

# Chronic heart failure in women

Brief review with a focus on new quality markers in therapy

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## KEY WORDS

female sex, heart failure, women

## ABSTRACT

The problem of cardiovascular diseases in women is often neglected. Current guidelines recommend the same treatment for chronic heart failure (HF) in all patients regardless of sex. However, prior studies demonstrated sex-related differences in many aspects of HF care. Female patients with HF are less likely than men to receive evidence-based, guideline-recommended treatment; on the other hand, the effect of patient's sex on the administration of treatment is eliminated when the objective reasons for not using these therapies are taken into account. Women with HF are not undertreated in comparison with men when considering objective reasons (this is the cardinal advantage of new HF quality markers). Despite known sex differences, recommendations for HF treatment are the same for women and men because prospective sex-specific clinical trials have not been conducted. There is an urgent need for further research specifically focused on women with HF.

**Introduction** The burden of heart failure (HF) is tremendous and the prognosis of patients with HF is still poor despite progress in treatment options. In order to further increase the public awareness of HF, the Heart Failure Association of the European Society of Cardiology has launched the European Heart Failure Awareness Day.

**Cardiovascular diseases in women** The issue of sex-related differences in HF has been attracting more and more attention. Cardiovascular diseases are often neglected in women because of the perception that women are protected against cardiovascular diseases by sex hormones. However, this protection fades after menopause, thus leaving women prone to experience myocardial infarction, HF, and stroke. It is a common misconception that cardiovascular disease is a male disease. In fact, it kills a higher percentage of women than men and kills more people than all cancers combined. Yet, women seem to think that they are more at a risk of cancer, especially breast cancer. In March 2005, the European Society of Cardiology launched the "Women at Heart" program<sup>1</sup> and the Slovak Society of Cardiology promoted the "Heart and Women" initiative (FIGURE).

## Underrepresentation of women in clinical trials

Women constitute the majority of patients with HF in the general population; however, primarily men are enrolled in clinical trials. There have been no large prospective randomized blinded studies in women with HF; all the available data come from retrospective studies or post-hoc and subgroup analyses of major trials. In clinical trials, the number of women reaches about the quarter of all HF patients; in registries, the number of women is nearly one-half of all patients (TABLE 1). Stringent entry criteria in these studies usually exclude minorities such as women or elderly patients. The available studies included patients with impaired systolic function, despite the fact that preserved systolic function is common among elderly women with HF. Large multicenter trials have not included the sufficient number of women to draw firm conclusions about the efficacy and safety of treatment in this group. Due to the underrepresentation of women, extrapolation of the results of these trials and their use to the treatment of women should be treated with caution. Currently, great efforts are being made to include a higher proportion of women in clinical trials on HF.<sup>2</sup>

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Received: April 16, 2012.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2012;

122 (Suppl 1): 42-46

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**FIGURE** Logo of the “Heart and Women” initiative in Slovakia



**Sex differences in heart failure** Prior studies demonstrated sex-related differences in many aspects of HF care, including epidemiology, etiology, diagnosis, prognosis, and treatment. Men and women with HF have different clinical characteristics. Women are older, have more preserved ejection fraction, and more advanced HF than men. A history of hypertension and diabetes was more prevalent among women, while men more often were smokers and more often had evidence of coronary heart disease. The risk of HF associated with hypertension is greater in women than in men (in terms of population attributable risk: 59% in women vs. 39% in men). Diabetes

seems to be a stronger risk factor for HF in women than in men.<sup>2</sup>

It is suggested that the diagnosis of HF in women is less accurate than in men. In patients older than 80 years, the false-positive diagnosis of HF was more common in women than in men.<sup>3</sup>

