Stage-Based Management of Type 2 Diabetes Mellitus with Heart Failure

Patricia Mejia Osuna, M.D.[a,b]; *Spandana J. Brown,* M.D.[a]; *Laila S. Tabatabai,* M.D.[a,b]; *Dale J. Hamilton,* M.D.[a,b]

[a]HOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS; [b]HOUSTON METHODIST RESEARCH INSTITUTE, HOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS

ABSTRACT: Type 2 diabetes negatively impacts heart failure outcomes. Insulin resistance, central adiposity, dyslipidemia, and altered cellular substrate metabolism each have a mechanistic role. Management strategies focused solely on glycemic control have had limited success. However, three new classes of drugs, each with several options, offer the promise of improved diabetes management in heart failure. Unlike earlier classes, these medications have had favorable cardiovascular outcomes. In this review, we present a therapeutic guide for metabolic treatment based on the stages of heart failure.

INTRODUCTION: DIABETES AND HEART FAILURE

Type 2 diabetes mellitus (T2DM) is a well-established risk factor for cardiovascular (CV) disease. It is also a growing pandemic. Although heart failure is tightly linked to T2DM, this complication is under recognized. In 1979, the Framingham Heart Study documented that men and women with prior evidence of diabetes had a 2- and 5-fold risk, respectively, of HF compared with age-matched controls.[1] In 2000, the U.K. Prospective Diabetes Study reported that patients with T2DM had HF incidence rates of 2.3 to 11.9 per 1000 patient-years over 10 years of follow-up.[2] Subsequent retrospective cohort studies such as the one conducted by Nichols et al. state an even higher incidence rate of HF in diabetic versus nondiabetic patients (30.9 vs 12.5).[3] The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) trial reported that more than 40% of individuals hospitalized with HF have T2DM.[4] Furthermore, for those without a prior diagnosis of T2DM, the presence of HF itself can cause diabetes.[5] It is clear that the two are often related, and the combination complicates the management of both.

Several mechanisms have been proposed to explain the relationship between T2DM and HF. Echocardiographic evaluations of patients with T2DM reveal an increase in left ventricular (LV) hypertrophy and systolic and diastolic dysfunction.[6] Studies have shown that these changes appear to occur even in the absence of coronary artery disease. Diastolic dysfunction is an important manifestation of diabetic cardiomyopathy, with a reported prevalence as high as 40% to 60%.[6] Indeed, systemic insulin resistance with compensatory hyperinsulinemia is a more important prognostic factor in HF incidence than hyperglycemia.[7] Insulin resistance results in a predominately fatty acid "substrate" oxidation phenotype of the diabetic heart, which leads to the accumulation of toxic lipid compounds (Figure 1).[8] Other established factors known to occur in T2DM patients—such as accelerated atherosclerosis, hypertension, and expansion of extracellular fluid volume—are also likely to contribute to HF pathogenesis in this population.

Agents that demonstrate not only CV safety but also improved CV outcomes have emerged as effective alternatives in the management of T2DM. This paper reviews antihyperglycemic agents that have been studied in HF patients, discusses their mechanisms of action and risk/benefit profiles, and provides recommendations based on HF stage.

DIABETIC THERAPIES AND HEART FAILURE: FROM TRADITIONAL DRUGS TO NEWER AGENTS

Sulfonylureas

Sulfonylureas are an older class of diabetic drugs that have been shown to increase HF risk in multiple studies. A large

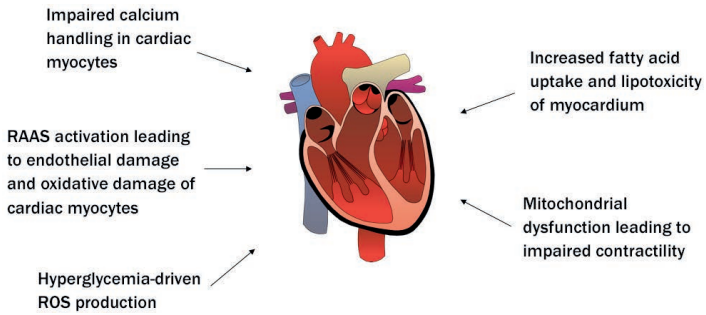

Figure 1.
Mechanisms underlying diabetic cardiomyopathy. RAAS: renin-angiotensin-aldosterone system; ROS: reactive oxygen species

