Predictors of Heart Failure Among Women With Coronary Disease

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Background—Although heart failure is common among women with coronary disease, the risk factors for developing heart failure have not been well studied. We determined the risk factors for developing heart failure among postmenopausal women with established coronary disease.

Methods and Results—This is a prospective cohort study using data from the Heart and Estrogen/progestin Replacement Study (HERS), a randomized, blinded, placebo-controlled trial of 4.1 years’ duration, and subsequent open-label observational follow-up for 2.7 years (HERS II), performed at 20 US clinical centers between 1993 and 2000. Of the 2763 postmenopausal women with established coronary disease in the HERS trial, we studied the 2391 women with no heart failure at baseline by self-report and physical examination. The primary outcome of this analysis was incident heart failure defined by hospital admission or death from heart failure. During the 6.3±1.4-year follow-up, 237 women (10%) developed heart failure. Nine predictors were identified: diabetes (defined as a self-reported history of diabetes on treatment), atrial fibrillation, myocardial infarction, creatinine clearance <40 mL/min, systolic blood pressure >120 mm Hg, current smoking, body mass index >35 kg/m², left bundle-branch block, and left ventricular hypertrophy. Randomization to estrogen/progestin was not associated with heart failure (hazard ratio = 1.0; 95% CI, 0.7 to 1.3). Diabetes was the strongest risk factor (adjusted hazard ratio = 3.1; 95% CI, 2.3 to 4.2). Diabetic women with elevated body mass index or depressed creatinine clearance were at highest risk, with annual incidence rates of 7% and 13%, respectively. Among diabetic women, hyperglycemia was associated with heart failure risk (adjusted hazard ratio = 3.0; 95% CI, 1.2 to 7.5 for fasting glucose >300 mg/dL compared with fasting glucose 80 to 150 mg/dL).

Conclusions—We identified 9 predictors of heart failure in postmenopausal women with coronary disease. Diabetes was the strongest risk factor, particularly when poorly controlled or with concomitant renal insufficiency or obesity. (Circulation. 2004;110:1424-1430.)

Key Words: coronary disease • diabetes mellitus • heart failure • prevention • women

Heart failure is a devastating disease, characterized by frequent hospitalizations, poor quality of life, and annual mortality rates as high as 20% to 30%. Despite declines in the incidence of other cardiovascular disease, incidence rates of heart failure have remained unchanged, with more than 500 000 new cases of heart failure diagnosed annually. Lifetime risk for developing heart failure is 1 in 5 among both men and women.

Because of the enormous impact of this disease, current recommendations emphasize the importance of prevention. Effective preventive interventions require a thorough understanding of the risk factors for developing heart failure. Unfortunately, little is known about these risk factors in women, perhaps because of the underrepresentation of women in cardiovascular clinical trials. Although coronary disease appears to be the most common cause in both men and women with heart failure, the prognostic factors that determine the progression of coronary disease to heart failure among women with coronary disease have not been well established and may be different from the risk factors among men.

We evaluated the risk factors for developing heart failure in a cohort of postmenopausal women with established coronary disease in the Heart and Estrogen/progestin Replacement Study (HERS). Our objective was to determine independent risk factors for heart failure in women, with the additional goal of identifying targets for preventive interventions.

Methods

HERS methods have been described. Briefly, participants were postmenopausal women with known coronary disease defined by
previous myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or angiographic evidence of ≥50% narrowing of 1 or more major coronary arteries. Women were excluded if they were >79 years of age, had a previous hysterectomy, had a coronary event within the 6 months before randomization, had a serum triglyceride level >3.39 mmol/L (300 mg/dL), had used hormones within 3 months, or had a history of conditions that would contraindicate estrogen therapy.14 Participants in HERS were randomly assigned within clinical centers to 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). The institutional review boards at the coordinating center and each of the 20 HERS clinical centers approved the protocol, and all participants provided written informed consent.

The HERS randomized controlled trial was conducted over a period of 4.1 years. After the conclusion of the trial, women were unblinded to treatment assignment and were observed for an additional 2.7 years on average (HERS II).15 Suspected outcome events either were reported by participants to the clinical center staff or were identified via participant interviews that were conducted every 4 months. Records of all hospitalizations were reviewed, and an independent morbidity and mortality subcommittee blinded to treatment assignment adjudicated all suspected outcome events, including hospitalizations for heart failure.

