**Objective**—The relationship between γ-glutamyl transferase (GGT) and heart failure (HF) in older adults is unknown. We have examined the relationship between GGT, other markers of hepatic function (alanine aminotransaminase, aspartate transaminase, and alkaline phosphatase), and incident HF in older men.

**Methods and Results**—This was a prospective study of 3494 men aged 60 to 79 years with no diagnosed HF or myocardial infarction followed up for a mean period of 9 years, in whom there were 168 incident HF cases. Elevated GGT (top quartile, ≥38 U/L) was associated with significantly increased risk of incident HF in men aged <70 years but not in men aged ≥70 years (test for age-GGT interaction, \(P<0.0001\)). The increased risk of HF associated with elevated GGT persisted after adjustment for a wide range of established and novel risk factors for HF, including diabetes, stroke, obesity, systolic blood pressure, atrial fibrillation, lung function, inflammation (C-reactive protein), endothelial dysfunction (von Willebrand factor), leptin, and NT-proBNP (adjusted hazard ratio [95% CI], 1.91 [1.07, 3.42]). Other liver function markers showed no significant associations with HF with similar adjustments.

**Conclusion**—Elevated GGT was associated with increased risk of HF in men aged <70 years. Additional studies are now needed to determine the mechanisms responsible. (Arterioscler Thromb Vasc Biol. 2012;32:00-00.)

**Key Words:** epidemiology ■ heart failure ■ risk factors ■ hepatic enzymes

Heart failure (HF) is a major and increasingly important public health problem in older people and is associated with considerable hospitalization and mortality. Although γ-glutamyl transferase (GGT) is commonly used in clinical practice as a marker of excessive alcohol consumption and liver dysfunction, several prospective studies and a meta-analysis of population-based studies have shown that high GGT levels are associated with increased risk of cardiovascular disease (CVD) events and mortality. Liver dysfunction is a common occurrence in HF. More recently, attention has turned to the potential role of GGT in HF. Several studies show GGT to be raised in established HF and to predict adverse outcome in those with HF and to 2 prospective studies have shown GGT to predict incident HF in the general population. GGT is strongly associated with many established risk factors for HF, including hypertension, obesity, diabetes, and inflammation. However, a recent prospective study conducted in men and women (mean age, 44 years) has shown that GGT predicts incident HF independently of these risk factors. HF incidence increases steeply with age, but the prospective association between GGT and HF has not been investigated in older adults. Moreover, the prognostic role of GGT in CVD appears strongly influenced by age such that GGT does not predict CVD mortality in the elderly. Whether the association between GGT and HF is similarly age dependent is not known. We have therefore examined the association between GGT and incident HF in a prospective study of older men aged 60 to 79 years, taking into account a wide range of potential and novel risk factors for HF, including NT-proBNP, interleukin-6 (IL-6), and leptin, all predictors of HF not previously examined in relation to the GGT-HF association. We also examined the associations between other markers of hepatic dysfunction—including alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP)—and incident HF.

**Subjects and Methods**

The British Regional Heart Study is a prospective study involving 7735 men aged 40 to 59 years drawn from 1 general practice in each of 24 British towns, who were screened between 1978 and 1980. The population studied was socioeconomically representative of British men and comprises predominantly white Europeans (>99%). In 1998 to 2000, all surviving men, now aged 60 to 79 years, were invited for a 20th year follow-up examination. All men completed a mailed questionnaire providing information on their lifestyle and medical history, had a physical examination, and provided a fasting blood sample. The samples were frozen and stored at \(-20^\circ\text{C}\) on the day of collection and transferred in batches for storage at \(-70^\circ\text{C}\) until analysis, carried out after no more than 1 freeze-thaw cycle. Twelve lead electrocardiograms were recorded using a Siemens Sicard 460 instrument and were analyzed using Minnesota Coding...
definitions at the University of Glasgow ECG core laboratory. The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (MI) (heart attack, coronary thrombosis), HF, or stroke; details of their medications were recorded at the examination. A total of 4252 men (77% of survivors) attended for examination. Blood measurements, including GGT, were available in 4036 men at the follow-up examination.

