Women, Heart Failure, and Heart Failure Therapies

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The landmark 2001 Institute of Medicine (IOM) report *Exploring the Biological Contributions to Human Health: Does Sex Matter?* confirmed that significant differences between the sexes affect the prevalence, incidence, and severity of a broad range of diseases and conditions. The report highlighted that sex differences must be considered when designing and analyzing research studies in all areas of biomedical and health-related research, with systematic study and elucidation of sex similarities and differences. The current topic serves as a fine example.

Examination of the underuse of beneficial cardiovascular therapies in women and in elderly persons, often overlapping populations, suggests that under-representation of these cohorts in the randomized clinical trials that provided the evidence for benefit was likely contributory. Exclusion of women from therapeutic trials of heart failure is exacerbated by exclusion of older participants, as heart failure predominates in older women; women with heart failure were further excluded because they did not have the lower ejection fraction to qualify for enrollment. Such exclusion compromises their quality of care. Although the analysis of women in MERIT-HF (Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure) reported in this issue of *Circulation* clarifies one aspect of the hazy landscape of heart failure in women, much remains to be learned.

Post Hoc Analysis of Women in MERIT-HF and Pooling of Mortality Data

Addition of β-blockers to diuretics, ACE inhibitors, and digoxin is described to improve clinical outcomes, mortality, and hospitalizations. The 23% of women enrolled in MERIT-HF was the only subgroup for whom mortality benefit was not demonstrated. As in other trials where women were under-represented, question arose as to whether β-blocker survival benefit was restricted to men or whether a mortality reduction for women was not apparent due to larger confidence intervals resulting from the small numbers of women studied and limited number of deaths available for analysis.

With pooling of mortality data from MERIT-HF, CIBIS-II (Cardiac Insufficiency Bisoprolol Study), and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study Group), which provided a larger number of deaths for analysis, comparable survival benefit was evident in both sexes. This information should enhance the application of β-blocking therapies for women with heart failure.

In most decision-analysis studies, although both patients and their physicians value the absence of clinical events and hospitalizations, survival benefit assumes the greatest importance. As documented by Ghali and associates, small sample size may limit ascertainment of survival benefit. However, even in an overview of 30 randomized trials of ACE inhibitor therapy in patients with a decreased left ventricular ejection fraction (LVEF), women did not share with men the significant reduction in mortality or in the combined endpoint of all-cause mortality and heart failure hospitalizations. Does this mean that women have less benefit from ACE inhibitor therapy? Or does this reflect under-enrollment of women and insufficient statistical power to ascertain benefit?

Sex Differences in the Clinical Spectrum of Heart Failure

Differing cardiac structural and functional changes between women and men may relate both to different etiologies of heart failure and to sex, per se. Sex-specific differences in animal models have been described for cardiac hypertrophy. Women are more likely to develop concentric hypertrophy in response to loading; do sex differences in the cardiac response to increased afterload influence survival? Do postinfarction differences in left ventricular remodeling as seen in female and male animals translate to differences in outcome in patients?

Risk factors for development of heart failure also differ by sex. Hypertension and diabetes mellitus have a greater role in women, with diabetes disproportionately increasing the risk in young women and coronary heart disease a greater role in men. Yet women in the Framingham cohort had a greater risk of symptomatic heart failure after myocardial infarction. Comparable randomized trial data were reported in the Multicenter Investigation of Limitation of Infarct Size (MILIS). An excess of heart failure and pulmonary edema in women after revascularization was reported both in the Coronary Artery Surgery Study (CASS) and in BARI (Bypass Angioplasty Revascularization Investigation), despite equivalent or better LVEF than in men.

Epidemiological data suggesting sex-related differences in the occurrence and prognosis of heart failure are conflicting and may be confounded both by differing etiologies of heart failure and by lack of separation of patients with preserved and impaired left ventricular systolic function. Women with heart failure in the Framingham Heart Study (even after

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controlling for age and etiology of heart failure), as well as women in National Health and Nutrition Examination Survey-I (NHANES-I) had improved survival compared with men. However, these epidemiological studies did not assess left ventricular function, and the population was less homogeneous than in many clinical trials; higher prevalence of ventricular systolic dysfunction in men was postulated as the basis for sex differences in mortality rates. Studies of Left Ventricular Dysfunction (SOLVD) data, which derive from patients with a reduced LVEF, did not demonstrate sex differences in heart failure survival.

