Clinical Investigations

The Effect of Gender on Outcome in Digitalis-Treated Heart Failure Patients

M. DOMANSKI, MD,[1] J. FLEG,[1] M. BRISTOW,[2] AND S. KNOX[3]

Bethesda, Maryland; Denver, Colorado

ABSTRACT

Background: The use of digitalis is recommended for the treatment of heart failure to reduce hospitalization. Recent data suggest that digitalis treatment may adversely affect survival in women but not in men. We studied patients with left ventricular dysfunction enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) to determine whether there was a gender-based survival difference in patients treated with digitalis.

Methods and Results: Symptomatic (n = 2569) and asymptomatic (n = 4228) patients with left ventricular ejection fraction ≤0.35 were studied. Digitalis use was assessed at baseline and baseline demographic variables were catalogued and compared. A multivariate analysis, incorporating known covariates of risk for adverse cardiovascular events, was used to examine the association of digitalis with all-cause mortality, cardiovascular death, death from heart failure, and arrhythmic death, with, or without, worsening heart failure in women compared with men. Analysis for an interaction between digitalis and gender on mortality was also performed. No interaction between gender and digitalis treatment on survival was found, and there was no significant difference in the hazard ratios for men and women on digitalis either with respect to all-cause mortality, cardiovascular mortality, heart failure mortality, or arrhythmic death with worsening heart failure. When mortality for arrhythmic death without worsening heart failure was adjusted for the probability of being treated with digitalis (propensity analysis), women fared better than men.

Conclusion: Data from the SOLVD trials suggest that digitalis treatment of heart failure does not result in a difference in survival between men and women. Because a randomized trial to definitively answer the question is unlikely, and perhaps inappropriate, examination of other heart failure populations for a gender-digitalis interaction is indicated.

Key Words: Heart failure, left ventricular dysfunction, digitalis.

The Digitalis Investigation Group (DIG) performed a large randomized, double-blinded, placebo-controlled trial to assess the impact of digitalis therapy on survival in patients with heart failure and sinus rhythm.[1] They found no difference between digoxin- and placebo-treated groups with respect to overall mortality, cardiovascular death, or death from worsening heart failure. However, both hospitalization for any cause and hospitalization for worsening heart failure were reduced in patients treated with digoxin. These investigators did not prespecify subgroups based on gender and did not report results by gender.

Rathore et al performed a post-hoc analysis of the 6800 patients in the DIG study to assess whether there was sex-based difference in the primary endpoint of death from any cause.[2] They used the Mantel-Haenszel tests of heterogeneity and a multivariable Cox proportional hazards model adjusted for demographic and clinical covariates. These investigators found that women randomly assigned to digitalis had a higher rate of death than those assigned to placebo. The overall mortality in men, on the other hand, was similar in patients treated with, or without, digitalis. The finding of a difference in mortality between men and women with heart failure treated with digoxin has significant clinical implications. Current guidelines incorporate digitalis as an important treatment modality in heart failure patients[3–5] and

From the [1]Clinical Trials Group, National Heart, Lung, and Blood Institute, Bethesda, MD; [2]Division of Cardiology, University of Colorado School of Medicine, Denver, Colorado; and the [3]Division of Epidemiology Statistics and Prevention Research, National Institute of Child Health and Human Development, Bethesda, Maryland.

Manuscript received April 23, 2004; revised manuscript received June 20, 2004; revised manuscript accepted July 6, 2004.

Reprint requests: Michael Domanski, MD, Clinical Trials Group, National Heart, Lung, and Blood Institute, Bethesda, MD 20892.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2004.07.002

would have to be altered if this gender difference was confirmed.

Sex-based differences in the outcome of patients with heart failure have been reported[6–8] but may have been related to a gender-based difference in the clinical profile of the patients. The report by Rathore et al uses appropriate statistical methodology and the sample size is large. However, a single post-hoc database analysis is a less than ideal basis for far-reaching conclusions; thus, further investigation of the finding seems indicated. The most definitive support or refutation would come from a randomized trial. However, no such study is, or is likely to become, available. Nearly as convincing would be similar findings in other databases of heart failure patients.