Cardiovascular Risk Factors

Anthropometric measurements, including body weight, height, and waist circumference, were carried out with subjects standing in light clothing without shoes. Details of measurement and classification methods for smoking status, physical activity, social class, alcohol intake, blood pressure, blood lipids, and measures of lung function (forced expiratory volume in 1 second) in this cohort have been described. Prevalent diabetes included men with a diagnosis of diabetes and men with fasting blood glucose ≥7 mmol/L. C-reactive protein (CRP) was assayed by ultrasensitive nephelometry (Dade Behring, Milton Keynes, United Kingdom). Plasma leptin was measured by an in-house radioimmunoassay validated against the commercially available Linco assay, as previously described. Predicted glomerular filtration rate (measure of renal function) was estimated from serum creatinine using the Modification of Diet in Renal Disease equation developed by Levy et al.

Results

During the mean follow-up period of 9 years, there were 168 incident HF cases (rate, 5.9/1000 person-years) in the 3494 men with no diagnosed HF and MI. Table 1 shows the baseline characteristics by quarters of GGT. Raised GGT was significantly associated with many cardiovascular risk factors, including adiposity (body mass index and waist circumference), physical inactivity, prevalent stroke, diabetes, atrial fibrillation, systolic blood pressure, forced expiratory volume in 1 second, blood lipids (cholesterol, high-density lipoprotein cholesterol, and triglycerides) homeostasis model assessment-IR, blood glucose, inflammation (CRP and IL-6), endothelial dysfunction (vWF), and leptin. However, GGT showed weak associations with NT-proBNP; no association was seen with predicted glomerular filtration rate. Incidence rates and relative HR for HF by quarters of GGT, using those in the lowest quarter as the reference group, are shown in Table 2. In all men, GGT was significantly associated with HF after adjustment for age, with risk increased only in the top quarter of the distribution. In age stratified analysis the men were initially divided into four 5-year age groups: 60 to 64, 65 to 69, 70 to 74, and 75 to 79 years. The positive association with GGT was only seen in the 2 younger age-groups. To maximize statistical power, the 2 younger groups were combined and the 2 older groups were combined, so that data for 2 age-groups, <70 and ≥70 years, are presented. The age-GGT HF interaction was highly significant (P<0.0001).

We examined the correlations between GGT and metabolic and biological risk markers stratified by age groups (Table 3). There was no evidence that the GGT associations with these variables differed by age (age-GGT interactions all P>0.05).

Table 4 shows the effect of adjustment for cardiovascular risk factors on the relationship between GGT and incident HF in men aged <70 years. Elevated GGT (highest quarter) was associated with significantly increased risk of HF after adjustment for cardiovascular risk factors: age, smoking status, physical activity, alcohol intake, body mass index, systolic blood pressure, cholesterol, forced expiratory volume in 1 second, atrial fibrillation, stroke, use of antihypertensive treatment, LVH, and diabetes. Although further adjustment for CRP, vWF, and leptin attenuated the association, GGT remained significantly associated with increased risk of HF. Adjustment for IL-6 instead of CRP (data not presented) yielded similar findings. Further adjustments for NT-proBNP and homeostasis model assessment-IR did not alter the findings. The increased relative risk of HF associated with
elevated GGT remained, even after adjusting for incident CHD or incident diabetes.

The addition of GGT to a multivariate model using routinely measured clinical variables and biomarkers to predict HF (including age, smoking, alcohol intake, body mass index, systolic blood pressure, use of antihypertensive treatment, prevalent diabetes, and lung function) increased the C-statistic slightly from 0.678 to 0.697, but this was not statistically significant ($P = 0.34$).

