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Diabetes and heart failure: Basic, translational, and clinical research

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Diabetes and heart failure: Basic, translational, and clinical research

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Editorial: Diabetes and heart failure: basic, translational, and clinical research

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diabetes, heart failure, sacubitril/valsartan, HFrEF–heart failure with reduced ejection fraction, HFpEF–heart failure with preserved ejection fraction, SGLT2 (sodium-glucose cotransporter 2) inhibitor, multiomics, translational reseach

Editorial on the Research Topic
Diabetes and heart failure: basic, translational, and clinical research

Diabetes mellitus (DM) and heart failure (HF) are complex and systemic diseases that often coexist and share pathophysiological pathways. DM and HF are clinically and pathophysiologically interdependent, such that worsening of one condition is frequently accompanied by worsening of the other. Patients with type 2 DM (T2DM) show a higher risk for developing HF while hospitalization as well as prognosis are worse for patients with DM and HF compared to non-diabetic HF patients. Therefore, there is an increasing unmet need to identify new molecular mechanisms involved in the development and progression of DM complications including heart disease and find specific clinical features in diabetic patients with HF.

Sacubitril/Valsartan (Sac/Val), an angiotensin receptor-neprilysin inhibitor, has been previously demonstrated to improve cardiac function and outcomes in patients with HF with reduced HF (HFrFE) and is currently under investigation to identify further applications in patients with heart disease. Armentaro et al. (*Long Term Metabolic Effects of Sacubitril/Valsartan in Non-Diabetic and Diabetic Patients With Heart Failure Reduced Ejection Fraction: A Real Life Study*) showed an improvement in metabolic profile in patients with HFrEF treated with Sacubitril/Valsartan (Sac/Val). Thirty month-long treatment with Sac/Val ameliorated glycometabolic parameters such as HbA1c, fasting glucose/insulin, IGF-1, the HOMA index, and LDL-cholesterol. In line with previously published data, the authors also found that long-term Sac/Val treatment improved renal function, NTpro-BNP levels, and echocardiographic parameters in HF patients. Moreover, Sac/Val significantly reduced the use of oral antidiabetic drugs and insulin in diabetic patients with HF. Li et al. (*Assessment of ultra-early administration of sacubitril valsartan to improve cardiac remodeling in patients with acute myocardial infarction following primary PCI: rational and design of a prospective, multicenter, randomized controlled trial*) discussed the hypothesis, study objective, inclusion criteria, design and outcome definition of an ongoing, prospective, multicenter, randomized controlled clinical trial aimed to assess the effects of an ultra-early administration of Sac/Val on cardiac remodeling in patients with acute myocardial infarction following primary percutaneous coronary intervention.

Heart failure with preserved ejection fraction (HFpEF) has a high prevalence in the population and accounts at least for half of all patients with HF. Dhore-patil et al. (*Diabetes*

mellitus and heart failure with preserved ejection fraction: role of obesity) analyzed the characteristics of the metabolic phenotype (DM-obesity) of HFpEF that is the most common in the clinical practice, with poor clinical outcomes and an urgent need for effective treatments. The authors examined how obesity and diabetes induce the development and progression of left ventricular remodeling. Pathophysiological mechanisms involved in the HFpEF phenotype include low-grade systemic inflammation, microvascular dysfunction and increase in visceral as well as pericardial/epicardial adipose tissue. In this review article, recent therapeutic advances were discussed, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), Sodium-glucose co-transporter 2 inhibitors (SGLT2i) and metabolic surgery. Ali et al. (*Temporal trends in outcomes of ST-elevation myocardial infarction patients with heart failure and diabetes*) investigated the temporal trends in demographics and outcomes in diabetic heart failure patients admitted with STEMI utilizing data from the national inpatient sample (NIS) database between 2005–2017. The mean age of patients with HFrEF and the rate of hospitalization for STEMI in this cohort decreased over time although the prevalence of traditional risk factors increased. In contrast, in patients with HFpEF hospitalization rates for STEMI steadily increased. Mortality rates remained stable in both HF entities with lower rates in patients with HFpEF compared to HFrEF. These findings in temporal trends are consistent with other studies and underpin that HF is a major public health problem with a significant financial and societal burden.

Mekhaimar et al. (*Diabetes outcomes in heart failure patients with hypertrophic cardiomyopathy*) investigated the prevalence and outcomes of diabetes in patients with hypertrophic cardiomyopathy. Data derived from the national inpatient sample (NIS) database between 2005–2015 a large all-payer database in the US. Almost one-third of patients with HCM had diabetes with an increasing prevalence over time, which corresponds to a general increase of diabetes and other traditional cardiovascular risk factors in the general population. Diabetes was associated with a lower risk of in-hospital mortality but an increased length of stay and total charges/stay. There are conflicting data with regards to a lower in-hospital mortality with diabetes. This finding cannot be easily explained. Further trial evidence is warranted to find conclusive answers to this question. Kreiner et al. (*The potential of glucagon-like peptide-1 receptor agonists in heart failure*) analyzed the beneficial effects of GLP-1 RAs in patients with DM and HF. In the last two decades, GLP-1 RAs have been shown to improve glycemic control in T2DM and to decrease body weight in subjects with overweight/obesity. Interestingly, GLP-1 RAs have also been recommended for patients with T2DM and cardiovascular diseases (CVDs) to improve CV outcomes. Moreover, this review article discussed the use of GLP-1 RA treatment for people with T2DM and HF particularly when SGLT2i are not well tolerated. Finally, the authors suggested that the cardioprotective effect of GLP-1 RAs may be particularly pronounced in patients with HFpEF and metabolic comorbidities such as obesity. Currently ongoing clinical trials are testing this hypothesis.

Tayanloo-Beik et al. (*Diabetes and heart failure: multi-omics approaches)* reviewed recent approaches used to detect specific molecular and cellular pathways involved in both HF and T2DM using a multiomics approach. They concentrated on oxidative stress with a particular focus on diminished myocardial perfusion linked to endothelial dysfunction, dysregulated glucose levels due to insulin resistance and reactive oxygen species (ROS) mediation. The main molecular targets discussed were protein phosphatase, sarcoplasmic/endoplasmic reticulum Ca2+ ATPase 2a and phosphorylated SERCA2a. This paper is indicative of the impact that the new omics technologies will bring to the table in the comprehension of the molecular pathways implicated in HF and T2DM.

Ge et al. (*The Serum Soluble Scavenger with 5 Domains Levels: A Novel Biomarker for Individuals with Heart Failure*) studied correlations between seric levels of the Soluble Scavenger with 5 Domains (SSC5D) and HF in a cohort of 276 HF patients or normal controls. Additionally, Ssc5d mRNA levels were quantified in murine heart tissue after cardiovascular disorder occurred. They found that SSC5D levels were significantly increased in pathological murine hearts compared to control. Accordingly, seric SSC5D levels were elevated in the HF group compared with healthy patients. Finally, they found that serum SSC5D levels were positively correlated with N-terminal pro-B-type natriuretic peptide while they were inversely correlated with left ventricular ejection fraction. Thus, this interesting study provides evidence indicating that SSC5D seric levels may be a novel biomarker for patients with HF.

Hebbard et al. (*Diabetes, heart failure, and COVID-19: an update*) endeavored to review the interactions between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, HF and T2DM. It is widely known that, when infected with SARS-CoV-2, there is a more severe prognoses for patients with existing cardiovascular disease than healthy counterparts. What is less known is that newly published studies hint at a correlation between SARS-CoV-2 infection and an enhanced incidence of new-onset HF and T2DM, regardless of disease severity. The authors interestingly point out new potential mechanisms that may explain how SARS-CoV-2 infection would trigger HF and T2DM in heretofore unaffected patients such as systemic inflammation, cytokine storm, hyperglycemia *etc.* This interesting review points out clues to use innovative ways to optimize old treatments to develop new preventative measures for patient care.

We hope that the manuscripts published within our Research Topic will contribute to a more accurate risk stratification for diabetic patients with HF and to identify appropriate and timely treatments for subjects with DM and heart disease.

Author contributions

LM, MW, and CL have written and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Diabetes and Heart Failure: Multi-Omics Approaches

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Diabetes and heart failure, as important global issues, cause substantial expenses to countries and medical systems because of the morbidity and mortality rates. Most people with diabetes suffer from type 2 diabetes, which has an amplifying effect on the prevalence and severity of many health problems such as stroke, neuropathy, retinopathy, kidney injuries, and cardiovascular disease. Type 2 diabetes is one of the cornerstones of heart failure, another health epidemic, with 44% prevalence. Therefore, finding and targeting specific molecular and cellular pathways involved in the pathophysiology of each disease, either in diagnosis or treatment, will be beneficial. For diabetic cardiomyopathy, there are several mechanisms through which clinical heart failure is developed; oxidative stress with mediation of reactive oxygen species (ROS), reduced myocardial perfusion due to endothelial dysfunction, autonomic dysfunction, and metabolic changes, such as impaired glucose levels caused by insulin resistance, are the four main mechanisms. In the field of oxidative stress, advanced glycation end products (AGEs), protein kinase C (PKC), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) are the key mediators that new omics-driven methods can target. Besides, diabetes can affect myocardial function by impairing calcium (Ca) homeostasis, the mechanism in which reduced protein phosphatase 1 (PP1), sarcoplasmic/endoplasmic reticulum Ca2+ ATPase 2a (SERCA2a), and phosphorylated SERCA2a expressions are the main effectors. This article reviewed the recent omics-driven discoveries in the diagnosis and treatment of type 2 diabetes and heart failure with focus on the common molecular mechanisms.

Keywords: diabetes mellitus type 2, heart failure, diabetic cardiomyopathies, metabolomics, oxidative stress

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INTRODUCTION

Diabetes mellitus is defined as a major metabolic disorder that is associated with considerable and long-term microvascular and macrovascular complications (Adeghate and Singh, 2014). Herein, heart failure (HF) has been identified in patients with diabetes since 1876 (Lee et al., 2019). Indeed, cardiovascular (CV) disease is a primary cause of disability and death due to diabetes

(Boudina and Abel, 2010). "Diabetic cardiomyopathy" (DC) can be manifested by diastolic dysfunction, cardiomyocyte hypertrophy, and apoptosis along with myocardial fibrosis (Huynh et al., 2014). Moreover, DC contributes to the higher incidence of HF in patients with diabetes (Aneja et al., 2008). Among different underlying mechanisms that are common between type 2 diabetes mellitus (T2DM) and HF, oxidative stress is a key contributor. Coenzyme Q (CoQ)10 supplementation and gene therapy, as well as targeting cardiac phosphoinositide-3-kinase (PI3K) (p110α) signaling, protein kinase-C (PKC) signaling, and dysregulated microRNAs (miRNAs), are newer promising therapeutic approaches (Huynh et al., 2014). On the other hand, the development of high-throughput techniques utilizing multi-omics data have provided a holistic study on complex biological processes, especially in disease subtyping and providing biomarkers (Subramanian et al., 2020). Although there are some challenges in utilizing multi-omics technologies, they are currently being used to uncover underlying biological pathways of disorder and molecular basis of complex phenotypes at different dimensions (Chakraborty et al., 2018), which are applied in different disorders such as cancer (Chaudhary et al., 2018; Yoo et al., 2018), CV diseases (V et al., 2015; Leon-Mimila et al., 2019), and diabetes. In this review, we first stated different aspects of T2DM as a chronic lifelong disease through its clinical features, consequences, epidemiology, and prognosis, especially concomitant with HF and CV events. Then, we explained the coexistence of T2DM and HF, focusing on their common underlying pathways. Lastly, we introduced omics studies as promising therapeutic technologies particularly targeting common mechanisms of these two major disorders.

T2DM: A CHRONIC LIFELONG DISEASE

Diabetes mellitus is an old human disorder that was first mentioned about 3,000 years ago. T2DM, the most common type of DM, was first reported in 1988 as part of metabolic syndrome (Olokoba et al., 2012). It is an important cause of mortality because of its associated CV complications and several other pathogenetic disturbances (Blaslov et al., 2018). Age, race, and ethnicity as well as physical activity, diet, and smoking can be linked to T2DM etiologies (Sami et al., 2017). However, the underlying direct pathological mechanism of T2DM is complex and has many different elements (Leahy, 2005). More knowledge of the pathophysiological mechanisms of T2DM can lead to better prediction, earlier diagnosis, and improved therapeutic approaches (Ma et al., 2018). Some other features of T2DM regarding its clinical characteristics, consequences, prognosis, and epidemiological aspects are explained in the next subsections.

Clinical Features and Consequences

First, there are some metabolic, genetic, and environmental risk factors that predispose individuals to T2DM. Overweight, CV events, hypertension, and dyslipidemia are some of the important risk factors for T2DM (Fletcher et al., 2002; Vijan, 2010). T2DM diagnosis can be performed by the measurement of venous plasma glucose and hemoglobin A1c (HbA1c), which are standardized and quality-assured laboratory approaches (Kerner and Brückel, 2014). As stated, most patients with diabetes have the T2DM form of the disease, which can have an asymptomatic and latent period of sub-clinical stages (DeFronzo et al., 2015). However, T2DM at very high stages of hyperglycemia can be accompanied by some symptoms such as polyuria, polydipsia, and polyphagia, which are classic symptoms of the disease (Ramachandran, 2014). Diabetes has a mentionable association with microvascular and macrovascular complications that can lead to organ damage (Cade, 2008; Chatterjee et al., 2017). It should be stated that cardiovascular autonomic neuropathy (CAN) has a major role in diabetic autonomic neuropathy complications (Vinik et al., 2003). Also, endothelium dysfunction due to DM can lead to other CV events, which predominantly affect coronary, peripheral, and carotid arteries (Stolar and Chilton, 2003). It is mentioned that intensive glycemic control has lesser effect on macrovascular complications compared with microvascular sequelae (Chatterjee et al., 2017).

Epidemiology and Prognosis

Diabetes mellitus as an epidemic of the century along with its accompanying complications has a major global health impact on economies. The number of patients with DM has quadrupled globally over the last three decades, making it a major concern worldwide. This estimation is predicted to rise even to 642 million by 2040 (Zheng et al., 2018). The significantly high burden of the disease can be seen in some specific regions of the world (island states of the Pacific, Western Europe) (Khan et al., 2020). CV complications are mentioned to be the major reasons for morbidity and mortality due to DM (Zheng et al., 2018). It has been estimated that 1% higher glycosylation of Hb is associated with about 8% higher risk for HF (Cas et al., 2015). HF can be mentioned as an independent risk factor for developing T2DM (Bell and Goncalves, 2019), and patients with diabetes are also at higher risk for HF development following myocardial infarction (Stone et al., 1989). Thus, the increased prevalence of HF can be seen in patients with diabetes along with worse prognosis (Lehrke and Marx, 2017; Norhammar et al., 2017; Zareini et al., 2018; Bell and Goncalves, 2019). Diabetes can also lead to worse outcomes of acute coronary syndromes in the early and late stages of the disease (Beckman et al., 2002). Moreover, other mentioned macrovascular and microvascular complications of DM can also result in death and reduce the quality of life through

Abbreviations: ACE, angiotensin converting enzyme; AGEs, advanced glycation end products; AIF, apoptosis-inducing factor; ATP, adenosine triphosphate; BPIFB4, bactericidal/permeability-increasing fold-containing family B member 4 (BPIFB4); CAN, cardiac autonomic neuropathy; CK, creatine kinase; CoQ, coenzyme Q; CV, cardiovascular; DM, diabetes mellitus; ER, endoplasmic reticulum; FA, fatty acids; GWASs, genome-wide association studies; HbA1c, hemoglobin A1c; HF, heart failure; IGF-1, insulin-like growth factor 1; IL, interleukin; LAV, longevity-associated variant; MiRNAs, microRNAs; MS, mass spectrometry; NMR, nuclear magnetic resonance; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOX, nicotinamide adenine dinucleotide phosphate- oxidases; *O*-GlcNAc, O-linked *N*-acetylglucosamine; PARP-1, poly [ADP-ribose] polymerase 1; PI3K, phosphoinositide 3-kinase; PKA, protein kinase a; PKC, protein kinase c; PP1, protein phosphatase 1; RAAS, rennin-angiotensin-aldosterone system; RNS, reactive nitrogen species; ROS, reactive oxygen species; SR, sacoplasmic reticulum; T2DM, type 2 DM; TNF tumor necrosis factor.

blindness, kidney failure, peripheral neuropathy, and several other consequences (Bailes, 2002; Cole and Florez, 2020). T2DM prevalence and incidence are still increasing, to which serious attention should be paid because of its severe consequences (Khan et al., 2020).

COEXISTENCE OF T2DM AND HF

Heart failure is a life-threatening clinical syndrome in which the heart is unable to provide blood flow sufficiently and could not meet metabolic requirements (Kemp and Conte, 2012). Pathogenesis mechanisms of HF in diabetes can be related to hypertension, cardiotoxic tetrad related to coronary artery disease, and extracellular fluid volume expansion (Gilbert and Krum, 2015). "DC" is the term that is used for the presence of myocardial dysfunction in the absence of CV associated risk factors (Lehrke and Marx, 2017). The metabolism, function, and structure of the cardiac system may be affected by the underlying pathways of both diabetes and HF (Wallner et al., 2018). In the early stages of DC, structure and morphology changes are not considerable, but in the late stages, both systolic and diastolic function may be affected with greater increases in size and wall thickness of the left ventricular mass (Jia et al., 2016). In the next subsections, diabetes and HF as two major diseases are brought together considering their common mechanisms and underlying molecular pathways (**Figure 1**).

Impaired Cardiac Glucose Metabolism

Hyperglycemia is mentioned to have important roles in triggering molecular and cellular pathways of diabetes (Mortuza and Chakrabarti, 2014; Borghetti et al., 2018). According to many reports, diabetes can cause abnormalities in the heart tissue directly without the necessity of vascular defects. In a diabetic state, impairments in glucose uptake and glycolysis and abnormalities in pyruvate oxidation, along with impairment of insulin function, can promote lipolysis and fatty acid (FA) release from adipose tissues. Thus, these events could lead to the development of cardiomyopathy because of the adaption of cardiac muscle to exclusive utilization of FA for ATP generation (An and Rodrigues, 2006). Indeed, accumulation of FA and lipotoxicity can affect heart function due to altered lipid signaling (Maisch et al., 2011). Taken together, higher FA metabolism, decreased amount of protective glucose metabolism, and insulin resistance along with neurohumoral activation can lead to some perturbations in myocardial energetic functions (Salabei et al., 2016). Also, activation of other pathways, such as increased polyol flux, increased advanced glycation end products (AGEs), and higher activity of PKC, in addition to higher mitochondrial dysfunction and oxidative stress can lead to the development of DC as a result of hyperglycemia. The induction of *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) modification (through increased hexosamine pathway) may result in altered Ca2+ sensitivity and cycling and, thus, impaired cardiac protein contractility (Brahma et al., 2017; Kaludercic and Di Lisa, 2020). Also, several studies have also suggested the effects of hyperglycemia in inducing apoptotic cell death (Cai et al., 2002). All events of glucose metabolism are related to higher oxidative stress, which contains the basis metabolic impairments of DC (Mandavia et al., 2013), which is explained in the following section.

Altered Oxidative Stress

Oxidative stress is stated as one of the most important causes for DC pathophysiology, which contributes to both onset and complications of diabetes (Khullar et al., 2010; Liu et al., 2014; Ding et al., 2019). Increased production of ROS and reactive nitrogen species (RNS) in mitochondria can be derived from hyperglycemia in both main types of diabetes. Also, lack of insulin-mediated glucose metabolism can result in increased FA concentrations that can cause higher production of ROS from nicotinamide-adenine-dinucleotide-phosphate (NADPH)-oxidases (NOX). The activation of NOX results in higher production of superoxide, which, in combination with nitric oxide (NO), can produce damaging peroxynitrite (Liu et al., 2014). Indeed, transport of FA through CD36 can activate PKC-2β, leading to NOX2 activation and promoting recruitment of NOX2 catalytic subunits, and superoxide production, inducing a positive feedback loop of ROS production (Hansen et al., 2018). Cardiac dysfunction can be also related to mitochondria uncoupling along with mitochondrial-electron transport chain leakage. Also, the activation of PKC, xanthine oxidase, and lipoxygenases has a role in ROS production in a diabetic heart (Varma et al., 2018). PKC-dependent activation of the reduced form of NADPH has roles in inducing cellular ROS (Lee et al., 2004). Indeed, promoting recruitment of NOX2 catalytic subunits and superoxide production have positive effects on ROS production (Hansen et al., 2018). Activation of GTP-binding protein Rac-1 takes part in this induced NAD(P)H oxidase activation (Inoguchi et al., 2003). Xanthine oxidase, a cytoplasmic enzyme, catalyzes the oxidation of hypoxanthine and xanthine (its substrates) to uric acid utilizing O^2 (as an electron acceptor), leading to O^2- and H_2O_2 production. This may present as an important source of ROS production in cardiomyocytes (Kayama et al., 2015). Lipoxygenases contain lipid-peroxidizing enzymes that form hydroperoxy derivatives by oxidizing free and esterified polyunsaturated FAs (Kühn and O'Donnell, 2006). Herein, oxidative damage of proteins, lipids, and DNA resulted from an imbalance in ROS production (Varma et al., 2018). Other abnormalities associated with ROS production include some dysfunctions in (Na,K)-ATPase, Ca2+ ATPase, and pump activities in addition to depressed creatine kinase (CK) activities of the heart. On the other hand, in diabetic rats, CoQ, which has a potential antioxidant activity, is shown to be decreased (particularly CoQ9 and CoQ10) in cardiac mitochondria (Cai and Kang, 2001). Additionally, toxic molecules in the oxidative stress state affect Ca2+ handling and subcellular remodeling. Impaired left ventricular function can be the result of decreased Ca2+ sensitivity, reduced sarco(endo)plasmic reticulum Ca2+ -ATPase (SERCA2a) activity, and shifting myosin heavy chain. All of these could as a result lead to DC (Trost et al., 2002; Suarez et al., 2008; Goyal and Mehta, 2013; Zarain-Herzberg et al., 2014). The SERCA pump plays a part in muscle relaxation

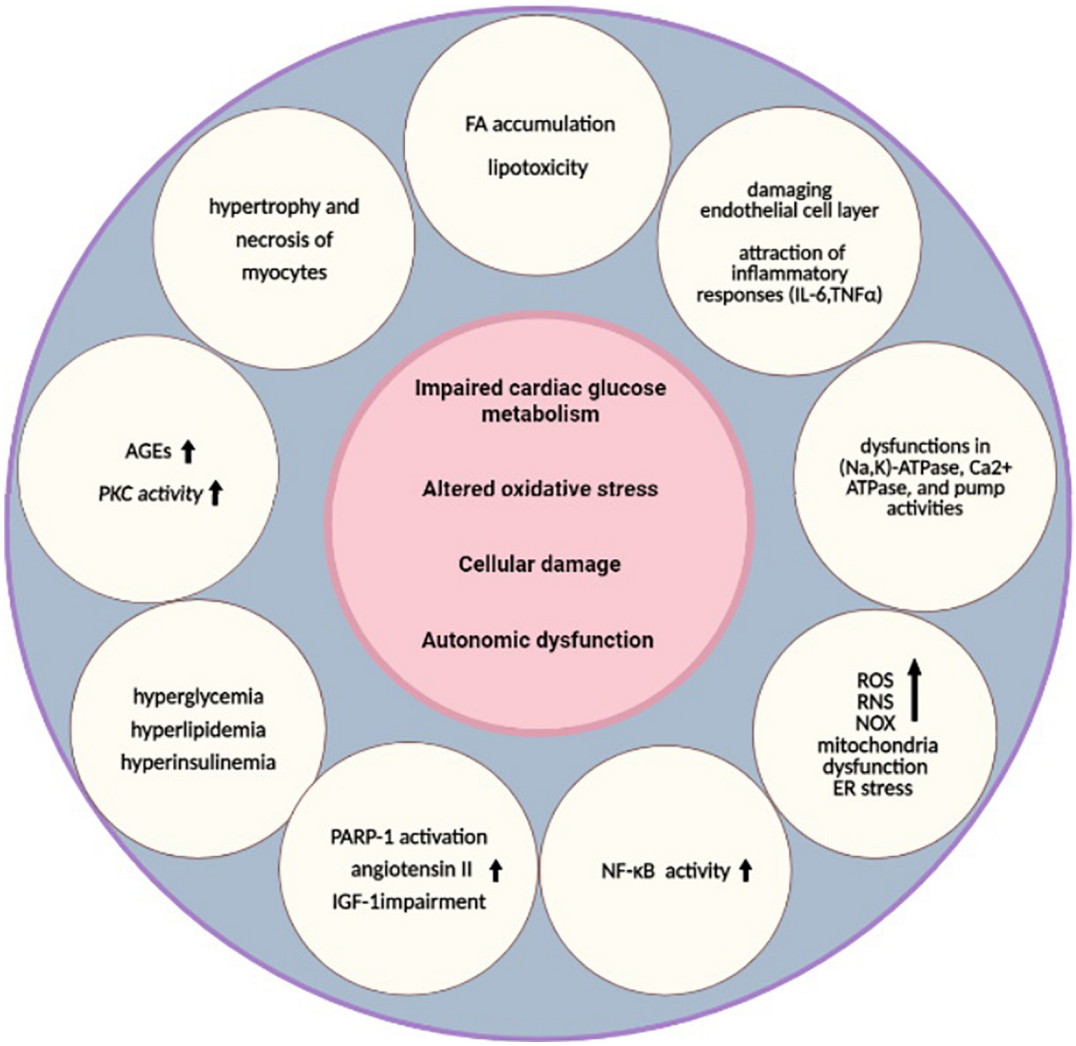

FIGURE 1 | Underlying pathways of diabetic cardiomyopathy. Impaired cardiac glucose metabolism (Mortuza and Chakrabarti, 2014), altered oxidative stress (Khullar et al., 2010), cellular damage (Cai and Kang, 2003), and autonomic dysfunction are the main pathological mechanisms that are common between T2DM and HF (Rodriguez-Saldana, 2019). Several other alterations, such as hyperglycemia, hyperlipidemia, hyperinsulinemia (Borghetti et al., 2018), higher AGEs, increased PKC activity (Brahma et al., 2017; Kaludercic and Di Lisa, 2020), FA accumulation, lipotoxicity (Maisch et al., 2011), damaged endothelial cell layer, attraction of inflammatory responses (IL-6, TNFα) (Lorenzo et al., 2011), higher NF-κB activity (Faria and Persaud, 2017), dysfunctions in (Na,K)-ATPase, Ca2+ ATPase, and pump activities, depressed CK activities (Cai and Kang, 2001), increased levels of ROS, RNS, NOX (Liu et al., 2014), mitochondria dysfunction (Varma et al., 2018), ER stress, hypertrophy and necrosis of myocytes (Jia et al., 2018), PARP-1 activation, increased angiotensin II, and IGF-1 impairment, are also related to these pathways (Bugger and Abel, 2014). These alterations can lead to diabetic cardiomyopathy as a result. HF, heart failure; AGEs, advanced glycation end products; ATP, adenosine triphosphate; CK, creatine kinase; ER, endoplasmic reticulum; FA, fatty acids; IGF-1, insulin-like growth factor 1; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOX, nicotinamide adenine dinucleotide phosphate-oxidases; PARP-1, poly [ADP-ribose] polymerase 1; PKC, protein kinase C; RNS, reactive nitrogen species; ROS, reactive oxygen species; T2DM, type 2 DM; TNF, tumor necrosis factor.

by means of lowering Ca2+ and also in restoration of sarcoplasmic reticulum (SR) Ca2+ load for muscle contraction. SERCA2a pump function is affected by inhibitory peptide phospholamban. Increasing the levels of this inhibitory function along with higher activity of protein phosphatase 1 (PP1) may result in inactivation/dephosphorylation of protein kinase A (PKA) targets related to SR Ca2+ uptake dysfunctions (Lipskaia et al., 2010; Zarain-Herzberg et al., 2014). On the other hand, increased ROS along with higher glucose levels and lipid changes leads to damaged endothelial layer and attraction of inflammatory responses. Cytokines such as interleukins (IL)-6 and tumor necrosis factor (TNF)α, adhesion molecules, and angiotensin-II are released from the endothelial cell layer, which causes migration of more leukocytes to subendothelial layers of inflammation. It could result in fibrosis and atherosclerotic plaque in which nuclear-factor kappa-light-chain-enhancer of activated B cells (NF-κB) has an important regulatory role (Lorenzo et al., 2011). Thus, NF-Kb can also be activated following oxidative stress, which causes cardiac fibrosis and hypertrophy. It can also lead to inflammation and

excessive oxidative stress related to DNA and membrane injury (Faria and Persaud, 2017).

Cellular Damage

Myocardial cell death has important effects on the pathophysiology of different cardiomyopathies, such as endothelial dysfunction, myocardial infarction, and DC. In this regard, ROS and RNS have important roles in inducing different apoptotic signaling pathways (Cai and Kang, 2003). Also, biochemical changes such as hyperglycemia in DC can lead to thickening of capillary-basement membrane as well as hypertrophy and necrosis of myocytes (Farhangkhoee et al., 2006). On the other hand, endoplasmic reticulum (ER) stress can result in unfolded protein reaction and its proteasomal degradation. ER stress could promote apoptosis and cellular damage and lower the function of sarcoplasmic reticulum-calcium pump, which takes part in Ca2+ sequestration (Yang et al., 2015; Jia et al., 2016). Indeed, ER stress in combination with oxidative stress and impaired calcium handling may lead to apoptosis, autophagy, and cellular necrosis (Jia et al., 2018). Moreover, normal autophagy can be affected by some impairments of autophagosome and lysosome fusion, which influences both the diastolic and systolic functions of the diabetic heart (Xie et al., 2011). The renin-angiotensin-aldosterone system (RAAS) also has notable roles in the progression of DC through higher oxidative damage along with cellular necrosis and apoptosis of diabetic heart (Murarka and Movahed, 2010). On the other hand, apoptotic cell death can be explained by higher inflammatory cytokines as well as Fas receptor-dependent apoptosis pathways. Excessive activation of poly [ADP-ribose] polymerase 1 (PARP-1) and impairment of insulin-like growth factor 1 (IGF-1), in addition to higher levels of angiotensin II, can also induce cellular necrosis pathways (Bugger and Abel, 2014). It should be noted that PARP-1 is involved in different physiological pathways such as cell death and DNA repair. Impaired DNA can activate PARP-1, which results in the cleaving of NAD+ into nicotinamide and ADP-ribose. Overactivation of PARP-1 can lead to irreversible cytotoxicity, cellular damage, and even death as a result of higher NAD+ and ATP depletion (Qin et al., 2016). On the other hand, caspase-independent cell death can be triggered by this enzyme, termed parthanatos, which is mentioned to be distinct from apoptosis/necrosis (or autophagy). This PARP-1-mediated cell death can be induced by apoptosis-inducing factor (AIF) nuclear translocation (Bugger and Abel, 2014).

Autonomic Dysfunction

Cardiovascular autonomic dysfunction can be defined as impaired autonomic control of the CV system in the diabetic state when other causes are excluded. Damages to nerve fibers can cause this abnormality of the CV system. There are several interactions of pathogenic pathways that have roles in CAN in which hyperglycemia is introduced as a major and initial cause. Oxidative/nitrosative stress, ER stress, impaired mitochondrial function and membrane permeability, inflammation, and calcium imbalance can be involved in this CAN pathway (Rodriguez-Saldana, 2019). Taken together, autonomic diabetic neuropathy as an important complication of DM can affect different organs (especially the CV system). As mentioned earlier, CAN can cause some clinical/functional manifestations that can be brought about by some alterations in vascular dynamics and uncontrolled heart rate (Flotats and Carrió, 2010). Hypertension, exercise intolerance, QT interval prolongation, and higher arterial stiffness are also associated with CAN. The peripheral vascular function can be also affected by this autonomic process (Rodriguez-Saldana, 2019). This autonomic dysfunction can predict CV risk and contributes to poor prognosis, higher mortality rates, and sudden death (Flotats and Carrió, 2010; Stables et al., 2013; Vinik et al., 2013). It has been found that there is an association between the dysfunction degree of the left ventricle and levels of cardiac autonomic dysfunction (Poirier et al., 2003). It has also been found that metabolic factors have important effects on this autonomic process (Valensi et al., 1997). Indeed, CAN could be seen early in the diabetes state, which can be a prognostic factor for microangiopathic complications (Valensi et al., 2003).

BRIEF REVIEW OF OMICS STUDIES

"OMICS" strategies are defined by providing high-throughput interfaces (in global-unbiased ways) to investigate millions of markers that represent similar biochemical identities simultaneously. These technologies can be used to find out the underlying molecular properties that exist behind complex phenotypes (Chakraborty et al., 2018; Conesa and Beck, 2019). There are several data types of omics technologies including genomics, transcriptomics, microbiomics, proteomics, epigenomics (Hasin et al., 2017; Manzoni et al., 2018), and metabolomics (Sun and Hu, 2016; **Figure 2**). Among the omics technologies, genomics, the most mature field, is the study of associated genetic variants to identify new therapeutic responses or disease prognosis. The human genome has important roles in personalized medicine with the aims of disease treatment and prevention considering genetic susceptibility (Burke and Psaty, 2007; Hasin et al., 2017; Ahmed, 2020). In this regard, the effects of genetic variant knowledge regarding genome-wide-association-studies (GWASs) along with omics findings have been found (Akiyama, 2021). Transcriptomics, another high-throughput technology, is responsible for the simultaneous examination of defined mRNA species qualitatively and quantitatively (Hegde et al., 2003). Proteomics is also another omics-related technology with the ability to examine the protein content of an organism, tissue, or cell with the aim of understanding the function or structure of a specific protein. This technology can be used in various research settings with different capacities to find diagnostic markers, vaccine production, and even interpretation of protein pathways of disorders (Aslam et al., 2017). Herein, large-scale protein characterization in this high-throughput proteomics strategy may benefit from MS-based technique (Bruce et al., 2013; Zhang et al., 2014). Moreover, other related technologies have been found to measure other biomolecules. For instance, epigenomics (for epigenetic markers) or metabolomics (for low-molecular-weight metabolites) can

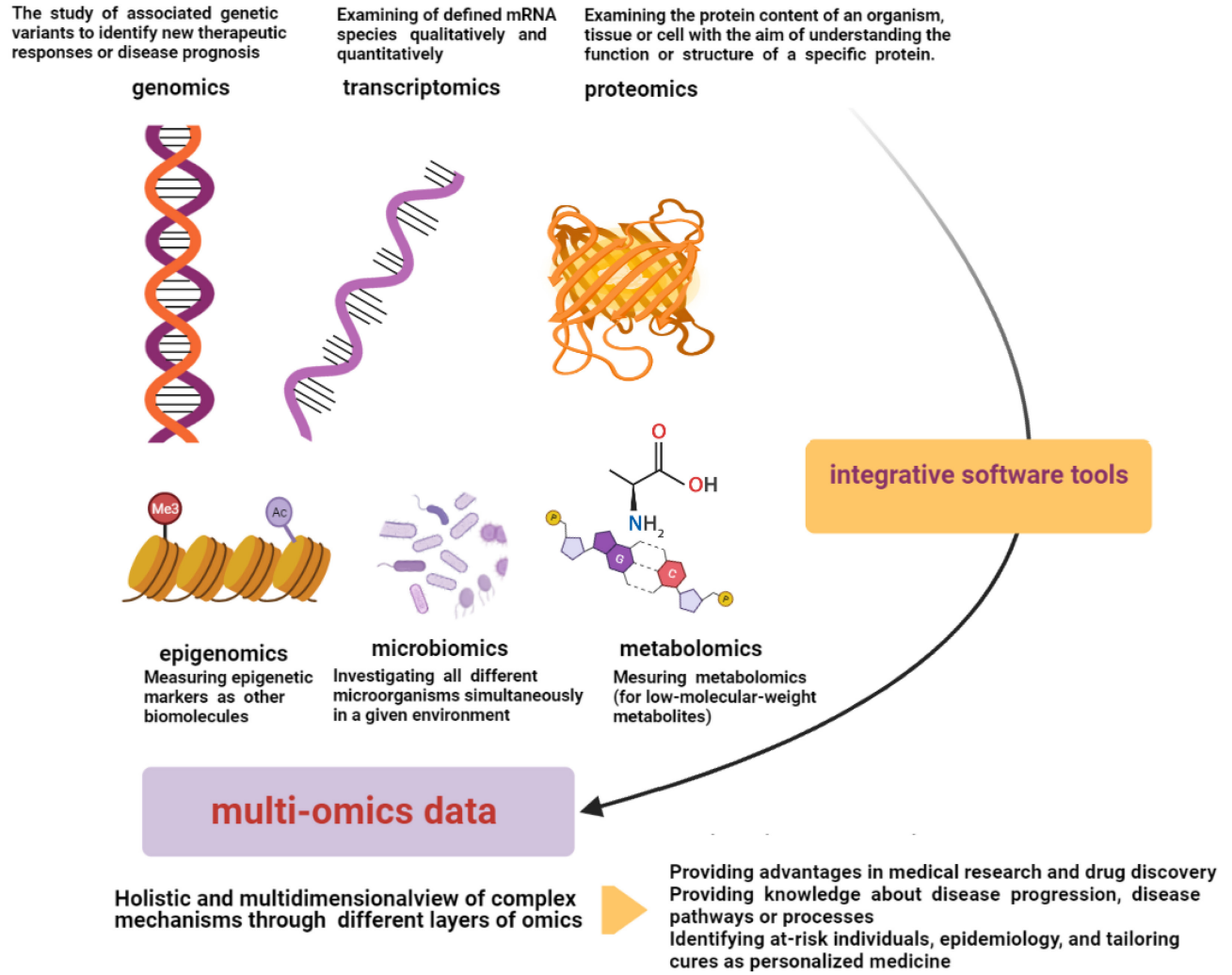

FIGURE 2 | Multi-omics data. Multi-omics technologies through different layers of omics data (genomics, transcriptomics, microbiomics, proteomics, epigenomics, and metabolomics) can provide a multidimensional analysis network to develop knowledge of interactive molecular basis and complex underlying pathophysiology of disorders. Electronic health records, imaging, and other integrative software tools can be helpful in integrative processes (Sun and Hu, 2016; Hasin et al., 2017).

be utilized in these fields (Sun and Hu, 2016). Microbiomics is another developed omics-related technology that investigates all different microorganisms simultaneously in a given environment (Wong et al., 2015; Hasin et al., 2017). Thus, omics technologies have different layers for a comprehensive study on a specific type of involvement, whereas human disorders consist of complex biological processes and diverse metabolic pathways, which have an interactive molecular basis and are affected by some environmental factors (Bersanelli et al., 2016; Sun and Hu, 2016). Therefore, these studies are relatively simple for that kind of analysis (Chen et al., 2012). Multi-omics technologies can help to achieve a holistic view and information on these complex mechanisms by studying different layers of omics information in a multidimensional network simultaneously. Multi-omics provides an analysis system to develop knowledge of the underlying interactive molecular basis to determine the pathophysiology of disorders and their associated longitudinal effects more accurately (**Figure 2**; Sun and Hu, 2016). Indeed, precision medicine may benefit from integrative omics providing data along with other helpful methods such as electronic health records, imaging, and other integrative software tools (Huang et al., 2017). Multi-omics may help to access novel approaches for diverse phases of the disorder including prevention, early diagnosis, and treatment. For instance, in the field of cancer treatment, the comprehensive single-cell survey may be effective to clarify underlying different biological and molecular basis finding in regional subdivisions of it (Sun and Hu, 2016). Integrative omics data derived from the cancer genome atlas have been shown to be helpful in profiling the druggability of cancer comprehensively (Sengupta et al., 2018). In addition, multi-omics data can provide novel approaches targeting drug resistance, which can be related to personalized medicine (Bock et al., 2016). In the next part, we are going to explain multi-omics technologies targeting T2DM and HF as two major human

disorders in addition to stating five different layers of it, namely, genomics, metabolomics, transcriptomics, proteomics, and epigenomics.

MULTI-OMICS STUDIES TARGETING T2DM AND HF COMMON MECHANISMS

Multi-omics technologies have promoted the knowledge of pathways of different disorders such as T2DM, obesity, cancer, and many others. Measurement of some relevant biomolecules can be helpful in the investigated environment. For instance, in metabolic disorders, important metabolites such as relevant biomolecules can reflect metabolic states (Chen et al., 2020). One of the growing fields for studying different metabolites (low molecular weight molecules) is metabolomics. Metabolomics assay techniques such as nuclear magnetic resonance (NMR) spectroscopy, MS, and chromatography help us to investigate the expression and posttranslational modification of transcription factors during different pathologic conditions (Kappel et al., 2016). Biologically, according to energy requirement, alterations in cardiac function occur. Herein, systems biology approaches such as metabolomics provide data to reveal how these metabolic changes during T2DM affect myocardial redox function (Cortassa et al., 2020). Indeed, both environmental influences and individual predisposition could be reflected by metabolite profiling, which makes it a useful method for investigating the pathophysiology of different diseases (Padberg et al., 2014). Herein, a study on multi-omics analysis on T2DM db/db mice aimed to characterize alterations in cardiac function, by investigating the effects of transferring longevity-associated-variant (LAV) of the human bactericidal/permeability-increasing fold-containing-Family-B member 4 (BPIFB4) gene. It was shown that alterations in heart lipid metabolism considering elevated levels of FA, acyl-carnitine, sphingolipid, ceramides, diacylglycerol, and triacylglycerides were notable metabolic changes in metabolic phenotyping investigations. Also, they were associated with impaired mitochondrial function with exertion of some effects on insulin sensitivity pathways (Faulkner et al., 2020). According to the results of previous studies, any disruption in lipid metabolism leads to deleterious effects on the diabetic heart. Understanding and managing this complication become possible by lipidomics profiling, which means observing lipids and providing an insight into their interactions. Indeed, lipidomics, which quantitatively analyzes lipids, is considered a subset of metabolomics (Tham et al., 2018). In recent times, a clear correlation between abnormal triglyceride accumulation and heart dysfunction, which are more prevalent in patients with obesity and diabetes, has been demonstrated. Lipidomics analysis of a diabetic heart demonstrated the important role of phospholipids in the development of this pathological condition (Dong et al., 2017). Lipid classes were also affected by the alterations in some lipid metabolites of the cellular membrane (glycerophospholipid and cardiolipin lipid classes), which suggests membrane composition changes with notable influences on cardiac functions. For instance, impaired cardiolipins have been shown to contribute to reduced contractility with effects on the mitochondrial electron-transport chain. Other associated changes were sarcomere rearrangement and loss of mitochondrial cristae and matrix volume (Paradies et al., 2019). One of the proposed mechanisms between DM and HF is attributed to excess activation of renin/angiotensin as well as sodium-glucose transporter 2, which can lead to exacerbation of overload volume in HF. Increased systemic inflammation is an additional common mechanism in DM and HF pathogenesis that results in an exacerbation of cardiac extracellular matrix remodeling and endothelial dysfunction. Decreased bioavailability of nitric oxide and microvascular dysfunction are consequences of hyperglycemia that are accompanied by production of glycated end products. Impaired function of myocyte mitochondria occurs following insulin resistance-induced increase in free FA consumption in the myocardium and toxic lipid intermediates accumulation (Hanff et al., 2021). Although several data on cellular and molecular mechanisms underlying cardiovascular disease have been obtained using genomics analysis techniques, more promising results are provided by proteomics technology. Proteomics outcomes together with genomics data broaden the knowledge of specific pathways involved in heart failure. For instance, identifying the alterations that occur in association with mitochondrial energy metabolism, stress response, and mitochondrial signaling is performed by proteomics. Indeed, cardiac proteome changes serve as an indicator of DC and are useful in assessing the consequences of different therapies for DM complications associated with heart disorders. Altogether, proteomics approaches have the potential to be applied in different study disciplines, from animal studies to cell culture systems, to address different questions (Karthik et al., 2014). Regarding multi-omics technology, utilizing LAV-BPIFB4 with stromal cell-derived factor-1/C-X-C chemokine receptor-type4 dependent effects influences cardiac contractility of diabetic db/db mice. Mitochondrial metabolism and function can be affected in this intervention with cardioprotective effects. RNA-seq analysis has also been performed to find transcriptional changes in metabolism- and immune-related genes, but alterations in protein level could not be observed in the progression of DC, which suggested the limited effects of metabolic enzyme expression at the time point of the study. Taken together, this study reveals the possible therapeutic benefits of LAV-BPIFB4 gene transfer due to its positive effects on mitochondrial FA handling along with energy production in treated mice (Faulkner et al., 2020). In the other multi-omics study, the effects of environmental glucose levels on the miRNA–mRNA dynamics have been shown by using high-throughput sequencing and qRT-PCR. The results suggest that miRNA-mediated gene regulation can be a useful biomarker for treatment and can promote knowledge of the development of diabetes (Chen et al., 2020). As mentioned before, cardiac dysfunction in the diabetic state can be related to mitochondria uncoupling along with mitochondrial-electron transport chain leakage (Varma et al., 2018). In this regard, multi-omics approaches regarding lipidomics and proteomics with functional investigations can be promising tools to understand the cause of mitochondria dysfunction and to use the underlying

knowledge for personalized treatments of different disorders such as diabetes and HF (Kappler and Lehmann, 2019). On the other hand, as stated earlier, inflammatory responses have effects on CAN (Rodriguez-Saldana, 2019). In another study on the identification of key genes involved in DM, it was established that underlying immunity and inflammation pathways have important roles in DM. This analysis using the Linked Omics database has shown that MMP9 (an important

TABLE 1 | Examples of recently performed multi-omics studies on diabetic heart disease.

	Article title	Type of studied disease model	Omics technique	Result	References
1	Posttranslational modulation of FoxO1 contributes to cardiac remodeling in post-ischemic heart failure	Acute myocardial infarction mice model	Metabolomics	Post translationally modification of cardiac FoxO1 by diabetes and ischemia	Kappel et al., 2016
2	Quantitative Proteomic Analysis of Diabetes Mellitus in Heart Failure With Preserved Ejection Fraction	Proteins with HFpEF and DM	Proteomics	Identifying proteins related to lipid metabolism, inflammation, and oxidative stress that are differentially expressed in patients with diabetes with HFpEF	Hanff et al., 2021
3	A proteomics approach to identify the differential protein level in cardiac muscle of diabetic rat	Diabetic rats	Proteomics	Identifying common mechanisms linked between DM and heart disease	Karthik et al., 2014
4	Investigation of the Protective Effects of Phlorizin on Diabetic Cardiomyopathy in db/db Mice by Quantitative Proteomics	db/db diabetic mice	Quantitative Proteomics	Probable protective effects of Phlorizin against diabetic cardiomyopathy	Cai et al., 2013
5	Mitochondrial dysfunction in the type 2 diabetic heart is associated with alterations in spatially distinct mitochondrial proteomes	Mitochondrial dysfunction in T2DM heart in db/db mice	Quantitative Proteomics	Association of mitochondrial dysfunction in T2DM heart with specific subcellular locale	Dabkowski et al., 2010
6	Proteomics of the Rat Myocardium during Development of Type 2 Diabetes Mellitus Reveals Progressive Alterations in Major Metabolic Pathways	Zucker diabetic fatty rat heart	MS based proteomics	Up-regulation of fatty acid degradation from onset to late T2DM	Edhager et al., 2018
7	Multi-proteomic approach to predict specific cardiovascular events in patients with diabetes and myocardial infarction: findings from the EXAMINE trial	Patients with diabetes and a recent MI	Proteomics	Better reclassification and risk prediction and event, better targeted treatment decisions and risk assessment	Ferreira et al., 2021
8	Changes of myocardial lipidomics profiling in a rat model of diabetic cardiomyopathy using UPLC/Q-TOF/MS analysis	Diabetic cardiomyopathy model in rats	UPLC/Q-TOF/MS	The suggestion of some changes in lipid biomarkers involved in hypertrophy of diabetic cardiomyopathy and cardiac dysfunction	Dong et al., 2017
9	Lipidomic Profiles of the Heart and Circulation in Response to Exercise versus Cardiac Pathology: A Resource of Potential Biomarkers and Drug Targets	Mice with physiological cardiac remodeling	Lipidomics	– Highlighting lipid profile adaptations in response to training versus pathology – Providing a resource to investigate of potential therapeutic targets and biomarkers	Tham et al., 2018
10	Diabetes changes gene expression but not DNA methylation in cardiac cells	Diabetic mice	Transcriptome analysis	Revealing differentially regulated gene programs associated with diabetes biological processes	Lother et al., 2021
11	Transcriptomic analysis of the cardiac left ventricle in a rodent model of diabetic cardiomyopathy: molecular snapshot of a severe myocardial disease	Diabetic cardiomyopathy model in rats	Transcriptomic analysis	Providing a molecular overview to processes leading to myocardial disease in diabetes	Glyn-Jones et al., 2007
12	Cardiac transcriptome profiling of diabetic Akita mice using microarray and next generation sequencing	Akita heart model in mice	Transcriptomic analysis	Providing a platform for future targeted studies to investigate genes involved in Akita heart and diabetic cardiomyopathy	Kesherwani et al., 2017
13	Divergent transcriptomic profiles in skeletal muscle of diabetics with and without heart failure	Patients with T2DM	Transcriptomic analysis	Confirming distinct transcriptome profiles of skeletal muscle in DM patients with and without HF	Wood et al., 2021

FOXO1, forkhead box O1; HFpEF, heart failure with preserved ejection fraction; T2DM, type 2 diabetes mellitus; HF, heart failure; DM, diabetes mellitus.

hub gene) can be helpful for the treatment of DM suggests as an inflammatory regulator in diabetic peripheral neuropathy. Herein, MMPs have notable effects on immunity responses by regulating cytokine function (Jian and Yang, 2020). Multi-omics analysis of integrative data from population-based genetic analysis, miRNA expression data collection, and DNA methylation has found several cardiometabolic-related miRNAs, which have roles in lipid metabolism. These miRNAs could be also defined as potential biomarkers for the earlier diagnosis of T2D and CHD or their development pathways. However, more research studies are needed to explain the connection between elevated blood glucose and these miRNAs (Mens et al., 2020). Some of the other studies performed are shown in **Table 1**.

