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Objective—To examine the association of serum $\gamma$-glutamyltransferase (GGT) with incident heart failure.

Methods and Results—We related serum GGT to the incidence of heart failure in 3544 (mean age, 44.5 years; 1833 women and 1711 men) Framingham Study participants who were free of heart failure and myocardial infarction. On follow-up (mean, 23.6 years), 188 participants (77 women) developed new-onset heart failure. In multivariable Cox proportional hazards regression models adjusting for standard risk factors and alcohol consumption as time-varying covariates (updated every 4 years), each SD increase in log-GGT was associated with a 1.39-fold risk of heart failure (95% CI, 1.20 to 1.62). The linearity of the association was confirmed by multivariable-adjusted splines, and the relations remained robust on additional adjustment for hepatic aminotransferases and C-reactive protein. Participants with a serum GGT level at the median or greater had a 1.71-fold risk of heart failure (95% CI, 1.21 to 2.41) compared with individuals with GGT concentrations less than the median. GGT marginally increased the model C-statistic from 0.85 to 0.86 but improved the risk reclassification modestly (net reclassification index, 5.7%; $P=0.01$).

Conclusion—In this prospective study of a large community-based sample, higher serum GGT concentrations within the “normal” range were associated with greater risk of heart failure and incrementally improved prediction of heart failure risk. (Arterioscler Thromb Vasc Biol. 2010;30:1855-1860.)

Key Words: epidemiology ■ heart failure ■ risk factors ■ oxidative stress ■ $\gamma$-glutamyl transferase

In clinical practice, serum $\gamma$-glutamyltransferase (GGT) is measured as a marker of excessive alcohol consumption or hepatic disease.1,2 Researchers,3,4 during the past 3 decades, have reported that GGT is not only secreted by the liver but also by several other tissues, including the kidneys and vascular pericytes in the brain. Indeed, GGT has a primary role in glutathione metabolism and acts as an antioxidant in the metabolism of amino acids to maintain intracellular glutathione levels.5 Experimentally, GGT may also have pro-oxidant activity by promoting the generation of free radical species in the presence of free metal ions, such as iron.6 Overall, evidence from epidemiological studies shows that higher serum GGT concentrations within the so-called normal range are associated with greater risk of hypertension,7 incident diabetes mellitus,8–10 metabolic syndrome,10,11 cardiovascular disease,11–14 cardiovascular disease–associated mortality,15,16 and all-cause mortality.17 These associations of GGT with adverse sequelae were independent of alcohol consumption.

More recently, investigators have focused on serum GGT concentrations in those with heart failure. Limited data indicate that GGT concentrations are higher in patients with prevalent heart failure18,19 and are a marker of increased mortality risk.15 However, the association of serum GGT concentrations with the incidence of heart failure has not been elucidated. Therefore, in the present study, we evaluated the association of serum GGT concentrations with the incidence of heart failure prospectively in a large community-based sample of individuals who were free of heart failure and myocardial infarction (MI).

Methods

Study Participants

The Framingham Heart Study began in 1948 with the enrollment of 5209 participants into the original cohort. In 1972, the children (and the respective spouses) of the original cohort participants were enrolled into the Framingham Offspring Study (N=5124).20 All participants from the Framingham Offspring Study (n=3792) who attended the second examination cycle (1978 to 1982) with available data on serum GGT concentrations were eligible for the present investigation (n=3696). In addition, we excluded participants with prevalent heart failure or a previous MI, yielding a final sample of...
Measurement of Risk Factors
At each Framingham Heart Study visit, attendees undergo a physical examination and complete a medical history form (by a heart study physician), take anthropometric tests, and undergo a laboratory assessment of vascular risk factors. For the present investigations, hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications.21 Participants who smoked cigarettes regularly during the year preceding the heart study visit were considered “current” smokers. Alcohol intake was assessed by averaging the self-reported weekly consumption of alcoholic drinks. Valve disease was defined as the presence of any diastolic murmur of grade 3/6 or greater on physical examination findings. Diabetes was defined as a fasting blood glucose level of 126 mg/dL or greater or the use of any hypoglycemic agent.

