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Heart Failure in Type 2 Diabetes Mellitus: Impact of Glucose Lowering Agents, Heart Failure Therapies and Novel Therapeutic Strategies

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Abstract

Patients with diabetes have greater than two-times the risk for developing heart failure (HFrEF and HFpEF). Cardiovascular outcomes, hospitalization and prognosis are worse for patients with diabetes relative to those without. Beyond the structural and functional changes that characterize diabetic cardiomyopathy, a complex underlying, and interrelated pathophysiology exists. Despite the success of many commonly used antihyperglycemic therapies to lower hyperglycemia in type 2 diabetes the high prevalence of heart failure persists. This, therefore, raises the possibility that additional factors beyond glycemia might contribute to the increased HF risk in diabetes. This review summarizes the state of knowledge regarding the impact of existing anti-hyperglycemic therapies on heart failure and discusses potential mechanisms for beneficial or deleterious effects. Second, we review currently approved pharmacological therapies for heart failure and review evidence that addresses their efficacy in the context of diabetes. Dysregulation of many cellular mechanisms in multiple models of diabetic cardiomyopathy and in human hearts have been described. These include oxidative stress, inflammation, endoplasmic reticulum (ER) stress, aberrant insulin signaling, accumulation of advanced glycated end-products, altered autophagy, changes in myocardial substrate metabolism and mitochondrial bioenergetics, lipotoxicity and altered signal transduction such as g-protein receptor kinase (GRK) signaling, renin angiotensin aldosterone signaling and beta2 adrenergic receptor signaling. These pathophysiological pathways might be amenable to pharmacological therapy to reduce the risk of heart failure in the context of type 2 diabetes. Successful targeting of these pathways could alter the prognosis and risk of heart failure beyond what is currently achieved using existing antihyperglycemic and heart failure therapeutics.

Keywords

Diabetes Mellitus; Heart Failure; Diabetes therapies; Diabetic cardiomyopathy

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EDA has consulted in the past for Novo Nordisk and Pfizer.

Heart failure (HF) risk is significantly increased in diabetes.

Type 2 Diabetes Mellitus (T2DM) is a global epidemic and is expected to affect over 592 million people worldwide by 2035, a dramatic increase from 382 million people with diabetes in 2013 [1], a prevalence that is likely underestimated [2]. In the United States alone, an estimated 30.2 million adults or 12.2% had diabetes in 2015, of which 7.2 million (23.3%) were not aware or did not report having diabetes [3]. Both type 1 and type 2 diabetes are heterogenous diseases in which clinical presentation and disease progression may vary considerably. Type 2 diabetes accounts for 90-95% of all diabetes cases [4], for this reason, this review will focus on pharmacological treatments for type 2 diabetes and their impact on heart failure development. Patients with diabetes have over twice the risk of developing heart failure (HF) than patients without diabetes [5, 6]. The Framingham Heart Study suggests that diabetes independently increases the risk of heart failure up to 2-fold in men and 5-fold in women compared to age matched controls [7, 8], highlighting a gender discrepancy that is incompletely understood. The increased incidence of heart failure in diabetic patients persists even after adjusting for other risk factors such as age, hypertension, hypercholesterolemia and coronary artery disease (CAD). Thus, the term ‘diabetic cardiomyopathy’ was coined over 40 years ago and was initially used to describe ventricular dysfunction in the absence of coronary artery disease (CAD) and hypertension in diabetic patients [9]. However, its use has been broadened to describe the increased vulnerability of the myocardium to dysfunction that characterizes individuals with diabetes. While 10-15% of diabetic patients have HF, a recent study suggested that 44% of patients hospitalized for HF have diabetes [10]. The coexistence of comorbidities pose unique clinical challenges [10]. While the association between mortality and HbA_{1c} in diabetes patients with heart failure appears to be U-shaped, with the lowest risk of death in patients with HbA_{1c} levels of ~ 7.1% [11], other studies suggest that diabetes is independently associated with greater risk of death and rehospitalization compared to non-diabetics with heart failure [12]. Additionally, observational data suggests a higher HbA_{1c} level was associated with increased incidence of HF [13]. Therefore, an important question to address is whether improved glycemic control improves HF outcomes.

Heart failure risk and glycemic control

Many landmark clinical trials have addressed the relationship between tight glycemic control and cardiovascular (CV) endpoints. The ADVANCE trial showed that intensive glucose control, which lowered HbA_{1c} to 6.5% in type 2 diabetics, showed no evidence of a reduction in macrovascular events with no increase in mortality [14]. In contrast, The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which targeted HbA_{1c} to 6% in the intensive therapy group, had an increased mortality of 22% suggesting a potentially unexpected increased risk of intensive glucose lowering in high risk patients with type 2 diabetes. The finding of higher mortality resulted in this arm of the trial being terminated [15]. These findings were further supported by intensive glycemic control in a veteran cohort over a 7.5-year period. They too reported intensive glycemic control in patients with poorly controlled type 2 diabetes (baseline HbA_{1c} of 9.4%) had no significant effect on rates of major CV events or death [16]. Similarly, the UK Prospective Diabetes Study (UKPDS) successfully reduced HbA_{1c} by 11% over a 10-year follow-up but did not substantially

reduce diabetes related mortality or myocardial infarction [17]. Together these studies suggested that despite the efficacy of diabetes therapies in achieving lower HbA_{1c}, these therapies were not necessarily advantageous from a CV standpoint and some studies even showed an increase in CV events. These findings underscore the important conundrum that normalization of glycemia might not restore risk of cardiovascular disease to the non-diabetic baseline. Although heart failure was not a primary endpoint of these studies, post-hoc analyses also suggested that intensive glucose lowering did not reduce and in some cases, increased the risk for heart failure or heart failure hospitalization [18]. Table 1 summarizes the relationship between diabetes therapy and heart failure. In summary, pharmacological agents that may have beneficial effects on CV outcomes include metformin, SGLT2i and certain GLP1RA. However, others such as sulfonylureas (SUs), thiazolidinediones (TZDs), insulin, some GLP1RAs and some DPP4i might exacerbate or increase the risk for HF.

The observations that blood glucose lowering might not be sufficient to prevent increased hospitalization and mortality from HF, reinforce the possibility that additional factors beyond glycemia might contribute to the increased HF risk in diabetes, or that independent mechanisms might exist linking anti-hyperglycemic therapies and LV remodeling. Beyond the structural and functional changes that occur with diabetic cardiomyopathy, a complex underlying and interrelated pathophysiology exists and may contribute to heart failure in the context of diabetes [19], some of which may be amenable to pharmacological therapy. These pathways will be discussed in greater detail later in this review. A consistently reported finding in the diabetic myocardium is cardiac hypertrophy, characterized by increase LV mass and wall thickness. Population studies have reported an independent association between diabetes and cardiac hypertrophy and systolic dysfunction [20, 21]. The Atherosclerosis Risk in Communities (ARIC) study provided evidence for subclinical myocardial damage in subjects with pre-diabetes and type 2 diabetes as measured by subclinical circulating concentrations of troponin T (TnT), using a highly sensitive assay. Subclinical myocardial damage increased in a linear manner across the glycemic spectrum from no diabetes to pre-diabetes and diabetes. This correlated with increased risk for CV events, HF or death, being highest in those with type 2 diabetes [22]. A correlation between microvascular complications of diabetes and heart failure has long been established [23]. More recently direct evidence of microvascular dysfunction and impaired myocardial perfusion reserve has been demonstrated [24, 25] implicating tissue hypoxia as another mechanism contributing to accelerated ventricular remodeling in diabetes. Although the correlation between glycemia and myocardial injury could represent “cause and effect”, it could also reflect the existence of additional risk factors for myocardial injury that track with glycemia. Therefore, any analysis of the relationship between antihyperglycemic therapies and heart failure risk must also account for the impact of these agents on other potential mechanisms that could lead to cardiac injury. Thus, direct or indirect mechanisms that could link current anti-hyperglycemic therapies with LV remodeling and myocardial injury that are independent of their blood glucose lowering effects may exist. The remainder of this review will examine current anti-hyperglycemic therapies and discuss potential mechanisms that could influence their efficacy in terms of modulating heart failure risk, and then will review

additional pathophysiological targets implicated in diabetic cardiomyopathy that could be amenable to therapeutic manipulation.

The effect of existing anti-hyperglycemic drugs on cardiovascular risk in type 2 diabetes

Although this section will emphasize potential direct effects of these therapeutic agents on myocardial function in the context of diabetes, it is important to note that often times, studies in which these agents are evaluated are confounded by the fact that these agents will alter systemic metabolism. Thus, beneficial effects observed, could represent direct effects or effects that are secondary to metabolic consequences of these agents such as reducing circulating glucose or triglycerides.

