Coagulation Disorders and Thrombotic Complications in Heart Failure With Preserved Ejection Fraction

Kacper Karaban [a], Dorota Słupik [a], Aleksandra Reda [a], Magdalena Gajewska [a], Bartosz Rolek [a], Josip A. Borovac [b], Panteleimon E. Papakonstantinou [c,d], Dario Bongiovanni [e,f,g,h], Hanne Ehrlinder [i], William A.E. Parker [j], Aleksander Siniarski [k,l], Aleksandra Gąsecka [a,*]

[a] Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
[b] Division of Interventional Cardiology, Cardiovascular Diseases Department, University Hospital of Split, Split, Croatia
[c] Second Cardiology Department, Evangelismos Hospital, Athens, Greece
[d] First Cardiology Clinic, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece
[e] Department of Internal Medicine I, Cardiology, University Hospital Augsburg, University of Augsburg, Augsburg, Germany
[f] Department of Cardiovascular Medicine, Humanitas Clinical and Research Center IRCCS and Humanitas University, Rozzano, Milan, Italy
[g] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[h] Department of Cardiovascular Medicine, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[i] Department of Clinical Sciences, Division of Cardiovascular Medicine, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
[j] Cardiovascular Research Unit, Division of Clinical Medicine, University of Sheffield, Sheffield, UK
[k] Department of Coronary Artery Disease and Heart Failure, Institute of Cardiology, Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland
[l] John Paul II Hospital, Cracow, Poland

A B S T R A C T

Heart failure with preserved ejection fraction (HFpEF) is associated with multiple cardiovascular and noncardiovascular comorbidities and risk factors which increase the risk of thrombotic complications, such as atrial fibrillation, chronic kidney disease, arterial hypertension and type 2 diabetes mellitus. Subsequently, thromboembolic risk stratification in this population poses a great challenge. Since date from the large randomized clinical trials mostly include both patients with truly preserved EF, and those with heart failure with mildly reduced ejection fraction, there is an unmet need to characterize the patients with truly preserved EF. Considering the significant evidence gap in this area, we sought to describe the coagulation disorders and thrombotic complications in patients with HFpEF and discuss the specific thromboembolic risk factors in patients with HFpEF, with the goal to tailor risk stratification to an individual patient.

Introduction

Heart failure (HF) is a clinical syndrome caused by structural and/or functional abnormalities of the cardiac muscle, leading to impaired cardiac function. HF is divided into 3 subtypes based on left ventricular ejection fraction (LVEF): (i) HF with reduced ejection fraction (HFrEF), (ii) HF with mildly reduced ejection fraction (HFmrEF), and (iii) HF with preserved ejection fraction (HFpEF).[1] The definition of HFpEF has changed in the recent years, from LVEF $\geq$40% to the currently applicable values of $\geq$50%.[1,2] Furthermore,

---

along with preserved systolic function, HFpEF patients should also have symptoms and/or signs consistent with HF and objective evidence of structural and/or functional cardiac abnormality such as increased LV filling pressures and elevated natriuretic peptides.

Data from the large randomized clinical trials mostly include both patients with truly preserved EF, and those with HFmrEF (LVEF 41%-49%), such as CHARM-Preserved (two-thirds of patients with LVEF ≥50%), I-PRESERVE (EF ≥45%), PARAGON-HF (EF ≥45%) and TOPCAT (EF ≥45%)]. Thus, there was an unmet need to characterize the patients with HF and LVEF ≥50%, as their clinical characteristics, comorbidities, prognosis, and treatment significantly differ from "canonical" heart failure phenotype which has been traditionally associated with HFrEF. Of note, patients with HFpEF are usually older, more often female and present with many cardiovascular and noncardiovascular comorbidities and risk factors such as atrial fibrillation (AF), chronic kidney disease (CKD), arterial hypertension and type 2 diabetes mellitus (Fig 1).[1] These risk factors both directly and indirectly increase the risk of thrombotic complications, and are also potent drivers and modifiers of heart failure outcomes. For example, in the above-mentioned clinical trials, 29%-32% of patients had a history of AF and 8.5%-11% had a history of previous stroke,[3-5] whereas the incidence of new stroke episodes ranged from 3.3% in the I-PRESERVE and TOPCAT trials to 6% in the PARAGON-HF trial during the mean follow-up period of 29 to almost 50 months.[2-7]

Considering the inherently high thromboembolic risk of patients with HFpEF due to underlying comorbidities, thromboembolic risk stratification in this population poses a great challenge. Considering the significant evidence gap in this area, we sought to describe the coagulation disorders and thrombotic complications in patients with HFpEF and discuss the specific thromboembolic risk factors this population, with the goal to tailor risk stratification to an individual patient.

Epidemiology

Increased lifespan and aging of the Western population and breakthrough improvements in the HF therapeutic approaches lead to a steady increase in the HF prevalence, currently ranging from 1.5% to 4% per 1000 patient-years.[8] HFpEF accounts for 34% of HF cases in the general population,[9,10] but more than 50% of HF cases among female patients and those >65 years of age.[11] Similarly, contemporary studies and registries report that HFpEF and HFmrEF together might together constitute about 50% of all patients hospitalized due to HF.[12] Women are more likely to develop HFpEF compared to men, while among those patients with HFpEF, women are significantly older than men (85 years vs 83 years), have greater prevalence of diastolic dysfunction, while men are more likely to have comorbidities including diabetes, coronary artery disease (CAD), hyperuricemia, and chronic kidney disease.[13] Women also have some unique sex-specific risk factors that might predispose them to heart failure such as hypertensive disorders of pregnancy.[14] The risk of death in patients with HFpEF is high and increases along with the burden of comorbidities, with 5-year survival rate of 35% after a HF-related hospitalization.[15]

