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Heart Failure and Diabetes:

Clinical significance and epidemiology of this two-way association

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Abstract

People with type 2 diabetes (T2DM) and those with pre-diabetes have an increased risk of heart failure (HF). Longer duration of T2DM correlates with a greater risk of HF, but HF is also seen in patients with recent onset diabetes. Insulin resistance is more likely to be present in patients with HF. The risk of HF persists even in the face of standard of care preventive treatments for atherosclerotic cardiovascular disease (ASCVD). HF is commonly the presenting symptom of cardiovascular disease (CVD) in people with diabetes and HF is the most expensive complication of diabetes due to the high cost of hospitalizations. Recently hospitalization for HF has been included in cardiovascular outcome studies (CVOT) including for medications that are used to treat T2DM which has led to new therapies for all HF patients. In addition, these CVOT trials have shown that many drugs, utilized in the therapy of diabetes, are either neutral or detrimental in the HF patient and should be used with caution in patients with existing HF or those at high risk for HF. Most recently the SGLT-2 receptor blockers have shown efficacy in both HFrEF and HFpEF. The only other oral or injectable diabetes agent shown to improve outcomes in both is metformin.

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Introduction

The prevalence of diabetes globally was 9.3% or 463 million in 2019 with a predicted prevalence of 10.2% or 700 million by 2045.[1,2] A recent study predicted a nearly 700% increase in T2DM in people under age 20 by 2060.[3] Of people affected by diabetes 90-95% meet the criteria for T2DM, and currently studies of HF outcomes are being performed in people with T2DM since of patients hospitalized with HF 44% have T2DM.[4] After the first hospitalization for heart failure in persons not having diabetes, the incidence of new onset diabetes is approximately 2% per year. New onset diabetes in these persons greatly increases their risk of death.[5]

Traditionally, HF was thought to occur as a result of myocardial damage from ischemia but while treatments directed to the prevention of coronary artery disease (CAD), including lipid and blood pressure management and lifestyle modification, have decreased CAD in persons with T2DM these therapies have not decreased the risk for HF.[6,7] In addition, HF is associated with a poor prognosis in people with T2DM. In the Swedish Heart Failure Registry, mortality was increased by 37% in those HF patients who had diabetes.[8] A Medicare study showed that people with T2DM and HF had a mortality of 32.7 per 1000 person-years compared with 3.7 per 1000 person-years in euglycemic HF patients.[9] Therefore, in persons with diabetes, not only therapy for HF but also prevention of the development or progression of HF is essential.

Etiology

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The classification of HF is based on both symptoms and the calculated left ventricular ejection fraction (LVEF). Approximately 40% of people who have HF and T2DM have a reduced ejection fraction, defined as LVEF of 40% or less (HFrEF), while 50% of people with HF and T2DM have preserved LVEF of 50% or greater (HFpEF) and 10% have moderately reduced LVEF of 40 – 50% (HFmrEF).[10]

The pathophysiological reasons for HF in patients with T2DM is not as clear as the epidemiology. The cardiac tetrad is made up of coronary artery disease (CAD), left ventricular hypertrophy (LVH), a specific diabetic cardiomyopathy and fluid overload.[11] Originally, it was thought that persons with HF who did not have significant CAD had microvascular ischemia. This theory was disproved in a study where rapid atrial pacing in this type of patient failed to increase lactate production.[12, 13] A more likely explanation for HF with non-obstructed coronary arteries is that coronary artery endothelial dysfunction leads to repetitive vasoconstriction, reperfusion injury and myocardial dysfunction (Figure 1). Endothelial dysfunction also leads to increased vascular permeability which leads in turn to interstitial edema, fibrosis, myocardial ischemia and ventricular dysfunction.[14, 15] Endothelial dysfunction is also the presumed etiology of microalbuminuria which has a strong association with HF and CAD.[16]

It has long been known that insulin induces an elevated left ventricular ejection fraction (LVEF) in normoglycemic persons but this is attenuated in persons having diabetes. The study documenting this was performed using radionuclide ventriculograms. It is postulated that insulin resistance inherent to persons with T2DM is the cause.[17]

HFpEF is believed to begin with LVH, with only a proportion of LVH being attributed to hypertension. The Scottish Tayside study which used echocardiography to define left

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ventricular size found that independent of hypertension, CAD and the use of ACE inhibitors, LVH was present in 32% of persons with T2DM, irrespective of known CAD and the use of ACE inhibitors.[18] A cross-sectional European echocardiography study included 371 persons with T2DM. Of the T2DM subjects 71% had LVH, 41% had left ventricular filling abnormalities and only 4.2% had systolic dysfunction.[19] Pediatric persons with T2DM have also been found to have a higher ventricular mass largely related to an increased BMI and elevated blood pressure.[20] In the Effects of linagliptin on Left Ventricular Dysfunction in Patients with Type 2 Diabetes and Concentric Left Ventricular Geometry (DYHA) study, subjects with T2DM and HF had an increased LV mass that was unrelated to blood pressure but did correlate with the metabolic syndrome (particularly triglyceride levels and increased body mass index [BMI]).[21] From these studies LVH can be hypothesized to be due to insulin driven cardiomyocyte growth.[22]

A study of 1,089 African American persons showed that LVH was an independent risk factor for cardiovascular mortality. With LVH there was a 2.4 relative risk of death compared to a 1.6 relative risk in patients with T2DM and multivessel coronary disease.[23] As hypertension develops in T2DM subjects there is continuing damage to myocardial contractile proteins which leads to myocardial hypertrophy.[24] Activation of the RAAS and the sympathetic nervous system also worsen LVH.

