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STATE-OF-THE-ART REVIEW

The Role of Coronary Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of the 64 million people living globally with heart failure and is associated with significant morbidity and mortality. Therapeutic options for HFpEF remain limited, largely due to an incomplete understanding of its complex pathophysiology. A growing body of evidence has highlighted coronary microvascular dysfunction (CMD) as a driver of both the development and progression of HFpEF. CMD is prevalent in up to 75% of HFpEF patients in the absence of obstructive epicardial disease and is associated with increased rates of rehospitalization and mortality. Despite this, CMD is often underdiagnosed in this patient population. A more comprehensive understanding of the link between HFpEF and CMD could provide novel targeted therapeutic strategies. This review aims to elucidate the prognostic significance of CMD in HFpEF, pathophysiologic links between these 2 conditions, and the role of CMD in current and future therapeutic interventions. (JACC Adv. 2025;4:102345)

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure (HF) diagnoses and is associated with significant morbidity and mortality.[1] HFpEF is a complex and heterogeneous entity encompassing diverse underlying pathophysiological mechanisms resulting in significant challenges in treatment.[2] A growing body of evidence

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ABBREVIATIONS AND ACRONYMS

ANOCA = angina with nonobstructive coronary artery disease

CAD = coronary artery disease

CBF = coronary blood flow

CFR = coronary flow reserve

CMD = coronary microvascular dysfunction

Ees = end-systolic elastance

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HMR = hyperemic microvascular resistance

ICFT = invasive coronary functional testing

IL = interleukin

IMR = index of microvascular resistance

INOCA = ischemia with nonobstructive coronary artery disease

LV = left ventricular

PET = positron emission tomography

TNF = tumor necrosis factor

VAC = ventriculoarterial couplinge

implicates coronary microvascular dysfunction (CMD) as a critical and highly prevalent comorbidity in HFpEF. CMD is predominantly characterized by impaired vasodilation or enhanced constriction in the coronary microcirculation through endothelial-independent and endothelial dependent mechanisms, which frequently coexist. CMD is prevalent in 75% of patients with HFpEF and correlates with higher rates of rehospitalization, mortality, and reduced quality of life for these patients.[3] This frequent co-occurrence suggests that CMD may represent a significant pathophysiological mechanism contributing to the adverse clinical outcomes observed in patients with HFpEF, although a causal relationship has not been established. In this review, we summarize contemporary data regarding the epidemiology, pathophysiology, diagnosis, prognostic implication, and potential therapeutic strategies for CMD in patients with HFpEF (**Central Illustration**).

HIGHLIGHTS

- The prevalence of CMD in patients with HFpEF and nonobstructive coronary artery disease is high.
- CMD is an independent predictor for future adverse outcomes in the HFpEF population.
- CMD and HFpEF share pathophysiological links, although a direct causal relationship remains unproven.
- Comprehensive CMD assessment in HFpEF can improve risk stratification and guide targeted therapeutic strategies.

EPIDEMIOLOGY

HFpEF incidence and prevalence have increased in tandem with the increasing age and prevalence of comorbidities accounting for nearly half of all HF cases. The estimated incidence of new-onset HFpEF is 26.9 cases per 10,000 person-years.[4] The incidence of HFpEF is nearly 2:1 incidence in women compared to men.[5]

