Relation of Alanine Aminotransferase Levels to Cardiovascular Events and Statin Efficacy

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The relation between hepatic serum markers within the normal range and cardiovascular risk is uncertain. We sought to address this issue within a prospective randomized trial of statin therapy. Men and women (n = 17,515) free of cardiovascular disease participating in a randomized placebo controlled trial of rosuvastatin 20 mg/day had baseline levels of alanine aminotransferase (ALT) below <40 IU/l and were followed prospectively for the first-ever cardiovascular events. Cox proportional hazards models were used to calculate the relative risks of these events according to increasing tertiles and each SD increase in baseline ALT levels. ALT levels at study entry, all within the normal range, were inversely associated with age, smoking status, and inflammation and were positively associated with male gender, alcohol use, and triglycerides. Incident cardiovascular event rates were highest in those in the lowest tertile of baseline ALT; specifically, incidence rates were 1.43, 0.98, and 0.85 per 100 person-years of exposure for those in the lowest, middle, and highest tertile of baseline ALT within the normal range, respectively (p <0.001). These inverse effects remained statistically significant after multivariate adjustment for a wide range of vascular risk factors risk markers such that each higher SD unit of ALT was associated with an 18% lower event rate (relative risk 0.82, 95% confidence interval 0.72 to 0.93, p = 0.002). The efficacy of statin therapy was not modified by baseline ALT level. In conclusion, increasing ALT levels within the normal range are inversely associated with future cardiovascular risk but had limited clinical utility and also did not modify the efficacy of statin therapy. **(Am J Cardiol 2016;118:49−55)**

Alanine aminotransferase (ALT) is released by the liver both in pathologic and normal physiological conditions. Clinically, levels of ALT above the upper limit of normality have been associated with increased risks for hepatic and cardiovascular events,[1] in part due to underlying nonalcoholic fatty liver disease (NAFLD) and its consequent effects on metabolic dysfunction and diabetes.[2,3] Besides, statin therapy can increase ALT levels and elevations over 3 times the upper normal limit of ALT have in turn been considered a relative contraindication for therapy with this class of lipid-lowering agent.[4] In contrast, recent data have suggested an apparent paradox between ALT levels within the normal range, incident vascular event rates, and the efficacy of statin therapy. In particular, prospective cohort studies have reported inverse relations between ALT levels within the normal range and subsequent risks for cardiovascular events and all-cause mortality such that those in higher ALT stratum have reduced event rates versus those in the lower ALT group.[5−7] Furthermore, reports from 2 statin trials have suggested that those with ALT levels higher than the upper limit of normal obtain a greater relative risk reduction from lipid-lowering therapy versus those with normal ALT levels.[8,9] Whether the efficacy of statin therapy is modified by ALT levels within the normal range, however, is uncertain. We addressed these issues in the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, a contemporary randomized double-blind placebo-controlled evaluation of rosuvastatin 20 mg. That trial included 17,515 apparently healthy men and women with ALT levels ≤40 IU/l who were followed prospectively for future vascular events.[10]

Methods

The sample was derived from JUPITER (ClinicalTrial.gov NCT00239681), a randomized, double-blind, placebo-controlled trial designed to investigate whether rosuvastatin 20 mg/day compared to placebo decreases the rate of the first-ever cardiovascular events in apparently healthy men aged >50 years and women >60 years with low-density lipoprotein (LDL) cholesterol <130 mg/dl who were at increased vascular risk because of a high-sensitivity C reactive protein (hsCRP) level ≥2 mg/l.[10] The full details of the trial protocol have been previously presented.[10] The trial exclusion criteria included diabetes, treatment with any lipid-lowering therapy in the 6 weeks preceding randomization, current use of postmenopausal hormonal replacement therapy, previously known ALT levels higher than 2 times the upper limit of normal, creatinine >2.0 mg/dl, uncontrolled hypertension or hypothyroidism, a history of

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See page 54 for disclosure information.

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Table 1
Baseline clinical characteristics of the study population according to increasing tertiles of alanine aminotransferase measured at study entry

