Aspirin for Primary Prevention of Coronary Artery Disease

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Abstract: Primary prevention of coronary artery disease (CAD) is an important means to reduce the burden of the disease. Aspirin has been widely prescribed over the last several decades as part of primary CAD prevention strategy. However, 3 recent hallmark trials - ARRIVE, ASCEND and ASPREE have raised serious questions about this common practice. Although, aspirin reduced incidence of non-fatal MI and stroke in these recent studies, bleeding risk was higher. In the present era, where regular exercise, healthy diet, smoking cessation, and statins are used to manage the risk factors of CAD, additional prescription of aspirin seems more harmful than beneficial. The guidelines of major societies such as European Society of Cardiology (ESC), American College of Cardiology (ACC), and American Heart Association (AHA) also reflect this shift. In this article, the authors aim to highlight the current evidence on aspirin use for primary prevention of CAD, in the context of evolving contrasting clinical trial data from the last 2 decades. We also highlight the pertinent sections of the most recent clinical guidelines of European Society of Cardiology,

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Introduction

Coronary artery disease (CAD) continues to be a major killer despite an overall decrease in cardiovascular disease (CVD) mortality. According to the 2016 Center for Disease Control and Prevention statistics, CAD accounted for approximately 13% of deaths in the US in 2016, causing a total of 363,452 deaths. The absolute number of deaths due to CAD decreased by 14.6% but its burden remains alarmingly high.[1] According to a 2016 report, with the ageing of the American population, the costs of CAD management are projected to double by 2035, from 188 to 366 billion dollars.[2]

Preventive medicine has been the most economically feasible solution to the growing burden of CAD, with specific focus on antiplatelet therapy with aspirin. Multiple tools, including the Framingham and atherosclerotic cardiovascular disease (ASCVD) risk scores, have been used to predict the risk of development of CAD in apparently healthy population, which assist with the clinical decision-making regarding initiation of primary prevention. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend classification of healthy adults between 40 and 79 years of age with no symptoms into four categories as per likelihood of development of ASCVD in the next 10 years: low (<5%), borderline (5%-7.5%), intermediate (7.5%-20%) and high (≥20%).[3] Of note, a study evaluating 5 risk-scoring tools showed that these tools may overestimate the actual ASCVD risk by about 25% to 115%.[4] This highlights the importance of improved risk factor modification in decreasing CV events.

Historically, aspirin has been used for primary prevention of CAD in individuals with high risk as per these calculators, and also for secondary prevention in patients of known CAD to slow further disease progression and mortality. Stuntz et al estimated that almost 30% of the population over the age of 40 years in the US (corresponding to 48.7 million Americans) takes over-the-counter aspirin for primary and secondary prevention, a declining yet staggering statistic. According to another study, consumption of aspirin for primary prevention is prevalent in over 20% of adults over 40 years, with its use being more common in elderly white males and those over 65 years.[5]

However, in the present era of aggressive CAD risk management with antihypertensive and statin therapy, the use of aspirin has been the subject of numerous clinical trials, reevaluating its role in primary prevention.

Three recent trials, all published in 2018, challenged this long-standing norm of prescribing aspirin for primary prevention. Aspirin in Reducing Events in the Elderly (ASPREE), Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) and A Study of Cardiovascular Events In Diabetes (ASCEND) all uniquely demonstrated a lack of positive impact in CVD outcomes that was expected with aspirin prescription.[6-8] Furthermore, the trials emphasized on the association of aspirin use with bleeding complications. The 2019 American College of Cardiology (ACC) guidelines correspondingly reflected this radical change in approach to CAD primary prevention by recommending restricted use of aspirin, applicable in selected population. Thus, in this review we attempt to examine the recent evidence in the context of older evidence and guidelines on aspirin use, and thereby explain the current status of aspirin in primary prophylaxis of CAD.

Pathophysiology of CAD and Mechanisms of Aspirin in its Prevention

CAD is primarily a chronic inflammatory process in which conditions like hyperlipidemia, hypertension, smoking, diabetes mellitus and obesity predispose to atherosclerotic plaque formation, as shown in Figure 1.[9] When an atherosclerotic plaque ruptures, platelets form a thrombus and enhance the interplay of inflammatory processes already existing between leukocytes, endothelium and smooth muscle cells of the mesothelium.[10] Thus, antiplatelet medication like aspirin can be used to mitigate the risk of disease progression in CAD.