The metabolic syndrome is associated with increased circulating free fatty acids (FFA) which “overflow” and are deposited in tissues other than adipocytes. Normal cardiac muscle uses varying energy sources (glucose, lactate, ketone bodies and amino acids) for ATP production but in the metabolic syndrome 70% of myocardial ATP production comes from the

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oxidation of free fatty acids which increases the cardiac workload. The switch to FFA metabolism for fuel stimulates the peroxisome proliferator-activated receptor alpha (ppar-alpha) which further reduces glucose utilization and increases FFA uptake in the mitochondria. In addition, FFAs accumulate in the myocardium which leads to structural myocardial damage including increased myocyte apoptosis and fibrosis through the breakdown of FFA to ceramide leading to mitochondrial dysfunction.[24, 25, 26]

The primary defect caused by myocardial lipid accumulation is mitochondrial dysfunction. Decreased free fatty utilization leads to the increased use of glucose which in turn leads to less ATP production and less efficient cardiac function. In addition, insulin resistance decreases the uptake of glucose by the cardiac muscle which also leads to an increased cardiac workload.[27] A biochemical candidate for myocardial mitochondrial dysfunction is overexpression of apolipoprotein O in the cardiac muscle.[28] This lipoprotein is localized in the mitochondria and promotes the uncoupling of oxidative metabolism from the phosphorylation of ADP.[28]

Increased visceral but not subcutaneous fat is linked to both metabolic syndrome and HF. Visceral fat produces inflammatory proteins which increase both myocardial apoptosis and fibrosis. Visceral fat also increases the activation of RAAS increasing the production of aldosterone.[29] A study with db/db mice infused with aldosterone showed vascular remodeling as evidenced by increased myogenic tone. These mice had preserved fractional shortening and EF but a decrease in contractility.[29]

Inflammatory markers are known to be elevated in patients with HF. Blockade of inflammation utilizing the interleukin IL1 beta inhibitor, canakinumab, was studied in 10,061

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persons with a prior myocardial infarction and high C-reactive protein. With canakinumab, there was a dose dependent reduction in hospitalization for heart failure (HHF) and the composite of HHF and HF mortality. However, studies utilizing drugs that suppress tumor necrosis factor alpha activity failed to affect these endpoints.[30.]

Chemokines and cytokines are released in increased amounts in the presence of hyperglycemia and activate the signaling pathway involving nuclear factor kappa beta (NF-kB) via the toll-like receptor (TLR)4. This results in multiple other pro-inflammatory cytokines being released. Additionally, this pathway is also activated by angiotensin 2 and leads to myocardial stiffness.[31]

Lastly, hyperglycemia leads to the formation of advanced glycosylation end products (AGE). When these products bind to the receptor for AGE (RAGE), this also triggers the release of cytokines through the NF-kB pathway. This results in reactive oxygen species (ROS) being produced which causes increased myocardiocyte apoptosis and fibrosis.[32]

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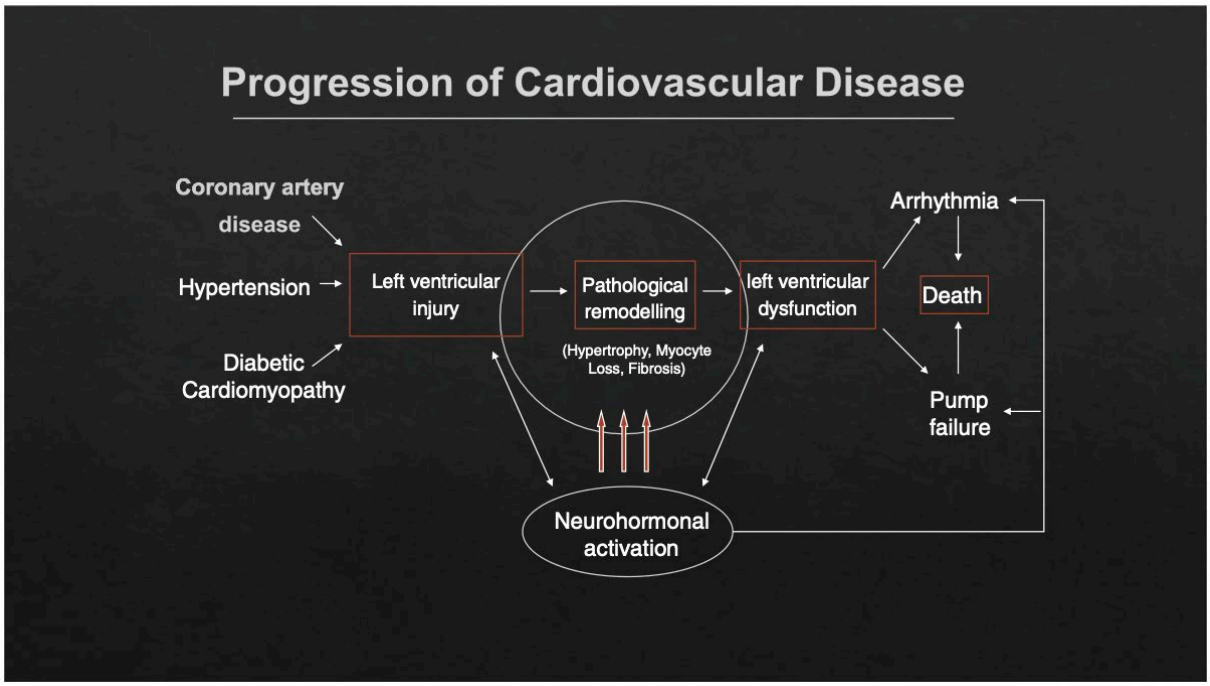


