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Hormone Replacement Therapy Is Associated With Improved Survival in Women With Advanced Heart Failure

JoAnn Lindenfeld, MD,* Jalal K. Ghali, MD,† Heidi J. Krause-Steinrauf, MS,‡ Steven Khan, MD,§ Kirkwood Adams, Jr, MD,‖ Steven Goldman, MD,¶ Mary Ann Peberdy, MD,# Clyde Yancy, MD,** Surai Thaneemit-Chen, MS,†† Rhonda L. Larsen, RN,‡‡ James Young, MD,§§ Brian Lowes, MD,* Yves D. Rosenberg, MD,‡ for the BEST Investigators

Denver, Colorado; Shreveport, Louisiana; Bethesda, Maryland; Los Angeles and Palo Alto, California; Chapel Hill and Durham, North Carolina; Tucson, Arizona; Richmond, Virginia; Dallas, Texas; and Cleveland, Ohio

OBJECTIVES We sought to determine whether hormone replacement therapy (HRT) is associated with an improved prognosis in women with advanced heart failure (HF) and systolic dysfunction.

BACKGROUND There are about two million postmenopausal women in the U.S. with HF. However, limited data are available to assess the effects of HRT on survival in this large group of patients.

METHODS A retrospective analysis of women age 50 years and over entered into the Beta-Blocker Evaluation of Survival Trial (BEST) was conducted using Cox regression analysis comparing survival in HRT users and non-users after correcting for baseline variables known to predict survival in women with HF and systolic dysfunction.

RESULTS In 493 women age 50 years and older, HRT was associated with a significant reduction in mortality—21% mortality in HRT users and 34% in non-users ($p = 0.025$). Multivariate analysis demonstrated a hazard ratio for mortality of 0.6 (95% confidence interval = 0.36 to 0.97) ($p = 0.039$) for HRT users. The benefits of HRT were noted only in women with a nonischemic etiology of HF ($n = 237$).

CONCLUSIONS Hormone replacement therapy is associated with a marked improvement in survival in postmenopausal women with advanced HF. A prospective, randomized trial of HRT should be performed in this large group of patients. (J Am Coll Cardiol 2003;42:1238–45) © 2003 by the American College of Cardiology Foundation

Heart failure (HF) is a common cause of morbidity and mortality in both men and women. It is estimated that four to five million people in the U.S. have HF and that one-half of these are women (1,2). Data from the Framingham Heart Study and the National Health and Nutrition Examination

See page 1246

and Survey-I suggest that at least 70% of women with HF are over age 50 years—the average age of menopause in the U.S. (3,4). Thus, there are at least two million menopausal women in the U.S. with HF. Mortality is high in women with HF, with estimates of 50% to 90% mortality over 10 years (3,4). Despite the frequency and severity of advanced HF in postmenopausal women, there is only one study investigating the effect of hormone replacement therapy (HRT) in these women. This retrospective study combined trials comparing vesnarinone with placebo in patients with advanced HF (5). After accounting for known predictors of mortality, estrogen use was associated with a 32% decrease in HF mortality. We sought to confirm whether HRT is associated with an improved prognosis in women with advanced HF and systolic dysfunction using data collected in the Beta-Blocker Evaluation of Survival Trial (BEST).

METHODS

The BEST study. The BEST trial was a multicenter, prospective, randomized trial comparing a nonselective beta-blocker, bucindolol, with placebo in patients with New York Heart Association (NYHA) functional class III or IV HF and an ejection fraction of ≤35%. The design of this trial and the study results have been published (6,7). Exclusion criteria included a reversible cause of HF and infarction within the previous six months (6). Other exclusion criteria included a coronary revascularization procedure within 60 days, patients who were candidates to be listed for heart transplantation, unstable angina defined as uncorrected thyroid disease, obstructive or hypertrophic cardiomyopathy, amyloidosis, active myocarditis, malfunctioning

From the *University of Colorado Health Sciences Center and Center for Women's Health Research, Denver, Colorado; †Cardiac Centers of Louisiana, Shreveport, Louisiana; ‡National Heart, Lung, and Blood Institute, Bethesda, Maryland; §Cedars-Sinai Medical Center, Los Angeles, California; ‖University of North Carolina, Chapel Hill, North Carolina; ¶Tucson SAVAHCS, Tucson, Arizona; #Virginia Commonwealth University, Medical College of Virginia, Richmond, Virginia; **University of Texas Southwestern, Dallas, Texas; ††VA Palo Alto Health Care System Cooperative Studies Program, Palo Alto, California; ‡‡Duke Clinical Research Institute, Durham, North Carolina; and the §§Cleveland Clinic Foundation, Cleveland, Ohio. The BEST trial was sponsored by the Division of Epidemiology and Clinical Applications of the National Heart, Lung, and Blood Institute and the Department of Veterans Affairs Cooperative Studies Program through an interagency agreement. Additional support was provided by Incara Pharmaceuticals Corporation, which also supplied bucindolol and placebo.