It acts by irreversibly inhibiting platelet cyclooxygenase by covalent acetylation, resulting in decreased biosynthesis of prostaglandin H_2 and its downstream product, thromboxane A_2. At doses less than 300 mg, aspirin inhibits platelet aggregation and release of pro-inflammatory molecules, thereby retarding thrombogenesis. It has a short half-life of 15 to 20 minutes, but its antiplatelet effect lasts until new platelets are formed.[11] Additional mechanisms supporting aspirin use in CAD have been demonstrated by recent animal models. Data shows that aspirin induces the formation of nitric oxide radicals in the body, which decreases leukocyte adhesion. It can also alter signaling through NF-κB gene, which encodes regulatory molecules involved in atherogenesis.[12] The antiplatelet property of aspirin has worrisome clinical consequences

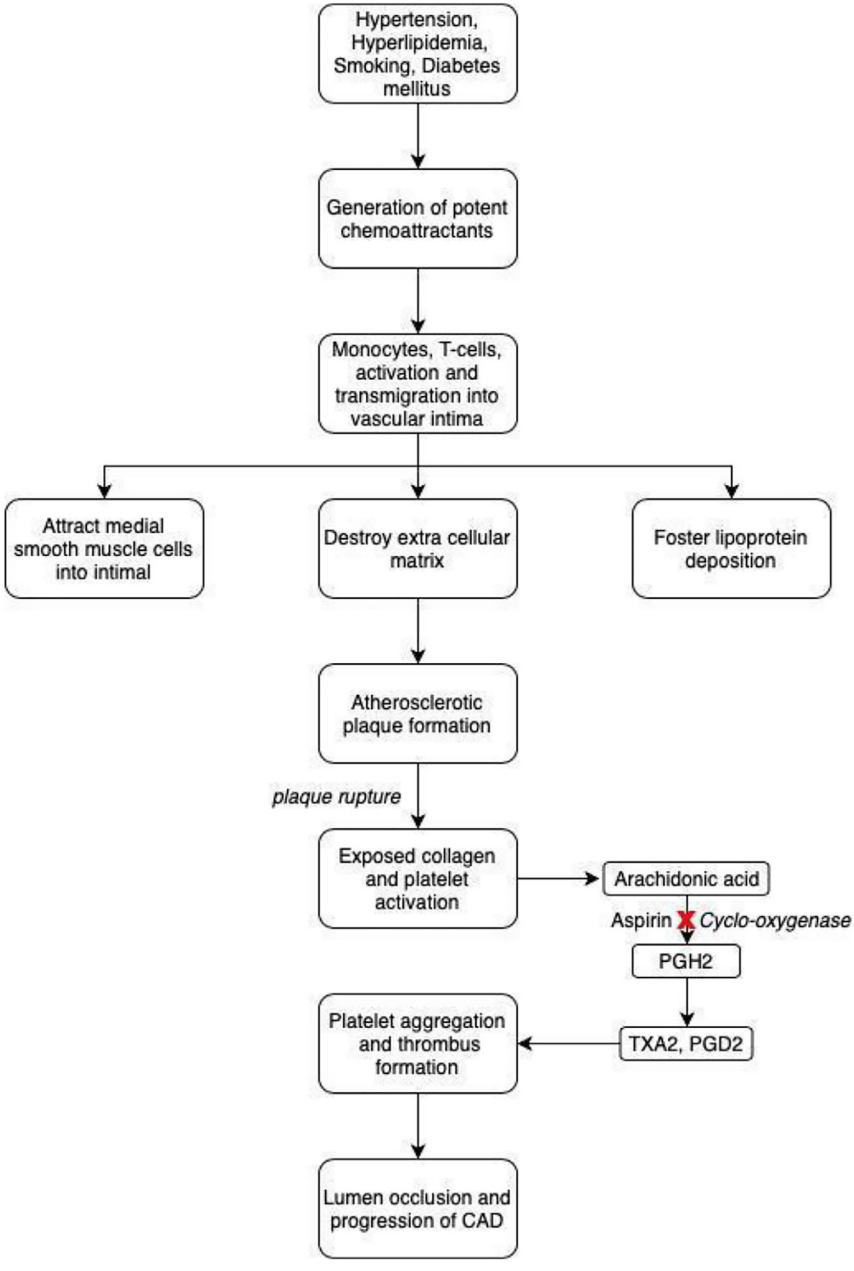

FIG 1. Role of aspirin in prevention of coronary artery disease. PGD_2, prostaglandin D_2; PGH_2, prostaglandin H_2; TxA_2, thromboxane A_2.

in the form of bleeding risk ranging from mild (epistaxis and hematuria) to severe (upper and lower gastrointestinal and intracranial hemorrhage). Risk of bleeding is also worsened with increasing age, even with low doses, adding to safety concerns of aspirin use.[13] Table 1 summarizes the pharmacological properties of aspirin.

