

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 also occurs at doses of 100 mg or less per day. Older adults seem to achieve a greater relative MI benefit.

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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, formulations, 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) 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	1
Editorial comment	2

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). 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

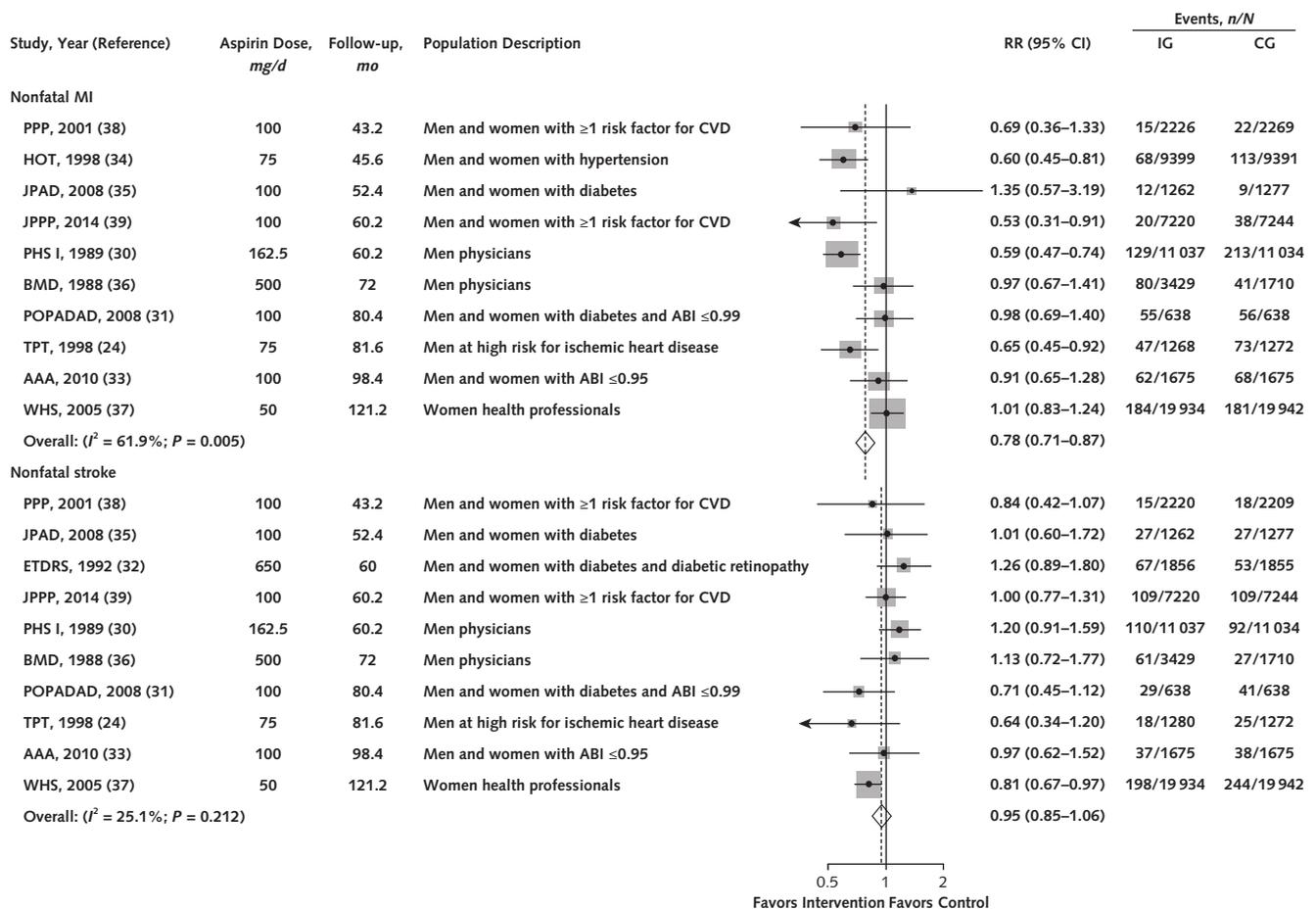
Description of Included Trials

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). 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