At the baseline interview, participants provided a self-report of their medical history. On baseline physical examination, a physician assessed signs (jugular venous distension, third heart sound, significant murmurs, pulmonary edema, and peripheral edema) and symptoms (NYHA classification) of heart failure. All participants received an NYHA classification. Those with no history of heart failure and no signs or symptoms of heart failure were classified as NYHA class 0.

Of the 2763 participants in HERS, we excluded 345 women who reported a previous history of heart failure and 133 women with evidence of heart failure signs or symptoms on baseline physical examination (NYHA class 1 to 4). We also excluded 24 women with less than normal body weight (body mass index <18.5 kg/m²), leaving 2391 women for this analysis.

Predictors
Demographic characteristics, behavioral risk factors, medical history, and medication use were determined by participant self-report. Diabetes was considered present if the participant reported that a physician told her that she had diabetes and she was using an oral hypoglycemic agent or insulin. We also investigated the risk associated with baseline hyperglycemia without a diagnosis of diabetes. Body mass index and systolic blood pressure were determined on baseline physical examination. Fasting serum specimens were collected at baseline, and a central laboratory measured glucose, total cholesterol, HDL, lipoprotein(a), triglycerides, and creatinine.13,14 Fasting glucose also was collected at the first, third, and final annual visits and included in this analysis as a time-dependent predictor. LDL was calculated by the Friedewald equation.16 Creatinine clearance was estimated by using the Cockcroft-Gault equation.17 Atrial fibrillation, left bundle-branch block, and left ventricular hypertrophy were diagnosed on the basis of ECG at the baseline visit; all ECGs were reviewed centrally by Epicare at Wake Forest University School of Medicine.

Previous myocardial infarction was determined by interview and medical record review. New nonfatal myocardial infarctions were diagnosed by use of an algorithm based on ischemic symptoms, ECG abnormalities, and elevated cardiac enzyme levels.14 Incident nonfatal myocardial infarctions during the observation period were treated as time-dependent predictors for the development of heart failure.

Outcome
Incident heart failure was the primary outcome for this analysis and was defined as hospitalization or death from heart failure. Both hospitalization for heart failure and death from heart failure were prespecified outcomes of the HERS trial. All HERS outcomes were independently adjudicated by 2 physicians who were not principal investigators of the study; disagreements were resolved by consensus. A hospitalization was attributed to heart failure if there was evidence of physical signs of heart failure (jugular venous distension, third heart sound, significant murmurs, pulmonary edema, and peripheral edema) and treatment during the hospitalization with intravenous diuretics.

The overall mean follow-up time from HERS and HERS II was 6.8 years. Among the 2391 women included in this analysis, average follow-up to incident heart failure, loss to follow-up, death, or the end of the study was 6.3 ± 1.4 years.

Statistical Analysis
We used a multivariable Cox proportional-hazards model to identify risk factors associated with incident heart failure.18 Candidate predictors were excluded from the final model by use of a backward selection procedure if the probability value was ≥0.1. We also compared this model with results from models using less stringent retention criteria of P ≥ 0.15 and P ≥ 0.2. The results of final models including and excluding medications reported at baseline were compared. An unadjusted, intention-to-treat Cox model was used to assess the effects of assignment to hormone therapy on risk of incident heart failure during HERS. We also used a Cox model to examine the trend in risk of heart failure with the observed number of independent risk factors. Cox models were estimated with SAS Version 8.2.

Using the formulas provided by Therneau and Grambsch,19 we had 80% power in 2-sided tests with an α level of 5% to detect hazard ratios (HRs) for 1.85, 1.58, and 1.44 for binary risk factors of 10%, 20%, and 40% prevalence, respectively. Our implementation uses the correction suggested by Hsieh and Lavori20 to adjust for the potential loss of precision because of adjustment for the effects of correlated predictors. These are fairly small effects.

To identify combinations of baseline risk factors that might best predict incident heart failure, we used regression trees fit to the Martingale residuals from an unadjusted Cox model.21,22 Continuous variables that had been categorized for the multivariable Cox model were entered as continuous values for this analysis, allowing the regression tree to “choose” the optimal cut point for dichotomizing the population. Cross-validation was used to remove “splits” from the final tree that did not substantially improve prediction of heart failure incidence. This analysis was performed in Splus Version 6.1 (Mathsoft Inc), using recursive partitioning functions developed by Therneau and Atkinson and available online at http://www.mayo.edu/hsr/Sfunc.html.