Pathophysiology

Association Between HFpEF Pathophysiology and Coagulation Disorders

Here, the pathophysiology of HFpEF has briefly been discussed to explain the association between HFpEF and coagulation disorders. The crucial components of HFpEF development include (i) left atrium (LA) myopathy, (ii) endothelial-to-mesenchymal
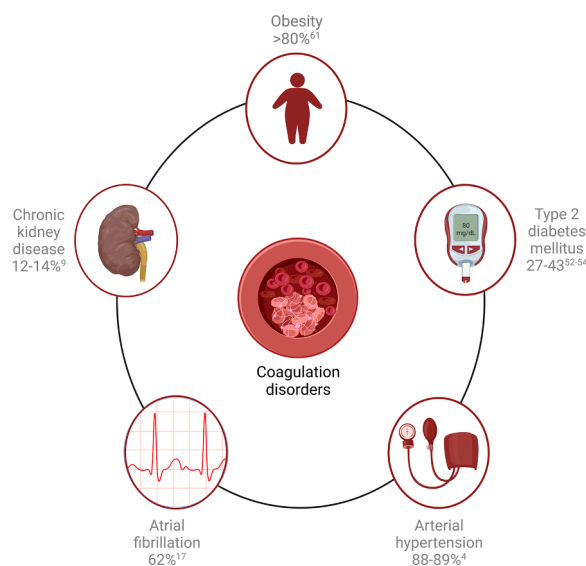
FIG 1. Cardiovascular and noncardiovascular comorbidities associated with coagulation disorders in patients with heart failure with preserved ejection fraction. Created with BioRender.com, licensed version by A.G. (Color version of figure is available online.)

transition, (iii) increased vascular stiffness, (iv) myocardial ischemia, (v) right ventricular (RV) failure and (vi) increased diastolic ventricular interaction (Fig 2).

High filling pressures in the LA and LV play an important role in the pathophysiology of HFpEF. Elevated filling pressures are caused by stiffening of the LV and delayed isovolumetric relaxation of this chamber that impairs the suction function. Consequently, the workload of LA increases to produce more pressure than in physiological conditions to ensure adequate LV filling. Under normal physiological conditions, 80% of the LV filling occurs during early diastole (isovolumetric relaxation) due to the suction of LV, indicated by the echocardiographic E wave. The remaining 20% is due to the contractile work of the LA, indicated by the A wave. In patients with HFpEF, the percentages of the filling are opposite, with most filling caused by the LA contraction. When the heart rate increases, for example during physical exercise or stress, there is a further decline in the isovolumetric relaxation and an increase in the LA filling pressure, which evokes HF symptoms in the early stage of the disease.[16] The concomitant renin-angiotensin-aldosterone system (RAAS) activation, oxidative stress, inflammatory cascades, and mechanical atrial stretch due to pressure and volume over-load lead to LA fibrosis.[17] Continuous volume overload, loss of atrial contractility and the stiffening of LA wall are symptoms of LA myopathy. This state promotes additional nonsinus impulses, substantially increasing the risk of AF. Moreover, LA myopathy pre-disposes to blood stasis and spontaneous thrombus formation. This state increases with AF risk of thromboembolism.[18]

Endothelial-to-mesenchymal transition (EndoMT) is a biological pathway connected with the remodeling of vascular and heart in, for example, pulmonary hypertension, vascular malformation, vascular calcification, and earlier mentioned, cardiac fibrosis.[19] EndoMT is crucial during the embryonic cardiac development, especially for the formation of the heart valves. Postnatal reactivation of EndoMT is a potential mechanism for adaptation to a new pathological environment, such as proinflammatory state.[20] In HFpEF, the expression of EndoMT biomarkers (such as SM22α and calponin) is increased.[21] Angiotensin II, known for its profibrotic effects, also activates EndoMT. In the rodent model, administration of angiotensin II receptor antagonist ibesartan reduced interstitial cardiac fibrosis and left ventricular hypertrophy by blocking EndoMT.[22] Hence, EndoMT activation is a crucial event in HFpEF and one of its comorbidities—chronic kidney disease.

Vascular stiffness due to endothelial dysfunction is another crucial factor in HFpEF pathophysiology. Multiple risk factors and comorbidities that coexist within the clinical syndrome of HFpEF, such as aging and metabolic syndrome lead to endothelial activation and impaired bioavailability of nitric oxide (NO). The molecular changes demonstrated in the cardiac biopsies of HFpEF patients included upregulation of E-selectin and intercellular adhesion molecule-1 expression levels and low levels of endothelial NO synthase, indicating systemic inflammation.[24] The loss of NO is associated with vasoconstriction and abnormal blood flow. The increased vascular stiffness, in turn, increases the afterload and leads to the blood pressure fluctuations, especially during physical exercise.[23] At the crossroads of myocardial fibrosis, LV and LA stiffening, and diastolic dysfunction is the microvascular dysfunction that occurs as the consequence of widespread systemic inflammation perpetuated by comorbidities that elicits injury to endothelial cells and through perivascular space induces cardiomyocyte injury.[25]

CAD is a common comorbidity in patients with HFpEF.[26] Myocardial ischemia is involved in the development of HFpEF and correlated with the abnormalities of ventricular function.[27] Although classically, myocardial ischemia more often leads to HFrEF instead of HFpEF, the diastolic function becomes impaired prior to the systolic function of the LV in any HF subtype.[28] The mismatch between oxygen supply and demand and coronary microvascular dysfunction explain the association between myocardial ischemia and HFpEF.[29]

