WHITEPAPER

Heart Failure with Preserved Ejection Fraction: Emerging Pharmacotherapies and Retrospective Data Review using Electronic Health Records

John Farah, PhD
Alan Wilk, BS
Alina Bogdanov, MA
Lee Kallenbach, PhD
Joe Vasey, PhD

TABLE OF CONTENTS

ABBREVIATIONS

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACEI	Angiotensin Converting Enzyme Inhibitor
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
BMI	Body Mass Index
BNP	B-Type Natriuretic Peptide
cGMP	Cyclic Guanosine Monophosphate
COPD	Chronic Obstructive Pulmonary Disease
CAD	Coronary Artery Disease
DHF	Diastolic Heart Failure
EF	Ejection Fraction
EHR	Electronic Health Record
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GWTG	Get with the Guidelines
HTN	Hypertension
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ICD-9	International Classification of Disease-Ninth Revision
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
NLP	Natural Language Processing
NO	Nitric Oxide
NT-proBNP	N-terminal pro-B-Type Natriuretic Peptide
NYHA	New York Heart Association
PKG	Protein Kinase G
RCT	Randomized Clinical Trial
RAAS	Renin-Angiotensin-Aldosterone System
RWD	Real-World Data
RWE	Real-World Evidence
SGLT2	Sodium-Glucose Cotransporter-2
T2DM	Type 2 Diabetes Mellitus
UACR	Urinary Albumin-to-Creatinine Ratio

EXECUTIVE SUMMARY

With a rising prevalence and high rates of morbidity and mortality, heart failure has become a prominent personal and public health burden. Recently, Veradigm™ published a whitepaper (https://www.veradigmhealth.com/veradigm-news/systolic-heart-failure-case-study/) that described heart failure with reduced ejection fraction (HFrEF), also known as systolic heart failure, and characterized ambulatory patients with HFrEF using de-identified real-world data from an EHR platform Practice Fusion, a Veradigm offering. That paper briefly touched on another type of heart failure, heart failure with preserved ejection fraction (HFpEF), also referred to as diastolic heart failure. Despite similarities in clinical expression, HFrEF and HFpEF differ in their etiologies, cardiac remodeling patterns, biomarker profiles, and responsiveness to pharmacotherapy. This paper addresses HFpEF, with a focus on major comorbidities and on two classes of emerging pharmacotherapies. A retrospective data review using de-identified patient data from the EHR Practice Fusion demonstrates how real world evidence may be leveraged to offer insights regarding HFpEF.

What is HFpEF?

Heart failure with preserved ejection fraction (HFpEF), also known as diastolic heart failure (DHF), is a heterogeneous syndrome with clinical signs and symptoms of congestive heart failure, impaired diastolic function, and a normal or near normal left ventricular ejection fraction (LVEF ≥50%) (Harper et al, 2018; McHugh et al, 2019). Epidemiologic studies and registries indicate HFpEF accounts for 30% to 75% of HF cases (Harper et al, 2018). Patients with HFpEF are generally older (>65 yr) and female; mortality in this population is often due to non-cardiovascular causes (Redfield, 2016; Upadhya and Kitzman, 2017). On presentation, exertional dyspnea and fatigue or exercise intolerance are common complaints (Borlaug and Redfield, 2011). When HFpEF is suspected, careful clinical evaluation, objective confirmation of structural and functional abnormalities using various tests (e.g., Doppler echocardiography, electrocardiography, chest radiography, measurement of natriuretic peptide levels), and specialized, invasive hemodynamic testing (e.g., cardiac catheterization) afford accurate diagnosis (Borlaug and Paulus, 2011; Redfield, 2016). While elevated left ventricular filling pressure during rest is a supportive finding, hemodynamic testing may need to be conducted with exercise, as hemodynamic compromise may surface only under stress (Mayo Clinic, 2014).

PATHOPHYSIOLOGY OF HFpEF

The diastolic dysfunction evident in HFpEF during rest or exertion arises from impairment of active relaxation or passive stiffness of the left ventricle (Mayo Clinic, 2014; Tam et al, 2017). Beyond diastolic dysfunction, a host of other abnormalities are apparent in HFpEF and include

- Systolic dysfunction
- Chronotropic incompetence
- Systemic and pulmonary vascular dysfunction

- Autonomic imbalance
- Left atrial dysfunction/atrial fibrillation
- Right ventricular dysfunction
- Skeletal muscle dysfunction
- Endothelial dysfunction (Borlaug, 2014; Mayo Clinic, 2014; Tam et al, 2017; Harper et al; 2018; McHugh et al, 2019).

The consequences of these abnormalities can be severe. Limitations in systolic reserve and chronotropic incompetence limit cardiac output during exercise and reduce end-organ perfusion (Mayo Clinic, 2014; Borlaug, 2018). Pulmonary hypertension, present in 70% to 80% of patients with HFpEF, is associated with higher rates of hospitalization and increased mortality (Borlaug, 2018). Left atrial dysfunction is associated with a greater burden of pulmonary hypertension, even among patients with normal sinus rhythm and without atrial fibrillation (Borlaug, 2018). Right ventricular failure, estimated to occur in one-third of patients and strongly predictive of poor outcomes, leads to systemic congestion, cardiorenal syndrome, malabsorption, and cardiac cachexia (Mayo Clinic, 2014; Harper et al, 2019). Endothelial dysfunction has been associated with more severe HF symptoms, diminished exercise capacity, and higher rates of adverse events (Borlaug, 2018).

COMORBIDITIES IN HFpEF

Comorbidities are risk factors for developing HF as well as complicating factors once HF is established (Bozkurt et al, 2016). They are common in patients with HFpEF and contribute to worsening prognosis. In a community study, comorbid conditions were strongly associated with hospitalizations, and hospital readmissions were frequently related to non-cardiovascular comorbidities (Dunlay et al, 2009). In a large ambulatory cohort study of patients with HF, a higher burden of non-cardiac comorbidity, lower rates of HF hospitalization, and higher rates of non-HF hospitalizations were demonstrated for patients with HFpEF than for patients with HFrEF, with similar overall rates of hospitalization reported for both (Ather et al, 2012). The authors concluded aggressive management of comorbidities may have greater prognostic effect in HFpEF than in HFrEF (Ather et al, 2012).

HFpEF was originally believed to arise from hypertension (HTN)-induced, left ventricular pressure overload causing concentric left ventricular hypertrophy, diastolic dysfunction, and fibrotic remodeling (Tam et al, 2017; Redfield, 2016; Harper et al, 2018). An alternative theoretical framework has evolved that places comorbidity-driven systemic inflammation at the forefront of HFpEF development, with coronary microvascular endothelial inflammation leading to decreased nitric oxide (NO) bioavailability, cyclic guanosine monophosphate (cGMP) content, and protein kinase G (PKG) activity in cardiomyocytes; myocardial hypertrophy and stiffening and interstitial fibrosis; global cardiac remodeling and dysfunction; and impaired coronary flow reserve (Paulus and Tschöpe, 2013; Redfield, 2016; Tam et al, 2017). Similar changes are proposed to occur in the vasculature and striated tissue of skeletal muscle (Redfield, 2016).

