

# Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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**Background:** Cardiovascular disease (CVD) is the leading cause of death in the United States.

**Purpose:** To update a systematic review about the benefits of aspirin for the primary prevention of cardiovascular events in adults aged 40 years or older and to evaluate effect modification in subpopulations.

**Data Sources:** MEDLINE, PubMed, Cochrane Central Register of Controlled Trials (January 2008 to January 2015), and Cochrane Database of Systematic Reviews.

**Study Selection:** Two investigators independently reviewed 3396 abstracts and 65 articles according to prespecified criteria. All included trials evaluated aspirin for the primary prevention of cardiovascular events.

**Data Extraction:** Two investigators assessed study quality; data were abstracted by 1 reviewer and checked by a second.

**Data Synthesis:** Two good-quality and 9 fair-quality randomized, controlled trials were identified. In analyses of all doses, aspirin reduced the risk for nonfatal myocardial infarction (MI) (relative risk [RR], 0.78 [95% CI, 0.71 to 0.87]) but not nonfatal stroke; aspirin showed little or no benefit for all-cause or cardio-

vascular mortality. Benefits began within the first 5 years. Older adults achieved greater relative MI reduction, but no other effect modifications were found in analyzed subpopulations. In trials with aspirin doses of 100 mg or less per day, the reduction in nonfatal MI benefit persisted (absolute risk reduction, 0.15 to 1.43 events per 1000 person-years) and a 14% reduction in nonfatal stroke benefit was noted, but no benefit was found for all-cause mortality (RR, 0.95 [CI, 0.89 to 1.01]) or cardiovascular mortality (RR, 0.97 [CI, 0.85 to 1.10]).

**Limitation:** Evidence for aspirin in primary prevention is heterogeneous and limited by rare events and few credible subgroup analyses.

**Conclusion:** The beneficial effect of aspirin for the primary prevention of CVD is modest and occurs at doses of 100 mg or less per day. Older adults seem to achieve a greater relative MI benefit.

**Primary Funding Source:** Agency for Healthcare Research and Quality.

*Ann Intern Med.* 2016;164:804-813. doi:10.7326/M15-2113 [www.annals.org](http://www.annals.org)  
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This article was published at [www.annals.org](http://www.annals.org) on 12 April 2016.

Cardiovascular disease (CVD) is the leading cause of mortality in the United States, accounting for about 1 in 3 deaths (1, 2). The evidence of net benefit of aspirin in secondary prevention is clear (3), and guidelines consistently recommend aspirin for persons with previous myocardial infarction (MI) or stroke (4–8). For primary prevention, however, guidelines vary about whether, and to which groups, aspirin should be recommended (6, 8–15). Recently, the U.S. Food and Drug Administration (16) stated that the primary prevention of MI should not be an indication for aspirin in any risk group (16).

In 2009, the U.S. Preventive Services Task Force (USPSTF) (17) endorsed aspirin for the primary prevention of CVD in sex-, age-, and outcome-specific recommendations. The current systematic review updates the evidence on the benefits of aspirin for the primary prevention of cardiovascular events with data from new trials. It also evaluates evidence for effect modification in subpopulations and varying aspirin dosages, formu-

lations, and durations of use. This review was used in conjunction with additional evidence about harms (18), a decision model (19), and concurrent reviews on aspirin and colorectal (20) and other types of cancer (21) to update USPSTF recommendations. Companion articles addressing these complementary issues should also be considered for a complete picture of the benefits and harms of aspirin for primary prevention of CVD.

## METHODS

We developed an analytic framework (Appendix Figure 1, available at [www.annals.org](http://www.annals.org)) that examined the effect of aspirin in reducing MI, stroke, or all-cause mortality (key question 1) and on associated increases in gastrointestinal bleeding, hemorrhagic stroke, or other serious harms (key question 2). This review addresses only key question 1; key question 2 is addressed in a review by Whitlock and colleagues (22) in this week's *Annals*. Potential effect modification in subpopulations was addressed a priori. Detailed methods and secondary outcome analyses are available in our full report (18).

## Data Sources and Searches

We searched MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials from Janu-

### See also:

Related articles . . . . . 777, 814, 826, 836  
Editorial comment . . . . . 846

ary 2008 to January 2015, which was supplemented by checking reference lists from relevant systematic reviews.

### Study Selection

Two reviewers independently reviewed 3396 citations and 65 full-text articles against a priori inclusion criteria (Appendix Figure 2, available at [www.annals.org](http://www.annals.org)). We included randomized, controlled trials (RCTs) and controlled clinical trials that examined the primary prevention of CVD with oral aspirin (a minimum of 75 mg every other day for 1 year or more) compared with placebo or no treatment in adults aged 40 years or older. We excluded interventions that included nonaspirin antithrombotic medications or aspirin as cotreatment with another active intervention. For multifactorial trials, we combined groups in which no evidence of interaction was found (23) and excluded cotreatment groups (24).

### Data Extraction and Quality Assessment

One reviewer extracted study-level data into standardized evidence tables, and a second checked data accuracy. Two independent reviewers critically appraised eligible articles using predefined criteria (25, 26), and a third resolved disagreements.

### Data Synthesis and Analysis

We examined 4 primary beneficial outcomes based on a priori decisions and the availability or consistency of outcome reporting across trials: nonfatal MI; nonfatal stroke (all types); CVD mortality, which was defined as a composite of death due to MI, stroke, and CVD; and all-cause mortality.

Due to the rarity of cardiovascular and all-cause mortality events (>1% but <10%), we used the Mantel-Haenszel fixed-effects model as the primary statistical analysis method (27). We assessed statistical heterogeneity using the  $I^2$  statistic.

For estimating absolute risk reduction and exploring potential variability among candidates for aspirin chemoprevention, we calculated absolute effects by simulating control group event rates for our primary outcomes. We simulated the event rate per 1000 person-years by dividing the number of events for each outcome by the person-years at risk (calculated by multiplying the sample size of the control group by the mean follow-up years), thereby assuming constant risks over time. We selected the minimum, median, and maximum event rates (excluding outliers and zeros) for each outcome and calculated the range of expected control event rates after aspirin intervention using the pooled relative risks (RRs) from the included CVD primary prevention trials evaluating aspirin doses of 100 mg or less per day (28).

### Subpopulation Methods

A priori subpopulations included age, sex, diabetes, smoking, race/ethnicity, CVD risk, decreased ankle-brachial index, elevated blood pressure, and elevated lipid levels. We abstracted subgroup analyses for these groups and considered their credibility based on the timing of planned analysis, interaction testing for heterogeneity

of treatment effect, baseline comparability, and control for confounders (29). To minimize confounding, we emphasized within-study comparisons over between-study comparisons. We evaluated subgroup analyses qualitatively because those reported were too limited to pool.

### Role of Funding Source

Agency for Healthcare Research and Quality staff provided oversight for the project and assisted in external review of the companion draft evidence synthesis. The USPSTF liaisons helped with scoping issues but were not involved in the conduct of the review.

