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Short Report

Is there a benefit of aspirin therapy for primary prevention to reduce the risk of atherosclerotic cardiovascular disease in patients with elevated Lipoprotein (a)—A review of the evidence

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HIGHLIGHTS

- Definition of lipoprotein(a) and screening recommendations.
- Mechanism of lipoprotein(a) increasing ASCVD.
- Potential mechanisms of aspirin therapy in individuals with elevated lipoprotein(a).
- Review of literature supporting the benefits of aspirin therapy in individuals with elevated lipoprotein(a).

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ABSTRACT

Aspirin has long been recognized as a beneficial treatment for atherosclerotic cardiovascular disease (ASCVD) due to its antiplatelet effects. However, there is a need to more precisely identify individuals who would benefit from aspirin therapy for primary prevention in order to reduce the risk of ASCVD. Those with elevated lipoprotein (a) [Lp(a)] levels are at increased risk of ASCVD. In this article, we provide an overview of studies that have explored the use of aspirin therapy in individuals with elevated Lp(a). We discuss the potential mechanisms by which aspirin therapy may reduce ASCVD risk, and present a review of the data on the effectiveness of aspirin therapy in reducing ASCVD risk in individuals with elevated Lp(a). The presented evidence suggests that individuals with elevated Lp(a) benefit more from aspirin therapy for reduction of ASCVD events than the general population.

1. Introduction

Lipoprotein a [Lp(a)] is a low-density lipoprotein (LDL) variant with an additional glycoprotein, apolipoprotein(a) [apo(a)], linked to apolipoprotein B. Elevated levels of Lp(a) (≥50 mg/dL) have been linked with increased risk of ASCVD). Lp(a) levels are primarily determined genetically through variations of the LPA gene, which is responsible for coding apo(a). Variations in the LPA gene includes kringle IV type 2 (KIV-2) repeats, which inversely correlate with Lp(a) levels, and single nucleotide polymorphisms (rs10455872 and rs3798220) [1,2].

Further data suggest that Lp(a) levels are affected by race and ethnicity. The UK Biobank showed variation in median Lp(a) levels in Chinese, White, South Asian, and Black individuals (16, 19, 31, and 75 and nmol/L, respectively) [3]. It was also observed that women have higher Lp(a) levels in comparison to men [3,4].

Currently, genotyping for Lp(a) is not routinely recommended. However, according to the most recent European and Canadian guidelines, measurement of Lp(a) levels should be done at least once in adults during their lifetime. We believe that a one-time screening measurement of Lp(a) in the general population is reasonable. This can help identify patients with extreme elevations that require aggressive ASCVD risk reduction, guide decisions on aspirin therapy, and will be even more useful in the future when novel RNA-targeting, Lp(a) lowering therapies are clinically available. A National Lipid Association (NLA) statement

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suggests selective screening for adults with a personal or family history in first-degree relatives of premature ASCVD, as well as adults with severe primary hypercholesterolemia (LDL-C $\geq$ 190) to aid treatment decisions for both primary and secondary prevention of ASCVD [2]. American College of Cardiology/American Heart Association guidelines recommend using elevated Lp(a) as a risk-enhancing factor that, if measured, would favor initiating statin therapy among individuals with borderline (5–7.4%) or intermediate (7.5–19.9%) 10-year predicted risk for ASCVD [5]. Additionally, testing should be highly considered in people with a blunted LDL-C lowering response to statins (i.e. "Statin-refractory") [6].

2. Association of elevated Lp(a) with ASCVD

Over the last few decades, several large studies have found a correlation between elevated Lp(a) levels and increased cardiovascular disease [4,7]. Multiple mechanisms are thought to be responsible for this increased risk, which include inhibition of plasminogen, inhibition of clot lysis and increasing cell growth [8]. Apo(a) has hydrophilic properties and can bind to exposed lysine on the vascular endothelium in a manner similar to plasminogen, allowing its entrance and accumulation into subintimal spaces to compete with plasminogen through molecular mimicry, thereby accelerating atherothrombosis [9]. Additionally, Lp(a) acts as a carrier for oxidized phospholipids, which adds to its proinflammatory and proatherogenic effects [10,11]. Elevated Lp(a) levels have been found to be highly influenced (80–90%) by genetics with little to no correlation with age and lifestyle. Generally, Lp(a) levels remain fairly constant throughout a person's life. Therefore, in the absence of acute illness, once in a lifetime measurement is usually sufficient for risk assessment, unlike LDL-C levels which rise as people age [6,12]. Lp(a) levels are associated with ASCVD risk in a linear and dose-dependent fashion, which has been evident in both observational and Mendelian randomization studies [13,14].