Among the cardiovascular and non-cardiovascular comorbidities associated with HFpEF, the following are notable for their prevalence and/or impact, with many (HTN, anemia, chronic renal

dysfunction, chronic obstructive pulmonary disorder [COPD], obesity, and diabetes mellitus [DM]) implicated in tissue inflammation and coronary microvascular dysfunction (Paulus and Tschöpe, 2013; Redfield, 2016; Borlaug, 2018):

- **Coronary Artery Disease** – One-quarter to two-thirds of patients with HFpEF have been reported to have comorbid coronary artery disease (CAD) (Upadhya and Kitzman, 2017; Borlaug, 2018). In a study of consecutive patients previously hospitalized for HFpEF, patients with CAD were more likely to be treated with anti ischemic medications but were similar to patients without CAD with regard to symptoms of angina and heart failure and in measures of cardiovascular structure, function, and hemodynamics (Hwang et al, 2014). CAD was also associated with increased mortality and left ventricular dysfunction; revascularization may improve cardiac function and clinical outcomes (Hwang et al, 2014). Others have shown coronary microvascular disease may cause ischemia in the absence of CAD (Bourlag, 2018; Mohammed et al, 2016).
- **Hypertension** – As a cardiovascular comorbidity, HTN is a prevalent risk factor for HF; its presence precedes a HF diagnosis in an estimated 75% to 85% of patients with established HF (Upadhya and Kitzman, 2017). Elevated systemic blood pressure, often caused by renal HTN, increases left ventricular wall stress and delays or impairs myocardial relaxation (Tam et al, 2017; Borlaug, 2019). In treating comorbid HTN, matching antihypertensive treatment to patient phenotype may confer important strategic advantages (Tam et al, 2017). Evidence from randomized clinical trials (RCTs) suggests long-term treatment of HTN prior to the onset of HFpEF may forestall its development (Kostis et al, 1997; ALLHAT, 2002; Bechet et al, 2008).
- **Atrial Fibrillation** – Atrial fibrillation is extremely common (in up to two-thirds of patients) in HFpEF (Mayo Clinic, 2014). Because left atrial contractility is essential to maintaining left ventricular filling for adequate stroke volume, atrial fibrillation is poorly tolerated (Mayo Clinic, 2014). The presence of atrial fibrillation is associated with diminished capacity for exercise, severe right ventricular dysfunction, and increased mortality (Borlaug, 2018).
- **Anemia** – Anemia, often caused by underlying chronic renal disease, is common in older patients, occurs more frequently in HFpEF than HFrEF, and is associated with increased morbidity and mortality (Mentz et al, 2014). Comorbid anemia may bring on an acute decompensated HFpEF that requires aggressive diuresis (Borlaug, 2018).
- **Renal Dysfunction** – With a prevalence of 30% to 60%, renal dysfunction (i.e., low estimated glomerular filtration rate [eGFR] and/or high urinary albumin-to-creatinine ratio [UACR]) is a common comorbidity in HFpEF (Gori et al, 2014). Reduced renal perfusion and venous congestion, neuroendocrine activation, therapeutic modulation of the renin-angiotensin-aldosterone system (RAAS), chronic low grade inflammation, endothelial dysfunction, and anemia have been associated with worsening renal function (Damman and Testani, 2015). Renal dysfunction elevates cardiovascular risk; it is associated with cardiac remodeling and diastolic dysfunction and the extent of dysfunction may be useful in establishing prognosis (Gori et al, 2014). Worsening renal function may precipitate acute decompensated HFpEF (Borlaug, 2018).
- **Chronic Obstructive Pulmonary Disease** – Approximately one-third of patients with HF have COPD, with a consistently noted higher prevalence in patients with HFpEF than in patients with HFrEF that suggests coexisting pulmonary and cardiac dysfunction may be particularly

important for the former group (Mentz et al, 2014). As an independent predictor of mortality in HFpEF, COPD increases non-cardiovascular mortality during HF hospitalization and following discharge (Mentz et al, 2014).

- **Obesity** – Fifty percent of patients with HFpEF are estimated to be obese (Altara et al, 2017). Obesity is a key risk factor as well as a distinct phenotype of HFpEF (Borlaug, 2018). Obese individuals are at markedly increased risk of heart failure, independent of ischemic cardiovascular injury (Packer and Kitzman, 2018). Among other deficits, obese patients with HFpEF have greater right heart dysfunction and remodeling than normal weight individuals (Borlaug, 2018).

  Obesity is an extra-cardiac cause of volume overload (Shah et al, 2014). Sodium retention is one pathophysiologic abnormality that contributes to the pronounced plasma volume expansion and HTN common to obesity-related HFpEF (Packer and Kitzman, 2018). Another obesity-related abnormality is systemic inflammation; inflammation of epicardial adipose tissue leading to myocardial fibrosis may prevent adequate ventricular dilation in response to plasma volume expansion, causing cardiac filling pressures to rise disproportionately and leading to congestion (despite minimal systolic dysfunction) and exercise intolerance (Packer and Kitzman, 2018). In addition, levels of natriuretic peptides are low in patients with obesity-related HFpEF (Packer and Kitzman, 2018). These features may relate to overproduction of adipocyte-derived molecules, including aldosterone and neprilysin (Packer and Kitzman, 2018).

- **Diabetes Mellitus** – There is a bi-directional, complex relationship between heart failure and DM, with DM affecting approximately 40% of HFpEF patients in registry and observational studies (Mentz et al, 2014). The links between DM and HF likely involve activation of RAAS, impaired calcium handling in cardiomyocytes, oxidative stress, myocardial fibrosis, and endothelial dysfunction (Zelniker and Braunwald, 2018). Type 2 diabetes mellitus (T2DM) related small vessel disease affecting the coronary microcirculation often contributes to HFpEF (Zelniker and Braunwald, 2018).

  Across large-scale trials, patients with HFpEF and comorbid DM were invariably reported to have higher BMIs and generally had higher rates of HTN than patients without comorbid DM (MacDonald et al, 2008; Aguilar et al, 2010; Lindman et al, 2014; Kristensen et al, 2017). In one of these studies (Digitalis Investigation Group [DIG] ancillary trial), there was a 68% increased risk of HF hospitalization or HF death for HFpEF patients with DM compared with HFpEF patients without DM (Aguilar et al, 2010). In a Get with the Guidelines in Heart Failure (GWTG-HF) registry of patients with HFpEF hospitalized for new or worsening HF, a significant increase in hospital and post discharge morbidity was associated with DM (McHugh et al, 2019). Another study (Candesartan in Heart-failure Assessment of Reduction in Mortality and Morbidity [CHARM] program) reported DM was associated with a greater relative risk of CV death or HF hospitalization for patients with HFpEF than for patients with HFrEF (MacDonald et al, 2008).

  In treating DM, some anti-hyperglycemic medications have been reported to have deleterious effects (McHugh et al, 2019). Of possible concern are insulin and insulin-sensitizing medications (e.g., sulfonylureas, thiazolidinediones) that facilitate uptake of fat and glucose into cardiac tissue; these agents may promote lipotoxicity and glucotoxicity (Riggs et al, 2015). A recent analysis of data from patients with HFpEF enrolled in the Americas region of the TOPCAT

trial identified male gender and insulin-treated DM as independent predictors of sudden death or aborted cardiac arrest (Vaduganathan et al, 2018). In a meta-regression analysis of observational studies (6 of 19 studies identified), use of sulfonylureas was associated with an increased risk of cardiovascular events and mortality (Azoulay and Suissa, 2017). Others have suggested the contribution of glucotoxicity to heart failure is minor based on lack of association between changes in glycemic control and the risk of heart failure when examining data from large randomized trials of glucose-lowering agents (Packer et al, 2017).

MANAGEMENT OF HFpEF

While substantial clinical evidence is available to guide treatment of HFrEF (Yancy et al, 2013; Yancy et al, 2016; Yancy et al; Yancy et al, 2017; Yancy et al, 2018), there is minimal evidence based guidance for the treatment of HFpEF. Clinical trials in HFpEF have been inconclusive, failing to identify therapies that reduce mortality (Martin et al, 2018). The neutral outcomes obtained in clinical trials may reflect, at least in part, the phenotypic heterogeneity of HFpEF.

Currently, management of HFpEF is directed toward reducing volume overload, treating coexisting comorbidities, increasing exercise tolerance, educating patients regarding diet and self-care, and managing chronic disease through structured programs (Redfield, 2016). Therapeutic goals include reduction or control of symptoms, prevention of hospitalization and mortality, and improvement in quality of life (Yancy et al, 2013).

According to the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline for the Management of Heart Failure, Class I recommendations for treating stage C HFpEF include the use of antihypertensive medications to control systolic and diastolic blood pressure and diuretics to relieve symptoms caused by hypervolemia; Class IIa recommendations include coronary revascularization in patients with coronary artery disease who, despite guideline-directed medical therapy, have symptoms or ischemia; management of atrial fibrillation according to published practice guidelines; and the use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (ARBs) in patients with HTN (Yancy et al, 2017). In 2017, an update to the 2013 guidelines included a recommendation for a target systolic blood pressure of less than 130 mm Hg for patients with stage C HFpEF and persistent HTN despite management of volume overload (Yancy et al, 2017). Although limited clinical trial data are available to guide the choice of antihypertensive agent, angiotensin converting enzyme inhibitors (ACEIs), ARBs, and possibly an angiotensin receptor-neprilysin inhibitor (ARNI), each of which inhibit RAAS, are the preferred choices (Yancy et al, 2017).

