Aspirin for the Primary Prevention of Cardiovascular Events: An Update of the Evidence for the U.S. Preventive Services Task Force

Tracy Wolff, MD, MPH; Therese Miller, DrPH; and Stephen Ko, MD, MPH

Background: Coronary heart disease and cerebrovascular disease are leading causes of death in the United States. In 2002, the U.S. Preventive Services Task Force (USPSTF) strongly recommended that clinicians discuss aspirin with adults who are at increased risk for coronary heart disease.

Purpose: To determine the benefits and harms of taking aspirin for the primary prevention of myocardial infarctions, strokes, and death.

Data Sources: MEDLINE and Cochrane Library (search dates, 1 January 2001 to 28 August 2008), recent systematic reviews, reference lists of retrieved articles, and suggestions from experts.

Study Selection: English-language randomized, controlled trials (RCTs); case–control studies; meta-analyses; and systematic reviews of aspirin versus control for the primary prevention of cardiovascular disease (CVD) were selected to answer the following questions: Does aspirin decrease coronary heart events, strokes, death from coronary heart events or stroke, or all-cause mortality in adults without known CVD? Does aspirin increase gastrointestinal bleeding or hemorrhagic strokes?

Data Extraction: All studies were reviewed, abstracted, and rated for quality by using predefined USPSTF criteria.

Data Synthesis: New evidence from 1 good-quality RCT, 1 good-quality meta-analysis, and 2 fair-quality subanalyses of RCTs demonstrates that aspirin use reduces the number of CVD events in patients without known CVD. Men in these studies experienced fewer myocardial infarctions and women experienced fewer ischemic strokes. Aspirin does not seem to affect CVD mortality or all-cause mortality in either men or women. The use of aspirin for primary prevention increases the risk for major bleeding events, primarily gastrointestinal bleeding events, in both men and women. Men have an increased risk for hemorrhagic strokes with aspirin use. A new RCT and meta-analysis suggest that the risk for hemorrhagic strokes in women is not statistically significantly increased.

Limitations: New evidence on aspirin for the primary prevention of CVD is limited. The dose of aspirin used in the RCTs varied, which prevented the estimation of the most appropriate dose for primary prevention. Several of the RCTs were conducted within populations of health professionals, which potentially limits generalizability.

Conclusion: Aspirin reduces the risk for myocardial infarction in men and strokes in women. Aspirin use increases the risk for serious bleeding events.

Cardiovascular disease (CVD) is the leading cause of death in the United States; it is the underlying or contributing cause in approximately 58% of deaths. In 2003, 1 in 3 adults had some form of CVD. In adults age 40 years or older, the lifetime risk for CVD increases to 2 in 3 for men and more than 1 in 2 for women. Mortality data from 2003 showed that CVD was an underlying cause of death in 1 of every 2.7 deaths, accounting for roughly 2.5 million deaths; the mortality rate from CVD was 308.8 per 100 000 (1).

The epidemiology of CVD events is different for men and women. Men have a higher risk for coronary heart disease and tend to have these events at a younger age than women. Men have a lifetime risk of 49% for a coronary heart disease event after the age of 40 years; for women, the lifetime risk is 32%. The median age for a first myocardial infarction is 65.8 years for men and 70.4 years for women. Women are more likely to die as a result of a myocardial infarction; 38% of women die within 1 year of their first myocardial infarction versus 25% of men. This may in part be because women are likely to be older when they have their first myocardial infarction (1, 2).

Although incidence rates of stroke are higher among men than women, more women die of stroke than men because of their longer life expectancy. According to the

Framingham data (2), the 10-year risk for initial ischemic stroke at age 55 years is 1.8% for women and 2.4% for men; at age 65 years, the risk increases to 3.9% for women and 5.8% for men. The lifetime risk for ischemic stroke for persons between the ages of 55 and 75 years is greater for women than for men (approximately 17% to 18% for women and 13% to 14% for men). After age 75 years, the risk decreases to 14% for women and 8% for men.

