Evidence Synthesis

Number 131

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA-290-2012-00015-4, Task Order No. 2

Prepared by:
Kaiser Permanente Research Affiliates Evidence-based Practice Center
Kaiser Permanente Center for Health Research
Portland, OR

Investigators:
Janelle M. Guirguis-Blake, MD
Corinne V. Evans, MPP
Caitlyn A. Senger, MPH
Maya G. Rowland, MPH
Elizabeth A. O'Connor, PhD
Evelyn P. Whitlock, MD, MPH

AHRQ Publication No. 13-05195-EF-1
September 2015

This systematic review was conducted in coordination with two other systematic reviews[1,2] and a decision model[3] to support the U.S. Preventive Services Task Force (USPSTF) in making updated clinical preventive service recommendations for aspirin in primary prevention. The original literature searches were completed in June 2014. In order to prepare a set of manuscripts derived from these reviews, we conducted updated literature searches through January 6, 2015 to identify newly published information since the original searches.

A single open-label randomized, controlled clinical trial in a cardiovascular disease (CVD) primary prevention population—the Japanese Primary Prevention Project (JPPP)[4]—was the only additional clinical research report located through the updated searches that met inclusion/exclusion criteria for any of the reviews. Outcomes from this study (nonfatal myocardial infarction [MI], nonfatal stroke [nonfatal cerebral infarction, intracranial hemorrhage, and undefined cardiovascular events], CVD mortality [fatal MI, cerebral infarction, intracranial hemorrhage, subarachnoid hemorrhage, and other fatal cardiovascular events], hemorrhagic stroke [fatal and nonfatal intracranial hemorrhage], and all-cause mortality) were incorporated into the final evidence reviewed by the USPSTF and resulted in updated inputs into the decision analysis.

This systematic review has NOT been updated to reflect the incorporation of results from JPPP. Updated results are reflected in the manuscript derived from this review, which is available for public comment at http://www.uspreventiveservicestaskforce.org. Results for this systematic review for outcomes unrelated to those reported in JPPP are current through January 6, 2015. No further updated literature searches have been undertaken.

References

1. Chubak J, Kamineni A, Buist DS, et al. 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.
2. Whitlock EP, Williams SB, Burda BU, et al. 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.
3. 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.
4. Ikeda Y, Shimada K, Teramoto T, 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(23):2510-20. PMID: 25401325.

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2012-00015-4, Task Order No. 2). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors acknowledge the following individuals for their contributions to this project: Robert McNellis, MPH, PA, at AHRQ; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Steven Teutsch, MD, Diana Petitti, MD, MPH, Nancy R. Cook, ScD, and Mark Alberts, MD, FAHA, who provided expert review of the report; and Smyth Lai, MLS, Kevin Lutz, MFA, and Keshia Bigler, BS, at the Kaiser Permanente Center for Health Research.

Suggested Citation

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. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

Structured Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in the United States, contributing to more than a third of deaths annually.

Purpose: To systematically review evidence for the effectiveness of aspirin to prevent myocardial infarction (MI)/coronary events, stroke, cardiovascular death, and all-cause mortality in those without a history of CVD. To review evidence for harms associated with aspirin use.

Data Sources: We searched MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials to identify literature that was published between January 2008 and June 2014. We supplemented our searches with reference lists from the previous review, relevant existing systematic reviews, suggestions from experts, and Clinicaltrials.gov to identify ongoing trials.

Study Selection: Two investigators independently reviewed identified abstracts and full-text articles against a set of a priori inclusion and quality criteria.

Data Analysis: One investigator abstracted data into an evidence table and a second investigator checked these data. We conducted Mantel-Haenszel fixed effects meta-analyses to estimate the effect size of aspirin chemoprevention in preventing MI/coronary events, stroke, CVD-related death and all-cause mortality. Additionally, we conducted sensitivity analyses using Peto odds ratios. We qualitatively synthesized the harms related to major gastrointestinal (GI) bleeding, hemorrhagic stroke, and age-related macular degeneration to estimate the harms associated with aspirin use.

Results: We included 10 fair- to good-quality randomized, controlled trials (RCTs) (N=103,787) examining the effectiveness of aspirin for the primary prevention of CVD. Aspirin reduces the risk of major CVD events (total MI, total stroke, CVD mortality) by 11 percent (relative risk [RR], 0.89 [95% confidence interval (CI), 0.84 to 0.95]), which appears to be largely driven by a 20 percent reduction in nonfatal MI/coronary events (RR, 0.80 [95% CI, 0.72 to 0.88]). Aspirin's effectiveness in reducing nonfatal MI/coronary events that were reported in trials of doses ranging from 100 mg every other day to 650 mg daily were also seen with trials using 100 mg or less daily. While primary prevention trials for doses 100 mg every other day to 650 mg daily demonstrated no reduction in stroke events with aspirin use, trials using 100 mg daily or less showed a reduction in total stroke (RR, 0.85 [95% CI, 0.76 to 0.96]). CVD mortality was unchanged with the use of aspirin in these 10 trials. All-cause mortality may be unchanged or slightly reduced with a statistically significant benefit not persistent in dose sensitivity analyses. All trials were powered for CVD composite outcomes. Increasing age being associated with greater RR reductions was the only consistent subgroup trend we identified. Trials of patients with diabetes showed no CVD benefit and trials with diabetes subgroup analyses showed no effect modification in this group. Given the paucity of data, we can draw no conclusions about treatment benefit modification based on aspirin formulation or duration. Aspirin's CVD benefit appears to begin within the first 5 years of administration; there are limited data for longer durations. We included nine of these RCTs to examine the major GI bleeding harms, hemorrhagic stroke, and other harms associated with aspirin use. Major GI bleeding was reported variably in the nine trials, with RRs ranging from 0.50 to 8.10. An individual participant data

meta-analysis reported a 50 percent increase in major GI bleeding and other extracranial bleeding (RR, 1.54 [95% CI, 1.30 to 1.82]) with aspirin use compared to controls. Seven trials reported hemorrhagic stroke as rare events (≤5% incidence) in both aspirin and control groups, making the numbers too unstable to precisely estimate the effect of aspirin on this harm. Two RCTs found no statistically significant difference in age-related macular degeneration in the aspirin group compared to controls. Both trials showed RRs of less than 1.

Conclusions: In primary prevention populations, aspirin modestly reduces nonfatal MI/coronary events and major CVD events, but also increases major GI bleeding risk. More precise real-world estimates for bleeding events, including major GI bleeding events and hemorrhagic stroke, are necessary to calculate the net benefit. At some absolute risk for 10-year CVD events, this absolute CVD benefit could potentially outweigh the bleeding risks. Models to identify these populations are needed.

Abbreviations

AAA	Aspirin for Asymptomatic Atherosclerosis
ABI	ankle brachial index
ACC/AHA	American College of Cardiology/American Heart Association
ACCEPT-D	Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes
ACE	angiotensin converting enzyme
adj	adjusted
AHRQ	Agency for Healthcare Research and Quality
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack
ARB	angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
ARMD	age-related macular degeneration
ASA	acetylsalicylic acid
ASCEND	A Study of Cardiovascular Events in Diabetes
ATP	Adult Treatment Panel
ATT	Antithrombotic Trialists
BMD	British Doctor's Trial
BMI	body mass index
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CCT	controlled clinical trial
CG	control group
CHD	coronary heart disease
CHF	congestive heart failure
CHS	Cardiovascular Health Study
CI	confidence interval
COX	cyclooxygenase
CVD	cardiovascular disease
DBP	diastolic blood pressure
dL	deciliter
DM	diabetes mellitus
ETDRS	Early Treatment Diabetic Retinopathy
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GI	gastrointestinal
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HOT	Hypertension Optimal Treatment
HR	hazard ratio
HTN	hypertension
ICD	International classification of disease
IG	intervention group
IHD	ischemic heart disease

IPD	individual patient data
ITT	intent-to-treat
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
k	number of studies
kg	kilogram
KQ	key question
L	liter
LDL	low-density lipoprotein
m^2	square meter
MA	meta-analysis
MESA	Multiethnic Study of Atherosclerosis
mg	milligram(s)
MI	myocardial infarction
mm	millimeters mercury
mmol	millimole
N	number
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NR	not reported
NS	not significant
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PAD	peripheral arterial disease
PHS	Physician's Health Study
POPADAD	Prevention of Progression of Arterial Disease and Diabetes
PPI	proton pump inhibitor
PPP	Primary Prevention Project
py	person-years
QOD	every other day
RCT	randomized controlled trial
RR	relative risk
SSRI	selective serotonin reuptake inhibitor
SBP	systolic blood pressure
TC	total cholesterol
TIA	transient ischemic attack
TPT	Thrombosis Prevention Trial
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization
WHS	Women's Health Study

Table of Contents

Figures

Tables

Appendixes

Chapter 1. Introduction

Prevalence

Heart disease is the leading cause of mortality in the United States for both men and women.[1] While the relative rate of cardiovascular disease (CVD) mortality declined by 31 percent from 2000 to 2010, the burden of disease remains high, with CVD accounting for about one in three deaths in the United States.[2] In addition to high rates of mortality, many persons live with a CVD diagnosis (16 million) and a large number of individuals are survivors of CVD-related events such as heart attack (7.9 million) or stroke (7 million).[3] Each year, an estimated 620,000 Americans have a first heart attack and about 610,000 experience a first stroke.[2] These high rates of CVD mortality and morbidity represent a significant economic burden to the health care system in the United States. In 2010, for example, the estimated direct and indirect cost of CVD was approximately $315 billion.[2]

Burden

While CVD impacts much of the population, the distribution of burden and risk factors is not equal among subpopulations. Age, sex, and race/ethnicity are nonmodifiable risk factors that are associated with an increased burden of CVD in the United States. The prevalence of CVD (including heart disease, stroke, and other vascular diseases) increases progressively with age, with a lifetime risk for any CVD of almost two in three for men and greater than one in two for women who are free of disease at age 45 years.[4] 2010 U.S.-based data showed that individuals age 65 years or older carry the highest prevalence of coronary heart disease (CHD) (19.8%), with those ages 45 to 64 and 18 to 44 years having a prevalence of 7.1 and 1.2 percent, respectively.[5] Men also bear a higher burden of heart disease than women, with higher incidence at each age strata[2] and prevalence rates of 7.8 and 4.6 percent, respectively.[5] While men carry a higher burden of heart disease, women experience higher mortality from certain cardiovascular incidents, such as stroke.[2] One cause of this difference is that men tend to experience CVD events earlier in life. For myocardial infarction (MI), the mean age of first event is 64.9 years for men and 72.3 years for women.[2] Perhaps due to their increased age at first MI, women are more likely than men to die within weeks of having an MI.[2] In addition to age and sex differences, race and ethnicity are also associated with an increased burden of CHD. From 2006 to 2010, American Indians and Alaska Natives had the highest prevalence (11.6%) of heart disease followed by blacks (6.5%), Hispanics (6.1%), whites (5.8%), and Asians or Native Hawaiians/other Pacific Islanders (3.9%).[5]

CVD Risk Factors and Risk Assessment

Risk factors for CVD are well established and include both modifiable and nonmodifiable components. Modifiable risk factors include: high cholesterol, high blood pressure, diabetes, overweight and obesity, smoking, lack of physical activity, and unhealthy diet.[6-8] Nonmodifiable risk factors include: age, sex, and family history.[6,7,9,10]

Diabetes is an important risk factor, as prevalence of diabetes is increasing in the U.S. population and patients with diabetes incur a greater risk for heart disease than those without diabetes. In 2010, for example, 8.3 percent of the general population and 26.9 percent of those age 65 years or older had been diagnosed with diabetes mellitus, and these prevalence rates are increasing dramatically.[2,11] This high prevalence of diabetes, especially among older populations, is noteworthy because adults with diabetes are at a two- to four-fold risk for CVD events compared with those without diabetes.[11-13]

There are a number of CHD and CVD risk assessment tools available to clinicians and patients.[6,8,14-22] These tools are based on risk prediction equations derived from large prospective cohort studies, randomized trials, and primary care databases. Investigators have cited several sources of heterogeneity among risk assessment tools, including: the definition of CHD or CVD outcomes predicted, risk factors included, and variation in the baseline risk and other characteristics of model derivation cohorts.[23,24] These differences in tools can lead to different risk scores in the same patient.[24]

Characteristics of these tools are provided in **Appendix A**. The American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equation[14] and one of the six Framingham-based models by Anderson[25] predict global CVD outcomes and have been externally validated in U.S.-based populations. Models predicting CHD that have been externally validated in U.S.-based populations include those based on Framingham data by Anderson,[26] Wilson,[8] and the Adult Treatment Panel (ATP) III.[15] No stroke prediction model has been externally validated in the United States (**Appendix E Table 5**).

Mechanism of Action

While aspirin has long been used as a pain reliever, it began to gain traction as an effective antiplatelet drug therapy during the 1980s as clinical trials showed promising results.[27] Over the past two decades, researchers gained insights into the mechanism of aspirin and its use as an anticlotting agent to prevent the development of CVD. This research has revealed that atherosclerosis associated with CVD causes narrowing of the arteries and blood vessels through the thickening of the arterial wall, which may lead to reduced blood flow to the tissues and organs of the body.[28] Additionally, plaques may form in these narrowed vessels and break or rupture causing blood clots that can block blood flow to the heart or brain resulting in a heart attack or stroke.[28] Aspirin therapy helps to reduce these blood clots and, because of this, is often prescribed as a primary or secondary preventive measure for persons at high risk for MI/coronary events or stroke.

Aspirin belongs to the family of nonsteroidal anti-inflammatory drugs (NSAIDs) and has been determined to be an irreversible cyclo-oxygenase (COX)-1 and -2 enzyme inhibitor, although unlike other NSAIDs, it affects more of the COX-1 variant than COX-2.[29] When used in low doses (≤100 mg/day), aspirin works by preferentially inhibiting COX-1 activity, which results in a decreased production of thromboxane A2.[30] Thromboxane promotes platelet clotting and vasoconstriction, which explains aspirin's anticlotting effects.[29] With low doses of aspirin, throughout this process, COX-2 activity remains intact, which allows prostaglandin I2 (a

vasodilator and platelet inhibitor) to continue to be produced. COX-2 typically helps to produce prostanoids, the majority of which are proinflammatory and are an important part of the inflammatory response system.[31] This resulting decrease in thromboxane A2 and continued production of prostaglandin I2 explains aspirin's potential ability to diminish arterial thrombosis and prevent MI/coronary events and stroke.[29] The COX-1 enzyme is also responsible for producing a variety of prostaglandins, some of which are actively involved in protecting the gastrointestinal (GI) mucosa.[32] By inhibiting this enzyme, aspirin use can leave the patient vulnerable to GI bleeding, which is a major harm to consider when weighing the benefits of regular aspirin therapy.[29] At higher doses (≥300 mg/day), aspirin begins to inhibit COX-2 activity, taking on greater anti-inflammatory effects, but also increases the inhibition of prostaglandins produced by COX-1, further increasing the risk of GI bleeding in the patient.[29-31]

Current Clinical Practice in the United States

Research has demonstrated that aspirin therapy can effectively reduce the recurrence of serious vascular events in patients with a history of a previous MI, stroke, or transient ischemic attack (TIA) by approximately 20 percent.[33] Because of this consistently reported benefit, which has been found to significantly outweigh the risk of major bleeding, aspirin therapy for secondary prevention has gained widespread clinical acceptance.[33,34] The potential benefit of aspirin in primary prevention, however, is smaller because of the lower absolute risk in this population.[33] Therefore, many recommendations have focused on identifying primary prevention patients at sufficiently high CVD risk to outweigh bleeding harms. As illustrated in **Appendix E Table 1**, U.S.-based recommendations published more than 3 years ago by the U.S. Preventive Services Task Force (USPSTF),[35] AHA,[36] and American Diabetes Association[37] recommend aspirin for patients meeting various CVD/CHD risk thresholds. In contrast, European recommendations published more recently[38-41] do not recommend the use of aspirin in primary prevention, with the exception of a weak consideration from the United Kingdom's National Institute for Health and Care Excellence for use in patients with hypertension age 50 years or older with a greater than 20 percent 10-year CVD risk or reduced renal function.

The Centers for Disease Control and Prevention released data from 2007–2008 that demonstrates that physicians prescribed aspirin and other antiplatelet medications at relatively few visits in the population recommended by the USPSTF: 16.2 percent in men and 21.7 percent in women.[3] Possible reasons for low uptake of the recommendation could include lack of knowledge about guidelines, competing demands during the clinical encounter, or the expectation that patients will not adhere to advice.

Previous USPSTF Recommendations

In 2002, the USPSTF found good evidence from five randomized, controlled trials (RCTs) that aspirin decreases the incidence of CHD in adults at increased risk for heart disease.[42] It also found good evidence that aspirin increases the incidence of GI bleeding and fair evidence that aspirin increases the incidence of hemorrhagic stroke. The USPSTF concluded that the balance of benefits and harms is most favorable in patients at high risk for CHD (those with a 5-year risk

≥3%) but is also influenced by patient preferences. As a result, the USPSTF strongly recommended that clinicians discuss aspirin with adults who are at increased risk for CHD.[42]

In contrast to the 2002 recommendations, in 2009, the USPSTF concluded that there was evidence to support variations in aspirin use by age and sex.[35] Based on data from six RCTs, the USPSTF concluded there was good evidence that aspirin decreases the risk of MI/coronary events in men and ischemic strokes in women. It also concluded there was good evidence that aspirin increases the risk of GI bleeding and fair evidence that aspirin increases the incidence of hemorrhagic stroke. The USPSTF determined that overall reduction in CVD events with aspirin use is dependent on both baseline CVD risk (specifically, CHD risk in men and stroke risk in women) and risk for GI bleeding.[35] The USPSTF found insufficient evidence to assess the balance of risks and benefits in men and women age 80 years or older. There was modest certainty that the benefits of reducing MI/coronary events or ischemic stroke do not outweigh harms in men age 44 years or younger and women age 54 years or younger. As a result, the USPSTF recommended aspirin use for men ages 45 to 79 years for prevention of MI and for women ages 55 to 79 years for prevention of ischemic stroke when the potential benefit outweighs the risk of an increase in GI hemorrhage. The USPSTF recommended against treatment in men and women age 80 years or older and did not issue a recommendation for men age 44 years or younger or women age 54 years or younger.[35]

Since the previous review, results are now available from three new trials conducted in populations selected for diabetes, asymptomatic peripheral artery disease, or both.[43-45]

Chapter 2. Methods

Scope and Purpose

This systematic review will provide updated evidence regarding the benefits and harms of aspirin for the primary prevention of cardiovascular events. The USPSTF will use this review to update its 2009 recommendation on this topic.[35] This review included all trials from the previous review that met current inclusion and exclusion criteria as well as newly identified studies.

