Plasma Homocysteine and Risk for Congestive Heart Failure in Adults Without Prior Myocardial Infarction

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CONGESTIVE HEART FAILURE (CHF) is a public health problem with considerable morbidity, mortality, and economic burden. Thus, identification of risk factors for CHF is a public health priority. Several epidemiological investigations have identified advancing age, myocardial infarction (MI), hypertension, valve disease, diabetes mellitus, and obesity as key risk factors for CHF.

In the last decade, plasma total homocysteine has emerged as a major vascular disease risk factor. Elevated total homocysteine levels have been related to greater risk of atherosclerotic sequelae, including cardiovascular mortality, coronary heart disease, and stroke. Prior investigations have not examined the relation of homocysteine to risk of CHF.

In small clinical series, patients with CHF have been reported to have elevated plasma homocysteine levels. Based on experimental evidence that the myocardium may be uniquely susceptible to homocysteine-induced injury and observations relating homocysteine to oxidative stress, we hypothesized that elevated plasma homocysteine levels would increase the risk of CHF. Accordingly, we investigated the relations of plasma homocysteine concentration to the risk of CHF in a community-based sample of adults free of prior MI.

Context Elevated plasma homocysteine levels are associated with increased risk of vascular disease. It is unclear whether elevated homocysteine levels are a risk factor for congestive heart failure (CHF).

Objective To study prospectively the association between nonfasting plasma homocysteine and incidence of CHF.

Design, Setting, and Participants Community-based prospective cohort study of 2491 adults (mean age 72 years, 1547 women) who participated in the Framingham Heart Study during the 1979-1982 and 1986-1990 examinations and were free of CHF or prior myocardial infarction (recognized or unrecognized) at baseline.

Main Outcome Measure Incidence of a first episode of CHF during an 8-year follow-up period.

Results During follow-up, 156 subjects (88 women) developed CHF. In multivariable analyses controlling for established risk factors for CHF including the occurrence of myocardial infarction (recognized or unrecognized) during follow-up, plasma homocysteine levels higher than the sex-specific median value were associated with an adjusted hazards ratio for heart failure of 1.93 in women (95% confidence interval, 1.19-3.14) and 1.84 in men (95% confidence interval, 1.06-3.17). The relation of plasma homocysteine levels to CHF risk was more continuous in women than in men. In analyses restricted to participants without any manifestation of coronary heart disease at baseline, the association of plasma homocysteine levels with risk of CHF was maintained in men and women.

Conclusions An increased plasma homocysteine level independently predicts risk of the development of CHF in adults without prior myocardial infarction. Additional investigations are warranted to confirm these findings.

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METHODS
Participants
The Framingham Heart Study began in 1948 as a prospective epidemiological investigation of 5209 women and men. Participants in the original cohort are examined every 2 years. Attendees of the 16th biennial examination (1979 through 1982, 2351 subjects) and the 20th examination (1986 through 1990, 1401 subjects) were available for the present investigation because plasma homocysteine measurements were routinely obtained at these examinations. We excluded 1261 participants (33.9%) for the following reasons: missing information on covariates (n = 730), lack of plasma homocysteine measurements (n = 235), prevalent CHF (n = 76), lack of follow-up (n = 11), and prior recognized or unrecognized MI (n = 209). Those with missing covariates were older and had slightly higher plasma homocysteine levels than those included in the sample. We chose to exclude individuals with a prior myocardial infarction because the demonstration of an association of homocysteine with CHF in such a sample would support the hypothesis that homocysteine promotes CHF risk even in the absence of clinically apparent preexisting myocardial injury. After the above exclusions, 2491 subjects (mean [SD] age was 72 [7] years [range, 60-95], 1547 women) remained eligible. Informed consent was obtained from study participants and the research protocol was reviewed and approved by the institutional review board of Boston University School of Medicine.

