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Sex-Related Differences in Heart Failure Diagnosis

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Abstract

Purpose of Review The literature on the importance of sex in heart failure diagnosis is scarce. This review aims to summarize current knowledge on sex differences regarding the diagnosis of heart failure.

Recent Findings Comorbidities are frequent in patients with heart failure, and their prevalence differs between sexes; some differences in symptomatology and diagnostic imaging techniques were also found. Biomarkers also usually show differences between sexes but are not significant enough to establish sex-specific ranges.

Summary This article outlines current information related to sex differences in HF diagnosis. Research in this field remains to be done. Maintaining a high diagnostic suspicion, actively searching for the disease, and considering the sex is relevant for early diagnosis and better prognosis. In addition, more studies with equal representation are needed.

Keywords Sex differences · Heart failure · Diagnosis · Biomarkers

Abbreviations

CA125	Carbohydrate 125
HF	Heart failure
NT-proBNP	N-terminal Pro-B type natriuretic peptide
sST2	Soluble isoform of suppression of tumorigenesis-2

Introduction

Heart failure (HF) has a similar overall prevalence in both sexes [1]. However, pronounced differences are found in age, comorbidity, etiology, mortality, and prognosis. Women with HF tend to present more diabetes, obesity, high blood pressure, anemia, or kidney diseases, while men are more prone, concomitantly, to develop stroke or to be smokers [2, 3]. Women are also more likely to be frail, although it

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has a worse prognosis in men [4, 5]. Considering those differences, it is reasonable to think there are discrepancies between those patients at the time of diagnosis. Nevertheless, studies comparing sex differences in HF diagnosis are scarce [6]. Moreover, women are underrepresented in clinical trials, and statistically significant comparisons between the sexes are complex [7].

This research aims to summarise the current knowledge on the differences between men and women regarding clinical presentation, imaging diagnosis, and biomarkers in HF diagnosis.

Diagnosis of HF and Sex Differences

The main red flags to consider when HF is suspected in women are shown in Table 1. All sex differences related to HF diagnosis are summarised in Fig. 1.

Sex-Specific Signs and Symptoms of Heart Failure

On admission for acute HF, symptoms of HF, such as dyspnea and edema, are common in both men and women.

Table 1 Most frequent characteristics in women with HF. Heart failure (HF), Heart failure with preserved ejection fraction (HFpEF), Cardiovascular Magnetic Resonance (CMR)

Most frequent characteristic in women with HF
• Advanced age compared to men
• Studies highlight dyspnea and orthopnea in women with HF
• HF is more frequently of non-ischemic HF etiology
• Higher incidence of HFpEF, which is better characterized by CMR
• It may lower the prevalence and amount of LGE in the CMR, lower ventricular volume, and higher ejection fraction
• May better systolic function and higher filling pressures are measured by echocardiography
• More symptomatic forms of HF
• Device implantations are less frequent than in men

