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Aspirin and lipoprotein(a) in primary prevention

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Abstract

Purpose of review—Lipoprotein(a) [Lp(a)] is causally associated with cardiovascular diseases, and elevated levels are highly prevalent. However, there is a lack of available therapies to address Lp(a)-mediated risk. Though aspirin has progressively fallen out of favor for primary prevention, individuals with high Lp(a) may represent a high-risk group that derives a net benefit.

Recent findings—Aspirin has been demonstrated to have a clear benefit in secondary prevention of cardiovascular disease, but recent primary prevention trials have at best demonstrated a small benefit. However, individuals with elevated Lp(a) may be of high risk enough to benefit, particularly given interactions between Lp(a) and the fibrinolytic system / platelets, and the lack of available targeted medical therapies. In secondary analyses of the Women's Health Study (WHS) and the Aspirin in Reducing Events in the Elderly (ASPREE) trial, aspirin use was associated with a significant reduction in cardiovascular events in carriers of genetic polymorphisms associated with elevated Lp(a) levels. Further studies are needed, however, as these studies focused on narrower subsets of the overall population and genetic markers.

Summary—Individuals with elevated Lp(a) may benefit from aspirin therapy in primary prevention, but further study with plasma Lp(a) levels, broader populations, and randomization of aspirin are needed.

Keywords

aspirin; cardiovascular disease; lipoprotein(a); primary prevention

INTRODUCTION

Lipoprotein(a) [Lp(a)] is causally associated with cardiovascular disease risk, particularly coronary artery disease and aortic stenosis. Lp(a) causes disease through multiple mechanisms including atherosclerosis, inflammation, and thrombosis (Fig. 1) [1]. Elevated Lp(a) is highly prevalent with levels >50 mg/dL present in approximately 24–29% of all individuals [2]. However, there are limited therapeutic options for elevated Lp(a), with no medical treatments specifically approved for Lp(a). Given its genetic nature, lifestyle measures are not effective for lowering Lp(a) [3]. Statins, a central aspect of cardiovascular

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Conflicts of interest

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disease prevention, do not lower Lp(a) [4]. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have been shown to modestly lower Lp(a) which may translate into an improvement in clinical outcomes based on secondary analyses of clinical trials [5,6]; however, PCSK9i are not specifically approved for this purpose. Multiple RNA therapies which lower Lp(a) significantly are in development or in clinical trials [7], but no outcomes data is yet available, and these drugs will initially be targeted towards a secondary prevention population. Given the large population at risk, there is a significant need for therapies which reduce risk associated with Lp(a) in primary prevention.

Aspirin has long been a cornerstone of the secondary prevention of cardiovascular disease. In the Antithrombotic Trialists' (ATT) meta-analysis of secondary prevention aspirin trials, aspirin use was associated with a 19% relative risk reduction, and 1.5% per year absolute risk reduction in serious vascular events [8]. However, the role of aspirin in primary prevention has become increasingly unclear. In the ATT meta-analysis of primary prevention trials, aspirin use was associated with a statistically significant 12% relative risk reduction in serious vascular events; however, the yearly absolute risk reduction was only 0.07%, offset by an increase in major bleeding [8]. Three recent primary prevention trials of aspirin, discussed in more detail below, failed to demonstrate a strong benefit to aspirin use, leading to weaker guideline recommendations for aspirin use in the primary prevention setting.

In this review, we will discuss the potential role for aspirin for the primary prevention of cardiovascular events in individuals with elevated Lp(a). We will review the recent primary prevention trials of aspirin, the rationale for a net benefit in those with elevated Lp(a), and the available studies addressing this question, including a recent secondary analysis of the Aspirin in Reducing Events in the Elderly (ASPREE) trial.

RECENT PRIMARY PREVENTION ASPIRIN TRIALS

There were three large randomized primary prevention trials of aspirin therapy in different populations published in 2018 – ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events), ASCEND (A Study of Cardiovascular Events in Diabetes), and ASPREE (Table 1).