Even among patients with a decreased LVEF, the etiology of heart failure differs between the sexes; the less prevalent ischemic etiology and history of prior myocardial infarction among women may correlate with improved survival and potentially a lesser ability to detect a mortality benefit of therapy. However, in the Ghali analysis from MERIT-HF, women had a significantly improved survival even after adjustment for baseline differences, including ischemic etiology. Female sex in CIBIS-II also significantly and independently predicted improved survival in patients with heart failure, independent both of β-blocker treatment and of baseline clinical profile. The mechanism(s) underlying an improved prognosis for women require elucidation.

Clinical Practice Guidelines: Should Sex Be a Variable?

Most large clinical trials of heart failure management strategies involved patients with a decreased LVEF. Older patients with heart failure, among whom women predominate, are more likely to have preserved ventricular systolic function, a problem not addressed in these major treatment trials.

The 2001 ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult Executive Summary delineate that heart failure with preserved systolic function is primarily a disease of elderly women, most of whom have hypertension. The small numbers of clinical outcome treatment trials of heart failure with preserved ventricular systolic function have failed to produce conclusive evidence for optimal pharmacological management. Because no clinical trial evidence is consistent, the Guidelines recommend a pathophysiological approach designed to control blood pressure and tachycardia, to decrease central blood volume, and to alleviate myocardial ischemia. Currently, patients with heart failure and intact ventricular systolic function, predominantly women, experience dyspnea and fatigue, exercise intolerance, and resultant impaired life quality; they are further disadvantaged by their frequent hospitalizations for symptomatic exacerbations, which also have unfavorable socioeconomic implications.

Other Heart Failure Therapies for Women

The limited numbers of women enrolled in other pharmacological treatment trials for ventricular systolic dysfunction lead to uncertainty regarding the efficacy and safety of these therapies for women and confound their application in clinical practice. For the total population (predominantly men), ACE inhibitors, β-blockers, and spironolactone impacted positively on morbidity and mortality and digitalis decreased hospitalizations and improved symptoms.

Sex-based differences in survival with ACE inhibitor therapy have already been addressed, with small numbers of women and lack of direct comparison with men limiting the interpretation of the data; neither were sex-based differences in beneficial responses or adverse effects reported for digitalis.

Although benefit of spironolactone added to digitalis, diuretic, and ACE inhibitor therapy was reported for patients with Class IV symptoms due to ventricular systolic dysfunction, outcomes were not specified for the 27% of women participants.

Heart Failure in Women: Additional Issues

Equally understudied is the ventricular systolic dysfunction associated with anthracycline chemotherapy for breast cancer, predominantly a problem for women. Subjects with this problem have been excluded from most randomized trials either by specific study design or by their limited survival likelihood. Are the current guideline-based heart failure therapies comparably applicable to this subpopulation?

Peripartum cardiomyopathy has a highly unpredictable outcome and variable recurrence in subsequent pregnancies. Impaired contractile reserve has been suggested, even in women who apparently recover. Should therapy for this condition parallel that for other etiologies of ventricular systolic dysfunction (save for avoidance of ACE inhibitor therapy during the pregnancy)? Should therapy persist after ventricular systolic function apparently recovers? Two years ago a National Heart, Lung, and Blood Institute Working Group recommended a Registry to explore the clinical spectrum of peripartum cardiomyopathy, with establishment of a serum and tissue bank to help investigate its pathogenesis. When will implementation occur?

Does menopausal status or postmenopausal hormone therapy confer benefit or risk for women with heart failure? One retrospective analysis suggested an association between estrogen use and improved survival in women with heart failure. These variables must be prospectively evaluated in sizable populations of women with heart failure, both with and without preserved ventricular systolic function. Because an excess risk of thrombotic events has been described in women with heart failure, subgroup analysis in anticoagulant trials for heart failure will be requisite to determine anticoagulant risk:benefit ratios for women and whether they differ from those for men.

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