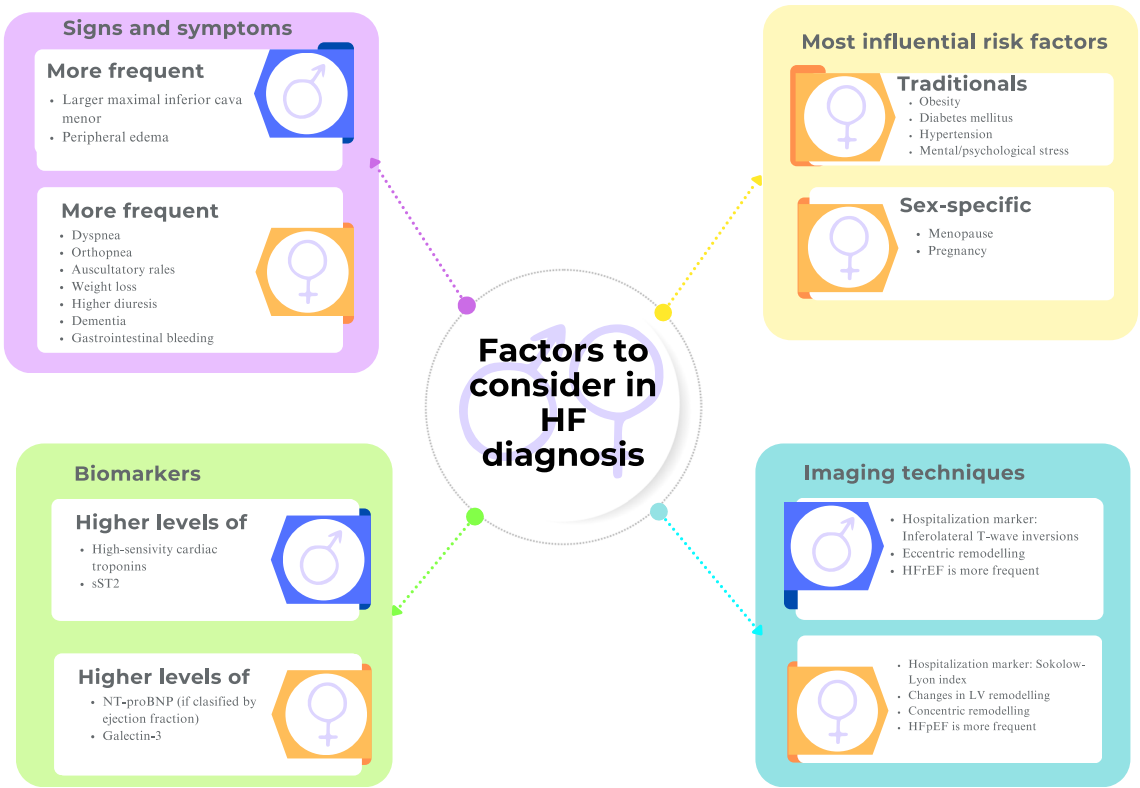

Fig. 1 Factors to consider in heart failure diagnosis. Heart failure reduced ejection fraction (HFrEF), Heart failure with preserved ejection fraction (HFpEF), Amino-terminal portion of pro-brain natriuretic peptide (NT-proBNP), Soluble suppression of tumorogénesis-2 (sST2), Left Ventricular (LV), Ejection fraction (EF)

However, women tend to present severe symptoms. Women more frequently suffer dyspnea, orthopnea, and auscultatory rales (intravascular congestion phenotype), while men more regularly manifest larger maximal inferior cava vena diameter and peripheral edema (tissue congestion phenotype) [8, 9].

Regarding the signs and symptoms of acute HF in hospitalized patients, women have more dyspnea on a scale of 0 (no dyspnea) to 10 (severe dyspnea at rest). Women have a mean of 5, while men have a mean score of 3. In addition, women experience more significant weight loss and higher diuresis. Concerning edema, 80% of men had lower extremity edema compared to 68% of women [10•, 11, 12].

At the time of diagnosis, apart from symptoms, more comorbidities are often found in women related to traditional and sex-specific cardiovascular risk factors [9]. Women suffer not only higher rates of obesity, diabetes mellitus, and hypertension but also mental disease or psychological stress added to sex-specific risk factors such as hormonal changes like early menopause [13]. Furthermore, women have a higher prevalence of gastrointestinal bleeding and a lower prevalence of peripheral vascular disease [11].

More differences between sexes arise when HF is secondary to myocardial infarction. Women tend to present more microvascular angina, and vagal symptoms accompany chest pain, which can act as a confounder and delay diagnosis.

In early menopause, the decline in endothelial function may be involved in the pathophysiology of chest pain and dyspnea, which is sometimes confused with stress. In the case of premenopausal women, admission of HF secondary to infarction is often related to myocardial infarction with no obstructive coronary artery (MINOCA). In contrast, postmenopausal women are more predisposed to Takotsubo cardiomyopathy. In both cases, comorbidities and the wide range of symptoms can lead to underdiagnosis. In addition, women with chest pain syndromes have a twofold increased risk of developing heart failure. All of this should be considered to improve the diagnosis [14, 15].

Sex Differences in Diagnostic Imaging Techniques in HF

Diagnostic imaging techniques are performed when HF is suspected. Among these, an electrocardiogram helps rule out HF, and its high sensitivity for detecting HF with reduced ejection fraction shows differences between sexes. However, sex dissimilarities probably result from hormonal factors, differences in the left ventricular mass, and wall thickness [16, 17]. Sokolow-Lyon index of left ventricular hypertrophy could predict HF hospitalization in females. In contrast, in males, it depends on inferolateral T-wave inversions [18]. This sex difference may be because inferolateral T-wave inversion is a more common electrocardiogram abnormality in HF due to type 1 myocardial infarction, the most common cause of HF in males [18].

