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Predictors of Mortality and Hospitalization in Women with Heart Failure in the Digitalis Investigation Groups Trial

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Abstract

Background—Heart failure (HF) differs in many ways between women and men.

Aim—To determine predictors of outcomes in women with HF.

Methods—We performed a retrospective follow up study of women with HF who participated in the Digitalis Investigation Group (DIG) trial. Using multivariable Cox proportion hazard models we identified independent predictors for all-cause mortality, hospitalization due to worsening HF, and all-cause hospitalization.

Results—In the DIG trial, 24.7% participants (1926/7788) were women whose mean ($\pm$ SD) age was 65.5 ($\pm$ 11.9) years, 18.4% (354/1926) were nonwhite, and 21.1% (407/1926) had a left ventricular ejection fraction (LVEF) $>45\%$. Adjusted hazard ratios and 95% confidence intervals for covariates that were significant independent predictors of all-cause mortality were: age in years (1.02; 1.01 – 1.03; $p<0.001$), NYHA class III-IV (1.56; 1.31 – 1.87), diabetes (1.63; 1.36 – 1.95), glomerular filtration rate in ml/min/1.73 meter² (0.99; 0.98 – 0.996; $p=0.001$), pulmonary congestion by chest x-ray (1.57; 1.22 – 2.02), LVEF (0.99; 0.98 – 0.993; $p<0.001$) and use of digoxin (1.20; 1.02 – 1.42). Covariates that were significant independent predictors of hospitalization due to worsening heart failure were: non-white race (1.28; 1.03 – 1.58), NYHA class III-IV (1.55; 1.30 – 1.84), diabetes (1.75; 1.47 – 2.09), glomerular filtration rate as ml/min/1.73 meter² (0.99; 0.986 – 0.996; $p<0.001$), pulmonary congestion by chest x-ray (1.42; 1.12 – 1.81), and use of ACE inhibitors (0.67; 0.49 – 0.91).

Conclusion—Longer duration of HF, higher NYHA classes, diabetes, chronic kidney disease, pulmonary congestion and lower LVEF were significant independent predictors of all-cause mortality, all-cause hospitalization, and hospitalization for heart failure in women with HF.

Keywords

digoxin; heart failure; outcomes; women

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1. Introduction

Heart failure differs in many ways between genders. Women with heart failure are generally older than men, more likely to have preserved left ventricular systolic function [1-5] and have lower mortality [6-9]. Compared with men, women with diabetes and hypertension, and after myocardial infarction are at higher risk of developing heart failure [10,11]. The age-adjusted rates for hospitalizations due to heart failure has increased significantly in the past decade for women, but not for men [12]. The risk of hospitalization and re-hospitalization for women with heart failure have been described as higher than or similar to those in men [7,13]. Use of digoxin has been shown to be associated with a significant increased risk of death in women with heart failure and a left ventricular ejection fraction of 45% or less [14]. The objective of this study was to determine predictors of all-cause mortality, hospitalization due to worsening heart failure and all-cause hospitalization in ambulatory women with chronic heart failure across a broad range of ejection fraction.

2. Methods

2.1. Subjects

The subjects of this study are 1,926 women who participated in the DIG trial. The trial involved 6,800 patients with systolic heart failure (ejection fraction $\leq 45\%$) and 988 with diastolic heart failure (ejection fraction $> 45\%$).

2.2. Data Source

The public use version of the DIG dataset was obtained from the National Heart, Lung and Blood Institute after an expedited review was approved by the Institutional Review Board of the University of Alabama at Birmingham. All patients provided signed informed consent forms during the main trial, and the original protocol was approved by the Institutional Review Boards of all the participating centers.

2.3. Study Design

This is a retrospective follow up study of women who participated in the DIG trial. The details of the design of the DIG trial have been reported [15,16]. The DIG trial was a prospective, randomized, double-blind placebo-controlled clinical trial that enrolled 7,788 ambulatory patients with chronic systolic heart failure patients at 302 clinical centers in the United States and Canada. Patients were randomized to receive digoxin or placebo. Most patients were receiving angiotensin-converting enzyme (ACE) inhibitors and diuretics. Data on beta blockers and aldosterone antagonists were not collected.

2.4. Study Outcomes

Outcomes of interest for the present analysis included all-cause mortality, hospitalization due to worsening heart failure, and all-cause hospitalization over the mean follow-up of 37 months (range 28 to 58 months).

