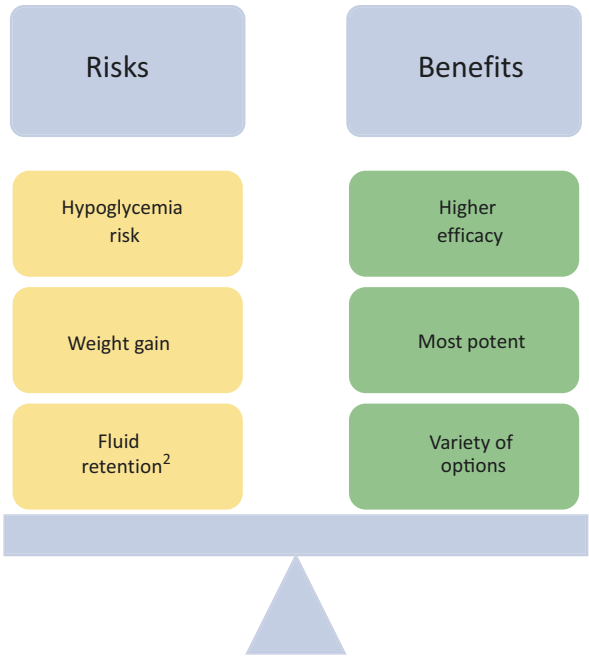

Fig. 12.8 Some potential benefits and risks for insulin [10, 11] (individual factors and priorities can shift the weight for the final decision)

DPP-4i and GLP-1 RA was not listed among recommended options in the ADA Standards of Medical Care-2021 [10]. Risk for hypoglycemia and weight gain is further increased when a sulfonylurea and insulin are combined [11]. The AACE/ACE 2020 insulin algorithm recommended providers consider discontinuing or reducing the dose of a sulfonylurea after starting basal insulin [11]. Further, even though metformin, GLP1-RA, SGLT2i, DPP4i, and TZD have lower hypoglycemia risks, if any of these are combined with insulin, the AACE/ACE recommended considering a lower dose of either drug to reduce the risk of hypoglycemia [11].

12.4 Conclusion

Individualizing pharmacotherapy and weighing risks and benefits are important steps in diabetes management. There are a variety of factors that may make one drug a better fit for a particular patient. For those with cardiovascular disease, certain drugs may have compelling indications. As discussed, GLP-1 receptor agonists and SGLT-2 inhibitors have important cardiovascular benefits for patients with T2DM [10], and SGLT-2 inhibitors should be considered for those with T2DM and HFrEF [2, 4, 10], due to their beneficial effects and potential to reduce hospitalizations [2, 4].

Though this chapter focuses on management of T2DM for those with HF, it is important to note that some SGLT-2 inhibitors, such as dapagliflozin and empagliflozin, have indications for HF, even without a diagnosis of T2DM [26, 27]. The 2022 AHA/ACC/HFSA HF guideline recommended SGLT2i for patients with symptomatic chronic HFrEF to reduce hospitalization for HF and cardiovascular

mortality, irrespective of the presence of T2DM [22]. In addition, this guideline added SGLT2i as a component of guideline-directed medical therapy (GDMT) for HFrEF [22]. The American College of Cardiology's (ACC) 2021 Expert Consensus Decision Pathway update outlined indications for an SGLT2i in HF (in conjunction with a background of GDMT), including: HfrEF (EF ≤40%) with or without T2DM and NYHA class II–IV HF [27].

The AHA/HFSA scientific statement stated, "There are many unanswered questions regarding the epidemiology, pathobiology, optimal pharmacotherapy, and co-disease management strategies for patients with DM and HF" [2, p. e313]. Further, DM and HF treatment options and recommendations are expected to change over time, as research reveals new information and new drugs are developed. Because of the dynamic nature of this content, it is important for providers to stay abreast of changes in updated, evidence-based literature and prescribing resources. There have been many exciting findings for some T2DM and HF therapies, and it will be interesting to see what new breakthroughs may be revealed in the future.

