

Aspirin for the Primary Prevention of Cardiovascular Events: Recommendations and Rationale

U.S. Preventive Services Task Force

Final Draft September 6, 2001

Word count: 1815 (includes all boilerplate material at beginning and end, plus table)

Corresponding Author: Alfred O. Berg, MD, MPH, Chair, U.S. Preventive Services Task Force, c/o David Atkins, MD, MPH, Scientific and Technical Editor, U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Center for Practice and Technology Assessment, 6010 Executive Boulevard, Suite 300, Rockville, MD 20852. (301) 594-4016, fax (301) 594-4027, Email <datkins@ahrq.gov>.

Members of the US Preventive Services Task Force are Alfred O. Berg, MD, MPH, Chair, USPSTF (Professor and Chair, Department of Family Medicine, University of Washington, Seattle, WA), Janet D. Allan, PhD, RN, CS, Vice-chair, USPSTF (Dean and Professor, School of Nursing, University of Texas Health Science Center, San Antonio, TX), Paul S. Frame, MD (Tri-County Family Medicine, Cohocton, NY, and Clinical Professor of Family Medicine, University of Rochester, Rochester, NY), Charles J. Homer, MD, MPH (Executive Director, National Initiative for Children's Healthcare Quality, Boston, MA), Mark S. Johnson, M.D., M.P.H. (Associate Professor of Clinical Family Medicine and Chairman Department of Family

Medicine, University of Medicine and Dentistry of New Jersey-New Jersey Medical School), Jonathan D. Klein, M.D., M.P.H. (Associate Professor of Pediatrics and of Community and Preventive Medicine, University of Rochester School of Medicine), Tracy A. Lieu, MD, MPH (Associate Professor, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School, Boston, MA), Cynthia D. Mulrow, MD, MSc (Professor of Medicine, University of Texas Health Science Center, Audie L. Murphy Memorial Veterans Hospital, San Antonio, TX), C. Tracy Orleans, PhD (Senior Scientist, The Robert Wood Johnson Foundation, Princeton, NJ), Jeffrey F. Peipert, MD, MPH (Director of Research, Women and Infants' Hospital, Providence, RI), Nola J. Pender, PhD, RN (Professor and Associate Dean for Research, School of Nursing, University of Michigan, Ann Arbor, MI), Albert L. Siu, M.D., M.S.P.H. (Professor of Medicine, Chief of Division of General Internal Medicine, and Medical Director of the Primary Care and Medical Services Care Center, Mount Sinai School of Medicine and The Mount Sinai Medical Center), Steven M. Teutsch, MD, MPH (Senior Director, Outcomes Research and Management, Merck & Company, Inc., West Point, PA), Carolyn Westhoff, MD, MSc (Associate Professor of Obstetrics, Gynecology and Public Health, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY), and Steven H. Woolf, MD, MPH (Professor of Family Medicine, Department of Family Practice, Medical College of Virginia, Fairfax, VA).

This statement summarizes the third U.S. Preventive Services Task Force (USPSTF) recommendations for aspirin for the primary prevention of cardiovascular events and the supporting scientific evidence. The complete information upon which this statement is based,

including evidence tables and references, is available in the accompanying article "Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force" and in the Systematic Evidence Review on this topic. Copies of this document, the summary of the evidence, and the Systematic Evidence Review can be obtained through the USPSTF Web site (<http://www.ahrq.gov/clinic/uspstfix.htm>) and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

SUMMARY OF RECOMMENDATION

- The USPSTF strongly recommends that clinicians discuss aspirin chemoprevention with adults who are at increased risk of coronary heart disease (see Clinical Considerations). Discussions with patients should address both the potential benefits and harms of aspirin therapy. (**A recommendation.**)

The USPSTF found good evidence that aspirin decreases the incidence of coronary heart disease in adults who are at increased risk for heart disease. They also found good evidence that aspirin increases the incidence of gastrointestinal bleeding and fair evidence that aspirin increases the incidence of hemorrhagic strokes. The USPSTF concluded that the balance of benefits and harms is most favorable in patients at high risk of CHD (5-year risk of greater than or equal to 3%) but is also influenced by patient preferences.

