Revisiting the Low-Dose Aspirin Benefit-Risk Discussion in the Context of New Risk Assessment Tools

Steven M. Weisman, PhD; Stephen Brunton, MD, FAAFP

doi:10.12788/fp.0778

Sponsorship: This activity is sponsored by Primary Care Education Consortium and supported by funding from Bayer.

FACULTY

Steven M. Weisman, PhD
Global President, Clinical and Regulatory
Lumanity
Morristown, NJ

Stephen Brunton, MD, FAAFP
Professor, Department of Family and Preventive Medicine
University of South Carolina
Columbia, SC

DISCLOSURES

Dr. Weisman discloses that he is the Global President, Clinical and Regulatory at Lumanity, a consultancy to the pharmaceutical industry, and he has received consultancy fees from Bayer related to the topic of this manuscript.

Dr. Brunton discloses that he serves on the advisory board and speakers bureau for Abbott Diabetes, AstraZeneca, and Novo Nordisk; on the speakers bureau for Lilly; and on the advisory board for Sanofi Adventis.

INTRODUCTION

Low-dose aspirin has been extensively studied for the prevention of major cardiovascular (CV) events. Aspirin consistently demonstrates meaningful reductions in both relative and absolute risk, with the highest absolute benefit in patients with the highest underlying risk of a CV event. The central challenge is not aspirin's effectiveness, but in the separation between potential benefit and risk without CV risk stratification. Accurately identifying high-risk but asymptomatic patients who would benefit from aspirin therapy has been challenging for those clinicians most dependent on population-based risk calculators.

Careful patient selection and a personalized approach to treatment may substantially improve the benefit-risk balance.[1] Individuals with a meaningful baseline CV risk are more likely to derive net benefit from aspirin therapy, making them appropriate candidates for consideration. To make informed recommendations, primary care clinicians must assess both the underlying risk of CV events and the potential benefits and risks of aspirin use.

This review examines the current evidence about the benefits and risks of low-dose aspirin, with a focus on practical application in primary care. It highlights newer data suggesting that adverse events may occur less frequently than is often assumed and discusses how newer analytical methods might be used to optimize the benefit-risk balance. It also outlines strategies for pretreatment evaluation to help more individuals benefit from aspirin in preventing CV events and demonstrates the importance of clinician awareness of available tools to better guide therapy.

Bleeding risks from aspirin are well known yet often misunderstood or exaggerated and may be a barrier to patient interest and clinician recommendations. This article aims to support clinicians in making informed, individualized decisions about aspirin therapy, helping them counsel patients effectively and enhance adherence where preventive benefit is likely to outweigh risk.

Key takeaways

- Aspirin retains clear value for patients at risk of ischemic CV events, both in those with a prior event and in those without a prior event but with an equivalent level of risk.
- While the use of aspirin for secondary prevention is well established, use for primary prevention should be based on patient-specific risk profiles.
- Reliance solely on conventional risk factors can miss many high-risk patients, resulting in both overtreatment (low-risk individuals exposed to bleeding risk without benefit) and undertreatment (high-risk patients not offered aspirin despite potential benefit).
- Imaging and emerging biomarkers are promising tools to identify patients in whom the absolute CV benefit of aspirin outweighs bleeding risk.
- Discussions between clinicians and patients are necessary to ensure that aspirin is used appropriately, safely, and in alignment with individual risk profiles.

BRIEF HISTORY OF ASPIRIN USE FOR CV EVENT PREVENTION

Building on observations from the 1960s that aspirin inhibits platelet aggregation and reduces thrombosis,[2,3] several large clinical trials established aspirin's role in the prevention of myocardial infarction (MI), stroke, and CV death (**TABLE 1**).