retrospective study in the United Kingdom looked at 91,521 patients with T2DM and found that second-generation sulfonylurea use was associated with an 18% increase in developing HF compared to patients using metformin.[9] Two other studies analyzing databases from the Cleveland Clinic and Saskatchewan found a similar increase in HF admissions in patients using sulfonylurea versus metformin.[10] Thus, this class of medications has fallen out of favor in HF patients and in those at risk for developing this condition.

Thiazolidinediones

Thiazolidinediones (TZDs) such as rosiglitazone are antihyperglycemic agents that were initially thought to be effective in patients at risk for CV disease.[11] Unfortunately, safety and efficacy trials, which excluded NYHA class III and IV patients, showed a significant increase in hospital admissions for HF. The fluid retention seen with this class is thought to result from activation of sodium channels in the collecting ducts (mediated by peroxisome proliferator-activated receptor gamma) and sodium transporters in the proximal tubule.[11] Additionally, factors such as higher perfusion pressure leading to increased fluid extravasation and increased vascular permeability are also thought to contribute to the edema and volume overload seen with TZDs.

Metformin

A cornerstone of T2DM therapy, metformin was initially contraindicated for HF due to concerns regarding lactic acidosis. However, observational studies, including an extensive meta-analysis by Eurich et al., have shown no increases in lactic acidosis in patients treated with metformin versus other therapies; in fact, this group reported that metformin-based therapies had a 20% relative risk reduction in all-cause mortality compared to other therapies. Furthermore, in patients with reduced LV ejection fraction (LVEF) (EF < 40%), metformin-based therapies did not increase mortality, and there was a trend towards improved survival. The absolute contraindication warning was removed by the U.S. Food and Drug Administration (FDA) in 2006 and by Health Canada in 2010.[12] Metformin is now one of the first-line agents in patients with both T2DM and HF.

Insulin

The relationship between insulin and HF is complicated. Although several observational studies point to a worse prognosis in insulin-treated patients with T2DM and HF, there are no specific studies evaluating insulin treatment in HF progression.[13] It is well known that insulin promotes sodium retention, likely through potentiation of sodium transporters in the kidney. While extensive edema is rare with insulin therapy, it is thought that milder volume expansion may predispose patients to develop HF.[10] Additionally, several observational studies found that insulin-treated T2DM patients have worse morbidity and mortality compared to their non–insulin-treated counterparts.[13,14] However, reports such as the U.K. Prospective Diabetes Study did not see such a difference in HF incidence when comparing insulin to noninsulin therapies.[10] Overall, it remains unclear whether insulin therapy is more common in higher-risk HF patients or if the therapy itself is detrimental to HF patients at all stages. Insulin therapy continues to be a last resort in patients with uncontrolled T2DM, which may limit alternate therapies in this patient population.

NEWER AGENTS, MECHANISM OF ACTION, AND DIRECT EFFECTS ON THE HEART

Three new classes of antihyperglycemic drugs have received considerable attention due to their CV and HF benefits (Table 1): dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitors. DPP-4 inhibitors and GLP-1 agonists achieve glycemic control by prolonging the action of the endogenous incretin hormones and by directly stimulating GLP-1 receptors, respectively. Incretin hormones, GLP-1 and gastric inhibitory polypeptide (GIP), are both decreased in T2DM but have several beneficial glucoregulatory effects; for example, they stimulate insulin release in response to glucose levels, inhibit glucagon secretion, increase beta-cell proliferation, and decrease beta-cell apoptosis.[15] GLP-1 receptors are located not only on the pancreatic islet cells but are also widely distributed across several organs, such as the heart, kidneys, gastrointestinal tract, endothelium, and pituitary and nervous systems.[16] In experimental models, GLP-1 has been shown to modulate heart rate, blood pressure, myocardial contractility, and vasodilation and protect against ischemia-reperfusion injury.[17] Additionally, GLP-1 agonists have demonstrated favorable effects in animal models of HF, including increased myocardial glucose uptake and improved parameters of LV function.[18] Small human studies have also shown compatible results, demonstrating an increase in LVEF and functional status.[19]