Metformin

Metformin is the most widely used oral antihyperglycemic agent and is considered first line therapy in type 2 diabetes due to its superior safety profile [26]. It is both safe and efficacious both as monotherapy and in combination with other antidiabetic agents and insulin. The United Kingdom Prospective Diabetes Study (UKPDS) reported that patients with type 2 diabetes on metformin had 36% reduced risk of all-cause mortality and 39% lower risk of myocardial infarction compared to type 2 diabetic patients treated otherwise [17]. This risk reduction was greater with metformin therapy than with insulin or sulfonylurea (SU) derivatives despite patients achieving similar glycemic control [17]. Other more recent analysis has supported the case for metformin having a survival benefit in diabetic patients with heart failure compared with alternative glucose-lowering regimens [27, 28]. Metformin was associated with better short term and long-term prognosis than any other anti-diabetic treatment in patients with acute coronary syndrome [29] and heart failure [30].

The cardioprotective actions of metformin in diabetic patients are not fully understood. Activation of AMPK is one putative mechanism of action of metformin. AMPK activation inhibits mTOR and represses protein synthesis, which could inhibit cardiac hypertrophy [31]. Metformin was reported to inhibit hypertrophy in a rat model of pressure overload [32], providing cardioprotection against ischemia-induced heart failure [33] and more recently was shown to protect against transverse aortic constriction-mediated cardiac hypertrophy independently of AMPK [34]. Diabetes is associated with reduced myocardial glucose utilization and increased fatty acid (FA) utilization. Metformin could increase myocardial glucose utilization in part by activating AMPK or by increasing myocardial insulin sensitivity [35]. Although AMPK activation could also increase FA oxidation, the extent of any increase in FA utilization might be tempered by improvements in peripheral insulin sensitivity, which would reduce the delivery of fatty acids to the heart. Cardiac fibrosis has also been shown to be attenuated in heart failure with metformin treatment in mice subjected to transverse aortic constriction (TAC) [36]. However, the metformin doses in these studies was greater than those used clinically, thus it is uncertain if similar changes occur in a clinical setting. In a human study examining the impact of metformin on myocardial function and metabolism in humans with type 2 diabetes, metformin modestly reduced myocardial FA utilization but did not change glucose utilization [37]. Taken together, clinical

studies suggest that metformin might have negligible effects on myocardial substrate utilization and function. However, population cohort and observational studies have consistently revealed that metformin treatment is associated with a reduction in the prevalence of heart failure in diabetic subjects [38, 39]. The mechanisms for this cardioprotection remain to be determined.

Sulfonylureas (SU)

SUs are insulin secretagogues that lower glucose by a glucose-independent release of insulin from pancreatic beta cells [40]. Frequently prescribed SUs include 2nd generation agents such as glyburide/glibenclamide, glipizide and glimepiride [41]. SUs bind to beta cell membrane SU receptors (SURs) leading to closure of ATP-sensitive potassium (KATP) channels. The subsequent membrane depolarization increases calcium influx and insulin release [42]. A second SU receptor SUR2 is highly expressed in cardiac and skeletal muscle [43, 44]. In vitro studies support a possible insulin mimetic action of SU, whereby SU drugs stimulated glycogenesis and lipogenesis [45]. As a direct extension of their mechanism of action, the major adverse effect of SUs is hypoglycemia [46, 47] Weight gain is another important side effect of SUs. Many studies have demonstrated increased weight gain in patients on SUs versus metformin [47] and the UKPDS study demonstrated an increase in weight gain with SUs but even more so with insulin [17], however not all studies have reported an increase in weight gain [48].

Although prior studies have suggested a link between first generation sulfonylureas and CV mortality [49], to date there is no definitive cardiovascular outcome trial that has specifically evaluated cardiovascular safety with SU versus placebo or other glucose lowering agents and for this reason the controversy regarding the effects of SU on CV outcome continues. Observational studies, systematic reviews and meta-analyses have attempted to inform the clinically relevant question regarding cardiovascular safety of SUs. Results are conflicting, whereby some suggest the presence of increased cardiovascular risk and others do not [50]. A meta-analysis of 47 RCTs was performed to explore the cardiovascular safety of SUs and reported no increased risk of any key outcomes; all-cause death, CV death, MI or stroke; nor was there any increased CV risk with SUs versus metformin [51]. Other studies have reported an increase in CV risk in patients on SU versus metformin [52]. These data should be interpreted with caution as the reduction in CV events with metformin may reflect the cardiovascular benefit of metformin. Few studies have directly examined the relationship between SU use and heart failure. An observational cohort study of > 500,000 patients, which revealed an increased risk of all-cause mortality in patients treated with SUs did not reveal a statistical increase in heart failure [38]. Potential reasons for adverse CV complications with SU therapy could include inhibition of myocardial preconditioning, hypoglycemia, weight gain and hypertension [50].

Thiazolidinediones (TZDs)

The glucose lowering effects of the TZDs are mediated primarily by decreasing insulin resistance in skeletal muscle and liver to increase glucose uptake and reduce hepatic glucose production respectively [53]. They have also been shown to be an acute inhibitor of the mitochondrial pyruvate carrier (MPC), thereby having a direct metabolic effect by increasing

glucose uptake [54]. TZDs directly activate peroxisome proliferator-activated receptor- γ (PPAR- γ). The binding of TZDs to PPAR- γ increases peripheral insulin sensitivity in the liver and skeletal muscle in part by promoting the release of adipokines such as adiponectin [55], while promoting adipogenesis [53]. Controversy exists regarding the specific extent to which TZD treatment increases cardiovascular risk. The recent IRIS trial reported that in non-diabetic patients with insulin resistance and a recent history of ischemic stroke or transient ischemic attack, treatment with pioglitazone reduced the risk for stroke or myocardial infarction [56]. These findings have been further supported by two recent meta-analyses [57, 58].

In terms of heart failure, the most commonly reported side effects of TZDs used either as monotherapy or in combination are weight gain [59, 60] and fluid retention [61, 62]. According to a meta-analysis, TZD treatment was associated with a 2-fold increase risk of edema versus placebo, other oral hypoglycemic drugs or insulin [63]. The PROactive trial suggested that pioglitazone was associated with 26.4% increase in edema compared to 15.1% for placebo [64]. TZD -induced edema is thought to be linked to increased vascular permeability, vasodilation and fluid retention by the kidney [65]. Activation of PPARs in the nephrons of the kidney by TZDs promotes the expression of epithelial sodium channels (ENaC) in the collecting duct which increases the retention of salt and water leading to fluid retention [66]. Zhang and colleagues reported that collecting duct specific PPAR- γ knock out were resistant to TZD-induced weight gain and plasma volume expansion [67] further supporting the role of ENaC in fluid retention. However, other studies have challenged this mechanism [68]. TZDs also failed to augment basal or insulin-stimulated Na^+ flux via ENaC in cell lines (A6, M-1 and mpkCCD$_{c14}$) [69]. Thus, additional mechanisms could contribute to adverse effects of TZDs on LV structure and function. Although increased myocardial insulin signaling could represent one mechanism, animal studies in mice lacking insulin receptors in cardiomyocytes revealed that cardiac hypertrophy still develops in animals treated with a PPAR-γ agonist [70]. Other animal studies have also suggested that direct activation of PPAR-γ could lead to ventricular dysfunction [71]. Finally, the inhibition of the MPC by TZDs, could increase mismatch between glycolysis and glucose oxidation, which could be maladaptive. Thus, the relationship between TZD use and ventricular remodeling is complex and may represent direct and indirect effects on the myocardium.

DPP-4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibition prevents the inactivation of the incretin hormone, glucagon-like peptide I (GLP-I), which promotes glucose-dependent insulin release from beta cells. DPP-4 inhibitors (DPP-4i) are effective glucose lowering agents when used as monotherapy or in addition to other agents [72-74]. Five DPP-4is are currently in clinical use (alogliptin, linagliptin saxagliptin, sitagliptin and vildagliptin). Although preclinical studies identified many potential mechanisms of action by which DPP-4 inhibition or GLP1 agonism could exhibit direct cardiovascular benefits [75-79], recent cardiovascular outcome trials have indicated that treatment with DDP4-is do not improve cardiovascular morbidity or mortality relative to placebo. The results of these trials have been recently reviewed [80]. However, with regard to heart failure, the SAVOR-TIMI-53 trial reported a significant increased risk of hospitalization for heart failure in patients on saxagliptin versus placebo [81].

The EXAMINE (alogliptin) and TECOS (sitagliptin) trials [82, 83] did not reveal a statistical increase in heart failure hospitalization, but meta-analyses including data from these trials have suggested a small effect of DPP-4is to increase heart failure hospitalization [80]. The mechanisms responsible for these observations are not understood. One possibility could be effects of other circulating peptides that are substrates for DPP-4 that could have independent cardiovascular effects, although this hypothesis remains to be proven. However, a consensus is emerging that DDP-4is might not be a preferred agent in patients with type 2 diabetes with increased risk for CVD with concomitant heart failure.