Current smokers, % & 12.6 & 12.6 & 13.5 & 13.1 & 0.64  \\
Inactive, % & 7.9 & 9.3 & 9.5 & 12.8 & 0.001  \\
Heavy drinkers, % & 1.4 & 2.1 & 3.0 & 8.2 & $<$0.0001  \\
Manual workers, % & 54.0 & 50.0 & 54.8 & 55.3 & 0.24  \\
Stroke, % & 3.8 & 3.9 & 4.8 & 5.9 & 0.02  \\
Atrial fibrillation, % & 2.4 & 2.7 & 3.2 & 4.7 & 0.006  \\
Diabetes, % & 7.8 & 8.0 & 10.2 & 16.9 & $<$0.0001  \\
On BP-lowering treatment, % & 16.4 & 19.0 & 23.1 & 26.7 & $<$0.0001  \\
LVH, % & 8.2 & 7.4 & 8.4 & 6.6 & 0.47  \\
FEV1, L & 2.65 (0.67) & 2.64 (0.69) & 2.58 (0.65) & 2.59 (0.64) & 0.03  \\
SBP, mm Hg & 148.0 (23.5) & 147.9 (25.1) & 150.5 (22.9) & 153.5 (23.4) & $<$0.0001  \\
Cholesterol, mmol/L & 5.80 (1.02) & 5.96 (0.98) & 6.13 (1.07) & 6.25 (1.11) & $<$0.0001  \\
HDL-C, mmol/L & 1.36 (0.33) & 1.33 (0.34) & 1.31 (0.33) & 1.32 (0.35) & 0.08  \\
Triglycerides, mmol/L* & 1.35 (1.01–1.78) & 1.52 (1.12–2.09) & 1.67 (1.24–2.25) & 1.86 (1.33–2.68) & $<$0.0001  \\
Glucose, mmol/L* & 5.69 (5.20–5.97) & 5.75 (5.23–5.98) & 5.87 (5.26–6.14) & 6.04 (5.33–6.28) & 0.0005  \\
HOMA* & 1.77 (1.13–2.44) & 2.05 (1.41–2.90) & 2.36 (1.51–3.34) & 2.61 (1.56–3.92) & $<$0.0001  \\
CRP, mg/L* & 1.16 (0.56–2.20) & 1.54 (0.72–3.14) & 1.90 (0.90–3.67) & 2.25 (1.06–4.42) & $<$0.0001  \\
IL-6, pg/mL* & 2.20 (1.47–3.06) & 2.36 (1.50–3.40) & 2.39 (1.55–3.31) & 2.59 (1.63–3.82) & $<$0.0001  \\
vWF, IU/dL* & 135.0 (49.5–115.6) & 133.5 (41.6–108.3) & 137.2 (44.3–110.5) & 144.9 (49.8–116.7) & $<$0.0001  \\
eGFR, mL/min per 1.73 m² & 77.5 (67.6–89.8) & 78.3 (66.9–89.4) & 79.8 (67.9–91.7) & 86.5 (71.5–104.4) & $<$0.0001  \\
WC indicates waist circumference; BMI, body mass index; BP, blood pressure; FEV1, forced expiratory volume in 1 second; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; CRP, C-reactive protein; IL, interleukin; vWF, von Willebrand factor; eGFR, predicted glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase.

*Geometric mean and interquartile range.

In age-adjusted analysis, ALT, AST and ALP were positively associated with risk of HF in those aged <70 years (Table 4) but not those ≥70 years. The age-adjusted HR (95% CI) for a SD increase in log ALT, log AST, and log ALP were 0.99 (0.82, 1.20), $P = 0.94$; 0.94 (0.78, 1.15), $P = 0.56$, and 1.05 (0.87, 1.26), $P = 0.63$, respectively. The associations between ALT, AST, ALP, and HF in those aged <70 years were attenuated after adjustment for variables in model 6 and indeed was abolished after adjustment for age and GGT alone (Table 4). Similarly null findings were seen when the associations between ALT, AST, ALP, and HF were examined in quartiles (Table 4). By contrast, adjustment for ALT or AST or ALP made little difference to the findings for GGT. Inclusion of the ratio AST/ALT also made little difference to the findings after exclusion of men with GGT levels above 61 U/L, the upper normal laboratory range in the study (adjusted HR [95% CI] for model 7, 1.99 [1.02, 3.93]).

**Discussion**

In this study of older men, elevated GGT was associated with a significant increase in risk of HF only in men <70 years independently of known risk factors for HF, including obesity, hypertension, atrial fibrillation, diabetes, and inflammation.18 Our findings are consistent with the limited evidence from prospective studies of the GGT-HF association in younger populations3,13 and extend the findings further by examining the roles of a wider range of potential risk factors associated with HF, including plasma leptin, NT-proBNP, IL-6, and endothelial dysfunction (vWF), and by contrasting the association with those of other markers of hepatic
The findings that only GGT and not AST or ALT (more specific markers of hepatic function) or ALP was associated with incident HF in adjusted models suggest that the GGT-HF association may not simply reflect the influence of fatty liver, as measured by ALT, although imaging studies would be useful to confirm. The lack of association between GGT and HF was shown to be independent of other risk factors.