The ARRIVE trial randomized 12,546 individuals at moderate estimated cardiovascular risk (10–20% 10-year risk of coronary heart disease) to aspirin 100 mg daily or placebo with a primary endpoint of time to cardiovascular death, myocardial infarction, unstable angina, stroke or transient ischemic attack (TIA). Of note, diabetics were excluded. After median follow-up of 60 months, aspirin was not associated with improvement in the primary endpoint (Hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.81–1.13) but was associated with increased gastrointestinal bleeding (HR 2.11, 95% CI 1.36–3.28). In a per protocol analysis, there was a significant reduction in myocardial infarctions (HR 0.53, 95% CI 0.36–0.79). Importantly, event rates for the primary endpoint were much lower than expected (4.5% in the placebo arm and 4.3% in the aspirin arm) [9].

The ASCEND trial randomized 15,480 individuals with diabetes to aspirin 100 mg daily or placebo with a primary endpoint of first serious vascular event (myocardial infarction, stroke, TIA or death from vascular cause excluding intracranial hemorrhage). At mean

follow-up of 7.4 years, aspirin was associated with reduced risk of the primary endpoint (rate ratio (RR) 0.88, 95% CI 0.79–0.97), offset by major bleeding (RR 1.29, 95% CI 1.09–1.52). Higher event rates were observed than in the other studies (9.6% in the placebo group, 8.5% in the aspirin group). When the components of the primary outcome were evaluated individually, the lowest (non-significant) hazard ratio was for TIA, and the primary outcome was no longer significant if TIA was excluded [10]. This is important as the diagnosis of TIA may be more subjective than for other included clinical outcomes.

The ASPREE trial randomized individuals >70 years of age (≥65 in US minorities) to 100 mg of aspirin or placebo; multiple endpoints were evaluated but the primary cardiovascular end point was cardiovascular disease (a composite of fatal coronary heart disease, nonfatal myocardial infarction, stroke or hospitalization for heart failure). After median 4.7-year follow-up in 19,114 people, aspirin was not associated with a reduction in cardiovascular events (HR 0.95, 95% CI 0.83–10.08) but was associated with increased major hemorrhage (HR 1.38, 95% CI 1.18–1.62). Again, event rates were low with an overall rate of the primary outcome of 4.8% [11].

A subsequent meta-analysis of primary prevention aspirin trials, including the three most recent trials, demonstrated a small benefit to aspirin use (HR 0.89, 95% CI 0.84–0.94] for cardiovascular events (cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke), again offset by increased major bleeding (HR 1.43, 95% CI 1.30–1.56). When individual outcomes were evaluated, there was a benefit for both myocardial infarctions (HR 0.85, 95% CI 0.73–0.99) and ischemic strokes (HR 0.81, 95% CI 0.76–0.87, Fig. 2) [12]. After the publication of these trials, the US Preventive Services Task Force released updated guidance stating that use of aspirin for primary prevention in individuals aged 40 to 59 with ≥10% 10-year cardiovascular disease (CVD) risk should be individualized, but the net benefit is likely small. They recommended against use of aspirin in adults ≥60 years of age [13]. This was similar to the prior recommendations in the American College of Cardiology/American Heart Association primary prevention guidelines which stated that aspirin may be considered in adults 40 to 70 years of age at higher ASCVD risk without bleeding risk with a IIb strength of recommendation. Aspirin for primary prevention for adults >70 or those with increased risk of bleeding was recommended against [14].

The lack of a clear net benefit from aspirin use in primary prevention may be due to improvements in other preventive therapies over time, including the use of lipid lowering therapies and more aggressive management hypertension and diabetes. However, the benefit from aspirin use in secondary prevention, and the small benefit in primary prevention, particularly in diabetics, suggest that there may be a higher risk group for whom aspirin in primary prevention is beneficial.