While no studies have demonstrated reductions in mortality, use of ARBs may reduce HF hospitalizations (Yancy et al, 2017; Bozkurt, 2018). The use of aldosterone antagonists may reduce HF hospitalizations in patients with HFpEF with elevated biomarker (i.e., brain natriuretic peptide and N-terminal pro-B-type natriuretic peptide) levels (Yancy et al, 2017; Bozkurt, 2018; Harper et al, 2018). A recent meta-analysis that included randomized and non-randomized controlled trials and a pre-post trial suggested exercise training is safe and confers benefits (improved exercise capacity and health-related quality of life) for patients with HFpEF (Taylor et al, 2012).

EMERGING PHARMACOTHERAPIES FOR HFpEF

Two drug classes with indications for other medical conditions have emerged as potential treatments for HFpEF: sodium-glucose cotransporter-2 (SGLT2) inhibitors and combination ARBs/neprilysin inhibitors (ARNI). Several SGLT2 inhibitors and a first-in-class ARNI are currently under evaluation in late-stage, randomized clinical trials.

Sodium-Glucose Cotransporter-2 Inhibitors

SGLT2 inhibitors increase urinary glucose excretion by binding to one of two symporters in the kidney nephron, both of which can cotransport glucose and sodium (Baar et al, 2018). Under physiologic conditions, low-affinity, high capacity SGLT2 located in proximal tubule epithelium facilitates reabsorption of the majority of glucose (~90%) filtered by the kidney, with the remaining 10% reabsorbed via the more distally located high-affinity, low capacity SGLT1 (Baar et al, 2018). By binding to SGLT2 and promoting glycosuria and natriuresis (with attendant osmotic diuresis and plasma volume contraction), SGLT2 inhibitors enhance lipolysis and shift substrate utilization from carbohydrates to lipids, reduce fat mass and body weight, and reduce blood pressure without increases in heart rate (Vallon and Thomson, 2017). SGLT2 inhibitors have been associated with reductions in arterial stiffness and vascular resistance and improvements in microvascular endothelial function (Altara et al, 2017). Four SGLT2 inhibitors—canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin—have received approval from the US Food and Drug Administration (FDA) as adjuncts to diet and exercise to improve glycemic control in adults with T2DM. These SGLT2 inhibitors are administered orally, either as monotherapy or as add-on therapy with other glucose-lowering drug classes (Baar et al, 2018; Davies et al, 2018). Late-stage clinical trials are ongoing for sotagliflozin, a dual SGLT1/SGLT2 inhibitor, in adults with T2DM (Lexicon Pharmaceuticals, 2019). Canagliflozin has a boxed warning for association with lower limb amputation in patients with T2DM who have established, or are at risk of, cardiovascular disease. A recent cohort study using nationwide registers in two countries reported use of SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) was associated with a two-fold increased risk of lower limb amputation and diabetic ketoacidosis compared with glucagon-like peptide 1 receptor agonists; no increased risk was associated with bone fracture, acute kidney injury, serious urinary tract infection, venous thromboembolism, or acute pancreatitis (Ueda et al, 2018).

Evidence for a possible therapeutic role of SGLT2 inhibitors in heart failure prevention or management was provided in RCTs conducted in patients with T2DM (see **Textbox**). These trials were designed to satisfy regulatory requirements for cardiovascular safety (Lytvyn et al, 2017). Currently, two SGLT2 inhibitors, canagliflozin and empagliflozin, are additionally indicated to reduce the risk of cardiovascular death or to reduce the risk of major adverse cardiovascular events, respectively, in adults with T2DM and established cardiovascular disease. The reductions in hospitalization for heart failure that were demonstrated across independent trial programs has led the American Diabetes Association and the European Association for the Study of Diabetes to recommend treatment with SGLT2 inhibitors for patients with T2DM and atherosclerotic disease "in whom HF coexists or is of special concern" (Davies et al, 2018).

SGLT2 INHIBITOR CARDIOVASCULAR SAFETY TRIALS

The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcomes and Mortality in T2DM) trial, which enrolled more than 7,000 patients from 42 countries with T2DM and established cardiovascular disease, reported for empagliflozin versus placebo a 14% reduced risk of three-point major adverse cardiovascular events (MACE, the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), driven by a 38% risk reduction of cardiovascular death, and a 35% reduced risk of hospitalization for heart failure (Zinman et al, 2015). Consistent benefits were noted for patients with and without heart failure at baseline (Fitchett et al, 2018).

In the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program (two studies combined), which enrolled over 10,000 patients with T2DM with high cardiovascular risk, canagliflozin reduced the risk of death from MACE and reduced the risk of hospitalization for heart failure by 14% and 33%, respectively, compared with placebo (Neal et al, 2017). Reductions in risk were noted across a broad range of patient subgroups, with benefits potentially greater for patients with a history of HF (Radholm et al, 2018).

In the DECLARE-TIMI 58 trial, which evaluated over 17,000 patients with T2DM who were at risk of or had a diagnosis of atherosclerotic cardiovascular disease, dapagliflozin reduced the risk of hospitalization for heart failure by 27% compared with placebo (Wiviott et al, 2019).

A meta-analysis of cardiovascular trials of three SGLT2 inhibitors in patients with T2DM (i.e., EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58 [including secondary analyses]) demonstrated a moderate reduction (11%) in the risk of MACE that appeared confined to a subset of patients with established atherosclerotic cardiovascular disease and that did not extend to patients with multiple risk factors; in contrast, there were robust reductions in the risk of hospitalization for heart failure (23%) and of progression of renal disease (45%), with these occurring regardless of existing atherosclerotic cardiovascular disease or history of heart failure (Zelniker et al, 2019).

The VERTIS CV Study, which is evaluating the effects of ertugliflozin on approximately 8,000 patients with T2DM and established vascular disease, is currently underway to evaluate the relative risk of MACE and hospitalization for heart failure compared with placebo. Study completion is anticipated in 2019 (4Q) (Clinical Trials.gov identifier: NCT01986881).

The SCORED Study was designed to assess the effects of sotagliflozin on cardiovascular (MACE, cardiovascular death or hospitalization for HF) and renal events in over 10,000 patients with T2DM and moderate renal impairment who are at cardiovascular risk. Completion of the study is expected in 2022 (1Q) (Clinical Trials.gov identifier: NCT03315143).

Consistent with the findings of RCTs are those obtained from a large multinational study (US and Europe) using real-world data collected from medical claims, primary care and hospital records, and national registries, which showed treatment with SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) was associated with a lower risk of heart failure hospitalization and death than treatment with other glucose-lowering drugs (Kosiborod et al, 2017). The benefits suggest a class effect that may be applicable across broad populations with T2DM in clinical practice (Kosiborod et al, 2017). Interim results from another real-world study (Empagliflozin Comparative Effectiveness and Safety Study [EMPRISE]) indicate empagliflozin was associated with a 44% reduction in relative risk for heart failure hospitalization compared with a glucose-lowering agent in patients with T2DM with and without cardiovascular disease (Boehringer Ingelheim, 2018).