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Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
CHF = congestive heart failure
CI = confidence interval
CTR = cardiothoracic ratio
HF = heart failure
HR = hazard ratio
HRT = hormone replacement therapy
LVEF = left ventricular ejection fraction
MAPK = mitogen-activated protein kinase
NYHA = New York Heart Association

prosthetic heart valve, or myocardial use of >6 nitroglycerin tablets per week, heart rate <50 beats/min, life expectancy of <3 years, or a serum creatinine level >3 mg/dl. Patients with decompensated HF, pulmonary edema, or systolic blood pressure <80 mm Hg were also excluded. Patients were excluded if they required a drug in one of four categories: 1) beta-adrenergic blocking agents within 30 days of baseline evaluation; 2) calcium channel blocking agents, theophylline, tricyclic antidepressants, monoamine oxidase inhibitors, or beta-adrenergic agonists within one week of baseline evaluation; 3) flecainide, encainide, propafenone, or disopyramide within two weeks of randomization; or 4) amiodarone within eight weeks of baseline evaluation.

Randomization at each clinical site was stratified by etiology of HF (ischemic or nonischemic), left ventricular ejection fraction (LVEF) (≤0.20 vs. >0.20), gender, and race. Follow-up visits occurred at 3, 6, and 12 months after randomization and at 6-month intervals thereafter. The primary end point was all-cause mortality. Secondary end points included cardiovascular mortality, all-cause and congestive heart failure (CHF)-specific hospitalization, the combination of death and cardiac transplantation, LVEF at 3 and 12 months, myocardial infarction, quality of life, and a change in the need for cotherapy.

We conducted a retrospective analysis to examine the effect of HRT in postmenopausal women on survival and to evaluate whether the effect varied according to etiology of HF. We also examined HRT-by-treatment effect (bucindolol-placebo) interactions for mortality.

Definition of postmenopausal and HRT. Women in this trial were considered to be postmenopausal if they were ≥50 years of age. Women were classified as using HRT if they were taking estrogen, progestin, or a combination of both at the baseline evaluation.

Assessment of compliance and health status. Compliance to follow-up was estimated by percent attendance at the three-month follow-up visit. Health status was estimated by the prevalence of current smoking and body mass index (BMI) at the baseline evaluation. Coronary artery disease (CAD) was defined as the presence of significant disease by angiography or evidence of a previous myocardial infarction.

Statistical analysis. Means and standard deviations or medians are reported for continuous data. Proportions are reported for categorical data. The p values reported for the comparisons of the HRT and non-HRT subgroups are from the *t* test, except when the data were non-normal and the Wilcoxon rank sum test for continuous variables was used. For categorical variables the chi-square test was used, except in cases when the expected cell counts were <5 and the Fisher's exact test was used. Two-sided tests of significance were performed using an alpha of 0.05. Cox proportional hazards regression was used to examine the effect of HRT on survival, adjusting for prespecified variables and to estimate risk (hazard) ratios and corresponding confidence intervals (CIs). A backward elimination process was used to derive the multivariate model, which examined the following predictors: LVEF, NYHA functional classification, etiology of HF (ischemia = CAD, no ischemia = no CAD), race, age, diabetes, cardiothoracic ratio (CTR), HRT, and treatment group assignment (bucindolol or placebo). Cox regression models were also used to examine HRT-by-CAD and HRT-by-treatment interactions. The model-based Kaplan-Meier curves were corrected for potential confounders, including CTR, NYHA functional classification, etiology (CAD vs. non-CAD), LVEF, and treatment group.

RESULTS

Patient characteristics. A total of 2,708 patients were randomized in the BEST study, including 593 women. Of the 593 women, 435 (73%) were ≥50 years of age and were considered to be postmenopausal. Subjects were considered to be using HRT if they were taking oral or transdermal estrogen alone, a progestin, or a combination of estrogen and progestin. Of the 435 women age 50 years or older, 122 (23%) were using HRT. No woman age 50 years or above was using oral contraceptives. Of the 102 HRT users, 72 were using estrogen alone, 3 were using a progestin alone, and 27 were using a combination of the two hormones. The baseline characteristics of the HRT users and non-HRT users are shown in Table 1. Hormone replacement therapy users were younger and more often non-black compared with the HRT non-users. Hormone replacement therapy users had a lower BMI compared with the non-HRT subgroup, primarily because of a height difference. Hormone replacement therapy users were less likely to have a history of hypertension and diabetes than the non-users. Systolic and diastolic blood pressure, heart rate, LVEF and right ventricular ejection fraction, and the prevalence of atrial fibrillation were not different between the two subgroups. Medications at baseline were similar, with the exception of fewer vasodilators being taken by HRT users compared with non-users (p = 0.047). Hormone replacement therapy users had slightly lower creatinine, serum sodium, and alanine aminotransferase levels than their non-HRT counterparts. Median plasma norepinephrine

