Current Heart Failure Reports (2024) 21:379–388
https://doi.org/10.1007/s11897-024-00665-x

REVIEW

Sex-based Differences in Heart Failure Biomarkers

Ainhoa Robles-Mezcua[1,2,3,4] · Nelsa González Aguado[1,2,3] · Antonia Pilar Martin de la Rosa[1,2] · Concepción Cruzado-Álvarez[1,2] · Clara Jiménez Rubio[1,2,3] · Alejandro IPérez Cabeza[1,2,3,4] · Juan José Gómez-Doblas[1,3,4,5] · Manuel F. Jiménez-Navarro[1,3,4,5] · Mora Murri Pierri[1,4,6,7,8] · José M. García-Pinilla[1,2,3,4,6]

Accepted: 24 April 2024 / Published online: 20 May 2024

Abstract

Purpose of Review Differences in HF biomarker levels by sex may be due to hormonal, genetic, and fat distribution differences. Knowledge of these differences is scarce, and it is not well established whether they may affect their usefulness in the management of HF.

Recent Findings The different biomarker profiles in women and men have been confirmed in recent studies: in women, markers of cardiac stretch and fibrosis (NP and galectin-3) are higher, whereas in men, higher levels of markers of cardiac injury and inflammation (cTn and sST2) are found.

The use of new biomarkers, together with growing evidence that a multimarker approach can provide better risk stratification, raises the question of building models that incorporate sex-specific diagnostic criteria.

Summary More and more research are being devoted to understanding sex-related differences in HF. The aim of this review is to review the dynamics of HF biomarkers according to sex and in different situations, to learn whether these sex differences may affect their use in the diagnosis and follow-up of HF patients.

Keywords Sex differences · Biomarkers · Heart failure

✉ Mora Murri Pierri
moramurri@gmail.com

1 Área del Corazón, Hospital Universitario Virgen de La Victoria, Málaga, Spain

2 Unidad de Insuficiencia Cardíaca y Cardiopatías Familiares, Cardiología. Hospital Universitario Virgen de La Victoria, Málaga, Spain

3 Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina (IBIMA Plataforma BIONAND), Málaga, Spain

4 Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain

5 Departamento de Medicina y Dermatología, Facultad de Medicina, Universidad de Málaga, Málaga, Spain

6 Endocrinology and Nutrition UGC, Hospital Universitario Virgen de La Victoria, Málaga, Spain

7 Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina-IBIMA Plataforma BIONAND, Hospital Clínico Virgen de La Victoria, Málaga, Spain

8 CIBER Fisiopatología de La Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Málaga, Spain

Abbreviations

BMI	Body mass index
CTn	Circulatory troponins
Gal-3	Galectin-3
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
hs-Tn	High-sensitivity troponin
NP	Natriuretic peptide
NT-proBNP	Amino-terminal pro-peptide fragment
sST2	Soluble suppression of tumorgenicity 2

Introduction

The current worldwide prevalence of heart failure (HF) stands at more than 64 million cases, or 8.5 per 1,000 population, making it a growing epidemic associated with significant morbidity, mortality and health care costs in both sexes [1–3]. This prevalence is higher as age increases, being more than 10% in the population over 70 years of age, and it is

estimated that the incidence of the disease is higher in the elderly [4]. Thus, HF is considered a major problem, since despite advances in treatment and prevention, it continues to be the leading cause of hospitalization in the world [5, 6] and it continues to be the leading cause of hospitalization in people over 65 years of age [7].

Although 50% of patients with HF are women, differences between sexes in the presentation and evolution of HF and in biomarker levels have been described, but the cause and its clinical implications are not fully understood [8]. The predominant phenotype in each sex is well known, with heart failure with preserved ejection fraction (HFpEF) being more prevalent in women, whereas the risk of heart failure with reduced ejection fraction (HFrEF) is higher in men. In addition, although women are hospitalized in more advanced stages of HF, hospitalizations for HF are more frequent in men [9••, 10].

The prevalence and impact of traditional cardiovascular risk factors also differ between men and women, with a different distribution across the lifespan [11••]. Diabetes mellitus, coronary microvascular dysfunction, and immunoinflammatory mechanisms play a greater role in the development of HF in women, whereas ischemic heart disease with macrovascular coronary disease is the main cause of HF in men [12, 13••]. In addition, it is known that even the myocardial response to ischemic damage and cardiovascular stress is also different between men and women [13••].

Despite adjusting for left ventricular ejection fraction (LVEF) and natriuretic peptide (NP) levels, clinical presentation also differs between sexes [14]. Women tend to show a more advanced clinical picture, with worse functional class, greater congestion and more severe symptoms [13••]. However, women have a better prognosis in terms of hospitalization and death than men [9••, 15, 16], postulating sex-specific regulation of mitochondrial function and energy metabolism as one of the causes of this sexual dimorphism in HF [17].

When analyzing the differences between women and men, hormonal reasons are always considered. When oestrogen production ceases, an increase in cardiovascular risk is demonstrated, which supports the idea of the protective role of this hormone. It is thought that the function of contractile proteins may be hormonally influenced, since oestrogenic and androgenic receptors have been detected in cardiac tissue; it has also been shown that endogenous oestrogens are relatively protective against apoptosis and cell death. All this could explain why women have a better response to acute coronary ischemia, with higher rates of successful reperfusion, smaller infarcts, and less cardiac remodelling with greater preservation of left ventricular function [8].

HF biomarker concentrations are known to differ between men and women, but the clinical significance of these differences remains poorly understood [18]. We cannot forget that women are still underrepresented in clinical trials, having less knowledge of their evolution, management and treatment, which may also contribute to the lack of knowledge on this issue. Furthermore, about cardiovascular disease in general, we should pay attention to sex and gender, as these are nuances that also influence clinical outcomes. Sex encompasses biological differences, from gene expression to hormonal influence; whereas gender involves culture, different roles and behaviour between men and women, which also vary across societies and historical periods [19].

The aim of this review is to analyse these sex-associated differences in HF, with emphasis on biomarkers and their novel aspects. Figure 1 shows a summary of the most characteristic sex differences in HF.