Results
Over a mean follow-up time of 6.3 ± 1.4 years, 237 of the 2391 women were hospitalized or died of heart failure. Those who developed heart failure were older, more likely to be African American, diabetic, obese, and to have elevated systolic blood pressure and lower creatinine clearance (Table 1). Women who developed heart failure were also more likely to have atrial fibrillation, left bundle-branch block, and left ventricular hypertrophy on baseline ECG.

After adjusting for age and medication use, we identified 9 factors that were independently associated with the development of heart failure (Table 2). Among these, diabetes had the largest HR, followed by atrial fibrillation, >1 myocardial infarction, creatinine clearance <40 mL/min, and systolic blood pressure >140 mm Hg. Other risk factors included current smoking, body mass index >35 kg/m², left bundle-branch block, and left ventricular hypertrophy. Changing the threshold for retention in the model did not alter the risk factors identified. Excluding aspirin, lipid-lowering medications, and antihypertensive medications from the model also...
TABLE 1. Baseline Characteristics of 2391 Postmenopausal Women With Coronary Heart Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women Who Did Not Develop Heart Failure</th>
<th>Women Who Developed Heart Failure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (mean ± SD)</td>
<td>66.6 ± 6.6</td>
<td>68.3 ± 6.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Race, % white</td>
<td>90</td>
<td>83</td>
<td>0.008</td>
</tr>
<tr>
<td>Risk factors, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120–139 mm Hg</td>
<td>42</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>140–159 mm Hg</td>
<td>27</td>
<td>35</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;159 mm Hg</td>
<td>10</td>
<td>15</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>6</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>9</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–7 drinks/wk</td>
<td>37</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;7 drinks/wk</td>
<td>5</td>
<td>4</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>49</td>
<td>49</td>
<td>0.74</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–30 kg/m²</td>
<td>39</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30–35 kg/m²</td>
<td>20</td>
<td>22</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;35 kg/m²</td>
<td>12</td>
<td>22</td>
<td>0.70</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>40–60 mL/min</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;40 mL/min</td>
<td>9</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>LDL &gt;130 mg/dL</td>
<td>63</td>
<td>65</td>
<td>0.48</td>
</tr>
<tr>
<td>HDL &lt;35 mg/dL</td>
<td>7</td>
<td>11</td>
<td>0.05</td>
</tr>
<tr>
<td>Triglycerides &gt;200 mg/dL</td>
<td>28</td>
<td>31</td>
<td>0.35</td>
</tr>
<tr>
<td>Lp(a) &gt;25.3 mg/dL</td>
<td>49</td>
<td>49</td>
<td>0.94</td>
</tr>
<tr>
<td>Serum sodium &lt;137 mEq/L</td>
<td>4</td>
<td>5</td>
<td>0.70</td>
</tr>
<tr>
<td>Myocardial infarctions at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44</td>
<td>44</td>
<td>0.008</td>
</tr>
<tr>
<td>&gt;1</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>History of CABG</td>
<td>40</td>
<td>49</td>
<td>0.004</td>
</tr>
<tr>
<td>History of PTCA</td>
<td>45</td>
<td>36</td>
<td>0.02</td>
</tr>
<tr>
<td>Medications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>81</td>
<td>74</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>13</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>33</td>
<td>37</td>
<td>0.22</td>
</tr>
<tr>
<td>Digoxin</td>
<td>6</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>22</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>54</td>
<td>60</td>
<td>0.13</td>
</tr>
<tr>
<td>Statin</td>
<td>38</td>
<td>31</td>
<td>0.05</td>
</tr>
</tbody>
</table>

P value for χ² test for dichotomous variables and Student's t test for continuous variables.

Over the 4 years of the HERS trial, randomization to estrogen/progestin use was not associated with the development of heart failure (adjusted HR = 1.0; 95% CI, 0.7 to 1.3; P = 0.75).

