ESC European Society of Cardiology

European Journal of Heart Failure (2020) **22**, 1551–1567
doi:10.1002/ejhf.1902

REVIEW

Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease

Milton Packer[1,2]*, Carolyn S.P. Lam[3,4,5], Lars H. Lund[6], Mathew S. Maurer[7], and Barry A. Borlaug[8]

[1]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA; [2]Imperial College London, London, UK; [3]National Heart Centre Singapore and Duke-National University of Singapore, Singapore; [4]University Medical Centre Groningen, Groningen, The Netherlands; [5]The George Institute for Global Health, Sydney, Australia; [6]Department of Medicine, Karolinska Institutet and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; [7]Columbia University Irving Medical Center, New York, NY, USA; and [8]Mayo Clinic, Rochester, MN, USA

Received 15 January 2020; revised 5 May 2020; accepted 17 May 2020; online publish-ahead-of-print 26 June 2020

Accumulating evidence points to the existence of an inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction (HFpEF), which is characterized by biomarkers of inflammation, an expanded epicardial adipose tissue mass, microvascular endothelial dysfunction, normal-to-mildly increased left ventricular volumes and systolic blood pressures, and possibly, altered activity of adipocyte-associated inflammatory mediators. A broad range of adipogenic metabolic and systemic inflammatory disorders – e.g. obesity, diabetes and metabolic syndrome as well as rheumatoid arthritis and psoriasis – can cause this phenotype, independent of the presence of large vessel coronary artery disease. Interestingly, when compared with men, women are both at greater risk of and may suffer greater cardiac consequences from these systemic inflammatory and metabolic disorders. Women show disproportionate increases in left ventricular filling pressures following increases in central blood volume and have greater arterial stiffness than men. Additionally, they are particularly predisposed to epicardial and intramyocardial fat expansion and imbalances in adipocyte-associated proinflammatory mediators. The hormonal interrelationships seen in inflammatory-metabolic phenotype may explain why mineralocorticoid receptor antagonists and neprilysin inhibitors may be more effective in women than in men with HFpEF. Recognition of the inflammatory-metabolic phenotype may improve an understanding of the pathogenesis of HFpEF and enhance the ability to design clinical trials of interventions in this heterogeneous syndrome.

Keywords Heart failure with preserved ejection fraction • Systemic inflammation • Obesity • Diabetes • Aldosterone • Neprilysin

Introduction

The most common cardiovascular disorder in the general population results from an inflammatory response to an ectopic accumulation of dysfunctional lipids. Hypercholesterolaemia is a major risk factor for coronary artery disease, but it is the inflammatory response to oxidized lipoproteins that leads to the formation of and undermines the stability of the atherosclerotic plaque. However, inflammation in atherosclerosis may not solely be a response to lipids that are imbibed from the bloodstream. Many systemic inflammatory diseases (e.g. rheumatoid arthritis and psoriasis) are characterized by accelerated coronary atherosclerosis

*Corresponding author. Baylor Heart and Vascular Institute, 621 N. Hall Street, Dallas, TX 75226, USA. Tel: +1 214 820-7500, Email: milton.packer@baylorhealth.edu

and a heightened risk of coronary ischaemic events.[1] In these disorders, the coronary vessels are the target of a systemic inflammatory response whose trigger resides outside of the cardiovascular system. Some have proposed that systemic inflammation induces transformational changes in epicardial adipose tissue; the resulting pockets of inflammation are transmitted to the immediately adjacent coronary vessels to cause occlusive lesions.[2]

Like the coronary arteries, the myocardium can be a target of a systemic inflammatory disorder that is initiated in non-cardiac tissues. These diseases can adversely affect the coronary microvasculature directly.[3] Additionally, these disorders are often accompanied by the accumulation and dysfunction of epicardial adipose tissue and intramyocardial lipids, which are poised to focus the effects of the systemic disorder onto the underlying cardiac tissues.[4] The epicardial release of proinflammatory mediators can cause microcirculatory dysfunction and fibrosis of the adjacent muscle.[5] When this process affects the atria, the resulting electroanatomical remodelling may lead to atrial fibrillation.[6] When the process adjoins the left ventricle, it may impair the chamber's distensibility and increase diastolic stiffness and left ventricular (LV) filling pressures.[7] This phenotype is designated herein as 'inflammatory-metabolic heart failure with a preserved ejection fraction' (HFpEF).

The myocardial inflammatory process in these patients often compromises systolic function, but in general, the LV ejection fraction is not severely depressed; typically, it is >40%. However, many patients with a LV ejection fraction of 40–50% do not have meaningful evidence of inflammation; instead, they have features of heart failure and a reduced ejection fraction (HFrEF), with evidence of cardiomyocyte injury and stretch.[8] These latter patients often respond favorably to drugs that produce important benefits in those with marked systolic dysfunction (i.e. LV ejection fraction <35–40%).[9] Therefore, the diagnosis of 'inflammatory-metabolic HFpEF' is not based on the measurement of LV ejection fraction, but instead, it is primarily determined by evidence of systemic and adipose tissue inflammation, microvascular endothelial dysfunction, and myocardial fibrosis.

Previous work on the influence of visceral fat and the actions of hormonal mediators has focused on HFpEF in obese people.[7,10] By contrast, this paper characterizes the pathophysiologic abnormalities that may lead to a distinctive form of HFpEF that is seen in a broad range of systemic inflammatory and metabolic disorders, potentially explaining why this HFpEF phenotype is predominantly a disease of women.

Characterization of the heart failure phenotype in patients with a systemic inflammatory or adipogenic metabolic disorder

A diverse range of disorders can cause heart failure with a LV ejection fraction in the normal range.[11] Some patients have surgically correctable lesions (e.g. valvular disease), and others have hypervolaemic or high-output states (e.g. obesity, cirrhosis and shunts).[10,12,13] Still others may have hypertrophic or an infiltrative cardiomyopathy. The most common infiltrative disease leading to a clinical picture that may mimic HFpEF is amyloidosis, which affects up to 15% of elderly people with heart failure, primarily men.[14] However, the majority of patients with HFpEF in clinical practice have a phenotype that is closely linked to systemic and adipose tissue inflammation, and is primarily seen in women.

Pathophysiological distinctions between inflammatory-metabolic heart failure with a preserved ejection fraction and hypertrophic or infiltrative cardiomyopathy

When first recognized, HFpEF was regarded as a form of hypertrophic cardiomyopathy,[15] a disorder that is characterized by excessive thickening of the LV walls and small LV volumes. The hypertrophic process may encroach into LV cavity, impeding the capacity of the left ventricle to accommodate blood. These patients have depressed stroke volumes and low blood pressures and may deteriorate clinically when plasma volumes are reduced by diuretics.[16] The LV end-diastolic pressure–volume relation is shifted upwards and to the left, so that cardiac filling pressures are elevated, even though cardiac filling is inadequate.

Many of these features are also present in patients with wild-type transthyretin amyloid cardiomyopathy. These individuals are generally men who have low-to-normal systolic blood pressures, a reduced LV cavity size, striking thickening of the ventricular walls, and disportionately increased levels of natriuretic peptides.[17–19] The LV end-diastolic pressure–volume relation is also shifted upwards and to the left as in hypertrophic cardiomyopathy, but in contrast with the latter, patients with cardiac amyloidosis often have right ventricular involvement as a result of amyloid infiltration.

In contrast, the HFpEF phenotype that accompanies a broad range of systemic inflammatory or metabolic diseases is primarily seen in older women with comorbidities, which may reflect the effects of the inflammatory or metabolic process on various end-organ functions.[20] The LV walls are often not thickened or only mildly so, and ventricular volumes (when indexed for body surface area and sex) are normal or modestly enlarged, and not decreased.[7,21,22] This HFpEF phenotype is frequently accompanied by sodium retention and possibly by a decrease in systemic venous capacitance, both of which can lead to an increase in central blood volume.[7,11,23] However, the ventricles cannot accommodate the expansion and redistribution of blood volume because cardiac distensibility is impaired,[7,11] most likely related to coronary microvascular dysfunction and myocardial fibrosis and/or pericardial restraint.[5,7] Inflammation-related phosphorylation of titin may also enhance myocardial stiffness.[24] The LV end-diastolic pressure–volume relationship is not necessarily shifted in these patients as it is in infiltrative cardiomyopathies;

Table 1 Contrasting features of cardiac amyloidosis and inflammatory-metabolic heart failure with a preserved ejection fraction

	Wild-type transthyretin amyloid cardiomyopathy	Inflammatory-metabolic heart failure with a preserved ejection fraction
Demographic features	Older adults, men > women	Middle-aged to elderly, women > men
Clinical presentation	Heart failure, typically with increased right-sided pressures	Heart failure, often with increased right-sided pressures
Obesity or visceral adiposity	Not characteristic	Characteristically present
Systolic blood pressure	Low to normal (often intolerant of antihypertensive drugs)	Modestly increased (or taking antihypertensive drugs)
Systemic inflammation	Not well characterized	Increased C-reactive protein and other inflammatory biomarkers
Systemic venous capacitance	Not impaired	Impaired, leading to increased central blood volume
Natriuretic peptides	Often strikingly increased	Disproportionately lower than cardiac filling pressures
Cardiac troponin	Typically increased	Occasionally increased
LV systolic function	Ejection fraction typically >40%	Ejection fraction typically >40%
Left atrial enlargement	Typically present	Typically (but not invariably) present
LV diastolic filling abnormalities	Typically present	Typically present, but often not at rest
LV wall thickness	Markedly increased (especially in men)	Often within the normal range or mildly increased
LV end-diastolic volumes (indexed for age and gender)	Typically reduced	Normal to mildly increased

LV, left ventricular.

Table 2 Principal clinical and pathophysiological characteristics of inflammatory-metabolic heart failure with a preserved ejection fraction

- Exertional dyspnoea due to heart failure with a left ventricular ejection fraction that is generally >40%
- Primarily a disease of women
- Generally accompanied by a chronic systemic inflammatory or metabolic disorder that is characterized by a derangement of adipose tissue biology (e.g. obesity, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, rheumatoid arthritis, psoriasis)
- Increased biomarkers reflecting systemic inflammation or insulin resistance (e.g. C-reactive protein)
- Mildly increased systolic blood pressure or taking medications for the treatment of hypertension
- Echocardiography reveals normal to modestly increased left ventricular volumes (indexed for gender and body surface area), generally with diastolic filling abnormalities, but without marked septal thickening
- Magnetic resonance imaging demonstrates increased epicardial adipose tissue volume, with variable degrees of fibrosis
- Coronary microvascular dysfunction, ideally measured by reduced coronary flow reserve during adenosine-induced hyperaemia, but approximated by provocative testing during non-invasive imaging
- Renal dysfunction (typically, an estimated glomerular filtration rate of 50–80 mL/min/1.73 m^2), with evidence of increased perirenal fat or renal microvascular disease related to systemic inflammation
- Potentially impaired systemic venous capacitance (often with plasma volume expansion) leading to an increase in central blood volume
- Potential reduction in adverse heart failure-related outcomes with mineralocorticoid receptor antagonists and neprilysin inhibitors

instead, patients operate on a steeper portion of the normal pressure–volume curve.[16,25] Cardiac filling pressures are increased in large part because of chamber overfilling.[16] Yet, cardiomyocyte stretch is limited, and thus, circulatory levels of natriuretic peptides are often lower than expected based on the increase in LV filling pressures.[7,11,12,20] In further contrast with hypertrophic or amyloid cardiomyopathy, patients with inflammatory HFpEF often have an elevated blood pressure, in part related to their plasma volume expansion (*Tables 1* and *2*).[11,12,17] *Table 3* provides a list of the diseases that have been linked to this form of HFpEF; importantly, these disorders are generally more prevalent in women.

Influence of sex on the mechanisms of inflammatory-metabolic heart failure with a preserved ejectin fraction

The pathways that drive inflammatory-metabolic HFpEF are particularly common in women. Women are prone to the systemic metabolic and autoimmune disorders that cause adipose tissue inflammation,[4] and they show a heightened systemic inflammatory response to the accumulation of body fat.[26] Women are particularly likely to develop myocardial steatosis in response to metabolic derangements,[27] and when compared with men, they are more susceptible to developing coronary microvascular dysfunction and

Table 3 Systemic inflammatory, metabolic and hormonal disorders that are accompanied by epicardial adipose tissue expansion and inflammation and an increased risk of heart failure with a preserved ejection fraction

Chronic systemic inflammatory disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Psoriasis
Systemic sclerosis
Inflammatory bowel disease
Chronic kidney disease
Late-onset asthma
Multiple sclerosis
Chronic adipogenic metabolic or hormonal disorders
Obesity
Diabetes
Metabolic syndrome
Non-alcoholic fatty liver disease
Hypothyroidism
Hypercortisolism (iatrogenic or endogenous)
Primary hyperaldosteronism

left atrial (LA) and LV structural and functional abnormalities in response to adiposity and systemic inflammation.[28–32]

Systemic inflammatory and metabolic disorders that lead to cardiac inflammation, diastolic filling abnormalities and heart failure

Many chronic systemic inflammatory and metabolic disorders are accompanied by an increased risk of heart failure, particularly HFpEF (*Table 3*), and this risk is independent of the development of macrovascular coronary heart disease. As noted earlier, most of these systemic disorders are more prevalent in women.