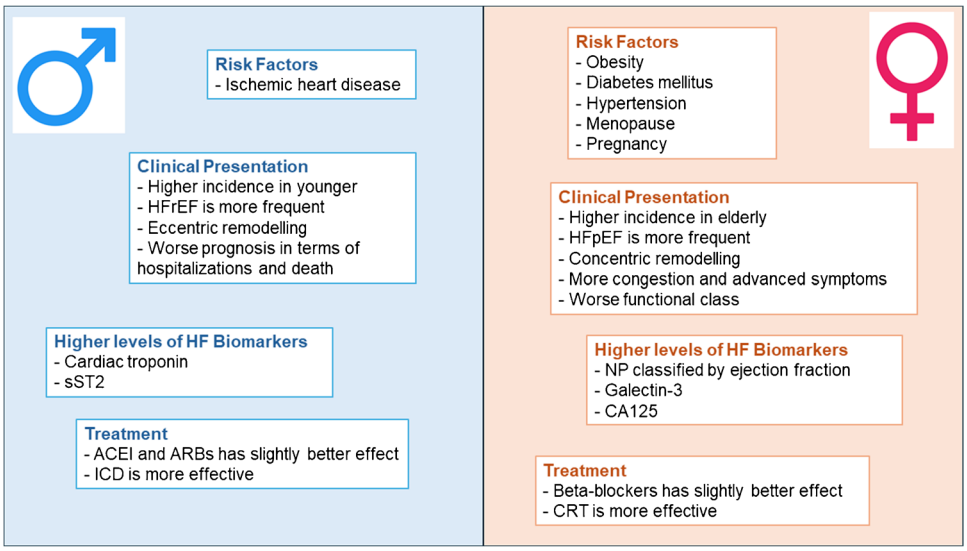

Fig. 1 Sex differences in Heart Failure. ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; CA125: Carbohydrate 125; CRT: cardiac resynchronization therapy; HFrEF: Heart failure reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; ICD: implantable cardioverter defibrillator; NP: Natriuretic peptides; sST2: Soluble suppression of tumorogenesis-2

Sex Differences in Biomarkers of Hear Failure

Plasma biomarkers are useful tools in the diagnosis and prognosis of HF. There are cardiac-specific biomarkers, such as natriuretic peptides (NP) and high-sensitivity troponins (hsTn), which are widely represented in clinical practice. However, other biomarkers have not yet been included in practical HF management, such as galectin-3 (Gal-3) and soluble suppression of tumorigenicity 2 (sST2) [20]. The large number of potential circulating biomarkers reflects the complexity of HF pathogenic pathways. Although ideally, each biomarker should correspond to a single point in the pathogenesis of HF, in reality, receiving an accurate clinical interpretation of peak concentrations is challenging due to the changes observed in most current biomarkers because of the extensive overlap of different phenotypes [21].

Sex-related differences in HF biomarker levels may be due to genetic, epigenetic and environmental differences, as well as the effect of sex hormones and the different distribution of body fat between men and women [13••, 22]. There is still a knowledge gap regarding the biology or physiology of these different marker concentrations, and they have an implication to consider in the diagnosis and follow-up of patients with HF, and it may be necessary to develop sex-specific diagnostic or predictive models [13••]. In general, women tend to have elevated levels of biomarkers associated with cardiac stretch and fibrosis, whereas men have higher levels of markers associated with cardiac injury and inflammation [23] (Table 1).

Natriuretic Peptides

Natriuretic peptides (NP) are a group of polypeptides secreted mainly by the heart, kidneys and vascular endothelium. They regulate cardiovascular homeostasis, controlling intravascular volume and blood pressure, with diuretic, natriuretic and vasodilator properties [13••]. NPs are mainly biomarkers of myocardial stretch, with BNP and NTproBNP being the most widely used in clinical practice for the diagnosis and prognosis of patients with HF [9••, 24].

It is widely known that HF is a complex phenotype, so we must carefully assess differences in NP levels between men and women, because these differences may be related to the differential prevalence of HFrEF vs. HFpEF between men and women [13••]. Female sex has been described as a strong predictor of elevated natriuretic peptides [18] as several studies have shown that NT-proBNP levels are higher in women than in men [2]. However, NT-proBNP appears to be a stronger predictor of risk in men than in women, demonstrating a greater presence of ICrEF in men and higher levels of NT-proBNP [2].

In the general population, basal NTproBNP levels have been found to be higher in women than in men, especially in premenopausal women [13••, 25, 26]. It appears that sex hormones play a role in this difference, and there is

Table 1 Sex differences in Heart Failure biomarkers

Biomarkers	Diagnostic value	Sex differences		Modulators
		General population	HF population	
BNP NT-proBNP	Cardiac stretching and congestion	Higher levels in women	Inconsistent results in several papers: Higher levels in women if classified by ejection fraction	Age and oestroges increase biomarker levels Obesity ante testosterone induced lower levels
Cardiac troponins	Myocyte injury	Lower leves in women	Lower levels in women	Testosterone-induced hypertrophy and apoptosis Oestrogen-induced suppression of cardiomyocyte apoptosis
sST2	Extracellular matrix remodeling and fibrosis	Lower leves in women	Higher levels in men with chronic HF	Sex hormones (testosterone and estradiol increase levels in men, estrogens decrease levels in women), obesity
Galectin-3	Extracellular matrix remodeling and fibrosis	Higher levels in women	No differences, but it is more associated with incident HF in women	Body fat increases biomarker levels
GDF-15	Inflammatory response	Lower levels in women	Unknown	Unknown
CA125	Congestion	Variation in women by the menstrual cycle	Higher in women than in men	Menstruation, endometriosis, and rise in ovarian cancer CA125 concentration

CA125: Carbohydrate 125; GDF-15: Growth differentiation factor-15; NT-proBNP: Amino-terminal molecule of Brain Natriuretic Peptide; sST2: soluble suppression of tumorogenesis-2

now strong clinical evidence that testosterone decreases cardiac NP levels, which may explain these lower NP levels in men [9••, 13••, 27]. One possible explanation for this is the up-regulation of neprilysin activity by testosterone, although this mechanism has not been fully elucidated [13••, 28]. This hypothesis could explain both the differences observed in premenopausal women compared to young men of the same age range, as well as the change in NP levels after menopause, since studies have shown that postmenopausal women have lower NT-proBNP levels than premenopausal women [9••, 13••].

In the HF population, the different levels of NP in terms of sex show inconsistent results in several papers. Some studies show that the mean NP concentration seems to be slightly higher in men [13••], this would imply that in this state of excessive NP production such as HF, the effects of sex hormones are overridden, and plasma levels may no longer reflect sex-specific changes. However, in other studies, it has been shown that women had moderately higher levels of NT-proBNP when comparing women and men with HF and the same LVEF [29, 30••].