The impact of sex differences on the prognosis of patients with HF is still controversial. Several observational studies and subanalyses of randomized controlled trials have reported that female patients have a better prognosis than male patients. In contrast to those findings, there have been several reports that describe a comparable prognosis in male and female patients with HF. Furthermore, the Studies of Left Ventricular Dysfunction (SVOLD) revealed that male patients had a significantly better prognosis than female patients. The reason for these inconsistencies remains unknown. However, different background factors of the study populations may have influenced the results, and the adjustment by a multivariate analysis may not be ideal to abolish the effect of the confounding factors such as HF etiology or patients' age. We speculate that the high proportion of elderly patients in the population of women with HF is the main reason for the apparently poor prognosis in this patient group in routine clinical practice in real life.<sup>3</sup>

**Sex differences in pharmacotherapy of chronic heart failure** Current guidelines recommend the same care for patients with chronic HF regardless of sex. There is no difference in the appropriate use and dosing of evidence-based therapy and in the individual response to pharmacological treatment between women and men with HF. In the future, however, HF care may need to be tailored to individual needs depending on sex as the best way to optimize outcomes for both men and women. In general, the benefit of  $\beta$ -blockers, angiotensin-converting enzyme

**TABLE 1** Women in large heart failure trials

Clinical study (drug)	Number of patients	Number of women (%)
V-HeFT I (hydralazine-ISDN)	642	0
V-HeFT II (enalapril)	804	0
V-HeFT III (felodipine)	450	0
DIG (digoxin)	6800	1520 (22.4)
CIBIS II (bisoprolol)	2647	515 (20)
COPERNICUS (carvedilol)	2287	469 (20)
MERIT-HF (metoprolol CR/XL)	3991	451 (23)
SENIORS (nebivolol)	2128	785 (37)
SOLVD-T (enalapril)	2569	504 (23)
TRACE (trandolapril)	1749	501 (22)
ELITE-II (losartan)	3152	966 (30)
Val-HeFT (valsartan)	5010	1002 (20)
CHARM (candesartan)	7599	243 (32)
RALES (spironolactone)	1663	446 (27)
SCD-HeFT (ICD, amiodarone)	2521	580 (23)

Abbreviations: CR/XL – controlled release/extended release, ICD – intracardiac defibrillator, ISDN – isosorbide-dinitrate

inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and spironolactone in clinical trials was similar regardless of sex. Several studies have documented a lower use of ACEIs in women with HF compared with men. Women may also have a different safety profile than men. ACEI-induced cough is not dose-dependent and is more frequent among women.<sup>4</sup> Women with HF have lower cough threshold leading to increased sensitivity to the cough reflex.<sup>5</sup> Women with HF appear to have significantly lower mortality rates on ARBs than on a more standard HF therapy (ACEIs); in men, there is no difference in survival whether on ARBs or ACEIs. These sex differences could be plausibly explained by genetic polymorphisms of the angiotensin-converting enzyme 2 gene (it has been identified on the X chromosome) and should be confirmed in a randomized trial before ARBs are preferentially prescribed to women with HF.<sup>6</sup> The use of spironolactone was inversely associated with fractures in men with chronic HF.<sup>7</sup> In a post-hoc subgroup analysis, digoxin was associated with an increased risk of death from any cause in women with HF, but not in men.<sup>8</sup> This increase was presumed to be due to digoxin toxicity, since the risk of death increased at higher serum drug levels: the levels of 1.2 to 2.0 ng/ml were associated with more deaths in both women and men.<sup>9</sup> Amiodarone-associated bradycardia requiring pacemaker implantation appears to be more common in women.<sup>10</sup>

**Sex differences in nonpharmacological therapy of chronic heart failure** There is seasonal variability in morbidity and mortality of HF with significant sex differences, partially due to respiratory diseases, which may be potentially preventable by vaccination. Quitting smoking is associated with a substantial decrease in morbidity and mortality in HF patients, which is similar in magnitude to the effect of using an appropriate  $\beta$ -blocker. Yet, little emphasis has been placed on smoking cessation strategies in women with HF and should be adopted as vigorously as proven medical therapy.<sup>11</sup> Fonarow et al.<sup>12</sup> showed that smokers have been at a lower risk of in-hospital mortality (the smoking paradox). Disease management programs probably narrow sex differences in the quality of care and survival among HF patients.<sup>13</sup> Women with HF have less access to cardiologists, although such consultation is associated with better quality of care, particularly for women. Complications of catheter ablation for atrial fibrillation were more frequent in women. Sex disparity exists in the use of implantable cardioverter-defibrillators and cardiac resynchronization therapy, although they are beneficial for both women and men. Smaller women have limited access to the left ventricular assist device because these devices require a minimum body surface to fit properly. Women were more likely than men to develop severe right ventricular failure after implantation of left ventricular assist device. A lower cut-off level of peak oxygen consumption