Systemic inflammatory disorders leading to heart failure with a preserved ejection fraction

Rheumatoid arthritis and systemic lupus erythematosus can lead to myocardial inflammation, coronary microcirculatory abnormalities, diastolic dysfunction, LA enlargement, and heart failure, particularly HFpEF; these abnormalities parallel the degree of clinical inflammation and are not explained by traditional cardiovascular risk factors or ischaemic heart disease.[33–39] Patients with psoriasis also exhibit coronary microvascular dysfunction, abnormal diastolic filling, and an increased risk of heart failure.[40–42] In systemic sclerosis, the myocardium is often affected by microcirculatory abnormalities and fibrosis, leading to diastolic dysfunction, abnormal LA mechanics, intolerance to volume loading, and heart failure.[43–45] Inflammatory bowel disease, chronic kidney disease, late-onset asthma and multiple sclerosis are accompanied by diastolic filling and coronary microvascular abnormalities and an increased risk of heart failure.[46–51] Regardless of the cause, biomarkers of systemic inflammation may precede the onset of HFpEF by years[52,53] and distinguish such patients from those with HFrEF.[20] Furthermore, measures of inflammation are elevated in proportion to the number of comorbidities[54]; are accompanied by abnormalities in LA structure and LV filling that are typical of HFpEF[55]; and have an adverse prognosis.[56]

Metabolic and hormonal derangements leading to heart failure with a preserved ejection fraction

In addition to systemic inflammation, numerous metabolic disorders that are accompanied by the expansion and inflammation of visceral adipose tissue have been linked to the development of HFpEF (*Table 3*). Obesity is predictably accompanied by diastolic filling abnormalities, microvascular dysfunction, and cardiac fibrosis.[57–59] An elevated body mass (especially visceral adiposity) presages a dramatic increase in the risk of heart failure (especially HFpEF)[7,10] and independent of any association with ischaemic cardiac injury.[60] Additionally, there is a strong mechanistic relationship between diabetes and heart failure; hyperglycaemia and insulin resistance are often accompanied by cardiac inflammation, coronary microvascular disease, myocardial fibrosis, and diastolic dysfunction,[61,62] which may collectively culminate in HFpEF.[63] Other disorders that are characterized by visceral adiposity and insulin resistance – e.g. the metabolic syndrome and non-alcoholic fatty liver disease – are also strongly associated with coronary microcirculatory dysfunction, ventricular fibrosis, abnormalities of diastolic filling, and an increased risk of heart failure.[64–68] Finally, patients with hypercortisolism, hypothyroidism and primary hyperaldosteronism manifest cardiac fibrosis, abnormalities of LV filling and an increased risk of heart failure, which may be ameliorated by treatment of the underlying hormonal derangement.[69–73] Each of these metabolic disorders is characterized by the expansion and inflammation of adipose tissue depots.[74–76]

The kidneys as a secondary target of inflammation

These systemic disorders may not only adversely affect the heart, but also the kidneys. The most common causes of inflammatory-metabolic HFpEF – diabetes and obesity – are important causes of chronic kidney disease.[77] Additionally, other diseases that are linked to HFpEF (e.g. rheumatoid arthritis, psoriasis and non-alcoholic steatohepatitis) increase the risk of chronic kidney disease, in proportion to the severity of the inflammatory derangement.[78–81] Chronic kidney disease is often accompanied by systemic inflammation, whose severity predicts the development of diastolic dysfunction and heart failure, including HFpEF.[82–84] Proinflammatory mediators that have been linked to HFpEF have been associated with a progressive decline in glomerular function.[85] Furthermore, the renal response to adipose tissue expansion and

inflammation can trigger changes in tubuloglomerular feedback that promote glomerular hyperfiltration and its adverse effects on renal function.[86,87]

Obesity as a link between systemic inflammation and metabolic disorders

Obesity provides an important link between systemic inflammation and metabolic disorders, and thus, is a major determinant of HFpEF, whether the primary mechanism is identified as inflammatory or metabolic.[10] Visceral adiposity amplifies the systemic inflammatory response even if its origins reside in non-adipocyte organs. As a result, concomitant obesity substantially increases the incidence and clinical severity of many inflammation-related disorders.

Obesity predicts adverse clinical outcomes and treatment responses in rheumatoid arthritis, systemic lupus erythematosus and psoriasis,[88–90] worsens functional capacity in systemic sclerosis,[91] increases the prevalence and worsens the severity of asthma,[92] has deleterious effects in inflammatory bowel disease and multiple sclerosis,[93,94] and contributes to the progression of diabetes, non-alcoholic steatohepatitis and chronic kidney disease.[95–97] By acting as a broad accelerant of systemic inflammation, obesity potentiates the likelihood of heart failure (particularly HFpEF) in patients who are already prone to its development. The predisposition to heart failure is particularly enhanced by an action of obesity to promote sodium reabsorption across multiple sites along the renal tubular epithelium.[10] Obese patients with HFpEF have plasma volume expansion that is directly proportional to body mass,[7] and additionally, obesity may limit systemic venous capacitance.[98] The resulting expansion of central blood volume is poorly tolerated when LV distensibility is impaired.[7]

Influence of sex on cardiac and vascular dysfunction leading to heart failure with a preserved ejection fraction

Women are not only at greater risk of the systemic inflammatory and metabolic disorders that are linked to HFpEF, but sex also influences the cardiovascular response to stresses that predispose to HFpEF.[99] As compared with men with HFpEF, women have more symptoms and disability,[100,101] but have more favourable long-term outcomes.[99] When compared with men, women (especially elderly women) exhibit greater impairment of LV diastolic reserve and show greater increases in pulmonary venous pressures with volume loading,[102] possibly because systemic venous capacitance is limited in women.[103] Furthemore, women show greater degrees of arterial stiffness, more impaired ventricular–vascular coupling, and more striking LV concentric remodelling with pressure overload than men.[104–106] Importantly, in the absence of HFpEF, LV volumes are smaller in women than in men (even when accounting for body surface area),[106–108] and thus, women are more reliant on a higher ejection fraction to maintain stroke volume and cardiac output,[109] an effect that may be exaggerated by aging.[110] In patients with established HFpEF, women show greater increases in pulmonary wedge pressure and abnormalities of diastolic filling at a given workload and manifest a greater LV wall thickness than men.[107,108]

Interestingly, the two most common harbingers of inflammatory-metabolic HFpEF – obesity and diabetes – have greater cardiac effects in women than men. Obesity causes greater structural changes in the hearts of women.[29,32] Central obesity exacerbates age-related ventricular-arterial stiffening in women, but not in men.[111] Both adiposity and diabetes are important determinants of LV mass and wall thickness in women, but not in men,[112,113] especially as they grow older. Similarly, obesity and other inflammatory states have a greater influence to increase LA size in women than in men,[114,115] particularly with aging.[116] Visceral adiposity is accompanied by coronary microvascular dysfunction in women, but not in men.[30] Obesity and diabetes accelerates the evolution of diastolic filling abnormalities during longitudinal follow-up more in women than men,[117] and diabetes exacerbates exercise-induced diastolic abnormalities more in women than men.[118] As a result – in obesity, diabetes and the metabolic syndrome – as compared with men, women show increased LV wall thickness and filling pressures by echocardiography and an enhanced risk of HFpEF.[119–124]

Deleterious biological transformation of epicardial adipose tissue in systemic inflammatory and metabolic disorders

Why do systemic inflammatory and adipogenic metabolic disorders target the heart? These diseases may lead to HFpEF through their common action to cause endothelial dysfunction of the coronary microvasculature.[3] Furthermore, each of these disorders also causes adipose tissue inflammation, which (if it involves the epicardial fat mass or intramyocardial lipids) may amplify and focus the systemic process onto the myocardium,[4] thus potentiating cardiac inflammation and coronary microcirculatory dysfunction, thereby impairing the distensibility of the left ventricle.

Adaptive and maladaptive roles of epicardial adipose tissue in nurturing and injuring underlying cardiovascular structures

The epicardium shares an unobstructed microcirculation with the underlying muscle, given the absence of a fascial plane between the two structures. Embryonically, it is a major source of mesenchymal stem cells for cardiac regeneration, and healthy epicardial fat has the biological properties of brown adipose tissue, which combusts proinflammatory fatty acids and secretes adipokines (e.g. adiponectin) that nourish the myocardium. However, under the influence of certain systemic inflammatory or metabolic disorders, mesenchymal cells in the epicardium are transformed into adipocytes, which develop features of white adipose tissue.[4,10] When overfilled with lipids, these adipocytes are prone to lipolysis, and the release of fatty acids triggers macrophage infiltration[125] and

the secretion of proinflammatory cytokines (leptin, tumour necrosis factor-α, interleukin-6, interleukin-1β and resistin).[10,126] The intimacy of its interface with the myocardium allows these biological derangements to be transmitted to the neighbouring muscle.[4] Proinflammatory cytokines synthesized in epicardial fat depots are ideally positioned to adversely influence the structure and function of the underlying tissues, i.e. the epicardium focuses the inflammation initiated in other organs onto the heart. Accordingly, in the presence or absence of HFpEF, the volume of epicardial adipose tissue is associated with the severity of coronary microvascular dysfunction, myocardial fibrosis and LV hypertrophy.[6,127–133] Lipids may also accumulate to an excess degree within the myocardium itself and be accompanied by adverse structural changes.[129,130]

Expansion of epicardial adipose tissue in patients with chronic systemic inflammatory and metabolic disorders and in patients with heart failure and a preserved ejection fraction

In light of the potential importance of epicardial adipose tissue expansion in the pathogenesis of HFpEF, it is noteworthy that each of the systemic inflammatory or adipogenic metabolic disorders that have been linked to HFpEF has been shown to be associated with an increase in epicardial fat volume (*Table 3*).

Specifically, rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis are accompanied by an increase in epicardial fat volume that is proportional to the duration and severity of the underlying disease and is paralleled by changes in diastolic filling parameters.[134–136] Epicardial adiposity is also seen in psoriasis,[137] inflammatory bowel disease,[138] and chronic pulmonary inflammation.[139] Similarly, in obesity, epicardial adipose tissue volume is increased[140] in relation to the degree of microvascular dysfunction, cardiac fibrosis, and ventricular hypertrophy[128] and to adverse changes in diastolic filling, LA dimensions and global longitudinal strain.[7,130,141] Diabetes is accompanied by epicardial adipose expansion and inflammation[142]; when diabetes and obesity coexist, each contributes to the volume of epicardial fat.[143] Epicardial adiposity is strongly associated with insulin resistance[144] and changes in ventricular structure and function.[145] The metabolic syndrome and non-alcoholic fatty liver disease are associated with increases in epicardial fat that are accompanied by proportional degrees of diastolic dysfunction and microvascular injury.[128,146,147] Other hormonal derangements that have been linked to HFpEF (primary hyperaldosteronism, Cushing's syndrome and hypothyroidism) exhibit increases in epicardial fat volume that parallel the severity of the underlying disorder.[148–150]

The systemic inflammatory or metabolic disorders that are linked to HFpEF are associated with epicardial adipose tissue expansion before the onset of heart failure, and thus, epicardial fat volume is increased in patients with established HFpEF[7,151] – a feature that may distinguish HFpEF from HFrEF.[152,153] [One report suggesting a decrease in epicardial fat volume in HFpEF evaluated obese patients who had an inexplicably low prevalence of atrial fibrillation and likely had a hypervolaemic (rather than an inflammatory) state.[154]] In patients with HFpEF, epicardial adipose tissue expansion has been associated with greater degrees of LA and LV dysfunction and a higher prevalence of atrial fibrillation.[152,153] Spread of the systemic inflammatory process to the kidneys may explain why epicardial fat is increased in chronic kidney disease.[155] Epicardial adipose tissue mass predicts the progressive decline in glomerular function and the onset of albuminuria in diabetic nephropathy.[156,157] Epicardial adiposity is associated with chronic kidney disease even in the absence of diabetes.[158]

Influence of sex on epicardial adipose tissue in inflammatory-metabolic heart failure with a preserved ejection fraction

Given the potential importance of epicardial adipose tissue inflammation in mediating the structural and functional changes in the myocardium in HFpEF, it is noteworthy that epicardial fat volume appears to be particularly increased in women, particularly as they age and become postmenopausal.[31,159,160] Epicardial fat is likely to be accompanied by evidence of systemic inflammation, increases in systolic blood pressure, coronary microcirculatory abnormalities and abnormalities of diastolic filling in women, but not in men.[31,127,161] Intramyocardial fat accumulation in HFpEF is also particularly characteristic of women.[129]

Challenges in assessing the role of epicardial adipose tissue derangements in inflammatory-metabolic heart failure with a preserved ejection fraction

Notwithstanding these observations, deciphering the role of epicardial adipose tissue inflammation in the pathogenesis of HFpEF is difficult. Imaging can quantify the volume of epicardial fat, but it cannot assess its biological activity, and thus, cannot determine if it is nutritive or proinflammatory. Furthermore, the increase in circulating proinflammatory adipocytokines in epicardial adiposity may reflect their release from non-cardiac visceral fat depots, which often increase in parallel with an expansion of epicardial adipose tissue. As in the case of epicardial fat, abdominal fat is closely associated with LV dysfunction.[111,162]

Nevertheless, epicardial fat depots (as well as intramyocardial lipids) are unique in their exceptionally close proximity to the myocardium, and fat expansion adjacent to cardiomyocytes may be particularly linked to cardiac derangements.[159,163] Furthermore, the premise that an expanded epicardial fat mass is biologically abnormal is supported by the analyses of tissue obtained during surgery and by the finding of an elevated transcardiac gradient for proinflammatory adipocytokines in states of epicardial adiposity.[164–167] Yet, the intimacy of epicardial fat and the myocardium can be bidirectional; conceivably, epicardial adipose tissue expansion may reflect the extension of inflammation originating in the heart to the epicardium. If so, then increases in epicardial fat would represent a biomarker rather than a cause of cardiac

inflammation. However, it is noteworthy that interventions that selectively remove epicardial fat (by excision or lipolysis) appear to reduce proinflammatory cytokines, ameliorate the severity of nearby coronary lesions and improve myocardial function, highlighting the likelihood of an inflammatory source within the epicardium, acting as a transducer of a systemic process.[168,169]

Role of aldosterone, natriuretic peptides and leptin in the genesis of adipose tissue inflammation and the development of heart failure with a preserved ejection fraction

Why does a broad range of systemic inflammatory and metabolic disorders lead to epicardial adipose tissue expansion? Systemic and adipose tissue inflammation has been linked to abnormalities in several hormonal mediators (i.e. aldosterone, leptin and natriuretic peptides) that may contribute to the development of epicardial adiposity. Previous work has focused on their contribution in the genesis of heart failure in obesity,[10] whereas this paper focuses on their role in the epicardial adipose tissue expansion and in mediating the inflammatory processes seen in the myriad of systemic disorders that are linked to HFpEF.

Aldosterone promotes epicardial adipose tissue expansion and its adverse effects on the myocardium. Mineralocorticoid receptor signalling is required for the differentiation of adipocytes and their transition to a proinflammatory state,[170] promoting epicardial adipogenesis and the secretion of proinflammatory cytokines.[150,171] Elevated tissue activity of aldosterone causes coronary microvascular dysfunction and fibrosis,[172,173] and the infusion of aldosterone contributes to the evolution of experimental HFpEF.[174] Circulating levels of aldosterone are increased in parallel with abnormalities of LV geometry,[175] although interestingly, hyperaldosteronism has not been noted in patients with established HFpEF,[176] supporting the hypothesis that aldosterone (if released by epicardial adipocytes) acts primarily in a paracrine manner.

