JACC Vol. 30, No. 6
November 15, 1997:1417–9

EDITORIAL

Where Are All the Women With Heart Failure?

JOANN LINDENFELD, MD, FACC, HEIDI KRAUSE-STEINRAUF, MS,* JUDITH SALERNO, MD†
Denver, Colorado; Menlo Park, California; and Washington, D.C.

In recent clinical trials of medical therapy for heart failure, only ~20% of patients enrolled were women. The reasons for the low enrollment of women have not been clear. Although the incidence of heart failure is higher in men than in women, the prevalence is equal. When men and women with heart failure and a low left ventricular ejection fraction are compared, the women are more symptomatic and have a similarly poor outcome. Because mortality is worse in men than in women in large populations of patients with heart failure, there may be important pathophysiologic differences. Substantial data suggest that women may have diastolic dysfunction more often than men. This difference would explain differences in mortality and the difficulty in enrolling women in studies of medical therapy for heart failure with underlying systolic dysfunction.

(J Am Coll Cardiol 1997;30:1417–9)

Investigators who have been involved in the conduct of clinical trials of heart failure know that it is difficult to enroll women with symptomatic heart failure due to systolic dysfunction. In recent clinical trials (1–10) of medical therapy for heart failure, only ~20% of the subjects were women (Table 1). This low enrollment of women has been a puzzling problem. Although the incidence of heart failure is higher in men than in women in every age group, the prevalence of heart failure is about the same in all age groups (Fig. 1) (11). Similar prevalence data were reported in the National Health and Nutrition Examination Survey (NHANES-I) (12). The National Institutes of Health has recommended that there be appropriate representation of subjects with respect to gender and racial or ethnic subgroups in clinical trials to provide the opportunity to detect major qualitative differences among these subgroups (13). Thus, finding and enrolling women with heart failure and systolic dysfunction is a problem that is being tackled by every steering committee directing a clinical trial of medical therapy for heart failure. These groups find themselves asking, "Where are all the women with heart failure?" Although the final answer to this question will await a formal evaluation, suggestive data are already available.

The Studies of Left Ventricular Dysfunction (SOLVD) registry (14) was implemented in several of the same centers participating in the SOLVD treatment and prevention trials. The registry was designed to include a broader spectrum of patients than those entered into the treatment and prevention trials. Patients entered into the registry were discovered by screening reports of cardiac catheterizations, nuclear gated blood pool scans, and echocardiograms as well as screening hospital discharge summaries. With this systematic approach, more women were entered into the registry than into either the SOLVD treatment or prevention trials. However, only 26% of the total registry population were women, and they had a substantially higher average left ventricular ejection fraction than patients entered into the treatment and prevention trials. Thus, even an intensive search may not provide equal numbers of men and women for clinical trials of heart failure with systolic dysfunction. These data suggest that although there are large numbers of both men and women with symptomatic heart failure, important pathophysiologic differences may exist.

Among patients with heart failure, women are more symptomatic than men despite an equivalent left ventricular ejection fraction (15). Surprisingly, symptoms of heart failure are more common in women than in men, even when rest systolic function is normal. In the Coronary Artery Surgery Study (CASS) (16), women had significantly more heart failure symptoms and used more diuretic drugs despite a better ejection fraction and less three-vessel coronary artery disease. Why does this difference in symptoms exist? Do women have more diastolic dysfunction than men?

In many clinical trials of heart failure with systolic dysfunction, the number of patients with hypertension as the primary etiology for heart failure is low, but the percent of patients with reported hypertension is high, often more than one-third (2,3). This incidence of hypertension in patients with heart failure is consistent with the incidence of hypertension in the United States, which is estimated to be >50% for patients >60 years old (17). Thus, hypertension may be underrecognized as an underlying cause of heart failure. Several studies suggest that women may have a qualitatively different left ventricular hypertrophic response to a pressure load than men. In reports of hypertensive cardiomyopathy of the elderly, >80% of

From the Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado; *Veterans Affairs Cooperative Studies Program Coordinating Unit, Palo Alto Veterans Affairs Health Care System, Menlo Park, California; and †Geriatrics and Extended Care, Department of Veterans Affairs, Washington, D.C.

Manuscript received July 30, 1997; accepted August 14, 1997.

Address for correspondence: Dr. JoAnn Lindenfeld, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, B130, Denver, Colorado 80262. E-mail: lindenfj@jove.uchsc.edu.