Concerning chest radiography, no significant sex differences have been observed in adults hospitalized for acute HF [10•]. However, differences in some echocardiographic parameters, like left ventricular ejection fraction, have been found. The controversy regarding the accuracy of ejection fraction for the classification of HF patients is due to its variability depending on factors such as sex, age, and ethnicity [19]. Common cut-off points for "normal" at 50% could include elderly women with a relatively reduced ejection fraction for their age and sex [19, 20]. It is proposed that the "average" ejection fraction should be $\geq 55\%$ for men and $\geq 60\%$ for women [20]. Other authors consider sex differences in systolic dysfunction diagnosing when the left ventricular ejection fraction is $< 52\%$ in men and the left ventricular ejection fraction $< 54\%$ in women [19].

Regarding the use of echocardiography in women's diagnosis, it should be considered that they have breast tissue and a higher prevalence of concave chest walls, which may hinder HF diagnosis [21, 22].

Cardiovascular magnetic resonance is recommended for the early diagnosis of patients with HF with preserved ejection fraction, primarily women, because it allows the characterization of HF with preserved ejection fraction etiology [23]. Cardiovascular magnetic resonance with late gadolinium enhancement reveals distinct phenotypes of female patients with ischemic and non-ischemic cardiomyopathy relative to male patients [24•].

Additionally, women with HF with preserved ejection fraction are more likely to experience changes in left ventricle remodeling and more severe diastolic dysfunction [14, 25, 26]. Left ventricle remodeling also differs between sexes. Women are more likely to develop concentric remodeling and HF with preserved ejection fraction, whereas men are more likely to develop eccentric remodeling and HF with reduced ejection fraction. Moreover, females have a higher systolic and diastolic left ventricular stiffness than males, which increases to a greater extent with age [7].

Finally, in terms of safety, particular care must be taken with the use of imaging techniques in women's diagnosis, with echocardiography and non-contrast gadolinium cardiovascular magnetic resonance being the safest imaging techniques during pregnancy and lactation, and for breast tissue, due to the absence of ionizing agents and radiation [21, 22, 27].

Sex Differences in Biomarkers

Some biomarkers are vital in diagnosing, risk stratifying, and managing patients if HF is suspected. Some of the most outstanding HF biomarkers are natriuretic peptides, carbohydrate 125 (CA125), high-sensitivity troponins, galectin-3, the soluble isoform of suppression of

tumorigenesis-2 (sST2), and osteopontin (Table 2) [28]. In 2019, The International Federation of Clinical Chemistry Committee on Clinical Applications of Cardiac Biomarkers recommended studying cardiac biomarkers, particularly natriuretic peptides, in various heterogeneous cohorts and stratifying upper reference limits by age and sex [29].

Sex Differences in Natriuretic Peptides

The levels of plasma natriuretic peptides should be measured if the diagnosis of HF is uncertain, NT-ProBNP being the best biomarker for the diagnosis and prognosis of HF [30, 31]. Several studies have shown that baseline NT-proBNP levels are higher in women than in men, especially in the case of premenopausal women [32, 33]. In a follow-up study of 78,657 individuals, it was seen that women had an average NT-proBNP concentration of almost twice the level found in men and that NT-proBNP was associated with a lower risk of HF in women than in men [34]. The exact mechanisms affecting these differences are unknown; one explanation could be the influence of sex hormones. It has been shown that testosterone is related to a lower level of NT-proBNP, while estrogens increase the marker levels, which could explain the difference between young men and women [35].

On the other hand, older ages were also associated with increasing levels of this marker. This age-related increment is higher in men than women, resulting in sex differences in NT-proBNP concentration decreasing with age. It is relevant to consider this since HF is more prevalent in older generations [33]. However, several studies have shown that the concentration remains higher in women than in men, regardless of age [36, 37•]. One recent cross-sectional study with 18,356 participants aged between 18 and 98 years found that, after adjusting for sociodemographic and cardiovascular risk factors including age, women still had a higher odds ratio of an elevated NT-proBNP (Odds Ratio:9.48; confidence interval 95%, 5.60–16.1) (Fig. 2) [37•].