Table 1. Baseline Clinical Characteristics by HRT User Status*

Characteristics	HRT User (n = 102)			HRT Non-User (n = 333)			Overall P Value
	Placebo (n = 49)	Bucindolol (n = 53)	Overall	Placebo (n = 165)	Bucindolol (n = 168)	Overall	
Demographic							
Age (yrs)	61.8 ± 7.5	61.2 ± 7.3	61.5 ± 7.4	63.8 ± 8.6	65.1 ± 9.0	64.5 ± 8.8	0.004
Range	50–78	50–77	50–78	50–86	50–93	50–93	
Weight (lbs)	150.3 ± 34.0	152.4 ± 27.1	151.4 ± 30.5	155.5 ± 37.7	156.5 ± 35.5	156.0 ± 36.5	0.204
Height (in)	64.0 ± 2.5	64.2 ± 2.5	64.1 ± 2.5	63.4 ± 2.6	63.1 ± 2.8	63.3 ± 2.7	0.007
Body mass index (kg/m^2)	25.9 ± 6.2	26.1 ± 5.1	26.0 ± 5.6	27.1 ± 6.0	27.6 ± 6.2	27.4 ± 6.1	0.048
Median duration of CHF (months)	48.0	46.0	47.5	36.0	40.5	39.0	0.178*
Range	1–240	1–288	1–288	1–199	1–456	1–456	–
Current smoker	5 (10%)	7 (13%)	12 (12%)	12 (7%)	19 (11%)	31 (9%)	0.467
Ever smoked	30 (61%)	32 (60%)	62 (61%)	83 (51%)	87 (53%)	170 (52%)	0.120
Race							
White non-Hispanic	41 (84%)	47 (89%)	88 (86%)	106 (64%)	105 (63%)	211 (63%)	0.000
Black non-Hispanic	7 (14%)	5 (9%)	12 (12%)	46 (28%)	52 (31%)	98 (29%)	
Hispanic or Latino	1 (2%)	1 (2%)	2 (2%)	10 (6%)	10 (6%)	20 (6%)	
Other	0 (0%)	0 (0%)	0 (0%)	3 (2%)	1 (1%)	4 (1%)	
NYHA functional class							
III	44 (90%)	50 (94%)	94 (92%)	149 (90%)	154 (92%)	303 (91%)	0.715
IV	5 (10%)	3 (6%)	8 (8%)	16 (10%)	14 (8%)	30 (9%)	
Heart failure etiology							
Ischemic	17 (35%)	23 (43%)	40 (39%)	74 (45%)	84 (50%)	158 (47%)	0.144
Nonischemic	32 (65%)	30 (57%)	62 (61%)	91 (55%)	84 (50%)	175 (53%)	
History of related illness							
Hypertension	24 (49%)	26 (49%)	50 (49%)	99 (60%)	107 (64%)	206 (62%)	0.021
Hyperlipidemia	25 (51%)	26 (49%)	51 (50%)	81 (49%)	74 (44%)	155 (47%)	0.541
Diabetes mellitus	12 (24%)	18 (34%)	30 (29%)	72 (44%)	73 (43%)	145 (44%)	0.011
Hemodynamics/ventricular function							
Heart rate (beats/min)	82.0 ± 11.0	81.4 ± 10.3	81.7 ± 10.6	83.4 ± 13.5	82.0 ± 11.4	82.7 ± 12.5	0.404
Blood pressure (mm Hg)							
Systolic	117.4 ± 17.1	119.8 ± 17.5	118.7 ± 17.3	119.0 ± 19.0	117.9 ± 18.7	118.5 ± 18.8	0.771