We found no evidence that diabetes altered the association of the risk factors in Table 2 with the incidence of heart failure (all probability values for interaction >0.1). We also explored the possibility that the association between diabetes and heart failure was mediated by more severe coronary disease. The increased risk associated with diabetes was unchanged in models in which we included myocardial infarction as a time-dependent covariate (HR = 3.0; 95% CI, 2.2 to 4.0; P < 0.001) or myocardial infarction at baseline only (HR = 3.1; 95% CI, 2.3 to 4.2; P < 0.001) and when myocardial infarction was eliminated from the model (HR = 3.1; 95% CI, 2.3 to 4.2; P < 0.001).

We explored whether baseline hyperglycemia (fasting blood sugar >110 mg/dL) without a diagnosis of diabetes was associated with incident heart failure. A total of 337 women (14%) had hyperglycemia at baseline without meeting HERS criteria for diabetes. In unadjusted analysis, women with hyperglycemia had an increased risk of heart failure (HR = 1.5; 95% CI, 1.0 to 2.2; P = 0.05), as did women with diagnosed diabetes (HR = 4.2; 95% CI, 3.2 to 5.5; P < 0.001) compared with normoglycemic, nondiabetic women. After adjustment for covariates in Table 2, hyperglycemia alone was no longer significantly associated with heart failure (adjusted HR = 1.3; 95% CI, 0.9 to 2.0; P = 0.18), whereas diabetes was associated with a 3-fold risk (adjusted HR = 3.3; 95% CI, 2.4 to 4.5; P < 0.001).

We observed a nearly monotonous association of increasing levels of fasting blood glucose with heart failure risk among diagnosed diabetics (Table 3). Diabetics with fasting blood glucose >300 mg/dL had a 3-fold adjusted risk of developing heart failure, compared with diabetics with controlled fasting blood sugar levels (80 to 150 mg/dL) (P for trend = 0.01).

The risk of developing heart failure increased steadily with the number of risk factors (Figure 1). Among nondiabetic women with no risk factors, the annual incidence rate was 0.4% (95% CI, 0.2% to 0.7%). This rate increased with the presence of each additional risk factor, and nondiabetic women with 5 or more risk factors had an annual incidence of 3.4% (95% CI, 2.3% to 5.1%; P for trend < 0.001). Among diabetic participants with no additional risk factors, the annual incidence of heart failure was 3.0% (95% CI, 1.5% to 6.2%), compared with 8.2% among diabetics with at least 3 additional risk factors (95% CI, 5.2 to 13.0%; P for trend < 0.001).

To explore further the relative influence of the risk factors we identified, we used recursive partitioning and found that diabetes was the most important determinant of heart failure risk (Figure 2). Among the diabetic women, concomitant renal insufficiency (creatinine clearance <42.8 mL/min) was associated with the highest annual incidence of heart failure (12.8%); diabetics with morbid obesity (body mass index >36 kg/m²) also had a high annual incidence (7.0%). These creatinine clearance and body mass index values were iden-
tified during the recursive partitioning as the optimal cut-points for dichotomizing the population; they mirror the categories chosen on clinical grounds used for the Cox models.

Diabetic women without renal insufficiency or morbid obesity had an annual incidence rate of 2.8%, slightly more than double the 1.2% annual incidence rate for all nondiabetic women. In this analysis, we could not identify a factor among the nondiabetic women that substantially improved the ability of this model to predict the risk of incident heart failure; this may stem in part from the relatively low rate of events among nondiabetic women.

**Discussion**

We identified 9 risk factors for the development of heart failure in postmenopausal women with established coronary disease: diabetes, atrial fibrillation, myocardial infarction, renal insufficiency, hypertension, obesity, current smoking, body mass index, and left bundle-branch block. Among diabetic women, left ventricular hypertrophy was also identified as a risk factor. These findings highlight the importance of comprehensive risk assessment in the prevention of heart failure in women.
smoking, left bundle-branch block, and left ventricular hypertrophy. Diabetes was the strongest predictor of heart failure, particularly in the setting of concomitant renal insufficiency or morbid obesity. Furthermore, we found a graded association of impaired glycemic control and increased risk for heart failure among diabetics. These findings highlight the importance of diabetes as a heart failure risk factor in women and suggest several potentially modifiable targets for preventive interventions, particularly among diabetic women.