CAD is also associated with reduced function of the right ventricle (RV),[28] with RV dysfunction present in 19% of HFpEF patients, defined as EF <47% and measured by cardiovascular magnetic resonance imaging.[30] To support this notion, in patients with HFpEF, 24% increase in moderate or severe tricuspid regurgitation, 20% increase in RV diastolic area and 10% decrease in RV fractional area change was shown during 6 months of follow-up, compared to baseline echocardiographical examination.[32] In addition, high LV filling
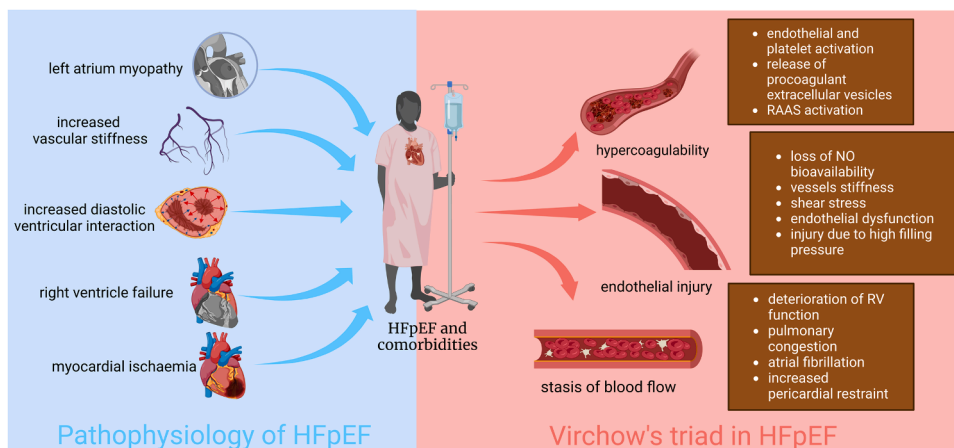
FIG 2. Pathophysiology and coagulation disorders in HFpEF (Virchow's triad). HFpEF, heart failure with preserved ejection fraction; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; RV, right ventricle. Created with BioRender.com, licensed version by A.G. (Color version of figure is available online.)

pressure leads to the combined postcapillary and precapillary (reactive) pulmonary hypertension, increasing the risk of RV failure, systemic venous congestion, congestive hepatopathy, cardiorenal syndrome and development of cardiac cachexia.[33,34] Consequently, RV dysfunction was the strongest single predictor of mortality in patients with HFpEF, increasing this risk nearly 2.5-fold. Patients with RV dysfunction have higher mortality compared to group of patients with HFpEF, but without RV dysfunction, with median 2-years survival of 56% vs 92%.[31]

The increased volume of the LA and right heart chambers leads to the increased total cardiac volume, without altering the size of the LV cavity. This increase in cardiac volume can be a factor of increased pericardial restraint and RV pressure and volume changes, affecting the LV.[35] Consequently, the left heart filling is elevated even though the left ventricular end-diastolic volume is normal or reduced. As a result, the heart of a HFpEF patient cannot increase stroke volume during exercise due to the pericardial restraint mechanism that prevents further preload, which aggravates venous congestion (one of the states that can promote thrombogenesis).[24,36] In light of this, heart rate increase during exercise might be protective mechanism in sustaining cardiac output as stroke volume cannot be increased and this creates a rationale to not use beta-blockers in this population unless there is a clear and specific indication.[37]

Pathophysiology of Comorbidities of HFpEF

Numerous comorbidities associated with HFpEF increase the risk of thromboembolic complications. In the LATTEE registry, patients with HFpEF had a higher median of CHA_2DS_2-VASc scores than populations with HFmrEF and HFrEF (5, 4, and 4, respectively).[38]

Chronic Kidney Disease

The Prevention of REnal and Vascular ENdstage Disease (PREVEND) study reported that chronic kidney disease (CKD) is present in 12%-14% of HFpEF patients.[9] CKD and HFpEF are both associated with hypertension, diabetes, and obesity which lead to inflammation, oxidative stress, arterial stiffening, and endothelial dysfunction.[39] What is more, these states are connected with coagulation disorders. Myocardial impairment influences kidney dysfunction and vice versa. The interaction between heart and renal dysfunction is often described in studies as cardiorenal syndrome (CRS).[39] Mice with HFpEF and CRS had elevated levels of Endo-MT biomarkers. The same findings are in serum taken from patients with HFpEF during the same study. That suggests the mechanism of Endo-MT plays a role in a pathway of not only cardiac but also kidney fibrosis.[40] Kidney fibrosis is one of the pathophysiological pathways in the development of CKD.

CKD including end-stage kidney disease are associated with an increased risk of thromboembolic complications such as stroke.[41,42] Recently, a meta-analysis of over 2 million subjects confirmed the strong association between kidney function and stroke incidence, showing a 7% increase in stroke risk with every 10 mL/min/1.73 m^2 decline in estimated glomerular filtration rate.[41,42] As the severity of chronic kidney disease increases, the incidence of HF increases. An estimated 44% of patients on hemodialysis have HF (10% with HFpEF, 13% with HFrEF, and 21% with unspecified).[43] Patients with end-stage kidney disease undergoing dialysis had the highest risk of stroke, which was 2-7-fold higher compared to non-CKD patients, with a 3-5-fold increase in mortality.[42,44] Finally, it was calculated that about two-thirds of patients aged over 75 years on dialysis will die within a year due to a stroke.[42,44]

There are many pathological pathways in which CKD can enhance the risk of cardiovascular incidents in patients with HFpEF. Patients with CKD present with both a hypercoagulable state and endothelial dysfunction, contributing to increased cardiovascular risk.[45] In patients with advanced CKD (stages 4 and 5), substantial changes in coagulation and anticoagulation pathways were shown, compared to healthy controls, including activation of the tissue factor pathway, increased prothrombin fragment 1+2 and substantial drop in antithrombin III and free protein S-to-total protein S ratio.[45] Other authors also showed increased levels of fibrinogen, D-Dimer, thrombin-antithrombin complexes, intercellular adhesion molecule-1, von Willebrand factor (vWF) concentration and activity, and factors VII and VIII in patients with different stages of CKD, compared with the control subjects.[46,47] However, there is still a lack of studies in the fields of thromboembolic incidents in CKD in which separate group of patients are patients with HFpEF.

Arterial Hypertension

Due to its hemodynamic consequences, arterial hypertension is one of the most prevalent risk factors not only for intracranial hemorrhage, but also for ischemic stroke.[48] Data from 30 studies described that hypertension was present in about 64% of patients with stroke.[48,49] The pathophysiological mechanisms underlying the prothrombotic profile of patients with hypertension remain elusive and may include (i) platelet activation, (ii) endothelial dysfunction, and (iii) dysregulation of the renin-angiotensin and kallikrein-kinin systems.