Evidence Supporting Aspirin Use

Used prehistorically as the key chemical component of willow (or *salix,* in Latin) bark, salicylic acid was first identified and refined in the first half of the 19th century. Following the revolution in the chemical dye industry, this molecule was further modified to acetyl salicylic acid or erstwhile aspirin. The role of aspirin in inhibition of prostaglandin formation was described in 1971 by John Vane, who was awarded the Nobel Prize in Medicine for his contribution.[14] In 1974, Elwood et al published the first ever, albeit non-significant evidence, indicating benefit of aspirin in secondary prevention of MI.[15] The first robust evidence supporting the effectiveness of aspirin in primary prevention of CAD surfaced shortly thereafter in 1989 with the emergence of results of the large-scale clinical trial called the US Physician Health Study. In this trial, there was risk reduction of 44% in the occurrence of first myocardial infarction (MI) noted in 22071 healthy male physicians followed for a mean period of 60.2 months, when the aspirin arm was compared to the placebo arm (RR 0.56; 95% CI 0.45 - 0.70; $P < 0.00001$). However, no change in CVD deaths was observed. The risk of ulcer and bleeding, although not significant, was higher with aspirin.[16] There was a notable difference in the outcome of this study from a similar trial conducted in 5139 healthy British male physicians, referred to as the British Doctors' Study, which concluded a nonstatistically significant reduction in incidence and mortality from MI, stroke or other vascular conditions in those receiving aspirin versus placebo.[17]

TABLE 1. Pharmacological properties of aspirin[11]

Target	Irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes
Duration of action	10 days
Dosing	75-100 mg
Prodrug	Yes
Half life	3 hours
Renal clearance	85%
Bioavailability	50% to 75%

To explore this relationship further, subsequent studies targeted subjects with increased CVD risk managed on a lower dose of aspirin. These included the Hypertension Optimal Treatment trial (HOT), Thrombosis Prevention Trial and the Primary Prevention Project and added to the growing body of evidence in favor of low-dose aspirin in CAD prevention.[18-20]

Based on these findings, USPSTF recommended consideration of low dose aspirin for individuals at high risk of CAD defined as 5-year risk of ≥3%.[21] Correspondingly, the AHA guidelines of 2002 agreed with USPSTF guidelines, but they defined higher CAD risk as a 10-year risk of ≥10%.[22] Although the Antithrombotic Trialists' Collaboration in the same year[23] also corroborated that the risk-benefit ratio favored aspirin and further consolidating use in CAD, the female population was overall underrepresented in the 5 studies, paving the way for future trials focusing on this population group.

Conflicting Evidence Regarding Aspirin Use

In 2005, Ridker et al.[24] published their findings from a 10-yearlong randomized, placebo-controlled trial titled "Women's Health Study (WHS)", that examined women aged 45 years or older with majority having a low (<5%) 10-year CVD risk. When compared with the placebo group, the authors did not find a significant decrease in the MI (fatal or nonfatal) or CVD mortality in women given aspirin (RR 1.02; 95% CI 0.84-1.25; *P* 0.83). While women over 65 years benefitted from aspirin, with a significant decrease in MI, major CVD events and ischemic stroke, it was accompanied with an overall increase in gastrointestinal bleeding (RR 1.40; 95% CI 1.07-1.83; *P* 0.02).

These 6 trials [16-20,24] were subsequently meta analyzed by Berger et al to conclude that aspirin prescription was related to a significant decrease in odds of occurrence of a CVD event, contributed by MI in men (OR 0.68; 95% CI 0.54-0.86; *P* 0.001) and stroke in women (OR 0.83; 95% CI 0.70-0.97; *P* = .02).[25] The total CVD mortality was found to be the same in both sexes, with the odds of major bleeding being higher with aspirin when compared to the control arm (OR 1.68; 95% CI 1.13-2.52; *P* 0.01). In the same year, the European Antithrombotic Trialists' Collaboration (ATT) published conflicting findings in their meta-analysis[26] of the same 6 clinical trials published between 1988 to 2005.[16-20,24] They found that aspirin decreased CVD events (mainly nonfatal MI) by 12%

per year, when compared to the control arm, but had no effect on net stroke or vascular mortality, and that it increased extracranial bleeding. The authors concluded that the role of aspirin was questionable given the lack of net benefit and likelihood of hemorrhage.