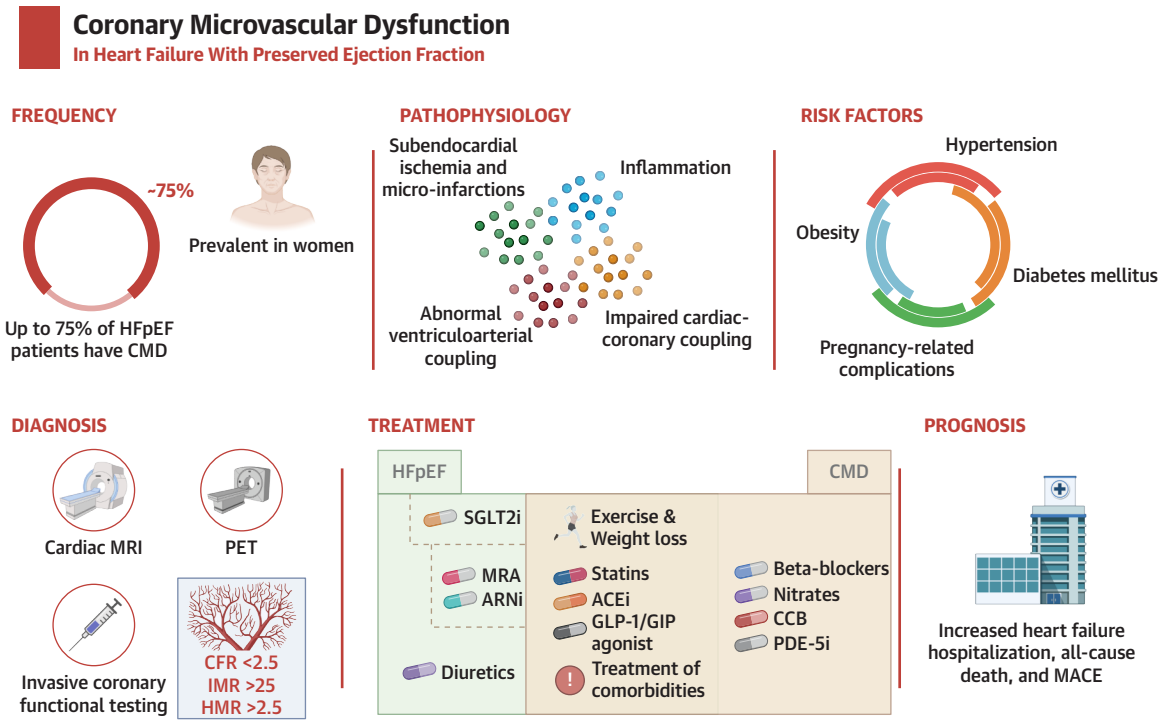
CMD is increasingly recognized in a spectrum of cardiovascular diseases including angina/ischemia with nonobstructive coronary artery disease (CAD) (ANOCA/INOCA), myocardial infarction with nonobstructive CAD, refractory angina post-revascularization, and cardiomyopathies including HFpEF. CMD is the predominant cause of angina and ischemia in ANOCA/INOCA patients and is diagnosed using invasive coronary functional testing (ICFT) and noninvasive modalities.[6]

CMD is characterized by abnormal coronary flow reserve (CFR $\leq$2.5) and is further classified into structural or functional CMD based on abnormal index of microvascular resistance (IMR $\geq$25 U) or hyperemic microvascular resistance (HMR >2.5 mm Hg cm^{-1} s). Structural CMD is characterized by abnormal CFR and abnormal IMR/HMR due to architectural changes in the microvasculature such as capillary rarefaction and arteriolar obliteration. Functional CMD refers to abnormal CFR in the presence of normal IMR/HMR and is related to an increased coronary resting flow due to an increased resting myocardial oxygen demand or disordered coronary autoregulation. CFR is the ratio of coronary flow during hyperemia induced by adenosine to the coronary flow at rest and it can be measured using both Doppler and thermodilution methods. In addition, surrogates of CFR can be measured noninvasively with adenosine vasodilatory positron emission tomography (PET), cardiac magnetic resonance imaging, and Doppler echocardiography. IMR is measured with the thermodilution method and HMR with the Doppler wire method.

ICFT allows for the complete assessment of CMD and vasomotor disorders including coronary endothelial dysfunction, microvascular spasm, and epicardial spasm which require intracoronary acetylcholine. In this review we focus on the link between HFpEF and both CMD and coronary endothelial dysfunction as the relationship with vasospasm remains poorly understood.