GLP-I Receptor Agonists (GLP1RA)

Direct GLP-1R agonists are effective glucose lowering agents that also promote weight loss. The landmark cardiovascular outcome trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER®)) that examined the impact of the GLP1RA liraglutide on cardiovascular outcomes in patients with diabetes with increased cardiovascular risk revealed a significant reduction in the composite endpoint of occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke [84]. However, the rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were non-significantly lower in the liraglutide group than in the placebo group. A subsequent meta-analysis of randomized and observational trials supported the conclusion that GLP-I receptor agonists might not increase the risk of heart failure or hospitalization for heart failure in patients with type 2 diabetes [85]. By contrast, in a small study of heart failure patients (stage 3 and 4 NYHA) with and without diabetes, who were randomized in the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial to receive Liraglutide or placebo, there was no impact of liraglutide on mortality or heart failure hospitalizations. However, in a prespecified subgroup analysis of patients who died or who were hospitalized for heart failure by type 2 diabetes diagnosis, there was a strong trend towards adverse outcomes in patients with diabetes and heart failure who received liraglutide (HR 1.54, 95% CI, 0.97-2.46; log-rank p=0.07) [86]. Thus, there remains uncertainty regarding the utility of liraglutide in patients with existing HF although in type 2 diabetes patients with high risk for CVD, liraglutide may be a suitable choice to prevent a future cardiovascular event. Although preclinical studies have suggested mechanisms by which GLP1RA may influence LV contractility in the short-term, little is known about the mechanisms that account for the potential worsening of heart failure when individuals with existing heart failure are treated with liraglutide.

Sodium-glucose cotransporters 2 (SGLT2)

Glucose that is filtered by the glomeruli is reabsorbed in the nephron by an active transport process that is mediated predominantly by SGLT2, which is a member of a larger family of sodium-glucose co-transporters. Inhibition of SGLT2 promotes glycosuria and represents a novel therapeutic strategy for treating type 2 diabetes [87]. Three SGLT2 inhibitors are currently in clinical use; dapagliflozin, canagliflozin and empagliflozin [3]. All of these agents are effective in lowering blood glucose as monotherapy in combination with other glucose lowering agents [88-92]. Recent cardiovascular outcomes trials revealed an unexpectedly strong cardioprotective signal of SGLT2 inhibition in high-risk patients with type 2 diabetes. Empagliflozin was the first SGLT2 inhibitor to show a reduction in CV mortality and

hospitalization from heart failure in the EMPA-REG OUTCOME trial [93]. The CANVAS trial also revealed similar benefits in terms of the composite endpoint of major adverse cardiovascular events and reduced heart failure hospitalization in subjects randomized to Canagliflozin [94]. While no large dapagliflozin cardiovascular outcome trial has been completed yet, a meta-analysis of cardiovascular events from dapagliflozin clinical trials also revealed a significant reduction in heart failure hospitalizations in patients treated with dapagliflozin [95]. Thus, SGLT2 inhibitors represent the first class of therapeutic glucose lowering agents that have definitively reduced the risk of heart failure in type 2 diabetes. The mechanisms by which SGLT2 inhibitors mediate these benefits are not understood. However potential mechanisms that have been proposed include increased natriuresis, reduced blood pressure, renal protection and a modest effect to increase circulating ketones, which might improve myocardial energetics [96]. It is important to note that these trials were designed primarily to evaluate cardiovascular safety. Trials designed to evaluate outcomes in subjects with heart failure (with or without diabetes) are ongoing, which will enable clinicians to better determine for example, if addition of SGLT2 inhibition to patients with diabetes and heart failure will increase survival and improve the outcomes in these patients. The results of recent cardiovascular outcomes trials have already influenced clinical guidelines that recommend the use of SGLT2 inhibitors in sub-optimally controlled patients with diabetes, at high risk for cardiovascular disease or with existing heart failure [80].

Insulin

In the management of type 2 diabetes, insulin therapy is often added when lifestyle and oral hypoglycemic agents fail to establish glycemic control. As such, it may not be surprising that individuals receiving insulin therapy are older and have greater risk for heart failure. Observational studies have suggested greater cardiovascular mortality and increased heart failure prevalence in insulin treated patients with type 2 diabetes [38]. A number of mechanisms linking hyperinsulinemia and heart failure have been proposed and reviewed [97]. Few trials have been designed to prospectively evaluate the relationship between insulin treatment and heart failure. Such studies are challenging because insulin therapy usually occurs in the context of or in addition to the use of other treatment approaches, which could confound or contribute in uncertain ways to clinical outcomes. A recent cardiovascular outcomes trial, the ORIGIN trial examined insulin glargine versus standard care in type 2 diabetics with high risk for CVD. After a median follow-up of 6.2 years, the results showed that early use of basal insulin to target fasting plasma glucose levels neither increased nor reduced cardiovascular outcomes compared with the standard care group [98]. A recent analysis of heart failure events in the ORIGIN trial suggested that randomization to insulin glargine did not increase heart failure hospitalization or heart failure recurrence [99]. Finally, the recently completed DEVOTE trial examined the efficacy and safety of degludec, an ultralong acting, once daily basal insulin in patients with type 2 diabetes and high CV risk. This trial compared degludec to glargine and demonstrated no difference between the two with respect to incidence of adverse cardiovascular events [100]. These trials are reassuring because they suggest that insulin usage in high-risk patients does not invariably lead to adverse cardiovascular outcomes or to increased heart failure. However, it is important to note improving glycemic control with insulin has not been shown to reduce the elevated risk of heart failure that exists in diabetes. Additionally, it has been suggested that exogenous

insulin by increasing myocardial glucose uptake in the absence of a compensatory reduction in free fatty acid uptake, could exacerbate insulin-mediated metabolic stress by increasing glucolipotoxicity [101]. We also do not understand the interaction between associated co-morbidities, insulin use and heart failure risk. Thus, additional research is required to further inform therapeutic guidelines that seek to balance metabolic control and cardiovascular outcomes in insulin requiring individuals.

Heart failure therapies and their effect on glycemic control

While it is important to determine the impact of antidiabetic drugs on heart failure, it is also important to address the effects of heart failure therapies on heart failure outcome measures and glycemic control in the setting of diabetes. We will briefly review the relationship between commonly used heart failure therapies and their potential relationship with glycemic homeostasis in diabetes.

Renin Aldosterone Angiotensin System (RAAS) Inhibition

It is widely accepted that induction of the renin angiotensin aldosterone system (RAAS) represents a mechanism linking diabetes and cardiovascular complications [102]. In addition to systemic activation of the RAAS, induction of this pathway also occurs locally in the heart both in diabetes and in heart failure [19]. Angiotensin converting enzyme inhibitors (ACE inhibitors) reduce the risk for new onset heart failure in patients with established cardiovascular disease or diabetes [103-105], and correlates with reduced urinary albumin excretion. Activation of RAAS in diabetes may also contribute to inflammation [106], cardiac fibrosis and oxidative stress [107] which all contribute to cardiac remodeling, and could be reversed or prevented by RAAS blockade [107, 108]. Thus, ACE inhibition and angiotensin II type 1 receptor blockade remain first line therapy for CVD prevention in patients with diabetes [109]. ACE inhibitors reduce CVD rates and all-cause mortality in patients with diabetes and increase insulin sensitivity in cells [110, 111]. ARBs, specifically candesartan improves calcium signaling parameters in atrial tissue with diabetic cardiomyopathy [112]. Moreover, renin inhibition improved left ventricular hypertrophy (LVH) and end-systolic volume (ESV) in patients with diabetes [113, 114]. A recent innovation in the management of heart failure has been the combination of RAAS inhibition and inhibition of neprilysin that degrades natriuretic peptides. These dual angiotensin receptor-neprilysin inhibitors (ARNis), such as valsartan in combination with the neprilysin inhibitor, sacubitril, improves cardiac function in experimental models of reperfusion injury [115] and reduces hospitalization in patients with HF and diabetes [116]. Natriuretic signaling has recently been shown to promote energy expenditure and augment systemic insulin sensitivity in animal models of obesity and insulin resistance [117]. Moreover, in human studies, reduced adipose tissue natriuretic peptide signaling correlated with insulin resistance [118]. Thus, it is plausible that these mechanisms of action could increase insulin sensitivity and metabolic control in subjects with type 2 diabetes and heart failure. As such, it will be of interest to rigorously determine if ARNis use could reduce the risk of heart failure progression in individuals with diabetes, particularly those at high-risk for CVD and heart failure. Increased aldosterone signaling has been implicated in heart failure, diabetic cardiovascular injury including diabetic cardiomyopathy and may also play a role in the pathophysiology of insulin resistance [119].

Inhibition of aldosterone receptor signaling with eplerenone may reduce indices of inflammation and markers of insulin resistance in HIV infected subjects [120]. Thus, it would be of interest to determine metabolic and cardiovascular outcomes (including heart failure incidence) in high-risk subjects with diabetes treated with aldosterone receptor antagonists. Other targets for modulating the RAAS are in development that could also impact glucose metabolism in addition to their cardiovascular effects.

Aliskiren a renin inhibitor has been successful in reducing blood pressure by reducing Ang II generation [121]. One potential concern is that aliskiren increases renin levels that could signal through the prorenin receptor (P) RR [122]. Blocking (P) RR may be more efficacious than blocking renin alone. To date, only one (P) RR agent has been developed called HRP (handle region peptide). Animal models have demonstrated promising results as recently reviewed [123] and may have benefits in high prorenin disease states such as diabetes. A novel approach to antagonize Ang II, is stimulation/activation of ACE2, which degrades Ang II to generate Ang 1-7. Animal models of ACE2 deficiency have demonstrated cardiac dysfunction [124]. Several experimental studies have suggested Ang 1-7 infusion may ameliorate diabetic cardiomyopathy, by improving LVH, fibrosis and inflammation and increasing cardiac output [125]. Despite the complex regulation of RAAS, a case can be made for further exploration of approaches to reduce Ang II and its adverse consequences while increasing the activity of beneficial pathways such as ACE2 or Ang 1-7 administration as a plausible therapeutic approach for improving cardiovascular outcomes and reducing heart failure risk in diabetes.