## RESULTS

### Description of Included Trials

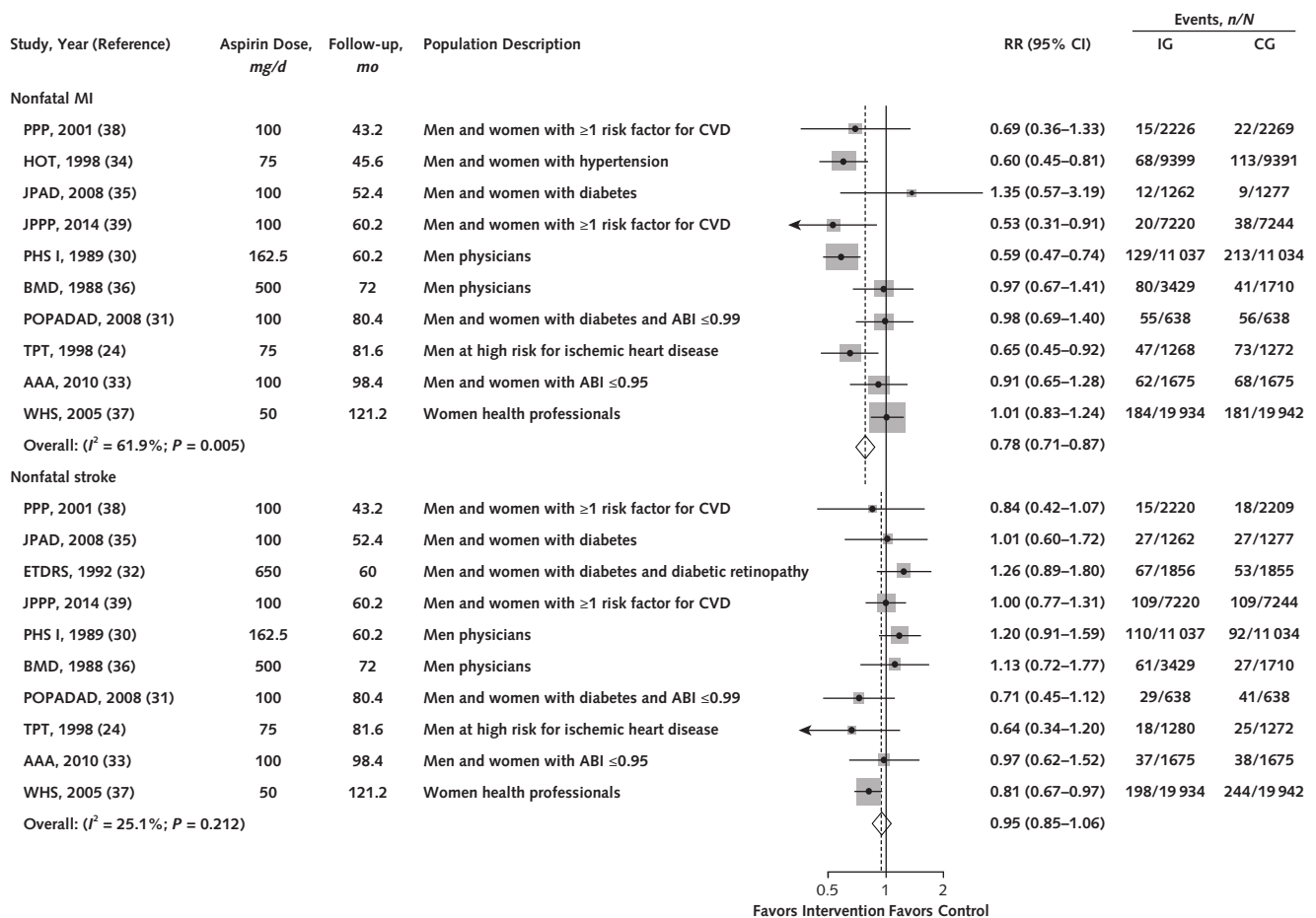
We found 11 eligible RCTs (2 good quality and 9 fair quality) that tested the benefits of aspirin for the primary prevention of cardiovascular events in 118 445 participants; trials ranged from 1276 to 39 876 participants (24, 30–39) (Appendix Table, available at [www.annals.org](http://www.annals.org)). Follow-up durations ranged from 3.6 to 10.1 years; most trials lasted 4 to 6 years. Eight of 11 trials studied aspirin doses of 100 mg or less per day or 100 mg or less every other day (24, 31, 33–35, 37–39). Older trials used higher doses (325 to 650 mg/d) (30, 32, 36). Three of 11 trials were conducted exclusively in men (24, 30, 36), and 1 was conducted exclusively in women (37). Where reported, the mean age of participants was 55 to 70.5 years, and the oldest participants recruited were aged 84 and 85 years (30, 35, 39).

Four trials (31, 33, 35, 39) published since the previous review for the USPSTF (17) focused on populations with cardiovascular risk factors, including diabetes and abnormal ankle-brachial index. The level of baseline cardiovascular risk in included populations, which was estimated by the annualized CVD event rate in control groups, varied widely—from 0.26% in the WHS (Women's Health Study) (37) to 4.09% in the ETDRS (Early Treatment Diabetic Retinopathy Study) (32).

### Effect of Aspirin on Nonfatal MI

Ten trials (24, 30, 31, 33–39) reported the effect of aspirin for the primary prevention of nonfatal MI. Meta-analysis showed a statistically significant 22% reduction in nonfatal MI, although heterogeneity was high (RR, 0.78 [95% CI, 0.71 to 0.87];  $I^2 = 61.9%$ ) (Figure 1, top). Three of the 4 largest trials (30, 34, 39) showed a statistically significant benefit despite being conducted in considerably different populations. The fourth large trial (WHS) showed an MI benefit in the older age group but not overall. One smaller trial conducted in high-risk men (40% were smokers) also showed an MI benefit, with additional smaller trials trending in this direction (33, 38). Two point estimates were near 1 (31, 36, 37), and 1 trial (35) that included few events showed a trend toward favoring the control group. Qualitative exploration of heterogeneity by aspirin dose, publication date, and cardiovascular risk as estimated by control group event rates did not clearly explain heterogeneity.

**Figure 1.** Benefits of aspirin for nonfatal MI and nonfatal stroke.



AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle-brachial index; BMD = British Male Doctors Trial; CG = control group; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; MI = myocardial infarction; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

**Effect of Aspirin on Nonfatal Stroke**

Ten trials that reported nonfatal stroke (all types) yielded mixed results, with RR estimates ranging from 0.64 to 1.26 (Figure 1, bottom). A pooled analysis from these 10 trials showed no difference in nonfatal stroke in the aspirin group compared with the control group, and heterogeneity was relatively low (RR, 0.95 [CI, 0.85 to 1.06];  $I^2 = 25.1\%$ ). Only the WHS (37) showed a statistically significant benefit for aspirin (RR, 0.81 [CI, 0.67 to 0.97]). This good-quality trial of 100 mg of aspirin every other day was conducted in a large sample of generally younger female health professionals (mean age was 55 years, with only 10% aged 65 or older). Other trials showed mixed results (24, 30–33, 35, 36, 38, 39).