12.5 Case Study

12.5.1 Subjective

Mr. P is a 59 year-old Causcasian male with the following past medical history:
- CAD-ischemic cardiomyopathy
- HFrEF
- Hyperlipidemia
- Hypertension
- T2DM

Family history
- Mother—early onset heart disease, deceased at age 53 due to myocardial infarction
- Father—T2DM, hypertension, deceased at age 75 due to stroke
- Sibling (alive) with CAD

Social history—lives with wife, works part-time in retail, denies ETOH, tobacco, illicit drug use

Medications
- Atorvastatin 80 mg once daily
- Coreg (carvedilol) 12.5 mg twice daily
- Entresto (sacubitril/valsartan) 24/26 mg twice daily
- Furosemide 40mg once daily in the morning
- Spironolactone 25 mg daily
- Aspirin 81 mg daily
- Metformin 1,000 mg twice daily with food

Allergies: No known drug allergies

HPI
Mr. P presents to the office today for 1 week post hospital follow-up for heart failure. He has a long-standing history of T2DM and was diagnosed with HFrEF and ischemic cardiomyopathy 1 year ago. He was hospitalized last week due to acute decompensated heart failure and fluid overload. This was his first heart failure hospitalization, thought to be secondary to dietary sodium indiscretion. His hospitalization was uncomplicated. An echocardiogram was obtained and left ventricular ejection fraction was unchanged at 35%. He was diuresed and discharged home 2 days later. Discharge weight was 225 pounds. Today, he reports NYHA class II symptoms. Able to walk to mailbox without limiting dyspnea. Denies orthopnea and or PND. He is attempting to limit sodium and fluid intake, but states he often feels thirsty. He reports that his home blood sugars are usually around 180–200 mg/dL throughout the day. No chest pain, palpitations, abdominal distention or pain, nausea, diarrhea, myalgias.

12.5.2 Objective

Vital signs: BP 124/72, weight: 225, ht: 70 inches, BMI: 33

Labs:

HbA_{1c}: 8.3%

BMP: Sodium 136, Potassium 4.0, BUN 15, Creatinine 1.06, eGFR 75 mL/minute/1.73 m^2

NT-Pro BNP: 2,500 pg/mL

Physical Examination
General: no acute distress, pleasant, communicates well, obese

Neck: Supple, JVD ~5 cm

Cardiovascular: regular rate and rhythm, normal S1 and S2, no S3 or S4, no murmur

Respiratory: lungs clear to auscultation with no increased work of breathing

GI: abdomen round without tenderness, normoactive bowel sounds, no hepatosplenomegaly, negative hepatojugular reflux (HJR)

Extremities: 1+ bilateral pitting lower extremity edema, no skin breakdown, no decreased sensation with monofilament test on both feet

12.5.3 Assessment

Diagnosis
1. Acute on chronic heart failure with reduced ejection fraction
2. Uncontrolled type 2 DM
3. Hypertension
4. Hyperlipidemia

12.5.4 Plan

Pharmacologic:

- Start SGLT-2i. Take Farxiga (dapagliflozin) 10 mg once daily in the morning. (Note: the target dose for HF recommended in an ACC report was also 10 mg daily [27].) Continue current Metformin therapy for T2DM and diuretic therapy for HFrEF, Furosemide 40 mg daily, with ongoing monitoring.