CLINICAL CONSIDERATIONS

- Decisions about aspirin therapy should take into account overall risk of coronary heart disease. Risk assessment should include asking about the presence and severity of the following risk factors: age, sex, diabetes, elevated total cholesterol levels, low levels of high-density lipoprotein (HDL) cholesterol, elevated blood pressure, family history (in younger adults), and smoking. Tools that incorporate specific information on multiple risk factors provide more accurate estimation of cardiovascular risk than categorizations based simply on counting the numbers of risk factors (<http://www.intmed.mcw.edu/clinical/heartrisk.html>)¹.

- Men over age 40, postmenopausal women, and younger persons with risk factors for coronary heart disease (e.g., hypertension, diabetes, or smoking) are at increased risk of heart disease and may wish to consider aspirin therapy. Table 1 shows how estimates of the type and magnitude of benefits and harms associated with aspirin therapy vary with an individual's underlying risk of coronary heart disease. Although balance of benefits and harms is most favorable in high-risk persons (5-year risk greater than 3%), some persons at lower risk may consider the potential benefits of aspirin to be sufficient to outweigh the potential harms.
- Discussions about aspirin therapy should focus on potential coronary heart disease benefits, such as prevention of myocardial infarction, and potential harms of gastrointestinal and intracranial bleeding. Discussions should take into account individual preferences and risk aversions concerning myocardial infarction, stroke, and gastrointestinal bleeding.

Table 1. Estimates of benefits and harms of aspirin therapy given for 5 years to 1000 individuals with various levels of baseline risk for coronary heart disease*

Benefits and Harms	Baseline risk for coronary disease over 5 years†		
	1%	3%	5%
Total mortality	No effect	No effect	No effect
CHD events†	1-4 avoided	4-12 avoided	6-20 avoided
Hemorrhagic Strokes**	0-2 caused	0-2 caused	0-2 caused
Major gastrointestinal bleeds⁺⁺	2-4 caused	2-4 caused	2-4 caused

*These estimates are based on a relative risk reduction of 28% for coronary heart disease events in aspirin-treated patients. They assume risk reductions do not vary significantly by age.

†Nonfatal acute myocardial infarction and fatal coronary heart disease. Five-year risks of 1%, 3% and 5% are equivalent to 10-year risks of 2%, 6%, and 10%, respectively.

** Data from secondary prevention trials suggest that increases in hemorrhagic stroke may be offset by reduction in other types of stroke in patients at very high risk of CVD (greater than or equal to 10% 5-year risk).

++ Rates of gastrointestinal bleeds may be 2 to 3 times higher in persons older than 70.

Source: Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: A summary of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* **xxxx**.

- Although the optimal timing and frequency of discussions related to aspirin therapy are unknown, reasonable options include every 5 years in middle-aged and older persons or when other cardiovascular risk factors are detected.
- Most participants in the primary prevention trials of aspirin therapy have been men between the ages of 40 and 75 years old. Current estimates of benefits and harms may not be as reliable for women and older men.
- Although older patients may derive greater benefits due to their higher risk of CHD and stroke, their risk of bleeding may be higher.
- Uncontrolled hypertension may attenuate the benefits of aspirin in reducing CHD.
- The optimum dose of aspirin for chemoprevention is not known. Primary and secondary prevention trials have demonstrated benefits of a variety of regimens including 75 mg per day, 100 mg per day, and 325 mg every other day. Doses of about 75 mg daily appear as effective as higher doses; whether doses below 75 mg daily are effective is not established. Enteric-coated or buffered preparations do not clearly reduce adverse gastrointestinal effects of aspirin. Uncontrolled hypertension and concomitant use of other nonsteroidal anti-inflammatory agents or anticoagulants increase risk for serious bleeding.