Key Questions and Analytic Framework

Using the USPSTF's methods (detailed in **Appendix B**),[46] we developed an analytic framework (**Figure 1**) and two key questions (KQs) in consultation with the Agency for Healthcare Research and Quality (AHRQ) Medical Officer and three members of the USPSTF. These KQs were adapted from questions addressed in the previous review.[35]

KQs

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 [ABI], 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 GI bleeding, hemorrhagic stroke, or other serious harms (e.g., age-related macular degeneration [ARMD])?
   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 ABI, or elevated blood pressure), GI bleeding or hemorrhagic stroke risk factors (including history of GI bleeding, ulcers, or NSAID use), or concomitant medication use (NSAIDs, selective serotonin reuptake inhibitors, or proton pump inhibitors [PPIs])?
   b. Does the effect vary by dose, formulation, or duration of aspirin use?

Data Sources and Searches

In addition to considering all studies from the previous review for inclusion in the current review, we performed a comprehensive search of MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials for studies published between January 2008 and June 3, 2014. We worked with a medical librarian to develop our search strategy (**Appendix B**). All searches were limited to articles published in the English language. We managed literature search results using version 12.0 of Reference Manager® (Thomson Reuters, New York, NY), a bibliographic management software database.

To ensure comprehensiveness of our retrieval strategy, we reviewed the reference lists of included studies and relevant systematic reviews and meta-analyses to identify relevant articles that were published before the timeframe of, or not identified in, our literature searches. We also obtained references from outside experts. In addition, we searched federal agency trial registries for ongoing trials (**Appendix D**).

Study Selection

Two reviewers independently reviewed the title and abstracts of all identified articles to determine if the study met the inclusion and exclusion criteria for design, population, intervention, and outcomes (**Appendix B Table 1**). Two reviewers then independently evaluated the full-text article(s) of all potentially relevant studies against the complete inclusion and exclusion criteria. Disagreements in the abstract and/or full-text review were resolved by discussion and consultation with a third reviewer if necessary. Excluded studies and reasons for exclusion are listed in **Appendix C**.

We developed an a priori set of criteria for inclusion and exclusion of studies based on criteria from the previous review and our understanding of the literature (**Appendix B Table 1**). For both KQs we considered studies examining the primary prevention of CVD (i.e., MI or stroke) in adults age 40 years or older. We excluded studies that included adult populations with an existing CVD diagnosis (heart failure, previous stroke, previous MI, TIA, angina, or previous bypass or angioplasty), atrial fibrillation, or hypercoagulable disorders. In addition, we did not consider studies in patients with familial hypercholesterolemia and other selected nongeneralizable populations. We included studies examining regular oral aspirin use (minimum of 75 mg every other day) compared to no treatment or a placebo. We excluded interventions including nonaspirin antithrombotic medications, aspirin as a cotreatment to another active intervention, and nonoral or nontablet forms of aspirin. In addition, we excluded studies that did not provide information on the dose of aspirin used or if limited to irregular or occasional aspirin use only. For KQ 1 (effectiveness of aspirin), we considered RCTs or controlled clinical trials reporting MI/coronary events (fatal and nonfatal), stroke (fatal and nonfatal), all-cause mortality, and quality of life. For KQ 2 (harms of aspirin), we considered RCTs, controlled clinical trials, or observational studies (i.e., cohort or case-control studies) reporting GI bleeding, hemorrhagic stroke (fatal and nonfatal), or other serious harms (e.g., ARMD).

Individual patient data (IPD) meta-analyses provide unique data that complement existing trial data, particularly for subpopulations. IPD meta-analyses were not pooled with primary trials due to double counting, but were discussed in relevant results sections when they provided data on subpopulations not available elsewhere.

For both KQs, we required a minimum of 1 year duration of aspirin treatment and study followup. We limited our included studies to those published in English and rated as good or fair quality using USPSTF quality rating standards.[47] We excluded studies that were rated as poor quality and those that did not publish results in English. The outcomes that were reviewed are fully listed in **Appendix B Table 1**.

Quality Assessment

Two reviewers independently assessed the methodological quality of each study using predefined criteria developed by the USPSTF[47] and supplemented with the National Institute for Health and Care Excellence methodology checklists for observational studies.[48] Disagreements in quality were resolved by discussion. Each study was given a final quality rating of good, fair, or poor.

Good-quality RCTs had adequate randomization procedures and allocation concealment, blinded outcome assessment, reliable outcome measures, similar groups at baseline (i.e., little to no statistically significant differences between groups in baseline characteristics), low attrition (≥90% of participants had followup data with <10 percentage point difference in loss to followup between groups), used intention-to-treat analysis, and reported diagnostic criteria for outcome ascertainment. Trials were downgraded to fair quality if they were unable to meet the majority of the good quality criteria. We rated trials as poor quality if attrition was greater than 40 percent or differed between groups by 20 percentage points, or if there were any other "fatal" flaws that seriously affected internal validity, as agreed upon by two independent investigators. We did not rate any trials as poor, however, based on these criteria.

Data Extraction

One reviewer extracted data from all included studies rated as fair or good quality into a standard evidence table (Microsoft Excel®; Microsoft Corporation, Redmond, WA) and a second reviewer checked data for accuracy. Elements abstracted included: population characteristics (e.g., baseline demographics, including CVD risk factors, concurrent conditions and medication use [i.e., antihypertension medications, lipid-lowering agents, selective serotonin reuptake inhibitors, PPIs, H2 blockers, or NSAIDs]); history of GI ulcers or treatment for *Helicobacter pylori*; study design (e.g., recruitment procedures, inclusion/exclusion criteria, followup, and adherence), intervention characteristics (i.e., aspirin dose, duration, formulation, and administration time), and outcomes as specified in the inclusion and exclusion criteria.

Health outcomes included the number and rate of participants experiencing an event and measures of association where reported; adjustments for confounders were noted as appropriate. For KQ 1 (effectiveness of aspirin), we abstracted the reported primary composite CVD outcomes from each included trial, describing in detail what elements composed each composite outcome. In addition, we abstracted fatal and nonfatal MI, coronary, and stroke events, separating by stroke type where reported. Furthermore, CVD-related and all-cause mortality data were abstracted for each included trial. For KQ 2 (harms of aspirin), we abstracted bleeding events with a focus on GI bleeding, intracranial bleeding, and hemorrhagic stroke.

Data Synthesis and Analysis

After the abstraction of data into evidence tables, we audited the outcomes reported across trials to assess heterogeneity of reporting. We identified 24 eligible outcomes (including variations for

fatal, nonfatal, and total events per category) that we prioritized into four primary outcomes based on a priori decisions from the criteria and the availability/consistency of outcome reporting across trials: 1) composite of death from MI/coronary events, stroke, and CVD, 2) nonfatal stroke, 3) nonfatal MI/coronary events, and 4) all-cause mortality. Seven secondary outcomes were also identified: 1) total stroke, 2) total MI/coronary events, 3) fatal MI/coronary events, 4) composite of fatal MI/coronary events and fatal stroke, 5) composite of nonfatal MI/coronary events and nonfatal stroke, 6) composite of MI/coronary events and stroke (fatal and nonfatal) combined with CVD mortality, and 7) CVD composites identified by the trial.

Because of substantial heterogeneity in the definition of trials' primary composite outcomes, and the fact that these composites included outcomes that were not eligible for our review (i.e., angina, revascularization) or not related to the aspirin pathway (i.e., abdominal aortic aneurysm, heart failure, pulmonary embolism), we constructed our own primary composite outcome of fatal MI/coronary events, fatal stroke, and cardiovascular death. When this outcome was not reported in primary studies, we combined fatal stroke, fatal MI/coronary events, and cardiovascular death. We also analyzed these outcomes individually. We defined fatal MI/fatal coronary events as fatal acute MI, sudden death (International Classification of Disease [ICD]-9 code 798: sudden death cause unknown), and all death attributable to ischemic heart disease (IHD) (ICD-9 codes 410–414). Where possible, we excluded abdominal aortic aneurysm, heart failure, and pulmonary embolism from the cardiovascular death composite. In some cases, however, these events were not reported separately and, as a result, it was possible that such events contributed to a trial's reported cardiovascular death composite. We assumed that these other causes of CVD-related mortality would represent few contributing events; this approach was preferable to excluding such trials in the analysis for the composite CVD mortality outcome.

When not reported, we calculated nonfatal (fatal) events by subtracting fatal (nonfatal) events from total events for an outcome category. Stroke type was not calculated from total stroke and another stroke type (i.e., calculate ischemic by subtracting hemorrhagic from total) unless the study reported that all strokes were ascertained or reported stroke of unknown type. If a combination of outcomes were not reported in a trial (i.e., total stroke), we added together its components where possible (i.e., fatal and nonfatal stroke).

For multifactorial trials with additional randomization to vitamins/antioxidants or placebo, we combined groups, as there was no evidence of interaction and evidence from systematic reviews supports that vitamins do not reduce the incidence of CVD.[49] In a trial with additional randomization to warfarin or placebo, we did not include these arms, as we considered warfarin a "cotreatment" that we excluded per inclusion criteria.

We limited our analysis of bleeding to major GI bleeding, defined as GI bleeding requiring transfusion or hospitalization or leading to death. If a trial reported transfusions and death from GI bleeding separately, we added these events together. If a trial only reported deaths from GI bleeding, we used that number for major GI bleeding (we recognize that these event rates will appear low compared to other studies also reporting nonfatal major GI bleeding). If a trial reported GI bleeding without any mention of severity, we did not include it in our analysis. While we considered minor GI bleeding, bleeding from other sites, and other serious harms, they are discussed in an accompanying systematic review.[50]

Because these studies were conducted in relatively healthy primary prevention populations, most outcomes were rare (i.e., generally <10% of participants experienced any given event, and <1% to 2% for some outcomes). Because of rare events, the Mantel-Haenszel fixed effects model was chosen as the primary statistical analysis method.[51] Sensitivity analyses were conducted using the Peto odds ratio (OR) method.[52] We assessed statistical heterogeneity using the I^2 statistic. We assessed small study bias using funnel plots and Peters test of bias for the four primary outcomes. None of these outcomes demonstrated a statistically significant relationship between effect size and study precision. The power was limited for these tests, however, because only nine to 10 studies were included for these outcomes.

Forest plots show adjusted values for relative risks (RRs) when primary studies adjusted for confounders, along with the Mantel-Haenszel pooled estimate. When measures of association were not reported, we calculated these measures using the number of individuals and the numbers of events in each randomized group. We used unadjusted values for sensitivity analyses using Peto ORs because of software/programming limitations. When events were reported as per unit of patient-years and the number of patient-years in each group was reported, we calculated the number of events in each group.

Given the small number of included trials, we chose not to pool several outcomes because of very small absolute numbers of events, which we believed could result in unstable and potentially misleading effect estimates. Although the outcomes we pooled were also rare events, large samples ensured that trials found at least 10 or more events in each treatment arm for most pooled outcomes. We did not pool outcomes, however, when a substantial number of trials reported fewer than 10 events in one or both treatment arms. We did not pool fatal stroke, for example, because of small numbers of events—six of nine contributing studies had fewer than 10 events in one or both groups. In contrast, we pooled the fatal MI/coronary event outcome, which had 10 contributing trials with only two having fewer than 10 events in each group. We did include the forest plots of outcomes we did not pool in a visual display of the data.

We used first-event analyses when trials reported both first and total event analyses. We chose this more conservative approach because after a first event, patients are more likely to have a second event in the same category. These patients are likely being treated for secondary prevention with other potentially confounding medical management, such as lipid therapy and administration of beta blockers or angiotensin-converting enzyme inhibitors. We identified both heterogeneity and a lack of reporting across trials regarding whether analyses were first event only or whether multiple events were allowed within or across outcome categories.

In order to explore the impact of heterogeneity in population characteristics and aspirin dose, we conducted sensitivity analyses to exclude four trials of special populations with diabetes, abnormal ABI, or both and aspirin doses of 325 mg or greater and greater than 100 mg. Forest plots were created that show daily aspirin dose. For trials using alternate day dosing, we divided the alternate day dose by two to generate the daily dose. Additionally, funnel plots were created to explore publication bias.

We did not pool the results of IPD meta-analyses with primary trials to avoid double counting. We discuss the results of these analyses separately. When results from long-term observational

followup were reported, these were not pooled, as followup was not randomized for the entire period. We addressed the results from these analyses qualitatively.

Subpopulation Methods

We prespecified subpopulations of interest in the KQs. These populations were selected based on analysis of subpopulation considerations in the previous review and recommendation, established characteristics associated with cardiovascular and/or bleeding risk, and subpopulations addressed in authoritative existing systematic reviews. During the data abstraction phase, we catalogued the availability and characteristics of subgroup analyses (i.e., whether analyses were a priori, post hoc, or unclear) for each subpopulation of interest for each trial and subsequently audited these results (**Appendix E Table 2**). Using this audit, formal subgroup analyses were prioritized based on the number of contributing studies and the credibility of subgroup analyses, with subpopulation-specific trials and a priori analyses given more weight.

We then entered data from subgroup analyses into evidence tables and further into summary tables for the prioritized analyses of sex, age, and diabetes. In addition to outcomes, subgroup summary tables included information relevant to the credibility of each trial's subgroup analyses, including timing of the analysis, interaction testing for heterogeneity of treatment effect, and if relevant, diagnostic criteria for the subgroup of interest. Direct evidence from within-study comparisons was emphasized over across-study comparisons, which can be confounded by differences in populations and their risk factors.

Based on a limited number of contributing studies for subgroup analyses, we did not pool results and instead analyzed them qualitatively.

Expert Review and Public Comment

A draft of the analytic framework, KQs, and inclusion/exclusion criteria was posted on the USPSTF Web site for public comment from July 11, 2013 to August 7, 2013. We received comments from 11 individuals or organizations. All comments were reviewed and addressed as appropriate. The final research plan was posted on the USPSTF Web site on October 3, 2013.

USPSTF Involvement

This research was funded by AHRQ under a contract to support the work of the USPSTF. The authors worked with three USPSTF liaisons at key points throughout the review process to develop and refine the scope, analytic framework, and KQs; to resolve issues around the review process; and to finalize the evidence synthesis. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the draft evidence synthesis, and distributed the initial evidence report for external review of content by outside

experts, including representatives of professional societies and federal agencies. We revised the final published systematic evidence review based on comments from these external reviewers.

Chapter 3. Results

Literature Search

Our literature search yielded 2,853 unique citations. From these, we provisionally accepted 61 articles for review based on titles and abstracts (**Appendix B Figure 1**). After screening the full-text articles, 10 trials (27 articles) were judged to have met the inclusion criteria for KQ 1 and nine trials (26 articles) met inclusion for KQ 2 (**Appendix B Figure 1**); the remaining articles were excluded (**Appendix C**).

Overview of Included Studies

Ten major RCTs (two good-quality and eight fair-quality) investigated the benefits of aspirin for the primary prevention of cardiovascular morbidity and mortality.[43-45,53-59] Nine of these studies examined the harms associated with aspirin use for primary prevention.[43-45,53,54,56-59] Details on study design and baseline participant characteristics are included in **Tables 1** and **2**.

KQ 1. Does Regular Aspirin Use in Patients Without Known CVD Reduce MI, Stroke, Death From MI or Stroke, or All-Cause Mortality?

Summary of Results

Based on a meta-analysis of the 10 primary prevention aspirin RCTs, aspirin appears to have a statistically significant, although modest, benefit on nonfatal MI/coronary events. It also showed a benefit for the composite outcomes of nonfatal stroke combined with nonfatal MI/coronary events and total stroke combined with total MI/coronary events (including CVD death). These composite findings were again largely driven by the reduction in nonfatal MI/coronary events. All-cause mortality may be unchanged or slightly reduced with aspirin; the statistically significant modest reduction was not persistent with sensitivity analyses in lower doses, nor was it seen in an IPD meta-analysis. A pooled analysis that only included low-dose aspirin trials (≤100 mg/day) showed a modest reduction in total stroke while still retaining much of the nonfatal MI benefit. All 10 trials were powered for composite outcomes, making it difficult to determine if the nonstatistically significant findings with some individual outcomes were due to lack of power. Each of the trials recruited participants from unique patient subpopulations, thereby making pooling potentially less useful for clinical application.

Trial Characteristics

Ten major RCTs (N=103,787), two good-quality and eight fair-quality, investigated the benefits of aspirin for the primary prevention of cardiovascular morbidity and mortality.[43-45,53-59] These

trials were conducted in the United Kingdom,[44,45,54,57] the United States, [53,55,58] Japan,[43] Italy,[59] or were multinational.[56] Six were conducted in the 1980s or 1990s,[53-57,59] with four trials starting recruitment in the mid-1990s or later.[43-45,58] Recent trials[44,45 ,43] published since the last review for the USPSTF[35] focus on special populations with diabetes, abnormal ABI, or both. While all 10 included studies were RCTs, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial [43] and the Primary Prevention Project (PPP)[59] were open-label trials.

