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Letters

RESEARCH LETTER

Lipoprotein(a) and Benefit of Antiplatelet Therapy

Insights From the PEGASUS-TIMI 54 Trial

Lipoprotein(a) [Lp(a)] is an independent risk factor for atherogenesis and has been postulated to exert a prothrombotic effect.[1,2] Studies have suggested that antiplatelet therapy may attenuate the risk conferred by higher levels of Lp(a).[3,4] An analysis of the Women's Health study suggested greater benefit with low-dose aspirin vs placebo in carriers harboring variants associated with elevated Lp(a) concentrations.[3] A smaller study from the ASPREE trial also suggested greater benefit with aspirin use in carriers harboring the same variant, but a similar interaction was not seen when applying a more comprehensive Lp(a) genetic risk score.[4] Whether prolongation or intensification of dual antiplatelet therapy is especially beneficial in a secondary prevention population with higher Lp(a) concentrations remains uncertain. We assessed the benefit of prolonged ticagrelor vs placebo on a background of low-dose aspirin as a function of baseline Lp(a) concentrations in PEGASUS-TIMI 54,[5] a randomized trial of stable patients enrolled 1 to 3 years after a myocardial infarction (NCT01225562).

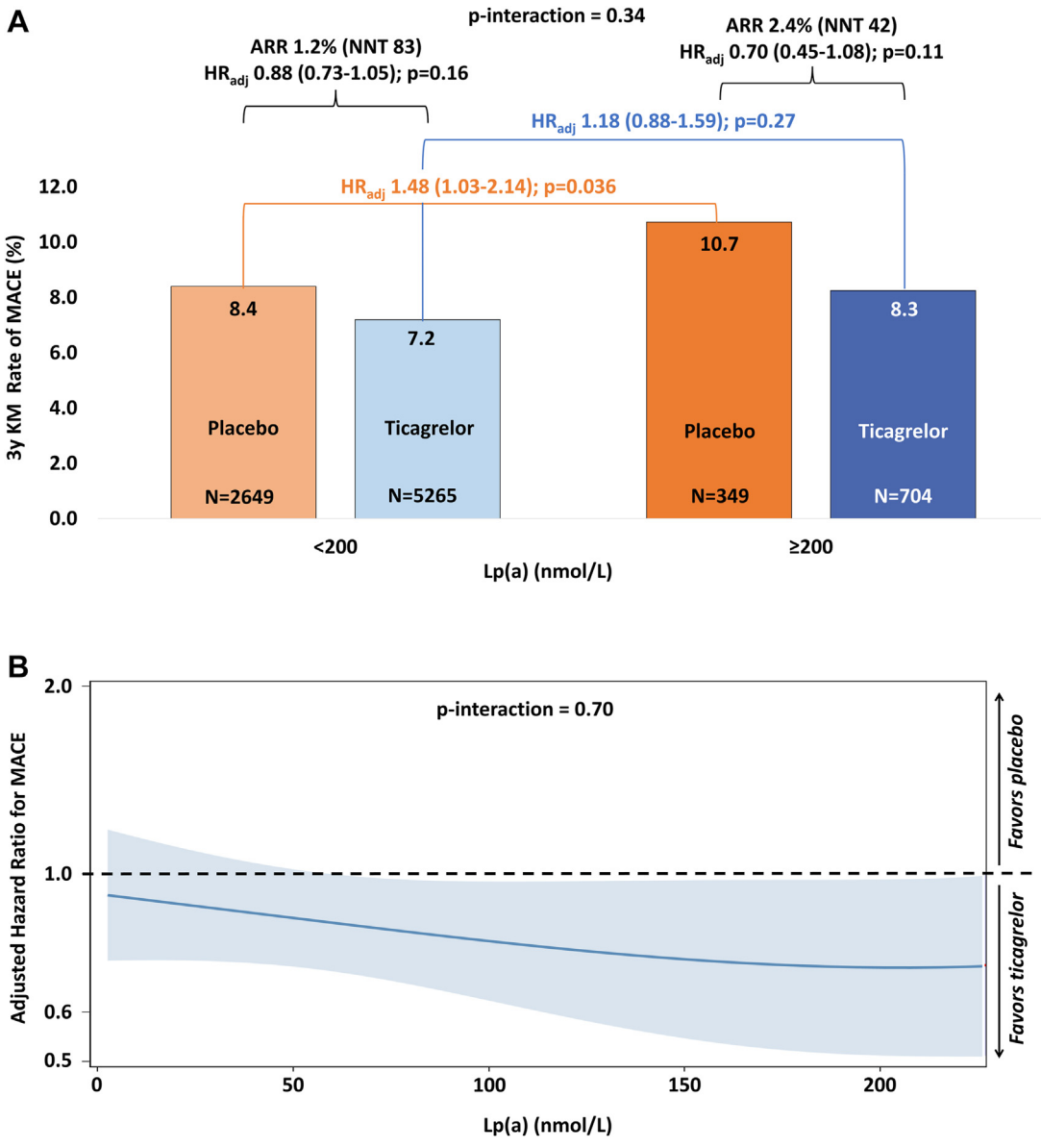
This analysis includes patients consenting to the biomarker substudy (conducted in a subset of countries participating in the parent trial) with available Lp(a) at randomization (n = 8,967), measured using an isoform-independent assay (Randox) on the Cobas 6000 analyzer (Roche). The outcome was major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, or stroke) at a median follow-up of 2.7 years, assessed as time-to-event. The ticagrelor 90 and 60 mg twice daily dosing arms were pooled for this analysis given nearly identical treatment effect on MACE observed in the primary trial results. Event rates are Kaplan-Meier estimates at 3 years. HRs were derived using a Cox model with adjustment for age, sex, race, hypertension, diabetes, smoking, creatinine clearance <60 mL/min, and apolipoprotein-B (apoB) at baseline. Lp(a) was categorized as high vs low using 200 nmol/L as a previously proposed threshold of risk[2] and modeled continuously. The prognostic associations of Lp(a) with MACE and treatment effect of ticagrelor vs placebo was assessed using 3 separate analyses. First, the prognostic associations of high vs low Lp(a) were evaluated separately in the placebo and the ticagrelor arm. Second, the treatment effect for ticagrelor vs placebo was evaluated separately in the high- and low-Lp(a) groups. Third, the treatment effect of ticagrelor vs placebo was evaluated across Lp(a) as a continuous variable using restricted cubic splines. Interaction testing was performed for treatment allocation by Lp(a) concentration.