Original cohort subjects who were eligible at the 16th examination cycle remained eligible for inclusion at the 20th biennial examination if they remained eligible for inclusion at the 16th examination cycle. Adjustment for MI on follow-up (as a recognized) on follow-up (as a time-dependent covariate), and examination cycle. Adjustment for MI on follow-up is important because elevated plasma homocysteine levels might predispose a person to the development of CHF by increasing risk of MI. Because serum creatinine values were not obtained at examination 16, values obtained at the previous examination were used.

Outcome
All subjects were under continuous surveillance for the development of cardiovascular disease events including CHF and MI. A panel of 3 experienced investigators reviewed all suspected cardiovascular disease events by examining hospital records, information from physicians, and pathology reports using previously described methods. The primary outcome for our investigation, was the occurrence of a first episode of CHF as defined by the Framingham Heart Study criteria. These validated criteria require the simultaneous presence of at least 2 major criteria, or 1 major criterion in conjunction with 2 minor criteria to establish a diagnosis. Major criteria included paroxysmal nocturnal dyspnea or orthopnea, jugular venous distension, pulmonary rales, radiographic cardiomegaly, acute pulmonary edema, third heart sound, estimated central venous pressure of more than 16 cm of H2O, hepatojugular reflux; and weight loss of 4.5 kg in 5 days in response to receiving treatment for CHF. Minor criteria included bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, and heart rate of at least 120/min. Minor criteria were acceptable only if they could not be attributed to another medical condition (such as chronic lung disease, extreme obesity, cirrhosis, ascites, or nephrotic syndrome). Criteria for recognized and unrecognized MI have been detailed.

Statistical Analysis
Follow-up was for 8 years. Sex-specific Cox proportional-hazards regression models were used to examine the association of plasma homocysteine (quartiles) with the incidence of CHF. Homocysteine levels increased markedly with age and differed slightly between the 2 sexes. Accordingly, plasma homocysteine quartiles were defined in 2 ways: (1) crude sex-specific quartiles, not adjusted for age and (2) age- and sex-specific quartiles, defined for each of several 5-year age categories.

The assumption of proportionality of hazards was met. Cox models adjusted for the following covariates (all defined at the baseline examinations with the exception of subsequent MI) that influence CHF risk and/or plasma homocysteine levels: age, body mass index (as an indicator of obesity), ratio of total cholesterol to high-density lipoprotein cholesterol levels, valve disease, current cigarette smoking status, alcohol consumption, systolic blood pressure, antihypertensive medication use, diabetes mellitus, serum creatinine, occurrence of an MI (recognized or unrecognized) on follow-up (as a time-dependent covariate), and examination cycle. Adjustment for MI on follow-up is important because elevated plasma homocysteine levels might predispose a person to the development of CHF by increasing risk of MI. Because serum creatinine values were not obtained at examination 16, values obtained at the previous examination were used.

Models using homocysteine quartiles compared risk of CHF in each of the 3 top quartiles with the first quartiles.
tile serving as a referent (multicategory models), and examined the trend across the quartiles (trend models). We also evaluated threshold models that compared the risk of CHF at select quartile-based cut points for plasma homocysteine levels, eg, values above vs those at or below the median, fourth quartile of plasma homocysteine vs the first 3 quartiles. Separate models were examined for crude sex-specific quartiles (model 1), and for age- and sex-specific quartiles (model 2) of plasma homocysteine concentration. We performed supplementary analyses treating homocysteine as a continuous variable (with natural logarithmic transformation); subjects with homocysteine values higher than 30 µmol/L were excluded for these analyses to avoid excessive influence of results by extreme values.

**Ancillary Analyses**

We tested for the presence of effect modification by age, systolic blood pressure, diuretic or cholesterol-lowering drug use, and the baseline examination by incorporating several interaction terms individually in multivariable models 1 (above median plasma homocysteine × covariate; plasma homocysteine × covariate). Because blood pressure is a key risk factor for CHF, we examined additional models that incorporated the average of several readings of systolic blood pressures obtained at Framingham study examinations in the decade preceding the baseline examination.

Although we excluded all subjects with a recognized or unrecognized prior MI, we did not exclude subjects with a history of angina or coronary insufficiency (n=249, 151 women). We performed secondary analyses excluding those with prevalent coronary heart disease at baseline.