In 1994, the Antiplatelet Trialists' Collaboration analyzed 174 clinical trials involving approximately 70,000 high-risk patients. Medium-dose aspirin (75-325 mg/day) consistently reduced major CV events, with similar efficacy across this dose range. There was no significant evidence that either a higher aspirin dose or alternative antiplatelet agents were more effective than a medium aspirin dose in preventing nonfatal MI, nonfatal strokes, or vascular deaths.[4]

Collectively, these findings informed the US Food and Drug Administration (FDA) approvals for aspirin use after stroke (1980), after MI (1985), and for suspected MI (1996) (**FIGURE 1**).[5]

Today, daily low-dose aspirin use is well established and widely recommended for the prevention of atherosclerotic CV disease (ASCVD) in patients who have had a previous CV event or who are at high risk of CV events (strength of recommendation IIb). Evidence suggests that the benefits of low-dose aspirin might outweigh the risks in individuals with a higher ASCVD risk but not an increased bleeding risk.[6] In contrast, clinical trials of aspirin for patients who have not had a previous event have provided less clarity. Most of these trials randomized patients to aspirin treatment based on conventional risk factors and yielded inconsistent results, leading to the conclusion that aspirin's net value in these patients remains uncertain.[7]

Given the collective findings from studies of at-risk patients, in 2016, the US Preventive Services Task Force (USPSTF) updated its guidance citing evidence that aspirin was beneficial to reduce risk of CV events in adults aged 50 to 69 years with increased CV disease (CVD) risk, but major bleeding risk also increased. The USPSTF also noted that absolute bleeding risk varied considerably depending on an individual's baseline risk profile. Based on this evidence, the Task Force recommended initiating low-dose aspirin for the primary prevention of CVD in adults aged 50 to 59 years with a 10% or greater 10-year CVD risk and not at an increased risk of bleeding.[8]

CURRENT CLINICAL PRACTICE GUIDELINES AND RECOMMENDATIONS

Three major trials published in 2018 had a substantial impact on the clinical approach to aspirin use for CV prevention in patients without a previous event. The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial evaluated low-dose aspirin (100 mg daily) in individuals at moderate estimated risk for a first CV event (defined by conventional risk assessment). Over an average follow-up of 60 months, the composite endpoint (i.e., time to first occurrence of CV death, MI, unstable angina, stroke, or transient ischemic attack [TIA]) occurred in 269 participants (4.29%) in the aspirin group vs 281 participants (4.48%) in the placebo group. Although predominantly mild, GI bleeding events occurred in 61 aspirin participants (0.97%) compared with 29 placebo participants (0.46%).[14]

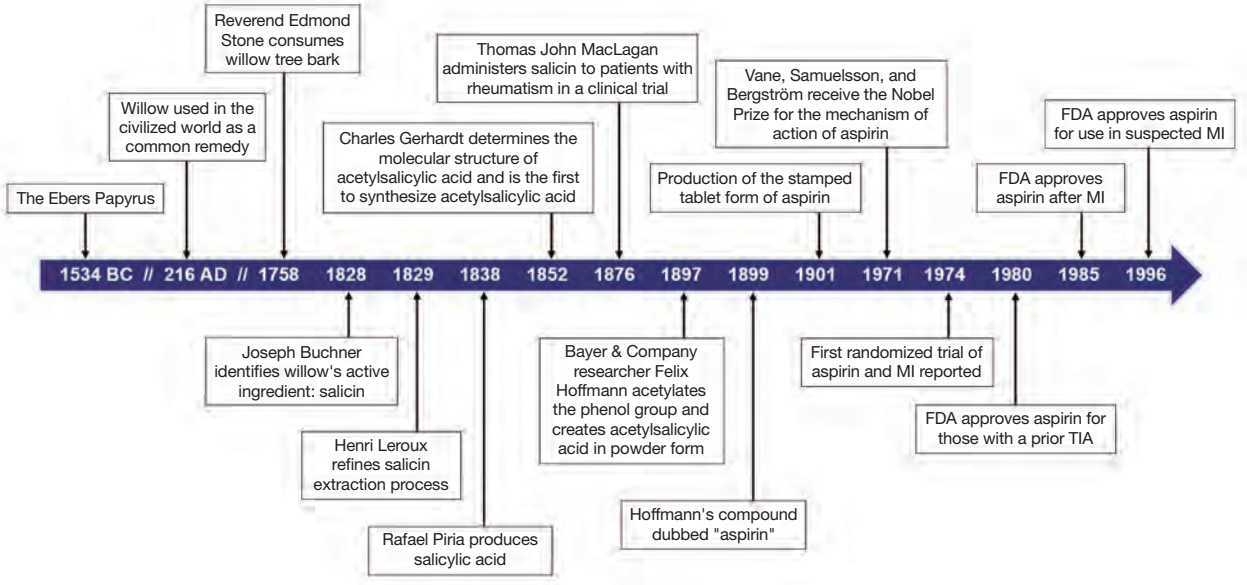
The A Study of Cardiovascular Events in Diabetes (ASCEND) trial assessed low-dose aspirin (100 mg daily) in individuals with diabetes but without established CVD. Over a mean follow-up of 7.4 years, aspirin significantly reduced the percentage of serious vascular events in the aspirin