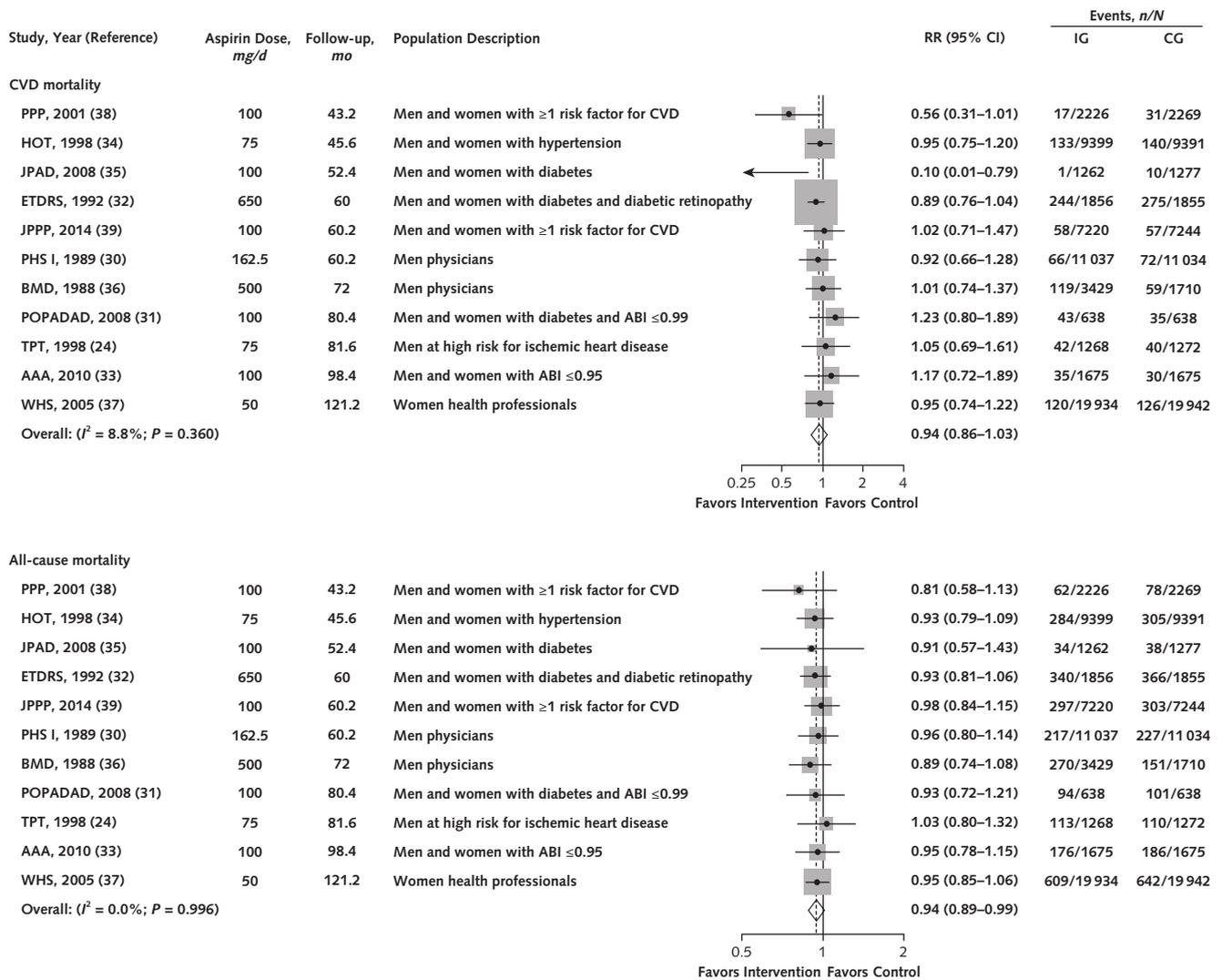
Eleven trials contributed to our composite CVD mortality analysis. Pooled analysis showed no statistically significant effect (RR, 0.94 [CI, 0.86 to 1.03]; $I^2 = 8.8\%$) (Figure 2, top). Two trials showed a statistically

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).