**Effect of Aspirin on CVD Mortality**

Eleven trials contributed to our composite CVD mortality analysis. Pooled analysis showed no statistically significant effect (RR, 0.94 [CI, 0.86 to 1.03];  $I^2 = 8.8\%$ ) (Figure 2, top). Two trials showed a statistically

significant benefit of aspirin for reducing CVD mortality. One of these was a small fair-quality study ( $n = 2539$ ) conducted in men and women with diabetes in Japan with only 11 total cardiovascular deaths (hazard ratio, 0.10 [CI, 0.01 to 0.79]) (35). In a fair-quality trial (38) of patients with at least 1 CVD risk factor, the unadjusted RR (using raw numbers from our plots) neared significance. Further, the RR was statistically significant only when baseline characteristics were adjusted for (odds ratio, 0.48 [CI, 0.26 to 0.88]).

**Effect of Aspirin on All-Cause Mortality**

Eleven trials (24, 30–39) reported all-cause mortality, with all showing nonstatistically significant results. Ten trials reported RRs of 0.81 to 0.98, and 1 trial (24) reported an RR greater than 1. When all trials using all doses were pooled, aspirin had little or no all-cause mortality benefit (RR, 0.94 [CI, 0.89 to 0.99];  $I^2 = 0\%$ ) (Figure 2, bottom).

**Effect Modification by Dose, Duration, and Formulation**

**Dose**

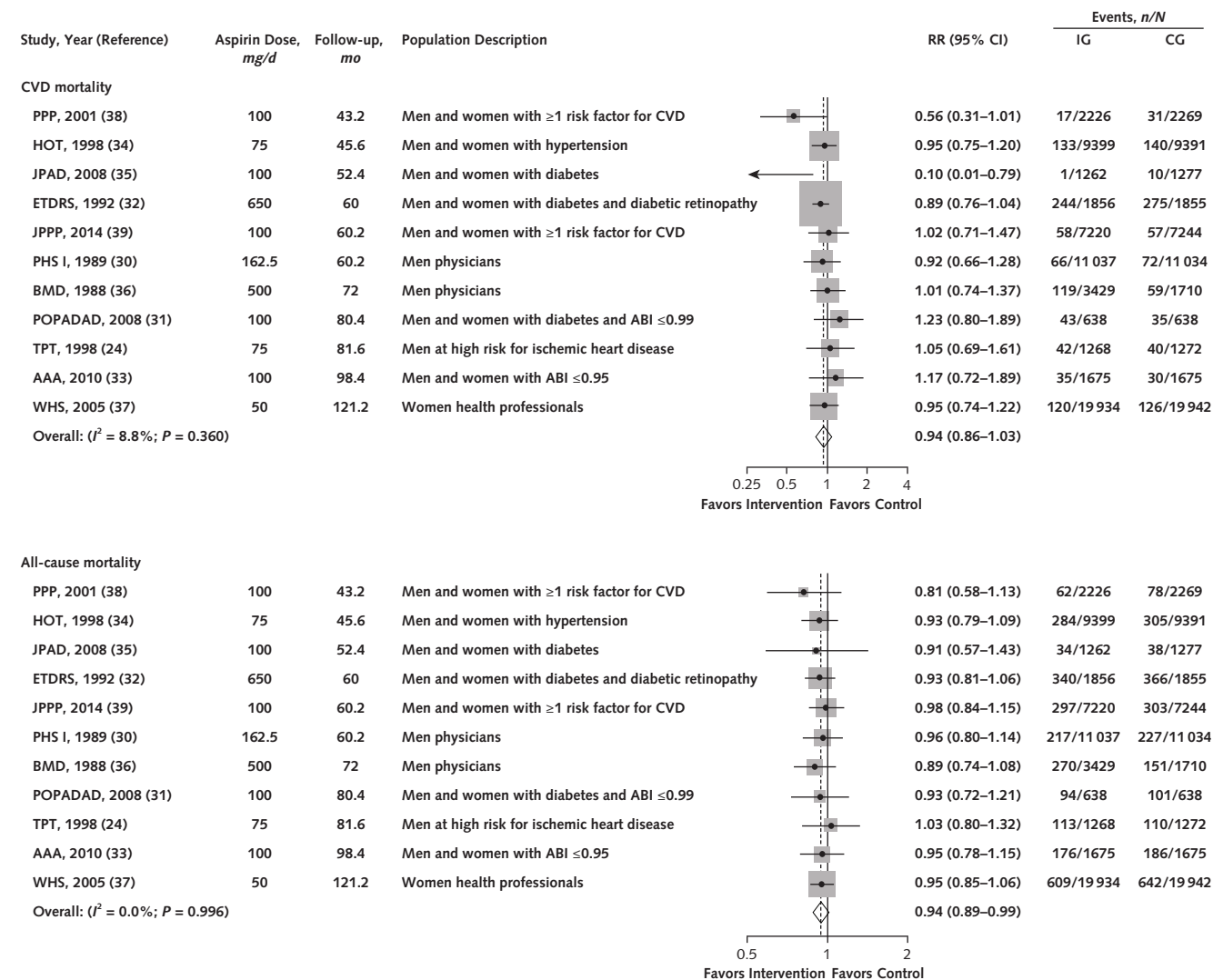
The 8 trials involving aspirin doses of 100 mg or less per day achieved a similar and statistically significant reduction in nonfatal MI (RR, 0.83 [CI, 0.74 to 0.94];  $I^2 = 54.5\%$ ). This mimics the trend we observed when pooling trials of all doses (RR, 0.78 [CI, 0.71 to 0.87];  $I^2 = 61.9\%$ ). Pooled analysis of trials using doses of 100 mg or less per day, however, showed a statistically significant reduction in nonfatal stroke ( $k = 7$ ; RR, 0.86 [CI, 0.76 to 0.98];  $I^2 = 0\%$ ) that was not observed when trials with all doses were pooled ( $k = 10$ ; RR, 0.95 [CI, 0.85 to 1.06];  $I^2 = 25.1\%$ ) (Table 1). Sensitivity analyses of trials with doses of 100 mg or less per day yielded similar

results for CVD mortality when compared with analyses using all doses. All-cause mortality achieved a similar point estimate in low-dose sensitivity analyses, but the CI widened to cross 1 ( $k = 8$ ; RR, 0.95 [CI, 0.89 to 1.01]).

**Duration**

Time-to-event data for various outcomes were available from 9 trials (24, 31-33, 35, 37, 39-41). Conclusions varied about the minimum time to benefit and benefit duration. Overall, available data suggest that any CVD benefit from aspirin begins within the first 1 to 5 years. We found no clear upper time limit to benefit because of inconsistent results and relatively short trial

**Figure 2.** Benefits of aspirin for CVD mortality and all-cause mortality.



AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle-brachial index; BMD = British Male Doctors Trial; CG = control group; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

**Table 1.** Pooled Estimates for All Included Trials and Trials With Aspirin Doses of  $\leq 100$  mg/d

Outcome	Studies, <i>k</i>	Participants, <i>n</i>	Mantel-Haenszel Fixed-Effects RR (95% CI)	<i>I</i> <sup>2</sup> , %
Nonfatal MI	10	114 734	0.78 (0.71-0.87)	61.9
	8	87 524	0.83 (0.74-0.94)	54.5
Nonfatal stroke	10	99 655	0.95 (0.85-1.06)	25.1
	7	68 734	0.86 (0.76-0.98)	0
CVD mortality	11	118 445	0.94 (0.86-1.03)	8.8
	8	87 524	0.97 (0.85-1.10)	30.0
All-cause mortality	11	118 445	0.94 (0.89-0.99)	0
	8	87 524	0.95 (0.89-1.01)	0

CVD = cardiovascular disease; MI = myocardial infarction; RR = relative risk.

durations. Five of these 9 trials had durations of 5 years or less.