In contrast to the actions of aldosterone, natriuretic peptides have direct effects to limit adipogenesis and restrain the proinflammatory transformation of adipose tissue[177–179]; natriuretic peptides are capable of reverting epicardial fat to its healthy state, thereby enhancing its nutritive functions.[180,181] By doing so, natriuretic peptide signalling opposes the actions of aldosterone to promote the expansion and inflammation of adipose tissue; circulating levels of natriuretic peptides are inversely related to epicardial as well as visceral fat mass.[182,183] However, dysfunctional adipocytes accelerate the clearance of natriuretic peptides and secrete neprilysin (which degrades natriuretic peptides), thus promoting a positive feedback loop that stimulates adipogenesis.[184,185] Attenuation of the actions of natriuretic peptides also leads to coronary microvascular dysfunction and cardiac fibrosis[186,187]; the resulting limitation of ventricular stretch further weakens the stimulus to natriuretic peptide synthesis.[7] Interestingly, circulating neprilysin levels have been reported to be increased in HFpEF in some studies[188] (but not others[189]); nevertheless, patients with HFpEF have accelerated breakdown of natriuretic peptides.[190] In any case, neprilysin inhibition attenuates atrial distension and ventricular wall stress in patients with HFpEF with obesity, and these benefits are particularly notable in those who have type 2 diabetes.[191]

The expansion and biological transformation of epicardial adipose tissue promotes its synthesis of proinflammatory adipocytokines, including leptin, tumour necrosis factor-α, interleukin-1β and interleukin-6.[4,126] These mediators are released locally (promoting cardiac inflammation) and systemically (potentially contributing to renal dysfunction).[5] Among the candidate adipocytokines, leptin is most likely to cause sodium retention and be linked to systemic inflammatory and adipogenic metabolic disorders.[10] Circulating levels of leptin are closely associated with those of aldosterone in population studies.[192] Leptin stimulates aldosterone secretion from the adrenal cortex[193] and promotes its proinflammatory actions[194]; in return, aldosterone can increase the synthesis of leptin.[195] In a counterregulatory manner, natriuretic peptides inhibit the synthesis of both leptin and aldosterone[196,197]; circulating levels of leptin and natriuretic peptides are inversely related.[182,198] Circulating leptin levels are correlated with epicardial fat mass[163] and are increased in patients with HFpEF.[198,199]

Role of aldosterone, leptin and natriuretic peptides in the pathogenesis of systemic inflammatory and adipogenic metabolic disorders

If derangements in aldosterone, natriuretic peptides and leptin contribute to the expansion of epicardial adipose tissue, it is not surprising that imbalances in these hormonal systems are seen in the systemic inflammatory and metabolic disorders linked to HFpEF. In fact, these adipocyte-associated mediators appear to play a central role in promoting and modulating the inflammatory process itself.

Aldosterone stimulates proinflammatory pathways in a broad range of cell types[171,200]; and mineralocorticoid receptor antagonism attenuates inflammasome activity and blocks the production of proinflammatory cytokines in adipocytes and macrophages.[201,202] Rheumatoid arthritis is characterized by increased levels of aldosterone in blood and inflamed tissues,[203,204] and spironolactone has been proposed as an anti-inflammatory treatment for the disorder.[205] The activity of aldosterone is increased in ulcerative colitis, multiple sclerosis, and pulmonary inflammation.[206–208] Finally, adipocytes are an important source of aldosterone,[209] and obesity is characterized by hyperaldosteronism[210]; increased levels of aldosterone precede the development of the metabolic syndrome[211] and predict the development of diabetes.[212] Spironolactone ameliorates insulin resistance[213]; and aldosterone contributes to the microvascular complications of diabetes.[214,215]

Leptin also plays a central role in immune responses and inflammation.[216] The adipokine stimulates the proliferation of monocytes and their production of proinflammatory cytokines, and

it fuels the activation of T cells.[217,218] Levels of leptin in blood and synovial fluid are increased in rheumatoid arthritis in proportion to the disease activity,[219] and leptin drives autommune responses in systemic lupus erythematosus.[220] Increased leptin is a marker of disease activity in chronic pulmonary disorders, inflammatory bowel disease and multiple sclerosis.[221–223] Additionally, leptin is increased in proportion to body mass and insulin resistance in obesity and diabetes.[224] Increased leptin levels are seen in hypercortisolism and primary aldosteronism and are reduced by treatment.[225,226]

Endogenous natriuretic peptides also play an important role in the pathogenesis of systemic inflammatory and adipogenic metabolic disorders, but in a manner opposite to that of aldosterone and leptin. Natriuretic peptides inhibit pathways involved in inflammation and attenuate the production of proinflammatory cytokines by macrophages and adipocytes.[179,227] Importantly, circulating levels of natriuretic peptides are decreased in obesity, diabetes, metabolic syndrome and non-alcoholic fatty liver disease, particularly in women[228–231]; in addition, these disorders are accompanied by impaired responsiveness to the actions of natriuretic peptides in adipose tissue, blood vessels and the kidney.[232–234] The impairment of natriuretic peptide signalling may be related to an increase in neprilysin that is seen in states of visceral adiposity[185]; enhanced neprilysin activity has been implicated in the end-organ injury seen in diabetes.[234] Furthermore, the activity of neprilysin is increased at sites of disease activity in rheumatoid arthritis and systemic sclerosis,[235,236] where it may negate the counterbalancing anti-inflammatory actions of locally active natriuretic peptides. The loss of the adaptive action of biologically active natriuretic peptides should not be confused with reports that circulating levels of N-terminal pro B-type natriuretic peptide (BNP) (an inactive prohormone) are increased in many systemic inflammatory disorders, where they primarily represent a biomarker of cardiac dysfunction.[237,238]

Sex and the neurohormonal response to adipose tissue inflammation

Given the potential role of adipocyte-associated inflammatory mediators in the development of HFpEF, it is noteworthy that sex influences their synthesis and their interactions. When compared with men, women have higher levels of leptin and aldosterone.[239] These relationships may be related to greater visceral adiposity in women,[240] but women also show higher levels of and are more sensitive to the effects of agonists of the secretion of aldosterone.[241,242] Furthermore, women manifest a heightened leptin response to inflammation and visceral adiposity.[242,243] Leptin activates the sympathetic nervous system and increases blood pressure; interestingly, women show greater sympathetic response to leptin than men,[244] and leptin is correlated with blood pressure in women, but not in men.[245] Conversely, although women have higher levels of natriuretic peptides than men when healthy, they have lower levels if they are obese,[228] and these are further reduced when they become postmenopausal.[246] Interestingly, natriuretic peptides are particularly decreased in visceral adiposity,[183,247] and the lower levels of natriuretic peptides in women are still apparent in patients with heart failure.[248] When compared with men, women with HFpEF have lower levels of the biologically active BNP[249] – but not the inactive prohormone, N-terminal proBNP[250] – consistent with increased adiposity-related neprilysin-mediated breakdown of the former, but not the latter.[185]

Thus, systemic inflammatory and metabolic disorders are characterized by an increase in proinflammatory mediators (aldosterone and leptin) and decrease in the counterbalancing effects of natriuretic peptides. The net result may be to transform the biology of the visceral (and particularly epicardial) adipocytes, thus focusing the systemic inflammatory process onto the myocardium and leading to HFpEF. These interactions are particularly prominent in women.

Potential therapeutic strategies for inflammatory-metabolic heart failure with a preserved ejection fraction

Patients with the inflammatory-metabolic phenotype of HFpEF may respond to the treatment of the underlying systemic disorder. Observational studies have noted favourable effects on the course of heart failure following bariatric surgery for obesity[251]; on the risk of death in patients with HFpEF who were prescribed statins for dyslipidaemia or diabetes[252]; and on the risk of heart failure hospitalization with the use of methotrexate in rheumatoid arthritis,[253] but these benefits have not been evaluated in randomized controlled trials. Interestingly, the effect of statins on the course of HFpEF is independent of any benefits on coronary heart disease,[254] a pattern that differs from that seen when statins are prescribed to patients with HFrEF.[255]

If increases in aldosterone and leptin along with decreases in natriuretic peptide signalling contribute to the development of inflammatory-metabolic HFpEF, then interventions that ameliorate these abnormalities might be expected to have favourable effects, and such benefits (if present) may be particularly notable in women.

Mineralocorticoid receptor antagonists

The findings of randomized controlled trials suggest that inhibition of the action of aldosterone may have benefits in HFpEF. Spironolactone improved LV filling dynamics and improved exercise tolerance in patients with HFpEF in some studies, but not in others.[256,257] In the TOPCAT trial, when the analyses were restricted to the regions where sites recruited patients with HFpEF and where patients received their study medication, mineralocorticoid receptor antagonism appeared to reduce the risk of cardiovascular death and hospitalization for heart failure.[258]

The proportion of patients with the inflammatory-metabolic form of HFpEF in the TOPCAT trial is not known. However, patients with a higher body mass index were more likely to respond to spironolactone[259]; a differential response might have been more readily distinguished if visceral adiposity had been assessed directly.[260] This possibility is supported by analyses indicating that

Table 4 Pathophysiological mechanisms and clinical observations demonstrating that women may be at greater risk for inflammatory-metabolic heart failure with a preserved ejection fraction than men

- Women predominate among community-based cohorts of HFpEF
- Women exhibit higher pulmonary venous pressures with volume loading, possibly because women have a greater limitation of systemic venous capacitance
- Women show greater degree of arterial stiffness, more impaired ventricular–vascular coupling, and more striking LV concentric remodelling with pressure overload than men
- LV volumes are smaller in women than in men (even when accounting for differences in body surface area), and thus, women are more reliant on a higher ejection fraction to maintain stroke volume and cardiac output
- In patients with HFpEF, women show greater increases in pulmonary wedge pressure and abnormalities of diastolic filling dynamics at a given workload and manifest greater LV wall thickness than men. Women with HFpEF have greater symptoms and disability than men
- Systemic inflammatory and metabolic disorders that are linked to HFpEF are more common in women than men
- Women are more likely than men to experience systemic inflammation and show increases in proinflammatory cytokines in response to increases in body fat
- As compared to men, women are more likely to develop myocardial steatosis in response to metabolic derangements, and women have greater volumes of epicardial or intramyocardial fat than men, particularly as they age and particularly if they have HFpEF
- Epicardial fat is accompanied by evidence of systemic inflammation, coronary microcirculatory abnormalities, abnormalities of diastolic filling and increases in blood pressure in women, but not in men
- As compared with men, women are more likely to show adverse changes in cardiac structure and function in response to systemic inflammation and metabolic disorders. Obesity causes greater structural changes in the hearts of women, and obesity and diabetes increases the risk of HFpEF more in women than in men
- Women have higher levels of leptin and aldosterone than men, and they are more sensitive to the effects of agonists of aldosterone secretion. Obesity is more likely to be accompanied by hyperaldosteronism in women, and women show heightened leptin response to inflammation and visceral adiposity
- In states of adipose tissue inflammation and insulin resistance, circulating levels of natriuretic peptides are decreased more in women than men. As compared with men with HFpEF, women with HFpEF have lower levels of B-type natriuretic peptide
- Women show greater increases in sympathetic activity in response to leptin than men, and leptin is correlated with blood pressure in women, but not in men
- Women with HFpEF may show a greater reduction in all-cause mortality with mineralocorticoid receptor antagonism than men
- Women with HFpEF may show a greater reduction in hospitalizations for heart failure with neprilysin inhibition than men

HFpEF, heart failure with a preserved ejection fraction; LV, left ventricular.

patients were more likely to benefit from spironolactone if they had circulating natriuretic peptides that were lower than the median value[261]; decreased levels likely identified patients with obesity- or inflammation-related HFpEF. Interestingly, low levels of natriuretic peptides also identified patients with HFpEF most likely to respond in the I-PRESERVE trial, which evaluated an inhibitor of aldosterone synthesis.[262] Furthermore, in TOPCAT, women (who are prone to inflammatory-metabolic HFpEF) responded more favourably than men on certain outcome measures.[263] Spironolactone reduced the risk of death by 34% in women, with no apparent benefit in men (interaction $P = 0.02$), although there was no treatment-by-sex interaction for the effect on hospitalizations for heart failure.

Inhibitors of neprilysin

Neprilysin inhibition increases levels of natriuretic peptides, potentially explaining its ability to ameliorate cardiac and renal injury, inflammation and fibrosis in states of sodium overload or diabetes.[186,237,264] In patients with HFpEF most of whom were obese, neprilysin inhibition reduced myocardial injury, biomarkers of LV filling pressures and LA size, and the effect was particularly notable in patients with diabetes.[191]

In a large-scale double-blind randomized trial (PARAGON-HF), neprilysin inhibition produced a modest decrease in the number of hospitalizations for heart failure.[265] As in TOPCAT, the trial enrolled both patients with inflammatory-metabolic HFpEF as well as other diseases that mimic HFpEF. Interestingly, the trial reported a sex-by-treatment interaction, which suggested a greater benefit of neprilysin inhibition in women. When compared with valsartan, sacubitril/valsartan reduced the likelihood of cardiovascular death and total hospitalizations for heart failure by 27% in women, but treatment did not influence this risk in men (interaction $P < 0.006$). Importantly, the treatment-by-sex interaction was independent of the influence of ejection fraction on the effects of neprilysin inhibition seen in the trial. Ongoing analyses are determining if this finding may be related to a favourable effect of neprilysin inhibition on the inflammatory-metabolic phenotype of HFpEF, particularly among women, or conversely, if the enrolment of patients with cardiac amyloidosis may have attenuated the benefit of neprilysin inhibition in men.

Sodium–glucose co-transporter 2 inhibitors

In both experimental and clinical studies, sodium–glucose co-transporter 2 (SGLT2) inhibitors reduce adipose tissue inflammation and epicardial fat mass; inhibit coronary microvascular

dysfunction and myocardial fibrosis; and improve LV diastolic filling, thus ameliorating the evolution of HFpEF.[266–268] In addition, these drugs inhibit sodium reabsorption in the proximal renal tubule, the site where metabolic disorders may act to cause sodium retention.[269] As a result of these effects, SGLT2 inhibitors may function as physiological antagonists of leptin.[270] These salutary actions may explain why SGLT2 inhibitors reduce the risk of heart failure hospitalizations in patients with type 2 diabetes[271]; these trials noted a decrease in new-onset HFpEF as well as a reduction in heart failure events in patients with established HFpEF.[63,272] Since all patients who had or developed HFpEF in these trials had some underlying cause of the inflammatory/metabolic HFpEF, no treatment-by-sex interaction might be expected. However, ongoing large-scale trials of SGLT2 inhibitors are enrolling non-diabetic patients with HFpEF, and they are likely to enrol patients without inflammatory/metabolic HFpEF; thus, they may be poised to find a sex-by-treatment interaction similar to that seen in other recent HFpEF trials.

Summary and conclusions

A broad range of chronic systemic inflammatory and adipogenic metabolic and hormonal disorders increase the risk of HFpEF. These diseases may cause HFpEF by virtue of their common action to promote global microvascular endothelial dysfunction and adipose tissue inflammation, particularly among epicardial adipocytes. The activation of aldosterone, leptin and neprilysin that is seen in systemic inflammatory and metabolic disorders may mediate the accumulation and dysfunction of epicardial (and other forms of visceral) fat. The transmission of inflammation related to the accumulation of epicardial adipose tissue or intramyocardial lipids to the adjacent cardiac tissues may cause microvascular dysfunction, cardiac fibrosis and impaired LV distensibility – the features of inflammatory-metabolic HFpEF.