Diastolic	70 ± 12	71 ± 10	71 ± 11	70 ± 11	69 ± 11	69 ± 11	0.290
LVEF (%)	24.9 ± 6.0	24.1 ± 7.2	24.5 ± 6.6	24.5 ± 7.0	24.6 ± 7.5	24.6 ± 7.3	0.917
RVEF (%)	40.8 ± 14.4	39.4 ± 12.7	40.1 ± 13.5	37.9 ± 14.3	36.1 ± 14.2	37.0 ± 14.2	0.081
Atrial fibrillation	2 (4%)	3 (6%)	5 (5%)	8 (5%)	12 (7%)	20 (6%)	0.675
Routine medications							
ACE inhibitor	43 (88%)	45 (85%)	88 (86%)	147 (89%)	153 (91%)	300 (90%)	0.277
Angiotensin receptor blocker	6 (12%)	7 (13%)	13 (13%)	18 (11%)	9 (5%)	27 (8%)	0.156
Digitalis	46 (94%)	50 (94%)	96 (94%)	152 (92%)	152 (90%)	304 (91%)	0.359
Diuretic	44 (90%)	50 (94%)	94 (92%)	156 (95%)	165 (98%)	321 (96%)	0.101
Aldactone (spironolactone)	4 (8%)	2 (4%)	6 (6%)	9 (5%)	4 (2%)	13 (4%)	0.101
Vasodilator	17 (35%)	23 (43%)	40 (39%)	90 (55%)	78 (46%)	168 (50%)	0.047
Hydralazine/isosorbide	13 (27%)	18 (34%)	31 (30%)	57 (35%)	63 (38%)	120 (36%)	0.295
Antiarrhythmic	2 (4%)	0 (0%)	2 (2%)	1 (1%)	1 (1%)	2 (1%)	0.235
Anticoagulant	18 (37%)	26 (49%)	44 (43%)	63 (38%)	65 (39%)	128 (38%)	0.396
Aspirin	21 (43%)	22 (42%)	43 (42%)	70 (42%)	61 (36%)	131 (39%)	0.611
Statin lipid-lowering agents	9 (18%)	13 (25%)	22 (22%)	41 (25%)	32 (19%)	73 (22%)	0.940
Laboratory values							
Creatinine (mg/dl)	1.0 ± 0.3	1.0 ± 0.4	1.0 ± 0.3	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.007*
Serum sodium (mg/dl)	138.6 ± 2.7	137.8 ± 2.8	138.2 ± 2.7	139.5 ± 3.4	139.3 ± 3.0	139.4 ± 3.2	0.001
Serum potassium (mg/dl)	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	0.607
Serum ALT (mg/dl)	19.3 ± 9.2	19.1 ± 8.5	19.2 ± 8.8	25.7 ± 16.3	25.4 ± 18.7	25.5 ± 17.5	0.0001*
Median plasma norepinephrine (pg/ml)	392.0	423.0	420.0	460.0	423.0	441.0	0.413*
ECG/X-ray							
QRS duration, (ms)	137.1 ± 32.3	137.5 ± 34.4	137.4 ± 33.2	131.4 ± 36.2	129.8 ± 34.7	130.6 ± 35.4	0.087
QT duration–corrected (ms)	450.6 ± 45.7	458.7 ± 53.0	454.8 ± 49.6	451.9 ± 45.8	446.0 ± 47.6	448.9 ± 46.7	0.273
LBBB	22 (45%)	24 (45%)	46 (45%)	60 (36%)	63 (38%)	123 (37%)	0.139
Cardio/thoracic ratio	58.6 ± 6.6	56.6 ± 7.6	57.6 ± 7.2	60.4 ± 8.0	60.2 ± 7.2	60.3 ± 7.6	0.002