DPP-4 Inhibitors

A novel class of oral antihyperglycemic agents, DPP-4 inhibitors target the incretin system and block the degradation of endogenous GLP-1 by inhibiting the DPP-4 enzyme. This, in turn, increases the concentrations of circulating GLP-1 and improves glycemic control.[20] DPP-4 inhibitors are increasingly prescribed because of their weight-neutral effects and favorable tolerability profiles.

ANTIHYPERGLYCEMIC CLASS	HBA1C LOWERING EFFECT	COMMON SIDE EFFECTS	WARNINGS/CONTRAINDICATIONS
DPP-4 inhibitors	0.5-0.8%	Headaches, upper respiratory tract infection, nasopharyngitis, joint pain, dizziness	Warnings: pancreatitis (avoid if history of chronic pancreatitis or discontinue if acute pancreatitis); heart failure (saxagliptin and alogliptin); arthalgias and bullous pemphigoid; hypersensitivity-related events; hepatotoxicity (alogliptin) Contraindications: serious hypersensitivity reactions to agent
GLP-1 agonists	1-1.5%	Nausea, vomiting, diarrhea (mostly self limited and dose related), antibody development (attenuated glycemic response), injection site reaction, headaches, sinus tachycardia, abdominal pain or distension	Warnings: pancreatitis (avoid if history of chronic pancreatitis or discontinue if acute pancreatitis); gallbladder and bile duct disease; severe gastroparesis, caution on renal impairment (risk of acute injury observed if severe GI symptoms); increased risk of complications from diabetic retinopathy (semaglutide) Contraindications: serious hypersensitivity reactions to agent, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (boxed warning)
SGLT2 inhibitors	0.7-1.0%	Genitourinary fungal infection, urinary tract infection, increased urine output, nausea, nasopharyngitis, hypotension	Warnings: euglycemic diabetic ketoacidosis, hypotension, acute kidney injury, urosepsis and pyelonephritis, increased LDL-C, genital mycotic infections, increased risk of bone fracture (canagliflozin), increased risk of lower limb amputation (canagliflozin) (boxed warning), avoid or use caution if active or history of bladder cancer, respectively (dapagliflozin) Contraindications: severe hypersensitivity reaction, severe renal dysfunction or end-stage kidney disease

Table 1.
Comparison of efficacy and safety profiles between antihyperglycemic classes DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter-2; LDL-C: low-density lipoprotein cholesterol

GLP-1 Receptor Agonists

GLP-1 agonists are a class of injectable drugs resistant to DPP-4 enzymatic degradation.[21] As with DPP-4 inhibitors, GLP-1 agonists target the incretin system and exert enhanced pancreatic and extra-pancreatic effects. For example, exocrine pancreatic changes noted in rodents include stimulation of beta cell neogenesis, replication, and acinar cell inflammation and are likely associated with the clinically significant finding of increased risk of pancreatitis found with this class.[22] In addition, the agents within this drug class have significant physiological and clinical differences with regard to efficacy and side effects (Table 2). DPP-4 inhibitors increase endogenous GLP-1 to physiological levels (10-25 pmol/L) while GLP-1 agonists reach significantly higher concentrations (60-90 pmol/L), which may account for their stronger glucose-lowering effect. These agonists delay gastric emptying and often result in nausea and decreased appetite, both of which contribute to the clinically significant weight loss distinctive of this class.[23]

SGLT2 Inhibitors

This new class of antihyperglycemic drugs has a unique mechanism of action that improves glycemic control. By inhibiting the SGLT2 cotransporters on renal tubules, these