Extremely elevated Lp(a) ($\geq$180 mg/dl) might be linked to a risk of ASCVD that is equivalent to people with heterozygous familial hypercholesterolemia, even in patients with an otherwise low estimated risk of ASCVD based on other traditional risk factors [15]. Even moderately elevated Lp(a) levels (between 50 and 150 mg/dl) carry intermediate-high risk [16], and in such individuals, it is reasonable to address other ASCVD risk factors aggressively (i.e. LDL-C levels, obesity and overweight, smoking, hypertension, etc.) [6].

3. Aspirin effect

Aspirin is the most commonly prescribed antiplatelet agent. High levels of Lp(a) may shift towards prothrombosis through the apo(a) moiety [17]. As described in more detail above, there are multiple mechanisms for this prothrombotic and proatherosclerotic state. This could suggest a role of using aspirin, which can attenuate part of the atherothrombotic process.

In addition to the antiplatelet and antithrombotic properties, aspirin may have an Lp(a)-lowering effect, particularly in patients with very elevated Lp(a) [18]. While the quality of clinical evidence regarding the Lp(a)-lowering effect of aspirin is currently lacking, there is some biological plausibility to this effect. The mechanism by which aspirin is thought to lower Lp(a) level is by inhibiting its production in the liver by suppressing apo(a) mRNA expression, independent of cyclooxygenase-1. Reduction of apo(a) production in hepatocyte cultures by aspirin has been demonstrated [8]. The size of this effect in clinical trials has not been well studied. There are a few small studies that have shown a quite significant Lp(a) lowering effect of aspirin therapy [18,19] with a wide range of effect size. These studies are limited due to their small size which makes it difficult to reduce confounding from a regression to the mean effect. In some cases, initial measurements were also taken at the time of an acute ischemic event which can lead to elevation in Lp(a) from baseline due to its role as an acute phase reactant [19]. Additional high-quality clinical studies are required to further evaluate this effect.

Clinical practitioners have been limiting the use of aspirin for primary prevention to patients with high cardiovascular risk. The use of aspirin for secondary prevention in ischemic events has been established; however, the role in primary prevention has been controversial over the past decades [20]. Historically, trials have shown only modest benefit in terms of reduction of ischemic events, mainly for myocardial infarction and to a lesser degree stroke, that usually comes at the expense of an increased risk of bleeding. Current USPSTF guidelines recommend an individualized approach to the decision to initiate aspirin in primary prevention. They recommend considering aspirin therapy for individuals aged 40–59 years with an estimated 10-year ASCVD risk 10% or greater using the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations for risk assessment (Grade C), and recommend against aspirin for primary prevention of CVD in individuals aged 60 years and above [21]. This shift in practice was a result of multiple clinical trials [ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events), ASCEND (A Study of Cardiovascular Events in Diabetes), and ASPREE (Aspirin in Reducing Events in the Elderly)] that showed no net clinically significant benefit in using aspirin and an increased risk of bleeding in the general population [22]. One specific population that may have a net benefit from aspirin for primary prevention is patients with elevated Lp(a) levels.

4. Evidence on ASCVD risk reduction with aspirin use in individuals with elevated Lp(a)

Only a few randomised controlled trials have been analysed to look at the effect of aspirin on the occurrence of cardiovascular disease in individuals with elevated Lp(a). The first randomised trial analysed was the Women's Health Study (WHS), published in 2010, in which 28,345 women, the majority of whom were Caucasian, were studied using a dose of 100 mg orally of aspirin every other day over a period of 9.9 years [23]. In this study, the effect of low-dose aspirin in a population that carried the minor allele of the rs3798220 polymorphism in the LPA gene, associated with elevated plasma Lp(a) and increased cardiovascular risk, was examined. The authors found that 3.7% of the study population carried the minor allele of the rs3798220 polymorphism in the Lp(a) gene. Carriers of the rs3798220-C variant had elevated Lp(a) levels with a mean level in carriers of 79.5 compared to 10.0 mg/dL in non-carriers. A doubling of the risk of major cardiovascular events was seen in carriers. The authors found an absolute risk reduction in aspirin users vs placebo of 2.69% for major cardiovascular events (MACE) compared to 0.12% in non-carriers (Fig. 1), effectively abolishing the increased risk with elevated Lp(a) in aspirin users. The relative risk reduction of MACE in carriers who used aspirin was 56% ($p = 0.033$), while among non-carriers it was 9% ($p = 0.3$), age-adjusted hazard ratio for MACE was 0.44 (95%CI: 0.20−0.94, $p = 0.033$) (Fig. 2A). This interaction between carrier status and aspirin allocation was significant (Pinteraction=0.048).