was suggested for women to determine optimal timing for heart transplantation.<sup>11</sup>

These sex differences could have potential widespread implications for routine HF care. Despite these known sex differences, recommendations for HF are the same for women and men, because prospective sex-specific clinical trials have not been performed. There is an urgent need to take specific action to address men's health, too. On 1 October 2005, the first ever men's health declaration was ratified, known as the Vienna Declaration on the health of men and boys in Europe.<sup>2</sup>

#### Undertreatment of women with chronic heart failure

Previous studies have suggested that female with HF are less likely to receive guideline-recommended therapies (in appropriate doses). In an observational survey conducted in Germany, a female patient was likely to receive the worst medical treatment from a male physician, whereas male patients were best treated by a female physician.<sup>14</sup> The effect of a patient's sex on the administration of these therapies was eliminated when the objective reasons for not using these therapies were taken into account.<sup>15,16</sup> In the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) from outpatient cardiology practices, the eligible patients were only those who had no contraindications, intolerance, or other documented reason for not providing a given therapy. The use of ACEIs, ARBs,  $\beta$ -blockers, aldosterone inhibitors, and cardiac resynchronization therapy was similar for men and women, but the rates for implantable cardioverter defibrillators, anticoagulation therapy for atrial fibrillation, and HF education were significantly lower in women. Older patients, particularly older women, were significantly less likely to receive guideline-recommended HF therapies.<sup>15</sup> In the Organized Program to Initiate Life-saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), hospitalized female patients with HF generally received similar medical care compared with male patients in the real-world setting when analysis comprised only eligible patients without documented contraindications or intolerance.<sup>16</sup>

**New quality markers for chronic heart failure** Guidelines are not cookbook medicine. New quality markers (QMs) are more favorable because they have qualitative attributes (are more flexible and adaptable for each patient with HF because they take into account the objective reasons for deviation from the guidelines). QMs are the quantitative measures that can be used to quantify the quality of care (TABLE 2). They measure the effect of quality improvement efforts, assess compliance with the guidelines (and compare the actual routine practice with the guidelines that represent the ideal practice). So all QMs have quantitative attributes: 1) they are valid – scientific evidence or professional consensus exists supporting better benefit for patients who receive higher rate

**TABLE 2** Standard and new quality markers for chronic heart failure

standard quality markers (quantitative approach)
prescription rate (Rx) is defined as the percentage of (ideal) HF patients with a drug; for ACEIs (ACEI Rx) and for $\beta$ -blockers (BB Rx)
target dose rate (target) is defined as the percentage of (ideal) patients with a drug only in target dose; for ACEIs (ACEI target) and for $\beta$ -blockers (BB target)
new quality markers (qualitative approach)
appropriate use is defined as the percentage of HF patients with a drug or without a drug because of objective reasons; for ACEIs (ACEI use) and for $\beta$ -blockers (BB use)
appropriate dose is defined as the percentage of chronic HF patients treated with a target dose and also chronic HF patients with lower than target dose due to objective reasons; for ACEIs (ACEI dose) and for $\beta$ -blockers (BB dose)

Abbreviations: ACEIs – angiotensin-converting enzyme inhibitors, HF – heart failure

of adherence to a QM, and higher percentage of adherence to a QM identifies higher quality; 2) they are feasible – data should be routine part of medical charts, and failure to document this is in itself an indicator of poor quality.