There are also conflicting data regarding prognosis and sex-specific differences in NP. There are studies that found no sex-specific differences [31, 32] but, at very high levels of NT-proBNP, there was a trend toward higher mortality in women compared to men at similar levels [32]. In other studies and meta-analyses, NT-proBNP was more strongly associated with the incidence of HF in men than in women [13••, 33].

Special mention should be made of obesity, which is known to favour a state of relative cardiac NP deficiency, perhaps associated with the fact that visceral fat appears to increase testosterone levels, which decrease cardiac NP levels [34, 35] perhaps associated with the fact that visceral fat appears to increase testosterone levels which decrease NP levels [29, 36]. Shutahar et al. have recently shown that, in the general population, the decrease in NT-proBNP levels associated with male sex was more important than the reduction in NT-proBNP levels associated with obesity [13••, 36]. These observations may have clinical implications regarding the choice of the optimal cut-off value to rule out HF, with sex-specific cut-off points being necessary to rule out HF in the general population (e.g., lower NT-proBNP cut-off points in men), and not so much considering obesity. In contrast, in the HF population, it has been shown that NT-proBNP levels are up to 60% lower in obese patients, with sex-related effects being more subtle and obesity playing a more important role [13••]. Therefore, in patients with HF it does seem interesting to establish a lower cut-off point in obese individuals to estimate the severity of the disease, the differences between men and women not being so necessary in this regard.

Cardiac Troponins

Cardiac troponins are mainly markers of myocardial ischemia, establishing as the specific marker of cardiac injury. Thus, troponin levels may be elevated in HF due to multiple mechanisms, not only because of ischemia caused by macrovascular and microvascular coronary artery disease, but also due to the state of inflammation and neurohormonal overactivation, leading to infiltrative processes and myocardial apoptosis. In healthy individuals, circulating troponin (cTn) levels are higher in men than in women [13••, 37].This has been attributed to differences in left ventricular mass and the protective antioxidant role of estrogens [30••].

Since the predominant use of high-sensitivity techniques, cTn has been found to be elevated in the majority of HF patients and high-sensitivity troponin (hs-Tn) has been established as a strong predictor in patients with chronic HF [38]. In most studies, there is no evidence of sex-specific differences in cTn levels, but the data are sometimes partial [39]. In the sex-specific analyses of Suthahar et al. cTn levels were higher in men and remained significantly associated with HF in men [31]. It has also been observed that when stratifying by sex and phenotype, there is a stronger predictive association of hs-Tn with outcome in men with HFpEF than in women, but the same association was not found in patients with HFrEF [40].

The pathophysiology of sex-related differences in cTn levels is not known. It is thought that perhaps the higher prevalence of cardiac comorbidities in men (e.g., atrial fibrillation, ventricular arrhythmias, coronary artery disease, cardiomyopathies, myocarditis), together with their specific hormonal mechanisms (e.g., testosterone-induced hypertrophy and cardiomyocyte apoptosis) could contribute to the higher cTn concentrations observed in male HF patients. In contrast, the different mechanisms of myocardial injury present in women (e.g., coronary microvascular disease), together with the cardioprotective effects of oestrogens (e.g., suppression of cardiomyocyte apoptosis), could explain the relatively lower cTn concentrations in women with HF [13••, 30••].

Although the diagnostic value of cTn in HF is limited, it does clearly predict the incidence of HF in the general population [13••] and its prognostic value in HF patients appears increasingly robust. However, we still have few data on sex-related differences in this prognostic value of cTn in patients with HF [5, 41]. In this regard, it is interesting to note that the T isoform (cTnT) appears to be similarly associated with adverse events in both sexes, whereas I (cTnI), which is measured with a more sensitive assay, is more associated with adverse events in men with HF-PEF than in women with HFpEF [40].

Obesity also influences cTn levels. According to Ndumele et al. data, obesity is strongly associated with

higher cTn levels [42]. It is hypothesized that adipokines could lead to adverse cardiac remodelling as a consequence of cardio-deleterious signals or even direct damage to cardiac tissue. It also seems important to take into account sex differences in this regard, given the differences in fat distribution between men and women and the higher overall prevalence of obesity in women [13••, 42].

Soluble Suppression of Tumorgenicity 2 (sST2)

ST2 is a member of the IL1 family and is proposed as a novel biomarker associated with ventricular fibrosis and remodelling. The ST2 gene encodes two isoforms, the transmembrane form or ligand (LST2) and the soluble form (sST2). The sST2 form is produced in cardiomyocytes in response to myocardial stretch, and acts as a "decoy" receptor for IL-33, thus promoting myocardial damage by inhibiting the cardioprotective effects of IL33-ST2L interaction [43].

In the general population, sST2 levels are higher in men, and a similar trend is observed in HF patients [18, 44, 45]. Data regarding these differences are scarce and contradictory, and although in general there appear to be higher levels of sST2 in males, this cannot be explained by hormonal influence alone. There is research indicating that both testosterone and oestradiol levels are significantly associated with sST2 levels. For example, in some work in women, oestrogen hormone therapy was associated with lower sST2 levels, while in other studies sex hormones did not correlate with sST2 levels [13••].

Elevated sST2 levels have prognostic implications in HF patients, but sex-specific data are limited [9••, 31]. It does not appear that the influence of sex hormones can explain sex differences in sST2, nor is the pathophysiology of these sex-specific differences in healthy individuals and HF patients known [46, 47]. In the multimarker study by Lew et al. no significant association between sexes was evident overall, but significantly lower levels were observed in postmenopausal women compared with men of the same age [48]. Recently, Arrieta et al. demonstrated that sST2 was an independent factor for fibrosis in patients with severe aortic stenosis. In this study, men had higher levels of fibrosis and sST2, with a positive correlation with greater ventricular dilatation and hypertrophy [49]. Despite these observations, it is still unknown whether sex-specific differences in sST2 levels have a clinical and prognostic implication in patients with HF.

At present, obesity has not been described as having a significant influence on sST2 levels. There is some data from animal studies indicating that sST2 expression is decreased in adipose tissue, heart and liver of obese mice compared to non-obese controls [13••].

Galectin-3 (Gal-3)

Galectin-3 is a profibrotic protein secreted mainly by macrophages, its expression being essential for tissue repair after injury. However, persistent elevation of galectin-3 generates a state of inflammation that leads to fibrosis and adverse remodeling [50]. Unlike NPs and cTn, plasma levels of Gal-3 come from sources other than the heart, such as adipose tissue, lungs, hematopoietic tissue and liver. Thus, its levels are less influenced by cardiac loading conditions and for this reason it is already included in American guidelines with a class II indication as a diagnostic and prognostic marker in patients with HF [41].