It was suggested that in hypertensive patients, the inflammatory cytokines may enhance the procoagulant activity of platelets and endothelial cells by triggering phosphatidylserine exposure on their surface.[50] In addition, the combination of chronic inflammation and shear stress may alter the normally acting endothelium into a procoagulant surface, expressing tissue factor.[51] Renin-angiotensin and kallikrein-kinin systems, in turn, interact at several levels to impact blood clotting, fibrinolysis, and vasodilatation and therefore may increase the risk of thrombotic complications.[51] It was demonstrated that the treatment of hypertensive patients with angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists may favorably alter both the renin-angiotensin and kallikrein-kinin axis, and as a result reduce the risk of thrombosis, which can partly explain the clinical efficacy of these groups of medications.[51]

Type 2 Diabetes Mellitus

In recent clinical trials on HFpEF, patients with type 2 diabetes accounted for 27%-43% of the study participants.[52-54] There is a bulk of evidence that type 2 diabetes is associated with an increased cardiovascular risk, which is not fully explained by the accumulation of classical cardiovascular risk factors.[55]

Recent evidence showed that fibrinogen is an independent risk factor for cardiovascular disease in the general population.[55] However, the influence of type 2 diabetes on atherothrombotic risk seems to extend beyond the increased fibrinogen levels and may act through the fibrin clot structure and function.[55] Hyperglycemia and protein glycation have important effects on fibrin clot structure and function, generating a clot with a denser structure, and more resistant to lysis.[56,57] In addition, patients with type 2 diabetes frequently present with platelet resistance to standard antiplatelet therapy, leading to increased platelet reactivity.[56] Finally, suppression of nitric oxide and prostacyclin synthesis might contribute to the development of endothelial dysfunction in diabetic patients.

Altogether, a combination of elevated circulating coagulation proenzymes, decreased fibrinolysis, differences in fibrin structure and function and increased platelet reactivity seem to increase the thrombotic risk in this subpopulation.[56] To support this statement, the rates of death from any cause and the rates of hospitalization are much higher in trials involving patients with HFpEF[3,52-54] than in trials involving patients with other cardiovascular risk factors such as hypertension,[58] diabetes[59] or chronic coronary syndrome.[60]

Obesity

Obesity or overweight occurs in up to 80% of patients with HFpEF in the USA.[61] Obesity affects both the development of HFpEF and the thromboembolic risk. Elevated inflammatory biomarkers, such as C-reaction protein or tumor necrosis factor, disrupt coagulation homeostasis in obese patients with HFpEF[62] and lead to higher platelet activation.[63] In morbidly obese patients loss of body mass reduces thrombin generation potential.[64]

Both obesity and diabetes mellitus type 2 increase the risk of thromboembolic events without AF in the group of patients with HFpEF. Adiposity and dysregulation of sugar metabolism are common comorbidities and both enhance the inflammation, fibrosis, and abnormality in epicardial adipose. All of the mentioned states lead to ventricular myopathy and LA myopathy. LA myopathy promotes the development of thrombus into the atria but also promotes the occurrence of AF (the relation between AF and atrial myopathy in the pathophysiology of cardioembolic incidents is still elucidated—more in section "Atrial fibrillation").[18] Nonetheless, LA myopathy and AF are both connected with cardiovascular incidents in HFpEF patients.

However, there is research that shows the existence of the "obesity paradox" in HFpEF. There is a decrease in mortality in the group of patients without AF, but with overweight and obesity and in patients with AF, only obesity (not overweight) is associated with decreased risk of all-cause death.[65]

Atrial Fibrillation

Atrial fibrillation (AF) is a very common comorbidity of HFpEF reported in 62% of patients with previous or postdiagnosis AF.[15] It is associated with an 11% increased risk of all-cause mortality in patients with HFpEF and is an independent predictor of cardiovascular death and stroke.[66]

AF and HFpEF not only have similar risk factors, but also many similar mechanisms that lead to the development of AF. As earlier mentioned LA myopathy is the joint step of the pathophysiology of HFpEF and AF. We still don't know which dysfunction - LA myopathy or AF is directly related to a higher risk of thromboembolism (especially stroke). If the main risk of thromboembolism is atrial myopathy, not AF, then control of rhythm should not lower the risk of thromboembolism.[18] On one hand, there are observational studies that suggest that it is not true[67] but on the other hand there are also meta-analyses that support the statement that control of rhythm has a lack of benefit in reducing stroke risk.[68] Nonetheless, this topic requires further study with studies including a group of patients with HFpEF.

Obesity is another common coexisting factor in the development of AF by increasing fibrosis of the atria.[69] Moreover, Berkovitch et al. showed that the higher risk is reversible—5 kg weight loss reduced the risk of the new onset of AF by 12%.[69] Fibrosis is associated with the occurrence of LA thrombus in patients with a long history of AF regardless of the size of the LA chamber. Akoum et al. suggest that the fibrotic tissue leads to a reduction of atrial contraction, blood stasis and tissue lesions that activate the thrombogenic cascade.[70] Moreover, Nattel et al. showed that there are calcium abnormalities in myocytes and electrical remodeling of dilated atria.[71] Both, calcium abnormalities and electrical remodeling, lead to completely symptomatic AF.

