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

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in the U.S.

Purpose: To update a systematic review about the benefits of aspirin for the primary prevention of cardiovascular events.

Data Sources: MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials (January 2008 to January 2015) and systematic reviews.

Study Selection: Two investigators independently reviewed 3,396 abstracts and 65 articles against pre-specified inclusion and quality criteria.

Data Extraction: Data from 11 trials were abstracted by 1 reviewer and checked by a second.

Data Synthesis: Aspirin reduces the risk of nonfatal myocardial infarction (MI) (relative risk, 0.78 [95% CI, 0.71 to 0.87]) and all-cause mortality (relative risk, 0.94 [95% CI, 0.89 to 0.99]) but does not reduce nonfatal stroke or CVD mortality. Benefits begin within the first 5 years. The only subpopulation for which there appears to be effect modification is older age groups that achieve greater relative MI reduction. When restricting to trials using daily doses of 100 milligrams or less, the nonfatal MI benefit persisted, a 14% nonfatal stroke benefit emerged and all-cause mortality was no longer statistically significant.

Limitations: Evidence for aspirin in primary prevention is heterogeneous in terms of dose, duration, and baseline CVD risk. Trials were powered for composite outcomes and individual events were rare. Very few credible subgroup analyses were available.

Conclusions: The beneficial impact of aspirin for the primary prevention of CVD is modest.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States (U.S) and accounts for about 1 in 3 deaths (1, 2). Despite a 15.5% reduction in cardiovascular deaths per year between 2001 and 2011, an estimated 525,000 Americans have a first myocardial infarction (MI) each year and about 610,000 experience a first stroke (2). There is clear evidence of net benefit for aspirin in secondary prevention (3) and guidelines consistently recommend aspirin for those with previous MI or stroke (4–8). For primary prevention, however, guidelines vary as to whether, and to which groups, aspirin should be recommended (6, 8–15). Recently, the U.S. Food and Drug Administration (FDA) denied primary prevention of MI as an indication for aspirin in any risk group (16).

In 2009, the U.S. Preventive Services Task Force (USPSTF) made sex-, age-, and outcome-specific recommendations for aspirin use. They recommended aspirin for men aged 45 to 79 years of age for prevention of MI, and for women aged 55 to 79 years of age for prevention of ischemic stroke when the potential benefit outweighs the risk of an increase in gastrointestinal (GI) hemorrhage (17). The current systematic review updates the evidence on the benefits of aspirin for the primary prevention of cardiovascular events with data from new trials published since the last recommendation. This review also evaluates evidence for effect modification in subpopulations, and for varying aspirin dosages, formulations and durations of use. This review was used in conjunction with the full evidence review including bleeding harms (18), a decision model (19) and concurrent reviews on aspirin and colorectal (20) and other cancers (21) to update USPSTF recommendations on aspirin use. Companion manuscripts addressing complementary issues of cancer benefits (22) and bleeding harm (23) should be considered

alongside this manuscript for a complete picture of benefits and harms in a CVD primary prevention population.

Methods

We developed an analytic framework with 2 key questions (Appendix, Figure 1) that examined the effect of aspirin in reducing MI, stroke, or all-cause mortality (question 1); and on associated increases in GI bleeding, hemorrhagic stroke, or other serious harms (question 2). This manuscript addresses question 1 only; question 2 is addressed in a manuscript by Whitlock et al in this issue (23). We addressed potential effect modification in *a priori* subquestions. Detailed methods are available in our full evidence report (18). The analytic framework, review questions, and methods for locating and qualifying evidence reflect public input after posting on the USPSTF website.

Data Sources and Searches

We searched MEDLINE, Pubmed, and the Cochrane Central Register of Controlled Trials from January 2008 to January 2015, supplemented by checking reference lists from relevant systematic reviews.

Study Selection

Two reviewers independently reviewed 3,396 citations and 65 full-text articles against *a priori* inclusion criteria (Appendix Figure 2). We included studies examining the primary prevention of CVD with oral aspirin use (minimum 75 mg every other day for at least 1 year) compared with placebo or no treatment in adults aged 40 years or older. We excluded interventions including non-aspirin antithrombotic medications or aspirin as a co-treatment to

another active intervention. For multifactorial trials, we combined arms when there was no evidence of interaction (24) and excluded arms considered co-treatment (25).

We considered RCTs and controlled clinical trials (CCTs) that reported eligible outcomes for question 1. We additionally considered cohort studies for question 2. We discussed, but did not pool, relevant individual patient-data (IPD) meta-analyses to provide additional subpopulation information.

Data Extraction and Quality Assessment

One reviewer extracted study-level data into standardized evidence tables and a second checked these data for accuracy. Two reviewers independently critically appraised eligible articles using predefined criteria (26, 27). Disagreements were resolved by a third investigator.

Data Synthesis and Analysis

We examined four primary beneficial outcomes based on *a priori* decisions and the availability/consistency of outcome reporting across trials: 1) nonfatal MI; 2) nonfatal stroke (all types); 3) CVD mortality, defined as a composite of death from MI, stroke, and CVD; and 4) all-cause mortality. Our full evidence report provides outcome definitions and data for secondary outcomes (18).

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 (28). We assessed statistical heterogeneity using the I^2 statistic.

For estimating absolute risk reduction and to explore potential variability among candidates for aspirin chemoprevention we calculated absolute effects by simulating control group event rates for our primary outcomes (**Table 3**). We simulated the event rate per 1,000 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 followup 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 dosage ≤ 100 mg/day.

