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Sex-related differences in chronic heart failure

Alberto Aimo [a,b,*], Giuseppe Vergaro [c], Andrea Barison [c], Silvia Maffei [c], Chiara Borrelli [a], Doralisa Morrone [b], Matteo Cameli [d], Alberto Palazzuoli [d], Giuseppe Ambrosio [e], Stefano Coiro [e], Ketty Savino [e], Elisabetta Cerbai [f], Rossella Marcucci [f], Roberto Pedrinelli [b], Luigi Padeletti [f], Claudio Passino [a,c], Michele Emdin [a,c], on behalf of the Società Italiana di cardiologia, sezione tosco-umbra

[a] Scuola Superiore Sant'Anna, Pisa, Italy
[b] University of Pisa, Italy
[c] Fondazione Toscana Gabriele Monasterio, Pisa, Italy
[d] University of Siena, Italy
[e] University of Perugia, Italy
[f] University of Florence, Italy

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ABSTRACT

The prevalence of chronic heart failure (CHF) is steadily increasing. Both sexes are affected, with significant differences in etiology, epidemiology and clinical presentation, prognosis, comorbidities, and response to treatment. Women tend to develop CHF at a more advanced age, present more often with HF with preserved ejection fraction, are more symptomatic, and have a worse quality of life than men, but also a better prognosis. In women, CHF has more frequently a non-ischemic etiology, and arterial hypertension and diabetes mellitus are leading comorbidities. Furthermore, many sex-related differences have been detected in the response to treatment, for example a greater prognostic benefit from angiotensin-receptor blockers in women, a higher incidence of complications after defibrillator implantation, and a greater response to cardiac resynchronization therapy. Furthermore, women are less likely to receive defibrillator therapy or heart transplantation. The significant underrepresentation of women in clinical trials limits our capacity to evaluate the extent of sex-related differences in CHF, although their characterization seems crucial in order to achieve the ultimate goal of a tailored therapy for this condition.

1. Introduction

The prevalence of chronic heart failure (CHF) is steadily increasing [1]. According to a recent American survey, women represented the 49.5% over 150,000 patients recruited [2]. Furthermore, CHF causes around 35% of deaths for cardiovascular (CV) causes in the female sex [3]. Despite these premises, women have been historically underrepresented in clinical research on CHF; for example, it has been estimated that only the 29% of randomized trials on CHF has enrolled women [4].

Such disparity limits the possibility to detect sex-related differences in CHF, and to evaluate their impact in current clinical practice. This review aims to summarize our current knowledge on the differences in clinical presentation and response to drug and device therapy. A detailed discussion of the molecular mechanisms underlying such differences goes beyond our scopes and can be found in dedicated reviews [5,6].

2. Epidemiology and clinical presentation

The incidence and prevalence of CHF have dramatically increased from 70s to 90s; [7] currently, the incidence of CHF seems to be stabilizing, whereas its prevalence continues to increase because of improved life expectancy [1]. While the prevalence of HF with reduced ejection fraction (HFrEF) is decreasing, the relative proportion of HF with preserved ejection fraction (HFpEF) is rising [8,9,10]. Compared to HFrEF, HFpEF shows major differences in pathophysiology and clinical presentation [11], while carrying a similar risk for hospital readmissions and mortality [12].

Recent epidemiological data suggest that CHF incidence in the United States amounts to 550,000 cases per year, equally distributed between sexes [2]. Again in the US, CHF affects 3.1 million men and 2.6 million women [4,13]. The prevalence increases with age in both sexes, but women tend to develop CHF at a more advanced age, with a higher probability to receive a diagnosis of CHF after 79 years [13]. The hospitalization rates for CHF are similar in both sexes, with an average longer hospital stay for women [13,14]. The differences in prognosis are discussed in the following paragraph.

* Corresponding author at: Scuola Superiore Sant'Anna and Cardiology Division, University of Pisa, Piazza Martiri della Libertà, 33, Pisa, Italy.
E-mail addresses: albertoaimo@libero.it, a.aimo@sssup.it (A. Aimo).

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There are also important sex-related differences in the clinical presentation of CHF. In population studies, female sex has been consistently associated with greater propensity to development of HFpEF, and male sex with new-onset HFrEF [15,16]. At diagnosis, women tend to be older and to have more symptoms of CHF; in particular, signs and symptoms of congestion (namely dyspnea on effort, peripheral edema, third heart sound, and jugular venous distention) are more frequent and more prominent in women [15,16]. Women have also greater functional impairment, worse quality of life, and more frequent depression [15,17,18]. These findings have been confirmed also in the elderly population [19].

3. Prognosis

A sub-analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) trial reported that female sex was an independent predictor of reduced all-cause and CV mortality (adjusted hazard ratio - HR - 0.64 in both cases) [20]. When considering CV death, women displayed a reduced mortality for CHF progression, whereas there were no significant differences between sexes in the risks of sudden cardiac death and fatal myocardial infarction (MI) [20].

Similar data about CHF prognosis have emerged from more recent studies. For example, in a sub-analysis of the Candesartan in Heart Failure-Assessment of Reduction in Morbidity and Mortality (CHARM) trial, women had a significantly lower risk of all-cause death (adjusted HR 0.77), CV death or CHF hospitalization (adjusted HR 0.83), sudden death (HR 0.70), death due to worsening of CHF (HR 0.72). Notably, the risk of death was lower in women irrespective of CHF etiology [21].

