Relation of Circulating Liver Transaminase Concentrations to Risk of New-Onset Atrial Fibrillation

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Heart failure, a strong risk factor for atrial fibrillation (AF), is often accompanied by elevated liver transaminases. The aim of this study was to test the hypothesis that elevated transaminases are associated with the risk for incident AF in the community. A total of 3,744 participants (mean age 65 ± 10 years, 56.8% women) from the Framingham Heart Study Original and Offspring cohorts, free of clinical heart failure, were studied. Cox proportional-hazards models adjusted for standard AF risk factors (age, gender, body mass index, systolic blood pressure, electrocardiographic PR interval, antihypertensive treatment, smoking, diabetes, valvular heart disease, and alcohol consumption) were examined to investigate associations between baseline serum transaminase levels (alanine transaminase and aspartate transaminase) and the incidence of AF over up to 10 years (29,099 person-years) of follow-up. During follow-up, 383 subjects developed AF. The 2 transaminases were significantly associated with greater risk for incident AF (hazard ratio expressed per SD of natural logarithmically transformed biomarker: alanine transaminase hazard ratio 1.19, 95% confidence interval 1.07 to 1.32, p = 0.002; aspartate transaminase hazard ratio 1.12, 95% confidence interval 1.01 to 1.24, p = 0.03). The associations between transaminases and AF remained consistent after the exclusion of participants with moderate to severe alcohol consumption. However, when added to known risk factors for AF, alanine transaminase and aspartate transaminase only subtly improved the prediction of AF. In conclusion, elevated transaminase concentrations are associated with increased AF incidence. The mechanisms by which higher mean transaminase concentrations are associated with incident AF remain to be determined. **(Am J Cardiol 2013;111:219–224)**

Heart failure is 1 of the strongest risk factors for atrial fibrillation (AF)[1] and commonly goes along with an elevation of liver transaminases.[2] We hypothesized that elevations of liver transaminases may also be a marker of subclinical heart failure and thus an indirect marker of AF risk. In addition, the current guidelines for the management of patients with AF of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommend the assessment of liver function for the evaluation of patients with initial, incident diagnoses of AF, at least if their heart rates are difficult to control.[3] Because many drugs prescribed in the context of AF management are metabolized hepatically or affect liver function,[4] presumably, the guidelines recommend the

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assessment of liver function for pharmacodynamic reasons. With the present study, we therefore sought to assess whether transaminases are associated with risk for new-onset AF in a community-based sample.

Methods

The Framingham Heart Study was founded in 1948 by enrolling 5,209 subjects, who were followed regularly every 2 years.[5] For the present study, we examined 1,401 participants who attended the 20th examination cycle (1986 to 1990). Starting in 1971, the offspring of the Original cohort and their spouses were enrolled in the Framingham Offspring Study (n = 5,124) and were followed every 4 to 8 years. Offspring participants who attended the 7th examination cycle (1998 to 2001) were eligible (n = 3,539). We combined participants from the Original and the Offspring cohorts and excluded 1,196 participants for the following indications (detailed in Supplemental Table 1): age <45 years at examination (because the incidence of AF below this threshold is very low, and to make the age distribution of the 2 cohorts more comparable), did not attend the examination on site, incomplete or missing follow-up, incomplete covariate information, prevalent AF or heart failure, and transaminases >3 times the upper limit of normal (>120 U/L) (suggestive of prevalent liver disease; values ≤120 U/L are considered only mildly elevated[6]). The Boston University Medical Center Institutional Review Board approved the study protocols, and participants provided written informed consent at each examination.

We studied AF risk over up to 10 years of follow-up from the baseline examinations (cohort 20th [1986 to 1990] and Offspring 7th [1998 to 2001] examination). An AF diagnosis was based on AF or atrial flutter on electrocardiography or medical record information from routinely collected Framingham Heart Study examinations and inpatient or outpatient medical visits. Health history updates during examination visits and between examinations also contained a routine question regarding AF. If any cardiovascular, cancer, or orthopedic diagnosis or AF was indicated, all available medical records to substantiate diagnoses were reviewed. All incident AF electrocardiograms were individually reviewed by ≥2 Framingham cardiologists.[7]