### Formulation

No conclusions can be made about treatment formulation, which reflects the heterogeneity of trial design and sparse reporting of tablet formation in some trials.

### Differences in Subpopulations

All 11 trials (24, 30-39) addressed effect modification for at least 1 of 9 predefined subpopulations of interest. We also examined the Antithrombotic Trialists' (ATT) Collaboration's individual-participant data (IPD) meta-analysis (3) that pooled IPD from 6 of the 11 trials ( $n = 95\,000$ ; 660 000 person-years) (24, 30, 34, 36-38). Our body of evidence was sufficient to draw conclusions for only age, sex, and diabetes.

### Age

Data from age-specific subgroup analyses provided limited evidence suggesting a greater relative total MI benefit of aspirin in older age groups; results were mixed for other outcomes. Eight trials (30, 31, 33, 35, 37, 39, 40, 42) reported age-specific results, but only 4 (33, 35, 37, 39) clearly prespecified subanalyses. All 3 trials (30, 37, 40) that reported total MI by age showed a consistent pattern of greater RR reduction with older age. Two of these showed statistically significant interactions for effect by age (30, 37, 40). Of note, the WHS (37) showed a statistically significant 34% reduction in total MI only among women aged 65 years or older (RR, 0.66 [CI, 0.44 to 0.97]). None of the 3 trials that reported age-specific stroke events showed statistically significant differences in effect by age group, although rare events limited all analyses. The WHS was the only a priori analysis; it reported more stroke events but had no interaction testing for this outcome (24, 37, 40, 42). Six trials (31, 33, 35, 37, 39, 40) reported variously defined composite cardiovascular outcomes by age strata with conflicting results. The ATT IPD meta-analysis (3) did not show any heterogeneity of effect for serious vascular events based on age (<65 years vs.  $\geq 65$  years), although data were not adjusted for other factors, such as sex.

### Sex

Our critical appraisal of the literature about sex-specific subgroups concludes that no strong evidence supports treatment benefit modification for aspirin by sex or outcome. All 11 trials (24, 30-33, 35-37, 39-41) reported sex-specific results. In the 7 trials (31-35, 38, 39) that included both men and women, only 3 (33, 35, 39) clearly specified sex as an a priori subgroup. Five trials (30, 32, 37-39) adjusted for confounders. Three trials (32, 40, 41) conducted in both men and women reported MI by sex. For total MI, only the HOT (Hypertension Optimal Treatment) trial (40) showed a beneficial effect in men, but not women, in unadjusted analyses (RR for men, 0.58 [CI, 0.41 to 0.81]; RR for women, 0.81 [CI, 0.49 to 1.31]). In adjusted analysis, the Primary Prevention Project (41) showed a trend toward reduction of total MI in men and harm in women, and ETDRS (32) showed a greater although not statistically significant reduction in total MI in men but not women. In both studies, interaction tests were not performed and CIs between men and women overlapped. The same 3 trials reported stroke by sex. Risk reductions were greater in women in 2 of 3 trials (40, 41), but the results were not statistically significant for either sex and interaction testing was not performed. The ATT IPD meta-analysis showed that sex-specific differences in MI were no longer statistically significant after controlling for multiple comparisons. Of note, no statistically significant sex-specific difference in stroke was found before or after multiple comparisons were controlled for (3). The 5 additional trials not included in the ATT IPD meta-analysis (31-33, 35, 39) showed no difference in composite cardiovascular outcomes between the sexes.

### Diabetes

Available evidence does not clearly support the heterogeneity of aspirin's treatment effect based on diabetes status. Although 3 trials (31, 32, 35) specifically recruited patients with diabetes, others included such patients in recruiting a high cardiovascular risk population (38, 39). An additional 6 trials (30, 33, 37, 39, 43, 44) performed subgroup analyses, and only 2 (37, 39) clearly designated analyses a priori. Three of these 6 trials (30, 43, 44) performed interaction testing, and 4 (30, 37, 39, 44) adjusted for confounders. Seven trials examined aspirin's total MI effect in participants with diabetes: 3 (31, 32, 35) were conducted exclusively in participants with diabetes, and 4 (30, 37, 43, 44) were subgroup analyses. These trials showed no statistical difference in aspirin's effect by diabetes status, including the large Physicians' Health Study, which was the only trial that performed heterogeneity testing for this outcome ( $P = 0.22$ ). Three RCTs (31, 32, 35) that were conducted in participants with diabetes only and 3 subanalyses (37, 43, 44) examined stroke. The 3 RCTs showed no statistically significant stroke difference, although they were underpowered for this outcome. In a priori subgroup analysis, the WHS showed that the beneficial effect of aspirin on total stroke (adjusted RR,

**Table 2.** Absolute Risk Reduction With Low-Dose Aspirin Use  $\leq 10$  Years

Outcome	Risk Level*	Baseline Risk for Outcome, events per 1000 person-years	RR (95% CI)†	Events Prevented per 1000 Person-Years (95% CI), n‡
All-cause mortality (k = 8)	Low	3.19	0.95 (0.89 to 1.01)	0.16 (−0.03 to 0.35)
	Median	8.55		0.43 (−0.09 to 0.94)
	High	13.54		0.68 (−0.14 to 1.49)
CVD mortality (k = 8)	Low	0.63	0.97 (0.85 to 1.10)	0.02 (−0.06 to 0.09)
	Median	2.18		0.07 (−0.22 to 0.33)
	High	4.62		0.14 (−0.46 to 0.69)
Nonfatal stroke (k = 7)	Low	1.21	0.86 (0.76 to 0.98)	<b>0.17 (0.02 to 0.29)</b>
	Median	2.83		<b>0.40 (0.06 to 0.68)</b>
	High	4.84		<b>0.68 (0.10 to 1.16)</b>
Nonfatal MI (k = 8)	Low	0.90	0.83 (0.74 to 0.94)	<b>0.15 (0.05 to 0.23)</b>
	Median	2.69		<b>0.46 (0.16 to 0.70)</b>
	High	8.44		<b>1.43 (0.51 to 2.19)</b>

CVD = cardiovascular disease; MI = myocardial infarction; RR = relative risk.

\* Low (minimum), median, and high (maximum) control group rate for each outcome, excluding zeros and outliers.

† Based on aspirin doses  $\leq 100$  mg/d in primary CVD prevention trials.

‡ Boldface data represent clearly prevented events (i.e., 95% CI does not include both caused and prevented events).

