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Aspirin in the primary prevention of cardiovascular disease: Current knowledge and future research needs

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ABSTRACT

In secondary prevention, among a very wide range of survivors of prior occlusive cardiovascular disease (CVD) events and those suffering acute myocardial infarction (MI) or occlusive stroke, aspirin decreases risks of MI, stroke, and CVD death. In these high risk patients, the absolute benefits are large and absolute risks are far smaller so aspirin should be more widely prescribed. In contrast, in primary prevention, aspirin reduces risks of first MI but the evidence on stroke and CVD death remain inconclusive. Based on the current totality of evidence from predominantly low risk subjects where the absolute benefits is low and side effects the same as in secondary prevention, any decision to prescribe aspirin for primary prevention should be an individual clinical judgment by the healthcare provider that weighs the absolute benefit in reducing the risk of a first MI against the absolute risk of major bleeding. If the ongoing trials of intermediate risks subjects show net benefits then general guidelines may be justified with several caveats. First, any decision to use aspirin should continue to be made by the healthcare provider. Second, therapeutic lifestyle changes and other drugs of life saving benefit such as statins should be considered with aspirin as an adjunct, not alternative. The more widespread and appropriate use of aspirin in primary prevention is particularly attractive, especially in developing countries where CVD is emerging as the leading cause of death. In addition, aspirin is generally widely available over the counter and is extremely inexpensive.

Introduction

The totality of evidence on aspirin in the primary prevention of cardiovascular disease is incomplete, whereas it is far more robust and clear in secondary prevention. Thus, any consideration of the benefits and risks of aspirin in primary prevention should be viewed in the context of the data in secondary prevention [1]. Further, all the data on aspirin should be viewed in the context of the contributions of different types of evidence in the conclusion of a valid statistical association from analytic studies designed a priori to test a hypothesis as well as a judgment of causality based on the totality of evidence [2].

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The need for randomized evidence concerning aspirin

For many hypotheses, randomized evidence is neither necessary nor desirable. For moderate to large treatment effects, which generally refers to relative risks of about 2.0 or greater, observational analytic studies, either case–control or cohort, designed a priori to test the hypothesis in the context of basic research provide a sufficient totality of evidence upon which to base rational clinical decisions for individual patients and policy decisions for the health of the general public. However, for small to moderate effects, the amount of uncontrolled and uncontrollable confounding inherent in all observational analytic study designs may be about as big as the most plausible effect size of the intervention. In fact, for most major drugs of proven benefit in the treatment and prevention of CVD, including aspirin, statins, angiotensin-converting enzyme inhibitors and blockers, and beta-adrenergic blockers, the benefits are small to moderate but of enormous clinical and public health importance. Thus, large-scale randomized trials designed a priori to test the hypothesis remain the most reliable design strategy to detect small to moderate effects. In addition, meta-analyses of such trials may be considered hypothesis testing. In contrast, meta-analyses of trials not designed a priori to test the hypothesis should be considered, at best, hypothesis formulating [3].

Randomized trials of secondary prevention and their meta-analyses

There are about 195 randomized trials of antiplatelet therapy, principally with aspirin, that have been completed among more than 135,000 high-risk patients defined as having prior evidence of a wide range of occlusive CVD events. These CVD events include prior or acute myocardial infarction (MI), prior or acute stroke or transient ischemic attacks (TIAs), or other high-risk events such as unstable angina, chronic stable coronary disease, peripheral artery disease, coronary artery bypass grafts, and percutaneous coronary interventions. Many of the individual trials show statistically significant and clinically important benefits of aspirin when given to survivors of a wide range of occlusive CVD events. In addition, the Antithrombotic Trialist's Collaboration (ATT) has performed the most comprehensive, worldwide meta-analysis of these 195 randomized trials that had been designed a priori to test the hypothesis of clinical benefits on CVD [4]. In the ATT meta-analysis, aspirin produced a statistically significant and clinically important 22% reduction in risk of subsequent vascular events. In this wide range of patients with prior CVD, there were absolute reductions of approximately 36 vascular events per 1000 patients with MI treated for a mean of 27 months, 36 events per 1000 patients with a previous stroke or TIA treated for 29 months, and 22 events per 1000 patients with other high-risk conditions treated for 22 months (Table 1).

With respect to the dose of aspirin, indirect comparisons showed the same results as direct comparisons. Specifically, in three trials testing the hypothesis, there were no significant differences in efficacy or safety between doses of 75–150 mg/day and 160–325 mg/day.

Randomized trials of aspirin in acute MI

The Second International Study of Infarct Survival (ISIS-2) randomized 17,187 patients within 24 h on onset of their symptoms of acute MI in a 2 × 2 factorial design to aspirin (162.5 mg), streptokinase (SK) (1.5 million units), both active treatments, or both placebos [5]. At 35 days, the primary prespecified endpoints of total mortality were proportionally reduced by 23% with aspirin, 25% with SK, and 42% with aspirin and SK together. For aspirin, the proportional reductions in mortality were similar regardless of whether administration was within 1 h or up to 24 h after onset of symptoms of acute MI. In contrast, the subgroup of patients treated within 6 h with SK had a 30% proportional reduction in mortality and with SK and aspirin a 52% reduction.

In addition, among those assigned at random to aspirin, there were statistically significant and clinically important proportional reductions on nonfatal reinfarction of 49% and nonfatal stroke of 46%. Major bleeds requiring transfusions were similar in the aspirin and placebo groups (0.4%). After 35 days of treatment with aspirin, there were no excess risks of cerebral hemorrhages and only a slight increase in major bleeds. In terms of absolute risk reductions of vascular events, there was an avoidance of 38 events per 1000 patients with an acute MI treated for 1 month (Table 2).

As regarding the benefit-to-risk ratio, aspirin given within 24 h of onset of symptoms of acute MI avoided 23 deaths with no increase in cerebral hemorrhage. In contrast, SK given within 12 h avoided 30 deaths but caused three cerebral hemorrhages. Regarding benefit to cost, the cost per life saved during acute MI is about $88,000 for tissue plasminogen activator, $12,000 for SK, and $13 for aspirin [6]. Thus, for all patients suffering acute MI, aspirin should be administered promptly and continued for long term [1]. In fact, there are

Table 1 – Antiplatelet therapy in secondary prevention of vascular events.

Reason for randomization	Antiplatelet therapy events/*n* (%)	Control events/*n* (%)	Absolute benefit per 1000 (SE)	Months	*P* value
Prior MI	1347/9984 (13.5)	1708/10,022 (17.0)	36 (5)	27	<0.00001
Prior stroke or TIA	2045/11493 (17.8)	2464/11527 (21.4)	36 (6)	29	<0.00001
Other high risk	1614/20169 (8.0)	2084/20367 (10.2)	22 (3)	22	<0.00001

Adapted with permission from Anti-Platelet Trialists Collaboration (Barnett H, Bousser M-G, Boysen G, Breddin K, Britton M, Cairns J, et al.). Secondary prevention of vascular disease by prolonged anti-platelet therapy. Br Med J 1988;296:320-31.