TABLE 1. Evidence establishing aspirin's role in CV prevention.[9-13]

Elwood et al, 1974	Canadian cooperative study, 1978	ISIS-2, 1988	SALT, 1991	UK-TIA, 1991
300 mg daily	325 mg QID	160 mg daily	75 mg daily	300 mg or 1200 mg daily
Patients with MI	Patients with threatened stroke	Patients within 24 hours of suspected acute MI	Patients 1 to 4 months after TIA or minor stroke	Patients with TIA or minor ischemic stroke
12% reduction in total mortality at 6 months 25% reduction in total mortality at 1 year	19% reduction in composite outcome of continuing TIAs, stroke, or death 31% reduction in stroke or death No bleeds observed	23% reduction in 5 week vascular mortality; 42% reduction when combined with streptokinase Lowered rates of nonfatal stroke and nonfatal reinfarction No significant increase in cerebral hemorrhage or bleeds requiring transfusion	18% reduction in stroke or death 16% to 20% reductions in secondary outcome events More frequent bleeding episodes	15% reduction in major stroke, MI, or vascular death More GI toxicity at 1200 mg

Abbreviations: GI, gastrointestinal; ISIS-2, Second International Study of Infarct Survival Collaborative Group; QID, four times daily; SALT, Swedish Aspirin Low-Dose Trial; UK-TIA, United Kingdom Transient Ischaemic Attack trial.

FIGURE 1. Timeline of events in the history of aspirin use.[5]



Note: years are not spaced to scale.
Abbreviation: MI, myocardial infarction
Adapted from Fuster V and Sweeny JM, 2011.[5]

group (658 participants or 8.5%) compared with placebo (743 or 9.6%). However, major bleeding events occurred in 314 aspirin participants (4.1%) vs 245 placebo participants (3.2%).[15]

The Aspirin in Reducing Events in the Elderly (ASPREE) trial investigated low-dose aspirin (100 mg daily) in healthy adults aged 70 years or older. Aspirin did not extend disability-free survival and was associated with a higher rate of major hemorrhage. These findings suggested that, in elderly individuals, aspirin use for primary prevention may be more harmful than beneficial.[16]

A subsequent meta-analysis of 13 primary prevention trials, including ARRIVE, ASCEND, and ASPREE, found that aspirin use was associated with a reduction in composite CV outcomes (hazard ratio, 0.89; 95% confidence interval [CI]: 0.84, 0.94; absolute risk reduction, 0.41%; 95% CI: 0.23, 0.59); however, in 11 trials, there were 2029 bleeding events in the aspirin groups vs 834 in the control groups. It should be noted that event rates in several of these trials were lower than anticipated, with an estimated 10-year risk of composite CV outcome <10% in 6 studies.[17] These findings underscore the importance of careful patient selection when considering aspirin as primary prevention in those with atherosclerosis and low bleeding risk.

Current guidelines discourage aspirin use for low-risk individuals. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) CVD prevention guidelines recommend infrequent use for primary prevention because of lack of net benefit, but in individuals aged 40 to 70 years who have higher ASCVD risk without increased bleeding risk, aspirin might be considered (see recommendation IIb, **TABLE 2**).[6]

TABLE 2. 2019 ACC/AHA recommendations for aspirin use.[6]

Recommendations	Class of Recommendation	Level of Evidence
Low-dose aspirin[a] might be considered for primary prevention of ASCVD among select adults 40 to 70 years of age at higher ASCVD risk but not at increased risk of bleeding.	**IIb (Weak)** Benefit ≥ Risk	**A** (High-quality RCT evidence)
Low-dose aspirin[a] should not be routinely used for primary prevention of ASCVD in adults older than 70 years of age.	**III: Harm** (Strong) Risk > Benefit	**B-R** (Moderate-quality RCT evidence)
Low-dose aspirin[a] should not be used for primary prevention of ASCVD in adults with increased bleeding risk.	**III: Harm** (Strong) Risk > Benefit	**C-LD** (Limited Data; observational or physiological/ mechanistic studies)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; RCT, randomized controlled trial
[a]Low-dose aspirin refers to 75-100 mg of aspirin by mouth daily.
Adapted from Arnett DK et al, 2019.