The mechanisms responsible for the beneficial effect of SGLT2 inhibitors on heart failure have yet to be determined. Synergistic interactions between improvements in blood glucose levels and reductions in blood pressure, body weight, and uric acid levels have been proposed to underlie class related cardio-protective effects (Vallon and Thomson, 2017). Of interest is the relatively rapid onset of HF risk reduction in RCTs, which suggests SGLT2 inhibitors may work directly on the cardiovascular system (Lytvyn et al, 2017; Zelniker and Braunwald, 2018). Some have proposed SGLT2

TABLE 1 | SGLT2 Inhibitor Clinical Trials for Patients with HFpEF

Trial/ Identifier	SGLT2 inhibitor	Description
EMPEROR-Preserved/ NCT03057951	**empagliflozin**	EMPEROR-Preserved, a phase 3 RCT of up to 38 months' duration, is assessing the effect of empagliflozin on long-term morbidity and mortality outcomes in patients (N=4,126) with chronic HFpEF. The primary outcome measure is the time to first event of composite CV death or HHF. Among secondary endpoints are occurrence of HHF (first and recurrent) and the time to first hospitalization for heart failure. Patients will also be monitored for time to onset of T2DM. The study is expected to be completed in 2020 (2Q).
EMPERIAL-Preserved/ NCT03448406	**empagliflozin**	EMPERIAL-Preserved, a phase 3 RCT, is evaluating the impact of empagliflozin on exercise ability and HF symptoms in patients (N=300) with chronic HFpEF, independent of T2DM status. Primary outcomes include the change from baseline to week 12 in exercise capacity, as measured by the distance walked in 6 minutes. Estimated completion date is 2019 (4Q).
EMPA-VISION/ NCT03332212	**empagliflozin**	EMPA-Vision is a phase 3 mechanistic RCT of 12 weeks' duration, designed to assess the effect of empagliflozin on cardiac physiology and metabolism; experimental cohorts include patients with HFpEF and patients with HFrEF (N=86). The primary outcome measure is the change from baseline to week 12 in myocardial creatine phosphate/adenosine tri-phosphate ratio in the resting state, as measured using magnetic resonance imaging. The study is expected to be completed in 2019 (4Q).
EMBRACE-HF/ NCT03030222	**empagliflozin**	EMBRACE-HF is a Phase 4 RCT evaluating the impact of empagliflozin on hemodynamic parameters in patients (N=60) with HF (HFpEF or HFrEF). The primary outcome measure is the change from baseline to end of treatment in pulmonary artery diastolic pressure. The study is scheduled for completion in 2019 (2Q).
PRESERVED-HF/ NCT03030235	**dapagliflozin**	PRESERVED-HF is a phase 3 RCT designed to evaluate the effects of dapagliflozin on levels of HF biomarkers (BNP and NT-proBNP), symptoms, health status, quality of life, and echocardiographic parameters in patients with chronic HFpEF (N=320). The primary outcome measure is the change from baseline in NT-proBNP at weeks 6 and 12; among secondary measures are the changes from baseline to week 12 in the KCCQ summary score and in a 6-minute walk test. The study runs through 2019 (4Q).
DELIVER/ NCT03619213	**dapagliflozin**	DELIVER, a phase 3 RCT of up to 33 months' duration, is evaluating whether dapagliflozin, when added to standard of care, reduces CV death or worsening HF in patients with HFpEF (N=4,700). Primary outcomes include the time to first occurrence of any component of a composite: CV cardiovascular death, HHF, or urgent heart failure visit (outpatient or emergency department). The total number of HHF (first and recurrent) and CV death is a secondary measure. Study completion is expected in 2021 (2Q).
ERADICATE-HF/ NCT03416270	**ertugliflozin**	ERADICATE-HF is a phase 2 safety and mechanistic RCT designed to assess how ertugliflozin modifies cardiorenal interactions that regulate fluid volume and neurohormonal activation in patients (N=36) with T2DM and HF (HFpEF or HFrEF). The primary outcome measure is the difference vs placebo in proximal sodium reabsorption (acute [week 1] and chronic [week 12]). The study will be completed in 2021 (1Q).
SOLOIST-WHF/ NCT03521934	**sotagliflozin**	SOLOIST-WHF is a phase 3 RCT designed to evaluate mortality and morbidity in hemodynamically stable patients (N=4,000) (HFrEF and HFpEF) with worsening HF (admitted to a hospital or urgent care visit) with T2DM. Primary measures include the time to first occurrence of either CV death or HHF in patients with HFrEF and in the total population. Study completion is expected in 2021 (1Q).

SGLT2=sodium glucose transporter-2, RCT=randomized clinical trial, HFpEF=heart failure with preserved ejection fraction, HFrEF=heart failure with reduced ejection fraction, CV=cardiovascular, HHF=hospitalization for heart failure, T2DM=diabetes mellitus, HF=heart failure, BNP=B-type natriuretic peptide, NT-proBNP=N-terminal pro-B type natriuretic peptide, KCCQ=Kansas City Cardiomyopathy Questionnaire.

inhibitors may exert their cardio-protective effects via inhibition of sodium-hydrogen exchange in both the heart and the kidneys (Packer et al, 2017; Zelniker and Braunwald, 2018). In addition, by decreasing accumulation of biologically active pericardial adipocytes, SGLT2 inhibitors may inhibit leptin-mediated cardiac and renal inflammation and reduce cardiac fibrosis (Packer, 2018).

Late-stage RCTs assessing SGLT2 inhibitors in HFpEF are summarized in **Table 1**.

Angiotensin Receptor-Neprilysin Inhibitor

Sacubitril/valsartan represents a first-in-class ARNI combination. As a neprilysin inhibitor, sacubitril augments plasma concentrations of natriuretic peptides (e.g., B-type natriuretic peptide [BNP]) that are involved in the long-term regulation of water and sodium balance and of blood volume and arterial pressure. In addition, sacubitril increases plasma levels of vasodilators such as bradykinin and adrenomedullin but also increases levels of vasoconstrictor peptides, including angiotensin I and II (Gori et al, 2018). Co-administration of the ARB valsartan counters vasoconstriction by inhibiting RAAS to reduce blood pressure (Bozkurt, 2018).

The results of a double blind, placebo-controlled RCT (PARADIGM) conducted in patients (N=8442) with Class II, III, or IV heart failure with ejection fraction ≤40% (i.e., HFrEF) showed sacubitril/valsartan to be superior to enalapril (an ACEI), with significant improvement in the primary end point of combined cardiovascular mortality or HF hospitalizations (McMurray et al, 2014). Following a median follow-up of 27 months, the trial was discontinued, having crossed the threshold for showing overwhelming benefit (McMurray et al, 2014). Sacubitril/valsartan has received FDA approval and is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association [NYHA] Class II-IV) and reduced ejection fraction. According to the American College of Cardiology Foundation/American Heart Association guidelines, sacubitril/valsartan represents an important advance in heart failure patient care and is recommended to replace ACEIs or ARBs (as appropriate and under specified conditions) to further reduce morbidity and mortality in patients with HFrEF (Yancy et al, 2017). For patient with HFpEF, current guidelines recommend sacubitril/valsartan as a possible preferred choice of anti-hypertensive agent for achieving target systemic blood pressure (<130mm Hg) (Yancy et al, 2017).

Because neprilysin inhibitors decrease sodium and water retention (limiting plasma volume expansion) and also inhibit the accumulation of inflammatory perivisceral adipose tissue, their use may limit pericardial and myocardial fibrosis leading to HFpEF (Packer and Kitzman, 2018). As discussed, systemic inflammation and coronary microvascular endothelial dysfunction with impaired NO-cGMP-PKG signaling in cardiomyocytes appear to drive global cardiac remodeling (Paulus and Tschöpe, 2013; Altara et al, 2017). Drugs such as sacubitril, which increase NO-dependent cGMP and PKG activity via natriuretic peptide enhancement (with PKG having anti-hypertrophic and anti-fibrotic effects in cultured myocytes and fibroblasts and in cardiac disease models) may be of use in treating diastolic dysfunction in HFpEF (Zouein et al, 2013; Shah et al, 2016; Altara et al, 2017).