LIPOPROTEIN(a), PLATELETS, BLEEDING

The overall association between Lp(a) and thrombotic risk remains unclear with inconsistent findings in various studies. However, Lp(a) has been suggested to have both antifibrinolytic properties as well as interactions with platelets. Lp(a) has been shown to inhibit fibrinolysis, primarily related to its homology with plasminogen, in experimental studies [15]. However,

this has not translated to increased venous thromboembolism risk in clinical studies [16,17]. If an association between Lp(a) and antifibrinolysis is confirmed, this may suggest that individuals with high Lp(a) are at lower bleeding risk. Lp(a) has been shown to stimulate platelet function and increase platelet aggregation in primarily in vitro studies involving various stimuli and platelet receptors [18,19–22]. In contrast, several other studies have suggested an antiplatelet effect of Lp(a). These studies, in general, were more limited in scope and in vivo data is lacking [23–27]. From these studies, the net effect of Lp(a) on platelet function remains unclear. One study, however, of individuals undergoing percutaneous coronary intervention (PCI), observed that individuals with higher Lp(a) had accelerated fibrin generation, greater clot strength, and increased platelet aggregation in vivo, suggesting a net pro-platelet effect of Lp(a) [28]. Another study of individuals undergoing PCI observed a benefit to prolonged dual antiplatelet therapy in individuals with high Lp(a) but not in individuals with normal Lp(a) [29]. The potential antifibrinolytic and pro-platelet effects of Lp(a) provide a rationale for a particular benefit from aspirin therapy with increased thrombotic risk and possibly decreased bleeding risk in this population.

STUDIES OF ASPIRIN AND LIPOPROTEIN(a)

Prior studies of aspirin use and Lp(a) have focused on genetic polymorphisms (Table 2). In an analysis of the Women's Health Study (WHS), which randomized healthy women ≥45 years of age to aspirin 100 mg every other day or placebo, investigators evaluated the single nucleotide polymorphism (SNP) rs3798220-C of the *LPA* gene. In the study, this SNP was associated with higher Lp(a) levels and greater CVD risk compared with noncarriers (HR 2.24, 95% CI 1.36–3.68). In carriers of the SNP who were assigned aspirin, however, the risk was significantly reduced compared to placebo (HR 0.44, 95% CI 0.20–0.94) after median 9.9 years of follow-up. In noncarriers, in contrast, aspirin use was not associated with a reduction in events compared with placebo. Of particular significance is the fact that the absolute risk in SNP carriers assigned aspirin was 2.14%, which was similar to the risk in noncarriers assigned aspirin (2.13%) and placebo (2.25%) [30].

A study of the same SNP in participants from the Atherosclerosis Risk in Communities study was also conducted. In this study, over median 7.2-year follow-up, the SNP was nonsignificantly associated with coronary heart disease (CHD) risk among non-users of aspirin (HR 1.57, 95% CI 0.92–2.69). Among aspirin users, however, the SNP was not associated with increased risk of CHD (HR 0.86, 95% CI 0.38–1.95) [31]. While this study was limited by self-report of aspirin and is likely subject to residual confounding as an observational study, the overall direction of the results was consistent with the WHS results.

Finally, a recent analysis was conducted in the more contemporary ASPREE trial (described above). Genotyping was performed in 12,815 individuals of European ancestry and two analyses were conducted – one involving the same rs3798220-C SNP, and another using a polygenic risk score for LPA (genetic risk score [GRS]). Again, the SNP and high GRS were both associated with increased risk of major adverse cardiovascular events (MACE) in the placebo group with HRs of 1.90 (95% CI 1.11–3.24) and 1.70 (95% CI 1.14–2.55), respectively. In the aspirin group, however, the SNP (HR 0.54, 95% CI 0.17–1.71) and high GRS (HR 1.41, 95% CI 0.90–2.23) were not associated with MACE. Among SNP carriers,

aspirin reduced MACE by 11.4 events per 1000 person-years with a bleeding risk of 3.3 events per 1000 person-years, equating to a net benefit of 8.1 events per 1000 person-years. Similarly, among those with high GRS, aspirin resulted in a net benefit of 1.7 events per 1000 person-years [32■]. These results extended the WHS results in a more contemporary setting with modern background therapy, to a broader population including men and women, by using a broader set of genetic markers with the GRS, and by also accounting for bleeding outcomes and calculating net benefit.