**Echocardiographic Insights**

To obtain insights into the type of CHF (systolic vs diastolic) associated with increasing plasma homocysteine concentration, we reviewed echocardiographic reports in a subgroup of participants who had evaluation of left ventricular systolic function within 30 days of their first hospitalization for CHF in a contemporary period (1989 to 1998). Heart failure was presumed to be due to systolic dysfunction (systolic CHF) if the estimated left ventricular ejection fraction was less than 50%, whereas a left ventricular ejection fraction of 50% or higher was considered consistent with diastolic CHF.29

A 2-sided P value of .05 was considered significant. All analyses were performed using version 8 of the SAS statistical package.30

**RESULTS**

**Clinical Characteristics**

About a quarter of our participants were hyperhomocysteinemic (>14 µmol/L) at baseline (Table 1). The sex-specific quartiles of plasma homocysteine overall and for 5-year age groups are in Table 2 (for pooled examinations).

**Homocysteine and CHF Risk**

During a follow-up period of 8 years, 156 subjects (88 women) developed CHF. The Figure indicates that the crude cumulative incidence of CHF in women and men in the top 2 homocysteine quartiles (values higher than the sex-specific median) was considerably higher than those in the lower 2 quartiles. During follow up, 6% of women and 12% of men in the sample experienced an MI (recognized or unrecognized). Of the incident CHF cases, 28 of the 88 women and 22 of the 68
men experienced an MI prior to the development of CHF.

TABLE 3 shows the results of multivariable analyses examining the relations of plasma homocysteine levels to risk of CHF after adjusting for covariates at baseline and additionally for the occurrence of MI on follow-up. Use of age-adjusted quartiles of homocysteine yielded similar results to the use of crude quartiles. Risk of CHF increased about 25% (men) to 49% (women) per quartile increment in plasma homocysteine level (Table 3, models 1 and 2, trend across quartiles).

Thresholds at which CHF risk increased in multcategory models (comparing each plasma homocysteine quartile with the first) were different for women and men (Table 3). In women, risk of CHF rose at the second plasma homocysteine quartile; the point estimates of the hazards ratios exceeded 2 for the second and the third quartiles relative to the lowest quartile. An additional increase in risk of CHF was observed at the top quartile of plasma homocysteine. Because of the increasing gradient of risk across plasma homocysteine quartiles, cut points at the median and the 75th percentile plasma homocysteine values were each associated with an about 2-fold risk of CHF relative to levels below these thresholds (P < .01 for both).

In men, risk of CHF increased only beyond the second quartile of plasma homocysteine; the point estimates of the hazards ratio for the third and fourth quartiles each exceeded 1 but were not statistically significant (in multcategory models). Values above the median were associated with an 84% to 92% increased risk of CHF (models 1 and 2, P < .03 for both). The top quartile was associated with a 60% increased risk relative to the lower 3 quartiles. When considered as a continuous variable, increased plasma homocysteine levels were predictive of CHF in men (adjusted hazard ratio per 1 SD [0.4] increment in log homocysteine, 1.66; 95% confidence interval, 1.20-2.29) and in women (adjusted hazards ratio per 1 SD [0.4] increment in log homocysteine, 1.34; 95% confidence interval, 1.04-1.71).

Figure. Plasma Homocysteine and Congestive Heart Failure Risk

![Figure](image-url)

Kaplan-Meier plots showing the cumulative incidence of heart failure in subjects with baseline plasma homocysteine levels above the median (quartiles 3-4) compared with plasma homocysteine levels at or below the median (quartiles 1-2).