Lipid lowering agents

Dyslipidemia is a major risk factor for cardiovascular disease in type 2 diabetes. The characteristics of diabetic dyslipidemia include high plasma triglycerides (TG), high low-density lipoproteins (LDL) and low high density lipoproteins (HDL). These changes can be attributed to increased fatty acid flux secondary to insulin resistance in adipocytes, in concert with altered hepatic lipid metabolism. While several classes of pharmacological agents are used to treat dyslipidemia, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial suggested a reduction in the risk of hospitalization for HF by 15-20% in patients on rosuvastatin [126]. The mechanism for the reduction in HF is not clear, but could represent reduced ischemic events or direct effects of the statin on endothelial or microvascular function. Many studies confirm that statin treatment of individuals with diabetes will reduce cardiovascular events linked to myocardial ischemia [127]. However, the specific question of cholesterol lowering in a diabetic population with heart failure as the pre-specified end point to our knowledge remains to be addressed in a clinical trial. Fibrates are PPAR-α agonists that lower TGs, LDL and raise HDL. They may also improve insulin sensitivity [128]. Fibrate therapy reduced CVD risk factors and has been shown to reduce coronary events in a diabetic population [129]. In sucrose fed insulin resistant rats, used as a model of diabetic cardiomyopathy, treatment with bezafibrate prevented metabolic abnormalities and cardiomyocyte dysfunction [130]. However, it is possible that the improvement in cardiomyocyte function described in this animal study resulted from reduced lipid delivery to the heart and improved systemic metabolic homeostasis. Although, these findings suggest that PPAR-α agonists therapy could be a reasonable therapeutic target

in subjects at risk for diabetic cardiomyopathy, further investigation of this question is necessary and trials examining the impact of specifically treating diabetic dyslipidemia on heart failure risk are warranted. A clinical trial (AleCardio) of a dual PPAR-α/PPAR-γ activation which had potent effects on reducing hypertriglyceridemia and increasing HDL, was discontinued because of increased cardiovascular mortality, including a trend towards increased risk of heart failure [131]. It is not known if these adverse effects were the consequence of PPAR-α versus PPAR-γ stimulation.

Beta Blockade

Beta blockade is central to the management of patients with heart failure with reduced ejection fraction. Although concerns were raised in the past regarding the potential increase in risk of hypoglycemia, when beta blockade is used in individuals with diabetes, there is little evidence that this is the case and contemporary clinical guidelines support the use of beta blockade in individuals with diabetes and heart failure [132]. Meta-analyses support the prognostic benefits of beta-blockade in heart failure patients with diabetes, although, the magnitude of benefit is attenuated in diabetes [133], perhaps due to associated autonomic dysfunction. Notably, carvedilol (a combined beta1/beta2 antagonist) improves both glycemic control, left ventricular ejection fraction [133, 134] and decreases oxidative stress in the failing human heart [135] and might be the beta blocker of choice. A role for aberrant beta 2 adrenergic signaling in diabetic cardiomyopathy has also been suggested in animal studies [136]. In this study, hyperinsulinemia induced phosphodiesterase 4D (PDE4D), by a mechanism involving insulin receptor substrate (IRS) and GRK2- dependent transactivation of a β_2AR-β-arrestin-ERK signaling pathway. PDE4D induction reduces cAMP activity and PKA phosphorylation of its substrates which contributed to cardiac dysfunction. Genetic deletion of the β_2AR or β-arrestin 2 or pharmacological inhibition of GRK2 or the β_2AR reversed the obesity-related cardiac dysfunction. These observations provide a rationale for targeting β_2AR or GRK2- mediated signaling as a potential therapy for diabetes-associated heart failure.

Pathophysiologic mechanisms that could be therapeutically targeted for treating heart failure in diabetes

Cardiac Metabolism in Diabetes and in Heart Failure.

Diabetes with or without heart failure is associated with profound changes in myocardial substrate utilization and this topic has been extensively reviewed [19, 97]. In brief, diabetes is associated with increased myocardial FA utilization, decreased glucose utilization (glycolysis and glucose oxidation), increased myocardial oxygen consumption and decreased cardiac efficiency. Despite increased rates of FA oxidation, triglycerides and other lipid metabolites such as ceramides accumulate in the diabetic heart. Cardiac metabolism in heart failure has also been studied by many groups and extensively reviewed [137, 138]. Similar to diabetes, glucose oxidation rates are generally reduced in the failing heart and changes in glycolysis are variable with glycolysis being increased early in the evolution from compensated cardiac hypertrophy to heart failure. However, in end stage heart failure, rates of glucose uptake might be reduced although the mis-match between glycolysis and glucose

oxidation likely persists [139]. In contrast to diabetes, fatty acid utilization and oxidation rates are reduced in heart failure, although evidence for accumulation of toxic lipid intermediates have been reported [140]. Thus, the combination of heart failure and diabetes could potentially exacerbate lipotoxicity and further reduce cardiac contractility, as was suggested by studies combining increased myocardial lipid utilization with increased glucose delivery [141]. Relatively few studies have rigorously examined myocardial substrate utilization in subjects with diabetes and heart failure. Animal studies have attempted to examine this issue and results are variable. For example, whereas transverse aortic constriction in high-fat fed mice was associated with reduced ventricular function and increased myocardial injury [142], recent studies in diabetic db/db mice revealed incredible resilience and preservation of myocardial energetics following transverse aortic constriction [143]. Moreover, studies in animal models of HF subjected to high fat diets suggested that high-fat feeding (which induced impaired glucose tolerance and insulin resistance) could be cardioprotective [144]. Metabolic modulation as an approach to treating heart failure has long been considered as an approach to treating heart failure and has been extensively reviewed [145, 146]. The rationale for modulating myocardial substrate utilization in HF, includes increasing glucose utilization while reducing FA utilization in an attempt to increase cardiac efficiency. The most widely studied approach has been with trimetazidine an inhibitor of 3-ketoacylcoenzyme A thiolase (3-KAT), which would shift substrate utilization from FFA to glucose oxidation. Meta-analyses of small clinical studies have revealed potential beneficial effects [147]. Earlier attempts to increase PDH flux thereby increasing glucose oxidation, with dichloroacetate have yielded mixed results in small human trials. Moreover, the long term use of DCA in humans is contraindicated due to the neuropathy associated with this drug [148]. However, similar studies of metabolic modulation in heart failure patients with established diabetes remain to be performed.

Recent studies have revealed that human failing hearts exhibit increased ketone body utilization [149]. Ketone bodies are an energy-efficient fuel generated primarily in the liver from acetyl-CoA derived from β oxidation of FA. It remains to be shown if this increase in ketone utilization in HF represents an adaptation in the face of reduced ability of the failing hearts to utilize other substrates. Moreover, whether ketone bodies could improve cardiac function in HF is unknown and is now an intense area of investigation. Less is known about ketone body utilization in diabetic cardiomyopathy, although a recent human study suggested that myocardial ketone utilization might be increased [150]. Studies examining ketone utilization in diabetics with heart failure would therefore be of great interest and could provide a strong rationale for studies designed to determine the impact of modulating myocardial ketone metabolism on the course of heart failure in diabetes.

Diabetes is associated with increased flux through the hexosamine biosynthetic pathway (HBP), leading to increased generation of glucosamine that is used by the enzyme O-GlcNAc transferase (OGT) to generate post-translational modifications on a diverse array of cellular proteins via a process known as O-GlcNAcylation. The relationship between protein O-GlcNacylation and cardiac structure and function is context dependent. For example, increased protein O-GlcNAcylation has been described in rodent models of hypertrophy and heart failure and in failing human hearts [137, 151, 152] which correlated with reduced cardiac mitochondrial function particularly in the context of diabetes [153]. In contrast, NOX4, which

is induced in the failing heart was shown to maintain myocardial FA utilization via a mechanism mediated by increased O-GLcNacylation of the fatty acid transporter CD36 [154]. Moreover, O-GlcNAcylation was shown to be protective in the context of ischemia [155] by inhibiting calcium overload and ROS generation [156] or by increasing cardiac stem cell survival [157]. As such, future work is needed to identify the specific targets of O-GlcNACylation in the diabetic heart to determine the impact of these changes on protein function and heart failure pathophysiology. This in-depth understanding would be a prerequisite to determining if pharmacological modulation of the HBP or of the activity of OGT or OGlcNACase may play a role in modifying heart failure outcomes particularly in the context of diabetes.