In the general population, several studies have shown that women have slightly higher levels of galectin-3 than men, without knowing the cause of this difference [13••, 51]. It is postulated that differences in fat mass may be an explanation, rather than differences in sex hormones [52].

In the HF population there are no consistent data regarding sex-specific differences in Gal-3 levels [31]. Some studies describe a trend of slightly higher galectin-3 levels in male HF patients; whereas in other studies Gal-3 levels were similar in both sexes or more associated with incident HF in women [13••, 18, 53]. Dekelva et al. in a cohort of percutaneously treated myocardial infarction patients, observed higher Gal-3 levels in women, together with a higher incidence of heart failure and left ventricular hypertrophy [54]. These are preliminary and unconfirmed data, without being able to establish their sex-specific implication for predicting the incidence of HF or disease progression [31, 55].

Growth Differentiation Factor-15 (GDF-15)

Growth differentiation factor-15 is a member of the transforming growth factor-β (TGF-β) superfamily of cytokines with antiapoptotic, antihypertrophic, and anti-inflammatory properties [21]. Its production is predominantly extracardiac (lungs, liver and kidneys) [56] and in general has anti-inflammatory, antioxidant and antiapoptotic properties, giving it a cardioprotective role [57]. Ischemia and reperfusion injury induces GDF15 expression in cardiomyocytes, which is associated with inflammation and cardiac fibrosis. Elevated concentrations of GDF15 also seem to predict the occurrence of atrial fibrillation, cardiac thrombosis and cardioembolic stroke [58–60]. GDF15 is thus considered a promising biomarker and a potential therapeutic target for the treatment of HF, and several studies are currently underway.

Although women appear to have slightly lower levels of GDF-15 than men, sex differences in plasma GDF-15 levels have not yet been clearly established. [13••, 61].

Carbohydrate Antigen 125 (CA125)

Carbohydrate antigen 125 (CA125, also called mucin 16 [MUC16]) is a high molecular weight glycoprotein encoded by the MUC16 gene and expressed on the surface of pleural, peritoneal and pericardial epithelial cells [62]. Although its use was initially based on the monitoring of ovarian oncologic processes, CA125 has also been shown to be elevated in many other situations related to volume expansion, such as cirrhosis, renal failure and heart failure [63]. It is thought that elevated hydrostatic pressure, mechanical stress and inflammatory stimuli in the context of congestion may activate mesothelial cells on serosa surfaces, inducing the production and plasma elevation of CA125 [62]. Recent studies have confirmed the usefulness of changes in plasma CA125 concentration in predicting mortality and readmission, especially during the first months after an episode of decompensated HF [62, 63]. In terms of therapeutic implications, it has been shown that patients at lower risk are those with a greater reduction in CA125 after the first month after admission; on the other hand, patients who maintain elevated levels or those whose levels increase during follow-up appear to be at higher risk [64].

It is important to note that there is a time interval between the onset of congestion and the release and rise of CA125 and that we must take this into account in order to correctly interpret CA125 as a surrogate marker of congestion. Consequently, we will find higher plasma CA125 levels in patients with more progressive and prolonged congestion (days to weeks) than in patients with more acute congestion (minutes to hours) [63]. An advantageous property of CA125 compared to NPs is that its levels are not significantly affected by age, LVEF and renal function, being this relevant in its clinical application for the evaluation of cardiorenal syndrome as well as in elderly patients and patients with HFpEF [63, 64].

We do have to keep in mind that CA125 can be elevated under physiological conditions such as pregnancy or menstruation and CA125 levels have been shown to differ during the menstrual cycle, with higher values during endometrial shedding in menstruation due to the inflammatory process [65]. However, this menstrual surge does not bring CA125 values to concentrations similar to those required for a diagnosis of HF [30••]. Recently, Menghoum et al. described significantly higher CA125 levels in women than in men, further demonstrating that CA125 levels were a strong and independent predictor of HF hospitalization in patients with HFpEF [66]. However, in this study, no differences in abnormal CA125 values were found between men and women, suggesting that sex does not appear to be an independent factor in elevating CA125 levels. The authors explain these findings by the higher proportion of women in the HFpEF population, and therefore this effect of sex on CA125 levels might be expected [66].

Also this study by Menghoum et al. revealed an inverse association between body mass index and CA 125 levels, a finding already reported in patients with metabolic syndrome [67]. The cause of this inverse correlation is not known, but the most convincing hypothesis suggests that a lower body mass index is associated with a poor prognosis in HF and therefore increased CA125 could be an indicator of poor prognosis, related to these metabolic changes in advanced disease with a lower body mass index [66, 67].

Female Specific Situations

Takotsubo cardiomyopathy is an entity that mainly affects women, especially postmenopausal women. It has been observed that these patients have lower troponin levels and higher NP levels than when the aetiology is coronary artery disease and may be of interest in the differential diagnosis [9••]. However, no prognostic association has been established with these different biomarker values [68].

NP levels could be nonspecific and elevated for other causes such as pulmonary embolism or preeclampsia in peripartum cardiomyopathy. However, it seems that higher baseline NT-proBNP levels predict lower recovery of cardiac function at 6 months [69–71]. Other more specific biomarkers have been studied in peripartum cardiomyopathy (e.g. prolactin, placental growth factor…) but although there is evidence that they may be elevated for a long time after the process and even correlate with recovery of cardiac function, their implementation in clinical practice has not been established [72].

Future Directions

Multiparametric assessment in the diagnosis and follow-up of HF is already a reality in the management of HF, along with precision medicine that allows us to more precisely define the patient's phenotype in order to choose the most beneficial treatment in each case [76–78]. Within this multiparametric assessment is the use of different biomarkers in combination (multimarker approach), and there are already data on sex differences, especially in the HFpEF spectrum [79–81].

There are some studies that investigated sex-differences in HF patients using high-throughput protein biomarker platform using Proximity Extension Assay (PEA) technologythe. Fatty acid binding protein 4 (FABP-4), secretoglobin family member 2 3A (SCGB3A2), paraoxonase 3 (PON3), and trefoil factor 3 (TFF-3) showed higher mean levels in women, whereas levels of matrix metalloproteinase-3 (MMP-3), ST2s, and myoglobin (MB) were higher in men. However, although multiple proteins related to cardiovascular disease

and HF showed sex differences at baseline, no relationship was found over time or with events at follow-up between women and men with HF [82, 83].

