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

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Structured Abstract

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 increase 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, meta-analysis, and systematic reviews of aspirin versus control for the primary prevention of cardiovascular disease were selected to answer the following questions: Does aspirin in adults without known cardiovascular disease decrease coronary heart events, strokes, death from coronary heart events or stroke, or all-cause mortality? 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 one good quality RCT, one good quality meta-analysis, and 2 fair quality sub-analyses of RCTs demonstrates that aspirin use in patients without known cardiovascular disease (CVD) reduces the number of CVD events. Men in these studies experienced a reduction in the number of myocardial infarctions and women experienced a reduction in the number of ischemic strokes. Aspirin does not appear 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 GIBs, 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: There is limited new evidence on aspirin for theprimary prevention of CVD. The dose of aspirin used in the RCTs varied preventing the estimation of the most appropriate dose for primary prevention. Several of the RCTs were performed in health professionals potentially limiting generalizability.

Conclusions: Aspirin reduces the risk of myocardial infarctions in men and strokes in women. The risk of serious bleeding is increased with aspirin use.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the U.S.; 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 ages 40 and 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 out 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: for women the lifetime risk is 32%. The median age of first myocardial infarction is 65.8 years in men and 70.4 years for women. Women are more likely to die as a result of an myocardial infarction; 38% of women die within 1 year of a first myocardial infarction versus 25% of men. This is likely due in part to the older age in women at first myocardial infarction.(1, 2)

While incidence rates of stroke are higher in men than women, more women die of stroke than men because of their longer life expectancy. According to Framingham data the 10-year risk for initial ischemic stroke at age 55 is 1.8% for women and 2.4% for men; at age 65 the risk increases to 3.9% in women and 5.8% in men. The lifetime risk for ischemic stroke is greater in women than men between the ages of 55-75 (approximately 17-18% in women and 13-14% in men). After age 75 the risk decreases: 14% in women and 8% in men.

In 2002, the USPSTF strongly recommended that clinicians discuss aspirin with adults who are at increased risk for coronary heart disease.(3) The previous USPSTF recommendation on the prophylactic use of aspirin to prevent CVD was based on data from five RCTs that showed a 28% reduction in myocardial infarctions with aspirin use. Only two of the five studies included women. In 2005, data from the Women's Health Study provided important information about the benefit of aspirin in women. The Women's Health Study was a trial of 39,876 women randomized to aspirin or placebo and followed for 10 years for cardiovascular events.(4) With the availability of new data on benefits in women, the USPSTF decided to update its previous recommendation by re-evaluating 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 (KQ):

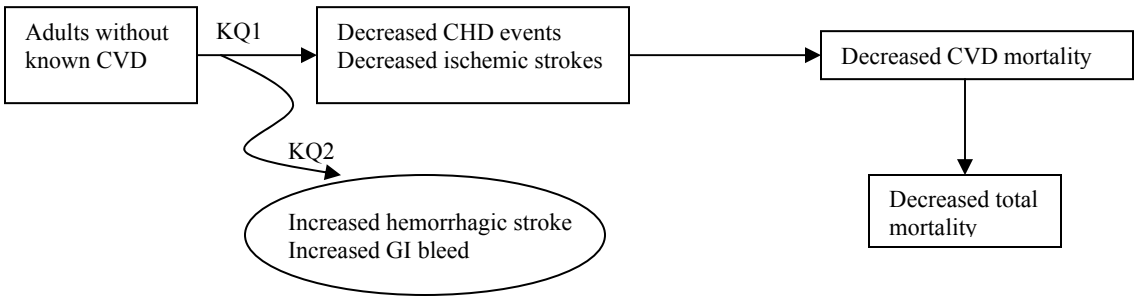
KQ1a. Does aspirin use in women without known cardiovascular disease decrease coronary heart events, strokes, death from coronary heart events or strokes, or all-cause mortality?

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?