Six of the 10 trials included 2x2 factorial designs with cotreatments of vitamins/antioxidants,[44,53,58,59] photocoagulation,[55] or warfarin.[54] One trial, the Hypertension Optimal Treatment (HOT) trial, was a 3x2 factorial design wherein patients were initially randomized to one of three diastolic blood pressure targets, then each of the target blood pressure groups were randomized to aspirin or placebo.[56]

The 10 primary prevention RCTs randomized a total of 103,787 participants with individual trial sizes ranging from 1,276 to 39,876 participants. The largest two trials were substantially larger than any other trials and both funded by the National Institutes of Health; the Women's Health Study (WHS) included more than 39,000 participants and its male counterpart, the Physicians' Health Study (PHS), included more than 22,000 participants.[53,58] Overall, followup times in the trials ranged from 3.6 to 10.1 years. PPP had the shortest followup time of less than 4 years.[59] The Aspirin for Asymptomatic Atherosclerosis (AAA) trial and WHS had the longest followup times of 8 and 10 years, respectively.[45,58]

Seven of the trials administered aspirin at a dosage of 100 mg or less daily or every other day;[43-45,54,56,58,59] one trial used 325 mg every other day,[53] one used 500 mg daily,[57] and one used 650 mg daily.[55] Half of the studies specified tablet formulation; two used enteric coated[45,59] and three trials used other or unspecified formulations.[43,44,56] Control groups received placebo,[44,45,53-56,58] nothing,[43,59] or were advised to avoid aspirin products.[57] Cotreatments included betacarotene,[53] antioxidant combination (alpha-tocopherol, ascorbic acid, pyridoxine hydrochloride, zinc sulphate, nicotinamide, lecithin, and sodium selenite),[44] vitamin E,[58,59] or warfarin.[54] Almost all of the trials were government sponsored, with the exception of HOT and the British Medical Doctor's (BMD) trial, which were industry sponsored.[56,57]

Primary outcomes for seven trials were cardiovascular event composites, which involved combining cardiovascular mortality events and nonfatal events defined variably;[43-45,54,56,58,59] two trials' primary outcomes were cardiovascular mortality event composites,[53,57] and one trial's primary outcome was all-cause mortality.[55] Secondary outcomes generally included several of the following: event rates for individual outcomes of fatal stroke, nonfatal stroke, fatal MI, nonfatal MI, cardiovascular mortality, or all-cause mortality. Eight studies specified stroke etiology as hemorrhagic versus ischemic.[43-45,53,54,57-59] It is important to note that all of the trials were only powered to detect differences in the composite outcomes. Harms outcomes were reported quite variably and included, for some (but not all) trials, one or more of the following: GI bleeding,[43-45,54,56-59] fatal GI bleeding,[53,56,58] subarachnoid/subdural hemorrhage,[43,45,56] major bleeding composites,[45,56 44,54] hemorrhagic/peptic ulcers,[43,45,57,58] bleeding requiring transfusion,[43,53,58] and/or minor bleeding.[43,45,53-56,58,59] Bleeding events were variably defined and ascertainment unreported for most trials.

MI and stroke were clearly defined using World Health Organization (WHO) or modified AHA criteria in all except two trials—BMD and the Early Treatment Diabetic Retinopathy Study (ETDRS).[55,57] Cardiovascular deaths were variably defined and often included events outside of fatal MI/coronary events or fatal stroke, such as deaths due to rheumatic fever, pulmonary embolism, abdominal aortic aneurysm, or hypertensive disease. Events were ascertained using a combination of death certificates, national registries, hospital and outpatient records, autopsies (when available), and physician and patient questionnaires. Independent blinded endpoint committees confirmed events in all trials.

PHS and WHS had run-in periods of 12 to 18 weeks.[53,58] Compliance with aspirin therapy in the intervention group was variably reported and ascertained from participant questionnaires in the eight studies reporting compliance. The Thrombosis Prevention Trial (TPT) was the only trial that used pill counts or salicylate levels to measure compliance/crossover. At 5 years, PHS, BMD, and ETDRS reported 70 to 89 percent of participants taking aspirin or other platelet affecting drugs.[53,55,57] Despite TPT's nearly 50 percent withdrawal rate, those continuing in both groups missed only 2 percent of tablets based on pill counts and only 6.8 percent in the intervention group had salicylate levels indicating no recent aspirin use. At the end of the trial (median, 4.37 years), JPAD reported 90 percent compliance in the aspirin group.[43] At 5 years, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial reported that 50 percent of the total participants were not taking their assigned tablets (placebo or aspirin).[44] Followup data on mortality events was available for 97 to 100 percent of participants in all RCTs except JPAD, which had 92.4 percent followup completion. Three trials reported less than 1 percent withdrawal rates.[43-45] TPT had a high withdrawal rate of 42 percent at 5 years.[54] Six trials did not report withdrawals.[53,55-59]

All trials used ITT analyses. All but one trial[55] clearly reported valid random assignment procedures. Proper allocation concealment was reported in seven trials.[43-45,53-56] Seven of the RCTs reported adequate blinding of providers, patients, and outcome assessors. One trial[57] did not clearly report blinding and two trials were open-label.[43,59] Trials reported outcome associations predominantly as RRs, with a few as hazard ratios (HRs), and only four trials adjusted their primary outcome for confounders.[45,53,55,58]

Participant Characteristics

Three trials were conducted in healthy male or female health care professionals.[53,57,58] Seven trials included participants who would be considered at higher than average cardiovascular risk: patients with diabetes;[43] patients with diabetic retinopathy;[55] patients with diabetes and ABI less than or equal to 0.99;[44] patients with hypertension;[56] individuals with abnormal ABI less than or equal to 0.95;[45] individuals with at least one CVD risk factor;[59] or those at high risk for ischemic disease based on the Northwick Park Heart Study algorithm.[54] The lower age limit of inclusion in ETDRS was 18 years, but it ranged from 30 to 40 years in other trials. HOT and JPAD specified age 80 and 85 years as upper limits, while POPADAD specified no upper age limit. All studies were intended to target primary prevention candidates and excluded participants with a history of stroke or MI, except HOT and TPT, which only excluded those with an MI/coronary event or stroke in the recent past or occurring in the 12 months prior to recruitment. All studies excluded those taking current or regular aspirin therapy, as well as those with aspirin contraindications or

allergies. Seven of the trials excluded those with a history of peptic ulcer disease,[43,44,53,54,57] GI hemorrhage,[55] or severe indigestion.[45] Four trials excluded those with poor survival prognosis.[44,55,56,59]

In the seven studies that reported mean ages, the mean age was relatively young and ranged from 54.6 to 64.5 years.[43-45,54,56,58,59] Ninety percent of WHS participants were younger than 65 years; 75 percent of PHS participants were younger than 60 years. Three trials recruited only men,[53,54,57] one trial recruited only women,[58] and six trials included both sexes, with 43.5 to 71.5 percent being women.[43-45,55,56,59] Only WHS and ETDRS, both U.S.-based RCTs, reported information on race. WHS reported 5.2 percent of participants were nonwhite and ETDRS reported 23.6 percent of participants were nonwhite.[55,58] Other than the JPAD trial that was conducted in Japan,[43] most of the trials, especially the European trials, probably recruited predominantly Caucasian participants.

Participants' baseline cardiovascular event risks varied widely, as evidenced by the incidence of a composite of CVD events (all MI/coronary events combined with all stroke and CVD death) in the control groups ranging from 2.6 percent over 10.1 years (annualized 0.2% per year, assuming a constant event rate) in WHS (a population of female health professionals) to 20.4 percent over 5 years (annualized 4.1% per year) in ETDRS, a population with diabetic retinopathy. All 10 RCTs reported the percent of current smokers at baseline, which ranged from 6.1 to 44.2 percent. Mean or median body mass index (BMI) at baseline was only reported in six trials and ranged from 24.0 to 29.2 kg/m^2.[54,56,58,59,43,44] Six trials reported the percent of patients with hypertension at baseline, which ranged from 9.9 to 68.0 percent in five trials,[43,55,57-59] and one trial was exclusively in participants with hypertension.[56] Only four trials reported dyslipidemia frequency at baseline, ranging from 29.5 to 53.0 percent.[43,55,58,59] Nine trials reported diabetes comorbidity, with four trials including 2.0 to 3.0 percent participants with diabetes,[53,57,58,45] one trial including 8.0 percent diabetes patients,[56] one trial including 17 percent diabetes patients,[59] and three trials were exclusively conducted in diabetes patients.[43,44,55] Three trials reported less than 10 percent of participants had prior CVD.[55-57]

Results by Outcome

Effect of Aspirin on All-Cause Mortality

Ten trials reported the outcome of all-cause mortality with all showing nonstatistically significant results.[43-45,53-59] Nine trials reported RRs of 0.81 to 0.96 and one trial reported an RR crossing 1 (**Figure 2**, **Table 3**).[54] A pooled analysis showed that aspirin has a statistically significant effect on all-cause mortality (RR, 0.94 [95% confidence interval (CI), 0.88 to 0.99]; I^2=0%). A sensitivity analysis using the Peto OR yielded similar results (OR, 0.93 [95% CI, 0.88 to 0.99]; I^2=0%) (**Table 4**). The Antithrombotic Trialists (ATT) IPD meta-analysis of six trials did not show an all-cause mortality benefit with aspirin use (RR, 0.95 [95% CI, 0.88 to 1.02]).[33]

Effect of Aspirin on MI/Coronary Events

Table 5 presents MI/coronary event results for the 10 trials included for this KQ.[43-45,53-59] Total MI/coronary event incidence in the control group ranged from 1 percent over 10.1 years in

WHS[43,58] (annualized 0.1% per year assuming constant event rate) to 15 percent over 5 years in ETDRS (annualized 3.1% per year),[55] which reflects a wide range of baseline risk. For total MI/coronary events (fatal combined with nonfatal), two trials showed a statistically significant benefit with aspirin[53,56] and the remaining eight trials had CIs crossing 1, with five trials favoring aspirin,[43,54,55,57,59] two trials favoring the control,[44,45] and one showing no effect (**Figure 3**, **Table 5**).[58] The two trials[53,56] that showed a statistically significant benefit reported an RR of 0.67 (95% CI, 0.55 to 0.80) and 0.74 (95% CI, 0.60 to 0.91). A pooled analysis for total MI/coronary events showed a statistically significant effect with high heterogeneity (RR, 0.85 [95% CI, 0.79 to 0.92]; I^2=52.1%) (**Figure 3**, **Table 4**). While diabetes status, aspirin dose, year of publication, and effect size were explored to explain the high heterogeneity, none of these variables elucidated its presence.

As with total MI/coronary events, fatal event rates in the control groups varied widely, with the lowest annualized incidence in WHS and highest in ETDRS[55,58] (**Figure 4**, **Table 5**). All trials reported no statistically significant effect of aspirin on fatal MI/coronary events. Six trials reported a trend favoring aspirin,[43,53,55-57,59] while the other four trials favored the control group.[44,45,54,58] A pooled analysis from these 10 trials showed a nonstatistically significant reduction in fatal MI/coronary events (RR, 0.94 [95% CI, 0.82 to 1.09]; I^2=15.5%) (**Figure 4**, **Table 4**). Sensitivity analyses using the Peto OR yielded similar results (**Table 4**).

Nonfatal MI/coronary event rates in the control group again varied among the nine trials, with the lowest annualized incidence in WHS and highest in POPADAD.[44,58] Three trials showed a statistically significant benefit for aspirin[53,54,56] and two additional trials showed results trending in this direction (**Figure 5**, **Table 4**).[45,59] While three trials' point estimates were near 1[44,57,58] and only one trial showed a trend toward favoring the control group, these results were based on few reported events (9/1,277 in the control group, 12/1,262 in the aspirin group).[43] A pooled analysis showed a statistically significant benefit for aspirin in preventing nonfatal MI/coronary events similar to that seen for total MI/coronary events and again, heterogeneity was high (RR, 0.80 [95% CI, 0.72 to 0.88]; I^2=62.8%) (**Figure 5**, **Table 4**). A sensitivity analysis using the Peto OR yielded similar results (Peto OR, 0.79 [95% CI, 0.71 to 0.88]; I^2=61.4%) (**Table 4**). Exploration of this heterogeneity by aspirin dose, date of publication, and diabetes status did not explain heterogeneity.

Effect of Aspirin on Stroke

Table 6 presents stroke results for the 10 trials. Total stroke incidence ranged from 1.3 percent over 10.1 years in WHS (annualized rate of 0.13% per year assuming a constant event rate) to 7.8 percent over 6.7 years in POPADAD (annualized rate of 1.2% per year) in the control groups.[44,58] For total stroke (fatal combined with nonfatal), one trial showed a statistically significant benefit favoring aspirin (RR, 0.83 [95% CI, 0.69 to 0.99]);[58] four trials showed a similar trend, although their results were not statistically significant (**Figure 6**, **Table 6**).[43,45,54,59] Conversely, three trials showed a nonstatistically significant trend favoring the control, with RR point estimates ranging from 1.16 to 1.22.[53,55,57] A pooled analysis examining aspirin's effect on total stroke events showed no effect (RR, 0.95 [95% CI, 0.86 to 1.05]; I^2=28.4%) (**Figure 6**, **Table 4**). Sensitivity analyses showed that pooling only trials using low-dose aspirin (defined as ≤100 mg) showed a modest statistically significant benefit (RR, 0.85 [95% CI, 0.76 to 0.96];

I^2=0), while pooling the high-dose trials alone showed no difference (RR, 1.19 [95% CI, 1.00 to 1.42]; I^2=0%), suggesting a stroke benefit using lower doses of aspirin (**Table 7**).

Fatal stroke events were rare in the control group and varied among the trials with the lowest annualized incidence in WHS and the highest in ETDRS (**Figure 7**, **Table 6**).[55,58] Four trials showed a nonstatistically significant trend favoring aspirin, with RR point estimates ranging from 0.17 to 0.89.[43-45,59] Two trials showed no difference with an RR of 1[55,58] and three trials[53,54,57] showed a nonstatistically significant trend favoring the control with RRs of 1.25 to 2.01. We did not conduct a pooled analysis examining aspirin's effect on fatal stroke events because of the rarity of the event (six RCTs reported ≤10 events in either treatment group).

The annualized incidence of nonfatal stroke reported in the control groups varied 10-fold between WHS with the lowest incidence and POPADAD with the highest (**Table 6**).[44,58] Results were mixed, however, with RR point estimates ranging from 0.64 to 1.26 (**Figure 8**).[54,55] One trial showed a statistically significant benefit for aspirin,[58] three trials showed a trend toward benefit with aspirin,[44,54,59] and two trials showed essentially no difference.[43,45] Three included trials, on the other hand, showed a nonstatistically significant trend favoring the control.[53,55,57] A pooled analysis from these nine trials showed no difference in nonfatal stroke effects in the aspirin group compared to the control group (RR, 0.94 [95% CI, 0.84 to 1.06]; I^2=32.3%) (**Figure 8**, **Table 4**).

In the four trials that reported total stroke by subtype,[45,53,54,58] one trial showed a statistically significant reduction in total ischemic stroke (fatal combined with nonfatal) in the aspirin group,[58] two trials showed a trend in this direction,[45,54] and one trial showed a nonstatistically significant trend favoring the control (**Figure 9**, **Table 6**).[53] We did not pool data for stroke by subtype because few studies reported this rare outcome.

The majority of ischemic strokes were nonfatal (**Table 6**). The two trials reporting both fatal and nonfatal ischemic strokes showed that fatal ischemic stroke represented only 3.6 and 13.4 percent of total ischemic strokes.[45,53] Fatal ischemic events were rare in the four trials reporting this outcome, with three to seven events in the control groups and mixed results with no statistically significant findings (**Figure 10**, **Table 6**).[44,45,53,57] Similarly, four trials reported nonfatal ischemic stroke outcomes and reported no statistically significant results in any of the trials with mixed results,[43,45,53,57] with the two trials with higher dosage aspirin trending toward favoring the control (**Figure 11**, **Table 6**).[53,57] Hemorrhagic stroke is later addressed as a harm in KQ 2 results.

Effect of Aspirin on Fatal MI/Coronary Events Combined With Fatal Stroke

Nine trials contributed events to the composite outcome of fatal MI/coronary events combined with fatal stroke (**Figure 12**).[43-45,53-55,57-59] Only one trial reported a statistically significant reduction in this fatal composite, appearing as an outlier with the most impressive RR in favor of aspirin and a wide CI (RR, 0.10 [95% CI, 0.01 to 0.79]).[43] The remaining eight trials showed no statistically significant difference. Of these, three trials showed trends in favor of aspirin, two in favor of the control,[53,55,59] and three trials with RRs near 1.[53,54,57,58] A pooled analysis showed a nonsignificant effect with aspirin treatment (RR, 0.96 [95% CI, 0.83 to 1.10]; I^2=29.5%) (**Figure**

12, **Table 4**). Sensitivity analyses revealed similar conclusions (Peto OR, 0.94 [95% CI, 0.82 to 1.09]; I^2=41.8%) (**Table 4**).

Effect of Aspirin on Fatal MI/Coronary Events Combined With Fatal Stroke and CVD Mortality

Ten trials contributed to the composite outcome of fatal MI/coronary events combined with fatal stroke and CVD mortality (**Figure 13**). Results for individual trials were not substantially different for this composite compared to the fatal MI/coronary events combined with fatal stroke composite. A pooled analysis showed no statistically significant effect with aspirin (RR, 0.94 [0.85 to 1.03]; I^2=16.4%) (**Figure 13**, **Table 4**). Sensitivity analyses yielded similar results (**Table 4**).

Effect of Aspirin on Nonfatal MI/Coronary Events Combined With Nonfatal Stroke

Eight trials contributed to the composite outcome of nonfatal MI/coronary events combined with nonfatal stroke (**Figure 14**). Two trials showed a statistically significant reduction in events,[53,54] four trials showed a nonsignificant trend in the same direction,[44,45,58,59] and two trials showed nonsignificant RRs just above 1.[43,57] A pooled analysis showed a statistically significant benefit in this nonfatal composite outcome (RR, 0.86 [95% CI, 0.79 to 0.93]; I^2= 16.2%) (**Figure 14**, **Table 4**). Sensitivity analyses yielded nearly identical results (**Table 4**).

Effect of Aspirin on Total MI/Coronary Events Combined With Total Stroke and CVD Mortality

Ten trials contributed to the composite outcome of total MI/coronary events combined with total stroke and CVD mortality (**Figure 15**).[43-45,53-59] Three trials showed a statistically significant benefit with RR point estimates ranging from 0.76 to 0.85,[53,54,59] while five trials had nonstatistically significant results in the same direction.[43,44,55,56,58] Two trials had RRs near 1.[45,57] A meta-analysis of these trials demonstrated that aspirin had a statistically significant beneficial effect on this composite outcome (RR, 0.89 [95% CI, 0.84 to 0.94]; I^2=0%) (**Figure 15**, **Table 4**). Sensitivity analyses yielded nearly identical results (**Table 4**).