TABLE 2 | Sacubitril/Valsartan Clinical Trials for Patients with HFpEF

Trial/ Identifier	Description
PARAGON-HF/ NCT01920711	PARAGON-HF, a multicenter, double-blind, parallel-group, active-controlled phase 3 RCT of up to 57 months' duration, is evaluating the efficacy and safety of sacubitril/valsartan in patients (N=4822) with HFpEF. The primary outcome measure is the cumulative number of composite event of CV death and total (first and recurrent) HHF. Secondary outcome measures include the change from baseline to month 8 in 1) the clinical summary score of the KCCQ, and 2) the NYHA functional class. Study completion is expected in 2019 (2Q).
PERSPECTIVE/ NCT02884206	PERSPECTIVE, a multicenter, double-blind, parallel-group, active-controlled phase 3 RCT, is assessing efficacy and safety of sacubitril/valsartan on cognitive function in patients (N=520) with HFpEF. The primary outcome measure is the change from baseline to week 156 in the CogState Global Cognitive Composite Score. Secondary measures are the change from baseline to week 156 in 1) cortical composite standardized uptake value ratio, 2) individual cognitive domains (memory, executive function, and attention), and 3) summary score of the instrumental activities of daily living. The study is anticipated to conclude in 2022 (2Q).
PARALLAX/ NCT03066804	PARALLAX, a multicenter, double blind, parallel-group, active-controlled phase 3 RCT, is evaluating the effect of sacubitril/valsartan on NT-proBNP, exercise capacity, symptoms, and safety compared to individualized medical management of comorbidities in patients (N=2500) with HFpEF. Primary outcome measures are 1) the change from baseline to week 12 in NT-proBNP and 2) the change from baseline to week 24 in 6-minute walk distance. The trial is expected to be completed in 2019 (4Q).
CNEPi/ NCT03506412	CNEPi, sponsored by the Mayo Clinic in collaboration with the National Institute on Aging, is a proof-of-concept mechanistic phase 4 study for determining efficacy of sacubitril/valsartan in patients (N=40) with high and low circulating neprilysin levels. The primary outcome measure is the change from baseline to week 5 in biomarkers based on neprilysin levels. Secondary measures are the change from baseline in NT-proANP, NT-proBNP, and NT-proCNP and the change from baseline in plasma cGMP. The study will conclude in 2019 (2Q).

RCT=randomized clinical trial, HFpEF=heart failure with preserved ejection fraction, CV=cardiovascular, HHF=hospitalization for heart failure, KCCQ=Kansas City Cardiomyopathy Questionnaire, NYHA=New York Heart Association, NT-proBNP=N-terminal pro-B type natriuretic peptide, NT-proANP=N-terminal pro-A type natriuretic peptide, NT-proCNP=N-terminal pro-C type natriuretic peptide, cGMP=cyclic guanosine monophosphate.

For patients with HFpEF, the PARAMOUNT study, a phase 2, double-blind, active-controlled proof-of-concept RCT demonstrated sacubitril/valsartan treatment was associated with a significantly greater reduction in the level of N-terminal B-type natriuretic peptide (NT-proBNP), a biomarker of left ventricular wall stress, at 12 weeks than valsartan treatment alone (Solomon et al, 2012). In addition, significant reduction in left atrial size and improvement in NYHA HF functional class were noted with sacubitril/valsartan at 36 weeks compared with valsartan alone (Solomon et al, 2012). Ongoing trials for sacubitril/valsartan in patients with HFpEF are shown in **Table 2**.

REAL-WORLD EVIDENCE: RETROSPECTIVE DATA REVIEW

The Food and Drug Administration (FDA) defines real-world evidence (RWE) as clinical evidence of the use and of the benefits or risks of medical products (Corrigan-Curay et al, 2018; US Food and Drug Administration, 2018). RWE enables research that may be used to identify gaps in provider care and patient self-care, provide input for system-wide or community-based HF programs, and inform medical coverage decisions. RWE also has potential to supplement the findings of RCTs, which are internally valid but may not adequately inform clinical practice (Sherman et al, 2016; Lund et al, 2017). Recently, the FDA has created a framework to evaluate how RWE may enable efficient, cost-effective support for new indications for drugs already approved or for regulatory efforts post-approval (US Food and Drug Administration, 2018). De-identified real world data (RWD) obtained from medical and prescription claims, patient and provider surveys, clinical registries and other observational studies, and electronic health records (EHRs) are viable sources of RWE (Sherman et al, 2016; Camm and Fox, 2017; US Food and Drug Administration, 2018).

To explore how real-world observations may provide insight into the challenges of and opportunities for managing HFpEF, a preliminary analysis of de-identified patient data from ambulatory patients was performed using an electronic health record (EHR) platform Practice Fusion, a Veradigm offering. Practice Fusion is the largest cloud-based EHR platform in the US (Practice Fusion, 2019). The objectives of this analysis were to characterize HFpEF patients according to key demographics and comorbidities and to evaluate use of SGLT2 inhibitors and sacubitril/valsartan in the management of these patients over a period of 24 months.

This retrospective data review evaluated de-identified data from ambulatory patients with evidence of treatment for symptomatic DHF. The study design is shown in **Figure 1**. Patients were included if they

- had a diagnostic code for DHF (e.g., diastolic, acute on chronic diastolic, combined systolic and diastolic) between Dec 2, 2016 and Dec 1, 2018
- had symptomatic heart failure as evidenced by at least one written prescription for or documented use of a diuretic
- were at least 18 years of age or older on Dec 1, 2018 (Index).

FIGURE 1 | Study Design

Eligible patients were evaluated as a group (symptomatic DHF) and were also stratified according to whether they had a comorbid diagnosis of DM (type 1 or type 2) or HTN, yielding the following four cohorts: symptomatic DHF with DM, symptomatic DHF without DM, symptomatic DHF with HTN, and symptomatic DHF without HTN.

Of the 91,757 patients with DHF identified at Index, 30,161 (32.9%) met additional symptom and age eligibility criteria. Among these eligible patients, 9,158 (30.4%) were diagnosed with comorbid DM and 13,168 (43.7%) were diagnosed with comorbid HTN during the 24 months prior to Index (**Table 3**).

TABLE 3 | Characteristics for Patients with Symptomatic DHF

CHARACTERISTICS	Patients with Symptomatic DHF				
	All N=30,161	**with DM** N=9,158	**w/o DM** N=21,003	**with HTN** N=13,168	**w/o HTN** N=16,993
AGE					
Mean Age (SD)	75.2 (11.6)	73.4 (11.1)	76.0 (11.7)	75.0 (11.8)	75.4 (11.4)
18-64 yr, n (%)	5,350 (17.7)	1,858 (20.3)	3,492 (16.6)	2,446 (18.6)	2,904 (17.1)
=>65 yr, n (%)	24,803 (82.2)	7,297 (79.7)	17,506 (83.3)	10,718 (81.4)	14,085 (82.9)
GENDER					
Female, n (%)	17,772 (58.9)	5,240 (57.2)	12,532 (59.7%)	7,967 (60.5)	9,805 (57.7)
Male, n (%)	12,342 (40.9)	3,899 (42.6)	8,443 (40.2%)	5,173 (39.3)	7,169 (42.2)
Not recorded, n (%)	46 (0.2)	19 (0.2)	27 (0.1%)	27 (0.2)	19 (0.1)
BMI					
BMI (%)	84.3	82.8	84.9	80.6	87.2
Mean BMI (SD)	31.7 (8.4)	33.6 (8.5)	30.9 (8.3)	32.0 (8.6)	31.5 (8.3)

Abbreviations: DHF=diastolic heart failure, DM=diabetes mellitus, HTN=hypertension, w/o=without, SD=standard deviation, yr=year, BMI=body mass index.

Patient demographics are shown in **Table 3**. The mean age (SD) of all patients was 75.2 (11.6) years (range of means for the four cohorts, 73.4 [11.1]-76.0 [11.7] yr), with most patients (82.2%) aged 65 years or older. More than one-half of patients (58.9%) were female (range of means, 57.2%-60.5%). Mean ages and/or percentages of females across the cohorts aligned with corresponding values for ambulatory HFpEF patients in RCTs (PEP-CHF Study [Cleland e al, 2006], I-PRESERVE Trial [Massie et al, 2008], and the ongoing PARAGON-HF Trial [Solomon et al, 2018]) and a retrospective, consecutive-enrollment outpatient study (Georgiopoulou et al, 2018). Mean

ages were also similar to those reported in real-world studies of ambulatory military veterans with HFpEF and in a Swedish national HF registry (Ather et al, 2012; Eriksson et al, 2018). Mean (SD) BMI for all patients was 31.7 (8.4) (range of means for the four cohorts, 30.9-33.6, all exceeding the "obese" threshold of 30), with the lowest mean BMI reported for the symptomatic DHF without DM cohort and the highest mean BMI reported for the symptomatic DHF with DM cohort. Mean BMIs were similar to or greater than mean values reported in the I-PRESERVE Trial (mean [SD] BMI, 29.6 [5.3] and 29.7 [5.3]) (Massie et al, 2008) and the ongoing PARAGON-HF Trial (mean [SD] BMI, 30.2 [5.0]) (Solomon et al, 2018).