Assessment of Heart Failure on Follow-Up
The follow-up for the current investigation was from the second examination (1979–1982) through December 2007. All Framingham Heart Study participants are under continuous surveillance for the development of new cardiovascular disease events, including heart failure. A team of 3 physician investigators reviews all medical records (findings from heart study examinations, physician office visits, and hospitalization records) for adjudicating possible heart failure events. A diagnosis of heart failure in the Framingham Heart Study is based on the presence of 2 major, or 1 major and 2 minor, criteria. Briefly, the major criteria include the presence of paroxysmal nocturnal dyspnea, jugular venous distension, orthopnea, hepatojugular reflux, pulmonary edema, third heart sound, cardiomegaly on a chest radiograph, central venous pressure of greater than 16 cm H2O, and weight loss of greater than 4.5 kg during the first 5 days of treatment for suspected heart failure. Minor criteria include bilateral ankle edema, exertional dyspnea, nocturnal cough, hepatomegaly, pleural effusion, and heart rate of greater than 120 bpm. A detailed description of the adjudication of heart failure events has been previously published.23

Table 1. Baseline Characteristics of Study Participants*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 1717)</th>
<th>Women (n = 1833)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.7 (10.3)</td>
<td>44.3 (9.9)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.0 (6.9)</td>
<td>161.0 (6.4)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.9 (12.2)</td>
<td>63.9 (13.1)</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>26.9 (3.7)</td>
<td>24.9 (4.8)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>126 (16)</td>
<td>119 (17)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81 (9)</td>
<td>75 (9)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>28.0</td>
<td>17.2</td>
</tr>
<tr>
<td>Treatment for hypertension, %</td>
<td>10.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>6.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>35.4</td>
<td>36.8</td>
</tr>
<tr>
<td>Alcohol, drinks/wk</td>
<td>5.1 (6.2)</td>
<td>2.2 (3.1)</td>
</tr>
<tr>
<td>Valve disease, %§</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Total to HDL cholesterol ratio</td>
<td>5.1 (1.6)</td>
<td>4.0 (1.3)</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>24 (12)</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>31 (19)</td>
<td>21 (19)</td>
</tr>
<tr>
<td>hsCRP, mg/dL</td>
<td>2.7 (5.3)</td>
<td>2.3 (4.4)</td>
</tr>
<tr>
<td>GGT, median (Q1–Q3), U/L$</td>
<td>16 (11–25)</td>
<td>9 (7–14)</td>
</tr>
<tr>
<td>Log GGT</td>
<td>2.8 (0.6)</td>
<td>2.3 (0.6)</td>
</tr>
</tbody>
</table>

GGT indicates γ-glutamyltransferase; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; Q, quartile.

*Data are given as mean (SD) unless otherwise indicated.
†Calculated as weight in kilograms divided by height in meters squared.
§Defined as the presence of any diastolic murmur or a systolic murmur of 3/6 or greater on physical examination findings.
$Q01 is 0.43 U/L; and Q3, 2.46 U/L.

Comparing categories at median or greater levels with less than median concentrations (that served as the referent category).

All models were adjusted for the following covariates in a hierarchical fashion: (1) age and sex; (2) age, sex, body mass index, diabetes, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total to HDL cholesterol ratio, valve disease, and history of MI; (3) all covariates in model 2 were updated every 4 years as time-dependent covariates; and (4) all covariates in model 3, with additional adjustment for aspartate aminotransferase, alanine aminotransferase, and hsCRP (all measured at the baseline examination).

Secondary Analyses
To assess for any potential nonlinearity of relations between serum GGT and incidence of heart failure, we examined multivariable generalized additive models using penalized splines,24,25 adjusting for all the covariates in multivariable model 2. We also evaluated for effect modification by age, body mass index, hypertension, and alcohol intake by incorporating interaction terms in the multivariable models examining the association of serum GGT (log-transformed) with heart failure risk. We examined the incidence of heart failure using Cox models by comparing heart failure incidence in the 2 groups, defined by the sex-specific median cutoff for GGT level (versus using the sex-pooled median threshold of our primary analyses).

We also assessed the incremental contribution of GGT levels to the prediction of congestive heart failure risk by estimating the increment in the model C-statistic (comparing multivariable models with and without GGT) by calculating the proportion of people at risk reclassified appropriately (risk reclassification) and calibration indexes.26 Because risk reclassification requires categorization of
Table 2. Age-Adjusted Cumulative Incidence Rates of Heart Failure According to Serum GGT Level

<table>
<thead>
<tr>
<th>Serum GGT Level</th>
<th>No. of Events</th>
<th>Age- and Sex-Adjusted Incidence Rates of Heart Failure per 1000 Person-Years (95% Poisson CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than the median</td>
<td>53</td>
<td>1.93 (1.45–2.53)</td>
</tr>
<tr>
<td>At or greater than the median</td>
<td>135</td>
<td>3.35 (2.81–3.96)</td>
</tr>
</tbody>
</table>

GGT indicates γ-glutamyltransferase.
*The median cut point for serum GGT concentration was 12 U/L.