The observation that GGT predicted HF only in those aged <70 years was also consistent with the suggestion that GGT in the normal range is of limited usefulness in predicting CVD mortality in older patients. By contrast, no association was seen with other hepatic markers, including ALT, AST, or ALP, after taking GGT into account or when adjusted for other risk factors.

Table 2. Heart Failure Rates/1000 Person-y and Age-Adjusted HRs for Heart Failure According to GGT Levels in All Men and by Age Group

<table>
<thead>
<tr>
<th>GGT Quartile (U/L)</th>
<th>No of Men (Cases)</th>
<th>Age-Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td>843 (54)</td>
<td>1.00</td>
</tr>
<tr>
<td>19–25.9</td>
<td>896 (48)</td>
<td>0.91 (0.57, 1.44)</td>
</tr>
<tr>
<td>26–37.9</td>
<td>879 (66)</td>
<td>1.34 (0.87, 2.06)</td>
</tr>
<tr>
<td>≥38</td>
<td>876 (70)</td>
<td>1.43 (0.93, 2.20)</td>
</tr>
</tbody>
</table>

1 SD increase: 1.24 (1.07, 1.44), P=0.004

Table 3. Correlation Coefficients Between GGT and Biological Markers Stratified by Age Group

<table>
<thead>
<tr>
<th>Aged &lt;70</th>
<th>Aged ≥70</th>
<th>Age-GGT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.03</td>
<td>−0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>0.22</td>
<td>0.18</td>
</tr>
<tr>
<td>WC</td>
<td>0.20</td>
<td>0.21</td>
</tr>
<tr>
<td>Leptin</td>
<td>0.21</td>
<td>0.18</td>
</tr>
<tr>
<td>FEV1</td>
<td>−0.07</td>
<td>−0.03</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.03</td>
<td>0.00</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>SBP</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.27</td>
<td>0.25</td>
</tr>
<tr>
<td>HOMA</td>
<td>0.20</td>
<td>0.18</td>
</tr>
<tr>
<td>eGFR</td>
<td>−0.04</td>
<td>−0.02</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>−0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>CRP</td>
<td>0.24</td>
<td>0.22</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>vWF</td>
<td>0.10</td>
<td>0.13</td>
</tr>
<tr>
<td>AST</td>
<td>0.30</td>
<td>0.27</td>
</tr>
<tr>
<td>ALT</td>
<td>0.43</td>
<td>0.38</td>
</tr>
<tr>
<td>ALP</td>
<td>0.17</td>
<td>0.14</td>
</tr>
</tbody>
</table>

GGT indicates γ-glutamyl transferase; BMI, body mass index; WC, waist circumference; FEV1, forced expiratory volume in 1 second; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; HOMA, homeostasis model assessment; eGFR, predicted glomerular filtration rate; CRP, C-reactive protein; IL, interleukin; vWF, von Willebrand factor; AST, aspartate transaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Test for age-GGT interaction, P<0.0001. HR indicates hazard ratio; GGT, γ-glutamyl transferase.

function. The observation that GGT predicted HF only in those aged <70 years was also consistent with the suggestion that GGT in the normal range is of limited usefulness in predicting CVD mortality in older patients. By contrast, no association was seen with other hepatic markers, including ALT, AST, or ALP, after taking GGT into account or when adjusted for other risk factors.

The findings that only GGT and not AST or ALT (more specific markers of hepatic function) or ALP was associated with incident HF in adjusted models suggest that the GGT-HF association may not simply reflect the influence of fatty liver, as measured by ALT, although imaging studies would be useful to confirm. The lack of association between ALT and HF is in keeping with the general finding that ALT is only weakly associated with CVD mortality. Liver dysfunction is also a clinical feature of HF, resulting particularly from hepatic venous congestion, which could lead to elevated GGT. Although we excluded men with diagnosed HF from analyses, it is possible that the increased risk is due to those with undiagnosed HF or asymptomatic left ventricular dysfunction, which may lead to increased GGT. However, GGT showed no association with NT-proBNP, a strong clinical measure of HF and left ventricular systolic dysfunction, which suggests that the association between GGT and incident HF appears unlikely to be due to undiagnosed HF. We did not have information on valvular heart disease. However, its prevalence in this study population would be expected to be low and its relevance to the present findings limited. It is of interest to note that a recent report showed GGT but not total bilirubin (a marker of hepatic dysfunction) to be predictive of adverse outcome in those with chronic HF and suggests that other pathways are likely to be operating.