Mitochondrial Bioenergetics

Many studies have examined mitochondrial bioenergetics either in heart failure or in diabetes. Both conditions are associated with impaired mitochondrial oxidative capacity and oxidative stress. However, diabetes might be more likely to be associated with increased mitochondrial uncoupling, which contributes to impaired cardiac efficiency in the diabetic heart [158]. There is considerable evidence linking heart failure with impaired myocardial energetics [137]. Reduced cardiac PCr/ATP ratio has been reported in explanted human hearts [159], in ^{31}P MRS studies in humans with HFrEF [160], in patients with HFpEF [161] and in animal models of pressure overload HF [162]. Similar changes in myocardial pCr/ATP ratios have been reported in subjects with diabetes with mild diastolic impairment. Impaired mitochondrial respiration and altered mitochondrial ultrastructure have been observed in rodent models of insulin resistance and diabetes and have been previously reviewed [163]. Thus, the possibility exists that the superimposition of diabetes and heart failure could further impair mitochondrial bioenergetics. Intriguingly, this specific question has not been widely studied. Although animal studies that have attempted to maintain expression levels of regulators of mitochondrial biogenesis such as PGC1-α have not led to preservation of myocardial function, additional mechanisms linking impaired mitochondrial bioenergetics and heart failure could potentially be targeted therapeutically. These include ROS-mediated mitochondrial uncoupling, a characteristic of diabetic cardiomyopathy that in animal studies could be ameliorated by treatment with anti-oxidants [164, 165]. Similar effects have been reported in animal models of heart failure [166, 167], but few studies have examined a role for ROS-scavenging when diabetes and heart failure co-exist. Another molecular target that is emerging as a potential treatment for heart failure are strategies that replete the myocardial pool of NAD^+ using for example nicotinamide riboside (NR) [168]. Although NR has also been studied in diabetic neuropathy, a role for therapeutic manipulation of this pathway in the context of diabetes and heart failure remains an important question for future studies. Finally, altered E-C coupling represents an important pathophysiological mechanism that is altered both in heart failure and in models of diabetic cardiomyopathy. Calcium re-uptake via SERCA-2 into the SR is an energy-dependent process, which is impaired in heart failure and in models of diabetic cardiomyopathy. For example, cardiomyocytes from ob/ob mice exhibited elevated cytosolic Ca^{2+}, delayed removal of Ca^{2+} and reduced amplitudes of Ca^{2+} transients related to reduced SERCA-2a activity and impaired Ca^{2+} reuptake [169-171]. Adenoviral overexpression of SERCA-2 was shown to improve E-C coupling in animal models of type 1 and type 2 diabetes [172].

Lipotoxicity and Glucotoxicity

The systemic metabolic perturbations associated with uncontrolled diabetes presents the myocardium with a surplus of fuels such as fatty acids, ketones and glucose. The inability of the heart to process these substrates stem in part from mitochondrial dysfunction leading to the accumulation of toxic byproducts of these cardiac fuels that may contribute to increased myocardial injury. The net effect of this imbalance between substrate supply and metabolic capacity and the aberrant signaling that ensues from metabolic byproducts of lipid or glucose metabolism has been termed lipotoxicity or glucotoxicity respectively, or when their effects occur in concert, the synergistic pathological consequences have been described as glucolipotoxicity. The topic of myocardial lipotoxicity has been extensively reviewed [173, 174]. There is a general consensus that lipotoxicity arises from the increased availability of lipid intermediates such as ceramides, diacylglycerol or oxidized phospholipids [19]. Lipotoxic cardiomyopathy has been achieved in many animal models by increasing FA uptake [19]. Excess lipid can be stored as triglycerides and are also shunted into non oxidative pathways, disrupting normal cellular signaling and leading to apoptosis and organ dysfunction [173]. Metabolites that arise from glycolysis such as sorbitol the product of aldose reductase, the initial step in the polyol pathway has been implicated in promoting oxidative stress. O-GlcNAC modifications of proteins as discussed earlier, resulting from increased flux through the hexosamine biosynthetic pathway has variable consequences which could be cardioprotective or deleterious [175]. Recent studies have also revealed that glucose or its metabolites might also impact myocardial gene expression by direct effects on transcription factors or by epigenetic mechanisms [176]. Although, in the context of diabetes, adaptations develop in the heart to reduce glucose uptake, persistent hyperinsulinemia, hyperglycemia and increased circulating fatty acids may conspire to limit “protective” adaptations leading to a cumulative impact of toxic byproducts of glucose and lipid metabolism, - “glucolipotoxicity”. From a therapeutic stand-point the most effective approaches to limit glucolipotoxicity will likely be those that limit excessive substrate delivery to the heart and mitigating hyperinsulinemia. As discussed elsewhere in this review, existing glucose lowering therapies address some but not all of these variables and might have independent effects on the myocardium, which depending on the agent may provide additional benefit (e.g. SGLT2 inhibitors) or generate adverse effects (e.g. TZDs). A non-pharmacological approach, namely bariatric surgery which represents a treatment that is most likely to lead to diabetes reversal may come close to addressing many of the metabolic abnormalities that promote glucolipotoxicity and is discussed next.

Obesity - impact of bariatric surgery or calorie restriction

Bariatric surgery has been proven to be the most effective long-term weight loss treatment, provoking changes in gut hormone physiology, the metabolic profile and improvements in insulin sensitivity [177, 178]. Considering the strong association between BMI, waist circumference with HF incidence [179], bariatric surgery may be an attractive therapeutic target in both HFrEF and HFpEF patients. Studies addressing the impact of bariatric surgery in patients with HF have comprised small sample sizes or have been mostly retrospective analyses. Weight loss induced by either Roux-en-Y gastric bypass (RYGB) or adjustable gastric banding (AGB) proved to be beneficial and normalized LV diastolic dysfunction in 42% of patients in one study [180]. In patients with HFrEF, RYGB, sleeve gastrectomy (SG) or

AGB was associated with significant improvements in LVEF six months' post-surgery. HF symptoms improved across all NYHA classes of HF [181]. Findings consistently report the positive effect of weight loss, achieved through different types of bariatric surgery on myocardial structure and function, HF and symptoms of HF. A better understanding of factors that positively mediate this clinical response is necessary to aid in the design of future interventions. Another way to achieve weight loss is calorie restriction (CR). In a randomized control trial (RCT) of obese older adults with HFpEF, calorie restriction plus exercise increased peak oxygen consumption [182]. Recently, de Lucia et al. examined the impact of CR, when started after the onset of HF in myocardial infarction or sham operated rats. They reported that CR using an intermittent fasting protocol over one year ameliorated cardiac dysfunction and improved inotropic reserve [183]. A similar study in humans with HF has yet to be completed but if true, would provide a relatively inexpensive therapeutic modality with favorable effects in the setting of HF.

Oxidative stress and pharmacological targeting of ROS

It is widely accepted that oxidative stress contributes importantly to the pathophysiology of diabetic cardiomyopathy and arises from mitochondrial and non-mitochondrial sources such as NADPH oxidase and xanthine oxidase [19, 184-186]. The association between redox abnormalities and heart failure in general, and its potential exacerbation by diabetes provides a rationale for targeted antioxidant therapy as an adjunct for managing heart failure in the context of diabetes [187, 188]. A large body of literature has examined the potential utility of diverse anti-oxidant strategies in heart failure. Although studies in animals have suggested utility, rigorous analysis in human clinical trials have been disappointing. For example, Vitamin E (α-tocopherol) supplementation was shown to have therapeutic efficacy in animal models of heart failure, although this was not replicated in human clinical trials of heart failure [189]. It has been argued that more targeted antioxidant approaches are warranted and should be selectively targeted to those circumstances where oxidative stress can be shown to be increased. Recent studies have attempted to use circulating biomarkers to estimate redox changes in the context of heart failure and have revealed that approximately 42% of heart failure patients exhibit evidence of oxidative stress whereas 41% do not. Moreover, 17% of subjects in this study revealed characteristics of a hyper-reductive state [190]. A similar analysis has not yet been performed to determine if diabetics with heart failure will exhibit a greater preponderance of markers consistent with myocardial oxidative stress. Thus, future studies in which antioxidants are targeted selectively only to those with evidence of increased oxidative stress are warranted. Another important consideration is the molecular target of anti-oxidant therapy. Given that oxidative stress in the context of diabetes-related heart failure could derive either from mitochondrial sources or from activation of NADPH oxidases (NOX), strategies that specifically target each source, either separately or in combination will need to be examined. Agents now exist that specifically target mitochondrial ROS by accumulating in mitochondria (e.g. MitoQ or mito-catalase) or by reducing ROS formation by respiratory complexes (SS-31). While preclinical trials have demonstrated amelioration of cardiac damage in response to stress [165, 167, 191], no clinical trial has tested the efficacy of mitochondrial ROS scavengers in the general heart failure population or in heart failure populations enriched with diabetes. The ever-evolving understanding of the complex interplay between difference sources of ROS and their effect

in heart failure have revealed novel and attractive targets for drug therapy. Further clinical investigations are required to identify the impact of ROS targeting in heart failure, particularly in the context of diabetes.