In 2002, the U.S. Preventive Services Task Force (USPSTF) strongly recommended that clinicians discuss aspirin with adults who are at increased risk for coronary
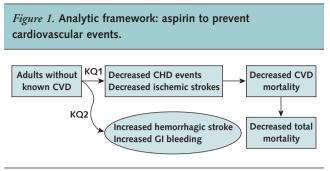
Figure 1. Analytic framework: aspirin to prevent cardiovascular events.

CHD = coronary heart disease; CVD = cardiovascular disease; GI = gastrointestinal; KQ = key question.

heart disease (3). The previous USPSTF recommendation for the prophylactic use of aspirin to prevent CVD was based on data from 5 randomized controlled trials (RCTs) that showed a 28% reduction in myocardial infarctions with aspirin use. Only 2 of the 5 studies included women. In 2005, data from the Women's Health Study (4) provided important information about the benefit of aspirin for women. The Women's Health Study was a trial of 39 876 women randomly assigned to receive aspirin or placebo and followed for 10 years for cardiovascular events. With the availability of new data on benefits for women, the USPSTF decided to update its previous recommendation by reevaluating the evidence for aspirin use in the primary prevention of CVD, with a focus on sex-specific harms and benefits. This review updates the previous review and focuses on new evidence on the benefits and harms of aspirin for the primary prevention of CVD published since the 2002 USPSTF review and recommendation (3).

Analytic Framework and Key Questions

In consultation with the USPSTF, we developed an analytic framework (Figure 1). From this analytic framework, we developed the following key questions (KQs):

KQ1a. Does aspirin use in women without known cardiovascular disease decrease coronary heart events, strokes, death from coronary heart events or strokes, or all-cause mortality?

KQ1b. Does aspirin use in men without known cardiovascular disease decrease coronary heart events, strokes, death from coronary heart events or strokes, or all-cause mortality?

KQ2a. Does aspirin use in women increase gastrointestinal bleeding or hemorrhagic strokes?

KQ2b. Does aspirin use in men increase gastrointestinal bleeding or hemorrhagic strokes?

Methods

Data Sources and Searches

For evidence on the benefits of aspirin for the primary prevention of CVD events (KQ1), we performed a litera-

ture search in PubMed by using the Medical Subject Heading terms *aspirin* and *cardiovascular diseases*. For evidence on the harms of aspirin for the primary prevention of CVD events (KQ2), we used the terms *aspirin, cardiovascular diseases, gastrointestinal hemorrhage*, and *cerebral-hemorrhage*. We searched for studies published between 1 January 2001 and 28 August 2008. We limited our search to English-language studies, human studies, and studies of nonpregnant adults and to the following study types for benefits: RCT, meta-analysis, and systematic review. For evidence on harms, we limited our search to RCTs, case–control studies, meta-analyses, and systematic reviews. In addition to the literature search, we looked for other relevant studies in the Cochrane Central Register of Controlled Trials, through the examination of reference lists from included and other important articles, and through consultation with experts.

Study Selection

Two reviewers independently reviewed the titles, abstracts, and full articles and selected articles on the basis of predefined inclusion criteria. We resolved disagreements on inclusion by consensus or by involving a third reviewer, if necessary. In general, we included studies that evaluated aspirin versus control for the primary prevention of cardiovascular disease events in adults, had a study population of patients without a history of CVD or who were not at very high risk for CVD (such as patients with atrial fibrillation) and was generalizable to the U.S. primary care population, and calculated risk estimates for 1 of the following outcomes: myocardial infarction, stroke, death from myocardial infarction or stroke, or all-cause mortality for benefits and gastrointestinal bleeding, serious bleeding episodes, hemorrhagic stroke, or cerebral hemorrhage for harms. We accepted studies that included patients with a history of CVD or patients who were at very high risk for CVD only if those studies reported separate results for patients without a history of CVD or who were not at very high risk for CVD.