Figure 1: Analytic framework: aspirin to prevent cardiovascular events



CVD = cardiovascular disease; CHD = coronary heart disease; GI – gastrointestinal

Methods

Data Sources and Searches

For evidence on the benefits of aspirin for the primary prevention of CVD events (KQ1), we performed a literature search in PubMed using the following MeSH terms: "aspirin" and "cardiovascular diseases." For evidence on the harms of aspirin for the primary prevention of CVD events (KQ2), we used the following MeSH terms: "aspirin," "cardiovascular diseases," "gastrointestinal hemorrhage," and "cerebral hemorrhage." We searched for studies published between January 1, 2001 and August 28, 2008. The literature search was limited to English language studies, human studies, non-pregnant adults, and the following study types for benefits: RCT, meta-analysis, and systematic review. For evidence on harms we limited the search to the following study types: RCT, case control, meta-analysis, and systematic review. In addition to the literature search, we looked for other relevant studies in the Cochrane database and 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. Disagreements on inclusion were resolved by consensus or the involvement of a third reviewer if necessary. In general, we included studies that met the following criteria: 1) evaluated aspirin versus control for the primary prevention of cardiovascular disease events in adults; 2) study population comprised only subjects with a history of CVD or at very high risk for CVD (e.g., patients with atrial fibrillation); 3) study population was generalizable to the United States primary care population; 4) risk estimates for 1 of the following outcomes were calculated: myocardial infarction, stroke, death from myocardial infarction or stroke, all-cause death for benefits; and gastrointestinal bleeding, serious bleeding episodes, and hemorrhagic stroke, cerebral hemorrhage for harms. We accepted studies that included subjects with a history of CVD or subjects at very high risk for CVD, but only if those studies reported separate results for subjects without a history of CVD or 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 from the studies: geographic location, duration of therapy, proportion of female subjects, dosage, control, blinding, outcome adjudication, additional therapies, demographics, and effect estimates on the previously listed outcomes. We evaluated the quality of the individual studies using previously published USPSTF criteria on internal and external validity (Appendix Table). (5-7) We evaluated RCTs on adequacy of randomization; maintenance of similar groups (includes attrition, crossovers, adherence, 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 study sample to the United States by consensus of 3 reviewers after discussions with the USPSTF on similarities between the healthcare 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 the baseline risk of 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.

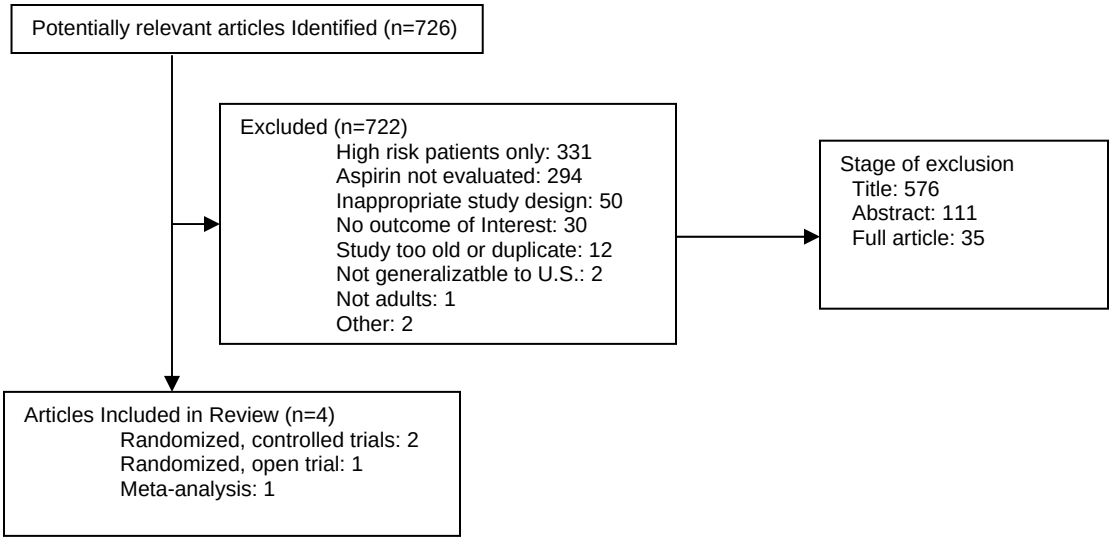
Role of the Funding Source

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

The 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.