Effect on Quality of Life

No included trial reported quality of life outcomes.

KQ 1a. Does the Effect Vary Between a Priori Subgroups: Age, Sex, Smoking Status, Race/Ethnicity, 10-Year Cardiovascular Risk, or Related Risk Conditions?

Summary of Results

All 10 trials described in KQ 1 addressed issues of effect modification by subgroup.[43-45,53-59] In

addition to these individual trials, the ATT IPD meta-analysis pooled the results from six of the aforementioned primary prevention trials[53,54,56-59] (n=95,000; 660,000 person-years), which provided additional information on subgroup related issues.[33] Our analysis defined a priori subpopulations of interest to include age, sex, diabetes status, smoking history, CVD risk status, patients with abnormal ABI, patients with elevated hypertension, and patients with elevated lipids.

Six trials reported age-specific results (**Tables 8–10**).[53,44,45,43,58,60] Three trials showed a consistent pattern of greater RR reduction in total MI/coronary events with older age,[53,58,60] with two of these trials showing statistically significant interactions.[58,60] Additionally, three trials showed aspirin had no effect on stroke events by age group. Likewise, none of the age strata showed a statistically significant benefit, and the one trial that performed interaction testing showed no interaction between age and stroke events.[54,58,60] Six trials showed conflicting results for the interaction between age and various measured composite CVD outcomes, and three trials performing interaction testing found no statistically significant interaction between age and reported CVD composite outcomes.[43-45,53,58,60] The ATT IPD meta-analysis did not show any heterogeneity of effect for composite CVD events based on age (<65 vs. ≥65 years).[33] Additionally, one trial showed no statistically significant difference in all-cause mortality in either patients age 65 years or younger or those age 65 years or older.[60]

Ten trials reported sex-specific results.[43-45,53-55,57,58,60,61] Three of these trials were conducted exclusively among men[53,54,57] and one trial was conducted exclusively among women (**Tables 11–13**).[58] In the six trials that included both men and women,[43-45,55,56,59] only two trials clearly specified sex as an a priori subgroup.[43,45] Three trials adjusted for confounders: ETDRS (adjusted for age, diabetes type, and clinical center), PHS, and WHS (adjusted for age and treatment assignment).[53,55,58] The ATT IPD meta-analysis showed that the apparent sex-specific differences in MI/coronary events and ischemic stroke events were no longer statistically significant after controlling for multiple comparisons.[33] The four additional trials not included in the ATT IPD meta-analysis[43-45,55] showed no difference in composite CVD outcomes between the sexes; the one trial that reported individual event outcomes by sex[55] showed no difference in the individual outcomes of total MI/coronary events or total stroke between the sexes.

Three trials specifically recruited patients with diabetes.[43,44,55] An additional five trials performed subgroup analyses on patients with diabetes,[45,53,58,62,63] although only one trial clearly designated the analysis a priori (**Tables 14–16**).[58] Three of these additional trials performed interaction testing[53,62,63] and two trials adjusted for confounders.[53,58] These trials reported no statistically significant benefit for aspirin in diabetes patients for all-cause mortality, MI/coronary events, or stroke. Likewise, the results for composite CVD outcomes were nonsignificant and conflicting. The ATT IPD meta-analysis analyzed a composite outcome of serious vascular events and showed no statistically significant effect of aspirin in patients with diabetes and no heterogeneity of effect by diabetes status.[33]

Six trials reporting subgroup results for smoking, CVD risk, and abnormal ABI showed varied results.[43-45,53,58,64] For smoking, two trials showed no interaction or statistically significant trend in MI/coronary events or stroke with smoking.[43,53] Conversely, another trial showed a trend of statistically significant benefit in patients who have never smoked, which was not seen in

current/past smokers for total stroke, ischemic stroke, and a CVD event composite.[58] Overall, no clear relationship between smoking status and aspirin effects was apparent. For CVD risk, two trials[58,64] performed risk-based subanalyses and a third trial was conducted in a high-risk CVD population.[54] None of these trials clearly reported interaction testing or adjustments for confounders and only one analysis was clearly reported as a priori.[58] One trial with subgroup analysis by CVD risk showed that only participants with greater than 20 percent 10-year risk had a statistically significant reduction in total MI and the trial's reported CVD composite;[56] one exclusively female trial showed that only participants with a greater than or equal to10 percent 10-year CVD risk had a statistically significant reduction in total stroke.[58] The one trial conducted in high-risk men showed a statistically significant reduction in nonfatal MI/coronary events and in a nonfatal composite CVD outcome.[54] The ATT IPD meta-analysis showed a statistically significant reduction in total serious vascular events only in the patients with less than 5 percent 5-year CVD risk, but heterogeneity testing revealed no statistical heterogeneity between the risk groups.[33] Based on two trials recruiting participants with an abnormal ABI, there appears to be no modification of treatment benefit based on ABI threshold.[44,45]

Trials examining the subgroup effects of patients with elevated blood pressure or lipid levels reported conflicting results, making it difficult to draw any conclusions about a differential benefit of aspirin in these groups. Five trials performed subgroup analyses in hypertensive and normotensive groups or for systolic blood pressure (SBP)/diastolic blood pressure (DBP) levels with varied results.[53,58,64-66] One of these trials, HOT, showed a trend of higher SBP and DBP being associated with a greater reduction in major cardiovascular events and total MI.[64] Conversely, another of these trials reported an interaction with lower SBP leading to a greater RR reduction in total stroke,[66] but the timing of their analysis is unclear. Further, one trial reported no trends in the RR of total MI/coronary events or CVD mortality by SBP/DBP level.[53] As a result, the results of these studies were inconsistent.

Four trials reported subgroup analyses by total cholesterol levels or by presence or absence of dyslipidemia (defined as total cholesterol ≥240 mg/dL in WHS; not defined in JPAD).[43,53,58,66] While two of these trials performed subgroup analyses a priori,[43,58] the other two trials do not specify the timing of their analyses.[53,66] Two trials were conducted exclusively in men and showed an interaction between aspirin use and lipid levels, with greater aspirin benefit seen in patients with the lowest cholesterol levels for total MI/coronary events or total stroke.[53,66] Another trial, which was conducted exclusively in women, showed a statistically significant reduction in composite CVD outcomes, total stroke, and ischemic stroke with aspirin therapy, which was not seen in the normal cholesterol group.[58]

Age

Trial Characteristics

In the seven studies that reported mean ages, the mean age was relatively young and ranged from 54.6 to 64.5 years.[43-45,54,56,58,59] Ninety percent of WHS participants were younger than age 65 years and 75 percent of PHS participants were younger than age 60 years. In three trials, approximately half of participants were older than age 60 to 65 years.[43,44,59] The upper age limit was specified in the inclusion criteria for six trials, ranging from 69 to 85 years.[43,45,53-56]

Three trials reported age as an a priori subgroup: JPAD (<65 and ≥65 years), AAA (<62 and ≥62 years), and WHS (45 to 54, 55 to 64, and ≥65 years).[43,45,58] The only two trials that compared the same age group strata were JPAD and HOT (<65 and ≥65 years).[43,60] The ATT IPD meta-analysis analyzed the composite outcome of serious vascular events (defined as MI, stroke, or death from a vascular cause, including sudden death, pulmonary embolism, and hemorrhage) by patients younger than age 65 and patients age 65 years or older.[33]

Results by Outcome

Effect of Aspirin on All-Cause Mortality by Age

Only one trial, HOT, reported all-cause mortality by age and reported no statistically significant effect of aspirin on all-cause mortality in either patients younger than age 65 years or those age 65 years or older (**Table 8**).[60]

Effect of Aspirin on MI/Coronary Events by Age

Three trials provided subgroup analyses by age for total MI, but only WHS had an a priori analysis (**Table 9**).[53,58,60] HOT and WHS both showed a statistically significant reduction in total MI/coronary event among patients age 65 years or older (HOT: RR, 0.62 [95% CI, 0.38 to 0.98];[60] WHS: adjusted (adj)RR, 0.66 [95% CI, 0.44 to 0.97][58]). PHS showed a greater RR reduction with older age: it decreased from 1.12 (ages 40 to 49 years) to 0.49 (ages 70 to 84 years), with a statistically significant trend (p=0.02).[53] These studies appear to show a consistent trend of greater RR reduction in total MI/coronary events with aspirin use with older age; both PHS and WHS reported p-values for interaction of 0.02 and 0.03 with age.[53,58] A 2011 post hoc analysis of WHS showed that aspirin treatment resulted in less than 1 percent absolute risk reduction in major cardiovascular events among the majority of patients (>90%); age was the strongest determinant of treatment effect, where older women (age ≥65 years) had the highest absolute treatment effects.[67]

The ATT IPD meta-analysis did not find any heterogeneity of effect on major coronary events by age.[33]

Effect of Aspirin on Stroke by Age

Three trials provided subgroup analyses by age for total stroke, but again, only WHS clearly specified theirs as an a priori analysis (**Table 10**).[54,58,60] None of these trials showed a statistically significant difference in stroke outcomes between the aspirin and control groups for any age strata. These trials revealed no trend in nonsignificant RRs. Of these trials, only TPT conducted interaction testing, showing no interaction between stroke and age (p=0.85 for interaction).[54] WHS showed no statistically significant benefit for ischemic stroke in any of the age strata (45 to 64, 55 to 64, or ≥65 years).[58]

Effect of Aspirin on Composite Outcomes by Age

Six trials provided subgroup analyses by age for composite outcomes (**Table 8**).[43-45,53,58,60]

JPAD, POPADAD, and WHS performed interaction testing; JPAD and POPADAD showed no interaction between age and composite outcomes measured, while WHS showed a borderline statistically significant interaction (p=0.05).[43,44,58] Additionally, AAA and HOT showed nonstatistically significant interactions for their fatal CVD composite outcome; however, both trials showed trends of benefit favoring aspirin among younger patients (<62 or 65 years) and among the older age groups (≥62 or 65 years) favoring control.[45,60] Further, HOT showed a statistically significant reduction in its total CVD composite among patients younger than age 65 years (RR, 0.79 [95% CI, 0.64 to 0.98]), but not in patients age 65 years or older.[60] Conversely, WHS showed a statistically significant reduction in its CVD event composite only among patients in the oldest age group (≥65 years) (adjRR, 0.74 [95% CI, 0.59 to 0.92]), which comprised only 10 percent of its total trial population.[58]

The ATT IPD meta-analysis showed a statistically significant reduction in its composite of serious vascular events (defined as MI, stroke, or death from a vascular cause, including sudden death, pulmonary embolism, and hemorrhage) among patients younger than age 65 years, but not among patients age 65 years or older, and found no heterogeneity of effect on serious vascular events by age.[33]

Sex

Trial Characteristics

All 10 trials included in this KQ reported sex-specific outcomes.[43-45,53-55,57,58,60,61] Four trials recruited a single sex: BMD, PHS, and TPT recruited only men, while WHS recruited only women.[53,54,57,58] Two trials reported outcomes for an a priori sex subgroup analysis.[43,45] Four trials reported outcomes by sex without specifying if the analysis was prespecified or post hoc.[44,55,60,61] WHS was the largest trial (n=39,876) with the longest followup (10.1 years) that contributed sex-specific information.[58] The six trials that included both sexes recruited study populations that were between 43.5 and 72.0 percent women.[43-45,55,56,59] The ATT IPD meta-analysis[33] included sex-specific results for the outcomes of ischemic stroke and major coronary events (defined as MI, coronary death, or sudden death), and performed interaction testing and adjustments for multiple comparisons. In 2013, 8 years after the completion of WHS, an observational followup of a median of 18 years comprising 33,682 patients out of the original 39,876 randomized trial participants (88.6%) was published using annual participant questionnaires and medical record review.[68] These results were similar to the previously published results and reported no differences between treatment groups for major CVD events, MI, total stroke, or CVD mortality. These results did find, however, a statistically significant reduction in ischemic stroke events.[68]

Results by Outcome

Effect of Aspirin on All-Cause Mortality by Sex

All-cause mortality by sex was reported in seven trials, with aspirin showing no effect when men and women were analyzed separately (**Table 11**).[53,57,58 54,55,60,61]

Effect of Aspirin on MI/Coronary Events by Sex

Seven trials reported total MI/coronary events by sex, with BMD, TPT, and PHS providing results for fatal and nonfatal MI/coronary events separately (**Table 12**).[53-55,57,58,60,61] For total MI, only HOT showed a beneficial effect in men, but not women (men: RR, 0.58 [95% CI, 0.41 to 0.81]; women: RR, 0.81 [95% CI, 0.49 to 1.31]).[60] PHS showed a reduction in total MI/coronary events with aspirin (RR, 0.67 [95% CI, 0.55 to 0.80]),[53] but the other two trials conducted exclusively in men[54,57] showed no effect of aspirin on total MI/coronary events. WHS showed no effect of aspirin on total MI/coronary events in women.[58] The ATT IPD meta-analysis reported major coronary events (defined as MI/coronary events, coronary death, or sudden death) and showed that after testing for heterogeneity or trend, the only statistically significant subgroup difference was between men and women (p=0.03). This finding, however, was no longer significant when adjusted for multiple comparisons (p=0.33).[33] All three of the trials conducted only in men showed no effect of aspirin for fatal MI.[53,54,57] Two of these trials showed a reduction in nonfatal MI/coronary events[53,54] and the remaining trial showed no effect of nonfatal MI/coronary events.[57]

Effect of Aspirin on Stroke by Sex

Seven trials reported total stroke events by sex (**Table 13**).[53-55,57,58,60,61] Only one trial showed a statistically significant reduction in total stroke in women.[58] The other six trials showed no statistically significant effect of aspirin in either men or women.[53,57 54 55,60,61] BMD, PHS, TPT, and WHS reported fatal and nonfatal stroke separately and all showed no statistically significant difference in fatal stroke events, which were relatively rare in most trials.[53,54,57,58] The three trials conducted exclusively in men showed no effect of aspirin on nonfatal stroke events[53,54,57] and the one trial conducted in women showed a statistically significant reduction in nonfatal stroke events (adjRR, 0.81 [95% CI, 0.67 to 0.97]).[58]

Five trials reported stroke subtype by sex, but interpretation is limited by the rarity of stroke events, especially when broken down by subtype and fatal versus nonfatal.[53,54,57,58,61] Looking at all ischemic stroke, only WHS showed a statistically significant reduction in all ischemic stroke among women (adjRR, 0.76 [95% CI, 0.63 to 0.93]).[58] The ATT IPD meta-analysis analyzed ischemic stroke by sex. After testing for heterogeneity of effect, this trial reported that any subgroup difference between men and women (p=0.08) was no longer significant when adjusted for multiple comparisons (p=0.88).[33]

Effect of Aspirin on Composite Outcomes by Sex

For composite CVD outcomes, trials reported no statistically significant effect of aspirin, with the exception of two trials conducted exclusively in men (**Table 11**).[53,54] Both of these studies—TPT and PHS—showed a statistically significant reduction in a total CVD composite (TPT: RR, 0.76 [95% CI, 0.60 to 0.97]; PHS: adjRR, 0.82 [95% CI, 0.70 to 0.96]) and a CVD composite comprised of nonfatal stroke/MI/coronary events (TPT: RR, 0.64 [95% CI, 0.47 to 0.88]; PHS: RR, 0.78 [95% CI, 0.66 to 0.93]). Additionally, WHS did not show a statistically significant benefit for any composite outcomes.[58] The ATT IPD meta-analysis of the composite outcome of serious vascular events (defined as MI, stroke, or death from a vascular cause, including sudden

death, pulmonary embolism, and hemorrhage) by sex revealed no significant heterogeneity between men and women (p=0.9).[33]

Diabetes

Trial Characteristics

Three trials only recruited patients with diabetes[43,44,55] and an additional five trials performed subgroup analyses on patients with diabetes.[45,53,58,62,63] ETDRS likely had participants with the most advanced diabetes out of the three diabetes trials, as more than 80 percent of participants were using daily insulin, more than 40 percent had a hemoglobin A1c level of 10 percent or higher, and all participants had diabetic retinopathy.[55] POPADAD's mean baseline hemoglobin A1c level was approximately 8 percent, and 30 percent of participants were treated with insulin.[44] JPAD, on the other end of the disease severity spectrum, likely had patients with the least severe diabetic disease, reporting a baseline mean hemoglobin A1c level of 7 percent, and 13 percent of participants taking daily insulin.[43]

Results by Outcome

Effect of Aspirin on All-Cause Mortality by Diabetes Status

Five trials reported all-cause mortality by diabetes status or were trials recruiting only diabetes patients, with no trials showing a statistically significant benefit with aspirin (**Table 14**).[43,44,55,62,63] HOT and PPP showed nonstatistically significant results for both patients with and without diabetes, with point estimates greater than 1 for diabetes patients (PPP: RR, 1.23; HOT: RR, 1.12).[62,63] The three trials conducted exclusively in diabetes patients showed nonstatistically significant results for all-cause mortality and reported point estimates in the range of 0.91 to 0.93.[43,44,55]

Effect of Aspirin on MI/Coronary Events by Diabetes Status

Seven trials reported total MI/coronary events,[43,44,53,55,58,62,63] with the three trials conducted exclusively in patients with diabetes further reporting fatal and/or nonfatal MI/coronary events (**Table 15**).[43,44,55] Of all the trials, only HOT showed a statistically significant reduction in total MI/coronary events among those without diabetes.[62] The remaining six trials reported nonstatistically significant results for both those with and without diabetes for MI/coronary events.[43,44,53,55,58,63] Only PHS performed a test for interaction, showing no differential effect by diabetes status (p=0.22).[53] The three trials that only recruited diabetes patients showed nonstatistically significant results for total MI, with two trials reporting RR point estimates of 0.85 and 0.87. The RR point estimate in the remaining trial was 1.10.[44] These three trials showed similar nonstatistically significant differences in fatal and nonfatal MI/coronary events.[43,44,55]

Effect of Aspirin on Stroke by Diabetes Status

For total stroke, five trials showed nonstatistically significant results in participants with diabetes, with all point estimates being less than 1 and ranging from 0.74 in POPADAD to 0.91

in HOT, except ETDRS, which reported a nonstatistically significant RR point estimate of 1.18 (**Table 16**).[43,44,55,62,63] WHS, on the other hand, reported a significant reduction in total stroke in patients with diabetes (RR, 0.46 [95% CI, 0.25 to 0.85]).[58] For fatal and nonfatal stroke, all three trials that were conducted exclusively in diabetes patients showed nonsignificant results, with inconsistency across studies for nonfatal and fatal events. This result was likely due the fact that fatal stroke events were rare and the populations were heterogeneous. ETDRS showed a nonstatistically significant RR point estimate of 1.00 for fatal stroke and 1.26 for nonfatal stroke, while JPAD reported an RR of 0.20 for fatal stroke and 1.01 for nonfatal stroke.[43,55] POPADAD reported an RR of 0.89 for fatal stroke and 0.71 for nonfatal stroke, with all results being statistically insignificant.[44] Three trials provided results for diabetes patients by stroke subtype.[43,55,58] WHS showed a statistically significant reduction in ischemic stroke among those with diabetes, but not those without (without diabetes: adjRR, 0.42 [95% CI, 0.22 to 0.82]). JPAD reported nonfatal ischemic strokes and found no difference among treatment groups. Likewise, POPADAD showed no difference in fatal ischemic strokes between treatment groups.[43,44]

Effect of Aspirin on Composite Outcomes by Diabetes Status

Seven trials contributed at least one composite outcome analyzed by diabetes status (**Table 14**).[43-45,55,58,62,63] All trials except JPAD and PPP reported nonstatistically significant findings in patients with diabetes, regardless of composite reported, without consistency in trends across studies. Five trials[44,55,58,62,63] showed fatal composite outcomes for the diabetes subgroup, with only two trials reporting RRs greater than 1.[44,63] Two trials reported a nonfatal CVD composite with conflicting, nonstatistically significant results—JPAD favoring the control and POPADAD favoring aspirin.[43,44] The ATT IPD meta-analysis looked at a composite of serious vascular events (defined as MI, stroke, or death from vascular causes, including sudden death, pulmonary embolism, and hemorrhage) and found a nonstatistically significant effect of aspirin in patients with diabetes (ratio of yearly event rates, with diabetes: 0.88 [95% CI, 0.67 to 1.15]; without diabetes: 0.87 [95% CI, 0.79 to 0.96]), but heterogeneity testing revealed no significant heterogeneity between any prespecified subgroups, including diabetes (global heterogeneity=0.7).[33]

Smoking

Trial Characteristics

Two trials reported a priori subgroup analyses for smoking status.[43,58] One additional trial[53] did not specify whether analysis was a priori or post hoc. PHS and WHS categorized smokers as never, past, or current. JPAD categorized individuals as current/past or nonsmoker.[43,53,58]

Results by Outcome

Effect of Aspirin on All-cause Mortality by Smoking Status

None of the trials reported smoking-specific results for all-cause mortality.