Data Extraction and Quality Assessment

Two reviewers independently abstracted and quality-rated the included articles. We extracted the following data: geographic location, duration of therapy, proportion of female patients, dosage, control, blinding, outcome adjudication, additional therapies, demographic characteristics, and effect estimates on the previously listed outcomes. We evaluated the quality of the individual studies by using previously published USPSTF criteria on internal and external validity (Appendix Table, available at www.annals.org) (5–7). We evaluated RCTs on adequacy of randomization; maintenance of similar groups (includes attrition, crossovers, adherence, and contamination); loss to follow-up; equality, reliability, and validity of measurements; clarity of intervention definitions; and appropriateness of outcomes. We evaluated systematic reviews on comprehensiveness of sources considered,

search strategy used, explicit selection criteria, standard appraisal of included studies, validity of conclusions, recency, and relevance. We excluded studies of poor quality. We determined generalizability of the study sample to the United States by consensus of 3 reviewers after discussions with the USPSTF on similarities between the health care system in the study country and that of the United States. Considerations about whether a population would be similar to the U.S. population include baseline risk for cardiovascular disease, general health status of the population, and the availability of acute medical care and treatment in a health system with available tertiary care centers.

Data Synthesis

We synthesized the studies qualitatively and organized them by key question. We did not synthesize quantitatively because of the availability of a good-quality meta-analysis by Berger and colleagues (8). We discuss the results of this meta-analysis in the Results section.

Role of the Funding Source

The general work of the USPSTF is supported by the Agency for Healthcare Research and Quality. This specific review did not receive separate funding.

RESULTS

Our literature search initially identified 726 potentially relevant articles (**Figure 2**). We excluded most studies because either the sample population comprised only patients at very high risk for CVD or with a history of CVD or the study did not evaluate aspirin for the primary prevention of CVD. We also excluded studies that were duplicates or provided no new information, were not of appropriate study design, or did not report outcomes of interest. We ultimately included 4 studies, which we discuss. The 4 studies provided information on both benefits and harms.

Key Question 1

Does aspirin use in men and women without known cardiovascular disease decrease coronary heart events, strokes, death from coronary heart events or strokes, or all-cause mortality?

New evidence from controlled trials is limited to 1 study in women, the Women's Health Study (4), that reported benefit in the reduction of ischemic strokes with aspirin use. The Women's Health Study was a good-quality, double-blind RCT that evaluated the risks and benefits of aspirin for the primary prevention of cardiovascular disease. The investigators reported a benefit from aspirin use for the reduction of strokes (relative risk [RR], 0.83 [95% CI, 0.69 to 0.99]), specifically ischemic strokes (RR, 0.76 [CI, 0.63 to 0.93]), and no statistically significant benefit in the reduction of combined cardiovascular events, myocardial infarctions, death from CVD, or all-cause mortality. We considered this study to be of good quality because a blinded end point committee of physicians reviewed medical records for all reported end points, analyses were completed by using an intention-to-treat process, and the follow-up rate was high. The investigators did not report information on rates of adherence or crossovers.

A recent good-quality meta-analysis (8) suggests differential benefits of aspirin by sex: Men derive benefit in the reduction of myocardial infarctions, and women derive benefit in the reduction of ischemic strokes. Although the meta-analysis includes studies that were published before our search dates, we include it here because it provides new estimates of sex-specific benefits and harms and is of sufficient quality that we thought it unnecessary to duplicate the updated calculations (5). Berger and colleagues' search
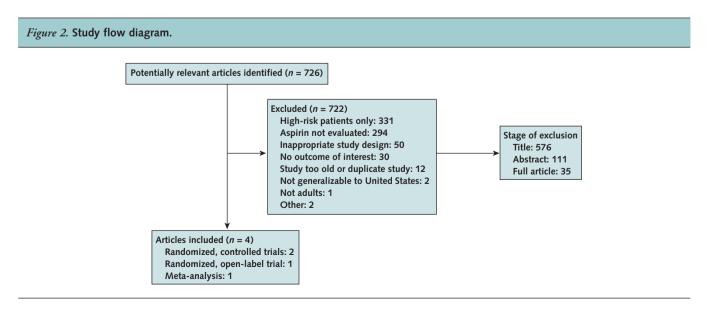
Figure 2. Study flow diagram.