Clinical covariates were routinely ascertained during the Framingham Heart Study examination visits. Physicians performed interviews and physical examinations and collected data on self-reported medication use (e.g., hypertension and statins), smoking status, and alcohol consumption. Participants were considered current smokers if they reported smoking cigarettes during the preceding year. Alcohol consumption was categorized as light or moderate to heavy drinking for men, if they consumed 1 to 14 or >14 drinks per week, respectively, and for women if they consumed 1 to 7 or >7 drinks per week, respectively. Systolic blood pressure was assessed as the average of 2 seated measurements. A systolic murmur of grade ≥3 on a scale of 6, or any diastolic murmur, was considered a clinically significant heart murmur. A dedicated end point committee adjudicated all diagnoses of heart failure on the basis of criteria published elsewhere.[8]

Fasting blood samples were drawn and processed immediately for storage at −70°C during the examination visits. Liver function tests assessed at the baseline examination included alanine transaminase (ALT; previously referred to as alanine aminotransferase or serum glutamic pyruvic transaminase) and aspartate transaminase (AST; previously referred to as aspartate aminotransferase or serum glutamic oxaloacetic transaminase). In the Original cohort, ALT and AST were measured using a Cobas Mira Analyzer using Roche Diagnostics reagents (Roche Diagnostics Corporation, Indianapolis, Indiana). In the Offspring cohort, ALT and AST were determined enzymatically using a Roche Hitachi 911 analyzer (Roche Diagnostics Corporation). For ALT, the intra- and interassay coefficients of variation were 3.8% and 4.4%, respectively. For AST, the intra- and interassay coefficients of variation were 3.1% and 4.5%, respectively. Details on the distribution of ALT and AST are provided in Supplemental Table 2 and Supplemental Figure 1. The 2 assays had comparable detection ranges. C-reactive protein (CRP) was available only in the Offspring cohort and was determined using the Dade Behring BN 100 high-sensitivity CRP reagent kit (Dade Behring, Deerfield, Illinois). Intra- and interassay coefficients of variation were 3.2% and 5.3%, respectively.

Table 1
Baseline characteristics of the study sample (n = 3,744)

Variable	Value
Clinical	
Age (yrs)	65 ± 10
Women	2,127 (56.8%)
Current smokers	454 (12.1%)
Light alcohol drinkers	1,769 (47.3%)
Moderate to heavy alcohol drinkers	636 (17.0%)
Body mass index (kg/m^2)	27.8 ± 5.2
Systolic blood pressure (mm Hg)	132 ± 21
Diastolic blood pressure (mm Hg)	75 ± 10
Heart rate (beats/min)	66 ± 11
PR interval (ms)	168 ± 28
Diabetes mellitus	360 (9.6%)
Antihypertensive treatment	1,408 (37.6%)
Statin medication use	532 (14.2%)
Significant cardiac murmur	120 (3.2%)
Biomarkers	
ALT (U/L)	19 (14−25)
Log$_e$ ALT	3.0 ± 0.4
AST (U/L)	21 (18−25)
Log$_e$ AST	3.1 ± 0.3
CRP (mg/L)*	2.2 (1.0−5.2)
Log$_e$ CRP*	0.8 ± 1.1

Data are expressed as mean ± SD, as number (percentage), or as median (interquartile range).

* Available in the Offspring cohort only.

Table 2
Incidence of AF

	n Event	n Total	Person-Years	AF Incidence/1,000 Person-Years
Total sample	383	3,744	29,099	13.2
≤40 U/L for both markers	348	3,492	27,204	12.8
>40 U/L for either marker	35	252	1,894	18.5

Table 3
Cox proportional-hazards models relating transaminases to incidence of AF

Adjustments	ALT		AST	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Primary models				
Age and gender	1.21 (1.09−1.34)	<0.001	1.11 (1.00−1.23)	0.05
Multivariable	1.19 (1.07−1.32)	0.002	1.12 (1.01−1.24)	0.03
Secondary models				
Multivariable model with additional adjustments				
CRP	1.18 (1.04−1.35)	0.01	1.10 (0.98−1.24)	0.12
Competing risk for death during follow-up	1.21 (1.08−1.35)	<0.001	1.12 (1.01−1.25)	0.03
Interim heart failure	1.19 (1.06−1.32)	0.002	1.12 (1.01−1.24)	0.03
Interim myocardial infarction	1.20 (1.07−1.34)	0.002	1.10 (0.99−1.22)	0.08
Restricting to transaminases ≤40U/L	1.14 (0.99−1.32)	0.07	1.06 (0.93−1.22)	0.39
Excluding moderate to heavy alcohol consumption	1.28 (1.10−1.39)	<0.001	1.18 (1.05−1.32)	0.005

Multivariable adjustment included age, gender, body mass index, alcohol consumption, smoking status, diabetes mellitus, antihypertensive treatment, cardiac murmur, PR interval, and systolic blood pressure. HRs are expressed per 1 SD of $\log_e$ ALT or $\log_e$ AST.
CI = confidence interval; HR = hazard ratio.

