HHS Public Access

Author manuscript

Thromb Haemost. Author manuscript; available in PMC 2015 March 06.

Published in final edited form as:

Thromb Haemost. 2009 July ; 102(1): 179–180. doi:10.1160/TH09-01-0037.

Coronary heart disease risk, aspirin use, and apolipoprotein(a) 4399Met allele in the Atherosclerosis Risk in Communities (ARIC) study

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Dear Sir,

The *LPA* gene encodes apolipoprotein(a), a component of the plasma lipoprotein Lp(a), and the Ile4399Met polymorphism (rs3798220) of this gene is associated with coronary heart disease (CHD). Carriers of the 4399Met allele (~3.5% of the European American population), compared with noncarriers, were shown to have increased risk of CHD and to have higher levels of plasma Lp(a) in case-control studies (1, 2) and in a prospective study of 4,522 older (>65) North Americans (3). Carriers of the 4399Met variant were also at increased risk of major cardiovascular events in the Women's Health Study (WHS), a randomised trial of low-dose aspirin and placebo in initially healthy women aged 45 years or older. A post-hoc genetic analysis of 25,131 participants in the WHS (4) revealed that in the placebo group carriers of the 4399Met allele, compared with noncarriers, had over two-fold increased risk for major cardiovascular events (hazard ratio [HR] 2.21, 95% confidence interval [CI] 1.39–3.52). Furthermore, this increased risk was essentially eliminated by low-dose aspirin treatment in the WHS.

However, in the Atherosclerosis Risk in Communities (ARIC) study, a prospective study of 15,792 African American and European American adults aged 45 to 64 years, this *LPA* polymorphism was not associated with CHD (HR: 1.01, p=0.98 among European Americans, HR: 1.46, p=0.45 among African Americans) (5). Because evidence from the WHS suggested that aspirin treatment could ameliorate the risk associated with the 4399Met allele of *LPA*, we asked whether aspirin use by ARIC participants affected the association

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between the Ile4399Met polymorphism and CHD. Specifically, we asked whether carriers of the 4399Met allele, compared with noncarriers, had a higher risk for CHD among aspirin nonusers than among aspirin users.

After recruitment, ARIC participants were invited to participate in three follow-up examinations, at approximately two-year intervals. Detailed information regarding regular aspirin use was first collected from ARIC participants during the third follow-up examination (visit 4), which occurred at a median of 8.9 years following recruitment. Therefore, we analysed the time from visit 4 to the first incident CHD event according to aspirin use. This analysis was limited to the 6,752 European American ARIC participants who had not had a CHD event prior to visit 4, and who had *LPA* genotype information as well as aspirin use information available. We defined aspirin users as those who at visit 4 reported regularly using aspirin seven days a week (n = 1,422; 4399Met carriers = 53). Aspirin nonusers were defined as those who at visit 4 reported that they did not use aspirin regularly (n = 5,330; 4399Met carriers = 168). CHD events included definite or probable myocardial infarction, definite CHD death, or coronary revascularisation. During a median follow-up of 7.2 years (after visit 4), 636 (9.4%) of the 6,752 ARIC participants in this analysis had a first incident CHD event: 385 events were among aspirin nonusers (7.2% of 5,330 nonusers) and 251 events were among aspirin users (17.7% of 1,422 users). For carriers of the 4399Met allele, compared with noncarriers, among nonusers of aspirin the HR for CHD was 1.57 (95%CI 0.92–2.69, p=0.098, Fig. 1), after adjusting for age and sex. Among aspirin users the hazard ratio was 0.86 (95%CI 0.38–1.95, p=0.73): p=0.22 for interaction between carrier status and aspirin use.

In summary, among self-reported nonusers of aspirin in ARIC we found increased risk for CHD among carriers of the 4399Met allele, compared with noncarriers. However, using a two-sided test, this increased risk did not reach statistical significance. Carriers, compared with noncarriers, were not at increased risk for CHD among self-reported regular users of aspirin. Thus, although further studies would be required to validate this finding, these observations in ARIC, which include both male and female participants, are in the same direction that was reported in the WHS, namely that aspirin treatment ameliorated the risk associated with 4399Met carrier status.

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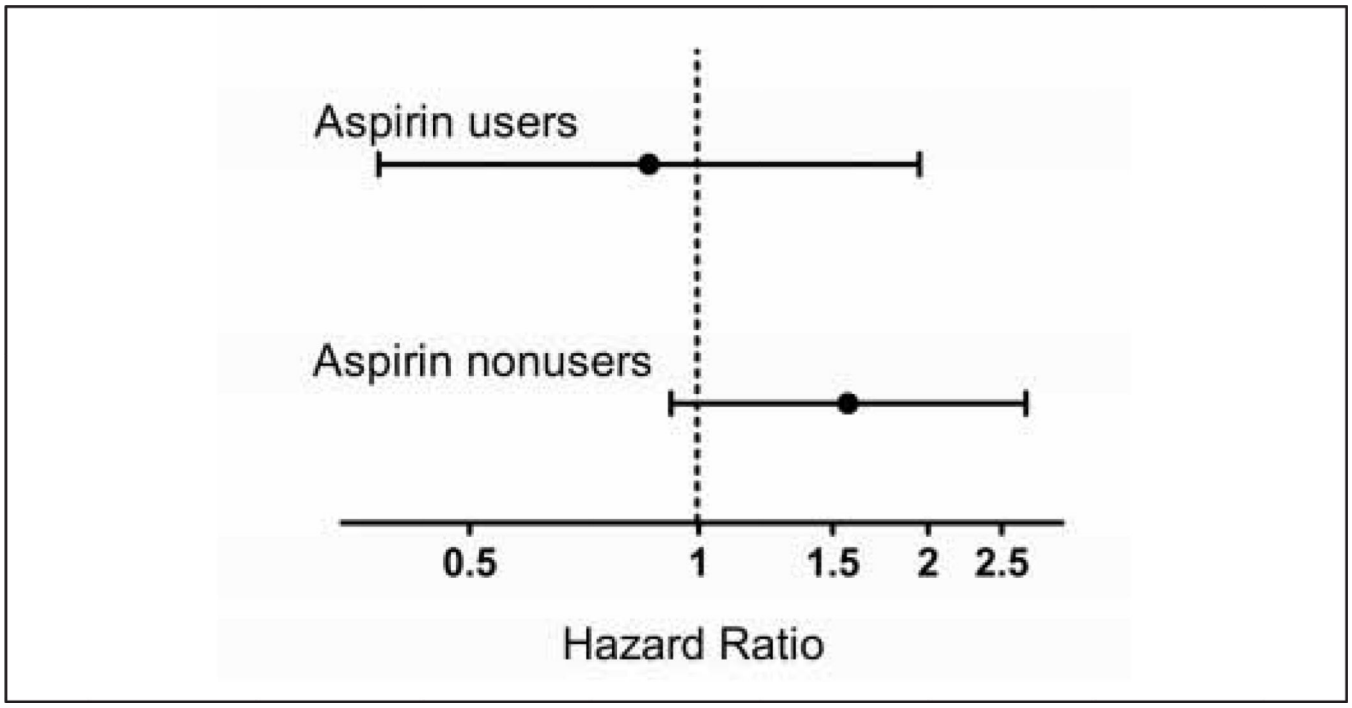

Figure 1.
Risk of incident coronary heart disease (CHD) among carriers of the 4399Met allele of *LPA* according to aspirin use; whiskers denote 95% confidence intervals.