Although a large proportion of the women who develop heart failure have coronary disease, the risk factors that determine the transition from coronary disease to heart failure have not been well investigated in women. The current focus on the prevention of heart failure requires a greater knowledge of the risk factors involved in the development of heart failure among patients with coronary disease. We have identified several risk factors that could be modified and have the potential to reduce the burden of heart failure in women with established coronary disease: diabetes, hypertension, renal insufficiency, elevated body mass index, and tobacco use.

Diabetes is known to be associated with the development of heart failure, particularly in women. Among heart failure patients, women are more likely than men to have concomitant diabetes. In the setting of acute myocardial infarction, diabetic patients, particularly diabetic women, are more likely to develop subsequent heart failure. Previous studies have suggested that diabetes may promote the development of heart failure independently of obstructive coronary disease. The Framingham investigators described a “diabetic cardiomyopathy” that is associated with heart failure particularly in diabetic women, independent of coronary disease. Although the pathophysiological basis for a distinct diabetic cardiomyopathy remains controversial, there is evidence that diabetes affects the myocardium, inducing increased left ventricular mass, diastolic dysfunction, alterations in endothelial function, and direct metabolic effects on myocytes. Our finding that diabetes is a potent risk factor for heart failure independent of coronary disease status may support the hypothesis that diabetes operates via direct effects on the myocardium. However, all the women in this cohort had underlying coronary disease, so we cannot exclude the possibility that the adverse effects of diabetes operated via the coronary vasculature.

In the United Kingdom Prospective Diabetes Study (UK-PDS), which included only type II diabetics, a graded association was observed between higher hemoglobin A1C and the risk of heart failure, although this risk was not modified by reducing hemoglobin A1C. Iribarren et al also report an association between higher hemoglobin A1C and heart failure risk among a large population-based study of diabetics, although this association was less strong among women than men. We found higher fasting blood glucose levels to predict a greater adjusted risk of heart failure among diabetic women with coronary disease. Clinical trials are needed to determine whether treatment of long-standing hyperglycemia decreases risk of developing heart failure.

In addition to diabetes, we identified other potentially modifiable risk factors for heart failure in women. Uncontrolled hypertension (systolic blood pressure \(>140 \text{ mm Hg}\)) was present in more than one third of the women included in this analysis and was associated with a 2-fold risk of heart failure. Even lower levels of systolic blood pressure (120 to 140 mm Hg) were associated with a significantly increased risk of heart failure. Clinical trials have found that hypertension therapy reduces heart failure risk, which indicates that blood pressure control should be an integral part of heart failure prevention. We observed an increased risk of heart failure associated with renal insufficiency and found this risk to be particularly high among diabetic women; halting the progression of renal disease in these patients through the use of ACE inhibitors and angiotensin receptor blockers may be important for modifying heart failure risk. Consistent
with previous studies, we found that severe obesity (body mass index >35 kg/m²) was associated with increased risk of heart failure.0.41 Thus, reduced risk for heart failure might be another benefit of weight reduction. In addition, current but not former tobacco use was associated with an increased risk for heart failure, which indicates that smoking cessation might reduce heart failure risk in women with coronary disease.

Our study has certain limitations. The outcome of our study was hospitalization or death from heart failure, which probably underestimates the actual rate of new heart failure cases and is biased toward more severe heart failure. However, such a bias is unlikely to result in differential associations among the risk factors identified. Individuals with diabetes are more likely than those without diabetes to be hospitalized, and we cannot exclude the possibility that heart failure was diagnosed at somewhat higher rates among diabetic patients because they spent more time in the hospital. Subjects in this analysis were postmenopausal women who participated in a prevention clinical trial, and thus results may not be generalizable to overall populations of women with coronary disease. Finally, because echocardiography data were not collected routinely as a part of the HERS trial, we are unable to distinguish between heart failure with preserved systolic function and heart failure with depressed systolic function. Both are highly prevalent in women, and heart failure with preserved systolic function appears to be more common among women than men.42 These clinical entities have distinct pathophysiology and may differ somewhat in their risk factors.

In conclusion, we have identified 9 risk factors for the development of heart failure in women with coronary disease. Diabetic women, particularly those with concomitant renal insufficiency, morbid obesity, or hyperglycemia, are at greatest risk and should be targeted for interventions to prevent heart failure. Further studies are needed to determine whether the high risk of heart failure in diabetic women can be reversed with glucose control, treatment to halt the progression of renal disease, weight loss, and smoking cessation.

References
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