Figure 1: Progression from left ventricular injury, pathological remodeling and left ventricular disfunction, leading to HF.[33]

Diagnosis of HF, Clinical Stages and Treatment Recommendations

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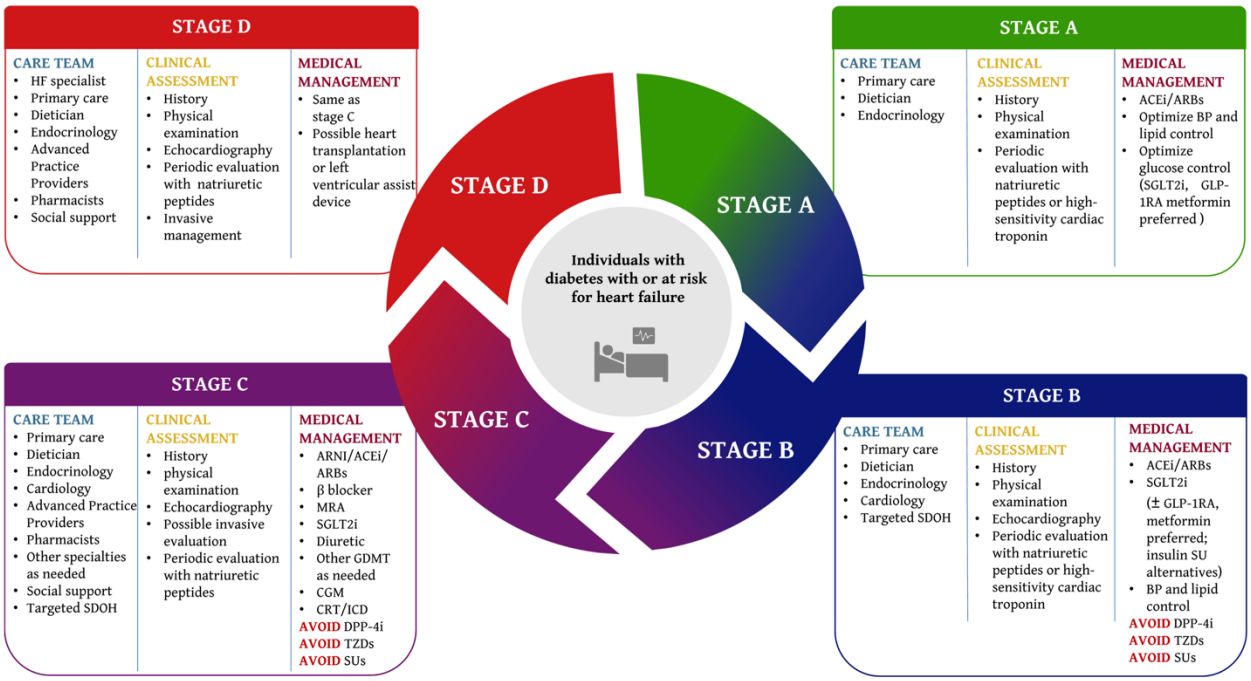


Figure 2: Chart Credit: Consensus Report, Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association, June 1, 2022.[36]

The means by which patients may be classified into the various stages of HF have been defined by the (ACC/AHA/HFSA) (Figure 2).[34,35,36] Use of echocardiography as a screen for early HF has not been shown to be cost effective.[36] Identifying patients at high risk but without symptoms may impede the relentless progression to cardiac failure through early therapeutic intervention (Stage A and Stage B). Such therapies would include RAAS blockade, use of beta blockers (for HFrEF) and SGLT2 inhibitors. Due to the high cost of echocardiography, the more economic use of biomarkers should be utilized to identify the early stages of HF. The commonly utilized biomarkers are BNP (Brain naturetic peptide) NTproBNP, and hsCTN (high-sensitivity cardiac troponin).

