Research Highlight

Aspirin in primary prevention: can we individualize care?

Anuradha Lala[1], William R. Hiatt[2,3], Jeffrey S. Berger[1]

[1]Department of Medicine, Leon Charney Division of Cardiology, New York University School of Medicine, New York, NY 10016; [2]Department of Medicine, Division of Cardiology, University of Colorado School of Medicine; [3]CPC Clinical Research, Aurora, CO 80045, USA

Corresponding to: William R. Hiatt, MD. Department of Medicine, Division of Cardiology, University of Colorado School of Medicine and, CPC Clinical Research, 13199 E Montview Blvd, Suite 200, Aurora, CO 80045. Tel/Fax: 201-341-9381. Email: Will.Hiatt@UCDenver.edu.

Submitted Apr 06, 2012. Accepted for publication Apr 26, 2012.
doi: 10.3978/j.issn.2223-3652.2012.04.07
Scan to your mobile device or view this article at: http://www.thecdt.org/article/view/639/688

Aspirin is very effective in preventing ischemic events in subjects with acute myocardial infarction, ischemic stroke or evidence of clinical cardiovascular disease, forming the basis of current evidence based guidelines (1-3). In this patient population, aspirin use results in a 10% relative reduction in vascular death and 20% relative reduction in any serious vascular event (absolute risk reduction of 1.5% in aspirin users). In fact, the number needed to treat to prevent a single death, myocardial infarction or stroke in subjects with established cardiovascular disease is lower for aspirin compared with other proven medications, such as statins or ACE-inhibitors (3). While aspirin therapy decreases incident cardiovascular events, it also increases risk of major bleeding and hemorrhagic stroke. For secondary prevention the magnitude of benefit outweighs the risk of major bleeding (4). In patients without clinical cardiovascular disease, however, the benefit to risk ratio for aspirin use in primary prevention of cardiovascular events is less clear.

From 1988 to 2008, there were a total of 6 randomized trials comparing aspirin versus placebo/control in the primary prevention of cardiovascular events. All trials included patients without clinical cardiovascular disease, which was defined as the absence of a history of a cardiovascular event or clinical symptoms of angina or transient ischemic attack. While the Physicians Health Study demonstrated a significant 44% decrease in non-fatal myocardial infarction leading to the widespread recommendation of aspirin in patients without clinical cardiovascular disease, aspirin failed to show a benefit in the reduction of the trial's primary endpoint of cardiovascular mortality raising the concern of informative censoring. In fact, none of the six trials were able to demonstrate a reduction in their respective primary endpoints (*Table 1*). When the data were pooled from these 6 trials, a modest 12% relative risk reduction in major adverse cardiovascular events was demonstrated, with no significant reduction in mortality (absolute risk reduction of 0.06%). In a sex-specific pooled analysis, aspirin conferred a significant 12% and 14% relative reduction and 0.3% and 0.4% absolute reduction in cardiovascular events in women and men, respectively (5).

The majority of subjects in the primary prevention trials were at low absolute risk of cardiovascular events and major bleeding. While the absolute bleeding risk in the secondary prevention trials was also low, the absolute risk of a cardiovascular event was much higher. Thus, the benefit-to-risk ratio for aspirin is considerably more favorable for the secondary prevention of cardiovascular events.

Over the last several years, three additional trials in higher risk "primary prevention" subjects (e.g., diabetics and/or patients with subclinical atherosclerosis defined as reduced ABI) have been published (6-8). Though the populations in these trials were also without clinical cardiovascular disease they were at higher risk than those in the original 6 primary prevention trials (9). Despite this higher risk population, all three newer trials also failed to demonstrate a significant benefit of aspirin in reducing their primary endpoint. Our group published a meta-analysis of all 9 trials to date of aspirin in subjects without clinical cardiovascular disease, and found a modest but significant 10% reduction in cardiovascular events but no significant difference in all-cause or cardiovascular mortality (10). The argument for aspirin in primary prevention may extend beyond the reduction of vascular

Table 1 The randomized trials comparing aspirin versus placebo/control in the primary prevention of cardiovascular events

Study	Year	Primary Efficacy Endpoint	P value
PHS	1989	Cardiovascular mortality	0.87
BDT	1988	CV death, nonfatal MI and stroke or TIA	NS
TPT	1998	All ischemic heart disease (coronary death and fatal and nonfatal MI)	0.04*
HOT	1998	CV death, nonfatal MI, stroke	0.17**
PPP	2001	CV death, MI, stroke	NS
WHS	2005	CV death, nonfatal MI, stroke	0.13
POPADAD	2008	CV death, nonfatal MI or stroke, or amputation for critical limb ischemia	0.86
JPAD	2008	CV death, nonfatal MI, stroke, UA, PVD, new angina	0.16
AAA	2010	CV death, MI, stroke, revascularization	NS

*after including silent MI, the reduction was no longer significant (P=0.07); **after exluding silent MI, the reduction became statistically significant (P=0.03)

events. Aspirin has also been shown to reduce nonvascular adverse outcomes as well - specifically the short and long-term incidence of cancer mortality - across multiple types of cancer including gastrointestinal, brain and lung cancers (11,12). To better understand the benefit of preventing serious adverse vascular events in addition to cancer mortality compared to the risk of major bleeding, Seshasai and colleagues conducted a meta-analysis of all 9 trials exploring the role of aspirin in primary prevention (13).