FEATURES	DPP-4 INHIBITORS	GLP-1 AGONISTS
Biological effect	Both GLP-1 and GIP enhanced Increased to physiological endogenous levels (10-25 pmol/L)	Pure GLP-1 effect Increased to supraphysiological levels (60-90 pmol/L)
Route of administration	Oral	Subcutaneous
Efficacy	Moderate efficacy	Enhanced efficacy
Impact on HBA1c	0.5-1%	1-1.5%
Tolerance	Usually well tolerated	Common tolerance issues at initiation (nausea, gastrointestinal upset)
Cardiovascular risk	Noninferior to traditional therapies	Decreased compared to traditional therapies
Cost	Less expensive (approximately $150-$450)	More expensive (approximately $600-$850)
Effect on weight	Neutral	Promotes weight loss

Table 2.
Major differences between incretin-based therapy classes: DPP-4 inhibitors and GLP-1 agonists.[23] DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1

drugs effectively decrease the threshold for renal reabsorption of glucose and sodium, thereby increasing urinary glucose and sodium excretion.[24] SGLT is a sodium glucose cotransporter present in two major isoforms, SGLT1 and SGLT2. SGLT2 is mainly found in the lumen of the small intestine and kidneys and regulates the absorption and reabsorption of glucose. SGLT1 is primarily present in the cardiac capillaries and cardiomyocytes and has an important role in glucose uptake into the myocardium.[25]

Despite the relative absence of SGLT2 cotransporters in the heart, SGLT2 inhibitors have been shown to have a positive impact on blood pressure control, arterial stiffness, vascular resistance, and microvascular remodeling.[26] A number of mechanisms have been proposed, including beneficial effects on ion hemostasis, calcium handling, reduction of cardiac oxidative stress, and vascular inflammation.[27] SGLT2 cotransporters also modulate myocardial metabolism by shifting away from glucose and lipid oxidation and instead utilizing ketone bodies, which is more energy efficient and ultimately improves cardiac contractility.[28] This leads to beneficial changes in weight, blood pressure, diuresis, and natriuresis with a decrease in glomerular hyperfiltration. The net effects of SGLT2 inhibition likely confer CV protection.[29,30]

STAGE-BASED RECOMMENDATIONS FOR ANTIHYPERGLYCEMIC THERAPY

Based on preclinical data, biological effects, and recent beneficial CV outcomes of large randomized clinical trials (RCT),[10] we propose a stepwise approach to incorporating novel T2DM therapies in the care of patients with HF (Table 3). Information regarding glucose-lowering efficacy, safety profile, dosing, and renal adjustments for commonly used agents is also provided (Tables 1, 4). These general recommendations should be used in conjunction with evidence-based guidelines and the physician's own clinical judgment based on the patient's glycemic control.[31]

STAGE A HEART FAILURE

For patients with diabetes and stage A HF, the cornerstone of therapy is dietary modification and weight reduction. Metformin is also recommended as monotherapy or in conjunction with other agents. DPP-4 inhibitors, GLP-1 agonists, or SGLT2 inhibitors would be reasonable agents to use either as add-ons or as monotherapy, with the latter two especially beneficial in overweight individuals. Insulin therapy can be considered if glycemic control is not achieved with the above therapies. If possible, sulfonylureas and thiazolidinediones (TZDs) should

HEART FAILURE STAGE	RECOMMENDATIONS
Stage A	Lifestyle interventions and metformin Consider incretin-based therapy or SGLT2 inhibitor for overweight or obesity
Stage B	Lifestyle interventions and metformin Consider incretin-based therapy with DPP-4 inhibitors Consider SGLT2 inhibitors
Stage C	Lifestyle changes and metformin Switch from DPP-4 inhibitors to GLP-1 agonists SGLT2 inhibitors
Stage D	Lifestyle changes Insulin as mainstay of therapy SGLT2 inhibitors and GLP-1 agonists, if tolerated

Table 3.
Recommendations for antihyperglycemic therapy based on heart failure stage.

be avoided. Consensus guidelines from the American Diabetes Association and American Heart Association do mention cautious low-dose use of TZDs in patients without symptomatic heart disease but with one or more risk factors for congestive heart failure.[11] If TZDs are used at this stage, patients should be carefully monitored for worsening signs/symptoms of HF.