TABLE 3. Current guidelines for aspirin use for primary prevention.[6,18]

	Adults younger than 40 years of age	Adults aged 40-70 with ≥10% CVD risk	Adults older than 70 years of age
2019 ACC/AHA guidelines	There is insufficient evidence to judge risk-benefit ratio of aspirin for primary prevention of ASCVD	Low-dose aspirin might be considered for primary prevention among adults at higher ASCVD risk but not increased bleeding risk	Low-dose aspirin should not be administered for primary prevention of ASCVD
	Adults aged 40 to 59 with ≥10% CVD risk	**Adults aged 60-69 with ≥10% CVD risk**	**Adults older than 60 years of age**
2022 USPSTF recommendation	The decision to initiate low-dose aspirin for primary prevention of CVD should be an individual one	The decision to initiate low-dose aspirin for primary prevention of CVD should be an individual one	Low-dose aspirin for primary prevention of CVD is not recommended

Similarly, in its 2021 CVD prevention guidelines, the European Society of Cardiology (ESC) concluded that aspirin should not be prescribed to individuals without ASCVD. However, in selected patients at high or very high CVD risk, the potential benefits of aspirin may outweigh the risks. For adults over 70 years of age with high CVD risk, the ESC advised that decisions be made on a case-by-case basis.[19]

In 2022, the USPSTF released an updated systematic review evaluating the effectiveness of aspirin in reducing CVD events. The Task Force concluded that for adults aged 40 to 59 years, with ≥10% estimated 10-year CVD risk, aspirin use for primary prevention offers a small net benefit. However, individuals who are not at increased risk for bleeding and take low-dose aspirin daily are more likely to derive benefit. Consistent with the 2019 ACC/AHA guidelines, the USPSTF recommends low-dose aspirin for primary prevention in adults ≥60 years of age.[18] Current guidelines emphasize the importance of determining individual net benefit of aspirin use for primary prevention (**TABLE 3**).

Nevertheless, physician and public perceptions have increasingly shifted toward caution in aspirin use, largely due to concerns over bleeding risk. This shift has resulted in underuse in patients who stand to benefit, and in some cases, overuse in low-risk individuals, exposing them to bleeding risk with few benefits.[20] These trends underscore the need for greater clarity in identifying the clinical characteristics of patients for whom aspirin's net benefit outweighs its risks. It also highlights the need to better educate clinicians on the importance of continued aspirin use in patients at risk of recurrent CV events.

Traditionally, aspirin recommendations were segmented based on either evidence of a previous event (secondary prevention) or usual or elevated risk (primary prevention). This approach presumed that aspirin's benefits outweighed its bleeding risks only once a patient had an event or was risk equivalent based on risk calculators largely built on data derived from epidemiologic studies. However, as demonstrated by primary prevention studies, the conventional tools that were used to select patients were not effective in identifying those at sufficient risk to benefit from aspirin use.[21]

Yet it is clearly understood that someone can have elevated CV risk without having had an event, as evidenced by the large number of first events that occur every year. The goal, therefore, should be to better identify these patients, as they are most likely to benefit from aspirin treatment. These patients, particularly those with subclinical atherosclerosis, while technically classified as "primary prevention," may have event risks comparable to or greater than patients who have had a previous event.[22]

A patient's CV risk is influenced by a combination of atherosclerotic disease and thrombotic risks; features that are not easily assessed by conventional risk factors, such as age, diabetes, hypertension, smoking, or family history. Evidence of subclinical atherosclerosis (e.g., coronary artery calcium [CAC] score, carotid plaque score [CPS]) or biomarkers (e.g., lipoprotein(a) [Lp(a)], platelet reactivity, genetic susceptibility) are individualized risk indicators that are becoming more clinically available.