Effect of Aspirin on MI/Coronary Events or Stroke by Smoking Status

PHS reported that smoking status had no consistent effect on MI/coronary events (p=0.99) and cigarette smoking did not modify the effect of aspirin on stroke (p-value not reported).[53] WHS showed a trend of lower RR point estimates in past or never smokers compared to current smokers for total MI, total stroke, and ischemic stroke, with statistically significant findings in the never smokers for all of these outcomes except total MI.

Effect of Aspirin on Composite Outcomes by Smoking Status

PHS reported that cigarette smoking modified the effect of aspirin for a cardiovascular mortality composite (defined as acute MI, other IHD, sudden death, stroke [ischemic, hemorrhagic, unknown], other [hypertensive heart disease, acute and subacute endocarditis, other diseases of endocardium, cardiomyopathy, heart failure ,complications from heart disease, other cerebrovascular disease, atherosclerosis, aortic aneurysm]) (p=0.05). Despite this result, neither the observed reduction in risk among nonsmokers (p=0.18) nor the increased risk among current smokers (p=0.20) were significant.

JPAD reported that the CIs overlapped for current/past smokers and nonsmokers for its primary composite outcome (composed of sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute MI; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease) in current or past smokers (RR, 0.73 [95% CI, 0.47 to 1.14]) and nonsmokers (RR, 0.83 [95% CI, 0.53 to 1.31]).[43]

WHS showed a trend of lower RR point estimates in past or never smokers compared to current smokers for the primary composite outcome of major cardiovascular events (nonfatal MI, nonfatal stroke, or CVD mortality) (RR, 0.80 [95% CI, 0.69 to 0.93]).[58]

Race/Ethnicity

None of the trials reported outcomes by race/ethnicity.

10-Year Cardiovascular Risk

Trial Characteristics

Two trials specifically reported outcomes by 10-year risk score for CHD or CVD: HOT and WHS.[58,64] TPT specifically recruited male participants in the top 20 percent risk stratum, based on the Northwick Park Heart Study algorithm, or those in the top 25 percent risk stratum if from regions with high IHD rates.[54] HOT reported outcomes by 10-year CVD risk score of 15 to 20 percent and greater than 20 percent based on established risk factors (age, sex, smoking, diabetes, high cholesterol, history of premature CVD, and history of cardiovascular or renal disease) and risk groups deemed low-, medium-, high-, and very high-risk per the 1999 WHO/International Society of Hypertension (ISH) guidelines. Half of the trial participants were

categorized as medium-risk and the other half were categorized as either high- or very high-risk.[64] WHS performed an a priori subgroup analysis using 10-year CHD risk based on Framingham risk score with three risk categories (<5.0%, 5.0% to 9.9%, and ≥10.0%).[58] Neither HOT nor WHS clearly reported interaction testing.[58,64,69]

Additionally, JPAD reported results of analyses stratified by cardiovascular risk, which was defined by age and the presence of risk factors in addition to diabetes. Specifically, high-risk was defined as men older than age 50 years and women older than age 60 years with one or more of the following additional risk factors: current smoking, hypertension, dyslipidemia, family history of coronary artery disease, or proteinuria. More than 70% of the population was classified as high-risk, with the most common risk factor being hypertension (prevalence of about 70%). Authors did not specify whether analyses were prespecified or post hoc, but interaction testing was performed.

Results by Outcome

Effect of Aspirin on All-Cause Mortality by 10-Year CVD Risk

None of the trials reported 10-year CVD risk-specific results for all-cause mortality.

Effect of Aspirin on MI/Coronary Events or Stroke by 10-Year CVD Risk

HOT, in a subgroup analysis, reported that that only participants with greater than 20 percent 10-year CVD risk had a statistically significant reduction in total MI (RR, 0.64 [95% CI, 0.45 to 0.91]), but not those in the medium-risk category (15% to 20% risk).[64] WHS's subgroup analysis showed there was no difference between the aspirin and control group for total MI/coronary events and total ischemic stroke in any of the three CHD risk categories, but did show that participants with a 10 percent or greater 10-year CVD risk had a statistically significant reduction in total stroke (RR, 0.54 [95% CI, 0.30 to 0.98]).[58] TPT, the one trial conducted exclusively in high-risk men, showed a statistically significant reduction in nonfatal MI/coronary events.[54]

Effect of Aspirin on Composite Outcomes by 10-Year CVD Risk

HOT showed that there was only a statistically significant reduction in its primary CVD composite (all MI/coronary events, all stroke, or other CVD deaths) seen in the high- to very high-risk CVD category patients (>20% risk) (RR, 0.78 [95% CI, 0.65 to 0.94]), but not in the medium-risk category (15% to 20% risk) (RR, 1.00 [95% CI, 0.77 to 1.30]).[64] Additionally, WHS reported that there was no difference between the aspirin and control group in any of the three CHD risk categories for its primary composite outcome of CVD events (nonfatal MI/coronary events, nonfatal stroke, or CVD death).[58] Conversely, TPT showed a reduction in a composite outcome of nonfatal MI/coronary events combined with nonfatal stroke (RR, 0.64 [95% CI, 0.47 to 0.88]).[54] JPAD showed no statistically significant benefit of aspirin for a broadly defined primary outcome of any atherosclerotic event in either the high-risk (adjHR, 0.78 [95% CI, 0.55 to 1.11]) or low-risk (adjHR, 0.53 [95% CI, 0.23 to 1.21]) group (p=0.26 for interaction).

While the ATT IPD meta-analysis showed a statistically significant reduction in total serious vascular events only among patients in the less than 5 percent 5-year CHD risk group (ratio of yearly event rates: 0.87 [95% CI, 0.76 to 0.99] in <2.5% risk group; 0.82 [95% CI, 0.68 to 0.98] in 2.5% to 5% risk group), the highest risk group was so small that estimates were unreliable, and testing for heterogeneity revealed no difference in effect based on risk strata (p=0.3).[33]

Decreased ABI

Trial Characteristics

POPADAD and AAA specifically recruited participants with reduced ABI.[44,45] POPADAD recruited men and women age 40 years or younger with type 1 or 2 diabetes and asymptomatic peripheral artery disease, as detected by an ABI of less than or equal to 0.99.[44] AAA recruited men and women ages 50 to 75 years with no history of MI, stroke, angina, or peripheral artery disease who also had an ABI of less than or equal to 0.95, as determined by screening by trialists.[45] Only one trial reported CVD mortality,[44] while both trials reported a primary composite outcome by ABI strata (for AAA: ≤0.95, ≤0.90, ≤0.85, and ≤0.80; for POPADAD: ≤0.90 and 0.91 to 0.99).[44,45] In AAA, this analysis was conducted post hoc. It is unclear if the analysis was post hoc or a priori in POPADAD. AAA reported no interaction testing and POPADAD reported testing for interactions.[45]

Results by Outcome

Effect of Aspirin on All-Cause Mortality by Decreased ABI

None of the trials reported ABI-specific results for all-cause mortality.

Effect of Aspirin on MI/Coronary Events or Stroke by Decreased ABI

None of the trials reported ABI-specific results for stroke or MI/coronary events.

Effect of Aspirin on Composite Outcome by Decreased ABI

AAA showed no statistically significant difference in its primary outcome (defined as initial [earliest] fatal or nonfatal coronary event or stroke or revascularization) for any of the four ABI groups.[45] Similarly, POPADAD showed no statistically significant difference in the trial's primary composite outcome (defined as death from CHD or stroke, nonfatal MI/coronary events or stroke, or above ankle amputation for critical limb ischemia) for either of the two ABI groups and found no significant interaction (p=0.089). POPADAD additionally reported CVD mortality (defined as death from CHD or stroke) and found no heterogeneity of treatment effect in ABI subgroups (p=0.17).[44]

Elevated Blood Pressure

Trial Characteristics

One trial[64] specifically recruited patients with hypertension and reported outcomes by blood pressure level. Four additional trials reported subgroup analyses by either hypertension status or blood pressure level.[53,58,65,66] JPAD reported subgroup analyses by hypertension status and WHS reported a priori subgroup analyses both by hypertension status and blood pressure level.[58,65] While TPT reported outcomes by SBP, we were not able to determine if the analysis was prespecified or post hoc.[66]

Results by Outcome

Effect of Aspirin on All-Cause Mortality by Blood Pressure Level

None of the trials reported all-cause mortality by blood pressure level.

Effect of Aspirin on MI/Coronary Events or Stroke by Blood Pressure Level

Four trials reported subgroup data for MI/coronary events and/or stroke by hypertension status. HOT found that total MI/coronary events were reduced in its subgroup analysis, with a greater benefit seen among the higher SBP and DBP levels; statistical significance was reached in the two higher SBP groups and the 104 to l07 mm Hg DBP group. These were all unadjusted RRs, so confounders, including medications used and age, could have contributed to these findings.[64]

PHS reported no significant interaction between SBP or DBP level and aspirin treatment for total MI/coronary events (p=0.88 for SBP and p=0.48 for DBP). Additionally, TPT reported a statistically significant interaction between SBP levels (<130, 130 to 145, and >145 mm Hg) and total stroke (p=0.006). Lower SBP levels were associated with a greater RR reduction when adjusting for age, smoking history, family history of premature CVD, BMI, total cholesterol, plasma fibrinogen, and plasma factor VII.[66] Similarly, WHS reported a statistically significant reduction in total stroke and ischemic stroke after adjusting for age and treatment group in the hypertensive group, but not the normotensive group (total stroke in hypertensive group: adjRR, 0.76 [95% CI, 0.59 to 0.98]; ischemic stroke in hypertensive group: adjRR, 0.73 [95% CI, 0.56 to 0.96]). This trial, however, did not report a statistically significant reduction in total MI.[58]

Effect of Aspirin on Composite Outcome by Blood Pressure Level

HOT found no statistically significant difference in major CVD events (defined as fatal and nonfatal MI/coronary events, all stroke, or other CVD death) in any of the SBP or DBP target groups, except the highest DBP level (≥107 mm Hg), but there appears to be a trend toward a lower RR with higher blood pressure levels (p-value not reported). Similarly, JPAD showed no statistically significant findings when comparing the hypertensive and normotensive subgroups for the primary composite outcome (defined as sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal MI; unstable angina; newly developed angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular

disease). It does appear that there is a trend toward a reduction in total stroke events among the aspirin group compared to the control group, but it was not statistically significant in the hypertensive group (3.3% vs. 5.2%; p-value not significant).[65]

Further, PHS reported that blood pressure levels had no consistent effect on CVD-related mortality (data not reported). Likewise, WHS reported no statistically significant reduction in its primary composite outcome (defined as nonfatal MI, nonfatal stroke, or CVD death).

Elevated Lipids

Trial Characteristics

Four trials reported subgroup analyses by total cholesterol levels or by the presence or absence of dyslipidemia (defined as total cholesterol ≥240 mg/dL in WHS; not defined in JPAD).[43,53,58,66] Two of these trials performed subgroup analyses a priori,[43,58] while the other two trials did not specify the timing of their analysis.[53,66] Two trials reported interaction testing or statistical testing for trends.[53,66]

Results by Outcome

Results of Aspirin on All-Cause Mortality by Lipid Level

None of the trials reported all-cause mortality by lipid levels.

Results of Aspirin on MI/Coronary Events or Stroke by Lipid Level

PHS showed a statistically significant trend with greater aspirin benefit in total MI/coronary events seen in the lowest total cholesterol quartile (<159 mg/dL: adjRR, 0.23; p=0.04 for trend).[53] The same trend was reported in TPT for total stroke, with a statistically significant interaction with greater aspirin benefit observed in the lowest total cholesterol tertile (<5.9 mmol/L: adjRR, 0.20; p for trend=0.036).[66] WHS, on the other hand, reported a consistent pattern of greater aspirin benefit that reached statistical significance in the hyperlipidemia group, but not the normal lipids group, for total stroke and total ischemic stroke.[58]

Results of Aspirin on Composite Outcome by Lipid Level

JPAD reported no statistically significant difference in its primary composite outcome (defined as sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal MI; unstable angina; newly developed angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease) in the aspirin and control groups for those with and without dyslipidemia.[43] Following the same trend reported for total stroke and total ischemic stroke, WHS reported a greater aspirin benefit (statistically significant in the hyperlipidemia group, but not the normal lipid group) for its primary composite outcome.[58]

KQ 1b. Does the Effect Vary by Dose, Formulation, or Duration of Aspirin Use?

Summary of Results

Trials using aspirin doses of 100 mg/day or less achieved a similar and statistically significant reduction in nonfatal MI/coronary events, mimicking the trend we observed when pooling trials of all doses. Additionally, when the trials using doses of 100 mg/day are pooled, a statistically significant reduction in nonfatal and total stroke is observed that is not apparent when trials with all doses are pooled. No conclusions can be made regarding treatment duration and formulation, however, which reflects the heterogeneity of the trials' populations and designs. Based on time-to-event data, any CVD-related benefit likely begins within the first 5 years of treatment, without any consistent data to support that benefit diminishes over time.

Dose

Seven trials administered aspirin at a dosage of 100 mg or less daily or every other day;[43-45,54,56,58,59] one trial used 325 mg every other day,[53] one used 500 mg daily,[57] and one used 650 mg daily.[55] The largest trials, WHS and PHS, used every other day dosing.

After stratifying forest plots by effect size (not shown), we examined whether any of our four primary outcomes of interest appeared to show an effect size difference for trials with the highest or lowest aspirin doses. Compared to our primary analysis using all trials, we found similar results when we pooled studies using doses of less than 325 mg daily for the outcomes of fatal CVD events, nonfatal stroke, and nonfatal MI/coronary events, which confirms the primary finding that nonfatal MI/coronary events is the only outcome for which there was a statistically significant reduction with aspirin (**Table 17**). For the outcome of all-cause mortality, despite a similar point estimate, results became nonsignificant when we pooled only the trials using doses of less than 325 mg/day. We found similar results to our primary analysis using all doses when we pooled only trials using 100 mg or less daily, except nonfatal stroke, which became statistically significantly beneficial in the aspirin group (RR, 0.82 [95% CI, 0.71 to 0.95]; I^2=0%). Again, all-cause mortality became nonsignificant after pooling only trials using doses of 100 mg or less (**Table 18**).

We performed other sensitivity analyses for the outcome of total stroke (**Table 7**). Pooling studies with aspirin doses of 100 mg or less daily revealed a statistically significant reduction in total stroke events (k=7; RR, 0.85 [95% CI, 0.76 to 0.96]; I^2=0%) that was not apparent when we combined high-dose trials (k=3; RR, 1.19 [95% CI, 1.00 to 1.42]; I^2=0%). These results were similar in a sensitivity analysis using the Peto OR equation. While this may reflect a lower risk of hemorrhagic stroke with lower doses of aspirin, hemorrhagic stroke events were rare in the seven trials reporting this outcome (**Table 19**). As such, we could not confirm this hypothesis.

Formulation

Half of the studies specified tablet formulation; two trials used enteric coated[45,59] and three trials used other or unspecified formulations.[43,44,56] Qualitatively, there does not appear to be any association between formulation and aspirin effect for any outcome analyzed.

Duration

Time-to-event data were available from eight trials that reported varying conclusions regarding minimum time-to-benefit and benefit duration with aspirin use for various select outcomes. Overall, available data suggest that any CVD benefit from aspirin begins within the first 1 to 5 years, without a clear upper time limit to benefit due to inconsistent results and relatively short trial durations; half of these eight trials had durations of 5 years or less.[43-45,54,55,58,60,61]

Four trials reported statistically significant HRs for varying CVD outcomes, with divergence of Kaplan-Meier curves beginning at 1 to 2 years.[54,56,58,59] In WHS, the effect appeared to continue through years 4 to 5, with the slope of the curves then remaining constant and parallel through trial end at 10 years.[58] Three trials showed an increasing beneficial effect over time through trial end: HOT (4 years), PPP (4 years), and TPT (8 years). Four trials[43-45,55] showed no statistically significant differences in HRs in their time-to-event analyses and two trials[53,57] did not report time-to-event data.

