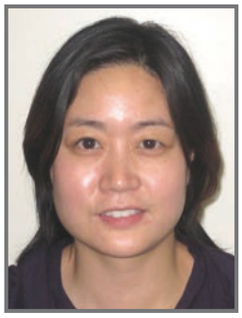
Aspirin to prevent incident cardiovascular disease: is it causing more damage than it prevents?

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Cardiovascular disease (CVD) principally encompasses fatal and nonfatal myocardial infarction (MI) and stroke. It remains a major challenge to healthcare with a high incidence, prevalence and mortality; hence, prevention is a highly relevant topic, with many clinical implications. This editorial will briefly cover the established role of aspirin in secondary prevention, then look at why it would be expected to be less useful in primary prevention and, finally, cover the evidence for this hypothesis.

There are two aspects to the prevention of CVD: primary and secondary prevention. Primary prevention refers to the reduction of incident disease in essentially healthy subjects believed to be at high risk, whereas secondary prevention refers to prevention of recurrent events in those with prevalent or established CVD. Both primary and secondary prevention involve the management of modifiable risk factors, starting with lifestyle changes (e.g., increasing exercise, improving the diet and smoking cessation). Pharmacological interventions have two different broad aims: drugs such as statins and antihypertensives focus on reducing low-density lipoprotein cholesterol and blood pressure, as a means of reducing the development or progression of atheroma and, hence, reducing risk of plaque rupture and a cardiovascular event. By contrast, antiplatelets such as aspirin purely target the final step in this pathway, reducing the likelihood of thrombus formation in patients with a ruptured atherosclerotic plaque.

It is important to clarify that the risk profiles of individuals in the primary and secondary prevention cohorts are very different. Patients who have already had an event such as a MI (i.e., secondary prevention) have demonstrated not only that they have atherosclerotic plaque but also that, as a result of genetic predisposition and acquired risk factors, they have a tendency to form acute thrombus. It therefore makes physiological sense that aspirin would be beneficial in this group, and this is supported

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by several trials and meta-analyses [1,2]. When data from these trials were combined in the Antithrombotic Trialists' (ATT) Collaboration meta-analysis of 2009 [1], it provided robust evidence that aspirin reduced any serious CVD event (e.g., cardiovascular death, nonfatal MI or stroke) by 19% (absolute risk reduction: 1.49% per year; number needed to treat [NNT]: 67 to prevent one CVD event over 1 year). When we looked at individual components aspirin reduced cardiovascular death by 9% (absolute risk reduction: 0.29% per year; NNT: 344) and nonfatal MI by 31% (absolute risk reduction: 0.66% per year; NNT: 151). The authors of this paper commented that bleeding events were incompletely reported in the secondary prevention trials with a more limited period of follow-up. In relative terms, the excess risk of hemorrhagic stroke was 67% and of major extracranial bleed was 169%, and the number of additional hemorrhagic strokes or major extracranial bleeds was approximately 0.16% per year (number needed to harm [NNH]: 632). Therefore, the net benefit of aspirin in secondary prevention more likely outweighs the risk at a population level.

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By contrast, in primary prevention, patients may have risk factors for cardiac disease, but they have not yet demonstrated propensity to have an event. Although there is a spectrum of risk amongst the primary prevention cohort, with some very-high-risk individuals, overall they are a group at significantly less risk of CVD events than the secondary prevention cohort. The aim in this group is again dual: to reduce atheroma formation and progression and to reduce thrombus in the event of plaque rupture; however, the risks of these events are lower. In particular, within the primary prevention group there will be a larger number of patients who do not have 'vulnerable plaques'. These patients may still benefit from treatments that reduce atheroma development, but they would be expected to gain less benefit from drugs that purely protect from thrombosis, as their risk of thrombosis is much less.

It is also important to look at absolute as well as relative risks of benefit and harm, and the associated NNT and NNH. The absolute risks associated with aspirin, and hence the NNH, are likely to be similar in the primary and secondary prevention groups. The absolute benefit, however, will be lower in the primary prevention group, as this is by definition a group with lower cardiovascular risk and therefore less to gain. Furthermore, risk of bleeding correlates with risk of thrombotic events (rather than remaining constant across the different levels of thrombotic risk) [3], making it difficult simply to pick a level of thrombotic risk at which one can be certain that bleeding risk will be outweighed. One could therefore hypothesize that the widespread use of aspirin in primary prevention will not provide enough benefit to outweigh the known risks of this drug. The rest of this editorial will focus on the evidence for this hypothesis.

The conclusion of the ATT Collaboration, based on six randomized trials, was that the role of aspirin in primary prevention was still uncertain. Since then three further trials have been conducted, and the recently published meta-analysis of Seshasai *et al.* has included these trials [3]. This meta-analysis, looking at use of aspirin in primary prevention in 102,621 subjects with approximately 700,000 person-years at-risk, did show that it reduced cardiovascular events. In total, cardiovascular events were reduced by 10%, primarily mediated by a 20% reduction in nonfatal MI. There was no significant effect on fatal MI, stroke, cardiovascular death or all-cause mortality. Even this significant relative risk reduction in nonfatal MI pertains to a small change in absolute risk in this low-risk population. The NNT to prevent any CVD event over 1 year was 720, and to prevent a nonfatal MI was 972. Furthermore, there was a significant increase in bleeding in the aspirin-treated patients. Aspirin was shown to increase the risk of all bleeding by 70%, and of nontrivial bleeding (such as any fatal bleeds, cerebrovascular and gastrointestinal bleeds, and those requiring transfusion or hospitalization) by over 30%. The NNH for one nontrivial bleed over 1 year was 438. This risk was even higher when only patients on daily aspirin (the usual practice for CVD) were included, with a relative risk increase of 48%.

Therefore, it seems that, in the primary prevention cohort as a whole, aspirin provides a small but statistically significant reduction in risk of cardiovascular events, primarily nonfatal MI. This is counterbalanced by numerically a far greater increase in nontrivial bleeds (~2.5 extra bleeds for every nonfatal MI prevented) [1,3–7]. This did not translate to an increase in mortality in the aspirin-treated patients, but nor

was there a statistically significant decrease in mortality in this group.

With this evidence it is hard to justify prescribing aspirin for primary prevention to the population as a whole; at best, the expectation would be that this would lead to a small reduction in nonfatal events, with no difference in cardiovascular or overall mortality, and a significant increase in bleeding, some of which would be clinically severe.

At an individual level there may be individuals in the primary prevention population who are at very high cardiovascular risk but at low bleeding risk, in whom the benefit of aspirin outweighs the risk of bleeding. Currently used risk prediction models are imprecise, and two-thirds of events occur in low-to-intermediate-risk groups. Similarly, there are no tools to predict net benefit and, in particular, bleeding risk with sufficient accuracy in low-risk populations. This is in contrast to treatments that carry lower risk of major adverse events such as statins and antihypertensives. These tools are urgently required if we are to identify individuals more likely to benefit on a case-by-case basis.

Finally, some authors have proposed that aspirin should be used for the prevention of cancer [8,9]. The majority of data on this subject pertain to cancer deaths and not to incident cancer, and may be a result of the bleeding risk with aspirin leading to earlier detection and detection bias. A small study in patients with a hereditary form of cancer has suggested that there is also a reduction in incident cancer [9]. However, longer-term data in more general primary prevention populations, taking into account the risks of aspirin as well as any possible anticancer effect, are required before this can be considered to have any clinical practice implications.

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