Based on sex-specific findings of WHS and subsequent meta-analysis, in 2009, the USPSTF revised previous recommendations of 2002 to limit low dose aspirin to men of 45-79 years and women of 55-79 years given the risk of MI or stroke superseded the bleeding risk.[27]

Evidence Against Aspirin Use in the Post-Stalin Era (Non-American Population)

To define the growing, yet unclear, scope of aspirin use in CAD, multiple small scale studies were designed to evaluate patient population with genetics and environmental factors different from those studied so far. In 2008, 2 clinical trials based in Scotland[28] and Japan[29] respectively, sought to investigate the role of aspirin in diabetics who were concomitantly being treated with antihypertensives and statins, as indicated. The authors concluded that aspirin had no added benefit in reducing CVD events or CVD mortality. In 2010, another Scotland-based study compared aspirin against placebo in patients with a risk of CAD, defined as low ankle brachial index, with endpoint of CAD events. The findings were statistically nonsignificant but clinically relevant: aspirin increased major bleeding and decreased CAD events when compared with the placebo.[30] Following this, in 2014, another study in Japan[31] published their findings on elderly Japanese patients at increased CVD risk and found aspirin to reduce nonfatal MI significantly at the cost of significantly increased risk of major extracranial hemorrhage.

These trials shed new light on the use of aspirin in diverse population groups, but a major weakness of these trials was that they were underpowered due to the lower event rates observed in the population. In the years between 2011 and 2016,[32-35] several meta-analyses were performed to evaluate the existing heterogeneous data. They all concluded that the protective benefit of aspirin was offset by its risk of causing a major bleed. Furthermore, on specifically examining the diabetic population, Kokoska and colleagues found similar statistics of mortality from any cause, individual atherosclerotic or bleeding events when aspirin was compared to placebo.[36]

In view of these new findings, the USPSTF in 2016 updated their guidelines to include aspirin only for patients aged 50 to 59 years with a calculated risk of development of ASCVD at 10% or more. Moreover,

patients started on aspirin were expected to take the medication for a minimum of 10 years, and had to be screened out for known bleeding risks.[37]

Most Recent Evidence Against Aspirin Use in the Post-Statin Era

The contradictions in the data, the Task Force recommendations and the advent of statins for risk factor management in CAD all fueled the debate on clinical utility of aspirin in CAD prevention. In the recent years, three randomized placebo-controlled, double-blinded trials (summarized in Table 1) attempted to investigate the preventive role of low-dose aspirin in specific patient cohorts to determine which subpopulation may benefit from aspirin, and whether such a benefit actually exists.

ASPREE: Aspirin in Reducing Events in the Elderly. Mc Neil, Nelson and colleagues studied the effect of aspirin (versus normal ageing) on the composite of disability, dementia and all-cause mortality in sample size comprising of healthy Australian and American adults exceeding the age of 70 years (or 65 years when including blacks and Hispanics in the US).[6] After a median follow-up period of 4.7 years, incidence of death (irrespective of cause) was found to be significantly more in the aspirin group (12.7 per 1000 person years) as compared to the placebo group (11.1 per 1000 person years), while the CV mortality was lower, albeit non significantly, with aspirin. Most deaths in the aspirin group, however, were attributable to cancer (3.1% vs 2.3%; HR 1.31, 95% CI 1.10-1.56) and not major bleeds. Deaths due to major bleeds including hemorrhagic stroke were found to be the same in both the groups (0.3%).

ARRIVE: Aspirin to Reduce Risk of Initial Vascular Events. In the multi-center Europe and US based study "ARRIVE", the investigators sought to determine the role of aspirin in preventing the first CVD event in subjects deemed to be at a moderately increased CVD risk.[7] The mean ASCVD score of 17.35% was attributable mainly to hypertension and hyperlipidemia. The endpoint of the trial was a composite of CVD death, MI, unstable angina, stroke, or transient ischemic attack. After a follow-up of 60 months (median), the primary endpoint in the aspirin arm and the placebo arm were comparable (4.29% vs 4.48%; HR 0.96; 95% CI 0.81-1.13; $P = 0.6$). Subgroup stratification on the basis of age, sex, body-mass index or smoking status did not yield any significant differences.