In a meta-analysis of 10 studies, 71% of HFpEF patients had comorbid CMD.[7] In the PROMIS-HFpEF (PRevalence Of MIcrovascular dySfunction in Heart Failure with Preserved Ejection Fraction) trial 75% of HFpEF patients had CMD which was associated with markers of volume overload severity and right ventricular strain.[3] In a recent study, the prevalence of CMD was similar in HFpEF and heart failure with reduced ejection fraction; however patients with HFpEF had higher IMR and lower CFR, suggestive of structural CMD.[8] Rush et al.[9] reported that 66% and 24% of hospitalized patients with HFpEF undergoing ICFT were found to have CMD and coronary endothelial dysfunction, respectively. Similarly, Ahmad et al.[10] reported that patients with HFpEF had a significantly lower CFR (2.5 $\pm$ 0.6 vs 3.2 $\pm$ 0.7; P = 0.0003) and a median %coronary blood flow

CENTRAL ILLUSTRATION Coronary Microvascular Dysfunction in HFpEF



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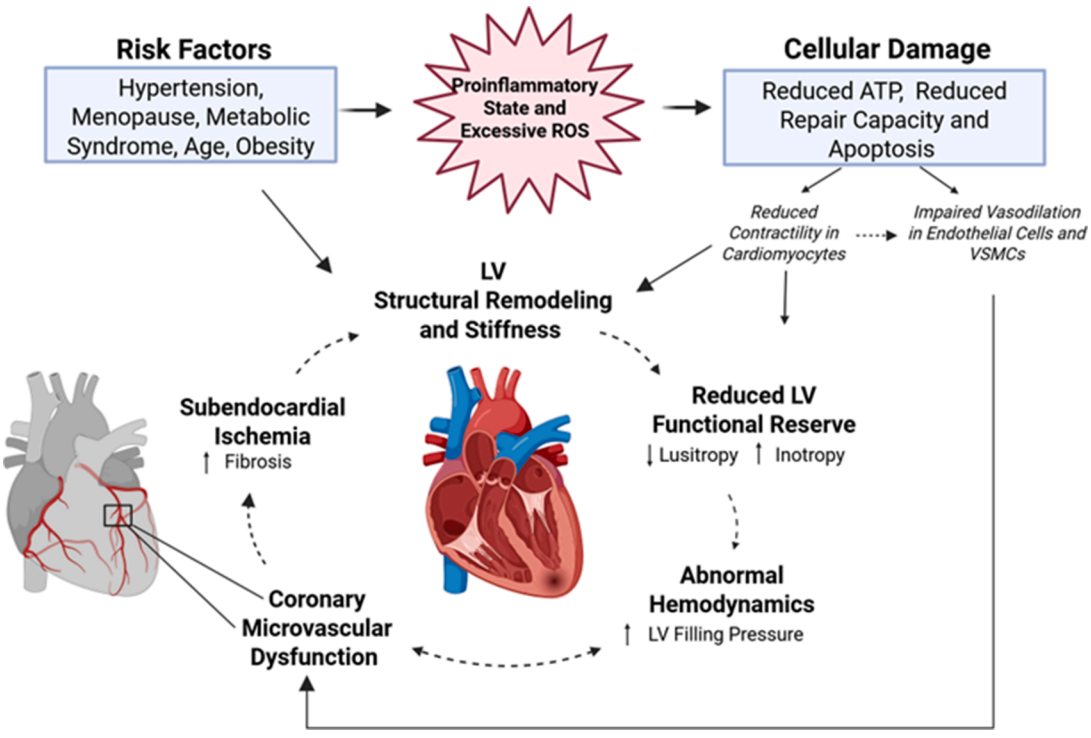
Summary of the prevalence, risk factors, pathophysiological mechanisms, diagnostic and therapeutic modalities and prognosis associated with CMD and HFpEF. ACEi = angiotensin-converting enzyme inhibitor; ARNi = angiotensin receptor-neprilysin inhibitor; CCB = Calcium channel blockers; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; GLP-1/GIP = Glucagon-Like Peptide-1/Glucose-dependent insulinotropic polypeptide; HFpEF = heart failure with preserved ejection fraction; HMR = hyperemic microvascular resistance; IMR = index of microvascular resistance; MACE = major adverse cardiovascular event; MRI = magnetic resonance imaging; PDE-5i = Phosphodiesterase-5 inhibitors; PET = positron emission tomography; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

