

COMMENTARY

Clin. Invest. (2013) 3(5), 447–449

The risks and benefits of prophylactic aspirin in vascular disease and cancer: what is a doctor to do?

Charles H Hennekens* & David J Bjorkman



“...any judgments about prescribing long-term aspirin therapy for apparently healthy individuals ... should be based on individual clinical judgments between the doctor and each of his or her patients...”

Department of Clinical Science & Medical Education, 777 Glades Road, Boca Raton, FL 33431, USA

*Author for correspondence:

Tel.: +1 561 393 8845

Fax: +1 561 620 2182

E-mail: profchmd@prodigy.net

In their recent ‘Therapeutic Perspective’ published in *Clinical Investigation*, Elwood and colleagues present their therapeutic perspective on the risks and benefits of prophylactic aspirin in vascular disease and cancer [1]. Nobody would disagree with the clinical implications of the cogent evidence in the secondary prevention of vascular diseases that aspirin reduces subsequent myocardial infarction (MI), stroke and cardiovascular (CV) death in a wide range of survivors of prior occlusive vascular disease events. These include survivors of prior MI, stable and unstable angina, occlusive stroke, transient ischaemic attacks, coronary artery bypass graft surgery, and percutaneous coronary interventions with and without stents. In all these high-risk subjects, the relative-risk reduction of approximately a quarter corresponds to an absolute risk-reduction of approximately ten to 20 important vascular events per 1000 people and to a smaller, but still definite, reduction in vascular death [2]. In all these high-risk patients, the absolute benefits of aspirin on important vascular events far exceed, by approximately tenfold, the absolute risks of major gastrointestinal or other major extracranial bleeds. Such cogent evidence is also available among even higher-risk patients undergoing acute MI, as well as acute occlusive stroke. Since their absolute risks of MI, stroke and vascular death are even higher than among survivors of prior occlusive vascular events, their absolute benefits from aspirin are even greater. In which the absolute benefits of aspirin are even greater than among longer-term survivors of prior occlusive vascular events.

Thus, the absolute benefits of aspirin are far greater than the absolute risks in acute MI or occlusive stroke, as well as in the secondary prevention of CV disease. In primary prevention, however, the balance is less clear. This situation is due, at least in part, to the fact that in apparently healthy subjects without prior evidence of clinical CV disease, their absolute risks of a first event and, as a consequence, the absolute benefits of aspirin are generally approximately tenfold lower than in secondary prevention patients receiving aspirin [3].

In primary prevention of vascular diseases, aspirin produces a conclusive and statistically significant reduction in the risk of a first MI. Nonetheless, there is substantial disagreement regarding whether this reduction clearly outweighs the bleeding risks in the low-risk individuals with no history of CV disease who have been randomized in the trials [4].

Several reputable, international organizations, including one in the UK [5] and one in the USA [6], have issued general guidelines for the use of aspirin in the primary prevention of a first MI. In most of these guidelines, aspirin is recommended for apparently healthy subjects whose absolute risk of a first coronary event is thought to exceed the absolute risk of major extracranial bleeding due to aspirin. In some

Keywords: aspirin • cancer • cardiovascular disease • primary prevention

guidelines, it has been assumed that aspirin affects men and women differently. At present, the available totality of evidence does not support this possibility. For example, men and women given aspirin have similar pharmacokinetic and pharmacodynamic responses. In the secondary prevention trials of aspirin, the data from which are more reliable and robust than in primary prevention, men and women have similar benefits regardless of whether they had an initial MI or stroke. Thus, whether there are gender differences in response to aspirin may turn out to be a 'beautiful hypothesis that is slain by ugly facts' [7]. These guidelines are also based on the assumptions that the absolute risks of bleeding do not vary either by age or other risk factors for a first coronary event. The Antithrombotic Trialists' Collaboration used individual participant data from six primary prevention trials of aspirin in a comprehensive meta-analysis, the results of which did not support this hypothesis. In this population of over 90,000 subjects, the average risk of a first event was less than 1% *per annum*. In fact, only 9% of individuals had a risk of a first coronary event above 1% per year.

Furthermore, although their absolute risks were low, those at increased risk of a first MI also appeared to be at increased risk of bleeding. Nonetheless, most would consider that a nonfatal MI or stroke is more likely to result in long-term disability than a nonfatal gastrointestinal or other extracranial bleed [3].

At present, randomized data are sparse among apparently healthy subjects at moderate risk whose net benefits from aspirin are more likely to be favourable. These include apparently healthy individuals with multiple risk factors for a first coronary event. Such individuals are at a moderate absolute risk of CV events, which lies between the levels observed in the completed trials of primary prevention (<1% per year) and the trials of secondary prevention (>2% per year). Four trials of aspirin in the primary prevention of CV disease are ongoing among individuals at intermediate risk. The ARRIVE trial has enrolled over 12,000 men and women with a predicted risk of a first coronary event of 1.5% per year using a modification of the Framingham Risk Score [101]. This large-scale, randomized, double-blind, placebo-controlled trial has a scheduled treatment and follow up of 5 years. In the ASPREE trial moderate risk is defined as elderly individuals aged 70 years and older [8]. ASCEND [102] and ACCEPT-D [9] define moderate risk as individuals with diabetes mellitus, but no known vascular disease. High levels of adherence and follow up are necessary in all these ongoing trials to provide reliable evidence about the absolute benefits and risks of aspirin for primary prevention in various groups of individuals at intermediate CV risk [4].