In a post hoc analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (ARISTOTLE) the rate of stroke or systemic embolism was for HFpEF 5.3 per 100 patient-years and is classified as intermediate contrary to patients with HFrEF (8 per 100 patient-years) and low for patients without AF (1.54 per 100 patient-years).[72] The ACTIVE-W trial showed that in patients with permanent AF, there is no significant difference between patients with reduced or preserved ejection fraction.[73] AF also increased the risk of incidence of fatal thromboembolic events almost 2-fold in the group of HFpEF.[66] Finally, patients with HFpEF and AF have a higher risk of developing pulmonary hypertension and right heart failure.[31,74] It is also important to note that ischemic stroke occurred in 3.7% of patients with HFpEF but without atrial fibrillation yielding a rate of 10.5 events per 1000 patient-years) while patients were followed for 3.6 years.[75]

Platelet Dysregulation

HFpEF is a clinical syndrome associated with a systemic proinflammatory state caused by comorbidities in which platelets are involved.[76] Elevated mean platelet volume (MPV) reflecting increased platelet activity in the ongoing inflammatory process, which may reflect a presumed role of platelets in the pathophysiology of HFpEF.[76]

Platelet proteins are altered in heart failure. Due to the lack of targeted therapies for HFpEF, it is crucial to identify biomarkers

associated with HFpEF. Elevated levels of serum amyloid A, lipopolysaccharide binding protein, S100A8 and apolipoprotein A have been identified in platelets from patients with HFpEF. This is the first study to link the presence of S100A8 protein to HFpEF.[77] However, data on platelet markers in HFpEF are still limited and the prognostic significance of MPV and S100A8 protein requires further study.

Complications of HFpEF-Associated Coagulation Disorders

The main complications of prothrombotic state in patients with HFpEF are: (i) cardioembolic stroke, (ii) venous thromboembolism, and (iii) pulmonary thromboembolism.

Cardioembolic Stroke Risk

Embolic materials originating from the heart are a major cause of ischemic strokes in the population of patients with HF (64.7%) to the contrary with patients without HF (26.8%).[78] Pathophysiology of thromboembolism is well known and described as abnormal blood flow, abnormality in the vessels wall or cardiac chambers and abnormal blood components (Virchow's triad).[79] Several mechanisms link the existence of AF and thromboembolism with stasis of blood especially in LA appendage, inducing formation of a thrombus. Approximately 25% of thromboembolic materials originally develop in the heart during AF episodes.[80] However, studies showed not only AF, but also atrial and/or ventricular remodeling and LV function increases the risk of cerebral vesicular events. This risk are similar between HFpEF and HFrEF.

AF, as mentioned earlier, is connected closely with stroke risk, but studies reported not only AF but also HFpEF without AF elevates this risk. In the analysis of CHARM-Preserved and I-Preserved trials point that even without AF there is elevated risk of stroke in patients with HFpEF (1.0% per year). This analysis involved 6701 patients with HFpEF, 4676 of them did not have AF. Interestingly, in the pooled analysis of this study in the highest tertile patients without AF have higher risk of stroke compared to with AF and receives of anticoagulant, but still lower than patients with AF but not treated by anticoagulants (sequentially 1.6% vs 1.5% and 2.2% per year).[81] These results also emphasize the significant role of appropriate treatment which can lower the risk of stroke in patients with HFpEF and AF. In the Atherosclerosis Risk in Communities (ARIC) Study involving 1527 participants who underwent echocardiography, brain resonance imaging and cognitive assessment showed that subclinical cerebral infarction (SCI) occurred in 49 from group of 167 patients (29.3%) with HFpEF but without prior history of AF. The odds ratio of having SCI were higher in the HFpEF group without AF than patients without HFpEF but no history of AF (OR 1.47, 95% CI 1.20-2.13).[82] That results indicate that SCIs are prevalent in patients with HFpEF with no history of AF and are associated with measurable cognitive deficits. However, Cogswell et al. suggest that the AF may be underdiagnosed in this population.[82]

It also seems that remodeling of the heart has significant influence on the frequency of stroke. In the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS), loss of reservoir function and enhanced stiffness correlated with worse infarct form—from SCI to full clinical stroke[83] and the importance of these 2 parameters rose with patient age. Furthermore, progressive deterioration of LA function (measured in LA global longitudinal strain values) and structure, decline of atrial shortening and contractility are common findings in elderly patients. All of these parameters are factors of enhanced LA clot formation and cause SCIs. With development of LA global dysfunction, this increases the frequency of clinical stroke.[83]

It has been suggested that heart function may play an important role in development of clots and future incidence of stroke. A post hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFIRM) trial showed that HFpEF is related to higher mortality in the AF group compared to systolic HF.[84] This trial also reported that stroke incidents (during mean follow-up duration of 3.5 years) was higher in the population with HFpEF than HFrEF (16.2% vs 10.9% $P = 0.04$). Age (≥ 75 years) and level of B-natriuretic peptide (BNP), produced by cardiac myocytes in response to wall stress (BNP 148-340 pg/mL and ≥ 341 pg/mL) are predictors of stroke and systemic thromboembolism in patients with AF.[85]

It should be noted that the prevalence of stroke between 2 groups with a AF - HFpEF and HFrEF are similar, as indicated by a meta-analysis of 33,773 patients. However, all-cause mortality was significantly higher in AF patients with HFrEF compared to HFpEF.[86] During the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trial which included 3400 patients with HF, the analysis showed that the risk of embolic events is 4.3% per 100 person-years and was similar to the population with HFrEF.[73] These results support the findings from the analysis of CHARM-Preserved and the I-Preserve trial that the left ventricular ejection fraction (LVEF) is not a good independent risk factor, though in this analysis only patients with LVEF $\geq 45\%$ were included).[81]

Venous Thromboembolism

Venous thromboembolism (VTE) consists of deep venous thrombosis and pulmonary embolism. There are several studies that indicate the influence of HF on VTE.[87-89] In the earlier mentioned ARIC study, HFrEF and HFpEF increased the long-term risk of VTE by 5 times.[87,89]

The pathophysiology of this state not contains the classic Virchow's triad but is exacerbated by additional factors. The literature indicates several potential mechanisms linking VTE with HFpEF, including pulmonary congestion which occurs in the process of HFpEF, blood stasis in the systemic circulation in advanced HFpEF (induced by RV dysfunction), elevated levels of prothrombotic microparticles and endothelial dysfunction of vessels.[23,32] Studies conducted so far mentioned the main factors which influence morbidity and occur incidents of VTE are: (i) stasis of blood and (ii) echocardiographic parameters.