(CBF) increase in response to intracoronary acetylcholine (1 [−35; 34] vs 64 [−4; 133]; P = 0.002) compared to patients without HFpEF.Taqueti et al.[11] first highlighted the prognostic significance of CMD in HFpEF in a prospective study of 201 symptomatic patients without a history of obstructive CAD with CFR <2 by vasodilatory PET perfusion. CMD was independently associated with a 2-fold higher risk of HFpEF hospitalizations (HR: 2.47; 95% CI: 1.09-5.62) and major adverse cardiovascular event (HR: 2.38; 95% CI: 1.21-4.67) in a median follow-up of 4.1 years.[11] Mohammed et al.[12] reported CMD in 64.2% of HFpEF patients, defined as IMR ≥25 and showed that CMD was independently predictive of the higher risk of the composite HF readmissions and all-cause death (HR: 2.93; 95% CI: 1.28-6.70) and a strong prognosticator (AUC: 0.767; 95% CI: 0.677-0.858). Although these studies report the high coexistence of CMD and coronary endotelial dysfunction in HFpEF patients and the associations with worse prognosis, causality remains unknown. Their results are also limited by the smaller sample size, differences in definitions of CMD and methods of assessment (invasive vs noninvasive), and cohorts predominanlty from Europe and North America which limits generalizability.

PATHOPHYSIOLOGY OF CMD AND HFpEF

The frequent coexistence of multiple mechanistic and pathophysiological links between CMD and HFpEF underscores the interplay between these conditions (Figure 1).[3] Although the precise causal vs associative role of CMD in the pathophysiology of HFpEF remains a subject of ongoing investigation, several potential mechanistic links have been proposed. The inherent heterogeneity of HFpEF is evidenced by the identification of 5 distinct phenotypic

FIGURE 1 Pathophysiological Links Between Coronary Microvascular Dysfunction and HFpEF



ATP = adenosine triphosphate; LV = left ventricular; ROS = reactive oxygen species; VSMCS = vascular smooth muscle cells.

clusters, driven by a confluence of comorbidities (including obesity, hypertension, coronary artery disease, and CMD), cardiac structural remodeling, and disparate inflammatory and molecular profiles. Notably, sex-specific differences exist in HFpEF pathophysiology.[1] Compared to men, women with HFpEF have smaller left ventricular (LV) chamber dimensions and a pattern of concentric rather than eccentric hypertrophy, alongside higher myocardial blood flow and oxygen consumption.[13] Although CMD predisposes to HFpEF in both sexes, emerging evidence suggests that inflammation may be a contributor of CMD in men, whereas abnormalities in ventricular remodeling and fibrosis appear to play a more crucial role in women.[14]

SUBENDOCARDIAL ISCHEMIA. At a pathophysiological level, CMD is characterized by structural and/or functional abnormalities within the coronary microvasculature, affecting both endothelial-dependent and endothelial-independent mechanisms. These alterations result in an inappropriate augmentation of CBF relative to myocardial oxygen demand, ultimately leading to myocardial ischemia.[15] Notably, patients with HFpEF often exhibit a decreased coronary microvascular density, a phenomenon known as microvascular rarefaction, which may arise from the loss or impaired regeneration of these small vessels.[16] CMD or microvascular rarefaction can result in repeated episodes of microinfarction, subtle areas of myocardial damage that can be detected using advanced cardiac imaging techniques such as cardiac magnetic resonance imaging with late gadolinium enhancement or PET perfusion imaging.[17] These microinfarctions can lead to subendocardial ischemia and adverse cardiac remodeling, affecting myocardial tension and compliance. These microinfarctions thereby contribute to the development and progression of impaired diastolic function, a hallmark of HFpEF.

Intriguingly, HFpEF and CMD share similar mechanistic underpinnings. Insufficient adenosine triphosphate production required for normal myocardial relaxation results in the inability to adequately augment CBF in response to stress.[18] It is plausible that CMD acts as a significant contributor to the development of HFpEF through ischemia-driven maladaptive changes in the myocardium.

Conversely, the diastolic dysfunction associated with HFpEF may itself perpetuate subendocardial ischemia and contribute to the coexistence and progression of CMD, suggesting a potential bidirectional relationship between these 2 conditions.