Anyone with T2DM and at least one of the following risk factors (obesity, hypertension, hyperlipidemia, diabetic kidney disease, CAD, female sex and high SDOH (social determinants of

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health) score are at high risk for HF (Stage A). These risk factors merit an annual biomarker assay and if elevated a chest Xray and/or an echocardiogram.[36]

Stage B HF is linked to both increased risks of all-cause mortality and CV mortality, even in the absence of symptoms. Stage B indicates the presence of a structural disorder i.e., LV systolic dysfunction, LV diastolic dysfunction, LVH, chamber enlargement, valvular disease, increased filling pressure or elevated biomarkers.[35] Screening of asymptomatic patients is indicated if they have evidence of structural heart disease, abnormal cardiac function or elevated biomarkers (NT pro BNP, BNP or hsCTN).[37] Serial measure of these biomarkers--i.e., levels taken six months apart--may help delineate those at highest risk for decompensation and HF.[38] It must be noted that the presence of obesity can decrease BNP levels, and BNP levels may also be elevated in patients with advanced age, advanced chronic kidney disease, anemia, obstructive sleep apnea, pulmonary hypertension, sepsis and atrial fibrillation. Studies have also indicated intensification of therapy for hypertension, hyperlipidemia and hyperglycemic may be helpful at both stage A and stage B HF.[39,40] A large cohort study to evaluate the hypertension strategies (intensified ACEI or ARB or beta blockade) is now underway.
The DAPA HF study[41] and the EMPEROR Preserved study[42] both indicated decreased hospitalization for HF in persons without T2DM who have HFrER and who utilized a SGLT-2 receptor blocker compared with placebo.

Heart failure stages C and D, are identified by the presence of previous or current symptoms.[36] The diagnosis rests upon the history of CV symptoms, physical findings known to be associated with HF and results of initial testing which should support the clinical diagnosis.

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Persons with HFrEF present with evidence of fluid retention, congestion and reduced cardiac output. Persons with HFpEF most often present with edema and dyspnea and fatigue on exertion.[34,35] In both HFrEF and HFpEF findings on physical examination include jugular venous distention (JVD), peripheral edema, increased weight, displacement to the left of the apical impulse, a third heart sound, decreased peripheral pulses and cool extremities.

The initial laboratory evaluation of HF stages C and D includes complete blood count, basic metabolic profile, HbA1C, urinalysis, lipid profile, liver function tests, iron studies and TSH.[36] These tests can identify and rule out secondary causes of HF, e.g., anemia, hemochromatosis and thyroid disease, as well as testing for exacerbating factors for HF such as CKD. In addition, the presence of microalbuminuria indicates more aggressive endothelial dysfunction and a more aggressive course of HF.

Evaluation of BNP or NT-proBNP is important because while a normal value excludes the diagnosis of decompensated HF, it is predictive for the presence of compensated HF.[43,44,45.46] An electrocardiogram and/or continuous cardiac monitoring will evaluate for arrhythmias, which can exacerbate HF, and show QT interval abnormalities, which could be improved with pacing.[36] Historically, most patients with HF have died from an arrythmia but with the advent of pacing the most common cause of death is an infection (particularly pneumonia).

Preforming an echocardiogram will determine a calculated LVEF and look for structural cardiac abnormalities.[34] Because of the connection between CAD and diabetes, screening for large vessel lesions is advisable. This may be done using noninvasive coronary artery imaging, reserving arteriography for those with high pretest probability of obstructive CAD who may benefit from revascularization.[36]

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Lifestyle Treatments for HF

All patients with HF should be strongly encouraged to avoid smoking and alcohol.[47,48] One of the leading reasons for an exacerbation of HF is fluid overload. Strict limitations on salt and water intake are indicated with overt fluid overload and in patients who are sensitive to fluid intake and respond incompletely to diuretics.[34,48] Patients with T2DM are at risk for hyperkalemia due to RAAS blockade (ACEI, ARB, valsartan/sacubitril, potassium sparing diuretics).[49] Patients should be instructed in appropriate potassium intake including the potassium content of food and dietary supplements and serum potassium levels should be followed regularly. There is a U-shaped curve for predicting mortality associated with potassium levels with both hypokalemia and hyperkalemia being associated with inferior outcomes.[50] NSAID's can increase fluid retention and worsen both HF and renal function and should be religiously avoided in HF patients.[47]

Dietary recommendations with the best study supported data are DASH (Dietary Approach to Stop Hypertension) and the Mediterranean diets.[51] Both diets eliminate trans fats, reduce the intake of saturated fats and promote intake of vegetables, fruits, poultry, fish, low fat dairy products, legumes, grains and nontropical vegetable oils.

Exercise in patients with HF was investigated in the HF-ACTION (Heart failure: A Controlled Trial investigating Outcomes of Exercise Training) study, where 2,331 patients with HF were enrolled of whom 32% had T2DM. They were assigned to aerobic exercise or usual activity and followed for 2.5 years. The patients enrolled in the exercise arm when compared with usual activity group, improved peak oxygen consumption and improved the 6-minute walk

distance test significantly. When exercise was utilized in patients with decreased ventricular compliance, the compliance was shown to be improved with aerobic exercise. Exercise in HF is recommended with tailoring of the individual exercise plans to baseline exercise tolerance.[52]