0.83 [CI, 0.69 to 0.99]) seemed to be largely driven by a benefit in participants with diabetes (adjusted RR, 0.46 [CI, 0.25 to 0.85]) rather than those without diabetes (adjusted RR, 0.87 [CI, 0.72 to 1.05]). These CIs overlapped, however, and no interaction testing was reported. Subgroup analysis in the HOT study reported nonsignificant interaction testing for total stroke based on diabetes status, and the trial's main findings showed no difference in total stroke in all participants receiving aspirin compared with the control group. Subgroup analyses in the Primary Prevention Project were post hoc, were limited by few events, and showed overlapping CIs in persons with and without diabetes. No clear difference was found in aspirin's effect on CVD mortality in populations with diabetes compared with those without diabetes because of mixed results and few events (31, 32, 35, 43, 44). Results for study-defined composite CVD outcomes were generally nonsignificant (31–33, 35, 37, 39, 43, 44). The ATT IPD meta-analysis of serious vascular events (3) similarly showed no heterogeneity of effect by diabetes status (ratio of yearly event rates for diabetic participants, 0.88 [CI, 0.67 to 1.15], and nondiabetic participants, 0.87 [CI, 0.79 to 0.96]). Three trials (31, 32, 35) conducted exclusively in participants with diabetes showed no all-cause mortality benefit of aspirin. Although 2 subanalyses (43, 44) showed no evidence for all-cause mortality effect modification, few trials were powered for this outcome.

### Absolute Risk Reduction

Persons with higher baseline CVD risk are expected to experience greater benefit (more events prevented) from aspirin. We simulated control group event rates for all primary beneficial outcomes within a 10-year period (Table 2), and the range of events prevented based on the low, median, and high baseline event rates seen in the included trials.

Across the range of baseline event rates, for each 1000 person-years of low-dose aspirin use, absolute benefits were modest for nonfatal MIs and nonfatal strokes prevented (0.15 to 1.43 person-years and 0.17 to 0.68 person-years, respectively); for all risk levels, these nonfatal events were prevented. Aspirin did not

clearly prevent all-cause mortality or CVD death for any risk level. Wide CIs around most of the estimated event rates suggest uncertainty due to small numbers and probably heterogeneity of aspirin's effect among groups that were relatively and crudely categorized by baseline event rates. These simulations do not include considerations of harm and the potential long-term benefit from reduced colorectal cancer incidence because of its delayed effect beyond 10 years; these issues are addressed in companion articles (22, 45).

### DISCUSSION

Our meta-analysis of 11 primary prevention trials showed that aspirin reduces the risk for nonfatal MI by 22%, which confirms the conclusions of several other published meta-analyses (3, 46–49). This nonfatal MI benefit begins sometime within the first 5 years of aspirin use. When pooling trials with average daily doses of 100 mg or less, this benefit persisted and a 14% benefit for nonfatal stroke emerged. Although some of the hemorrhagic strokes caused by aspirin can be mitigated by reducing the dose, they were so rare that we cannot confirm this hypothesis. Given that this nonfatal stroke benefit is not seen with all doses of aspirin, the certainty of the stroke benefit is weaker than the persistent nonfatal MI benefit across all doses. Our analysis showed little or no benefit on CVD mortality or all-cause mortality, which is consistent with other findings (46, 47, 49).

Our critical appraisal of the subpopulation literature aimed to identify any subpopulation for whom the net benefit would be maximized—subpopulations for whom either the RR reduction achieved from aspirin is higher than that of the average population or the baseline risk for CVD events is higher than that for the average population and high enough to outweigh the serious bleeding risks. We found that very few a priori subgroup analyses were available, even fewer trials performed interaction testing, and none adequately controlled for important confounders. The best information came from controlled multivariable analyses

based on IPD meta-analysis from all available, applicable trials. The ATT IPD meta-analysis suggests that, among the 6 CVD primary prevention trials examined, there is no heterogeneity of effect for serious vascular events by sex, age, or diabetes.

On the basis of relatively limited and generally lower-quality evidence, we conclude that the most consistent evidence of subpopulation differences in aspirin use was an enhanced effect on MI in older age groups. A large ongoing trial of 19 000 participants aged 70 years or older may confirm this finding (50). We found no clear effect modification based on diabetes status, although the 3 trials that were conducted exclusively in patients with diabetes found nonstatistically significant results for the composite CVD outcomes that the trials were designed to detect (31, 32, 35). Prior systematic reviews that have pooled 3 to 6 trials in populations or subpopulations with diabetes have shown no statistically significant reduction in CVD events, total MI, or total stroke (51–55). Our best conclusion is that persons with diabetes will have similar benefits as those with similar CVD risk profiles. Two large RCTs (together enrolling >20 000 patients with diabetes) (56, 57) that are in progress may definitively answer the question about aspirin's primary prevention effectiveness in populations with diabetes. Our critical appraisal of sex-specific evidence showed that the conclusions of prior study-level meta-analyses (41) (that women achieve a stroke benefit and men achieve an MI benefit from aspirin) were based on subanalyses with serious limitations. In the WHS, aspirin reduced ischemic stroke in women; however, MI benefit was also achieved in those aged 65 years or older (37). Thus, lack of age adjustment and that WHS participants were relatively young could have led to prior sex- and outcome-specific conclusions. The ATT IPD and subsequent meta-analyses (41, 49) have confirmed the findings of no robust sex- or outcome-specific differences in major CVD events. Further, the lack of heterogeneity of treatment effect in the literature about secondary aspirin prevention puts such sex-specific findings in question (3).

An accompanying article by Whitlock and colleagues (22) reports findings from a systematic review about the harms of aspirin. Taken together, these data suggest that individual consideration of the potential for harms and benefits is prudent, particularly for persons at low to moderate CVD risk. Recent guidelines for aspirin use in primary prevention are conflicting. Although some recommend aspirin for persons meeting age, 10-year CVD, coronary heart disease, or stroke risk thresholds (11, 58, 59), others recommend against aspirin for primary prevention (6, 10, 14).

Tools that effectively identify patients at higher CVD risk are recommended in primary prevention (60) and may reduce potential overuse of aspirin by persons not likely to benefit (61). As we have reported elsewhere (18), consideration of 10-year CVD risk (as opposed to coronary heart disease or stroke risk separately) may simplify clinical application. Although no current tool is ideal, the American College of Cardiology/American Heart Association pooled cohort equations

(60) predict 10-year risk for a first hard atherosclerotic CVD event, which is defined as nonfatal MI, coronary heart disease death, and fatal or nonfatal stroke. This tool is derived from a more racially and ethnically diverse, contemporary population than the Framingham calculator, enabling race- and sex-specific equations for black and white persons (although not Hispanic, Asian, or other persons), and has been externally validated in U.S. populations (60, 62–64). Critics have voiced concerns about the model's calibration because of overprediction (62–65). Several investigators have characterized the model's discrimination as moderate at best using c-statistics (62–65). A more recent analysis, however, found that use of the pooled cohort equations (as part of the American College of Cardiology/American Heart Association treatment guidelines) more accurately and efficiently identified increased CVD risk than the Framingham risk score (as part of the Adult Treatment Panel III treatment guidelines) (66). Its application clinically and in policy recommendations, however, should be informed by the potential for overprediction.

The literature has several limitations. The 11 primary prevention studies are heterogeneous in terms of aspirin dose; duration of therapy; baseline population characteristics; comorbid conditions; and, most important, baseline CVD risk at trial entry. Moreover, many included trials are decades old and could reflect populations with higher smoking rates and lower use of risk-modifying medications, such as statins and antihypertensive agents. In addition, trials were powered for composite outcomes combining fatal and nonfatal events of varying severity (67), with limited power for relatively rare individual outcomes in these primary prevention populations. Nonetheless, we carefully coded these outcomes to enhance comparability across trials and pooled results. Because of the relatively short trial durations and lack of similar time-to-event data reporting, we could not precisely determine the minimum time to benefit other than to conclude that the cardiovascular-related benefits (that is, nonfatal MI) occur during the first 5 years of therapy. As such, whether the nonfatal MI benefit continues to accrue at a constant rate after 5 to 10 years of aspirin use remains unclear because follow-up in most studies was 4 to 6 years. One trial provided extended observational follow-up at 18 years and confirmed the results of its outcomes at 10 years (68). We found that sufficient aspirin dosing for primary prevention is probably 75 to 100 mg/d. Limited data suggest that dosing every other day may also achieve CVD benefits.

