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## Meta-Analysis Questions Use of Aspirin in Primary Prevention CME



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June 9, 2009 — The authors of a new meta-analysis of aspirin use in primary prevention say their results "do not seem to justify general guidelines advocating the routine use of aspirin in all healthy individuals above a moderate level of risk for coronary heart disease. [1]"

The meta-analysis, published in the May 30, 2009 issue of the *Lancet*, was conducted by the Antithrombotic Trialists' (ATT) Collaboration, led by **Dr Colin Baigent** (Clinical Trial Service Unit, Oxford University, UK).

Baigent commented to **heartwire**: "The present data that we have reported here have not been previously available. The current guidelines are based on previous meta-analyses, which have limitations. We have shown for the first time that the very same people at higher risk of heart disease are also at higher bleeding risk with aspirin, which is a very important piece of information and should influence the way in which aspirin is used."

He added: "Medicine has moved on in recent years, and we now know that we can safely reduce risk of heart disease by lowering cholesterol and blood pressure, and the drugs used to lower these risk factors are probably safer than aspirin. A person wanting to lower their risk might well consider taking a statin or an antihypertensive first and only after that add in a less safe drug like aspirin."

Baigent pointed out that the present guidelines, recommending aspirin for primary prevention in all people above a certain risk, are not supported by this new meta-analysis. "It is not for us to recommend changes in guidelines, but I would think the guidelines committees would now want to review their recommendations in light of these new findings," he said. "I'm not saying you should never use aspirin for primary prevention, and certain individuals may wish to still take it after discussing the risks and benefits with their doctor, which I think is fine. But our data suggest there is not good evidence of substantial benefit that outweighs risk enough to justify a public policy recommending routine use above a moderate CHD risk in primary prevention."

He added that this advice does not affect recommendations for secondary prevention, where the absolute benefit of aspirin is much greater and vastly outweighs the risk of bleeding.

### Decision Should be Made on Individual Basis?

Commenting on the paper for **heartwire**, **Dr Deepak Bhatt** (Brigham and Women's Hospital, Boston, MA) agreed with Baigent. He described the meta-analysis as "very well-done" with "robust" findings. "The authors identify a benefit of aspirin in primary prevention on nonfatal ischemic events that is largely counterbalanced by an increase in bleeding events, including a small increase in hemorrhagic stroke, with no net effect on vascular mortality. That the risk factors for ischemic events were similar for bleeding events is an interesting observation on its own. The effects in men and women were more similar than dissimilar, which makes biological sense for antiplatelet therapy," Bhatt noted.

"Therefore, I think for now, the decision of whether to use aspirin for primary prevention should be based on a thoughtful assessment of ischemic and bleeding risks by the physician and patient on an individual basis. I think it is a mistake for patients to decide to start aspirin for primary prevention without consulting their physicians. Ongoing trials should help clarify which patients in the large primary-prevention universe really ought to be on aspirin," he added.

### Previous Meta-Analyses Had Limitations

In the paper, the authors explain that for patients who already have occlusive vascular disease, the benefit of long-term aspirin treatment in reducing vascular events has been clearly shown to be much greater than the risk of bleeding, but for primary prevention, the balance of risk and benefit is less clear. This is because the patients are at lower risk of vascular disease and the absolute benefits of aspirin are therefore an order of magnitude lower than in secondary prevention.

They point out that previous meta-analyses of aspirin primary-prevention trials were not based on individual participant data, so they could not reliably compare the benefits and risks of aspirin in prognostically important groups (such as older people and others at increased risk of coronary heart disease) and could not quantify reliably the extent to which people at increased risk of coronary heart disease might also be at increased risk of bleeding. Therefore, current guidelines largely ignore any differences in bleeding risk and recommend that aspirin be used widely for primary prevention in those at moderately raised risk of heart disease, and, as age is a major determinant of the risk of coronary heart disease, the guidelines recommend that daily aspirin should be started in all people above a specific age, they add.

In view of the limitations of the analyses underlying current guidelines, the authors collated a meta-analysis of individual participant data, established involving the principal investigators of all large trials of primary prevention with aspirin.

Results from the six primary-prevention trials showed that serious vascular events occurred at a rate of 0.51% per year in people allocated to aspirin compared with 0.57% per year in controls. This absolute reduction of 0.07% per year represented a 12% proportional reduction. The risk of major bleeds was increased with aspirin from 0.07% to 0.10% per year, an absolute increase of 0.03%.