The use of proteomics, metabolomics and circulating microRNAs is a promising strategy for early diagnosis and risk stratification of patients with HF [84]. This more basic research is also increasingly taking sex and gender differences into account [85]. The use of microRNAs (miRNAs) as biomarkers for diagnosis, follow-up and prognosis in HF is being studied. These miRNAs are small non-coding RNAs that play an important role in the regulation of gene expression [86]. It seems that the expression of these miRNAs is significantly influenced by sex: on the one hand, with the direct effect of oestrogens driving the expression of some of these miRNAs, which also seem to have protective functions [86, 87]; and on the other hand, because the X chromosome encodes more than 100 miRNAs that could escape the inactivation of this chromosome, so they would be expressed at a higher level [88], with many of these miRNAs X-linked associated with microvascular and myocardial involvement [86]. This knowledge of miRNAs and the influence that sex has on them could contribute to the differences in the pathophysiology of HF between men and women, especially in HFpEF [86]. In addition, with the increasing advances in gene therapy with RNA, being able to silence or activate regulatory pathways, we are invited to think about possible future treatments in this sense [85, 86].

Artificial intelligence and machine learning are also being used as tools in HF management [89]. There are already some data in this regard, with studies in which machine learning models have been applied to predict the incidence of HF in asymptomatic individuals and in which some differences by sex have been revealed, with markers of inflammation (such as FABP4 and interleukin-6) being higher in the female population with a higher risk of developing HF or cardiovascular death. In contrast, in a male-dominated phenotype, biomarkers of remodelling such as troponin, sST2 and C-type natriuretic peptide were elevated and the risk increased fivefold [90].

Conclusion

Although it is well known that there are sex differences in the pathophysiology, presentation, and progression of HF, these differences in the levels and clinical interpretation of HF biomarkers are less well established.

It appears that the influence of sex on biomarker levels is greater or best known in the general population than in HF patients and the different biomarker profiles in women and men have been described in recent studies: in women, markers of cardiac stretch and fibrosis (NP and galectin-3) are higher, whereas in men, higher levels of markers of cardiac injury and inflammation (cTn and sST2) are found. However, it remains to be elucidated whether these differences have clinical significance and whether it is necessary to identify sex-specific cut-off points for the diagnosis and follow-up of HF.

This, together with the growing evidence that multiparametric assessment using different biomarkers (multimarker approach), in addition to the use of artificial intelligence and machine learning can provide better risk stratification and should lead us to build models that incorporate sex-specific diagnostic criteria. This will allow us to achieve equitable care for men and women and ultimately improve HF treatment and patient care.

Acknowledgements This study has been funded by the Instituto de Salud Carlos III (ISCIII) through project "PI23/00293" and co-funded by the European Union. MM is supported by the Miguel Servet II program (CPII22/00013) and ARM has a Río Hortega contract [CM23/00125] funded by the Instituto de Salud Carlos III. The editors would like to thank Dr. Kai M. Eggers for handling the review of this manuscript.

Author Contributions All authors contributed significantly to the preparation of the manuscript. All authors reviewed the manuscript.

Declarations

Conflict of Interest Ainhoa Robles-Mezcua, Nelsa González Aguado, Antonia Pilar Martin de la Rosa, Concepción Cruzado-Álvarez, Clara Jiménez Rubio, Alejandro I Pérez Cabeza, Juan José Gómez-Doblas, Manuel F. Jiménez-Navarro, Mora Murri Pierri, José M. García-Pinilla declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any human or animal studies conducted by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. AME Med J. 2020;5(0). https://doi.org/10.21037/AMJ.2020.03.03/COIF.
2. Magnussen C, Niiranen TJ, Ojeda FM, et al. Sex-specific epidemiology of heart failure risk and mortality in Europe: results from the biomarCaRE consortium. JACC Heart Fail. 2019;7(3):204–13. https://doi.org/10.1016/J.JCHF.2018.08.008.
3. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020;22(8):1342–56. https://doi.org/10.1002/EJHF.1858.
4. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014;63(12):1123–33. https://doi.org/10.1016/J.JACC.2013.11.053.

5. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2023;44(37):3627–39. https://doi.org/10.1093/EURHEARTJ/EHAD195.
6. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56–528. https://doi.org/10.1161/CIR.0000000000000659.
7. Díez-Villanueva P, Jiménez-Méndez C, Alfonso F, Díez-Villanueva P, Jiménez-Méndez C, Alfonso F. Heart failure in the elderly. J Geriatr Cardiol. 2021;18(3):219–32. https://doi.org/10.11909/J.ISSN.1671-5411.2021.03.009.
8. Postigo A, Martínez-Sellés M. Sex Influence on Heart Failure Prognosis. Front Cardiovasc Med. 2020;7:616273. https://doi.org/10.3389/FCVM.2020.616273/BIBTEX.
9.•• Rao RA, Bhardwaj A, Munagala M, et al. Sex differences in circulating biomarkers of heart failure. Curr Heart Fail Rep. Published online December 7, 2023. https://doi.org/10.1007/s11897-023-00634-w. **Excellent review of the most significant sex differences in biomarkers of HF.**
10 Marra AM, Salzano A, Arcopinto M, Piccioli L, Raparelli V. The impact of gender in cardiovascular medicine: Lessons from the gender/sex-issue in heart failure. Monaldi Arch chest Dis = Arch Monaldi per le Mal del torace. 2018;88(3):48–52. https://doi.org/10.4081/MONALDI.2018.988.
11.•• Díez-Villanueva P, Jiménez-Méndez C, Bonanad C, et al. Sex differences in the impact of frailty in elderly outpatients with heart failure. Front Cardiovasc Med. 2022;9:1000700. https://doi.org/10.3389/FCVM.2022.1000700/BIBTEX. **This study describes gender differences in frailty in the older HF population and highlights the most important differential characteristics.**
12. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. Eur Heart J. 2019;40(47):3859–68. https://doi.org/10.1093/EURHEARTJ/EHZ835.
13.•• Suthahar N, Meems LMG, Ho JE, de Boer RA. Sex-related differences in contemporary biomarkers for heart failure: a review. Eur J Heart Fail. 2020;22(5):775–88. https://doi.org/10.1002/EJHF.1771. **Extensive and comprehensive review on HF biomarkers and sex-based differences. Very easy to read and a wealth of knowledge.**
14. Dewan P, Rørth R, Jhund PS, et al. Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women. J Am Coll Cardiol. 2019;73(1):29–40. https://doi.org/10.1016/J.JACC.2018.09.081.
15. Levinsson A, Dubé MP, Tardif JC, de Denus S. Sex, drugs, and heart failure: a sex-sensitive review of the evidence base behind current heart failure clinical guidelines. ESC Hear Fail. 2018;5(5):745–54. https://doi.org/10.1002/EHF2.12307.
16. Stolfo D, Uijl A, Vedin O, et al. Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and prognostic and therapeutic implications. JACC Hear Fail. 2019;7(6):505–15. https://doi.org/10.1016/J.JCHF.2019.03.011.
17. Regitz-Zagrosek V. Sex and gender differences in heart failure. Int J Hear Fail. 2020;2(3):157–81. https://doi.org/10.36628/IJHF.2020.0004.
18. Meyer S, Van Der Meer P, Van Deursen VM, et al. Neurohormonal and clinical sex differences in heart failure. Eur Heart J. 2013;34(32):2538–47. https://doi.org/10.1093/EURHEARTJ/EHT152.
19. Díez-Villanueva P, Jiménez-Méndez C, López-Lluva MT, et al. Heart failure in the elderly: the role of biological and sociocultural aspects related to sex. Curr Heart Fail Rep. 2023;20(5):321–32. https://doi.org/10.1007/s11897-023-00619-9.
20. Piek A, Du W, de Boer RA, Silljé HHW. Novel heart failure biomarkers: why do we fail to exploit their potential? Crit Rev Clin Lab Sci. 2018;55(4):246–63. https://doi.org/10.1080/10408363.2018.1460576.
21. Berezin AE, Berezin AA. Biomarkers in heart failure: from research to clinical practice. Ann Lab Med. 2023;43(3):225–36. https://doi.org/10.3343/alm.2023.43.3.225.
22. Mongraw-Chaffin ML, Anderson CAM, Allison MA, et al. Association between sex hormones and adiposity: qualitative differences in women and men in the multi-ethnic study of atherosclerosis. J Clin Endocrinol Metab. 2015;100(4):E596–600. https://doi.org/10.1210/JC.2014-2934.
23. Lau ES, Binek A, Parker SJ, et al. Sexual dimorphism in cardiovascular biomarkers: clinical and research implications. Circ Res. 2022;130(4):578–92. https://doi.org/10.1161/CIRCRESAHA.121.319916.
24. Zile MR, Desai AS, Agarwal R, et al. Prognostic value of brain natriuretic peptide vs history of heart failure hospitalization in a large real-world population. Clin Cardiol. 2020;43(12):1501–10. https://doi.org/10.1002/CLC.23468.
25. Cesaroni G, Mureddu GF, Agabiti N, et al. Sex differences in factors associated with heart failure and diastolic left ventricular dysfunction: a cross-sectional population-based study. BMC Public Health. 2021;21(1):1–13. https://doi.org/10.1186/S12889-021-10442-3/FIGURES/2.
26. Fradley MG, Larson MG, Cheng S, et al. Reference limits for N-terminal-pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). Am J Cardiol. 2011;108(9):1341–5. https://doi.org/10.1016/j.amjcard.2011.06.057.
27. Chang AY, Abdullah SM, Jain T, et al. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the dallas heart study. J Am Coll Cardiol. 2007;49(1):109–16. https://doi.org/10.1016/J.JACC.2006.10.040.
28. de Lemos JA, Das SR. Closing the book on androgens and natriuretic peptides. J Am Coll Cardiol. 2019;73(11):1297–9. https://doi.org/10.1016/J.JACC.2018.12.061.
29. Cediel G, Codina P, Spitaleri G, et al. Gender-related differences in heart failure biomarkers. Front Cardiovasc Med. 2021;7:617705. https://doi.org/10.3389/FCVM.2020.617705/BIBTEX.
30.•• Maidana D, Bonanad C, Ortiz-Cortés C, et al. Sex-related differences in heart failure diagnosis. Curr Heart Fail Rep. 2023;20(4):254–62. https://doi.org/10.1007/S11897-023-00609-X/METRICS. **Article reviewing the key issues in sex-based differential diagnosis in HF.**
31. Suthahar N, Lau ES, Blaha MJ, et al. Sex-specific associations of cardiovascular risk factors and biomarkers with incident heart failure. J Am Coll Cardiol. 2020;76(12):1455–65. https://doi.org/10.1016/J.JACC.2020.07.044.
32. Franke J, Lindmark A, Hochadel M, et al. Gender aspects in clinical presentation and prognostication of chronic heart failure according to NT-proBNP and the Heart Failure Survival Score. Clin Res Cardiol. 2015;104(4):334–41. https://doi.org/10.1007/S00392-014-0786-Z/FIGURES/1.
33. Myhre PL, Claggett B, Yu B, et al. Sex and race differences in N-Terminal Pro–B-type natriuretic peptide concentration and absolute risk of heart failure in the community. JAMA Cardiol. 2022;7(6):623–31. https://doi.org/10.1001/JAMACARDIO.2022.0680.
34. Ndumele CE, Matsushita K, Sang Y, et al. N-Terminal Pro-brain natriuretic peptide and heart failure risk among individuals with