Comorbidities observed during the 24-month period for patients with symptomatic DHF are shown in **Table 4**. The retrospective data review indicated a comorbidity if a patient had one or

TABLE 4 | Observed Comorbidities in Patients with Symptomatic DHF

	Patients with Symptomatic DHF				
COMORBIDITIES n(%)	All N=30,161	with DM N=9,158	w/o DM N=21,003	with HTN N=13,168	w/o HTN N=16,993
Anemia	3,444 (11.4)	1,529 (16.7)	1,915 (9.1)	2,133 (16.2)	1,311 (7.7)
Atrial fibrillation, Arrhythmia	7,724 (25.6)	2,440 (26.6)	5,284 (25.2)	4,368 (33.2)	3,356 (19.7)
Chronic obstructive pulmonary disease	1,851 (6.1)	786 (8.6)	1,065 (5.1)	933 (7.1)	918 (5.4)
Coronary artery disease	2,276 (7.5)	1,036 (11.3)	1,240 (5.9)	1,305 (9.9)	971 (5.7)
DM with or w/o complications	9,158 (30.4)	9,158 (100.0)	0 (0.0)	5,455 (41.4)	3,703 (21.8)
Hyperlipidemia	8,995 (29.8)	4,253 (46.4)	4,742 (22.6)	6,511 (49.4)	2,484 (14.6)
HTN	13,167 (43.7)	5,455 (59.6)	7,712 (36.7)	13,167 (100.0)	0 (0.0)
Myocardial infarction	257 (0.9)	116 (1.3)	141 (0.7)	171 (1.3)	86 (0.5)
Obesity	4,836 (16.0)	2,365 (25.8)	2,471 (11.8)	2,953 (22.4)	1,883 (11.1)
Obstructive sleep apnea	2,665 (8.8)	1,322 (14.4)	1,343 (6.4)	1,614 (12.3)	1,051 (6.2)
Peripheral vascular disease	2,455 (8.1)	1,161 (12.7)	1,294 (6.2)	1,341 (10.2)	1,114 (6.6)
Renal dysfunction, Chronic kidney disease	2,093 (6.9)	944 (10.3)	1,149 (5.5)	1,343 (10.2)	750 (4.4)
Valvular heart disease	8 (0.0)	2 (0.0)	6 (0.0)	6 (0.0)	2 (0.0)

Abbreviations: DHF=diastolic heart failure, DM=diabetes mellitus, w/o=without, HTN=hypertension.

more visits during the observation period with a diagnosis for the condition, regardless of when the condition was first diagnosed. For all patients, the most commonly occurring comorbidities were HTN (43.7%), DM (30.4%), hyperlipidemia (29.8%), atrial fibrillation/other arrhythmias (25.6%), and obesity (16.0%). HTN has been shown to be the most frequently occurring comorbidity among patients with HFpEF in RCTs (Cleland et al, 2006; Massie et al, 2008; Solomon et al, 2018) and in real-world studies (Ather et al, 2012; Eriksson et al, 2018; Georgiopoulou et al, 2018). With the exception of atrial fibrillation/arrhythmia and myocardial infarction, comorbidities appeared to occur more frequently in patients with symptomatic DHF with DM than in patients with symptomatic DHF without DM. A greater percentage of symptomatic DHF patients with DM had a diagnosis of HTN than DHF patients without DM (59.6% vs 36.7%). Additionally, 46.4% of patients with symptomatic DHF with DM had a diagnosis of hyperlipidemia compared with 22.6% of patients with DHF without DM.

TABLE 5 | Prescription Medication Summary for Patients with Symptomatic DHF

MEDICATION SUMMARY, NO. PATIENTS (%)	Patients with Symptomatic DHF				
	All N=30,161	**with DM** N=9,158	**w/o DM** N=21,003	**with HTN** N=13,168	**w/o HTN** N=16,993
PRELOAD REDUCERS	30,161 (100.0)	9,158 (100.0)	21,003 (100.0)	13,168 (100.0)	16,993 (100.0)
Loop diuretics	24,149 (80.1)	7,542 (82.4)	16,607 (79.1)	10,755 (81.7)	13,394 (78.8)
Aldosterone receptor antagonists	5,241 (17.4)	1,589 (17.4)	3,652 (17.4)	2,087 (15.8)	3,154 (18.6)
Other potassium-sparing diuretics	40 (0.1)	17 (0.2)	23 (0.1)	16 (0.1)	24 (0.1)
Thiazide diuretics & carbonic anhydrase inhibitors	6,404 (21.2)	1,984 (21.7)	4,420 (21.0)	2,716 (20.6)	3,688 (21.7)
VASODILATORS	4,137 (13.7)	1,735 (18.9)	2,402 (11.4)	2,114 (16.1)	2,023 (11.9)
AFTERLOAD REDUCERS	15,582 (51.7)	5,369 (58.6)	10,213 (48.6)	7,143 (54.2)	8,439 (49.7)
Angiotensin Converting Inhibitors	7,818 (25.9)	2,706 (29.5)	5,112 (24.3)	3,633 (27.6)	4,185 (24.6)
Angiotensin II receptor blockers	7,996 (26.5)	2,808 (30.7)	5,188 (24.7)	3,676 (27.9)	4,320 (25.4)
BETA-BLOCKERS	19,881 (65.7)	6,508 (71.1)	13,303 (63.3)	9,252 (70.3)	10,559 (62.1)
SGLT2 INHIBITOR	483 (1.6)	307 (3.4)	176 (0.8)	193 (1.5)	290 (1.7)
SACUBITRIL/VALSARTAN	716 (2.4)	210 (2.3)	506 (2.4)	222 (1.7)	494 (2.9)

Abbreviations: DHF=diastolic heart failure, DM=diabetes mellitus, w/o=without, HTN=hypertension.

A summary of selected medications is shown in **Table 5**. As a requirement for study entry, all patients had written prescriptions for or documented use of diuretic medications. The percentage of patients with prescriptions for or documented use of medications within the category of preload reducers was highest for loop diuretics (80.1%), followed by thiazide diuretics and carbonic anhydrase inhibitors (21.2%), and aldosterone receptor antagonists (17.4%). Approximately one-half of patients had prescriptions for or documented use of afterload reducers (i.e., ACEIs [25.9%] and ARBs [26.5%]). The percentage of patients with prescriptions for or documented use of beta-blockers was 65.7%.

During the 24-month period, 483 patients (1.6%) had written prescriptions for or documented use of SGLT2 inhibitors. Approximately two-thirds of these patients (n=307 [63.6%]) had a diagnosis of DM. A total of 716 patients (2.4%) had written prescriptions for or documented use of sacubitril/valsartan. Of these, 222 patients (31.0%) had a diagnosis of HTN.

DISCUSSION

Because there are few effective treatments and minimal evidence based guidance, management of HFpEF is directed toward reducing volume overload, controlling blood pressure, and treating comorbidities. Improving exercise tolerance and managing chronic disease through structured care programs and initiatives promoting health and wellness literacy are also recommended. Reduction or control of symptoms, improvement in quality of life, and prevention of hospitalization and premature death are chief aims of therapy; however, no completed studies to date have demonstrated reductions in mortality (Yancy et al, 2013; Bozkurt, 2018).

This retrospective analysis demonstrates how de-identified ambulatory patient data from an EHR platform, in this instance Practice Fusion from Veradigm, may be used to generate actionable and meaningful RWE. Several findings were notable: that mean BMI values for all symptomatic DHF cohorts exceeded the threshold for Class 1 obesity, that the highest mean BMI was reported for the cohort with comorbid DM, and that multiple comorbidities appeared to occur more frequently in the patients with DM cohort than in the patients without DM cohort. Comorbidities were indicated if a patient had one or more visits during the 24-month observation period with a diagnosis for a condition, regardless of when the condition was first diagnosed. A higher percentage of symptomatic DHF patients with DM had a diagnosis of HTN than DHF patients without DM (59.6% vs 36.7%). These real-world findings closely align with findings from large-scale RCTs, in which patients with HFpEF and comorbid DM were reported to have higher BMIs and generally higher rates or prevalence of HTN than patients without comorbid DM (MacDonald et al, 2008; Aguilar et al, 2010; Lindman et al, 2014; Kristensen et al, 2017).