Table. Summary of Primary Prevention Trials in the Meta-analysis by Berger and Colleagues*

Variable	BMD (9)	PHS (10)	TPT (11)	HOT (12)	PPP (13)	WHS (4)
Year of publication	1988	1989	1998	1998	2001	2005
Location	United Kingdom	United States	United Kingdom	Worldwide	Italy	United States
Sample	Male physicians	Male physicians	Men at high risk for heart disease	Men and women with diastolic blood pressure 100–115 mm Hg	Men and women with >1 cardiovascular risk factor	Female health professionals
Patients, n	5139	22 071	5085	18 790	4495	39 876
Women, %	0	0	0	47	58	100
Age, y	<60 (46.9%) 60–69 (39.3%) 70–79 (13.9%)	Mean, 53 (range, 40–84)	Mean, 57.5 (range, 45–69)	Mean, 61.5 (range, 50–80)	<60 (29%) 60–69 (45%) 70–79 (24%)	Mean, 54.6 45–54 (60.2%) 55–64 (29.5%) ≥65 (10.3%)
Duration of therapy, y†	5.8	5	6.8	3.8	3.6	10.1
Aspirin dosage	500 mg/d	325 mg every other day	75 mg/d (controlled release)	75 mg/d	100 mg/d	100 mg every other day
Additional therapies	None	β-Carotene (50% of patients)	Warfarin‡	Felodipine with or without ACE inhibitor or β-blocker	Vitamin E (300 mg/d)	Vitamin E (600 IU every other day); β-carotene (discontinued after 22.8 mo)
Control	No placebo	Placebo	Placebo	Placebo	No placebo	Placebo
Blinding	Open-label	Double-blind	Double-blind	Double-blind	Open-label	Double-blind
Adjudication	Cardiologist or neurologist blinded to treatment reviewed reported myocardial infarctions, strokes, and TIAs and classified them as definite, probable, or doubtful	End points committee of physicians, including 2 internists, 1 cardiologist, and 1 neurologist, all blinded	Research nurse annually searched notes for possible end points whether the man was still taking trial treatment; Office of National Statistics provided information on end points for men who had moved away from their GP	Verification of all reported events by the blinded Independent Clinical Event Committee	End points assured by ad hoc committee	Medical records reviewed by blinded end points committee of physicians
Study quality	Fair§	Good§	Good§	Good§	Fair§	Good

ACE = angiotensin-converting enzyme; BMD = British Male Doctors' trial; GP = general practitioner; HOT = Hypertension Optimal Treatment trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.
* See reference 8.
† Values given are means, except for the TPT value, which is a median.
‡ Data for patients receiving warfarin are not included in this table.
§ Quality rating from a U.S. Preventive Services Task Force review conducted in 2002.

differed from ours in that we searched for recent studies published since 2001 and we used the broader term *cardiovascular disease*, whereas Berger and colleagues used the specific terms *myocardial infarction* and *stroke*. We also used additional terms to search for studies on the harms of aspirin and accepted study types other than RCTs. Berger and colleagues' meta-analysis (8) reported on the sex-specific benefits of aspirin in 51 342 women and 44 114 men enrolled in 6 primary prevention trials. This meta-analysis included the Women's Health Study and 5 older RCTs that were published before our search dates but were part of the previous 2002 USPSTF review: the British Male Doctors' trial (9), the Physicians' Health Study (10), the Thrombosis Prevention Trial (11), the Hypertension Optimal Treatment trial (12), and the Primary Prevention Project (13). The **Table** lists the trial characteristics included in the meta-analysis. Aspirin use in women was associated with statistically significant reductions in cardiovascular events (odds ratio [OR], 0.88 [CI, 0.79 to 0.99]) and ischemic strokes (OR, 0.76 [CI, 0.63 to 0.93]); no statistically significant benefit was found in the reduction of myocardial infarctions or cardiovascular mortality. In men, aspirin use was associated with a statistically significant reduction in cardiovascular events (OR, 0.86 [CI,

0.78 to 0.94]) and myocardial infarctions (OR, 0.68 [CI, 0.54 to 0.86]); no statistically significant benefit was found in the reduction of ischemic strokes or cardiovascular mortality. Total mortality was not significantly reduced by aspirin use in men or women. We rated Berger and colleagues' study as good quality because of its comprehensive sources, use of established quality-rating criteria, recency, relevance, and the validity of its conclusions.