HOT published Kaplan-Meier curves for total MI showing a statistically significant divergence of aspirin and control curves for men (p=0.001), patients younger than age 65 years (p=0.02), and patients age 65 years or older (p=0.04). These results suggest that benefit begins with treatment of 1 year or less and continues until study end at approximately 4 years.[60] PPP reported Kaplan-Meier curves for the trial's composite CVD outcome, showing a statistically significant benefit for patients without diabetes in the aspirin group compared to the nonaspirin group (p=0.03), with separation in the curves beginning between 1 and 2 years, with no suggestion that the benefit diminishes over time.[59] TPT showed cumulative incidence curves for all IHD, fatal IHD, and nonfatal IHD in the aspirin and placebo groups, with total and nonfatal IHD curves showing divergence after 1 year.[54] WHS showed cumulative incidence curves for ischemic and total stroke, with statistically significant divergence for ischemic stroke (p=0.009) and total stroke (p=0.04) starting at approximately 2 years of this 10-year trial, while the curves for MI and the primary CVD composite showed no difference in the aspirin and control groups.[58]

AAA provided Kaplan-Meier curves for its primary composite CVD outcome showing similar aspirin and control curves (HR, 1.03 [95% CI, 0.84 to 1.27]).[45] JPAD's time-to-event data for its composite CVD outcome showed no statistically significant difference in the aspirin and control groups (HR, 0.80 [95% CI, 0.58 to 1.10]).[43] POPADAD provided Kaplan-Meier curves for the outcomes of CVD death, all-cause mortality, and the trials' composite CVD outcome and showed very similar curves for the aspirin and control groups, with nonstatistically significant HRs confirming no difference over 8 years.[44] ETDRS reported that its time-dependent analysis suggested that the HR for MI benefit with aspirin declined with time; however, data were not shown for adjusted HRs, although this appears to be true for unadjusted RRs reported for MI, composite CVD events, and total mortality beyond 5 years. The authors postulated that this could

be attributed to declines in adherence over time, delay rather than prevention of events, or random chance.[55]

Qualitatively, stratifying forest plots for our primary outcomes by followup time (equivalent to treatment duration in the trials) does not appear to suggest an association between treatment duration and aspirin effect.

KQ 2. Does Regular Aspirin Use Increase GI Bleeding, Hemorrhagic Stroke, or Other Serious Harms?

Summary of Results

The nine RCTs addressing the harms of aspirin in primary prevention populations reported harms variably and reported different outcomes. Additionally, some trials did not define bleeding type or severity and no trial reported ascertainment methods.[43-45,53,54,56-59] Qualitatively, it appears that aspirin was associated with an increased risk of total hemorrhagic stroke in the seven trials reporting this outcome, with RRs ranging from 0.68 to 4.01 (**Table 19**). The incidence of this outcome was so rare (≤0.5%), however, that precise estimates are not possible. Major GI bleeding reported in the seven trials was rare (≤0.8%), and RRs were greater than 1 in all but one trial, ranging from 1.13 to 8.10. The ATT IPD meta-analysis showed a 50 percent increase in major GI and other extracranial bleeding in patients taking aspirin (RR, 1.54 [95% CI, 1.30 to 1.82]).[33]

Study Characteristics

Nine of the 10 trials that addressed the effectiveness of aspirin in primary prevention also addressed the harms of aspirin in primary prevention populations.[43-45,53,54,56-59] These nine trials (two good-quality and seven fair-quality) are discussed at length in KQ 1. Assessing harms in many trials was difficult as they did not define bleeding events or bleeding severity, and none of the trials reported ascertainment methods for these bleeding harms, although they were presumably gathered by participant questionnaire and/or medical records.

Results by Outcome

Hemorrhagic Stroke

Total hemorrhagic stroke events were far less common than ischemic strokes. Seven trials reported this outcome, with incidence rates ranging from 0 over 6.8 years in TPT to 0.5% over 4.4 years in JPAD in the control groups (**Table 19**).[45,53,54,56-59] With these rare events, all studies showed nonstatistically significant results and mixed results, with RR point estimates ranging from 0.68 in PPP to 5.02 in TPT and wide CIs (**Figure 16**, **Table 19**).[54,59] Similarly, fatal hemorrhagic stroke events were rare, and the six trials reported mixed results, with RRs ranging from 0.25 to 3.5, wide CIs, and no statistical significance (**Figure 17**, **Table 19**).[43-45,53,56,57] Five RCTs reported nonfatal hemorrhagic stroke.[43,45,53,56,57] Four out of the five trials reported a rare

event rate of approximately 0.1 percent in both the aspirin and the control groups. RRs of nonfatal hemorrhagic stroke ranged from 0.75 to 2.00, with wide CIs (**Figure 18**, **Table 19**). The ATT IPD meta-analysis showed a nonstatistically significant trend of a higher incidence of hemorrhagic stroke in the aspirin group compared to the control group (RR, 1.32 [95% CI, 0.91 to 1.91]).[33]

Major GI Bleeding

For the purposes of this review, major GI bleeding was defined as any GI bleeding requiring hospitalization or blood transfusion or resulting in death. Seven trials reported major GI bleeding events, and these events were rare (<1%) in both the aspirin and control groups (**Table 19**).[43,45,53,54,56-58] Three trials reported statistically significant increases in major GI bleeding events, with RRs ranging from 1.37 to 2.08,[53,56,58] and three trials showed nonsignificant trends in the same direction (**Figure 19**).[43,45,54] Only one trial showed a nonstatistically significant RR of less than 1, reporting more frequent major GI bleeding in the control group compared with the aspirin group (0.1% vs. 0.2%); this finding is likely due to the rarity of events rather than a true finding, as this was the trial with a higher aspirin dose (500 mg/day).[57] The ATT IPD meta-analysis showed a 50 percent increase in major GI and other extracranial bleeding (RR, 1.54 [95% CI, 1.30 to 1.82]).[33]

Intracranial Bleeding

Four trials reported intracranial bleeding, which included subdural and/or subarachnoid bleeding, and again the events were rare (≤0.4% in aspirin and control groups) (**Figure 20**, **Table 19**).[43,45,54,59] Three of four trials reported RRs greater than 1, ranging from 2.00 to 4.08;[43,45,59] only one trial[54] reported an RR of less than 1. The RRs reported in all four trials were nonsignificant.[43,45,54,56,59]

ARMD

Two trials reported ARMD as ascertained from participant self-report, confirmed by medical records after randomization.[58,70] WHS reported two secondary endpoints of advanced ARMD (exudative neovascular ARMD combined with geographic atrophy) and ARMD with or without vision loss. Visually significant ARMD after adjustment for age and beta carotene use was similar in the aspirin and placebo groups (adjRR, 0.82 [95% CI, 0.64 to 1.06]). Advanced ARMD and ARMD with or without vision loss were similar in both groups (advanced ARMD: adjRR, 0.90 [95% CI, 0.53 to 1.52]; ARMD with or without vision loss: RR, 1.03 [95% CI, 0.88 to 1.21]). PHS reported no statistically significant difference in ARMD with or without visual loss in the aspirin versus placebo group (RR, 0.77 [95% CI, 0.54 to 1.11]) or with visual loss (RR, 0.78 [95% CI, 0.46 to 1.32]).[70]

KQ 2a. Does the Effect Vary Between a Priori Subgroups: Age, Sex, Smoking Status, Race/Ethnicity, 10-Year Cardiovascular Risk, Related Risk Conditions, GI Bleeding or Hemorrhagic Stroke Risk Factors, or Concomitant Medication Use?

Summary of Results

Few trials reported GI bleeding or hemorrhagic stroke by subgroup. Because of the rare harm events in the entire populations studied, it is not possible to make conclusions regarding a possible differential harms profile among subpopulations. Only two trials reported ARMD, with subgroup analyses limiting any generalizable conclusions.

Major GI Bleeding by Subgroup

Age

One trial reported major GI bleeding events by age subgroup (<65 or ≥65 years) without reporting statistical significance testing.[60] For fatal bleeding events (GI combined with cerebral), the events were identical in the aspirin and control groups for patients younger than age 65 years (0.2 cases per 1,000 person-years). Events were similar in the aspirin and control groups for patients age 65 years or older (0.3 vs. 0.4 cases per 1,000 person-years). For nonfatal major bleeding requiring hospitalization (including GI, cerebral, and nasal sources), the trial reported more events in the aspirin group compared to the placebo group, and these results were similar in both age groups (3.0 vs. 1.7 cases per 1,000 person-years in patients younger than age 65 years; 4.3 vs. 2.6case per 1,000 person-years in patients age 65 years or older) (**Table 8**).[60]

Sex

Four trials conducted either exclusively in men or women[53,57,58,66] and two trials including both men and women[59,60] performed sex subgroup analyses for bleeding harms (**Table 11**). HOT reported fatal bleeding events (GI combined with cerebral) by sex, showing that fatal bleeding was similarly rare in men and women in the aspirin and control groups (men: 0.3 vs. 0.2 cases per 1,000 person-years, respectively; p=NS; women: 0.1 vs. 0.2 cases per 1,000 person-years, respectively; p=NS). Nonfatal major bleeding requiring hospitalization (including GI, cerebral, and nasal bleeding) was higher in the aspirin group compared to the control group in both men and women. These events were more frequent in men than women, although no statistical testing for sex-specific interaction was performed (men: 4.1 vs. 2.5 cases per 1,000 person-years in aspirin and control groups, respectively; p=0.010; women: 2.7 vs. 1.3 cases per 1,000 person-years in aspirin and control groups, respectively; p=0.006).[60] PPP showed the same trend with major bleeding (not defined in the trial but reported to be predominantly GI bleeding) and reported that these events occurred more frequently in men than women. The authors, however, did not perform statistical testing for sex-specific interaction (men: OR, 3.85 [95% CI, 1.27 to 11.64]; women: OR, 4.63 [95% CI, 1.00 to 21.46]).[59]

The three trials that were conducted exclusively in men all reported that major GI bleeding events were rare (<1%), and TPT and PHS reported a higher bleeding risk in the aspirin group, although only PHS reached statistical significance (**Table 11**).[53,57,66] BMD showed rare major GI bleeding events, with only three events in the aspirin and control groups, making these numbers unstable for conclusions (aspirin: 0.09%; control: 0.2%; RR, 0.50 [95% CI, 0.10 to 2.47]). TPT also showed more frequent, but rare, major GI bleeding events in the aspirin group compared to the control group (aspirin: 0.5%; control: 0.2%; RR, 3.01 [95% CI, 0.61 to 14.88]).[66] PHS reported death from GI hemorrhage combined with bleeding requiring transfusion, with relatively rare events, but reaching statistical significance (aspirin: 0.4%; control: 0.2%; RR, 1.75 [95% CI, 1.10 to 2.78]).[53] Similarly, the trial conducted in exclusively women reported slightly more deaths from GI hemorrhage and bleeding requiring transfusion in those taking aspirin, but with relatively rare events (aspirin: 0.6%; control: 0.5%; RR, 1.37 [95% CI, 1.05 to 1.79]).[58]

Diabetes

GI bleeding in patients with diabetes was variably reported in two trials that exclusively recruited this population.[43,44] There were no subgroup analyses of GI bleeding in diabetes patients in other trials. JPAD reported severe bleeding requiring transfusion more commonly in the aspirin group compared with the control group, with wide CIs (0.3% vs. 0%; RR, 8.10 [95% CI, 0.43 to 152.96]) (**Table 14**).[43] Conversely, POPADAD reported more GI bleeding without specifying severity in the control group, but the results were not significant (4.4% vs. 4.9%; OR, 0.90 [95% CI, 0.53 to 1.52]).[44]

Hypertension

Only HOT reported bleeding events relating to hypertensive subgroups based on SBP and DBP levels (SBP ≥180, 160 to <180, or <160 mm Hg; DBP ≥107, 104 to <107, or <104 mm Hg).[64] This trial defined a "fatal and nonfatal major bleeding" composite outcome as fatal, life-threatening, disabling, or requiring hospitalization, but did not specify the source of the bleeding (GI, cerebral, nasal, or other). These fatal and nonfatal major bleeding events occurred in 1.0 to 1.8 percent of the aspirin group in all blood pressure levels, and there was no clear trend in RR related to degree of hypertension (range, 1.38 to 2.10).[64]

10-Year CVD Risk

HOT reported its fatal and nonfatal major bleeding composite by 10-year CVD risk, based on a Framingham risk calculator from the 1999 WHO/ISH guidelines. Major bleeding events occurred in 1.1 percent of the 15 to 20 percent risk group taking aspirin and in 1.6 percent of the 20 percent or greater risk group taking aspirin (RR, 2.08 [95% CI, 1.29 to 3.35] vs. 1.45 [95% CI, 1.01 to 2.06], respectively).[64] JPAD reported GI bleeding stratified by high- and low-risk groups, which were defined by age and the presence of risk factors in addition to diabetes; the severity of bleeding was not defined.[71] There was no statistically significant difference in bleeding in the aspirin and no aspirin groups at either risk level; however, there were few events. GI bleeding occurred in 0.4 percent of the high-risk group taking aspirin and 0.3 percent of the low-risk group taking aspirin (RRs not reported).

Other Subgroups

No trials reported GI bleeding or other bleeding by smoking status, race/ethnicity, lipid status, or ABI.

Hemorrhagic Stroke by Subgroup

Age

None of the trials reported hemorrhagic stroke events by age.

Sex

Three trials conducted exclusively in men reported hemorrhagic stroke, [53,54,57] as did one trial conducted in women;[58] PPP performed a subanalysis of men and women, but the specification of the analysis is not reported (**Table 20**).[61] All trials reported rare total hemorrhagic stroke events ranging from 0 to 0.2 percent in the aspirin groups. Because of rare events, all results were nonstatistically significant. The total hemorrhagic stroke OR/RR reported in men were 2.03, 2.14, and 4.01 in the PPP, PHS, and TPT trials, respectively.[53,54,57] In women, the PPP subanalysis showed a total hemorrhagic stroke OR of 0.20 (95% CI, 0.01 to 4.26). In WHS, the adjRR was 1.24 (95% CI, 0.82 to 1.87).[58]

Diabetes

Two trials conducted exclusively in diabetes patients reported hemorrhagic stroke (**Table 21**).[44,43] JPAD reported that the risk of hemorrhagic stroke was similar in both groups (RR, 0.87 [95% CI, 0.29 to 2.57]), with an additional two subdural hematomas reported in the aspirin group and none in the control group.[43] In POPADAD, there were rare fatal hemorrhagic strokes in both groups (0.31 vs. 0.47%; RR, 0.67 [95% CI, 0.11 to 3.98]).[44]

Other Subgroups

No trials reported hemorrhagic stroke by hypertensive status or blood pressure level, lipid status, abnormal ABI, smoking status, or race/ethnicity. No trial reported hemorrhagic stroke by 10-year CVD risk, but JPAD did report a stratified analysis of intracerebral hemorrhage stratified by high- and low-risk groups, which were defined by age and the presence of risk factors in addition to diabetes.[71] There was no statistically significant difference in intracerebral hemorrhage between the aspirin and no aspirin groups at either risk level. There were few events in those taking aspirin in the high- and low-risk groups (six in the high-risk group [0.6%] and 0 in the low-risk group; RRs not reported). About 70% of the high-risk group had hypertension.

ARMD by Subgroup

WHS reported ARMD for the following subgroups: age (45 to 54, 55 to 64, or ≥65 years), smoking status, alcohol use (<1 or ≥1 drink per week), BMI, hypertension status, hyperlipidemia

status, diabetes status, menopausal status, parental history of premature MI, multivitamin use, and patients having an eye examination in the past 2 years. While it was unclear if these subgroup analyses were a priori, the analyses were explored using interaction terms with trend testing. Among nonusers of multivitamins, those in the aspirin group had a 32 percent reduction in ARMD (RR, 0.68 [95% CI, 0.49 to 0.95]). Among current multivitamin users, however, there was a nonsignificant 14 percent increase in risk of ARMD in the aspirin group (RR, 1.14 [95% CI, 0.76 to 1.70]; p=0.53 for interaction).[58]

PHS reported stratified analyses and tests of interactions to evaluate the possible effect modification by the following risk factors: cigarette smoking (ever or never), hypertension status, hypercholesterolemia, and alcohol use (daily, weekly, or rarely). Additionally, PHS reported ARMD events stratified by age group. Of these risk factors, only hypertension status altered the treatment effect, with hypertensive men having a statistically significant 65 percent reduction in ARMD (RR, 0.35 [95% CI, 0.15 to 0.83]; p=0.04).[53]

KQ 2b. Does the Effect Vary by Dose, Formulation, or Duration Of Aspirin Use?

Summary of Results

Bleeding events were rare in all trials, making it difficult to draw generalizable conclusions regarding the relationship between aspirin dose, duration, and formulation and bleeding events.

Dose

In the seven primary prevention trials reporting hemorrhagic stroke or major GI bleeding, there appears to be no qualitative association between these outcomes and aspirin dose (**Figures 16–19**, **Table 19**). This result is likely due to such few events being reported (four out of seven trials reported <10 events in the aspirin group), making the numbers unstable. This is illustrated by BMD, which had the highest dose (500 mg/day), but showed a trend toward reduced major GI bleeding (RR, 0.5 [95% CI, 0.10 to 2.47]). Again, this is likely due to small numbers of events being reported and the point estimate being unstable.[57]

Formulation

Half of the studies specified tablet formulation—two trials used enteric coated formulations[45,59] and three trials used other or unspecified formulations.[43,44,56] Qualitatively, there is no apparent association of formulation and aspirin effect for major GI bleeding or hemorrhagic stroke.

Duration

For the 10 trials included in this KQ, mean trial duration ranged from 3.6 to 10 years, which coincides with aspirin treatment. No trials reported time-to-event data for major GI bleeding

outcomes. Only one trial, WHS, provided cumulative incidence data for hemorrhagic stroke, showing a nonsignificant 24 percent increase with aspirin treatment over the 10-year trial duration (p=0.31).[58]

Qualitatively, stratifying trials' results by duration showed no apparent association between treatment duration and hemorrhagic stroke or major GI bleeding.