Importantly, the inflammatory-metabolic phenotype of HFpEF is primarily seen in women. When compared with men, women are at greater risk of the systemic inflammatory and metabolic disorders that are linked to HFpEF, and women experience exaggerated cardiovascular responses to the haemodynamic and inflammatory stresses that predispose to HFpEF. Epicardial fat volume is particularly increased in women, and such expansion is more likely to be accompanied by systemic inflammation, coronary microcirculatory abnormalities and abnormalities of LV diastolic filling in women than in men. Furthermore, when compared with men, women have higher levels and exhibit exaggerated responses to leptin and aldosterone and show greater relative deficiency of natriuretic peptides. Accordingly, systemic inflammation and metabolic disorders linked to adipose tissue inflammation are more likely to have adverse cardiovascular effects in women than men (*Table 4*).

If adipose tissue inflammation drives the pathogenesis of HFpEF in systemic inflammatory and adipogenic metabolic disorders, then interventions directed at reducing the influence of aldosterone or potentiating the actions of natriuretic peptides might have favourable effects in those with inflammatory-metabolic HFpEF. This hypothesis may explain sex differences in outcomes observed in trials of mineralocorticoid receptor antagonism and neprilysin inhibition in HFpEF.

Conflict of interest: M.P. has recently consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi-Sankyo, Gilead, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance. None of these relationships are related to this work or to the topic of this manuscript. C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, WebMD Global LLC, Radcliffe Group Ltd and Corpus. None of these relationships are related to this work or to the topic of this manuscript. L.H.L. reports personal fees from Abbott, AstraZeneca, Bayer, Medscape, Merck, Mundipharma, Novartis, Pharmacosmos, Relypsa, Sanofi and Vifor-Fresenius and grants from AstraZeneca, Boehringer Ingelehim, Boston Scientific, Mundipharma, Novartis, Relypsa and Vifor-Frenenius. None of these relationships are related to this work or to the topic of this manuscript. M.S.M. receives grant support from NIH R01HL139671–01, R21AG058348 and K24AG036778. He has had consulting income from Pfizer, GSK, Eldos, Prothena, Akcea and Alnylam, and institution received clinical trial funding from Pfizer, Prothena, Eidos and Alnylam. None of these relationships are related to this work or to the topic of this manuscript. B.A.B. has received grant support from the NIH/NHLBI (RO1 HL128526 and U10 HL110262), Medtronic, Tenax, GlaxoSmithKline, Mesoblast, AstraZeneca, Novartis, Corvia.

References

1. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, Troxel AB, Hennessy S, Kimmel SE, Margolis DJ, Choi H, Mehta NN, Gelfand JM. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;**74**:326–332.
2. Mancio J, Azevedo D, Saraiva F, Azevedo AI, Pires-Morais G, Leite-Moreira A, Falcao-Pires I, Lunet N, Bettencourt N. Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2018;**19**:490–497.
3. 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.
4. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *J Am Coll Cardiol* 2018;**71**:2360–2372.
5. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation* 2015;**131**:550–559.
6. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F, Amour J, Leprince P, Dutour A, Clément K, Hatem SN. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. *Eur Heart J* 2015;**36**:795–805a.
7. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6–19.

8. Moliner P, Lupón J, Barallat J, de Antonio M, Domingo M, Núñez J, Zamora E, Galán A, Santesmases J, Pastor C, Bayes-Genis A. Bio-profiling and bio-prognostication of chronic heart failure with mid-range ejection fraction. *Int J Cardiol* 2018;**257**:188–192.
9. Butler J, Anker SD, Packer M. Redefining heart failure with a reduced ejection fraction. *JAMA* 2019;**322**:1761–1762.
10. Packer M. Leptin-aldosterone-neprilysin axis: identification of its distinctive role in the pathogenesis of the three phenotypes of heart failure in people with obesity. *Circulation* 2018;**137**:1614–1631.
11. Maurer MS, King DL, El-Khoury Rumbarger L, Packer M, Burkhoff D. Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. *J Card Fail* 2005;**11**:177–187.
12. Packer M. The conundrum of patients with obesity, exercise intolerance, elevated ventricular filling pressures and a measured ejection fraction in the normal range. *Eur J Heart Fail* 2019;**21**:156–162.
13. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Di Mario U, Leonetti F. Adapted changes in left ventricular structure and function in severe uncomplicated obesity. *Obes Res* 2004;**12**:1616–1621.
14. Griffin JM, Maurer MS. Cardiac amyloidosis a rare disease in older adults hospitalized for heart failure? *Circ Heart Fail* 2019;**12**:e006169.
15. Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. *N Engl J Med* 1985;**312**:277–283.
16. Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? *Circulation* 2003;**107**:656–658.
17. Damy T, Maurer MS, Rapezzi C, Planté-Bordeneuve V, Karayal ON, Mundayat R, Suhr OB, Kristen AV. Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy. *Open Heart* 2016;**3**:e000289.
18. Brun S, Cariou E, Fournier P, Ribes D, Faguer S, Huart A, Carrié D, Galinier M, Lairez O; Toulouse Amyloidosis Research Network Collaborators. Value of natriuretic peptides and tissue Doppler imaging in the estimation of left ventricular filling pressure in patients with cardiac amyloidosis. *Open Heart* 2019;**6**:e000980.
19. Lee SP, Lee ES, Choi H, Im HJ, Koh Y, Lee MH, Kwon JH, Paeng JC, Kim HK, Cheon GJ, Kim YJ, Kim I, Yoon SS, Seo JW, Sohn DW. 11C-Pittsburgh B PET imaging in cardiac amyloidosis. *JACC Cardiovasc Imaging* 2015;**8**:50–59.
20. Tromp J, Khan MA, Klip IT, Meyer S, de Boer RA, Jaarsma T, Hillege H, van Veldhuisen DJ, van der Meer P, Voors AA. Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. *J Am Heart Assoc* 2017;**6**:e003989.
21. Maurer MS, Burkhoff D, Fried LP, Gottdiener J, King DL, Kitzman DW. Ventricular structure and function in hypertensive participants with heart failure and a normal ejection fraction: the Cardiovascular Health Study. *J Am Coll Cardiol* 2007;**49**:972–981.
22. Santos AB, Kraigher-Krainer E, Gupta DK, Claggett B, Zile MR, Pieske B, Voors AA, Lefkowitz M, Bransford T, Shi V, Packer M, McMurray JJ, Shah AM, Solomon SD; PARAMOUNT Investigators. Impaired left atrial function in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014;**16**:1096–1103.
23. Balmain S, Padmanabhan N, Ferrell WR, Morton JJ, McMurray JJ. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. *Eur J Heart Fail* 2007;**9**:865–871.
24. Zile MR, Baicu CF, Ikonomidis JS, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, Redfield MM, Bull DA, Granzier HL, LeWinter MM. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. *Circulation* 2015;**131**:1247–1259.
25. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003;**107**:714–720.
26. Khera A, Vega GL, Das SR, Ayers C, McGuire DK, Grundy SM, de Lemos JA. Sex differences in the relationship between C-reactive protein and body fat. *J Clin Endocrinol Metab* 2009;**94**:3251–3258.
27. Iozzo P, Lautamaki R, Borra R, Lehto HR, Bucci M, Viljanen A, Parkka J, Lepomaki V, Maggio R, Parkkola R, Knuuti J, Nuutila P. Contribution of glucose tolerance and gender to cardiac adiposity. *J Clin Endocrinol Metab* 2009;**94**:4472–4482.
28. Wei J, Nelson MD, Szczepaniak EW, Smith L, Mehta PK, Thomson LE, Berman DS, Li D, Bairey Merz CN, Szczepaniak LS. Myocardial steatosis as a possible mechanistic link between diastolic dysfunction and coronary microvascular dysfunction in women. *Am J Physiol Heart Circ Physiol* 2016;**310**:H14–H19.
29. Lai YH, Liu ME, Su CH, Yun CH, Liu CY, Hou CJ, Hu KC, Hung CL, Yeh HI, Lam CS. Obesity-related changes in cardiac structure and function among Asian men and women. *J Am Coll Cardiol* 2017;**69**:2876–2878.
30. Hall ME, Brinkley TE, Chughtai H, Morgan TM, Hamilton CA, Jordan JH, Stacey RB, Soots S, Hundley WG. Adiposity is associated with gender-specific reductions in left ventricular myocardial perfusion during dobutamine stress. *PLoS One* 2016;**11**:e0146519.
31. Kim SA, Kim MN, Shim WJ, Park SM. Epicardial adipose tissue is related to cardiac function in elderly women, but not in men. *Nutr Metab Cardiovasc Dis* 2017;**27**:41–47.
32. Kuch B, Muscholl M, Luchner A, Döring A, Riegger GA, Schunkert H, Hense HW. Gender specific differences in left ventricular adaptation to obesity and hypertension. *J Hum Hypertens* 1998;**12**:685–691.
33. Amigues I, Russo C, Giles JT, Tugcu A, Weinberg R, Bokhari S, Bathon JM. Myocardial microvascular dysfunction in rheumatoid arthritis. Quantitation by ^{13}N-ammonia positron emission tomography/computed tomography. *Circ Cardiovasc Imaging* 2019;**12**:e007495.
34. Davis JM 3rd, Roger VL, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. *Arthritis Rheum* 2008;**58**:2603–2611.
35. Davis JM 3rd, Lin G, Oh JK, Crowson CS, Achenbach SJ, Therneau TM, Matteson EL, Rodeheffer RJ, Gabriel SE. Five-year changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population. *Int J Cardiol* 2017;**240**:379–385.
36. Kim CH, Al-Kindi SG, Jandali B, Askari AD, Zacharias M, Oliveira GH. Incidence and risk of heart failure in systemic lupus erythematosus. *Heart* 2017;**103**:227–233.
37. Sandhu VK, Wei J, Thomson LEJ, Berman DS, Schapira J, Wallace D, Weisman MH, Bairey Merz CN, Ishimori ML. Five-year follow up of coronary microvascular dysfunction and coronary artery disease in systemic lupus erythematosus: results from a community-based lupus cohort. *Arthritis Care Res* 2020;**72**:882–887.
38. Elnady BM, Abdelghafar AS, Khalik ES, Algethami MM, Basiony AS, Al-Otaibi MD, Al-Otaibi ME. The implication of tissue Doppler echocardiography and cardiopulmonary exercise in early detection of cardiac dysfunction in systemic lupus erythematosus patients. *Eur J Rheumatol* 2016;**3**:109–117.
39. Mantel Ä, Holmqvist M, Andersson DC, Lund LH, Askling J. Association between rheumatoid arthritis and risk of ischemic and nonischemic heart failure. *J Am Coll Cardiol* 2017;**69**:1275–1285.
40. Gullu H, Caliskan M, Dursun R, Ciftci O, Guven A, Muderrisoglu H. Impaired coronary microvascular function and its association with disease duration and inflammation in patients with psoriasis. *Echocardiography* 2013;**30**:912–918.
41. Ozden HK, Polat M, Ozturk S, Bugdayci G. Assessment of subclinical cardiac damage in chronic plaque psoriasis patients: a case control study. *Arch Med Sci Atheroscler Dis* 2016;**1**:e126–e132.
42. Khalid U, Ahlehoff O, Gislason GH, Kristensen SL, Skov L, Torp-Pedersen C, Hansen PR. Psoriasis and risk of heart failure: a nationwide cohort study. *Eur J Heart Fail* 2014;**16**:743–748.
43. Rodríguez-Reyna TS, Morelos-Guzman M, Hernández-Reyes P, Montero-Duarte K, Martínez-Reyes C, Reyes-Utrera C, Vazquez-La Madrid J, Morales-Blanhir J, Núñez-Álvarez C, Cabiedes-Contreras J. Assessment of myocardial fibrosis and microvascular damage in systemic sclerosis by magnetic resonance imaging and coronary angiotomography. *Rheumatology (Oxford)* 2015;**54**:647–654.
44. D'Alto M, Romeo E, Argiento P, Mattera Iacono A, Vettori S, Riccardi A, Allanore Y, D'Andrea A, Rea G, Bossone E, Valentini G, Naeije R, Golino P. Hemodynamic changes after acute fluid loading in patients with systemic sclerosis without pulmonary hypertension. *Pulm Circ* 2019;**9**:2045894018816089.
45. Porpáczy A, Nógrádi Á, Kehl D, Strenner M, Minier T, Czirják L, Komócsi A, Faludi R. Impairment of left atrial mechanics is an early sign of myocardial involvement in systemic sclerosis. *J Card Fail* 2018;**24**:234–242.
46. Caliskan Z, Gokturk HS, Caliskan M, Gullu H, Ciftci O, Ozgur GT, Guven A, Selcuk H. Impaired coronary microvascular and left ventricular diastolic function in patients with inflammatory bowel disease. *Microvasc Res* 2015;**97**:25–30.
47. Aniwan S, Pardi DS, Tremaine WJ, Loftus EV Jr. Increased risk of acute myocardial infarction and heart failure in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2018;**16**:1607–1615.e1.
48. Yeh JJ, Wei YF, Lin CL, Hsu WH. Association of asthma-chronic obstructive pulmonary disease overlap syndrome with coronary artery disease, cardiac dysrhythmia and heart failure: a population-based retrospective cohort study. *BMJ Open* 2017;**7**:e017657.
49. Jadidi E, Mohammadi M, Moradi T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. *Mult Scler* 2013;**19**:1336–1340.
50. Joyce E, Mulroy E, Scott J, Melling J, Goggin C, McGorrian C, O'Rourke K, Lynch T, Mahon N. Subclinical myocardial dysfunction in multiple sclerosis patients remotely treated with mitoxantrone: evidence of persistent diastolic dysfunction. *J Card Fail* 2013;**19**:571–576.