New evidence about whether specific subpopulations benefit from aspirin use to a greater or lesser extent than the general population is limited to 3 subgroup analyses of RCTs: the Women's Health Study (4) and 2 subanalyses of RCTs whose original report was published before the dates of our search (14, 15). We have therefore not included the original RCT reports in this review. No consistent evidence from recent studies indicates whether subpopulations may benefit to a greater or lesser extent than the general population. The Women's Health Study performed subgroup analyses by smoking status and age and reported a greater benefit among former and never smokers, who had a greater reduction in risk for ischemic strokes with aspirin use than current smokers, and among women 65 years of age or older, who had a greater reduction in the risk for major cardiovascular events, ischemic strokes, and

myocardial infarctions (RR for myocardial infarction, 0.66 [CI, 0.44 to 0.97]). A fair-quality subgroup analysis of the Hypertension Optimal Treatment study (14) reported a greater-than-average reduction in myocardial infarctions among subgroups of aspirin users with systolic blood pressure of 180 mm Hg or higher, systolic blood pressure of 160 to 179 mm Hg, diastolic blood pressure of 107 mm Hg or higher, diastolic blood pressure of 104 to 106 mm Hg, or serum creatinine level greater than 115 μmol/L (>1.3 mg/dL). Methodological issues—most important, the performance of subanalyses on groups not considered in the randomization process—led to a fair-quality rating. Finally, a fair-quality subgroup analysis of the larger, previously published Primary Prevention Project (15) reported no benefit of aspirin in the reduction of any cardiovascular end points among diabetic patients (hazard ratio for the main combined cardiovascular end point, 0.9 [CI, 0.49 to 1.67]). The results of this study are difficult to interpret because a large number of participants had crossed over to the other group by the end of the trial: 28% of diabetic patients in the aspirin group had discontinued use of the medication, and 12% of diabetic patients in the control group were taking aspirin. We assigned the study a fair-quality rating because the crossover rate was high and the original randomization process did not seem to account for the presence or absence of diabetes mellitus.

Key Question 2

Does aspirin use in women and men increase gastrointestinal bleeding or hemorrhagic strokes?

New evidence on the harms of aspirin for the primary prevention of CVD events consistently shows that aspirin increases the risk for major bleeding events, primarily gastrointestinal bleeding, in men and women. Limited new evidence suggests that hemorrhagic strokes are significantly increased among men but not among women. Four studies provided information on the harms of aspirin for this key question.

The Women's Health Study (4) reported that serious gastrointestinal bleeding events (requiring transfusion) were more common among the women assigned to the aspirin group than among those assigned to the placebo group (RR, 1.40 [CI, 1.07 to 1.83]). Five women died in the study because of gastrointestinal bleeding: 3 in the placebo group and 2 in the aspirin group. In addition to serious gastrointestinal bleeding events, episodes of peptic ulcer, self-reported hematuria, easy bruising, and epistaxis were significantly more common among the women randomly assigned to receive aspirin than among those randomly assigned to receive placebo. Increases in hemorrhagic strokes were not statistically significant in the aspirin group (RR, 1.24 [CI, 0.82 to 1.87]). The meta-analysis of RCTs discussed for the key question on benefits (8) reported adverse events with aspirin use in the primary prevention of cardiovascular events in 51 342 women and 44 114 men. Major bleeding events occurred in 301

women (OR, 1.68 [CI, 1.13 to 2.52]) and 288 men (OR, 1.72 [CI, 1.35 to 2.20]). The odds of a hemorrhagic stroke were not significantly increased for women assigned to the aspirin group but were significantly increased for men (OR, 1.69 [CI, 1.04 to 2.73]).

New evidence as to whether specific subpopulations are harmed to a greater or lesser extent than the general population is limited to 2 subgroup analyses of previously published RCTs. The subgroup analysis of the Hypertension Optimal Treatment study (14) reported that bleeding events did not differ by blood pressure at baseline. Sacco and colleagues' subgroup analysis of data from the Primary Prevention Project trial on diabetic patients (15) reported 10 bleeding episodes in the aspirin group and 1 in the control group; no intracranial hemorrhages occurred during the study in either group.