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.

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

Table 1. Pooled Estimates for All Included Trials and Trials With Aspirin Doses of ≤100 mg/d

Outcome	Studies, k	Participants, n	Mantel-Haenszel Fixed-Effects RR (95% CI)	I^2 , %
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.

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 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. ≥ 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 ≤ 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)	0.17 (0.02 to 0.29)
	Median	2.83		0.40 (0.06 to 0.68)
	High	4.84		0.68 (0.10 to 1.16)
Nonfatal MI (k = 8)	Low	0.90	0.83 (0.74 to 0.94)	0.15 (0.05 to 0.23)
	Median	2.69		0.46 (0.16 to 0.70)
	High	8.44		1.43 (0.51 to 2.19)

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 ≤ 100 mg/d in primary CVD prevention trials.

‡ Boldface data represent events clearly prevented (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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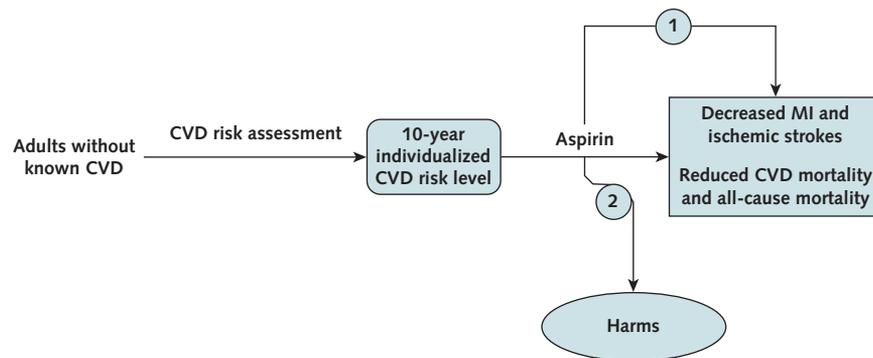
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Appendix Figure 1. Analytic framework with key questions.

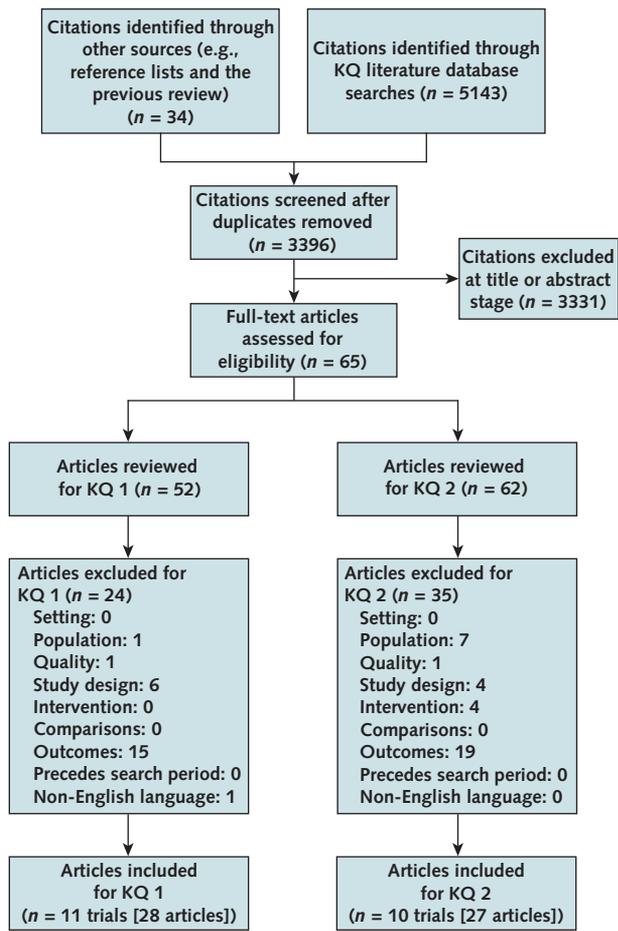


Key Questions

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, % [¶]
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.