51. Jain A, Scott C, Chen HH. The renal-cardiac connection in subjects with preserved ejection fraction: a population based study. *ESC Heart Fail* 2017;**4**:266–273.
52. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, Liu Y, Hoffmann U, Bauer DC, Newman AB, Kritchevsky SB, Harris TB, Butler J; Health ABC Study Investigators. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. *J Am Coll Cardiol* 2010;**55**:2129–2137.
53. AlBadri A, Lai K, Wei J, Landes S, Mehta PK, Li Q, Johnson D, Reis SE, Kelsey SF, Bittner V, Sopko G, Shaw LJ, Pepine CJ, Bairey Merz CN. Inflammatory biomarkers as predictors of heart failure in women without obstructive coronary artery disease: a report from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE). *PLoS One* 2017;**12**:e0177684.
54. DuBrock HM, Redfield MM, AbouEzzeddine OF. High-sensitivity C-reactive protein in heart failure with preserved ejection fraction. *PLoS One* 2018;**13**:e0201836.
55. Kloch M, Stolarz-Skrzypek K, Olszanecka A, Wojciechowska W, Bednarski A, Stefaniak J, Czarnecka D. Inflammatory markers and left ventricular diastolic dysfunction in a family-based population study. *Kardiol Pol* 2019;**77**:33–39.
56. Koller L, Kleber M, Goliasch G, Sulzgruber P, Scharnagl H, Silbernagel G, Grammer T, Delgado G, Tomaschitz A, Pilz S, März W, Niessner A. C-reactive protein predicts mortality in patients referred for coronary angiography and symptoms of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014;**16**:758–766.
57. Kurnicka K, Domienik-Karłowicz J, Lichodziejewska B, Bielecki M, Kozłowska M, Goliszek S, Dzikowska-Diduch O, Lisik W, Kosieradzki M, Pruszczyk P. Improvement of left ventricular diastolic function and left heart morphology in young women with morbid obesity six months after bariatric surgery. *Cardiol J* 2018;**25**:97–105.
58. Sorop O, Olver TD, van de Wouw J, Heinonen I, van Duin RW, Duncker DJ, Merkus D. The microcirculation: a key player in obesity-associated cardiovascular disease. *Cardiovasc Res* 2017;**113**:1035–1045.
59. Eschalier R, Rossignol P, Kearney-Schwartz A, Adamopoulos C, Karatzidou K, Fay R, Mandry D, Marie PY, Zannad F. Features of cardiac remodeling, associated with blood pressure and fibrosis biomarkers, are frequent in subjects with abdominal obesity. *Hypertension* 2014;**63**:740–746.
60. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002;**347**:305–313.
61. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, Beussink-Nelson L, Ljung Faxén U, Fermer ML, Broberg MA, Gan LM, Lund LH. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J* 2018;**39**:3439–3450.
62. Fontes-Carvalho R, Ladeiras-Lopes R, Bettencourt P, Leite-Moreira A, Azevedo A. Diastolic dysfunction in the diabetic continuum: association with insulin resistance, metabolic syndrome and type 2 diabetes. *Cardiovasc Diabetol* 2015;**14**:4.
63. Figtree GA, Rådholm K, Barrett TD, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Matthews DR, Shaw W, Neal B. Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes: results from the CANVAS Program. *Circulation* 2019;**139**:2591–2593.
64. Tang ZH, Wang L, Zeng F, Zhang K. Association and predictive value analysis for metabolic syndrome on systolic and diastolic heart failure in high-risk patients. *BMC Cardiovasc Disord* 2014;**14**:124.
65. Vita T, Murphy DJ, Osborne MT, Bajaj NS, Keraliya A, Jacob S, Diaz Martinez AJ, Nodoushani A, Bravo P, Hainer J, Bibbo CF, Steigner ML, Taqueti VR, Skali H, Blankstein R, Di Carli MF, Dorbala S. Association between nonalcoholic fatty liver disease at CT and coronary microvascular dysfunction at myocardial perfusion PET/CT. *Radiology* 2019;**291**:330–337.
66. Pirat B, Bozbas H, Simsek V, Yildirir A, Sade LE, Gursoy Y, Altin C, Atar I, Muderrisoglu H. Impaired coronary flow reserve in patients with metabolic syndrome. *Atherosclerosis* 2008;**201**:112–116.
67. Wijarnpreecha K, Lou S, Panjawatanan P, Cheungpasitporn W, Pungpapong S, Lukens FJ, Ungprasert P. Association between diastolic cardiac dysfunction and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Dig Liver Dis* 2018;**50**:1166–1175.
68. Zhang Z, Wang P, Guo F, Liu X, Luo T, Guan Y, Chen H, Wang Z, Zhao L, Ma X, Lv Q, Zhang Y, Kang J, Liu T, Liu X, Dong JZ, Bai R. Chronic heart failure in patients with nonalcoholic fatty liver disease: prevalence, clinical features, and relevance. *J Int Med Res* 2018;**46**:3959–3969.
69. Yiu KH, Marsan NA, Delgado V, Biermasz NR, Holman ER, Smit JW, Feelders RA, Bax JJ, Pereira AM. Increased myocardial fibrosis and left ventricular dysfunction in Cushing's syndrome. *Eur J Endocrinol* 2012;**166**:27–34.
70. Fardet L, Petersen I, Nazareth I. Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study. *BMJ* 2012;**345**:e4928.
71. Shatynska-Mytsyk I, Rodrigo L, Cioccocioppo R, Petrovic D, Lakusic N, Compostella L, Novak M, Kruzliak P. The impact of thyroid hormone replacement therapy on left ventricular diastolic function in patients with subclinical hypothyroidism. *J Endocrinol Investig* 2016;**39**:709–713.
72. Biondi B. Mechanisms in endocrinology: heart failure and thyroid dysfunction. *Eur J Endocrinol* 2012;**167**:609–618.
73. Lorenzo Romero JG, Salinas Sánchez AS, Segura Martín M, Hernández Millán I, Ruíz Mondejar R, López Rubio E, Virseda Rodríguez JA. The Conn syndrome. The clinical and surgical aspects of 18 cases of adrenal adenoma. *Actas Urol Esp* 1999;**23**:14–21.
74. Wu C, Zhang H, Zhang J, Xie C, Fan C, Zhang H, Wu P, Wei Q, Tan W, Xu L, Wang L, Xue Y, Guan M. Inflammation and fibrosis in perirenal adipose tissue of patients with aldosterone-producing adenoma. *Endocrinology* 2018;**159**:227–237.
75. Sorisky A, Antunes TT, Gagnon A. The adipocyte as a novel TSH target. *Mini Rev Med Chem* 2008;**8**:91–96.
76. Barahona MJ, Sucunza N, Resmini E, Fernández-Real JM, Ricart W, Moreno-Navarrete JM, Puig T, Farrerons J, Webb SM. Persistent body fat mass and inflammatory marker increases after long-term cure of Cushing's syndrome. *J Clin Endocrinol Metab* 2009;**94**:3365–3371.
77. Lakkis JI, Weir MR. Obesity and kidney disease. *Prog Cardiovasc Dis* 2018;**61**:157–167.
78. Tokoroyama T, Ando M, Setoguchi K, Tsuchiya K, Nitta K. Prev-alence, incidence and prognosis of chronic kidney disease classified according to current guidelines: a large retrospective cohort study of rheumatoid arthritis patients. *Nephrol Dial Transplant* 2017;**32**:2035–2042.
79. Ungprasert P, Raksasuk S. Psoriasis and risk of incident chronic kidney disease and end-stage renal disease: a systematic review and meta-analysis. *Int Urol Nephrol* 2018;**50**:1277–1283.
80. Gigante A, Barbano B, Granata G, Quarta S, Amoroso A, Salsano F, Cianci R, Rosato E. Evaluation of estimated glomerular filtration rate and clinical variables in systemic sclerosis patients. *Clin Nephrol* 2016;**85**:326–331.
81. Nampoothiri RV, Duseja A, Rathi M, Agrawal S, Sachdeva N, Mehta M, Dhaliwal HS, Dhiman RK, Chawla Y. Renal dysfunction in patients with nonalcoholic fatty liver disease is related to the presence of diabetes mellitus and severity of liver disease. *J Clin Exp Hepatol* 2019;**9**:22–28.
82. Gupta J, Dominic EA, Fink JC, Ojo AO, Barrows IR, Reilly MP, Townsend RR, Joffe MM, Rosas SE, Wolman M, Patel SS, Keane MG, Feldman HI, Kusek JW, Raj DS; CRIC Study Investigators. Association between inflammation and cardiac geometry in chronic kidney disease: findings from the CRIC study. *PLoS One* 2015;**10**:e0124772.
83. He J, Shlipak M, Anderson A, Roy JA, Feldman HI, Kallem RR, Kanthety R, Kusek JW, Ojo A, Rahman M, Ricardo AC, Soliman EZ, Wolf M, Zhang X, Raj D, Hamm L; CRIC (Chronic Renal Insufficiency Cohort) Investigators. Risk factors for heart failure in patients with chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) study. *J Am Heart Assoc* 2017;**6**:e005336.
84. Nayor M, Larson MG, Wang N, Santhanakrishnan R, Lee DS, Tsao CW, Cheng S, Benjamin EJ, Vasan RS, Levy D, Fox CS, Ho JE. The association of chronic kidney disease and microalbuminuria with heart failure with preserved vs. reduced ejection fraction. *Eur J Heart Fail* 2017;**19**:615–623.
85. Pedone C, Roshanravan B, Scarlata S, Patel KV, Ferrucci L, Incalzi RA. Longitudinal association between serum leptin concentration and glomerular filtration rate in humans. *PLoS One* 2015;**10**:e0117828.
86. Favre G, Anty R, Canivet C, Clément G, Ben-Amor I, Tran A, Gugenheim J, Gual P, Esnault VLM, Iannelli A. Determinants associated with the correction of glom-erular hyperfiltration one year after bariatric surgery. *Surg Obes Relat Dis* 2017;**13**:1760–1766.
87. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S. The number of metabolic syndrome components is a good risk indicator for both early- and late-stage kidney damage. *Nutr Metab Cardiovasc Dis* 2014;**24**:277–285.
88. Levitsky A, Brismar K, Hafström I, Hambardzumyan K, Lourdudoss C, van Vollenhoven RF, Saevarsdottir S. Obesity is a strong predictor of worse clinical outcomes and treatment responses in early rheumatoid arthritis: results from the SWEFOT trial. *RMD Open* 2017;**3**:e000458.
89. Maglio C, Peltonen M, Rudin A, Carlsson LM. Bariatric surgery and the incidence of psoriasis and psoriatic arthritis in the Swedish Obese Subjects study. *Obesity (Silver Spring)* 2017;**25**:2068–2073.
90. Tedeschi SK, Barbhaiya M, Malspeis S, Lu B, Sparks JA, Karlson EW, Willett W, Costenbader KH. Obesity and the risk of systemic lupus erythematosus among women in the Nurses' Health Studies. *Semin Arthritis Rheum* 2017;**47**:376–383.
91. Caramaschi P, Biasi D, Caimmi C, Barausse G, Gatti D, Ferrari M, Pieropan S, Sabbagh D, Adami S. Relationship between body composition and both cardiovascular risk factors and lung function in systemic sclerosis. *Clin Rheumatol* 2014;**33**:77–82.