CARDIAC-CORONARY COUPLING AND IMPAIRED LUSITROPY. Cardiac-coronary coupling, the dynamic and tightly regulated relationship between LV contraction and relaxation and intramyocardial CBF, is a primary determinant of myocardial perfusion. In healthy individuals, exercise triggers a relative increase in accelerating flow waves, largely due to the decompression of the microcirculation during ventricular diastole. However, in patients with LV diastolic dysfunction, there is a predominance of decelerating flow waves within the coronary microvasculature, resulting from both the blunted transmission of accelerating waves from the aorta and the accentuated compression of microvessels during the isovolumetric contraction phase of the cardiac cycle.[19] Consequently, the impaired LV relaxation characteristic of HFpEF can disrupt this delicate cardiac-coronary coupling, leading to a blunted CBF response to stress and ultimately predisposing the subendocardium to ischemia.[2] Factors such as subendocardial ischemia itself, impaired nitric oxide (NO) signaling, LV hypertrophy, and fibrosis can all contribute to impaired lusitropy resulting in diastolic dysfunction.[20] This impaired relaxation, in turn, can reduce early diastolic coronary flow, the period of maximal coronary perfusion, thereby creating a "vicious cycle" where reduced flow worsens ischemia, which further impairs relaxation, perpetuating and exacerbating diastolic dysfunction and potentially contributing to the progression of HFpEF.

VENTRICULOARTERIAL COUPLING. The interaction between the LV and the arterial system is known as ventriculoarterial coupling (VAC) and is an important determinant of net cardiovascular function. VAC is most frequently assessed with LV pressure-volume loop as the ratio of arterial elastance (Ea), net arterial load against which the heart ejects blood, to ventricular end-systolic elastance (Ees), LV chamber contractility, and systolic stiffness at the end of systole.[21] In HFpEF abnormal VAC is predominantly driven by arterial hypertension, but as HFpEF progresses the ratio of both arterial elastance and Ees may become insensitive to changes. Therefore, novel VAC markers, such as LV global longitudinal strain and pulse wave velocity have been proposed for more accurate VAC assessment.[21] In acute myocardial infarction patients, Løgstrup et al.[22] reported an independent association between higher osteoprotegrin levels and both higher VAC and impaired CFR, suggesting a pathophysiological link between these. The pathophysiologic role of VAC in link between CMD and HFpEF is likely bidirectional. Subendocardial ischemia in CMD may result in increased LV stiffness resulting in abnormal VAC. Increased arterial stiffness in HFpEF increases pulsatile load and pressure transmission to microvasculature, leading to microvascular damage and impaired vasodilatory reserve and CMD.

INFLAMMATION. A novel paradigm for HFpEF proposes that comorbidities drive myocardial dysfunction and remodeling via coronary microvascular endothelial inflammation.[20] Elevated circulating levels of various inflammatory biomarkers, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, have been consistently observed in HFpEF.[23] Similarly, circulating inflammatory biomarkers (including IL-1, IL-6, TNF-α, soluble TNF receptor 1, and vascular cell adhesion molecule-1) are consistently associated with CMD in patients with ANOCA.[24] Systemic inflammation promotes increased endothelial expression of cell adhesion molecules and selectins, facilitating subendothelial leukocyte migration and the production of reactive oxygen species. These processes, in turn, lead to impairments in NO signaling pathways, endothelial dysfunction, and an increase in arterial stiffness leading to increased arterial elastance in parallel to myocardial stiffening (increased Ees), resulting to abnormal VAC that contributes to progression of HF.

SEX DIFFERENCES. Women tend to have smaller epicardial coronary arteries adjusted for body surface area, higher CBF at rest, and higher endothelial shear stress which predisposes them to diffuse coronary atherosclerosis instead of focal epicardial coronary disease, global reduction of CFR, and development of CMD.[25,26] In a cohort of 434 patients with ANOCA, women had less obstructive epicardial disease but significantly lower CFR (2.69 [IQR: 2.08-3.90] vs 3.20 [IQR: 2.20-4.31]) compared to men.[27]

The prevalence of HFpEF and CMD increases significantly in postmenopausal women.[28] Endogenous estrogen appears to plays a critical role in regulating inflammation, NO signaling, and endothelial function.[29] The decline in estrogen levels during menopause contributes to a state of systemic inflammation, endothelial dysfunction and may partially account for the lower CFR compared to premenopausal women and age-matched men.[30] Among postmenopausal women, a more androgenic circulating sex hormone profile is associated with reduced peripheral endothelial function,[31] and a higher

testosterone/estradiol ratio is associated with a greater risk of HF.[32] In addition, estrogen deficiency is associated with an increased visceral adiposity,[33] which is linked to concentric LV remodeling and reduced exercise tolerance in patients with both CMD and HFpEF.