This more analytical perspective reframes the benefit-risk calculation for aspirin use. The question is no longer whether a patient has had a clinical event, but rather how their absolute CVD risk compares to their bleeding risk. Applying new analytical tools may offer a more personalized approach to determine a patient's position on the CVD risk continuum and improve the ability to identify individuals whose absolute benefit outweighs bleeding harm in primary prevention. These approaches are reviewed below.

Imaging

Coronary imaging modalities, such as CAC or CPS, are increasingly used to identify asymptomatic, higher-risk individuals (i.e., those with advanced subclinical atherosclerosis) who may be appropriate candidates for aspirin use as primary prevention. Research has shown that ASCVD risk rises sharply with higher CAC scores, while bleeding risk

does not appear to increase proportionally.[22-24] Studies suggest that aspirin may be beneficial in individuals with a CAC score >100 or moderate plaque burden on carotid ultrasound (CPS ≥2), provided they have no major bleeding risk factors.[25] Similarly, a recent systematic review found that, in the absence of significant bleeding risk, both elevated ASCVD risk and higher CAC scores correlated with greater net benefit from aspirin use.[26]

Biomarkers

Lp(a)

In individuals with elevated Lp(a), aspirin use has been associated with a reduction in CV events. For example, recent evidence suggests that aspirin for primary prevention may benefit elderly individuals with elevated Lp(a)-associated genotypes. In an analysis of more than 12,000 participants enrolled in the ASPREE trial, low-dose aspirin (100 mg daily) reduced major adverse CV events (MACE) by 1.7 events per 1000 person-years, while increasing clinically significant bleeding by 1.7 events per 1000 person-years. However, in subgroups carrying Lp(a)-associated genotypes, specifically rs3798220-C and Lp(a) genomic risk score, aspirin reduced MACE by 11.4 and 3.3 events per 1000 person-years, respectively, without a statistically significant increase in bleeding risk.[27]

Similarly, findings from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort showed a relationship between aspirin use and CV events in individuals with elevated Lp(a). A subgroup of participants with Lp(a) concentrations >50 mg/dL had a higher burden of traditional CVD risk factors, more frequent aspirin use, and a significantly higher rate of coronary heart disease incidents. Aspirin use was associated with a significant reduction in coronary heart disease events. Although overall bleeding risk was increased with aspirin use, no significant differences in bleeding rates were observed between those with elevated Lp(a) and those without.[28]

Platelet activity

Aspirin's CV benefits stem from its antithrombotic effects, raising the possibility that assessing platelet activity could enable more targeted patient selection for therapy. Individuals with elevated platelet reactivity may be at higher risk for thrombotic events and, therefore, would be more likely to derive meaningful benefit from aspirin for primary prevention. Conversely, those with low platelet reactivity are generally more prone to bleeding and less likely to experience net benefit. Prospective clinical studies are needed to determine whether a platelet-guided approach can reliably identify candidates for aspirin as primary prevention. The development of protein biomarker signatures that predict both platelet activity and CV event risk could make such an approach scalable in routine practice.[29,30]

Genetic predisposition

Genetic markers may offer another approach to personalized aspirin therapy. Recent research suggests that low-dose aspirin (100 mg) for primary prevention may be beneficial in high-risk individuals with an elevated genetic predisposition to coronary artery disease (CAD). Using data from the ASPREE trial, it was shown that among participants with the highest CAD polygenic risk score (GPSMult), there was a 47% reduction in risk of CAD events with aspirin (P =.02) without a statistically significant increase in bleeding risk (P =.80).[31]

SUMMARY

While aspirin use is well established for the prevention of recurrent stroke and MI (secondary prevention) and acute or evolving MI, its role in individuals without an event (primary prevention) remains uncertain. In line with the 2019 ACC/AHA guidelines, recent trends show a decline in aspirin use for primary prevention, particularly among adults ≥70 years. Nevertheless, about one-third of adults in this age group continue to use aspirin for primary prevention.[32] Conversely, a decline in use has been observed among adults <60 years with ASCVD risk factors.[33]