Autophagy as a therapeutic target in diabetes and heart failure

Autophagy is an intracellular catabolic pathway in which long-lived proteins, ribosomes, lipids and cellular organelles are sequestered by the autophagosome and then targeted to the lysosome for degradation [192]. Basal autophagy is important in the heart to maintain normal cellular function and protein and organelle quality control [193]. Autophagy is induced in response to environmental stressors such as starvation and in this context, represents an important cell survival mechanism. There is some controversy regarding whether or not autophagy is cardioprotective or deleterious in the context of heart failure, and has been recently reviewed [194]. The role of autophagy in promoting cellular survival or cell death is context specific. For example, the presence of autophagic structures in dying cells has led to the hypothesis that excessive autophagy may play a causative role in stress-induced cell death. Moreover, in mice with cardiomyocyte-restricted deletion of insulin receptor substrates 1 and 2 (IRS1/2) excessive autophagy contributed to accelerated heart failure [195]. However, there are many reports indicating that induction of autophagy in animal models of pressure-overload-induced or post-ischemic heart failure may be protective and an inhibition in autophagy could mark a transition from compensated to de-compensated heart failure [196, 197]. Conversely, while specific mechanisms might differ between models of type I and type 2 diabetes, autophagic flux is believed to be impaired in the heart in diabetes [198-200]. Mechanisms for autophagic impairment include lipid-induced impairment of lysosomal function, altered insulin signaling or mTORC1 activation and impaired activation of AMPK [201, 202]. In animal models of type 2 diabetes, inhibition of mTOR either by AAV-mediated overexpression of PRAS40 [203], rapamycin [204] or in Akt2 deficient mice increased autophagy which correlated with reduced hypertrophy and improved cardiac function. Mitophagy refers to selective degradation of damaged mitochondria. Considering mitochondrial dysfunction and mitochondrial ROS production are hallmarks of diabetic cardiomyopathy, a potential approach for reducing diabetic cardiac injury could be to increase the removal of dysfunctional mitochondria as an approach to limiting mitochondrial ROS overproduction by increasing mitophagy.

Although it is possible that either excessive or impaired autophagy may play a role in the development of heart failure, it is still notable that none of the current approved treatments for diabetes or heart failure, target autophagy as a specific mechanism of action and little is known of the impact of these agents on myocardial autophagy. Angiotensin II type 1 Receptor (AT1R) blockade or AT2R stimulation was reported to modulate hypertrophy-associated cardiomyocyte autophagy [205]. Chronic activation of AMPK by metformin restored cardiac autophagy in parallel with improved cardiac function in type 1 diabetic mouse hearts, an effect that was absent in diabetic AMPKα2 deficient mice [201]. The polyphenol resveratrol, may promote autophagy via SIRT1 [206] or AMPK [207]. Thus, on the basis of preclinical studies there are a number of potential therapeutic agents that could modulate myocardial autophagy, thereby providing a rationale for future studies to

determine their efficacy in preventing diabetic cardiomyopathy or in modifying the course of heart failure in patients with heart failure and diabetes.

ER stress as a therapeutic target in diabetes and heart failure

Activation of the endoplasmic reticulum (ER) stress response also known as the unfolded protein response (UPR), or the integrated stress response in which signaling mediators downstream of the UPR may be activated in the absence of ER stress, have been described in animal models of heart failure or myocardial inflammation [208-210]. Hyperglycemia has been associated with ER stress induction in vascular smooth muscle cells [211]. Hyperglycemia-associated increases in ER stress is correlated with oxidative stress [212]. Moreover, ER stress activation has been implicated as a novel risk factor for CVD in humans [213]. Few studies have investigated the impact of therapeutically modulating ER stress pathways in the context of diabetic cardiomyopathy. Genetic inhibition of CHOP, which is downstream of eif2α phosphorylation, which is increased by ER stress, attenuated pressure overload cardiac hypertrophy in mice [209]. Salubrinal a small molecule that prevents dephosphorylation of eif2α in neurons [214], has not yet been tested in the setting of heart failure. It is possible that normalizing diabetes-related oxidative stress might be sufficient to normalize ER stress [212]. This has not yet been formally tested in the context of diabetic cardiomyopathy. The use of chemical chaperones or overexpression of chaperone proteins have been used experimentally to attenuate ER stress [215]. For example, overexpression of the chaperone GRP78 reduced cardiac dysfunction and ER stress in the context of ischemia reperfusion [216]. Chemical chaperones such as sodium phenylbutyrate (PBA) and Tauroursodeoxycholic acid (TUDCA) have been shown to enhance ER protein folding ability and to improve insulin resistance in vitro and in humans [217], but no studies to date have examined the impact of modulating ER stress pathways on the course or risk of diabetic cardiomyopathy. Angiotensin II type I receptor antagonism might indirectly modulate ER stress in the heart as evidenced by CHOP inhibition when mice with pressure overloaded hearts were treated with an ARB [218]. AMPK activation also reduces ER stress [219], however, it remains to be established if potential beneficial effects of AMPK activation in the context of diabetic cardiomyopathy is secondary to modulation of ER stress or to other targets of AMPK. Taken together, additional studies are warranted both to explore the contribution of aberrant ER stress in diabetes-related heart failure and its utility as a therapeutic target.

Inflammation as a Therapeutic Target in Diabetic Cardiomyopathy

Pro-inflammatory cytokines have been implicated in the pathogenesis of heart failure [220]. Increased circulating levels of proinflammatory cytokines and cytokine receptors correlate with mortality in patients with HFrEF [221, 222] and HFpEF [223]. Both circulating and intracardiac levels of pro-inflammatory cytokines, primarily TNFα, IL-6 and IL-18, are elevated in patients with heart failure [224]. The inflammation burden in a given tissue reflects the balance between pro and anti-inflammatory cytokines, such as IL-1RA, IL-10 and IL-13 and changes in these cytokines have also been recognized in heart failure [225]. Cytokines implicated in cardiac remodeling can originate in the heart i.e. cardiokines, [226] or originate from peripheral sites such as the spleen or bone marrow [227]. Although inflammation has long been considered an important player in the pathogenesis of heart failure and a potential therapeutic target for heart failure treatment, no anti-inflammatory approaches have to date

proved effective in modifying the course or prognosis of heart failure in clinical trials [228-230].

Myocardial inflammation has also been implicated in the pathophysiology of diabetic cardiomyopathy [229, 231]. In diabetes, visceral adipocytes secrete cytokines and chemokines which may contribute to low grade inflammation in many tissues including the heart. Hyperglycemia may induce cytokine secretion from cardiac cells which promotes the recruitment of monocytes and lymphocytes, that may contribute to a chronic inflammatory state and activation of signaling pathways that contribute to cardiac hypertrophy [229, 232, 233]. Diabetes may promote cardiac inflammation by modulating a number of signaling pathways which converge on NF-ƙB. These include activation of the renin angiotensin aldosterone system (RAAS), advanced glycated end-products (AGEs) and damage-associated molecular patterns (DAMPs), which have been reviewed in detail elsewhere [234]. Toll-Like receptors are present in cardiomyocytes and are implicated in immune signaling [235]. High levels of glucose and FFA, activate TLR2 and TLR4 [236]. Diabetic TLR2 and TLR4 deficient mice demonstrated reduced cardiomyocyte TG accumulation, reduced leukocyte infiltration and decreased NF-ƙB signaling [237]. Hyperglycemia also induces TLR2 and TLR4 in monocytes from type 2 diabetic patients [238, 239]. TLR antagonists ameliorate NF-ƙB activation, leukocyte infiltration and myocardial contractile dysfunction in murine hearts following ischemia/reperfusion injury [240]. Thus, specific targeting of TLR signaling could represent a potential therapeutic target in diabetic cardiomyopathy. Inflammasomes are multimeric protein complexes, the best characterized being NLRP3. NLRP3 oligomerization leads to the recruitment of procaspase-1. Active caspase-1 processes IL-1ß and IL-18 precursors to enhance proinflammatory pathways. Like TLRs, NLRP3 can be activated by hyperglycemia and long chain free fatty acids and ceramides [241]. NLRP3 inflammasome formation has been implicated as a contributor to increased systemic inflammation that is characteristic of insulin resistance and type 2 diabetes [242]. NLRP3 enhances myocardial cytokine production and infiltration by macrophages [243, 244]. Given a potential role for the NLRP3 inflammasome in linking inflammation and metabolic heart disease, targeting the inflammasome could represent a plausible target for reducing the burden of heart failure in diabetes. Although targeting inflammatory pathways have been proposed as a tool to reduce cardiovascular disease in general [245], evidence for a specific role in heart failure prevention has been lacking. However, whether or not subsets of patients with heart failure such as diabetics or others with a greater inflammatory burden will benefit from targeted inhibition of these inflammatory pathways remain to be determined. Although anti-inflammatory strategies might modulate the progression of insulin resistance and dysglycemia, it remains to be proven that these will translate into reducing the cardiovascular complications of diabetes or to altering the course of diabetic cardiomyopathy. It is important to note that some commonly used therapeutic agents in heart failure or diabetes exhibit anti-inflammatory properties. For example, both statins and valsartan, an angiotensin II receptor blocker may attenuate TLRs, inhibit NF-ƙB and reduce circulating levels of cytokines in mouse models of dilated cardiomyopathy and rat models of ischemic cardiomyopathy [246-248]. Evidence linking anti-inflammasome properties of anti-diabetic drugs like metformin, SUs and GLP-1 have been recently reviewed [241]. However, the extent to which

these pathways are modulated when these agents are used clinically remain to be determined.