The sex differences found in the general population NT-proBNP levels seem to fade in patients with HF. However, when comparing the levels of this marker between women and men with HF and the same left ventricular ejection fraction, it was found that women had moderately higher levels of NT-proBNP [30, 38, 39]. HF with preserved ejection fraction is more frequent in women than in men. This type of HF is related to lower levels of NT-proBNP than HF with reduced ejection fraction, which could partly explain why there are no sex differences in the general population with HF [30, 36, 40, 41]. Thus, special care should be taken with patients with HF with preserved ejection fraction because they often have NT-proBNP levels below the cut-off point and alone cannot exclude the diagnosis of HF in these patients.

A trial with 1936 participants recently showed how age-specific and sex-specific cut-offs for NT-proBNP improved the diagnosis of unrecognized HF. In this study, the following cut-off points were established at 125 pg/mL for men and 192 pg/mL for women under 60 years and 228 pg/mL for men, and 285 pg/mL for women over 60 years [42]. In

Table 2 Biology, diagnostic value, sex differences, and modulators of important HF biomarkers. Amino-terminal molecule of Brain Natriuretic Peptide (NT-proBNP), Carbohydrate 125 (CA125), Heart Failure (HF), Acute Coronary Syndrome (ACS), Coronary Artery Disease (CAD), interleukin 1β (IL-1β), interleukin 6 (IL-6), Myocardial Infarction (MI), Not Applicable (NA), soluble suppression of tumorogénesis-2 (sST2), tumor necrosis factor α (TNF- α)

Biomarkers	Sex differences		Modulators	Diagnostic value
	General population	HF population		
BNP/NT-proBNP	Higher levels in women	Higher levels in women if classified by ejection fraction	Obesity, sex hormones, age. More information is in Fig. 2	HF, congestion
CA 125	Variation in women by the menstrual cycle	NA	Menstruation, endometriosis, and rise in ovarian cancer CA125 concentration	HF, congestion
High-sensitivity cardiac troponins	Lower in women than in men	Lower in women than in men	Testosterone-induced hypertrophy and cardiomyocyte apoptosis. Estrogen-induced suppression of cardiomyocyte apoptosis	MI, HF, CAD
Galectin-3	Higher in women than in men	No differences, but it is more associated with incident HF in women	Body fat increases biomarker levels	HF
sST2	Lower in women than in men	sST2 concentration is higher in men with chronic HF	Sex hormones (testosterone and estradiol increase levels in men, estrogens decrease levels in women), obesity	HF, congestion
Osteopontin	Lower in women than in men	NA	Estrogens in vascular smooth muscle suppress osteopontin	HF