The risk of nonfatal MI, when compared between aspirin and placebo, was statistically nonsignificant but slightly lower in the group receiving aspirin. The incidence of gastrointestinal bleeding, however, was double with aspirin than with placebo (0.97% vs 0.46%; $P = 0.0007$). Most of these bleeds were mild and the incidence of other serious adverse events and deaths was similar in both the arms.

ASCEND: A Study of Cardiovascular Events in Diabetes. In another Europe-based trial "ASCEND", the investigators sought to study the effect of aspirin in decreasing the incidence of CVD events and gastrointestinal cancer in 15,480 diabetic adults lacking any diagnoses CVD disease, when compared with placebo (or omega-3 fatty acid).[8] 82.75% participants of this study were at low-moderate CV risk, with approximately 75% of patients taking concomitant treatment with statins. The authors found a 12% decrease in serious CVD events including nonfatal MI, transient ischemic attack and stroke in aspirin users (8.5% vs 9.6%; Rate ratio 0.88; 95% CI 0.79-0.97; *P* 0.01), findings similar to the conclusions from the ATT meta-analysis from 2009. This was accompanied with a 29% increase in major bleed in patients on aspirin (4.1% vs 3.2%; RR 1.29; 95% CI 1.09-1.52; *P* 0.003), of which 41.3% were GI bleeds, 21.1% were intraocular and 17.2%, intracranial bleeds. Interestingly, the number needed to treat was 91 while the number needed to harm was 112 with aspirin in this study, as highlighted in Table 5. Although statistically nonsignificant, the risk of nonfatal MI was the same in both groups while the risk of nonfatal stroke was slightly lower in the group receiving aspirin as compared to the placebo group. The incidence of fatal bleeds and hemorrhagic stroke was found to be the same in both groups.

Discussion and Future Direction

Aspirin has come a long way (as reflected in Table 3 and 4) in the management of CVD disease since the initial interest shown in the late 1980s when it was recommended for primary prevention of CAD in high risk individuals. Over the years, although this recommendation was tailored multiple times, it was never abandoned altogether. However, recent trials designed to find clear evidence for a benefit in primary prevention showed that although it reduced incidence of nonfatal MI and stroke, bleeding risk was higher bringing into question its use for primary prevention. Added to this is an age-complicated increased risk of GI bleeding, which some researchers argue can be controlled by PPIs, but requires further evidence before any practice can be adopted.

Thus, patient specific assessment of aspirin's effects on bleeding risks and expected benefits to account for variability from patient to patient is important to ensure safe prescription.[38] As a result, although aspirin stays as an integral part of pharmacotherapy for secondary prevention of CAD or clinical ASCVD even though its role in primary prevention is not 'one size fits all'. The current 2019 guidelines on primary CVD prevention by ACC, framed after the meta-analysis of three recent trials that proved that harm by aspirin exceeded benefit, recommends the use of aspirin in 40 to 70-year age group with higher ASCVD scores, provided there is no existing risk factors that could cause bleeding. The latest USPSTF guidelines still encourages use of low dose aspirin for primary prevention of CAD when the 10-year ASCVD risk score is equal to or greater than 10%, assign a grade B recommendation in adults of age 50 to 59 years and grade C in adults between 60 and 69 years.[37] However, the USPSTF guideline was published before the 3 recent trials that generated evidence against the use of aspirin in primary prevention of CAD and are likely pending an update. Although published before the completion of the 3 recent trials, the European Society of Cardiology (ESC) guidelines of 2016 do not recommend aspirin use unless CAD is confirmed, in view of higher chances of bleeding.[39] It is noteworthy, that although aspirin has lost support over the years as a therapy for primary prevention as per society guidelines across the world, the US FDA never approved aspirin for primary prevention.