CONCLUSION AND FUTURE PERSPECTIVES

Taken together, HF, an important comorbidity/complication of diabetes, has a high incidence and a high mortality rate in diabetic patients (Bertoni et al., 2004; Bowes et al., 2019). HF most commonly occurs following other CV events such as ischemia and hypertension (Bowes et al., 2019). Patients with DM and HF have specific manifestations of metabolic, structural, and neurohormonal abnormalities, which may worsen HF outcomes (Dei Cas et al., 2015). Alterations in insulin signaling, lipid accumulation, mitochondrial dysfunction, higher AGEs, and oxidative stress are some of the underlying mechanisms of this DC (Tarquini et al., 2011; Voors and van der Horst, 2011), which were explained before. Herein, lifestyle modification, blood glucose control, considering and eliminating risk factors for CV events, and treatment of HF can be helpful to achieve better outcomes regarding DC (Trachanas et al., 2014). On the other hand, omics studies have been developed as high-throughput technologies that have revolutionized medical research. Each layer of the omics studies can provide an associated list of differences with the disorder. Data derived from the single layer of omics data could be used as the biological markers of disease progression along with providing knowledge about disease pathways or processes. For instance, in the field of epigenomics, differentially methylated DNA regions can be helpful as disease indicators in the different disorders of metabolic syndrome or CV disease (Kim et al., 2010; Hasin et al., 2017). In addition to the benefits associated with omics technologies, multi-omics techniques provide improved and integrated characterization of biological pathways through different omics layers (Argelaguet et al., 2018). Drug discovery using omics technologies can be helpful through non-invasive data collection to manifest disease progression in order to achieve direct and translatable phenotype modeling of disorder (mapping disease phenotypes). It could also show the molecular basis and biomarkers of disorders. These technologies can also be effective to identify at-risk individuals, epidemiology, and tailoring cures as personalized medicine (Cisek et al., 2016). More knowledge of biological pathways utilizing multi-omics data can reveal the relationship between a disease and environmental factors. That may lead to earlier and more accurate diagnosis utilizing biomarkers of diseases along with more developed pharmacological and improved interventions for specific groups of patients (Koh and Hwang, 2019). T2DM and HF as two major disorders with some common underlying mechanisms that can also benefit from these advantages of omics/multi-omics approaches targeting their mentioned common pathways (Faulkner et al., 2020). Indeed, the development of next-generation sequencing along with mass-spectrometric techniques strategies provide large-scale research on whole cellular systems (Chakraborty et al., 2018). Nevertheless, efficiently utilizing multi-omics data requires proper data combination of different omics layers as well as effective bioinformatics strategies and standardized protocol (Koh and Hwang, 2019). A large amount of data and lack of related research for prioritizing tools and analysis utilized in multi-omics approaches, as well as lack of established standards for data filtering, are other challenges associated with multi-omics techniques (Subramanian et al., 2020).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Diabetes, Heart Failure, and COVID-19: An Update

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the WHO in March 2020. As of August 2021, more than 220 countries have been affected, accounting for 211,844,613 confirmed cases and 4,432,802 deaths worldwide. A new delta variant wave is sweeping through the globe. While previous reports consistently have demonstrated worse prognoses for patients with existing cardiovascular disease than for those without, new studies are showing a possible link between SARS-CoV-2 infection and an increased incidence of new-onset heart disease and diabetes, regardless of disease severity. If this trend is true, with hundreds of millions infected, the disease burden could portend a potentially troubling increase in heart disease and diabetes in the future. Focusing on heart failure in this review, we discuss the current data at the intersection of COVID, heart failure, and diabetes, from clinical findings to potential mechanisms of how SARS-CoV-2 infection could increase the incidence of those pathologies. Additionally, we posit questions for future research areas regarding the significance for patient care.

Keywords: diabetes, heart failure, COVID-19, pandemic, CVD (cardio vascular disease), Long-COVID, SARS-CoV-2, diabetic cardio

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INTRODUCTION

November 2019 marked the appearance of a novel human infectious RNA virus that has precipitated worldwide crises and left indelible marks on society, science, and healthcare. Named as the second of its kind and for its effects on the human respiratory system, severe acute respiratory syndrome coronavirus (SARS-CoV-2) has, to date, infected over an estimated 200 million persons (Dong et al., 2020). Acute manifestations of the disease range from asymptomatic infection to acute hypoxic respiratory failure and death. While up to 5% of infections result in critical illness (Guan et al., 2020), most acute infections seem to present with few-to-no symptoms (Wu et al., 2020). Though the rate of COVID-19 deaths had declined in the last months throughout most of the world, new variants have appeared, and an accumulating body of epidemiologic and basic science suggests that COVID-19's aftermath on human health may be longer-lasting than first imagined. We now know that, in addition to causing respiratory illness, SARS-CoV-2 directly and indirectly (and sometimes by unknown methods) can affect multiple organ systems: cardiac, hematologic, pancreatic, renal, and others (Gupta et al., 2020; Siddiqi and Mehra, 2020). Important questions going forward are *what are the long-term effects of SARS-CoV-2 infection; what will be the burden on patients and the healthcare system*; and *how we will continue to best screen and treat patients who*

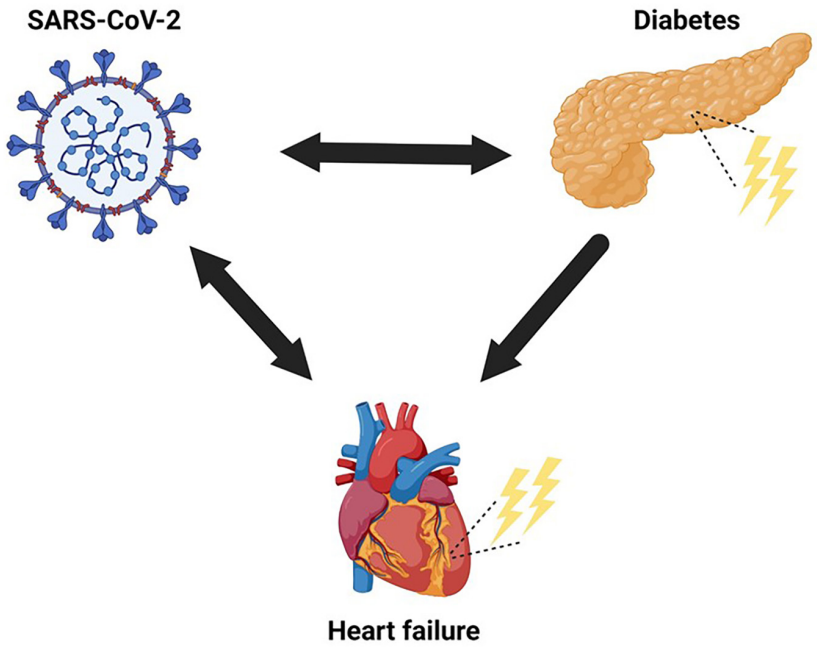

FIGURE 1 | Interconnection between diabetes, heart failure, and SARS-CoV-2.

have been affected by the disease. Given the breadth of this topic, in this work, we focus on reviewing the relationships among heart failure, diabetes, and SARS-CoV-2 infection (**Figure 1**).

A review of the available literature was performed using multiple databases, including PubMed, Google Scholar, bioRxiv, medRxiv, and real-time resources (e.g., WHO reports). Search terms included SARS-CoV-2, Heart failure, diabetic heart failure, mechanisms of infection, long-COVID-19, post-COVID, chronic COVID, post-COVID syndrome, and long-haul COVID, viral illness following COVID-19, post-COVID illness, COVID recovery, predictors of long-COVID-19. Additional literature was found by reading references in those articles as well. Articles and Reviews were curated individually by the authors.

Current Heart Failure Epidemiology

Heart failure (HF) is a clinical syndrome that carries heavy morbidity and mortality for patients and high healthcare costs for the US health system. In patients over 65 years old, HF exacerbation is a common reason for hospital admission from the Emergency Department, and the risk of death or re-hospitalization in the sixty-to-ninety-day period following the admission is estimated to be as high as 45% (Gheorghiade et al., 2011). The associated yearly healthcare cost of HF in 2012 was estimated to be around $ 40 billion US dollars (Gheorghiade et al., 2011). According to data collected from 2015 to 2018 (Virani et al., 2021), over 6 million Americans have HF and, for the last 11 years, HF prevalence has been on the rise globally (Virani et al., 2021). A silver lining, of course, is that one contributing factor to the increased prevalence is the general increase in life expectancy (with increased age comes increased incidence of HF); However, HF continues to be one of the leading causes of death and fastest-growing categories of heart disease. Pre-COVID data predict a US population prevalence increase from 2.4 to 3.0% by 2030 (Heidenreich et al., 2013).

HF is ubiquitous in the medical setting and, generally, recognizable, contributing to the erroneous impression that "heart failure" is a single entity or disease. Instead, it is a syndrome that can result from different pathophysiologic causes and etiologies and, likely, for that reason, has had a definition that continually undergoes revisions as we discover new information (Bozkurt et al., 2021). However, as analyzed, reviewed, and categorized by Bozkurt et al. (2021), combinations of three fundamental factors unite the various HF presentations: biophysical evidence of cellular and architectural pathophysiology (e.g., elevated brain-natriuretic peptide, fibrosis) (Gjesdal et al., 2011), patient-reported symptomology (e.g., fatigue, shortness of breath, decreased exercise tolerance etc.), and physician-observed signs (e.g., leg swelling, pulmonary edema). This information is pertinent because, given the various current tools we use to look for HF, we have seen signs of heart damage from SARS-CoV-2 with a form of each modality.

A standard first-line imaging method that helps delineate structure and function is echocardiography. This method employs sound waves through the chest wall, producing an image as some waves return and others do not. This provides real-time images of the heart beating and allows for calculating both architectural and functional parameters such as muscle thickness and ejection fraction (**Figure 2**). Magnetic Resonance Imaging (MRI) can provide information about organ structure and give important information about tissue health. Myocarditis, for example, can often be appreciated on MRI. When cardiac tissue or vessels are damaged and/or stressed, specific biomarkers rise.

Cardiac troponin, for example, is indicative of myocardiocyte damage and is used with electrocardiogram in standard first-line evaluation of acute myocardial infarction. Brain Natriuretic Peptide (Pro-BNP) is a less reliable protein marker but measures stretch of the vascular system (as might happen if a person were retaining extra fluid from HF).

Association Between Severe Acute Respiratory Syndrome Coronavirus 2 and Heart Failure

There is growing evidence of a correlation between SARS-CoV-2 infection and myocardial injury (Madjid et al., 2020), even in seemingly healthy individuals. Puntmann et al. (2020), for example, demonstrated through MRI studies that there is an elevated incidence of myocardial injury in people who have recovered from COVID-19, even after controlling for preexisting conditions. Other researchers measured a four-to-five-fold higher increase in poor outcomes for patients with underlying cardiovascular disease (CVD) who are infected with SARS-CoV-2 than for patients without CVD (Li X. et al., 2020; Wu and McGoogan, 2020); and in one United Kingdom study, patients with previously diagnosed CVD had a 50.0% mortality while those without known CVD had only 10.6% (Chatrath et al., 2020). There are even questions as to what long-term cardiac damage the virus might cause to the healthiest of individuals: Rajpal et al. (2020), found evidence of active myocarditis in 15% of young athletes who had tested positive for SARS-CoV-2 infection after 11–53 days of quarantine, raising general questions about recovery times from the virus (discussed later).

Evidence of Global Cardiac Dysfunction After Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Various clinical data modalities show mixed support for the epidemiologic and statistical findings that SARS-CoV-2 infection could be causing or exacerbating myocardial damage, possibly permanently in some cases. In a prospective echocardiography study of 100 patients admitted to the hospital with COVID-19, 69% showed signs of heart failure. Among these, 39% had right ventricular (RV) dilation or dysfunction, 16% had left ventricular (LV) diastolic dysfunction, and 10% had LV systolic dysfunction (Szekely et al., 2020). Areas of significant difference between patients who developed echocardiographic signs of heart failure included admission levels of creatinine (a marker of kidney function and/or perfusion), pro-BNP, systolic blood pressure, and C-reactive protein (a marker of inflammation and important topic discussed later). A retrospective study from New York on 110 patients with COVID-19 (Argulian et al., 2020) also identified RV dilation in 31% of patients who underwent echocardiography. The patients also showed a significant impairment in kidney function. As noted by Szekely et al. (2020) the likeliest explanation for the preponderance of right-heart failure in these patients is an acute increase in pulmonary resistance secondary to multiple mechanisms involved during COVID-19 (**Figure 2**), though, in a paper by Graziani et al. (2020), patients with COPD had higher mortality with COVID than those without but a similar incidence of HF. When patients were stratified by worsening clinical grade, there was not a difference in the LV dysfunction seen (Szekely et al., 2020). An interesting comparison might be a retrospective cohort of case-controls (prior to 2019) with echocardiographic RV and LV data.

Evidence of Tissue Cardiac Damage After Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Cardiac magnetic resonance imaging (CMR) techniques combined with serum biomarkers have identified cardiac tissue damage in patients recovering from COVID-19 infection. Puntmann et al. (2020) produced a prospective cohort study of 100 German patients who had tested positive for SARS-CoV-2 infection but were symptomatically recovered and subsequently had tested negative since their infection. Of 100 patients considered "recovered" from SARS-CoV-2, 78% had abnormal CMR images consistent with myocardial inflammation, heart scarring, or pericardial abnormalities, and this was true even after controlling for preexisting conditions. Additionally, there was a significant increase in serum troponin levels in patients who recovered from infection when compared to persons who never had SARS-CoV-2 infection. Similar to Argulian et al. (2020) and Szekely et al. (2020), Puntmann et al. (2020) found some RV dysfunction in some of these patients. Dissimilarly, however, Puntmann et al. (2020) did find evidence that patients also had lower left ventricular ejection fraction and higher left ventricle volumes when compared to controls. Particularly salient details of this work are that the authors excluded from the study any patients who were being worked up by their doctors for cardiac disease, which means there is a group of individuals who symptomatically really have not yet recovered from infection despite subsequent negative tests. Sobering, too, is that 67% of the patients studied had mild/moderate-to-no symptoms. In another study, 26 Ohio State University (OSU) athletes who tested positive for SARS-CoV-2 infection did not show any elevation in cardiac biomarkers, yet CMR imaging showed evidence of myocarditis in 15% of the athletes and cardiac scarring in 30% (though, unknown if that scarring is COVID-related or exercise-related change) (Rajpal et al., 2020). Many of the athletes were asymptomatic and it would be interesting to know how this compared to hearts from athletes who had not contracted SARS-CoV-2. In a meta-analysis of studies from the United States, Asia, Europe, and Brazil, Toraih et al. (2020) found elevated levels of Troponin I and NT-proBNP and others have reported similar findings (Shi et al., 2020; Zhou et al., 2020).

Clinical Signs and Symptoms of Possible Heart Dysfunction After Severe Acute Respiratory Syndrome Coronavirus 2 Infection

We now know that some people who have had a SARS-CoV-2 infection have long-persisting symptoms—such as fatigue and dyspnea—or fail to recover from the infection entirely. "Long-COVID" was noticed anecdotally first by individuals communicating in blogs and Social Media but since has been corroborated by large data sets from phone applications, and the NIH recently have launched initiatives to study the biological causes of this phenomenon [as reviewed by Nath (2020),

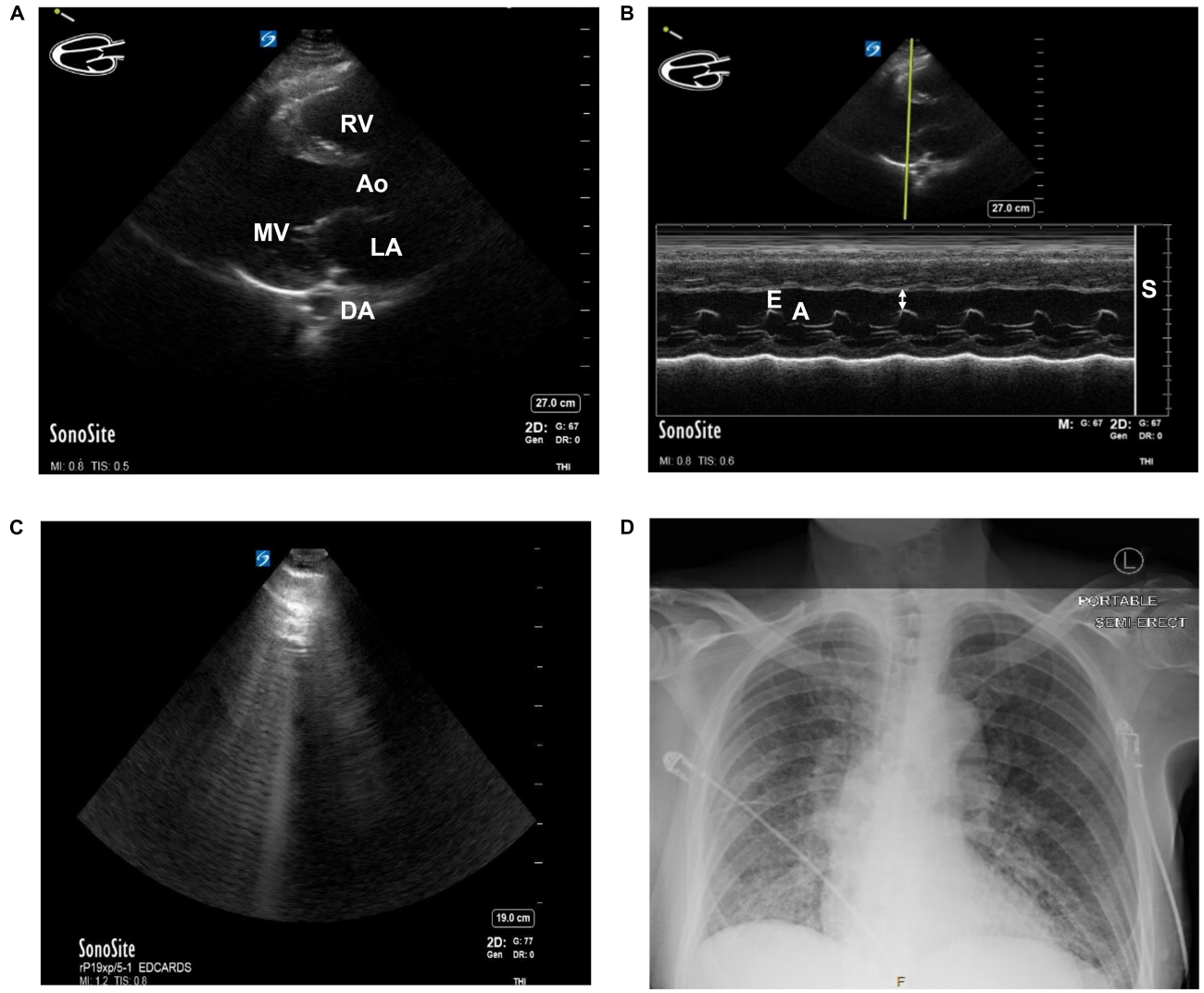

FIGURE 2 | (A) Parasternal Long Axis (PLAX) view of the heart of a patient with known heart failure and diabetes using Point of Care Ultrasound (POCUS) imaging technique. MV, mitral valve. Ao, Aortic outflow. DA, descending aorta. LA, left atrium. RV, Right ventricle. **(B)** E-point Septal Separation (EPSS) calculation of the same patient with known heart failure and diabetes using POCUS. M-Mode doppler tracing. Estimated ejection fraction of 32%. Double arrow = EPSS. E = E wave. A = A wave. S = septum. **(C)** B-lines seen while performing cardiac ultrasound in a patient with COVID-19. A patient presented to the Emergency Department in acute hypoxic respiratory failure secondary to SARS-CoV-2 infection. The B-lines pattern seen above is indicative of lung pathology and, in the setting of SARS-CoV-2 infection, often correlates with ground-glass opacities on CT. **(D)** Chest x-ray of the same patient. Findings of bilateral ground-glass airspace disease. With no prior known hypercoagulable risk factors other than age and SARS-CoV-2 infection, this patient was found to have ground-glass opacities on CT and a new pulmonary embolism. Patient consent was obtained for publication and discussion of ultrasound and x-ray imaging.

Sudre et al. (2021)]. It may be that Long-COVID is a form of post-sepsis syndrome (Prescott and Girard, 2020; Gritte et al., 2021), and, if so, we might expect increased re-hospitalization of these patients who have prior comorbidities. It will be interesting to study these individuals' demographics, risk factors, biomarkers, and cardiac imaging and evaluate whether there might be lingering myocarditis or even pre-heart failure.

Though question-provoking, these results of cardiac abnormalities may not be surprising. During the 2002–2004 SARS outbreak, researchers discovered increases in patients' cardiovascular complications following SARS-CoV-1 infection (Peiris et al., 2003; Chong et al., 2004). To date, the SARS-CoV-2 virus has had a wider reach than the SARS-CoV-1 virus, infecting an estimated population total of over one-hundred million people (worldmeters, 2021). It is unclear if SARS-CoV-2 infection is unmasking underlying heart failure and/or causing direct myocardial damage, and, if the latter, if that damage will have permanent long-term health effects for the individual. *Does cardiac involvement occur and persist in people with mild to moderate COVID-19 infections, even after recovery from symptoms?* No matter the answer to these questions, we need to consider and anticipate what, if any, consequences SARS-CoV-2

infection may bring to morbidity and mortality for patients and cost to healthcare systems.

Association Between Severe Acute Respiratory Syndrome Coronavirus 2 and Diabetes

There appears to be an increase in diabetes incidence in patients who have been infected with SARS-CoV-2 (Al-Aly et al., 2021). Though an increase in power would be needed before definitive conclusions are drawn, there are multiple reports of increases in previously undiagnosed type I diabetes in adults (Accili, 2021) and children (Unsworth et al., 2020) during the COVID-19 pandemic. In one United Kingdom study of a few hospital units, a significantly higher increase in new-onset type I diabetes was observed in children aged 23 months to 16.8 years of age (Unsworth et al., 2020). In a study from China (Li J. et al., 2020), patients with COVID-19, with or without previously diagnosed diabetes, had a higher prevalence of ketosis and ketoacidosis. Acute illness is one of the most common precipitating factors of new diagnoses of type I diabetes, a characteristic way in which diabetes first might be discovered in children or adolescents. Despite SARS-CoV-2 causing reportedly mild symptoms in children compared to adults, one might reasonably hypothesize that a virus with high infectivity and infection incidence naturally could cause a concomitant increase in type I diabetes incidence and prevalence in predisposed individuals. There is, however, also a well-documented but less understood relationship between hyperglycemia and infection with coronaviruses, with or without diabetes, and an increased incidence of mortality. A few proposed mechanisms include viral binding to ACE2 receptors—receptors found in nasopharyngeal tissue, pancreatic cells, and others. More on proposed mechanisms will follow. Additionally, in a study of thousands of adult patients from the US Department of Veterans Affairs, Al-Aly et al. (2021) did find an increase in diabetes and insulin prescriptions. As the authors note, it is difficult to explain the root cause of the increase (inactivity during COVID quarantine, better follow up direct infection of the virus causing diabetes, etc.). What we do know, though, is that having diabetes does increase a person's risk of having heart failure.

Diabetic Heart Disease

DHD is defined as the presence of heart disease specifically in patients with diabetes that encompasses coronary artery disease, heart failure, and/or cardiomyopathy (Marwick, 2008; Lew et al., 2017). DHD is a broad definition that encapsulates many myocardial diseases due to the varying etiology and the poorly understood mechanisms. Therefore, DHD should be considered as a distinct clinical entity and not limited to one particular type of myocardial disease (Lew et al., 2017). A recent systemic literature review conducted pre-covid era identified that CVD affects approximately 32.2% of individuals with type 2 diabetes, and, significantly, 14.9% of them developed HF. Of note, CVD was the cause of death in 9.9% of individuals with type 2 diabetes, representing 50.3% of all deaths, demonstrating that diabetes is an independent risk factor for CVD and associated mortality (Einarson et al., 2018). This is only expected to increase, especially with the incidence of type 2 diabetes affecting over 592 million people globally by 2035, a sharp increase from 382 million in 2013 (Guariguata et al., 2014).

The underlying mechanisms leading to DHD development remain unclear, although increasing evidence suggests that hyperglycemia and insulin resistance lead to DHD development. Hyperglycemia activates the polyol pathway, protein kinase C, advanced glycation end products, and hexosamine pathway, while insulin resistance activates Ras/MAPK pathway. These induce myocardial lipotoxicity and augment oxidative stress and systemic inflammation, resulting in endothelial cell dysfunction, cardiac hypertrophy, fibrotic scarring, and apoptotic cell death, thereby compromising cardiac function. Interestingly, the clinical treatment of DHD is solely dependent on a cocktail of medications and symptomatic treatment approaches. There is no single drug that specifically and effectively treats/prevents DHD. This is likely due to the multifactorial nature of the underlying mechanisms.

Individuals with diabetes have more than two times the risk of developing HF compared to non-diabetic individuals. The Framingham Heart Study suggested diabetes independently increases the risk of HF up to two-fold in men and five-fold in women even after adjusting for other risk factors such as age, hypertension, hypercholesterolemia, and coronary artery disease (Kannel, 1979). While an association of diabetes in HF with reduced ejection fraction (HFrEF) is well established, recent evidence suggests heart failure with preserved ejection fraction (HFpEF) is a common comorbidity of diabetes (Solomon et al., 2018), with a prevalence of almost 45% (Echouffo-Tcheugui et al., 2016). Furthermore, outcomes following HFpEF are poor and comparable to HFrEF, and sudden death accounts for around 20% of mortality in persons with diabetes who also have HFpEF (Vaduganathan et al., 2018).

Adding to the insult, patients with heart failure may be particularly susceptible to COVID-19 complications. Along these lines, recent reports suggest mortality rates were significantly higher for patients with HF with COVID-19 across broad cohorts, including those with active cancer on chemotherapy. However, mortality attenuated due to increased testing, disease-modifying therapy, and improved COVID-19 care. Despite all these, patients with underlying HF who contract COVID remain at high-risk for in-patient mortality (Panhwar et al., 2019; Alvarez-Garcia et al., 2020; Chatrath et al., 2020; Lee L. Y. et al., 2020; Bhatt et al., 2021; Group et al., 2021).

There Is an Increased Risk of Heart Failure in Patients With Diabetes Who Contract COVID-19

Available evidence suggests that COVID-19 has poor outcomes for patients with diabetes (**Table 1**) and is likely to exacerbate heart failure in individuals with diabetes (Freaney et al., 2020). Patients with diabetes and CVD have a higher propensity for severe outcomes when infected with SARS-CoV-2 than those with diabetes or heart failure alone. In a meta-analysis of six studies with > 1,500 patients (Li B. et al., 2020), cardiac-cerebrovascular disease and diabetes were present in 16.5 and

TABLE 1 | Characteristics COVID-19 patient's grouped number of patients admitted, gender, age,% diabetes,% CVD and% mortality.

Study name	Date	# of COVID positive patients admitted	Percent Male	Percent Female	Median Age	Mean Age	Percent Diabetes	Percent CVD	Percent. Mortality
Wang G. et al. (2020)	Mar-20	242	49.20	50.80	45		6.20	3.70	0.80
Qi et al. (2020)	Mar-20	267	55.80	44.20	48		9.70	4.90	1.50
Cao et al. (2020)	Mar-20	198	51.00	49.00			7.60	6.00	NA
Liu S. et al. (2020)	Mar-20	620	52.60	47.40			6.50	2.60	NA
Chen M. et al. (2020)	Mar-20	123	49.60	50.40	53 (discharged) 72 (death)		11.40	16.00	25.20
Chen X. et al. (2020)	Mar-20	291	49.80	50.20	46		7.60	4.10	0.70
Hong et al. (2020)	Mar-20	140	51.00	49.00		45.66	9.00	3.00	NA
Wang S. et al. (2020)	Apr-20	165	55.80	44.20	44		8.20	4.80	0.60
Zheng et al. (2020)	Apr-20	30	43.30	56.70	44.5		10.00	3.30	NA
Yuan et al. (2020)	Mar-20	417	47.50	52.50		45.40	7.70	6.70	0.72
Petrilli et al. (2020)	Mar-20	1,999	62.60	37.40	62		25.20	44.60	14.60
Guan et al. (2020)	Mar-20	1,099	58.10	41.90	47		7.40	2.50	1.40
Bai et al. (2020)	Dec-20	1,833	66.10	33.90	70		19.50	17.90	100.00

9.7% of the patient population. In patients in the ICU or with severe cases, the prevalence of cardio-cerebrovascular disease and diabetes was present at three- and two-fold higher rates. In a large United Kingdom study (61,414,470 individuals) on COVID-19 mortality (23,698 deaths), 30.9% of individuals who died had preexisting coronary artery disease, and 17.8% had heart failure. 31.4% of individuals who died had type 2 diabetes, 1.5% had type 1 diabetes, and 0.3% had other types of diabetes (Barron et al., 2020). It is estimated to be about five times greater than the percentage of diabetes in the United Kingdom. Notably, individuals with type 1 and type 2 diabetes who died were younger than those without diabetes.

Recently, Abe et al. (2021) showed that patients with diabetes admitted with COVID-19 had increased incidence of acute myocarditis, acute heart failure, acute myocardial infarction, and new-onset atrial fibrillation. They concluded that diabetes was associated with worse cardiovascular outcomes. Furthermore, COVID-19 appears to increase the risk of HFpEF, which, as described above, is beginning to be recognized as one of the major forms of HF (Freaney et al., 2020). Since HFpEF is high in individuals who have diabetes, there may be a positive relationship between COVID-19, HFpEF, and diabetes. While no direct data support this notion yet, indirectly, the central pathogenesis shared by HFpEF and COVID-19 appears to be inflammation. Infection with SARS-CoV-2 increases the release of pro-inflammatory cytokines such as IL-1 and IL-6, which directly affect both the respiratory system and myocardium (Freaney et al., 2020). Therefore, when an individual with diabetes and HFpEF contracts COVID-19, it is likely to exacerbate the pathology of HFpEF in these patients. In addition to inflammation, obesity is a significant risk factor for COVID-19 severity. Further, more than 20% of patients with diabetes struggle with obesity and obesity is also a risk factor of HFpEF. Combined, inflammation and obesity could increase the risk of HF in diabetic patients with COVID-19.

Taken together, available evidence suggests that COVID-19 may induce myocardial damage and HF and, significantly, is particularly detrimental to individuals with diabetes. Further, COVID-19 may directly induce diabetes. Some propose that there is perhaps a common mechanism by which the virus worsens diabetes and HF concomitantly and synergistically, and the next section will review the main potential mechanisms.

MECHANISMS

The Virus

Understanding the structure and targets of coronaviruses helps frame the mechanism of the virus's attack and some of the pathophysiology caused by the virus's aftermath (**Figure 3**). All coronaviruses are positive-sense, single-strand RNA-based viruses with crown-like spikes. This *crown* of spikes is what gives the virus its name. Coronaviruses share the same overall structure, its genome - SARS-CoV-2's being large for RNA viruses (ranging from 27 to 32 kb) – is found inside a capsid formed by the nucleocapsid protein and surrounded by an envelope. Three proteins are attached to the envelope: the membrane protein and envelope protein are involved in virus assembly, whereas the spike protein (S) is responsible for viral attachment and entry. The spike protein comprises S1, which includes the receptor-binding domain (RBD), and S2, which allows the fusion between the virus and the host membranes (Li, 2016).

While the coronavirus family is quite large, SARS-CoV, SARS-CoV-2, and MERS belong to the same genus, Betacoronavirus. Even though these viruses share clinical similarities, there are critical differences among them. SARS-CoV-2 shares 79% sequence similarity to SARS-CoV and only 50% to MERS (Lu et al., 2020). SARS-CoV-2 has higher infectivity but lower mortality (<2%) compared to MERS (∼34%) and SARS-CoV (∼9%). MERS bind to the dipeptidyl peptidase (DPP4) receptor,

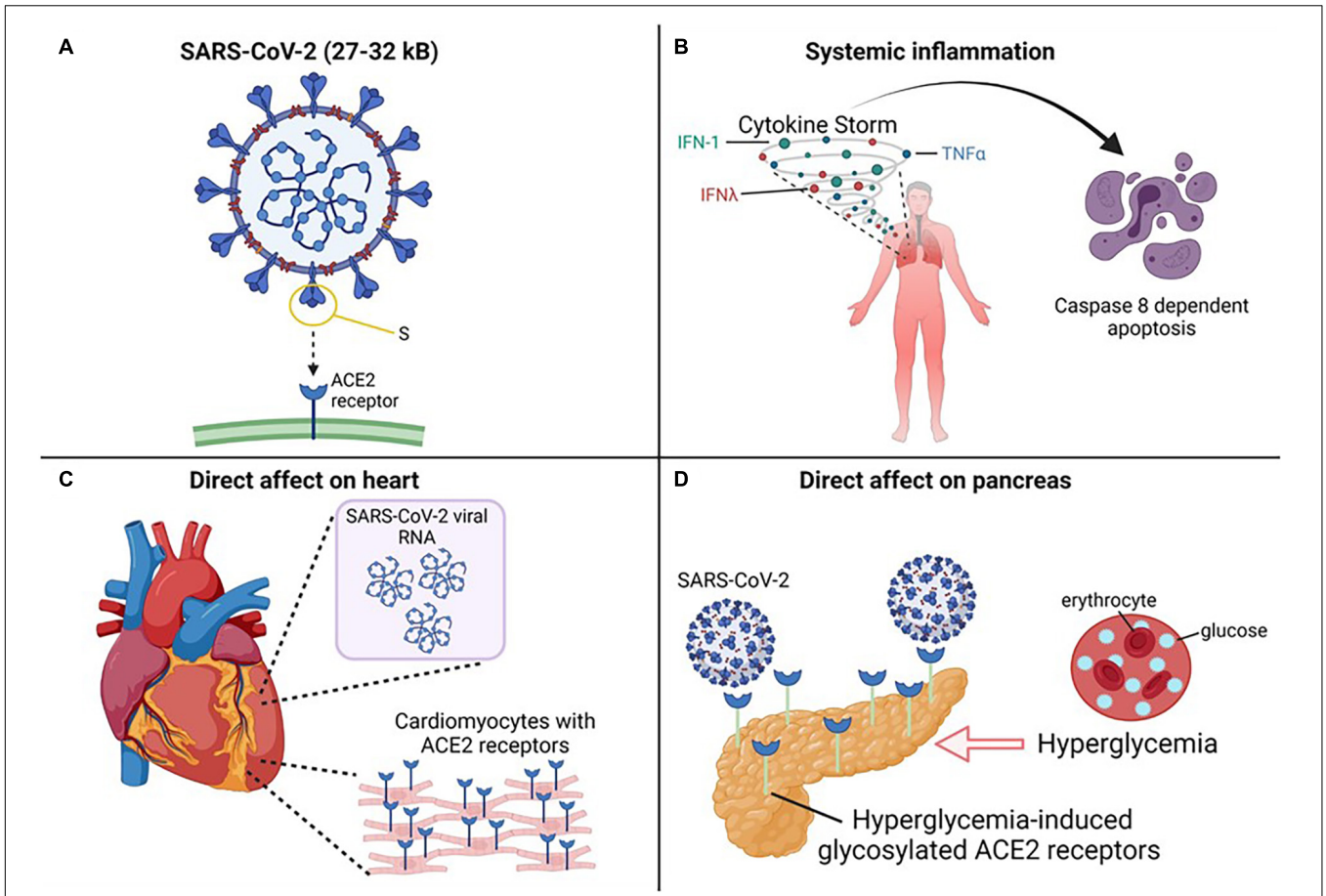

FIGURE 3 | Molecular mechanisms of SARS-CoV-2 infection.

while SARS-CoV-2 and SARS-CoV bind to the ACE2 receptor (Petrosillo et al., 2020). Even in binding to ACE2, key differences have been observed where the differences in the mechanism are possibly speculated to help explain the difference in infectivity between SARS-Cov2 and SARS-CoV (Shang et al., 2020; Ozono et al., 2021). Even considering these significant differences, the long-lasting effects on people infected with these viruses share similarities (Li et al., 2003; Peiris et al., 2003; Hui, 2005; Ahmed et al., 2020; Chasouraki et al., 2020; Xiong et al., 2020) which are worth investigating to understand if there is a common underlying mechanism. Researchers have proposed a few potential mechanisms of how SARS-CoV2 is involved in causing severe outcomes for people with cardiovascular disease and/or diabetes mellitus (**Figure 3**). These are discussed below.

Systemic Inflammation

Systemic inflammation is one of the most common findings in autopsies of patients who had COVID-19. Findings include focal pancreatitis, myocardial inflammation, and others (Eketunde et al., 2020). Researchers also observed inflammation in the brain (Lee L. Y. et al., 2020). While virus infections are known to cause direct damage to heart cells, Lee M. H. et al. (2020) concluded the brain inflammation likely was caused through an indirect mechanism secondary to the systemic response to SARS-CoV-2 infection. Providing support for this hypothesis, Hadjadj et al. (2020) observed an impaired interferon type I response in patients with COVID-19 with a high viral load and heightened inflammatory response. Clinically, inflammation and immune response are often two-edged swords, necessary to help the body fight and apparent infection, but sometimes resulting in damage to organs.

The acute hypoxic respiratory failure and ARDS-like picture seen in patients with severe COVID-19 is thought to be triggered by a cytokine storm (Hojyo et al., 2020). Additionally, cytokine storm has been put forward as a mechanism contributing to left ventricular dysfunction in patients with SARS (Li et al., 2003). Therefore, it is possible that hyper-inflammation and a modulated immune response could also explain cardiovascular damage in COVID-19 patients. In a study of 217 patients, IL-6 and lactate dehydrogenase were detected within 24 h of hospital admittance (Zeng et al., 2020). Because IL-6 has pro-inflammatory properties, this has been proposed as one factor responsible for severe diabetes mellitus and COVID-19 infection (Lim et al., 2021). However, recent clinical trials targeting IL-6 with tocilizumab or sarilumab have shown mixed results (Stone et al., 2020; Cavalli et al., 2021; Hermine et al., 2021; Parr,

2021; Salvarani et al., 2021). Cavalli et al. further showed that inhibiting IL-1 with anakinra significantly reduced mortality risk compared to inhibiting IL-6. In this study, IL-6 inhibition seemed to be only effective in patients either with high C-reactive protein or lactate dehydrogenase concentrations (Cavalli et al., 2021). In another study, multiple cytokines were detected in COVID-19 patients with mild or moderate symptoms, namely IL-1α, IL-1β, IL-17A, IL-12 p70, and IFNα (Yale et al., 2020). In the same study, patients with severe symptoms also were shown to have IL-33, IL-16, IL-21, IL-23, IFN-λ in their blood, as well as thrombopoietin (TPO) eotaxin, and eotaxin 3 (Yale et al., 2020).

Recently, researchers studying COVID-19 cytokine storm in bone marrow-derived macrophages (BMDMs) have proposed a possible mechanism linked to programmed cell death that can explain systemic inflammation not only in COVID-19 but also potentially in MERS, SARS, and other viruses where cytokine storm has been observed (Channappanavar and Perlman, 2017; Karki et al., 2021; Ryabkova et al., 2021). The researchers demonstrated cell death only when both TNF-α and IFN-λ were applied as a treatment, and not in any other combination of cytokines, individually or in combinations that did not include TNF-α and IFN-λ; furthermore, in their analysis of data from Silvin et al. (2020), they observed that while TNF-α production peaked in patients with moderate disease, IFN-λ only peaks in patients with severe COVID-19. This observation is also supported by RNA-seq data that suggests the increase in production of TNF-α and IFN-λ is driven by immune cells (Lee J. S. et al., 2020). The researchers also showed that a combination of TNF-α and IFN-λ production causes inflammatory cell death *via* IRF1/STAT1 pathway expression. IRF1/STAT1 expression results in the production of iNOS and NO, which ultimately activates caspase-8 dependent apoptosis. This programmed cell death was demonstrated not to be caused by suppression of NF-κB, nor was it due to intrinsic apoptosis in macrophages.

Direct Injury

Viral particles have been found within cardiomyocytes in patients infected with SARS-CoV-2 (Dolhnikoff et al., 2020; Tavazzi et al., 2020). Viral RNA of SARS-CoV-2 has also been detected in cardiac tissue during autopsies (Lindner et al., 2020; Liu P. P. et al., 2020). This is similar to what was observed in SARS-CoV-1 infection as well (Oudit et al., 2009). Researchers have also observed *in vitro* direct infection by SARS-CoV-2 in human iPSC-derived cardiac cells (Pérez-Bermejo et al., 2020). In this study, the researchers observed cytopathic damage by SARS-Cov-2, resulting in myofibrillar fragmentation and nuclear DNA loss in intact cells, even if the virus was not actively replicating. The same researchers also observed similar cytopathic results in myocardium cells of patients with COVID-19. These data suggest that SARS-CoV-2 can directly infect cardiac cells, and the prevailing hypothesis of SARS-CoV-2 entry into cells is through the ACE2 receptor (Liu P. P. et al., 2020). A recent study showed that the virus could gain entry into a human cell line *via* the ACE2 receptor (Hoffmann et al., 2020). In a protein profiling study using immunohistochemistry, researchers profiled over 150 proteins and found ACE2 was significantly expressed in cardiomyocytes and renal tubules (Hikmet et al., 2020). While ACE2 was detected by both immunohistochemistry and transcriptomics in the pancreas, expression was not as high as in the heart or kidneys (Hikmet et al., 2020).

It is conceivable that direct injury mediated through ACE2 could explain a link between heart failure and diabetes mellitus in COVID-19 patients, which would explain how the virus could be directly involved in damaging the heart and pancreas. However, in a recent analysis of transcriptomic data, the presence of ACE2 in the pancreatic islet β cells were not conclusive: TMPRSS2 was not co-expressed with ACE2 in these cells, which is a necessary co-factor to facilitate SARS-CoV-2 cellular entry (Coate et al., 2020; Hoffmann et al., 2020; Ozono et al., 2021); however, with SARS, diabetes was in some cases was shown to persist for 3 years after infection, indicating potential damage to islet β cells (Yang et al., 2010).

Role of Renin–Angiotensin–Aldosterone System

ACE2 is part of the Renin–angiotensin–Aldosterone System (RAAS) system, and its role in potential direct injury by the virus has been discussed above. While ACE is involved in causing a cascade that results in vasoconstriction and inflammation *via* converting angiotensin I to angiotensin II, ACE2 breaks down angiotensin II and thus simultaneously decreases the afterload on the heart (*via* vasodilation) and promotes glucose tolerance (Chappel and Ferrario, 2006; Chhabra et al., 2013). Thus, ACE2 may help protect the cardiovascular system from the remodeling that occurs secondary to increased afterload. Previously, SARS-CoV-1 was shown to reduce ACE2 expression (Kuba et al., 2005), leading to cardiac injury. Perhaps SARS-CoV-2 affects the RAAS system similarly (Luo et al., 2021), which could explain a link between diabetes and cardiac injury seen in COVID-19 patients. This protective effect of ACE2 seems contradictory to its role in virus entry in cells. This contradiction can be explained by hyperglycemia-induced glycosylation (discussed below).

Hyperglycemia

Hyperglycemia has frequently been found in COVID-19 patients with severe outcomes (Bode et al., 2020). Interestingly, a history of diabetes and hyperglycemia was also found to result in severe outcomes with patients infected with SARS (Yang et al., 2006); thus, a proposed mechanism for hyperglycemia in SARS involved the hyperglycemia-induced glycosylation of ACE2 and the viral spike protein, potentially modulating the binding ability of the virus to the receptor. A similar hypothesis has been proposed to SARS-CoV-2 as well (Brufsky, 2020).

Brufsky notes a discrepancy in gene expression in recent survey studies where ACE2 expression was an inverse correlation of ACE2 expression to disease severity (Chen J. et al., 2020). This discrepancy can be explained by protein glycosylation, a posttranslational modification that gene expression cannot detect. This would suggest that the glycosylated ACE2 receptor is responsible for virus binding and fusion while still explaining the benefit provided by non-glycosylated ACE2.

CONCLUSION AND FUTURE DIRECTIONS

In this work we reviewed recent reports supporting that SARS-CoV-2 infection was directly and indirectly associated with adverse health outcomes among all people, but especially for those with HF and/or diabetes. There is a link among diabetes and heart failure and SARS-CoV-2 infection that stretches beyond mere pre-infection comorbidity (**Figure 1**) and has the potential to have long-lasting effects on the global health system. Just a small increase in the incidence of diabetes or cardiac dysfunction could have profound consequences in overall health burden and number of required screening exams. Currently, some members of the European Society of Cardiology posit that we reasonably might screen (or continue to monitor) for cardiac dysfunction in (1) patients who had demonstrated cardiac dysfunction during their COVID infection; (2) patients with clinical symptoms of dyspnea, exercise intolerance, long COVID symptoms; (3) anyone who had elevated cardiac troponin levels during infection (Richter et al., 2021). Arguments for screening the latter group seem supported by the evidence in Puntmann et al. (2020). Puntmann et al. (2020) and Rajpal et al. (2020) also noted tissue-level signs of cardiac stress in a large percentage of asymptomatic or mildly symptomatic individuals.

We find more questions than answers with the available data, especially regarding patient care and screening in the post-COVID era. *In the acute setting, when the treatment for one aspect of the disease can exacerbate another (such as glucocorticoids dampening inflammation but causing hyperglycemia), can we optimize treatments for diabetes and heart failure using the familiarity with the patient, understanding of pharmaco-kinetics/-dynamics in illness, and consideration of the practicalities in practicing medicine (Bornstein et al., 2020; Hartmann-Boyce et al., 2020; Korytkowski et al., 2020; Solerte et al., 2020; Dagan et al., 2021). Is there a role for TNF-α and IFN-λ inhibition (Lee J. S. et al., 2020)?* There is growing acceptance of and interest in the chronic, symptomatic long-term effects of COVID-19, or "Long-COVID" with multiple trials and studies initiated. *What is "Long-COVID" and is it similar to or a form of post-sepsis syndrome, and does it have cardiac components? Is it possible that a common mechanism explains the multi-organ effects and links SARS and MERS with COVID-19? Are we seeing a real increase in diabetes incidence (Al-Aly et al., 2021), and if so, what is the root cause and type of diabetes? Could it be direct or indirect damage to pancreatic cells, increased detection from increased healthcare screening for the disease, ramifications of inactivity during quarantine, or something entirely different?* The answers to these and like questions are important because the answers dictate treatment and guide screening. Primary care physicians and bodies such as the US Preventive Services Task Force, who help create evidence-based guidelines for physicians caring for patients, will undoubtably be monitoring the developments. Importantly, too, *what is the true incidence of infection and what are the long-term sequelae for asymptomatic individuals?* We saw the preliminary data in one study that 67% of mildly symptomatic to asymptomatic patients still have physiologic evidence of disease damage post-infection (Puntmann et al., 2020). Are they at risk for developing HF or diabetes earlier than before or at all? That answer might help us to calculate the cost-benefit to screening for SARS-CoV-2 antibodies, or prior infection. With more data, we may begin to answer some of these questions.

Armed with new and old knowledge about potential coronavirus infection mechanisms, we may begin to discover new ways to optimize old treatments in the setting of coronavirus infection or even develop entirely new preventative measures. As the fight continues, we look forward to progress in science and medicine.

AUTHOR CONTRIBUTIONS

CH, BL, and RK collected the material and wrote the manuscript. VNSG provided critical feedback and helped to shape the manuscript. All authors contributed to the article and approved the submitted version.

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Temporal Trends in Outcomes of ST-Elevation Myocardial Infarction Patients With Heart Failure and Diabetes

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Aims: We aimed to assess temporal trends in outcomes of ST-elevation myocardial infarction (STEMI) patients with diabetes and heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) and compared both groups.

Methods: Data from the National Inpatient Sample was analyzed between 2005 and 2017. We assessed hospitalizations rate and in-hospital mortality, ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation (AF), cardiogenic shock (CS), ischemic stroke, acute renal failure (ARF), and revascularization strategy. Socio-economic outcomes consisted of the length of stay (LoS) and total charges/stay.

Results: Hospitalization rate steadily decreased with time in STEMI patients with diabetes and HFrEF. Mean age (SD) decreased from 71 ± 12 to 67 ± 12 ($p < 0.01$), while the prevalence of comorbidities increased. Mortality was stable (around 9%). However, VT, VF, AF, CS, ischemic stroke, and ARF significantly increased with time. In STEMI patients with HFpEF and diabetes, the hospitalization rate significantly increased with time while mean age was stable. The prevalence of comorbidities increased, mortality remained stable (around 4%), but VF, ischemic stroke, and ARF increased with time. Compared to patients with HFrEF, HFpEF patients were 2 years older, more likely to be females, suffered from more cardio-metabolic risk factors, and had a higher prevalence of cardiovascular diseases. However, HFpEF patients were less likely to die [adjusted OR = 0.635 (0.601-0.670)] or develop VT [adjusted OR = 0.749 (0.703-0.797)], VF [adjusted OR = 0.866 (0.798-0.940)], ischemic stroke [adjusted OR = 0.871 [0.776-0.977)], and CS [adjusted OR = 0.549 (0.522-0.577)], but more likely to develop AF [adjusted OR = 1.121 (1.078-1.166)]. HFpEF patients were more likely to get PCI but less likely to get thrombolysis or CABG. Total charges per stay increased by at least 2-fold in both groups. There was a slight temporal reduction over the study period in the LoS of the HFpEF.

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Conclusion: While hospitalizations for STEMI in patients with diabetes and HFpEF followed an upward trend, we observed a temporal decrease in those with HFrEF. Mortality was unchanged in both HF groups despite the temporal increase in risk factors. Nevertheless, HFpEF patients had lower in-hospital mortality and cardiovascular events, except for AF.

Keywords: heart failure, diabetes, HFREF, HFPEF, STEMI, cardiovascular disease, NIS, mortality

INTRODUCTION

Heart failure (HF) has been described as a growing pandemic with a significant economic burden. It is estimated that 2.4% of the population currently suffers from HF, which is expected to rise to 3.0% in 2030 (Heidenreich et al., 2013), coupled with an increase in over 100% of the total cost reaching 69.8 billion USD (Heidenreich et al., 2013).

HF is associated with increased morbidity and mortality, especially in the elderly, who are subject to frequent re-hospitalizations (Thrainsdottir et al., 2005; Roth et al., 2015). HF and myocardial infarction (MI) are a common and hazardous combination, with ischemic heart disease remaining the most common cause of HF and a common consequence of it (Torabi et al., 2014; Cahill and Kharbanda, 2017). In a study that examined the association between HF and mortality in patients discharged after their first MI, the 1-year mortality rate was 13.9% in patients with HF compared to 2.4% in patients with no HF (Dunlay et al., 2019). Another study found that up to 10% of patients presenting with the acute coronary syndrome (ACS) have underlying heart failure, which predisposed them to higher in-hospital mortality (Jeger et al., 2017).