#### Proportional Reduction in Vascular Events Similar in All Subgroups

This proportional reduction in serious vascular events did not depend significantly on age, sex, smoking history, blood pressure, total cholesterol, body-mass index, history of diabetes, or predicted risk of coronary heart disease. The authors point out that there was not even a significant trend in the proportional effects of aspirin in people at very low, low, moderate, and high estimated risk of coronary heart disease. "If the proportional risk reductions in these different subgroups really are similar, then the absolute risk reductions will depend chiefly on an individual's absolute risk without treatment," the authors comment.

They calculate that irrespective of age or sex, the absolute reduction in occlusive events in the primary-prevention population would be only about twice as large as the absolute increase in bleeding. And they further point out that most people in these trials were not taking statins, which would have reduced both MI and stroke with little hazard. Noting that generic statins are now widely available at low cost, they suggest that because of their efficacy and safety, primary prevention by a statin could well be preferred to primary prevention only by aspirin. "If so, then one of the main questions for aspirin in primary prevention nowadays is whether it is worthwhile to add it to a statin," they write.

They add that if the risk of vascular disease is already approximately halved by statins, then the further absolute benefit of adding aspirin could well be only about half as large as was suggested by these primary-prevention trials, but the main bleeding hazards could well remain. "In that case, the benefits and hazards of adding long-term aspirin in people without preexisting disease might be of approximately similar magnitude," they write.

#### Same Factors Determine Risk of Heart Disease and Bleeding

They also say that their analysis suggests that the same factors that determine risk of heart disease also determine the risk of bleeding with aspirin, so that, even for people at moderately increased risk of coronary heart disease, the major absolute benefits and hazards of adding aspirin to a statin-based primary-prevention regimen could still be approximately evenly balanced.

"Drug safety is of particular importance in public-health recommendations for large, apparently disease-free populations; there should be good evidence that benefits exceed risks by an appropriate margin. Hence, although the currently available trial results could well help inform personally appropriate judgments by individuals about their own use of long-term aspirin, they do not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals above a moderate level of risk of coronary heart disease," the authors conclude.

#### Editorial Tries to Define Groups That Would Benefit

In an accompanying editorial [2], **Drs Ale Algra** and **Jacoba Greving** (University Medical Center, Utrecht, the Netherlands) use the data from the current meta-analysis to update a cost-effectiveness analysis that they performed previously. Whereas the authors of the current meta-analysis analyzed data from men and women together to draw their main conclusions, Algra and Greving used the slightly different risk ratios for cardiac events and ischemic stroke for women and men separately. They summarize their results in the following table, which suggests that aspirin should be recommended for the higher-risk primary-prevention populations.

#### Risk of Vascular Disease and Aspirin Recommendations for Aspirin Use in Men and Women of Different Ages

Age, y	Women	Women	Men	Men
	10-y vascular risk (%)	Aspirin recommended	10-y vascular risk (%)	Aspirin recommended
<b>40 - 49</b>				
Average risk	1	No	4	No
2× average risk	3	No	7	No
5× average risk	7	No	18	No
<b>50 - 59</b>				
Average risk	3	No	8	No
2× average risk	6	No	15	No
5× average risk	15	No	34	Yes
<b>60 - 69</b>				
Average risk	6	No	14	No
2× average risk	15	No	26	Yes

5× average risk	34	Yes	53	Yes
70 - 79				
Average risk	16	No	20	Yes
2× average risk	30	Yes	35	Yes
5× average risk	60	Yes	66	Yes

### Baigent Unimpressed With Editorial

But Baigent told [heartwire](#) that he did not agree with the editorialists' table. "I don't know exactly how they have done their calculations, but I don't think they have considered our data in a consistent enough way. They have used a model with some assumptions in it, and these models generally don't perform well. I don't think it is a particularly helpful way of interpreting the data we've published," he said.

He pointed out that unfortunately there is no easy way to define who should take aspirin for primary prevention. "There is no easy formula, but this is not an easy question," he commented. When asked how he would advise primary-care doctors to make this decision, Baigent answered: "If a patient has lots of risk factors—eg, they are overweight, smoke, and have high cholesterol, then aspirin would be reasonable on top of statin therapy. It may well be that the level of risk that GPs consider justifies aspirin use just increases somewhat," he suggested.

### References

1. 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: 1849–1860. [Abstract](#)
2. Algra A and Greving JP. Aspirin in primary prevention: sex and baseline risk matter. *Lancet* 2009; 373: 1821-1822. [Abstract](#)

### Clinical Context

In persons with a previous MI or stroke, the decrease in stroke risk associated with aspirin use typically corresponds to an absolute reduction of approximately 10 to 20 per 1000 in the yearly incidence of nonfatal events and to a smaller reduction in vascular death; these benefits outweighed the small risk of bleeding. However, for primary prevention in healthy persons, the evidence of benefits vs risks for MI and stroke is less clear.