Modulating Insulin Signaling Pathways

A strong association exists between insulin resistance and HF [249]. These two conditions tend to coexist and the impact of one disorder on the other results in bidirectional effects relating to causation and outcome [250]. On one hand, evidence from clinical studies exist to support the notion that insulin resistance predicts the development of heart failure [251]. Genetic mouse models with cardiomyocyte-restricted knockouts of the insulin receptor, insulin receptor substrates or the glucose transporter GLUT4, have further supported a role for altered insulin signaling in the development of HF. Together, these observations have implicated insulin resistance as a contributing factor to the development of heart failure [252-254]. Conversely, the presence of heart failure may predict the development of abnormalities in glucose regulation considering 28% of non-DM HF patients developed T2DM over a 3 year follow up [255]. These findings were also supported by others who reported that HF patients developed T2DM with the largest increase in those in the most severe NYHA class for HF [256, 257]. It is however unclear if insulin resistance is a cause or a consequence of HF and most clinical studies were not designed to discern the relationship between antecedent insulin resistance and subsequent heart failure. However, the presence of either condition likely exacerbates the other.

Defective myocardial insulin signaling in diabetic cardiomyopathy has been described in both animal models [258] and humans [259]. The relationship between myocardial insulin signaling, diabetes and heart failure is complex and has been recently reviewed in-depth [97]. Briefly, hyperinsulinemia or cardiomyocyte stretch can cause hyperactivation of the insulin signaling pathway, increasing IRS1 phosphorylation and Akt activation which can exacerbate cardiac dysfunction in response to pressure overload [260]. Moreover, our group has recently shown that the constitutive activation of PI3K, while it leads to compensated hypertrophy, also results in a desensitization of insulin mediated glucose uptake [261]. Interestingly, short-term Akt activation resulted in reversible hypertrophy, however long-term Akt activation results in heart failure. When the Akt stimulus was reduced in these failing hearts, the rate of progression to death was accelerated [262]. Hyperinsulinemic activation of Akt/mTOR signaling could also lead to LV hypertrophy by inhibiting autophagy [97]. Activation of such growth promoting pathways by hyperinsulinemia that characterizes type 2 diabetes could contribute to accelerating left ventricular remodeling. Hyperinsulinemia might also activate GRK2 signaling, which may accelerate LV remodeling. Whether or not approaches that reduce hyperinsulinemia or attenuate growth signaling in diabetes may directly modulate the outcome of heart failure in diabetic subjects is not known. It is interesting to speculate however, that one potential mechanism for the robust effect of SGLT2 inhibition on heart failure outcomes in high risk patients with diabetes could be the consequence of reduced hyperinsulinemia.

A well-studied downstream mediator of insulin signaling that has been studied in the context of heart failure are members of the Forkhead bo*x*-containing protein, *O* subfamily (FOXO) of transcription factors. FOXOs have also been implicated in the pathophysiology of obesity

and diabetes-related heart failure [263, 264]. The phosphorylation of FOXO1 (Ser265) and FOXO3 (Thr32 and Ser235) by Akt promotes their translocation from the nucleus to the cytoplasm where they become sequestered and bound by 14-3-3, thereby reducing their transcriptional activity. Conversely, the activation of FOXOs due to the disruption of the interaction with 14-3-3 by acetylation mediated by p300 [265, 266] or AMPK [267], or by deacetylation of FOXO1 by SIRT1 [268] induces its nuclear localization and increases its transcriptional activity. Nuclear localized FOXO1 or FOXO3 promotes cardiac atrophy and autophagy [269]. Conversely, FOXO3 inhibition is associated with pathological hypertrophy [270]. Constitutively nuclear FOXO1 has been implicated in the pathophysiology of obesity-related cardiomyopathy in mice and genetic reduction of FOXO1 signaling was cardioprotective in this context [263]. At present, there are no approved targets for therapeutically targeting FOXO1. However, as these agents are identified there is a strong rationale for examining their role in diabetes-associated cardiovascular disease.

Advanced Glycated End Products

Increased formation of advanced glycation end products (AGEs) have been implicated to play a pathophysiological role in diabetic cardiovascular injury, including diabetic cardiomyopathy [271]. Mechanistically, AGEs crosslinks with extracellular matrix proteins to increase fibrosis and impair myocardial relaxation. AGEs also transactivate their receptors (RAGE) to activate inflammatory signaling, increase ROS production and promote myosin isoform switching via an NF-ĸB signaling-dependent mechanism [272-274]. Studies in animal models of diabetes have suggested that pharmacological inhibition of AGEs or RAGE signaling might ameliorate myocardial dysfunction. For example, treatment of STZ-induced diabetic rats and ZDF rats using dehydroepiandrosterone (DHEA) counteracted hyperglycemia-mediated oxidative stress-induced RAGE activation which normalized NF-ĸB signaling and reversed the MHC isoform switch [272]. In another study using STZ induced type I diabetes, AGE accumulation impaired SR Ca^{2+} reuptake in cardiomyocytes and long term treatment with an AGE crosslink breaker partially normalized SR Ca^{2+} handling [275]. RAGE gene knockdown prevented hemodynamic impairments in STZ-induced diabetic mice [276]. More recently, inhibition of AGE in STZ diabetic mice using aminoguanidine alleviated or reversed diabetes induced cardiac dysfunction. Diabetes also inhibited autophagy and induced ER stress which were also reversed by inhibiting AGEs. This study suggested that AGE-induced cardiac dysfunction may be mediated through ER stress and autophagy [277]. Targeting AGE/RAGE axis might thus represent another potential therapeutic approach, however, the precise cellular mechanisms underlying AGE-mediated pathogenesis of diabetic cardiomyopathy remains unknown.

Concluding Remarks

The pathophysiology of heart failure in diabetes is complex and represents a cardiovascular complication of diabetes that contributes importantly to morbidity and mortality. The recent realization that various classes of approved anti-hyperglycemic agents may have divergent effects on heart failure, and that some classes of agents might actually reduce heart failure risk, has led to a closer examination of the relationship between treatments and outcomes. This review has provided an overview of the current state of knowledge regarding the mechanisms linking approved diabetes therapies and heart failure. While recent data have

provided a rationale for preferential use of certain agents in diabetic patients at high-risk for developing cardiovascular disease or heart failure, a rationale for therapeutic decision making in individuals with co-existent diabetes and heart failure is less clear and will await the results of future clinical trials designed to specifically address this question. We have also discussed additional molecular targets, the modulation of which could play a role in designing therapeutic strategies to reverse or treat this challenging condition. There are many approaches now available to achieve glycemic control in individuals with diabetes. However, as we enter an era of personalization in the management of diabetes, the next challenge will be the identification of therapeutic strategies that will not only achieve and maintain glycemic control, but that will also reverse existing complications. Given the high prevalence of heart failure in diabetes, there is a strong imperative to advance this agenda, with the view of identifying robust strategies that will not only improve long-term outcomes in subjects with diabetes and heart failure but also limit the likelihood of developing heart failure in the first place.

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Nonstandard Abbreviations and Acronyms:

AGE	Advanced glycated end-products
AMPK	AMP activated protein kinase
ARBs	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
cAMP	cyclic adenosine monophosphate
DAMP	Damage-associated molecular pattern
DPP4i	Dipeptidyl peptidase 4 inhibitor
GLP1RA	Glucagon-like peptide 1 receptor agonist
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3	Nucleotide-binding domain, leucine rich-containing family, pyrin domain-containing 3
NOX	nicotinamide adenine dinucleotide phosphate oxidase
PDE4D	Phosphodiesterase 4D
PKA	Protein Kinase A

PPAR-α	Peroxisome proliferator-activated receptor alpha
PPAR-γ	Peroxisome proliferator-activated receptor gamma
RAAS	Renin Angiotensin Aldosterone System
SGLT2	Sodium glucose cotransporter 2
SU	Sulfonylurea
TLR	Toll like receptor
TUDCA	Tauroursodeoxycholic Acid
TZDs	Thiazolidinediones
β_2AR	Beta 2 adrenergic receptor