2.5. Statistical Analysis

We compared baseline characteristics among patients randomized to digoxin versus placebo and tested statistical significance using Pearson Chi-square tests and Student's t tests as appropriate. Because the balance in baseline covariates achieved during randomization in the original trial might have been disrupted in the subgroup of our current study, we estimated propensity scores for the receipt of ACE inhibitors, and matched patients based on propensity scores. There was no difference in baseline covariates between the groups before or after propensity score matching. Therefore, all subsequent analyses were based on all women, and

on those matched by propensity scores. Next, we used multivariable Cox proportional hazard regression analyses to estimate risk of all-cause mortality, all-cause hospitalization and heart failure related hospitalization. Covariates used in the multivariable Cox regression model included age, sex, race, duration heart failure in months, etiology of heart failure i.e. ischemic, hypertensive, idiopathic, and others, comorbidities i.e. myocardial infarction, current angina, hypertension, and diabetes, medications i.e. ACE inhibitors, and non-potassium sparing diuretic, New York Heart Association (NYHA) functional class, jugular venous distension, third heart sound, pulmonary râles, and lower extremity edema, and pulmonary congestion by chest x-ray, glomerular filtration rate in ml/min/1.73 meter² as determined by the Dietary Modification in Renal Disease formula,[17] serum potassium level, and left ventricular ejection fraction. We also conducted subgroup analyses to determine the effects of digoxin on all-cause mortality. All statistical tests were done using an intention to treat approach with two-tailed 95% confidence intervals (CI), and a $p < 0.05$ was required to reject the null hypothesis. Analyses were performed using SPSS for Windows (Release 12.02) [18].

3. Results

3.1 Patient characteristics

Patients (N=1,926) had a mean ($\pm$ SD) age of 65.5 ($\pm$ 11.9) years, 18.4% were non-white and 21.1% had an ejection fraction greater than 45%. Nine hundred sixty two (49.9%) were receiving digoxin while 964 (50.1%) were receiving placebo. Five hundred sixty nine (29.5%) patients died from all causes, 1,260 (65.4%) were hospitalized from all causes, and 599 (31.1%) were hospitalized due to worsening heart failure. Table 1 demonstrates that there was reasonable balance in patient characteristics between the digoxin and placebo groups at randomization. However, women receiving digoxin were more likely to have symptoms and signs of heart failure. In the propensity score matched cohort, there were no significant differences in baseline covariates between the two treatment groups.

3.2 Predictors of all-cause mortality

Independent predictors for all-cause mortality in these ambulatory women with heart failure (Table 2) included age (adjusted hazard ratio, 1.02; 95% CI 1.01 – 1.03; $p < 0.001$), duration of heart failure (adjusted hazard ratio, 1.003; 95% CI 1.001 – 1.005; $p = 0.017$), NYHA functional class III-IV (adjusted hazard ratio, 1.56; 95% CI 1.31 – 1.87; $p < 0.001$), presence of diabetes (adjusted hazard ratio, 1.63; 95% CI 1.36 – 1.95; $p < 0.001$), diastolic blood pressure (adjusted hazard ratio, 0.990; 95% CI 0.981 – 0.999; $p = 0.029$), glomerular filtration rate (adjusted hazard ratio, 0.986; 95% CI 0.979 – 0.996; $p = 0.0001$), pulmonary congestion by chest x-ray (adjusted hazard ratio, 1.57; 95% CI 1.22 – 2.02; $p < 0.001$), left ventricular ejection fraction (adjusted hazard ratio, 0.986; 95% CI 0.979 – 0.993; $p < 0.001$), and digoxin use (adjusted hazard ratio, 1.20; 95% CI 1.02 – 1.42; $p = 0.032$).

3.3 Predictors of hospitalization due to worsening heart failure

Independent predictors for hospitalization due to worsening heart failure (Table 3) included non-white race (adjusted hazard ratio, 1.28; 95% CI 1.03 – 1.58; $p = 0.024$), duration of heart failure (adjusted hazard ratio, 1.003; 95% CI 1.001 – 1.005; $p = 0.028$), NYHA class III-IV (adjusted hazard ratio, 1.55; 95% CI 1.30 – 1.84; $p < 0.001$), diabetes (adjusted hazard ratio, 1.75; 95% CI 1.47 – 2.09; $p < 0.001$), glomerular filtration rate (adjusted hazard ratio, 0.991; 95% CI 0.986 – 0.996; $p = 0.0001$), pulmonary congestion by chest x-ray (adjusted hazard ratio, 1.42; 95% CI 1.12 – 1.81; $p = 0.004$), left ventricular ejection fraction (adjusted hazard ratio, 0.986; 95% CI 0.979 – 0.992; $p < 0.001$), and use of ACE inhibitors (adjusted hazard ratio, 0.67; 95% CI 0.49 – 0.91; $p = 0.011$).