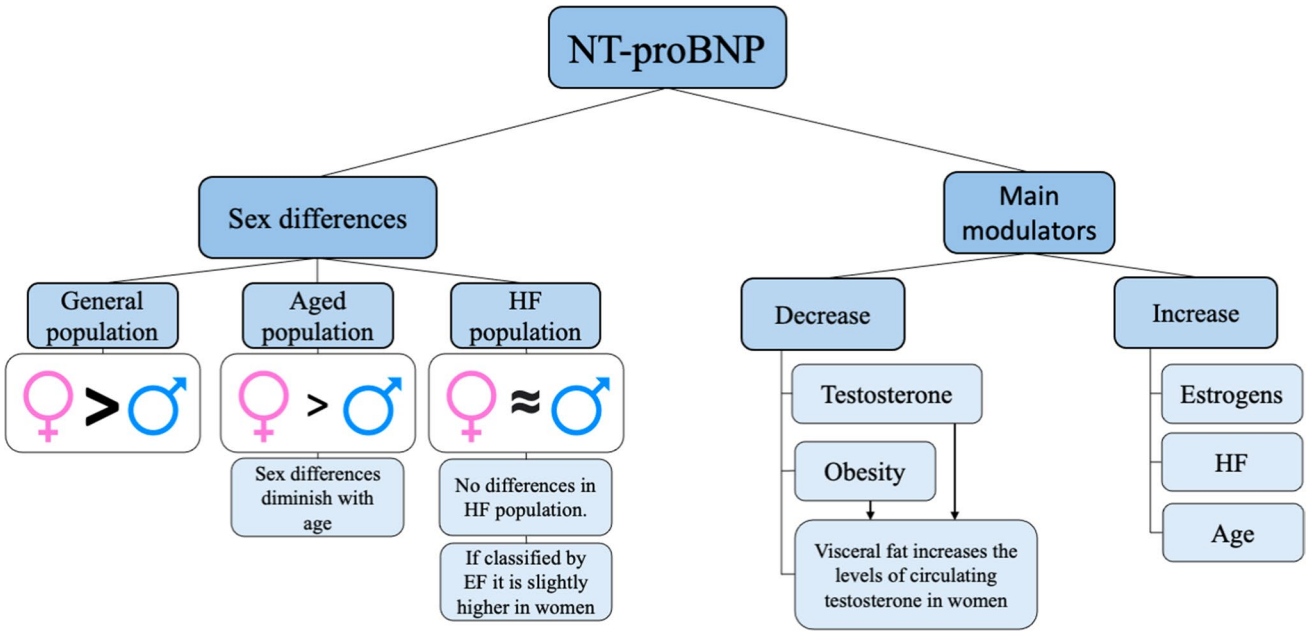

Fig. 2 Sex differences and central modulators of NT-proBNP concentration. Heart failure (HF), amino-terminal portion of pro-brain natriuretic peptide (NT-proBNP)

addition, other comorbidities could alter NT-proBNP levels, such as obesity [19, 43]. Several articles have proven that the reduction associated with obesity is influenced by sex, being higher in women than in men [30, 33]. In the case of abdominal obesity, it was associated with minor levels of NT-proBNP in women but not in men. In women, visceral fat increases circulating testosterone levels, explaining a decrease in the ranks of NT-proBNP.

In contrast, in men, visceral adiposity is associated with reduced androgen levels (Fig. 2) [33]. In a cohort of 18,356 individuals, it has been shown that around 10% of young women without classic cardiovascular risk factors exceeded the cut-off point of 125 pg/mL, below which the diagnosis of HF became unlikely [37•]. Thus, rather than exclude the diagnosis of HF, this biomarker was used to establish an early diagnosis in an asymptomatic population. It would be necessary to take sex differences into account since there are healthy women whose NT-proBNP levels exceed the current cut-off points [37•, 38].

Sex Differences in CA125

Currently, indistinctly of the sex, levels of CA125 higher than 35 U/mL could indicate acute HF [44]. When using CA125 as a marker of HF, it is essential to consider that it can be elevated under physiological conditions such as pregnancy or menstruation [45]. It has been shown that CA125 values vary during the menstrual cycle, being higher during menstruation due to the inflammatory process induced by endometrial desquamation. However, several studies observed that despite the increase in CA125 concentration during menstruation, the mean values did not reach concentrations relevant for the diagnosis of HF, with mean concentrations of 12.2 U/ml and 16.6 U/ml [46, 47]. Also, the presence of diseases such as endometriosis, ovarian cancer, or inflammatory diseases of the peritoneum can cause an increase in this biomarker [45]. In the case of endometriosis, CA125 levels in the menstrual phase exceeded the threshold of 35 U/mL. Specifically, it was observed that the levels of CA125 increased from 12 to 35.8 U/mL, and this increase was even more pronounced in women with deep infiltration endometriosis, reaching levels of 65.8 U/mL [46]. In addition, 80% of women with epithelial ovarian cancer had CA125 levels higher than 35 U/mL [48]. Thus, although the clinical presentations are different, it is necessary to keep in mind that the values of this biomarker in HF may be like other common conditions in women that frequently are diagnosed late. Because of this, when in diagnostic doubt, not only between men and women but also between women, it is necessary to look for specific symptoms and perform other tests to confirm the diagnosis of elevated CA125, as other undiagnosed conditions can act as confounders, as in the case of endometriosis [47]. It would be necessary to investigate further how these conditions affect CA125 levels in the context of HF.