DISCUSSION

The practice of prescribing aspirin to asymptomatic women for the prevention of myocardial infarction has been called into question after the publication of a recent large study in women and a meta-analysis that reported no benefit (4, 8). In the past, many organizations have recommended aspirin for the prevention of first myocardial infarctions in both men and women. These recommendations were based on studies primarily of men. The new evidence from the Women's Health Study and the meta-analysis with sex-specific calculations (4, 8) help clarify the differing benefits of aspirin for men and women. This evidence demonstrates that aspirin use reduces the number of CVD events in both men and women without known CVD. Men in these studies experienced fewer myocardial infarctions, and women experienced fewer ischemic strokes. Aspirin does not seem to affect CVD mortality or all-cause mortality in either men or women. Aspirin use for the primary prevention of CVD events probably provides more benefits than harms to men at increased risk for myocardial infarction and women at increased risk for ischemic stroke. The reason for the differences by sex is unknown. Several potential explanations have been posited (8), including differences in aspirin metabolism, differences in rates of myocardial infarction and stroke, and higher likelihood of aspirin resistance in women.

The use of aspirin in primary prevention increases the risk for major bleeding events, primarily gastrointestinal bleeding events, in both men and women. Men have an increased risk for hemorrhagic strokes with aspirin use, whereas a new RCT and meta-analysis (4, 8) suggest that the risk for hemorrhagic strokes in women is not significantly increased. Some factors, such as whether the patient is receiving proton-pump inhibitors, may modify the risk for gastrointestinal bleeding. We did not specifically review this evidence. Future reviews should include a thorough review of the effect of proton-pump inhibitors and other factors on the incidence of gastrointestinal bleeding.

We found 1 study, a subgroup analysis of the previously published Primary Prevention Project study (15), that suggests that aspirin may have less benefit in diabetic patients than in nondiabetic patients. As a subgroup analysis, it has inherent limitations. Further research is needed to establish the benefit of aspirin use in diabetic patients for the primary prevention of CVD events. Another subgroup analysis, of the Hypertension Optimal Treatment study (14), reported that patients with higher baseline blood pressures had a greater-than-average benefit in the reduction of cardiovascular events without an increased risk for major bleeding events. These findings contrast with those of 2 other primary prevention trials, the Physicians' Health Study and the Thrombosis Prevention Trial (10, 11), which found less benefit for patients with higher systolic blood pressure. Further research is needed to clarify the benefit of aspirin in the prevention of CVD events in relation to blood pressure.

The dosages used in the primary prevention trials ranged from 75 mg/d to 500 mg/d. The Women's Health Study used 100 mg every other day. Some experts have suggested that the low dose used in the Women's Health Study may be a reason why no effect was seen in the reduction of the combined outcome of CVD events or in the reduction of heart attacks.

In summary, consistent evidence from randomized clinical trials indicates that aspirin use reduces the risk for CVD events in adults without a history of CVD. Men have a reduced risk for myocardial infarctions, and women have a reduced risk for ischemic strokes. Consistent evidence shows that aspirin use increases the risk for gastrointestinal bleeding events, and limited evidence shows that aspirin use increases the risk for hemorrhagic strokes. The overall benefit in the reduction of CVD events with aspirin use depends on baseline CVD risk and risk for gastrointestinal bleeding.

References

1. **Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006;113:e85-151. [PMID: 16407573]

2. **Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB.** Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991;22:312-8. [PMID: 2003301]

3. **U.S. Preventive Services Task Force.** Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med. 2002; 136:157-60. [PMID: 11790071]

4. **Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al.** A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293-304. [PMID: 15753114]

5. **Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA.** Using existing systematic reviews in complex systematic reviews. Ann Intern Med. 2008;148: 776-82. [PMID: 18490690]

6. **Harris R, Atkins D, Berg AO, Best D, Eden KB, Feightner JW, et al.** US Preventive Services Task Force Procedure manual. Rockville, MD: Agency for Healthcare Research and Quality; 2001.