*Mean ± SD unless otherwise indicated. p Value based on Wilcoxon rank sum test.

ACE = angiotensin converting enzyme; ALT = alanine aminotransferase; CHF = congestive heart failure; ECG = electrocardiogram; HRT = hormone replacement therapy; LBBB = left bundle blanch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction.

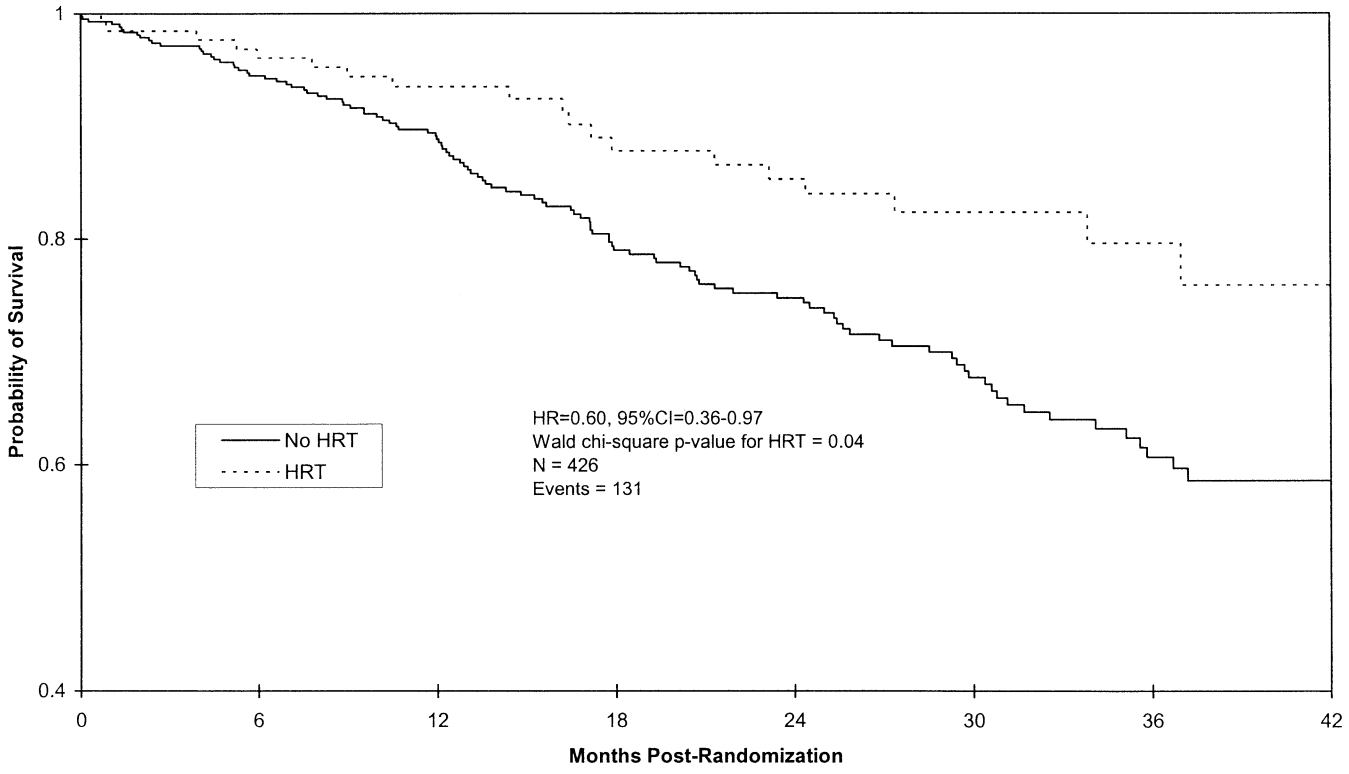

Figure 1. Model-based survival curves for survival by hormone replacement therapy (HRT) use in postmenopausal women. Difference between HRT subgroups is significant. (Wald chi-square p value for HRT = 0.04) Adjustment was made for etiology of disease (coronary artery disease vs. non-coronary artery disease), cardiothoracic ratio, New York Heart Association functional classification, left ventricular ejection fraction, and treatment group. CI = confidence interval; HR = hazard ratio.

values were not different between the two subgroups. There were no differences in the QRS or corrected QT durations or the incidence of left bundle branch block. Hormone replacement therapy users had a smaller CTR compared with non-HRT users (p = 0.002).

Figure 1 depicts the model-based survival curves adjusted for potential confounders for HRT users and non-users. There were 134 deaths in the 435 women age 50 and over with a mean follow-up of 2 years. Twenty-one deaths (21%) occurred in the 102 HRT users and 113 deaths (34%) in the 333 non-HRT users. There was a significant difference in survival favoring HRT users (Wald chi-square p value for HRT = 0.04). Table 2 presents the results from the multivariate analysis using prespecified risk factors known to predict mortality in patients with HF and adjusting for treatment group assignment (bucindolol or placebo). Significant factors predicting higher mortality included NYHA functional class IV vs. III and an ischemic etiology of HF. A higher LVEF and HRT use were associated with a lower mortality. After adjusting for the effect of HRT, treatment group assignment and etiology of CHF, we found no significant effect of HRT-by-treatment interaction (p = 0.85) or HRT-by-etiology of CHF (CAD vs. no CAD) interaction (p = 0.09) on mortality.

Survival curves adjusted for potential confounders comparing HRT users with non-HRT users by etiology of disease are presented in Figure 2. Of the 198 women with ischemic etiology, there was no difference in survival between HRT users and non-users (HR = 0.74, 95% CI = 0.41 to 1.33, Wald chi-square p value = 0.31). However, there was a significant survival benefit for HRT users in the 237 nonischemic postmenopausal women (HR = 0.35, 95% CI = 0.14 to 0.87, Wald chi-square p value = 0.02).

We compared the survival between unopposed estrogen HRT users (n = 72) to those users on a combination of estrogen plus progestin (n = 27). A total of 21 deaths occurred, 15 (21%) in unopposed estrogen users and 6 (22%) in those using combination estrogen and progestin.

Table 2. Multivariate Predictors of Mortality Including Treatment Group Assignment

Covariate	Relative Risk	95% CI	p Value
NYHA (IV vs. III)	2.610	1.659–4.107	0.0001
CAD (ischemic vs. nonischemic)	2.492	1.737–3.573	0.0001
LVEF (per 1 EF unit increase)	0.961	0.935–0.988	0.0042
HRT (taking vs. not taking)	0.595	0.364–0.973	0.0387
Cardio/thoracic ratio	1.026	1.000–1.053	0.0502
Treatment (bucindolol vs. placebo)	0.710	0.502–1.005	0.0534

n = 426, total deaths = 131. Estimates from Cox proportional hazards regression model. Model derived using a backwards elimination process considering the following covariates: left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) classification, etiology of heart failure (ischemia = coronary artery disease [CAD] or no ischemia = no CAD), race, age, diabetes, cardiothoracic ratio, hormone replacement therapy (HRT), and treatment group assignment (bucindolol or placebo).

CI = confidence interval; EF = ejection fraction.