Pooled analysis from 11 trials in healthy and higher-risk populations shows that low-dose aspirin has little or no effect on CVD mortality or all-cause mortality. Aspirin does provide a modest benefit in reducing nonfatal MI and nonfatal stroke events.

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**Note:** This review was conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ). The staff of AHRQ provided oversight for the project and assisted in the external review of the companion draft evidence synthesis.

**Disclaimer:** The views expressed in this manuscript do not represent and should not be construed to represent a determination or policy of the AHRQ or the U.S. Department of Health and Human Services.

**Acknowledgment:** The authors thank the following persons for their contributions to this project: AHRQ staff; the U.S. Preventive Services Task Force; Steven Teutsch, MD, Diana Petitti, MD, MPH, Nancy R. Cook, ScD, Mark Alberts, MD, FAHA, and colleagues at the Centers for Disease Control and Prevention's National Center for Chronic Disease Prevention and Health Promotion who provided expert review of the report; and Maya Rowland, MPH, Brittany Burda, MPH, Keshia Bigler, BS, Kevin Lutz, MFA, and Smyth Lai, MLS, at the Kaiser Permanente Center for Health Research.

**Financial Support:** By contract HHS-290-2012-00015-EPC4, Task Order 2, from AHRQ.

**Disclosures:** The authors report a contract with AHRQ during the conduct of the study. Disclosures can also be viewed at [www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-2113](http://www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-2113).

**Reproducible Research Statement:** *Study protocol:* Available at [www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan-aspirin-to-prevent-cardiovascular-diseases/aspirin-to-prevent-cardiovascular-disease-and-cancer](http://www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan-aspirin-to-prevent-cardiovascular-diseases/aspirin-to-prevent-cardiovascular-disease-and-cancer). *Statistical code:* Not available. *Data set:* Available at [www.ncbi.nlm.nih.gov/books/NBK321623](http://www.ncbi.nlm.nih.gov/books/NBK321623).

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## References

- Heron M. Deaths: leading causes for 2010. *Natl Vital Stat Rep*. 2013;62:1-96. [PMID: 24364902].
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-322. [PMID: 25520374] doi:10.1161/CIR.0000000000000152
- Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al; Antithrombotic Trialists' (ATT) Collaboration. 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. [PMID: 19482214] doi:10.1016/S0140-6736(09)60503-1
- Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al; World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other

Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124:2458-73. [PMID: 22052934] doi:10.1161/CIR.0b013e318235eb4d

- Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160-236. [PMID: 24788967] doi:10.1161/STR.0000000000000024
- Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al; European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635-701. [PMID: 22555213] doi:10.1093/eurheartj/ehs092
- National Institute for Health and Care Excellence. Secondary prevention in primary and secondary care for patients following a myocardial infarction. Partial update of NICE CG48. London: Royal College of Physicians; 2013. Accessed at [www.nice.org.uk/guidance/cg172/resources/myocardial-infarction-secondary-prevention-full-guideline3](http://www.nice.org.uk/guidance/cg172/resources/myocardial-infarction-secondary-prevention-full-guideline3) on 8 March 2016.
- JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart*. 2014;100 Suppl 2:ii1-ii67. [PMID: 24667225] doi:10.1136/heartjnl-2014-305693
- Matthys F, De Backer T, De Backer G, Stichele RV. Review of guidelines on primary prevention of cardiovascular disease with aspirin: how much evidence is needed to turn a tanker? *Eur J Prev Cardiol*. 2014;21:354-65. [PMID: 23610452] doi:10.1177/2047487312472077
- Scottish Intercollegiate Guidelines Network. SIGN 129: Anti-thrombotics: indications and management. Edinburgh, Scotland: SIGN; 2013. Accessed at [www.sign.ac.uk/guidelines/fulltext/129](http://www.sign.ac.uk/guidelines/fulltext/129) on 8 March 2016.
- Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al; American Heart Association Stroke Council. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:517-84. [PMID: 21127304] doi:10.1161/STR.0b013e3181fcb238
- Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, et al; American Diabetes Association. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care*. 2010;33:1395-402. [PMID: 20508233] doi:10.2337/dc10-0555
- Guidelines and Protocols Advisory Committee. Cardiovascular disease: primary prevention. Victoria, British Columbia, Canada: British Columbia Ministry of Health; 2014. Accessed at [www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/cardiovascular-disease](http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/cardiovascular-disease) on 8 March 2016.
- Guidelines and Protocols Advisory Committee. Diabetes care. Victoria, British Columbia, Canada: British Columbia Ministry of Health; 2015. Accessed at [www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/diabetes](http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/diabetes) on 8 March 2016.
- World Health Organization. Cardiovascular disease: prevention of cardiovascular disease (CVDs): pocket guidelines for assessment and management of cardiovascular risk. Geneva: World Health Organization; 2007. Accessed at [www.who.int/cardiovascular\\_diseases/publications/Pocket\\_GL\\_information/en](http://www.who.int/cardiovascular_diseases/publications/Pocket_GL_information/en) on 16 April 2014.
- U.S. Food and Drug Administration. Citizen Petition Denial Response From FDA to Bayer Healthcare LLC. Docket ID: FDA-1977-N-