Subpopulation Methods

A priori subpopulations included: age, sex, diabetes status, smoking history, race/ethnicity, CVD risk, decreased ankle brachial index (ABI), elevated blood pressure, and elevated lipids. We abstracted subgroup analyses for these groups and considered their credibility based on timing of planned analysis, interaction testing for heterogeneity of treatment effect, baseline comparability, and control for confounders (29). We emphasized within-study comparisons over between-study comparisons to minimize confounding. We analyzed subgroup analyses qualitatively because those reported were too limited to pool.

Role of Funding Source

Agency for Healthcare Research and Quality (AHRQ) staff provided oversight for the project and assisted in external review of the companion draft evidence synthesis. USPSTF liaisons helped to resolve issues around the scope of the review but were not involved in the conduct of the review.

Results

Description of Included Trials

We found eleven 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 in individual

trials ranging from 1,276 to 39,876 participants (25, 30–39) (**Table 1**). Follow-up times ranged from 3.6 to 10.1 years and most trials lasted 4 to 6 years. Eight of 11 trials administered aspirin at a dosage of 100 mg or less daily or every other day (25, 31, 33–35, 37–39). Older trials used higher doses (325 mg to 650 mg daily) (30, 32, 36). Three of 11 trials were conducted exclusively in men (25, 30, 36) and 1 was conducted exclusively in women (37). Mean participant ages in trials were generally in the mid-50s to mid-60s with maximum recruited ages of 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 ABI. The level of baseline cardiovascular risk in included populations, as estimated by the annualized CVD event rate in control groups varied widely, from 0.26% in the Women's Health Study (WHS) (37) to 4.09% in the Early Treatment Diabetic Retinopathy Study (ETDRS) (32). The full report includes individual trial-level detail (18).

Effect of Aspirin on Nonfatal MI

Ten trials reported the effect of aspirin for the primary prevention of nonfatal MI (25, 30, 31, 33–39). Meta-analysis showed a statistically significant 22% reduction in nonfatal MI, although heterogeneity was high (relative risk, 0.78 [95% CI, 0.71 to 0.87]; I^2=61.9%) (**Figure 1, Panel A**). Three of the four largest trials (PHS, HOT, JPPP) showed a statistically significant benefit despite being conducted in considerably different populations. The fourth large trial (WHS) showed no MI benefit overall but did in the older age group (discussed below). One smaller trial conducted in high-risk men (40% 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 that included few events showed a trend toward favoring the control group (35). Qualitative

exploration of heterogeneity by aspirin dose, publication date, and cardiovascular risk as estimated by control group event rates did not clearly explain heterogeneity.

Effect of Aspirin on Nonfatal Stroke

Ten trials that reported nonfatal stroke (all types) yielded mixed results with relative risk estimates ranging from 0.64 to 1.26 (**Figure 1, Panel B**). A pooled analysis from these ten trials showed no difference in nonfatal stroke in the aspirin group, compared with the control group, with relatively low heterogeneity (relative risk 0.95 [95% CI, 0.85 to 1.06]; I^2=25.1%). Only 1 trial (WHS) showed a statistically significant benefit for aspirin (relative risk, 0.81 [95% CI, 0.67 to 0.97]) (37). This good-quality trial of 100 mg aspirin every other day was conducted in a large sample of generally younger female health professionals (mean age of 55 years with only 10% aged 65 or older). Other trials showed mixed results (25, 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 (relative risk, 0.94 [0.86 to 1.03]; I^2=8.8%) (**Figure 1, Panel C**). Two individual trials showed a statistically significant benefit of aspirin for reducing CVD mortality. One of these was a small study (N=2,539) of fair-quality conducted in men and women with diabetes in Japan with only 11 total cardiovascular deaths (hazard ratio 0.10 [0.01 to 0.79]) (35). In a fair-quality trial of patients with at least 1 CVD risk factor, the unadjusted relative risk (using raw numbers from our plots) neared significance, but was significant when adjusted for baseline characteristics (OR 0.48 [0.26 to 0.88]) (38).

Effect of Aspirin on All-Cause Mortality

Eleven trials reported all-cause mortality with all showing non-statistically significant results (25, 30–38). Ten trials reported relative risks of 0.81 to 0.98 and 1 reported a relative risk greater than 1 (25). When all trials using all doses were pooled, aspirin had a statistically significant

benefit for all-cause mortality (relative risk, 0.94 [95% CI, 0.89 to 0.99]; I^2=0%) (**Figure 1, Panel D**).

Effect Modification by Dose, Duration, and Formulation

Dose. The eight trials that administered aspirin doses of 100 mg/day or less achieved a similar and statistically significant reduction in nonfatal MI (relative risk, 0.83 [95% CI, 0.74 to 0.94]; I^2=54.5%), which mimics the trend we observed when pooling trials of all doses (relative risk, 0.78 [95% CI, 0.71 to 0.87]; I^2=61.9%). Pooled analysis of trials using doses of 100 mg/day or less, however, showed a statistically significant reduction in nonfatal stroke (k=7; relative risk, 0.86 [95%CI, 0.76 to 0.98)]; I^2=0%) that was not observed when trials with all doses were pooled (k=10; relative risk, 0.95 [95% CI, 0.85 to 1.06]; I^2=25.1%) (**Table 2**). Sensitivity analyses of trials with doses 100 mg/day or less yielded similar results for CVD mortality when compared to analyses using all doses. All-cause mortality achieved a similar point estimate in low-dose sensitivity analyses, but the confidence interval widened to cross 1 (k=8; relative risk, 0.95 [0.89 to 1.01]).