Involuntary weight loss in patients with HF is a poor prognostic sign and in its severest form (cardiac cachexia) has a very poor prognosis. Weight loss in patients with T2DM has cardiometabolic advantages related to lowering blood pressure and improving glycemic control and potentially may prevent progression from stage A HF. The Look AHEAD trial investigated the possible prevention of adverse cardiovascular outcomes in patients who were overweight or obese. The trial showed that a BMI reduction was associated with a lower risk of HF and loss of visceral fat (as indicated by reduction in waist circumference) correlated with a reduced risk for HFpEF.[53]

Weight loss pharmacotherapy has a history of being associated with worsening of CV outcomes i.e., phentermine/fenfluramine[54], sibutramine[55], and locaserin and this class of drugs should not be used in HF patients.[54,55,56] Phentermine is also not recommended in HF. GLP1 receptor agonists (GLP1-RA) are approved for weight loss in obese patients with comorbidities and offer an option for weight loss assistance which may if utilized at an early stage decrease the risk of HF. The currently approved GLP1-RAs for weight loss are liraglutide (Saxenda) and injectable semaglutide (Wegovey). Orlistat (Alli) is also approved as an over-the-counter weight loss drug through decreasing the absorption of dietary fat. However, its use is limited by diarrhea and malabsorption of fat-soluble vitamins.

Bariatric surgery has been evaluated for the potential to decrease the risk of HF. From the Swedish Obesity Surgery registry, 25,804 persons who had undergone bariatric surgery

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were compared with 13,701 persons who were treated with lifestyle modification who lost 12 kg over four years. The average weight loss with bariatric surgery was 18.8 kg after one year with an additional 22.6 kg average weight loss after 2 years. During a median follow-up of 4.1 years the bariatric surgery group had one half the incidence of HF when compared with the lifestyle modification group. Also, when data from both treatment groups was combined, the decreased risk for HF was proportional to the degree of weight loss.[57]

Glycemic Control: The UKPDS evaluated people with new onset diabetes and showed that for every 1% reduction in HgbA1C there was a 16% decrease in the development of HF but "intensive control" during this study was not associated in a reduction of hospitalizations for HF.[58] Tight glycemic control also failed to reduce HF in the ACCORD, ADVANCE and VADT trials when hypoglycemic events are excluded.[59,60,61] Therefore, it is clear that tight glycemic control does not protect against the development of HF. However chronic hyperglycemia through glycosylation of myocardial proteins, can cause myocardial collagen cross-linking leading to an increase in fibrosis and a higher risk of HF.[62]

Pharmacologic Therapy of HF: In patients with HF, stages A and B, pharmacologic therapy is directed toward risk factor modification and treatment to prevent worsening of myocardial structural abnormalities. Risk factor modification which includes lifestyle changes, weight loss, control of hypertension and dyslipidemia can reduce the risk of worsening HF but achieving these goals outside of clinical trials has not been inconsistent and usually suboptimal.

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However, when these risk factors are reduced, persons with stage B HF have remained stable for many years.

Hypertension control which includes ACEI and ARBs is preferred for the management of hypertension in patients with T2DM particularly if microalbuminuria or CKD are present.[62] The model of HF development implicates overactivation of the RAAS in the cascade leading to cardiac remodeling. ACEI reduce the risk of developing HF in patients with established CVD or T2DM. Most of the effect is through reducing circulating and tissue levels of angiotensin 2 which through vasoconstriction is also associated with overload-induced proliferative signaling. Elevation of bradykinin and prostacyclin levels secondary to ACEI results in increasing levels of nitrous oxide and vasodilatation. Unfortunately, with ACEI and most ARBs the improvement in HF is seen only in patients with HFrEF and not in patients with HFpEF. However, ACEI should still be used as a therapy for hypertension in patients with HFpEF.

In HF, ARB therapy is the alternative to ACEI and is more efficacious. The effect on HF of ARBs was best studied with candesartan in the CHARM trials (Candasartan in Heart Failure: Assessment of Reduction in Mortality) trials. These included CHARM-ADDED[64] where candesartan was added to standard of care including ACEI, CHARM-ALTERNATIVE[65] where candesartan was substituted for patients who were intolerant to ACEI, and CHARM-PRESERVED[66] in patients with HFpEF, 28% of whom had T2DM. There was an overall 15% decrease in first HF hospitalization with 15% and 23% reductions in the CHARM-ADDED and CHARM-ALTERNATIVE groups. In the CHARM-PRESERVED study there was a significant (17.7% p=0.017) decrease in hospital admission with HF. Candasartan may also have a HF reducing

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effect through improving calcium signaling in the myocardium especially in patients with diabetic cardiomyopathy.

Dual inhibition with neprilysin and ARB in HF patients has been shown to decrease both CV and total mortality when compared to the ACEI enalapril in both diabetic and non-diabetic subjects with HFrEF. The dual inhibitor, sacubitril, was tested in the PARADIGM-HF trial, where a post-hoc analysis also revealed positive effects on insulin sensitivity and improved glycemic control compared to the ACEI enalapril in patients with T2DM. Sacubitril's mode of action is to increase the availability of natriuretic peptides and assists bradykinin in achieving vasodilation and naturesis in addition to lowering blood pressure.[67,68] Like ACEIs and ARBs, sacubitril is associated with angioedema and is contraindicated in patients who have had ACEI induced angioedema. Because of superiority over ACEI and ARB alone, sacubitril/valsartan is now first line in treatment of symptomatic HFrEF.