Diabetes is associated with higher cardiovascular events (Huang et al., 2017). Patients with HF, MI, or both often encounter diabetes, as they share similar cardio-metabolic risk factors. In adult diabetic patients, the prevalence of HF is estimated to be 9–22%, which is almost 3–4 times the prevalence in the general population (Kaul et al., 2013). On the other side, the prevalence of diabetes in HF patients ranges from 10 to 47%, according to the age and underlying comorbidities (Nichols et al., 2004). Further, HF patients with diabetes have worse clinical outcomes than their non-diabetic counterparts (Allen et al., 2013). Furthermore, diabetes is an independent risk factor for death and re-hospitalizations (Einarson et al., 2018). An improvement in the prevalence, incidence, and outcome of CVD has been noted in the past decades in the general population (Pocock et al., 2013) and diabetes individuals (Abi Khalil et al., 2012). This was fueled by the emergence of new treatments and the comprehensive implementation of prevention guidelines. However, this gradual progress was counteracted by a continuous rise in the costs of the CVD care (Pocock et al., 2013). We, therefore, assessed the temporal trend in cardiovascular and economic outcomes of patients with heart failure with reduced ejection fraction (HfrEF) and with preserved ejection fraction (HFpEF), hospitalized for ST-elevation myocardial infarction (STEMI), and compared both HF entities.

MATERIALS AND METHODS

Data Source

Data were extracted from the national inpatient sample (NIS) database between the years 2005–2017. The database represents almost 20% of de-identified inpatient hospitalizations in the US and about 95% after weighting. The NIS contains clinical and economic data elements related to patients' demographics, diagnosis, and comorbidities, coded using the International Classification of Disease—9th edition (up till 2014) and ICD-10th edition afterward. The study received administrative IRB approval as it contains only de-identified data (record number 18-00017).

Diagnosis and Outcomes

The primary diagnosis for this study was STEMI in patients known to have HF and diabetes at inclusion. HF patients were divided into HFrEF and HFpEF based on ICD-9 and ICD-10 used and validated in heart failure studies from the NIS database (Goyal et al., 2018; Lemor et al., 2018; see **Appendix**). We first assessed temporal trends in baseline characteristics and in-hospital cardiovascular and socio-economic outcomes of STEMI patients with diabetes and either HFrEF or HFpEF between 2005 and 2017. Then, we combined all HFrEF patients and compared them to HFpEF patients for the same outcomes during the observation period. Cardiovascular outcomes included hospitalization rate per 100,000 adults and in-hospital mortality, ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation (AF), ischemic stroke, acute renal failure (ARF), and cardiogenic shock. The revascularization strategy included percutaneous coronary intervention (PCI), thrombolysis, and coronary artery bypass grafts (CABG). Socio-economic outcomes included length of stay (LoS) and total charges per stay.

Statistical Analysis

Data for categorical variables are presented using frequency distributions and cross-tabulations and means (standard deviation) and medians (with interquartile range) for continuous variables. Data weighting was used to allow for representative nationwide population estimates as recommended by the Healthcare Cost and Utilization Project, to which the NIS belongs (AHRQ, 2021). Patient-level discharge trend weights consisted of applying the DISCWT variable before 2012 and the TRENDWT variable from 2012 to 2017. Temporal changes were assessed using Trends were analyzed using generalized linear models. Hospitalization costs were adjusted for inflation using numbers provided by the United States Bureau of labor statistics.

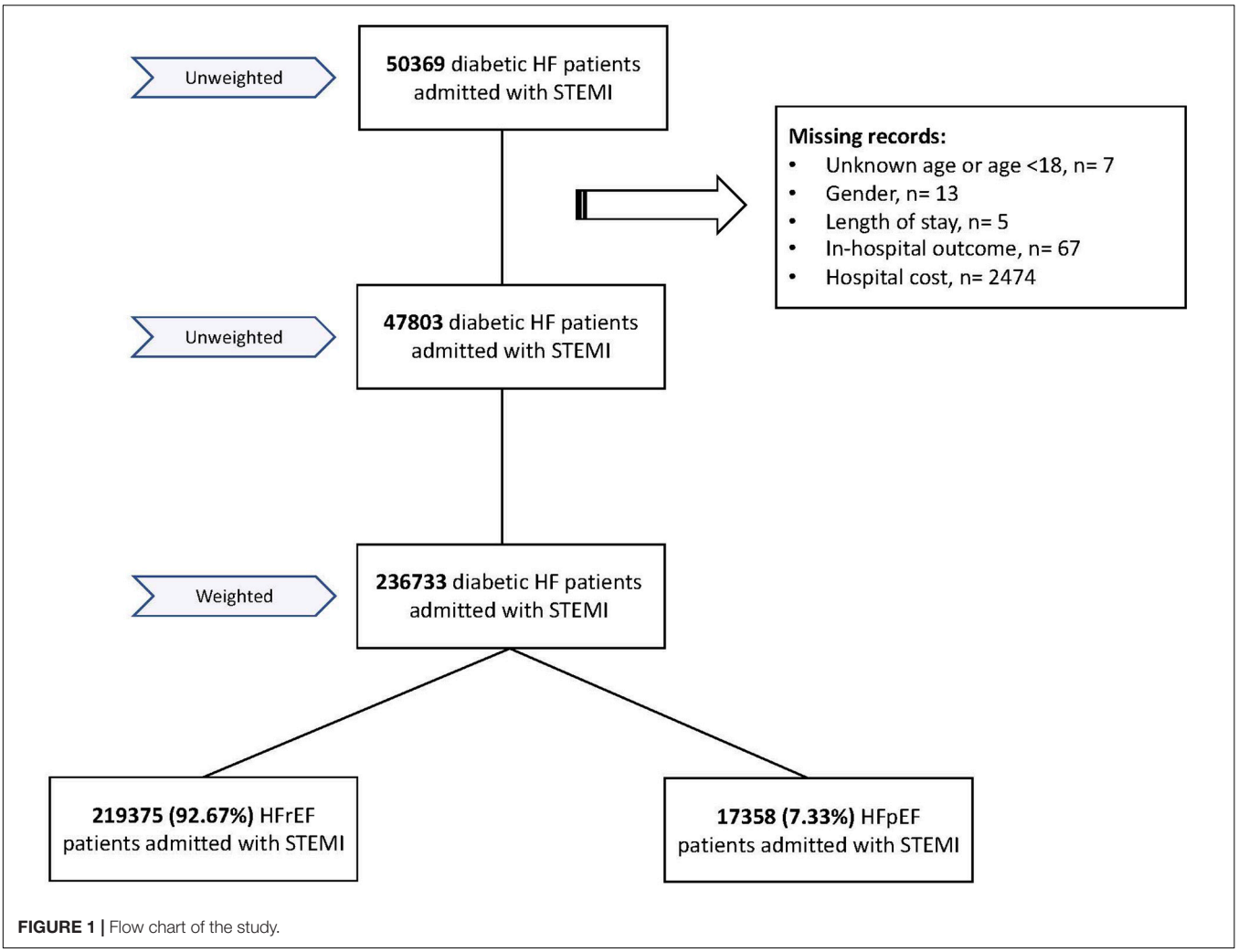

FIGURE 1 | Flow chart of the study.

Comparison of HFrEF with HFpEF patients was performed using a Student's *t*-test for continuous data and a χ^2-test for categorical data. Multivariable logistic regression analysis was performed to assess predictors of mortality in both groups. Cardiovascular events were adjusted for baseline characteristics and comorbidities that were statistically different between groups, including age, gender, race, obesity, hypertension, smoking dyslipidemia, peripheral vascular disease, renal failure, and coronary artery disease. We also calculated the Elixhauser comorbidity score, which measures patients' comorbidities. Initially developed in 1998 by Elixhauser et al. (1998), the score is based on 31 variants and assesses the association of comorbidity with death and future cardiovascular events. Statistical analyses were performed using SPSS (IBM, version 26).

RESULTS

Population

A total of 47,803 diabetic HF patients admitted for STEMI between 2005 and 2017 were included in our analysis after excluding patients with missing or incomplete records (**Figure 1**). After weighing the data, our patient population consisted of 236,733 HF patients. Interestingly, most HF patients (92.67%) had HFrEF patients, while only 7.33% had HFpEF.

Temporal Trend in Characteristics and Outcomes of Heart Failure With Reduced Ejection Fraction Patients

Hospitalization rate for HFrEF decreased from 10.81/100,000 adults to 7.12/100,000 adults (**Figure 2**, p trend < 0.001). Over the study period, the mean age (SD) in the HFrEF group decreased from 71.8 (12.5) to 67 (12.6) years old (**Table 1**, p trend < 0.001). The age distribution in the HFrEF group showed significant changes over time: The percentage of patients in the age intervals 75–84 and > 85 gradually decreased, whereas those in the age intervals < 55, 55–64 gradually increased (p trend < 0.001 for all). By 2017, 30% of the patients were older than 75 years of age compared to 47% in 2005. The racial distribution changed as well over time as the percentage of white patients decreased from 75.60 to 66.80% ($p < 0.001$), while the percentage of Blacks, Hispanics, and Asians slightly but significantly increased

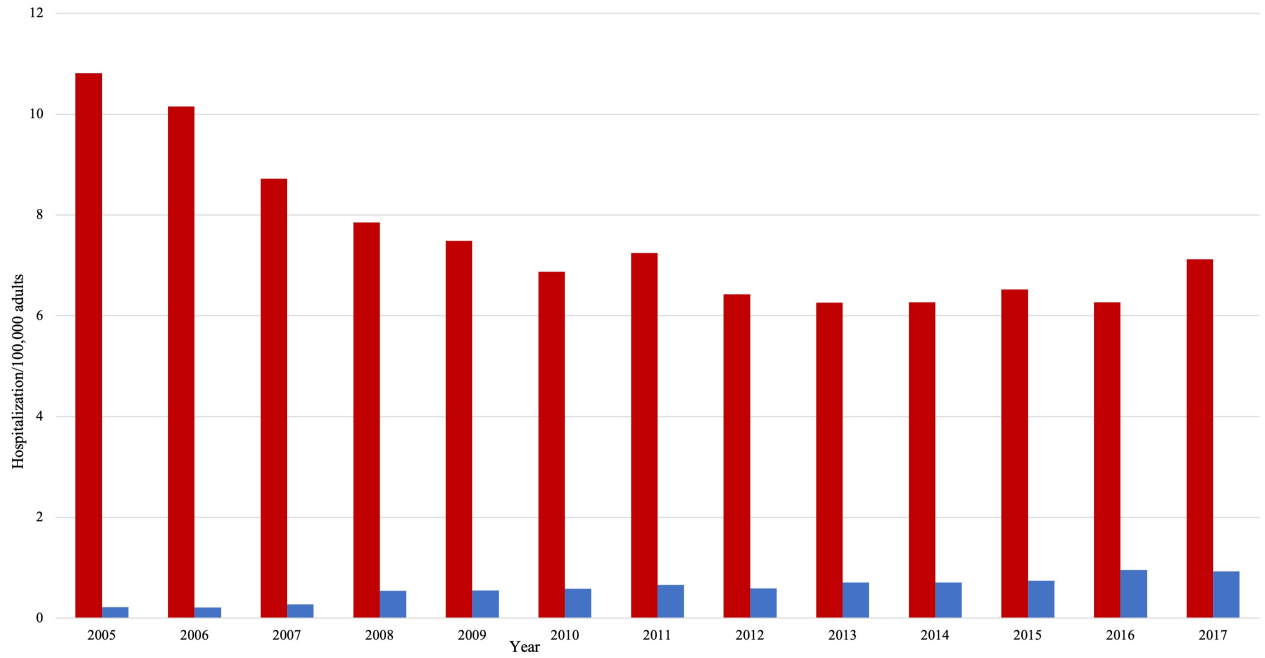

FIGURE 2 | Hospitalizations per 100,000 adults in HFrEF patients (red color) and HFpEF patients (blue color).

(p trend < 0.001 for all). The prevalence of cardiometabolic risk factors such as obesity, hypertension, smoking, and dyslipidemia increased over the study period ($p < 0.001$ for all), which was translated into a substantial increase in the mean (SD) of the Elixhauser comorbidity index. A similar trend was observed in renal failure and coronary artery disease (CAD). Age-adjusted mortality was unchanged, neither was the sex distribution. However, ventricular fibrillation, ventricular tachycardia, atrial fibrillation, ischemic stroke, and acute renal failure increased with time ($p < 0.001$ for all). In terms of revascularization, PCI significantly increased by almost 3-fold ($p < 0.001$) at a time when CABG slightly- and non-significantly- decreased.

Temporal Trend in Characteristics and Outcomes of Heart Failure With Preserved Ejection Fraction Patients

The hospitalization rate in HFpEF increased by almost 4 folds, from 0.22/100,000 adults to 0.93/100,000 adults (p trend < 0.001). However, there was no statistically significant change in the temporal trend of age and gender (**Table 2**). By 2017, 38% of the patients were older than 75 years of age compared to 40% in 2005. In a pattern similar to HFrEF patients, cardiovascular risk factors and comorbidities significantly increased with time. For instance, smoking prevalence increased by more than fourfolds ($p < 0.001$). There were no significant changes in age-adjusted mortality and sex distribution. Only ventricular fibrillation and acute renal failure significantly increased among other cardiovascular outcomes ($p < 0.01$ for both). There was a twofold increase in the likelihood of having a PCI during that time (p trend < 0.001), but the rates of thrombolysis and CABG were unchanged.

Comparison of Both Heart Failure Categories

As seen in **Table 3**, HFpEF patients were 2 years older, more likely to be females, Blacks, and less likely to be Hispanic (p trend < 0.001). They were more likely to smoke and have cardio-metabolic risk factors, such as obesity, hypertension, and dyslipidemia. Cardiovascular diseases, such as PVD, renal failure, and CAD, were more prevalent in HFpEF. Nevertheless, they were less likely to die [adjusted OR = 0.635 (0.601-0.670)] or develop ventricular tachycardia [adjusted OR = 0.749 (0.798-0.940)], ventricular fibrillation [adjusted OR = 0.866 (0.798-0.940)], cardiogenic shock [adjusted OR = 0.549 (0.522-0.577)] or ischemic stroke [adjusted OR = 0.871 (0.776-0.977)] (**Table 4**). However, atrial fibrillation was significantly higher in HFpEF patients [adjusted OR = 1.121 (1.078-1.166)]. Significant differences were also observed in the treatment of STEMI between the two groups. HFpEF patients were more likely to get PCI [adjusted OR = 1.106 (1.066-1.147)] but less likely to get thrombolysis or CABG [adjusted OR = 0.720 (0.620-0.836), 0.750 (0.703-0.801); respectively] compared to HFrEF patients.

Predictors of Mortality

The predictors of mortality in both groups are shown in **Table 5**. As expected, increasing age is associated with increased mortality risk in both groups. Females were slightly protected compared to males in the HFrEF group [OR = 0.93 (0.904–0.956), $p < 0.001$], but no difference in mortality based on gender was reported in HFpEF. Racial characterization showed

TABLE 1 | Baseline characteristics, outcomes, and temporal trend of HFrEF patients with diabetes admitted for STEMI between 2005 and 2017.

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	P-Trend
Age														
Mean age (SD)	71.84 (12.52%)	71.35 (12.86%)	71.12 (12.94%)	70.96 (12.83%)	70.53 (12.99%)	70.14 (13.13%)	69.43 (13.22%)	68.51 (12.94%)	68.38 (12.81%)	67.80 (12.83%)	67.37 (12.75%)	67.13 (12.70%)	67.05 (12.61%)	< 0.001
<55	2,238 (9.90%)	2,564 (11.80%)	2,130 (11.50%)	1,960 (11.50%)	2,078 (12.60%)	1,989 (13.10%)	2,272 (13.90%)	2,210 (15.00%)	2,190 (15.10%)	2,455 (16.70%)	2,500 (16.60%)	2,570 (17.10%)	2,935 (16.80%)	< 0.001
55–64	4,136 (18.20%)	3,985 (18.40%)	3,678 (19.90%)	3,249 (19.10%)	3,275 (19.90%)	3,163 (20.90%)	3,749 (23.00%)	3,520 (23.90%)	3,455 (23.80%)	3,585 (24.40%)	3,820 (25.30%)	3,895 (25.90%)	4,380 (25.10%)	< 0.001
65–74	5,670 (25.00%)	5,349 (24.70%)	4,405 (23.80%)	4,512 (26.50%)	4,366 (26.50%)	3,960 (26.20%)	4,116 (25.20%)	3,860 (26.20%)	3,920 (27.00%)	3,795 (25.90%)	4,180 (27.70%)	3,990 (26.50%)	5,010 (28.70%)	0.002
75–84	6,957 (30.70%)	6,263 (28.90%)	5,266 (28.40%)	4,706 (27.60%)	4,145 (25.10%)	3,657 (24.20%)	3700 (22.70%)	3,245 (22.00%)	3,145 (21.60%)	3,145 (21.40%)	2,925 (19.40%)	3,075 (20.40%)	3,550 (20.30%)	< 0.001
>84	3,666 (16.20%)	3,491 (16.10%)	3,049 (16.50%)	2,600 (15.30%)	2,633 (16.00%)	2,366 (15.60%)	2464 (15.10%)	1,915 (13.00%)	1,830 (12.60%)	1,690 (11.50%)	1,680 (11.10%)	1,515 (10.10%)	1,585 (9.10%)	< 0.001
Gender														
Male	11,659 (51.40%)	11,217 (51.80%)	9,752 (52.60%)	8,848 (52.00%)	9,005 (54.60%)	8,499 (56.20%)	8978 (55.10%)	8,400 (56.90%)	8,435 (58.00%)	8,760 (59.70%)	9,275 (61.40%)	9,425 (62.60%)	10,920 (62.50%)	< 0.001
Female	11,009 (48.60%)	10,434 (48.20%)	8,776 (47.40%)	8,179 (48.00%)	7,492 (45.40%)	6,636 (43.80%)	7,323 (44.90%)	6,350 (43.10%)	6,105 (42.00%)	5,910 (40.30%)	5,830 (38.60%)	5,620 (37.40%)	6,540 (37.50%)	< 0.001
Race														
White	12,573 (75.60%)	12,051 (74.00%)	9,953 (72.00%)	10,550 (74.70%)	10,359 (70.60%)	9,220 (69.10%)	10,128 (69.20%)	9,625 (69.00%)	9,655 (70.00%)	9,670 (69.90%)	9,640 (67.80%)	9,560 (66.50%)	11,170 (66.80%)	< 0.001
Black	1,369 (8.20%)	1,549 (9.50%)	1,393 (10.10%)	1,211 (8.60%)	1,512 (10.30%)	1,392 (10.40%)	1,795 (12.30%)	1,595 (11.40%)	1,390 (10.10%)	1,445 (10.40%)	1,660 (11.70%)	1,710 (11.90%)	1,930 (11.50%)	0.003
Hispanic	1,633 (9.80%)	1,689 (10.40%)	1,490 (10.80%)	1,192 (8.40%)	1,517 (10.30%)	1,546 (11.60%)	1,561 (10.70%)	1,560 (11.20%)	1,650 (12.00%)	1,605 (11.60%)	1,710 (12.00%)	1,845 (12.80%)	2,070 (12.40%)	0.001
Asian	369 (2.20%)	432 (2.70%)	384 (2.80%)	467 (3.30%)	456 (3.10%)	487 (3.70%)	488 (3.30%)	375 (2.70%)	460 (3.30%)	425 (3.10%)	520 (3.70%)	495 (3.40%)	750 (4.50%)	0.004
Native American	98 (0.60%)	111 (0.70%)	136 (1.00%)	171 (1.20%)	120 (0.80%)	170 (1.30%)	59 (0.40%)	185 (1.30%)	80 (0.60%)	90 (0.70%)	125 (0.90%)	115 (0.80%)	95 (0.60%)	0.662
Other minority	588 (3.50%)	448 (2.80%)	470 (3.40%)	539 (3.80%)	715 (4.90%)	527 (3.90%)	611 (4.20%)	605 (4.30%)	550 (4.00%)	595 (4.30%)	555 (3.90%)	645 (4.50%)	695 (4.20%)	0.033
Comorbidities														
Obesity	2,288 (10.10%)	2,264 (10.50%)	2,073 (11.20%)	2,573 (15.10%)	2,787 (16.90%)	2,620 (17.30%)	3,172 (19.50%)	3,150 (21.40%)	3,235 (22.20%)	3,395 (23.10%)	3,695 (24.50%)	3,820 (25.40%)	4,490 (25.70%)	< 0.001
Hypertension	14,746 (65.10%)	14,399 (66.50%)	12,844 (69.30%)	12,065 (70.90%)	12,679 (76.90%)	11,677 (77.20%)	12,774 (78.40%)	11,795 (80.00%)	11,740 (80.70%)	11,875 (80.90%)	12,675 (83.90%)	11,520 (76.60%)	11,520 (76.60%)	< 0.001
Smoking	3,113 (13.70%)	3,478 (16.10%)	3,489 (18.80%)	3,392 (19.90%)	4,272 (25.90%)	4251 (28.10%)	4,870 (29.90%)	4,900 (33.20%)	4,900 (33.70%)	5,470 (37.30%)	6,040 (40.00%)	5,970 (39.70%)	7,225 (41.40%)	< 0.001
Dyslipidemia	7,912 (34.90%)	8,117 (37.50%)	7,907 (42.70%)	7,764 (45.60%)	8,962 (54.30%)	8595 (56.80%)	9,666 (59.30%)	9,030 (61.20%)	9,100 (62.60%)	9,650 (65.80%)	10,150 (67.20%)	10405 (69.20%)	12,170 (69.70%)	< 0.001
PVD	2,517 (11.10%)	2,469 (11.40%)	2,464 (13.30%)	2,442 (14.30%)	2,608 (15.80%)	2170 (14.30%)	2,560 (15.70%)	2,385 (16.20%)	1,990 (13.70%)	2,360 (16.10%)	2,220 (14.70%)	2030 (13.50%)	1,810 (10.40%)	0.588

(Continued)

TABLE 1 | (Continued)

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	P-Trend
Renal failure	3,940 (17.40%)	5,497 (25.40%)	5,470 (29.50%)	4,682 (27.50%)	5,058 (30.70%)	4846 (32.00%)	5,142 (31.50%)	4,750 (32.20%)	4,580 (31.50%)	4,805 (32.80%)	4,760 (31.50%)	5000 (33.20%)	6,085 (34.90%)	0.001
CAD	14,662 (64.70%)	14,301 (66.10%)	12,770 (68.90%)	12,346 (72.50%)	12,621 (76.50%)	12015 (79.40%)	13,221 (81.10%)	12,005 (81.40%)	11,980 (82.40%)	12,425 (84.70%)	12,915 (85.50%)	13780 (91.60%)	15,715 (90.00%)	< 0.001
Elixhauser comorbidity index	36,518 (7.2593)	4.2675 (7.5304)	4.6763 (7.8733)	4.6712 (7.9058)	5.2804 (8.5712)	5.4112 (8.4923)	6.0003 (9.0120)	5.8506 (8.9929)	5.5151 (8.7784)	5.9824 (9.1458)	6.2877 (9.2685)	9.8288 (6.9981)	10.3547 (7.3043)	< 0.001
Cardiovascular outcomes														
Mortality (Age-adjusted)	8.79%	8.54%	9.68%	9.14%	7.26%	8.09%	9.60%	10.85%	9.07%	9.72%	10.94%	9.85%	9.28%	0.099
Mortality (Age-adjusted, male)	7.73%	8.35%	9.43%	8.65%	6.27%	8.72%	8.72%	10.53%	8.65%	9.91%	10.40%	9.26%	8.88%	0.09
Mortality (Age-adjusted, female)	8.24%	8.75%	10.04%	9.89%	8.84%	6.40%	11.04%	11.53%	9.88%	10.03%	10.56%	10.67%	9.98%	0.104
Ventricular tachycardia	1,509 (6.70%)	1,714 (7.90%)	1,528 (8.20%)	1,489 (8.70%)	1464 (8.90%)	1,675 (11.10%)	1,720 (10.60%)	1,625 (11.00%)	1,515 (10.40%)	1,855 (12.60%)	1,880 (12.40%)	1,935 (12.90%)	2,380 (13.60%)	< 0.001
Ventricular fibrillation	655 (2.90%)	714 (3.30%)	782 (4.20%)	696 (4.10%)	690 (4.20%)	830 (5.50%)	859 (5.30%)	915 (6.20%)	1,100 (7.60%)	990 (6.70%)	1,175 (7.80%)	1120 (7.40%)	1225 (7.00%)	< 0.001
Atrial fibrillation	4,723 (20.80%)	4,529 (20.90%)	3,900 (21.00%)	3,519 (20.70%)	3,327 (20.20%)	3,404 (22.50%)	3,881 (23.80%)	3,450 (23.40%)	3,405 (23.40%)	3,610 (24.60%)	3,570 (23.60%)	3,610 (24.00%)	4300 (24.60%)	< 0.001
Cardiogenic chock	2,497 (11.00%)	2,659 (12.30%)	2,680 (14.50%)	2,717 (16.00%)	3,164 (19.20%)	3,219 (21.30%)	3,828 (23.50%)	3,485 (23.60%)	3,660 (25.20%)	3,835 (26.10%)	4,080 (27.00%)	3,960 (26.30%)	4,740 (27.10%)	< 0.001
Ischemic stroke	431 (1.90%)	546 (2.50%)	345 (1.90%)	341 (2.00%)	292 (1.80%)	329 (2.20%)	351 (2.20%)	350 (2.40%)	305 (2.10%)	410 (2.80%)	420 (2.80%)	440 (2.90%)	480 (2.70%)	0.003
Acute renal failure	3,370 (14.90%)	3,881 (17.90%)	3,730 (20.10%)	3,839 (22.50%)	4,548 (27.60%)	4,201 (27.80%)	5,049 (31.00%)	4,705 (31.90%)	4,540 (31.20%)	5,330 (36.30%)	5,455 (36.10%)	5,705 (37.90%)	6,615 (37.90%)	< 0.001
Revascularization strategies														
PCI	5,789 (25.5%)	6,382 (29.50%)	6,235 (33.70%)	6,331 (37.20%)	6,848 (41.50%)	6,624 (43.80%)	7,821 (48.00%)	7,695 (52.20%)	8,040 (55.30%)	8,570 (58.40%)	9,145 (60.50%)	10,320 (68.60%)	12,425 (71.20%)	< 0.001
Thrombolysis	374 (1.6%)	428 (2.00%)	283 (1.50%)	278 (1.60%)	261 (1.60%)	185 (1.20%)	211 (1.30%)	265 (1.80%)	235 (1.60%)	265 (1.80%)	185 (1.20%)	280 (1.90%)	275 (1.60%)	0.89
CABG	2,100 (9.3%)	2,228 (10.30%)	2,172 (11.70%)	1,657 (9.70%)	1,817 (11.00%)	1,595 (10.50%)	1,913 (11.70%)	1,445 (9.80%)	1,485 (10.20%)	1,415 (9.60%)	1,370 (9.10%)	1,360 (9.00%)	1,455 (8.30%)	0.061

TABLE 2 | Baseline characteristics, outcomes and temporal trend of HFpEF patients with diabetes admitted for STEMI between 2005–2017.

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	P-Trend
Age														
Mean age (SD)	70.65 (13.161)	71.35 (13.096)	73.71 (11.103)	72.98 (12.352)	72.28 (12.724)	73.46 (12.729)	72.69 (12.246)	70.81 (12.885)	71.77 (12.259)	72.25 (12.073)	70.45 (13.017)	70.02 (12.532)	69.90 (12.794)	0.084
<55	54 (11.90%)	54 (12.00%)	30 (5.30%)	96 (8.30%)	121 (10.00%)	106 (8.50%)	127 (8.70%)	125 (9.30%)	130 (8.10%)	135 (8.30%)	220 (12.90%)	310 (13.60%)	315 (13.90%)	0.184
55–64	79 (17.40%)	106 (23.50%)	104 (18.50%)	195 (16.90%)	230 (19.10%)	217 (17.40%)	254 (17.40%)	295 (21.90%)	330 (20.60%)	270 (16.60%)	330 (19.40%)	470 (20.60%)	425 (18.80%)	0.891
65–74	139 (30.70%)	68 (15.10%)	123 (21.90%)	281 (24.30%)	303 (25.10%)	325 (26.10%)	349 (23.90%)	360 (26.80%)	435 (27.20%)	445 (27.40%)	470 (27.60%)	615 (26.90%)	660 (29.20%)	0.097
75–84	109 (24.10%)	167 (37.00%)	208 (37.10%)	398 (34.40%)	322 (26.70%)	310 (24.90%)	448 (30.60%)	350 (26.00%)	370 (23.10%)	510 (31.40%)	355 (20.80%)	530 (23.20%)	505 (22.30%)	0.028
>84	72 (15.90%)	56 (12.40%)	96 (17.10%)	187 (16.20%)	231 (19.10%)	289 (23.20%)	285 (19.50%)	215 (16.00%)	335 (20.90%)	265 (16.30%)	330 (19.40%)	360 (15.80%)	355 (15.70%)	0.589
Gender														
Male	224 (49.40%)	191 (42.40%)	290 (51.60%)	534 (46.20%)	614 (50.90%)	561 (45.00%)	661 (45.20%)	610 (45.40%)	725 (45.30%)	815 (50.20%)	810 (47.50%)	1,045 (45.70%)	1,110 (49.10%)	0.99
Female	229 (50.60%)	259 (57.60%)	272 (48.40%)	623 (53.80%)	593 (49.10%)	686 (55.00%)	802 (54.80%)	735 (54.60%)	875 (54.70%)	810 (49.80%)	895 (52.50%)	1,240 (54.30%)	1,150 (50.90%)	0.99
Race														
White	244 (72.80%)	197 (61.90%)	308 (77.80%)	764 (74.30%)	766 (74.80%)	748 (66.30%)	920 (68.70%)	955 (74.60%)	1,020 (66.90%)	1,105 (72.00%)	1,105 (68.60%)	1,505 (68.70%)	1,510 (69.90%)	0.577
Black	64 (19.10%)	68 (21.40%)	44 (11.10%)	112 (10.90%)	104 (10.20%)	160 (14.20%)	208 (15.50%)	125 (9.80%)	200 (13.10%)	165 (10.70%)	225 (14.00%)	255 (11.60%)	275 (12.70%)	0.116
Hispanic	17 (5.10%)	28 (8.80%)	35 (8.80%)	84 (8.20%)	61 (6.00%)	117 (10.40%)	110 (8.20%)	120 (9.40%)	160 (10.50%)	155 (10.10%)	125 (7.80%)	235 (10.70%)	245 (11.30%)	0.015
Asian	0 (0.00%)	10 (3.10%)	9 (2.30%)	25 (2.40%)	26 (2.50%)	52 (4.60%)	47 (3.50%)	25 (2.00%)	65 (4.30%)	45 (2.90%)	60 (3.70%)	90 (4.10%)	85 (3.90%)	0.02
Native American	5 (1.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	21 (2.10%)	20 (1.80%)	5 (0.40%)	5 (0.40%)	15 (1.00%)	5 (0.30%)	20 (1.20%)	5 (0.20%)	25 (1.20%)	0.902
Other	5 (1.50%)	15 (72.80%)	0 (0.00%)	43 (4.20%)	46 (4.50%)	32 (2.80%)	50 (3.70%)	50 (3.90%)	65 (4.30%)	60 (3.90%)	75 (4.70%)	100 (4.60%)	20 (0.90%)	0.519
Comorbidities														
Obesity	73 (16.10%)	49 (10.90%)	68 (12.10%)	236 (20.40%)	174 (14.40%)	251 (20.10%)	260 (17.80%)	305 (22.70%)	410 (25.60%)	440 (27.10%)	560 (32.80%)	745 (32.60%)	730 (32.30%)	< 0.001
Hypertension	303 (66.90%)	334 (74.20%)	401 (71.40%)	882 (76.20%)	962 (79.70%)	988 (79.30%)	1,254 (85.80%)	1,170 (87.00%)	1,395 (87.20%)	1,375 (84.60%)	1,540 (90.30%)	1,940 (84.90%)	1,940 (84.90%)	< 0.001
Smoking	43 (9.50%)	62 (13.80%)	63 (11.20%)	177 (15.30%)	291 (24.10%)	281 (22.50%)	342 (23.40%)	430 (32.00%)	460 (28.70%)	490 (30.20%)	610 (35.80%)	810 (35.40%)	960 (42.50%)	< 0.001
Dyslipidemia	182 (40.30%)	169 (37.60%)	212 (37.70%)	465 (40.20%)	681 (56.40%)	735 (58.90%)	877 (59.90%)	800 (59.50%)	1,050 (65.60%)	1,065 (65.50%)	1,255 (73.60%)	1,690 (74.00%)	1,575 (69.70%)	< 0.001
PVD	71 (15.70%)	49 (10.90%)	112 (20.00%)	215 (18.60%)	213 (17.60%)	207 (16.60%)	264 (18.00%)	250 (18.60%)	225 (14.10%)	255 (15.70%)	335 (19.60%)	355 (15.50%)	290 (12.80%)	0.803
Renal failure	92 (20.40%)	138 (30.70%)	215 (38.30%)	409 (35.40%)	460 (38.10%)	480 (38.50%)	553 (37.80%)	570 (42.40%)	640 (40.00%)	685 (42.20%)	715 (41.90%)	1,010 (44.20%)	950 (42.00%)	0.001

(Continued)

TABLE 2 | Continued

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	P-Trend
CAD	271 (59.80%)	289 (64.20%)	390 (69.50%)	778 (67.20%)	923 (76.50%)	978 (78.40%)	1,122 (76.70%)	1,115 (82.90%)	1,290 (80.60%)	1,240 (76.30%)	1,370 (80.40%)	2,015 (88.20%)	2,030 (89.80%)	< 0.001
Elixhauser comorbidity index	3.6518 (7.2593)	4.2675 (7.5304)	4.6763 (7.8733)	4.6712 (7.9058)	5.2804 (8.5712)	5.4112 (8.4923)	6.0003 (9.0120)	5.8506 (8.9929)	5.5151 (8.7784)	5.9824 (9.1458)	6.2877 (9.2685)	9.8288 (6.9981)	10.3547 (7.3043)	< 0.001
Cardiovascular outcomes														
Mortality (Age-adjusted)	4.12%	3.60%	14.18%	6.08%	6.94%	7.64%	11.99%	3.55%	6.15%	8.15%	12.84%	3.27%	4.61%	0.947
Mortality (Age-adjusted, Male)	0.54%	2.65%	3.86%	11.07%	7.26%	10.89%	9.54%	3.13%	6.78%	3.80%	12.74%	3.43%	6.39%	0.415
Mortality (Age-adjusted, female)	4.16%	4.20%	23.96%	2.99%	6.33%	3.93%	16.86%	3.88%	3.54%	13.19%	13.21%	2.52%	2.79%	0.723
Ventricular tachycardia	25 (5.50%)	34 (7.60%)	37 (6.60%)	133 (11.50%)	107 (8.90%)	75 (6.00%)	122 (8.30%)	90 (6.70%)	125 (7.80%)	140 (8.60%)	115 (6.70%)	150 (6.60%)	195 (8.60%)	0.867
Ventricular fibrillation	15 (3.30%)	18 (4.00%)	5 (0.90%)	29 (2.50%)	44 (3.60%)	37 (3.00%)	42 (2.90%)	75 (5.60%)	75 (4.70%)	75 (4.60%)	110 (6.50%)	95 (4.20%)	125 (5.50%)	0.01
Atrial fibrillation	73 (16.10%)	116 (25.80%)	171 (30.40%)	199 (17.20%)	241 (20.00%)	287 (23.00%)	392 (26.80%)	390 (29.00%)	465 (29.10%)	525 (32.30%)	490 (28.70%)	525 (23.00%)	615 (27.20%)	0.092
Cardiogenic chock	29 (6.40%)	39 (8.70%)	48 (8.50%)	150 (13.00%)	146 (12.10%)	171 (13.70%)	199 (13.60%)	180 (13.40%)	255 (15.90%)	260 (16.00%)	255 (15.00%)	255 (11.20%)	310 (13.70%)	0.006
Ischemic stroke	15 (3.30%)	15 (3.30%)	14 (2.50%)	30 (2.60%)	15 (1.20%)	15 (1.20%)	46 (3.10%)	25 (1.90%)	30 (1.90%)	25 (1.50%)	50 (2.90%)	50 (2.20%)	40 (1.80%)	0.173
Acute renal failure	79 (17.40%)	94 (20.90%)	105 (18.70%)	311 (26.90%)	354 (29.30%)	375 (30.10%)	453 (31.00%)	445 (33.10%)	540 (33.80%)	600 (36.90%)	565 (33.10%)	795 (34.80%)	765 (33.80%)	<0.001
Revascularization strategies														
PCI	123 (27.20%)	140 (31.10%)	144 (25.70%)	365 (31.50%)	426 (35.30%)	464 (37.20%)	701 (47.90%)	670 (49.80%)	845 (52.80%)	810 (49.80%)	955 (56.00%)	1,335 (58.40%)	1,420 (62.80%)	<0.001
Thrombolysis	5 (1.10%)	16 (3.60%)	0 (0.00%)	24 (2.10%)	0 (0.00%)	21 (1.70%)	17 (1.20%)	15 (1.10%)	25 (1.60%)	5 (0.30%)	20 (1.20%)	30 (1.30%)	35 (1.50%)	0.599
CABG	22 (4.90%)	44 (9.80%)	68 (12.10%)	98 (8.50%)	73 (6.10%)	102 (8.20%)	128 (8.70%)	75 (5.60%)	120 (7.50%)	115 (7.10%)	110 (6.50%)	180 (7.90%)	155 (6.90%)	0.372

TABLE 3 | Comparison of baseline characteristics of HFrEF and HFpEF patients with diabetes admitted for STEMI.

		HFrEF	HFpEF	
Age	Mean (SD)	69.53 (12.96)	71.47 (12.614)	<0.001
	<55	13.7%	10.50%	<0.001
	55–64	21.80%	19.00%	<0.001
	65–74	26%	26.40%	<0.001
	75–84	24.50%	26.40%	<0.001
	> 84	13.90%	17.70%	<0.001
Gender	Male	56.10%	47.20%	<0.001
	Female	43.90%	52.80%	<0.001
Race	White	70.50%	70.20%	<0.321
	Black	10.50%	12.60%	<0.001
	Hispanic	11.10%	9.40%	<0.001
	Asian	3.20%	3.40%	0.176
	Native American	0.80%	0.80%	0.664
	Other minorities	4.00%	3.50%	0.006
Comorbidities	Obesity	18.00%	24.80%	<0.001
	Hypertension	72.30%	78.90%	<0.001
	Smoking	28.00%	28.90%	0.006
	Dyslipidemia	54.40%	62.00%	<0.001
	PVD	13.70%	16.40%	<0.001
	Renal failure	29.50%	39.90%	<0.001
	CAD	77.80%	79.60%	<0.001
	Elixhauser comorbidity index	5.85 (8.4)	6.94 (8.4)	<0.001

significant effects on mortality in both groups. In patients with HFrEF, Blacks and Asians had a slightly lower mortality risk compared to White Americans [OR = 0.946 (0.902-0.993), 0.768 (0.706-0.835); respectively], while in the HFpEF group, mortality was increased by almost 50% in Hispanics [OR = 1.579 (1.320–1.888)]. Surprisingly, comorbidities such as hypertension, smoking, and dyslipidemia were associated with decreased mortality in patients with HFrEF ($p < 0.001$ for all). In contrast, obesity was associated with higher mortality risk [OR = 1.145 (1.1–1.191)]. In HFpEF patients, dyslipidemia was also associated with a significant decrease in mortality [OR = 0.551 (0.493–0.615)]. In both groups, the presence of CAD was associated with almost 50% decrease in mortality risk [OR = 0.641 (0.622–0.662) for HFrEF, OR = 0.498 (0.442–0.561) for HFpEF], while the presence of PVD was associated with increased mortality [OR = 1.131 (1.089–1.174) for HFrEF, OR = 1.161 (1.013-1.331) for HFpEF]. Renal failure was associated with significantly higher mortality risk in patients with HFpEF [OR = 1.564 (1.384-1.766)], but not in HFrEF. As expected, a higher Elixhauser comorbidity score was associated with a higher risk of death in both groups. In terms of revascularization, PCI and CABG reduced mortality by almost 50%, but thrombolysis did not have a statistically significant impact.

Temporal Trend in Socio-Economic Outcomes

Total charges gradually increased with time in both groups. In patients with HFrEF, total charges per stay increased by almost threefold, from 33,161 (14,193–73,770) to 104,166 (59,052–183,912) USD (adjusted for inflation, p trend < 0.001) (**Figure 3**). In patients with HFpEF, total charges per stay also increased by almost twofold, from 37,892 (18,720–74,254) to 87,972 (47,731–148,151) USD (adjusted for inflation). Of note, total charges were not statistically different between both groups in 2005

TABLE 4 | Comparison of outcomes between patients with diabetes admitted for STEMI, either with HFrEF or with HFpEF.

	HFrEF	HFpEF		
	N (%) Unadjusted OR (95% CI)	N (%) Unadjusted OR (95%CI)	Adjusted OR (95% CI)	*P*-Value
In-hospital events				
Mortality	31,728 (14.50%) OR = 1	1,895 (10.90%) OR = 0.713 (0.679-0.749)	0.635 (0.601-0.670)	< 0.001
Ventricular tachycardia	22,290 (10.20%) OR = 1	1,348 (7.80%) OR = 0.732 (0.692-0.776)	0.749 (0.703-0.797)	< 0.001
Ventricular fibrillation	11,752 (5.40%) OR = 1	747 (4.30%) OR = 0.78 (0.723-0.842)	0.866 (0.798-0.940)	0.001
Atrial fibrillation	49,229 (22.40%) OR = 1	4,488 (25.90%) OR = 1.222 (1.18-1.267)	1.121 (1.078-1.166)	< 0.001
Cardiogenic shock	44,524 (20.30%) OR = 1	2,297 (13.20%) OR = 0.582 (0.557-0.609)	0.549 (0.522-0.577)	< 0.001
Ischemic stroke	5,040 (2.30%) OR = 1	370 (2.10%) OR = 0.918 (0.825-1.022)	0.871 (0.776-0.977)	0.019
Acute renal failure	60,967 (27.80%) OR = 1	5,481 (31.60%) OR = 1.212 (1.172-1.253)	0.961 (0.924-1.000)	0.05
Revascularization strategy				
PCI	102,224 (46.60%) OR = 1	8,400 (48.40%) OR = 1.074 (1.041-1.107)	1.106 (1.066-1.147)	< 0.001
Thrombolysis	3,526 (1.60%) OR = 1	212 (1.20%) OR = 0.745 (0.648-0.857)	0.720 (0.620-0.836)	< 0.001
CABG	22,012 (10.00%) OR = 1	1,290 (7.40%) OR = 0.706 (0.666-0.748)	0.750 (0.703-0.801)	< 0.001

TABLE 5 | Predictors of mortality in both entities of heart failure.

Age		HFrEF		HFpEF	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
	<55	Ref	Ref	Ref	Ref
	55–64	1.387 (1.308-1.472)	<0.001	1.170 (0.885-1.547)	0.27
	65–74	1.673 (1.572-1.78)	<0.001	1.084 (0.821-1.430)	0.57
	75–84	2.28 (2.14-2.429)	<0.001	1.512 (1.146-1.996)	0.004
	> 84	2.974 (2.78-3.181)	<0.001	1.979 (1.486-2.636)	< 0.001
Gender	Male	Ref	Ref	Ref	Ref
	Female	0.93 (0.904-0.956)	<0.001	0.940 (0.841-1.051)	0.278
Race	White	Ref	Ref	Ref	Ref
	Black	0.946 (0.902-0.993)	0.024	0.962 (0.807-1.146)	0.663
	Hispanic	0.999 (0.954-1.047)	0.982	1.579 (1.320-1.888)	< 0.001
	Asian	0.768 (0.706-0.835)	<0.001	1.273 (0.939-1.725)	0.12
	Native American	1.111 (0.945-1.306)	0.203	1.508 (0.854-2.663)	0.157
	Other minorities	1.047 (0.975-1.123)	0.206	1.198 (0.880-1.631)	0.252
Obesity	No	Ref	Ref	Ref	Ref
	Yes	1.145 (1.1-1.191)	<0.001	0.882 (0.757-1.027)	0.106
HTN	No	Ref	Ref	Ref	Ref
	Yes	0.876 (0.848-0.904)	<0.001	0.969 (0.836-1.123)	0.676
Smoking	No	Ref	Ref	Ref	Ref
	Yes	0.762 (0.736-0.788)	<0.001	0.988 (0.868-1.125)	0.853
Dyslipidemia	No	Ref	Ref	Ref	Ref
	Yes	0.637 (0.62-0.656)	<0.001	0.551 (0.493-0.615)	< 0.001
PVD	No	Ref	Ref	Ref	Ref
	Yes	1.131 (1.089-1.174)	<0.001	1.161 (1.013-1.331)	0.032
Renal Failure	No	Ref	Ref	Ref	Ref
	Yes	1.01 (0.979-1.043)	0.48	1.564 (1.384-1.766)	< 0.001
CAD	No	Ref	Ref	Ref	Ref
	Yes	0.641 (0.622-0.662)	<0.001	0.498 (0.442-0.561)	< 0.001
Elixhauser score		1.038 (1.032-1.045)	<0.001	1.084	< 0.001
PCI	No	Ref	Ref	Ref	Ref
	Yes	0.513 (0.485-0.543)	<0.001	0.424 (0.337-0.534)	0.032
CABG	No	Ref	Ref	Ref	Ref
	Yes	0.413 (0.367-0.465)	0.48	0.344 (0.186-0.635)	< 0.001
Thrombolysis	No	Ref	Ref	Ref	Ref
	Yes	0.867 (0.696-1.081)	0.226	0.860 (0.305-2.423)	0.775

but became significantly higher in the HFrEF group over time ($p < 0.001$). In 2005 both groups had a similar median (IQR) LoS of 5 (3–9) days in patients with HFrEF and 6 (3–9) days in patients with HFpEF. There was a slight temporal reduction in the LoS of the HFpEF group, reaching 4 (2–8) days (p trend = 0.003). At the same time, no statistically significant changes were observed in the HFrEF group over the study period.

DISCUSSION

To the best of our knowledge, we report in this analysis that most cases of patients with STEMI with diabetes with pre-existing heart failure are HFrEF. Nevertheless, the percentage of HFpEF significantly increased by almost 4-fold with time while that of HFrEF decreased. Our data is aligned with several other international studies. Tsao et al. (2018) reported a decrease in the incidence rate ratio of HFrEF in the US between 1990 and 2009 while that of HFpEF increased. The Swedish heart failure registry analysis reported similar results between 2000 and 2012 (Chen et al., 2019). The increased recognition of HFpEF as a clinical entity might explain its increasing prevalence, but this explanation is difficult to prove (Oktay et al., 2013). Another possibility could be the temporal increase in cardiovascular risk factors such as diabetes, obesity, and hypertension—primary etiologies of HFpEF—while age-adjusted rates of ischemic heart disease—the most common etiology of HFrEF—are declining in industrialized countries (Dai et al., 2020). Interestingly, in our study that is only focused only on patients with diabetes hospitalized for STEMI, cardiometabolic risk factors significantly increased during the observation period, CAD by 28% in HFrEF and 33% in HFpEF Patients with STEMI and diabetes with pre-existing

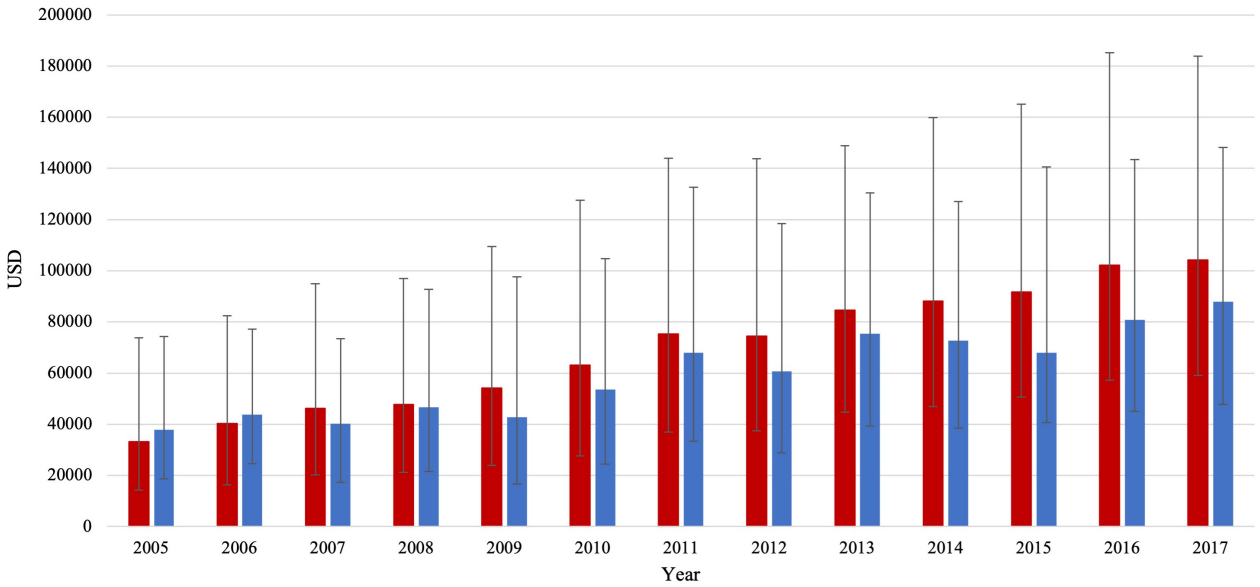

FIGURE 3 | Total charges/stay (median IQR) in HFrEF patients (red color) and HFpEF patients (blue color).

HFpEF had lower in-hospital mortality than HFrEF patients, concordant with HF patients without STEMI or diabetes studies. In an analysis of 3 multi-national cohorts, lower in-hospital and 2-year mortality was observed in the HFpEF group (Lam et al., 2018). Further, HFpEF patients were older, had a predominance of the female gender, and had a higher prevalence of cardio-metabolic factors than HFrEF, which is aligned with our data.