Traditionally, patients were categorized as either high risk (secondary prevention) or moderate risk (primary prevention). However, this approach can potentially overlook a subset of individuals who have not had a CV event but who are risk equivalent due to the presence of subclinical atherosclerosis and may benefit from aspirin. Emerging evidence supports tailoring treatment decisions to a patient's atherosclerotic/thrombotic status using more precise analytical methods. Using such tools will allow improved decision-making regarding initiating aspirin therapy and provide a better ability to weigh potential benefits against possible harms, integrating clinical characteristics, CV and bleeding risks, and other relevant factors.[1]

The challenge lies in identifying individuals with sufficiently high CV event risk in which aspirin's benefits outweigh potential harms. Reliance solely on conventional risk factors often underestimates aspirin's potential benefit and overstates its risks. While patient-facing CV risk-assessment tools can help initiate discussions between clinician and patient, they may be inadequate for guiding treatment decisions. Current risk stratification tools may be refined by the addition of more personalized emerging imaging and biomarkers.

Incorporating CAC and CPS scoring into clinical practice is an effective strategy for improving clinician-patient decision-making in primary prevention. CAC is a highly reli-

able method for identifying asymptomatic, higher-risk individuals who are likely to benefit from aspirin. A score ≥100 offers a practical threshold for considering aspirin, whereas a score of 0 generally supports avoiding use due to the low expected net benefit. Making CAC-guided aspirin therapy a standard of care will require integrating CAC data into electronic medical records, opportunistically using prior imaging to calculate scores, and enhancing clinician education on interpreting results in the context of both bleeding risk and overall CV risk.

Targeted education for health care professionals, covering appropriate imaging and interpretation for prevention decisions, is essential. Equally important are informed, shared discussions between clinicians and patients to ensure aspirin is used appropriately, safely, and in alignment with individual risk profiles. Communication must be simple and precise.

For clinicians: If a patient has documented atherosclerosis and low bleeding risk, aspirin should be considered. For the public, the message becomes: *aspirin can help prevent heart attacks and strokes in certain higher-risk individuals, but it is not appropriate for everyone.*

Ultimately, an integrated approach combining clinical risk factors, imaging, and biomarkers is needed to identify patients in whom aspirin's benefits outweigh its risks. Current guidelines do not yet incorporate imaging-based risk stratification, though this may represent the future of preventive care. Until such tools become routine, clinician education and individualized decision-making are key. ●