Duration. Time-to-event data for various outcomes were available from 9 trials (25, 31–33, 35, 37, 39–41). Conclusions varied regarding 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. There was no clear upper time limit to benefit due to 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 regarding treatment formulation, which reflects the heterogeneity of the trials' designs and sparse reporting of tablet formation in some trials.

Differences in Subpopulations

All 11 trials addressed effect modification for at least 1 of our 9 predefined subpopulations of interest (25, 30–39). In addition to evaluating subgroup analyses from individual trials, we examined the Antithrombotic Trialists' (ATT) IPD meta-analysis that pooled individual patient data from 6 of the 11 aforementioned primary prevention trials (25, 30, 34, 36–38) (n=95,000; 660,000 person-years) and provided additional subpopulation analyses (3). Our body of evidence was sufficient to draw conclusions for only 3 subpopulations—age, sex and diabetes. Evidence was insufficient for other subpopulations because of inconsistent and imprecise results or sparse or no data.

Age. While data from age-specific subgroup analyses provides limited evidence suggesting that aspirin may have an overall greater relative total MI benefit in older age groups, mixed results were reported for other outcomes. Eight trials reported age-specific results (30, 31, 33, 35, 37, 39, 40, 42), but only 4 trials clearly pre-specified their subanalyses (33, 35, 37, 39). All 3 trials that reported total MI by age showed a consistent pattern of greater relative risk reduction with older age (30, 37, 40).Two of these trials, PHS and WHS, showed statistically significant interactions for effect by age (30, 37, 40). Of note, WHS showed a statistically significant 34% reduction in total MI only among women 65 or older (relative risk, 0.66 [0.44 to 0.97]) (37). None of the 3 trials that reported age-specific stroke events showed statistically significant differences in effect by age group, although the rarity of these events limited all analyses including WHS. The WHS was the only *a priori* analysis; it reported more stroke events but had no interaction testing for this outcome (25, 37, 40, 42). Six trials (31, 33, 35, 37, 39, 40) reported variously defined composite cardiovascular outcomes by age strata with 4 trials performing analyses a priori (33, 35, 37, 39) and showed conflicting results. Only 3 of these trials performed interaction testing (31, 35, 37). While POPADAD and JPAD found no statistically significant

interaction between age and aspirin use for their cardiovascular composite outcomes (31, 35), the WHS suggested effect modification by age (p for interaction=0.05), where women 65 years or older experienced a statistically significant 26% reduction in total cardiovascular events (37). The ATT IPD meta-analysis 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 (3). Additionally, 1 trial (HOT) showed no statistically significant difference in all-cause mortality based on age (<65 years vs ≥65 years), although these analyses were not prespecified and there was no interaction testing (40).

Sex. Our critical appraisal of the sex-specific subgroup literature concludes that there is no strong evidence supporting a CVD treatment benefit modification for aspirin by sex or outcome. All 11 included trials reported sex-specific results (25, 30–33, 35–37, 39–41). In the 7 trials that included both men and women (31–35, 38, 39), only 3 trials clearly specify sex as an *a priori* subgroup (33, 35, 39). Five trials adjusted for confounders: ETDRS, PHS, WHS, PPP and JPPP (30, 32, 37–39). Three trials conducted in both men and women reported MI by sex (32, 40, 41). For total MI, only a single trial (HOT) showed a beneficial effect in men, but not women in unadjusted analyses (men: relative risk, 0.58 [95% CI, 0.41 to 0.81]). For women the relative risk was 0.81 [95% CI, 0.49 to 1.31]) (40). In adjusted analysis, PPP showed a trend towards reduction of total MI in men and harm in women (41), and ETDRS showed a greater although not statistically significant reduction in total MI in men but not women (32). In each of these studies, interaction tests were not performed and confidence intervals between men and women were overlapping. The same 3 trials reported stroke outcomes separately for men and women. Risk reductions were greater in women in 2 of 3 trials (40, 41), but the results were not statistically significant for any sex in these studies and interaction testing was not performed.

The ATT IPD meta-analysis showed that the apparent statistically significant differences in sex-specific differences in MI were no longer statistically significant after controlling for multiple comparisons. There was no statistically significant sex-specific difference in stroke before or after controlling for multiple comparisons (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. The single trial that reported individual event outcomes by sex (30) showed no difference in the individual outcomes of total MI or total stroke between the sexes.

Diabetes. Available subpopulation literature and limited subgroup analyses do not clearly support heterogeneity in aspirin's CVD treatment effect based on diabetic status. While three trials specifically recruited patients with diabetes (31, 32, 35), other trials clearly included diabetics in recruiting a high cardiovascular risk population (38, 39). An additional 6 trials performed subgroup analyses (30, 33, 37, 39, 43, 44) and only 2 clearly designated analyses *a priori* (37, 39). Three of these 6 trials performed interaction testing (30, 43, 44) and 4 trials adjusted for confounders (30, 37, 39, 44). Seven trials examined ASA's total MI effect in diabetics—3 were conducted exclusively in diabetics (31, 32, 35) and 4 were subgroup analyses (30, 37, 43, 44). These trials showed no statistical difference in aspirin's effect by diabetes status, including the large PHS trial, which was the only trial that performed heterogeneity testing for this outcome (p=0.22). Three trials that were conducted in diabetics only (31, 32, 35) and 3 subanalyses (37, 43, 44) examined stroke outcome in diabetics. The three RCTs in diabetics showed no statistically significant stroke difference in diabetics taking aspirin compared to control, although these trials were underpowered for this individual outcome. In *a priori* subgroup analysis, WHS showed that the beneficial effect of aspirin on total stroke (adj RR 0.83 (95% CI, 0.69 to 0.99) appeared to largely be driven by a benefit in those with diabetes (adj