Sacubitril/valsartan has been recommended as a possible choice of antihypertensive agent in patients with HFpEF (Yancy et al, 2017). A recent RCT that compared sacubitril/valsartan with an ARB (olmesartan) alone demonstrated the superiority of sacubitril/valsartan in reducing central aortic and brachial pressures in elderly clinic and ambulatory patients with stiff arteries and systolic hypertension (Williams et al, 2017). Interestingly, in the present analysis, most patients with prescriptions for or documented use of sacubitril/valsartan did not have comorbid HTN. A consensus

report (US and European) recommends treatment with SGLT2 inhibitors for T2DM patients with atherosclerotic disease "in whom HF coexists or is of special concern" (Davies et al, 2018). In this analysis, approximately two-thirds of patients with prescriptions for or documented use of SGLT2 inhibitors had a diagnosis of comorbid DM.

Comorbidities such as obesity, DM, and HTN figure prominently in the conceptualization of HFpEF as a disorder of phenotypic heterogeneity and multi-factorial pathophysiology (Upadhya and Kitzman, 2017). Of interest is obesity-related HFpEF with comorbid DM, hyperlipidemia, or other metabolic disorders, which has been identified as a distinct HFpEF phenotype arising from overproduction of aldosterone, neprilysin, and inflammatory cytokines from adipocytes (Packer and Kitzman, 2018). Mineralocorticoid receptor antagonists, neprilysin inhibitors, and SGLT2 inhibitors, which inhibit plasma volume expansion and pro-inflammatory and pro-fibrotic processes, may prove useful in treating this important phenotype (Packer and Kitzman, 2018).

Diagnosis of HFpEF minimally requires careful evaluation of clinical signs and symptoms of heart failure, evidence of structural abnormalities or diastolic dysfunction, and documentation of ejection fraction (LVEF >50%). In the retrospective study, selection of patients was based on International Classification of Disease-Ninth Revision (ICD-9) codes encompassing probable DHF (e.g., diastolic, acute on chronic diastolic, combined systolic and diastolic) and symptomatic evidence, specifically, written prescriptions for or documented use of diuretics. These diagnoses and prescription data are available in the structured fields of de-identified patient records. Evolving natural language processing (NLP) capability of EHRs may enable efficient data capture and transformation of patient information stored as free text within semi-structured or unstructured data fields. For patients with HFpEF, such de-identified data may include NYHA functional classification, left ventricular ejection fraction, and hemodynamic parameters; these may be found in provider notes on patient history, examination, and progress; from consultation notes and discharge summaries; and from echocardiographic, nuclear medicine, and cardiac catheterization descriptive reports to generate inclusive and specific patient cohorts for supporting clinical research and in guiding clinical management and quality improvement initiatives (Nath et al, 2016; Patel et al, 2018; Udelsman et al, 2019). Development of definitive cohorts is especially important for HFpEF given the phenotypic heterogeneity that may have confounded the results of some clinical trials.

CONCLUSION

A retrospective data review using de-identified patient data from an EHR platform Practice Fusion, from Veradigm, demonstrates how RWE aligns with findings from RCTs and may provide insights regarding HFpEF. RWE may be complementary to findings from RCTs that are currently evaluating SGLT2 inhibitors and ARNI in patients with HFpEF. Future studies that leverage RWD and RWE from electronic health information platforms may offer insight into hospitalizations, quality of life, and survival in well-defined HFpEF phenotypic cohorts.

REFERENCES

Aguilar D, Deswai A, Ramasubbu K, et al. Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus. Am J Cardiol 2010;105(3):373-377.

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. JAMA 2002;288(23):2981-2997.

Altara R, Giordano M, Norden ES, et al. Targeting obesity and diabetes to treat heart failure with preserved ejection fraction. Front Endocrinol 2017;8:160. doi: 10.3389/fendo.2017.00160

Ather S, Wenyaw C, Bozkurt B, et al. Impact of non-cardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59(11):998-1005.

Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. Diabetes Care 2017;40(5):706-714.

Baar MJB, van Ruiten CC, Muskiet MHA, et al. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care 2018;41(8):1543 1556. doi: 10.2337/dc18-0588.

Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887-1898.

Boehringer Ingelheim. Initial results from EMPRISE real-world evidence study show Jardiance was associated with reduced risk for hospitalization for heart failure compared with DPP-4 inhibitors in people with type 2 diabetes with and without cardiovascular disease. https://www.boehringer-ingelheim.us/press-release/initial-results-emprise-real-world-evidence-study-show-jardiance-was-associated
Accessed 2019 Mar 3.

Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart Journal 2011;32:670-679.

Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes of the heart failure syndrome. Circulation 2011;123(18):2006-2014. doi:10.1161/CIRCULATIONAHA.110.954388.

Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2014;11:507-515.

Borlaug, BA. Pathophysiology of heart failure with preserved ejection fraction. 2018; https://www.uptodate.com/contents/pathophysiology-of-heart-failure-with-preserved-ejection-fraction Accessed 2019 Feb 22.

Borlaug, BA. Clinical manifestation and diagnosis of heart failure with preserved ejection fraction. 2019; https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-heart-failure-with-preserved-ejection-fraction
Accessed 2019 Feb 22.

Bozkurt B, Aguilar D, Deswal A, et al. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. Circulation 2016;134:e535-e578.

Bozkurt B. What is new in heart failure management in 2017? Update on ACC/AHA heart failure guidelines. Curr Cardiol Rep 2018;20(6):39. doi: 10.1007/s11886-018-0978-7.

Camm AJ, Fox KAA. Strengths and weaknesses of 'real world' studies involving non-vitamin K antagonist oral anticoagulants. Open Heart 2018;5(1):e000788. doi: 10.1136/openhrt-2018-000788. eCollection 2018.

Cleland JGF, Tendera M, Adamus J, et al. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. Eur Heart J 2006;27:2338-2345.

Corrigan-Curry J, Sacks L, Woodcock J. Real-world evidence and real-world data for evaluating drug safety and effectiveness. J Am Med Assoc 2018;320(9):867-868.

Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J 2015;36(23):1437-1444.doi: 10.1093/eurheartj/ehv010.

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41(12):2669-2701. doi.org/10.2337/dci18-0033.

Drescher CS, Desai AS. Sacubitril/Valsartan combination drug: 2 years later. Am Coll Cardiol 2017; https://www.acc.org/latest-in-cardiology/articles/2017/03/03/09/30/sacubitril-valsartan-combination-drug
Accessed 2019 Mar 5.

Dunlay SM, Redfield MM, Weston SA, et al. Hospitalizations after heart failure diagnosis: a community perspective. J Am Coll Cardiol 2009;54(18):1695-1702.

Ericksson B, Wändell P, Dahlström U, et al. Comorbidities, risk factors and outcomes in patients with heart failure and an ejection fraction of more than or equal to 40% in primary care- and hospital care-based outpatient clinics. 2018;36(2):207–215. doi: 10.1080/02813432.2018.1459654.

Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME trial. Eur Heart J 2018;39(5):363-370. doi: 10.1093/eurheartj/ehx511.

Georgiopoulou VV, Velayati A, Burkman G, et al. Comorbidities, sociodemographic factors, and hospitalizations in outpatients with heart failure and preserved ejection fraction. Am J Cardiol 2018;121:1207-1213.

Gori M, Senni M, Gupta DK, et al. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. Eur Heart J 2014;35(48):3442-3451.

Gori M, D'Elia E, Senni M. Sacubitril/valsartan therapeutic strategy in HFpEF: Clinical insights and perspectives. Int J Cardiol 2018;281:158–165. doi: 10.1016/j.ijcard.2018.06.060.

Harper AR, Patel HC, Lyon AR. Heart failure with preserved ejection fraction. Clin Med 2018;18(2):s24 s29.

Hwang S-J, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63(25):2817-2827.

Kosiborod M, Cavender MA, Fu AZ, et al. Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation 2017;136(3):249-259. doi: 10.1161/CIRCULATIONAHA.117.029190.

Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. JAMA 1997;278(3):212-216.

