In the Literature

Does sex affect how patients respond to ASA?

Berger JS, Roncaglioni MC, Avanzini F, et al. 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.

Background: The role of ASA in the primary prevention of cardiovascular disease is unclear, in particular whether women and men derive the same benefit from taking it. This meta-analysis was designed to assess the impact of sex on response to ASA for the primary prevention of cardiovascular events.

Design: Prospective randomized controlled trials of ASA therapy for patients without cardiovascular disease reporting on myocardial infarct (MI), stroke and cardiovascular death were identified for the meta-analysis.

Results: Six trials were identified with a total of 95 456 participants (of which 51 342 were women and 44 144 were men). Three included only men, 1 included only women and 2 included both sexes. The weighted mean duration of follow-up was 6.4 years. Table 1 shows key findings from the meta-analysis.

Among participants taking ASA, major cardiovascular events — defined as nonfatal MI, nonfatal stroke or cardiovascular death — were reduced in both sexes in all of the trials, although there was no reduction in all-cause death for either men or women. Other clinical outcomes showed different results for men and women. The risk of stroke was reduced among women, but this reduction was related mainly to ischemic stroke (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.63–0.93); there was no effect on hemorrhagic stroke. For men, there was no overall effect on stroke (OR 1.00, 95% CI 0.96–1.33), including ischemic stroke; however, the risk of hemorrhagic stroke was increased by 69% (OR 1.69, 95% CI 1.04–2.73). The risk of MI was reduced among men but not among women.

Table 1: Clinical outcomes by sex of 6 trials of ASA therapy for the primary prevention of cardiovascular events

	Absolute risk reduction (NNT)*		Odds ratio (95% CI)	
Outcome	Women *n = 51 342*	Men *n = 44 114*	Women *n = 51 342*	Men *n = 44 114*
Major cardiovascular event†	0.30 % (333)	0.33% (303)	0.88 (0.79-0.99)	0.86 (0.78-0.94)
Nonfatal stroke	0.24% (416)	No change	0.83 (0.7-0.97)‡	No change
Nonfatal myocardial infarct	No change	0.85% (117)	No change	0.68 (0.54-0.86)
Cardiovascular death	No change	No change	No change	No change
Major bleeding§	0.25% (400)	0.33% (303)	1.68 (1.13-2.52)	1.72 (1.35-2.20)

Note: NNT = number needed to treat, CI = confidence interval.
*NNT is the number of patients who would have to receive ASA therapy for one to receive the benefit (or harm).
†Defined as cardiovascular death, nonfatal myocardial infarct or nonfatal stroke.
‡Reflects decreased rate of ischemic stroke (odds ratio 0.76, 95% CI 0.63-0.93).
§Absolute risk increase (number needed to harm).

Major bleeding was associated with ASA therapy in both women and men and usually occurred in the gastrointestinal tract.

Commentary: The findings of this meta-analysis show important sex-related differences in the effect of ASA on the primary prevention of cardiovascular events. Although ASA therapy reduces the overall risk of cardiovascular events in both sexes, the reduction takes a different form in each sex: the risk of ischemic stroke is reduced among women and the risk of MI reduced among men.

Sex-related differences in response to ASA have recently been identified. The Women's Health Study, the first primary prevention trial of ASA therapy specific to women, also found that the risk of stroke was decreased but not that of MI or cardiovascular death.[1] Similarly, the Hypertension Optimal Therapy trial, which involved men and women with hypertension, found no effect on MI in women (although there was a significant benefit for men).[2]

Berger and colleagues present several possible explanations for these differences, including differing ASA metabolism in women and men and increased ASA resistance in women (e.g., ASA does not produce an anticipated effect, such as inhibiting biosynthesis of thromboxane or platelet aggregation). Event rates for stroke and MI are also different between the sexes, and it is possible that small numbers of these events in the trials meant that it was not possible to detect statistically significant benefits of ASA therapy for MI in women and stroke in men.

Practice implications: The benefits of ASA therapy need to be weighed against the risk of major bleeding. Although ASA therapy for 6.4 years may prevent 2 strokes per 1000 women and 8 MIs per 1000 men, in the same period 2.5 and 3 major bleeding events per 1000 women and men respectively would occur. Also, because different doses and treatment durations were used in the trials, no firm recommendation regarding doses for primary prevention can be derived. However, current guidelines recommend 75–162 mg/day for primary prevention for both men and women.[3]

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