Results
The baseline characteristics of study participants are given in Table 1 according to sex. Median GGT concentrations in our young middle-aged sample ranged from 9 U/L (women) to 16 U/L (men). As previously reported, the clinical correlates of circulating GGT included age, male sex, smoking, alcohol consumption, body mass index, low-density lipoprotein cholesterol concentration, triglyceride levels, diastolic blood pressure, and use of antihypertensive medications.

On follow-up (mean, 23.6 years; range, 0 to 28.2 years), 188 participants (77 women) developed heart failure. Age- and sex-adjusted incidence rates of heart failure were approximately 75% higher for participants with a serum GGT concentration at the median or greater (versus those with a concentration less than the median) (Table 2).

Continuous Increase in Serum GGT Concentration and Heart Failure Risk
In age- and sex-adjusted Cox models, each SD increase in log GGT was associated with a 49% higher risk of heart failure (Table 3). In multivariable models, each SD increase in log GGT was associated with a 26% to 36% higher risk of heart failure in models with baseline and time-varying covariates, respectively. These results remained unchanged after adjustment for hsCRP and other liver enzymes (aminotransferases). Additional adjustment for alkaline phosphatase also did not change our primary results (hazard ratio per SD increase in log GGT, 1.31; 95% CI, 1.09 to 1.57). Penalized splines demonstrated a graded linear increase in the risk of heart failure with increasing serum GGT concentrations (Figure 1).

In addition, when individuals with a serum GGT concentration higher than the normal levels (>40 U/L in women and >50 U/L in men) were excluded (n=3162), the association of higher log GGT with incident heart failure remained robust (hazard ratio, 1.36; 95% CI, 1.08 to 1.67; P=0.007).

Serum GGT Concentration at or Greater Versus Less Than the Median and Heart Failure Risk
Cumulative incidence curves demonstrated a greater risk of new-onset heart failure among individuals with a serum GGT concentration at or greater than the median compared with those with levels less than the median (P<0.001, log-rank test) (Figure 2). In Cox regression models adjusting for age and sex, participants with a median or greater serum GGT concentration had a more than 2-fold risk of heart failure compared with individuals with concentrations less than the median (Table 3). After adjustment for baseline covariates, the risk of heart failure was attenuated, with a 55% higher risk in those with GGT concentrations at or greater than the median. These results remained robust when covariates were updated every 4 years and after adjusting for liver enzymes and hsCRP (Table 3).

Secondary Analyses
We did not observe any effect modification by age, sex, hypertension, body mass index, or alcohol intake in the relations of log GGT to incident heart failure (P>0.05 for all probability values for interaction terms). When individuals were dichotomized using the sex-specific median concentrations of serum GGT, the association of GGT with heart

Table 3. Cox Proportional Hazard Regression Models Examining the Relations of Serum GGT Concentration to the Incidence of Heart Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age- and Sex-Adjusted</th>
<th>Multivariable Model 1*</th>
<th>Multivariable Model 2†</th>
<th>Multivariable Model 3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazards Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazards Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Log GGT per SD increment</td>
<td>1.49 (1.30–1.69)</td>
<td>&lt;0.001</td>
<td>1.26 (1.09–1.46)</td>
<td>0.002</td>
</tr>
<tr>
<td>Categorical model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than the median</td>
<td>Referent</td>
<td>&lt;0.001</td>
<td>Referent</td>
<td>0.02</td>
</tr>
<tr>
<td>At or greater than the median</td>
<td>2.19 (1.57–3.01)</td>
<td></td>
<td>1.55 (1.09–2.20)</td>
<td></td>
</tr>
</tbody>
</table>

GGT indicates γ-glutamyltransferase.
*Multivariable model 1 was adjusted for age, sex, body mass index, diabetes mellitus, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total to high-density lipoprotein cholesterol ratio, valve disease, and history of myocardial infarction.
†Multivariable model 2 was adjusted for all covariates in model 1 in time-varying fashion (updating every 4 years), except for age and sex.
‡Multivariable model 3 was adjusted for all covariates in model 2 plus aspartate aminotransferase, alanine aminotransferase, and high-sensitivity C-reactive protein.
failure risk remained robust (hazard ratio, 1.68; 95% CI, 1.20 to 2.34) compared with those with levels less than the median (results for models adjusted for time-varying covariates, as in model 3 [described in the “Statistical Analyses” subsection of the “Methods” section]).