In our study, the prevalence of men has gradually increased while that of women decreased in HFrEF patients with diabetes. However, no gender-related temporal changes were noted in the HFpEF group. Previous data have demonstrated an apparent gender effect in HF and associated outcomes. Male gender predisposes to HFrEF, probably due to the higher prevalence of the macrovascular coronary disease. In contrast, females tend to develop HFpEF, fueled by coronary microvascular disease and endothelial dysfunction (Lam et al., 2019). There is also an apparent association between gender and mortality in heart failure patients. In our study, the female gender was associated with modest protection against mortality in HFrEF but not in HFpEF. Concordant with our findings, Duca et al. (2018) found that the male gender was associated with increased cardiac mortality in HFrEF. Interestingly, the STAR study reported earlier that females had lower mortality in HFrEF of non-ischemic etiology (Ghali et al., 2003).

Using the NIS database, Ahmed et al. (2014) showed that age-adjusted mortality decreases in diabetic patients hospitalized for acute MI; all categories included. We have recently reported a steady decline in age-adjusted mortality in heart failure and diabetes for the same period (Mekhaimar et al., 2021). Interestingly, mortality is unchanged in our population consisting of diabetic heart failure patients hospitalized for STEMI. One of the plausible reasons is that the increase in the prevalence of risk factors might have counteracted any potential improvement in the outcome of those patients. It is also possible that those patients with three comorbidities (heart failure, diabetes, and STEMI) did not receive the optimal treatment as witnessed by the relatively low revascularization despite its significant increase in recent years when the combination of PCI/thrombolysis was approximately 72% in HFrEF and < 64% in HFpEF.

Contrary to our expectation, several cardio-metabolic risk factors such as hypertension, dyslipidemia, obesity, and strikingly smoking were associated with lower mortality risk. Nevertheless, this paradoxical association has been previously reported in the NIS database in studies assessing the outcome of diabetes patients hospitalized either for MI (Ahmed et al., 2014), heart failure (Mekhaimar et al., 2021), or stroke (Tabbalat et al., 2021). This might be since patients with several risk factors are usually given more cardioprotective medications and have their treatments intensified. Another possible explanation would be the possibility that in most sick patients these cardio-metabolic risk factors are most likely were not accounted for compared to healthier patients with fewer comorbidities, which might give rise to a false impression that these factors are protective.

The continuously growing economic burden of heart failure, STEMI, and diabetes on the healthcare system in the United States is considerable; costs of CVD care are expected to increase by threefold by 2030 (Heidenreich et al., 2011). Further, the simultaneous presence of diabetes in any cardiovascular pathology significantly increases the costs (Nichols and Brown, 2002). We report in this analysis that total charges/stay increased by almost twifold in HFpEF and threefold in HFrEF. Further, total charges/stay were higher in HPrEF patients. This difference aligns with previously reported results in the literature.

In a systemic review of the economic costs of heart failure in America, the total charge of hospitalization was 4–9% higher in HFrEF patients than those with HFpEF (Urbich et al., 2020). Another recently published cohort study reported that HFrEF patients had an overall higher economic cost over a 2-year follow-up than those with HFpEF (Vemmos et al., 2012). We anticipate a continuous rise in healthcare spending of both HF types, mainly due to population aging and advances in the medical technologies (Jayawardana et al., 2019).

HFrEF and HFpEF differ in pathophysiology and management. Therefore, it is not surprising that they differ in the risk of some cardiovascular outcomes following hospitalization. While a higher risk of VT (Alvarez et al., 2019), VF (Saour et al., 2017), cardiogenic shock (van Diepen et al., 2017), and ischemic stroke (Murphy et al., 2020) is expected and already known to be associated with a lower LVEF, HFpEF patients had a significantly higher risk of atrial fibrillation. Data in the literature about the risk of AF in STEMI and HF patients is limited. Still, it has been previously reported that AF is generally more prevalent in HFpEF patients than HFrEF. In a study involving more than 40,000 patients with heart failure in the Swedish heart failure registry between 2000 and 2012, Kannel et al. (1983) found that higher ejection fraction correlated with a higher incidence of atrial fibrillation. This might be because HFpEF patients are more obese, knowing that obesity increases the risk of AF by 20–30% (Vyas and Lambiase, 2019).

Several limitations were identified in our study. The retrospective nature of the study design and the absence of randomization limits our ability to reach definitive conclusions. Additionally, several cofounders are missed in the NIS database and could not be considered in our analysis and multivariable regression model. For instance, many strong predictors of mortality in diabetes and heart failure were not available, particularly the left ventricular ejection fraction, glycemic control, and baseline medications. The cause of death in HF patients—and all other patients included in the NIS database—is a weakness in our analysis. Further, our classification of HFpEF and HFrEF was based on systolic and diastolic HF, respectively, as reported in the NIS database. It is not clear what definition was used and whether it was updated with time in the light of newer cardiac guidelines; hence, we cannot exclude the possibility of misclassification between those HF entities in the absence of a LVEF, especially in earlier years when the diagnosis of HFpEF was not well established. Despite these limitations, we believe that our study provided a clear trend in the outcome of diabetic heart failure patients hospitalized for STEMI in a large sample representative of the US population.

CONCLUSION

In conclusion, most patients with STEMI with diabetes with pre-existing heart failure are HFrEF patients. While the hospitalization rate of HFpEF patients is steadily increasing, that of HFrEF patients is on a descending slope. Despite the increase in the prevalence of cardiometabolic risk factors in both groups, mortality was unchanged. Finally, HFpEF patients had lower mortality and better cardiovascular outcome except for atrial fibrillation and hemorrhagic stroke. The advances in cardiovascular medicine come at the displayed cost of ongoing medical expenses, which is notably higher in HFrEF patients, even though HFpEF patients were older and had a higher prevalence of CVD and cardiometabolic risk factors.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

CA conceived the study. BA performed the analysis with SD, CA, JA, and wrote the study. All authors reviewed the final draft and approved it.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

Coding of the Diagnosis

STEMI

ICD-9 codes: All 410 except 410.7 and its subgroups; ICD-10 codes: I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I22.0, I22.1, I22.2, I22.8, I22.9

HFrEF

ICD-9 codes: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.1, 428.20-428.23; ICD-10 codes: I11.0, I13.0, I13.2, I50.1, I50.20-I50.23, I50.40-I50.43, I50.80, I50.81 with its subgroups, I50.82, I50.83, I50.84, I50.89

HFpEF

ICD-9 codes: 428.30-428.33; ICD-10 codes: I50.30-I50.33

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Assessment of Ultra-Early Administration of Sacubitril Valsartan to Improve Cardiac Remodeling in Patients With Acute Myocardial Infarction Following Primary PCI: Rational and Design of a Prospective, Multicenter, Randomized Controlled Trial

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Background: Despite coronary re-vascularization, the common complications of acute myocardial infarction (AMI), cardiac remodeling, and heart failure (HF), is increasing globally. Sacubitril valsartan (SV), an angiotensin receptor-neprilysin inhibitor (ARNI), has been previously demonstrated to improve HF. We further hypothesize that ultra-early SV treatment is also effective in preventing cardiac remodeling for patients with AMI following primary percutaneous coronary intervention (PCI).

Methods: The Assessment of ultra-early administration of Sacubitril Valsartan to improve cardiac remodeling in patients with Acute Myocardial Infarction following primary PCI (ASV-AMI) trial is a prospective, multicenter, randomized controlled trial in China planning to enroll at least 1,942 eligible patients from 10 centers. After successful primary PCI of culprit artery within 24 h, AMI patients are randomized to 2 h group or 3–7 days group with SV treatment. The major endpoints are echocardiographic measurement, cardiothoracic ratio, and N-Terminal pro-B-Type Natriuretic Peptide (NT pro-BNP) at baseline, 1, 3, 6, and 12 months. The secondary endpoints included MACE (cardiac arrest, cardiogenic death, myocardial infarction, and target vessel re-vascularization), in-/out-patient HF, EuroQol Five Dimensions Questionnaire (EQ-5D), and Kansas City Cardiomyopathy Questionnaire (KCCQ).

Discussion: The ASV-AMI trial is the first clinical trial of ultra-early administration of SV in the treatment of post-PCI AMI, adding more clinical evidence. Early application of SV to prevent cardiac remodeling in AMI patient is a major focus of this trial.

Clinical Trial Registration: Trial registration Chinese Clinical Trial Registry (http://www.chictr.org.cn; ChiCTR2100051979). Registered on 11 October 2021.

Keywords: acute myocardial infarction, sacubitril valsartan, cardiac remodeling, echocardiographic measurement, NT pro-BNP, cardiothoracic ratio (CTR)

INTRODUCTION

Acute myocardial infarction (AMI), including ST-segment elevated myocardial infarction (STEMI) and non-STEMI, remains a serious life-threatening event (Xu et al., 2020). The rate of death, heart failure (HF), and recurrent ischemic events occurring in the first years after myocardial infarction remains elevated in the high risk population (Ferreira et al., 2021). Despite coronary re-vascularization of culprit coronary artery, there is currently no excellent treatment for cardiac remodeling after coronary artery patency recovery. Growing evidence from clinical trials shows that AMI has a great impact on cardiac remodeling and HF (Duengen et al., 2020; Tripolt et al., 2020; Wang et al., 2020). According to Swede Heart Registration, heart failure after AMI accounted for 13–31% over 1 year (Desta et al., 2015). The risk of subsequent heart failure caused by cardiac remodeling is very high. It is urgent to optimize the management measures for high-risk AMI population in order to improve the prognosis.

Sacubitril valsartan (SV), an angiotensin receptor-neprilysin inhibitor (ARNI), has been previously demonstrated to improve cardiac remodeling and heart failure (Massimo et al., 2021a). The 2018 Chinese Heart Failure Diagnosis and Treatment Guidelines recommend that ARNI (Class I recommendation, Level B evidence) reduces the morbidity and mortality for heart failure with reduced ejection fraction (HFrEF). AMI, especially anterior wall MI, probably promotes the progress of cardiac remodeling. The Association of Change in N-Terminal pro-B-Type Natriuretic Peptide (NT pro-BNP) Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction (PROVE HF) trail reported that SV improved NT-proBNP concentrations, left ventricular ejection faction (LVEF), left ventricular end-diastolic volume index (LVEDVi), and left ventricular end-systolic volume index (LVESVi) in HFrEF patients (Januzzi et al., 2019). Available evidence may support SV as a first-line therapy in outpatient or in-hospital HFrEF patients (Massimo et al., 2021b). The Effect of Sacubitril-Valsartan vs. Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial (EVALUATE-HF) trail found that SV improved left atrial volume index (LAVi), LVEDVi, and LVESVi compared with enalapril (Desai et al., 2019). So, ARNI has sufficient evidence to improve cardiac remodeling and clinic outcomes (Giovanna et al., 2020a).

Cardiac remolding is central to the progression of HF and occurs in response to AMI, which consists of the changes in cardiac geometry, function, or both, manifested by the reduced LVEF, LVEDVi, and LVESVi (Duengen et al., 2020). The pathological mechanism of the poor prognosis of AMI is cardiac remodeling, which often starts between 24 and 72 h after AMI. Cardiac remodeling is associated with risk of heart failure, cardiac death, and re-hospitalization, represented an important target for HF therapy. In the studies of guideline-directed medical therapies for HF, such as β-blocker, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA), increased LVEF, decreased LV volumes or both are associated with improved prognosis (Bao et al., 2021). In the process of cardiac remodeling post-AMI, we believe that the earlier we block the process of cardiac remodeling, the better the prognosis. We need a series of operation preparation post-PCI, such as random and drug preparation, so that our research can enter the next step. We choose 2 h post-PCI as our experimental group. However, the effects of SV on ultra-early preventing cardiac remodeling in patients with AMI remain unclear.

The pathophysiologic mechanism responsible for benefits of ARNI remains unclear. Neprilysin inhibition enhances circulating level of biologically active natriuretic peptides, which may have antihypertrophic, antifibrotic, and vasodilatory effects (Docherty et al., 2021). In PROVE HF and EVALUATE HF trails, the benefits of SV are associated with a decreased NT pro-BNP concentration, LVEDVi, LVESVi, cardiothoracic ratio, and increased LVEF. Reducted NT pro-BNP concentrations for HF is associated with reversed cardiac remodeling and HF. However, SV treatment has not established such a link. This trial examines the mechanism of the changes in NT pro-BNP concentrations, LVEF, LVEDVi, LVESVi, and cardiothoracic ratio after ultra-early administration of SV treatment in post-PCI AMI patients.

METHODS AND ANALYSIS

Study Objective and Hypothesis

The objective of ASV-AMI is to test whether SV treatment prevents cardiac remodeling more effectively in 2 h group than in 3–7 days in post-PCI AMI patients. The working hypothesis is that SV improves LVEDVi, LVESVi, and NT-proBNP concentration in EVALUATE HF and PROVE HF trial. AMI stimulates the progression of cardiac remodeling and heart failure, which is demonstrated by the changes of echocardiographic parameters (LVEDVi, LVESVi, LAVi, E/e', LVEDV, LVESV, LVEF, etc.), NT-proBNP concentrations, and cardiothoracic ratio.

The secondary objective is to study whether the effect of SV in 2 h group than in 3–7 days group is better in reducing in-/out-patient HF and major cardiovascular event (MACE), including cardiac arrest, cardiogenic death, myocardial infarction, and target vessel re-vascularization. The health quality of life is evaluated by EuroQol Five Dimensions Questionnaire (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ).

The primary safety assessment includes laboratory values, all adverse events within baseline, 1, 3, 6, and 12 months follow-up, hypotension, and vascular edema.

Study Design

This is a prospective, multicenter, randomized controlled trial in China. The steering and executive committee is responsible for scientific, operational, and medical process of the trial. The executive committee is also responsible for the integrity of data analysis and reporting results. The protocol has been approved by the Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine

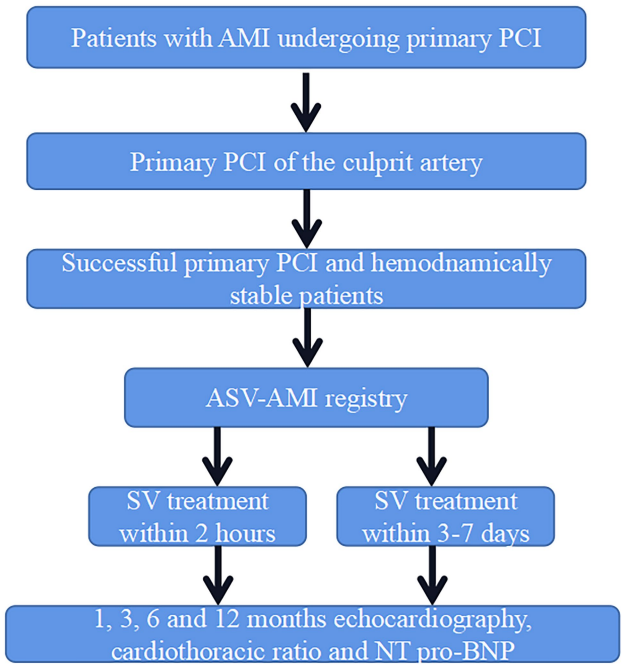

FIGURE 1 | Study design.

(No. Keyan 20210907-9). ASV-AMI has been registered at www.chictr.org.cn (ChiCTR2100051979) on 11 October 2021. The trial starts recruitment in January 2022. The study flowchart is shown in **Figure 1**. Prior to the start of any trial procedure, each subject will be given written informed consent. In all, 1,942 patients are collected from 10 participating centers.

Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine is the initiator of the investigator-initiated clinical trial. Department of cardiology in Sir Run Run Shaw Hospital is the clinical and data coordination center. Meanwhile, department of cardiology in Sir Run Run Shaw Hospital is responsible for the design and implementation, relevant statistical analysis, and preparation, including the drafting and editing of the document and its final version.

Trial Population, Criteria, and Procedures

All patients aged 18 years or above with first-time or recurrent AMI undergoing primary PCI will be qualified by attending physicians. The PCI procedure will be carried out according to the standard procedures of the treatment hospital. The inclusion and exclusion of patients will be implemented by the attending physicians of PCI centers. After successful primary PCI of culprit artery, AMI patients are allocated to 2 h group or 3–7 days group after PCI. All other documented secondary therapeutic medication, including dual antiplatelet therapy, statins, β-blockers, etc., will be prescribed in accordance with existing guidelines judged by attending physicians.

The premise for participation is that there is no indication of cardiac shock, a past history of angioedema, bilateral renal artery stenosis, serum potassium > 5.2 mmol/L, estimating Glomerular Filtration Rate (eGFR) < 30 ml/min/1.73 m^2, allergy to ARNI, ACEI, ARB, or other similar chemical drugs, any organ system in past 3 years and less than 1 year of life expectancy. Previous treatment with SV is not an exclusion criteria. Patients can participate in any other trial that does not directly alter the effect of SV or valsartan treatment. Further details on inclusion and exclusion criteria are summarized in **Table 1**.

TABLE 1 | Key eligibility criteria for the ASV-acute myocardial infarction (AMI) study.

Inclusion criteria
Informed consent
Age ≥ 18 years
Patients with AMI presenting within 24 h of symptom onset
Successful primary PCI within 24 h of symptom onset
Medication within 24 h of symptom onset
Exclusion criteria
Cardiac arrest within 24 h
A history of angioedema
Known or suspected bilateral renal artery stenosis
eGFR < 30 ml/min/1.73 m^2
Potassium > 5.2 mmol/L
A history of allergy to SV, ACEI, ARB, or NEP inhibitors or other similar chemical drugs
A history of malignancy in any organ system (except localized basal cell carcinoma of skin) in the past 3 years, with a life expectancy of less than 1 year
Patients are considered unsuitable to participate in the trial, including mental, behavioral, or cognitive impairment, which is enough to affect the ability of patients to understand, obey the protocol instructions, or complete the follow-up operation

Interventions With Study Drug

If all eligibility criteria are met and written informed consent is provided, the patient will be registered as a SV treatment prescription. The dosage will be based on the clinical condition. Acceptable drugs and dosages include SV (400 mg daily total dose). Patients will be encouraged to continue taking SV until the end of the trial. Patients with hypotension after taking medication are advised to reduce or stop medication.

All study patients will receive an information letter to obtain and contact information about the sponsor from the local primary investigator and the central supervisor of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine. Patients will be contacted by a dedicated person to prevent medical contact or primary care visits that may affect treatment compliance.

Data Collection and Monitoring

Detailed overview of data collected during follow-up is shown in **Table 2**. Baseline data will be obtained from hospital records and discharge letters (medication, comorbidity, cardiac rehabilitation, blood pressure, and weight and height measurements), echocardiography, and self-report EQ-5D and KCCQ. PCI hospitals will analyze the relevant standard blood samples (hematology, blood lipids, and clinical chemistry). Besides, blood samples will be sent to the central laboratory for NT-pro BNP concentrations test. The parameters of

TABLE 2 | Data collection and schedule of assessments.

Phage	Screening	Treatment			
Month	**0**	**1**	**3**	**6**	**12**
Informed consent	×				
Demographics	×				
Medical history	×				
Vital signs	×	×	×	×	×
Electrocardiogram	×	×	×	×	×
Myocardial enzymes	×	×	×	×	×
Stand chest X-ray	×	×	×	×	×
Myocardial enzymes	×	×	×	×	×
Echocardiography	×	×	×	×	×
NT pro-BNP	×	×	×	×	×
Killip/NYHA classification	×	×	×	×	×
Height	×				×
Weight	×				×
AE/SAEs		×	×	×	×
Biomarkers*	×			×	
Angioedema	×	×	×	×	×
EQ-5D**	×	×	×	×	×
KCCQ***	×	×	×	×	×
eCRF	×	×	×	×	×

**Hematology, clinical chemistry, and blood lipids.*
***EuroQol Five Dimensions Questionnaire (EQ-5D).*
****Kansas City Cardiomyopathy Questionnaire (KCCQ).*

echocardiography will be analyzed in the core laboratory too. Standing chest radiographs are used to measure the cardiothoracic ratio.

An Case Report Form (CRF) will be provided for these patients to fill in at baseline, 1, 3, 6, and 12 months of follow-up. If there is a lack of responders, a reminder will be issued. EQ-5D and KCCQ will be provided and sent to patients. Vital signs and dosage of drugs are recorded during the follow-up. Each clinical trial site will be monitored by Office of Clinical Trial Institution, Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine.

Safe Monitoring and Reporting

After registration, all selected patients will be contacted by outpatient visits or telephone and interviewed on side effects after a standardized written agreement. The local PI will check the secure endpoint in the hospital records if patients do not response to the telephone call. Besides, PI of every center is responsible for reporting suspected serious adverse reactions and serious adverse events to the Data and Safety Monitoring Board according to Good Clinical Practice and the Office of Clinical Trial Institution, Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine.

OUTCOME DEFINITIONS AND MEASUREMENTS

The primary and secondary endpoints will be followed up for at least 1 year. Evaluation of main results will be obtained from echocardiography parameter, NT-pro BNP concentrations, and cardiothoracic ratio. Assessment of safety endpoints will be determined by administrative registries (adverse events, hyperkalemia, renal insufficiency, angioedema, and hypotension). All the registries have a reporting system and a unique personal identification number enabling us to link the participants to the registry.

SAMPLE SIZE CALCULATION AND STATISTIC ASSESSMENT

Sample size is based on the available evidence published to date. We use https://www.cnstat.org/samplesize/4/ to generate the calculated sample size. We assume that baseline LVEDVi in 2 h group with SV was 70.3 ml/m^2, while 75.6 ml/m^2 in 3–7 days group used enalapril as a reference according to ELEVALUATE HF trial. The SD between the two groups was 37.6 ml/m^2. Thus, patients in each group would at least offer 80% power at a one sided 0.05 significance level according to a 1:1 ratio of random group. Considering the maximum follow-up loss rate of 2.5% 1 year in both groups, it is anticipated that a total of 1,710 patients need to be recruited with 855 cases in each group. Based on the least squares mean of covariance model analysis, the treatment effect is estimated according to the ratio of the geometric mean with logarithmic baseline value as covariate and the bilateral 95% CI is reported. The analysis is based on all available data points assume that data is lost randomly.

The ASV-AMI trial is conducted by department of cardiology, Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine. The ASV-AMI Steering

Committee Overall is fully responsible for the overseeing independent academic researchers. The ASV-AMI Data and Safety Monitoring Board, which includes ACS experts and an independent statistician, actively monitors safety data, including all adverse and serious adverse events. The authors are fully responsible for the design and implementation of this trial, all research analysis, the drafting and editing of the trial, and its final content.

Ethical Assessments

The ASV-AMI trial complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. The scheme is independently approved by the institutional review committee of the participating center, and the written informed consent is obtained before registration. The trial protocol has been approved by the Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine (No. Keyan 20210907-9) and registered at www.chictr.org.cn (ChiCTR2100051979) on 11 October 2020.

Analysis

All data will be presented as percentages, mean ± SD or median (quartile range). Pearson correlation coefficients and the corresponding two-sided 95% credibility intervals (CIs) and *p* values will be calculated to examine the association between change in log-transformed NT-proBNP levels and each structural cardiac parameters (LVEDVi, LVESVi, LAVi, E/e', LVEDV, LVESV, LVEF, and cardiothoracic ratio) from baseline to 1-, 3-, 6-, 12-month. The analyses will be repeated from baseline to 1-, 3-, 6-, 12-month. Sensitivity analyses will be performed using the last observation carried forward method used to impute missing data at 1 year.

An ANOVA will be conducted to compare the mean change in the EQ-5D and KCCQ scores between the two groups at baseline, 1-, 3-, 6-, 12-month. It is likely that groups defined in this way will be different with respect to characteristics that are also associated with the EQ-5D and KCCQ scores, including age (<75 vs. ≥75 years), LVEF (≤median vs. N median), and AMI types (STEMI vs. non-STEMI). Multivariable regression will be used to compare the mean change in EQ-5D and KCCQ scores by NT-proBNP and structural cardiac measurement groups, accounting for variability in individual patient characteristics by including them as covariates in the model. In addition, an optional sensitivity analysis using propensity score stratification (or matching) may be performed to provide an estimate of the differences by NT-pro BNP and structural cardiac measurement group between patients who are more similar with respect to baseline characteristics.

Pearson correlation co-efficients and their two-sided 95% CIs will be used to examine the association between both NT-proBNP and structural cardiac measurement and change from baseline. Echocardiographic variables will be calculated using values from follow up at baseline, 1-, 3-, 6-, 12-month.

Ethics and Dissemination

The ASV-AMI trial is a prospective, multicenter, randomized controlled trial designed to assess the efficacy, safety, and tolerance of ultra-early SV treatment in post-PCI AMI. This is a vital clinical problem because of the lack of scientific evidence for the treatment of post-PCI AMI patients around the world. Although, it has been approved by China Food and Drug Administration and recommended by Chinese clinical guidelines in heart failure, the experience of SV administration in hospitalized AMI patients is limited. Meanwhile, it is well recognized that the results of initiating evidence-based drugs in hospital are consistent in greater long term. Considering the burden of cardiac remodeling and the unacceptably high incidence of post charge events, safely starting SV in this case may meet a vital unmet clinical need. The remarkable features of the ASV-AMI trial further strengthen the existing evidence base and collective understanding of ARNI in AMI and prevent cardiac remodeling in daily practice.

The ASV-AMI trial predominantly recruits AMI patients with primary PCI within 24 h of onset, requiring participants to take SV within 2 h or 3–7 days after PCI. Early cardiac remodeling often occurs in AMI within 24–72 h, including the infarct margin and distal non-infarcted myocardium. Cardiac remodeling includes cardiac hypertrophy and changes in ventricular structure to more evenly distribute increased wall stress, as extracellular matrix produces collagen scars to stabilize dilation and prevent more deformation (Rezq et al., 2021). Cardiac remodeling is determined by cardiac stretch, neurohormonal activation, paracrine and/or autocrine factors and activation of renin angiotensin aldosterone system (RAAS; Rouleau et al., 1993). The RAAS system is the main pathophysiological factor of cardiac remodeling. A large number of experiments have shown that RAAS inhibition can improve the prognosis of AMI (The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, 1993; Kober et al., 1995; Dickstein and Kjekshus, 2002; Velazquez et al., 2003). The natriuretic peptide system reverses the harmful effect of the RAAS upregulation on AMI, prevents the secretion of arginine and vasopressin and has a good regulatory on autonomic nervous system. Before early cardiac remodeling, AMI patients receive SV administration to prevent the progress of cardiac remodeling. This is the biggest highlight of this clinic trial.

In the early stage, oral administration was tried to inhibit neprilysin, which successfully elevated excretion of atrial natriuretic peptide (Gros et al., 1989). However, a study of long-term use of neprilysin inhibitor shows that the initial decline in blood pressure is not compulsorily. This may be due to the fact that neprilysin decomposes Angiotensin II (Hubers and Brown, 2016). Hence, in addition to increasing natriuretic peptides level, it can also increases angiotensin II level, which may counteract the effect of the former peptides. There is a strategy to eliminate the unnecessary effect of loneliness on neprilysin inhibition. ARNI can block the renin-angioten system and enhance the action of natriuretic peptide through angiotensin receptor antagonist, and ultimately prevent cardiac remodeling.

The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) is performed that SV is superior to enalapril in reducing the main endpoint of cardiovascular death and HF hospitalization (Mogensen et al., 2018). Compared with enalapril group, the risk of cardiac death and cardiac mortality in SV group is significantly lower, so the trial is terminated earlier. In fact, the reduction of HF mainly depends on cardiac remodeling. The clinical benefits of ACEI, ARB, β-blockers, and cardiac resynchronization therapy (CRT) are due to their effects on adaptive ventricular dilation and hypertrophy, as well as systolic dysfunction. According to the result of PARAMOUNT II trial, SV can significantly reduce the left atrial size and volume compared with valsartan (Solomon et al., 2012). Preclinical AMI trial also shows that neprilysin inhibitors can improve cardiac remodeling. In HF patients treated with SV, mitral regurgitation and left ventricular end diastolic filling volume are significantly improved. The results of PROVE-HF trail shows that the absolute increase of LVEF in patients with heart failure is 9.4%, which is related to the decrease of NT pro-BNP. These studies also suggest that the clinical benefit of SV may be related to its reversal cardiac remodeling. The latest PARADIGM-MI trial suggests that for patients who receive tablets from 12 h to 7 days (average 4.3 days) after the occurrence of AMI events, SV has a gradual improvement, and the longer the treatment time, the more benefits (Giovanna et al., 2020b). SV is better than ramipril in reducing the total event rate and the risk of main endpoint events reported by researchers (Khachfe et al., 2019). However, our experiment is more prospective. AMI patients start SV treatment much earlier in our trial. AMI patients undergoing primary PCI within 24 h of onset receives SV treatment within 2 h after PCI, which is the first known clinical trial of ultra-early SV administration in post-PCI AMI. This results in the prevention of cardiac remodeling at an ultra-early stage of AMI, which is the most brilliant innovation of this trial.

There are no data on the safety and efficacy of ARNI for AMI nowadays. According to our clinical conjecture, SV may improve the prognosis of AMI by preventing cardiac remodeling. RAAS/ARB therapy may be the standard treatment for AMI patients after PCI, which is one of the cornerstones of preventing cardiac remodeling after AMI. Compared with the standard ACEI/ARB regimens, the dual effect of inhibition of Angiotensin II receptors and neprilysin may play an important role in the prevention of cardiac remodeling after AMI.

As far as we know, this trial is the first clinical trial of ultra-early administration of SV in the prevention of cardiac remodeling post-PCI AMI. However, our study is not without limitations. This is a small-scale experiment with fewer events, so type 1 errors cannot be completely eliminated. In addition, our trial is not a multilateral trial, so the results may not be applicable to all post-PCI AMI patients in the worldwide. A larger ongoing randomized trial is waiting to confirm our results.

In conclusion, the ultra-early administration of SV in the treatment of post-PCI AMI may improve cardiac remodeling. Although this will add a new indication, this new drug needs to be further confirmed in a larger scale cohort of patients and follow up to ensure safety and efficacy for a longer time.

TRIAL STATUS

The trial will be conducted according to the protocol version 1.0 of 11 October 2021. Patient recruitment started in January 2021 and is expected to run consecutively until December 2023. Data collection of the intervention phase is expected to be completed in January 2024 and data analysis in February 2024.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine (Approved No. Keyan 20210907-9). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZL and GF were broadly involved in the conception and design of the study and drafted the manuscript. Furthermore, GF will be responsible for the logistic preparation and protocol-conform implementation of the study, the recruitment of patients, and the performance of training sessions. ZL critically reviewed the manuscript. The co-principal investigators of this study are ZL and GF. All authors have read and approved the final version of the manuscript and gave their consent for publishing this study protocol.

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REVIEW
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Diabetes Mellitus and Heart Failure With Preserved Ejection Fraction: Role of Obesity

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Heart failure with preserved ejection fraction is a growing epidemic and accounts for half of all patients with heart failure. Increasing prevalence, morbidity, and clinical inertia have spurred a rethinking of the pathophysiology of heart failure with preserved ejection fraction. Unlike heart failure with reduced ejection fraction, heart failure with preserved ejection fraction has distinct clinical phenotypes. The obese-diabetic phenotype is the most often encountered phenotype in clinical practice and shares the greatest burden of morbidity and mortality. Left ventricular remodeling plays a major role in its pathophysiology. Understanding the interplay of obesity, diabetes mellitus, and inflammation in the pathophysiology of left ventricular remodeling may help in the discovery of new therapeutic targets to improve clinical outcomes in heart failure with preserved ejection fraction. Anti-diabetic agents like glucagon-like-peptide 1 analogs and sodium-glucose co-transporter 2 are promising therapeutic modalities for the obese-diabetic phenotype of heart failure with preserved ejection fraction and aggressive weight loss *via* lifestyle or bariatric surgery is still key to reverse adverse left ventricular remodeling. This review focuses on the obese-diabetic phenotype of heart failure with preserved ejection fraction highlighting the interaction between obesity, diabetes, and coronary microvascular dysfunction in the development and progression of left ventricular remodeling. Recent therapeutic advances are reviewed.

Keywords: obesity, heart failure with preserved ejection fraction, diabetes mellitus, weight loss surgery, visceral adipose tissue, epicardial adipose tissue

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INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a growing epidemic (Owan and Redfield, 2005). Unlike heart failure with reduced ejection fraction (HFrEF), myocardial contractility is near normal in HFpEF, and impaired left ventricular (LV) relaxation/increased stiffness leads to pulmonary congestion and thereby dyspnea, pulmonary hypertension, and exercise intolerance (Becher et al., 2013; Andersson and Vasan, 2014; Borlaug, 2014). Currently, HFpEF is the leading cause of hospitalizations in patients > 65 years. It will overcome HFrEF as the leading cause of heart failure (HF) within the next 10 years (Lam et al., 2011; Liu et al., 2013). The increasing prevalence of HFpEF and lack of guideline-directed therapy, has rekindled interest in its pathophysiology (Borlaug, 2020; Mishra and Kass, 2021).

The cornerstone of HF is LV remodeling. In HFrEF, systolic dysfunction leads to eccentric hypertrophy with LV wall thinning and replacement fibrosis. In HFpEF, the LV wall thickens leading to concentric hypertrophy (LVH) (Heinzel et al., 2015) with impaired myocardial relaxation/increased stiffness leading to LV diastolic dysfunction (LVDD) (LeWinter and Meyer, 2013) and ultimately HFpEF. Age (Cheng et al., 2009), hypertension (Verdecchia et al., 1995), obesity (Woodiwiss et al., 2008), diabetes (T2D) (Eguchi et al., 2005), and renal dysfunction (Pluta et al., 2015) contribute to LV concentric remodeling. Distinct clinical HFpEF phenotypes are increasingly being recognized (Samson et al., 2016). Phenotyping HFpEF allows tailoring therapeutic modalities for concentric LV remodeling reversal and eventually, better outcomes. The obese-diabetic phenotype of HFpEF is extremely common (Samson et al., 2016) and associated with poor outcomes (Yusuf et al., 2003).

Obesity is the main driver of T2D with 90–95% of patients with T2D being obese (Mozaffarian et al., 2015). Obesity and T2D overlap in the development and progression of HFpEF (Altara et al., 2017). In the present review, we reviewed articles related to HFpEF and T2D. We conducted a literature search using PubMed, Embase, Ovid, and Cochrane databases and searched terms like "HF," "T2D," "HFpEF," "Obesity," "LVDD," "epicardial adipose tissue (EAT)," and "visceral adipose tissue (VAT)." Arranged by hierarchy we reviewed randomized clinical trials, followed by registries and then cohort studies. This review first addresses how obesity affects LV remodeling and fosters low-grade systemic inflammation/microvascular dysfunction and thereby HFpEF (McHugh et al., 2019; Piche et al., 2020). Specific contributions of T2D to inflammation (Tsalamandris et al., 2019), coronary microvascular dysfunction (CMD) (Di Carli et al., 2003), and cardiac myocytes diastolic Ca^{2+} handling (Eisner et al., 2020) are then reviewed. Last, we address the clinical implications of obesity and T2D on HFpEF outcomes before reviewing emerging therapeutic options.

EFFECTS OF OBESITY ON THE HEART

Obesity and Left Ventricular Concentric Remodeling

The obesity-LV concentric remodeling association was first reported in observational studies and later confirmed in several community-based cohorts (Peterson et al., 2004b; Wong et al., 2004; Powell et al., 2006; Avelar et al., 2007; Woodiwiss et al., 2008; Turkbey et al., 2010; Gidding et al., 2013; Kishi et al., 2014; Reis et al., 2014; Bello et al., 2016; Fliotsos et al., 2018; Razavi et al., 2020; Yan et al., 2020). The correlation between weight loss and decrease in LV mass and not between weight loss and decline in blood pressure (BP) after metabolic surgery is further evidence of the central role of obesity in the pathogenesis of LV concentric remodeling (Jhaveri et al., 2009; Rider et al., 2009; Owan et al., 2011; Kurnicka et al., 2018). However, the loose correlation between obesity-induced LV concentric remodeling and LVDD suggests that obesity may impair LV diastolic function through other mechanisms than obesity heightened cardiac pre- and afterload (Russo et al., 2011). Obesity-induced increase in myocardial triglycerides (TGs) content and myocardial energetics impairment may worsen LVDD (Peterson et al., 2004a; Rider et al., 2013; Piche and Poirier, 2018; Rayner et al., 2018).

Not unexpectedly, obesity is now a recognized risk factor for incident HFpEF (Packer and Kitzman, 2018; Pandey et al., 2018; Savji et al., 2018). Incident HFpEF correlates more closely with visceral adipose tissue (VAT) mass than body mass index (BMI) (Neeland et al., 2013; Cordola Hsu et al., 2021). Peak aerobic capacity is inversely and independently related to intra-abdominal fat, abdominal adiposity is a strong risk factor for all-cause mortality, and CT measured VAT predicts incident hospitalization in patients with HFpEF (Tsujimoto and Kajio, 2017; Haykowsky et al., 2018; Rao et al., 2018). In the Irbesartan in heart failure with preserved ejection fraction (I-PRESERVE) trial (Massie et al., 2008) 71% of the patients had a BMI > 26.5 kg/m^2 and 55% of the patients in the Phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in HFpEF (RELAX) trial had a BMI > 35 kg/m^2 (Haass et al., 2011; Reddy et al., 2019). Women had a relatively greater waist circumference (an indirect measure of VAT) than men in the prospective comparison of angiotensin receptor -neprilysin inhibitor with ARB global outcomes in HFpEF (PARAGON-HF) trial (McMurray et al., 2020). A table regarding the salient features of important trials in HFpEF has been listed in **Table 1**.

Obesity and Sodium Retention

Obesity leads to HFpEF by increasing renal tubular sodium reabsorption and plasma volume expansion (Bickel et al., 2001; Kotsis et al., 2010; Obokata et al., 2017). The overproduction of aldosterone in obesity occurs through 2 pathways: 1- renin-angiotensin system activation stimulates aldosterone secretion from the adrenal cortex and the adipocytes (Faulkner et al., 2018). 2-leptin directly stimulates adrenal cortical cells (Faulkner et al., 2018). Natriuretic peptides reduce aldosterone levels but in obesity, there is increased neprilysin activity that curtails their impact on reducing aldosterone secretion (Wang et al., 2004).

Hyperaldosteronism also stimulates the accumulation and inflammation of EAT leading to increased loco-regional and systemic inflammation (Iacobellis et al., 2016; Packer, 2018b).

Obesity and Low-Grade Systemic Inflammation

White adipose tissue (AT) accumulates in multiple depots. The subcutaneous depot accounts for around 80% of the total AT (Chait and den Hartigh, 2020). Visceral and other ectopic AT depots (EAT, perivascular, hepatic pancreas renal, and skeletal muscle) accounts for the remaining 20% (Chait and den Hartigh, 2020). Visceral AT refers to the intra-abdominal accumulation of mesenteric and omental AT that can be measured by single-slice CT at the level of L4–L5 or the umbilicus and by multiple slice imaging by MRI (Le Jemtel et al., 2018).

Weight gain leads to AT accumulation through adipocyte hypertrophy or hyperplasia. While expanding VAT becomes dysfunctional and inflamed thereby promoting low-grade systemic inflammation (Lumeng et al., 2007). Increasing BMI correlates with a circulating level of inflammatory markers like

TABLE 1 | Major heart failure with preserved ejection fraction trials with role of obesity in outcomes.

Major heart failure with preserved ejection fraction trials					
Name	**Study type**	**N**	**N (BMI > 30 kg/m^2)**	**Treatment modality**	**Main outcomes**
I-PRESERVE (Haass et al., 2011)	RCT	4,128	1,409 (34%)	Irbesartan	• Irbesartan did not improve outcomes • BMI >35 kg/m^2 associated with worse CV outcomes (HR 1.27, *p* 0.011)
PARAGON-HF (McMurray et al., 2020)	RCT	4,796	2,357 (49.1%)	Sacubitril-Valsartan	Sacubitril-Valsartan did not improve outcomes • No subgroup analysis in obese population (HR 0.87, *P* 0.06)
RELAX (Reddy et al., 2019)	RCT	216	81 (38%)	Sildenafil	• Sildenafil did not improve quality of life or exercise capacity • BMI >35 kg/m^2 associated with greater systemic inflammation, worse exercise capacity and worse quality of life
TOPCAT (Huynh et al., 2019)	RCT	1,751	1,135 (64.8%)	Spironolactone	• In patients from the Americas with obesity (BMI >30 kg/m^2) spironolactone did improve outcomes (HR 0.62 *p* 0.001)
EMPEROR PRESERVED (Anker et al., 2021)	RCT	2,997	1,343 (45%)	Empagliflozin	• Empagliflozin improved composite of CV death or HF hospitalization (HR 0.73 $p < 0.001$) • Did not improve all cause death Not as effective in BMI > 30 KG/m^2 (HR 0.85 $p > 0.05$)

HR, Hazard ratio; RCT, Randomized clinical trial.

C-reactive protein (CRP), interleukin (IL) -6, P selectin, vascular cell adhesion molecule 1, plasminogen activator inhibitor 1, and tumor necrotic factor-alpha (TNF-α) (Osborn and Olefsky, 2012; McNelis and Olefsky, 2014). However, circulating inflammatory markers do not reliably reflect the degree of VAT and systemic inflammation (Le Jemtel et al., 2018).

After undergoing hypertrophy, VAT shifts from an anti-inflammatory state that facilitates AT angiogenesis and lipid storage to a pro-inflammatory state with production of monocyte chemoattractant protein- (MCP1), C-X-C motif chemokine 12 leukotriene B4, and colony-stimulating factor 1 that promote proliferation of classically activated macrophages and macrophages AT infiltration (McLaughlin et al., 2017; Reilly and Saltiel, 2017).

Adipogenesis modulates the AT remodeling process and hypoxia is the trigger behind angiogenesis, extracellular matrix remodeling, and inflammation (Crewe et al., 2017; Vishvanath and Gupta, 2019). Inflammatory VAT mediates the production of reactive oxygen species (ROS) and low nitric oxide (NO) that induce mitochondrial dysfunction and activate Nod-like receptor protein 3 (NLRP3) inflammasome (Abad-Jimenez et al., 2020) (**Figure 1**).

Low-Grade Inflammation and Microvascular Dysfunction

Low-grade systemic inflammation worsens cardiovascular diseases (Dhorepatil et al., 2019; Ghoneim et al., 2020a,b). It triggers/heightens an endothelial inflammatory response in the coronary microvasculature (Paulus and Tschope, 2013). In turn, inflammation of the coronary microvascular endothelium alters cardiomyocyte elasticity/function and increases myocardial deposition of collagen that impairs myocardial relaxation and enhances myocardial fibrosis resulting in LVDD and HFpEF (Franssen et al., 2016). Endothelial adhesion molecules enable the infiltration of inflammatory cells that generate hydrogen peroxide (H_2O2). High oxidative stress uncouples NO synthase (eNOS), reduces NO availability, and decreases soluble guanylate cyclase (sGC) stimulation that lowers the activity of cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG). Low PKG activity leads to cardiomyocytes hypertrophy and decreases titin phosphorylation that increases LV stiffness (Franssen et al., 2016).

Microvascular inflammation is associated with increased production of inducible NOS (iNOS that reduces the protein unfolded response (Paulus, 2020). Suppression of the unfolded protein response may lead to interstitial accumulation of destabilized protein (Paulus, 2020). Microvascular inflammation with macrophages and secretion of transforming growth factor-beta (TGF) results in LV deposition of high tensile collagen (Paulus, 2020).

Lastly, microvascular rarefaction and Sirtuin 3 (SIRT 3) dependent defect in the endothelial cell metabolic programing and angiogenesis may affect the progression of perivascular and myocardial fibrosis in HFpEF (Zeng and Chen, 2019) (**Figure 1**).

Adipocyte Dysfunction and Heart Failure With Preserved Ejection Fraction

The role of adipocyte dysfunction in the development of obese-HFpEF is still evolving. Adipocyte homeostasis is maintained by the modulation of pro-inflammatory and anti-inflammatory cytokines. Obesity leads to an excess of pro-inflammatory cytokines and adipokine dysregulation. Adipose tissue exerts an endocrine effect via adipokines. Adipocyte dysfunction caused by obesity leads to alteration in adipokine levels that promotes LV remodeling and ultimately, HfpEF (Berezin et al., 2020). Elevated leptin levels in obesity are associated with cardiac/renal fibrosis (Packer, 2018a) and increased aldosterone production and sodium retention.

Low adiponectin levels in obesity contribute to an increase in the risk for cardiovascular (CV) disease (Shibata et al., 2009).

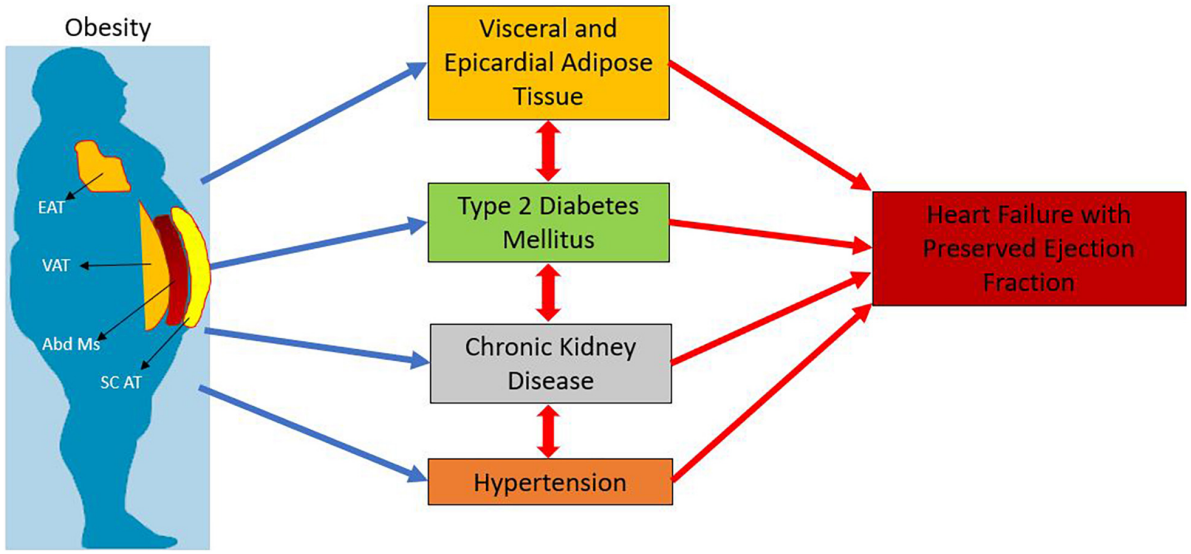

FIGURE 1 | Interplay of obesity and type 2 diabetes with heart failure with preserved ejection fraction. EAT: Epicardial Adipose Tissue; VAT: Visceral Adipose Tissue; Abd Ms : Abdominal Muscles; SC AT : Subcutaneous Adipose Tissue.

Adiponectin levels are reduced HFpEF and elevated in HFrEF. *In vitro* adiponectin has multiple beneficial effects such as stimulation of AMP-activated protein kinase (AMPK)-dependent and extracellular-signal-regulated kinase (Barouch et al., 2003) signaling in cardiac myocytes and endothelial cells. Adiponectin reduces LVH and fibrosis, activates endothelial nitric oxide synthase system to and increases NO production (Kobayashi et al., 2004; Ouchi et al., 2004). These beneficial effects have led to an increasing interest in adiponectin as a therapeutic target (Achari and Jain, 2017).

Resistin is an adipocytokine secreted in macrophages by pro-inflammatory cytokines (Lau et al., 2017). Increased resistin levels promote microvascular inflammation, endothelial dysfunction, and vascular smooth muscle proliferation (Acquarone et al., 2019). In elderly patients without HF, serum levels of resistin predict incident HFpEF and HFrEF (Butler et al., 2009). Resistin levels are elevated in patients with HF, but it does not independently predict an adverse outcome (Brankovic et al., 2018). The roles of visfatin, omentin, and other adipocytokines are less well established and an area of active research (Berezin et al., 2020).

Visceral Adipose Tissue and Heart Failure With Preserved Ejection Fraction

Accumulation of VAT when obesity worsens plays a major role in the development and progression of cardiometabolic conditions. In T2D, VAT is a strong predictor of insulin resistance (Lebovitz and Banerji, 2005) and increased cardiometabolic risk (Rawshani et al., 2020). The inability of the body to cope with unrestricted energy intake leads to VAT expansion that mediates most of the detrimental impact of obesity on clinical outcomes.

In the Multi-Ethnic Study of Atherosclerosis (MESA) (Rao et al., 2018), patients with increased VAT had an independently increased risk of incident HFpEF hospitalization (HR 2.24; 95% C.I. 1.44–3.49). Subcutaneous AT (Sc AT) was not associated with HFpEF. Both VAT and EAT were associated with incident HFpEF hospitalization in the Jackson Heart Study population of African Americans (Rao et al., 2021). Epicardial AT was the only significant variable which predicted all-cause mortality and there was a trend toward increased all-cause mortality seen in VAT (Rao et al., 2021). There was no significant trend seen with S c. AT (Rao et al., 2021) (**Table 2**). These findings point toward the additive effects of VAT and EAT in the obese-HFpEF phenotype.

In patients with obese-HfpEF, VAT accumulation is associated with LVDD and positively correlates with increased LV mass (Abbasi et al., 2015), sphericity, and lower end-diastolic volumes (Neeland et al., 2013). Effects of VAT are also gender specific, with women at baseline tending to have higher VAT% and in HFpEF having worse hemodynamics (Sorimachi et al., 2021). Women with increased VAT and HFpEF have higher exercise-induced LV filling pressures compared with their counterparts with lesser VAT (Sorimachi et al., 2021).

Pericardial/Epicardial Adipose Tissue and Heart Failure With Preserved Ejection Fraction

Increased pericardial/EAT is independently associated with both obesity and T2D (Yafei et al., 2019). EAT is twice as metabolically active as normal white AT and is involved a great degree of lipolysis and free fatty acid release (FFA) (Marchington et al., 1989). Excess circulating FFA levels lead to increased cardiac TG deposition. As EAT directly lies on the myocardium, FFAs released by EAT may have a direct effect on the myocytes and coronaries due to a complete lack of a fibrous fascial layer between the two. A large release of FFA may lead to cardiac lipotoxicity (Iacobellis et al., 2011).

TABLE 2 | Relationship of visceral and epicardial adipose tissue with incident heart failure with preserved ejection fraction.