We have investigated a wide range of possible mediators of the GGT-HF association. GGT is strongly influenced by alcohol intake, and excessive alcohol can lead to HF. However, less than 3% of the men in this study were deemed heavy drinkers (>6 drinks/day), and adjustment for alcohol intake did not affect the findings. The increased risk of HF is unlikely to reflect excessive alcohol drinking. The association between GGT and HF was shown to be independent of diabetes and metabolic abnormalities, including insulin resistance and blood pressure, which are associated with incident HF, and exclusion of men who developed diabetes during follow-up made little difference to the association seen. GGT is strongly influenced by obesity, an established risk factor for HF. However, the association between GGT and HF was independent of body mass index and leptin, a hormone derived from adipose tissue that is a strong blood surrogate for percentage fat mass. Both we and others have shown obesity to be a significant risk factor in elderly men suggesting that the GGT-HF association, observed only in those aged <70 years, is not necessarily reflecting obesity-related pathways. Another possible mechanism linking GGT to HF may be through its association with inflammation and endothelial dysfunction, which have been associated with the
The reasons for the age-GGT HF interaction are not clear. GGT showed similar associations with risk factors for HF in both the younger and older men. Speculatively, it has been postulated that serum GGT may reflect the amount of xenobiotics conjugated with glutathione.40 The cytochrome P450 class of enzymes are key metabolizers of xenobiotics that have been identified in the heart, and their levels have been reported to be altered during cardiac hypertrophy and HF.41 Clinical studies have suggested that certain cytochrome P450 enzymes may be involved in the disease process leading to HF.41 This particular hypothesis may partly explain the age interaction in our findings because hepatic metabolizing capacity of xenobiotics decreases with age,17 an observation potentially explaining the stronger association of GGT with incident CVD at younger ages.

It has been suggested that GGT may be useful for risk stratification for HF at least in younger populations.13 Although elevated GGT was associated with significant increased risk of HF we did not find GGT to significantly improve risk prediction in terms of C-statistics beyond routine clinical CVD biomarkers. However, the number of cases in those aged <70 in our study was relatively small (n = 66). Additional, larger studies and more formal prediction analyses are therefore needed to assess the usefulness of GGT in identifying those at high risk of HF in the younger elderly (60–70 years) population in clinical practice.

Our study has some limitations. It was based on an older, predominantly white male population of European extraction, so that the results cannot be generalized directly to women, younger populations, or other ethnic groups. However, the results observed here are consistent with reports from studies including women and younger subjects.13 The current findings are based on doctor diagnosed HF. Although this may underestimate the true incidence of HF, our estimates of incidence are close to those for the earlier Framingham Study42 and for a recent European study based on a community register.43 Moreover, the validity of HF ascertainment in the present study is supported by the consistency of the associations between risk factors and HF, both in the present report and in our previous report on obesity and HF,40 which generally accord with previous reports from other investigators.18,36

In conclusion, we have shown that elevated GGT predicted HF in men aged 60 to 69 years but not in those aged ≥70 years, independently of inflammation, obesity markers, and established risk factors for HF. By contrast, other markers of hepatic function (ALT, AST, and ALP) were more weakly associated HF in this older population. Additional, larger studies are needed to assess the potential of GGT for use in identifying individuals at high risk of HF in primary care settings and to determine the mechanisms responsible for this association.

Sources of Funding
The British Regional Heart Study is a British Heart Foundation (BHF) research group and receives support from BHF Programme Grant RG08/013/25942. The examination of study men aged 60 to 79 years was supported by BHF Project Grant 97012.

Disclosures
None.

References
6 Arterioscler Thromb Vasc Biol March 2012

γ-Glutamyltransferase, Hepatic Enzymes, and Risk of Incident Heart Failure in Older Men
S. Goya Wannamethee, Peter H. Whincup, A. Gerald Shaper, Lucy Lennon and Naveed Sattar

Arterioscler Thromb Vasc Biol. published online January 5, 2012;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2012/01/05/ATVBAHA.111.240457

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/