Only new QMs have qualitative attributes (are more flexible and adaptable for an individual patient because they take into account the objective reasons for deviation from the guidelines): 1) they are flexible – respect the clinical judgment of physicians (guidelines do not represent cookbook medicine; they supplement rather than replace clinical judgment); 2) they are adaptable – take into consideration individual characteristics of each patient with chronic HF.<sup>17</sup>

We retrospectively compared clinical characteristics and treatment between women and men in 695 consecutive patients (women, 45%) with systolic HF (ejection fraction,  $\leq 45\%$ ) hospitalized in a regional hospital from January 2005 to December 2009. After excluding patients with valvular etiology and terminal noncardiac illness (88 patients), we analyzed standard and new QMs for ACEIs and  $\beta$ -blockers (TABLE 2). Compared with men, women were significantly ( $P < 0.001$ ) older ( $83 \pm 4$  vs.  $69 \pm 8$  years), more often hypertensive (78.7% vs. 64%), and diabetic (46.2% vs. 31.8%). They also had more preserved ejection fraction ( $38\% \pm 5\%$  vs.  $28\% \pm 6\%$ ) and more advanced HF (New York Heart Association class III–IV: 63.4% vs. 42.8%). Women had lower prevalence of ischemic etiology of HF (61.5% vs. 79%,  $P < 0.001$ ) and atrial fibrillation (15.3% vs. 24.4%,  $P = 0.004$ ). There were no sex-differences in QMs for ACEIs, but men were significantly more likely to receive  $\beta$ -blockers ( $\beta$ -blocker rate, 80.3% vs. 69.8%;  $P = 0.003$ ) and target dose of  $\beta$ -blockers ( $\beta$ -blocker target, 34.9% vs. 25.3%;  $P = 0.033$ ). Nevertheless, new QMs were similar in women and men (nonsignificant):  $\beta$ -blocker use, 96.8% in women vs. 96% in men,  $P = 0.771$ ;  $\beta$ -blocker dose, 89.7% in women vs. 90.4% in men,  $P = 0.924$ . Digoxin was used significantly more frequently in women (17.8% vs. 11.8%,  $P < 0.01$ ), but at a lower dose (0.125 mg in 86% of women vs. in 74.8% of men). Thus, women with HF are not undertreated in comparison with men when considering

the objective reasons. This is the key advantage of new QMs in HF.<sup>18</sup>

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# Przewlekła niewydolność serca u kobiet

Krótki przegląd ukierunkowany na nowe wskaźniki jakości leczenia

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## SŁOWA KLUCZOWE

kobiety, niewydolność  
serca, płeć żeńska

## STRESZCZENIE

Problem występowania chorób układu sercowo-naczyniowego u kobiet jest często niedoceniany. Aktualne wytyczne zalecają ten sam sposób leczenia przewlekłej niewydolności serca (*heart failure* – HF) u wszystkich pacjentów, niezależnie od płci. Wcześniejsze badania wykazały jednak, że w wielu aspektach leczenia HF występują zależne od płci różnice. Prawdopodobieństwo, że kobiety z HF będą leczone zgodnie z wytycznymi było mniejsze niż w przypadku mężczyzn; z drugiej jednak strony wpływ płci pacjenta na decyzję o niestosowaniu zalecanego leczenia był nieistotny, jeżeli uwzględniono się inne, obiektywne przesłanki. Kobiety z HF nie są leczone gorzej niż mężczyźni jeżeli wzięto pod uwagę obiektywne przyczyny niestosowania odpowiedniej terapii (to jest główna zaleta nowych wskaźników jakości leczenia HF). Niezależnie od różnic związanych z płcią pacjenta, zalecenia dotyczące leczenia HF są jednakowe dla kobiet i mężczyzn, ponieważ nie ma prospektywnych badań nad wpływem płci na wyniki leczenia. Istnieje pilna potrzeba przeprowadzenia dalszych badań skupiających się na kobietach z HF.

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Praca wpłynęła: 16.04.2012.  
Nie zgłoszono sprzeczności  
interesów.

Pol Arch Med Wewn. 2012;  
122 (Suppl 1): 42-46  
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