relative risk, 0.46 [95% CI, 0.25 to 0.85]) rather than those without diabetes (adj, RR, 0.87 [95% CI, 0.72 to 1.05]. These confidence intervals overlapped, however, and no interaction testing was reported. Subgroup analysis in HOT, which was not explicitly prespecified, 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 taking aspirin compared to control. Subgroup analyses in PPP were *post-hoc*, limited by few events, and showed overlapping confidence intervals in those with and without diabetes. There was no clear difference in aspirin's effect on CVD mortality in diabetics when compared with non-diabetics, due to mixed results and few events (31, 32, 35, 43, 44). Results for study-defined composite CVD outcomes were generally non-significant (31–33, 35, 37, 39, 43, 44). The ATT IPD meta-analysis analyzed a composite of serious vascular events and showed no heterogeneity of effect by diabetes status (ratio of yearly event rates, diabetes: 0.88 [95% CI, 0.67 to 1.15]; no diabetes: 0.87 [95% CI, 0.79 to 0.96]) (3). Three trials that were conducted exclusively in diabetics (31, 32, 35) showed no all-cause mortality benefit of aspirin compared to control. While 2 subanalyses (43, 44) showed no evidence for all-cause mortality effect modification based on diabetes status, few trials were powered for this outcome.

Absolute Risk Reduction

For CVD benefit, those with higher baseline CVD risk are expected to experience higher benefits (more events prevented) with aspirin. We simulated control group event rates for all primary beneficial outcomes within a 10-year period (**Table 3**) and simulated the range of events prevented, based on the low, median, and high baseline event rates seen in included trials.

Across the range of baseline event rates, for each 1,000 person-years of low-dose aspirin use, absolute benefits were modest for nonfatal MIs and nonfatal strokes prevented (0.15 to 1.43 and

0.17 to 0.68, respectively); for all risk levels, these nonfatal events were prevented. For no risk level did aspirin clearly prevent all-cause mortality or CVD death. Wide confidence intervals around most of the estimated event rates suggest uncertainty, due to small numbers and probably also heterogeneity of aspirin effect among groups relatively crudely categorized by baseline event rates. These simulations do not include considerations of harm and the potential long-term benefit from reduced CRC incidence, due to its delayed effect beyond 10 years; these issues are addressed in companion manuscripts (22, 23).

Discussion

Our meta-analysis of 11 primary prevention trials showed that aspirin reduces the risk of nonfatal MI by 22%, which confirms the conclusions of several other published meta-analyses (3, 45–48). This nonfatal MI benefit begins sometime within the first 5 years of use. When pooling trials with average daily doses of 100 mg or less, this benefit for nonfatal MI persisted, and a 14% benefit for nonfatal stroke emerged. While it is plausible that some of the hemorrhagic strokes caused by aspirin can be mitigated by lowering the dose, hemorrhagic stroke events were so rare that we cannot confirm this hypothesis.

The statistically significant 6% reduction in all-cause mortality was unexpected because we did not find a CVD mortality benefit. Other CVD primary prevention meta-analyses of nine trials, however, have reported all-cause mortality benefit trend with confidence interval upper bounds of 1.00 (45, 46, 48). This all-cause mortality benefit did not persist in sensitivity analyses of primary prevention trials with aspirin doses of 100 mg/day or less. Analyses of primary and secondary prevention trials demonstrated a similar 6-7% statistically significant all-cause mortality benefit regardless of whether all dosages or only dosages of 100 mg or less are

included (21). These modest reductions in all-cause mortality do not appear to be completely explained through cardiovascular and/or cancer mortality reduction (21).

Our critical appraisal of the subpopulation literature aimed to identify any subpopulation for whom the net benefit would be maximized; that is, those for whom either: 1) the relative risk reduction realized from aspirin is higher than the average population, or 2) the baseline risk of CVD events is higher than 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 performed interaction testing, and none adequately controlled for important confounders. The best information would come from controlled multivariable analyses based on IPD MA from all available, applicable trials. The ATT IPD meta-analysis suggests that, among the six CVD primary prevention trials examined, there is no heterogeneity of effect for serious vascular events by sex, age, or diabetes. The suggestion of possible heterogeneity of effect for sex for major coronary events and ischemic stroke was no longer present when controlled for multiple comparisons (3).

Based on relatively limited and generally lower-quality evidence, we conclude that the most consistent evidence of subpopulation differences in aspirin use was an enhanced impact on MI in older age groups. A large ongoing trial of 19,000 participants aged 70 or older may confirm this finding (49). We found no clear effect modification based on diabetes status for any CVD-related outcomes, although the three trials that were conducted exclusively in diabetic patients found nonstatistically significant results for the composite CVD outcomes that the trials were designed to detect (31, 32, 35). Our best conclusion is that diabetics will benefit similarly to others with comparable CVD risk profiles. Diabetics were included in many trials and between-trial comparisons are a relatively weak basis for subpopulation conclusions when trials have

substantial methodological and other clinical heterogeneity, as characterized by the trials we reviewed. Two large RCTs (together enrolling over 20,000 patients with diabetes) that are currently in progress may definitively answer the question regarding whether or not aspirin is effective for primary prevention of any type of CVD events in this population (50, 51). We were unable to confirm conclusions of a prior study-level meta-analysis that showed sex- and outcome-specific differences whereby women achieved a stroke benefit from aspirin while men achieved an MI benefit (41). Our critical appraisal of sex-specific subgroup analyses showed that these prior conclusions were based on analyses with serious limitations including lack of: pre-specified analyses, baseline comparability reporting, adjustment for confounders (particularly age, which is critical for sex-specific CVD considerations), and interaction testing. In WHS, aspirin reduced ischemic stroke in women, however, MI benefit was also achieved in those 65 or older (37). Thus, lack of age adjustment and the relatively young age of the WHS trial could have led to prior sex- and outcome-specific conclusions. The ATT IPD and subsequent meta-analyses have confirmed the findings of no robust sex-specific, outcome-specific differences in major CVD events (41, 48). Furthermore, the lack of heterogeneity of treatment effect in the secondary aspirin prevention literature puts such sex-specific findings in question (3).