0018. Silver Spring, MD: U.S. Food and Drug Administration; 2014. Accessed at [www.regulations.gov/#!documentDetail;D=FDA-1977-N-0018-0101](http://www.regulations.gov/#!documentDetail;D=FDA-1977-N-0018-0101) on 3 March 2016.
17. **U.S. Preventive Services Task Force.** Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2009;150:396-404. [PMID: 19293072]
18. **Guirguis-Blake JM, Evans CV, Senger CA, Rowland MG, O'Connor EA, Whitlock EP.** Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 131. AHRQ Publication No. 13-05195-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015. Accessed at [www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079304](http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079304) on 3 March 2016.
19. **Dehmer SP, Maciosek MV, Flottemesch TJ.** Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: A Decision Analysis. AHRQ Publication No. 15-05229-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015. Accessed at [www.ncbi.nlm.nih.gov/books/NBK321651](http://www.ncbi.nlm.nih.gov/books/NBK321651) on 3 March 2016.
20. **Chubak J, Kamineni A, Buist DSM, Anderson ML, Whitlock EP.** Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 133. AHRQ Publication No. 15-05228-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
21. **Whitlock EP, Williams SB, Burda BU, Feightner A, Beil T.** Aspirin Use in Adults: Cancer, All-Cause Mortality, and Harms. A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 132. AHRQ Publication No. 13-05193-EF-1. Rockville, MD: Agency for Healthcare Research and Quality 2015. Accessed at [www.ncbi.nlm.nih.gov/books/NBK321643](http://www.ncbi.nlm.nih.gov/books/NBK321643) on 3 March 2016.
22. **Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV.** Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2016;164:826-34. doi:10.7326/M15-2112
23. **Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP.** Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer. An updated systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2013;159:824-34. [PMID: 24217421]
24. 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]
25. **U.S. Preventive Services Task Force.** U.S. Preventive Services Task Force procedure manual. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
26. **National Institute for Health and Care Excellence.** The guidelines manual. London: National Institute for Health and Care Excellence; 2012.
27. **Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ, et al.** Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol.* 2011;64:1187-97. [PMID: 21477993] doi:10.1016/j.jclinepi.2010.08.010
28. **Cochrane Handbook for Systematic Reviews of Interventions.** Chichester, UK: J Wiley; 2009.
29. **Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F, et al.** Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ.* 2012;344:e1553. [PMID: 22422832] doi:10.1136/bmj.e1553
30. **Steering Committee of the Physicians' Health Study Research Group.** Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med.* 1989;321:129-35. [PMID: 2664509]
31. **Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al; Prevention of Progression of Arterial Disease and Diabetes Study Group.** 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. [PMID: 18927173] doi:10.1136/bmj.a1840
32. **Early Treatment Diabetic Retinopathy Study report 14. ETRS Investigators.** Aspirin effects on mortality and morbidity in patients with diabetes mellitus. *JAMA.* 1992;268:1292-300. [PMID: 1507375]
33. **Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, et al; Aspirin for Asymptomatic Atherosclerosis Trialists.** 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. [PMID: 20197530] doi:10.1001/jama.2010.221
34. **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]
35. **Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators.** Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA.* 2008;300:2134-41. [PMID: 18997198] doi:10.1001/jama.2008.623
36. **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]
37. **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]
38. **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]
39. **Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, et al.** Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA.* 2014;312:2510-20. [PMID: 25401325] doi:10.1001/jama.2014.15690
40. **Kjeldsen SE, Kolloch RE, Leonetti G, Mallion JM, Zanchetti A, Elmfeldt D, et al.** Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid. The HOT study. *Hypertension Optimal Treatment. J Hypertens.* 2000;18:629-42. [PMID: 10826567]
41. **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]
42. **Meade TW, Brennan PJ.** Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. *BMJ.* 2000;321:13-7. [PMID: 10875825]
43. **Zanchetti A.** Aspirin and antiplatelet drugs in the prevention of cardiovascular complications of diabetes. In: Mogensen CE, ed. *Pharmacotherapy of Diabetes: New Developments: Improving Life and Prognosis for Diabetic Patients.* New York: Springer Science and Business Media; 2007:211-18.
44. **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]
45. **Chubak J, Whitlock EP, Williams SB, Kamineni A, Burda BU, Buist DSM, et al.** Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2016;164:814-25. doi:10.7326/M15-2117
46. **Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al.** Effect of aspirin on vascular and nonvascular

- outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med.* 2012;172:209-16. [PMID: 22231610] doi:10.1001/archinternmed.2011.628
47. Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med.* 2011;124:621-9. [PMID: 21592450] doi:10.1016/j.amjmed.2011.01.018
48. Bartolucci AA, Tendera M, Howard G. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol.* 2011;107:1796-801. [PMID: 21481826] doi:10.1016/j.amjcard.2011.02.325
49. Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR. 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. [PMID: 21742097] doi:10.1016/j.ahj.2011.04.006
50. Nelson M, Reid C, Beilin L, Donnan G, Johnston C, Krum H, et al; Aspirin in Reducing Events in the Elderly (ASPREE) Study Group. Rationale for a trial of low-dose aspirin for the primary prevention of major adverse cardiovascular events and vascular dementia in the elderly: Aspirin in Reducing Events in the Elderly (ASPREE). *Drugs Aging.* 2003;20:897-903. [PMID: 14565783]
51. Zhang C, Sun A, Zhang P, Wu C, Zhang S, Fu M, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. *Diabetes Res Clin Pract.* 2010;87:211-8. [PMID: 19853947] doi:10.1016/j.diabres.2009.09.029
52. Younis N, Williams S, Ammori B, Soran H. Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus: a meta-analysis. *Expert Opin Pharmacother.* 2010;11:1459-66. [PMID: 20429671] doi:10.1517/14656561003792538
53. Stavrakis S, Stoner JA, Azar M, Wayangankar S, Thadani U. Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Am J Med Sci.* 2011;341:1-9. [PMID: 21191260] doi:10.1097/MAJ.0b013e3181f1fba8
54. De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ.* 2009;339:b4531. [PMID: 19897665] doi:10.1136/bmj.b4531
55. Butalia S, Leung AA, Ghali WA, Rabi DM. Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2011;10:25. [PMID: 21453547] doi:10.1186/1475-2840-10-25
56. ASCEND: A Study of Cardiovascular Events in Diabetes [clinical trial]. Accessed at <https://clinicaltrials.gov/ct2/show/NCT00135226> on 8 March 2016.
57. De Berardis G, Sacco M, Evangelista V, Filippi A, Giorda CB, Tognoni G, et al; ACCEPT-D Study Group. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials.* 2007;8:21. [PMID: 17725825]
58. Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg FA, Alonso-Coello P, et al; American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e637S-68S. [PMID: 22315274] doi:10.1378/chest.11-2306
59. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American heart association. *Circulation.* 2011;123:1243-62. [PMID: 21325087] doi:10.1161/CIR.0b013e31820faaf8
60. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2935-59. [PMID: 24239921] doi:10.1016/j.jacc.2013.11.005
61. VanWormer JJ, Miller AW, Rezkalla SH. Aspirin overutilization for the primary prevention of cardiovascular disease. *Clin Epidemiol.* 2014;6:433-40. [PMID: 25506245] doi:10.2147/CLEP.S72032
62. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. *JAMA.* 2014;311:1406-15. [PMID: 24682252] doi:10.1001/jama.2014.2630
63. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA.* 2014;311:1416-23. [PMID: 24681960] doi:10.1001/jama.2014.2632
64. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med.* 2015;162:266-75. [PMID: 25686167] doi:10.7326/M14-1281
65. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet.* 2013;382:1762-5. [PMID: 24268611] doi:10.1016/S0140-6736(13)62388-0
66. Pursnani A, Massaro JM, D'Agostino RB Sr, O'Donnell CJ, Hoffmann U. Guideline-Based Statin Eligibility, Coronary Artery Calcification, and Cardiovascular Events. *JAMA.* 2015;314:134-41. [PMID: 26172893] doi:10.1001/jama.2015.7515
67. Ferreira-González I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *BMJ.* 2007;334:786. [PMID: 17403713]
68. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Ann Intern Med.* 2013;159:77-85. [PMID: 23856681] doi:10.7326/0003-4819-159-2-201307160-00002

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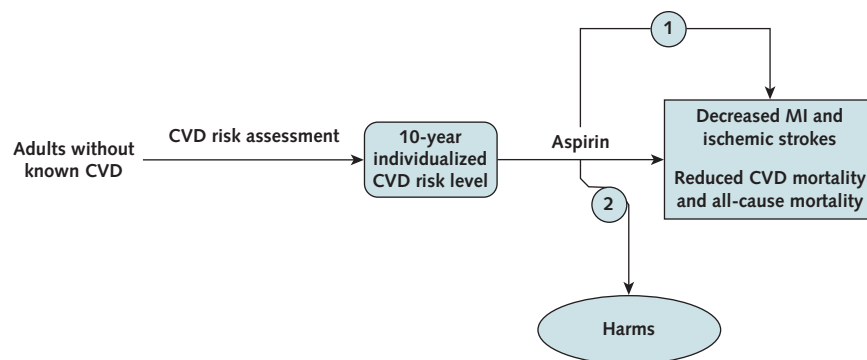
Final approval of the article: J. Guirguis-Blake, C.V. Evans, C.A. Senger, E.A. O'Connor, E.P. Whitlock.