Activation of the sympathetic nervous system (SRS) accelerates the decline in function of the failing heart. The benefit of beta blockade in HF is primarily seen in patients with HFrEF[69] and may be contraindicated in HFpEF[70] where it has been shown to increase the risk of HF hospitalization. The effect of beta blockade on diabetic control and the risk of hypoglycemic events has probably been overstated. However, the effect of first- and second-generation beta blockade on heart failure is not as robust in persons with T2DM as it is when diabetes is absent.[71,72] Selective vasodilating beta blockers (third generation) block not only beta1, beta2, but also beta3 and alpha receptors to increase blockade of the SNS. These third-generation vasodilating beta blockers are nebivolol and carvedilol. Carvedilol has been shown to improve

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glycemic control, improve LVEF and decrease oxidative stress in the heart. The EF may drop slightly when therapy is initiated but improves progressively thereafter.[70]

Mineralocorticoid receptor (MRA) overactivation is intrinsically linked to heart failure progression. The addition of aldosterone blockade using spironolactone and eplerenone has been shown to improve HF outcomes in HFrEF (RALES[73] and EMPHASIS-HF[74]). The TOPCAT study in patients with HFpEF did not confirm this benefit in HFpEF.[75] Finerenone, which is a nonsteroidal MRA receptor antagonist has been shown to reduce the risk of HF in patients with T2DM, CKD and reduced ejection fraction.[76] It is recommended that patients with HFrEF and perhaps with HFpEF have an aldosterone antagonist added to RAAS blockade. However, close and careful monitoring of potassium is essential.

In African American persons with HF, hydralazine combined with isosorbide dinitrate has been shown to be efficacious in persons with HFrEF who were intolerant to ACEI and ARB therapy. The results of this study, A-HeFT (African American Heart Failure Trial) resulted in this combination therapy being added as an AHA class 1 recommendation for African American patients receiving optimal HF medical therapy.[77]

Diabetic Drug Therapy that Worsens Heart Failure: Insulin resistance and high endogenous levels of insulin correlate with the development of HF. Sodium retention due to exogenous insulin was first documented 1975. In healthy volunteers, a 50% reduction in sodium excretion through reabsorption in the distal tubule was seen with insulin without increasing blood pressure. Retrospective and observational studies have shown a worse prognosis in persons with HF treated with insulin.[78] This may vary with the patient populations and individual

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characteristics, since prospective trials of long-acting insulins, such as glargine (ORIGIN trial[79]) and degludec (DEVOTE trial[80]), have not shown an increase in HF. Metabolic defects such as glucolipotoxicity and the associated sodium retention may play a role in exacerbations of HF with insulin.

Sulfonylureas are insulin secretagogues which bind to the sulfonylurea receptor (SUR) on the beta islet cells. This closes the ATP dependent potassium channels and releases insulin in a glucose independent fashion.[81] Acting as an insulin mimetic, the drugs stimulate glycogenesis and lipogenesis and are associated with hypoglycemia and weight gain.[82] A second sulfonylurea receptor (SUR2) is present on skeletal and cardiac muscle and with stimulation of this receptor the cardiac output and cardiac workload are increased.[83,84] Studies regarding HF have been conflicting, with an increased frequency of HF usually being seen with sulfonylureas when compared to metformin. However, these outcomes could be due to metformin's cardioprotective actions rather than a detrimental effect of the sulfonylurea.[85] Data from a large retrospective cohort study using data from the National Veterans Health Administration, Medicare, Medicaid and the National Death Index included 24,685 patients on metformin and 24,805 patients on sulfonylureas. There were significantly more hospitalizations for HF with sulfonylurea utilization than with metformin.[86] Due to these findings and the risk of hypoglycemia and weight gain, sulfonylureas are not recommended for use in patients with HF, stages B, C and D.

Dipeptidyl Peptidase 4 Inhibitors (DPP-4I) produce glucose reduction by inhibiting the breakdown of endogenous GLP1. There are five available drugs in the class: sitagliptin, saxagliptin, linagliptin, alogliptin, and vildagliptin. All have been subjected to cardiovascular

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trials which included HF as an outcome. Saxagliptin did not increased MACE events but was associated with increased risk for hospitalizations for HF without an increase in CV death. In the SAVOR-TIMI 53 trial[87] (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus- Thrombolysis in Myocardial Infarction 53) there was a 27% increase in the risk of hospitalization for HF with saxagliptin and those with a preexisting risk or a high risk for HF were most likely to be hospitalized.[88] In the EXAMINE study (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome), the use of alogliptin also increased the risk of hospitalization for HF without increasing MACE.[89,90] A third prospective study was the VIVIDD trial of vildagliptin (Effects of Vildagliptin on Ventricular Function in Patients with Type 2 Diabetes Mellitus and Heart Failure). This study showed that while vildagliptin had no effect on LVEF, it did increase left ventricular filling pressures and there was a non-statistically significant increase in HF of 19%.[91] A meta-analysis of these three studies and several smaller studies of DPP4 inhibitors revealed an overall statistically significantly increased risk for HF of 16%.[92] A further meta-analysis showed an increase in HF of 13 - 19% which was also statistically significant even when the SAVOR-TIMI data was excluded.[93,94,95]