Table 2. Distribution of Baseline Plasma Homocysteine Levels Within 5-Year Age Groups and Overall*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. of Women</th>
<th>Homocysteine Quartile, µmol/L</th>
<th>Mean (SD)</th>
<th>No. of Men</th>
<th>Homocysteine Quartile, µmol/L</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>60-64</td>
<td>276</td>
<td>4.2-8.5</td>
<td>8.6-10.2</td>
<td>10.3-12.3</td>
<td>12.4-15.5</td>
<td>11.1 (5.0)</td>
</tr>
<tr>
<td>65-69</td>
<td>319</td>
<td>4.1-8.6</td>
<td>8.7-10.5</td>
<td>10.6-12.8</td>
<td>12.9-14.3</td>
<td>11.3 (4.2)</td>
</tr>
<tr>
<td>70-74</td>
<td>430</td>
<td>4.3-8.5</td>
<td>8.6-10.9</td>
<td>11.0-13.4</td>
<td>13.5-16.4</td>
<td>11.9 (5.6)</td>
</tr>
<tr>
<td>75-79</td>
<td>285</td>
<td>3.5-9.1</td>
<td>9.2-11.4</td>
<td>11.5-14.3</td>
<td>14.4-16.9</td>
<td>12.3 (4.5)</td>
</tr>
<tr>
<td>80-84</td>
<td>158</td>
<td>6.1-9.7</td>
<td>9.8-11.5</td>
<td>11.6-15.5</td>
<td>15.6-19.9</td>
<td>13.3 (6.6)</td>
</tr>
<tr>
<td>≥85</td>
<td>79</td>
<td>5.4-10.8</td>
<td>10.9-13.9</td>
<td>14.1-18.9</td>
<td>19.0-25.6</td>
<td>15.6 (7.2)</td>
</tr>
<tr>
<td>All ages</td>
<td>1547</td>
<td>3.5-8.9</td>
<td>9.0-11.0</td>
<td>11.1-13.6</td>
<td>13.7-16.4</td>
<td>12.0 (5.4)</td>
</tr>
</tbody>
</table>

*Downloaded From: by a Non-Human Traffic (NHT) User on 10/27/2018
Effect Modification

Associations of homocysteine levels with CHF risk did not vary with age, systolic blood pressure, diuretic or cholesterol-lowering drug use, or baseline examination (P values for all interactions exceeded .10). Additionally, the relations of elevated homocysteine levels and CHF risk were maintained in analyses adjusting for the average of multiple systolic blood pressure readings obtained at examinations in the decade preceding the baseline examination.

In secondary analyses excluding all individuals with any prevalent coronary heart disease at baseline, the relations of elevated homocysteine and CHF risk remained robust in women (Table 4). In men, the associations of the median-based threshold of plasma homocysteine with increased risk of CHF observed in primary analyses were maintained (Table 4).

Echocardiographic Evaluation

Of the 32 participants (20% of CHF cases) who underwent echocardiographic evaluation within 30 days of their first hospitalization for CHF, 13 (62%) of 21 individuals with plasma homocysteine higher than the median, and 7 (64%) of 11 of those with plasma homocysteine levels below the median had a left ventricular ejection fraction of less than 50% (indicative of systolic CHF).

COMMENT

Principal Findings

To our knowledge, this is the first report in the general population examining prospectively the relations of plasma homocysteine levels and risk of subsequent CHF in individuals without a prior MI. In our sample, elevated plasma homocysteine concentration was related positively and strongly to CHF risk in continuous fashion in women; risk of CHF doubled at the second quartile and a 4-fold risk was observed for those with values in the top quartile vs those whose values were in the lowest quartile. In men, the association of plasma homocysteine with risk of CHF became evident only at values exceeding the median. In both men and women, the increased risk of CHF associated with plasma homocysteine was consistent regardless of the method of defining quartiles (age-adjusted vs age-pooled). In analyses restricted to a subset of individuals without any clinical coronary disease at baseline, the association of plasma homocysteine with CHF risk was maintained in both men and women. In a small subgroup of individuals who underwent echocardiographic evaluation within 30 days of their first CHF hospitalization, elevated homocysteine levels (values >median) were associated with both systolic and diastolic CHF.