HORMONAL EFFECTS. Beyond sex hormones, mineralocorticoid receptor (MR) signaling is associated with impaired endothelial function. MR signaling has also been associated with LV hypertrophy, adverse remodeling, diastolic dysfunction, and fibrosis, largely independent of blood pressure.[34]

RISK FACTORS IN HFpEF AND CMD

Hypertension significantly elevates the risk for the codevelopment of both HFpEF and CMD.[17,35] Hypertension predisposes to increased arterial stiffness, development of concentric LV hypertrophy, vascular remodeling of intramural arterioles, and interstitial fibrosis within the myocardium.[29] These structural alterations lead to a reduction in microvascular density and arterial compliance, establishing hypertension as a critical etiological factor for CMD.[25] Beyond its direct impact on the microvasculature, hypertension has also been implicated in augmenting myocardial inflammation, a key process contributing to the subsequent myocardial remodeling characteristic of HFpEF. In postmenopausal women, the strong association between endothelial dysfunction and hypertension is further exacerbated by the loss of the sympathoinhibitor effects of estrogen.[36]

Cardiometabolic risk factors—obesity and diabetes mellitus—are highly prevalent in both HFpEF and CMD, and disproportionately affect women. Excess epicardial adipose tissue leads to insulin resistance, oxidative stress, systemic inflammation resulting in impaired myocardial perfusion and endothelial dysfunction, contributing to CMD; and increases myocardial stiffness, diastolic dysfunction, and left atrial dilation—all established hallmarks of HFpEF.[37] Diabetes mellitus is associated with a 5-fold increased risk of HFpEF in women and 2.4-fold in men[29]; and lower CFR in patients with nonobstructive CAD.[38] Diabetes enhances generation of reactive oxygen species and decreased NO bioavailability, leading to systemic inflammation and CMD. Reduced NO production also contributes to impaired myocardial relaxation and cardiomyocyte hypertrophy, both key features of diastolic dysfunction. Diabetic patients frequently exhibit concentric remodeling of the coronary microvasculature, characterized by vascular wall thickening, reduced luminal diameter, and decreased myocardial capillary density—structural alterations strongly associated with the development of CMD.[39]

Adverse pregnancy outcomes, including hypertensive disorders of pregnancy, preterm birth, and intrauterine growth restriction, are sex-specific risk factors for both CMD and HFpEF. Hypertensive disorders of pregnancy, including pre-eclampsia, are linked to endothelial dysfunction characterized by reduced NO bioavailability and subsequent LV remodeling[29] and HFpEF.[13] Notably, patients with severe preeclampsia exhibit diminished CFR postpartum.[40] Furthermore, impaired inflammatory and coagulation pathways contribute to the development of HFpEF and CMD in women with adverse pregnancy outcomes.[29]

THERAPEUTIC STRATEGIES IN HFpEF AND CMD

The treatment of HFpEF, particularly in patients with concurrent CMD, may necessitate a comprehensive strategy that addresses both conditions (**Table 1**).

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITION. Renin-angiotensin-aldosterone system inhibitors have been studied in several HFpEF trials and they were not associated with the improvement in the reduction of HF hospitalization or death; however, results on sex-specific treatment effects were not reported.[41,42] The WISE (Women's Ischemia Syndrome Evaluation) trial reported in 61 women with INOCA that angiotensin-converting enzyme inhibitor therapy significantly improved CFR and angina.[43]

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS. The angiotensin receptor-neprilysin inhibitor (ARNi) sacubitril-valsartan did not significantly reduce the risk of primary outcome of HF hospitalization and cardiovascular mortality compared to valsartan in the PARAGON-HF (Prospective Comparison of ARNI (angiotensin receptor-neprilysin inhibitor) with ARB (angiotensin receptor blockers) Global Outcomes in Heart Failure with Preserved Ejection Fraction) trial; however significant benefit was suggested in the lower range of ejection fraction (45% to 57%) and in women.[44] The PARALLAX (Prospective Comparison of ARNI vs Comorbidity-Associated Conventional Therapy on Quality of Life and Exercise Capacity) clinical trial showed a significant sex interaction with improvement in walking distance observed in women.[45] Direct activation of natriuretic peptide receptors of cardiac myocyte and cardiac fibroblast by opposing pathologic growth and maladaptive gene expression may explain improved outcomes in