3.4 Predictors of all-cause hospitalization

Table 4 displays the independent predictors for all-cause hospitalization. In addition to duration of heart failure, NYHA class, use of ACE inhibitors, diabetes, diastolic blood pressure, and pulmonary congestion, angina at the time of randomization was associated with higher risk of all-cause hospitalization (adjusted hazard ratio, 1.25; 95% CI 1.10 – 1.42; $p = 0.001$). Age, renal function, and left ventricular systolic function were not independent predictors of all-cause hospitalization.

4. Discussion

This analysis from the DIG trial, based on a large cohort of ambulatory women with chronic heart failure from multiple centers in the US and in Canada, identified several important predictors of mortality and hospitalization. Older age, longer duration of heart failure, higher NYHA class, diabetes, lower kidney function and ejection fraction, pulmonary congestion by X-ray and digoxin use were associated with greater all-cause mortality. Most of these same variables except age and digoxin use were also predictive of all-cause and heart failure hospitalizations, ACE inhibitors were protective against these latter outcomes.

4.1 Heart failure in women

There is increasing evidence that the risk factors, pathogenesis, prognosis, and response to treatment may be different in women than in men with heart failure. Even though the incidence and prevalence of heart failure are somewhat lower in women than in men [19-21], the proportion of women with heart failure increases with age, and many of these women have preserved left ventricular systolic function [19]. The proportion of women among hospitalized heart failure patients is also high [7]. However, heart failure patients who are elderly and women are often not enrolled in clinical trials [22]. In addition, women with heart failure might respond differently than men [23]. Women are more likely to experience adverse effects from the use of ACE inhibitors, such as cough, taste disturbance, skin rash, gastrointestinal upset and a greater rise in creatinine [24,25]. Among patients with myocardial infarction and left ventricular systolic dysfunction, female patients were less likely to experience survival benefits from the use of an ACE inhibitors [26]. A subgroup analysis of data from the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) suggests a preferential survival benefit in men but not in women [27] Rathore et al. demonstrated that in women with heart failure and an ejection fraction of 45% or less, use of digoxin was associated with increased all-cause mortality (adjusted hazard ratio, 1.23; 95% confidence interval, 1.02 - 1.47) [14].

4.1 Mortality in women with heart failure

Our analysis confirms that women share many of the independent predictors of all-cause mortality as men, namely, increased age, longer duration of heart failure, higher NYHA classes, presence of diabetes mellitus, lower diastolic blood pressure, higher serum creatinine, presence of pulmonary congestion by chest x-ray, and lower ejection fraction [28,29]. Martinez-Selles reported that ejection fraction was a predictor of mortality in men with heart failure, but not in women [30]. Other investigators have reported that women with heart failure and an abnormal LVEF have a higher mortality than women with a normal LVEF [2,4,5,31,32]. In our study, use of ACE inhibitors was associated with a non-significant 17% reduction in the risk of all-cause death. This is very likely due to the fact that the vast majority of patients in the DIG trial were taking ACE inhibitors, and only about 7% of the participants were not receiving ACE inhibitors. However, the non-significant effect of ACE inhibitors in women noted in our study is similar to that reported by a meta-analysis of randomized trials of ACE inhibitors [33]. In that study, there were 2,506 deaths in 10,367 men with systolic heart failure, and use of ACE inhibitors was associated with a significant 21% reduction in the odds for death (adjusted odds

ratio, 0.79; 95% CI, 0.72–0.87). However, in 2,396 women, there were 671 deaths, and use of ACE inhibitors was associated with a non-significant 15% reduction in death (adjusted odd ratio, 0.85, 95% CI, 0.71–1.02) [33]. This underlies the importance of including more women in future clinical trials involving heart failure.