The sex-related differences in the thresholds of plasma homocysteine at which risk increases merits comment. It is well known that ischemic heart disease is a more important contributor to CHF risk in men, whereas hypertension accounts for a greater proportion of CHF risk in women.4 This study design specifically examined the possibility that homocysteine may promote CHF through nonschismic mechanisms by excluding individuals with prior MI and by adjusting for interim development of MI. It is important to note that although the relative risk for CHF associated with the top quartile of plasma homocysteine vs the lowest quartile is higher in women than in men, the absolute risk of CHF is lower in women (Figure).31

Table 3. Multivariable Cox Proportional Hazard Models for Risk of Congestive Heart Failure According to Plasma Homocysteine Levels*

<table>
<thead>
<tr>
<th>Quartile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Trend Across Quartiles</th>
<th>Above Median vs Below Median</th>
<th>Quartile 4 vs Quartiles 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women with CHF/No. at risk (%)</td>
<td>10/386 (2.6)</td>
<td>16/389 (4.1)</td>
<td>20/385 (5.2)</td>
<td>42/387 (10.9)</td>
<td>2.18 (0.94-5.06)</td>
<td>.07</td>
<td>.05</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>Referent</td>
<td>2.21 (0.99-4.93)</td>
<td>3.74 (1.77-7.89)</td>
<td>1.47 (1.19-1.82)</td>
<td>1.93 (1.19-3.14)</td>
<td>2.11 (1.33-3.33)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.07</td>
<td>.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.008</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>No. of men with CHF/No. at risk (%)</td>
<td>13/236 (5.5)</td>
<td>9/235 (3.8)</td>
<td>19/237 (8.0)</td>
<td>27/236 (11.4)</td>
<td>0.61 (0.26-1.46)</td>
<td>.27</td>
<td>.44</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>Referent</td>
<td>1.34 (0.64-2.79)</td>
<td>1.57 (0.77-3.22)</td>
<td>1.25 (0.99-1.59)</td>
<td>1.84 (1.06-3.17)</td>
<td>1.58 (0.94-2.68)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.27</td>
<td>.44</td>
<td>.22</td>
<td>.07</td>
<td>.03</td>
<td>.09</td>
<td></td>
</tr>
</tbody>
</table>

Models With Crude Sex-Specific Quartiles of Homocysteine

Archivations: CI, confidence interval; HR, hazards ratio.

*All models are adjusted for age, smoking, valve disease, systolic blood pressure, antihypertensive medication use, echocardiographic left ventricular hypertrophy, diabetes, ratio of total cholesterol to high-density lipoprotein, alcohol intake, body mass index, serum creatinine, interim recognized or unrecognized myocardial infarction, and baseline examination.

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Mechanisms

The strength of the association (hazard ratio of about 2.0 for values greater than median), the demonstration of a temporal sequence (increased homocysteine levels preceded the development of CHF), and the consistency of results in multiple analyses raise the possibility of a causal relation between increased plasma homocysteine levels and risk of CHF. An alternative interpretation is that individuals with subclinical left ventricular dysfunction have elevated plasma homocysteine levels, perhaps due to renal hypoperfusion, and these participants develop overt CHF on follow-up (reverse causality).

Recent experimental studies have underscored that the myocardium is uniquely susceptible to homocysteine-induced injury. Neither cystathionine β synthase (the key enzyme for the transsulfuration pathway of homocysteine metabolism) nor betaine-homocysteine methyltransferase (major enzyme for the alternate remethylation pathway) are expressed in myocardial cells, rendering cardiac myocytes critically dependent on the methionine synthase remethylation pathway. Elevated homocysteine levels may promote CHF through several mechanisms. First, elevated homocysteine concentration is a risk factor for coronary atherosclerosis and MI, the latter being a key antecedent of CHF. Furthermore, homocysteine may cause myocardial ischemia in the absence of infarction by promoting endothelial dysfunction of coronary resistance vessels. Second, elevated homocysteine levels in patients with acute coronary syndromes are associated with greater myocardial injury as evidenced by higher troponin levels. As noted above, we accounted for these possibilities to some extent by excluding all individuals with an MI (recognized or unrecognized) at baseline, and by further adjusting for interim MI (either recognized or unrecognized) on follow-up. Third, investigators have emphasized the critical role of homocysteine as a source of increased oxidative stress, a factor known to promote myocardial dysfunction. Fourth, hyperhomocysteinemic rats have increased cardiac fibrosis and increased activation of matrix metalloproteinases, which in turn promote left ventricular remodeling, a known precursor of CHF. A similar adverse effect of homocysteine on left ventricular remodeling has been noted in the setting of renal failure in humans. Although all these mechanisms may be operative, our study design would support the importance of nonischemic mechanisms in addition to the well-recognized ischemic mechanisms. Additional experimental investigations are warranted to examine the relative contributions of ischemic and nonischemic to the increased risk of CHF associated with elevated plasma homocysteine levels.