Hospitalized patients with HF typically have multiple risk factors for VTE, for example, stasis of blood in the legs. According to the

Worcester Venous Thromboembolism study,[88] hospitalization with diagnosed VTE and a history of HF have been associated with a doubling of in-hospital deaths and risk of death by 60% within 30 days of VTE diagnosis.[88] Also, immobility was found a predictor of in-hospital mortality and death 30 days after VTE diagnosis.[88]

A substudy of ARIC showed that greater left atrial volume index (LAVi) and left ventricular wall remodeling are independently associated with higher risk of thromboembolic events.[87,89]

Pulmonary Thromboembolism

A study of comparing the risk of death in patients with pulmonary embolism and either HFrEF or HFpEF showed that the presence of a history of HFpEF is not an independent factor for increased risk of 7-day mortality.[90]

Diagnosis of Coagulation Disorders

Markers of endothelial dysfunction, including vWF, vascular cell adhesion molecule 1 and adhesion molecule 1 have been shown to influence the prognosis of patients with HFpEF.[91] A high proportion of deaths in patients with HFpEF are associated with advanced age and comorbidities. Plasma levels of vWF are higher with advancing age and also in patients with comorbidities such as nondialysis-dependent chronic kidney disease.[92-94] In addition, correlations have been found between elevated vWF levels and the occurrence of cardiovascular events and stroke in patients with HFpEF and AF.[92,95]

Furthermore, in patients with HFpEF and comorbidities, the levels of the tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) complex are significantly higher, which is associated with increased embolic risk.[91,96] Whether the measurement of vWF and tPA/PAI-1 complex may have a practical value in the diagnosis, stratification and treatment of HFpEF requires further study.

Treatment of Coagulation Disorders in HFpEF

HFpEF is associated with frequent coexistence of other diseases, which may further increase the risk of thrombosis or bleeding. For this reason, treatment of HFpEF is much more difficult. Compared to other HF phenotypes, thromboembolic risk in patients with HFpEF, is associated with a higher incidence of AF.[1] The CHA$_2$DS$_2$-VASc score is used to assess the risk of thromboembolic complications in patients with AF. Patients with HFpEF and AF should have anticoagulant treatment included because of the increased risk of systemic embolism and stroke.[17] Patients with HFpEF and AF should be anticoagulated with nonvitamin K antagonist oral anticoagulants (NOACs) or warfarin, as per AF guidelines.[97,98] A study comparing the use of NOACs and warfarin in patients with HFpEF and AF on the incidence of stroke and systemic embolism showed no statistically significant difference, while the use of NOACs reduced the risk of major bleeding from any cause compared to warfarin.[99]

Conclusions

It is essential to assess the global cardiovascular and thromboembolic risk in patients with HFpEF, knowing that these patients are characterized by a mosaic of clinical presentations and concomitant medical conditions that all increase both overall cardiovascular and thromboembolic risk. However, given the lack of guidelines and the limited number of studies on anticoagulant therapy in patients with HFpEF, large randomized trials are needed. As recently suggested by A. Zain et al., comprehensive evaluation of platelet function, clotting and fibrinolytic factors and their association with HFpEF severity, anticoagulant or antiplatelet therapy and outcomes might improve the management of coagulation disorders in HFpEF and inspire future research.[100]

Declaration of Competing Interest

References

1 TA M, M M, M A, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726.
2 Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: The CHARM-overall programme. *Lancet.* 2003;362:759–766.
3 Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-preserved trial. *Lancet.* 2003;362.
4 Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med.* 2008;359.
5 Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med.* 2019;381.
6 B P, MA P, SF A, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370:10.
7 Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation.* 2006;114.