The median Lp(a) was 29 (IQR: 12-137) nmol/L. Those with Lp(a) ≥200 (11.7%) vs <200 nmol/L were less likely to be White (94.6% vs 96.8%) or male (63.7% vs 78.2%), with higher prevalence of hyperlipidemia (87.0% vs 83.2%), lower prevalence of diabetes (25.5% vs 30.4%), and higher baseline apoB (median: 0.8 [IQR: 0.7-1.0] mg/dL vs 0.7 [IQR: 0.6-0.9] mg/dL) ($P < 0.01$ for each). No significant differences were observed in baseline characteristics between treatment allocation arms within Lp(a) groups ($P \geq 0.05$ for each).

A total of 621 MACE events occurred during follow-up. In the complete trial population, ticagrelor (pooled) vs placebo reduced the risk of MACE (HR: 0.84 [95% CI: 0.76-0.94]) overall, with consistent treatment effect in this subset of patients with available Lp(a) (HR_{adj}: 0.85 [95% CI: 0.72-1.004]). After multivariable adjustment, patients with high Lp(a) concentration randomized to placebo had 48% greater risk of MACE compared with those with low Lp(a) (≥200 vs <200 nmol/L: HR_{adj}: 1.48 [95% CI: 1.03-2.14]; $P = 0.036$) (Figure 1A). In contrast, the risk conferred by high vs low Lp(a) for MACE tended to be attenuated in those randomized to ticagrelor (HR_{adj}: 1.18, 95% CI: 0.88-1.59; $P = 0.27$; P interaction = 0.34) (Figure 1A).

The treatment effect (HR_{adj}) of ticagrelor vs placebo on MACE was 0.70 (95% CI: 0.45-1.08; $P = 0.11$) in those with high Lp(a) compared with 0.88 (95% CI: 0.73-1.05; $P = 0.16$) in those with low Lp(a)

FIGURE 1 Treatment Benefit of Ticagrelor vs Placebo Across Lipoprotein(a) Concentrations



(A) depicts the prognostic associations and the treatment effect of ticagrelor compared with placebo across lipoprotein(a) analyzed dichotomously. (B) depicts the treatment effect of ticagrelor vs placebo across lipoprotein(a) analyzed continuously. ARR = absolute risk reduction; MACE = major adverse cardiovascular event composite of cardiovascular death, myocardial infarction or stroke; NNT = number needed to treat.

(*P* interaction = 0.34) (Figure 1A), with absolute risk reductions of 2.4% and 1.2%, respectively. The effect of ticagrelor on MACE by continuous Lp(a) is shown in Figure 1B.

These data reaffirm the prognostic associations of Lp(a) with cardiovascular events in a secondary prevention population, highlighting a potential role for emerging Lp(a)-lowering therapies. Moreover, these findings suggest ticagrelor may partially mitigate the risk conferred by higher Lp(a), and that Lp(a) may potentially help identify those who derive greater absolute benefit from prolonged dual antiplatelet therapy. Despite numerically greater absolute risk reduction with ticagrelor vs placebo in those with higher Lp(a), it should be noted that treatment interaction by Lp(a) did not achieve statistical

significance, which may be due to limited power for interaction testing. As such, our findings should be considered hypothesis-generating. In conclusion, long-term secondary preventive therapy with ticagrelor reduces MACE across the range of Lp(a), with a potential for greater benefit in those with higher Lp(a) that warrants further investigation in larger studies.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society Consensus Statement. *Eur Heart J*. 2022;43:3925–3946.

2. Cegla J, Neely RDG, France M, et al. HEART UK consensus statement on Lipoprotein(a): a call to action. *Atherosclerosis*. 2019;291:62–70.

3. Chasman DI, Shiffman D, Zee RY, et al. Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. *Atherosclerosis*. 2009;203:371–376.

4. Lacaze P, Bakshi A, Riaz M, et al. Aspirin for primary prevention of cardiovascular events in relation to lipoprotein(a) Genotypes. *J Am Coll Cardiol*. 2022;80:1287–1298.

5. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.