SCIENTIFIC EVIDENCE

Epidemiology and Clinical Background

Cardiovascular disease, including ischemic coronary heart disease, stroke, and peripheral vascular disease, is the leading cause of death in the United States.² Yearly, over 1 million Americans experience new or recurrent myocardial infarction or fatal coronary heart disease. Most events occur in older persons and those with recognized risk factors for cardiovascular disease, including high cholesterol, high blood pressure, diabetes, or a history of smoking. The early-documented and clear success of aspirin in preventing further clinical disease in some patients with known heart disease (secondary prevention) raised interest in aspirin as a potential primary preventive intervention in men and women without known heart disease.³ Two early randomized trials of aspirin had conflicting results, however, and lacked sufficient power to estimate major harms, such as gastrointestinal bleeding and hemorrhagic stroke.^{4,5} Thus the role of aspirin in primary prevention has remained controversial. The new USPSTF recommendation incorporates additional data from 3 recent trials and provides more reliable estimates of both benefits and harms of aspirin in patients without known heart disease.

Efficacy of Chemoprevention

Five trials have examined the effects of daily or every-other-day aspirin for the primary prevention of cardiovascular events over periods of 4 to 7 years.^{4,5,6,7,8} Most participants were over age 50 and male. Meta-analysis of pooled data from all of the studies showed that aspirin

therapy reduced the risk of CHD by 28% (summary odds ratio (OR) 0.72, 95% CI 0.60 to 0.87). Summary estimates showed no significant effects of aspirin on total mortality (OR 0.93, 95% CI 0.84 to 1.02) and stroke (OR 1.02, 95% CI 0.85 to 1.23).

Harms of Chemoprevention

These 5 primary prevention trials, and a larger number of secondary prevention randomized controlled trials (RCTs) enrolling patients with heart disease or stroke, demonstrate that aspirin increases rates of gastrointestinal bleeding. Estimated rates of major gastrointestinal bleeds are approximately 2 to 4 per 1000 middle-aged individuals (4 to 12 for older individuals) given aspirin for 5 years.^{9, 10, 11}

These controlled trials in primary and secondary prevention settings also suggest that aspirin increases rates of hemorrhagic strokes by a small amount (0-2 per 1000 individuals given aspirin for 5 years).^{4,5,6} Such estimates are less reliable than those of gastrointestinal bleeding because few strokes were reported in the trials.

RECOMMENDATIONS OF OTHERS

In 1994, the Canadian Task Force on Preventive Health Care concluded that the evidence was not strong enough to recommend for or against use of aspirin for primary prevention of heart disease in men or women and recommended that physicians and patients balance the reduced rate of nonfatal myocardial infarction against potential adverse effects.¹² In 1997, the American Diabetes Association recommended low-dose aspirin for diabetic patients with 1 or more risk factors for cardiovascular disease who were older than 30 years and had no contraindications to

aspirin therapy.¹³ In 1997, the American Heart Association concluded that aspirin may be warranted for patients at high risk of myocardial infarction, but that health care providers must take into account a patient's particular cardiovascular risk profile, the demonstrated benefits of aspirin on reducing risk of a first myocardial infarction, and known as well as unknown side effects of aspirin.¹⁴ In 1998 the European Society of Cardiology recommended low dose aspirin (75 mg) for well-controlled hypertensives and men at "particularly" high risk for coronary heart disease, but not for all individuals at high risk.¹⁵

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**U.S. PREVENTIVE SERVICES TASK FORCE
RECOMMENDATIONS AND RATINGS**

The U.S. Preventive Services Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

- A.** The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
- B.** The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
- C.** The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
- D.** The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
- I.** The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

**U.S. PREVENTIVE SERVICES TASK FORCE
STRENGTH OF OVERALL EVIDENCE**

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.