While the prospective TECOS study of sitagliptin did not show an increased risk of HF, this could have been due to the protective effect from concomitant use of metformin since 79.2% of subjects in this trial were utilizing metformin.[96] In contrast to TECOS several observational retrospective studies of sitagliptin have shown an increase in heart failure ranging from 21 - 84%.[97,98,99] The Linagliptin in the Carmelina trials did not show an increased risk for hospitalization for HF, so this may not be a class effect.[100,101] However, if the effect is

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prevalent in the class, what is the pathological basis for the increased frequency of HF? When GLP1 levels are increased by DPP4 inhibitors, they may also increase cyclic AMP in cardiomyocytes.[102] This may lead to calcium overload in the myocardium which may adversely affect cardiac function. A more likely explanation for HF with DPP4 inhibitors is that DPP4 inhibitors may also increase sympathetic nervous system activity which increases ventricular hypertrophy and increases the risk of arrhythmias.[103,104] However, the most likely explanation is that DPP4 inhibition increase stromal cell-derived factor-1 (SDF-1). Patients with HF already have increased levels of SDF-1 and its receptor. These elevations of SDF-1 in the myocardium increases the migration of mesangial cells which may then be transformed into fibroblasts leading to myocardial fibrosis.[105,106,107] DPP-4 inhibitor drugs are therefore not recommended in patients with HF, classes B, C and D.

Thiazolidinediones (TZDs) have a paradoxical effect on the heart. They improve ventricular diastolic function but also cause reabsorption of sodium in the distal nephron, causing volume expansion which may worsen HF. The effect is due to activation of the collecting duct epithelium's sodium channel (ENaC), and more proximally, sodium transporters such as NHE3 may play a role.[108,109] Because of the distal sodium retention, traditional diuretics (thiazide and loop diuretics) have no effect on the subsequent volume expansion,[110] although aldosterone receptor blockers and SGLT2 inhibitors may be effective.[111] Studies of pioglitazone appear to show improvement in ventricular diastolic function by decreasing inflammation factors and reducing triglyceride accumulation in the cardiomyocytes.[112] TZDs may be helpful in patients with T2DM and HFpEF (stage A) but at this time they cannot be recommended in HF, stages B, C and D.

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Diabetic Drug Therapy with a Neutral Effect on HF: Alpha-glucosidase inhibitors (AGIs) slow the breakdown of complex carbohydrates to glucose. They are frequently used in Asian countries where rice is a large part of the diet and through slowing the absorption of rice carbohydrates significantly improve glycemia excursions. A meta-analysis of seven placebo-controlled trials showed a reduction in MI of 64%, without a reduction in HF with AGIs.[113] Animal studies had suggested this drug class might have a favorable effect on ventricular function but that has not been confirmed in human subjects.

GLP-1 receptor agonists (GLP-1RA) produce a robust reduction in HgbA1C due to glucose dependent stimulation of insulin secretion and suppression of glucagon secretion. They also slow gastric emptying, which promotes less caloric intake and weight loss and stimulate the proinsulin gene which protects beta islet cell mass.[114] They also reduce RAAS activity, reduce oxidative stress, decrease blood pressure, reduce triglycerides and LDL cholesterol, and improve endothelial function. However, they have the potential for a negative effect on the myocardium due to increased sympathetic nervous system activity and sinoatrial node stimulation which results in an increase in heart rate. Increased heart rate is clearly deleterious in patients with HFrEF, but a higher heart rate induced by pacemaker placement improved quality of life and functional capacity in patients with HFpEF.[115] In the CVOTs of liraglutide, semaglutide, exenatide, lixisenatide and dulaglutide, no reduction in HF was seen when compared to placebo in patients with T2DM and HFrEF. This is despite a reduction in MACE with liraglutide, semaglutide and dulaglutide. Because of the effect of GLP-1RAs on multiple comorbidities, they should be used in patients with HF without any anticipation of

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improvement or deterioration in HFrEF.[116] Further evaluation of GLP1RA in treatment of HFpEF is indicated.

Diabetic Drug Therapy That May Prevent or Ameliorate HF: Metformin is the most commonly used glycemic agent in the world and is first line therapy in T2DM due to its low cost and superior safety profile. The data on metformin's effect on CV outcomes began with the UKPDS where patients with T2DM on metformin had a 36% decrease in all-cause mortality and a 39% lower risk of MI when compared to patients on sulfonylureas and insulin. There was not a decrease in heart failure noted on this study.[117] After approval metformin was contraindicated in HF because of a perceived increased risk for lactic acidosis, but newer data has shown that patients utilizing metformin do have a survival benefit in HF when compared to patients on other glucose lowering regimens. Use of metformin is still contraindicated in patients with unstable or acute heart failure.[118]