These studies have important limitations. In both the WHS and ASPREE studies, the analysis was limited to Caucasians, and the SNP was only present in 3.7% of women in the WHS and in 3.2% of individuals in ASPREE, limiting the generalizability of these results. Furthermore, Lp(a) levels were not available in these studies. Lp(a) levels are more clinically useful as they account for genetic and nongenetic influences, are inexpensive, and measurement is much more widely available.

CONCLUSIONS

Elevated Lp(a) remains a significant unmet need in cardiovascular disease prevention. While multiple new therapies are in development or under investigation, these will primarily be targeted towards secondary prevention initially. Given the high prevalence of elevated Lp(a), there is a need for strategies to reduce the associated risk today. While aspirin therapy in primary prevention has progressively fallen out of favor, the significant reduction in risk in secondary prevention and the smaller reduction in primary prevention (particularly in diabetics) suggests that a high-risk primary prevention group may benefit from aspirin therapy. Given the lack of available therapies for elevated Lp(a) and purported associations between Lp(a) and platelet function as well as decreased bleeding risk, those with elevated Lp(a) may be the ideal group to derive a net benefit from aspirin therapy.

The WHS and ASPREE studies demonstrated consistent results – increased CVD risk in carriers of genetic polymorphisms associated with high Lp(a) levels, as well as a significant reduction in events in those assigned aspirin therapy. The ASPREE trial provided additional bleeding outcomes to suggest a net benefit to aspirin. The limitations of these studies, however, prevent us from making a broad recommendation for aspirin use in this population. In particular, the use of genetic variants (particularly one SNP present in <4% of Caucasians) without Lp(a) levels, and the restriction to those of Caucasian ancestry limit the generalizability of these results. However, they do suggest a benefit to aspirin, and the choice to use aspirin in those with high Lp(a) should be individualized until further data is available. In particular, those with low bleeding risk and high Lp(a) without other significant cardiovascular risk factors to address may benefit. Further studies are needed utilizing Lp(a) levels, with broader, multiethnic populations and randomization of aspirin. For now, aspirin represents a potential therapy to prevent cardiovascular events in a population that badly needs one.

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KEY POINTS

- Elevated Lp(a) is a significant unmet need in primary prevention of cardiovascular disease.
- While aspirin therapy in primary prevention has fallen out of favor, prior studies suggest there are high-risk groups which may benefit.
- In secondary analyses of the WHS and ASPREE trials, aspirin was associated with a reduction in cardiovascular events in primary prevention in those with genetic polymorphisms associated with high Lp(a) levels.
- Further studies are needed to evaluate the use of aspirin in primary prevention in those with elevated plasma Lp(a) levels; until then, the decision to use aspirin should be individualized.