8   Stretti L, Zippo D, Coats AJS, et al. A year in heart failure: an update of recent findings. *ESC Heart Fail*. 2021;8:4370–4393.
9   Meyer S, Brouwers FP, Voors AA, et al. Sex differences in new-onset heart failure. *Clin Res Cardiol*. 2015;104:342–350.
10 Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J*. 2013;34:1424–1431.
11 Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients >or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol*. 2001;87:413–419.
12 Li P, Zhao H, Zhang J, et al. Similarities and differences between HFmrEF and HFpEF. *Front Cardiovasc Med*. 2021;8, 678614.
13 Sakai T, Motoki H, Suzuki S, et al. Gender difference in heart failure with preserved ejection fraction: clinical profiles, examinations, and prognosis. *Heart Vessels*. 2022;37:1710–1718.
14 O'Kelly AC, Lau ES. Sex differences in HFpEF. *Curr Treat Options Cardiol Med*. 2020;22:73.
15 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;62:263–271.
16 Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014;11:507–515.
17 Patel RB, Vaduganathan M, Shah SJ, et al. Atrial fibrillation in heart failure with preserved ejection fraction: insights into mechanisms and therapeutics. *Pharmacol Ther*. 2017;176:32–39.
18 Packer M. HFpEF is the substrate for stroke in obesity and diabetes independent of atrial fibrillation. *JACC Heart Fail*. 2020;8:35–42.
19 Evrard SM, Lecce L, Michelis KC, et al. Endothelial to mesenchymal transition is common in atherosclerotic lesions and is associated with plaque instability. *Nat Commun*. 2016;7:11853.
20 Bischoff J. Endothelial-to-mesenchymal transition. *Circ Res*. 2019;124:1163–1165.
21 Huang Y, Zhang K, Liu M, et al. An herbal preparation ameliorates heart failure with preserved ejection fraction by alleviating microvascular endothelial inflammation and activating NO-cGMP-PKG pathway. *Phytomedicine*. 2021;91, 153633.
22 Kovacic JC, Mercader N, Torres M, et al. Epithelial-to-mesenchymal and endothelial-to-mesenchymal transition: from cardiovascular development to disease. *Circulation*. 2012;125:1795–1808.
23 Reddy YNV, Andersen MJ, Obokata M, et al. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2017;70:136–148.
24 Franssen C, Chen S, Unger A, et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2016;4:312–324.
25 D'Amario D, Migliaro S, Borovac JA, et al. Microvascular dysfunction in heart failure with preserved ejection fraction. *Front Physiol*. 2019;10:1347.
26 Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014;63(Part A):2817–2827.
27 Obokata M, Reddy YNV, Melenovsky V, et al. Myocardial injury and cardiac reserve in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2018;72:29–40.
28 Gorter TM, Hoendermis ES, van Veldhuisen DJ, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail*. 2016;18:1472–1487.
29 Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J*. 2018;39:3439–3450.
30 Kanagala P, Arnold JR, Singh A, et al. Prevalence of right ventricular dysfunction and prognostic significance in heart failure with preserved ejection fraction. *Int J Cardiovasc Imaging*. 2021;37:255–266.
31 Melenovsky V, Hwang SJ, Lin G, et al. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J*. 2014;35:3452–3462.
32 Obokata M, Reddy YNV, Melenovsky V, et al. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J*. 2019;40:689–698.
33 Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019;124:1598–1617.
34 Borovac JA, Glavas D, Susilovic Grabovac Z, et al. Right ventricular free wall strain and congestive hepatopathy in patients with acute worsening of chronic heart failure: a CATSTAT-HF echo substudy. *J Clin Med*. 2020;9:1317.
35 Schwarz K, Singh S, Dawson D, et al. Right ventricular function in left ventricular disease: pathophysiology and implications. *Heart Lung Circ*. 2013;22:507–511.
36 Stray-Gundersen J, Musch TI, Haidet GC, et al. The effect of pericardiectomy on maximal oxygen consumption and maximal cardiac output in untrained dogs. *Circ Res*. 1986;58:523–530.
37 Meyer M, LeWinter MM. Heart rate and heart failure with preserved ejection fraction: time to slow β-blocker use? *Circ Heart Fail*. 2019;12, e006213.
38 Wybraniec MT, Mizia-Szubryt M, Cichoń M, et al. Heart failure and the risk of left atrial thrombus formation in patients with atrial fibrillation or atrial flutter. *ESC Heart Fail*. 2022;9.
39 Shah KS, Fang JC. Is heart failure with preserved ejection fraction a kidney disorder? *Curr Hypertens Rep*. 2019;21:86.
40 Valero-Muñoz M, Oh A, Faudoa E, et al. Endothelial-mesenchymal transition in heart failure with a preserved ejection fraction: insights into the cardiorenal syndrome. *Circ Heart Fail*. 2021;14, e008372.
41 Masson P, Webster AC, Hong M, et al. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2015;30: 1162–1169.
42 Arnold J, Sims D, Ferro CJ. Modulation of stroke risk in chronic kidney disease. *Clin Kidney J*. 2016;9:29–38.
43 House AA, Wanner C, Sarnak MJ, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int*. 2019;95:1304–1317.
44 Wang HH, Hung SY, Sung JM, et al. Risk of stroke in long-term dialysis patients compared with the general population. *Am J Kidney Dis*. 2014;63:604–611.
45 Adams MJ, Irish AB, Watts GF, et al. Hypercoagulability in chronic kidney disease is associated with coagulation activation but not endothelial function. *Thromb Res*. 2008;123:374–380.
46 Abdelmaguid A, Roberts LN, Tugores L, et al. Evaluation of novel coagulation and platelet function assays in patients with chronic kidney disease. *J Thromb Haemost*. 2022;20:845–856.
47 Huang MJ, Wei RB, Wang Y, et al. Blood coagulation system in patients with chronic kidney disease: a prospective observational study. *BMJ Open*. 2017;7: e014294.
48 Wajngarten M, Silva GS. Hypertension and stroke: update on treatment. *Eur Cardiol*. 2019;14:111–115.
49 Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res*. 2017;120:439–448.
50 Li J, Tong D, Chen F, et al. Inflammatory cytokines enhance procoagulant activity of platelets and endothelial cells through phosphatidylserine exposure in patients with essential hypertension. *J Thromb Thrombolysis*. 2021;51:933–940.
51 Dielis AWJH, Smid M, Spronk HMH, et al. The prothrombotic paradox of hypertension: role of the renin-angiotensin and kallikrein-kinin systems. *Hypertension*. 2005;46:1236–1242.
52 Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.
53 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.
54 Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381: 1609–1620.
55 Dunn EJ, Ariëns RAS. Fibrinogen and fibrin clot structure in diabetes. *Herz*. 2004;29:470–479.
56 Grant PJ. Diabetes mellitus as a prothrombotic condition. *J Intern Med*. 2007;262:157–172.
57 Bryk-Wiązania AH, Undas A. Hypofibrinolysis in type 2 diabetes and its clinical implications: from mechanisms to pharmacological modulation. *Cardiovasc Diabetol*. 2021;20:191.

58 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid-lowering treatment to prevent heart attack trial. 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 (ALLHAT). *JAMA*. 2002;288:2981–2997.

59 Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.

60 Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058–2068.

61 Kitzman DW, Lam CSP. Obese heart failure with preserved ejection fraction phenotype: from pariah to central player. *Circulation*. 2017;136:20–23.

62 Putko BN, Wang Z, Lo J, et al. Circulating levels of tumor necrosis factor-alpha receptor 2 are increased in heart failure with preserved ejection fraction relative to heart failure with reduced ejection fraction: evidence for a divergence in pathophysiology. *PLoS One*. 2014;9.

63 Santilli F, Vazzana N, Liani R, et al. Platelet activation in obesity and metabolic syndrome. *Obes Rev*. 2012;13:27–42.

64 Ay L, Kopp H-P, Brix J-M, et al. Thrombin generation in morbid obesity: significant reduction after weight loss. *J Thromb Haemost*. 2010;8:759–765.

65 Guo L, Liu X, Yu P, et al. The "obesity paradox" in patients with HFpEF with or without comorbid atrial fibrillation. *Front Cardiovasc Med*. 2022;8.

66 Liu G, Long M, Hu X, et al. Meta-analysis of atrial fibrillation and outcomes in patients with heart failure and preserved ejection fraction. *Heart Lung Circ*. 2021; 30:698–706.