STAGE B HEART FAILURE

In patients with stage B HF and T2DM, we recommend initiating early therapy with newer agents, beginning with DPP-4 inhibitors. Most of these agents have demonstrated an improved safety profile, including low risk of hypoglycemia and neutral weight effect when compared with traditional diabetic therapy.

An important caution was displayed in one of the earliest large CV trials studying the safety of these agents. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, saxagliptin showed noninferiority regarding a composite of CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke, but it also showed an unexpected early increase of 27% in HF hospitalization.[32]

In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, alogliptin demonstrated noninferiority regarding CV safety in a high-risk patient population but also displayed a nonstatistically significant 19% increase in hospitalization for HF.[33] Both studies found a higher proportion of hospitalization for HF events in the top baseline quartile with B-type natriuretic peptide, suggesting a higher susceptibility of patients with underlying significant hemodynamic disturbances. Conversely, another RCT involving DPP-4 inhibitors did not show statistical difference regarding risk of HF hospitalization, which suggests that this is not a class effect.[34] Their ease of use and simple dosing regimens make DPP-4 inhibitors an attractive option in the early stages of HF management, with the cautions mentioned above. Early use of SGLT2 inhibitors should also be considered based on robust clinical data (as discussed below).

STAGE C HEART FAILURE

At this stage, we recommend intensifying therapy by switching from DPP-4 inhibitors to GLP-1 agonists and avoiding the simultaneous use of two incretin-based agents. The injectable drugs have greater potency and have not been associated with adverse HF outcomes.

GLP-1 agonists have become increasingly recognized for their weight loss effect and improvement in glycemic and metabolic profiles, especially in overweight and obese patients. Although initial outcomes comparing lixisenatide and placebo in acute coronary syndrome were no different,[35] more recent studies have demonstrated cardioprotective effects. For example, liraglutide showed a decrease in composite death from CV causes, nonfatal myocardial infarction, nonfatal stroke and a nonstatistically decreased rate of hospitalization for HF.[36] Also, a recent RCT studying CV outcomes with the newest agent on this class, semaglutide, demonstrated significant decreased rates of CV death, nonfatal myocardial infarction, or nonfatal stroke.[37] It is important to consider cost and patient preference, as these agents are injectable with variable dosing frequency (Table 4).

SGLT2 inhibitors are a promising class of antihyperglycemic agents based on their robust beneficial effect on CV risk, including HF. The landmark Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial was the first to show a statistically significant decrease in composite risk of death from CV causes, nonfatal myocardial infarction, and risk of HF hospitalization.[38] This has created a significant impact on current clinical practices as reflected in the recent clinical guidelines regarding management of T2DM.[31]

MEDICATION	BRAND NAME	DOSING	RENAL ADJUSTMENT
DPP-4 inhibitors			
Sitagliptin	Januvia	100 mg daily	eGFR (mL/min/1.73 m^2) 30-45: 50 mg daily < 30: 25 mg daily ESRD on HD or PD: 25 mg daily
Alogliptin	Nesina	25 mg daily	CrCl (mL/min) 30-60: 12.5 mg daily < 30: 6.25 mg daily ESRD on HD: 6.25 mg daily
Saxagliptin	Onglyza	5 mg daily	eGFR (mL/min/1.73 m^2) < 45: 2.5 mg daily ESRD: 2.5 mg daily (post-dialysis)
Linagliptin	Tradjenta	5 mg daily	Not necessary
GLP-1 agonists – short acting			
Lixisenatide	Lyxumia, Adlyxin	Starting dose of 10 mg every day, titrate up to 20 mg daily	eGFR (mL/min/1.73 m^2) < 30: cautious use < 15: not recommended
Exenatide	Byetta	5-10 mg BID	CrCl (mL/min) < 30 or ESRD: not recommended
GLP-1 agonists – long acting			
Albiglutide	Tanzeum	30-50 mg every week	Not necessary
Dulaglutide	Trulicity	0.75-1.5 mg every week	Not necessary
Liraglutide	Victoza	Initial dose of 0.6 mg for 1 week, titrate up to 1.2 mg daily Increase to 1.8 mg daily if inadequate glycemic control	Not necessary
Exenatide	Bydureon	2 mg every week	CrCl (mL/min) 30-50: caution < 30: not recommended
Semaglutide	Ozempic	Initial dose of 0.25 mg once a week for 4 weeks, increase to 0.5 mg every week. Increase to 1 mg every week if inadequate glycemic response.	Not necessary
SGLT2 inhibitors			
Empagliflozin	Jardiance	10-25 mg daily	eGFR (mL/min/1.73 m^2) 30-45: not recommended < 30: contraindicated
Canagliflozin	Invokana	100-300 mg daily	eGFR (mL/min/1.73 m^2) 45-60: max 100 mg daily 30-45: not recommended < 30: contraindicated
Dapagliflozin	Farxiga	5-10 mg daily	eGFR (mL/min/1.73 m^2) 30-60: not recommended < 30: contraindicated