The strengths of our investigation include the large community-based sample, the standardized measurement of homocysteine, the use of consistent criteria for the diagnosis of CHF, and the use of measurements of plasma homocysteine concentrations at 2 different time points. Nonetheless, it is important to acknowledge several limitations. Plasma homocysteine levels were obtained on participants in a nonfasting state and, therefore, were likely to be slightly higher than if fasting specimens had been obtained. Use of a single estimation of plasma homocysteine may underestimate plasma homocysteine levels.

Table 4. Multivariable Cox Proportional Hazard Models for Risk of Congestive Heart Failure According to Plasma Homocysteine Levels: Excluding All Prevalent Coronary Heart Disease at Baseline

<table>
<thead>
<tr>
<th>Quartile</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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<th>Quartile 4 vs Quartiles 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartiles 1-3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>Trend Across Quartiles</td>
<td>Above Median vs Below Median</td>
<td>Quartile 4 vs Quartiles 1-3</td>
</tr>
<tr>
<td>No. of women with CHF/No. at risk (%)</td>
<td>9/351 (2.6)</td>
<td>11/349 (3.2)</td>
<td>17/346 (4.9)</td>
<td>37/350 (10.6)</td>
<td>HR (95% CI)</td>
<td>Referent</td>
<td>1.50 (0.54-4.86)</td>
</tr>
<tr>
<td>P value</td>
<td>.41</td>
<td>.14</td>
<td>.007</td>
<td>.003</td>
<td>.01</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>No. of men with CHF/No. at risk (%)</td>
<td>10/205 (4.9)</td>
<td>9/217 (4.2)</td>
<td>16/214 (7.5)</td>
<td>23/210 (11.0)</td>
<td>HR (95% CI)</td>
<td>Referent</td>
<td>0.85 (0.34-2.14)</td>
</tr>
<tr>
<td>P value</td>
<td>.73</td>
<td>.24</td>
<td>.20</td>
<td>.09</td>
<td>.05</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>No. at risk (%)</td>
<td>8/345 (2.3)</td>
<td>15/349 (4.3)</td>
<td>21/351 (6.0)</td>
<td>30/351 (8.6)</td>
<td>HR (95% CI)</td>
<td>Referent</td>
<td>1.91 (0.76-4.83)</td>
</tr>
<tr>
<td>P value</td>
<td>.17</td>
<td>.02</td>
<td>.004</td>
<td>.002</td>
<td>.004</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>No. of men with CHF/No. at risk (%)</td>
<td>10/203 (4.9)</td>
<td>10/218 (4.6)</td>
<td>17/215 (7.9)</td>
<td>23/210 (11.0)</td>
<td>HR (95% CI)</td>
<td>Referent</td>
<td>0.75 (0.30-1.83)</td>
</tr>
<tr>
<td>P value</td>
<td>.52</td>
<td>.25</td>
<td>.24</td>
<td>.07</td>
<td>.03</td>
<td>.19</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazards ratio.

*All models are adjusted for age, smoking, valve disease, systolic blood pressure, antihypertensive medication use, echocardiographic left ventricular hypertrophy, diabetes, ratio of total cholesterol to high-density lipoprotein, alcohol intake, body mass index, serum creatinine, interim recognized or unrecognized myocardial infarction, and baseline examination.
HOMOCYSTEINE AND RISK OF CONGESTIVE HEART FAILURE

REFERENCES


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