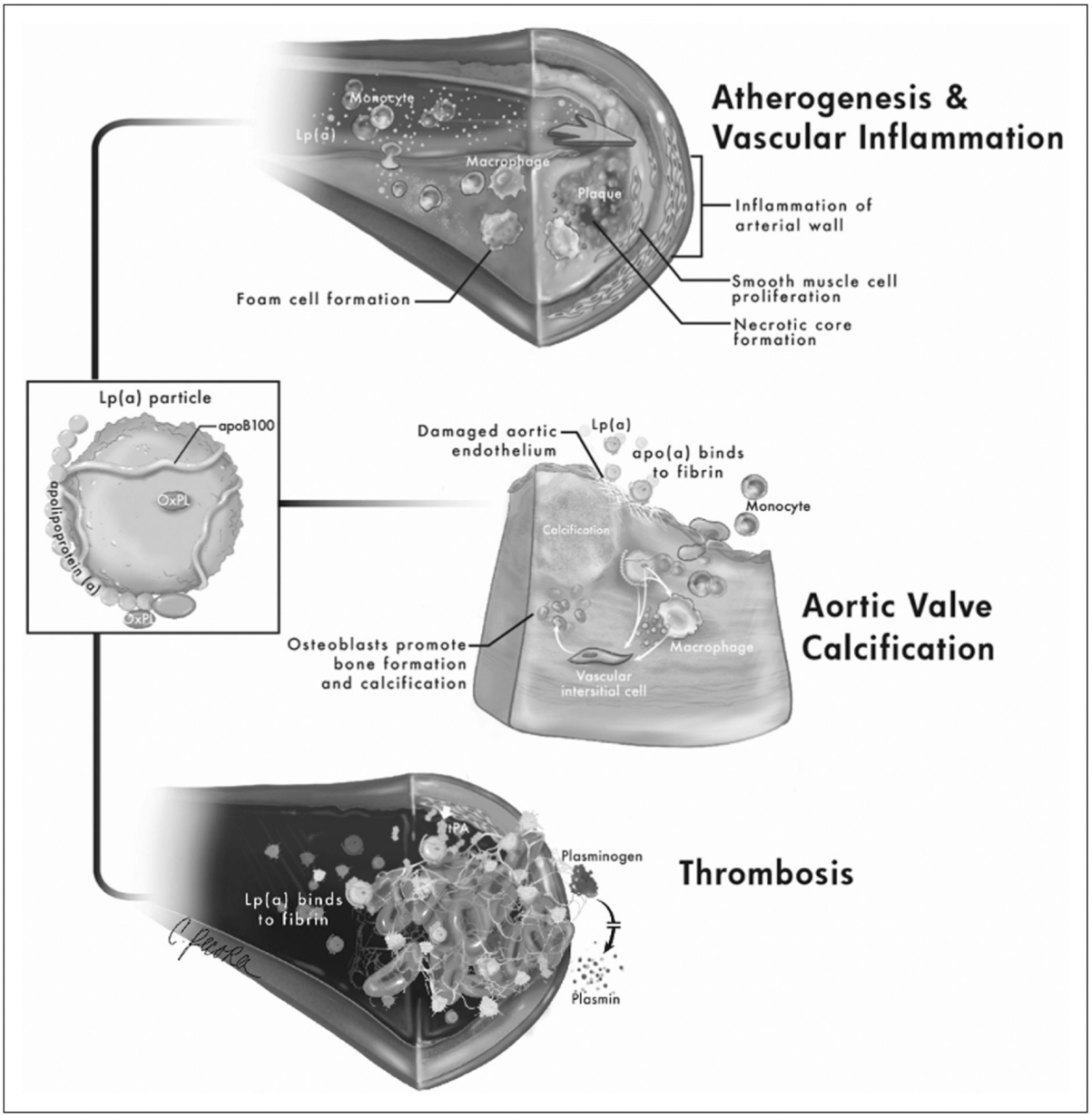
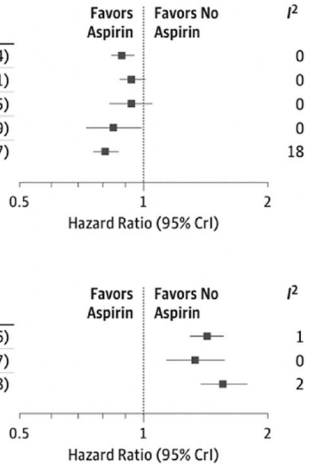


FIGURE 1.
Lipoprotein(a) and mechanisms of disease. Reproduced from Bhatia, *et al.* JCM 2022 [1].