Table 2 summarizes the key findings of this review and emphasizes on potential gaps that require further exploration, while Table 3 describes the changes in the guidelines over the years. Tables 4 and 5 are a summary of major trials based on aspirin over the last few decades and provide an overview of change of data reflected in the evolving guidelines. Rather than aspirin, recent primary prevention guidelines and contemporary clinical trials emphasize more on moderate to high intensity statin based on borderline, intermediate and high ASCVD risk scores. Clearly, older patients have higher risks of bleeding, so the benefits of low dose aspirin typically do not outweigh the risks.[40] In certain very high-risk patients, including those with very high coronary artery calcium scores (eg in the 90th percentile) or strongly positive stress tests or known significant carotid disease determined by noninvasive testing, the benefits versus risks of low dose aspirin require risk assessment at individual level.

TABLE 2. Key highlights of trials in favor of aspirin in primary prevention of CAD

No	Title, year	Sample pop.	FU period (years)	CVD risk	Inclusion criteria	Exclusion criteria	Predetermined outcom	Observations
1.	British Doctors' Study (1988)[15]	5139, male doctors	5.5 (median)	Healthy	All healthy male doctors born in the UK born in the 20th century who were listed in the medical directory of 1977	1. History of stroke, definite MI or PUD 2. Those unwilling to take aspirin	Primary endpoints: Fatal MI and stroke Secondary endpoints: non-fatal MI and stroke	No significant decrease in mortality, increase in disabling stroke but decrease in non-fatal stroke and MI with aspirin
2.	US Physician Health Study (1989)[14]	22071, male doctors	5 (median)	Healthy			Primary endpoints: death due to cardiovascular cause Secondary endpoints: non-fatal MI or stroke	44% reduced risk of MI but no reduction in mortality while non significantly increased hemorrhagic stroke, PUD and need for blood transfusion with aspirin
3.	Hypertension Optimal Treatment trial (1998)[16]	18790, males 53%	3.8 (mean)		1. 50-80 years 2. Hypertension (diastolic BP 100-115 mm Hg)		Primary endpoint: major cardiovascular events (excluding silent MI) Secondary endpoint: Stroke, MI, cardiovascular mortality	Reduced cardiovascular events and MI, no effect on stroke or fatal bleeding but higher incidence of non-fatal bleeding
4.	Thrombosis Prevention Trial (1998)[17]	5085, males	6.8 (median)	High	1. 45-69 years	1. Current or previous PUD 2. Probable or definite MI or stroke 3. Ongoing medication with interaction with aspirin/warfarin	Primary endpoint: Ischemic heart disease (IHD) Secondary endpoint: Stroke	Reduced non-fatal IHD, with addition of warfarin beneficial in reduction of IHD

(*continued on next page*)

TABLE 2. (*continued*)

No	Title, year	Sample pop.	FU period (years)	CVD risk	Inclusion criteria	Exclusion criteria	Predetermined outcom	Observations
5.	Primary Prevention Project (2001)[18]	4495, males 43%	3.6 (mean)	High	1. ≥5 years 2. Hypertension (SBP ≥160, DBP ≥95) 3. Hypercholesterolemia (total blood cholesterol ≥6.4 mmol/L) 4. DM (fasting venous glucose ≥7.8 mmol/L) 5. Obesity (BMI ≥30) 6. Family history of MI <55 years	1. Treatment with antiplatelet therapy for previous vascular event 2. Chronic history if anticoagulant or anti inflammatory 3. CI to aspirin 4. Disease with poor prognosis	Primary endpoint: major cardiovascular events Secondary endpoint: total cardiovascular events, cardiovascular mortality, all-cause mortality	Reduced major and total cardiovascular endpoints but was associated with higher rates of severe bleeding
6.	Women's Health Study (2005)[22]	39876, females	10.1 (mean)	Healthy	1. ≥45 years 2. No history of previous CAD, stroke/TIA, cancer or other major chronic illnesses	1. Aspirin or NSAID use more than once a week; or anticoagulants or corticosteroid 2. History of side effects to study drugs 3. Supplements of vitamin A.E or beta carotene more than once a week	Primary endpoint: major cardiovascular events Secondary endpoint: fatal MI and stroke, cardiovascular mortality	Reduced risk of stroke with no effect on risk of MI or mortality

TABLE 3. Key highlights of recent trials against aspirin in primary prevention of CAD