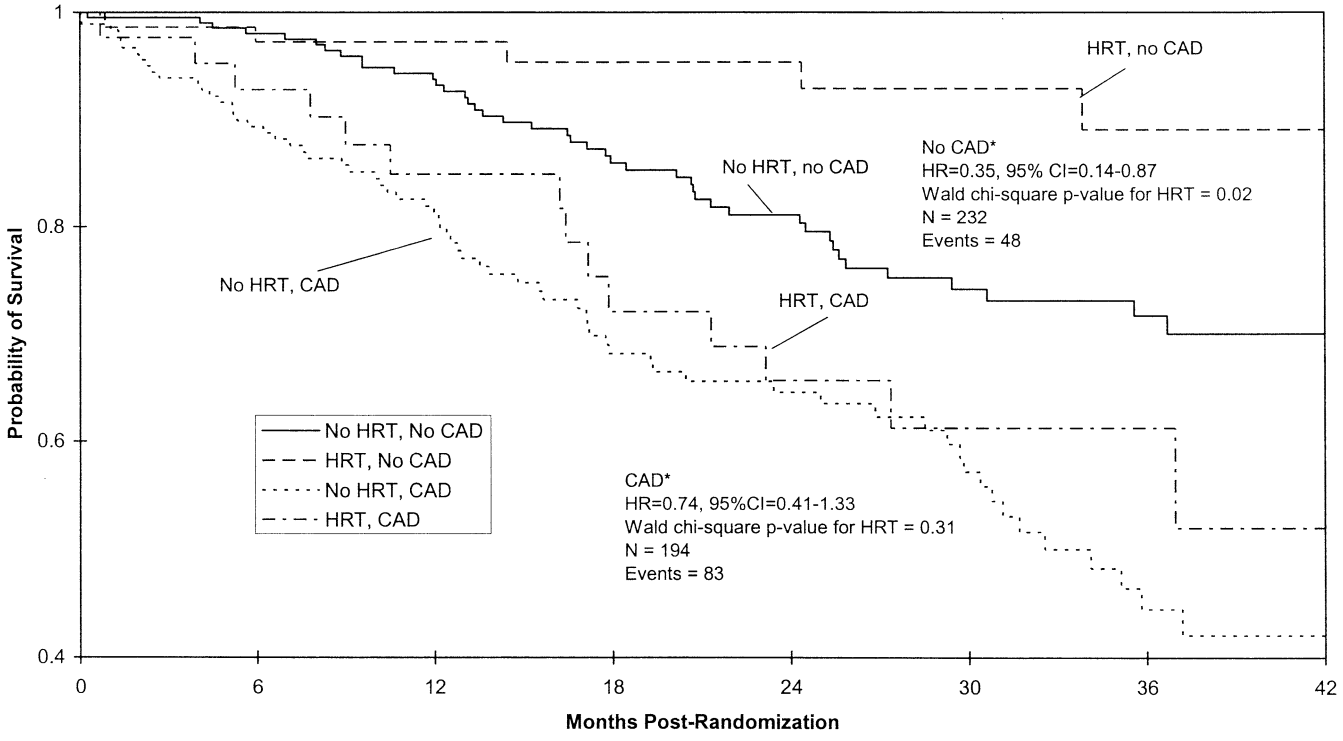

Figure 2. Model-based survival curves by hormone replacement therapy (HRT) use within etiology of disease. Differences are significant for women with a non-coronary artery disease (CAD) etiology but not for those with a CAD etiology. Adjustment was made for cardiothoracic ratio, New York Heart Association functional classification, left ventricular ejection fraction, and treatment group. CI = confidence interval; HR = hazard ratio.

There was no difference in survival between combination HRT and unopposed estrogen subgroups (HR = 1.09, 95% CI = 0.42 to 2.82, p = 0.86).

The results of the multivariate analysis including BMI and current smoking status as measures of health status and using attendance at the three-month visit as a measure of compliance are presented in Table 3. The frequency of current smoking status and the BMIs for HRT users and non-users are shown in Table 1. Attendance at the three-month clinic visit was 93% among both HRT users and non-users. Forcing measures of health status and compliance into the multivariate analysis resulted in an estimated relative risk for mortality for HRT of 0.54 (95% CI = 0.33 to 0.91) and p value of 0.019.

Table 3. Multivariate Predictors of Mortality Including Measures of Compliance and Health Status

Covariate	Relative Risk	95% CI	P Value
NYHA functional class (IV vs. III)	2.766	1.738–4.402	0.0001
CAD (ischemic vs. nonischemic)	2.171	1.494–3.155	0.0001
Compliance (yes vs. no)	0.235	0.142–0.389	0.0001
LVEF (per 1 EF unit increase)	0.952	0.925–0.980	0.0007
Current smoker (yes vs. no)	0.464	0.224–0.959	0.0381
BMI (per kg/m^2)	0.970	0.939–1.003	0.0742
Cardio/thoracic ratio	1.020	0.994–1.047	0.1379
HRT (taking vs. not taking)	0.544	0.327–0.906	0.0193
Treatment (bucindolol vs. placebo)	0.697	0.489–0.994	0.0462

*Table 2 model with BMI + smoker + compliance with treatment. N = 425, total deaths = 130. estimates from Cox proportional hazards regression model. Compliance at three-month visit defined as a patient attending her three month visit and having a physical exam completed.

BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; HRT = hormone replacement therapy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

DISCUSSION

Our study suggests that the use of HRT in women with advanced HF and systolic dysfunction is associated with a significant survival benefit. Hormone replacement therapy users had a number of baseline features that are known to predict a better prognosis. These included a younger age, a higher percentage of non-black subjects, less hypertension and diabetes, and a higher frequency of nonischemic etiology. When these factors are accounted for in a multivariate analysis, HRT remains a significant predictor of mortality with a relative risk of 0.60 (p = 0.039).