TABLE 1 Therapeutic Strategies and Mechanisms of Action in HFpEF and CMD

Treatment	Primary Target	Summary of Evidence
RAAS inhibition	CMD	↗ Improves CFR and angina in ANOCA patients with CMD × No improvement in HFpEF hospitalization • No studies in HFpEF patients with CMD
Angiotensin receptor-neprilysin inhibitors	HFpEF	↗ Improves function (walking distance) in women with HFpEF • Potential for improvements in HFpEF patients with CMD, no conclusive studies
Mineralocorticoid receptor antagonists	HFpEF	↗ Reduces HFpEF mortality in women, but not men • No studies in CMD or HFpEF patients with CMD
Sodium-glucose cotransporter 2 inhibitors (SGLT2i)	HFpEF	↗ Reduces mortality and hospitalization for HFpEF patients • Improves myocardial flow reserve in T2DM patients • No studies in HFpEF patients with CMD
Statins	HFpEF and CMD	↗ Reduces hospitalization and all-cause mortality in HFpEF patients ↗ Improves CFR in ANOCA patients • No studies in HFpEF patients with CMD
Nitrates	CMD	↗ Improves coronary endothelial dysfunction and angina in ANOCA patients × Null hemodynamic benefits in HFpEF with limited studies
Phosphodiesterase-5 (PDE) inhibitors	CMD	↗ Improvements in CFR in ANOCA population with CMD • Mixed and limited results in HFpEF
Incretins (GLP-1/GIP agonists)	HFpEF	↗ Decreases worsening heart failure and CVD death in HFpEF • No studies in CMD or HFpEF patients with CMD

ANOCA = angina with non-obstructive coronary artery disease; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; CVD = cardiovascular disease; HFpEF = heart failure with preserved ejection fraction.

HFpEF.[46] HFpEF patients with CMD might benefit more from ARNi therapy, since neprilysin inhibition can affect microvascular function independent of NO through enhancement of natriuretic peptide bioavailability in the cardiomyocyte level.[47] The PRISTINE HF trial (NCT 04128891) designed to assess the effect of ARNi on CMD and myocardial fibrosis was never conducted.

MINERALOCORTICOID RECEPTOR ANTAGONISTS. There are notable sex-based differences to treatment of HFpEF with MR antagonists. In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial), spironolactone was associated with reduced all-cause mortality in women with HFpEF but not in men.[48] Recent results from the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) trial showed potentially outsized effect of finerenone in women (rate ratio: 0.78; 95% CI: 0.65-0.95) compared with men (rate ratio: 0.88; 95% CI: 0.74-1.04) with HFpEF.[49] To date, MR antagonists have not been studies in CMD patients.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are the single approved treatment for HFpEF with evidence of improvement in the composite of HF hospitalization and mortality, mainly driven by reduction in HF hospitalizations in diabetic and nondiabetic patients.[50,51] Although the pathophysiologic mechanisms of their benefit are still being investigated, reduction in myocardial glucose toxicity and glucosuric effects improves congestion symptoms in HFpEF patients. The Dapagliflozin improves myocardial flow reserve in patients with type 2 diabetes: the DAPAHEART trial showed beneficial effects of SGLT-2i in myocardial flow reserve in patients with type 2 diabetes mellitus.[52] In animal models SGLT2i improves CMD and coronary endothelial dysfunction.[53] SGLT2i have been shown to reverse endothelial dysfunction via reduction in inflammation and inhibition of excessive reactive oxygen species production which ultimately results in increase in NO production and increase in flow-mediated dilation.[54]