No	Title, year	Sample pop.	FU period (years)	CVD risk	Inclusion criteria	Exclusion criteria	Predetermined outcomes	Observations
1	ASPREE: (2018)[6]	19114, males 43.5%	4.7	Low-moderate	1. ≥70 years (≥65 years if US Hispanic or African-American) 2. Free of cardiovascular disease, dementia and disability	Life expectancy > 5 years History of cardiovascular or cerebrovascular disease Cognitive impairment	Primary outcome: Diagnosis of dementia or persistent physical disability (difficulty in performing basic ADLs) Secondary outcome: Death from any cause	No change in disability-free period, increase in all-cause mortality (with most deaths attributed to cancer)
2	ARRIVE: (2018)[7]	12546, males 70.5%	6	Moderate (10-20%)	1. ≥ 55 year in females and ≥60 year in males 2. Known moderate CV risk with no known diabetes mellitus	1. Known indication for aspirin or anticoagulation 2. History of diabetes, MI, stroke or revascularization 3. GI ulcer or GI bleed	Primary efficacy outcome: Diagnosis of CV death, MI, unstable angina, stroke or TIA Primary safety outcome: GI bleed (mild, moderate or severe)	No added benefit of aspirin in those on treatment with antihypertensives and statins
3	ASCEND: (2018)[8]	15480, males 77%	7.4	Low-moderate (majority with <10%)	>40 years Well treated diabetic (Type 1 or 2) Uncertainty about benefit of aspirin	Evident cardiovascular disease Clear indication of aspirin CI to aspirin	Primary efficacy outcome: non-fatal MI or stroke, TIA, vascular death (excluding intracranial hemorrhage Primary safety outcome: first major bleed Secondary outcome: GI cancer, any serious vascular event or revascularization procedure	Aspirin decreased vascular events in diabetics but increased major bleeds. NNT: 91 NNH: 112

TABLE 4. Changes in the ACC/AHA/ ESC/USPSTF guidelines over the years

Society, year	Strength of recommendation	Recommendation
ACC/AHA, 2019[3]	IIb	Low dose aspirin in adults of age 40-70 years with higher ASCVD scores
	III	Adults over 70 years of age or with bleeding risks are not to be given aspirin.
USPSTF, 2016[35]	B	Low dose aspirin was recommended if 10-year ASCVD risk score is ≥10%, in adults of age 50 to 59 years
	C	Low dose aspirin was recommended if 10-year ASCVD risk score is ≥10%, in adults between 60 and 69 years
ESC, 2016[37]	III	Do not recommend aspirin due to bleeding risk and unproven efficacy in primary prevention of CAD
ESC, 2012[38]	III	Do not recommend aspirin due to bleeding risk and unproven efficacy in primary prevention of CAD
USPSTF, 2009[25]	A	Low dose aspirin was recommended to men of 45-79 years and women of 55-79 years given the risk of MI or stroke superseded the bleeding risk
ACC/AHA, 2002[20]		Low dose aspirin in higher CAD risk defined as a 10-year risk of ≥10%
USPSTF, 2002[19]	A	Low dose aspirin was recommended for all adults with 5-year risk of CAD ≥3%

TABLE 5. Key points of the review article

1. Primary prevention strategies are based on ASCVD risk score, which is valid for the group of 40-75 years of age.
2. In the current age of heavy emphasis on lipid and blood pressure control, aspirin is gradually losing favor as the drug of choice for primary prophylaxis of CAD.
3. Aspirin use restricted in patients with high ASCVD score (>10%) and low bleeding risk.
4. Routine use of aspirin above age 70 years not recommended.
5. Moderate-high intensity statin cornerstone of primary CAD prevention strategy.
6. Coronary artery calcium score to further risk stratify primary prevention strategy.
7. Aspirin remains an integral part of secondary prevention of known CAD, acute coronary syndrome and following percutaneous intervention.
8. Non-fatal MI and stroke benefit from aspirin are offset by the increase in bleeding risk.