Sex Differences in Cardiac Troponins

High-sensitivity cardiac troponin levels, vary according to sex, with higher concentrations in men than in women [49, 50]. Even after the increase due to HF, it has been observed that men continue to have higher cardiac troponin levels than women. Indeed, it has been shown that establishing age-specific and sex-specific cut-off points for high-sensitivity troponin T could rule out subclinical HF in a general population. It was also observed that the set cut-off points of 14 ng/L for high-sensitivity troponins only applied to men under 50 [42]. Several factors may cause this difference. It is known that cardiac troponin concentrations are related to greater left ventricular mass, and women have less left ventricular mass than men [51]. Male-specific hormonal mechanisms, such as testosterone-induced hypertrophy and cardiomyocyte apoptosis, may favor higher cardiac troponin levels. In contrast, estrogen-induced suppression of cardiomyocyte apoptosis and subtler mechanisms of myocardial injuries, such as coronary microvascular disease, may influence lower cardiac troponin levels in women [28].

Sex Differences Among Other HF Biomarkers

In the general population, Galectin-3 levels may vary according to sex, with a slightly higher concentration in women than in men [28, 30, 52]. It was observed in a cohort of 947 individuals from the general population that there were significant differences with higher levels in women than in men (mean difference: 0.97 ng/ml; $p < 0.001$) [53]. A possible explanation for the observed differences could be the association between total body fat and galectin-3 levels, considering that for the same body mass index, women have 10% more body fat [30]. In patients with HF, there is an increase in galectin-3 levels, and sex differences are inconsistent [28, 30]. However, within a population of 22,756 individuals, galectin-3 was related to incident HF only in women (HR: 1.13; 95% CI: 1.05 to 1.22) [54].

Sex-related differences have been found in concentration levels of a soluble isoform of suppression of tumorigenesis-2 (sST2) in healthy populations, being higher in men than in age-matched women [30, 55, 56]. Similarly, in a cohort of 4540 patients with chronic HF, sST2 was also found to be higher in men than in women in the overall cohort (27 ng/mL (20–40) vs. 24 ng/mL (17–36), $p < 0.001$). In contrast, no differences have been found in the elderly or underweight patients and those with HF with midrange or preserved ejection fraction or history of atrial fibrillation [57]. It was also noted that sex-specific sST2 cut-offs were significantly more predictive of incident HF, even with an adjustment for cardiac biomarkers and comorbidities [58]. Some studies have seen a slight association between testosterone, estradiol, and levels of sST2 in men that could explain the differences. In addition, low levels of sST2 have also been observed in women with exogenous estrogen therapy. However, given that the abovementioned associations are not seen in every study, other hypotheses must be considered [28, 30]. Since sex hormones are produced by adipose tissue, it is also necessary to consider obesity as a relevant factor [59].

Osteopontin is under-expressed in the cardiac tissue, but it is overexpressed in those patients with HF [28, 60, 61]. It has been proposed that the concentration of osteopontin in plasma is higher in healthy men than in women, probably due to the suppression of osteopontin induced by estrogens in vascular smooth muscle. In addition, levels of osteopontin were higher in men than in women with stable coronary artery disease and were associated with adverse cardiovascular incidents such as HF [30, 62].

Conclusions

Regarding signs and symptoms of HF, there is conflicting evidence on sex differences. However, a predominance of dyspnea in women and peripheral edema in men has been observed. Based on left ventricular ejection fraction, there is controversy about when to diagnose HF in men and women due to its variability depending on factors such as sex. Regarding biomarkers, some studies have shown differences by sex, but there is insufficient evidence to establish different concentration ranges for men or women in the current clinical practice. The information provided by biomarkers should always be considered together with symptomatology and echocardiographic parameters. More studies evaluating these differences between men and women might provide ways to improve the diagnosis of HF patients.

Data Availability All data supporting the findings of this study are available within the paper.

Declarations

Conflict of interest The authors, Daniela Maidana, Clara Bonanad-Lozano, Andrea Arroyo-Álvarez, Guillermo Barreres-Martín, Carles Muñoz-Alfonso, Cristina García-Pérez, Eva Maicas-Alcaine, Andrea Aparici-Redal, Victòria Freitas-Durks, and Alberto Esteban-Fernández, declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by authors.

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• Of importance.

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