Only one previous study has addressed the issue of HRT in women with HF. Using data combined from three trials of patients with advanced HF comparing vesnarinone with placebo, the relative risk of HRT for survival was 0.68 (5). The baseline characteristics in that study were similar to our study with HRT users being younger, less often black, and more frequently having a nonischemic etiology. In both studies, 21% to 22% of women age 50 years and older were using HRT. In both studies, multivariate analysis did not alter the apparent association of HRT with survival. Our study had a mean follow-up of two years, compared with a mean follow-up of <1 year in the study of Reis et al. (5). Thus, our findings confirm the study of Reis et al. (5) and

also suggest that the association of HRT with improved mortality in women with advanced HF is present even with prolonged follow-up.

Hormone replacement therapy was associated with a marked improvement in survival in women with a nonischemic etiology of HF (HR = 0.35, 95% CI = 0.14 to 0.87, p = 0.02) but no improvement in women with an ischemic etiology (HR = 0.74, 95% CI = 0.41 to 1.33, p = 0.31) (Fig. 2). This effect of etiology differs from the study of Reis et al. (5), in which etiology of HF did not impact the benefit of HRT. However, in that study the benefits of HRT were not statistically significant in either ischemic or nonischemic etiologies when the groups were considered separately. A test of interaction of benefit of HRT by etiology had a p value of 0.09. Although not statistically significant, this p value certainly does not exclude the possibility of an interaction between etiology of CHF and HRT. Indeed, a larger study will be necessary to be certain if etiology of HF is important for the benefits of HRT.

We found no difference in the benefits of combination estrogen and progestin versus unopposed estrogen. Reis et al. (5) reported a trend for estrogen alone to be associated with improved mortality. The small numbers of patients in both studies do not allow firm conclusions.

Potential mechanisms of benefit of HRT. Hormone replacement therapy may improve survival in postmenopausal women with advanced HF through effects on endothelial function, neurohormonal activation, myocardial remodeling, CAD, or any combination of these. Postmenopausal women have impaired endothelial function as measured by flow-mediated vasodilation (8,9). Chronic HRT with estrogen alone or with the combination of 17β-estradiol and norethisterone acetate improves endothelial-dependent vasodilation in postmenopausal women (9–11). Improved endothelial function may result in lower systemic vascular resistance and improved cardiac output in women with advanced HF, although no studies of HRT have been conducted in postmenopausal women with HF.

Neurohormonal activation is associated with a poorer prognosis in patients with HF (12,13). Increasing levels of norepinephrine, renin, angiotensin II, and endothelin have all been correlated with poorer survival in patients with HF (12–14). Hormone replacement therapy, particularly estrogen, is associated with reduced activation of a number of neurohormonal systems. Estrogen is known to suppress muscle sympathetic nerve activity, both at rest and after exercise in postmenopausal women (15). It is not known if cardiac sympathetic activity is also suppressed by estrogen, but muscle sympathetic nerve activity is known to reflect cardiac sympathetic activity (16). Estrogen supplementation to perimenopausal women for eight weeks decreased systolic and diastolic blood pressure and total body norepinephrine spillover in response to mental stress (17). Estrogen and progesterone decrease angiotensin-converting enzyme levels while increasing bradykinin levels in hypertensive postmenopausal women (18,19). Estrogen is known to decrease endothelin levels in healthy postmenopausal women (9,11). Thus, there is evidence that HRT might reduce activation of a number of neurohormonal systems that are known to be associated with increased mortality in HF. There are no data addressing the effects of HRT on neurohormonal activation in women with HF. However, if HRT provides similar benefits in women with advanced HF as in healthy postmenopausal women, an effect of HRT on mortality in HF might be expected.

There are substantial gender differences in myocardial remodeling due, at least in part, to the influence of sex hormones. In the general population there is a progressive age-related increase in myocardial mass in healthy women that is not seen in their male counterparts (20). These findings were confirmed in a healthy, nonobese, normotensive subset of the Framingham Heart Study (21). These studies demonstrate the increase in myocardial mass occurs primarily in postmenopausal women. Indeed, premenopausal women with essential hypertension have thinner posterior left ventricular walls, smaller left ventricular mass, and better cardiac function than age-matched men (22). In one study, women using HRT for more than 10 years had a significant reduction in septal and posterior left ventricular wall thickness when compared with controls (23). Elderly (postmenopausal) women with systolic hypertension or aortic stenosis have more concentric remodeling and better preserved left ventricular systolic function than their male counterparts both at rest and with exercise (24–28). These data suggest that female sex hormones, estrogen and progesterone, influence myocardial hypertrophy and myocardial remodeling by suppressing cardiac hypertrophy and preserving myocardial function. Studies in animals subjected to a left ventricular pressure load also demonstrate a substantial effect of female sex hormones on myocardial remodeling. Female rats subjected to pressure loads demonstrate less hypertrophy than male rats (29). Furthermore, female mice subjected to pressure overloads have less progression to HF than do the males (29–31). Female rats demonstrate gene expression changes in beta-myosin and sarcoplasmic reticulum calcium adenosine triphosphatase expression consistent with less hypertrophy and preserved systolic function (32). It is known that estrogen receptors are present in the myocardium (33). Recently two studies have contributed information linking 17β-estradiol with cardiac hypertrophy. van Eickels et al. (34) have shown that 17β-estradiol reduces left ventricular hypertrophy in ovariectomized mice subjected to aortic constriction. Estrogen therapy was associated with reduced levels of p38 mitogen-activated protein kinase (MAPK). The MAPK proteins are important in the activation and maintenance of cardiac hypertrophy and p38MAPK may be important in the progression to HF (35). In another study, Xin et al. (36) have demonstrated that male FKBP 12.6 knockout mice develop left ventricular hypertrophy, whereas the female knockouts do not. FKBP 12.6 is an intracellular binding protein that modulates the