Kristensen SL, Mogensen UM, Jhund PS, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve trial (Irbesartan in Heart Failure with Preserved Ejection Fraction). Circulation 2017;135(8):724-735.

Lexicon Pharmaceuticals. FDA to review Zynquista™ (sotagliflozin) as potential treatment for type 1 diabetes. 2018; http://www.lexpharma.com/media-center/news/673-fda-to-review-zynquista-sotagliflozin-as-potential-treatment-for-type-1-diabetes
Accessed 2019 Mar 3.

Lexicon Pharmaceuticals. Type 2 Diabetes. http://www.lexpharma.com/pipeline/sotagliflozin/t2d-clinical-results
Accessed 2019 Mar 3.

Lindman BR, Davila-Roman VG, Mann DL, et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. J Am Coll Cardiol 2014;64:541-549.

Lund LH, Oldgren J, James S. Registry-based pragmatic trials in heart failure: current experience and future directions. Curr Heart Fail Rep 2017;14:59-70.

Lytvyn Y, Bjornstad P, Udell JA, et al. Sodium Glucose Cotransporter-2 Inhibition in Heart Failure: Potential Mechanisms, Clinical Applications, and Summary of Clinical Trials. Circulation 2017;136(17):1643-1658. doi: 10.1161/CIRCULATIONAHA.117.030012.

MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM). Eur Heart J 2008;29(11): 1377-1385.

Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018;137(4):323-334. doi: 10.1161/CIRCULATIONAHA.117.032038.

Martin N, Manoharan K, Thomas J, et al. Cochrane Database Syst Rev. 2018;6: CD012721. doi: 10.1002/14651858.CD012721.pub2.

Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-2467.

Mayo Clinic. Heart failure with preserved ejection fraction (HFpEF): more than diastolic dysfunction. https://www.mayoclinic.org/medical-professionals/cardiovascular-diseases/news/heart-failure-with-preserved-ejection-fraction-hfpef-more-than-diastolic-dysfunction/mac-20430055
Accessed 2019 Feb 15.

McHugh K, DeVore AD, Wu J, et al. Heart failure with preserved ejection fraction and diabetes: JACC state-of-the-art review. J Am Coll Cardiol 2019;73(5):602-611.

McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004. doi: 10.1056/NEJMoa1409077.

Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol 2014;64(21):2281-2293.

Mohammed SF, Majure MD, Redfield MM. Zooming in on the microvasculature in heart failure with preserved ejection fraction. Circ Heart Failure 2016;9(7). doi:10.1161/CIRCHEARTFAILURE.116.003272.

Nath C, Albaghdadi MS, Jonnalagadda SR. A natural language processing tool for large-scale data extraction from echocardiography reports. PLoS One. 2016;11(4):e0153749. doi: 10.1371/journal.pone.0153749.

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-657. doi: 10.1056/NEJMoa1611925.

Packer M, Anker SD, Butler J, et al. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. JAMA Cardiol 2017;2(9):1025-1029. doi: 10.1001/jamacardio.2017.2275.

Packer M. Should we be combining GLP-1 receptor agonists and SGLT2 inhibitors in treating diabetes? Am J Med. 2018 May;131(5):461-463. doi: 10.1016/j.amjmed.2017.11.052.

Packer M, Kitzman DW. Obesity-related heart failure with a preserved ejection fraction: the mechanistic rationale for combining inhibitors of aldosterone, neprilysin, and sodium-glucose transporters. JACC Heart Fail 2018;6(8):633-639. doi: 10.1016/j.jchf.2018.01.009.

Patel YR, Robbins JM, Kurgansky KE, et al. Development and validation of a heart failure with preserved ejection fraction cohort using electronic medical records. BMC Cardiovascular Disorders 2018;128. doi: 10.1186/s12872-018-0866-5.

Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62(4):263-271.

Practice Fusion, 2019; https://www.practicefusion.com/about/
Accessed 2019 Mar 26.

Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus. Circulation 2018;138(5):458-468. doi: 10.1161/CIRCULATIONAHA.118.034222.

Redfield MM. Heart failure with preserved ejection fraction. New Engl J Med 2016;375:1868-1877.

Riggs K, Hiba A, Taegtmeyer H, et al. The use of SGLT-2 inhibitors in type 2 diabetes and heart failure. Metab Syndr Relat Disord 2015;13(7):292-297. doi: 10.1089/met.2015.0038.

Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 2016;143(1):73-90. doi:10.1161/CIRCULATIONAHA.116.021884.

Sherman RE, Anderson SA, Dal Pan GJ. Real-world evidence—what is it and what can it tell us? N Engl J Med 2016;375:2293-2297.

Solomon SD, Zile M, Pieske B, et al. The angiotensin neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387-1395.

Solomon SD, Rizkala AE, Lefkowitz MP, et al. Baseline characteristics of patients with heart failure and preserved ejection fraction in the PARAGON-HF Trial. Circulation Heart Failure 2018;11. doi.org/10.1161/CIRCHEARTFAILURE.118.004962

Tam MC, Lee R, Cascino TM, et al. Current perspectives on systemic hypertension in heart failure with preserved ejection fraction. Curr Hypertens Rep 2017;19(2). doi:10.1007/s11906-017-0709-2.

Taylor RS, Davies EJ, Dalal HM, et al. Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies. Int J Cardiol 2012;162(1):6-13.

Udelsman B, Chien I, Ouchi K, et al. Needle in a haystack: natural language processing to identify serious illness. J Palliat Med 2019;22(2):179-182. doi: 10.1089/jpm.2018.0294.

Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. BMJ 2018;363:k4365.

Upadhya B, Kitzman D. Management of heart failure with preserved ejection fraction: current challenges and future directions. Am J Cardiovasc Drugs 2017;17(4):283-298.

Upadhya B, Pisani B, Kitzman DW. Evolution of a geriatric syndrome: pathophysiology and treatment of heart failure with preserved ejection fraction. J Am Geriatr Soc 2017;65(11): 2431-2440.

US Food and Drug Administration. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes: study links Jardiance to improved survival in patients with type 2 diabetes with cardiovascular disease. 2016; https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm531517.htm
Accessed 2019 Mar 2.

US Food and Drug Administration. Framework for FDA's Real-World Evidence Program. 2018; https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf
Accessed 2019 Mar 12.

US National Library of Medicine. Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF). 2013; https://clinicaltrials.gov/ct2/show/NCT01920711
Accessed 2018 Dec 11.

Vaduganathan M, Claggett BL, Chatterjee NA, et al. Sudden death in heart failure with preserved ejection fraction: a competing risk analysis from the TOPCAT trial. JACC Heart Fail 2018;6(8):653-661. doi: 10.1016/j.jchf.2018.02.014.

Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 2017;60:215-225. doi 10.1007/s00125-016-4157-3.

Williams B, Cockcroft JR, Kario K, et al. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension: the PARAMETER Study. Hypertension 2017;69(3):411-420. doi: 10.1161/HYPERTENSIONAHA.116.08556.

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes N Engl J Med 2019;380:347-357. doi:10.1056/NEJMoa1812389

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:1810-1852.

Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2016;134:e282-e293.

Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-e161.

Yancy CW, Januzzi JL, Allen LA, et al. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction. J Am Coll Cardiol 2018;71(2):201-230.

Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. J Am Coll Cardiol 2018;72(15):1845-1855.

Zelniker TA, Wiviott SD, Raz I, et al. SGLT-2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-39.

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720.

Zouein FA, de Castro Bras LE, da Costa DV, et al. Heart failure with preserved ejection fraction: emerging drug strategies. J Cardiovasc Pharmacol 2013;62(1):13-21. doi:10.1097/FJC.0b013e31829a4e61.

ABOUT VERADIGM™

Veradigm is an integrated data systems and services company that combines data-driven clinical insights with actionable tools for clinical workflow, research, analytics and media. Our solutions are designed to help key healthcare stakeholders to improve the quality, efficiency, and value of healthcare technology partners, and most importantly, the patients they serve.

We are dedicated to simplifying the complicated healthcare system with next-generation healthcare solutions. This is how we are transforming health, insightfully.

veradigm™

FOR MORE INFORMATION
VISIT US ONLINE

veradigmhealth.com