Chapter 4. Discussion

Summary

Table 22 presents a summary of evidence for each KQ, which we discuss briefly next. Our meta-analysis of 10 primary prevention trials confirmed the conclusions from several other published meta-analyses, showing that aspirin reduces the risk of major CVD events (total MI, total stroke, or CVD death) by about 11 percent, which appears to be largely driven by a 20 percent reduction in nonfatal MI (**Appendix E Table 3**).[33,72-75] This effect on nonfatal MI/coronary events persisted when pooling only trials using aspirin with average daily doses of 100 mg or less. When pooling trials with doses of 100 mg or less, a nonfatal stroke benefit emerged as statistically significant. Our meta-analysis showed a modest, statistically significant reduction in all-cause mortality, which was not persistent in sensitivity analyses of lower-dose aspirin (≤100 mg/day). This finding was not reported in other meta-analyses.[33,72-75] A concurrent review concluded that modest reductions in all-cause mortality cannot completely be explained through CVD and/or cancer mortality reduction.[50] It appears that the nonfatal MI/coronary event benefit begins sometime within the first 5 years of use. While we did not pool major GI bleeding events because of study heterogeneity and rarity of events, we qualitatively found that most trials supported an increased risk similar to those reported in four prior meta-analyses that showed an increase in major bleeding events, with statistically significant measures of association ranging from 1.54 to 1.70.[33,72,73,75] Thus, in a primary prevention population, the net impacts on CVD prevention are modest and closely matched by increases in major bleeding risks.

Risk-Based Approach

In any given population, the benefits of aspirin for primary prevention are directly related to the RR reduction realized from aspirin and the baseline risk of CVD events balanced by the serious harms of GI bleeding and hemorrhagic strokes. To maximize the effectiveness side of the equation, we must identify a subpopulation for whom either: 1) the RR 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. Our systematic review aimed to critically appraise the subpopulation literature to answer these questions and found that very few a priori subgroup analyses were available, even fewer performed interaction testing, and none adequately controlled for important confounders. There are four specific subpopulations of greatest interest: age, sex, diabetes, and baseline CVD risk. Given the few available subgroup analyses, we focused on within-study comparisons and did not pool data for any individual population subgroups because of few contributing studies, small numbers of events, trial design, and population heterogeneity.[76-79]

Sex

For sex, our qualitative analysis of the 10 RCTs showed no pattern for sex- and outcome-specific trends in composite CVD events, MI/coronary events, or stroke outcomes, except in WHS,

which was the largest primary prevention population of women studied to date (90% of whom were younger than age 65 years). WHS showed that while aspirin reduced ischemic stroke, it did not reduce total MI/coronary events, except in the oldest age group of women (65 years or older), where MI/coronary events were reduced by 34 percent in the aspirin group compared with the control group (RR, 0.66 [95% CI, 0.44 to 0.97]).[58] Sex-specific meta-analyses of six of the 10 trials showed conflicting results: while one meta-analysis showed a sex-specific difference, with women realizing benefit for total and ischemic stroke and men realizing benefit for reduction in total MI, interaction testing and multivariate adjustment for other risk factors were not performed. Additionally, these findings were predominantly driven by the WHS results.[61] It is possible that the relatively young age of the WHS population, together with lack of adjustment for confounders, including age, led to a sex- and outcome-specific conclusion in this meta-analysis.[61] The ATT IPD meta-analysis of the same six trials showed that after controlling for multiple comparisons, the apparent sex-specific differences in MI/coronary events and ischemic stroke events were no longer statistically significant.[33] Subsequent to the ATT publication, other meta-analyses have confirmed the findings of no sex-specific, outcome-specific differences in major CVD events.[75] Furthermore, the lack of heterogeneity of treatment effect in the secondary aspirin prevention literature puts such sex-specific findings in question.[33] **Appendix E Table 4** provides a timeline of publications to illustrate the changing findings for sex-specific conclusions about aspirin for CVD prevention.

Diabetes

From six trials with evidence on patients with diabetes, our qualitative synthesis found no effect modification based on diabetes status for any of our CVD-related outcomes. This confirms the findings from five prior systematic reviews that pooled three to six trials in populations or subpopulations with diabetes and showed no statistically significant reduction in CVD events, total MI, or total stroke,[80-84] as well as a large Swedish observational study showing no CVD event, CVD mortality, or all-cause mortality benefit among diabetes patients.[85] The suggested biologic plausibility of a lack of effect of aspirin in patients with diabetes could be based on aspirin resistance and possibly increased platelet turnover.[86,87] Patients with diabetes are at a two- to four-fold risk for CVD events compared to those without diabetes;[11-13] however, evidence suggests that is not a CHD risk equivalent, since diabetes patients have a 43 percent lower risk of CHD events compared with those with a known history of CHD events.[88] Some have suggested that the use of aspirin in diabetes, therefore, lies somewhere between primary and secondary prevention. Results from two European cohorts further complicate the discussion of aspirin's net benefit for diabetes patients. One of these studies, an Italian population-based cohort using administrative data from more than 4 million individuals, showed that diabetes patients have an increased risk of major bleeding compared to those without diabetes regardless of aspirin use. This study did show, however, that aspirin use only marginally increases major bleeding rates in patients with diabetes compared to nonaspirin users with diabetes.[89] The other study, a Swedish patient registry of 58,465 individuals, showed that aspirin use was associated with increased all-cause mortality in diabetes patients without CVD, particularly among older patients, after controlling for confounders.[90] Both of these cohort studies have the major limitations of being administrative database analyses, which are particularly prone to erroneous conclusions of causality. Two large in progress RCTs enrolling more than 20,000 patients with diabetes may definitively answer this question regarding whether or not aspirin is effective for primary

prevention in this population (A Study of Cardiovascular Events in Diabetes [ASCEND][91] and Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes [ACCEPT-D]).[92]

Age

Older adults were the only subpopulation for which there appears to be a differential benefit from aspirin. Studies consistently showed a greater RR reduction in total MI/coronary events among older age groups based on three trials,[53,58,60] with WHS and HOT showing a statistically significant one-third reduction in total MI/coronary events for those age 65 years or older. Likewise, PHS showed similar reductions at age 50 years and older. Both PHS and WHS reported statistically significant p-values for heterogeneity of treatment effect for age for total MI/coronary events, and this statistic was not reported for HOT. This trend was not seen in the ATT IPD meta-analysis, however, as this trial did not find any heterogeneity of composite CVD events or coronary events based on age (<65 years compared to ≥65 years).[33] Concerns about a greater absolute bleeding risk with increasing age, regardless of aspirin use,[93] makes it important to quantify the RR reduction and balance it with higher bleeding risk. This is especially important for this subpopulation, as it appears that each decade of age confers a 50 percent increase in hemorrhagic stroke risk and doubles the risk of major extracranial bleeding.[33] The ongoing Aspirin in Reducing Events in the Elderly (ASPREE) trial has recruited 19,000 men and women age 70 years or older and randomized them to aspirin (100 mg daily) versus placebo, with a primary outcome of all-cause mortality, dementia incidence, or physical disability and will hopefully provide more precise estimates of harms and benefits in the older adult population.[94]

CVD Risk Approach

Given the lack of apparent treatment effectiveness modification based on individual risk characteristics, many international guideline panels have proposed a multiple risk factor-based approach. This approach uses a 10-year CVD risk calculator to identify a group with high risk for CVD events, thereby maximizing the absolute net benefits from aspirin.[95] Comparisons of international guidelines reveal that there is wide variation in the risk threshold for aspirin primary prevention recommendations, ranging from 4 to 30 percent 10-year CHD or CVD risk, with several panels recommending against aspirin use for primary prevention, regardless of CVD risk category (**Appendix E Table 1**). The previous USPSTF recommendation recommended aspirin (75 mg/day) for various 10-year CHD or stroke risk thresholds based on age and sex.

The U.S. Food and Drug Administration (FDA) recently denied primary prevention of MI as an indication for aspirin in any risk group. This decision was based on a review of six primary prevention trials, study-level and IPD meta-analyses, and newer trials in special populations, from which the FDA concluded there was insufficient evidence to support this indication.[96] In the rationale for its decision, the FDA stated that pooled results are generally not a basis for reaching effectiveness conclusions and furthermore that primary endpoints are given the greatest weight in interpreting evidence; in the case of aspirin for primary prevention, no study achieved statistically significant results for its planned primary endpoint as interpreted by FDA statistical

reviewers.[96]

Clinical guideline implementation requires selection of a specific risk prediction tool. Available risk prediction tools vary widely across a number of domains, including the definition of CHD or CVD outcomes predicted, risk factors included, and variation in the baseline risk and other characteristics of model derivation cohorts (**Appendix A**, **Appendix E Table 5**). Limitations of risk equations include: nonrepresentative or historically dated populations, limited ethnic diversity in derivation populations, narrowly defined endpoints, endpoints influenced by provider preferences, endpoints with poor reliability, and inclusion or exclusion of novel risk factors.[14,19,97]

In November 2013, the ACC/AHA Guideline on the Assessment of Cardiovascular Risk was released. This guideline included a new "pooled cohort equation" for predicting 10-year risk of a first hard atherosclerotic CVD event, defined as nonfatal MI, CHD death, and fatal or nonfatal stroke.[14] The derivation population included participants from four National Heart, Lung, and Blood Institute-sponsored community-based cohort studies (Atherosclerosis Risk in Communities [ARIC], Cardiovascular Health Study [CHS], Coronary Artery Risk Development in Young Adults [CARDIA], and Framingham/Framingham-Offspring), and this tool represented a departure from the previous narrower outcome focus of risk assessment for CHD.[15] Additionally, while the inclusion of multiethnic populations in the derivation cohorts enabled race- and sex-specific equations for blacks and whites, this was not the case for Hispanics, Asians, and other ethnic subpopulations.[14]

Critics have voiced several concerns about the model's calibration, citing overprediction that was most notable in the highest risk group of greater than or equal to 10 percent 10-year risk. They also point out the model's discrimination has been summarized as moderate, at best, using c-statistics.[14,98-100] In an unpublished in-process analysis, external validations of the ACC/AHA pooled cohort equation were performed for Hispanic men and women in the Multiethnic Study of Atherosclerosis (MESA) cohort and the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) trial. Preliminary results of this analysis appear to be consistent with other studies that have suggested overprediction in populations other than non-Hispanic Caucasians (K. Shum, personal communication, 2014).[14]

Other externally validated U.S.-based models include CHD calculators based on Framingham data by Anderson, Wilson, and ATP III.[8,15,16,25] Systematic reviews show that external validations of the Anderson and Wilson models have generally found that they overestimate risk in groups with low observed risk and underpredict risk in groups with higher risk.[101,102] Evidence from direct comparisons of risk assessment tools suggests potentially small differences in performance across models,[100,103] while others have argued that it is not appropriate to compare models head-to-head because of wide variation in outcome definitions, years of followup, and absolute risk categories.[104]

Despite the aforementioned shortcomings, the ACC/AHA pooled cohort calculator is, to date, the only U.S.-based CVD calculator that has published its external validations in other U.S.-based populations. Ideally, one could develop a model to apply the risk prediction equation for clinical care that would guide shared decisionmaking with patients regarding the risks and benefits of

aspirin. Currently, a contemporaneous AHRQ-commissioned model hoping to address these needs is under development.[105]

Harms

Our qualitative analysis, which was limited to major GI bleeding as defined by transfusion, hospitalization, or death, showed an increase in bleeding risk, although given trial heterogeneity, we were unable to estimate the effect with any precision; trials reported RRs between 0.50 and 8.10. Other published meta-analyses showed major bleeding ORs/RRs in the primary prevention trials ranging from 1.54 to 1.70.[33,72,73,75] Given the rarity of hemorrhagic strokes, we were unable to precisely estimate this harm in aspirin users. Based on the emergence of a total stroke benefit with lower doses of aspirin, however, it is plausible that some of the hemorrhagic strokes caused by aspirin can be mitigated by lowering the dose.

An association with aspirin use and ARMD has been reported in one large U.S.-based cohort study[106] and one cross-sectional European study[107] of nonprimary prevention populations. This association, however, was not reported by our two included trials reporting this outcome.[53,58]

Cotreatment With Statins or PPIs

Experts have suggested that additional considerations should inform aspirin treatment in patients taking other medications, such as statins and PPIs. While none of our 10 trials reported outcomes in statin users compared with nonusers, authoritative evidence shows that statins provide a 25 percent reduction in major vascular events in primary prevention populations.[108] It is not clear whether the modest absolute benefit of aspirin seen in the primary prevention population would be further enhanced by concomitant use of statins, but there is an in progress trial assessing this issue in populations with diabetes.[92] Until these results are published, it remains unclear how statins may modify aspirin-associated benefits or bleeding events.[89]

Our systematic review did not identify any eligible RCTs to address whether PPIs modify CVD effects with aspirin or bleeding risk in primary prevention populations. Co-administration of PPIs with low-dose aspirin to mitigate associated bleeding risks is being primarily pursued in those with indications for aspirin treatment (i.e., postCVD procedure or secondary prevention). For primary prevention populations without disease, trials of PPI/low-dose aspirin would be needed to determine the net effect, including whether the primary prevention aims are affected by this additional medication.

Limitations of the Literature

There are several limitations of the literature. The 10 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. Additionally, trials were powered for composite outcomes combining fatal and nonfatal events of varying

severity,[109] where individual outcomes of MI and stroke were rare enough in this primary prevention population to make any findings of nonstatistical significance potentially due to lack of power. We were unable to draw any conclusions regarding formulation—specifically whether or not enteric coated aspirin has diminished GI bleeding risks. 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 CVD-related benefits (i.e., nonfatal MI) occur during the first 5 years of therapy. As such, it remains unclear whether the nonfatal MI benefit continues to accrue at a constant rate beyond 5 to 10 years of use. Followup in most studies was 4 to 6 years, although only one trial provided extended observational followup at 18 years.[67] As a result, we cannot exclude larger benefits conferred over a longer time period in a primary prevention population. While we found that ideal dosing for primary prevention is likely 100 mg per day or less, it is unclear if every other day dosing versus daily dosing makes a difference for CVD benefits. Additionally, some literature suggests that every other day dosing may not be sufficient for other types of aspirin benefit (i.e., cancer benefits).[110] At this point, there is scant data to support any effect modification in any population. Subgroup analyses rarely reported interaction testing, never adequately controlled for confounders, and commonly did not specify timing of subgroup analyses, lending it to bias.[110,111] Bleeding outcomes were variably reported, and given the general underreporting of harms[112] and the restrictive inclusion criteria in RCTs, these trials likely underestimate bleeding risks in real practice.

Limitations of Our Review

We limited our review to English-language, primary prevention literature for both effectiveness and harms; therefore, we only examined a subset of the harms literature. Moreover, we limited our review of bleeding to major GI bleeding, defined as requiring transfusion or hospitalization or leading to death; bleeding of lesser severity and trials that did not specify bleeding severity were not addressed. We did not examine other potential nonCVD benefits from aspirin (i.e., cancer benefits). Two contemporaneous AHRQ-commissioned systematic reviews, however, are addressing all of these issues.[50,113]

Conclusions and Future Research Needs

Nearly half of the primary prevention trials recruited patients in the 1980s, and most trials reflect usual clinical care administered more than 20 years ago. Aspirin's potential role in primary prevention will continue to evolve based on the magnitude of a modest relative benefit balanced with bleeding risks in the context of declining smoking rates, increasing statin use, and more aggressive hypertension management. Recent trials[44,45,43] published since the last review for the USPSTF[35] focus on special populations for whom absolute risk reduction could outweigh bleeding harms; however, these trials failed to show any CVD benefit, even for the composite outcomes they were powered to detect. Nonetheless, we identified this question about aspirin's benefit in subpopulations as the area with the greatest evidence gaps. There remains a role for future research to identify subpopulations who may realize a clinically important net benefit from aspirin.

We identified the following research gaps:

- *Concomitant therapy with statins or PPIs:* RCT-level data are needed that examine the absolute benefit of aspirin with concurrent statin use in those deemed at elevated CVD risk. These data could further elucidate the nature of the effect of aspirin and statins combined in primary prevention populations, but it is crucial that these trials are sufficiently powered to assess hard CVD outcomes with long-term followup (>10 years). This research could also determine whether there are populations at high enough risk to realize a moderate benefit from aspirin use in primary prevention. Similarly, the impact of co-therapy with PPIs on the net effect of low-dose aspirin in primary prevention populations would inform this potential approach.
- *Subpopulations with diabetes:* Diabetes patients are an important subpopulation that needs further study. The pending ASCEND and ACCEPT-D trials could provide evidence for a role for aspirin in primary prevention for any subpopulations with diabetes.
- *Racial/ethnic subpopulations:* To date, there is no data available or in process RCTs addressing the role of aspirin used for primary prevention in racial/ethnic subpopulations; trials are needed to inform current practice.
- *IPD meta-analyses*: IPD meta-analyses provide important data that complement existing trial data. An updated IPD meta-analysis that includes the three new trials published since the ATT IPD meta-analysis[33] and adjusts for confounders is needed to fully evaluate aspirin's effect in important subpopulations.

References

1. Heron, M. Deaths: Leading causes for 2010. National vital statistics reports; vol 62 no 6. Hyattsville, MD: National Center for Health Statistics; 2013.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014 Jan 21;129(3):e28-e292. PMID: 24352519.
3. George MG, Tong X, Sonnenfeld N, et al. Recommended use of aspirin and other antiplatelet medications among adults--National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, United States, 2005-2008. MMWR Morb Mortal Wkly Rep 2012 Jun 15;61 Suppl:11-8. PMID: 22695458.
4. Wilkins JT, Ning H, Berry J, et al. Lifetime risk and years lived free of total cardiovascular disease. JAMA 2012 Nov 7;308(17):1795-801. PMID: 23117780.
5. Fang J, Shaw Kate M, Keenan NL. Prevalence of coronary heart disease--United States, 2006-2010. MMWR Morb Mortal Wkly Rep 2011 Oct 14;60(40):1377-81. PMID: 21993341.
6. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008 Feb 12;117(6):743-53. PMID: 18212285.
7. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004 Sep 11;364(9438):937-52. PMID: 15364185.
8. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation 1998 May 12;97(18):1837-47. PMID: 9603539.
9. Berry JD, Dyer A, Cai X, et al. Lifetime Risks of Cardiovascular Disease. N Engl J Med 2012 Jan 26;366(4):321-9. PMID: 22276822.
10. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001 May 16;285(19):2486-97. PMID: 11368702.
11. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011. PMID: None.
12. Fox CS, Coady S, Sorlie PD, et al. Trends in cardiovascular complications of diabetes. JAMA 2004 Nov 24;292(20):2495-9. PMID: 15562129.
13. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007 Mar 27;115(12):1544-50. PMID: 17353438.
14. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 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 2013 Nov 12 PMID: 24239921.