This is a meta-analysis of randomized clinical studies to examine the benefit vs risk of using aspirin for primary and secondary prevention of MI and stroke in patients with and without a history of cardiovascular conditions.

### Study Highlights

- Primary or secondary prevention trials were included only if they involved a randomized comparison of aspirin vs no aspirin (with no other antiplatelet drug).
- Primary prevention trials excluded individuals with any history of occlusive disease at entry.
- Primary prevention trials were included if they recruited at least 1000 nondiabetic participants with at least 2 years of treatment.
- Individual participant data were provided from 6 published trials.
- Secondary prevention trials were included if they involved individuals with previous MI (6 trials) or stroke or transient cerebral ischemia (10 trials) and had contributed individual participant data to the 2002 ATT report.
- Primary outcomes were serious vascular event, defined as MI, stroke, or death from a vascular cause (including sudden death; pulmonary embolism; hemorrhage; and, for secondary prevention trials only, death from an unknown cause); major coronary event (MI, coronary death, or sudden death); any stroke; death from any cause; and major extracranial bleed, mainly gastrointestinal tract bleed requiring transfusion or resulting in death.
- 6 primary prevention trials were available (95,000 individuals, 3554 serious vascular events).
- 1 trial recruited people with hypertension, and 2 recruited people with coronary risk factors.
- The results contrasted with those from the 16 secondary prevention trials (17,000 individuals, 3306 vascular events).
- In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0.51% aspirin vs 0.57% control per year;  $P = .0001$ ) mainly because of a reduction of approximately 20% in nonfatal MI (0.18% vs 0.23% per year;  $P < .0001$ ).
- The net effect on stroke was not significant.
- Aspirin had no net effect on strokes of known cause (hemorrhagic plus ischemic), strokes of unknown cause, or the aggregate of all strokes.
- There was evidence of an adverse effect on hemorrhagic stroke (relative risk, 1.39;  $P = .01$ ) but a protective effect on ischemic stroke (relative risk, 0.83;  $P = .005$ ).
- Vascular mortality rate did not differ significantly (0.19% vs 0.19% per year).
- Aspirin allocation increased major gastrointestinal tract and extracranial bleeds (0.10% vs 0.07% per year;  $P < .0001$ ), and the main risk factors for coronary disease were also risk factors of bleeding.

- In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6.7% vs 8.2% per year;  $P < .0001$ ).
- There was a nonsignificant increase in hemorrhagic stroke but overall reductions of approximately 20% in total stroke (2.08% vs 2.54% per year;  $P = .002$ ) and in coronary events (4.3% vs 5.3% per year;  $P < .0001$ ).
- In the secondary prevention trials, aspirin significantly reduced the aggregate of all strokes.
- In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events were similar for men and women.
- The most important predictor of risk was older age, and the mean age at entry for those in the highest risk group was 69 years.
- The authors concluded that aspirin was of benefit in secondary prevention, but in primary prevention, aspirin was of uncertain net value, and the small reduction in occlusive events has to be weighed against any increase in major bleeds.

### Clinical Implications

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- The risk of bleeding associated with aspirin may outweigh potential benefits when used for primary prevention of MI and stroke.
- Aspirin is of benefit for secondary prevention in patients with a history of MI or stroke.

### CME Test

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Which of the following is *most* likely to be a benefit of using aspirin for primary prevention of MI and stroke?

- Reduced mortality rate
- Reduced risk for serious vascular events
- Reduced risk for all strokes
- All of the above

Which of the following outcomes is *least* likely to be associated with the use of aspirin for secondary prevention of MI and stroke?

- Reduced risk for coronary events
- Reduced risk for hemorrhagic stroke
- Reduced risk for ischemic stroke
- Reduced risk for all stroke

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This activity is intended for primary care clinicians, cardiologists, neurologists, and other specialists who care for patients at risk for myocardial infarction or stroke.

#### Goal

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The goal of this activity is to provide medical news to primary care clinicians and other healthcare professionals in order to enhance patient care.

#### Learning Objectives

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Upon completion of this activity, participants will be able to:

- Describe the benefit vs risk of using aspirin for the primary prevention of myocardial infarction and stroke.
- Describe the benefit vs risk of using aspirin for the secondary prevention of myocardial infarction and stroke.

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