Name	Study design	N	M	F	Incident HFpEF			Key findings
					N	HR	95% C.I.	
$MESA_{EAT}$ (Kenchaiah et al., 2021)	Prospective Cohort Study	6,785	47%	53%	167	1.42	1.25–1.62	• EAT associ ated with increased risk of HFpEF not HFrEF • Elevated EAT conferred a greater risk of HF in women when compared to men
$MESA_{VAT}$ (Rao et al., 2018)	Prospective Cohort Study	1,806	48.4%	51.6%	34	2.24	1.44–3.49	• VAT associated with incident HFpEF but not HFrEF • No gender-specific differences in HFpEF incidence
Jackson heart $study_{EAT}$ (Rao et al., 2021)	Prospective Cohort Study	1,386	34%	66%	77	1.15	1.08–1.22	• In African American patients, EAT and VAT are independently associated with incident HFpEF
Jackson heart $study_{VAT}$ (Rao et al., 2021)	Prospective Cohort Study	2,844	35%	65%	168	1.12	1.06–1.18	• Increased EAT is independently associated with all-cause mortality even after adjusting for comorbidities • Increased VAT is also associated with all-cause mortality, but the association is not significant after adjusting for comorbidities •SC AT is not associated with incident HFpEF or all-cause mortality

EAT, Epicardial Adipose tissue; VAT, Visceral Adipose tissue; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; SC AT, Subcutaneous Adipose tissue.

Patients with increased EAT (measured on computed tomography; CT) have increased LV mass index (LVMI), large left atrial size (LA), and high E/e' velocity by echocardiography (Butler et al., 2009; Brankovic et al., 2018; Acquarone et al., 2019). The association between EAT and LV parameters persist upon adjusting for obesity markers (BMI, waist circumference), and traditional CV risk factors (Kim et al., 2021). Epicardial AT may increase the myocardial fat content and interstitial fibrosis that likely affects myocardial contractility as evidenced by reduced global longitudinal strain (Ng et al., 2018). Elevated EAT also results in reduced peak VO^2 consumption and peripheral extraction in patients with HfpEF, indicating a worse hemodynamic profile in these patients (Pugliese et al., 2021b).

Finally, in a recent analysis of MESA, EAT also was associated with an increased risk of incident HF (Kenchaiah et al., 2021). High EAT volumes defined as > 70 cm^3 for women and > 120 cm^3 for men correlated with a twofold increased incidence of HF in women and 53% higher risk in men. Increased EAT predominantly enhanced the risk of HFpEF ($p < 0.001$) and not HFrEF (p.31) (**Table 2**).

Role of Chronic Kidney Disease in Heart Failure With Preserved Ejection Fraction

Nearly 50% of patients with HFpEF have chronic kidney disease (CKD) (Redfield et al., 2003; Yancy et al., 2006). The etiology of CKD is multifactorial in HFpEF (van de Wouw et al., 2019). Comorbidities and HF contribute to microvascular dysfunction that causes and perpetuates both renal dysfunction and LV remodeling (van de Wouw et al., 2019). Chronic kidney disease is associated with premature vascular aging (Laurent et al., 2006) leading to macrovascular and microvascular dysfunction. Advanced atherosclerosis and arteriosclerosis worsen HTN that increases LV workload and exacerbates LVH and LVDD (Borlaug and Kass, 2011). Arteriosclerosis also leads to pulsatility (Mitchell, 2008) in the coronary microvascular bed that promotes microvascular disruption and CMD (Safar et al., 2015; van de Wouw et al., 2019). At a molecular level, CKD worsens the above mentioned pro-inflammatory pathways leading to increased ROS production, reduced local NO availability, and CMD (Rosner et al., 2012; Paulus and Tschope, 2013).

Obesity itself leads to a glomerulopathy, i.e., obesity-related glomerulopathy (ORG) that is characterized by maladaptive glomerular hypertrophy and focal segmental glomerulosclerosis (D'Agati et al., 2016). Other pathways of obesity-related CKD involve alteration of adipokines (Briffa et al., 2013), activation of Renin-Angiotensin-Aldosterone System (RAAS) (Upadhya et al., 2020), and ectopic lipid accumulation within the kidneys (Escasany et al., 2019) (**Figure 2**).

Management of CKD in patients with obesity and HFpEF is challenging. Targeting the RAAS showed promise in retrospective studies with a greater reduction of proteinuria seen in obese than non-obese individuals (Praga et al., 2001; Mallamaci et al., 2011; Tsuboi et al., 2013). However, there is still resistance in initiating RAAS inhibitors due to the fear of downstream CKD progression and hyperkalemia.

Weight loss improves proteinuria and has a favorable effect on the estimated glomerular filtration rate (Saiki et al., 2005; Shen et al., 2010; Friedman et al., 2013). Bariatric surgery markedly reduces proteinuria (Fowler et al., 2009; Huan et al., 2009). However, bariatric surgery is associated with long-term renal complications like nephrolithiasis and oxalate nephropathy (Turgeon et al., 2012; Lieske et al., 2015).

Linking Diabetes Mellitus, Obesity, and Heart Failure With Preserved Ejection Fraction: A Clinical Perspective

Besides T2D macrovascular complications, the direct effects of T2D on the myocardium have received increased attention over the last decade (Jia et al., 2018).

At a molecular level, patients with T2D-HFpEF have increased t-tubule density and lower collagen deposition when

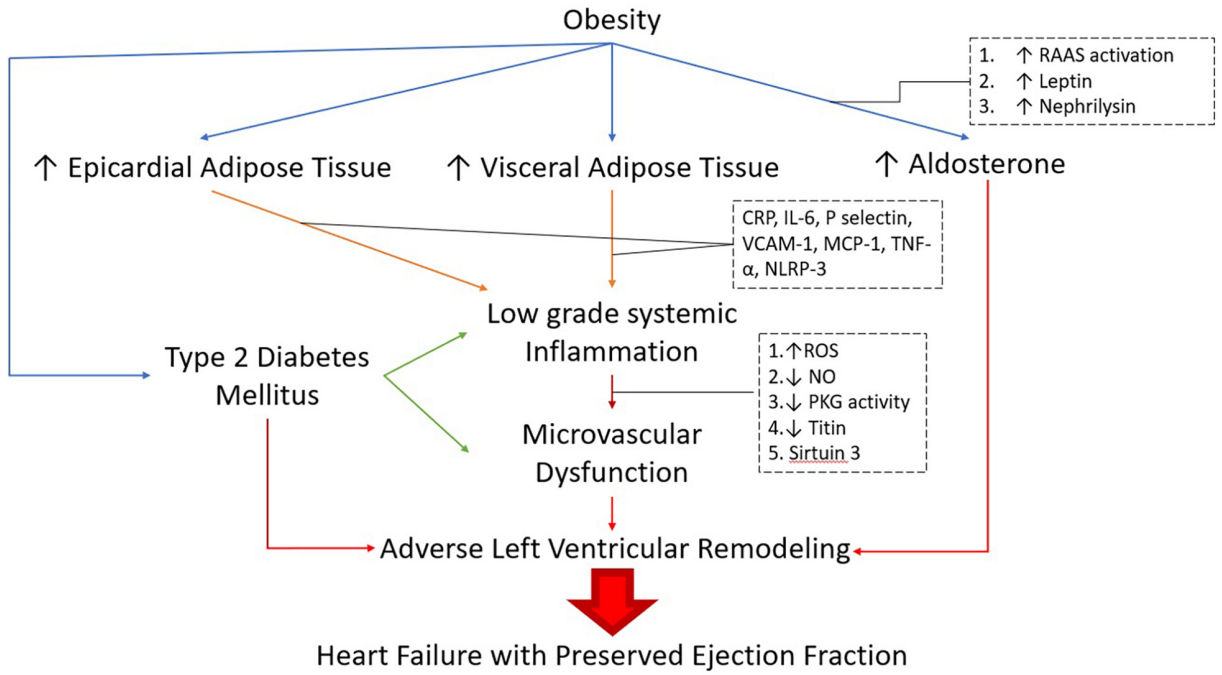

FIGURE 2 | Pathogenesis of obese-DM-HFpEF. RAAS: Renin-Angiotensin-Aldosterone system, CRP: C-Reactive Protein, IL -6: Interleukin-6, VCAM-1: Vascular cell adhesion molecule 1, MCP-1: monocyte chemoattractant protein-1,TNF-α: Tumor Necrosis Factor alpha, NLRP-3: Nod-Like receptor protein 3, ROS: Reactive oxygen species, NO: Nitric Oxide, PKG: Protein Kinase G.

compared with HFrEF. Patients with T2D-HFpEF also have impaired diastolic calcium homeostasis including reduced sarco/endoplasmic reticulum Ca^{2+}-ATPase activity indicating a different pathophysiological process when compared to non-T2D HFpEF (Frisk et al., 2021).

Though BMI is a poor marker of VAT and EAT (Le Jemtel et al., 2018), elevated BMI indirectly suggests a high prevalence of both. MESA, BMI, and VAT was significantly elevated in patients with incident HFpEF (29.9 vs. 27.8, p 0.01; 230.7 cm^3 vs. 162.6 cm^3 $p < 0.001$, respectively) (Rao et al., 2018). Patients with EAT have elevated BMIs and increased VAT, further linking BMI as an indirect measure of VAT and EAT (Kenchaiah et al., 2021).

In HFpEF, patients with T2D commonly have higher BMIs than their non-diabetic counterparts. In an ancillary study of the Phosphodiesterase-5 inhibition to improve clinical status and Exercise capacity in Diastolic HF (RELAX) trial (Redfield et al., 2013; Reddy et al., 2019), BMI were 37.1 and 30.7 kg/m^2 vs. 30.7 kg/m^2 in patients with and without T2D. Unsurprisingly, patients with T2D-HFpEF had more severe initial presentations and more frequent hospitalizations. They also had more LVH and higher filling pressures (E/e') by echocardiography. Cardiac Magnetic Resonance Imaging (CMR) reveals a trend toward higher LV Mass and higher levels of fibrosis in T2D than patients with non-T2D HFpEF (Lejeune et al., 2021). Patients with diabetes had high BMIs (31 vs. 27 kg/m^2, p 0.001) and had an increased rate of mortality and hospitalization for HF (HR 1.72 95% C.I. 1.1–2.6, p 0.011).

A common feature of both T2D and HFpEF is exercise intolerance (EI) (Upadhya et al., 2015a; Pandey et al., 2021). The cause of exercise training (ET) is multifactorial (Pandey et al., 2021) in T2D and HFpEF with impairment in cardiac performance (Pugliese et al., 2021a) and skeletal muscle metabolism/perfusion (Espino-Gonzalez et al., 2021). Obesity and T2D significantly contribute to EI in HFpEF. Obesity-induced sarcopenia exacerbates muscle mass loss due to aging and worsens EI (Upadhya et al., 2015b). Type 2 diabetes lowers exercise capacity through impaired cardiac energetics (Levelt et al., 2016) and skeletal muscle oxygen extraction and metabolism (Nesti et al., 2020). Clinically, EI leads to poor quality of life (Salzano et al., 2021), frequent re-hospitalizations, and early mortality in T2D and HFpEF (Pugliese et al., 2020). Thus, reversal of EI is an important therapeutic target in patients with T2D-HFpEF. improves peak VO^2 (Demopoulos et al., 1997) and quality of life in patients with systolic dysfunction (Fleg et al., 2015). In HFpEF, ET improves peak VO^2 and quality of life independent of improvement in cardiac systolic or diastolic function (Pandey et al., 2015b). The effects of ET on skeletal muscle perfusion and metabolism warrant investigation in T2D-HFpEF.

Patients with T2D HFpEF have an increased risk of mortality (Yusuf et al., 2003; MacDonald et al., 2008; Massie et al., 2008). In the I-PRESERVE trial, patients with T2D also had a higher prevalence of coronary artery disease (CAD) and percutaneous coronary intervention/ coronary artery bypass graft (PCI/CABG) indicating an increased risk of macrovascular disease (Massie

et al., 2008). Of note, patients with and without T2D had similar LVEFs, and patients with T2D had significantly greater LV Mass and DD despite having a lower prevalence of hypertension (HTN) (Kristensen et al., 2017). The greater LV remodeling in patients with T2D was likely related to greater BMIs (31 + /6 vs. 29 ± 5 kg/m^2, respectively). Moreover, in the T2D cohort, 52% of the patients had a BMI > 30 kg/m^2 vs. 38% of the patients in the non-T2D cohort (Kristensen et al., 2017).

Lastly, the duration and severity of T2D in HFpEF affect outcomes. In a sub-analysis of the Treatment Of Preserved Cardiac function heart failure with an Aldosterone Antagonist (TOPCAT) trial (Pitt et al., 2014), patients from the Americas (n = 1765 patients) were analyzed into 3 subgroups, patients with T2D treated with insulin (ITDM, n = 390 patients), patients with T2D not on insulin (NITDM, n = 406 patients), and patients withoutT2D (n = 969 patients) (Huynh et al., 2019). The ITDM cohort had a longer duration of T2D and higher BMI when compared with NITDM and non-T2D patients. The ITDM cohort also had worse LVDD and increased LV Mass. Unsurprisingly, ITDM patients had the worst outcome profile with a 50% increase in all-cause and CV mortality that was elevated when compared to NITDM patients alone. The risk of adverse outcomes was similar in NITDM and non-T2D. Thus, obesity and T2D are additive risk factors in patients with T2D-HFpEF (Huynh et al., 2019). However, obesity directly impacts the severity of T2D as well as HFpEF. Obesity clearly worsens outcomes in T2D. Increasing insulin resistance leads to increased production of insulin from pancreatic β-cells that eventually cannot meet glycemic demands. The ectopic pancreatic fat deposition also contributes to β-cell dysfunction and thereby to T2D (Ishibashi et al., 2020). Thus, treatment of the obese HFpEF phenotype needs to target obesity and T2D.

THERAPEUTIC ADVANCES FOR OBESE-T2D-HEART FAILURE WITH PRESERVED EJECTION FRACTION PHENOTYPE

Targeting Coronary Microvascular Dysfunction

Therapy in HfpEF, specifically in the obese-T2D-HfpEF phenotype is searching for novel therapeutic approaches. Targeting CMD is an innovative approach but so far results have not been promising (Redfield et al., 2013, 2015; Borlaug et al., 2018). Increasing NO availability and enhancing cGMP have been disappointing. In multiple trials looking at phosphodiesterase inhibitors and oral nitrates, increasing NO has failed to improve quality of life or exercise capacity in HfpEF. Most trials recruited patients with high BMI, severe LV concentric remodeling, and advanced LVDD at baseline. Hence, extensive collagen deposition and LV stiffness may account for the neutral findings (Samson and Le Jemtel, 2021).

Given the neutral findings of the above trials, increasing NO may not be the most effective way to remedy endothelial dysfunction. Vericiguat, an sGC stimulator bypasses NO production and can stimulate the production of cGMP that as previously mentioned prevents further LV remodeling. Vericiguat did not improve the primary endpoints of NT-ProBNP levels and left atrial volumes but did improve quality of life in a clinical trial (Pieske et al., 2017). A lower BMI than in prior trials (∼30 kg/m^2 in all groups) hints at a low prevalence of VAT and EAT in this population.

Regardless, despite the high prevalence of CMD in HFpEF (Shah et al., 2018), targeting CMD does not seem to be therapeutically fruitful.

Targeting Mineralocorticoid Receptors

Sodium retention secondary to increased aldosterone production plays a major role in obese-HFpEF. It accounts for the responsiveness to diuretics but excess natriuresis can accelerate renal dysfunction (Gupta et al., 2012). Experimentally, MRAs reduce oxidative stress (Gorini et al., 2019), cardiac inflammation (Tesch and Young, 2017) and fibrosis (Borlaug and Kass, 2011), and improve diastolic LV filling pressures (Pandey et al., 2015a). Spironolactone improved LV filling pressures and exercise capacity in patients with HFpEF. In T2D, spironolactone improves insulin resistance (Olatunji et al., 2017) and albuminuria (Makhlough et al., 2014; Selvaraj et al., 2018). The effects on diabetic nephropathy are mixed with delayed progression in type 1 (Schjoedt et al., 2005) but not T2D (Tofte et al., 2020).

In the TOPCAT trial, patients with obesity and T2D benefited the most from spironolactone (Cohen et al., 2020). Maximum reduction of the primary endpoint (All-cause death and HF hospitalization) was noted in patients with a BMI > 33 kg/m^2 (Elkholey et al., 2021). A similar benefit was seen in patients with high waist circumference (HWC) (Men > 102 cm and women > 88 cm) indicating that spironolactone was more beneficial in patients with increased VAT. The beneficial effect of spironolactone in obese and HWC patients is a reduction in HF hospitalization. Quantification of VAT may help better risk stratify patients who benefit from MRAs. The promising pre-clinical favorable metabolic effects of finerenone (Marzolla et al., 2020) suggest that MRAs may benefit adjunct obese-T2D-HFpEF phenotype.

Targeting Obesity and Diabetes Mellitus

The pathophysiology of HFrEF highlights worsening LVEF due to the progression of eccentric LV remodeling which leads to symptom deterioration and eventual patient decline. The success of neurohormonal modulation in HFrEF is based on the ability of pharmacotherapy and device therapy ability to reserve LV eccentric remodeling. In contrast, neurohormonal modulation does not reverse LV concentric remodeling in HFpEF (Lam et al., 2018; Upadhya and Kitzman, 2020). Hence, the most effective therapies in HFrEF do not lower mortality in HFpEF (Massie et al., 2008; Pitt et al., 2014; Solomon et al., 2019). As previously mentioned, obesity, specifically VAT and EAT, drive LV remodeling (Yan et al., 2020). Obesity leads to T2D hence aggressive weight management will benefit patients with HFpEF and T2D.

Treating obesity is complex and involves lifestyle/behavioral modifications (LBM) as the first step, then pharmacotherapy and bariatric surgery as the next step. Newer advances in anti-diabetic medications have led to a successful strategy of targeting obesity and HF in patients with T2D changing the management paradigm for these patients.

Glucagon-Like Peptide-1 Analogs

Glucagon-like peptide-1 (GLP-1) analogs are coming back in T2D and recent trials demonstrate efficacy in CV disease (Verma et al., 2018) and weight loss (Wilding et al., 2021). GLP-1 receptors are expressed in various organs like the heart, kidney, and pancreas. GLP-1 agonists reduce ROS production by the endothelium and systemic inflammation. It may contribute to their beneficial effect on LV diastolic function studies (Nguyen et al., 2018; Bizino et al., 2019).

GLP-1 agonists have also been shown to be effective in reducing EAT which is a target in HFpEF (Dutour et al., 2016; Iacobellis et al., 2017). In 95 patients with T2D, liraglutide plus metformin was associated with a 36% reduction in EAT when compared with metformin alone (Iacobellis et al., 2017). In 44 patients, exenatide was also associated with a ∼10% reduction in EAT when compared to 1.2% in the standard of care arm (Dutour et al., 2016).

Reduction of adiposity is an essential therapeutic aim in obese-T2D-HFpEF. Before recent semaglutide trials, pharmaceutical agents approved for weight loss by the Food and Drug Administration (FDA) at best resulted in 7% weight loss (Srivastava and Apovian, 2018). GLP-I analogs have been shown to cause an average weight loss of 2.9 kg 95% C.I. 2.2–3.6 kg in 21 trials and 6,411 patients (Vilsboll et al., 2012). The finding of the recent Four Semaglutide Treatment Effect in People with Obesity (STEP 1–4) trials was more promising (Davies et al., 2021; Rubino et al., 2021; Wadden et al., 2021; Wilding et al., 2021). Subcutaneous semaglutide was compared with intensive LBM in successive steps in patients with and without T2D. Semaglutide reduced body weight by 10% in 75% of patients, 15% in 56% of patients, and 20% in 36% of patients. In contrast in a veteran's affairs study (Maciejewski et al., 2016), patients with gastric bypass (GB) reduced weight by 27.5% (95% C.I. 23.8–31.2%), sleeve gastrectomy (SG) by 17.8% (95% C.I. 9.7–25.9%) underlining the magnitude of weight loss achieved by semaglutide. The cardiovascular and outcome effects of GLP-1 analogs need to be investigated in patients with obese-T2D-HFpEF.

Sodium-Glucose Co-transporter 2 Inhibitors

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) are extremely beneficial in HFrEF (McMurray et al., 2019; Packer et al., 2020). The actions are multiple (Lopaschuk and Verma, 2020) and include weight loss, increased diuresis, improved endothelial function, reduced inflammation, and cardiac remodeling prevention. Weight loss is modest (Mean 1.5–2 kg) (Liu et al., 2015; Maruthur et al., 2016; Zaccardi et al., 2016), and slightly greater in patients with T2D than those non-T2D (Pereira and Eriksson, 2019). Weight-loss lasts up to 4 years (Del Prato et al., 2015) and is dose-dependent (Cai et al., 2018). However, the weight loss induced by glycosuria leads to a compensatory increase in appetite and thereby caloric intake (Ferrannini et al., 2015). Thus, SGLT-2i must be combined with other medications for a lasting effect on weight (Leibel et al., 1995). SGLT-2i reduces perivascular AT thereby lowering leptin release and loco-regional inflammation (Iborra-Egea et al., 2019). In patients with T2D with CAD, SGLT2i reduces EAT, TNF-α, and plasminogen activator inhibitor-1 (Sato et al., 2018). SGLT2i effect on TNF-α leads to the improved endothelial secretion of NO and reduced CMD (Juni et al., 2019). Several experimental models have demonstrated the benefits of SGLT-2i on cardiac remodeling (Lambers Heerspink et al., 2013; Verma et al., 2016; Connelly et al., 2019). In a randomized clinical trial, patients treated with empagliflozin had a significantly lower LV mass index when compared with placebo at 6 months (Connelly et al., 2019). Reduced cardiac fibrosis and inhibition of the mammalian target of rapamycin pathway may alleviate LV remodeling (Lee et al., 2019; Kang et al., 2020).

TABLE 3 | Major studies addressing role of bariatric surgery in heart failure.

Bariatric surgery						
Study name	**Study type**	**Treatment modality**	**N**		**Median follow up**	**Main outcomes**
			GB	**LBM**		
Sundstrom et al. (2017)	Nationwide Registry	GB vs. LBM	25,804	13,701	4.1 years	• Patients undergoing GB lost 18.8 kg more weight at year 1 and 22.6 kg more weight at year 2 • HR for incident HF was 0.54 (C.I. 0.36–0.82) in GB patients • 10 kg weight loss was associated with a 23% reduction in incidence of HF (HR 0.77 C.I. 0.6–0.97) in both arms
Utah obesity study (Adams et al., 2005)	Prospective Cohort Study	GB vs. LBM	423	733	2 years	• Patients undergoing GB had marked weight loss (reduction in BMI with GB 15 kg/m^2 vs. 0.03 kg/m^2 in LBM) • The GBS group had reductions in LV mass index and RV cavity area • GBS group also had increased LV midwall fractional shortening and RV fractional area change

GB, Gastric Bypass; LBM, Lifestyle and behavioral modifications; HR, Hazard ratio; HF, Heart Failure; LV, Left ventricle; RV, Right Ventricle.

Recently, in the empagliflozin in HFpEF (EMPEROR-PRESERVED) trial (Anker et al., 2021), empagliflozin did reduce the combined endpoint of CV death or hospitalization but did not reduce significantly reduce CV death alone. The results were underwhelming for patients with typical HFpEF as the benefits were mostly noted in patients with LVEF < 50% compared to LVEF > 60% i.e., HF mid-range-EF. Of note, patients with BMI > 30 kg/m^2 (HR 0.85 C.I 0.7–1.03) did not derive as much benefit as those with BMI < 30 kg/m^2 (HR.7 C.I 0.62–0.88). The findings of the awaited dapagliflozin trials (Solomon et al., 2021) may strengthen EMPEROR-HF (Packer et al., 2020).

Role of Metabolic Surgery

Metabolic surgery, specifically GB, is the most effective intervention for weight loss. It prevents the occurrence of HFpEF in patients with severe obesity. However metabolic surgery has complications and requires careful and long-term monitoring. Compared with LBM, metabolic surgery results in a greater weight loss and a 23% risk reduction in HF (Sundstrom et al., 2017). Exercise-induced weight loss, an integral part of LBM, reduces EAT and thereby, the incidence of HF (Kim et al., 2009).

Weight loss has not been so far a therapeutic target in the management of HFpEF. Of note, regular aerobic exercise training is an arduous undertaking for severely or morbidly obese patients. Weight loss improved LV mass index (LVMI) in MESA with every 5% weight loss being associated with a 1.3% decrease in LVMI and LV mass-to volume ratio ($p < 0.0001$) measured by cardiac MRI (Shah et al., 2015). The Utah obesity study examined patients undergoing metabolic surgery and compared them with control patients with morbid obesity who did not undergo surgery. All patients underwent 2D echocardiography, and close monitoring (Adams et al., 2005). Mean baseline BMI was 48 and 44 kg/m^2 in metabolic surgery and control patients. At 2 years, BMI was 32 and 44 kg/m^2 in metabolic surgery and control patients. Patients who underwent metabolic surgery had significant reductions in LVMI and increases in right ventricular (RV) fractional area change at 2 years (Owan et al., 2011). Smaller studies reported similar findings (Karason et al., 1997; Ippisch et al., 2008; Aggarwal et al., 2016). The effects of caloric restriction and/or exercise were reported in older patients with obesity and HFpEF. After 20 weeks, body weight decreased by 4 kg (3%) in the exercise group, 7 kg (7%) in the caloric restriction group, and 11 kg (10%) in the combined group while it increased by 1 kg (1%) in the control group. Both caloric restriction and exercise independently improved exercise capacity [as measured by peak oxygen consumption (VO^2)] and the effects of caloric restriction and exercise were additive. However, there was no difference in the quality of life (as reported on the Minnesota Living with Heart Failure Questionnaire) or LVMI in either group. High intensity and moderate continuous exercise regimens do not significantly improve in peak VO^2 compared with guideline-directed exercise regimens (Mueller et al., 2021) (**Table 3**).

Adherence to LBM is strongly recommended for patients with obesity, T2D, and HFpEF and physicians need to be pro-active to effectively help patients lose weight. Metabolic surgery though beneficial is marred by strict indications (Ayinapudi et al., 2020) and multiple complications (Ma and Madura, 2015; Surve et al., 2018). Randomized controlled trials of metabolic surgery and LVM are clearly needed in patients with severe and morbid obesity with HFpEF.

CONCLUSION

Heart failure with preserved ejection fraction remains a therapeutic conundrum. The obese-T2D phenotype has distinct pathophysiology encompassing inflammation, CMD, and LV remodeling. Obesity is at the crux of the pathophysiology and weight reduction must be prioritized in these patients. Quantification of VAT and EAT may better help risk-stratify patients at greatest risk of HFpEF and further studies are needed to assess their impact on management. Mineralocorticoid receptor antagonists and anti-diabetic agents like semaglutide and SGLT-2 inhibitors hold promise as useful adjunct agents for obese-T2D-HFpEF and should be studied in randomized clinical trials. Lifestyle and behavioral modifications should be offered to all patients and metabolic surgery may be considered in patients with BMI > 35 kg/m^2.

AUTHOR CONTRIBUTIONS

AD-P and TL contributed to conception and design of the article, wrote the manuscript, and drafted the figures. TT and RS edited certain sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Long Term Metabolic Effects of Sacubitril/Valsartan in Non-Diabetic and Diabetic Patients With Heart Failure Reduced Ejection Fraction: A Real Life Study

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Sacubitril/Valsartan (sac/val) has improved clinical prognosis in patients affected by heart failure (HF) with reduced ejection fraction (HFrEF). HF and type 2 diabetes mellitus (T2DM) frequently coexist, with a prevalence of T2DM of 35%–40% in patients with HF. T2DM is the third co-morbidities in patients with HF and a strong independent risk factor for the progression of HF. In a post hoc analysis of PARADIGM-HF, improved glycemic control was shown in patients with T2DM and HFrEF receiving sac/val compared to enalapril at 12 months of follow-up. The aim of the present study was to evaluate, in a series of repeated observations in 90 HFrEF patients, the long term effect of sac/val treatment on renal function, glycometabolic state and insulin sensitivity parameters, according to diabetic status. We studied 90 patients (74 men and 16 women, mean age 68 ± 10 years, 60 diabetics and 30 non-diabetics) suffering from HFrEF and still symptomatic despite optimal pharmacological therapy. Patients with left ventricular ejection fraction (LVEF) <35% and II-III NYHA functional class were enrolled. All patients underwent clinical-instrumental and laboratory determinations and Minnesota Living with HF Questionnaire (MLHFQ) every 6 months until 30 months to evaluate benefits and adverse events. After 30 months follow-up, we observed a significant improvement in glycometabolic parameters including HbA1c, fasting glucose and insulin, insulin-like growth factor-1 (IGF-1), HOMA index, and LDL cholesterol. Moreover, renal function, NTpro-BNP levels and echocardiographic parameters significantly improved. In diabetic patients a significant reduction in use of oral antidiabetic drugs and insulin was observed after 30 months of sac/val treatment. In the whole population, multivariate analysis shows that the evolution of cardiac index (CI) was significantly associated to simultaneous changes in HOMA, IGF-1 and visit; per each visit and for 1 ng/ml increase in IGF-1 there was an increase in CI of 64.77 ml/min/m^2 ($p < 0.0001$) and 0.98 ml/min/m^2 ($p = 0.003$), respectively, whereas 1 point increase in HOMA was associated with a −7.33 ml/min/m2 ($p = 0.003$) reduction in CI. The present data

confirm persistent metabolic improvement in patients with HFrEF after treatment with sac/val and highlights its potential therapeutical role in patients with metabolic comorbidities.

Keywords: sacubitril/valsartan, type 2 diabetes mellitus, HbA1c, cardiac index, global longitudinal strain, heart failure with reduced ejection fraction

INTRODUCTION

Heart failure (HF) and type 2 diabetes mellitus (T2DM) frequently coexist, with a prevalence of T2DM as high as 35%–40% in patients with HF, independent of the degree of impairment in ejection fraction (McMurray et al., 2014a). Recent data from the Center for Medicare Services demonstrate that 55% of Medicare patients affected by HF have five or more chronic comorbidities (Tisminetzky et al., 2018). In addition, data from the European Society of Cardiology (ESC) Heart Failure Pilot Survey indicate that the majority of chronic HF patients had at least 1 comorbidity with renal disease, anemia, and T2DM being the most common ones and T2DM is the third most important comorbidity and an independent risk factor for hospital admission and death, expecially in elderly (Kristensen et al., 2016; Rosano et al., 2017; Sciacqua et al., 2021). On the other hand, according to Framingham Heart Study, diabetic patients have a 2.4-fold increased risk of HF in males and 5-fold increased risk in women regardless of other comorbidities (Artham et al., 2009; Seferovic et al., 2018). In addition, the degree of risk has further been related to the level of glycaemic control in patients with HF, and more severe hyperglycaemia has been associated with worsening of cardiac structure and function. In particular, as UKPDS has reported that for each 1% decrease in HbA1c there is a 16% decrease in risk of HF (Stratton et al., 2000). Finally, in people with T2DM, HF is a more common initial presentation of CVD than myocardial infarction (Kenchaiah and Vasan. 2015).

TD2M may cause myocardial damage indirectly through the promotion of coronary atherosclerosis, but also directly through hyperglycemia, insulin resistance, mitochondrial dysfunction, and oxidative stress involving chronic inflammation that underlies diabetic cardiomyopathy (DCM) (Jia et al., 2018; Kaur et al., 2021). In the early stages of DCM, cardiac function is preserved; however, a reduction in global longitudinal strain (GLS) can be detected. (Marwick et al., 2018; Sciacqua et al., 2019; Sciacqua et al., 2011).

In the PARADIGM-HF trial, it has been shown that compared with the angiotensin-converting enzyme inhibitor (ACEi) enalapril, sacubitril/valsartan (sac/val), an angiotensin receptor-neprilysin inhibitor (ARNI), improved morbidity and mortality in patients with HF and reduced ejection fraction (HFrEF) after a median follow-up of 27 months (McMurray et al., 2014b).

In a post hoc analysis of the PARADIGM-HF trial, it has been shown that patients with T2DM treated with sac/val exhibited an improved glycemic control as compared to those treated with enalapril at 12 months of follow up (Seferovic et al., 2017). A post-hoc analysis of the PARAGON-HF study showed that patients with HF and preserved ejection fraction (HFpEF) treated with sac/val exhibited a significantly reduction in triglyceride and an increase in HDL-cholesterol levels as compared with those treated with valsartan after a follow-up of 16 weeks (Selvaraj et al., 2021).

Natriuretic peptides (NPs), which are increased by neprilysin inhibition, might have a crucial role in insulin sensitivity and metabolism. Neprilysin is known to promote lipid mobilization from adipose tissue, increased postprandial lipid oxidation, adiponectin release, and enhanced muscular oxidative capacity (Engeli et al., 2012). According with this, blood glucose concentrations have been shown to decrease after infusion of B-type natriuretic peptide (BNP) (Heinisch et al., 2012).

In patients with chronic HF, there is an important desensitization of NPs receptors, with a significant deficiency of the active forms of NPs, leading to reduced natriuresis and diuresis, vasoconstriction, hyperactivation of the renin angiotensin aldosterone system (RAAS), and subsequent activation of the sympathetic nervous system (SNS), enhanced release of angiotensin II and aldosterone with further worsening of renal function, hemodynamic and metabolic conditions (Singh et al., 2017).

In this context, the dual inhibition of RAAS and neprilysin by sac/val effectively counteracts the neurohormonal mechanisms active in patients with HFrEF resulting in improving metabolic and hemodynamic state. A secondary analysis of the PARADIGM-HF trial has shown a beneficial effects of sac/val on renal function with patients treated with sac/val exhibiting lower decline in renal function than those treated with enalapril, an improvement that was more pronounced in diabetic patients compared to non-diabetics (Packer et al., 2018). Accordingly, a 24-month follow-up real-life study has demonstrated the efficacy and durability of sac/val treatment in patients with HFrEF not only in terms of clinical, haemodynamic and echocardiographic parameters but also regarding the renal function (Armentaro et al., 2021). Data on the improvement of metabolic parameters with sac/val treatment, in particular in diabetic patients, derive mainly from post-hoc analysis of the large clinical trials. However, whether these metabolic effects are also observed in real-life patients is still unsettled.

To this aim, we evaluate the long term effect of sac/val treatment on renal function, glycometabolic state and insulin sensitivity parameters according to diabetic status in a series of repeated observations in 90 patients with HFrEF.

MATERIALS AND METHODS

Among 150 outpatients eligible for this study, we enrolled and performed a longitudinal, observational, one-center study on 90 consecutive HFrEF Caucasian outpatients referred to the Geriatrics Department of the University Hospital of Catanzaro, 74 men and 16 females with an average age of

68 ± 10 years. The enrollment period began in March 2018 and ended in June 2018; and the follow-up period ended in December 2020. Subjects with NYHA II or III class were included by appropriate clinical tests. Other inclusion criteria were Age >18 years, LVEF <35%, treatment with stable doses of ACE-I or ARB for at least 4 weeks, according to the International Guidelines recommendations (Ponikowski et al., 2016).

According to American Diabetes Association (ADA) guidelines, diabetes mellitus can be defined as fasting plasma glucose ≥126 mg/dl, oral glucose tolerance test (OGTT) 2 h plasma glucose ≥200 mg/dl, and HbA1C ≥ 6.5%, or if antidiabetic medications were used (American Diabetes Association, 2019). No patient had clinical history of severe renal [estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2] or hepatic impairement (Child-Pugh Class C), angioedema, side effects to ACE-I or ARB. None of patient was pregnant or breastfeeding, none of them had potassium levels >5.4 mmol/L or systolic blood pressure (SBP) <100 mmHg. All patients underwent an accurate medical history and a complete objective examination with the determination of the main anthropometric [weight, height, and body mass index (BMI)] and hemodynamic parameters, assessment of the NYHA functional class, quality of life with the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a 12-lead electrocardiogram (ECG) using a Philips PageWriter T10 electrocardiograph and Echocardiographic recordings using a Vivid E-95 (GE Medical Systems, Milwaukee, United States) ultrasound using a 2.5 MHz transducer. Ethics Committee approved the protocol (code protocol number 2012.63) and informed consent was obtained from all participants. All investigations were carried out to accordance with the principles of the Helsinki Declaration.

Patients elegible for sac/val, in addition to their therapy after suspension of ACE-I (at least 36 h before) or ARB, received initial dosage of 24/26 mg or 49/51 mg in double administration; increasing dosage after 2–4 weeks to maximum dosage of 97/103 mg bid, according to patient tolerance. Clinical evaluation, laboratory tests, ECG, and Echocardiogram-color-Doppler were evaluated at baseline (T0) and every 6 months up to 30 months (T6, T12, T18, T24, and T30) to extimate the possible benefits and the possible occurrence of any adverse events. Furthermore, seven patients were lost to follow-up: in particular six patients died during the study, among these only three for CV causes and one patient experienced symptomatic hypotension which required withdrawal of treatment with sac-val. In addition to sac/val, the following CV drug classes were also considered: ACE-I and ARBs at baseline; while beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), loop diuretics, statins, antiplatelet agents, and oral anticoagulants (OACs) at baseline and during follow-up; furthermore the reduction of the diuretic drugs, insulin therapy and other oral antidiabetic drugs (OADs) during the follow-up was analyzed.

Blood Pressure

Blood pressure (BP) measurements made on the supine patient's non-dominant arm after 5 mins of rest. Three measurements minimum were obtained in three different visits in 2 weeks one from another. The values of the SBP and diastolic BP (DBP) were recorded, respectively, in the first (phase I) and last (phase V) tone of Korotkoff. Baseline BP values represent the average of three measurements obtained at 3 min intervals.

Echocardiograms

All patients were examined at rest and in the left lateral decubitus position. The measurements were obtained according to the international guidelines (Lang et al., 2015). Echocardiographic examinations were performed with a monoplane ultrasound probe 2.5 MHz of Vivid E-95 (GE Medical Systems, Milwaukee, United States) by a single trained operator, who was blinded to treatment protocol. Exclusively tests of excellent technical quality were used in the study, the values represented the mean of at least three and five measurements for patients with sinus rhythm and arrhythmias, respectively.

The left ventricular ejection fraction (LVEF) was calculated by the Simpson biplane method according to the following formula: LVEF = [left ventricular end-diastolic volume (LVEDV)-LV end-systolic volume (LVESV)/LVEDV*100] as mean of two measures in 4 and 2 apical chambers Both volumes were subsequently indexed for body surface area (BSA) and expressed in ml/m^2. Cardiac output has been calculated as a continuity equation, and the cardiac index (CI) expressed in ml/min/m^2 by means of continuity equation and the dP/dT as parameters of global systolic left ventricular function, as suggested by the guidelines (Ladipo et al., 1980; Lang et al., 2015). Left atrial volume (LAV) was measured with the area-length method and indexed for BSA (LAVI). Diastolic dysfunction was assessed by recording pulse-wave Doppler patterns at the mitral, in order to obtain early (E) and late (A) diastolic filling velocities from the 4-chamber view. Tissue Doppler imaging was performed to evaluate septal E' and the E/E' ratio was also calculated (Nagueh et al., 2016).

Right ventricular systolic parameters were also estimated, assessed by calculating the tricuspid annulus plane systolic excursion (TAPSE) and the systolic pulmonary artery pressure (s-PAP) estimate. The TAPSE was assessed using the M-Mode on the tricuspidal ring and expresses the longitudinal systolic function of shortening the right ventricle, a parameter assessed on the basis of ventricular interdependence. The diameter and collapsibility of the inferior vena cava (IVC) during the inhalation-expiratory phase in subcostal projection was used to estimate of the right atrial pressure. Tricuspid regurgitant velocity (TRV) was obtained by continuous Doppler at the level of the atrioventricular plane of the tricuspid valve in projection with the four apical chambers or, in the case of eccentric jets, in parasternal short axis: therefore the s-PAP was derived through the Bernoulli equation: s-PAP = 4 (TRVpeak)2 + Right atrial pressure (RAP). The evaluation of the diameter of the outflow tract of the right ventricle (RVOT) was assessed in the long axis parasternal projection. The area of the right atrium (RAA) was evaluated in apical four chambers projection (Lang et al., 2015).

For speckle tracking analysis digital loops were captured, recording at least three consecutive beats, and analyzed off-line using a dedicated software (EchoPAC 20.0; GE Medical Systems, Milwaukee, United States) by two operators who were blinded to the clinical characteristics of the patients. The same operators derived bidimensional, Doppler and speckle tracking parameters according

TABLE 1 | Baseline characteristics of patients that completed the study.

	Whole population (N = 90)	Non diabetic (N = 30)	Diabetic (N = 60)	*p*
Demographic and clinical parameters				
Age, years	68 ± 10	69 ± 10	67 ± 10	0.556
Gender (males), %	82%	83%	81%	0.845
BMI, Kg/m^2	**32 ± 5**	**31 ± 5**	**33 ± 5**	**0.043**
Smokers, %	39%	47%	35%	0.285
Systolic BP, mmHg	122 ± 12	121 ± 12	123 ± 13	0.378
Diastolic BP, mmHg	73 ± 8	73 ± 7	73 ± 8	0.741
Heart rate, beats/min	76 ± 11	74 ± 10	77 ± 11	0.268
Respiratory rate, breath/min	18 ± 3	18 ± 3	17 ± 3	0.477
MLHFQ, total score	90 ± 4	89 ± 4	90 ± 3	0.385
Biochemical parameters				
Na, mmol/l	140.4 ± 2.2	140.4 ± 2	140.5 ± 2.4	0.755
K, mmol/l	4.4 ± 0.3	4.4 ± 0.4	4.4 ± 0.3	0.272
Creatinine, mg/dl	1.1 (0.9–1.2)	1.1 (1–1.2)	1.1 (0.9–1.3)	0.942
e-GFR, ml/min/1.73m^2	67.3 ± 19.0	67.5 ± 17.2	67.2 ± 20	0.832
NT- proBNP, pg/ml	1904 (900–3,461)	1,608 (800–3,378)	2016 (1,050–3,488)	0.336
Fasting glucose, mg/dl	**112 (98–145)**	**101 (96–118)**	**120 (102–159)**	**0.004**
Fasting Insulin, μU/ml	27 (21–40)	25 (20–32)	29 (21.5–44.5)	0.155
IGF-1, ng/ml	82 (75.5–93.5)	82 (78–100)	82 (75–89.5)	0.662
HbA1c, %	**6.8 (5.8–7.7)**	**5.9 (5.7–6.6)**	**7.3 (6–8.2)**	**<0.001**
HOMA	**7.6 (5.6–12)**	**6.5 (5.3–9.1)**	**8.8 (5.9–16.7)**	**0.027**
Uric acid, mg/dl	6.6 ± 0.9	6.8 ± 1	6.6 ± 0.8	0.894
hs-CRP, mg/l	7.7 (7.2–7.8)	7.7 (7.1–7.8)	7.7 (7.3–7.8)	0.747
LDL cholesterol, mg/dl	78 (56.6–94.6)	80.5 (61.4–94.4)	75 (55.9–94.6)	0.697
HDL cholesterol, mg/dl	81.3 ± 33.5	44.4 ± 8.6	42.2 ± 10.6	0.231
Triglycerides, mg/dl	**130.5 (110–189)**	**114.5 (93–150)**	**132.5 (112–190)**	**0.041**
Echocardiographic parameters				
LVEDV/BSA, ml/m^2	**87.8 (83.1–95)**	**92 (87–98.3)**	**85.5 (82–93.4)**	**0.007**
LVESV/BSA, ml/m^2	**60.4 (56–65.2)**	**63 (60–68)**	**58 (56–64)**	**0.003**
LVEF, %	31.8 (30.8–32.9)	31.3 (30.5–32.7)	31.9 (31.2–33.2)	0.084
Cardiac index, ml/min/m^2	1,667 (1,534–1887)	1,656 (1,569–1807)	1,667 (1,529–1903)	0.467
E/e'	17 (16–18)	17.5 (16–18)	17 (16–18)	0.084
GLS, %	−7.8 (from −8.8 to −7)	−7.9 (from −8.9 to −7)	−7.7 (from −8.75to −7)	0.587
TAPSE, mm	16 (15.5–17)	16 (15–17)	16 (16–17)	0.589
s-PAP, mmHg	44.5 (41–48)	44.5 (42–48)	44.5 (40–48)	0.612
IVC, mm	19.6 (19.4–21)	19.7 (19.5–21)	19.6 (19.4–21)	0.615

BMI, body mass index; BP, blood pressure; MLHFQ, minnesota living with heart failure questionnaire; Na, Sodium; K, potassium; e-GFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; IGF-1, insulin-like growth factor-1; HbA1c, glycated haemoglobin; HOMA, homeostatic model assessment; hs-CRP, highly sensitive c-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEDV/BSA, left ventricular end-diastolic volume index/body surface area; LVESV/BSA, left ventricular end-systolic volume index/body surface area; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; TAPSE, Tricuspid annular plane systolic excursion; s-PAP, systolic pulmonary arterial pressure; IVC, inferior vena cava.

Variables that differed significantly between the two groups in the study population at baseline are shown in bold.

to the most recent recommendations. If the software was not able to assess a segment due to poor image quality after manual correction of endocardial border, the segment considered as inadequate was excluded from the analysis. Briefly, each ventricular wall was analyzed into three segments with a total of 17 segments for the whole myocardium. Longitudinal strain was calculated for each segment, considering the higher value; thus the global longitudinal strain (GLS) was obtained as the mean of all 17 segments (Badano et al., 2018).

Laboratory Determinations

All laboratory measurements were performed after a minimum fasting period of 12 h on peripheral blood samples. Uric acid and creatinine were derived by URICASE/POD and the Jaffé reaction method. To evaluate renal function, the eGFR was calculated using the CDK-EPI equation (Levey et al., 2009). NT-pro-BNP values were measured by enzyme-linked immunosorbent assay (Elecsys proBNP assay, Roche Diagnostics). Serum sodium and potassium levels were measured by indirect potentiometry (Cobas, Roche). The levels of blood glucose, triglycerides, and cholesterol were determined by enzymatic methods (Roche, Basel, and Switzerland). Plasma insulin levels were recorded by chemiluminescence method (Immulite, Siemens Healthcare, GmbH, Erlangen, and Germany). Insulin resistance was evaluated by the Homeostasis Model Assessment (HOMA) method, considering fasting insulin and glucose concentrations, according to the following formula: fasting insulin (μU/ml) × fasting glucose (mmol/L)/22.5. In addition, glycated hemoglobin (HbA1c) was measured by high performance liquid

chromatography certified by the national glycohemoglobin standardization program (NGSP) and using an automatic analyzer (Adams HA-8160 HbA1c analyzer, Menarini, Italy). Insulin like growth factor-1 (IGF-1) levels were evaluated by enzyme immunoassay chemiluminescent assay (CLIA) and, finally, high sensitivity C reactive protein levels (hs-CRP) were estimated by the immunoturbidimetric method (CardioPhase hsCRP, Milan, Italy).

STATISTICAL ANALYSIS

Normally distributed continuous variables were summarized as mean and standard deviation and non-normally distributed data as median and interquartile range. Categorical variables were expressed as percentages. Comparisons between patients with and without diabetes mellitus were performed by unpaired Student's t-test for normally distributed continuous variables, Mann-Whitney U-test for non-normally distributed continuous variables or χ^2 test for categorical data, as appropriate. The evolution of therapies across the follow up time was investigated by Cochran's Q test. The longitudinal changes of variables were analyzed by the linear mixed model (LMM). All variables which deviate from the normal distribution were log-transformed (nl) before to be introduced into LMM as dependent variables. Multifactorial hypotheses were addressed by multiple LMMs. In these models, data were expressed as regression coefficients, 95% confident intervals (95% CIs) and *p*-values. Data analyses were performed by a commercially available statistical softwares: SPSS version 22 for Windows (Chicago, IL, United States) and STATA statistical package (version 13, TX, United States).

RESULTS

The study population included 90 patients attending at the Geriatrics Department at the University Hospital of Catanzaro. At baseline, the mean age was 68 ± 10 years, 82% were males and 39% active smokers (**Table 1**). The most frequent comorbidities associated with study population were: chronic coronary artery disease (74.4%), hypertension (83.3%), dyslipidaemia (87.7%), and T2DM (66.6%). In addition, 32.2% had valvular heart disease, 34.3% atrial fibrillation, 35.5% chronic obstructive pulmonary disease (COPD), and 45.5% of patients renal dysfunction. Finally, 47% of patients had an electronic device [implantable cardioverter defibrillator (ICD) or cardiac resynchronisation therapy defibrillator (CRTd)]. These patients had been implanted at least 12 months prior to the start of sac/val treatment. In addition, patients who met the indication for CRTd or ICD implantation during the follow-up study were not considered for data analysis. However, none of the enrolled patients met this indication.

Baseline clinical, biochemical and echocardiographic characteristics of the study population are reported in **Table 1**.

The study group was stratified according to diabetes mellitus. Sixty patients had history of T2DM (66.6%), while the remaining 30 (33.4%) did not have T2DM. These two groups of patients had similar baseline characteristics except for BMI, fasting glucose, HbA1c, HOMA, and triglycerides values that were significantly higher in diabetic than in non-diabetic patients (**Table 1**). In addition, patients with T2DM showed lower values of IGF-1, LVEDV, and LVESV indexed for BSA (**Table 1**).

At baseline, 62.2% of patients started the lowest dose of sac/val (100 mg/die), and 37.8% 200 mg/die. At 30-months of follow-up, 19% of patients were taking the lowest dose of sac/Val (100 mg/die), 55% of the patients the intermediate dose (200 mg/die), and 26% the highest dose (400 mg/die) (**Table 2**). Regarding NYHA functional class, at baseline 58% of patients had NYHA class III and 42% NYHA class II. At 30 months follow-up, 7.8% of patients reverted to NHYA class I, 82.2% were in NHYA class II, and 10% remained in NYHA class III. Regarding adverse events, there were only four episodes of symptomatic hypotension but only one required drug discontinuation.

TABLE 2 | Evolution of therapies across time.

	Time (months)						
	0 (%)	6 (%)	12 (%)	18 (%)	24 (%)	30 (%)	p*
MRAs	**50**	**41**	**37**	**34**	**31**	**30**	**<0.001**
Statins	78	78	78	79	78	79	1.000
Beta-blockers	99	99	99	99	99	99	1.000
OACs	33	33	33	32	32	32	1.000
Antiplatelet therapy	57	57	57	58	58	56	1.000
Diuretics	**100**	**90**	**86**	**82**	**79**	**78**	**<0.001**
OADs**	**100**	**92**	**83**	**79**	**72**	**65**	**<0.001**
Insulin therapy**	**30**	**27**	**24**	**21**	**18**	**13**	**<0.001**
Sac/val Dose mg							
100	**62**	**20**	**20**	**19**	**19**	**19**	**<0.001**
200	**38**	**58**	**58**	**58**	**58**	**55**	
400		**22**	**22**	**23**	**23**	**26**	

*p*derived by Test di Cochran' Q on listwise; derived by Friedman test for entresto doses. MRAs, mineralocorticoid receptor antagonists; OACs, oral anticoagulants; OADs, oral antidiabetic drugs; Sac/val, Sacubitril-Valsartan. **only on diabetic patients.*

The percentage changes in drug classes taken by patients at baseline and during follow-up are shown in bold.