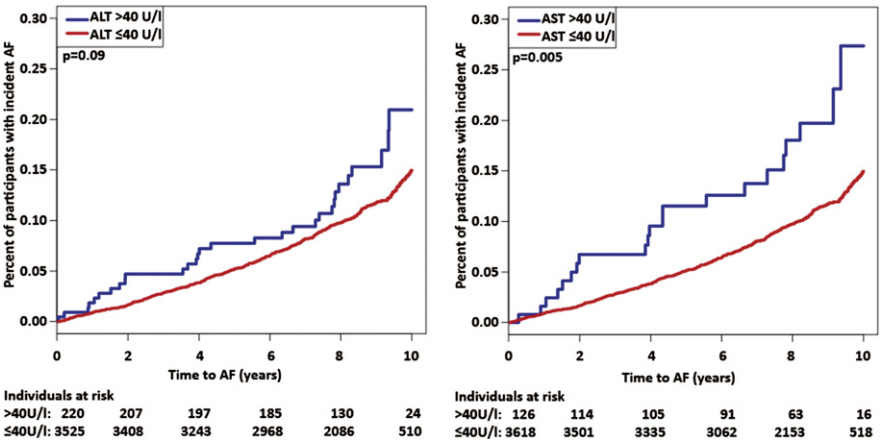

Figure 1. Cumulative hazard curves for the incidence of AF depicted by transaminase values ≤40 U/L versus >40 U/L; p values are derived from log-rank tests. *(Left)* ALT, *(right)* AST.

All discrete variables are expressed as frequencies and percentages. Untransformed biomarkers are expressed as medians with 25th and 75th percentiles; all other continuous variables, including natural logarithmically transformed ALT, AST, and CRP, are summarized as mean ± SD. Log-transformed ALT and AST were standardized to a mean of 0 and an SD of 1.

Interaction testing did not suggest effect modification by gender, so Cox models are gender pooled. We used Cox proportional-hazards models to assess the relations between ALT and AST and the incidence of AF. The follow-up time was up to 10 years; participants were followed from their baseline examinations until the development of AF. Censoring occurred at the time of death or at the end of follow-up. All models adjusted for age, gender, and cohort. Further multivariable models additionally adjusted for baseline risk factors included in the Framingham AF risk prediction model: body mass index, systolic blood pressure, electrocardiographic PR interval, antihypertensive treatment, smoking, diabetes, and valvular heart disease.[7] To account for its potential involvement in liver pathology, we also incorporated alcohol consumption into the model. We assessed the assumption of proportional hazards by calculating a supremum test on the basis of the cumulative sums of Martingale-based residuals.[9] Correlation between the clinically related transaminases was assessed using Pearson's correlation; models including the 2 transaminases were not assessed, because of potential collinearity. Instead, we forced the inclusion of previously established AF risk factors and used a stepwise, automated selection process with $p = 0.05$ to determine which transaminase would be selected. Effect estimates and confidence intervals for ALT and AST are shown for a 1-SD increase in the log-transformed biomarker values. For graphical presentation, we used cumulative hazard plots and spline plots with 3 knots around the untransformed median biomarker values of 18.0 U/L for ALT and 21.0 U/L for AST.

In secondary analyses, we assessed whether inflammation as measured by CRP might partially mediate the risk associated with elevated transaminases. As sensitivity analyses, we restricted our association analysis to subjects at the baseline examination with transaminases within the reference range (transaminase values ≤40 U/L), and we excluded participants with moderate or heavy alcohol

consumption. We also adjusted for the competing risk for death during follow-up. Further analyses additionally adjusted for the interim occurrence of heart failure and myocardial infarction, respectively.