Statistical expertise: E.A. O'Connor.

Administrative, technical, or logistic support: C.V. Evans, C.A. Senger.

Collection and assembly of data: J. Guirguis-Blake, C.V. Evans, C.A. Senger, E.P. Whitlock.

**Appendix Figure 1.** Analytic framework with key questions.

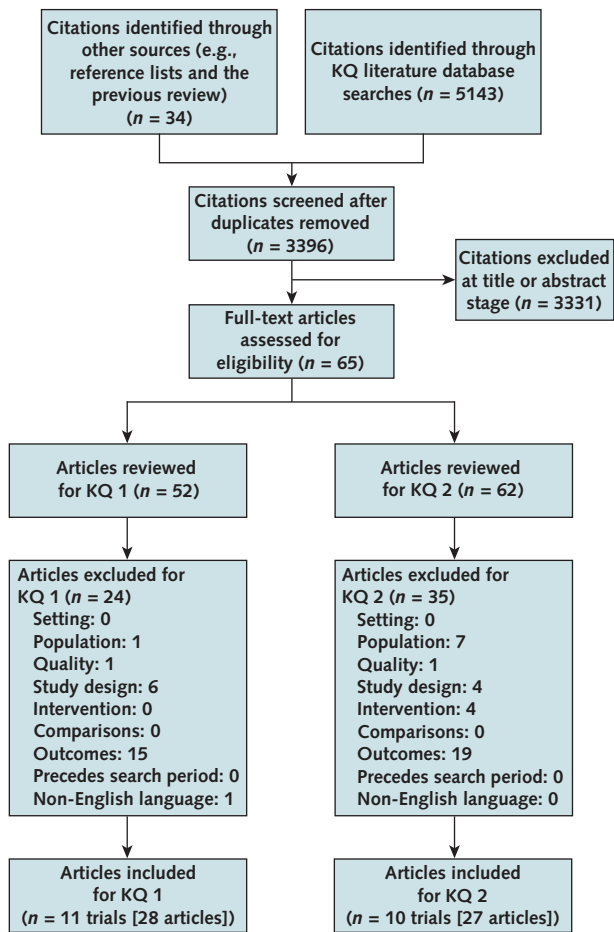


#### Key Questions

1. Does regular aspirin use in patients without known CVD reduce MI, stroke, death from MI or stroke, or all-cause mortality?
  - a. Does the effect vary between a priori subgroups: age, sex, smoking status, race/ethnicity, 10-year cardiovascular risk, or related risk conditions (e.g., diabetes mellitus, decreased ankle brachial index, or elevated blood pressure)?
  - b. Does the effect vary by dose, formulation (i.e., enteric-coated), or duration of use?
2. Does regular aspirin use increase gastrointestinal bleeding, hemorrhagic stroke, or other serious harms (e.g., age-related macular degeneration)?
  - a. Does the effect vary between a priori subgroups: age, sex, smoking status, race/ethnicity, 10-year cardiovascular risk, related risk conditions (e.g., diabetes mellitus, decreased ankle brachial index, or elevated blood pressure), gastrointestinal bleeding or hemorrhagic stroke risk factors (including a history of gastrointestinal bleeding, ulcers, or NSAID use), or concomitant medication use (NSAIDs, SSRIs, or PPIs)?
  - b. Does the effect vary by dose, formulation, or duration of use?

CVD = cardiovascular disease; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PPI = protein-pump inhibitor; SSRI = selective serotonin reuptake inhibitor.

**Appendix Figure 2.** Summary of evidence search and selection.



KQ = key question.

**Appendix Table. Methodological and Intervention Characteristics of Included Trials for Primary Prevention of Cardiovascular Events**

Study, Year (Reference)	Quality	Country	Randomly Assigned, n	Study Design	Inclusion	Aspirin Dose and Formulation	Mean Follow-up, y	Control Group CVD Event Rate per Year, % <sup>¶</sup>
BMD, 1988 (36)	Fair	United Kingdom	5139	RCT	Male physicians	500 mg/d, unspecified*	6	1.24
PHS I, 1989 (30)	Good	United States	22 071	2 × 2 RCT, β-carotene	Male physicians aged 40-84 y	325 mg every other day, tablet, not enteric-coated†	5	0.67
ETDRS, 1992 (32)	Fair	United States	3711	2 × 2 RCT, early or delayed photocoagulation	Diabetics with diabetic retinopathy aged 18-70 y	650 mg/d, tablet, not enteric-coated	5	4.09
HOT, 1998 (34, 40, 43)	Fair	26 countries§	18 790	3 × 2 RCT, hypertension treatment goals	Hypertensive men and women aged 50-80 y	75 mg/d, unspecified	3.8	1.03
TPT, 1998 (24, 42)	Fair	United Kingdom	2540	2 × 2 RCT, warfarin	Men at the top 20% or 25% of CVD risk score aged 45-69 y	75 mg/d, controlled release capsule	6.8	1.60
PPP, 2001 (38, 41, 44)	Fair	Italy	4495	2 × 2 RCT, vitamin E	Men and women aged ≥50 y with ≥1 CVD risk factor	100 mg/d, enteric-coated tablet	3.6	0.78
WHS, 2005 (37, 69)	Good	United States	39 876	2 × 2 RCT, vitamin E	Women health professionals aged ≥45 y	100 mg every other day, tablet, not enteric-coated	10.1	0.26
JPAD, 2008 (35)	Fair	Japan	2539	RCT	Men and women with diabetes aged 30-85 y	100 mg/d, tablet, not enteric-coated‡	4.37	0.82
POPADAD, 2008 (31)	Fair	United Kingdom	1276	2 × 2 RCT, antioxidant	Men and women with diabetes and asymptomatic PAD (ABI ≤0.99) aged ≥40 y	100 mg/d, tablet, not enteric-coated	6.7	3.09
AAA, 2010 (33)	Fair	United Kingdom	3350	RCT	Men and women with ABI of ≤0.95 aged 50-75 y	100 mg/d, tablet, enteric-coated	8.2	0.99
JPPP, 2014 (39)	Fair	Japan	14 658	RCT	Men and women aged 60-85 y with hypertension, dyslipidemia, or diabetes	100 mg/d, tablet, enteric-coated	5.02	0.57

AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle-brachial index; BMD = British Male Doctors Trial; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PAD = peripheral arterial disease; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RCT = randomized, controlled trial; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

\* Patients had the option to select either effervescent aspirin, 500 mg/d, or an enteric-coated tablet, 300 mg/d.

† General tablet formulation unspecified; however, 624 patients in the intervention group requested enteric-coated preparation.

‡ Patients could take either 81 or 100 mg/d.

§ 26 countries in Europe, North and South America, and Asia.

|| Median.

¶ Percentage with major cardiovascular events (fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and CVD death) in the control group divided by the years of follow-up.