In this context, the available data from randomized trials of primary prevention regarding cancer are intriguing but far less conclusive than the available evidence concerning aspirin in the primary prevention of CV diseases. The most conclusive evidence on the risks and benefits of prophylactic aspirin in cancer are in colorectal cancer. Multiple trials suggest that aspirin use may decrease the recurrence of adenomatous colonic polyps in patients with a history of polyps or colorectal cancer. A Cochrane review of the available data in 2004 concluded that low-dose aspirin reduced the risk of recurrent colon adenoma after 1–3 years [10]. A more recent retrospective review of four randomized trials, which had not been designed *a priori* to test cancer end points, suggested that aspirin conferred a small decrease in the incidence and mortality for proximal colon cancers, but not rectal cancer [11]. The totality of evidence supporting the hypothesis that aspirin reduces the risks of other cancers is less reliable and will require randomized trials of longer durations than those that are sufficient to detect a reliable benefit-to-risk ratio for aspirin in the primary prevention of CV disease of approximately 5 years. The available observational data for the most plausible small to moderate effects of aspirin should be considered hypothesis formulating, not testing as the amount of uncontrolled and uncontrollable confounding inherent in these designs can be as big as the effect sizes [12].

Based on the current totality of evidence, in the primary prevention of vascular disease and cancer, any judgments about prescribing long-term aspirin therapy for apparently healthy individuals at intermediate CV risk should be based on individual clinical judgments between the doctor and each of his or her patients based on the results of the large-scale individual trials designed *a priori* to test aspirin for primary prevention. General guidelines that advocate the routine use of aspirin in all apparently healthy individuals do not seem to be justified for the primary prevention of either CV disease or cancer. The increasing burden of CV disease in developed and developing countries underscores the need for more widespread therapeutic lifestyle changes as well as the adjunctive use of drug therapies of proven net benefit in the primary prevention of CV disease. These should include statins to lower LDL-cholesterol levels, and various drugs necessary to achieve control of high blood pressure [4].

Financial & competing interests disclosures

CH Hennekens reports funding by the Charles E. Schmidt College of Medicine, Florida Atlantic University (FL, USA), as principal investigator on two investigator-initiated research grants funded to Florida Atlantic University by Bayer; serving in an advisory role to investigators and sponsors as chair of the data and safety monitoring boards of randomized trials funded by Actelion, Amgen, Anthera,

Bristol-Myers Squibb and Sunovion, and as a member of the data and safety monitoring boards of randomized trials funded by AstraZeneca, Bayer and the Canadian Institutes of Health Research; serving in an advisory role to the US FDA, US NIH and UpToDate; serving as an independent scientist in an advisory role to legal counsel for GlaxoSmithKline and Stryker; serving as a speaker for the Association of Research in Vision and Ophthalmology, National Association for Continuing Education, PriMed, and the International Atherosclerosis Society; receiving royalties for authorship or editorship of three textbooks and as co-inventor on patents for inflammatory

markers and cardiovascular disease that are held by Brigham and Women's Hospital; and having an investment management relationship with the West-Bacon Group within SunTrust Investment Services, which has discretionary investment authority.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Elwood PC, Mustafa M, Almonte M, Morgan G. The risks and benefits of prophylactic aspirin in vascular disease and cancer. *Clin. Invest.* 2, 1177–1184 (2012).
- 2 Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high-risk patients. *Br. Med. J.* 324, 71–86 (2002).
- 3 Antithrombotic Trialists Collaboration Primary Prevention Writing Group. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 373, 1849–1860 (2009).
- 4 Hennekens CH, Baigent C. Aspirin in primary prevention: good news and bad news. *Nat. Rev. Cardiol.* 9, 262–263 (2012).
- 5 British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: joint British societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 91(Suppl. 5), v1–v52 (2005).
- 6 US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force Recommendation Statement. *Ann. Intern. Med.* 150, 396–404 (2009).
- 7 Hennekens CH, Hollar D, Baigent C. Sex-related differences in response to aspirin in cardiovascular disease: an untested hypothesis. *Nat. Clin. Pract. Cardiovasc. Med.* 3, 4–5 (2006).
- 8 Nelson M, Reid C, Beilin L *et al.* Rationale for a trial of low-dose aspirin for the primary prevention of major adverse cardiovascular events and vascular dementia in the elderly. Aspirin in Reducing Events in the Elderly (ASPREE). *Drugs Aging* 20, 897–903 (2003).
- 9 De Berardis G, Sacco M, Evangelista V. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials* 8, 21 (2007).
- 10 Asano TK, McLeod RS. Non steroidal anti-inflammatory drugs (NSAID) and Aspirin for preventing colorectal adenomas and carcinomas. *Cochrane Database Syst. Rev.* (2), CD004079 (2004).
- 11 Rothwell PM, Wilson M, Elwin E *et al.* Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomized trials. *Lancet* 376, 1741–1750 (2010).
- 12 Hennekens CH, DeMets D. The need for large scale randomized evidence without undue emphasis on small trials, meta-analyses or subgroup analyses. *JAMA* 302, 2361–2362 (2009).

■ Websites

- 101 Bayer HealthCare. ARRIVE. Aspirin to Reduce Risk of Initial Vascular Events. www.arrive-study.com/EN/study.cfm
- 102 University of Oxford. ASCEND. A Study of Cardiovascular Events in Diabetes. www.ctsu.ox.ac.uk/ascend/