Meta-analysis questions use of aspirin in primary prevention

JUNE 3, 2009 Sue Hughes

Oxford UK - 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 10-y vascular risk (%)	Women Aspirin recommended	Men 10-y vascular risk (%)	Men Aspirin recomm
40–49				
Average risk	1	No	4	No
2x average risk	3	No	7	No
5x average risk	7	No	18	No
50–59				
Average risk	3	No	8	No
2x average risk	6	No	15	No
5x average risk	15	No	34	Yes
60–69				
Average risk	8	No	14	No
2x average risk	15	No	26	Yes
5x average risk	34	Yes	53	Yes
70–79				
Average risk	16	No	20	Yes
2x average risk	30	Yes	35	Yes
5x average risk	60	Yes	66	Yes

To download table as a slide, click on slide logo above

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.