REFERENCES

1. Santilli F, Albrecht G, Blaha M, et al. Needs-based considerations for the role of low-dose aspirin along the CV risk continuum. *Am J Prev Cardiol*. 2024;18:100675. doi:10.1016/j.ajpc.2024.100675
2. Weiss H, Aledort L. Impaired platelet/connective-tissue reaction in man after aspirin ingestion. *The Lancet*. 1967;290(7514):495-497. doi:10.1016/s0140-6736(67)91658-3
3. Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. *J Clin Invest*. 1968;47(9):2169-2180. doi:10.1172/JCI105903
4. Antiplatelet Trialists' Collaboration. *Co*llaborative overview of randomised trials of antiplatelet therapy. I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994; 308(6921):81-106.
5. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation*. 2011;123(7):768-778. doi:10.1161/circulationaha.110.963843
6. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):1376-1414. doi:10.1016/j.jacc.2019.03.009
7. Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *The Lancet*. 2009;373(9678):1849-1860. doi:10.1016/S0140-6736(09)60503-1
8. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2016;164(12):836-845. doi:10.7326/M16-0577
9. Elwood PC, Cochrane AL, Burr ML, et al. A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. *Br Med J*. 1974;1(5905):436-440. doi:10.1136/bmj.1.5905.436
10. Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med*. 1978;299(2):53-59. doi:10.1056/NEJM197807132990201
11. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *J Am Coll Cardiol*. 1988;12(6 suppl A):3A-13A. doi:10.1016/0735-1097(88)92635-6
12. The SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *The Lancet*. 1991;338(8779):1345-1349.
13. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54(12):1044-1054. doi:10.1136/jnnp.54.12.1044
14. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *The Lancet*. 2018;392(10152):1036-1046. doi:10.1016/S0140-6736(18)31924-X
15. ASCEND Study Collaborative Group; Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379(16):1529-1539. doi:10.1056/NEJMoa1804988
16. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med*. 2018;379(16):1499-1508. doi:10.1056/NEJMoa1800722
17. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA*. 2019;321(3):277-287. doi:10.1001/jama.2018.20578
18. US Preventive Services Task Force; Davidson KW, Barry MJ, et al. Aspirin use to prevent cardiovascular disease: US Preventive Services Task Force recommendation statement. *JAMA*. 2022;327(16):1577-1584. doi:10.1001/jama.2022.4983
19. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for Cardiovascular Disease Prevention in Clinical Practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Rev Esp Cardiol (Engl Ed)*. 2022;75(5):429. doi:10.1016/j.rec.2022.04.003
20. Luepker RV, Oldenburg NC, Misialek JR, et al. Aspirin use and misuse for the primary prevention of cardiovascular diseases. *Am J Prev Med*. 2021;60(4):513-519. doi:10.1016/j.amepre.2020.10.025
21. Verma KP, Inouye M, Meikle PJ, Nicholls SJ, Carrington MJ, Marwick TH. New cardiovascular risk assessment techniques for primary prevention: JACC review topic of the week. *J Am Coll Cardiol*. 2022;80(4):373-387. doi:10.1016/j.jacc.2022.05.015
22. Blaha MJ, Abdelhamid M, Santilli F, Shi Z, Sibbing D. Advanced subclinical atherosclerosis: a novel category within the cardiovascular risk continuum with distinct treatment implications. *Am J Prev Cardiol*. 2022;13:100456. doi:10.1016/j.ajpc.2022.100456
23. Ajufo E, Ayers CR, Vigen R, et al. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2021;6(2):179-187. doi:10.1001/jamacardio.2020.4939
24. Dzaye O, Razavi AC, Dardari ZA, et al. Carotid ultrasound-based plaque score for the allocation of aspirin for the primary prevention of cardiovascular disease events: the Multi-Ethnic Study of Atherosclerosis and the Atherosclerosis Risk in Communities study. *J Am Heart Assoc*. 2024;13(12):e034718. doi:10.1161/JAHA.123.034718
25. Blaha MJ, Santilli F, Sibbing D, et al. Advanced subclinical atherosclerosis and low-dose aspirin: guideline-based extension into asymptomatic chronic coronary syndromes. *JACC Adv*. 2025;4(7):101855. doi:10.1016/j.jacadv.2025.101855
26. Doshi A, Gandhi H, Patel KN, Majmundar M, Doshi R. Aspirin for primary prevention in patients with elevated coronary artery calcium score: a systematic review of current evidences. *Am J Cardiol*. 2024;220:9-15. doi:10.1016/j.amjcard.2024.03.021
27. 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(14):1287-1298. doi:10.1016/j.jacc.2022.07.027
28. Bhatia HS, Trainor P, Carlisle S, et al. Aspirin and cardiovascular risk in individuals with elevated lipoprotein(a): the multi-ethnic study of atherosclerosis. *J Am Heart Assoc*. 2024;13(3):e033562. doi:10.1161/JAHA.123.033562
29. Berger JS. Aspirin for primary prevention—time to rethink our approach. *JAMA Netw Open*. 2022;5(4):e2210144. doi:10.1001/jamanetworkopen.2022.10144
30. Cofer LB, Barrett TJ, Berger JS. Aspirin for the primary prevention of cardiovascular disease: time for a platelet-guided approach. *Arterioscler Thromb Vasc Biol*. 2022;42(10):1207-1216. doi:10.1161/ATVBAHA.122.318020
31. Yu C, Natarajan P, Patel AP, et al. Polygenic risk, aspirin, and primary prevention of coronary artery disease. *Eur Heart J Cardiovasc Pharmacother*. 2025;11(1):84-91. doi:10.1093/ehjcvp/pvae085
32. Boakye E, Uddin SMI, Obisesan OH, et al. Aspirin for cardiovascular disease prevention among adults in the United States: trends, prevalence, and participant characteristics associated with use. *Am J Prev Cardiol*. 2021;8:100256. doi:10.1016/j.ajpc.2021.100256
33. Murugiah K, See C, Huang C. Recent trends in aspirin use for cardiovascular disease prevention in the United States, 2015 to 2023. *JACC Adv*. 2025;4(6 Pt 2):101699. doi:10.1016/j.jacadv.2025.101699