92. Barros R, Moreira P, Padrão P, Teixeira VH, Carvalho P, Delgado L, Moreira A. Obesity increases the prevalence and the incidence of asthma and worsens asthma severity. *Clin Nutr* 2017;**36**:1068–1074.
93. Jain A, Nguyen NH, Proudfoot JA, Martin CF, Sandborn WJ, Kappelman MD, Long MD, Singh S. Impact of obesity on disease activity and Patient-Reported Outcomes Measurement Information System (PROMIS) in inflammatory bowel diseases. *Am J Gastroenterol* 2019;**114**:630–639.
94. Sebastião E, Motl RW. Body mass index and cardiorespiratory fitness in persons with multiple sclerosis. *Acta Neurol Scand* 2018;**138**:315–319.
95. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009;**122**:248–256.
96. Shouhed D, Steggerda J, Burch M, Noureddin M. The role of bariatric surgery in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Expert Rev Gastroenterol Hepatol* 2017;**11**:797–811.
97. Kato S, Nazneen A, Nakashima Y, Razzaque MS, Nishino T, Furusu A, Yorioka N, Taguchi T. Pathological influence of obesity on renal structural changes in chronic kidney disease. *Clin Exp Nephrol* 2009;**13**:332–340.
98. Stepniakowski K, Egan BM. Additive effects of obesity and hypertension to limit venous volume. *Am J Physiol* 1995;**268**(2 Pt 2):R562–R568.
99. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, McKelvie RS, McMurray JJ, Zile MR, Massie BM, Kitzman DW. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail* 2012;**5**:571–578.
100. Faxén UL, Hage C, Donal E, Daubert JC, Linde C, Lund LH. Patient reported outcome in HFpEF: sex-specific differences in quality of life and association with outcome. *Int J Cardiol* 2018;**267**:128–132.
101. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W, Lefkowitz MP, Shi VC, Anand IS, Ge J, Lam CS, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, McMurray JJ, Solomon SD; PARAGON-HF Investigators. Health-related quality of life in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail* 2019;**7**:862–874.
102. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, Carrick-Ranson G, Levine BD. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. *Circulation* 2013;**127**:55–62.
103. Monahan KD, Ray CA. Gender affects calf venous compliance at rest and during baroreceptor unloading in humans. *Am J Physiol Heart Circ Physiol* 2004;**286**:H895–H901.
104. Piro M, Della Bona R, Abate A, Biasucci LM, Crea F. Sex-related differences in myocardial remodeling. *J Am Coll Cardiol* 2010;**55**:1057–1065.
105. Najjar SS, Schulman SP, Gerstenblith G, Fleg JL, Kass DA, O'Connor F, Becker LC, Lakatta EG. Age and gender affect ventricular-vascular coupling during aerobic exercise. *J Am Coll Cardiol* 2004;**44**:611–617.
106. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. *J Am Coll Cardiol* 2013;**61**:96–103.
107. Gori M, Lam CS, Gupta DK, Santos AB, Cheng S, Shah AM, Claggett B, Zile MR, Kraigher-Krainer E, Pieske B, Voors AA, Packer M, Bransford T, Lefkowitz M, McMurray JJ, Solomon SD; PARAMOUNT Investigators. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014;**16**:535–542.
108. Beale AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, Vizi D, Evans S, Lam CS, Kaye DM. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart Fail* 2019;**7**:239–249.
109. Chung AK, Das SR, Leonard D, Peshock RM, Kazi F, Abdullah SM, Canham RM, Levine BD, Drazner MH. Women have higher left ventricular ejection fractions than men independent of left ventricular volume: the Dallas Heart Study. *Circulation* 2006;**113**:1597–1604.
110. Gebhard C, Buechel RR, Stähli BE, Gransar H, Achenbach S, Berman DS, Budoff MJ, Callister TQ, Chow B, Dunning A, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Rubinshtein R, Marques H, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Shaw LJ, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Chang HJ, Leipsic J, Min JK, Kaufmann PA. Impact of age and sex on left ventricular function determined by coronary computed tomographic angiography: results from the prospective multicentre CONFIRM study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:990–1000.
111. Wohlfahrt P, Redfield MM, Lopez-Jimenez F, Melenovsky V, Kane GC, Rodeheffer RJ, Borlaug BA. Impact of general and central adiposity on ventricular-arterial aging in women and men. *JACC Heart Fail* 2014;**2**:489–499.
112. Kuch B, von Scheidt W, Peter W, Döring A, Piehlmeier W, Landgraf R, Meisinger C. Sex-specific determinants of left ventricular mass in pre-diabetic and type 2 diabetic subjects: the Augsburg Diabetes Family Study. *Diabetes Care* 2007;**30**:946–952.
113. Foppa M, Duncan BB, Arnett DK, Benjamin EJ, Liebson PR, Manolio TA, Skelton TN. Diabetes, gender, and left ventricular structure in African-Americans: the Atherosclerosis Risk in Communities study. *Cardiovasc Ultrasound* 2006;**4**:43.
114. Yu HT, Lee JS, Kim TH, Uhm JS, Joung B, Hong GR, Lee MH, Shim CY, Pak HN. Advanced left atrial remodeling and appendage contractile dysfunction in women than in men among the patients with atrial fibrillation: potential mechanism for stroke. *J Am Heart Assoc* 2016;**5**:e003361.
115. Halland H, Lønnebakken MT, Pristaj N, Saeed S, Midtbø H, Einarsen E, Gerdts E. Sex differences in subclinical cardiac disease in overweight and obesity (the FATCOR study). *Nutr Metab Cardiovasc Dis* 2018;**28**:1054–1060.
116. Losi MA, Izzo R, Canciello G, Giamundo A, Manzi MV, Strisciuglio T, Stabile E, De Luca N, de Simone G, Trimarco B. Atrial dilatation development in hypertensive treated patients: the Campania-Salute Network. *Am J Hypertens* 2016;**29**:1077–1084.
117. Nayor M, Enserro DM, Xanthakis V, Larson MG, Benjamin EJ, Aragam J, Mitchell GF, Vasan RS. Comorbidities and cardiometabolic disease: relationship with longitudinal changes in diastolic function. *JACC Heart Fail* 2018;**6**:317–325.
118. Ha JW, Lee HC, Park S, Choi EY, Seo HS, Shim CY, Kim JM, Ahn JA, Lee SW, Rim SJ, Oh JK, Chung N. Gender-related difference in left ventricular diastolic elastance during exercise in patients with diabetes mellitus. *Circ J* 2008;**72**:1443–1448.
119. Bouthoorn S, Valstar GB, Gohar A, den Ruijter HM, Reitsma HB, Hoes AW, Rutten FH. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: a systematic review and meta-analysis. *Diab Vasc Dis Res* 2018;**15**:477–493.
120. Savji N, Meijers WC, Bartz TM, Bhambhani V, Cushman M, Nayor M, Kizer JR, Sarma A, Blaha MJ, Gansevoort RT, Gardin JM, Hillege HL, Ji F, Kop WJ, Lau ES, Lee DS, Sadreyev R, van Gilst WH, Wang TJ, Zanni MV, Vasan RS, Allen NB, Psaty BM, van der Harst P, Levy D, Larson M, Shah SJ, de Boer RA, Gottdiener JS, Ho JE. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *JACC Heart Fail* 2018;**6**:701–709.
121. Kim HL, Kim MA, Oh S, Kim M, Park SM, Yoon HJ, Shin MS, Hong KS, Shin GJ, Shim WJ. Sex difference in the association between metabolic syndrome and left ventricular diastolic dysfunction. *Metab Syndr Relat Disord* 2016;**14**:507–512.
122. Nicolini E, Martegani G, Maresca AM, Marchesi C, Dentali F, Lazzarini A, Speroni S, Guasti L, Bertolini A, Venco A, Grandi AM. Left ventricular remodeling in patients with metabolic syndrome: influence of gender. *Nutr Metab Cardiovasc Dis* 2013;**23**:771–775.
123. Cioffi G, Faggiano P, Lucci D, Di Lenarda A, Mureddu GF, Tarantini L, Verdecchia P, Comaschi M, Giorda CB, Velussi M, Chinali M, Latini R, Masson S, De Simone G; DYDA Investigators. Inappropriately high left ventricular mass in patients with type 2 diabetes mellitus and no overt cardiac disease. The DYDA study. *J Hypertens* 2011;**29**:1994–2003.
124. De Simone G, Devereux RB, Chinali M, Roman MJ, Barac A, Panza JA, Lee ET, Howard BV. Sex differences in obesity-related changes in left ventricular morphology: the Strong Heart Study. *J Hypertens* 2011;**29**:1431–1438.
125. Grant RW, Dixit VD. Adipose tissue as an immunological organ. *Obesity (Silver Spring)* 2015;**23**:512–518.
126. Gruzdeva OV, Akbasheva OE, Dyleva YA, Antonova LV, Matveeva VG, Uchasova EG, Fanaskova EV, Karetnikova VN, Ivanov SV, Barbarash OL. Adipokine and cytokine profiles of epicardial and subcutaneous adipose tissue in patients with coronary heart disease. *Bull Exp Biol Med* 2017;**163**:608–611.
127. Alam MS, Green R, de Kemp R, Beanlands RS, Chow BJ. Epicardial adipose tissue thickness as a predictor of impaired microvascular function in patients with non-obstructive coronary artery disease. *J Nucl Cardiol* 2013;**20**:804–812.
128. Bakkum MJ, Danad I, Romijn MA, Stuijfzand WJ, Leonora RM, Tulevski II, Somsen GA, Lammertsma AA, van Kuijk C, van Rossum AC, Raijmakers PG, Knaapen P. The impact of obesity on the relationship between epicardial adipose tissue, left ventricular mass and coronary microvascular function. *Eur J Nucl Med Mol Imaging* 2015;**42**:1562–1573.
129. Wu CK, Lee JK, Hsu JC, Su MM, Wu YF, Lin TT, Lan CW, Hwang JJ, Lin LY. Myocardial adipose deposition and the development of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:445–454.
130. Ng AC, Strudwick M, van der Geest RJ, Ng AC, Gillinder L, Goo SY, Cowin G, Delgado V, Wang WY, Bax JJ. Impact of epicardial adipose tissue, left ventricular myocardial fat content, and interstitial fibrosis on myocardial contractile function. *Circ Cardiovasc Imaging* 2018;**11**:e007372.
131. Abe I, Teshima Y, Kondo H, Kaku H, Kira S, Ikebe Y, Saito S, Fukui A, Shinohara T, Yufu K, Nakagawa M, Hijiya N, Moriyama M, Shimada T, Miyamoto S, Takahashi N. Association of fibrotic remodeling and cytokines/chemokines content in epicardial adipose tissue with atrial myocardial fibrosis in patients with atrial fibrillation. *Heart Rhythm* 2018;**15**:1717–1727.

132. Petta S, Argano C, Colomba D, Cammà C, Di Marco V, Cabibi D, Tuttolomondo A, Marchesini G, Pinto A, Licata G, Craxì A. Epicardial fat, cardiac geometry and cardiac function in patients with non-alcoholic fatty liver disease: association with the severity of liver disease. *J Hepatol* 2015;**62**:928–933.
133. Şeker T, Türkoğlu C, Harbalıoğlu H, Gür M. Epicardial fat thickness is associated with abnormal left ventricle geometry in newly diagnosed hypertension. *Acta Cardiol Sin* 2018;**34**:280–287.
134. Alpaydın S, Buyukterzi Z, Akkurt HE, Yılmaz H. Impaired left ventricular diastolic functions and thickened epicardial adipose tissue in rheumatoid arthritis patients is correlated with DAS-28 score. *Acta Cardiol Sin* 2017;**33**:182–187.
135. Lipson A, Alexopoulos N, Hartlage GR, Arepalli C, Oeser A, Bian A, Gebretsadik T, Shintani A, Stillman AE, Stein CM, Raggi P. Epicardial adipose tissue is increased in patients with systemic lupus erythematosus. *Atherosclerosis* 2012;**223**:389–393.
136. Long BD, Stojanovska J, Brown RKJ, Attili AK, Jackson EA, Ognenovski V. Increased epicardial fat volume is independently associated with the presence and severity of systemic sclerosis. *Acad Radiol* 2017;**24**:1473–1481.
137. Wang X, Guo Z, Zhu Z, Bao Y, Yang B. Epicardial fat tissue in patients with psoriasis: a systematic review and meta-analysis. *Lipids Health Dis* 2016;**15**:103.
138. Uysal F, Akbal E, Akbal A, Cevizci S, Arık K, Gazi E. Epicardial adipose tissue is increased in patients with inflammatory bowel disease. *J Ultrasound Med* 2016;**35**:1859–1864.
139. Ozde C, Dogru M, Erdogan F, Ipek IO, Ozde S, Karakaya O. The relationship between adiponectin levels and epicardial adipose tissue thickness in non-obese children with asthma. *Asian Pac J Allergy Immunol* 2015;**33**:289–295.
140. Rabkin SW. The relationship between epicardial fat and indices of obesity and the metabolic syndrome: a systematic review and meta-analysis. *Metab Syndr Relat Disord* 2014;**12**:31–42.
141. Iacobellis G, Leonetti F, Singh N, Sharma AM. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. *Int J Cardiol* ;**115**:272–273.
142. Bambace C, Sepe A, Zoico E, Telesca M, Olioso D, Venturi S, Rossi A, Corzato F, Faccioli S, Cominacini L, Santini F, Zamboni M. Inflammatory profile in subcutaneous and epicardial adipose tissue in men with and without diabetes. *Heart Vessel* 2014;**29**:42–48.
143. Groves EM, Erande AS, Le C, Salcedo J, Hoang KC, Kumar S, Mohar DS, Saremi F, Im J, Agrawal Y, Nadeswaran P, Naderi N, Malik S. Comparison of epicardial adipose tissue volume and coronary artery disease severity in asymptomatic adults with versus without diabetes mellitus. *Am J Cardiol* 2014;**114**:686–691.
144. Arpaci D, Ugurlu BP, Aslan AN, Ersoy R, Akcay M, Cakir B. Epicardial fat thickness in patients with prediabetes and correlation with other cardiovascular risk markers. *Intern Med* 2015;**54**:1009–1014.
145. Kazlauskaite R, Doukky R, Evans A, Margeta B, Ruchi A, Fogelfeld L, Kelly RF. Predictors of diastolic dysfunction among minority patients with newly diagnosed type 2 diabetes. *Diabetes Res Clin Pract* 2010;**88**:189–195.
146. Fracanzani AL, Pisano G, Consonni D, Tiraboschi S, Baragetti A, Bertelli C, Norata GD, Dongiovanni P, Valenti L, Grigore L, Tonella T, Catapano A, Fargion S. Epicardial adipose tissue (EAT) thickness is associated with cardiovascular and liver damage in nonalcoholic fatty liver disease. *PLoS One* 2016;**11**:e0162473.
147. Park HE, Choi SY, Kim M. Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: assessment using 2-dimensional echocardiography. *BMC Cardiovasc Disord* 2014;**14**:3.
148. Maurice F, Gaborit B, Vincentelli C, Abdesselam I, Bernard M, Graillon T, Kober F, Brue T, Castinetti F, Dutour A. Cushing syndrome is associated with subclinical LV dysfunction and increased epicardial adipose tissue. *J Am Coll Cardiol* 2018;**72**:2276–2277.
149. Korkmaz L, Sahin S, Akyuz AR, Ziyrek M, Anaforoglu I, Kose M, Erkan H, Ağaç MT, Acar Z. Epicardial adipose tissue increased in patients with newly diagnosed subclinical hypothyroidism. *Med Princ Pract* 2013;**22**:42–46.
150. Iacobellis G, Petramala L, Marinelli C, Calvieri C, Zinnamosca L, Concistrè A, Iannucci G, De Toma G, Letizia C. Epicardial fat thickness and primary aldosteronism. *Horm Metab Res* 2016;**48**:238–241.
151. van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. *Eur J Heart Fail* 2018;**20**:1559–1566.
152. Watanabe K, Kishino T, Sano J, Ariga T, Okuyama S, Mori H, Matsushima S, Ohtsuka K, Ohnishi H, Watanabe T. Relationship between epicardial adipose tissue thickness and early impairment of left ventricular systolic function in patients with preserved ejection fraction. *Heart Vessel* 2016;**31**:1010–1015.
153. Doesch C, Streitner F, Bellm S, Suselbeck T, Haghi D, Heggemann F, Schoenberg SO, Michaely H, Borggrefe M, Papavassiliu T. Epicardial adipose tissue assessed by cardiac magnetic resonance imaging in patients with heart failure due to dilated cardiomyopathy. *Obesity (Silver Spring)* 2013;**21**:E253–E261.
154. Haykowsky MJ, Nicklas BJ, Brubaker PH, Hundley WG, Brinkley TE, Upadhya B, Becton JT, Nelson MD, Chen H, Kitzman DW. Regional adipose distribution and its relationship to exercise intolerance in older obese patients who have heart failure with preserved ejection fraction. *JACC Heart Fail* 2018;**6**:640–649.
155. Çolak H, Kilicarslan B, Tekce H, Tanrisev M, Tugmen C, Aktas G, Kursat S. Relationship between epicardial adipose tissue, inflammation and volume markers in hemodialysis and transplant patients. *Ther Apher Dial* 2015;**19**:56–62.
156. Reinhardt M, Cushman TR, Thearle MS, Krakoff J. Epicardial adipose tissue is a predictor of decreased kidney function and coronary artery calcification in youth- and early adult onset type 2 diabetes mellitus. *J Endocrinol Invest* 2019;**42**:979–986.
157. Christensen RH, von Scholten BJ, Hansen CS, Heywood SE, Rosenmeier JB, Andersen UB, Hovind P, Reinhard H, Parving HH, Pedersen BK, Jørgensen ME, Jacobsen PK, Rossing P. Epicardial, pericardial and total cardiac fat and cardiovascular disease in type 2 diabetic patients with elevated urinary albumin excretion rate. *Eur J Prev Cardiol* 2017;**24**:1517–1524.
158. Ozturk MT, Ebinç FA, Okyay GU, Kutlugün AA. Epicardial adiposity is associated with microalbuminuria in patients with essential hypertension. *Acta Cardiol Sin* 2017;**33**:74–80.
159. Baragetti A, Pisano G, Bertelli C, Garlaschelli K, Grigore L, Fracanzani AL, Fargion S, Norata GD, Catapano AL. Subclinical atherosclerosis is associated with epicardial fat thickness and hepatic steatosis in the general population. *Nutr Metab Cardiovasc Dis* 2016;**26**:141–153.
160. Cakir E, Ozkaya E, Korkmaz V, Goktas I, Kucukozkan T. Comparison of the effects of surgical and natural menopause on epicardial fat thickness and γ-glutamyltransferase level. *Menopause* 2011;**18**:901–905.
161. Shim IK, Cho KI, Kim HS, Heo JH, Cha TJ. Impact of gender on the association of epicardial fat thickness, obesity, and circadian blood pressure pattern in hypertensive patients. *J Diabetes Res* 2015;**2015**:924539.
162. Selvaraj S, Martinez EE, Aguilar FG, Kim KY, Peng J, Sha J, Irvin MR, Lewis CE, Hunt SC, Arnett DK, Shah SJ. Association of central adiposity with adverse cardiac mechanics: findings from the Hypertension Genetic Epidemiology Network study. *Circ Cardiovasc Imaging* 2016;**9**:e004396.
163. Iacobellis G, Diaz S, Mendez A, Goldberg R. Increased epicardial fat and plasma leptin in type 1 diabetes independently of obesity. *Nutr Metab Cardiovasc Dis* 2014;**24**:725–729.
164. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003;**108**:2460–2466.
165. Mach L, Bedanova H, Soucek M, Karpisek M, Konecny T, Nemec P, Orban M. Impact of cardiopulmonary bypass surgery on cytokines in epicardial adipose tissue: comparison with subcutaneous fat. *Perfusion* 2017;**32**:279–284.
166. Vrselja Z, Šram M, Andrijevic D, Takač B, Lekšan I, Radić R, Curic G. Transcardial gradient of adiponectin, interleukin-6 and tumor necrosis factor-α in overweight coronary artery disease patients. *Cytokine* 2015;**76**:321–327.
167. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, Kumar S, McTernan PG. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. *Cardiovasc Diabetol* 2006;**5**:1.
168. Chang HX, Zhao XJ, Zhu QL, Hou Q, Li Y. Removal of epicardial adipose tissue after myocardial infarction improves cardiac function. *Herz* 2018;**43**:258–264.
169. McKenney-Drake ML, Rodenbeck SD, Bruning RS, Kole A, Yancey KW, Alloosh M, Sacks HS, Sturek M. Epicardial adipose tissue removal potentiates outward remodeling and arrests coronary atherogenesis. *Ann Thorac Surg* 2017;**103**:1622–1630.
170. Nguyen Dinh Cat A, Antunes TT, Callera GE, Sanchez A, Tsiropoulou S, Dulak-Lis MG, Anagnostopoulou A, He Y, Montezano AC, Jaisser F, Touyz RM. Adipocyte-specific mineralocorticoid receptor overexpression in mice is associated with metabolic syndrome and vascular dysfunction: role of redox-sensitive PKG-1 and rho kinase. *Diabetes* 2016;**65**:2392–2403.
171. Kraus D, Jäger J, Meier B, Fasshauer M, Klein MJ. Aldosterone inhibits uncoupling protein-1, induces insulin resistance, and stimulates proinflammatory adipokines in adipocytes. *Horm Metab Res* 2005;**37**:455–459.
172. Garg R, Rao AD, Baimas-George M, Hurwitz S, Foster C, Shah RV, Jerosch-Herold M, Kwong RY, Di Carli MF, Adler GK. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. *Diabetes* 2015;**64**:236–242.
173. Minnaard-Huiban M, Hermans JJ, Essen Hv, Bitsch N, Smits JF. Comparison of the effects of intrapericardial and intravenous aldosterone infusions on left ventricular fibrosis in rats. *Eur J Heart Fail* 2008;**10**:1166–1171.
174. Valero-Muñoz M, Li S, Wilson RM, Hulsmans M, Aprahamian T, Fuster JJ, Nahrendorf M, Scherer PE, Sam F. Heart failure with preserved ejection fraction induces beiging in adipose tissue. *Circ Heart Fail* 2016;**9**:e002724.