TABLE 3 | Linear mixed models of study variables over time.

	Time (months)						
	0	6	12	18	24	30	P
BMI, Kg/m^2	32 ± 5	31 ± 5	30 ± 5	30 ± 5	29 ± 5	29 ± 4	<0.001
Systolic BP, mmHg	122 ± 12	119 ± 12	118 ± 10	116 ± 8	115 ± 8	113 ± 7	<0.001
Diastolic BP, mmHg	73 ± 8	70 ± 7	69 ± 7	67 ± 7	66 ± 6	66 ± 6	<0.001
Heart rate, beats/min	76 ± 11	72 ± 8	69 ± 8	66 ± 7	65 ± 7	64 ± 6	<0.001
Respiratory rate, breath/min	17 ± 3	16 ± 2	15 ± 2	13 ± 2	13 ± 2	13 ± 1	<0.001
MLHFQ, total score	89.7 ± 3.6	84.1 ± 4.9	80.5 ± 4.4	77.4 ± 4.5	75.3 ± 3.7	73.1 ± 3.9	<0.001
e-GFR, ml/min/1.73 m^2	67.3 ± 19	72.8 ± 17.9	81.4 ± 17.5	83.8 ± 15.8	85.5 ± 16	86.4 ± 13.2	<0.001
NT- proBNP, pg/ml	1904 (900–3,461)	1,281 (678–2,873)	979 (432–1845)	770 (411–1,670)	712 (411–1,476)	628.5 (389–1,245)	<0.001
Glycemia, mg/dl	112 (98–145)	102 (92–136)	95 (89–101)	91 (88–100)	90 (85–96)	88.5 (81–93)	<0.001
Insulinemia, μU/ml	27 (21–40)	22 (18–35)	19.5 (15–25)	19 (15–23)	18 (15–20)	17 (15–19)	<0.001
IGF-1, ng/ml	82 (76–92)	88 (81–106)	99.5 (90–116)	103 (96–125)	109 (100–129)	116 (106–134)	<0.001
HbA1c, %	6.8 (5.8–7.7)	5.9 (5.4–7.5)	5.6 (5–6.2)	5.6 (5–6.2)	5.6 (5–6.2)	5.4 (5–6)	<0.001
HOMA, (mmol/L*[μU/ml]/22.5)	7.55 (5.63–11.93)	5.99 (4.44–9.41)	4.71 (3.64–6.42)	4.44 (3.64–5.87)	4.13 (3.44–5.21)	3.75 (3.08–4.19)	<0.001
Uric acid, mg/dl	6.63 ± 0.89	5.9 ± 1.08	5.71 ± 1.12	5.62 ± 0.99	5.49 ± 0.82	5.41 ± 0.75	<0.001
hs-CRP, mg/l	7.65 (7.2–7.8)	6.8 (6.4–7)	6.175 (5.74–6.31)	5.61 (5.27–5.74)	5.02 (4.61–5.15)	4.33 (3.78–4.61)	<0.001
LDL cholesterol, mg/dl	81 ± 33	77 ± 30	72 ± 28	71 ± 29	69 ± 20	67 ± 19	<0.001
HDL cholesterol, mg/dl	43 ± 10	44 ± 9	45 ± 12	46 ± 11	47 ± 10	46 ± 9	<0.001
Triglycerides, mg/dl	130.5 (110–189)	128.5 (100–167)	110 (88–125)	110 (88–121)	110 (87–115)	99.5 (84–106)	<0.001
LVEDV/BSA, ml/m^2	89.48 ± 8.24	87.97 ± 7.67	85.01 ± 10.16	83.4 ± 10.33	82.9 ± 10.33	82.34 ± 10.35	<0.001
LVESV/BSA, ml/m^2	60.96 ± 5.9	57.75 ± 5.32	54.6 ± 6.53	51.83 ± 6.62	50.88 ± 6.61	50.01 ± 6.56	<0.001
LVEF, %	31.88 ± 1.47	34.37 ± 1.53	35.76 ± 1.59	37.87 ± 1.65	38.66 ± 1.67	39.3 ± 1.6	<0.001
Cardiac index, ml/min/m^2	1,698.19 ± 201.49	1879.83 ± 205.74	1972.97 ± 200.05	2029.97 ± 209.63	2,103.27 ± 209.63	2,158.89 ± 211.15	<0.001
E/e'	17 (16–18)	16 (14–17)	15 (13–16)	14 (13–15)	14 (13–15)	14 (13–15)	<0.001
GLS, %	−7.81 ± 1.26	−9.04 ± 1.6	−10.85 ± 1.54	−11.64 ± 2.1	−12.88 ± 2.06	−13.92 ± 1.73	<0.001
TAPSE, mm	16.2 ± 1.3	17.1 ± 1.8	17.8 ± 1.8	18.2 ± 2.1	19 ± 2.5	19.3 ± 2.3	<0.001
s-PAP, mmHg	45.4 ± 7.3	42.4 ± 7.3	40.4 ± 7.3	37.5 ± 6.3	34.6 ± 5.6	33.6 ± 4.9	<0.001
IVC, mm	19.6 (19.4–21)	19 (17–21)	19 (18–20)	18 (18–20)	18 (18–20)	18 (17–19)	<0.001

BMI, body mass index; BP, blood pressure; MLHFQ, minnesota living with heart failure questionnaire; Na, Sodium; K, potassium; e-GFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; IGF-1, insulin-like growth factor-1; HbA1c, glycated haemoglobin; HOMA, homeostatic model assessment; hs-CRP, highly sensitive c-reactive protein; LDL, low density lipoprotein; HDL, high density lipoprotein; LVEDV/BSA, left ventricular end-diastolic volume index/body surface area; LVESV/BSA, left ventricular end-systolic volume index/body surface area; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; TAPSE, Tricuspid annular plane systolic excursion; s-PAP, systolic pulmonary arterial pressure; IVC, inferior vena cava.

Evolution of Pharmacological Treatment Over Time

The main drugs taken by the patients and their evolution during follow-up are described in **Table 2**. At baseline 50% of patients were taking mineral receptor antagonists (MRA), whose intake decreased by 20% at 30 months of follow-up ($p < 0.001$); and 100% of patients were taking loop diuretics, which showed a statistically significant reduction of 22% of intake at the follow-up ($p < 0.001$).

At baseline, all patients with T2DM were treated with oral antidiabetic drugs (OADs), whereas at 30 months follow up only 65% were still taking OADs. In addition, at baseline 30% of diabetic patients were treated with insulin whereas at 30 months follow up only 13% continued the insulin treatment. At baseline, 18 (30%) diabetic patients were treated with OADs and insulin concomitantly, while at 30 months only 8 (13%). None of the patients with T2DM were treated with glucagon-like peptide 1 receptor agonist (GLP-1 RA) and only three (5%) patients were treated with sodium glucose cotransporter 2 inhibitors (SGLT2i).

Evolution of Study Biomarkers Over Time

During the follow-up period there was a significant improvement in clinical, echocardiographic and in particular laboratory parameters (**Table 3**). A significant decrease in BMI from 32 ± 5 to 29 ± 4 kg/m^2 was observed, $p < 0.001$. There was also a marked decrease in heart rate (HR) from 76 ± 11 to 64 ± 6 beats/min, $p < 0.001$, and in respiratory rate (RR) from 18 ± 3 to 13 ± 1 breath/min, $p < 0.001$. SBP also decreased from 122 ± 12 to 113 ± 7 mmHg, $p < 0.001$ as well as DBP from 73 ± 8 to 66 ± 6 mmHg, $p < 0.001$. In addition, the introduction of sac/val therapy led to an improvement in several echocardiographic parameters, with a reduction in left ventricular volumes: LVEDV/BSA from 89.4 ± 8.2 to 82.3 ± 10.3 ml/m^2, $p < 0.001$; LVESV/BSA from 60.9 ± 5.9 to 50.0 ± 6. 5 ml/m^2, $p < 0.001$; resulting in an increase in LVEF 31.8% ± 1.4% vs. 39.3% ± 1.6%, $p < 0.001$; in CI from 1698.1 ± 201.4 ml/min/m^2 to 2158.8 ± 211.1 ml/min/m^2, $p < 0.001$; and in left ventricular myocardial deformation indices: GLS from −7.8% ± 1.2% to −13.9% ± 1.7%, $p < 0.001$. In addition, there was also an improvement in right heart parameters, in particular an increase in TAPSE from 16.2 ± 1.3 mm to 19.3 ± 2.3 mm, $p < 0.001$ and a decrease in s-PAP 45.4 ± 7.3 mmHg vs. 33.6 ± 4.9 mmHg, $p < 0.001$. All these findings indicate a reduction in systemic and pulmonary congestion as confirmed by the decrease in NT-proBNP median values 1,904 (900–3,461) pg/ml vs. 628.5 (389–1,245) pg/ml, $p < 0.001$; IVC diameter 19.6 (19.4–21) mm vs. 18 (17–19) mm, $p < 0.001$. Finally, there was also a reduction in left ventricular filling pressures E/e' from 17 (16–18) to 14 (13–15),

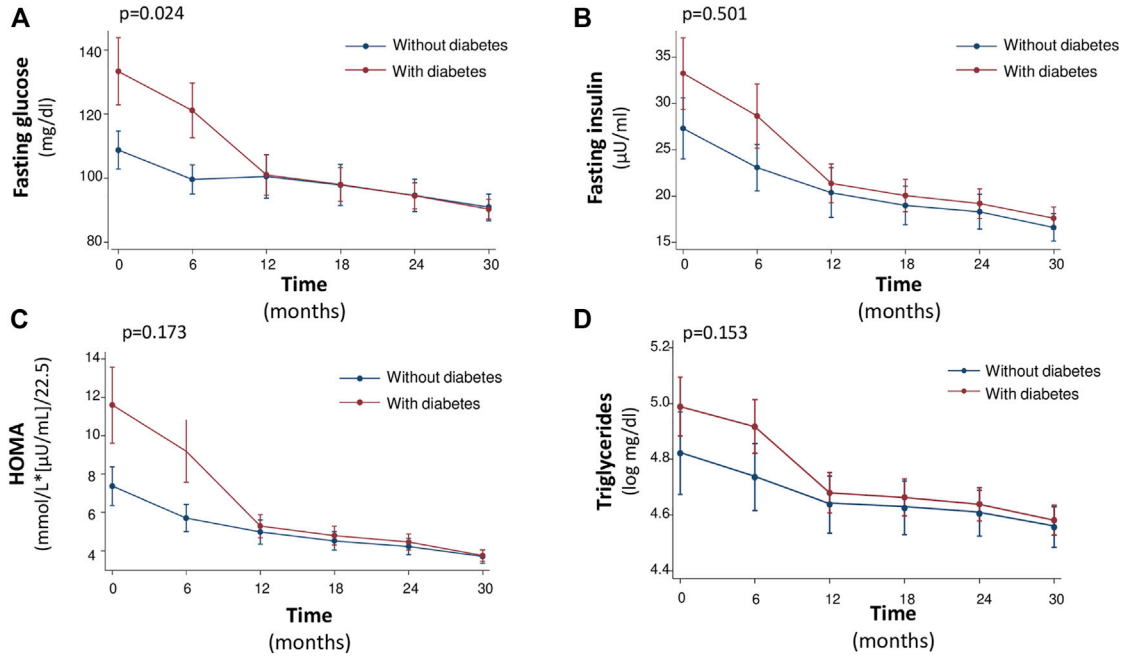

FIGURE 1 | Median values of Fasting glucose (mg/dl) **(A)**, Fasting Insulin (µU/ml) **(B)**, HOMA [mmol/L*(µU/ml)/22.5] **(C)** and Triglycerides (log mg/dl) **(D)** at baseline and every 6 months, during the 30-month follow-up.

$p < 0.001$. The amelioration of haemodynamic conditions may justify, through increase in systemic flow and renal perfusion, the improvement in eGFR from 67.3 ± 19 ml/min/1.73 m^2 to 86.4 ± 13.2 ml/min/1.73 m^2, $p < 0.001$ with a rate of increase of 3.89 ml/min/1.73 m^2 (95% CI: 3.12–4.66) every 6 months.

Notably, during the entire follow-up period, we observed marked changes of several metabolic parameters with improvement of glycemic control and insulin resistance. Fasting glucose decreased from 112 (98–145) to 88.5 (81–93) mg/dl, $p < 0.001$, fasting insulin from 27 (21–40) to 17 (15–19) µU/ml, $p < 0.001$, and HOMA index from 7.5 (5.6–11.9) to 3.7 (3.0–4.1), $p < 0.001$. There was also a reduction in HbA1c values from 6.8 (5.8–7.7)% to 5.4 (5–6)%, $p < 0.001$, and an increase in IGF-1 values 82 (76–92) vs. 116 (106–134) ng/ml, $p < 0.001$, with a rate increase of 6.78 ng/ml (95% CI: 5.84–7.72) per semester indicating an improvement in insulin sensitivity. Also lipid parameters significantly improved, in particular HDL-cholesterol increased, whereas LDL-cholesterol and triglycerides significantly decreased (**Table 3**). hs-CRP decreased from 7.6 (7.2–7.8) to 4.3 (3.7–4.6) mg/L, $p < 0.001$, with a significant reductions of −0.68 mg/L per semester (95% CI: from −0.72 to −0.64 together with a reduction in uric acid values from 6.6 ± 0.8 mg/dl to 5.4 ± 0.7 mg/dl, $p < 0.001$.

Notably, the rate of improvement of glycometabolic parameters in particular HbA1c, triglycerides, fasting glucose, insulin and HOMA was significantly steeper in patients with T2DM that in non-diabetic patients (**Figures 1**, **2**). In particular, fasting glucose, insulin and HOMA in patients with T2DM achieved almost the same values of non-diabetics from 12th month onwards. In addition the reduction of HbA1c and triglycerides was of higher magnitude in diabetic than in non-diabetic patients from baseline to 12th month, with a plateau observed from 12th month onwards.

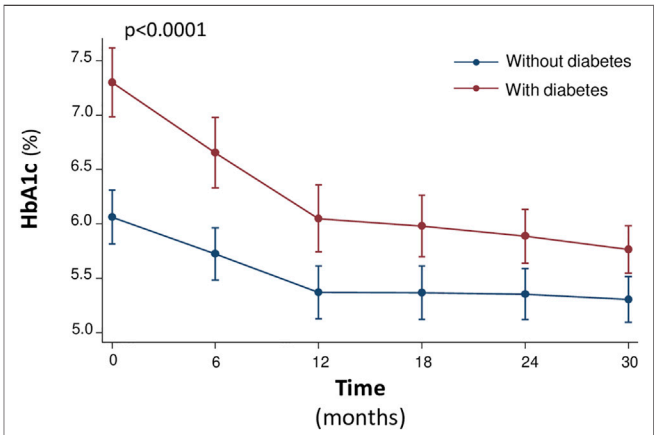

FIGURE 2 | Median values of the HbA1c (%) at baseline and every 6 months, during the 30-month follow-up.

Independent correlates of repeated measurements of left ventricular end-diastolic volume/BSA, LVESV/BSA, GLS, and Cardiac index

To assess the independent correlates of LVEDV/BSA, LVESV/BSA, GLS, and CI over time, a multiple linear mixed model was

TABLE 4 | Multivariate linear mixed models of LVEDV/BSA over time.

	Regression coefficient (95%CI)	*p*-value
Visit	−1.30 (from −1.54 to −1.06)	<0.001
BMI, Kg/m^2	−0.03 (from −0.31 to 0.25)	0.854
HOMA, (mmol/L*[μU/ml]/22.5)	−0.07 (from −0.16 to 0.01)	0.086
e-GFR, ml/min/1.73 m^2	−0.03 (from −0.08 to 0.02)	0.260
Uric acid, mg/dl	0.49 (from −0.14 to 1.11)	0.128
IGF-1, ng/ml	**−0.03 (from −0.06 to 0.003)**	**0.030**
HbA1c, %	0.16 (from −0.24 to 0.56)	0.425

BMI, body mass index; HOMA, homeostatic model assessment; e-GFR, estimated glomerular filtration rate; IGF-1, insulin-like growth factor-1; HbA1c, glycated haemoglobin.
The dependent variables that significantly correlate with the dependent variable of each Multivariate linear mixed models are shown in bold.

TABLE 5 | Multivariate linear mixed models of LVESV/BSA over time.

	Regression coefficient (95%CI)	*p*-value
Visit	−1.87 (from −2.04 to −1.70)	<0.001
BMI, Kg/m^2	0.12 (from −0.07 to 0.31)	0.215
HOMA, (mmol/L*[μU/ml]/22.5)	−0.04 (from −0.10 to 0.03)	0.282
e-GFR, ml/min/1.73 m^2	**−0.03 (from −0.07 to 0.0003)**	**0.050**
Uric acid, mg/dl	**0.49 (from 0.01 to 0.96)**	**0.045**
IGF-1, ng/ml	−0.02 (from −0.04 to 0.001)	0.063
HbA1c, %	**0.32 (from 0.01 to 0.63)**	**0.042**

BMI, body mass index; HOMA, homeostatic model assessment; e-GFR, estimated glomerular filtration rate; IGF-1, insulin-like growth factor-1; HbA1c, glycated haemoglobin.
The dependent variables that significantly correlate with the dependent variable of each Multivariate linear mixed models are shown in bold.

TABLE 6 | Multivariate linear mixed models of GLS over time.

	Regression coefficient (95%CI)	*p*-value
Visit	−1.08 (from −1.19 to −0.96)	0.000
BMI, Kg/m^2	0.08 (from 0.04 to 0.12)	0.000
HOMA, (mmol/L*[μU/ml]/22.5)	0.002 (from −0.03 to 0.03)	0.878
e-GFR, ml/min/1.73m^2	**−0.01 (from −0.02 to −0.00)**	**0.026**
Uric acid, mg/dl	0.13 (from −0.05 to 0.31)	0.149
IGF-1, ng/ml	−0.003 (from −0.009 to 0.004)	0.412
HbA1c, %	0.10 (from −0.08 to 0.27)	0.283

BMI, body mass index; HOMA, homeostatic model assessment; e-GFR, estimated glomerular filtration rate; IGF-1, insulin-like growth factor-1; HbA1c, glycated haemoglobin.
The dependent variables that significantly correlate with the dependent variable of each Multivariate linear mixed models are shown in bold.

TABLE 7 | Multivariate linear mixed models of CI over time.

	Regression coefficient (95%CI)	*p*-value
Visit	**64.77 (from 57.67 to 71.87)**	**0.000**
BMI, Kg/m^2	**−7.27 (from −13.78 to −0.76)**	**0.029**
HOMA, (mmol/L*[μU/ml]/22.5)	**−6.33 (from −10.12 to −2.53)**	**0.001**
e-GFR, ml/min/1.73 m^2	0.63 (from −0.25 to 1.51)	0.161
Uric acid, mg/dl	−12.75 (from −28.04 to 2.53)	0.102
IGF-1, ng/ml	**0.98 (from 0.34 to 1.62)**	**0.003**
HbA1c, %	−3.34 (from −19.98 to 13.29)	0.694

BMI, body mass index; HOMA, homeostatic model assessment; e-GFR, estimated glomerular filtration rate; IGF-1, insulin-like growth factor-1; HbA1c, glycated haemoglobin.
The dependent variables that significantly correlate with the dependent variable of each Multivariate linear mixed models are shown in bold.

applied including a number of covariates, specifically the different metabolic parameters and the impact of the visit at every follow-up. In multivariate LMMs, the longitudinal changes of LVEDV/BSA were significantly associated to concomitant changes of IGF-1 and visit. In fact, for each visit and for each 1 ng/ml increase in IGF1, a −1.3 ml/m^2 ($p < 0.001$) and −0.03 ml/m^2 ($p = 0.03$) reduction in LVEDV/BSA over time was observed, respectively (**Table 4**). Furthermore, the changes of LVESV/BSA were significantly related to simultaneous changes of eGFR, uric acid, HbA1c, and visit; in fact, for each visit and for each 1 ml/min/1.73 m^2 increase in eGFR, a −1.87 ml/m^2 ($p < 0.001$) and −0.03 ml/m^2 ($p = 0.05$) reduction in LVESV/BSA was observed, respectively, whereas a 1 mg/dl increase in uric acid and a 1% increase in HbA1c were associated with a 0.49 ml/m^2 ($p = 0.045$) and 0.32 ml/m^2 ($p = 0.042$) increase in LVESV/BSA, respectively (**Table 5**). The eGFR was also a correlate of GLS over time together with BMI and visit; in fact, for each visit and for each 1 ml/min/1.73 m^2 increase in eGFR, a −1.08% ($p = 0.001$) and −0.01% ($p = 0.026$) reduction in GLS was observed, respectively, whereas a 1 kg/m^2 increase in BMI was associated with a 0.08% increase in GLS (**Table 6**). Finally, the evolution of CI was significantly associated to simultaneous changes in BMI, HOMA, IGF-1, and visit; per each visit and for 1 ng/ml increase in IGF-1 there was an increase in CI of 64.77 ml/min/m^2 ($p < 0.0001$) and 0.98 ml/min/m^2 ($p = 0.003$), respectively, whereas a 1 kg/m^2 increase in BMI and 1 point increase in HOMA were associated with a −7.27 ml/min/m^2 ($p = 0.029$) and −7.33 ml/min/m^2 ($p = 0.003$) reduction in CI, respectively (**Table 7**).

Evolution of Variables Over Time Between Diabetics and Nondiabetics

Moreover, during the study there was a different evolution over time of the natural logarithm (nl) of fasting glucose ($p = 0.024$), fasting insulin (0.501), HOMA ($p = 0.173$), and triglycerides ($p = 0.153$) in diabetic versus nondiabetic patients, according with this a different trend was indeed observed until or at 12 months after initiation of sac/val therapy, after which the trend of these variables was similar between diabetics and nondiabetics, see **Figure 1**. On the other hand, HbA1c had a different trend between the two groups with respect to the other variables. In fact, there was an important reduction in the natural logarithm of HbA1c in both groups up to 12 months, after 12 months the variation of the variable was not superimposable between the two groups ($p < 0.0001$), see **Figure 2**.

DISCUSSION

In this longitudinal-observational, single-center study, considering 90 HFrEF patients with optimal medical therapy but still symptomatic, sac/val treatment demonstrated efficacy, safety and durability every 6 months up to 30 months of follow-up, with an important improvement in clinical and echocardiographic parameters confirming previous evidence (Armentaro et al., 2021). Notably, sac/val showed also a significant betterment in renal function, glycometabolic state and insulin sensitivity parameters and this effect was particularly noticeable in T2DM patients who represented about 67% of the entire population.

After a 30-month follow-up, 81% of the patients was taking the intermediate/high dose of sac/val and an important improvement in both NYHA class and MLHFQ score was observed. These findings were related to the hemodynamic state improvement as demonstrated by the positive changes of the morphological and functional right and left myocardial parameters and by the reduction of pulmonary and systemic venous congestion as demonstrated by decreased NT-proBNP levels and lower use of loop diuretics and MRAs.

The favorable effect of sac/val on renal function has been well demonstrated in the PARADIGM-HF study, in fact patients treated with sac/val showed a slower decline in eGFR compared to enalapril and the benefit was higher in diabetics than in non-diabetics (McMurray et al., 2014a; Packer et al., 2018) and confirmed in a recent meta-analysis.

In the present study, improvement in renal function is already significant after 6 months, consistent with our previous work (Pelaia et al., 2022), and mean changes in e-GFR remain statistically significant until 30 months. If at least part of the eGFR increase can be ascribed to betterment in hemodynamic conditions and renal blood flow by the contemporary modulation of RAAS and NEP, that leads to reduction of intraglomerulary pressure and direct antioxidant, anti-inflammatory and antifibrotic effects respectively, however it may be due to a direct protective effect on the kidney (Judge et al., 2015) (Ruggenenti and Remuzzi, 2015). This finding is clinically relevant because renal dysfunction has an important prognostic role in HF patients (Damman et al., 2014).

The improvement of renal function and the progressive reduction in the use of loop diuretics and MRAs may, at least in part, justify an important reduction in uric acid levels, a known cardiovascular risk factor, especially when associated with other metabolic abnormalities so as insulin resistance (Cassano et al., 2020).

Notably, during the follow-up period significant changes in metabolic parameters, together with hs-CRP levels reduction, have been also observed. In particular, fasting glucose, insulin and HbA1c levels significantly reduced with lowering of HOMA and increase of IGF-1 levels, thus indicating a significant betterment of insulin sensitivity. According with this, also lipid profile significantly improved with reduction of LDL-cholesterol and triglycerides and increase of HDL-cholesterol. Taken together, this better glycemic control accounted for the reduction of OADs and insulin therapy use. Of interest, the improvement of glycometabolic parameters was more evident in diabetic patients and their values achieved almost the same value of non-diabetics from 12th months onwards, indicating a greater effective of the treatment in diabetic setting. Moreover, the longitudinal changes of LV volumes, GLS and CI were significantly associated to simultaneous variations of BMI, HOMA, and IGF-1 and this association was consistent for every visit; emphasizing the effect of the drug on glyco-metabolic parameters and how these determine an important improvement in cardiac volumes, function and global left myocardial strain indices.

Our data are in agreement with results of a post-hoc analysis from the PARADIGM-HF trial showing that treatment with sac/val for the 1st year resulted in a significant reduction in HbA1c in comparison with enalapril. This benefit persisted during the follow-up as demonstrated by a 23% and a 29% reduction in new OADs and insulin therapy use, respectively (Seferovic et al., 2017). This is particularly relevant because patients with a history of diabetes or with previously undiagnosed diabetes, had a 38% greater risk of CV death or HF hospitalization than those without diabetes, moreover an increased risk for poor outcome is also observed in pre-diabetes than non-diabetic patients (HbA1c < 6.0%) (Kristensen et al., 2016).

Thus, this additional effect of sac-val on glycemic control and insulin sensitivity parameters makes this drug not only safe and effective on symptoms control and cardiac reverse remodeling in patients with HFrEF, but also suggests a possible favorable metabolic effect in the entire population with particular regard to diabetic subjects (de Diego et al., 2018; Martens et al., 2019).

In our study, there is also a significant reduction in LDL cholesterol and triglyceride levels and a modest increase in HDL cholesterol levels. This is not surprising, in fact a post-hoc analysis of the PARAGON-HF study showed that HF patients with preserved ejection fraction (HFpEF) treated with sac/val compared with valsartan at 16 weeks from baseline had significantly lower triglycerides and higher HDL-cholesterol levels. These metabolic effects were directly related to NPs activity in fact they were no longer evident after adjustment for urinary cGMP/creatinine (a biomarker of natriuretic peptide activation). However, in addition to these beneficial effects, an increase in LDL-cholesterol, that cannot be attributed to sac/val, was observed. (Selvaraj et al., 2021). However, PARAGON-HF analysis was conducted considering a follow-up of only 16 weeks, on the contrary in the present real life study, we observed the increase in HDL cholesterol levels and a significant reduction in triglycerides and LDL cholesterol levels during a 30-month follow-up.

Even if the positive metabolic effects of sac/val treatment could be partly justified by the reduction of diuretic drugs and by the improvement in quality of life and NYHA class which could have favored an increase in physical activity, however the modulation of RAAS and NPs system by sac/val may affect directly several pathophysiological mechanisms.

In particular, it's known that sustained RAAS activation and NPs deficiency are common conditions in HF thus promoting a proinflammatory state, metabolic dysfunction and IR. Sac/val

may improve the glycometabolic profile and insulin sensitivity through both inhibition of NEP and blocking angiotensin II type 1 receptors. NEP is practically ubiquitous, in fact it is abundantly expressed, as well as in the kidney, also in adipocytes, pancreatic islets, cardiomyocytes, and endothelial vascular cells; furthermore NEP recognizes about fifty substrates therefore its inhibition can have important implications. In particular, the increase of NPs levels can favour lipid mobilization and postprandial oxidation, increased adiponectin synthesis and browing of white adipose tissue, all mechanisms that promote insulin sensitivity. Moreover also other substances are affected by NEP inhibition, in particular bradykinin and glucagon like peptide-1 (GLP-1) increase and endothelin-1 decrease. This is clinically relevant because bradykinin may positively affect insulin signaling, glucose uptake, free fatty acids synthesis, and adiponectin expression in adipose tissue thus improving insulin sensitivity and glycemic control. In addition, GLP-1 may regulate insulin secretion and stimulate extrapancreatic glucoregulation; moreover it may affect appetite and food intake. Finally, lower edothelin-1 levels are associated with reduced lipolysis and improved insulin sensitivity (Giamouzis and Butler, 2017; Singh et al., 2017; Seferovic et al., 2020).

Taken together, the results of the present study might suggest that the improvement of inflammatory and metabolic conditions during sac/val treatment could represent another important mechanism by which the drug exerts its positive effects on cardiac reverse remodeling and hemodynamic balance. These additional metabolic effects of sac/val may have clinical relevance for several reasons; in particular the improvement in insulin sensitivity and HbA1c may favour a reduced use of harmful OADs, such as sulfanilureas, particularly in elderly (Giamouzis and Butler, 2017; Sciacqua et al., 2021). Moreover the progressive reduction in OADs and insulin therapy may reduce drug interactions improving compliance to pharmacological treatment.

The strengths of this study are represented by the fact that it is a real life study with patients showing important comorbidities and a polypharmacological therapy compared to RCTs. In addition, during a fairly consistent follow-up of 30 months sac/val treatment confirmed not only safety but also efficacy and durability, showing also new potential metabolic effects, that were never evaluated in real life studies before. Furthermore, considering that none of diabetic patients were treated with GLP-1 RA and only 5% of patients were treated with SGLT2i, OADs particularly relevant on metabolic and CV profile, it's possible hypothesize that the long-term changes in the study variables can be predominantly attributed to sac/val.

The present study have also several limitations; at first it is not a randomized clinical trial and a matched control group is not available. However, we can consider each patient as a control of himself as before enrollment every patient was treated with the best possible therapy according to current guidelines, but patients were still symptomatic. Other important limitations are represented by the relatively small sample size and the lack of information regarding the physical activity level of enrolled patients. The study protocol did not contemplate a sample size calculation and for this reason our findings, particularly those which did not attain the statistical significance, should be interpreted with very caution. The imbalance of the number of patients between diabetic and non-diabetic patients represents an intrinsic limitation of our study because a 1:1 ratio between the two groups (instead of 2:1) would have been the ideal one. In addition, the reduction of systemic and pulmonary congestion was assessed clinically and echocardiographically and not by a more accurate method such as: bioelectrical impedance vector analysis (Massari et al., 2018). A final limitation is the low percentage of patients on Dapagliflozin or Empagliflozin therapy.

CONCLUSION

To our knowledge, this real-life study is the only one with 30-month follow-up in which the safety, efficacy, and durability of sac-val were demonstrated throughout the follow-up period with a good tolerability profile. Furthermore, this is the first study in which not only the long-term effects of sac-val on reverse remodeling, but also on glycemic control, insulin-sensitivity, lipid parameters, and renal function have been evaluated. Considering present findings, the study results support the need to initiate sac/val treatment as early as possible and optimizing HF treatment particularly before ICD implantation, as recommended by current guidelines (McDonagh et al., 2021). An early use of sac/val in HFrEF patients with numerous comorbidities, in particular T2DM, would allow not only to improve QoL, but also to act on the pathophysiological mechanisms of the disease, promoting reverse cardiac remodeling, preserving renal function and improving insulin resistance and dyslipidemia thus allowing a positive and substantial intervention on prognosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato etico Regione Calabria "Area Centro." The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, AS, GA, GDA, SM, VC, MP, RM, AM, FA, AC, GT, and GS. Methodology, GA, SM, and AS. Statistical analysis, GDA and GT. Validation, AM, GT, AC, FA, GS, and AS. Writing—original draft preparation, GA, GS, and AS. Writing—review and editing, GA, GT, AC, FA, GS, and AS. Visualization, GA, GDA, SM, VC, MP, RM, AM, FA, AC, GT, GS, and AS. Supervision, AS. Project administration, AS. All authors have read and agreed to the published version of the manuscript.

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The potential of glucagon-like peptide-1 receptor agonists in heart failure

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Heart failure (HF) remains one of the cardiovascular diseases (CVDs) associated with a high unmet medical need due to high morbidity and mortality rates and lack of efficacious interventions. HF is closely related to cardiometabolic diseases such as diabetes, obesity and chronic kidney disease, and strategies that address most or all these intertwined conditions are desirable. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are approved for type 2 diabetes (T2D), and some are also indicated for reduction of the risk of atherosclerotic CVD in T2D and for weight management. As we summarise in this concise review, preliminary evidence suggests that the cardioprotective benefits of GLP-1 RAs may also extend to HF. The most robust clinical evidence arguably originates from the large cardiovascular outcomes trials (CVOTs) completed for most GLP-1 RAs, of which the latest showed a significant relative risk reduction (RRR) of 39% (HR) with once-weekly efpeglenatide on HF requiring hospitalisation, corroborating a meta-analysis which found a significant RRR across eight GLP-1 RA CVOTs of 11%. Further, although incompletely described, multiple studies are available to provide insights into the mechanistic underpinnings, which appear to be associated mostly with indirect cardioprotective benefits owing to the ability of GLP-1 RAs to address hyperglycaemia, and reduce body weight, and, amongst others, inflammation. In sum, current evidence positions GLP-1 RAs as a potential cardioprotective strategy in HF, with HF with preserved ejection fraction emerging as the clinically most relevant phenotype for the drug class, especially when occurring in people with obesity with and without diabetes.

KEYWORDS

heart failure, GLP-1, glucagon-like peptide-1, clinical trials, cardiovascular disease, cardiovascular outcome studies, diabetes, obesity

Introduction

Strategies to prevent or ameliorate heart failure (HF) remain urgently needed (Shah et al., 2020). Whereas pharmacotherapeutic and other interventions have steadily improved the prognosis of other types of cardiovascular disease (CVD) and associated sequelae, HF remains associated with more pronounced morbidity and mortality, constituting one of the most

pronounced unmet needs in cardiovascular medicine (Shah et al., 2020). Furthermore, alongside the increasing prevalence of related cardiometabolic diseases such as diabetes, obesity and chronic kidney disease (CKD), the number of people with HF has increased to around 64 million globally, amongst whom most are also living with type 2 diabetes or obesity (Groenewegen et al., 2020). Considering their intertwined epidemiological and pathophysiological associations, interventions that simultaneously address many or all of these diseases are arguably desirable.

Within the past 2 decades, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have emerged as effective agents to improve glycaemic control in type 2 diabetes and to reduce body weight in people with overweight or obesity (Müller et al., 2019; Nauck et al., 2020). In addition, three specific GLP-1 RAs are approved and recommended in several treatment guidelines to improve established CVD or CVD risk factors in people with type 2 diabetes (Arnett et al., 2019; Dunlay et al., 2019; Buse et al., 2020; Honigberg et al., 2020; Sattar et al., 2021; American Diabetes Association Professional Practice Committee, 2022). However, unlike for sodium-glucose co-transporter 2 (SGLT2) inhibitors (McDonagh et al., 2021; Heidenreich et al., 2022)–another novel drug class widely used in type 2 diabetes–a benefit for GLP-1 RAs in HF remains to be fully established in dedicated studies in people with type 2 diabetes as highlighted in some clinical guidelines (Dunlay et al., 2019). Nevertheless, reflecting theoretical and clinical evidence, other guidelines highlight the use of GLP-1 RA treatment for people with type 2 diabetes and HF (Buse et al., 2020; Cosentino et al., 2019), for example, the ADA/EASD consensus statement have hitherto recommended the use of GLP-1 RA treatment in situations where HF (and/or chronic kidney disease [CKD]) is predominant and SGLT2 inhibitors not tolerated (Buse et al., 2020).

In this article, we review current evidence suggesting a potential benefit of GLP-1 RAs in HF as well as the current understanding of the putative mechanistic underpinnings. Amongst the three predominant HF phenotypes (HF with preserved, mildly reduced or reduced ejection fraction; HFpEF, HFmrEF or HFrEF, respectively), we focus the review on HFpEF and HFrEF. Overall, results from the cardiovascular outcomes trials (CVOTs) completed for all marketed GLP-1 RAs in type 2 diabetes support a benefit in HF specifically in addition to the approved use in broad CVD risk reduction in people with type 2 diabetes (Sattar et al., 2021). However, additional trials are needed to increase the strength and granularity of the evidence in terms of, for example, safety considerations as well as benefits in people with comorbidities such as diabetes and obesity, and across HF phenotypes.

The biology and pharmacology of GLP-1

GLP-1 is a major peptide hormone of the incretin system. For an in-depth description of the biology of GLP-1, readers are referred to a recent review by Müller et al. (2019). Briefly, upon food intake, L cells in the intestine secrete GLP-1 into the circulation. The GLP-1 receptor (GLP-1R), which mediates the biological effects of the hormone with relevance for and beyond CVD, is present across many organs and tissues in humans (Figure 1). A major role of the hormone is to regulate the glucose homeostasis in a glucose-dependent manner as a result of its insulinotropic and glucagonostatic actions. GLP-1 effects in certain areas of the brain ultimately lead to weight loss, and in addition to the cardioprotective and renoprotective effects discussed in this article, evidence also points towards neuroprotective and other medically desirable properties (Müller et al., 2019; Nørgaard et al., 2022).

Currently, two main classes of GLP-1 RAs are available (Müller et al., 2019; Nauck et al., 2020): Compounds based on the lizard-derived exendin-4 peptide and compounds based on the human GLP-1 peptide. Both compound classes activate the human GLP-1R and have been engineered to have action profiles compatible with once-daily or once-weekly administration. Both classes are resistant to the enzymatic degradation seen for native GLP-1, which is cleaved by the DPP-IV enzyme to generate inactive metabolites and intact GLP-1 forms with low affinity for the GLP-1R. Most available GLP-1 RAs are given as subcutaneous injections. A second-generation GLP-1 RA (semaglutide) was introduced for oral administration as the world first's large peptide in a tablet (Aroda et al., 2019). The safety and tolerability profiles of the GLP-1 RA drug class are consistent across indications and drug class members (Müller et al., 2019; Nauck et al., 2020). Side effects primarily include gastrointestinal events such as nausea, which can be mitigated using dose-escalation regimens that improve tolerance.

In accordance with their mechanism of action, all marketed GLP-1 RAs are indicated to improve glycaemic control in people with type 2 diabetes (Müller et al., 2019; Nauck et al., 2020). In addition, GLP-1 RAs liraglutide and semaglutide are indicated for weight management in people with obesity or overweight (Jensterle et al., 2022). Furthermore, CVOTs have documented the cardiovascular safety of the GLP-1 RA drug class in type 2 diabetes (Sattar et al., 2021); for some [dulaglutide (Gerstein et al., 2019), liraglutide (Marso et al., 2016) and semaglutide (Marso et al., 2017)], the CVOTs also confirmed a cardiovascular benefit and eventually led to the approved use of these GLP-1 RAs to reduce cardiovascular risk in people with type 2 diabetes and established CVD or at high cardiovascular risk (Honigberg et al., 2020). A recent meta-analysis by Sattar et al. (2021) of the CVOTs found that the GLP-1 RAs are associated with a significant 14% relative risk reduction in terms of major adverse cardiovascular events (MACE, a standard 3-component composite endpoint) (hazard ratio [HR] 0.86; 95% CI: 0.80–0.93) as well as in terms of the three individual components (cardiovascular death, myocardial infarction, and stroke). As discussed below, the CVOTs and the meta-analysis also indicated a benefit on HF.

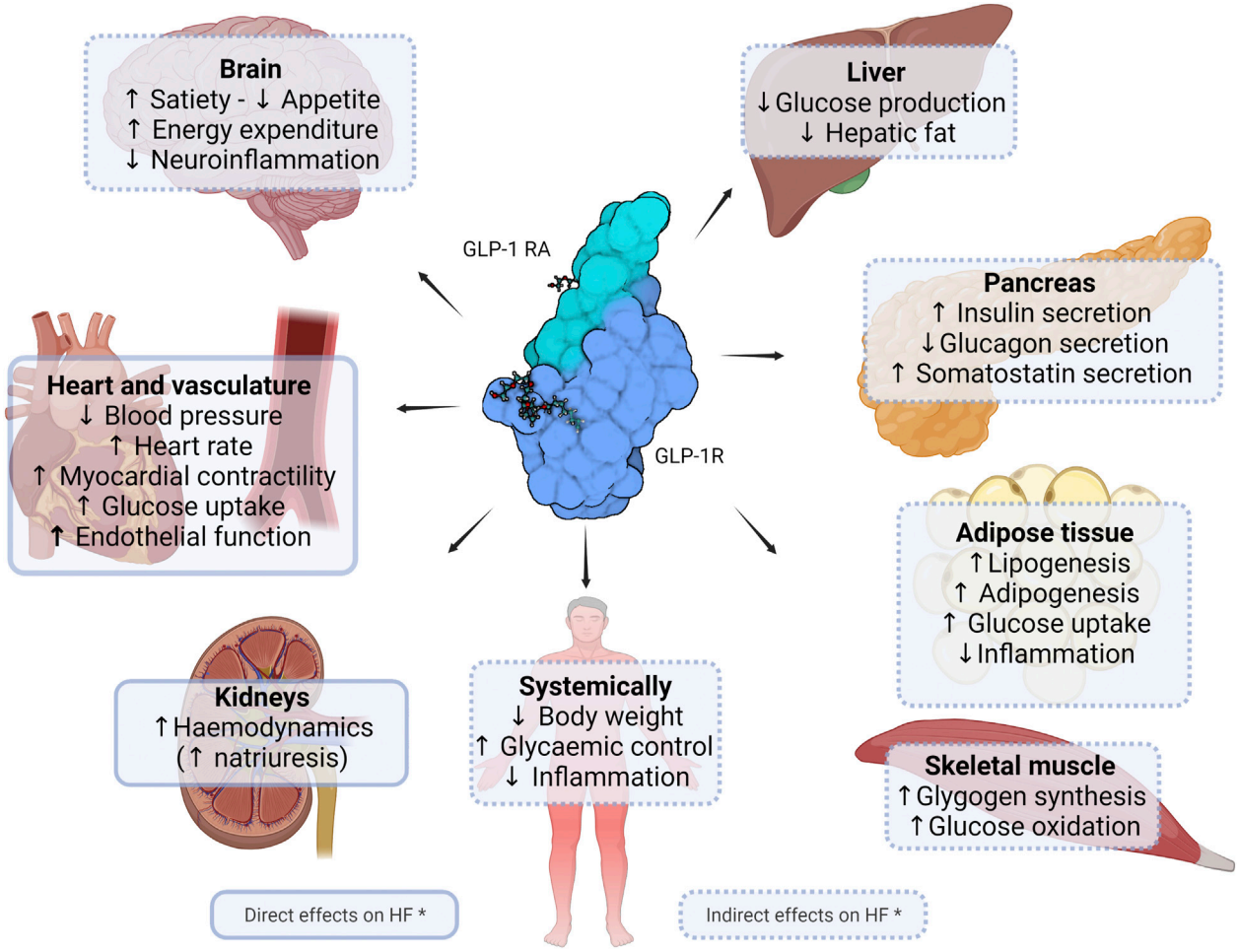

FIGURE 1
Potential direct and indirect effects of GLP-1 receptor agonists in heart failure. Figure shows currently known or suggested direct and indirect effects of glucagon-like peptide (GLP-1) receptor agonists of clinical relevance in heart failure. * Figure is not exhaustive and includes potential effects. Created with Biorender.com.

Epidemiology and pathophysiology of heart failure

As one of the most prevalent consequences of CVD and other cardiometabolic conditions such as diabetes and hypertension, HF remains associated with high mortality rates (Bragazzi et al., 2021). Estimates suggest that in 2017, approximately 64 million people world-wide suffered from varying degrees of HF (Groenewegen et al., 2020). In age-standardised numbers, the global prevalence was 831 individuals per 100.000 people (Bragazzi et al., 2021); despite a growing absolute number of cases, this represents a prevalence decrease of around 7% since 1990.

As outlined earlier, cardiometabolic diseases or risk factors such as type 2 diabetes (Nichols et al., 2004), obesity (Powell-Wiley et al., 2021) and hypertension (Oh and Cho, 2020) are major predictors for HF. Amongst people with HF, up to 50% are estimated to have type 2 diabetes and, vice versa, around 20% of the over 500 million people living with type 2 diabetes have been shown to have comorbid HF (Khan et al., 2020). Amongst people living with the HF with preserved ejection fraction phenotype (HFpEF; see below), 70% also live with obesity (Groenewegen et al., 2020) and 30% live with both type 2 diabetes and obesity (Lam et al., 2011) according to data from 2011. Accordingly, and in line with currently ongoing trials in HFpEF (ClinicalTrials.gov IDs NCT04916470 and NCT04788511), it may be relevant to consider obesity-related HFpEF as a specific (sub)phenotype, whether coexisting with type 2 diabetes or not.

Age is another major risk factor: HF has been reported to affect around 1%–2% of all adults (Groenewegen et al., 2020), rising to 10% in those over 75 years of age (Metra and Teerlink, 2017; Groenewegen et al., 2020; Weldy and Ashley, 2021).

Further, in the Framingham Heart Study, almost all people with hypertension (91%) had or developed HF, the risk of which was 2-3-fold higher in hypertensive than in normotensive individuals (Vasan et al., 2001). Finally, CKD, including even mild kidney disease, is also associated with increased risk of developing CVD, including HF (Ataklte et al., 2021).

The pathophysiology of HF has been extensively reviewed by others (Metra and Teerlink, 2017; Weldy and Ashley, 2021). Briefly, HF refers to a malfunctioning heart that fails to pump blood at a sufficient rate relative to the demands of organs and tissues. Classification of HF is usually done by symptom severity or disease progression stage (McDonagh et al., 2021; Heidenreich et al., 2022). In the early stages of HF, compensatory mechanisms reduce the impact of the cardiac dysfunction; eventually, however, the progressive dysfunction results in clinical symptoms such as fatigue, reduced exercise capacity, dyspnoea, and congestion ("decompensation"). HF is directly related to the thickening and stiffening of the arteries as the results of, for example, atherosclerosis. Other common structural changes include aortic stenosis, myocardial fibrosis and myocyte stiffness. Eventually, these changes lead to increased peripheral resistance, left ventricular hypertrophy and atrial dilation. In addition, atrial fibrillation can occur, which, especially chronically, is associated with increased mortality.

As mentioned earlier, HF is traditionally considered as three main phenotypes: HFrEF, HFmrEF and HFpEF (Weldy and Ashley, 2021; Metra and Teerlink, 2017; Savarese et al., 2022). As implied by the terms, HFrEF represents HF where the left ventricular (LV) EF is markedly reduced (40% or lower), HFmrEF describes a mildly reduced LV EF of 40%–49%, whereas in HFpEF the LV EF is preserved at around 50% or more. HFpEF appears to be the most common type of HF, representing around 50% of the cases, with HFmrEF accounting for 10%–25% (Savarese et al., 2022). HFpEF is especially associated with age as well as female sex and conditions such as diabetes, obesity, hypertension, coronary heart disease and CKD.

Currently available pharmacotherapeutics options in HF mostly remain focused on HFrEF, where treatments strategies aim at relief of symptoms, improving quality of life, and prolonging the life of the affected individual (McDonagh et al., 2021; Heidenreich et al., 2022; Savarese et al., 2022). Mainstay treatments are renin-angiotensin-aldosterone system inhibitors, mineralocorticosteroid antagonists and β-blockers, and, as mentioned earlier, SGLT-2 inhibitors, especially in people with comorbid diabetes. Other options include vasodilators and diuretics. In HFpEF and HFmrEF, these drugs are also widely used, but their effect on clinical outcomes such as survival and hospitalisation is limited. In patients in whom the above-mentioned interventions are insufficient to control the manifestations of HF, additional mechanical circulatory support and/or cardiac transplantation may be indicated. A full overview of the indications of the specific treatments has been described in recent guidelines (McDonagh et al., 2021; Heidenreich et al., 2022).

GLP-1 receptor agonism in heart failure

Clinical evidence

Only a few clinical investigations studying the effects of GLP-1 RAs specifically in HF (all in HFrEF) have been reported as briefly discussed below. Accordingly, the bulk of the clinical evidence of the effects of the drug class on HF have been collected in the placebo-controlled CVOTs in people with type 2 diabetes and established CVD or CVD risk (Table 1) (Pfeffer et al., 2015; Marso et al., 2016; Holman et al., 2017; Marso et al., 2017; Hernandez et al., 2018; Gerstein et al., 2019; Husain et al., 2019; Gerstein et al., 2021). Integrating the result from the CVOTs in their meta-analysis, Sattar and colleagues found that the GLP-1 RA drug class may reduce the risk of hospital admission for HF by 11% (HR vs. placebo of 0.89, 95%CI 0.82–0.98) (Sattar et al., 2021). This reflects HRs <1 in all eight CVOTs except SUSTAIN 6 (HR 1.11, 95%CI 0.77–1.61), although statistical significance for this secondary outcome was shown for only efpeglenatide in AMPLITUDE-O (31) and albiglutide in HARMONY Outcomes, which also found the lowest HR (0.71, 95%CI 0.53–0.94) (Hernandez et al., 2018). This may suggest that the observation of a benefit of the GLP-1 RAs on heart failure hospitalisation as found in the meta-analysis by Sattar and colleagues is driven by data from AMPLITUDE-O and Harmony Outcomes. AMPLITUDE-O with efpeglenatide, the latest GLP-1 RA CVOT to report (Gerstein et al., 2021), indeed indicated a benefit on HF, with post hoc analyses showing a significant 39% relative risk reduction on HF requiring hospitalisation (HR 0.61; 95%CI 0.38–0.98) (Sattar et al., 2021). Further, whilst efpeglenatide was associated with a relative risk reduction of 30% in those who were not on SGLT2 inhibitors at trial entry (HR 0.70; 95%CI 0.42–1.17), for those who were treated with such agents at enrolment, the HR was as low as 0.23 and statistically significant in the post-hoc testing (95%CI 0.05–0.97) (Lam et al., 2021).