STATINS. Statins have lipid lowering and anti-inflammatory effects that can be of benefit in the therapeutic management of HFpEF and CMD. Statin use in patients with HFpEF without epicardial CAD significantly reduced HF rehospitalization and all-cause mortality[55]; similar to results of prior meta-analyses.[56,57] Mechanisms for benefit in HFpEF include antiremodeling effects of LV hypertrophy, regression of fibrosis, reduced arterial stiffness, and improved endothelial function.[58,59] In patients with CMD statins have been associated with significant improvement of CFR.[60] A trial combining statin with RAAS inhibitor therapy in 19 ANOCA patients found improved markers of oxidative stress and improved quality of life compared with placebo.[61]

NITRATES. NO is the key in the pathophysiology of coronary endothelial dysfunction.[39] Nitrates are first line antianginal treatment in patients with microvascular or epicardial spasm.[62] Administration of oral L-arginine (precursor of NO vasodilator) in ANOCA patients improved coronary endothelial dysfunction and symptomatic scores compared to placebo.[63] NO-donating treatment have been studied in HFpEF with promising results in smaller placebo controlled randomized controlled trials (NO3-rich beetroot juice, infusion of sodium nitrite) but neutral results in larger randomized controlled trials (inhaled nitrites and isosorbide mononitrate).[64] Targeting the NO pathway with nitrates may be beneficial in the CMD-HFpEF phenotype or ischemic HFpEF associated with microvascular or epicardial spasm.

PHOSPHODIESTERASE-5 INHIBITORS. Phosphodiesterase-5-5 inhibitors can increase protein kinase G activity and in animal studies were shown to have beneficial effects on LV structure.[65] However, clinical trials have failed to show any clinical or hemodynamic benefit with sildenafil use[66]; and results on vericiguat (soluble guanylate cyclase stimulator) are inconsistent.[67] In a small ancillary study of the WISE trial, 23 symptomatic women with CMD received a phosphodiesterase-5 inhibitor (oral sildenafil) with acute improvement in CFR and with the greater response among patients with lower baseline CFR.[68]

INFLAMMATION. In the CIRT (Cardiovascular Inflammation Reduction Trial) sub study of low-dose methotrexate in individuals with cardiometabolic disease, circulating IL-6 was inversely associated with myocardial flow reserve ($r = -0.44$, $P = 0.002$).[69]

INCRETINS (GLUCAGON-LIKE PEPTIDE-1/ GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE AGONISTS). Both semaglutide and tirzepatide have been shown to have favorable effects on obese patients with HFpEF. Both achieved weight loss, improved symptoms, and quality of life; in addition, tirzepatide significantly decreased the composite of worsening HF and CV death.[70,71] Although there are no data on HFpEF patients with CMD, results from small cohorts indicate that incretins can produce coronary vasodilatory effect through adenosine-independent mechanisms.[72]

LIFESTYLE INTERVENTIONS. Physical activity in HFpEF can improve exercise capacity by improving chronotropic incompetence and oxygen use by oxygen muscles.[73] Exercise training, cardiac rehabilitation, and weight loss have been shown to reduce angina frequency and improve CFR, functional capacity, and quality of life in patients with CMD.[74,75] The benefits of nonpharmacologic interventions extend to behavioral changes like smoking cessation and stress management with psychotherapy and cognitive behavioral therapy in the prevention and management of symptoms of HFpEF and CMD.

CONCLUSIONS

Despite significant advancements in our understanding of both CMD and HFpEF over the last decade, critical knowledge gaps persist. Recent progress in HFpEF research has underscored the crucial gaps in our knowledge regarding the precise role of CMD in the pathophysiology and natural history of these comorbid conditions. Consequently, the causal relationships between CMD and HFpEF are uncertain, making it difficult to determine whether CMD predisposes to HFpEF, HFpEF promotes CMD, or if they frequently coexist due to shared cardiometabolic risk factors and overlapping pathophysiology. The lack of standardized diagnostic criteria for both conditions likely contributes to their under-recognition and an imprecise estimation of their true prevalence. Therefore, a comprehensive algorithm to guide the assessment of CMD in HFpEF patients, incorporating specific indications for biomarkers, noninvasive imaging, and ICFT in needed. A key area for future investigation is whether therapeutically targeting CMD in individuals at risk for HFpEF and those with established HFpEF can improve their clinical prognosis. Future large-scale clinical trials are essential to evaluate the efficacy of novel therapeutic agents specifically designed for the management of comorbid CMD and HFpEF.

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