175. Edelmann F, Tomaschitz A, Wachter R, Gelbrich G, Knoke M, Düngen HD, Pilz S, Binder L, Stahrenberg R, Schmidt A, März W, Pieske B. Serum aldosterone and its relationship to left ventricular structure and geometry in patients with preserved left ventricular ejection fraction. *Eur Heart J* 2012;**33**:203–212.
176. Reddy YN, Lewis GD, Shah SJ, Obokata M, Abou-Ezzedine OF, Fudim M, Sun JL, Chakraborty H, McNulty S, LeWinter MM, Mann DL, Stevenson LW, Redfield MM, Borlaug BA. Characterization of the obese phenotype of heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Mayo Clin Proc* 2019;**94**:1199–1209.
177. Wu W, Shi F, Liu D, Ceddia RP, Gaffin R, Wei W, Fang H, Lewandowski ED, Collins S. Enhancing natriuretic peptide signaling in adipose tissue, but not in muscle, protects against diet-induced obesity and insulin resistance. *Sci Signal* 2017;**10**:eaam6870.
178. Bae CR, Hino J, Hosoda H, Son C, Makino H, Tokudome T, Tomita T, Hosoda K, Miyazato M, Kangawa K. Adipocyte-specific expression of C-type natriuretic peptide suppresses lipid metabolism and adipocyte hypertrophy in adipose tissues in mice fed high-fat diet. *Sci Rep* 2018;**8**:2093.
179. Moro C, Klimcakova E, Lolmède K, Berlan M, Lafontan M, Stich V, Bouloumié A, Galitzky J, Arner P, Langin D. Atrial natriuretic peptide inhibits the production of adipokines and cytokines linked to inflammation and insulin resistance in human subcutaneous adipose tissue. *Diabetologia* 2007;**50**:1038–1047.
180. Tsukamoto O, Fujita M, Kato M, Yamazaki S, Asano Y, Ogai A, Okazaki H, Asai M, Nagamachi Y, Maeda N, Shintani Y, Minamino T, Asakura M, Kishimoto I, Funahashi T, Tomoike H, Kitakaze M. Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. *J Am Coll Cardiol* 2009;**53**:2070–2077.
181. Bordicchia M, Liu D, Amri EZ, Ailhaud G, Dessì-Fulgheri P, Zhang C, Takahashi N, Sarzani R, Collins S. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *J Clin Invest* 2012;**122**:1022–1036.
182. Karayannis G, Giamouzis G, Tziolas N, Georgoulias P, Skoularigis J, Mikhailidis DP, Triposkiadis F. Association between epicardial fat thickness and weight homeostasis hormones in patients with noncachectic heart failure. *Angiology* 2013;**64**:173–180.
183. Sugisawa T, Kishimoto I, Kokubo Y, Nagumo A, Makino H, Miyamoto Y, Yoshimasa Y. Visceral fat is negatively associated with B-type natriuretic peptide levels in patients with advanced type 2 diabetes. *Diabetes Res Clin Pract* 2010;**89**:174–180.
184. Shibasaki I, Nishikimi T, Mochizuki Y, Yamada Y, Yoshitatsu M, Inoue Y, Kuwata T, Ogawa H, Tsuchiya G, Ishimitsu T, Fukuda H. Greater expression of inflammatory cytokines, adrenomedullin, and natriuretic peptide receptor-C in epicardial adipose tissue in coronary artery disease. *Regul Pept* 2010;**165**:210–217.
185. Standeven KF, Hess K, Carter AM, Rice GI, Cordell PA, Balmforth AJ, Lu B, Scott DJ, Turner AJ, Hooper NM, Grant PJ. Neprilysin, obesity and the metabolic syndrome. *Int J Obes* 2011;**35**:1031–1040.
186. Pu Q, Larouche I, Schiffrin EL. Effect of dual angiotensin converting enzyme/neutral endopeptidase inhibition, angiotensin converting enzyme inhibition, or AT1 antagonism on coronary microvasculature in spontaneously hypertensive rats. *Am J Hypertens* 2003;**16**(11 Pt 1)::931–937.
187. Tamura N, Ogawa Y, Chusho H, Nakamura K, Nakao K, Suda M, Kasahara M, Hashimoto R, Katsuura G, Mukoyama M, Itoh H, Saito Y, Tanaka I, Otani H, Katsuki M. Cardiac fibrosis in mice lacking brain natriuretic peptide. *Proc Natl Acad Sci U S A* 2000;**97**:4239–4244.
188. Goliasch G, Pavo N, Zotter-Tufaro C, Kammerlander A, Duca F, Mascherbauer J, Bonderman D. Soluble neprilysin does not correlate with outcome in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2016;**18**:89–93.
189. Lyle MA, Iyer SR, Redfield MM, Reddy YN, Felker GM, Cappola TP, Hernandez AF, Scott CG, Burnett JC Jr, Pereira NL. Circulating neprilysin in patients with heart failure and preserved ejection fraction. *JACC Heart Fail* 2020;**8**:70–80.
190. Lanfear DE, Chow S, Padhukasahasram B, Li J, Langholz D, Tang WH, Williams LK, Sabbah HN. Genetic and nongenetic factors influencing pharmacokinetics of B-type natriuretic peptide. *J Card Fail* 2014;**20**:662–668.
191. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;**380**:1387–1395.
192. Allison MA, Jenny NS, McClelland RL, Cushman M, Rifkin D. The associations of adipokines with selected markers of the renin-angiotensinogen-aldosterone system: the Multi-Ethnic Study of Atherosclerosis. *J Hum Hypertens* 2015;**29**:127–133.
193. Huby AC, Antonova G, Groenendyk J, Gomez-Sanchez CE, Bollag WB, Filosa JA, Belin de Chantemèle EJ. Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. *Circulation* 2015;**132**:2134–2145.
194. Gutiérrez-Tenorio J, Marín-Royo G, Martínez-Martínez E, Martín R, Miana M, López-Andrés N, Jurado-López R, Gallardo I, Luaces M, San Román JA, González-Amor M, Salaices M, Nieto ML, Cachofeiro V. The role of oxidative stress in the crosstalk between leptin and mineralocorticoid receptor in the cardiac fibrosis associated with obesity. *Sci Rep* 2017;**7**:16802.
195. Hoppmann J, Perwitz N, Meier B, Fasshauer M, Hadaschik D, Lehnert H, Klein J. The balance between gluco- and mineralocorticoid action critically determines inflammatory adipocyte responses. *J Endocrinol* 2010;**204**:153–164.
196. Fain JN, Kanu A, Bahouth SW, Cowan GS, Lloyd Hiler M.. Inhibition of leptin release by atrial natriuretic peptide (ANP) in human adipocytes. *Biochem Pharmacol* 2003;**65**:1883–1888.
197. Miura S, Nakayama A, Tomita S, Matsuo Y, Suematsu Y, Saku K. Comparison of aldosterone synthesis in adrenal cells, effect of various AT1 receptor blockers with or without atrial natriuretic peptide. *Clin Exp Hypertens* 2015;**37**:353–357.
198. Faxén UL, Hage C, Andreasson A, Donal E, Daubert JC, Linde C, Brismar K, Lund LH. HFpEF and HFrEF exhibit different phenotypes as assessed by leptin and adiponectin. *Int J Cardiol* 2017;**228**:709–716.
199. Abd El-Aziz TA, Mohamed RH, Mohamed RH, Pasha HF. Leptin, leptin gene and leptin receptor gene polymorphism in heart failure with preserved ejection fraction. *Heart Vessel* 2012;**27**:271–279.
200. Bene NC, Alcaide P, Wortis HH, Jaffe IZ. Mineralocorticoid receptors in immune cells: emerging role in cardiovascular disease. *Steroids* 2014;**91**:38–45.
201. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, Li J, Williams GH, Adler GK. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation* 2008;**117**:2253–2261.
202. Kato Y, Kamiya H, Koide N, Odkhuu E, Komatsu T, Dagvadorj J, Watarai A, Kondo M, Kato K, Nakamura J, Yokochi T. Spironolactone inhibits production of proinflammatory mediators in response to lipopolysaccharide via inactivation of nuclear factor-κB. *Immunopharmacol Immunotoxicol* 2014;**36**:237–241.
203. Rovensky J, Kvetnansky R, Radikova Z, Imrich R, Greguska O, Vigas M, Macho L. Hormone concentrations in synovial fluid of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005;**23**:292–296.
204. Guy A, Sharif K, Bragazzi NL, Krosser A, Gilburd B, Zeruya E, Shovman O, Watad A, Amital H. Low levels of renin and high aldosterone-to-renin ratio among rheumatoid patients and ankylosing spondylitis patients: a prospective study. *Isr Med Assoc J* 2018;**20**:632–636.
205. Bendtzen K, Hansen PR, Rieneck K; Spironolactone/Arthritis Study Group. Spironolactone inhibits production of proinflammatory cytokines, including tumour necrosis factor-alpha and interferon-gamma, and has potential in the treatment of arthritis. *Clin Exp Immunol* 2003;**134**:151–158.
206. Garg M, Burrell LM, Velkoska E, Griggs K, Angus PW, Gibson PR, Lubel JS. Upregulation of circulating components of the alternative renin-angiotensin system in inflammatory bowel disease: a pilot study. *J Renin Angiotensin Aldosterone Syst* 2015;**16**:559–569.
207. Avsar T, Durası IM, Uygunoğlu U, Tütüncü M, Demirci NO, Saip S, Sezerman OU, Siva A, Tahir Turanlı E.. CSF proteomics identifies specific and shared pathways for multiple sclerosis clinical subtypes. *PLoS One* 2015;**10**:e0122045.
208. Lieber GB, Fernandez X, Mingo GG, Jia Y, Caniga M, Gil MA, Keshwani S, Woodhouse JD, Cicmil M, Moy LY, Kelly N, Jimenez J, Crawley Y, Anthes JC, Klappenbach J, Ma YL, McLeod RL. Mineralocorticoid receptor antagonists attenuate pulmonary inflammation and bleomycin-evoked fibrosis in rodent models. *Eur J Pharmacol* 2013;**718**:290–298.
209. Briones AM, Nguyen Dinh Cat A, Callera GE, Yogi A, Burger D, He Y, Corrêa JW, Gagnon AM, Gomez-Sanchez CE, Gomez-Sanchez EP, Sorisky A, Ooi TC, Ruzicka M, Burns KD, Touyz RM. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. *Hypertension* 2012;**59**:1069–1078.
210. Bentley-Lewis R, Adler GK, Perlstein T, Seely EW, Hopkins PN, Williams GH, Garg R. Body mass index predicts aldosterone production in normotensive adults on a high-salt diet. *J Clin Endocrinol Metab* 2007;**92**:4472–4475.
211. Musani SK, Vasan RS, Bidulescu A, Liu J, Xanthakis V, Sims M, Gawalapu RK, Samdarshi TE, Steffes M, Taylor HA, Fox ER. Aldosterone, C-reactive protein, and plasma B-type natriuretic peptide are associated with the develop-ment of metabolic syndrome and longitudinal changes in metabolic syndrome components: findings from the Jackson Heart Study. *Diabetes Care* 2013;**36**:3084–3092.
212. Joseph JJ, Echouffo Tcheugui JB, Effoe VS, Hsueh WA, Allison MA, Golden SH. Renin-angiotensin-aldosterone system, glucose metabolism and incident type 2 diabetes mellitus: MESA. *J Am Heart Assoc* 2018;**7**:e009890.

