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Editorial

Sex-Specific Differences in New York Heart Association Classification and Outcomes of Decompensated Heart Failure

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See article by Kajimoto et al., pages 30–36 of this issue.

The New York Heart Association (NYHA) classification is widely used for grading heart failure (HF) symptom severity. Since its conception in 1928,[1] NYHA classification has undergone multiple revisions and has been used as a tool for phenotypic ordering in a variety of settings such as risk prediction models, clinical trials, and determination of eligibility for therapies in evidence-based practice guidelines.[2] For chronic HF, NYHA class is a strong predictor of mortality and forms a component in mortality risk prediction models such as the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) and Seattle Heart Failure model.[3,4] Despite its widespread use in clinical and research settings, the reliability and reproducibility of the NYHA classification have been called into question[5] because it is based on subjective assessment of patients' reported dyspnea and exercise tolerance. Concurrent medical comorbidities, such as respiratory diseases and obesity, may also affect interpretation of symptom severity.[6] For chronic HF with reduced ejection fraction (HFrEF), studies have found that NYHA class IV compared with NYHA class III is a predictor of mortality in women but in not men.[7] This raises the possibility that the underlying pathophysiology and risk factors for HF may be sex specific. In other cardiac diseases, such acute coronary syndrome, it has been well documented that women have different risk-factor profiles, present with atypical symptoms, have longer door-to-balloon time, and have worse outcomes compared with men.[8] However, there is a paucity of information about the association between NYHA class, sex, and outcomes in decompensated acute HF.

In this issue of the *Canadian Journal of Cardiology*, Kajimoto et al. report the results of a multicentre prospective observational study using the Acute Decompensated Heart Failure Syndromes (ATTEND) registry on the impact of sex on the association between NYHA class symptoms at the time of hospital admission and mortality in patients with acute decompensated HF and preserved ejection fraction (HFpEF) and HFrEF.[9] In total, 4717 Japanese patients (2730 men, 1987 women; mean age 73; 45.2% had preserved left ventricular ejection fraction [LVEF]) were enrolled in the study at their admission for HF and subsequently followed for median of 527 (391 to 821) days. Reduced LVEF was defined as 40% or moderate-to-severe systolic dysfunction by qualitative assessment. Men and women were stratified into 6 groups, based on LVEF (HFpEF vs HFrEF) and NYHA class (II, III, and IV) symptoms on admission. The primary outcome was all-cause death after admission, whereas the secondary endpoints were cardiac death from HF, sudden cardiac death, or other cardiac death after admission. Among men and women with HFpEF, those with NYHA class IV symptoms had higher all-cause mortality than those of the same sex with NYHA class II symptoms. In women with HFrEF, NYHA class IV symptoms were associated with higher all-cause mortality compared with NYHA class II symptoms. However, among men with HFrEF, all-cause mortality was similar among those in NYHA class II, III, or IV. Similar observations were made for cardiovascular mortality. These findings suggest that, in context of acute decompensated HF, NYHA class IV is an important symptomatic stage associated with higher all-cause mortality in both men and women with HFpEF, whereas in HFrEF, NYHA class IV is an independent predictor of all-cause mortality in women but not men.

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This is the first study to closely examine the interaction between NYHA class, sex, and mortality in acute decompensated HF, using a contemporary, multicentre nationwide patient registry. Yet one must be mindful of several study limitations. First, this study only recorded NYHA class on admission and not following treatment. As early improvement of symptoms after treatment in the hospital is associated with shorter hospitalization and reduced 60-day cardiovascular mortality, potential differential response to therapy may have confounded the results on mortality.[10] Second, details regarding treatments in hospital were not completely captured. Differential treatment by sex and NYHA class might have confounded the results of the interaction test. Third, NYHA class on admission was determined by the treating physician, and data on reproducibility were not available. In addition, B-type natriuretic peptide, which directly correlates with NYHA class and HF mortality in acute decompensated HF,[11] was not reported in this study.

The findings of interaction among sex, severity of symptoms, and mortality in acute decompensated HFrEF by Kajimoto et al. are, nonetheless, similar to those reported by others for patients with chronic HFrEF.[7] Women admitted to hospitals with decompensated HF tended to receive fewer guideline-directed therapies, lower doses of diuretics, less aggressive diuresis regimens during hospitalization, and less fluid removal compared with men.[12] The current study shows a similar trend, in which women with HFrEF and NYHA class IV symptoms received less β-blocker therapy at admission than women with HFrEF and NYHA class II symptoms. This differential treatment, which might have persisted at discharge and accentuated the mortality differences across NYHA classes in women with HFrEF, was not present among men with HFrEF. In addition, patients in the current study with NYHA class IV and HFrEF were more likely to have ischemia as the cause of their HFrEF compared with the same-sex patients with NYHA class II symptoms. Given significant mortality benefits of HFrEF and ischemic heart disease treatments, gaps in HF and coronary artery disease care may explain why NYHA class IV is a predictor of worse outcome in women with HFrEF and not men. In comparison, HFpEF is a more heterogeneous clinical syndrome, composed of diverse clinical phenotypes, with no therapies proved to prolong survival significantly.[13] Although women with HFpEF have different comorbidities and physiology compared with men owing to the role of estrogen in vasodilation and alterations in the renin-aldosterone-angiotensin system, studies have not found any differences in mortality between men and women in acute decompensated HFpEF.[14,15] The paucity of effective therapies for HFpEF may have annulled any potential impact of sex-related gaps in treatment and care in this study. The observation by Kajimoto et al., that NYHA class IV symptoms were associated with higher mortality in HFpEF regardless of sex, is consistent with previous reports that NYHA class is an independent predictor of poor outcome.[16]

This study holds important implications for future research. The underlying mechanisms driving the sex-specific outcomes in HF are complex and warrant further investigations. Kajimoto et al. have reported previously, in a study using the ATTEND registry, that increased left ventricular end diastolic dimension in the setting of acute decompensated HFrEF was associated with worse cardiac mortality in men but not women.[17] Taken together, these findings suggest a possible interaction among sex, symptom burden, and left ventricular size in acute decompensated HF, which warrants further study. Furthermore, this study highlights the need for future trials with increasing representation of women to examine sex-specific responses to therapeutics.[18] Emerging data suggest that women with HFrEF may require significantly lower doses of guideline-directed medical therapy to achieve similar mortality benefit and are at greater risk of experiencing adverse effects from medication compared with men.[19] However, the optimal doses for women are poorly understood at present because of under-representation of women in many pivotal trials of HF therapy, and this remains a key future research direction.[20,21] Finally, given the interaction between sex and NYHA class on mortality in acute decompensated HF, it would be worthwhile to explore similar interaction in the MAGGIC and Seattle HF risk models for chronic HF.[3,4] Overall, this study serves as yet another sobering reminder of the important gender differences in cardiovascular medicine, and more gender-specific research is urgently needed.

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