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Composite CV outcome	13	2911	79717	3342	80057	0.41 (0.23 to 0.59)	0.89 (0.84-0.94)	0
All-cause mortality	13	3622	81623	3588	80057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)	0
CV mortality	13	995	81623	997	80057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)	0
Myocardial infarction	13	1469	81623	1599	80057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)	0
Ischemic stroke	10	831	65316	942	63752	0.19 (0.06 to 0.30)	0.81 (0.76-0.87)	18

Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Major bleeding	11	1195	74715	834	73143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)	1
Intracranial bleeding	12	349	80985	257	79419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)	0
Major GI bleeding	10	593	70336	380	70465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)	2



The composite cardiovascular (CV) outcome consisted of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Hazard ratios (HRs) and 95% credible interval variables (CrIs) were calculated using Bayesian meta-analysis of trial-level event counts. The absolute risk reductions and increases were calculated by multiplying the control event risk by the relative risk and 95% CIs derived by frequentist meta-analysis (eFigure 4 in Supplement 2). GI indicates gastrointestinal.

FIGURE 2.

Meta-analysis of aspirin primary prevention trials. Reproduced from Zheng, *et al.* JAMA 2019 [12].

Table 1.

Recent trials of aspirin for primary prevention.

Trial	Year	Population / Size	Primary Outcome	Event Rate	Risk	Primary Bleeding Outcome	Primary Bleeding Outcome / Events	Risk
ARRIVE [9]	2018	10–20% 10-year risk of coronary heart disease (*n* = 12,546)	Time to first cardiovascular death, myocardial infarction, unstable angina, stroke or transient ischemic attack	4.3% aspirin vs. 4.5% placebo	HR 0.96 (95% Cl 0.81–1.13)	Gastrointestinal bleeding	1.0% aspirin vs. 0.5% placebo	HR 2.11 (95% Cl 1.36–3.28)
ASCEND [10]	2018	Diabetics (*n* = 15,480)	First myocardial infarction, stroke or transient ischemic attack, death from vascular cause excluding intracranial hemorrhage	8.5% aspirin vs. 9.6% placebo	Rate ratio 0.88 (95% Cl 0.79–0.97)	Major bleeding event (intracranial hemorrhage, sight-threatening bleeding in eye, gastrointestinal bleeding, other serious bleeding)	4.1% aspirin vs. 3.2% placebo	Rate ratio 1.29 (95% Cl 1.09–1.52)
ASPREE [11]	2018	≥70 years of age (≥65 for minorities in the US, *n* = 19,1 14)	Fatal coronary heart disease, nonfatal myocardial infarction, stroke, hospitalization for heart failure	4.7% aspirin vs. 4.9% placebo	HR 0.95 (95% Cl 0.83–1.08)	Major hemorrhage (hemorrhagic stroke, symptomatic intracranial bleeding, clinically significant extracranial bleeding)	3.8% aspirin vs. 2.8% placebo	HR 1.38 (95% Cl 1.18–1.62)

Table 2.

Aspirin and lipoprotein(a) studies.

Study	Year / Author	Population	Genetic Polymorphism	Aspirin Dosage	Primary Outcome	Bleeding Outcomes
WHS [30]	2009 / Chasman	Healthy Caucasian women ≥45 years old (*n* = 25,131)	rs3798220-C	100 mg every other day	Major cardiovascular events (myocardial infarction, ischemic stroke, cardiovascular death) HR with aspirin use 0.44 (95% CI 0.20–0.94)	--
ARIC [31]	2009 / Shiffman	European Americans without prior CHD event (*n* = 6,752)	rs3798220-C	Unknown, defined as aspirin use 7 days a week	CHD (myocardial infarction, CHD death, coronary revascularization) HR for carriers with aspirin use 0.86 (95% CI 0.38–1.95)	--
ASPREE [32■]	2022 / Lacaze	European descent (*n* = 12,815)	rs3798220-C and GRS	100 mg daily	MACE (fatal CHD, nonfatal myocardial infarction, stroke) HR for SNP in aspirin arm (0.54, 95% CI 0.17–1.71) HR for high-GRS in aspirin arm (1.41, 95% CI 0.90–2.23)	Major hemorrhage and intracranial bleeding HR for SNP in aspirin arm (1.14, 95% CI 0.54–2.41)

CHD, coronary heart disease; GRS, genetic risk score; MACE, major adverse cardiovascular events; SNP, single nucleotide polymorphism.