AMP dependent kinase (AMPK) is present in nucleated human cells where it plays a key role in energy homeostasis. Dysfunction or loss of this enzyme is associated with metabolic disorders including T2DM. Based on animal and cell culture experiments, metformin probably activates AMPK by inhibiting the actions of mitochondrial respiratory chain complex 1 and by increasing the phosphorylated versus un phosphorylated AMPK ratio. Activation of AMPK signals a low energy state causing a switch from high energy ATP utilization for anabolic pathways to ATP generating pathways to stabilize energy homeostasis. This inhibits hepatic gluconeogenesis the production of triglycerides and proteins and stimulates glucose transport, glycolysis and the clearance of free fatty acids. Insulin resistance in the heart is improved by

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enhanced translocation of the glut 4 transporter and increased glucose uptake by cardiomyocytes.[118]

Metformin activates AMPK which inhibits mTOR and decreases myocardial protein synthesis and myocardial growth. AMPK may also increase glucose utilization by cardiac muscle thus decreasing the cardiac workload.[119] In the process of inhibiting hepatic gluconeogenesis, metformin reduces the risk factors of high triglycerides and LDL cholesterol and improves insulin sensitivity. When associated with weight loss, metformin decreases the production and activation of inflammatory factors and improves insulin sensitivity. It improves salt induced hypertension in nondiabetic patients. Atherogenesis is likely affected by the decrease in triglycerides and LDL cholesterol.[118]

Oxidative stress causes significant damage to failing cardiomyocytes. Metformin also ameliorates this by increasing the production of NO. Oxidative stress is also linked to activating stress in the endoplasmic reticulum which promotes cellular autophagy and apoptosis. NO also improves cardiac perfusion.[118]

Metformin is recommended as first line therapy in most patients being used with caution and at half dose in patients with eGFR of less than 40 and avoided at an eGFR of 30. It is at a minimum safe to use in the early stages of HF.[120,121,122,123]

SGLT2 is an enzyme that causes glucose and sodium reabsorption in the proximal tubules of the kidney. Inhibition of SGLT2 promotes glucosuria, naturesis and weight loss. This class of drugs produces a significant reduction in glycemia excursion and HbA1C. The first CVOT of SGLT2 inhibitors was the Empa-Reg study[42] where empagliflozin showed a 35% reduction in hospitalization for heart failure in addition to a reduction in 3-point MACE.[124] Canagliflozin in

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the CANVAS study showed a 33% reduction in hospitalization for heart failure and a reduction in 3-point MACE.[125] DECLARE-TIMI 58 with dapagliflozin included over 17,000 patients, including 10,000 without any evidence of cardiac disease. It did not meet superiority on 3-point MACE, but it did show reduction in CV mortality and hospitalization for HF.[126] The DAPA-HF quickly followed, showing a reduction in hospitalization for HF in patients with HFrEF with and without T2DM.[41] As a result, dapagliflozin received FDA approval for use in patients with HFrEF.[127] In patients with HFpEF, in the EMPEROR-Preserved with empagliflozin[124] and the PRESERVED-HF study with dapagliflozin,[127] both drugs lowered the risk of cardiovascular death and HF hospitalizations.

Subsequent to publishing the CVOT data, empagliflozin, dapagliflozin and canagliflozin published studies on renal outcomes which proved that SGLT2I drugs are protective against the progression of diabetic CKD and in the case of dapagliflozin in persons with CKD with or without T2DM.[128,129,130] This protection occurred in persons with proteinuria at all stages of CKD and was independent of glycemic control. A decelerated decline in renal function should improve the outcomes in HF patients utilizing SGLT2 inhibitors.

Multiple mechanisms are clearly involved in achieving both cardiac and renal protection with SGLT2 inhibitors. Inhibition of the sodium-glucose co-transporter promotes natriuresis and reduces plasma volume and decreases cardiac preload.[131] This results in a reduction in blood pressure and increased compliance of the vasculature, which does not entirely explain stabilization or improvement in HF with SGLT2I since this is not seen with thiazide or loop diuretics.[131] SGLT2 inhibitors but not thiazide or loop diuretics, decrease sodium hydrogen exchange in cardiac muscle. Sodium hydrogen exchange is increased in the cardiac muscle of

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patients with HF and is associated with increased cardiac injury, hypertrophy, remodeling, fibrosis and increasing systolic dysfunction. Inhibition of sodium hydrogen exchange is therefore a likely primary mechanism in the reduction of heart failure in patients utilizing SGLT2 inhibitors.[132]

SGLT2 inhibition also may also improve left ventricular function by a metabolic shift to ketogenic metabolism. The metabolism of ketones produces more ATP than glucose or free fatty acids and decrease the workload of both the heart and kidney.[133]

Conclusion: HF is very common in people with T2DM with a slight majority having HFrEF. 40% have HFpEF, which is more difficult to treat and fails to respond to many treatments which are effective in HFrEF. Treatments which improve HF in patients with HFrEF are less effective or even ineffective in treating HFpEF. The best treatment for both HFrEF and HFpEF may be identifying patients at risk for HF at its earliest stages before irreversible myocardial changes occur. Because hospitalization for HF is the most expensive aspect of diabetes care, early efficacious prophylactic treatments of patients will also control healthcare costs especially as the number of patients with T2DM patients increase. Utilization of evidence-based treatments for HFrEF and HFpEF may prolong lives, but management is a team effort between primary care providers and specialists.

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