7. **Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al; Methods Work Group, Third US Preventive Services Task Force.** Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. [PMID: 11306229]

8. **Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL.** 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. [PMID: 16418466]

9. **Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al.** Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed). 1988;296:313-6. [PMID: 3125882]

10. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med. 1989;321:129-35. [PMID: 2664509]

11. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. Lancet. 1998;351:233-41. [PMID: 9457092]

12. **Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al.** Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-62. [PMID: 9635947]

13. **de Gaetano G; Collaborative Group of the Primary Prevention Project.** Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet. 2001;357:89-95. [PMID: 11197445]

14. **Zanchetti A, Hansson L, Dahlöf B, Julius S, Ménard J, Warnold I, et al; HOT Study Group.** Benefit and harm of low-dose aspirin in well-treated hypertensives at different baseline cardiovascular risk. J Hypertens. 2002;20:2301-7. [PMID: 12409970]

15. **Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A; PPP Collaborative Group.** Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care. 2003;26:3264-72. [PMID: 14633812]

Annals of Internal Medicine

Current Author Addresses: Drs. Wolff and Miller: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, Maryland 20850.

Dr. Ko: Department of Pediatrics, New York Presbyterian Hospital–Cornell, 525 East 68th Street, M-610, New York, NY 10065.

Hierarchy of research design
  I: Properly conducted randomized, controlled trial (RCT)
  II-1: Well-designed controlled trial without randomization
  II-2: Well-designed cohort or case–control analytic study
  II-3: Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
  III: Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees
Design-specific criteria and quality category definitions
  Systematic reviews
    Criteria:
      Comprehensiveness of sources considered/search strategy used
      Standard appraisal of included studies
      Validity of conclusions
      Recency and relevance are especially important for systematic reviews
    Definition of ratings from above criteria:
      Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included
        studies; and valid conclusions.
      Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
      Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.
  Case–control studies
    Criteria:
      Accurate ascertainment of cases
      Nonbiased selection of cases/controls with exclusion criteria applied equally to both
      Response rate
      Diagnostic testing procedures applied equally to each group
      Measurement of exposure accurate and applied equally to each group
      Appropriate attention to potential confounding variables
    Definition of ratings based on criteria above:
      Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants, exclusion criteria applied equally to cases and controls,
        response rate equal to or greater than 80%, diagnostic procedures and measurements accurate and applied equally to cases and controls, and
        appropriate attention to confounding variables.
      Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rates less than 80% or attention to some but not all
        important confounding variables.
      Poor: Major section or diagnostic work-up biases, response rates less than 50%, or inattention to confounding variables.
  Randomized, controlled trials and cohort studies
    Criteria:
      Initial assembly of comparable groups
        For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
        For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception
          cohorts
      Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
      Important differential loss to follow-up or overall high loss to follow-up
      Measurements: equal, reliable, and valid (includes masking of outcome assessment)
      Clear definition of the interventions
      All important outcomes considered
    Definition of ratings based on above criteria:
      Good: Evaluates relevant available screening tests, uses a credible reference standard, interprets reference standard independently of screening test,
        reliability of test assessed, has few or handles indeterminate results in a reasonable manner, includes large number (more than 100) and broad
        spectrum of patients.
      Fair: Evaluates relevant available screening tests, uses reasonable although not best standard, interprets reference standard independent of screening test,
        moderate sample size (50–100 subjects) and a "medium" spectrum of patients.
      Poor: Has fatal flaw, such as use of an inappropriate reference standard, screening test improperly administered, biased ascertainment of reference standard,
        or very small sample size or very narrowly selected spectrum of patients.
  Diagnostic accuracy studies
    Criteria:
      Screening test relevant, available for primary care, adequately described
      Study uses a credible reference standard, performed regardless of test results
      Reference standard interpreted independently of screening test
      Handles indeterminate result in a reasonable manner
      Spectrum of patients included in study
      Sample size
      Administration of reliable screening test
    Definition of ratings based on above criteria:
      Good: Evaluates relevant available screening test, uses a credible reference standard, interprets reference standard independently of screening test, reliability
        of test assessed, has few or handles indeterminate results in a reasonable manner, includes large number (more than 100) and broad spectrum of
        patients with and without disease.
      Fair: Evaluates relevant available screening test, uses reasonable although not best standard, interprets reference standard independent of screening test,
        includes moderate sample size (50–100 subjects) and a "medium" spectrum of patients.
      Poor: Has fatal flaw, such as use of inappropriate reference standard, screening test improperly administered, biased ascertainment of reference standard, or
        very small sample size or very narrowly selected spectrum of patients.

* See references 6 and 7.