Aspirin for Primary Prevention of Heart Disease: Benefits Overestimated?


Study Overview

Objective. To determine the relative benefit or harm from low-dose aspirin used for primary prevention of coronary heart disease (CHD) and stroke.

Design. Subgroup analysis of the U.K. thrombosis prevention trial [1], a double-blind, placebo-controlled trial that examined the effects of aspirin and warfarin using a 2 × 2 factorial design. Analyses were by intention to treat.

Setting and participants. 108 group practices throughout the United Kingdom identified 10,557 men with no history of myocardial infarction or stroke who were at high risk for one of these events. Researchers used results from the Northwick Park Heart Study [2] to assess risk. The model included smoking history, family history of premature ischemic heart disease (not included in the Northwick study but estimated to increase risk by 50%), body mass index (BMI), blood pressure, total cholesterol, plasma fibrinogen, and plasma factor VII activity. Exclusionary criteria included current or recent history of suspected peptic ulcers and use of medication incompatible with trial treatment (medications not specified). Of the high-risk patients identified, 5499 men (52%) entered the trial.

Intervention. Patients received warfarin (goal INR about 1.5) or matched placebo and 75 mg of aspirin or matched placebo, resulting in 4 treatment groups.

Main outcome measures. Myocardial infarction and coronary death. Stroke was a secondary outcome.

Main results. The mean (SD) age of participants was 57.5 (6.7) years. Of these subjects, 41% were current smokers and 15.5% had a family history of premature coronary artery disease. Patients’ mean (SD) BMI was 27.4 (3.6). Mean systolic blood pressure (SBP) was 139 mm Hg at entry and 135 mm Hg at follow-up. 245 men used antihypertensive drugs at baseline; 1421 used these drugs at some point during the study.

There was a strong interaction between SBP (presumably at entry, though not clearly stated in the article) and either aspirin group (ie, with or without warfarin). Among subjects with SBP less than 130 mm Hg, there was a 45% risk reduction for nonfatal coronary events (number needed to treat for 1 year was approximately 160 based on information in the article). However, no significant reduction was noted for patients whose SBP was more than 145 mm Hg. The authors found a marginally significant (P = 0.5) interaction with age, although there was an increased risk for subjects between 65 and 69 years (relative risk, 2.13; P = 0.018). No interaction with cholesterol levels was observed.

For strokes, Meade and Brennan found interactions between SBP and the aspirin-only group similar to those associated with coronary events. Interaction between the aspirin-only group and cholesterol was marginally significant and suggested decreasing benefit with increasing cholesterol levels. For combined cardiovascular outcomes, the relationship between aspirin therapy and systolic and diastolic blood pressure was similar to that seen in the other results.

Conclusion

Aspirin, when used for primary prevention of cardiovascular diseases, may only be of benefit to certain high-risk patients. There may be no benefit and a possible increased risk for significant bleeding events [3] for patients with elevated blood pressures.

Commentary

The original study [1] was well designed. The main flaw was the drop-out rate (approximately 50% by year 5). Nonetheless, the study provided excellent evidence supporting an important benefit of aspirin for primary prevention of CHD for the entire study population. Moreover, the magnitude of effect was similar to that found in the Physicians’ Health Study [4], despite the trials’ different populations. The 2 studies, however, had substantially different findings on subgroup analysis. The Physicians’ Health Study found benefit only for subjects older than 50 years and showed an inverse relationship between benefit and cholesterol levels. The UK thrombosis prevention trial found an inverse relationship between blood pressure and risk reduction but marginal or no associations with age and cholesterol levels.
Subgroup analyses must be viewed with some suspicion, especially when they are carried out post hoc. It should be noted that Meade and Brennan do not state whether or not their analysis was planned. Generally, secondary analyses like theirs should be evaluated using a much lower threshold for significance ($P \leq 0.01$). The interaction between blood pressure and aspirin satisfies this caveat. Another important consideration is that Meade and Brennan used baseline blood pressure measurements in their analysis. Whether this single measurement accurately ascertained hypertension and its control is unknown.

**Applications for Clinical Practice**

The current study muddies the primary prevention waters. While it seems clear that some men without known cardiovascular disease will benefit from aspirin, some may be harmed. Determining which patients will benefit and which will be harmed may be difficult. However, both studies suggest that aspirin works best when part of an overall risk reduction plan. In appropriate patients, careful attention to blood pressure control and lipid management together with aspirin use should substantially reduce cardiovascular morbidity and mortality. Aspirin should be used carefully in patients not willing or able to control other risk factors.

**References**