An accompanying manuscript by Whitlock and colleagues reports findings from a systematic review of harms of aspirin and explores variability of harms in hypothetical populations with varying baseline cardiovascular and major bleeding event risks (23). Taken together with our findings, these data suggest that individualized consideration of potential for harms as well as benefits is prudent, particularly for those at low-to-moderate CVD risk. Recent guidelines for aspirin use in primary prevention are conflicting. While some recommend ASA for those

meeting age or 10-year CVD, CHD or stroke risk thresholds (11, 52, 53), others recommend against ASA for primary prevention (6, 10).

Tools that effectively identify patients at higher CVD risk are generally recommended in primary prevention (54) and may reduce potential overuse of aspirin by those not likely to benefit (55). 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 (ACC/AHA) "Pooled Cohort Equations" predict 10-year risk of a first hard atherosclerotic CVD event, defined as nonfatal MI, coronary heart disease death, and fatal or nonfatal stroke (54). This tool is derived from a more racially and ethnically diverse, contemporary population than the Framingham calculator, enabling race- and sex-specific equations for blacks and whites (although not Hispanics, Asians, and other ethnic subpopulations), and has been externally validated in U.S. populations (54, 56–58). Critics have voiced concerns about the model's calibration, citing over-prediction (56–59). Several investigators have characterized the model's discrimination as moderate, at best, using c-statistics (56–59). A more recent analysis, however, found that use of the Pooled Cohort Equations (as part of ACC/AHA treatment guidelines) more accurately and efficiently identified a population at increased CVD risk compared with the Framingham Risk Score (as part of ATP III treatment guidelines) (60). Its application clinically and in policy recommendations, however, should be informed by potential for over-prediction.

There are several limitations of the literature. The 11 primary prevention studies are heterogeneous in terms of aspirin dose, duration of therapy, baseline population characteristics, comorbid conditions, and most importantly 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. Additionally, trials were powered for composite outcomes combining fatal and nonfatal events of varying severity, (61) with limited power for relatively rare individual outcomes of MI and stroke 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 comparable time-to-event data reporting in the trials, we could not precisely determine the minimum time-to-benefit other than to conclude that the cardiovascular-related benefits (i.e., nonfatal MI) occur during the first 5 years of therapy. As such, whether the nonfatal MI benefit continues to accrue at a constant rate beyond 5 to 10 years of 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 10 year trial outcomes (62). We found that sufficient dosing for primary prevention is likely 75-100 mg per day. Limited data suggest that dosing every other day may also achieve CVD benefits. Others have suggested such dosages and regimens may not be effective in diabetics, in whom aspirin resistance has been documented (12). Additional research and further IPD MA could help resolve these questions.

Conclusions

Pooled analysis from 11 trials in healthy and higher-risk populations (including diabetics, those with low ankle-brachial index, and hypertensives) demonstrates that low dose aspirin does not reduce CVD mortality. Aspirin does provide a modest benefit in reducing nonfatal MI and nonfatal stroke events, and perhaps all-cause mortality.

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Figure 1, Panel A: Nonfatal MI