Table 4.
Newer agents, brand name, dosing, and recommended renal adjustments. eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; CrCl: creatinine clearance; HD: hemodialysis; PD: peritoneal dialysis.

STAGE D HEART FAILURE

Management of diabetes in advanced HF raises significant challenges. Common antihyperglycemic agents are restricted at this stage due to significant accompanying comorbidities, including renal dysfunction, systemic hypoperfusion, lactic acidosis risk, and other hemodynamic abnormalities. This frequently leaves insulin as the primary therapy,[39] despite concerns regarding its impact on HF, as explained above. The judicious use of insulin is advised, and less-strict glycemic goals should be considered, especially in elderly patients.[40] Use of SGLT2 inhibitors and GLP-1 agonists could be considered as combined or monotherapy if tolerated, but more studies evaluating their safety in this population are ongoing.

CONCLUSION

Heart failure is an important and under-recognized complication of T2DM. Multiple studies have shown that patients with T2DM and congestive heart failure have poor outcomes, and basic science studies have revealed pathophysiologic mechanisms that may underlie this relationship. Therefore, it is important to understand and use appropriate T2DM therapies in this population. If appropriate, agents such as metformin, GLP-1 agonists, and SGLT2 inhibitors should be considered in HF patients. Conversely, agents such as TZDs and sulfonylureas should be avoided, if possible. Close monitoring and judicious use of diabetic therapies should be constantly reviewed in HF patients at various stages of their disease. Ultimately, further studies are needed to better guide hyperglycemia management in this population.

KEY POINTS

- Type 2 diabetes (T2DM) and heart failure (HF) pathophysiology have a strong relationship, resulting in an increased incidence of HF in patients with T2DM and a significant negative impact on HF outcomes.
- Several traditional antihyperglycemic agents demonstrated detrimental effects regarding HF outcomes, thus restricting their use and complicating the management of patients with HF and T2DM.
- Current management options for glycemic control have expanded and include agents that show promise of improved diabetes and cardiovascular outcomes in HF; however, they are often underused due to lack of familiarity by physicians outside of the endocrinology field.
- We present a stage-based approach to management of type 2 diabetes with HF and suggest early incorporation of newer agents, including DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.

Conflict of Interest Disclosure:
Dr. Hamilton is a principal investigator in a clinical research trial for Ultragenyx Pharmaceutical, Inc.; Dr. Tabatabai is on the speakers' bureau for Radius Health and Eli Lilly.