67 Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J*. 2016;37:2478–2487.

68 Sethi NJ, Feinberg J, Nielsen EE, et al. The effects of rhythm control strategies versus rate control strategies for atrial fibrillation and atrial flutter: a systematic review with meta-analysis and trial sequential analysis. *PLoS One*. 2017;12, e0186856.

69 Berkovitch A, Kivity S, Klempfner R, et al. Body mass index and the risk of new-onset atrial fibrillation in middle-aged adults. *Am Heart J*. 2016;173:41–48.

70 Akoum N, Fernandez G, Wilson B, et al. Association of atrial fibrosis quantified using LGE-MRI with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013;24:1104–1109.

71 Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol*. 2008;1:62–73.

72 McMurray JJV, Ezekowitz JA, Lewis BS, et al. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail*. 2013;6:451–460.

73 Sandhu RK, Hohnloser SH, Pfeffer MA, et al. Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. *Stroke*. 2015;46:667–672.

74 Mohammed SF, Hussain I, Abou Ezzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation*. 2014;130:2310–2320.

75 Kondo T, Jering KS, Jhund PS, et al. Predicting stroke in heart failure and preserved ejection fraction without atrial fibrillation. *Circ Heart Fail*. 2023;16, e010377.

76 Menghoum N, Beauloye C, Lejeune S, et al. Mean platelet volume: a prognostic marker in heart failure with preserved ejection fraction. *Platelets*. 2023;34, 2188965.

77 Raphael R, Purushotham D, Gastonguay C, et al. Combining patient proteomics and in vitro cardiomyocyte phenotype testing to identify potential mediators of heart failure with preserved ejection fraction. *J Transl Med*. 2016;14:18.

78 Vemmos K, Ntaios G, Savvari P, et al. Stroke aetiology and predictors of outcome in patients with heart failure and acute stroke: a 10-year follow-up study. *Eur J Heart Fail*. 2012;14:211–218.

79 Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009;373:155–166.

80 Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135: e146–e603.

81 Abdul-Rahim AH, Perez AC, MacIsaac RL, et al. Risk of stroke in chronic heart failure patients with preserved ejection fraction, but without atrial fibrillation: analysis of the CHARM-Preserved and I-Preserve trials. *Eur Heart J*. 2017;38:742–750.

82 Cogswell RJ, Norby FL, Gottesman RF, et al. High prevalence of subclinical cerebral infarction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2017;19:1303–1309.

83 Bianco F, de Caterina R, Chandra A, et al. Left atrial remodeling and stroke in patients with sinus rhythm and normal ejection fraction: ARIC-NCS. *J Am Heart Assoc*. 2022;11.

84 Badheka AO, Rathod A, Kizilbash MA, et al. Comparison of mortality and morbidity in patients with atrial fibrillation and heart failure with preserved versus decreased left ventricular ejection fraction. *Am J Cardiol*. 2011;108:1283–1288.

85 Sobue Y, Watanabe E, Lip GYH, et al. Thromboembolisms in atrial fibrillation and heart failure patients with a preserved ejection fraction (HFpEF) compared to those with a reduced ejection fraction (HFrEF). *Heart Vessels*. 2018;33:403–412.

86 Kotecha D, Chudasama R, Lane DA, et al. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol*. 2016;203:660–666.

87 Goldhaber SZ. Venous thromboembolism in heart failure patients: pathophysiology, predictability, prevention. *J Am Coll Cardiol*. 2020;75:159–162.

88 Piazza G, Goldhaber SZ, Lessard DM, et al. Venous thromboembolism in heart failure: preventable deaths during and after hospitalization. *Am J Med*. 2011;124: 252–259.

89 Fanola CL, Norby FL, Shah AM, et al. Incident heart failure and long-term risk for venous thromboembolism. *J Am Coll Cardiol*. 2020;75:148–158.

90 Slobodan O, Boris D, Bojana S, et al. Predictive value of heart failure with reduced versus preserved ejection fraction for outcome in pulmonary embolism. *ESC Heart Fail*. 2020;7:4061–4070.

91 Winter MP, Kleber ME, Koller L, et al. Prognostic significance of tPA/PAI-1 complex in patients with heart failure and preserved ejection fraction. *Thromb Haemost*. 2017;117:471–478.

92 Kleber ME, Koller L, Goliasch G, et al. Von Willebrand factor improves risk prediction in addition to N-terminal pro-B-type natriuretic peptide in patients referred to coronary angiography and signs and symptoms of heart failure and preserved ejection fraction. *Circ Heart Fail*. 2015;8:25–32.

93 Patel TV, Mittal BV, Keithi-Reddy SR, et al. Endothelial activation markers in anemic non-dialysis chronic kidney disease patients. *Nephron Clin Pract*. 2008;110: c244–c250.

94 Conlan MG, Folsom AR, Finch A, et al. Associations of factor VIII and von Willebrand factor with age, race, sex, and risk factors for atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) study. *Thromb Haemost*. 1993;70:380–385.

95 Roldán V, Marín F, Muiña B, et al. Plasma von Willebrand factor levels are an independent risk factor for adverse events including mortality and major bleeding in anticoagulated atrial fibrillation patients. *J Am Coll Cardiol*. 2011;57:2496–2504.

96 Nordenhem A, Leander K, Hallqvist J, et al. The complex between tPA and PAI-1: risk factor for myocardial infarction as studied in the SHEEP project. *Thromb Res*. 2005;116:223–232.

97 Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.

98 Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.

99 Wulamiding K, Xu Z, Chen Y, He J, et al. Non-vitamin K antagonist oral anticoagulants versus warfarin in atrial fibrillation patients with heart failure and preserved, mildly reduced, and reduced ejection fraction: a systemic review and meta-analysis. *Front Cardiovasc Med*. 2022;9.

100 Zain A, Naseem MA, Qadeer A. Comment on: blood coagulation disorders in heart failure: from basic science to clinical perspectives. *Curr Probl Cardiol*. 2023, 101929.