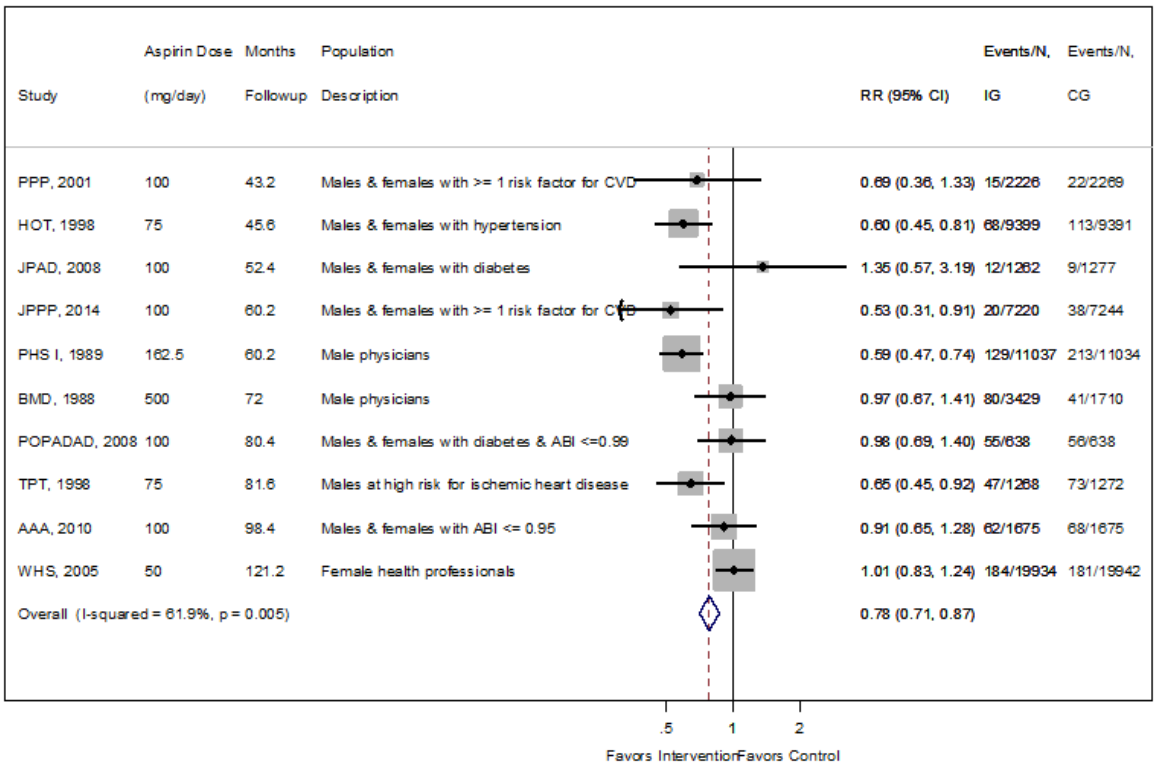


Figure 1, Panel B: Nonfatal Stroke

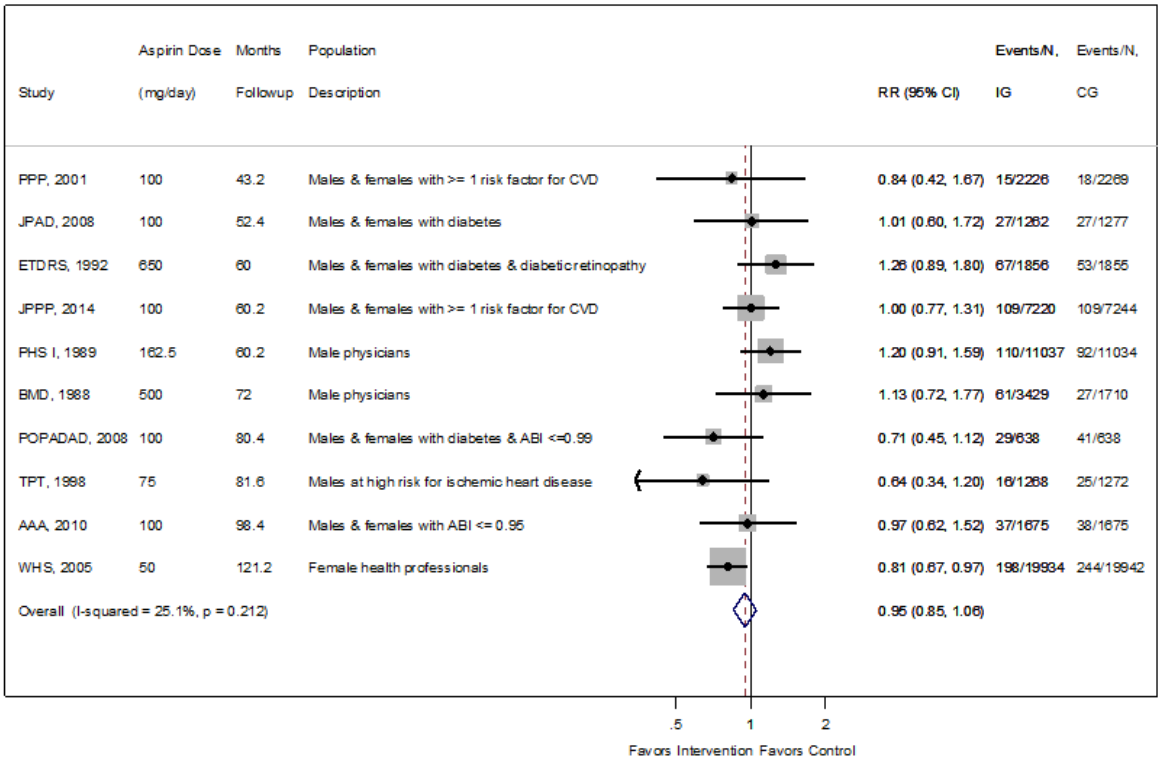


Figure 1, Panel C: CVD Mortality

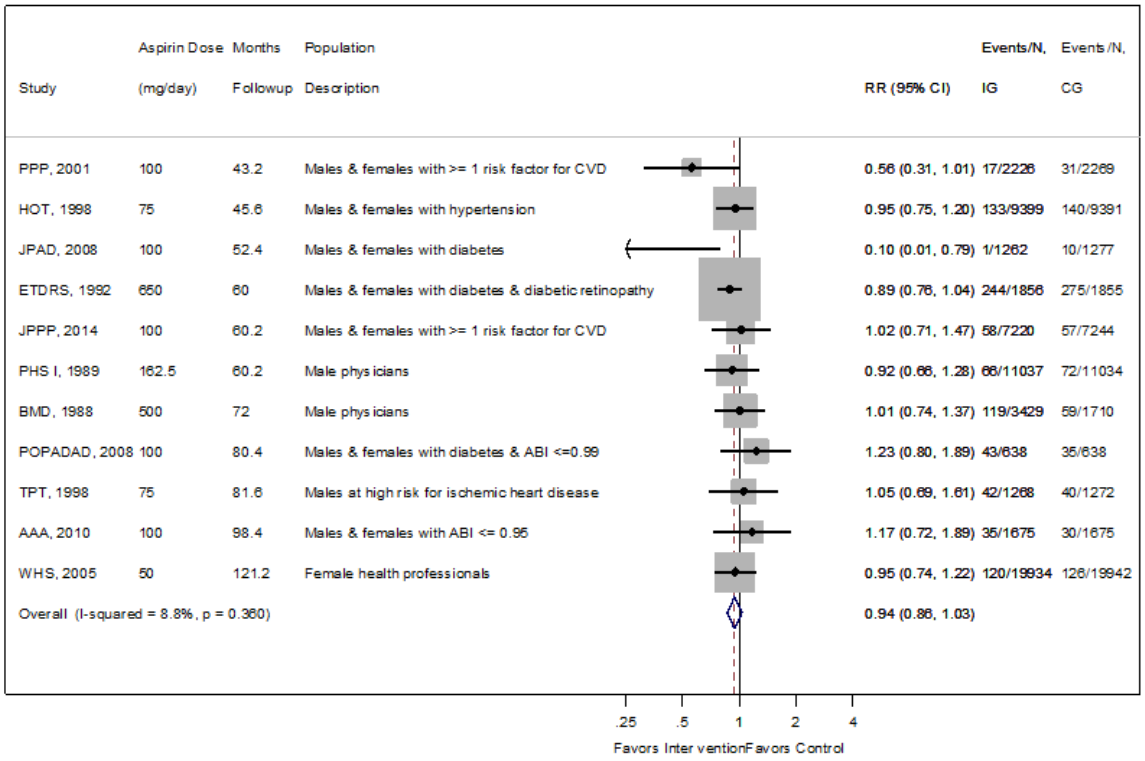