It should be noted that evidence for HF specifically from the CVOTs are all associated with a number of limitations. First, none of the trials included HF as a component of the primary composite endpoint (usually 3-component MACE); many, however, stringently captured HF events as secondary endpoints. Nevertheless, for this reason alone, current evidence is not confirmatory. Second, although the CVOTs in general included a meaningful count of people with type 2 diabetes and HF at enrolment, the definition of HF was somewhat vague and varied across the trials; moreover, most were not analysed for outcomes based on presence of HF at

TABLE 1 Key cardiovascular outcomes results for selected GLP-1 receptor agonists.

GLP-1 RA (class, regimen)	CVOT (years of follow-up)	Population		Outcomes, hazard ratio (95%CI)		
		N	History of heart failure (established CVD[b])	Hospitalisation for heart failure	3-point MACE[c]	Kidney outcomes (Sattar et al., 2021; von Scholten et al., 2022)
Efpeglenatide (exendin-4, s.c. OW[a])	AMPLITUDE-O (31) (1.8 years)	4,076	18% (90%)	0.61 (0.38–0.98)	0.73 (0.58–0.92)	0.68 (0.57–0.79)
Lixisenatide (hGLP-1, s.c. OD[a])	ELIXA (32) (2.1 years)	6,068	22% (100%)	0.96 (0.75–1.23)	1.02 (0.89–1.17)	0.84 (0.68–1.02)
Exenatide ER (exendin-4, s.c. OW)	EXSCEL (33) (3.2 years)	14,752	16% (73%)	0.94 (0.78–1.13)	0.91 (0.83–1.00)	0.88 (0.76–1.01)
Albiglutide (hGLP-1, s.c. OD[a])	HARMONY(34) (1.5 years)	9,463	20% (100%)	0.71 (0.53–0.94)	0.78 (0.68–0.90)	N/A
Liraglutide (hGLP-1, s.c. OD)	LEADER (18) (3.8 years)	9,340	18% (81%)	0.87 (0.73–1.05)	0.87 (0.78–0.97)	0.78 (0.67–0.92)
Semaglutide, oral (hGLP-1, p.o. OD)	PIONEER 6 (35) (1.3 years)[d]	3,183	12% (85%)	0.86 (0.48–1.55)	0.79 (0.57–1.11)	N/A
Dulaglutide (hGLP-1, s.c. OW)	REWIND(17) (5.4 years)	9,901	9% (31%)	0.93 (0.77–1.12)	0.88 (0.79–0.99)	0.85 (0.77–0.93)
Semaglutide, s.c. (hGLP-1, s.c. OW)	SUSTAIN 6 (19) (2.1 years)	3,297	24% (83%)	1.11 (0.77–1.61)	0.74 (0.58–0.95)	0.64 (0.46–0.88)
Meta-analysis				**0.89 (0.82 to 0.98)** (Sattar et al., 2021)	**0.86 (0.80–0.93)** (Sattar et al., 2021)	**0.79 (0.73–0.87)** (Sattar et al., 2021)

CI, confidence interval; CVD; cardiovascular disease; CVOT, cardiovascular outcomes trial; GLP-1, glucagon-like peptide-1; hGLP-1, GLP-1, receptor agonist based on human GLP-1; MACE, major adverse cardiovascular event; OD, once-daily dosing; OW, once-weekly dosing; p.o., per oral administration in a tablet; RA, receptor agonist; s.c., subcutaneous injection.
[a]not marketed.
[b]trials enrolled people with established cardiovascular disease and/or elevated cardiovascular risk factors (see original publications).
[c]primary 3-point composite outcome (first occurrence of either cardiovascular death, myocardial infarction, or stroke; in ELIXA, also hospital admission for unstable angina).
[d]PIONEER, 6 was designed to document cardiovascular safety only.

enrolment. Third, none of the CVOTs discriminated between the HF phenotypes. Thus, whilst the CVOTs provide valuable and supportive evidence of a benefit of GLP-1 RAs on HF in people with type 2 diabetes, additional trials are required to fully understand the magnitude and nature of such a potential effect, including if it applies to both prevention and treatment of the condition.

As mentioned, trials focusing on GLP-1 RA treatment in HFrEF are few and of a smaller scale; further, those that have been reported in general showed a neutral or even seemingly detrimental effect of GLP-1 RA in this HF phenotype. Albiglutide was tested in an 82-person placebo-controlled trial but did not improve LVEF or other HF-related outcomes such as the 6-min walking distance test in people with type 2 diabetes and HF with LV EF <40% (Lepore et al., 2016). Liraglutide has been tested in two trials in people with HF and reduced LV EF. In the 24-week LIVE trial in people with stable chronic HF (with or without diabetes), liraglutide did not meaningfully improve LV EF or other variables including quality of life (Jorsal et al., 2017). Further, in the FIGHT trial, which was the only trial sufficiently comprehensive to allow for the evaluation of hard outcomes, even though the HR was above 1 for the composite endpoint of hospital admission due to HF, the treatment effect did not reach statistical significance (HR [liraglutide vs. placebo at 6 months] 1.3, 95%CI 0.89–1.88) in 300 people with HF, with and without type 2 diabetes and with recent decompensation (Margulies et al., 2016). The three trials in HFrEF are in themselves insufficient to conclude on the effects of GLP-1 RA treatment in this HF phenotype, and additional trials are therefore needed.

In HFrEF, an issue remains that because GLP-1 RAs have been shown to modestly increase heart rate (2-3 beats per minute) owing to their chronotropic effects (see "Mechanisms") (Sun et al., 2015), GLP-1 RA treatment in HFrEF may be problematic considering that, in line with the use of beta-blockers to ameliorate HFrEF (11, 12), heart rate elevations may result in a worse outcome (DeVore et al., 2016; Ibrahim et al., 2019). In addition, although overweight and obesity is markedly more common, some individuals with advanced HF like HFrEF are also cachexic (Rossignol et al., 2015) and may therefore not benefit from the weight-reducing effect of GLP-1 RAs. These aspects likely need to be elucidated in future trials; however, to our knowledge, no larger clinical trials with GLP-1 RAs in HFrEF are ongoing.

Mechanisms

The exact basis of the benefits on CVD risk of GLP-1 RA treatment (including the potential positive effects in HF) as discussed above remains incompletely elucidated.

Arguably, the most clinically relevant basis for the potential of GLP-1 RAs in HF could be their effect on multiple cardiometabolic parameters that play intertwined roles across the HF-related diseases such as diabetes and obesity, which often co-exist. Accordingly, GLP-1 RA treatment has been shown to directly or indirectly improve cardiometabolic risk factors that characterise diabetes and obesity, and which play central roles in the development or exacerbation of CVD, including HF. These factors include systemic inflammation (Bray et al., 2021; Zobel et al., 2021), hyperglycaemia (Mapanga and Essop, 2016), increased endothelial production of reactive oxygen species (ROS) (Ceriello et al., 2011; Li et al., 2017; Oh and Jun 2017; Lambadiari et al., 2018; Bray et al., 2021) and impaired vasodilation due to low nitrogen oxide bioavailability (Ceriello et al., 2011; Correale et al., 2021). As noted earlier, endothelial dysfunction from increased vessel thickness and stiffness due to for example atherosclerosis may induce or exacerbate cardiac dysfunction. GLP-1 RAs have been shown to improve endothelial function (Lambadiari et al., 2018), at least in part due to reduced atherosclerosis owing predominantly to the anti-inflammatory properties of the drug class (Rakipovski et al., 2018; Bray et al., 2021; Zobel et al., 2021) and perhaps to lowering of triglyceride levels (Hermansen et al., 2013; Song et al., 2015).

In concordance with the above, weight loss of a magnitude obtainable with bariatric surgery, or with newer agents such as semaglutide (Enebo et al., 2021; Wilding et al., 2021) or the GIP/GLP-1 dual receptor agonist tirzepatide (Rosenstock et al., 2021; Jastreboff et al., 2022), have been shown to be associated with lower risk of incident HF and to improve established severe HF (Sundström et al., 2017; Kindel and Strande, 2018; Aminian et al., 2020; Yang et al., 2020). Moreover, liraglutide 3.0 mg (i.e., the dose level approved for weight management for this GLP-1 RA) in combination with lifestyle intervention markedly reduced the presence of visceral fat over a period of 40 weeks (Neeland et al., 2021). It is especially this kind of adipose tissue that is believed to drive a large part of the pathological effects of excess body weight (Fox et al., 2007).

The reductions in ROS and systemic inflammation, in combination with improvements in the other cardiometabolic parameters, are also thought to mediate the substantiated but so far formally unconfirmed kidney-protective effects of GLP-1 RAs, which may also directly or indirectly carry a HF-related benefit, considering that CKD is a prominent risk factor for HF (von Scholten et al., 2022). Thus, in a recent meta-analysis (Table 1), the results of which resembles our and another similar recent analysis (von Scholten et al., 2022; Kristensen et al., 2019; Cha et al., 2021), Sattar et al. (2021) showed that the GLP-1 RA drug class may be associated with a relative risk reduction for clinical kidney outcomes of 21% (HR 0.79; 95%CI 0.73–0.87). The potential HF benefit associated with better kidney function may in part also be due to improved haemodynamic parameters that essentially relieve the failing heart of stress factors and workload. In this context, GLP-1 RA treatment has been shown to reduce diastolic filling pressures and other measures of diastolic performance (Saponaro et al., 2016; Bizino et al., 2019), although another study did not show such an effect, perhaps reflecting a shorter treatment period (Bojer et al., 2021).

Direct effects of GLP-1 receptor agonism on the heart is likely not a major contributor. This is in line with the fact that, although some studies have shown the presence of the GLP-1R in other parts of the heart (Wei and Mojsov, 1995; Wei and Mojsov, 1996; Ban et al., 2008), current evidence overall suggests that the receptor in humans is expressed predominantly in the sinoatrial node (Pyke et al., 2014; Richards et al., 2014). This understanding is in line with the chronotropic effects of GLP-1 RA treatment, which in a large meta-analysis was shown to be associated with heart rate increases of up to 3.35 beats/min (Sun et al., 2015).

Apart from the chronotropic effects, direct effects of GLP-1 specifically on the heart have not been comprehensively documented, although evidence exists to suggest that GLP-1 RAs may improve cardiac output as well as cardiomyocyte survival (Ravassa et al., 2012; DeNicola et al., 2014; Du et al., 2016; Zhang et al., 2016; Ma et al., 2020). GLP-1 has been shown to increase glucose uptake in the myocardium (Nikolaidis et al., 2005a; Zhao et al., 2006) and to improve LV function in dogs with dilated cardiomyopathy (Nikolaidis et al., 2005a), in which GLP-1 also attenuated reperfusion-related mechanical ventricular dysfunction not associated with irreversible myocardial damage ("myocardial stunning") (Nikolaidis et al., 2005b). In line with the latter, GLP-1 have been shown to protect from ischaemia/reperfusion injuries in isolated perfused rat hearts (Bose et al., 2005). Taken together, additional studies are needed to fully clarify any cardioprotective effects of GLP-1 RA treatment directly on the heart.

It should be noted that one of the two major DPP-IV-generated truncated forms of GLP-1 (GLP-1 [9-36amide]) has been shown to have direct beneficial cardiac effects in mice, which is representative of the hypothesis that a GLP-1R-associated response can be elicited also by these metabolites and thus not only via the classic incretin pathway (Müller et al., 2019). However, in addition to a lack or ambiguity of similar findings in humans, GLP-1 RAs are resistant to enzymatic cleavage as noted earlier (Müller et al., 2019; Cherney et al., 2021). Thus, in the context of pharmacotherapeutic use of modern GLP-1 RAs and in terms of understanding the cardiovascular effects of such treatment, the biology of the truncated GLP-1 metabolites can be disregarded (Cherney et al., 2021).

Future perspectives

In summary, the cardiovascular safety of all currently marketed GLP-1 RAs has been thoroughly established in large CVOTs (Sattar et al., 2021), of which some also suggested a substantial cardioprotective benefit. Accordingly, dulaglutide, liraglutide and semaglutide are indicated to reduce cardiovascular risk in people with type 2 diabetes. Further, the CVOTs in general also suggested a potential benefit of GLP-1 RAs on HF, positioning GLP-1 RAs as another advanced option alongside SGLT2 inhibitors in the otherwise sparse treatment armamentarium for especially HFpEF. Furthermore, smaller clinical trials as well as pre-clinical studies have provided some, albeit not conclusive, support for the clinical outcomes-based evidence of the benefit of GLP-1 RAs in HF. However, as discussed next, a bona fide indication for GLP-1 RAs to reduce the risk of developing HF or to treat chronic HF arguably requires the resolution of several unknowns.

As noted by others (Khan et al., 2020), it remains to be clarified if use of GLP-1 RAs is safe across the HF phenotypes. At present, the safety of the drug class in HFrEF needs to be further investigated (Khan et al., 2020). Thus, clinical trials are needed to establish the benefits/risk profile in HF, considering that no properly designed, HF-specific randomised clinical trials have been completed with GLP-1 RAs in any of the HF phenotypes. Whilst such trials are required to ensure medically appropriate adoption of the drug class in HF, they are also strongly warranted considering the current scarcity of pharmacotherapeutic options in HF (especially HFpEF), which remains one of the CVDs with markedly unaddressed medical needs. Further, whilst real barriers persist, available evidence has indeed corroborated the potential clinical utility of GLP-1 RAs in HF(5), with the most recent GLP-1 RA CVOT (Amplitude-O with once-weekly efpeglenatide) indicating a relative risk reduction for hospitalisation-requiring HF of at least 30% in people with type 2 diabetes (Gerstein et al., 2021).

Of note, the finding of a markedly greater benefit on HF of efpeglenatide amongst trial participants using SGLT2 inhibitors at enrolment in the AMPLITUDE-O CVOT highlights another important point (Lam et al., 2021). That is, investigations are warranted to better understand the potential benefit of combined use of GLP-1 RAs and SGLT2 inhibitors in HF with specific focus on the sequence of treatment initiation and the suitable population, including by HF phenotype and presence of diabetes. Combination with SGLT2 inhibitors to augment the benefits of this drug class in HFrEF with, for example, the weight-lowering effects of GLP-1 RA could offer a clinically valuable and feasible option addressing the spectrum of abnormalities associated with this HF phenotype.

Another drug class widely used to treat type 2 diabetes is inhibitors of the enzyme dipeptidyl peptidase-4 (DPP4), which mediates enzymatic breakdown of GLP-1. A study in rats (Ramírez et al., 2018) has showed that the DPP4 inhibitor sitagliptin induces a lowering of fatty acid utilization in cardiomyocytes in favour of glucose. This finding suggests that DPP4 inhibitors, owing to their GLP-1-enhancing actions, may have a direct beneficial effect on cardiomyocyte function. Conversely, data from clinical trials have showed an increased risk of incident heart failure with DPP4 inhibitors compared to placebo. This may be related to sympathetic activation by DPP4 inhibition (Packer, 2018). Overall, GLP-1 RAs appear to be more efficacious than DPP4 inhibitors in people with type 2 diabetes in terms of improving glycaemic control and reducing body weight (Gilbert and Pratley, 2020).

Yet another aspect to consider is the recurring theme of precision medicine. It is likely that more granular subphenotypes exist beyond the HFrEF/HFmrEF/HFpEF trichotomy. For example, an HFpEF phenotype characterised by pronounced expansion of epicardial adipose tissue (EAT) has been suggested (Elsanhoury et al., 2021). People with HFpEF with EAT might benefit specifically from EAT-directed intervention. To that end, GLP-1 RAs might be useful in light of studies demonstrating EAT reductions following treatment with dulaglutide, liraglutide or semaglutide (Yang et al., 2013; Beiroa et al., 2014; Iacobellis et al., 2017; Iacobellis and Villasante Fricke, 2020; Rasmussen et al., 2021). In addition, other patient-specific treatment strategies tailoring the use of GLP-1 RAs and other options to the HF phenotype and stage are likely also valuable to study and validate.

Finally, although most of the evidence of a potential benefit of GLP-1 RAs in HF originates from CVOTs in type 2 diabetes, it may likely be in the weight management setting that the drug class could be of the highest clinical value, particularly in people with HFpEF. In fact, as outlined above, HF is even more prevalent amongst people with obesity than amongst those with type 2 diabetes, and the consequences of excess body weight (i.e., adipose tissue) most likely play direct and indirect key roles in the development of HF. Accordingly, currently ongoing trials in HF (HFpEF) with the GLP-1 RA semaglutide (2.4 mg for once-weekly subcutaneous injection, i.e., the dose approved for weight management) enrols people with obesity with (STEP-HFpEF DM trial; Clinicaltrials.gov ID NCT04916470) or without (STEP-HFpEF trial; Clinicaltrials.gov ID NCT04788511) diabetes. In addition, the SUMMIT trial evaluates the effect of tirzepatide (the GLP-1/GIP dual receptor agonist) in people with obesity-related HFpEF (Clinicaltrials.gov ID NCT04847557).

Conclusion

Taken together, it presently appears that amongst individuals with HF, those most likely to benefit from GLP-1 RA treatment are people living with or at risk of developing obesity-related (with or without diabetes) HFpEF. If in fact future studies robustly establish a beneficial effect of the drug class in HF, it may allow for broader adoption of GLP-1 RAs in the prevalent CVD, ultimately contributing to addressing the unmet medical need that continues to persist in the prevention or management of, in particular, HFpEF.

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Diabetes outcomes in heart failure patients with hypertrophic cardiomyopathy

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Aims: We aimed to assess diabetes outcomes in heart failure (HF) patients with hypertrophic cardiomyopathy (HCM).

Methods: The National Inpatient Sample database was analyzed to identify records from 2005 to 2015 of patients hospitalized for HF with concomitant HCM. We examined the prevalence of diabetes in those patients, assessed the temporal trend of in-hospital mortality, ventricular fibrillation, atrial fibrillation, and cardiogenic shock and compared diabetes patients to their non-diabetes counterparts.

Results: Among patients with HF, 0.26% had HCM, of whom 29.3% had diabetes. Diabetes prevalence increased from 24.8% in 2005 to 32.7% in 2015. The mean age of patients with diabetes decreased from 71 ± 13 to 67.6 ± 14.2 ($p < 0.01$), but the prevalence of cardiovascular risk factors significantly increased. In-hospital mortality decreased from 4.3% to 3.2% between 2005 and 2015. Interestingly, cardiogenic shock, VF, and AF followed an upward trend. Age (OR = 1.04 [1.03–1.05]), female gender (OR = 1.50 [0.72–0.88]), and cardiovascular risk factors were associated with a higher in-hospital mortality risk in diabetes. Compared to non-diabetes patients, the ones with diabetes were younger and had more comorbidities. Unexpectedly, the adjusted risks of in-hospital mortality (aOR = 0.88 [0.76–0.91]), ventricular fibrillation (aOR = 0.79 [0.71–0.88]) and atrial fibrillation (aOR 0.80 [0.76–0.85]) were lower in patients with diabetes, but not cardiogenic shock (aOR 1.01 [0.80–1.27]). However, the length of stay was higher in patients with diabetes, and so were the total charges per stay.

Conclusion: In total, we observed a temporal increase in diabetes prevalence among patients with HF and HCM. However, diabetes was paradoxically associated with lower in-hospital mortality and arrhythmias.

KEYWORDS

hypertrophic cardiomyopathy, heart failure, diabetes, cardiovascular disease, NIS database, heart failure, diabetes

1 Introduction

Hypertrophic cardiomyopathy (HCM) is a structural disease of the heart; it can be caused by genes affecting the heart muscle, defined by an increase in myocardial wall thickness of >15 mm in adults (or >13 mm in adults with a first-degree relative with HCM) (Seferović et al., 2019). HCM can also be seen as a result of longstanding hypertension and metabolic disease, causing remodeling of the heart (Olivotto et al., 2013). The structural abnormalities lead to many complications, including arrhythmias, angina, outflow tract obstruction, and heart failure (HF). While in these patients, the leading cause of death is arrhythmias causing sudden cardiac death (SCD) (Tripathi et al., 2019), HF exacerbations account for a common presentation in symptomatic patients, usually with dyspnea on exertion being the primary symptom (Wigle et al., 1995).

Macrovascular complications are the leading cause of death in patients with diabetes (Huang et al., 2017) despite the recent temporal decrease in complications-related mortality (Abi Khalil et al., 2012). Diabetes increases the risk of HF in the general population; it is associated with higher long-term mortality in patients with established HF(Lehrke and Marx, 2017; Kenny and Abel, 2019). Further, a new entity called "diabetic cardiomyopathy" has been recently recognized as a separate entity having concentric hypertrophy and diastolic dysfunction as the main hallmarks, even in the absence of coronary artery disease (CAD) (Dillmann, 2019). Diabetes is often encountered in heart failure with preserved ejection fraction (HFpEF) and is associated with a worse outcome (Lehrke and Marx, 2017).

Gven the increasing prevalence and incidence of diabetes (Seferović et al., 2018), it is inevitable that the proportion of patients with cardiac diseases also increases. We, therefore, assessed the temporal changes in diabetes prevalence in patients with HCM and subsequent cardiovascular and socio-economic outcomes.

2 Methods

2.1 Data source

Data were extracted from the national inpatient sample (NIS) database between 2005 and 2015. The database is the largest all-payer database in the US, representing almost 20% of inpatient hospitalizations in the US, containing de-identified data, and providing confidentiality. Data is coded using the International Classification of Disease (ICD) ninth edition until 2014, then the 10th edition. This study received approval from Weill Cornell Medicine's IRB (18-00017).

2.2 Diagnosis and outcomes

We analyzed admissions for HF (primary diagnosis), aged 18 or more, with previously reported HCM (secondary diagnosis). Patients were further divided into two groups according to diabetes. All diagnoses were based on ICD-9 and 10 (see Supplementary Appendix). The primary outcome was the prevalence of diabetes in all patients with HF and HCM. Secondary outcomes were in-hospital mortality, cardiogenic shock, ventricular fibrillation (VF), and atrial fibrillation (AF), knowing that sudden cardiac death and ventricular arrhythmias are the most serious and lethal complications of HCM (Houston and Stevens, 2014). Secondary outcomes included socio-economic outcomes, which are the total charges/stay and the length of stay (LoS). We first analyzed the baseline characteristics and cardiovascular and socioeconomic trends of all patients with HCM hospitalized for HF. We then stratified them into two groups according to the presence of diabetes. Further, we merged both groups for intercomparison. Finally, we assessed the predictors of outcomes in patients with diabetes, HF, and HCM.

2.3 Statistical methods

Data weighting was performed for the results to be more representative of the nationwide population (around 95% after weighting), as recommended by the Healthcare Cost and Utilization Project, the custodian of the NIS database (AHRQ, 2021). Data analysis was performed using the methodological standards in research using the NIS database (Khera et al., 2017). Trend weight was used for weighting data prior to 2012 and discharge weight from data from 2012 to 2015. Variables were presented using means (standard deviations), medians (interquartile ranges), or numbers (percentages) as deemed appropriate. Temporal trends were analyzed using a linear model. Comparisons of diabetic and non-diabetic patients were made using a Student's t-test or Chi-square test. We also calculated the Elixhauser score, which includes 31 characteristics that are predictors of poor long-term prognosis and higher mortality risk (Elixhauser et al., 1998). Cardiovascular events were adjusted for factors that were different between both groups, which included: age, gender, race, income, primary expected payer, obesity, hypertension, dyslipidemia, peripheral vascular disease (PVD), chronic kidney disease (CKD), and coronary artery disease (CAD). Multivariable logistic regression was used to assess predictors of cardiovascular events. Total charges/stay were adjusted for yearly inflation, relying on US Bureau of Labor Statistics numbers. Analysis was done using SPSS (IBM, version 26).

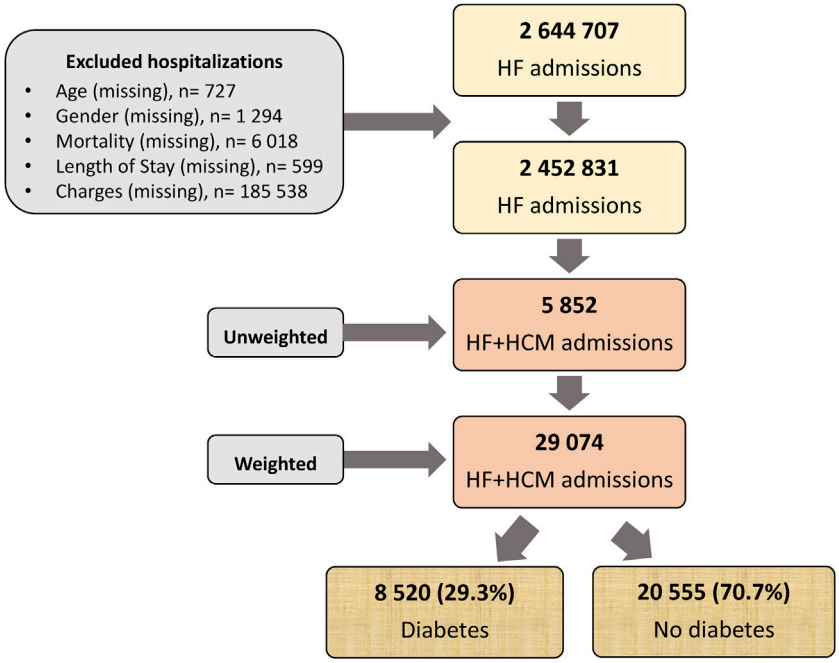

FIGURE 1
Flow chart of the study. HCM, Hypertrophic cardiomyopathy; HF, heart failure.

3 Results

3.1 Studied population

We initially included 2 644 707 admissions for HF between 2005 and 2015, of which we assessed 2 452 831 after excluding those with missing records (Figure 1), 5.852 (0.26%) had HCM. Weighted, the number amounted to 29.074 patients being analyzed with HF and HCM. Of those, 8.520 (29.3%) had diabetes and 20.555 (70.7%) did not.

3.2 Diabetes prevalence, trends, and outcomes in heart failure patients with hypertrophic cardiomyopathy

First, we looked at the prevalence of diabetes in patients and HF and HCM. As shown in Supplementary Table S1, the prevalence of diabetes increased from 24.8% in 2005 to 33% in 2015 ($p < 0.001$). The same applies to the age-adjusted prevalence, which increased from 22.3% to 32.6%, and the age and sex-adjusted from 22% to 32.9% ($p < 0.001$ for all).

Concomitantly, a temporal increase in the prevalence of hypertension, dyslipidemia, smoking, and other CVD was also noted. In diabetes patients with HCM, the mean (SD) age decreased during the observation period from 71 (13) to 67.6 (14) ($p = 0.027$), with the proportion of those aged <55 increasing over time from 11.2% to 20.9% ($p < 0.001$) (Table 1). There were more females than males. However, the percentage of males increased from 33.2% to 37.8% ($p = 0.001$). White Americans represented up to 75% of the patients in 2005. However, this number decreased to 54.3% in 2015, coupled with an increase in the proportion of Blacks ($p < 0.001$). All cardiovascular risk factors–except hypertension and a history of CAD-increased with time, which was translated to an increase in the Elixhauser score from 1.8 (6) in 2005 to 6.2 (8) in 2015 ($p < 0.001$).

When looking at the temporal trends of outcomes, we found that crude in-hospital mortality decreased from 4.3% to 3.2% (<0.001) in patients with diabetes (Figure 2). Interestingly, cardiogenic shock, VT, and AF followed an upward trend ($p < 0.001$ for all). Similar temporal trends exist regarding decreasing age, gender distribution, and rising prevalence of obesity, smoking, and dyslipidemia in patients without diabetes (Supplementary Table S2). In-hospital crude mortality also significantly decreased during the observation period in non-diabetes patients (3.9% in 2005 vs 2.7% in 2015, $p = 0.009$) (Figure 2).

3.3 Comparing diabetes to non-diabetes patients

After merging all years, we first compared the baseline characteristics of diabetes to non-diabetes patients. Most

TABLE 1 Baseline characteristics and temporal trends of diabetes patients with heart failure and hypertrophic cardiomyopathy, from 2005 to 2015.

Years	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P (trend)
Age												
Mean Age (SD)	71.0 (13.0)	68.5 (12.8)	70.7 (14.1)	69.5 (14.0)	69.8 (16.0)	67.7 (11.3)	70.1 (13.8)	67.4 (13.9)	68.1 (14.7)	69.0 (13.8)	67.6 (14.2)	0.027
Age: <55	51 (11.2%)	48 (11.7%)	66 (15.6%)	78 (16.5%)	69 (19.4%)	72 (15.3%)	91 (14.7%)	180 (15.2%)	250 (18.2%)	255 (18.8%)	290 (20.9%)	<0.001
Age: 55–64	69 (15.2%)	90 (21.9%)	43 (10.2%)	92 (19.5%)	63 (17.7%)	111 (23.6%)	98 (15.7%)	255 (21.5%)	240 (17.5%)	180 (13.2%)	275 (19.8%)	<0.001
Age: 65–74	147 (32.4%)	139 (33.8%)	125 (29.6%)	86 (18.2%)	73 (20.6%)	147 (31.3%)	154 (24.6%)	325 (27.4%)	315 (23.0%)	315 (23.2%)	325 (23.4%)	<0.001
Age: 75–84	133 (29.3%)	86 (20.9%)	130 (30.7%)	138 (29.2%)	73 (20.6%)	117 (24.9%)	203 (32.4%)	275 (23.2%)	355 (25.9%)	430 (31.6%)	320 (23.0%)	<0.001
Age: >85	54 (11.9%)	48 (11.7%)	59 (13.9%)	79 (16.7%)	97 (27.3%)	23 (4.9%)	79 (12.6%)	150 (12.7%)	210 (15.3%)	180 (13.2%)	180 (12.9%)	<0.001
Gender												
Male	151 (33.2%)	131 (31.8%)	164 (38.8%)	141 (29.8%)	132 (37.2%)	132 (28.1%)	232 (37.1%)	450 (38.0%)	570 (41.6%)	530 (39.0%)	525 (37.8%)	0.001
Race												
White	272 (74.5%)	201 (60.5%)	201 (60.2%)	282 (72.7%)	170 (61.4%)	248 (55.6%)	339 (59.5%)	630 (57.0%)	805 (61.9%)	785 (60.2%)	720 (54.3%)	<0.001
Black	49 (13.4%)	110 (33.1%)	71 (21.3%)	72 (18.6%)	51 (18.4%)	98 (22.0%)	145 (25.4%)	340 (20.8%)	335 (25.8%)	390 (29.9%)	410 (30.9%)	<0.001
Hispanic	26 (7.1%)	5 (1.5%)	29 (8.7%)	14 (3.6%)	37 (13.4%)	81 (18.2%)	63 (11.1%)	55 (5.0%)	90 (6.9%)	80 (6.1%)	95 (7.2%)	0.001
Asian	13 (3.6%)	0 (0.0%)	16 (4.8%)	5 (1.3%)	11 (4.0%)	19 (4.3%)	14 (2.5%)	15 (1.4%)	25 (1.9%)	10 (0.8%)	40 (3.0%)	0.003
Income												
Low	92 (20.2%)	112 (27.2%)	152 (36.4%)	98 (21.9%)	85 (24.8%)	196 (44.5%)	205 (32.7%)	355 (30.2%)	350 (26.3%)	425 (31.6%)	465 (35.0%)	<0.001
Low-Mid	133 (29.2%)	97 (23.5%)	77 (18.4%)	130 (29.0%)	118 (34.4%)	93 (21.1%)	155 (24.8%)	300 (25.5%)	350 (26.3%)	390 (29.0%)	360 (27.1%)	<0.001
High-Mid	98 (21.5%)	98 (23.8%)	80 (19.1%)	112 (25.0%)	94 (27.4%)	69 (15.7%)	164 (26.2%)	255 (21.7%)	275 (20.7%)	240 (17.8%)	315 (23.7%)	<0.001
High	133 (29.2%)	105 (15.5%)	109 (26.1%)	108 (24.1%)	46 (13.4%)	82 (18.6%)	102 (16.3%)	265 (22.6%)	355 (36.7%)	290 (21.6%)	190 (14.3%)	<0.001
Insurance												
Medicare	332 (72.8%)	295 (71.6%)	322 (76.3%)	338 (72.1%)	233 (65.6%)	297 (62.2%)	478 (76.2%)	780 (66.1%)	930 (67.9%)	1050 (77.2%)	910 (65.5%)	<0.001
Medicaid	43 (9.4%)	44 (10.7%)	22 (5.2%)	24 (5.1%)	46 (13.0%)	92 (19.6%)	59 (9.4%)	130 (11.0%)	115 (8.4%)	90 (6.6%)	205 (14.7%)	<0.001
Private	60 (13.2%)	64 (15.5%)	59 (14.0%)	83 (17.7%)	66 (18.6%)	56 (11.9%)	62 (9.9%)	225 (19.1%)	270 (19.7%)	185 (13.6%)	215 (15.5%)	<0.001
Self-Pay	16 (3.5%)	4 (1.0%)	10 (2.4%)	5 (1.1%)	0 (0.0%)	25 (5.3%)	23 (3.7%)	25 (2.1%)	20 (1.5%)	25 (1.8%)	40 (2.9%)	0.001
Comorbidities												
Obesity	85 (18.7%)	81 (19.7%)	79 (18.7%)	415 (12.4%)	80 (22.5%)	137 (29.1%)	158 (25.3%)	395 (33.3%)	430 (31.4%)	475 (34.9%)	500 (36.0%)	<0.001
Hypertension	292 (64.2%)	245 (59.5%)	282 (66.8%)	302 (63.8%)	249 (70.1%)	350 (74.3%)	426 (68.1%)	835 (70.5%)	940 (68.8%)	945 (69.5%)	1060 (76.3%)	0.085
Smoking	47 (10.3%)	63 (5.3%)	9 (2.1%)	53 (11.2%)	49 (13.8%)	112 (23.8%)	149 (23.8%)	345 (29.1%)	355 (25.9%)	395 (29.0%)	455 (32.7%)	<0.001
Dyslipidemia	142 (31.1%)	114 (27.7%)	182 (43.1%)	157 (33.1%)	176 (49.6%)	242 (51.4%)	338 (54.0%)	655 (55.3%)	765 (55.8%)	790 (58.1%)	855 (61.5%)	<0.001
Past Medical History												
PVD	33 (7.2%)	19 (4.6%)	37 (8.7%)	50 (10.6%)	44 (12.4%)	45 (9.6%)	73 (11.7%)	100 (8.4%)	160 (11.7%)	165 (12.1%)	170 (12.2%)	<0.001

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics and temporal trends of diabetes patients with heart failure and hypertrophic cardiomyopathy, from 2005 to 2015.

Years	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P (trend)
CKD	59 (13.0%)	85 (20.6%)	111 (26.2%)	192 (40.5%)	100 (28.2%)	145 (30.8%)	278 (44.5%)	580 (48.9%)	600 (43.8%)	650 (47.8%)	725 (52.2%)	<0.001
CAD	193 (42.3%)	136 (33.0%)	114 (27.0%)	166 (35.0%)	163 (46.0%)	171 (36.3%)	258 (41.2%)	525 (44.3%)	560 (40.9%)	575 (42.3%)	525 (37.8%)	0.309
Elixhauser score Mean (SD)	1.8764 (6.78)	1.7439 (7.02)	1.4576 (6.89)	4.2394 (7.86)	4.4835 (8.93)	4.4835 (8.93)	4.4692 (7.09)	4.5150 (8.82)	4.6765 (8.26)	5.2900 (7.96)	6.2188 (8.64)	0.001
Outcomes												
Cardiogenic shock	11* (0.6%)	12 (0.3%)	11* (0.7%)	11* (1.0%)	11* (0.4%)	11* (1.9%)	11 (1.8%)	25 (2.1%)	30 (2.2%)	20 (1.5%)	30 (2.2%)	<0.001
Ventricular fibrillation	11* (2.2%)	43 (10.4%)	15 (3.5%)	9 (1.9%)	24 (6.8%)	34 (7.2%)	38 (6.1%)	105 (8.9%)	95 (6.9%)	110 (8.1%)	110 (7.9%)	<0.001
Atrial fibrillation	175 (38.5%)	142 (34.5%)	130 (30.7%)	209 (44.1%)	122 (34.4%)	144 (30.6%)	294 (47.0%)	485 (40.9%)	645 (47.1%)	715 (52.6%)	660 (47.5%)	<0.001

CAD , coronary artery disease; CKD , chronic kidney disease; PVD , Peripheral vascular disease. *Per the requirements of the HCUP, cells less or equal to 10 are noted as < 11.

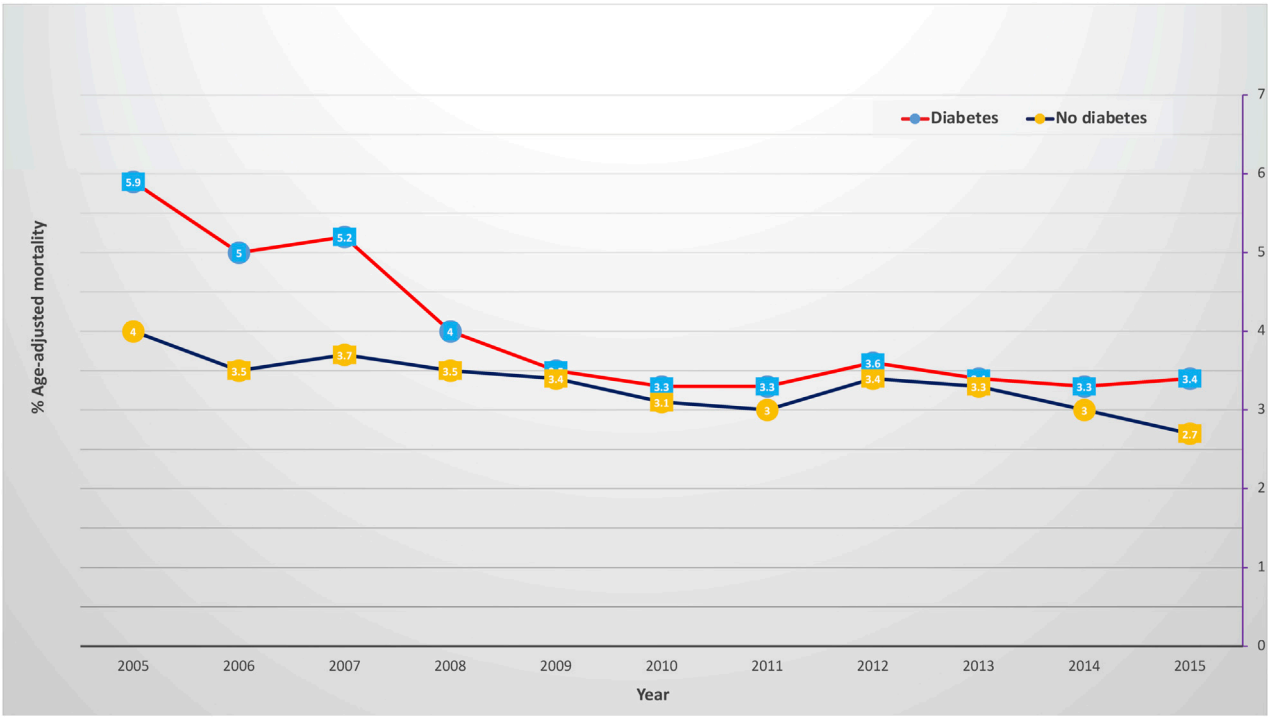

FIGURE 2
In-hospital mortality trend in patients with hypertrophic cardiomyopathy, heart failure, and diabetes (red color) and without diabetes (blue color). The X-axis represents the percentage of in-hospital mortality. The Y-axis represents the year.

patients are within the 75–84 age group in both populations. Non-diabetes patients tended to be older, with 24.1% of them aged >85 compared to 13.1% in the diabetes group ($p < 0.001$) (Table 2). There were more females than males in all patients; however, a higher percentage of females is observed in the non-diabetes group (66% vs 62.9%, $p < 0.001$). As expected, a

TABLE 2 Baseline characteristics of patients with heart failure and hypertrophic cardiomyopathy, with and without diabetes.

	Non-diabetes N = 20,555	Diabetes N = 8,520	*p* value
Age			
Mean (SD)	70.44 (16.66)	68.99 (13.97)	<0.001
<55	3916 (19.1%)	1453 (17.1%)	<0.001
55–64	2945 (14.3%)	1516 (17.8%)	<0.001
65–74	3395 (16.5%)	2150 (25.2%)	<0.001
75–84	5345 (26.0%)	2285 (26.8%)	<0.001
>85	4954 (24.1%)	1116 (13.1%)	<0.001
Gender			
Male	6994 (34.0%)	3158 (37.1%)	<0.001
Female	13560 (66.0%)	5362 (62.9%)	<0.001
Race			
White	13404 (73.8%)	4652 (60.1%)	<0.001
Black	3115 (17.2%)	2070 (26.7%)	<0.001
Hispanic	788 (4.3%)	574 (7.4%)	<0.001
Asian	337 (1.9%)	168 (2.2%)	<0.001
Income			
Low	5116 (25.5%)	2535 (30.5%)	<0.001
Low-Mid	5192 (25.8%)	2204 (26.5%)	<0.001
High-Mid	4780 (23.8%)	1799 (21.6%)	<0.001
High	5011 (24.9%)	1784 (21.4%)	<0.001
Insurance			
Medicare	14329 (69.8%)	5965 (70.1%)	<0.001
Medicaid	1508 (7.3%)	870 (10.2%)	<0.001
Private Insurance	3794 (18.5%)	1346 (25.8%)	<0.001
Self-Pay	587 (2.9%)	192 (2.3%)	0.004
Comorbidities			
Obesity	2831 (13.8%)	2480 (29.1%)	<0.001
Hypertension	12006 (58.4%)	5927 (69.6%)	<0.001
Smoking	5059 (24.6%)	2033 (23.9%)	0.171
Dyslipidemia	7360 (35.8%)	4416 (51.8%)	<0.001
Past Medical History			
PVD	1628 (7.9%)	897 (10.5%)	<0.001
CKD	5553 (27.0%)	3525 (41.4%)	<0.001
CAD	6243 (30.4%)	3385 (39.7%)	<0.001
Elixhauser score	4.53 (8.07)	5.48 (8.29)	<0.001

CAD , coronary artery disease; CKD , chronic kidney disease; PVD , peripheral vascular disease.

significantly higher number of patients with diabetes were obese and had hypertension and dyslipidemia. Additionally, PVD and CKD were more prevalent in the diabetes group. Unexpectedly, diabetes patients hospitalized for HF with HCM had significantly lower in-hospital mortality (3.9%) compared to non-diabetic ones (3.3%) ($p < 0.001$). After adjustments on characteristics that were different among both groups (Table 3), diabetes was associated with an adjusted lower in-hospital mortality rate (aOR = 0.84 [0.74–0.96]) (Table 4). The adjusted risk of cardiogenic shock was similar in both groups (aOR = 1.01 [0.80–1.27]. However, patients with diabetes also had a lower adjusted risk of ventricular fibrillation (aOR 0.79 CI [0.71–0.88]) and atrial fibrillation (aOR 0.8 CI [0.76–0.85]).

3.4 Socioeconomic outcomes

In diabetes and non-diabetes patients, hospitalization charges significantly increased between 2005 and 2015. The cost of hospitalizations in diabetes patients was lower up to 2007, but by 2008, diabetes patients had significantly higher charges, which continued until 2015 (Figure 3). We did not observe a temporal change in the length of stay (LoS). Further,

TABLE 3 Multivariable regression of in-hospital mortality among diabetes patients with heart failure and hypertrophic cardiomyopathy.

	Or (95% CI)	*p*-value
Age		
<55	Ref	Ref
55–64	1.21 (0.87–1.67)	0.258
65–74	1.45 (1.04–2.01)	0.028
75–84	1.59 (1.23–2.34)	0.001
>85	2.93 (2.13–4.05)	<0.001
Mean	1.66 (1.44–1.99)	<0.001
Gender		
Male	Ref	Ref
Female	1.38 (1.16–1.64)	<0.001
Race		
White	Ref	Ref
Black	0.97 (0.78–1.21)	0.812
Hispanic	0.93 (0.64–1.34)	0.678
Asian	0.926 (0.53–1.61)	0.784
Income		
Low	Ref	Ref
Low-Mid	1.02 (0.82–1.26)	0.874
High-Mid	1.03 (0.82–1.27)	0.827
High	109 (0.88–1.36)	0.437
Insurance		
Medicare	Ref	Ref
Medicaid	0.46 (0.28–0.75)	0.002
Private Insurance	0.91 (0.70–1.18)	0.479
Self-Pay	1.47 (0.89–2.42)	0.135
Comorbidities		
Obesity	1.85 (1.48–2.30)	<0.001
Hypertension	0.79 (0.68–0.92)	0.002
Smoking	Not in model	-
Dyslipidemia	0.73 (0.62–0.86)	<0.001
Past Medical History		
PVD	1.32 (1.07–1.62)	0.01
CKD	0.88 (0.75–1.04)	0.138
CAD	0.79 (0.67–1.03)	0.051
Elixhauser score	1.10 (1.09–1.11)	<0.001

CAD , coronary artery disease; CKD , chronic kidney disease; PVD , peripheral vascular disease.

patients with diabetes had a higher median (IQR) length of stay (5 [3–7] vs 4 [3–6] days, diabetes *versus* non-diabetes, $p < 0.001$).

3.5 D- predictors of outcomes in patients with diabetes

In-hospital mortality increased by almost 8-fold in those aged >85 years old (OR 7.49 [2.88–19.45], $p < 0.001$) and in females compared to males (OR 1.50 [1.08–2.08], $p = 0.016$). As expected, it also increased with concomitant renal failure (OR 1.35 [1.004–1.82], $p = 0.047$), CAD (OR 1.54 [1.14–2.07], $p = 0.004$), and those with PVD (OR 2.98 [2.11–4.21], $p < 0.001$) (Supplementary Table S3). Consequently, the Elixhauser score increased the in-hospital mortality risk (OR 1.09 [1.07–1.11], $p < 0.001$).

Increasing age did not predict cardiogenic shock (Supplementary Table S4), but the female gender was protective (OR 0.47 [0.31–0.71], $p < 0.001$). Asians and Native Americans had a higher risk compared to Whites. Obesity was also associated with higher rates of cardiogenic shock (OR 2.27 [1.42–3.65], $p < 0.001$), and so was having CAD (OR 2.41 [1.57–2.30], $p < 0.001$) and renal failure (OR 1.31 [1.19–1.50], $p < 0.001$).

Patients aged 55 to 74 had a higher risk of developing ventricular fibrillation (Supplementary Table S5) than those younger than 55. However, the female gender was associated with 37% less risk. Age was also associated with a higher risk of atrial fibrillation (OR 1.84 [0.63–0.71] and women had a lower risk (OR 0.67 [0.63–0.71] (Supplementary Table S5). Among cardiovascular risk factors, obesity was the strongest predictor of developing AF (OR 1.42 [1.12–1.95), $p < 0.001$).

4 Discussion

We report in this study that the incidence of diabetes is gradually increasing in patients with heart failure and hypertrophic cardiomyopathy. Furthermore, diabetes was surprisingly associated with a lower risk of in-hospital mortality and arrhythmias. However, the length of stay and total charges/stay were higher in patients with diabetes.

Diabetes has deleterious effects on cardiac function. Although the exact mechanism is unclear, there is damage to cardiac cells, and initially, patients have diastolic dysfunction, which eventually progresses to systolic dysfunction (Kenny and Abel, 2019). Diabetic cardiomyopathy is one of the types of non-ischemic cardiomyopathies, and commonly cardiovascular mortality is a cause of progressive HF(Bertoni et al., 2003). This study reports an increase in diabetes prevalence among HF patients with HCM, which corresponds to the rising prevalence of diabetes in the general population and other cardiovascular disorders (Collaboration, 2016). Conrad et al. reported an average 8% increase in diabetes prevalence over 10 years in a cohort of 4 million HF patients in the United Kingdom (Conrad et al., 2018). We recently reported that diabetes prevalence in patients with HF is also increasing in the US(Mekhaimar et al., 2021). Further, diabetes patients in our study are older and have more CVD risk factors, which is also concordant with other studies (Wasserstrum et al., 2019).

Despite the increasing prevalence and the worsening of the cardio-metabolic profile in patients with diabetes, we observed a

TABLE 4 Cardiovascular outcomes of patients with heart failure and hypertrophic cardiomyopathy, with and without diabetes.

	Non-diabetes	Diabetes	Adjusted OR (95% CI)
In-hospital mortality, n (%)	678 (3.3%)	332 (3.9%)	0.88 (0.76–0.91)
OR (95% CI)	1	0.84 (0.74–0.96)	
Ventricular fibrillation n (%)	1745 (8.5%)	594 (7.0%)	0.79 (0.71–0.88)
OR (95% CI)	1	0.81 (0.73–0.89)	
Atrial fibrillation, n (%)	10028 (48.8%)	3636 (42.7%)	0.80 (0.76–0.85)
OR (95% CI)	1	0.79 (0.74–0.83)	
Cardiogenic shock, n (%)	442 (2.2%)	151 (1.9%)	1.01 (0.80–1.27)
OR (95% CI)	1	0.84 (0.72–0.89)	

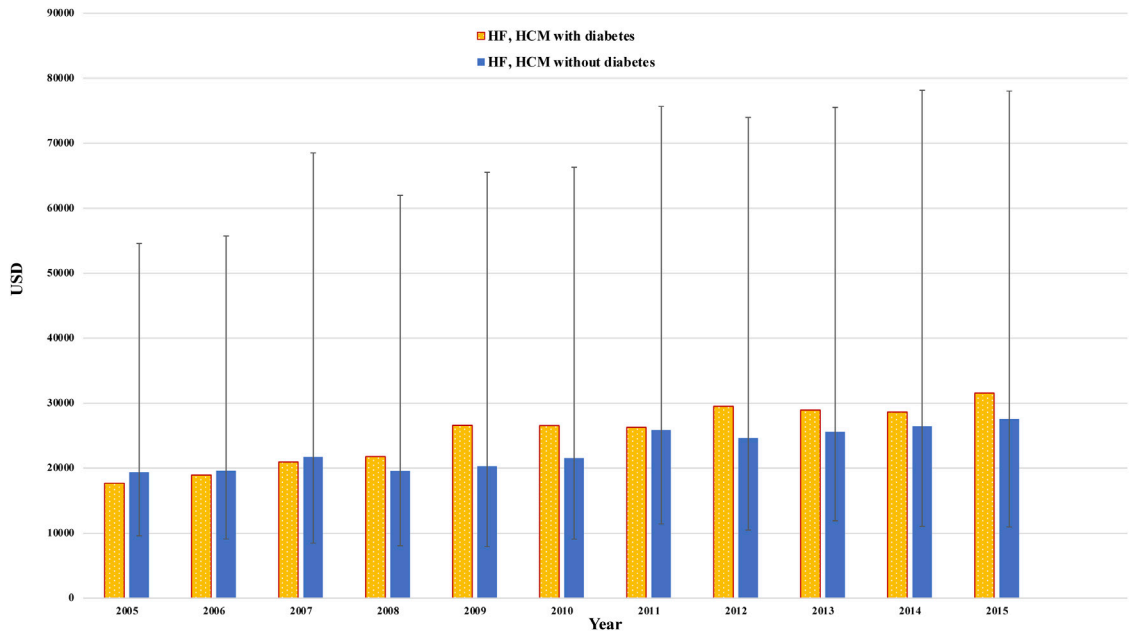

FIGURE 3
Temporal change in total charges/stay (median +/− IQR) in heart failure patients with diabetes (yellow color) and without diabetes (blue color). The X-axis represents the amount in USD. The Y-axis represents the year.

significant decline in in-hospital mortality, which has been reported in myocardial infarction (Ahmed et al., 2014; Ali et al., 2022), stroke (Tabbalat et al., 2021), HF (Mekhaimar et al., 2021), and valvular heart disease (Khan et al., 2022). In our study, in-hospital mortality in all patients decreased over time, similar to other reported trends for patients with HCM (Elliott et al., 2006; Maron et al., 2015). This could be due to more contemporary procedures specific to HCM, including myomectomies and earlier ICD placement in primary prevention (Maron et al., 2016).