The Studies of Left Ventricular Dysfunction (SOLVD)[9,10] were designed to evaluate the effect of the angiotensin-converting enzyme inhibitor enalapril on survival in symptomatic and asymptomatic patients with left ventricular dysfunction. We investigated the 6797 patients entered into the SOLVD Treatment and Prevention trials to determine whether there was evidence of an interaction between gender and digoxin therapy on survival.

Methods

Patients

Patients entered into the SOLVD Treatment and Prevention Trials were examined. These trials have been reported elsewhere.[9,10] Briefly, the SOLVD consisted of a pair of concurrent, double-blinded, randomized, controlled trials in which patients ages 21 to 80 years with left ventricular ejection fraction ≤0.35 were randomly assigned to treatment with enalapril or placebo. Symptomatic patients (n = 2569) were followed for a mean of 41.4 months, and asymptomatic patients (n = 4228) were followed for a mean of 37.6 months.

Digitalis Use

Digitalis use (100% digoxin) was determined at the time of enrollment in the study. Information on the use of digitalis was available for all patients in the Treatment Trial (symptomatic patients) and all but 1 patient in the Prevention Trial (asymptomatic patients).

Endpoints

The primary endpoint of the study was all-cause mortality. The cause of death was assessed in a masked fashion by the SOLVD investigators. The cause of death was classified as the result of worsening heart failure with or without an arrhythmia, an arrhythmia in the absence of worsening heart failure, myocardial infarction, a cardiovascular cause different from the foregoing, or to a noncardiovascular cause.

Statistical Methods

Baseline characteristics of men and women taking digitalis were compared using chi-squared (for categorical variables) and *t*-tests. Hazard ratios for all-cause mortality and various cardiac-specific mortality endpoints in patients on digitalis versus those not on the drug were calculated separately for men and women. Regression analyses of survival, based on a Cox proportional hazards model, were calculated separately for different types of events, using the SAS PHREG procedure.[11] The proportional hazards analyses were adjusted for age, race, left ventricular ejection fraction, New York Heart Association functional class, serum creatinine, systolic blood pressure, history of diabetes, diuretic use, angiotensin-converting enzyme inhibitor use, and a history of coronary artery disease, defined as a history of angina, myocardial infarction, or coronary intervention (percutaneous intervention or coronary bypass), by adding these variables as covariates in the equations. Analyses of these same events and covariates were also calculated for the entire cohort adding a "gender × digitalis" interaction term.

Because the patients in this trial were not randomized to digitalis, propensity analyses were also performed to adjust for the probability of being treated with digitalis. These analyses are reported separately.

Results

Patients

As a group, men were slightly younger, and had a lower heart rate, higher creatinine, and lower systolic blood pressure than women (Table 1). Among men, there was a higher proportion of whites, and men more frequently had a history of prior myocardial infarction or revascularization (percutaneous intervention or coronary bypass). However, diabetes and use of diuretics were more common in women. More men were in New York Heart Association functional Class 1 and fewer were in Class 3 compared with women.

Cardiovascular Outcomes

For the cohort as a whole, there was no statistically significant interaction of digitalis and gender. Further, there

Table 1. Characteristics of Patients on Digitalis

Characteristic	Men (n = 1874)	Women (n = 370)	*P* Value
Mean age (y)	60.4	61.8	.02
Mean left ventricular ejection fraction	25.0	25.4	.25
Race (% white)	85.5	72.7	.0001
New York Heart Association functional class (%)			
1	24.2	14.3	
2	51.8	52.4	
3	22.5	31.6	
4	1.2	1.6	
Serum creatinine	1.24	1.07	.0001
Heart rate (beats/min)	78.5	81.4	.0002
Systolic blood pressure (mm Hg)	124.9	127.0	.06
Diabetes (%)	22.4	29.7	.0025
Diuretic use (%)	71.2	81.9	.0001
Randomized to angiotensin-converting enzyme (%)	48.7	47.6	.70
Congestive heart disease history (%)*	76.3	66.8	.0001

*History of angina, myocardial infarction, or coronary artery bypass graft/percutaneous transluminal coronary angioplasty.