ALT Range (IU/L)	Lower	Intermediate	Higher	p value
	≤11 N = 5505	12-16 N = 5896	>16 N = 6114	
Age (years)	68.8 (7.7)	66.4 (7.4)	63.6 (7.1)	<0.001
Men	48.2%	60.5%	74.6%	<0.001
Body mass index (kg/m^2)	27.9 (6.0)	28.9 (5.4)	30.0 (5.7)	<0.001
Waist Circumference (cm)	95.5 (13.6)	98.7 (14.1)	102.3 (13.2)	<0.001
Alcohol ≥1 drink per day	13.3%	18.3%	23.4%	<0.001
Current Smoker	18.6%	15.0%	14.1%	<0.001
Estimated Glomerular Filtration Rate (ml/min)	74.3 (18.8)	74.9 (17.1)	76.6 (16.3)	<0.001
Family History of Early Coronary Heart Disease	10.8%	11.6%	12.2%	0.068
Metabolic Syndrome	33.9%	39.5%	50.5%	<0.001
Hypertension	57.2%	56.6%	57.9%	0.361
Systolic Blood Pressure (mmHg)	135 (17)	136 (17)	136 (17)	<0.001
Diastolic Blood Pressure (mmHg)	80 (9)	81 (9)	82 (9)	<0.001
Fasting Glucose (mg/dl)	92.7 (11.1)	94.7 (11.5)	96.8 (11.9)	<0.001
HbA1C (%)	5.7 (0.5)	5.7 (0.4)	5.7 (0.4)	0.200
Total Cholesterol (mg/dl)	182 (25)	184 (24)	184 (24)	<0.001
HDL Cholesterol (mg/dl)	53.3 (15.6)	51.7 (15.0)	49.2 (14.9)	<0.001
LDL Cholesterol (mg/dl)	104 (19)	105 (18)	104 (19)	0.748
Triglycerides (mg/dl)*	107 (80 − 149)	117 (84 − 166)	132 (93 − 193)	<0.001
Apolipoprotein-a (mg/dl)	167 (31)	166 (31)	164 (30)	<0.001
Apolipoprotein-b (mg/dl)	105 (21)	109 (21)	112 (22)	<0.001
High sensitive C Reactive Protein (mg/L)*	4.7 (3.0 - 8.3)	4.2 (2.8 - 6.8)	4.1 (2.8 - 6.5)	<0.001
Framingham Risk Score*	10 (5 − 16)	10 (6 − 16)	11 (6 − 16)	<0.001
Reynolds Risk Score*	10.0 (5.5 − 17.3)	9.6 (5.6 − 16.1)	9.4 (5.9 − 15.5)	0.009
Drug (Rosuvastatin)	50.0%	50.2%	49.6%	0.801
Delta LDL Cholesterol (mg/dL)	-14 (-49 − +6)	-12 (-51 − +7)	-14 (-51 - +7)	0.521

Continuous variables expressed by means (standard deviations) or median (interquartile range) signaled by *; meanwhile categorical ones expressed by percentage unless otherwise specified. Delta LDL cholesterol = LDL cholesterol at 12 months − baseline LDL cholesterol.

malignancy within 5 years, or another serious medical condition that might compromise patient safety or successful completion of the study.

Of 17,783 participants enrolled in this trial, 268 had baseline ALT levels >40 IU/l, the upper normal limit cutoff in the trial. Thus, the present analysis included 17,515 participants with baseline ALT levels within the study normal limits. Differences in clinical characteristics and 10-year predicted risk Framingham-based ATP-III risk estimator[11] and Reynolds risk score[12,13] between those in each ALT tertile were tested for trend by linear regression if normal and Jonckheere-Terpstra for nonparametric or categorical variables. We displayed the age- and gender-adjusted cumulative incident cardiovascular events curves for ALT tertiles and the age- and gender-adjusted hazard ratios (HRs) of the second and third tertiles versus the first. The relation of baseline ALT levels with future vascular events was addressed by its tertiles and SD units in Cox proportional hazards models to calculate crude and adjusted incidence rates for the composite end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina pectoris, or death from cardiovascular causes. Models were adjusted for age, gender, waist circumference, smoking status, alcohol consumption, systolic blood pressure, fasting glucose, plasma lipid levels, statin treatment, and hsCRP. Effect modification was addressed by stratified analyses according to age categories (<65 and ≥65 years), gender, smoking status, waist circumference categories (normal ≤102 cm for men and ≤88 cm for women, and abnormal otherwise), alcohol consumption categories (no or infrequent use if less than weekly consumption and regular otherwise), metabolic syndrome, and Reynolds risk score (<7.5% and ≥7.5%) categories. Rosuvastatin relative risk reductions were compared to placebo for each ALT tertile to evaluate effect modification. We also displayed the age- and gender-adjusted cumulative incident cardiovascular events curves for treatment arms within each ALT tertile and the age- and gender-adjusted HRs for rosuvastatin versus placebo. To address the HR for events across the ALT range in a more flexible way, we plotted adjusted smoothed spline with ALT knots at the 5, 25, 50, 75, and 95 percentiles values.

Cardiovascular risk prediction based on Reynolds risk score was compared in models with and without the addition of ALT in nonstatin users. The Reynolds risk score predicts cardiovascular death, myocardial infarction, stroke, and coronary revascularization. We compared *C*-statistics for the 2 models and computed the integrated discrimination improvement (IDI) and relative IDI and categorical net reclassification improvement (NRI). The group cutoffs for NRI were 1% and 1.5%, which correspond to 5% and 7.5% risk in 10 years of follow-up assuming events accumulate linearly every 2 years.

JUPITER was an investigator-initiated trial. The sponsor of the study collected the trial data and monitored the study sites but had no access to unblinded data until after the drafting of the trial primary report. All statistical analyses