Education:

- May experience increased urination, given SGLT2i mechanism of action.
- Monitor weight daily and notify provider of weight changes that are outside of recommended parameters, such as less than or greater than 5 pounds.
- Periodically monitor BG at home, which can give insight into changes in glycemic control in addition to HbA_{1c}. Both metformin and dapagliflozin have low risk for hypoglycemia [10]. One possible regimen is to test BG a few times a week at alternating times, such as fasting, before evening meal, and/or bedtime. Keep BG log; call if BG under 80 or over 200 mg/dL.
- Call if any new symptoms, such as dizziness; genitourinary infections; nausea or abdominal pain; weight change, such as rapid loss or gain of more than 5 pounds; increased swelling in legs, ankles, or feet.
- Discuss symptoms of DKA and when to seek care. It is recommended that patients avoid a low carbohydrate/ketogenic diet while taking Farxiga due to potential risks [30].

Non-pharmacologic:

- Discuss strategies to support integration of self-care and healthy behaviors for both DM and HF, such as medication adherence, dietary modification as needed, physical activity, weight and stress management [2].

Follow-up:

- Return to clinic in 2 weeks to reassess fluid status, obtain labs (BMP and NT-Pro BNP); discuss progress with new medication, Farxiga (dapagliflozin)-assess medication adherence, inquire about adverse effects, review BG logs; assess weight and review weight logs, monitor BP. Return sooner or call if needed.
- Repeat hemoglobin A_{1c} testing in 3 months. Continue routine monitoring of renal function and volume status as clinically indicated.

Referral considerations:

- A referral to cardiac rehabilitation professional may be considered for specific evaluation, recommendations, and rehabilitation sessions. An exercise specialist can also help with strategies to safely and effectively increase physical activity.
- A registered dietitian can be a valuable resource to plan and support implementation of appropriate dietary recommendations for HF and T2DM.
- Endocrinology can be a valuable resource when more complex insulin therapies are needed or a patient is not achieving glycemic goals. The AHA/HFSA [2] scientific statement stated, “Endocrinology consultation is strongly advised for patients with end-stage HF, DM, and poor glycemic control undergoing evaluation for advanced HF therapies” (p. e313).

12.6 Clinical Pearls

- The 2022 AHA/ACC/HFSA HF guideline added SGLT2i as a component of GDMT for HFrEF and recommended SGLT2i for patients with symptomatic chronic HFrEF to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of T2DM [22].
- Certain SGLT-2i have shown demonstrated benefits for patients with HFrEF and should be an initial pharmacologic consideration. Consider current research and recommendations—dapagliflozin and empagliflozin currently have HF indications [26] and were recommended by the ACC's 2021 expert consensus decision pathway for HF [27], in conjunction with a background of guideline-directed medial therapy (GDMT), for those with HFrEF (EF ≤40%) with or without T2DM and NYHA class II–IV HF [27].
- Consider safety recommendations for SGLT-2i, such as potential genitourinary infections and risk of DKA [10, 22].
- There is a risk of volume depletion and hypotension with SGLT-2 inhibitors [10]. Providers should weigh renal cautions in the context of individual factors when an SGLT2i is prescribed for a patient with HF and consider close follow-up as appropriate. Patients can also monitor BP outpatient, keep logs, and notify the provider if new symptoms (such as lightheadedness or dizziness) develop, or BP drops below recommended parameters.
- Given the drug's mechanism of action, an SGLT-2i can increase diuresis [11]. Monitor for changes in fluid status, BP, renal function, and potassium. Diuretic adjustments should be patient-specific and followed with close monitoring.
- Be mindful of thirst mechanism in hyperglycemic state with T2DM, which can lead to increased fluid intake and subsequently causing volume overload and challenging fluid balance. This has been described as a common issue seen in HF patients with diabetes that is uncontrolled.
- Metformin can be continued for many patients with T2DM and stable HF, but it is important to consider cautions, such as risk factors for lactic acidosis, and ensure renal function is appropriate for use [2]. Avoid if unstable or acute heart failure or shock [29], and it is not recommended for those with HF who are hospitalized [10].
- The AHA/HFSA scientific statement noted carvedilol could be used preferentially if a patient with HFrEF has poor glycemic control, due to more favorable effects on glycemic control than metoprolol succinate and bisoprolol [2].

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