Seshasai found that during a mean follow up of 6.0±2.1 years of over 100,000 patients, aspirin conferred a modest 10% reduction in cardiovascular events (OR 0.90; 95% CI, 0.85-0.96) with a number needed to treat (NNT) of 120. This reduction was driven primarily by a reduction in nonfatal MI (OR 0.80; 95% CI, 0.67-0.96). There was no significant reduction in cardiovascular death or cancer related death. Nontrivial or major bleeding events were increased by 31% (OR 1.31, 95% CI, 1.14-1.50) with a number needed to harm (NNH) of 73. Similarly, our group found that for every 1,000 subjects treated with aspirin over a 5 year period, aspirin prevented 2.9 major adverse cardiovascular events and caused 2.8 major bleeds (3). In regards to the nonvascular outcome of cancer mortality, they found a trend toward lower non-cardiovascular mortality (OR 0.92; 95% CI, 0.88-1.00) which failed to reach statistical significance.

It has been speculated that each of the 9 studies failed to show a mortality benefit because event rates are so low in primary prevention populations and they were not sufficiently powered to detect this difference. The pooled analyses however reflect outcomes in over 100,000 subjects and still failed to show a significant reduction in cardiovascular death or total death in aspirin users.

How do we process these findings into our clinical practice? Should aspirin be used for primary prevention?

If patients for whom the benefit-to-risk equation is more favorable can be identified, then the role of aspirin in primary prevention could be justified. Risk factors such as diabetes, low screening ankle-brachial index, hypertension, increasing age, and others are used to predict future cardiovascular event risk but do not seem to predict effectiveness of aspirin therapy. In fact, many of the same risk factors that identify an individual at increased risk for a cardiovascular event also increase the risk of major bleeding (14). We need novel and better ways to identify the patient population who have the most favorable benefit-to-risk ratio for aspirin therapy (e.g., identify high risk for thrombosis and low risk for major bleeding). One such example may be platelet activity. There are data to suggest that individuals with increased platelet activity are at increased risk for cardiovascular events from platelet mediated thrombosis (15,16) and may be at low risk for platelet mediated bleeding events. Perhaps we could use such measures of platelet activity to identify low risk patients who will derive the most benefit from aspirin. Rather than using traditional risk factors for inclusion criteria, an adequately powered study of aspirin in primary prevention using a patient's unique nascent platelet activity profile would shed light on this important field of study.

The evidence in support of aspirin for secondary prevention in preventing cardiovascular events and

mortality remains clear and should be routinely prescribed according to current guidelines. In contrast, pooled data from the current meta-analysis and others do not support the routine use of aspirin in patients without evidence of clinical cardiovascular disease. Physicians must continue to engage in dialogue with their patients as to the potential benefits and harms of aspirin. Furthermore, advocating more avidly for other measures such as diet, lifestyle modification, and other pharmacotherapies such as statins, (which have been shown to confer substantial benefit in the primary prevention population) may have a more profound impact on this unique population.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116:e148-304.
2. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. Circulation 2008;117:296-329.
3. Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. Am J Med 2008;121:43-9.
4. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
5. 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.
6. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840.
7. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134-41.
8. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010;303:841-8.
9. Patrono C, Baigent C, Hirsh J, et al. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:199S-233S.
10. Berger JS, Lala A, Krantz MJ, et al. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. Am Heart J 2011;162:115-24.e2.
11. Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31-41.
12. Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. Nat Rev Clin Oncol 2012. [Epub ahead of print].
13. Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012;172:209-16.
14. Lip GY, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation:

the HAS-BLED (Hypertension, Abnormal Renal/ Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/ Alcohol Concomitantly) score. J Am Coll Cardiol 2011;57:173-80.
15. Chu SG, Becker RC, Berger PB, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost 2010;8:148-56.
16. Sharma G, Berger JS. Platelet activity and cardiovascular risk in apparently healthy individuals: a review of the data. J Thromb Thrombolysis 2011;32:201-8.

Cite this article as: Lala A, Hiatt WR, Berger JS. Aspirin in primary prevention: can we individualize care? Cardiovasc Diagn Ther 2012;2(2):169-172. doi: 10.3978/j.issn.2223-3652.2012.04.07