In supplemental analyses, we assessed the ability of the transaminases to improve risk prediction of AF. To ensure complete follow-up for all subjects, we calculated all prediction analyses restricted to 8-year risk for AF. We calculated C-statistics and the difference in the C-statistic between the models with and without the respective transaminase.[10] To assess calibration, we calculated a Hosmer-Lemeshow statistic adapted for survival analyses.[11] In addition, we investigated the integrated discrimination improvement and the relative integrated discrimination improvement for each transaminase.[12] Reclassification of AF cases on the basis of the risk score including transaminases versus the score without the biomarkers was determined using a continuous and a user-defined net reclassification improvement analysis.[12] Eight-year risk categories for net reclassification improvement were selected as 5%, 5% to 10%, and 10%. Confidence intervals for prediction analyses were calculated using bootstrapping and 1,000-times resampling.

Results

Our overall study consisted of 3,744 participants, 875 of whom were derived from the Original cohort and 2,869 from the Offspring cohort. Clinical characteristics and the distributions of biomarkers are provided in Table 1. The mean follow-up duration was 7.77 ± 2 years (minimum 0.04, maximum 10.00) in 29,099 person-years of observation. During follow-up, 383 participants developed AF (Table 2). The mean age at the time of AF diagnosis was 76 years. At baseline, participants who subsequently developed AF were on average 6.8 years older than those who remained AF free.

In an age-, gender-, and cohort-adjusted model, ALT was significantly associated with incident AF; AST slightly missed statistical significance. In the multivariable-adjusted model, ALT and AST were significantly associated with incident AF (Table 3). Cumulative hazard curves illustrate the incidence of AF for subjects with baseline transaminase levels within reference limits (≤40 U/L) compared to those with elevated levels (>40 U/L) (Figure 1). Spline plots illustrate the increased risk for AF by increased transaminase values (Supplemental Figure 2). For ALT, a hazard ratio of 2 was reached at untransformed values of about 80 U/L, a hazard ratio of 3 at about 120 U/L, and a hazard ratio of 4 at about 150 U/L. ALT and AST were highly correlated ($r = 0.73$). In the Offspring cohort, neither of the transaminases was significantly correlated with CRP (ALT $r = -0.07$, and AST $r = 0.05$). By stepwise regression, ALT but not AST reached statistical significance for risk for AF once established risk factors were considered.

Secondary analyses are presented in Table 3. We additionally adjusted our model for CRP (available in the Offspring cohort only); the effect estimates minimally changed, and ALT remained significantly associated with new-onset AF, but AST did not. Consideration of death as a competing risk did not affect the associations. The incorporation of interim heart failure into the multivariable-adjusted model did not change the association of transaminases with AF risk. After the inclusion of interim myocardial infarction during follow-up, hazard ratios were slightly diminished; ALT remained significantly associated, but AST was not statistically significantly associated with AF. Restricting our analyses to subjects with transaminases within normal limits at baseline, the effect estimates for ALT and AST remained in the same direction but failed to reach statistical significance. Finally, we excluded participants with moderate to severe alcohol consumption, and both assessed transaminases remained significantly associated with incident AF after multivariable adjustment.

We assessed the ability of transaminases to improve AF risk prediction after 8 years of follow-up as supplemental analyses (Supplemental Tables 3 and 4). Models showed good calibration for ALT and AST. The predictive ability of ALT and AST, determined by an increase in the C-statistic, the absolute and relative integrated discrimination improvement, and the user-defined net reclassification improvement, failed to reach significance. Only the continuous net reclassification improvement metric suggested modest significant prediction improvement (17.8% for ALT, 16.3% for AST).

Discussion

In our study, we found evidence that impaired liver function as assessed by elevation of transaminases was significantly associated with incident AF over a 10-year follow-up period with multivariable adjustment for risk factors from a widely validated AF risk score. We further report that ALT and AST only subtly improved the prediction of AF when added to risk factors from an established AF risk score.

To date, numerous risk factors for AF have been described,[1] but the published research on AF and liver function is sparse. Only 1 case report describes a relation between the occurrence of AF in the context of manifest liver disease.[13] Another study reported that almost 28% of outpatients with AF presented with transaminase elevations >40 U/L; however, no suggestion was made regarding the causality or temporality of this observation.[14]

We found that transaminase elevation was associated with a moderate increased risk for incident AF. However, we are uncertain why ALT appeared to be more consistently associated with AF than AST. ALT is highly liver specific and localized in the cytosol,[15] whereas AST is present also in the mitochondria of various organs.[16] The 2 biomarkers indicate disintegration of liver cells, but ALT may be released more readily and thus occur more frequently.