The addition of GGT to a multivariable model incorporating baseline covariates increased the C-statistic from 0.85 to 0.86 and improved the risk reclassification (net reclassification index, 5.7%; \( P = 0.01 \)) (Figure 3).

**Discussion**

**Principal Findings**

Our results were 3-fold. First, within the so-called normal range of serum GGT, higher concentrations were associated with greater risk of heart failure in a graded fashion. Values greater than the median level of serum GGT were associated with a 55% to 71% greater risk of heart failure compared with individuals with less than median levels. Second, relations of higher serum GGT to heart failure risk were maintained in models adjusting for MI and other covariates on follow-up and on adjustment for aspartate aminotransferase or alanine aminotransferase and hsCRP. Third, GGT modestly improved prediction of heart failure risk, as judged by an improvement in the C-statistic and risk reclassification.

In prior studies, higher serum GGT concentration has been associated cross-sectionally with impaired coronary reserve flow in hypertensive patients and in patients with cardiomyopathy and longitudinally with greater mortality in patients who experienced heart failure. To our knowledge, the present study is the first to examine the relations of serum GGT and risk of developing heart failure in a community-based sample.
Mechanisms
Several mechanisms are postulated in relation to serum GGT with greater cardiovascular disease risk, which may also be implicated in the development of heart failure. Higher serum GGT activity has been reported in atherosclerotic plaques and foam cells. Because higher serum GGT levels have been associated with greater incidence of metabolic syndrome and incident diabetes, GGT may also reflect the development of fatty liver and greater insulin resistance. However, our results were independent of the development of MI or diabetes on follow-up and remained robust in analysis adjusting for other liver enzymes and hsCRP.

Serum GGT has also been associated with production of reactive oxygen species and subsequent oxidation of lipids, nucleic acids, and transcription factor proteins. These findings have suggested that GGT levels may be a marker of greater oxidative stress, which has also been postulated as a mechanism for the development of heart failure. In addition, serum GGT levels are inversely associated with several antioxidants, such as beta carotene, lycopene, and vitamin C, and positively related to other biomarkers of oxidative stress, such as F-2 isoprostanes. Thus, it is plausible that serum GGT concentrations reflect systemic oxidative stress and, therefore, can predict the development of heart failure. Another possible explanation of these relations could be the association of serum GGT with inflammation and atherogenesis. Last, hepatic congestion as the result of heart failure could increase serum GGT levels, although this would likely happen in patients with chronic heart failure. It is unclear whether the first episode of heart failure (as opposed to chronic heart failure) would have significant hepatic sinusoidal injury and would elevate serum GGT levels.

Overall, the exact mechanism of GGT to predict the incidence of heart failure remains unclear. However, GGT does provide incremental risk prediction and the current information may warrant testing this biomarker in relation to other biomarkers (eg, B-type natriuretic peptide and growth-differentiating factor-15) for the prediction of heart failure using a multimarker approach.

Strengths and Limitations
The present study has several strengths, including the community-based sample of men and women, a prospective design with a long follow-up, comprehensive adjustment for covariates at baseline, accounting for MI on follow-up as a time-varying covariate, and consistency of results in multiple analyses. However, there are several study limitations. We did not measure other biomarkers that reflect oxidative stress (eg, isoprostanes), which may have enabled us to elucidate the mechanisms underlying the observed association. Given the long follow-up, we were unable to characterize separately the association of GGT with incidence of heart failure with reduced versus preserved ejection fraction. Also, participants in our study were white Americans of European descent, which limits the generalizability of our results to other ethnic groups.

In conclusion, in a community-based sample, higher concentrations of serum GGT within the normal range were associated with greater risk of developing heart failure in individuals without a history of MI. Additional studies are needed to confirm our findings and to elucidate the underlying pathogenetic mechanisms.

Acknowledgments
We had full access to the data, take responsibility for its integrity, and have read and agree to the manuscript as written.

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Disclosures
None.
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