4.2 Hospitalization in women with heart failure

To our knowledge, no other study has documented independent predictors of hospitalization in women with prevalent heart failure. We found significant predictors of increased risk for hospitalization due to worsening heart failure in this cohort of ambulatory women were (age is $p>0.05$), longer duration of heart failure, higher NYHA classes, absence of myocardial infarction, presence of diabetes, higher heart rate, lower diastolic blood pressure, glomerular filtration rate, and left ventricular ejection fraction and presence of pulmonary congestion by X-ray. These same factors plus the presence of angina pectoris were also predictors of hospitalization due to all causes.

4.3 Diabetes, chronic kidney disease, and heart failure outcomes

Diabetes appears to be an important factor that not only increases the risk of death, but also of hospitalization, among ambulatory women with chronic heart failure. Several prior studies have reported an adverse effect of diabetes on survival in heart failure. Aronow et al. demonstrated the adverse effect of diabetes in heart failure patients with prior myocardial infarction [31,32]. The deleterious effects of diabetes on outcomes in heart failure patients have been reported to be particular worse among those with ischemic cardiomyopathy [34,35]. Among hospitalized heart failure patients, the effect of diabetes on mortality has been reported to be worse among women [36]. The strong association of diabetes with mortality and hospitalization found in the present analysis highlights the need for aggressive management of women with heart failure and diabetes.

Rising serum creatinine has been cited as a reason for underutilization of ACE inhibitors in heart failure patients [37]. The risk of increasing serum creatinine is higher for heart failure patients with diabetes [38]. However, the survival benefit of ACE inhibitors in heart failure patients and advanced kidney disease has been reported.[39] All women with heart failure and diabetes should be treated with ACE inhibitor [40].

4.3 Strengths and weaknesses

To our knowledge, this is the first analysis to examine predictors of outcomes in ambulatory women with chronic heart failure. Women in this study were recruited from over 300 centers in the US and Canada. Thus the results of this study are generalizable to a sizeable proportion of women with heart failure. Whereas nearly all large clinical trials in heart failure have included only individuals with reduced ejection fraction, almost half of the women with heart failure have preserved systolic function. Our study included women with heart failure across the spectrum of ejection fractions. Limitations of this study include lack of data on use of beta blockers, and all women were in sinus rhythm due to selection criteria for the DIG trial. Atrial fibrillation is common in heart failure and associated with poor outcomes [31,41]. The benefits of beta blockers are now well established [42,43].

4.4 Conclusions

In conclusion, we demonstrated that diabetes, NYHA class III-IV, pulmonary congestion by X-ray, decreasing glomerular filtration rate and reduced ejection fraction were predictors of increased all-cause mortality and heart failure related hospitalization among ambulatory women with chronic heart failure. Women with heart failure and diabetes have one of the

highest risks for both outcomes, and special attention should be paid to the care these patients. Use of ACE inhibitors should be maximized in these patients.

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Table 1
Baseline characteristics in ambulatory women with heart failure

	Placebo (n=964)	Digoxin (n=962)	P value
Age (years)	65.5±11.6.	65.5±12.2	0.970
Nonwhite	179 (18.6%)	175(18.2%)	0.831
Duration of heart failure (months)	26.5±30.6	26.4±26.4	0.956
Heart failure due to ischemic heart disease	558 (57.9%)	577 (60.0%)	0.350
Prior myocardial infarction	483 (50.1%)	498 (51.8%)	0.465
Current angina pectoris	284 (29.5%)	269 (28.0%)	0.467
Diabetes mellitus	335 (34.8%)	315 (32.8%)	0.352
Systemic hypertension	535 (55.5%)	555 (57.7%)	0.331
Angiotensin-converting enzyme inhibitors	894 (92.7%)	895 (93.0%)	0.800
Prior digoxin use	414 (43.0%)	421 (43.8%)	0.732
Diuretics	807 (83.7%)	812 (84.4%)	0.677
Potassium sparing diuretics	77 (8.0%)	85 (8.8%)	0.502
Dyspnea at rest	709 (73.5%)	744 (77.3%)	0.053
Elevated jugular venous pressure	491 (50.9%)	537 (55.8%)	0.032
Pulmonary râles	710 (73.7%)	748 (77.8%)	0.036
Lower extremity edema	176 (23%)	97 (45%)	<0.001
Blood pressure, systolic (mm Hg)	130±22	131±22	0.570
Blood pressure, diastolic (mm Hg)	75±15	75±12	0.666
Pulmonary congestion on chest x-ray	681 (70.6%)	720 (74.8%)	0.038
Glomerular filtration rate (ml/min/1.73 meter ²)	58.48 ±30.91	58.63±21.00	0.903
Serum potassium (mEq/l)	4.30±0.40	4.30±0.44	0.400
Left ventricular ejection fraction (%)	35.8±14	35.0±14	0.823