0735-1097/97/$17.00
PII S0735-1097(97)00343-4

Table 1. Age and Gender Distribution in Heart Failure Trials

Trial (ref no.)	Year	No. of Pts	No. (%) Women	Average Age (yr)
Captopril-Digoxin (1)	1988	300	51 (17%)	57
SOLVD (prevention) (2)	1992	4,228	486 (11.5%)	59
SOLVD (symptomatic) (3)	1991	2,569	594 (23%)	61
CONSENSUS-I (4)	1987	253	75 (30%)	70
MDC (5)	1993	383	105 (27%)	49
PROMISE (6)	1991	1,088	235 (22%)	64
Vesnarinone (7)	1993	477	63 (13%)	58
RADIANCE (8)	1993	178	42 (24%)	60
DIG (9)	1997	6,800	1,520 (22.4%)	64
Carvedilol (10)	1996	1,094	256 (23%)	48
Total		17,370	3,427 (19.7%)	62

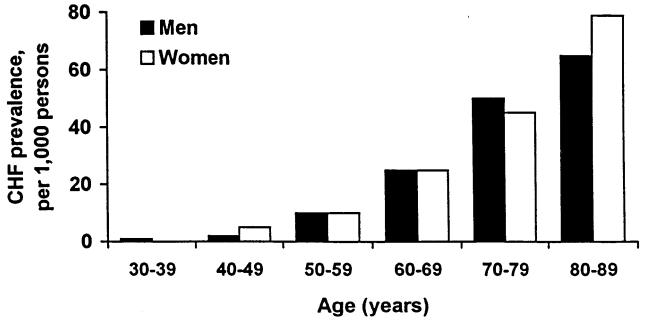
CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; DIG = Digitalis Investigation Group; MDC = Metoprolol in Dilated Cardiomyopathy; Pts = patients; RADIANCE = Randomized Assessment of Diogoxin on Inhibitors of the Angiotensin-Converting Enzyme; ref = reference; SOLVD = Studies of Left Ventricular Dysfunction.

patients are women (18). Carroll et al. (19) reported that women with severe aortic stenosis have more concentric hypertrophy and better preserved left ventricular systolic function than men with a similar degree of aortic stenosis. More eccentric hypertrophy and poorer left ventricular systolic function were found in the men. In women with isolated systolic hypertension, concentric hypertrophy was most common, whereas eccentric hypertrophy was more commonly found in men (20). If, as suggested by these data, women are more likely to develop concentric hypertrophy in response to a variety of loading conditions, one might expect symptoms of heart failure but with preserved systolic function and thus a better prognosis than men with more abnormal systolic function. Indeed, hypertension increases the risk of symptoms of heart failure in both men and women, but the mortality risk is higher in men (21,22).

Thus, the data are consistent with the hypothesis that there is substantially more heart failure due to diastolic dysfunction in women than in men. An excess of diastolic dysfunction in women would explain the equal prevalence of heart failure in men and women in the United States while accounting for the difficulty in actually finding equal numbers of women and men with heart failure due to systolic dysfunction. A preponderance of diastolic dysfunction might also help explain the better prognosis of women with heart failure. The results of ongoing clinical trials should provide answers to whether there are important differences in etiology and pathophysiology in women compared with men with heart failure.

If differences do exist, there may be differences in morbidity and mortality and in the response to medical therapy.

Figure 1. Prevalence rates of congestive heart failure (CHF) among Framingham Heart Study subjects, by gender and age. Reprinted, with permission, from Ho et al. (11).



References

1. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539–44.
2. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection. N Engl J Med 1992;327:685–91.
3. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
4. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
5. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993;342:1441–6.
6. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468–75.
7. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. N Engl J Med 1993;329:149–55.
8. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. N Engl J Med 1993;329:1–7.
9. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.
10. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on mortality and morbidity in patients with chronic heart failure. N Engl J Med 1996;334:1349–55.
11. Ho KKL, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22: Suppl A:6A–13A.
12. Shocken DD, Arrieta MI, Leaverton PE, Rosse A. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992;20:301–6.
13. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in

Clinical Research. Federal Register, Part VIII (59FR 14508-14513), March 28, 1994.

14. Bangdiwala SI, Weiner DH, Bourassa MG, Friesinger GC, Ghalai JK, Yusuf S. Studies of Left Ventricular Dysfunction (SOLVD) Registry: Rationale, design, methods and description of baseline characteristics. Am J Cardiol 1992;70:347–53.
15. Limacher MC, Yusuf S, for the SOLVD Investigators. Gender differences in presentation, morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD): a preliminary report. In: Wenger NK, Speroff L, Packard B, editors. Cardiovascular Health and Disease in Women. Greenwich (CT): Le Jacq Communications, 1993:345–8.
16. Fisher LD, Kennedy JW, David KB, et al. Association of sex, physical size, and operative mortality after coronary artery bypass in the Coronary Artery Surgery Study (CASS). J Thorac Cardiovasc Surg 1982;84:334–41.
17. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the U.S. adult population: results from the Third National Health and Nutrition Examination Survey, 1998–1991. Hypertension 1995;25:305–13.
18. Aurigemma GP, Gaasch WH. Gender differences in older patients with pressure-overload hypertrophy of the left ventricle. Cardiology 1995;86: 310–7.
19. Carroll JD, Carroll EP, Feldman T, et al. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. Circulation 1992;86: 1099–107.
20. Krumholz HM, Larson M, Levy D. Sex differences in cardiac adaptation to isolated systolic hypertension. Am J Cardiol 1993;72:310–3.
21. Liao Y, Cooper RS, Mensah GA, McGee DL. Left ventricular hypertrophy has a greater impact on survival in women than in men. Circulation 1995;92:805–10.
22. Kannel WB. Metabolic risk factors for coronary heart disease in women: perspective from the Framingham Study. Am Heart J 1987;114:413–9.