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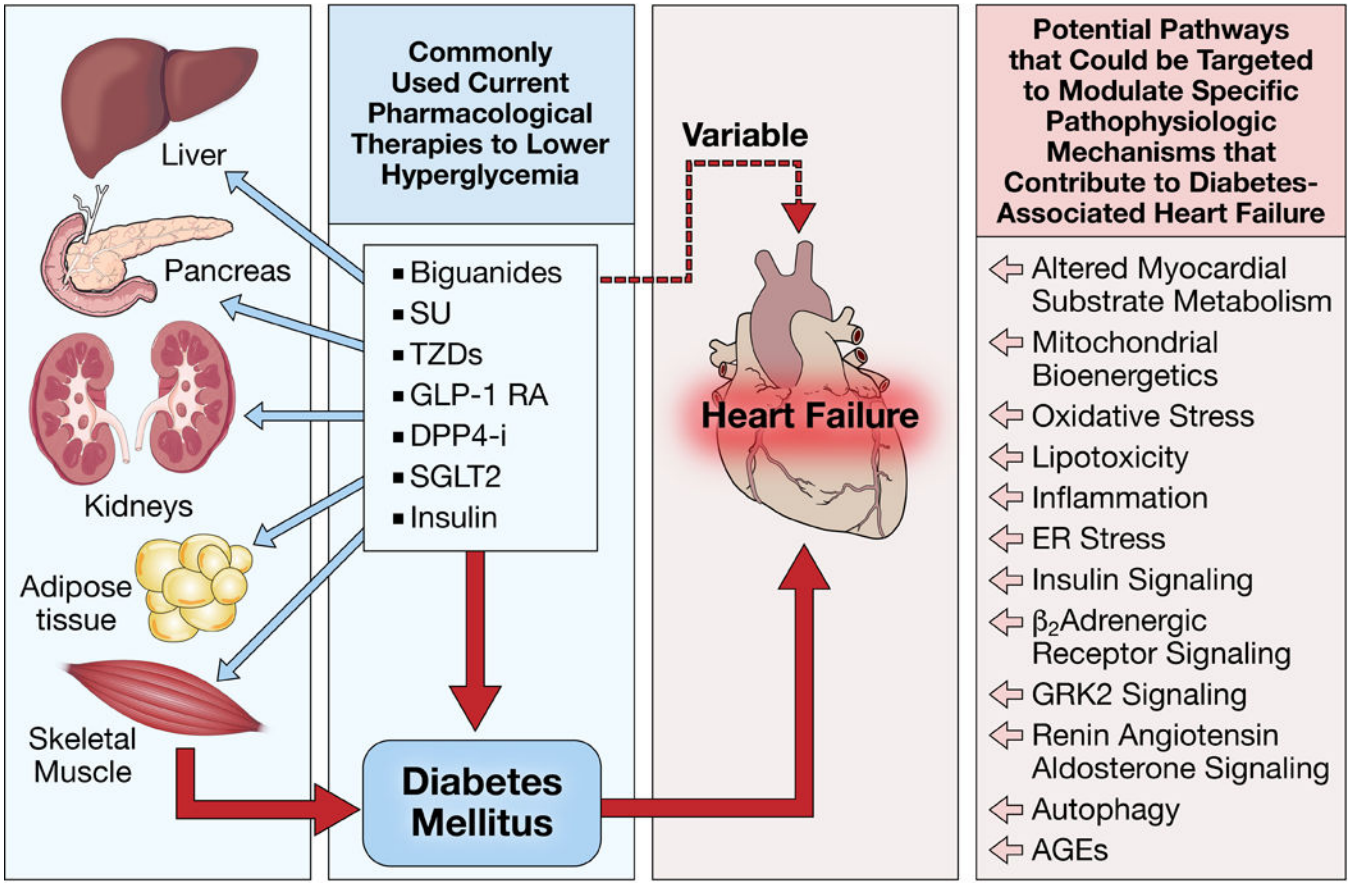

Figure 1. Current antihyperglycemic therapies and potential therapeutic targets that could modulate diabetes associated heart failure.

Diabetes mellitus is a multi-organ disease state characterized by hyperglycemia and dyslipidemia. Current commonly used therapies may achieve normoglycemia, but they have variable effects on heart failure risk and outcomes. Alternative targets, that could be amenable to pharmacological treatment and that may increase the risk of heart failure in diabetes are summarized.

Table 1.

Summary of Effects of Diabetes Treatments on Risk of Heart Failure

DM therapy	Effects of Diabetes Treatments on Risk Heart Failure
Biguanide (Metformin)	• Associated with better short-term and long-term prognosis in patients with HF [30] • Associated with reduced mortality in heart failure patients [30] • Reduces cardiac hypertrophy by AMPK-mediated repression of mTOR and as a consequence protein synthesis [31] • AMPK activation by metformin can stimulate cardiac glucose uptake [35]
Sulfonylureas (SU)	• Originally thought to increase mortality [49] • No definitive CV outcome trial to evaluate CV safety of SUs versus placebo or other diabetic agents • Meta-analysis reports no increased CV risk with SU treatment versus metformin [51] • Retrospective cohort study reported an increased CV risk in patients on SU versus metformin or DPP4 inhibitor [278] • No definitive CV outcome trials examining SUs in heart failure have been conducted
Thiazolidinediones (TZDs)	• Reports on effects of TZDs on CV safety are conflicting. • Beneficial effects were anticipated given improvements in glycemic control, inflammatory biomarkers, BP, TG levels and HDL [279] • PROactive trial showed no reduction in CV outcomes in patients on pioglitazone [280] • A meta-analysis reported an increased risk of MI with rosiglitazone [281] • IRIS trial reported lower risk of stroke and MI in patients on pioglitazone versus placebo [56] • Occurrence of fluid retention and weight gain is a reproducible side-effect of TZD therapy, which precludes its use in NYHA III and IV heart failure [60, 62]
Glucagon like peptide-I (GLP-I) receptor agonist	• Meta-analysis reports no increase risk in HF or hospitalization for HF among type 2 diabetics [85, 282] • A meta-analysis revealed a modest improvement in ejection fraction in heart failure patients [283] • Trial of GLP1 agonist in advanced heart failure revealed a trend towards increased hospitalization in diabetes subgroup [284]
Dipeptidyl peptidase 4 (DPP-4) Inhibitors	• SAVOR-TIMI-53 Trial reported a significant increase in hospitalization for heart failure in patients on saxagliptin versus placebo [81] • EXAMINE and TECOS trials do not reveal increased heart failure risk [83, 285] • Experimental studies in humans and animals show improvements in cardiac function when GLP-1 was activated by DPP-4 inhibitor [75, 76] • DPP-4 knock out mice showed induction of cardio-protective gene signature post MI [78]
Sodium-glucose cotransporters 1 and 2 (SGLT1 and 2) Inhibitors	• SGLT-2 improves CV risk factors (weight reduction, reduction in SBP and improved lipid profile) [96] • EMPA-REG OUTCOME trial reported a reduction in CV mortality and hospitalization from HF using empagliflozin [93] • CANVAS trial reported similar results for canagliflozin [94] • Meta-analysis of CV events in type 2 diabetics on dapagliflozin reported no increased risk for CV events [95]

DM therapy	Effects of Diabetes Treatments on Risk Heart Failure
Insulin	• Some observational trials have suggested a relationship between insulin use and heart failure risk [5, 38] • CVOT with long acting insulin analogs do not demonstrate increased CV event rate or heart failure [98, 100]

Table 2.

Diabetes Therapies and their Mode of Action and Physiological Effects

DM therapy	Mode of action and physiological effect
Biguanide (Metformin)	• Glucose lowering effect through the reduction in hepatic glucose production by suppressing gluconeogenesis [286] • This is achieved by inhibition of complex I of the mitochondrial respiratory chain [26] • This reduces ATP production and results in accumulation of AMP [26] • Changes in AMP/ATP ratio activates AMPK [26, 287] • AMPK activation promotes glucose uptake at skeletal muscle and inhibits glucose production by hepatocytes [288, 289] • Metformin also reduces circulating TGs and VLDL and increases HDL [290]
Sulfonylureas (SU)	• Closes K_{ATP} channels on pancreatic β-cell plasma membrane by binding to SU receptors (SUR) [42] • Membrane depolarization, promotes calcium influx and release of insulin [42] • Extrahepatic actions: SUR2 exists in cardiac and skeletal muscle [45] • Associated with reduced mortality in heart failure patients [30] • Reduces cardiac hypertrophy by AMPK-mediated repression of mTOR and as a consequence
Thiazolidinediones (TZDs)	• Mediated through the activation of the ligand activated transcription factor, PPAR-γ primarily expressed in adipose tissue [291] • Increases skeletal muscle glucose uptake thereby reducing insulin resistance [41] • Reduces hepatic glucose uptake, hepatic glucose production and postprandial gluconeogenesis [53]
Glucagon like peptide-I (GLP-I) receptor agonist	• GLP-I is an incretin hormone whose secretion is increased with an oral glucose load [292] • GLP-I receptor agonists activate GLP-I receptors which stimulates glucose dependent insulin secretion in response to oral glucose load [292] • Stimulates proinsulin gene in the islets to replenish insulin and may promote beta cell proliferation
Dipeptidyl peptidase 4 (DPP-4) Inhibitors	• DPP-4 inhibits GLP-1 [295] • DPP-4 inhibition increases postprandial active incretin (GLP-I) concentrations [295] • Improves glucose dependent insulin secretion [295] • Inhibits secretion of glucagon, suppressing hepatic glucose production and improves insulin sensitivity [295]
Sodium-glucose cotransporters 1 and 2 (SGLT1 and 2) Inhibitors	• SGLT2 causes renal glucose reabsorption across the luminal membrane of the epithelial cells of the proximal convoluted tubule (PCT) [296] • SGLT2 inhibitors block SGLT2 in the proximal nephron and therefore glucose reabsorption causing glucosuria [297]
Insulin	• Insulin administration activates insulin receptors • This results in increased glucose disposal and reduced hepatic glucose production [3]