To our knowledge, we are the first to assess the cardiovascular impact effect of diabetes on HF patients with HCM. Wasserstrum et al. showed that concurrent HCM and diabetes, in the absence of HF, lead to worse outcomes, including mortality (Wasserstrum et al., 2019). However, the difference in mortality was only significant in the last 5 years of the 15-year follow-up; the first 5 years of the study showed lower mortality in the presence of diabetes, which is concordant with our results. Another study looking at outcomes after septal myectomy in 201 HCM patients and comparing diabetes *versus* non-diabetes patients found identical mortality in both groups (Wang et al., 2020). Analysis of the OPTIMIZE-HF registry found that diabetes did not affect in-hospital mortality (Greenberg et al., 2007). We recently reported a lower in-hospital mortality risk in diabetes patients with HF compared to non-diabetes in the NIS database (Mekhaimar et al., 2021). It might be possible that the

Coding of the diagnosis

Diagnosis	ICD9 Codes	ICD10 Codes
Hypertrophic cardiomyopathy	425.1, 425.11, 425.18	I42.1, I42.2
Heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and all 428 sub-groups (428.30 to 33)	I11.0, I13.0, I13.2, I50.814, I50.9, I150.1, I150.20, (I150.21 to 23), (I150.40 to 43), (I150.810 to 813), (I150.82 to 84), I1590.89, I50.9, I50.30+I50.31+I50.32+I50.33
Ventricular fibrillation	427.1	I47.2
Atrial fibrillation	427.31	I48.91
Cardiogenic shock	785.51	R57.0

lower in-hospital mortality observed in HF patients with diabetes also applies to patients with HF and HCM.

It is not clear why diabetes was associated with lower in-hospital mortality risk. It might be possible that diabetes patients are closely monitored and better taken care of, including earlier initiation of guideline-directed medical therapy and implantable cardioverter defibrillators (ICD) placement, which would mitigate sudden cardiac death and fatal arrhythmias (Maron et al., 2003; Ranka et al., 2019; Ommen et al., 2020). This would also explain the higher charges and longer LOS we observed. Patients with HCM but without diabetes may appear compensated for longer and more rarely progress to end-stages of heart failure; therefore, they may be less likely to be getting care actively (Maron et al., 2000).

Limitations of this study include the retrospective nature of our data; therefore, we cannot make any conclusions about causality. Further, the NIS is an administrative database that was initially designed to produce national estimates of inpatient utilization, access, cost, quality, and outcomes; hence, there could be potential errors in its utilization in clinical investigations, such as–but not limited to - the accuracy or the lack of accuracy of ICD codes. Furthermore, our data set cannot tell the severity of heart failure, diabetes parameters (type, $HBA_{1c,}$ and duration), and HCM parameters (medications, septal thickness, left ventricular ejection fraction, and the etiology). This information would have allowed us to delineate the relationship between the two disease entities and make further conclusions about why the results came out.

5 Conclusion

In this analysis of the National Inpatient Sample database, we report an increase in the prevalence of diabetes in heart failure patients with concomitant hypertrophic cardiomyopathy. The in-hospital mortality in those patients is on a descending slope despite the temporal increase in cardiovascular risk factors. Diabetes was paradoxically associated with a lower in-hospital mortality rate which might be due to early aggressive treatment of those patients as reflected in higher charges and longer lengths of stay compared to their non-diabetic counterparts. Our results must be validated in different populations and, most importantly, in cardiovascular cohorts.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Weill Cornell Medicine's institutional review board, number 18-00017. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CAK conceived the study concept and design. MM and MAM acquired data and performed statistical analyses with SD. MM, MAM, JS, HJ, and CAK analyzed and interpreted data. MM wrote the first draft and conducted the literature search. All authors contributed to the critical revision of the manuscript. CAK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.976315/full#supplementary-material

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The serum soluble scavenger with 5 domains levels: A novel biomarker for individuals with heart failure

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Background: We aimed to explore the relationship between the serum Soluble Scavenger with 5 Domains (SSC5D) levels and heart failure (HF).

Methods and Results: We retrospectively enrolled 276 patients diagnosed with HF or normal during hospitalization in Shanghai General Hospital between September 2020 and December 2021. Previously published RNA sequencing data were re-analyzed to confirm the expression profile of *SSC5D* in failing and non-failing human and mouse heart tissues. Quantitative real-time polymerase chain reaction assay was used to quantify *Ssc5d* mRNA levels in murine heart tissue after myocardial infarction and transverse aortic constriction surgery. To understand the HF-induced secreted proteins profile, 1,755 secreted proteins were investigated using human dilated cardiomyopathy RNA-seq data, and the results indicated that *SSC5D* levels were significantly elevated in failing hearts compared to the non-failing. Using single-cell RNA sequencing data, we demonstrated that *Ssc5d* is predominantly expressed in cardiac fibroblasts. In a murine model of myocardial infarction or transverse aortic constriction, *Ssc5d* mRNA levels were markedly increased compared with those in the sham group. Similarly, serum SSC5D levels were considerably elevated in the HF group compared with the control group [15,789.35 (10,745.32–23,110.65) pg/mL, 95% CI (16,263.01–19,655.43) vs. 8,938.72 (6,154.97–12,778.81) pg/mL, 95% CI (9,337.50–11,142.93); $p < 0.0001$]. Moreover, serum SSC5D levels were positively correlated with N-terminal pro-B-type natriuretic peptide ($R = 0.4$, $p = 7.9e\text{-}12$) and inversely correlated with left ventricular ejection fraction ($R = -0.46$, $p = 9.8e\text{-}16$).

Conclusion: We concluded that SSC5D was a specific response to HF. Serum SSC5D may function as a novel biomarker and therapeutic target for patients with HF.

KEYWORDS

heart failure, SSc5D, biomarker, LVEF, NT-ProBNP

1 Introduction

Heart failure (HF) is a systolic or diastolic dysfunction of the heart, which is the terminal stage of various cardiovascular diseases. Despite improvements in medication and management, the morbidity and mortality of HF remain high worldwide (Tedeschi et al., 2020). Currently, the clinical diagnosis of HF is mainly based on the patient's symptoms, signs and left ventricular ejection fraction (LVEF) (Heidenreich et al., 2022).

Plasma B-type natriuretic peptide (BNP) and serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) have been recommended as the gold standards for HF diagnosis in HF guidelines (Yancy et al., 2017). However, other non-cardiac diseases, such as renal failure (Tsutamoto et al., 2006), obesity (Das et al., 2005), *etc.*, can also change plasma BNP and serum NT-proBNP levels. Therefore, it is particularly important to find more biomarkers with higher specificity and sensitivity to improve the value of prediction and diagnosis of HF. In addition to classical HF biomarkers, studies on serum biomarkers of HF have increased. MicroRNAs are endogenous small non-coding RNAs that play a crucial role in cardiovascular diseases (Huang et al., 2018) and have been proven to be biomarkers for HF diagnosis and prognosis (Yang et al., 2021). Moreover, serum LL-37/cathelicidin-related antimicrobial peptide (CRAMP) (Zhou et al., 2020) and soluble ST2 receptor (Weinberg et al., 2003) have been shown to promote the diagnostic and prognostic value of HF. Given the deadly conditions of HF, the investigation of HF-specific responders and regulators will contribute to the diagnosis and treatment of clinical patients. In this study, we explored the secreted proteins of patients with HF and demonstrated that serum Soluble Scavenger with 5 Domains (SSC5D) was overly elevated in failing hearts compared to control group.

SSC5D is a member of the scavenger receptor cysteine-rich superfamily (SRCR-SF) (Gonçalves et al., 2009). Studies have demonstrated that numerous SRCR-SF members play essential roles in inflammation and immunity (Lee et al., 2019; Wang et al., 2021). Additionally, SRCR-SF has been reported to be associated with various cardiovascular diseases, such as collagen deposition, angiogenesis (Umana-Diaz et al., 2020), and atherosclerosis (Silva et al., 2016). However, the function of SSC5D in cardiovascular disease remains unknown. Therefore, this study investigates the diagnostic value of serum SSC5D for patients with HF.

2 Materials and methods

2.1 Patient's characteristics

A total of 276 patients who were diagnosed with HF or control during hospitalization in Shanghai General Hospital between September 2020 and December 2021 were enrolled in this study. This study was approved by the Ethics Committee of Shanghai General Hospital (2018KY250). The study was performed under the Declaration of Helsinki and written informed consent was obtained from all patients.

HF is classified into the following categories based on LVEF: HFrEF (HF with reduced EF), LVEF≤40%; HFimpEF (HF with improved EF), previous LVEF≤40% and a follow-up measurement of LVEF>40%; HFmrEF (HF with mildly reduced EF), LVEF 41%–49%; HFpEF (HF with preserved EF), LVEF≥50% (Heidenreich et al., 2022). In this study, patients were grouped based on their symptoms and LVEF values: the HF group, LVEF<50% with typical symptoms of HF (Ponikowski et al., 2016), and the control group, LVEF≥50% without typical symptoms of HF. Patients who were diagnosed with acute infections, cancers, age<18 years, acute coronary syndrome, pregnancy, autoimmune diseases, or surgery within 1 month were prospectively excluded. Table 1 presents patient's characteristics.

2.2 RNA-sequencing (RNA-seq) and single-cell RNA sequencing (scRNA-seq) data analysis

RNA-seq data of humans (Accession number: GSE165303, GSE46224, and GSE116250) and mice (Accession number: GSE95755) were downloaded from Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/). Raw data were transformed into fragments per kilobase of exon model per million mapped fragments (FPKM), reads per kilobase per million mapped reads (RPKM), and counts per million (CPM) using the R statistical software for further analysis. The expression pattern of *Ssc5d* was derived from previously published scRNA-seq data (Zhuang et al., 2020). The human cardiac single nucleus RNA sequencing (snRNA-seq) transcriptomics data from the Kuppe et al. study was downloaded from: https://cellxgene.cziscience.com/collections/8191c283-0816-424b-9b61-c3e1d6258a77) (Kuppe et al., 2022). To re-analyze the scRNA-seq data, we performed a quality control of single cell by choosing individual live cell among each dataset. In brief, both the count of features and mitochondria were defined as the cut-offs. Then the data from all individual cell was screened based on the original article criteria prior to further analysis. When the quality control was completed, we normalized each cell characteristic by dividing or multiplying all unique molecular identifiers by 10,000 to get the value in per million transcripts, and then performed logarithmic transformation using RStudio.

2.3 Secreted proteins data analysis

The secreted proteins data were downloaded from the IUPHAR/BPS Guide to Pharmacology website (https://www.guidetopharmacology.org/).

2.4 Myocardial infarction (MI) and transverse aortic constriction (TAC) model

Male C57BL/6 mice (6–8 weeks old) were purchased from Sipper-BK Laboratory Animal Co., Ltd (Shanghai, China). All animal experimental procedures were approved by the Animal Welfare and Ethics Committee of Shanghai General Hospital

TABLE 1 Clinical characteristics of patients.

Characteristics	Controls (*N* = 148)	HF (*N* = 128)	*p*-Value
Age, years	61 (50–66)	61 (52–68)	0.4398
Male, n (%)	89 (60.1)	94 (73.4)	0.0197
Smoker, n (%)	24 (16.2)	23 (18.0)	0.6993
BMI, kg/m^2	24.8 (22.8–27.1)	25.0 (22.9–27.3)	0.9217
SBP, mmHg	134 (120–146)	125 (113–137)	0.0004
DBP, mmHg	78 (70–84)	75 (68–83)	0.3011
Heart rate, bpm	78 (73–88)	82 (72–92)	0.2364
Medical history, n (%)			
Hypertension	67 (45.3)	64 (50.0)	0.4326
Diabetes mellitus	26 (17.6)	46 (35.9)	0.0005
Hypercholesterolemia	48 (32.4)	14 (10.9)	<0.0001
Atrial fibrillation	11 (7.4)	33 (25.8)	<0.0001
COPD	2 (1.4)	3 (2.3)	0.5376
Myocardial infarction	4 (2.7)	62 (48.4)	<0.0001
Anemia	0	5 (3.9)	0.0152
Treatment, n (%)			
ACE-I/ARB	59 (39.9)	118 (92.2)	<0.0001
Beta-blocker	49 (33.1)	109 (85.2)	<0.0001
Digoxin	1 (0.7)	17 (13.3)	<0.0001
Statin	94 (63.5)	100 (78.1)	0.0081
Antiplatelet/anticoagulant	71 (48.0)	76 (59.4)	0.0583
CCB	30 (20.3)	13 (10.2)	0.0209
Loop diuretic	1 (0.7)	71 (55.5)	<0.0001
Laboratory measurements			
NT-proBNP, pg/mL	48.6 (21.0–107.3)	1,147.0 (495.0–2,249.3)	<0.0001
HDL-c, mmol/L	1.1 (0.9–1.3)	1.0 (0.9–1.2)	0.0089
LDL-c, mmol/L	2.6 (2.1–3.2)	2.5 (1.9–3.2)	0.5810
eGFR, mL/min/1.73 m^2	92.2 (79.6–99.3)	79.5 (67.3–94.5)	<0.0001
hs-CRP, mg/L	0.9 (0.3–1.9)	1.6 (0.8–5.0)	<0.0001
Sodium, mmol/L	142 (141–143)	141 (139–143)	0.0010
Creatinine, μmol/L	74 (65–84)	86 (71–100)	<0.0001
BUN, mmol/L	5.4 (4.5–6.5)	6.7 (5.1–8.1)	<0.0001
Cystatin C, mg/L	0.97 (0.85–1.08)	1.15 (1.03–1.33)	<0.0001
Hemoglobin, g/dL	138 (127–151.8)	140 (130–152)	0.6807
Total bilirubin, μmol/L	12.6 (9.9–16.8)	14.7 (10.7–20.4)	0.0063
Echocardiographic parameters			
LVEDd (mm)	48 (46–50)	63 (59–68)	<0.0001
LVESd (mm)	30 (28–31)	51 (46–57)	<0.0001
LAd (mm)	37 (35–40)	46 (43–51)	<0.0001
LVEF, %	68 (65–70)	37 (30–43.8)	<0.0001

Categorical variables are presented as n (percentage, %), and continuous variables are presented as median (interquartile range). *p*-value < 0.05 was considered statistically significant. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitors; ARB, Angiotensin II, receptor blocker; CCB, calcium channel blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; hs-CRP, hypersensitive C-reactive protein; BUN, blood urea nitrogen; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LAd, left atrial diameter; LVEF, left ventricular ejection fraction.

(2021AW035) and conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. TAC and MI surgery were performed based on the previous literature to construct failing heart model (n = 5–7) (Du et al., 2020; Zhuang et al., 2022).

2.5 RNA extraction and real-time quantitative PCR (RT-qPCR) assays

Heart tissues were collected from mice after MI (14 and 28 days) or TAC (1 and 4 weeks) surgery and the sham group. Total RNA was

extracted using RNAiso Plus (Takara, Japan) and cDNA was amplified using the PrimeScript™ RT Master Mix kit (Takara, Japan) according to the manufacturer's protocol. Quantitative PCR analysis was performed using the TB Green® Premix Ex Taq™ kit (Takara, Japan) and the QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems Co., United States). The specific qPCR primer sequences were as follows (5′-3′):

Mouse *Ssc5d* Forward primer: GCGTCGTCTGTGTAGGTC AG; Mouse Ssc5d Reverse primer: AGCGTGAGTTATAGGGGG CT; Mouse Gapdh Forward primer: CCGCATCTTCTTGTGCAGT; Mouse Gapdh Reverse primer: CATCACCTGGCCTACAGGAT; Gapdh was used as an endogenous control and the $2^{-\Delta\Delta CT}$ method was used to analyze the data.

2.6 Blood samples collection and ELISA assays

Blood samples were collected from patients with HF and the control group, centrifuged at 3,000 rpm for 20 min to obtain serum, and stored at −80°C for further ELISA assays. Serum SSC5D concentrations were measured using the Human SSC5D/Soluble scavenger receptor cysteine-rich domain-containing protein SSC5D ELISA Kit (catalog no: #EK21098, SAB, United States), according to the manufacturer's instructions. Human serum samples were diluted 1:100 in sample diluent. All serum samples were measured by a researcher who was oblivious to the patient's clinical data.

2.7 Statistical analysis

IBM SPSS Statistics (version 26, 2019) and R statistical software (version 4.0.4, 2021) were used to analyze data. The experimental data were represented as mean ± SEM. Two-tailed unpaired Student's t-test was performed to compare the difference between 2 groups. One-way ANOVA followed by the Tukey *post hoc* test was used to evaluate the difference between ≥3 groups. Categorical variables were presented as numbers (percentages, %) and were compared using the chi-square test. The Kolmogorov-Smirnov test was used to assess the normality of the continuous variables. If the continuous variables did not conform to the normality distribution, they were presented as median (interquartile range) and compared with the Mann-Whitney *U* test. The SSC5D concentration values were transformed into a normal distribution using a logarithm of 10 and divided into quartiles for further analysis. Spearman's rank correlation coefficients were used to evaluate the relationships between serum SSC5D levels and NT-proBNP, LVEF, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), cystatin c, and creatinine. A logistic regression model was performed to evaluate the association between HF and risk factors of HF. Sex, age, body mass index (BMI), diabetes mellitus, hypertension, hemoglobin, creatinine, low-density lipoprotein cholesterol (HDL-c), hypersensitive C-reactive protein (hs-CRP), BUN, Haemoglobin A1c (HbA1c), and eGFR were adjusted. The receiver operating characteristic (ROC) curve was used to assess the diagnostic value and determine the optimal cut-off value with or without SSC5D. The two-sided p-value < 0.05 was considered statistically significant.

3 Results

3.1 *SSC5D* transcript is elevated in failing heart

To investigate the role of secreted proteins in cardiovascular diseases, we first collected a list of secreted proteins data. Subsequently, we re-analyzed their expression patterns in failing and non-failing (NF) heart tissue RNA-seq (GSE165303) data (Feng et al., 2022). We identified 1,459 genes in common (Figure 1A). Furthermore, by setting p < 0.05 and $|\log_2 FoldChange|>1$, we identified 190 secreted proteins that were differentially expressed in the hearts of patients with HF, and *SSC5D* was one of the most differentially upregulated genes (Figure 1B). Furthermore, through Pearson correlation analysis in R, we discovered a significant positive correlation between *SSC5D* and the cardiac hypertrophy marker genes A-type natriuretic peptide (*NPPA*) (R = 0.6, p = 3.1e-11) and B-type natriuretic peptide (*NPPB*) (R = 0.46, p = 1.3e-6) (Figures 1C, D). To verify the results of increased *SSC5D* expression, a series of human failing heart tissues (GSE165303, GSE46224, and GSE116250) RNA-seq data were re-analyzed to compare the expression of *SSC5D*. From RNA-seq data analysis, we found that *SSC5D* expression was significantly upregulated in the failing group (dilated cardiomyopathy, DCM; ischemic cardiomyopathy, ICM) compared to the NF group (Figures 1E–G).

To further verify the human failing heart RNA-seq data, we constructed mouse TAC and MI models and collected cardiac tissue at different times after surgery. We found that the *Ssc5d* mRNA expression was significantly elevated at 4 weeks (approximately 2-fold, p < 0.0001) after TAC surgery compared to that in the sham group (Figure 2A). Similarly, compared with the sham group, *Ssc5d* mRNA levels were significantly elevated at 14 and 28 days after MI surgery, and the highest fold increase (approximately 11-fold, p < 0.0001) was observed at day 28 (Figure 2B). To further determine the origin of *Ssc5d*, we re-analyzed mouse heart RNA-seq data (GSE95755) (Quaife-Ryan et al., 2017), which sorted cardiac cardiomyocytes, fibroblasts, leukocytes, and vascular endothelial cells for RNA-seq analysis. We discovered that *Ssc5d* levels were significantly higher in fibroblasts than in other cell populations in both neonatal (P1) and adult (P56) mouse hearts (Figure 2C). Additionally, Zhuang et al. have integrated three representative mouse heart scRNA-seq datasets, including 27,349 non-cardiomyocytes (macrophages, fibroblasts, endothelia, and lymphocytes) isolated from myocardial infarction or sham heart tissue (Zhuang et al., 2020). We contacted the authors and re-analyzed their data to explore the expression profile of *Ssc5d* in non-cardiomyocytes and revealed that *Ssc5d* was markedly co-expressed with *Col1a1*-positive fibroblasts. Moreover, we re-analyzed the previous published human cardiac single-nucleus RNA sequencing data (snRNA-seq) (Kuppe et al., 2022). By analyzing this snRNA-seq data, we showed that *SSC5D* was expressed predominantly in fibroblasts, to the less extent in endothelial cells or myeloid cells (Supplementary Figures S1A, B). This is

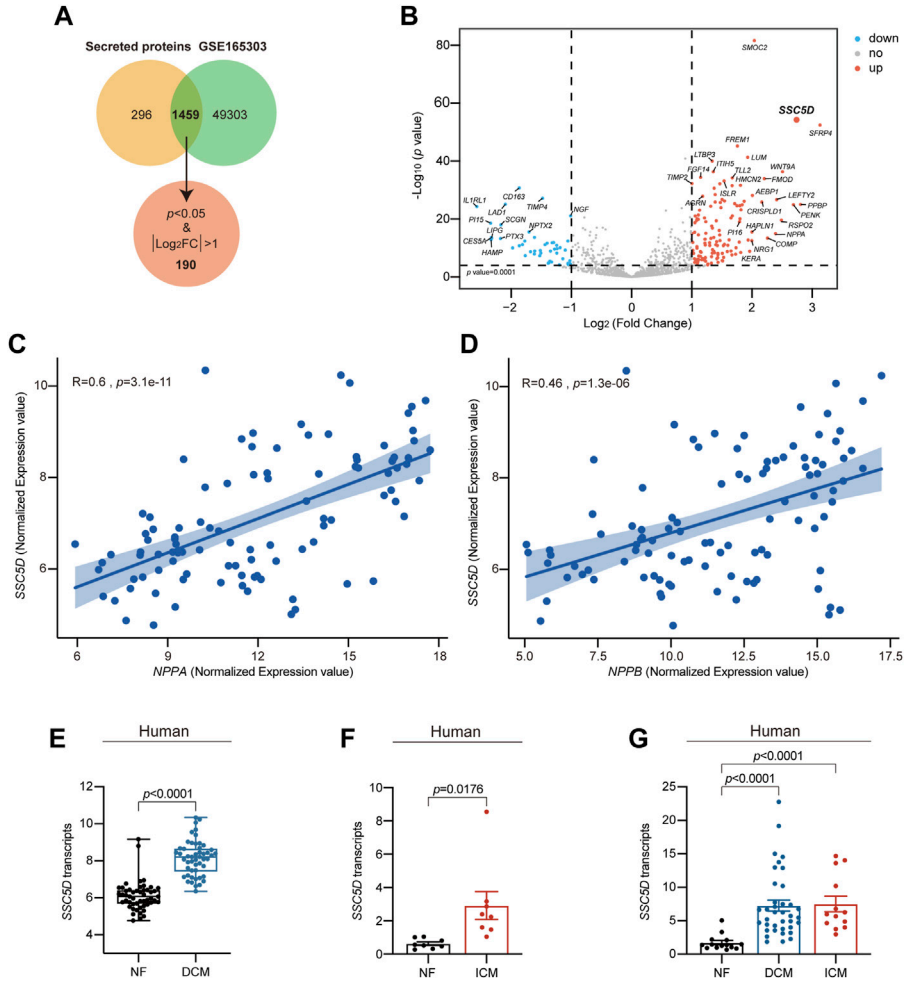

FIGURE 1
SSC5D transcript is highly elevated in failing hearts. **(A)** The Venn diagram shows the common genes between the secreted proteins and GSE165303 data. **(B)** The volcano map shows the significantly differentially expressed genes among 1,459 common genes. Red dots, significantly elevated genes; Blue dots, significantly downregulated genes; Grey dots, non-significantly altered genes. **(C, D)** The correlation between *SSC5D* (log2 [normalized counts]) and *NPPA*, *NPPB* (log2 [normalized counts]) in 51 NF and 50 DCM hearts RNA-seq data (GSE165303). **(E)** Normalized *SSC5D* expression values (log2 [normalized counts]) in 51 NF and 50 DCM human hearts RNA-seq data (GSE165303). **(F)** Normalized *SSC5D* expression (RPKM) in 8 NF and 8 ICM human hearts RNA-seq data (GSE46224). **(G)** Normalized *SSC5D* expression (RPKM) in 14 NF, 13 ICM and 37 DCM human hearts RNA-seq data (GSE116250). NF, non-failing; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; p-value < 0.05 was considered statistically significant.

consistent with our previous findings that SSC5D is mainly expressed in fibroblasts. Although it is possible that circulating Ssc5d is synthesized by other cells, our results demonstrated that it is mainly present in fibroblasts in the heart. Taken together, these results suggest that cardiac Ssc5d was mainly derived from fibroblasts and was markedly upregulated after MI and TAC surgery.

3.2 Patient's baseline characteristics

To further clarify the relationship between serum SSC5D and HF, we collected 276 blood samples and measured serum SSC5D concentrations in all patients using an ELISA Kit. The 276 enrolled patients were grouped into two based on their symptoms and LVEF values. Table 1 presents the baseline data of the patients. There were no significant differences in age, smoking status, BMI, diastolic blood pressure (DBP), and heart rate between the control and HF groups. More men were included in the HF group than in the control group and more HF patients have a medical history of diabetes mellitus, anemia, atrial fibrillation, and myocardial infarction. The number of patients treated with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I/ARB), beta-blockers, digoxin, statins, calcium channel blockers (CCB), and loop diuretic drugs was significantly higher in the HF group than in the control group. However, no significant difference was observed in patients receiving antiplatelet or anticoagulant drug treatment. Compared with the control group, blood creatinine, total bilirubin, NT-proBNP, hs-CRP, and BUN levels were higher in the HF group, whereas eGFR, high-density lipoprotein cholesterol (HDL-c), and sodium levels were slightly lower in the HF group. Furthermore, the echocardiographic results indicated a

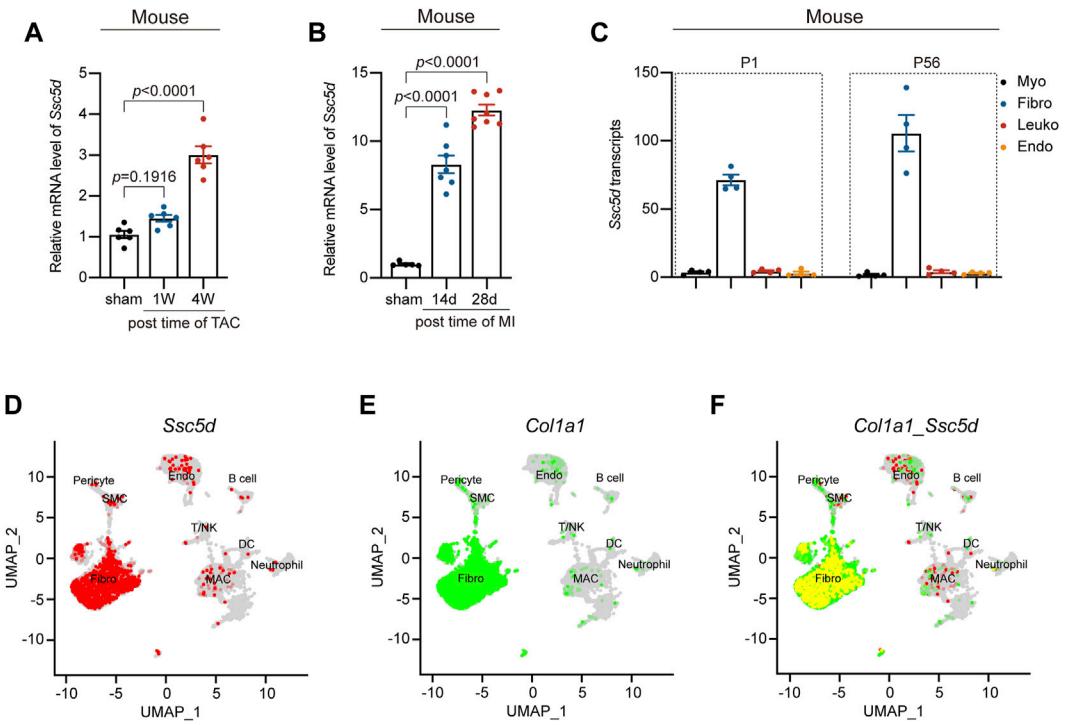

FIGURE 2
Ssc5d mRNA levels were significantly elevated in MI and TAC mouse models. **(A,B)** The relative mRNA expression of *Ssc5d* after TAC (1 and 4 W) (n = 6) and MI (14 and 28 days) (n = 5–7) surgery. **(C)** Normalized *Ssc5d* expression (CPM) in each cell type at neonatal (P1) or adult stages (P56) mouse hearts (GSE95755). Myo (black), cardiomyocytes; Fibro (blue), fibroblasts; Leuko (red), leukocytes; Endo (orange), endothelial cells. **(D–F)** UMAP plot of *Ssc5d* and *Col1a1* co-expression in sham mice cardiac non-cardiomyocyte clusters. Red, *Ssc5d*; Green, *Col1a1*; Yellow, *Ssc5d* and *Col1a1* co-expression. Fibro, fibroblasts; SMC, smooth muscle cell; MAC, macrophage; DC, dendritic cell; Endo, endothelial; CPM, counts per million; W, week; d, day. *p*-value < 0.05 was considered statistically significant.

significant decrease in LVEF but an increased left ventricular end-diastolic dimension (LVEDd), left ventricular end-systolic dimension (LVESd), and left atrial diameter (LAd) in the HF group compared with the control group.

3.3 Association of serum SSC5D with risk factors of HF

We discovered that the SSC5D levels were significantly elevated in the HF group compared with the control group [15,789.35 (10,745.32–23110.65) pg/mL, 95% CI (16,263.01–19655.43) vs. 8,938.72 (6,154.97–12778.81) pg/mL, 95% CI (9,337.50–11142.93); $p < 0.0001$] (Figure 3A). Furthermore, patients with HF were grouped into two, HFmrEF (n = 37) and HFrEF (n = 86) groups, and we discovered that the serum SSC5D levels in the HFmrEF and HFrEF groups were significantly higher than those in the control group (Figure 3B). However, no statistical difference was observed between the HFmrEF and HFrEF groups (Figure 3B).

We then analyzed the relationship between serum SSC5D levels and clinical HF risk factors. We discovered that serum SSC5D levels were higher in patients aged ≥65 years than those aged <65 years (Figure 3D). Patients with a history of hypertension and diabetes had higher serum SSC5D levels (Table 2). Moreover, elevated NT-proBNP and decreased LVEF were highly correlated with higher serum SSC5D levels (R = 0.4, p = 7.9e-12, and R = −0.46, p = 9.8e-16, respectively) (Figures 3E, F). Serum SSC5D levels were significantly correlated with indicators of renal dysfunction, such as eGFR, BUN, cystatin c, and creatinine (Figures 3G–J). However, no statistical difference in serum SSC5D levels was observed between the sexes and smoking status (Figure 3C; Table 2).

3.4 Predictive value of serum SSC5D

These results clarified that serum SSC5D levels were significantly elevated in patients with HF. Further, we explored the diagnostic value of serum SSC5D in patients with HF. Through univariate and multivariate binary logistic regression models analysis, we discovered that log-transformed serum SSC5D levels were strongly positively associated with the prevalence of HF (OR:3.23, 95% CI:2.32–4.50, $p < 0.001$) (Table 3). Meanwhile, we divided the log-transformed SSC5D into tertiles and discovered that the highest SSC5D tertile was associated with a higher risk of HF (OR:11.02, 95% CI:5.53–21.97, $p < 0.001$). Subsequently, we adjusted the covariates to analyze the correlation between the SSC5D score and HF. After adjusting age and sex in Model 1 and other covariates (sex, age, BMI, diabetes mellitus, hypercholesterolemia, hypertension, hemoglobin, creatinine, LDL-c, hs-CRP, BUN,

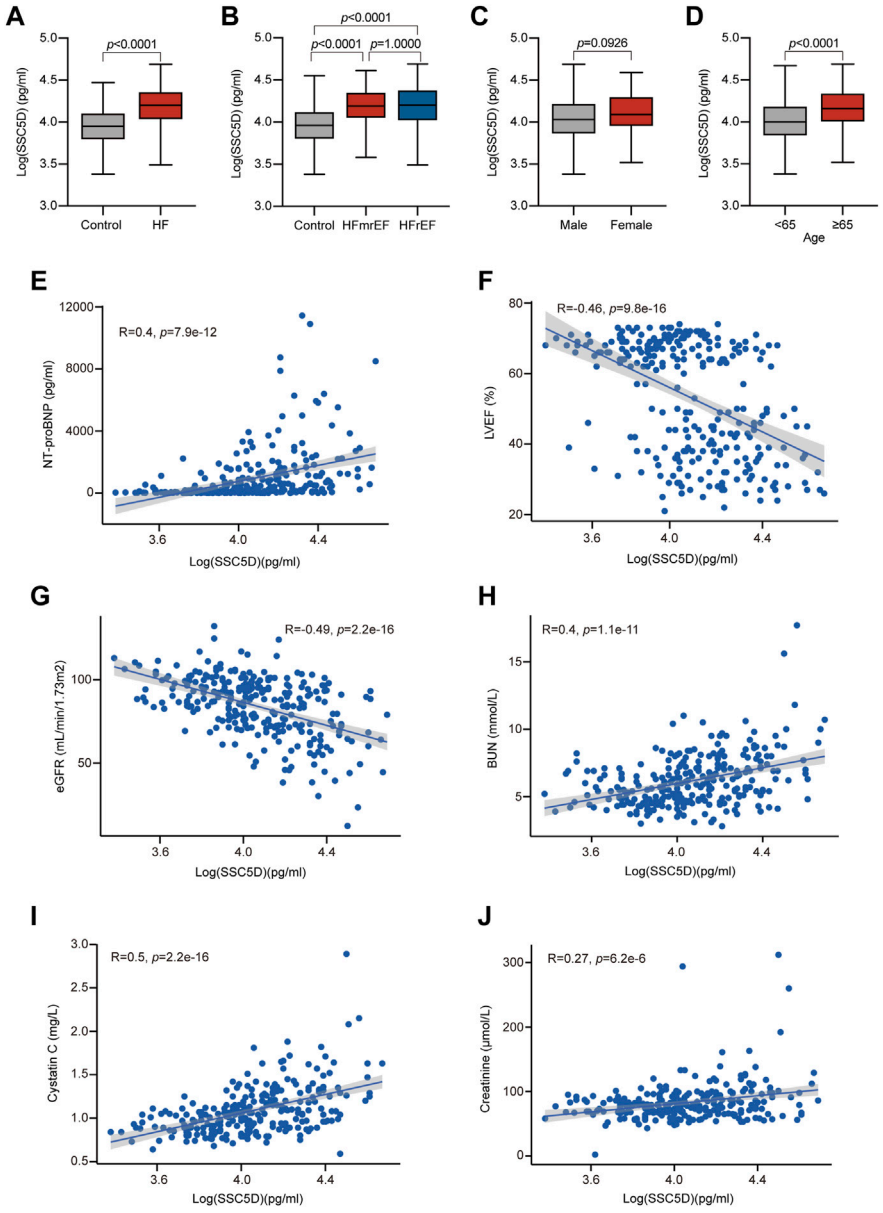

FIGURE 3
Serum SSC5D levels increased in HF patients. **(A)** Serum SSC5D levels in HF patients compared with control. **(B)** Serum SSC5D levels in control, HFmrEF, and HFrEF subjects. **(C, D)** Serum SSC5D levels in male and female, <65 and ≥65 years old subjects, respectively. **(E–J)** The correlation between serum SSC5D levels and NT-proBNP, LVEF, eGFR, BUN, cystatin c, and creatinine. The SSC5D concentrations were transformed by a logarithm of 10 to obtain normality. p-value < 0.05 was considered statistically significant.

HbA1c, and eGFR) in Model 2, log-transformed serum SSC5D levels were highly positively associated with a higher risk of HF (OR:3.60, 95% CI:2.53–5.11, $p < 0.001$ and OR:3.40, 95% CI:2.10–5.51, $p < 0.001$, respectively) (Table 3). Additionally, the highest SSC5D tertile had a higher risk of HF in Models 1 and 2 (OR:17.70, 95% CI: 7.78–40.24, $p < 0.001$ and OR:11.83, 95% CI:4.30–33.09, $p < 0.001$, respectively) (Table 3).

Receiver operating characteristic (ROC) curves were generated to investigate the diagnostic accuracy of the SSC5D for HF. First, we determined the diagnostic accuracy of individual SSC5D value on heart failure, and the ROC curve results showed that the sensitivity and specificity value was 0.750 and 0.676, respectively, and the AUC value was 0.773 (Supplementary Figure S2). In addition, we discovered that the area under the curve (AUC) value of SSC5D was 0.831, which was markedly improved compared to that without SSC5D (AUC: 0.768) in Model 2 (Figure 4; Table 4). The ROC curve analysis showed that the specificity and sensitivity were 0.723 and 0.843, respectively, and the optimal cut-off value of SSC5D concentration for predicting HF was 10,853.98 pg/mL in Model 2 (Figure 4; Table 4). Taken together, these results indicate that SSC5D is a sensitive indicator of HF and may serve as a therapeutic target for treating HF.

TABLE 2 Correlation analysis between HF risk factors and SSC5D concentrations.

Variables	SSC5D (pg/mL)	*p*-Value
Gender		
Male (n = 183)	10,816.41 (7,292.48–16,740.40)	0.0956
Female (n = 93)	12,256.01 (8,949.68–20,167.58)	
Age		
<65 (n = 173)	10,102.50 (6,889.57–15,352.32)	<0.0001
≥65 (n = 103)	14,575.00 (9,912.62–21,872.13)	
Smoking		
Yes (n = 47)	10,696.58 (6,799.49–14,196.77)	0.2587
No (n = 229)	11,543.20 (7,876.62–18,328.31)	
Hypertension		
Yes (n = 131)	14,120.30 (10,053.31–21,035.89)	<0.0001
No (n = 145)	9,561.05 (6,459.68–14,248.90)	
Hypercholesterolemia		
Yes (n = 62)	9,764.05 (7,331.49–13389.56)	0.0017
No (n = 214)	12,113.56 (7,892.27–19,868.04)	
Diabetes		
Yes (n = 72)	15,790.19 (11,298.94–23,199.95)	<0.0001
No (n = 204)	10,075.91 (6,977.58–15,562.41)	
LVEF (R = -0.46, p = 9.8e-16)		
≥50% (n = 153)	9,117.39 (6,294.03–13,132.71)	
41%–49% (n = 37)	15,507.25 (11,187.34–22,366.36)	$p^1 < 0.0001$
≤40% (n = 86)	15,789.35 (10,373.27–23,843.91)	$p^2 < 0.0001$
NT-proBNP (R = 0.4, p = 7.9e-12)		
<125 pg/mL (n = 116)	8,488.70 (5,824.16–12,065.34)	<0.0001
≥125 pg/mL (n = 156)	14,813.76 (10,102.50–21,660.74)	

Data are shown as median (interquartile range) and used Mann-Whitney U test between two groups. p-value < 0.05 was considered statistically significant.
p^1 and p^2 were the results of comparison between LVEF≥50% group with LVEF, 41%–49% and≤40% group in serum SSC5D levels, respectively.
Pearson correlation coefficient in R was used to analyze the correlation between serum SSC5D levels with the continuous LVEF, and NT-proBNP, level.

TABLE 3 Serum SSC5D levels were highly associated with the risk factors of HF.

	Unadjusted	*p*-Value	Model 1	*p*-Value	Model 2	*p*-Value
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
logSSC5D (per SD)	3.23 (2.32–4.50)	<0.001	3.60 (2.53–5.11)	<0.001	3.40 (2.10–5.51)	<0.001
SSC5D tertiles	3.31 (2.35–4.66)	<0.001	4.16 (2.77–6.26)	<0.001	3.41 (2.05–5.67)	<0.001
Tertile 1	1 (referent)		1 (referent)		1 (referent)	
Tertile 2	3.61 (1.87–6.97)	<0.001	4.90 (2.38–10.10)	<0.001	4.03 (1.71–9.48)	0.001
Tertile 3	11.02 (5.53–21.97)	<0.001	17.70 (7.78–40.24)	<0.001	11.83 (4.30–33.09)	<0.001

SSC5D concentration was normalized by $\log_{10}$ transformation to obtain normality and divided into tertiles.
Model 1: Adjusted for age and sex.
Model 2: Adjusted for sex, age, BMI, diabetes mellitus, hypercholesterolemia, hypertension, hemoglobin, creatinine, low-density lipoprotein cholesterol, hypersensitive C-reactive protein, blood urea nitrogen, HbA1c, and estimated glomerular filtration rate.

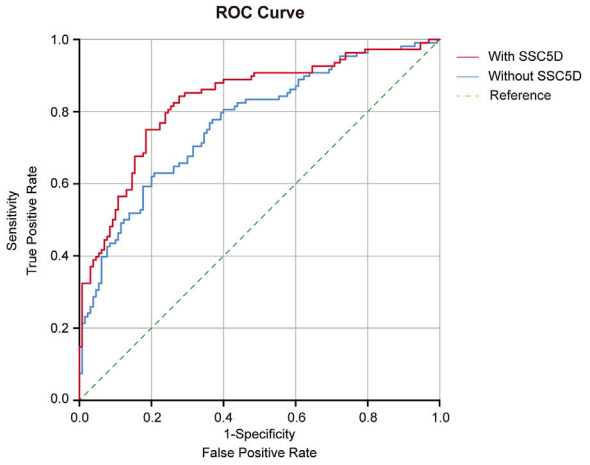

FIGURE 4
Receiver operating characteristic (ROC) curve with area under the curve (AUC) for Model 2 with SSC5D or without SSC5D. Red curve: ROC curve for Model 2 with SSC5D; Blue curve: ROC curve for Model 2 without SSC5D; Green curve: Reference. Model 2: sex, age, BMI, diabetes mellitus, hypercholesterolemia, hypertension, hemoglobin, creatinine, LDL-c, hs-CRP, BUN, HbA1c, and eGFR.

4 Discussion

In this study, we identified a sensitive indicator of HF by screening for the expression of secreted genes in a human RNA-seq dataset. The transcriptional level of *SSC5D* was significantly higher in the failing heart than in the non-failing heart in both clinical and pre-clinical models. Furthermore, we demonstrated that the *Ssc5d* mRNA levels were markedly elevated after TAC and MI surgery. Combining the scRNA-seq data and published RNA-seq data, we demonstrated that *Ssc5d* is predominantly expressed in cardiac fibroblasts in the mouse heart. Notably, the measurement of serum SSC5D concentrations revealed that patients with HF had higher SSC5D levels than those in the control group, which may serve as a therapeutic target for treating HF.

SSC5D is a new soluble protein that has been identified as a new family member of glycoproteins of the scavenger receptor cysteine-rich superfamily. A previous study indicated that SSC5D is predominantly expressed in monocytes/macrophages and T lymphocytes (Gonçalves et al., 2009).

However, our results demonstrated that *Ssc5d* was predominantly expressed in cardiac fibroblasts but was rarely expressed in cardiomyocytes, leukocytes, and endothelial cells. We speculate that this may be attributed to differential expression patterns in various tissues. However, whether *Ssc5d* is derived from cardiac fibroblasts must be verified in the future. Furthermore, studies have shown that abnormal expression of SSC5D is associated with various diseases, such as multiple myeloma (Laï et al., 1995), primary megakaryoblastic leukemia, and acute myeloid leukemia (Alvarez et al., 2001). Additionally, SSC5D is associated with inflammation. The protein level of SSC5D is significantly increased in the synovial fluid of patients with osteoarthritis (Balakrishnan et al., 2014). To date, no reports on the correlation between serum SSC5D levels and the incidence of HF exist. By re-analyzing the RNA-seq data of HF, this study demonstrated for the first time that fibroblast-derived SSC5D was remarkably upregulated in failing conditions.

Similar to SSC5D, S4D-SRCRB is a soluble member of group B SRCR-SF, which is considered to resemble SSC5D in amino acid composition and domain organization (Gonçalves et al., 2009). S4D-SRCRB plays a crucial role in innate immunity (Padilla et al., 2002). CD5L is also one of the SRCR-SF domains and contains three SRCR domains. The elevated CD5L levels often occur in infectious and inflammatory processes (Sanchez-Moral et al., 2021). Agra-Bermejo et al. suggested that isoproterenol treatment of patients with HF or atrial fibrillation significantly increased CD5L secretion from epicardial adipose tissue, which may activate the toll-like receptor 4/nuclear factor-kappa B (NF-κB) signaling pathway and produce pro-inflammatory cytokines (Agra-Bermejo et al., 2020). Circulating CD5L is highly correlated with the risk of cardiovascular events in patients with chronic kidney dysfunction (Castelblanco et al., 2021). Moreover, CD5L promotes atherosclerosis by increasing the formation of macrophage foam cells and CD36-mediated oxidized low-density lipoprotein uptake (Amézaga et al., 2014). Similarly, Scavenger Receptors Stabilin-1 and Stabilin-2 were associated with atherosclerosis, and inhibition of Stabilin-1/Stabilin-2 can significantly reduce Erg1 expression in mononuclear macrophages, thus reducing the progression of atherosclerosis (Manta et al., 2022). Lysyl Oxidase-like2 (LOXL2), one of SRCR-SF, plays a key role in cardiovascular diseases, and directedly interacted with collagen IV and fibronectin to regulate deposition of extracellular matrix (ECM) components (Umana-Diaz et al., 2020). Additionally, LOXL2 regulates the PI3K/AKT/mTORC1 signaling pathway to stimulate myofibroblast transformation in cardiac fibroblasts (Yang et al., 2016). Thus, we hypothesized that SSC5D may contribute to the augmentation of the cardiac immune response and ECM deposition *via* NF-κB and PI3K/AKT/mTORC1 or other pathways, further exacerbating cardiac dysfunction, which should be validated in the future.

5 Limitations

This study has some limitations: 1) Although we discovered that serum SSC5D levels are significantly increased in patients with HF, the role of SSC5D in HF remains unknown. 2) Although our findings suggest that SSC5D is mainly expressed in cardiac fibroblasts, it remains unclear whether SSC5D is associated with

TABLE 4 ROC curve analysis for SSC5D to predict the diagnosis of HF.

	ROC aera (AUC)	95% CI	Specificity	Sensitivity
Without SSC5D	0.768	0.708–0.828	0.792	0.630
With SSC5D	0.831	0.777–0.884	0.723	0.843

fibrosis during cardiac remodeling after HF and the underlying pathways. Therefore, further studies are required to elucidate the function and mechanisms of SSC5D in HF progression. 3) We did not validate the role of serum SSC5D in heart failure with a new validation cohort. Therefore, in future studies, a bigger sample size would be used to clarify the diagnostic and prognostic values of SSC5D on clinical heart failure patients.

6 Conclusion

In conclusion, this study demonstrates that elevated serum SSC5D levels are markedly associated with HF and function as a novel biomarker of clinical HF. Targeting SSC5D may provide therapeutic benefits for patients with HF in the future.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ Supplementary Material.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai General Hospital (2018KY250). The patients/participants provided their written informed consent to participate in this study. The animal study was reviewed and approved by the Animal Welfare and Ethics Committee of Shanghai General Hospital (2021AW035).

Author contributions

YG analyzed the data and drafted the manuscript. XL performed data statistical analysis. HC, GL, and XX collected blood samples, extracted serum, and recorded clinical data. JL and CZ drafted the tables and figures. YZG designed the study and provided critical revision of the manuscript. FW supervised the study, and wrote, reviewed and edited the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2023.1140856/full#supplementary-material

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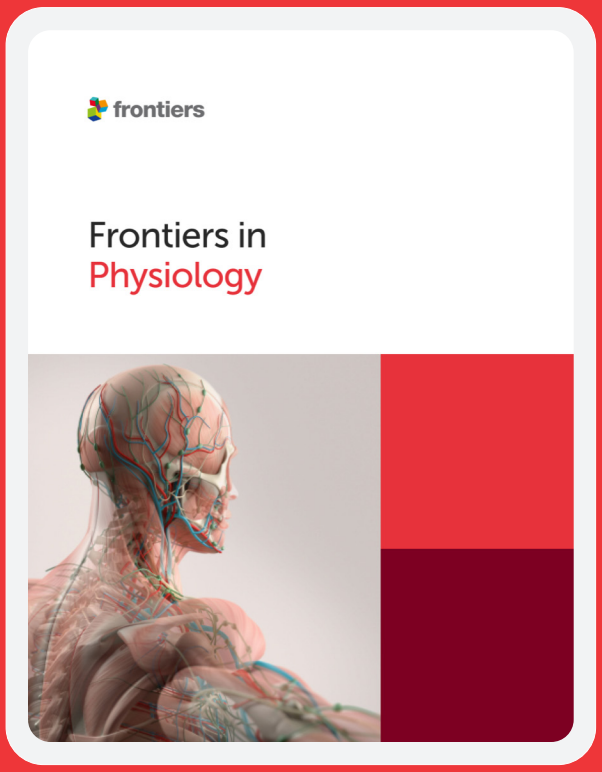

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