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EDITORIAL COMMENT

Lp(a)

Are Antithrombotic Therapies the Key to Event Reduction?*

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Elevated levels of lipoprotein(a) [Lp(a)] are now accepted as an independent risk factor for cardiovascular disease, owing to significant research advancements in recent years. However, no specific measurements are indicated in primary prevention, and patients with high Lp(a), who are known to have higher cardiovascular risk, are managed no differently from the general population. From the lipid-lowering therapies available today, only proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce Lp(a) levels, being translated into a greater benefit in this specific population.[1,2] Effects of statins in this specific population are controversial because they do not reduce Lp(a) levels, but rather they increase them.[3] New RNA-based therapeutics are being developed with good prospects, but they are not yet available.[4] In order to promote clinical guidelines regarding the treatment of elevated Lp(a) levels, we must first understand its mechanism of action.

The pathogenic mechanism of Lp(a) has been widely studied, and yet there is still no scientific consensus. Classically, a combination of prothrombotic and proatherogenic effects has been observed; these 2 mechanisms of action were usually found together. The main hypothesis about the prothrombotic effects of Lp(a) was a potential antifibrinolytic effect by inhibiting plasminogen activation; this hypothesis had its origin in the strong resemblance between the Lp(a) and the plasminogen molecules. However, a prothrombotic effect appears to occur only in the presence of atherosclerotic lesions, in a very focal pattern. No evidence of systemic venous thrombosis has been found in the presence of elevated Lp(a) levels.[5]

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In this issue of the *Journal of the American College of Cardiology*, the study by Lacaze et al[6] reveals a potentially different prothrombotic mechanism related to Lp(a): that Lp(a) is actually influencing platelet aggregation.[6] Although this had been hypothesized before, prior studies have only led to contradictory findings.[7,8] In this landmark study, a primary prevention treatment for patients carrying the rs3798220-C *LPA* gene variant, namely the use of low-dose aspirin, is proposed for the first time. The results are of interest, indicating that platelet inhibition by aspirin produces a significant reduction of events in subjects with elevated Lp(a) genotype. These findings support the hypothesis that the prothrombotic mechanism of Lp(a) is mediated by platelet aggregation rather than by loss of fibrinolytic activity as previously postulated, which would explain the occurrence of thrombotic events in the presence of atherosclerosis. Elevated Lp(a) levels may induce platelet adhesion and aggregation to the activated atherosclerotic plaque, thus enhancing the atherothrombotic process. Moreover, activated platelets release several mediators that result in cell adhesion and attraction of chemokines and proinflammatory cytokines, driving an inflammatory response and mediating atherosclerosis progression.[9] Furthermore, prior studies have attributed

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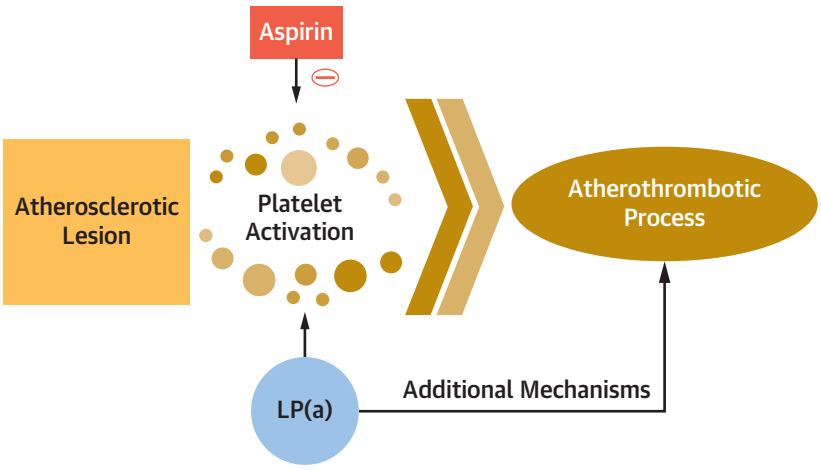
FIGURE 1 Prothrombotic Mechanism of Lp(a)



In the presence of atherosclerotic plaque, lipoprotein(a) [Lp(a)] would induce platelet aggregation and activation. The activated platelets release inflammatory cytokines and activate cell adhesion, leading to an inflammatory response that favors the atherothrombotic process. This pathway is attenuated by the use of aspirin.

proinflammatory and proatherogenic effects to Lp(a).[10] Such properties of Lp(a), including the attraction of chemokines, the increase of oxidized phospholipids, the formation of a necrotic core, and the calcification of lesions, would accelerate the process (Figure 1).[10] The inhibition of platelet aggregation by aspirin would attenuate part of this process; however, further actions might be needed to decrease the risk in these patients. Whether strategies that decrease the levels of circulating Lp(a) will be effective is yet to be proven. Moreover, if the atherosclerotic plaque is the common substrate for the development of events, focusing on plaque reduction would help to eradicate the root cause of the problem.

Interestingly, Lacaze et al[6] showed that in the aspirin group, carriers of the *LPA* gene variant had a lower risk of events than noncarriers. They also calculated a lipoprotein(a) genetic risk score (LPA-GRS) and showed that high quintiles of LPA-GRS had a lower risk of events than low quintiles. This suggests that these events are mainly led by some prothrombotic mechanism that is attenuated by low-dose aspirin. On the other hand, the authors found a significant interaction with aspirin when comparing carriers with noncarriers. However, this interaction was not significant when comparing high LPA-GRS quintiles to low quintiles. This could suggest that the presence of the genetic variant implies a specific risk that does not fully overlap with that conferred by the elevated circulating Lp(a) levels.

As Lacaze et al[6] point out, the genotype-based assessment of Lp(a) is an important limitation of the study. Whereas around 30% of the population is estimated to have elevated Lp(a) levels,[10] only 3.2% of the >12,000 subjects included in this study presented the *LPA* genetic variant. Further, because the study excluded non-European ancestries, the results are difficult to extrapolate to other populations. Also, it is of note that the study is limited to a population ≥70 years of age; however, these results complement those of the Womeńs Health Study that was performed in a younger female population, and showed that a subgroup of women with elevated Lp(a) levels benefited from aspirin.[11]

In conclusion, Lacaze et al[6] are to be congratulated for a study of very high clinical relevance that represents a first indication for primary prevention for patients at high cardiovascular risk. The next steps in clinical practice should be defined, and there are still questions to be answered. Will every patient benefit from antithrombotic therapies? Should all patients who have elevated Lp(a) levels be treated with aspirin?

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