A recent analysis of the ASPREE trial by Lacaze et al. showed that the use of aspirin may also be of benefit in older individuals with high risk Lp(a) genotypes [24]. The study analysed 12,815 individuals aged above 70 with no prior cardiovascular disease events, who were enrolled in the ASPREE trial. The dose of aspirin used in this trial was 100 mg per day. The participants were stratified based on rs3798220-C carrier status and quintiles of a Lp(a) genomic risk score (LPA-GRS). Outcomes studied were MACE and clinically significant bleeding. The study showed no net benefit of aspirin in all genotyped individuals with no stratification. In the rs3798220-C quintile subgroup, hazard ratio for MACE in aspirin users vs placebo was 0.24 (95%CI: 0.07−0.82, $p = 0.024$) (Fig. 2A), aspirin reduced MACE by 11.4 per 1000 person-years. Absolute risk reduction was found to be 5.09% in carriers and 0.60% in non-carriers with relative risk reduction of 76% and 16%, respectively (Fig. 1), without significantly increasing the bleeding risk. The net benefit (MACE minus significant bleeding events) with aspirin use was most

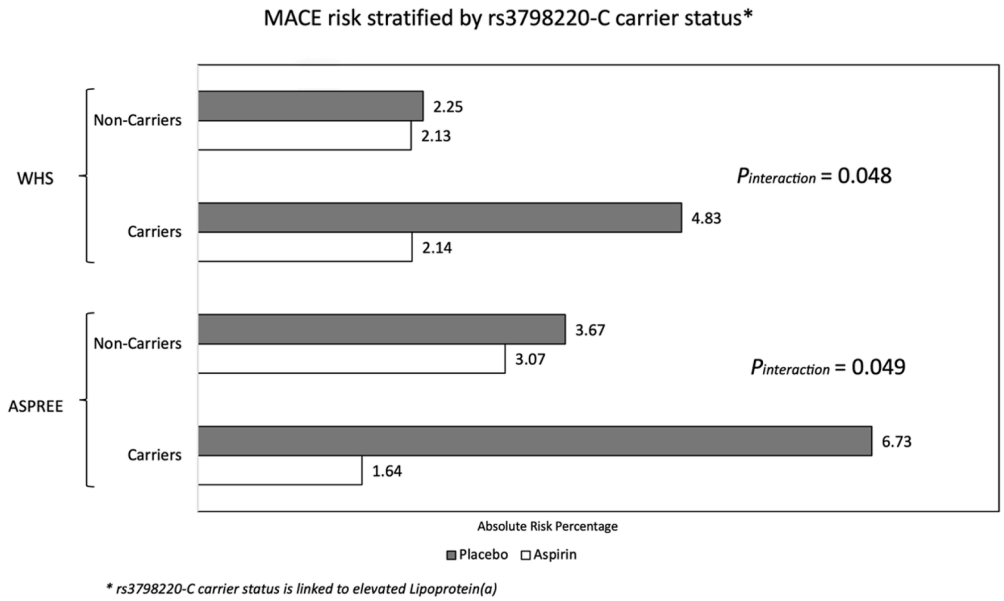

Fig. 1. WHS: Women Health Study [23] ASPREE: ASPirin in Reducing Events in the Elderly trial[24].

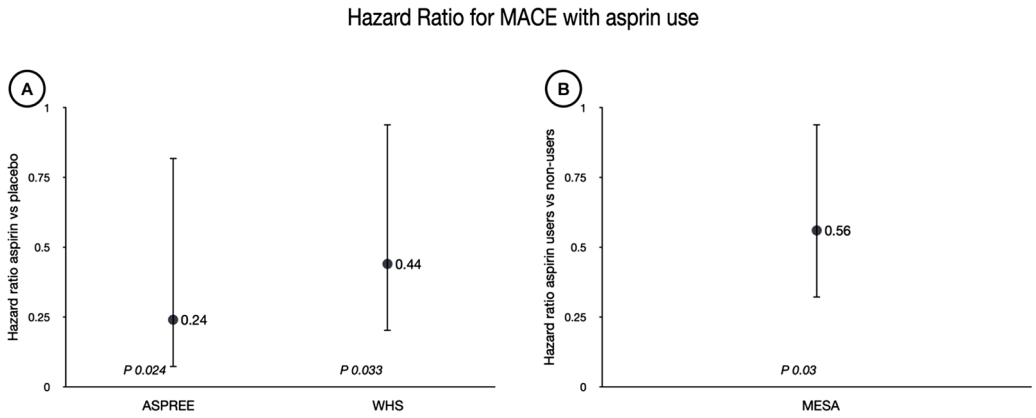

Fig. 2. A: WHS (Women's Health Study) and ASPREE (ASPirin in Reducing Events in the Elderly) trial were randomized control trials in which the relationship between rs3798220-C carrier status and aspirin was studied using Cox proportional hazard models [23,24]. B: MESA (Multi-Ethnic Study of Atherosclerosis) was a prospective cohort study that evaluated the use of aspirin in relation to Lp(a) levels (≤50 mg/dL vs >50 mg/dL) using Cox proportional hazards models [25].

