EDITORIAL

Aspirin for Secondary Prevention of Atherosclerosis—Evidence or Dogma?

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Decades of recommendations to give aspirin for primary prevention of cardiovascular events, based on overoptimistic interpretation of inconclusive data, were recently overturned after a randomized clinical trial with approximately 100 000 person-years of follow-up found that aspirin increased all-cause mortality; several other primary prevention trials of aspirin also failed to show meaningful reductions in cardiovascular events.[1,2] Furthermore, a trial[3] of 17 444 patients undergoing orthopedic surgery suggested increases in myocardial infarction (MI) with aspirin 160 mg per day. Many people randomized in primary prevention trials undoubtedly had undiagnosed atherosclerotic cardiovascular disease (ASCVD). Now that recommendations for prophylactic use of aspirin for primary prevention have been largely reversed, the stage is set to reconsider the strength of evidence for giving aspirin for secondary prevention.

No single trial provides conclusive evidence that long-term administration of aspirin improves outcomes for chronic ASCVD. Belief in aspirin for this indication is based on flawed meta-analyses that evolved over decades.[4] A meta-analysis is useful for confirming that relevant trials with seemingly conclusive results are consistent with the totality of evidence, but no such trial exists. A meta-analysis of inconclusive trials does not provide robust evidence of efficacy or safety but can be used to plan future trials that might provide definitive results. Most clinicians trust that trials included in a meta-analysis are of reasonable quality, that at least some of the trials included will show a clearly positive result, and that reporting is unbiased; those who read the original articles on chronic aspirin therapy will be disappointed. However, peer pressure and concerns about litigation often compel physicians to practice defensive medicine. Consequently, even if doubts about efficacy exist, aspirin may be prescribed by physicians to treat their own anxieties rather than for a patient's benefit. Strangely, some argue that aspirin should be used for chronic ASCVD because the evidence that it is ineffective is inconclusive, but surely this is a reason for more trials rather than prescribing a treatment with potentially serious adverse effects.

It is widely taught that thrombosis is the primary mechanism underlying acute vascular events. However, plaque hemorrhage leading to rupture and ulceration may often be the primary trigger for thrombosis.[5] There is little downside to giving antithrombotic agents to prevent secondary thrombosis on an ulcerated plaque but once the plaque has healed, any benefit from a reduction in platelet aggregation with aspirin may be balanced or outweighed by increases in plaque hemorrhage, suppression of endothelial prostacyclin-mediated protection, and increases in clinically overt bleeding. Moreover, long after most placebo-controlled trials of aspirin were conducted, the widespread introduction of lipid-lowering agents will have reduced the lipid content of the plaque, reducing the risk of rupture of lipid gruel through a thin fibrous cap and increasing the proportion of ruptures due to plaque hemorrhage. The pathological substrate underlying vascular occlusion has evolved, reducing the relevance of ancient trials. Plaque hemorrhage might also increase the proportion of coronary occlusions presenting as sudden death, thereby reducing the rate of nonfatal MI without reducing mortality. Similarly, cerebral infarction is often not associated with clinically obvious neurological events. Disability due to vascular events is rarely reported in aspirin trials. When trials of antiplatelet therapy fail to show concordant effects on vascular events and mortality, the results should be treated with deep suspicion.

Surprisingly, there are only 2 substantial, placebo-controlled trials[6,7] of aspirin that enrolled patients with chronic ASCVD in the absence of a recent vascular event (**Table**). In the

Table. The 2 Largest, Randomized, Placebo-Controlled Trials of Aspirin in Patients With Chronic Atherosclerotic Coronary Disease

Variable	Trial name (source)	
	AMIS (AMIS Study Group,[6] 1980)[a]	SAPAT (Juul-Möller et al,[7] 1992)[b]
Year	1980	1992
No. of patients	4524	2035
Dose, mg/d	1000	75
Duration, mo	>36	50
Myocardial infarction, No. of patients with an event (rate per 1000 p-y)		
Placebo	183 (27)	93 (22)
Aspirin	143 (21)	72 (17)
Result	6 Fewer per 1000 p-y (NS) No benefit for 994 patients	5 Fewer per 1000 p-y ($P < .01$) No benefit for 995 patients
Stroke, No. of patients with an event (rate per 1000 p-y)		
Placebo	45 (7)	38 (9)
Aspirin	27 (4)	28 (7)
Result	3 Fewer per 1000 p-y (NS) No benefit for 997 patients	2 Fewer per 1000 p-y (NS) No benefit for 998 patients
Death, No. of patients with an event (rate per 1000 p-y)		
Placebo	219 (29)	106 (25)
Aspirin	245 (32)	82 (19)
Result	3 More per 1000 p-y (NS) No benefit for any patient	6 Fewer per 1000 p-y (NS) No benefit for 994 patients

Abbreviations: AMIS, Aspirin Myocardial Infarction Study; NS, not statistically significant; p-y, patient-year; SAPAT, Swedish Angina Pectoris Aspirin Trial.