Figure 2. Study flow diagram.



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 one 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 in 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 using an intention-to-treat process, and the follow-up rate was high. The investigators did not report information on rates of compliance 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 this 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 appropriate quality that we thought it unnecessary to duplicate the updated calculations. (5) Berger and colleagues' search differed from ours in that we searched for recent studies published since 2001 and we used the broader term *cardiovascular disease,* whereas Berger 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 prior to 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 Berger 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 in myocardial infarction (OR, 0.68 [CI, 0.54 to 0.86]); no statistically significant benefit was found in the reduction of ischemic stroke or cardiovascular mortality. Total mortality was not significantly reduced by aspirin use in men or women. We rated the Berger 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 two 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 in the group of former and never smokers compared to current smokers, who had a greater reduction in risk for ischemic strokes, 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 the following: systolic blood pressure 180 mm Hg or higher, systolic blood pressure 160 to 179 mm Hg, diastolic blood pressure 107 mm Hg or higher, diastolic blood pressure 104 to 106 mm Hg, or serum creatinine greater than 115 μmol/L (>1.3 mg/dL). Methodologic 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 diabetics 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 statistically significantly increased among men but not increased in women. Four studies provided information on the harms of aspirin for this key question.

The Women's Health Study (4) report that serious gastrointestinal bleeds (requiring transfusion) were more common in the women assigned to the aspirin 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 bleeds, episodes of peptic ulcer, self-reported hematuria, easy bruising, and epistaxis were statistically significantly more common in the group of women randomized to aspirin than in the women randomized to 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 above for the key question on benefits reported adverse events with aspirin use in the primary prevention of cardiovascular events in 51,342 women and 44,114 men.(8) 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 hemorrhagic strokes were not significantly increased in women but were significantly increased in 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 two 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. The Sacco 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 infarctions 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 likely 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 infarctions 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 CV events without an increased risk for major bleeding events. These findings contrast with the findings 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 trails 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 is dependent on baseline CVD risk and risk for gastrointestinal bleeding.

Table 1. 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)
Publication Date	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 to 115 mm Hg	Men and women with > 1 risk cardiovascular risk factor	Female health professionals
Patients *n*	5,139	22,071	5,085	18,790	4,495	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%)
Mean Duration of Therapy, *y*[a]	5.8	5	6.8	3.8	3.6	10.1
Aspirin Dosage	500 mg daily	325 mg every other day	75 mg daily (controlled release)	75 mg daily	100 mg daily	100 mg every other day
Additional Therapies	None	Beta-carotene (50% of patients)	Warfarin[b]	Felodipine with or without ACE inhibitor or beta blocker	Vitamin E (300 mg every day)	Vitamin E (600 IU every other day); beta-carotene (discontinued after 22.8 months)
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 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 or not 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.
Quality	Fair *	Good *	Good *	Good *	Fair *	Good

a Values given are means, except for the TPT value which is a median
b Data for patients on Warfarin not included in this table
* Quality rating from a USPSTF review conducted in 2002.
ACE = angiotensin-converting enzyme; BMD = British Male Doctors' Trial; GP = general practitioner; HOT = Hypertension Optimal Treatment trial; PHS = Physicians' Health Study; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; PPP = Primary Prevention Project; WHS = Women's Health Study

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Appendix

USPSTF Hierarchy of Research Design and Quality Rating Criteria (6, 7)

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
- 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 equally to or greater than 80 percent; 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 percent or attention to some but not all important confounding variables.

Poor: Major section or diagnostic work-up biases, response rates less than 50 percent, 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, 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 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 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has fatal flaw such as: Uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow 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) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; 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: Uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum patients.