and without obesity: the atherosclerosis risk in communities (ARIC) study. Circulation. 2016;133(7):631–8. https://doi.org/10.1161/CIRCULATIONAHA.115.017298.
35. Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides. Circulation. 2005;112(14):2163–8. https://doi.org/10.1161/CIRCULATIONAHA.105.555573.
36. Suthahar N, Meijers WC, Ho JE, et al. Sex-specific associations of obesity and N-terminal pro-B-type natriuretic peptide levels in the general population. Eur J Heart Fail. 2018;20(8):1205–14. https://doi.org/10.1002/EJHF.1209.
37. Romiti GF, Cangemi R, Toriello F, et al. Sex-specific cut-offs for high-sensitivity cardiac troponin: Is Less More? Cardiovasc Ther. 2019;2019. https://doi.org/10.1155/2019/9546931.
38. Januzzi JL, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. Eur Heart J. 2012;33(18):2265–71. https://doi.org/10.1093/EURHEARTJ/EHS191.
39. Evans JDW, Dobbin SJH, Pettit SJ, Di Angelantonio E, Willeit P. High-sensitivity cardiac troponin and new-onset heart failure: a systematic review and meta-analysis of 67,063 patients with 4,165 incident heart failure events. JACC Hear Fail. 2018;6(3):187–97. https://doi.org/10.1016/J.JCHF.2017.11.003.
40. Gohar A, Chong JPC, Liew OW, et al. The prognostic value of highly sensitive cardiac troponin assays for adverse events in men and women with stable heart failure and a preserved vs. reduced ejection fraction. Eur J Heart Fail. 2017;19(12):1638–47. https://doi.org/10.1002/EJHF.911.
41. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the american college of cardiology/American heart association joint committee on clinical practice guidelines. Circulation. 2022;145(18):E895–1032. https://doi.org/10.1161/CIR.0000000000001063.
42. Ndumele CE, Coresh J, Lazo M, et al. Obesity, subclinical myocardial injury, and incident heart failure. JACC Hear Fail. 2014;2(6):600–7. https://doi.org/10.1016/J.JCHF.2014.05.017.
43. Bayés-Genis A, González A, Lupón J. ST2 in Heart Failure. Circ Heart Fail. 2018;11(12):e005582. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005582.
44. Dieplinger B, Januzzi JL, Steinmair M, et al. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma — The Presage™ ST2 assay. Clin Chim Acta. 2009;409(1–2):33–40. https://doi.org/10.1016/J.CCA.2009.08.010.
45. Anand IS, Rector TS, Kuskowski M, Snider J, Cohn JN. Prognostic value of soluble ST2 in the Valsartan heart failure trial. Circ Hear Fail. 2014;7(3):418–26. https://doi.org/10.1161/CIRCHEARTFAILURE.113.001036/-/DC1.
46. Coglianese EE, Larson MG, Vasan RS, et al. Distribution and clinical correlates of the interleukin receptor family member soluble ST2 in the framingham heart study. Clin Chem. 2012;58(12):1673–81. https://doi.org/10.1373/CLINCHEM.2012.192153.
47. Dieplinger B, Egger M, Poelz W, Gabriel C, Haltmayer M, Mueller T. Soluble ST2 is not independently associated with androgen and estrogen status in healthy males and females. Clin Chem Lab Med. 2011;49(9):1515–8. https://doi.org/10.1515/CCLM.2011.239/MACHINEREADABLECITATION/RIS.
48. Lew J, Sanghavi M, Ayers CR, et al. Sex-based differences in cardiometabolic biomarkers. Circulation. 2017;135(6):544–55. https://doi.org/10.1161/CIRCULATIONAHA.116.023005/-/DC1.
49. Arrieta V, Jover E, Navarro A, et al. Soluble ST2 levels are related to replacement myocardial fibrosis in severe aortic stenosis. Rev Esp Cardiol (Engl Ed). Published online December 2022. https://doi.org/10.1016/J.REC.2022.12.007.
50. Sharma UC, Pokharel S, Van Brakel TJ, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation. 2004;110(19):3121–8. https://doi.org/10.1161/01.CIR.0000147181.65298.4D.
51. Suthahar N, Meijers WC, Silljé HHW, Ho JE, Liu FT, de Boer RA. Galectin-3 activation and inhibition in heart failure and cardiovascular disease: an update. Theranostics. 2018;8(3):593–609. https://doi.org/10.7150/THNO.22196.
52. Lau ES, Liu E, Paniagua SM, et al. Galectin-3 inhibition with modified citrus pectin in hypertension. JACC Basic to Transl Sci. 2021;6(1):12–21. https://doi.org/10.1016/J.JACBTS.2020.10.006.
53. Jagodzinski A, Havulinna AS, Appelbaum S, et al. Predictive value of galectin-3 for incident cardiovascular disease and heart failure in the population-based FINRISK 1997 cohort. Int J Cardiol. 2015;192:33–9. https://doi.org/10.1016/j.ijcard.2015.05.040.
54. Dekleva M, Djuric T, Djordjevic A, et al. Sex related difference in heart failure development in patients after first myocardial infarction; role of galectine-3. Eur Heart J. 2022;43(Supplement_2). https://doi.org/10.1093/EURHEARTJ/EHAC544.816.
55. Motiwala SR, Szymonifka J, Belcher A, et al. Serial measurement of galectin-3 in patients with chronic heart failure: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. Eur J Heart Fail. 2013;15(10):1157–63. https://doi.org/10.1093/EURJHF/HFT075.
56. Wang T, Liu J, McDonald C, et al. GDF15 is a heart-derived hormone that regulates body growth. EMBO Mol Med. 2017;9(8):1150–64. https://doi.org/10.15252/EMMM.201707604.
57 Rochette L, Dogon G, Zeller M, Cottin Y, Vergely C. GDF15 and cardiac cells: current concepts and new insights. Int J Mol Sci. 2021;22(16):8889. https://doi.org/10.3390/IJMS22168889.
58. Li N, Feng Q, Yu F, Zhou J, Guo X. Plasma growth differentiation factor-15 in patients with "lone" atrial fibrillation. J Clin Lab Anal. 2022;36(5):e24373. https://doi.org/10.1002/JCLA.24373.
59. Matusik PT, Małecka B, Lelakowski J, Undas A. Association of NT-proBNP and GDF-15 with markers of a prothrombotic state in patients with atrial fibrillation off anticoagulation. Clin Res Cardiol. 2020;109(4):426–34. https://doi.org/10.1007/S00392-019-01522-X/FIGURES/1.
60. Wang Z, Yang F, Ma M, et al. The impact of growth differentiation factor 15 on the risk of cardiovascular diseases: two-sample Mendelian randomization study. BMC Cardiovasc Disord. 2020;20(1):1–7. https://doi.org/10.1186/S12872-020-01744-2/TABLES/1.
61. Ho JE, Mahajan A, Chen MH, et al. Clinical and genetic correlates of growth differentiation factor 15 in the community. Clin Chem. 2012;58(11):1582–91. https://doi.org/10.1373/CLINCHEM.2012.190322.
62 Núñez J, de la Espriella R, Rossignol P, et al. Congestion in heart failure: a circulating biomarker-based perspective. A review from the biomarkers working group of the heart failure association, European society of cardiology. Eur J Heart Fail. 2022;24(10):1751–66. https://doi.org/10.1002/EJHF.2664.
63. Núñez J, de la Espriella R, Miñana G, et al. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. Eur J Heart Fail. 2021;23(9):1445–57. https://doi.org/10.1002/EJHF.2295.
64. Núñez J, Núñez E, Bayés-Genís A, et al. Long-term serial kinetics of N-terminal pro B-type natriuretic peptide and carbohydrate