[a] AMIS: Numbers and rates recalculated from percentages with events reported in the article assuming follow-up of 3 years.

[b] SAPAT: Numbers reported in the article; rates recalculated based on median follow-up of 50 months.

Aspirin Myocardial Infarction Study (AMIS),[6] 4524 patients were randomized to aspirin 1000 mg per day or placebo, with a mean delay after MI of 25 months. Cardiovascular events were not reduced over the following 3 years, but there was a trend to increased mortality, especially among women. The authors concluded: "… aspirin is not recommended for routine use in patients who have survived an MI." Maybe the dose was too high, but that does not prove that smaller doses are effective. In the Swedish Angina Pectoris Aspirin Trial (SAPAT),[7] 2035 patients with a clinical diagnosis of angina were randomized to aspirin 75 mg per day or placebo by their primary care physicians. Investigations, such as exercise tests, radionuclide scans, or coronary angiography, were not required to confirm the presence of disease. Over a median follow-up of 50 months, there were approximately 5 fewer MIs per 1000 patient-years follow-up in those assigned to aspirin with no effect on stroke, vascular deaths, or mortality.

Lasting benefits can be delivered by short-term interventions given at the right time. The Second International Study of Infarct Survival (ISIS-II) trial, published in 1988, randomized 17 187 patients with an acute MI to aspirin 162.5 mg per day or placebo, double-blind, for just 28 days, after which aspirin was stopped; there was no reason to initiate aspirin due to a lack of evidence.[5,8] Those randomized to aspirin had a similar reduction in mortality at both 35 days and 10 years, in the absence of long-term aspirin therapy.[8] The US Veterans Administration trial of unstable angina showed similar results.[9] After 3 months, mortality was slightly lower with aspirin 324 mg per day, but 9 months after stopping aspirin, the reduction in mortality was clear.[9] These trials suggest that aspirin should be given after an acute cardiovascular event in much the same manner as antibiotics for infection; usually a short course rather than life-long treatment.

The Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness (ADAPTABLE) trial compared the effects of aspirin 81 mg per day to 325 mg per day on MI, stroke, or death in patients with chronic, stable ASCVD and found no difference in such events.[10] Unfortunately, no patients were randomized to avoidance of antiplatelet therapy, although many patients with ASCVD do not take aspirin, perhaps because they are less convinced by the evidence than their doctors.[5] The ADAPTABLE trial was a lost opportunity to get some evidence that some dose of aspirin is effective long-term for chronic ASCVD.

The edifice of antiplatelet trials for chronic ASCVD has no solid foundations but is built on shifting sands. Forty years ago, dogma dictated that ventricular ectopy after an MI should be treated with class I antiarrhythmic drugs; many believed a placebo-controlled trial was unethical. When the results of the Cardiac Arrhythmia Suppression Trial (CAST) were published in the *New England Journal of Medicine* showing a 250% increase in mortality with class I agents, the accompanying editorial said that the results "… have astounded most observers and challenge much of the conventional wisdom about antiarrhythmic drugs…."[11] For many decades, routine, lifelong administration of β-blockers after MI was also recommended by guidelines. Recent randomized trials of withholding or withdrawing β-blockers after MI cast doubt on this advice.[12,13] Antiplatelet therapy dogma should now be subjected to the same scrutiny.

Randomized trials withdrawing all antiplatelet therapy 3 to 6 months after a vascular event or procedure should be done. There is no randomized trial comparing antiplatelet therapy with placebo in patients who have received a coronary stent, but short-term suspension of antiplatelet therapy appears safe,[14] and therefore, such patients should be included. Given an accurate account of the evidence and in the absence of physician bias, patients should be happy to be randomized to placebo. However, despite the lack of evidence, many clinicians are trapped by the antiplatelet dogma. Perhaps a trial comparing 75 mg of aspirin once daily to a less intense antithrombotic intervention, such as aspirin or clopidogrel 75 mg once or twice per week, might not be too heretical? If this showed no substantial difference in disability or mortality, it would pave the way to placebo-controlled trials of complete withdrawal of long-term antiplatelet therapy for ASCVD.

ARTICLE INFORMATION

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Correction: This article was corrected on January 8, 2025, to fix the reported rates of death per 1000 patient-years for placebo and aspirin in the Table.

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