4. Etiology and comorbidities

In a recent case series evaluating over 150,000 patients hospitalized for CHF, patients with ischemic CHF were more often men (55.6% vs. 43.2%) [2]. It is known that several CV risk factors (most notably smoking and dyslipidemia, and arterial hypertension) are more common in men. For this reason and for the anti-atherogenic effects of estrogens, women show a lower prevalence of stable coronary heart disease and acute coronary syndromes, and of ischemic CHF [22].

Nonetheless, the burden of ischemic heart disease becomes significant among women in their post-menopausal years. For example, the worldwide INTERHEART Study, a large cohort study of >52,000 individual with MI, have revealed that women have their first presentation of coronary heart disease approximately 10 years later than men, most commonly after menopause [23]. Women are more likely than men to die after a first myocardial infarction, also because women are only half as likely as men to receive aspirin, beta-blockers or thrombolytic therapy or to be referred for revascularization procedure [24]. Furthermore, surviving women have a higher risk of HF development and death [25]. In the Framingham heart study the one-year mortality following an MI was 44% in women vs. 27% in men [24]. The overall short- and long-term coronary artery disease mortality, following an infarction are about 40% higher in women after adjustment for age and other risk factors [24].

Non-ischemic CHF may recognize several different causes. In a study on hospitalized HF patients stratified by etiology of cardiomyopathy, women accounted for the majority of patients with HF due to arterial hypertension (58.7%), chemotherapy (67.7%, most often cardiotoxic medications for the treatment of breast cancer), as well as idiopathic HF (57.8%) or HF due to other etiologies (57%) [2]. On the other hand, several etiologies were less represented among women, namely substance abuse (21% of women) and viral infections (41.8%). Around one half of familial forms occurred in women (49.8%), denoting a transmission pattern that is not sex-related [2,26]. Finally, *peripartum* cardiomyopathy, a very rare form of CHF (0.4% of patients in this case series) [2], is obviously a disease with exclusive involvement of the female sex.

With respect to CHF comorbidities, diabetes mellitus, arterial hypertension, and thyroid disease are prevalent among women, although atrial fibrillation is more frequent in men [6,27,28]. Diabetes mellitus and arterial hypertension are considered the main risk factors for CHF for women, while obesity seems equally relevant for both sexes [29]. Finally, male CHF patients are more often affected by coronary artery disease, peripheral vasculopathy, and chronic obstructive pulmonary disease [28,29].

5. Therapy

At present, evidence-based therapy of CHF is largely restricted to HFrEF. The mainstay of pharmacological treatment of this condition is represented by neuro-hormonal modulation, which aims to limit those neuro-endocrine axes that exacerbate symptoms and signs of CHF, and contribute to disease progression. The drug classes are: beta blockers (BBs), inhibitors of angiotensin-converting enzyme (ACE-I), or angiotensin-receptor blockers (ARBs), angiotensin receptor blockers/neprylisin inhibitors, mineralocorticoid receptor antagonists (MRAs), diuretics and digoxin. Furthermore, patients with advanced CHF typically require non-pharmacological approaches, represented by one or more of the following therapies: implantable cardiac defibrillator (ICD), cardiac resynchronization therapy (CRT), ventricular assist device (VAD), and heart transplantation.

From large population surveys, no significant sex-related differences in the prescription of evidence-based drug therapies for HF emerged [30]. On the other hand, several differences have been detected in the response to several treatments.

BBs play a crucial role in the treatment of CHF, as they improve the prognosis of these patients [31]. In all main clinical trials on beta-blockade in CHF, female sex has been markedly under-represented: 24% in the CIBIS II trial [32], (20%) in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial [33], 29% in the Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT-HF) [34].

Despite the modest representation of women, sub-analyses of these trials provided evidence of several sex-related differences in the prognostic benefit from BBs. According to the CIBIS II trial, in the bisoprolol arm women displayed a greater reduction in mortality. After adjustment for age, New York Heart Association class, CHF etiology, left bundle branch block, all-cause mortality was 36% lower among women than men; women had also a 39% lower risk of death for CV causes and a 70% lower risk of death for CHF progression [20].

In the COPERNICUS trial, treatment with carvedilol caused a 27% reduction of the risk of death or hospitalization for CV causes and a 31% reduction of the risk of death or hospitalization for CHF, without significant differences between sexes [33].

In a post hoc analysis of the MERIT-HF trial, treatment with metoprolol caused a 21% reduction in the composite endpoint “all-cause death or hospitalization” in women, whereas this reduction was 18% in men; there was also a marked difference in the reduction of the risk of HF hospitalization (−42% in women, −10% in men) [35]. However, the reduction in all-cause mortality alone was not significant among women, whereas the prognostic benefit was significant in the male sex [35].

In this latter sub-analysis, data from the CIBIS II, COPERNICUS and MERIT-HF were combined; beta-blockade resulted in a significant reduction of all-cause mortality, without differences between sexes (relative risk - RR - 0.69 in women, 0.66 in men) [35].

The first indication of sex-related differences in the response to ACE-I was provided by a sub-analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) trial, which revealed a reduction in the combined outcome of CHF-related death or hospitalization from 39.5% in the placebo arm to 29.7% in the treatment arm (enalapril) in men, and a non-significant reduction (from 38.7% to 37.0%) in women [36]. A meta-analysis of 30 randomized clinical trials on the use of ACE-I, which evaluated the data from 5399 men and 1587 women, revealed a significant reduction (24%) in the risk of death in men, and a non-significant