Figure 1, Panel D: All-Cause Mortality

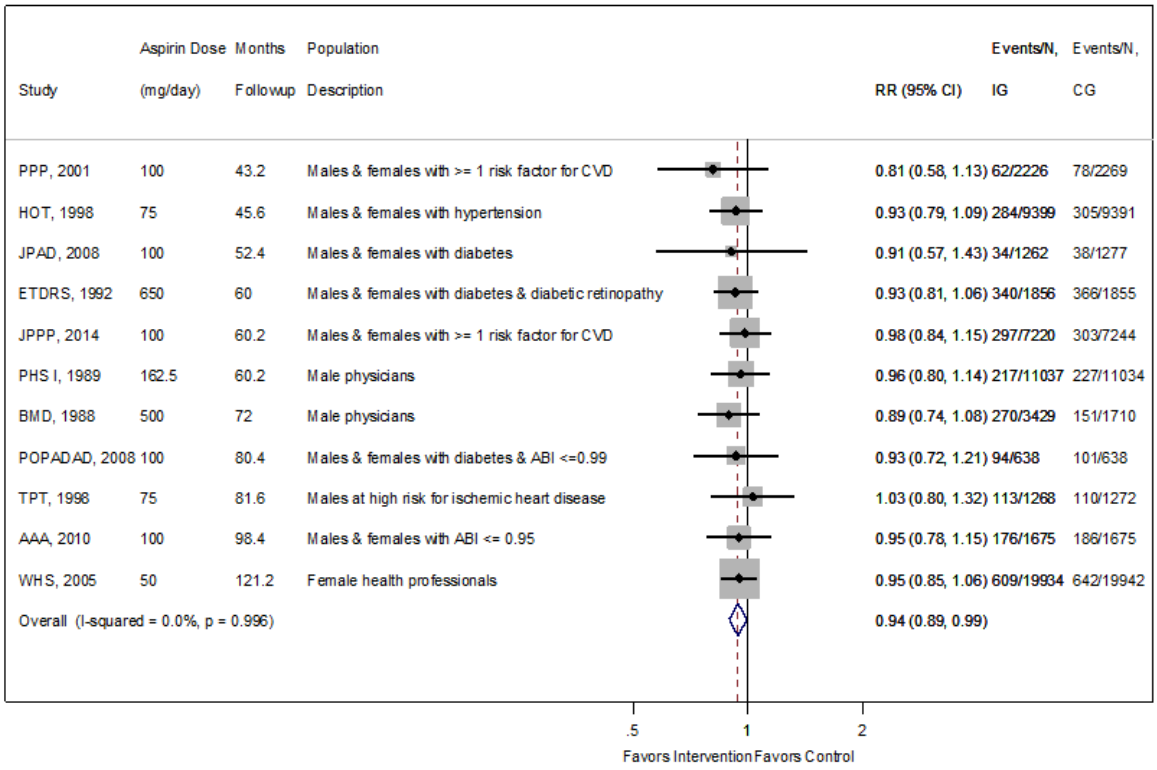


Table 1. Methodological and intervention characteristics of included trials for primary prevention of cardiovascular events