Keywords:
heart failure, type 2 diabetes, therapeutic options, DPP-4 inhibitors, GLP-1 agonists, SGLT2 inhibitors

REFERENCES

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979 May 11;241(19):2035-8.
2. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405-12.
3. 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 Aug;27(8):1879-84.
4. Greenberg BH, Abraham WT, Albert NM, et al. 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). Am Heart J. 2007 Aug;154(2):277.e1-8.
5. Tenenbaum A, Motro M, Fisman EZ, et al. Functional class in patients with heart failure is associated with the development of diabetes. Am J Med. 2003 Mar;114(4):271-5.
6. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007 Jun 26;115(25):3213-23.
7. Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. Circulation. 2007 Jul 24;116(4):434-48.
8. Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord. 2010 Mar;11(1):31-9.
9. Tzoulaki I, Molokhia M, Curcin V, et al. 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 Dec 3;339:b4731.
10. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. Lancet. 2015 May 23;385(9982):2107-17.
11. Nesto RW, Bell D, Bonow RO, et al.; American Heart Association; American Diabetes Association. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association

and American Diabetes Association. October 7, 2003. Circulation. 2003 Dec 9;108(23):2941-8.

12. 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 Oct;28(10):2345-51.

13. Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. Am Heart J. 2005 Jan;149(1):168-74.

14. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006 Jan;27(1):65-75. Epub 2005 Oct 11.

15. Koliaki C, Doupis J. Incretin-based therapy: a powerful and promising weapon in the treatment of type 2 diabetes mellitus. Diabetes Ther. 2011 May;2(2):101-21.

16. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007 May;132(6):2131-57.

17. Grieve DJ, Cassidy RS, Green BD. Emerging cardiovascular actions of the incretin hormone glucagon-like peptide-1: potential therapeutic benefits beyond glycaemic control? Br J Pharmacol. 2009 Aug;157(8):1340-51.

18. Nikolaidis LA, Elahi D, Hentosz T, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. Circulation. 2004 Aug 24;110(8):955-61.

19. Veitenhansl M, Stegner K, Hierl FX, et al. 40th EASD Annual Meeting of the European Association for the Study of Diabetes: Munich, Germany, 5-9 September 2004. Diabetologia. 2004 Aug;47(Suppl 1):A1-A464.

20. Standl E, Schnell O, McGuire DK. Heart Failure Considerations of Antihyperglycemic Medications for Type 2 Diabetes. Circ Res. 2016 May 27;118(11):1830-43.

21. White WB, Baker WL. Cardiovascular Effects of Incretin-Based Therapies. Annu Rev Med. 2016;67:245-60.

22. Pabreja K, Mohd MA, Koole C, Wootten D, Furness SG. Molecular mechanisms underlying physiological and receptor pleiotropic effects mediated by GLP-1R activation. Br J Pharmacol. 2014 Mar;171(5):1114-28.

23. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Diabetes Obes Metab. 2016 Mar;18(3):203-16.

24. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016 Sep 6;134(10):752-72.

25. Vrhovac I, Balen Eror D, Klessen D, et al. Localizations of Na(+)-D-glucose cotransporters SGLT1 and SGLT2 in human kidney and of SGLT1 in human small intestine, liver, lung, and heart. Pflugers Arch. 2015 Sep;467(9):1881-98.

26. Chilton R, Tikkanen I, Cannon CP, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab. 2015 Dec;17(12):1180-93.

27. Kaplan A, Abidi E, El-Yazbi A, Eid A, Booz GW, Zouein FA. Direct cardiovascular impact of SGLT2 inhibitors: mechanisms and effects. Heart Fail Rev. 2018 May;23(3):419-37.

28. 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 Jul;39(7):1115-22.

29. Secrest MH, Udell JA, Filion KB. The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. Trends Cardiovasc Med. 2017 Apr;27(3):194-202.

30. Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 Inhibitors in Heart Failure: Diabetes and Beyond. Curr Treat Options Cardiovasc Med. 2017 Mar;19(3):23.

31. Garber AJ, Abrahamson MJ, Barzilay JI, et al. 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 Jan;24(1):91-120.

32. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.

33. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35.

34. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42.

35. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015 Dec 3;373(23):2247-57.

36. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22.

37. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-44.

38. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.

39. Friedrich EB, Böhm M. Management of end stage heart failure. Heart. 2007 May;93(5):626-31.

40. Huang ES. Management of diabetes mellitus in older people with comorbidities. BMJ. 2016 Jun 15;353:i2200.