significant in rs3798220 carriers with 8.1 less events per 1000 person-years. The interaction between carrier status and aspirin allocation was significant (Pinteraction=0.049). The use of genotype-based assessment of Lp(a) was one of the limitations in this study, as only 3.2% of the >12,000 subjects were carriers of the high-risk rs3798220-C LPA genetic variant, whereas elevated Lp(a) levels are estimated to be present in up to around 20% of the population [2]. Another limitation was that the study limitation was limited to individuals with European ancestries aged ≥70 years.

These findings correlate with an observational study which was done on 6632 participants from the Multi-Ethnic Study of Atherosclerosis (MESA). Currently, only an abstract of this study has been published, however, it adds to the existing evidence supporting the benefits of aspirin therapy for patients with elevated Lp(a). This study was conducted on a more diverse population from 4 ethnicities (White, 28% African American, 23% Hispanic, and 11% Asian) aged 45–84 years [25,26]. These participants had no identified cardiovascular disease and were studied to evaluate the effect of aspirin on coronary heart disease (CHD) events (CHD death, non-fatal myocardial infarction) after stratification based on Lp(a) levels; 20% of the study participants had elevated Lp(a) >50 mg/dL. The study showed a significant higher incidence of CHD events with Lp(a) >50 mg/dL (9.0% vs 7.3%). After propensity matching, it showed reduction in CHD events in participants using aspirin who had elevated levels of Lp(a) (HR 0.54, 95% CI, p = 0.03) (Fig. 2B). This reduction was significant and, it was in fact noted that with aspirin use in participants with high Lp(a), their CHD event rate became similar in incidence to those with Lp(a) ≤50 mg/dL.

There is a growing body of evidence supporting the use of aspirin to mitigate the risk of ASCVD in individuals with elevated Lp(a) levels (≥50 mg/dL) and specifically in carriers of the rs3798220-C genetic variant. Carriers of this variant represent a much smaller proportion of the population (approximately 3–4%) than all individuals with elevated Lp(a) ≥50 mg/dL (approximately 20%). Carriers of this variant had a mean Lp(a) level of 79.5 mg/dl in the WHS. Genotypes associated with elevated Lp(a) have been used as a proxy to estimate elevated Lp(a) levels. However, it is not well established if carriers of the rs3798220-C genetic variant have any specific risk above and beyond that conferred by just the elevated Lp(a) levels associated with the variant [24] and would benefit more from aspirin therapy. Further research is needed to answer this question with direct measurements of Lp(a) levels.

It is worth noting that the net benefit with aspirin therapy may be even more pronounced in individuals who have higher levels of Lp(a)

within these sub-groups. As previously mentioned, the ASCVD risk associated with Lp(a) is linear and dose dependent. The existing studies have limited data on further stratifying the effect across different levels of elevation in Lp(a). Ideally, a randomized control trial designed to assess ASCVD outcomes in an intermediate risk, racially and ethnically diverse, primary prevention population with elevated Lp(a) treated with aspirin vs placebo would help answer many of the remaining questions in this area and help establish a threshold for treatment.

5. Conclusion

Considering the complex interplay of the effects of aspirin therapy and the atherothrombotic implications of elevated Lp(a) it is hypothesized that individuals with elevated Lp(a) benefit more from low-dose aspirin therapy than the general population for primary prevention of ASCVD. While this benefit must be balanced against the individualized bleeding risks, there is an overall net clinical benefit that has been demonstrated in carriers of the rs3798220-C polymorphism in the LPA gene. A reduction in coronary heart disease with aspirin therapy has also been observed in individuals with Lp(a) $\geq$50 mg/dL. Additional randomised control studies are needed for further evaluation of the effect of aspirin on decreasing risk of ASCVD in individuals with elevated Lp(a). In individuals in whom the decision on use of aspirin therapy for primary prevention for ASCVD risk reduction is uncertain, identifying elevated Lp(a) levels can help further inform this decision.

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Mohamad Hekmat Sukkari: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Basma Al-Bast:** Conceptualization, Methodology, Writing – original draft. **Raad Al Tamimi:** Writing – review & editing. **William Giesing:** Writing – original draft. **Momin Siddique:** Writing – review & editing, Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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