	Quality	Country	N Randomized	Study Design	Inclusion	ASA Dose & Formulation	Mean Followup, years	Per year Control Group CVD Event Rate (%)¶
BMD, 1988 (36)	Fair	UK	5,139	RCT	Male physicians	500 mg daily, unspecified*	6	1.24
PHS I, 1989 (30)	Good	US	22,071	2x2 RCT, Beta-carotene	Male physicians aged 40-84 years	325 mg QOD, tablet, not enteric coated†	5	0.67
ETDRS, 1992 (32)	Fair	US	3,711	2x2 RCT, early or delayed photo-coagulation	Diabetics with diabetic retinopathy aged 18-70	650 mg daily, tablet, not enteric coated	5	4.09
HOT, 1998 (34, 40, 43)	Fair	26 Countries§	18,790	3x2 RCT, hypertension treatment goals	Hypertensive men & women aged 50-80 years	75 mg daily, unspecified	3.8	1.03
TPT, 1998 (25, 42)	Fair	UK	2,540	2x2 RCT, Warfarin	Men at the top 20 or 25% of CVD risk score aged 45-69	75 mg daily, controlled release capsule	6.8‖	1.60
PPP, 2001 (38, 41, 44)	Fair	Italy	4,495	2x2 RCT, Vitamin E	Men & women aged 50 years or older with at least one CVD risk factor	100 mg daily, enteric coated tablet	3.6	0.78
WHS, 2005 (37, 63)	Good	US	39,876	2x2 RCT, Vitamin E	Women health professionals aged 45 years or older	100 mg QOD, tablet, not enteric coated	10.1	0.26
JPAD, 2008 (35)	Fair	Japan	2,539	RCT	Men & women with diabetes aged 30-85 years	100 mg daily, tablet, not enteric coated‡	4.37‖	0.82
POPADAD, 2008 (31)	Fair	UK	1,276	2x2 RCT, Antioxidant	Men & women with diabetes & asymptomatic PAD (ABI ≤0.99) aged 40 years or older	100 mg daily, tablet, not enteric coated	6.7‖	3.09
AAA, 2010 (33)	Fair	UK	3,350	RCT	Men & women with ABI of ≤0.95 aged 50-75 years	100 mg daily, tablet, enteric coated	8.2	0.99
JPPP, 2014 (39)	Fair	Japan	14,658	RCT	Men & women aged 60 – 85 with hypertension, dyslipidemia, or diabetes	100 mg daily, tablet, enteric coated	5.02‖	0.57

* Patients had the option to select either 500 mg per day or 300 mg per day of either effervescent aspirin or an enteric coated tablet.
†General tablet formulation unspecified, however 624 in IG requested enteric-coated preparation and 16 requested Ecotrin
‡Patients could take either 81 or 100 mg daily
§26 countries in Europe, North and South America, and Asia.
‖median
¶% with major cardiovascular events (fatal and nonfatal stroke, fatal and nonfatal MI and CVD death) in the control group divided by the years of follow-up

Table 2. Pooled estimates for all included trials (top rows), and trials with dose ≤100 mg (bottom rows)

Outcome	k	N	Mantel-Haenszel Fixed Effects Relative Risk (95% CI)	I^2 (%)
Nonfatal MI	10	114,734	0.78 (0.71 to 0.87)	61.9
	8	87,524	0.83 (0.74 to 0.94)	54.5
Nonfatal Stroke	10	99,655	0.95 (0.85 to 1.06)	25.1
	7	68,734	0.86 (0.76 to 0.98)	0
Cardiovascular Disease Mortality	11	118,445	0.94 (0.86 to 1.03)	8.8
	8	87,524	0.97 (0.85 to 1.10)	30.0
All-cause Mortality	11	118,445	0.94 (0.89 to 0.99)	0
	8	87,524	0.95 (0.89 to 1.01)	0

Abbreviations: CI = confidence interval; Mg= milligrams; MI = myocardial infarction; RR = relative risk

Table 3. Absolute risk reduction with low-dose aspirin use up to 10 years

Outcome	Risk Level*	Baseline Risk of Outcome, Events per 1,000 person-years	Relative Risk (95% CI)†	Events Prevented per 1,000 person-years (95% CI)
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)**

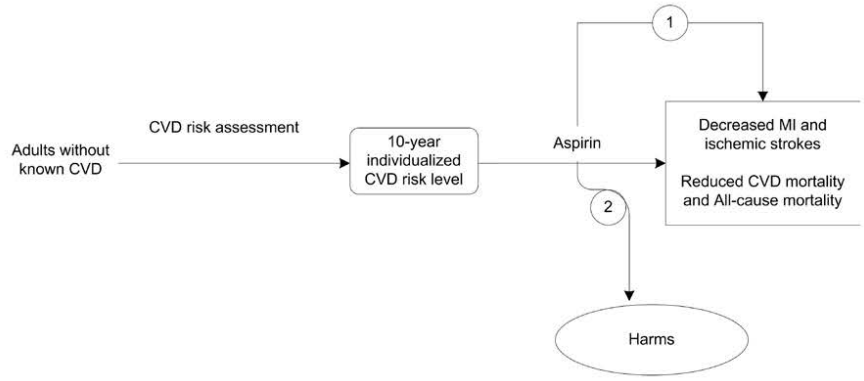
*Lowest (minimum), median, and high (maximum) control group rate for each outcome excluding zeros and outliers

†Based on ≤ 100 mg/day in primary CVD prevention trials

Bolding represents events clearly prevented (i.e., 95% CI does not include both caused and prevented events)

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; mg = milligram(S); MI = myocardial infarction

Appendix Figure 1. Analytic Framework



Abbreviations: CVD = cardiovascular disease; MI = myocardial infarction

Key Questions:

1. Does regular aspirin use in patients without known cardiovascular disease reduce myocardial infarction, stroke, death from myocardial infarction 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 aspirin 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, or related risk conditions (e.g. diabetes mellitus, decreased ankle brachial index, elevated blood pressure), gastrointestinal bleeding or hemorrhagic stroke risk factors (including history of gastrointestinal bleeding, ulcers, or NSAID use), concomitant medication use (NSAIDs, SSRIs, or PPIs)?
    b. Does the effect vary by dose, formulation, duration of aspirin use?

Appendix Figure 2. Literature Flow Diagram