antigen 125 for mortality risk prediction following acute heart failure. Eur Hear J Acute Cardiovasc Care. 2017;6(8):685–96. https://doi.org/10.1177/2048872616649757.
65. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res. 2019;12(1):1–9. https://doi.org/10.1186/S13048-019-0503-7/TABLES/2.
66. Menghoum N, Badii MC, Deltombe M, et al. Carbohydrate antigen 125: a useful marker of congestion, fibrosis, and prognosis in heart failure with preserved ejection fraction. ESC Hear Fail. Published online February 9, 2024. https://doi.org/10.1002/EHF2.14699.
67. Méndez AB, Ordoñez-Llanos J, Ferrero A, et al. Prognostic value of increased carbohydrate antigen in patients with heart failure. World J Cardiol. 2014;6(4):205–12. https://doi.org/10.4330/wjc.v6.i4.205.
68. Arao K, Yoshikawa T, Isogai T, et al. A study of takotsubo syndrome over 9 years at the Tokyo Cardiovascular Care Unit Network Registry. J Cardiol. 2023;82(2):93–9. https://doi.org/10.1016/j.jjcc.2022.12.011.
69. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(2):207–21. https://doi.org/10.1016/J.JACC.2019.11.014.
70. Paynter NP, Chasman DI, Paré G, et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA. 2010;303(7):631–7. https://doi.org/10.1001/JAMA.2010.119.
71. Azibani F, Sliwa K. Peripartum cardiomyopathy: an update. Curr Heart Fail Rep. 2018;15(5):297–306. https://doi.org/10.1007/S11897-018-0404-X/FIGURES/1.
72. Ersbøll AS, Goetze JP, Johansen M, et al. Biomarkers and their relation to cardiac function late after peripartum cardiomyopathy. J Card Fail. 2021;27(2):168–75. https://doi.org/10.1016/j.cardfail.2021.01.002.
73. Stone JR, Kanneganti R, Abbasi M, Akhtari M. Monitoring for chemotherapy-related cardiotoxicity in the form of left ventricular systolic dysfunction: a review of current recommendations. JCO Oncol Pract. 2021;17(5):228–36. https://doi.org/10.1200/OP.20.00924/ASSET/IMAGES/LARGE/OP.20.00924F2.JPEG.
74. Wilcox NS, Rotz SJ, Mullen M, et al. Sex-specific cardiovascular risks of cancer and its therapies. Circ Res. 2022;130(4):632–51. https://doi.org/10.1161/CIRCRESAHA.121.319901.
75. Demissei BG, Hubbard RA, Zhang L, et al. Changes in cardiovascular biomarkers with breast cancer therapy and associations with cardiac dysfunction. J Am Heart Assoc. 2020;9(2). https://doi.org/10.1161/JAHA.119.014708.
76 Riccardi M, Myhre PL, Zelniker TA, Metra M, Januzzi JL, Inciardi RM. Soluble ST2 in heart failure: a clinical role beyond B-Type natriuretic peptide. J Cardiovasc Dev Dis. 2023;10(11):468. https://doi.org/10.3390/JCDD10110468.
77. Pérez-Sanz TM, Gómez-Salvador I, Codina P, et al. Soluble ST2, BCN-Bio-HF calculator and MAGGIC-HF score in long-term risk prediction after an urgent visit for heart failure. Heart Vessels. Published online October 23, 2023:1–10. https://doi.org/10.1007/S00380-023-02327-9/METRICS.
78. Alma LJ, Bokslag A, Maas AHEM, Franx A, Paulus WJ, de Groot CJM. Shared biomarkers between female diastolic heart failure and pre-eclampsia: a systematic review and meta-analysis. ESC Hear Fail. 2017;4(2):88–98. https://doi.org/10.1002/EHF2.12129.
79. Takvorian KS, Wang D, Courchesne P, et al. The association of protein biomarkers with incident heart failure with preserved and reduced ejection fraction. Circ Hear Fail. 2023;16(1):E009446. https://doi.org/10.1161/CIRCHEARTFAILURE.121.009446.
80. Chandramouli C, Ting TW, Tromp J, et al. Sex differences in proteomic correlates of coronary microvascular dysfunction among patients with heart failure and preserved ejection fraction. Eur J Heart Fail. 2022;24(4):681–4. https://doi.org/10.1002/EJHF.2435.
81. Chirinos JA, Zhao L, Reese-Petersen AL, et al. Endotrophin, a Collagen VI Formation–Derived Peptide, in Heart Failure. NEJM Evid. 2022;1(10). https://doi.org/10.1056/EVIDOA2200091.
82. Raafs A, Verdonschot J, Ferreira JP, et al. Identification of sex-specific biomarkers predicting new-onset heart failure. ESC Hear Fail. 2021;8(5):3512–20. https://doi.org/10.1002/EHF2.13476.
83. de Bakker M, Loncq de Jong M, Petersen T, et al. Sex-specific cardiovascular protein levels and their link with clinical outcome in heart failure. ESC Hear Fail. 2024;11(1):594–600. https://doi.org/10.1002/EHF2.14578.
84. Woolley RJ, Ceelen D, Ouwerkerk W, et al. Machine learning based on biomarker profiles identifies distinct subgroups of heart failure with preserved ejection fraction. Eur J Heart Fail. 2021;23(6):983–91. https://doi.org/10.1002/EJHF.2144.
85. Ventura-Clapier R, Dworatzek E, Seeland U, et al. Sex in basic research: concepts in the cardiovascular field. Cardiovasc Res. 2017;113(7):711–24. https://doi.org/10.1093/CVR/CVX066.
86. Florijn BW, Bijkerk R, Van Der Veer EP, Van Zonneveld AJ. Gender and cardiovascular disease: are sex-biased microRNA networks a driving force behind heart failure with preserved ejection fraction in women? Cardiovasc Res. 2018;114(2):210–25. https://doi.org/10.1093/CVR/CVX223.
87. Carroll JS, Meyer CA, Song J, et al. Genome-wide analysis of estrogen receptor binding sites. Nat Genet. 2006;38(11):1289–97. https://doi.org/10.1038/NG1901.
88. Song R, Ro S, Michaels JD, Park C, Mccarrey JR, Yan W. Many X-linked microRNAs escape meiotic sex chromosome inactivation. Nat Genet. 2009;41(4):488–93. https://doi.org/10.1038/NG.338.
89. Chirinos JA, Orlenko A, Zhao L, et al. multiple plasma biomarkers for risk stratification in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol. 2020;75(11):1281–95. https://doi.org/10.1016/J.JACC.2019.12.069.
90. Kobayashi M, Huttin O, Magnusson M, et al. Machine learning-derived echocardiographic phenotypes predict heart failure incidence in asymptomatic individuals. JACC Cardiovasc Imaging. 2022;15(2):193–208. https://doi.org/10.1016/J.JCMG.2021.07.004.