action of the cardiac ryanodine receptor complex, which regulates sarcoplasmic reticulum calcium release. Blocking estradiol receptors in the female mice resulted in hypertrophy similar to that seen in the male mice. Thus, estrogen may have effects on more than one pathway influencing cardiac hypertrophy.

Myocyte apoptosis may also be important in myocardial remodeling. Olivetti et al. (37), in an autopsy study, demonstrated that myoctye number and volume are better preserved in women than in men. This intriguing study is supported by recent findings that estrogen may be important in the activation of the antiapoptotic protein AKT in the heart (38). Thus HRT, and particularly estrogen, positively effect myocardial hypertrophy and remodeling, and this mechanism seems the most plausible explanation for the improved survival with HRT in women with advanced HF.

Recent studies differ about whether HRT alters the natural history of CAD in women. Data from the Heart and Estrogen/progestin Replacement Study (HERS) and Heart and Estrogen/progestin Replacement Study follow-up demonstrated no increase in the rate of primary coronary heart disease events or secondary cardiovascular events with combination estrogen and progesterone therapy in postmenopausal women with known coronary heart disease (39,40). However the Women's Health Initiative (WHI) found a HR of 1.29 for coronary heart disease with combined HRT in healthy postmenopausal women (41). Our study did not demonstrate any benefit of HRT on survival in women with an ischemic etiology for HF. The absence of benefit in this subgroup may represent the sum of the positive benefit seen in women with a nonischemic etiology and a negative effect on CAD, such as was noted in WHI. Both the WHI and HERS studies have demonstrated a >2-fold risk in thromboembolic disease in women on combination HRT (39–41). However, the baseline risk of thromboembolic disease was about two-fold higher in the women with coronary disease enrolled in HERS than in the healthy postmenopausal women enrolled in WHI. In the Studies Of Left Ventricular Dysfunction (SOLVD) trials, women with HF had an increasing rate of thromboembolic events with decreasing ejection fraction that was not seen in the men (42). Most of the subjects in SOLVD had underlying coronary disease, and it is not known if the excess in thromboembolic events in the women in SOLVD was related to etiology of CHF. Our results could be explained if there were an excess risk of thromboembolic events in women with an ischemic etiology of disease compared with those with a nonischemic etiology. Although the test for interaction between the effect of HRT and etiology of disease was not statistically significant ($p = 0.09$), the number of women in these subgroups was small, and, accordingly, the power to detect an interaction effect was low.

Our results may also reflect a difference in the health status or compliance of HRT users compared with nonusers. It is known that women who take HRT have healthier lifestyles than do non-HRT users and that this may be an explanation of the reported benefits of HRT in retrospective studies (43). Furthermore, compliance bias may have influenced our study (44,45). However, when we attempted to correct for the "healthy subject" bias and for compliance bias as measured by compliance to treatment visits, the benefit of HRT was the same or even larger. Although these adjustments are rudimentary, they do not suggest a "healthy subject" or compliance bias in our study participants.

We have demonstrated a significant benefit of HRT use on survival in postmenopausal women with advanced HF. It will be important to determine if this benefit is confirmed in a prospective, randomized trial of HRT in postmenopausal women with HF because there are more than two million postmenopausal women in the U.S. with HF, and this number will continue to increase as our population ages (46).

Study limitations. This was a retrospective study and menopausal status was not collected prospectively. Hormone replacement therapy use was only documented at randomization and not during follow-up. This study could not completely address the possibility that either prevention bias or compliance bias or other factors not controlled for could have influenced these results, as has been suggested in studies of HRT and CAD (43–45). Although there was no statistically significant interaction between the effect of HRT and etiology of disease, there was low power to detect an interaction effect because of the small number of women in these subgroups.

Conclusions. We have demonstrated an association of HRT with improved survival in postmenopausal women with advanced HF and systolic dysfunction over a follow-up of two years. The 40% reduction in mortality is nearly identical to the 38% reduction noted in a previous study. Our finding that this benefit is noted in women with a nonischemic etiology of HF requires confirmation. With more than two million postmenopausal women with HF in the U.S., a prospective, randomized trial evaluating the benefits of HRT in this population, particularly those with a nonischemic etiology of HF, would be important.

Reprint requests and correspondence: Dr. JoAnn Lindenfeld, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, B-130, Denver, Colorado 80262. E-mail: JoAnn.Lindenfeld@UCHSC.edu.

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