213. Raheja P, Price A, Wang Z, Arbique D, Adams-Huet B, Auchus RJ, Vongpatanasin W. Spironolactone prevents chlorthalidone-induced sympathetic activation and insulin resistance in hypertensive patients. *Hypertension* 2012;**60**:319–325.
214. Takata H, Takeda Y, Zhu A, Cheng Y, Yoneda T, Demura M, Yagi K, Karashima S, Yamagishi M. Protective effects of mineralocorticoid receptor blockade against neuropathy in experimental diabetic rats. *Diabetes Obes Metab* 2012;**14**:155–162.
215. Wilkinson-Berka JL, Tan G, Jaworski K, Miller AG. Identification of a retinal aldosterone system and the protective effects of mineralocorticoid receptor antagonism on retinal vascular pathology. *Circ Res* 2009;**104**:124–133.
216. Abella V, Scotece M, Conde J, Pino J, Gonzalez-Gay MA, Gómez-Reino JJ, Mera A, Lago F, Gómez R, Gualillo O. Leptin in the interplay of inflammation, metabolism and immune system disorders. *Nat Rev Rheumatol* 2017;**13**:100–109.
217. Santos-Alvarez J, Goberna R, Sánchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. *Cell Immunol* 1999;**194**:6–11.
218. Saucillo DC, Gerriets VA, Sheng J, Rathmell JC, Maciver NJ. Leptin metabolically licenses T cells for activation to link nutrition and immunity. *J Immunol* 2014;**192**:136–144.
219. Cao H, Lin J, Chen W, Xu G, Sun C. Baseline adiponectin and leptin levels in predicting an increased risk of disease activity in rheumatoid arthritis: a meta-analysis and systematic review. *Autoimmunity* 2016;**49**:547–553.
220. Lourenço EV, Liu A, Matarese G, La Cava A. Leptin promotes systemic lupus erythematosus by increasing autoantibody production and inhibiting immune regulation. *Proc Natl Acad Sci U S A* 2016;**113**:10637–10642.
221. Bruno A, Alessi M, Soresi S, Bonanno A, Riccobono L, Montalbano AM, Albano GD, Gjomarkaj M, Profita M. Increased leptin/leptin receptor pathway affects systemic and airway inflammation in COPD former smokers. *J Inflamm Res* 2011;**4**:51–59.
222. Trejo-Vazquez F, Garza-Veloz I, Villela-Ramirez GA, Ortiz-Castro Y, Mauricio-Saucedo P, Cardenas-Vargas E, Diaz-Baez M, Cid-Baez MA, Castañeda-Miranda R, Ortiz-Rodriguez JM, Solis-Sanchez LO, Martinez-Fierro ML. Positive association between leptin serum levels and disease activity on endoscopy in inflammatory bowel disease: a case-control study. *Exp Ther Med* 2018;**15**:3336–3344.
223. Matarese G, Carrieri PB, La Cava A, Perna F, Sanna V, De Rosa V, Aufiero D, Fontana S, Zappacosta S. Leptin increase in multiple sclerosis associates with reduced number of CD4+CD25+ regulatory T cells. *Proc Natl Acad Sci U S A* 2005;**102**:5150–5155.
224. Wauters M, Considine RV, Yudkin JS, Peiffer F, De Leeuw I, Van Gaal LF. Leptin levels in type 2 diabetes: associations with measures of insulin resistance and insulin secretion. *Horm Metab Res* 2003;**35**:92–96.
225. Leal-Cerro A, Soto A, Martínez MA, Dieguez C, Casanueva FF. Influence of cortisol status on leptin secretion. *Pituitary* 2001;**4**:111–116.
226. Iacobellis G, Petramala L, Cotesta D, Pergolini M, Zinnamosca L, Cianci R, De Toma G, Sciomer S, Letizia C. Adipokines and cardiometabolic profile in primary hyperaldosteronism. *J Clin Endocrinol Metab* 2010;**95**:23918.
227. Chiurchiù V, Izzi V, D'Aquilio F, Carotenuto F, Di Nardo P, Baldini PM. Brain natriuretic peptide (BNP) regulates the production of inflammatory mediators in human THP-1 macrophages. *Regul Pept* 2008;**148**:26–32.
228. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004;**109**:594–600.
229. Goharian TS, Goetze JP, Faber J, Andersen LB, Grøntved A, Jeppesen JL. Associations of proatrial natriuretic peptide with components of the metabolic syndrome in adolescents and young adults from the general population. *Am J Hypertens* 2017;**30**:561–568.
230. De Souza LR, Ye C, Hanley AJ, Connelly PW, Sermer M, Zinman B, Retnakaran R. Circulating B-type natriuretic peptide in women with and without recent gestational diabetes: the impact of current glucose intolerance. *Clin Endocrinol* 2018;**88**:227–233.
231. Johansen ML, Schou M, Rasmussen J, Rossignol P, Holm MR, Chabanova E, Dela F, Faber J, Kistorp C. Low N-terminal pro-brain natriuretic peptide levels are associated with non-alcoholic fatty liver disease in patients with type 2 diabetes. *Diabetes Metab* 2019;**45**:429–435.
232. Kovacova Z, Tharp WG, Liu D, Wei W, Xie H, Collins S, Pratley RE. Adipose tissue natriuretic peptide receptor expression is related to insulin sensitivity in obesity and diabetes. *Obesity (Silver Spring)* 2016;**24**:820–828.
233. Marrachelli VG, Miranda FJ, Centeno JM, Miranda I, Castelló-Ruiz M, Burguete MC, Jover-Mengual T, Salom JB, Torregrosa G, Alborch E. Mechanisms underlying the diabetes-induced hyporeactivity of the rabbit carotid artery to atrial natriuretic peptide. *Pharmacol Res* 2011;**63**:190–198.
234. Packer M, Claggett B, Lefkowitz MP, McMurray JJV, Rouleau JL, Solomon SD, Zile MR. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2018;**6**:547–554.
235. Matucci-Cerinic M, Lombardi A, Leoncini G, Pignone A, Sacerdoti L, Spillantini MG, Partsch G. Neutral endopeptidase (3.4.24.11) in plasma and synovial fluid of patients with rheumatoid arthritis. A marker of disease activity or a regulator of pain and inflammation? *Rheumatol Int* 1993;**13**:1–4.
236. Matucci-Cerinic M, Iannone F, Carossino A, Pignone A, Leoncini G, Generini S, Lapadula G, Cagnoni M. Discrepant expression of neprilysin on fibroblasts in diffuse systemic sclerosis. *J Rheumatol* 1999;**26**:347–351.
237. Peters MJ, Welsh P, McInnes IB, Wolbink G, Dijkmans BA, Sattar N, Nurmo-hamed MT. Tumour necrosis factor alpha blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: results from a prospective cohort study. *Ann Rheum Dis* 2010;**69**:1281–1285.
238. Pietrzak A, Bartosinska J, Blaszczyk R, Chodorowska G, Brzozowski W, Hercogova J, Donica H, Lotti T. Increased serum level of N-terminal pro-B-type natriuretic peptide as a possible biomarker of cardiovascular risk in psoriatic patients. *J Eur Acad Dermatol Venereol* 2015;**29**:1010–1014.
239. Ferrario CM, Jessup JA, Smith RD. Hemodynamic and hormonal patterns of untreated essential hypertension in men and women. *Ther Adv Cardiovasc Dis* 2013;**7**:293–305.
240. Tonstad S, Sandvik E, Larsen PG, Thelle D. Gender differences in the prevalence and determinants of the metabolic syndrome in screened subjects at risk for coronary heart disease. *Metab Syndr Relat Disord* 2007;**5**:174–182.
241. Giacché M, Vuagnat A, Hunt SC, Hopkins PN, Fisher ND, Azizi M, Corvol P, Williams GH, Jeunemaitre X. Aldosterone stimulation by angiotensin II: influence of gender, plasma renin, and familial resemblance. *Hypertension* 2000;**35**:710–716.
242. Abdullah SM, Khera A, Leonard D, Das SR, Canham RM, Kamath SA, Vega GL, Grundy SM, McGuire DK, de Lemos JA. Sex differences in the association between leptin and CRP: results from the Dallas Heart Study. *Atherosclerosis* 2007;**195**:404–410.
243. Breyer MK, Rutten EP, Vernooy JH, Spruit MA, Dentener MA, Van der Kallen C, van Greevenbroek MM, Wouters EF. Gender differences in the adipose secretome system in chronic obstructive pulmonary disease (COPD): a pivotal role of leptin. *Respir Med* 2011;**105**:1046–1053.
244. Flanagan DE, Vaile JC, Petley GW, Phillips DI, Godsland IF, Owens P, Moore VM, Cockington RA, Robinson JS. Gender differences in the relationship between leptin, insulin resistance and the autonomic nervous system. *Regul Pept* 2007;**140**:37–42.
245. Ma D, Feitosa MF, Wilk JB, Laramie JM, Yu K, Leiendecker-Foster C, Myers RH, Province MA, Borecki IB. Leptin is associated with blood pressure and hypertension in women from the National Heart, Lung, and Blood Institute Family Heart Study. *Hypertension* 2009;**53**:473–479.
246. Maffei S, Del Ry S, Prontera C, Clerico A. Increase in circulating levels of cardiac natriuretic peptides after hormone replacement therapy in postmenopausal women. *Clin Sci (Lond)* 2001;**101**:447–453.
247. Neeland IJ, Winders BR, Ayers CR, Das SR, Chang AY, Berry JD, Khera A, McGuire DK, Vega GL, de Lemos JA, Turer AT. Higher natriuretic peptide levels associate with a favorable adipose tissue distribution profile. *J Am Coll Cardiol* 2013;**62**:752–760.
248. Emdin M, Passino C, Del Ry S, Prontera C, Galetta F, Clerico A. Influence of gender on circulating cardiac natriuretic hormones in patients with heart failure. *Clin Chem Lab Med* 2003;**41**:686–692.
249. Harada E, Mizuno Y, Kugimiya F, Shono M, Maeda H, Yano N, Yasue H. Sex differences in heart failure with preserved ejection fraction reflected by B-type natriuretic peptide level. *Am J Med Sci* 2018;**356**:335–343.
250. Faxén UL, Lund LH, Orsini N, Strömberg A, Andersson DC, Linde C, Dahlström U, Savarese G. N-terminal pro-B-type natriuretic peptide in chronic heart failure: the impact of sex across the ejection fraction spectrum. *Int J Cardiol* 2019;**287**:66–72.
251. Sundström J, Bruze G, Ottosson J, Marcus C, Näslund I, Neovius M. Weight loss and heart failure: a nationwide study of gastric bypass surgery versus intensive lifestyle treatment. *Circulation* 2017;**135**:1577–1585.
252. Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. *Circulation* 2005;**112**:357–363.
253. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. *Rheumatology (Oxford)* 2005;**44**:677–680.
254. Alehagen U, Benson L, Edner M, Dahlström U, Lund LH. Association between use of statins and mortality in patients with heart failure and ejection fraction of ≥50. *Circ Heart Fail* 2015;**8**:862–870.

255. Alehagen U, Benson L, Edner M, Dahlström U, Lund LH. Association between use of statins and outcomes in heart failure with reduced ejection fraction: prospective propensity score matched cohort study of 21 864 patients in the Swedish Heart Failure registry. *Circ Heart Fail* 2015;**8**:252–260.
256. Kosmala W, Rojek A, Przewlocka-Kosmala M, Wright L, Mysiak A, Marwick TH. Effect of aldosterone antagonism on exercise tolerance in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2016;**68**:1823–1834.
257. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B; Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013;**309**:781–791.
258. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay Pitt B.. Regional variation in patients and outcomes in the Treatment of Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT). *Circulation* 2015;**131**:34–42.
259. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
260. Olivier A, Pitt B, Girerd N, Lamiral Z, Machu JL, McMurray JJV, Swedberg K, van Veldhuisen DJ, Collier TJ, Pocock SJ, Rossignol P, Zannad F, Pizard A. Effect of eplerenone in patients with heart failure and reduced ejection fraction: potential effect modification by abdominal obesity. Insight from the EMPHASIS-HF trial. *Eur J Heart Fail* 2017;**19**:1186–1197.
261. Anand IS, Claggett B, Liu J, Shah AM, Rector TS, Shah SJ, Desai AS, O'Meara E, Fleg JL, Pfeffer MA, Pitt B, Solomon SD. Interaction between spironolactone and natriuretic peptides in patients with heart failure and preserved ejection fraction: from the TOPCAT trial. *JACC Heart Fail* 2017;**5**:241–252.
262. Anand IS, Rector TS, Cleland JG, Kuskowski M, McKelvie RS, Persson H, McMurray JJ, Zile MR, Komajda M, Massie BM, Carson PE. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. *Circ Heart Fail* 2011;**4**:569–577.
263. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: a secondary analysis of TOPCAT trial. *JACC Heart Fail* 2019;**7**:228–238.
264. Kusaka H, Sueta D, Koibuchi N, Hasegawa Y, Nakagawa T, Lin B, Ogawa H, Kim-Mitsuyama S. LCZ696, angiotensin II receptor-neprilysin inhibitor, ameliorates high-salt-induced hypertension and cardiovascular injury more than valsartan alone. *Am J Hypertens* 2015;**28**:1409–1417.
265. Solomon SD, McMurray JJ, Anand IS, Ge J, Lam CS, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund P, Boytsov SA, Colet JC, Cleland J, Duengen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620.
266. Díaz-Rodríguez E, Agra RM, Fernández ÁL, Adrio B, García-Caballero T, González-Juanatey JR, Eiras S. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production and differentiation ability. *Cardiovasc Res* 2018;**114**:336–346.
267. Adingupu DD, Göpel SO, Grönros J, Behrendt M, Sotak M, Miliotis T, Dahlqvist U, Gan LM, Jönsson-Rylander AC. SGLT2 inhibition with empagliflozin improves coronary microvascular function and cardiac contractility in prediabetic Ob/Ob−/− mice. *Cardiovasc Diabetol* 2019;**18**:16.
268. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, Matsumoto K, Shite J, Takaoka H, Doi T, Hirata KI. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol* 2018;**17**:132.
269. Packer M. Activation and inhibition of sodium-hydrogen exchanger is a mechanism that links the pathophysiology and treatment of diabetes mellitus with that of heart failure. *Circulation* 2017;**136**:1548–1559.
270. Packer M. Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis. *Diabetes Obes Metab* 2018;**20**:1361–1366.
271. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RH, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Sabatine MS. SGLT2 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.
272. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RH, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019;**139**:2528–2536.