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REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association. *Circulation* 2019:139. https://doi.org/10.1161/CIR.0000000000000659.
2. Nelson S, Whitsel L, Khavjou O, Phelps D, Leib A. Projections of cardiovascular disease prevalence and costs. n.d.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, 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. *Circulation* 2019. https://doi.org/10.1161/CIR.0000000000000678.
4. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al. An Analysis of Calibration and Discrimination Among Multiple Cardiovascular Risk Scores in a Modern Multiethnic Cohort. *Ann Intern Med* 2015;162:266–75. https://doi.org/10.7326/M14-1281.
5. Stuntz M, Bernstein B. Recent trends in the prevalence of low-dose aspirin use for primary and secondary prevention of cardiovascular disease in the United States, 2012-2015. *Prev Med Rep* 2017;5:183–6. https://doi.org/10.1016/j.pmedr.2016.12.023.
6. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med* 2018;379:1519–28. https://doi.org/10.1056/NEJMoa1803955.
7. Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, 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. *Lancet* 2018;392:1036–46. https://doi.org/10.1016/S0140-6736(18)31924-X.
8. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018;379:1529–39. https://doi.org/10.1056/NEJMoa1804988.
9. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005;111:3481–8. https://doi.org/10.1161/CIRCULATIONAHA.105.537878.
10. Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res* 2003;110:255–8.
11. Eikelboom J, Hirsh J, Spencer F, Baglin T, Weitz J. Antiplatelet drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141. https://doi.org/10.1378/chest.11-2293. e89S-e119S.
12. Steinhubl SR, Badimon JJ, Bhatt DL, Herbert J-M, Lüscher TF. Clinical evidence for anti-inflammatory effects of antiplatelet therapy in patients with atherothrombotic disease. *Vasc Med* 2007;12:113–22. https://doi.org/10.1177/1358863X07077462.
13. García Rodríguez LA, Martín-Pérez M, Hennekens CH, Rothwell PM, Lanas A. Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies. *PLoS ONE* 2016;11:e0160046. https://doi.org/10.1371/journal.pone.0160046.

14. Elwood PC, Cochrane AL, Burr ML, Sweetnam PM, Williams G, Welsby E, et al. A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. *Br Med J* 1974;1:436. https://doi.org/10.1136/bmj.1.5905.436.
15. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation* 2011;123:768–78. https://doi.org/10.1161/CIRCULATIONAHA.110.963843.
16. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129–35. https://doi.org/10.1056/NEJM198907203210301.
17. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)* 1988;296:313–6. https://doi.org/10.1136/bmj.296.6618.313.
18. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *HOT Study Group. Lancet* 1998;351:1755–62. https://doi.org/10.1016/s0140-6736(98)04311-6.
19. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998;351:233–41.
20. de Gaetano G. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet* 2001;357:89–95. https://doi.org/10.1016/s0140-6736(00)03539-x.
21. U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002;136:157–60. https://doi.org/10.7326/0003-4819-136-2-200201150-00015.
22. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002;106:388–91. https://doi.org/10.1161/01.cir.0000020190.45892.75.
23. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86. https://doi.org/10.1136/bmj.324.7329.71.
24. Ridker PM, Cook NR, Lee I-M, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293–304. https://doi.org/10.1056/NEJMoa050613.
25. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006;295:306–13. https://doi.org/10.1001/jama.295.3.306.

26. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–60. https://doi.org/10.1016/S0140-6736(09)60503-1.
27. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;150:396–404. https://doi.org/10.7326/0003-4819-150-6-200903170-00008.
28. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840. https://doi.org/10.1136/bmj.a1840.
29. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134–41. https://doi.org/10.1001/jama.2008.623.
30. Fowkes FGR, Price JF, Stewart MCW, Butcher I, Leng GC, Pell ACH, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA* 2010;303:841–8. https://doi.org/10.1001/jama.2010.221.
31. Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA* 2014;312:2510–20. https://doi.org/10.1001/jama.2014.15690.
32. Halvorsen S, Andreotti F, ten Berg JM, Cattaneo M, Coccheri S, Marchioli R, et al. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol* 2014;64:319–27. https://doi.org/10.1016/j.jacc.2014.03.049.
33. Seshasai SRK, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172:209–16. https://doi.org/10.1001/archinternmed.2011.628.
34. Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. *Am Heart J* 2011;162:115–24. https://doi.org/10.1016/j.ahj.2011.04.006. e2.
35. Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med* 2011;124:621–9. https://doi.org/10.1016/j.amjmed.2011.01.018.
36. Kokoska LA, Wilhelm SM, Garwood CL, Berlie HD. Aspirin for primary prevention of cardiovascular disease in patients with diabetes: A meta-analysis. *Diabetes Res Clin Pract* 2016;120:31–9. https://doi.org/10.1016/j.diabres.2016.07.012.
37. 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;164:836–45. https://doi.org/10.7326/M16-0577.

38. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016;164:826–35. https://doi.org/10.7326/M15-2112.
39. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–81. https://doi.org/10.1093/eurheartj/ehw106.
40. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2012;33:1635–701. https://doi.org/10.1093/eurheartj/ehs092.