Whereas we found an association between transaminases and AF, the underlying pathophysiological pathways remain unclear, and there are several plausible possibilities. The association might be due to preclinical heart failure. Heart failure and AF are closely related and share the burden of risk factors. Transaminase elevation is common in heart failure,[2] particularly in advanced stages.[17] We excluded subjects with clinical heart failure at baseline. Also, adjustment for clinically relevant interim heart failure during follow-up did not change our effect estimates for ALT or AST. Yet we hypothesize, but cannot prove, that alterations

in hepatic function presage heart failure. Regarding other potentially involved pathways, several investigations consistently found increased concentrations of transaminases in the context of the metabolic syndrome,[18–20] oxidative stress, and inflammation, and nonalcoholic fatty liver disease has been reported to be the most common cause.[21] When we adjusted for CRP, marking oxidative stress and inflammation,[22] the significance of the association with AF diminished for ALT and vanished for AST. Other factors possibly linking nonalcoholic fatty liver disease, oxidative stress or inflammation, and AF are a deranged adipokine profile, hypercoagulability, endothelial dysfunction, and accelerated progression of atherosclerosis.[23]

Alcohol consumption, leading to transaminase elevation,[24] was a last mechanism we considered to explain the relation between transaminase elevation and AF risk. To reflect the importance of alcohol, all of our multivariable models incorporated adjustment for alcohol consumption. Our sensitivity analysis excluded all participants with moderate or heavy alcohol intake, and the associations between transaminases and AF risk remained largely unchanged. Yet it is possible that the true extent of alcohol use was misclassified because of participants' nondisclosure of their true drinking habits.

Overall, the association between transaminases and AF is likely to be multifactorial. We acknowledge that residual confounding may partially or completely explain the association. For instance, natriuretic peptides (which were unavailable at the index examination) are a valuable diagnostic and predictive marker of cardiac dysfunction,[25] are correlated with the degree of liver dysfunction[26] and also are strongly associated with AF.[27,28]

We were also interested in the association between transaminases and AF because of guideline-based recommendation to assess liver function in patients with incident first episodes of AF.[3] We note that the recommendation is undoubtedly for pharmacodynamic reasons. Almost all antiarrhythmic and anticoagulant drugs are at least partly eliminated hepatically, and their half-lives and clearance are affected in the setting of impaired liver function.[4] Impaired liver function constitutes an increased risk for bleeding complications, a circumstance that led to the incorporation of liver function into clinical scores such as HAS-BLED to assess the risk for bleeding.[29]

In our supplemental analysis, we also aimed to identify the potential of transaminases to contribute to AF risk prediction. ALT and AST subtly improved the prediction of AF beyond previously established factors. The discrepancy between a transaminase-AF association and weak predictive abilities requires careful interpretation. One reason might be that transaminases only are an imperfect marker of a truly underlying condition.

Our study results benefit from a well-phenotyped sample with highly systematic follow-up and detailed outcome ascertainment. However, a number of limitations need to be considered. Our sample was predominantly of European descent. We thus cannot comment on subjects of different ethnic and racial backgrounds. Despite careful assessment of each AF event, the arrhythmia is often asymptomatic and might thus have been missed during case ascertainment. Furthermore, different subtypes of AF exist. We investigated overall AF only and therefore cannot comment on the association of transaminases depending on AF type (e.g., paroxysmal AF, permanent AF, or atrial flutter). Also, we cannot comment on whether transaminase levels influence the progression of AF from a paroxysmal to a permanent type. Our study was limited by a fixed sample size, the lack of a validation sample, and the availability of CRP in the Offspring cohort only. Liver function in its entirety is only partly reflected by transaminases. Other liver related biomarkers, in particular bilirubin, alkaline phosphate, and γ-glutamyltransferase, were not consistently available in the investigated examination cycles. Also, transaminases were assessed at baseline only; we could not investigate the relation of variation in transaminases over time to incident AF risk. Furthermore, complete 10-year follow up was not available for all participants; we thus had to restrict our risk prediction analysis to 8 years of follow-up. We cannot exclude residual confounding.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amjcard.2012.09.021.

Disclosures

The authors have disclosed no conflicts of interest.

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