Table 2

Predictors for all-cause mortality in ambulatory women with heart failure

	Hazard Ratio[*]	95% Confidence Intervals	P Value
Age (years)	1.02	1.01 - 1.03	<0.001
Race (nonwhite)	1.12	0.88 - 1.41	0.364
Duration of heart failure (months)	1.003	1.001 – 1.005	0.017
New York Heart Association (class III-IV)	1.56	1.31 – 1.87	<0.001
Diabetes mellitus	1.63	1.36 – 1.95	<0.001
Use of ACE inhibitors	0.76	0.56 – 1.05	0.093
Use of digoxin	1.20	1.02 – 1.42	0.032
Diastolic blood pressure (mm mercury)	0.990	0.981 – 0.999	0.029
Glomerular filtration rate (ml/min/1.73 meter ²)	0.991	0.981 – 0.996	0.001
Pulmonary congestion (by chest x-ray)	1.57	1.22 – 2.02	<0.001
Left ventricular ejection fraction (%)	0.986	0.979 – 0.993	<0.001

^{*} Other covariates in the multivariable Cox regression model included etiology of heart failure, past myocardial infarction, current angina, hypertension, diuretic use, heart rate, systolic blood pressure, jugular venous distension, third heart sound, and lower extremity edema, and serum potassium level.

Table 3

Predictors of hospitalization due to worsening heart failure in ambulatory women with heart failure

	Hazard Ratio[*]	95% Confidence Intervals	P Value
Age (years)	1.01	1.00 - 1.02	0.079
Race (nonwhite)	1.28	1.03 - 1.58	0.024
Duration of heart failure (months)	1.003	1.000 - 1.005	0.028
New York Heart Association (class III-IV)	1.55	1.30 - 1.84	<0.001
Use of ACE inhibitors	0.67	0.49 - 0.91	0.011
Use of digoxin	0.87	0.74 - 1.02	0.083
Myocardial infarction	0.79	0.64 - 0.98	0.028
Diabetes mellitus	1.75	1.47 - 2.09	<0.001
Heart rate (beats per minute)	1.008	1.0010 - 1.014	0.024
Diastolic blood pressure (mm mercury)	0.989	0.981 - 0.998	0.018
Glomerular filtration rate (ml/min/1.73 meter ²)	0.991	0.986 - 996	<0.001
Pulmonary congestion (by chest x-ray)	1.42	1.12 - 1.81	0.004
Left ventricular ejection fraction (%)	0.986	0.979 - 0.992	<0.001

^{*} Other covariates in the multivariable Cox regression model included etiology of heart failure, past current angina, hypertension, diuretic use, systolic blood pressure, jugular venous distension, third heart sound, and lower extremity edema, and serum potassium level.

Table 4

Predictors of all-cause hospitalization in ambulatory women with heart failure

	Hazard Ratio[*]	95% Confidence Intervals	P Value
Age (years)	1.00	0.99 - 1.01	0.840
Race (nonwhite)	1.11	0.95 - 1.29	0.190
Duration of heart failure (months)	1.003	1.001 – 1.004	0.002
New York Heart Association (class III-IV)	1.36	1.20 - 1.53	<0.001
Use of ACE inhibitors	0.77	0.62 - 0.95	0.015
Use of digoxin	1.00	0.89 - 1.11	0.957
Angina	1.25	1.10 - 1.42	0.001
Diabetes mellitus	1.44	1.27 - 2.63	<0.001
Diastolic blood pressure (mm mercury)	0.992	0.986 - 0.998	0.008
Glomerular filtration rate (ml/min/1.73 meter ²)	0.997	0.994 – 1.000	0.094
Pulmonary congestion (by chest x-ray)	1.24	1.06 - 1.44	0.006
Left ventricular ejection fraction (%)	0.999	0.994 - 1.003	0.547

^{*} Other covariates in the multivariable Cox regression model included etiology of heart failure, past myocardial infarction, hypertension, diuretic use, heart rate, systolic blood pressure, jugular venous distension, third heart sound, and lower extremity edema, and serum potassium level.