15. National Cholesterol Education Program. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. *NIH Publication No. 02-5215*. National Heart, Lung, and Blood Institute; 2002. PMID: 12485966.
16. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. Am Heart J 1991 Jan;121(1 Pt 2):293-8. PMID: 1985385.
17. Chambless LE, Folsom AR, Sharrett AR, et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. J Clin Epidemiol 2003 Sep;56(9):880-90. PMID: 14505774.
18. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003 Jun;24(11):987-1003. PMID: 12788299.
19. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007 Feb 14;297(6):611-9. PMID: 17299196.
20. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation 2008 Nov 25;118(22):2243-51, 4p. PMID: 18997194.
21. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008 Jun 28;336(7659):1475-82. PMID: 18573856.
22. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 2002 Jan 22;105(3):310-5. PMID: 11804985.
23. Matheny, M, McPheeters, ML, Glasser, A, et al. Systematic Review of Cardiovascular Disease Risk Assessment Tools. AHRQ Publication No. 11-05155-EF-1. 2011. PMID: 21796824.
24. Berger JS, Jordan CO, Lloyd-Jones D, et al. Screening for cardiovascular risk in asymptomatic patients. J Am Coll Cardiol 2010 Mar 23;55(12):1169-77. PMID: 20298922.
25. Anderson KM, Wilson PW, Odell PM, et al. An updated coronary risk profile. A statement for health professionals. Circulation 1991 Jan;83(1):356-62. PMID: 1984895.
26. Larson MK, Ashmore JH, Harris KA, et al. Effects of omega-3 acid ethyl esters and aspirin, alone and in combination, on platelet function in healthy subjects. Thrombosis & Haemostasis 2008 Oct;100(4):634-41. PMID: 18841286.
27. Bayer AG. History of Bayer HealthCare. 2013.
28. American Heart Association. What is Cardiovascular Disase (Heart Disease)? 2013. Accessed May 9, 2014.
29. Nemerovski CW, Salinitri FD, Morbitzer KA, et al. Aspirin for primary prevention of cardiovascular disease events. Pharmacotherapy 2012 Nov;32(11):1020-35. PMID: 23019080.
30. Abramson S, Howard R. Aspirin: mechanism of action, major toxicities, and use in rheumatic diseases. 2014.
31. Golden BD, Abramson SB. Selective cyclooxygenase-2 inhibitors. Rheum Dis Clin North Am 1999 May;25(2):359-78. PMID: 10356423.
32. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? Physiol Rev 2008 Oct;88(4):1547-65. PMID: 18923189.

33. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009 May 30;373(9678):1849-60. PMID: 19482214.
34. Parekh AK, Galloway JM, Hong Y, et al. Aspirin in the secondary prevention of cardiovascular disease. N Engl J Med 2013 Jan 17;368(3):204-5. PMID: 23323896.
35. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009 Mar 17;150(6):396-404. PMID: 19293072.
36. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011 Feb;42(2):517-84. PMID: 21127304.
37. Pignone M, Alberts MJ, Colwell JA, et al. 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 Jun;33(6):1395-402. PMID: 20508233.
38. National Institute for Health and Clinical Excellence. Clinical Knowledge Summaries. Antiplatelet treatment. When to prescribe antiplatelet treatment (primary prevention). 2013. http://cks.nice.org.uk/antiplatelet-treatment#!scenariorecommendation. Accessed April 15, 2014. PMID: None.
39. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014 Apr;100(Suppl 2):ii1-ii67. PMID: 24667225.
40. Scottish Intercollegiate Guidelines Network (SIGN). Antithrombotics: indications and management. SIGN Publication No. 129. Edinburgh: SIGN; 2013. PMID: None.
41. Perk J, De BG, Gohlke H, et al. 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 Jul;33(13):1635-701. PMID: 22555213.
42. U.S.Preventive Services Task Force. Aspirin for the Primary Prevention of Cardiovascular Events: Recommendation and Rationale. Annals of Internal Medicine 2002;136(2):157-60. PMID: None.
43. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial.[Erratum appears in JAMA. 2009 May 13;301(18):1882]. JAMA 2008 Nov 12;300(18):2134-41. PMID: 18997198.
44. Belch J, MacCuish A, Campbell I, et al. 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.
45. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010 Mar 3;303(9):841-8. PMID: 20197530.
46. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. PMID: 11306229.

47. U.S.Preventive Services Task Force. U.S. Preventive Services Task Force procedure manual. AHRQ Publication No. 08-05118-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2008. PMID: None.
48. National Institute for Health and Clinical Excellence. The Guidelines Manual. London: National Institute for Health and Clinical Excellence; 2006. PMID: None.
49. Fortmann SP, Burda BU, Senger CA, et al. 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 Dec 17;159(12):824-34. PMID: 24217421.
50. Whitlock, E, Williams, S, Burda, B, et al. Aspirin use in adults: total cancer, all-cause mortality, and harms. Rockville, MD: 2014. PMID: None.
51. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol 2011 Nov;64(11):1187-97. PMID: 21477993.
52. Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985 Mar;27(5):335-71. PMID: 2858114.
53. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989 Jul 20;321(3):129-35. PMID: 2664509.
54. 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 Jan 24;351(9098):233-41. PMID: 9457092.
55. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA 1992 Sep 9;268(10):1292-300. PMID: 1507375.
56. Hansson L, Zanchetti A, Carruthers SG, 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 Jun 13;351(9118):1755-62. PMID: 9635947.
57. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1988 Jan 30;296(6618):313-6. PMID: 3125882.
58. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005 Mar 31;352(13):1293-304. PMID: 15753114.
59. 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. The Lancet 2001 Jan 13;357(9250):89-95. PMID: 11197445.
60. Kjeldsen SE, Kolloch RE, Leonetti G, 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 May;18(5):629-42. PMID: 10826567.
61. Berger JS, Roncaglioni MC, Avanzini F, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006 Jan 18;295(3):306-13. PMID: 16418466.

62. Zanchetti A. Aspirin and Antiplatet Drugs in the Prevention of Cardiovascular Complications of Diabetes. Pharmacotherapy of diabetes: new developments: improving life and prognosis for diabetic patients. New York, New York: Springer Science and Business Media; 2007. p. 211-8. PMID: None.
63. Sacco M, Pellegrini F, Roncaglioni MC, et al. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general Practice. Diabetes Care 2003 Dec 1;26(12):3264-72. PMID: 14633812.
64. Zanchetti A, Hansson L, Dahlof B, et al. Benefit and harm of low-dose aspirin in well-treated hypertensives at different baseline cardiovascular risk. J Hypertens 2002 Nov;20(11):2301-7. PMID: 12409970.
65. Soejima H, Ogawa H, Morimoto T, et al. Aspirin reduces cerebrovascular events in type 2 diabetic patients with poorly controlled blood pressure. Subanalysis from the JPAD trial. Circ J 2012;76(6):1526-32. PMID: 22447019.
66. 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 Jul 1;321(7252):13-7. PMID: 10875825.
67. Dorresteijn JA, Visseren FL, Ridker PM, et al. Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects. European Heart Journal 2011 Dec;32(23):2962-9. PMID: 22090661.
68. Cook NR, Lee IM, Zhang SM, et al. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann Intern Med 2013 Jul 16;159(2):77-85. PMID: 23856681.
69. Rexrode KM, Lee IM, Cook NR, et al. Baseline characteristics of participants in the Women's Health Study. J Womens Health Gend Based Med 2000 Jan;9(1):19-27. PMID: 10718501.
70. Christen WG, Glynn RJ, Ajani UA, et al. Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians. Arch Ophthalmol 2001 Aug;119(8):1143-9. PMID: 11483080.
71. Okada S, Morimoto T, Ogawa H, et al. Effect of low-dose aspirin on primary prevention of cardiovascular events in Japanese diabetic patients at high risk. Circulation Journal 2013;77(12):3023-8. PMID: 24042256.
72. Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012 Feb 13;172(3):209-16. PMID: 22231610.
73. Raju N, Sobieraj-Teague M, Hirsh J, et al. Effect of Aspirin on Mortality in the Primary Prevention of Cardiovascular Disease. Am J Med 2011 Jul;124(7):621-9. PMID: 21592450.
74. Bartolucci AA, Tendera M, Howard G. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. Am J Cardiol 2011 Jun 15;107(12):1796-801. PMID: 21481826.
75. Berger JS, Lala A, Krantz MJ, et al. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. Am Heart J 2011 Jul;162(1):115-24. PMID: 21742097.
76. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007 Feb;28(2):105-14. PMID: 16807131.

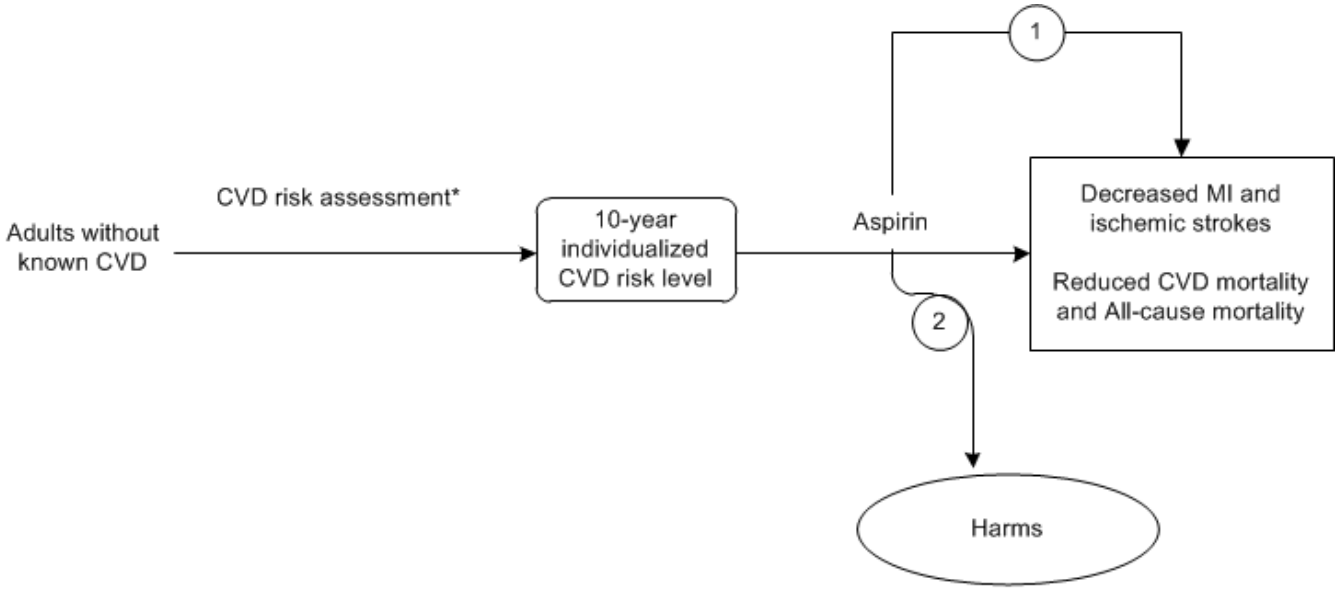
77. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med 1996 Dec 30;15(24):2733-49. PMID: 89811683.
78. Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. PLoS One 2013;8(7):e69930. PMID: 23922860.
79. Guolo A. Higher-order likelihood inference in meta-analysis and meta-regression. Stat Med 2012 Feb 20;31(4):313-27. PMID: 22173666.
80. Zhang C, Sun A, Zhang P, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pract 2010 Feb;87(2):211-8. PMID: 19853947.
81. Younis N, Williams S, Ammori B, et al. Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus: a meta-analysis. Expert Opin Pharmacother 2010 Jun;11(9):1459-66. PMID: 20429671.
82. Stavrakis S, Stoner JA, Azar M, et al. Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. Am J Med Sci 2011 Jan;341(1):1-9. PMID: 21191260.
83. De Berardis G, Sacco M, Strippoli GF, 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.
84. Butalia S, Leung AA, Ghali WA, et al. Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis. [Review]. Cardiovascular Diabetology 2011;10:25. PMID: 21453547.
85. Ekstrom N, Cederholm J, Zethelius B, et al. Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register. BMJ Open 2013;3(4) PMID: 23604419.
86. Coccheri S. Antiplatelet therapy: controversial aspects. Thromb Res 2012 Mar;129(3):225-9. PMID: 22119155.
87. Pulcinelli FM, Biasucci LM, Riondino S, et al. COX-1 sensitivity and thromboxane A2 production in type 1 and type 2 diabetic patients under chronic aspirin treatment. Eur Heart J 2009 May;30(10):1279-86. PMID: 19346231.
88. Bulugahapitiya U, Siyambalapitiya S, Sithole J, et al. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med 2009 Feb;26(2):142-8. PMID: 19236616.
89. De Berardis G, Lucisano G, D'Ettorre A, et al. Association of aspirin use with major bleeding in patients with and without diabetes. JAMA 2012 Jun 6;307(21):2286-94. PMID: 22706834.
90. Welin L, Wilhelmsen L, Bjornberg A, et al. Aspirin increases mortality in diabetic patients without cardiovascular disease: a Swedish record linkage study. Pharmacoepidemiology & Drug Safety 2009 Dec;18(12):1143-9. PMID: 19672841.
91. Bowman L. ASCEND: A Study of Cardiovascular Events iN Diabetes. http://clinicaltrials gov/ct2/show/NCT00135226?term=cardiovascular+events+prevention+trial+in+diabetes &rank=4 2011 PMID: None.
92. De Berardis G, Sacco M, Evangelista V, et al. 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.
93. Lanas A, Garcia-Rodriguez LA, Polo-Tomas M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol 2009 Jul;104(7):1633-41. PMID: 19574968.
94. Nelson M, Reid C, Beilin L, et al. 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(12):897-903. PMID: 14565783.
95. Matthys F, De BT, De BG, et al. 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(3):354-65. PMID: 23610452.
96. Food and Drug Administration. Citizen Petition Denial Response from FDA to Bayer Healthcare, LLC. Department of Health and Human Services; 2014. PMID: None.
97. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. Circulation 2011 Mar 22;123(11):1243-62. PMID: 21325087.
98. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet 2013 Nov 30;382(9907):1762-5. PMID: 24268611.
99. Muntner P, Colantonio LD, Cushman M, et al. Validation of the Atherosclerotic Cardiovascular Disease Pooled Cohort Risk Equations. JAMA 2014 Mar 29 PMID: 24682252.
100. Kavousi M, Leening MJ, Nanchen D, 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 Mar 29 PMID: 24681960.
101. Brindle P, Beswick A, Fahey T, et al. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart 2006 Dec;92(12):1752-9. PMID: 16621883.
102. Beswick, AD, Brindle, P, Fahey, T, et al. A Systematic Review of Risk Scoring Methods and Clinical Decision Aids Used in the Primary Prevention of Coronary Heart Disease. 2008. PMID: 21834196.
103. Siontis GC, Tzoulaki I, Siontis KC, et al. Comparisons of established risk prediction models for cardiovascular disease: systematic review. BMJ 2012;344:e3318. PMID: 22628003.
104. Ridker PM, Cook NR. Refining the American guidelines for prevention of cardiovascular disease - Authors' reply. Lancet 2014 Feb 15;383(9917):600. PMID: 24529467.
105. Maciosek, M, Dehmer, S, Flottemesch, T. Aspirin use to prevent cardiovascular disease and cancer: a decision analysis. Rockville, MD: Agency for Healthcare Research and Quality; 2014. PMID: None.
106. Liew G, Mitchell P, Wong TY, et al. The Association of Aspirin Use With Age-Related Macular Degeneration. JAMA Intern Med 2013 Jan 21:1-7. PMID: 23337937.
107. de Jong PT, Chakravarthy U, Rahu M, et al. Associations between aspirin use and aging macula disorder: the European Eye Study. Ophthalmology 2012 Jan;119(1):112-8. PMID: 21920607.

108. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005 Oct 8;366(9493):1267-78. PMID: 16214597.
109. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ 2007 Apr 14;334(7597):786. PMID: 17403713.
110. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005 Jan 8;365(9454):176-86. PMID: 15639301.
111. Sun X, Briel M, Busse JW, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ 2012;344:e1553. PMID: 22422832.
112. Pitrou I, Boutron I, Ahmad N, et al. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med 2009 Oct 26;169(19):1756-61. PMID: 19858432.
113. Chuback, J, Kamineni, A, Buist, D, et al. Aspirin use for the prevention of colorectal cancer: an evidence update for the US Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2014. PMID: None.
114. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989 Apr;129(4):687-702. PMID: 2646917.
115. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41(11):1105-16. PMID: 3204420.
116. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991 Feb;1(3):263-76. PMID: 1669507.
117. D'Agostino RB, Sr., Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001 Jul 11;286(2):180-7. PMID: 11448281.
118. Bastuji-Garin S, Deverly A, Moyse D, et al. The Framingham prediction rule is not valid in a European population of treated hypertensive patients. J Hypertens 2002 Oct;20(10):1973-80.
119. Folsom AR, Chambless LE, Duncan BB, et al. Prediction of coronary heart disease in middle-aged adults with diabetes. Diabetes Care 2003 Oct;26(10):2777-84. PMID: 14514579.
120. Bhopal R, Fischbacher C, Vartiainen E, et al. Predicted and observed cardiovascular disease in South Asians: application of FINRISK, Framingham and SCORE models to Newcastle Heart Project data. J Public Health (Oxf) 2005 Mar;27(1):93-100. PMID: 15749725.
121. Stephens JW, Ambler G, Vallance P, et al. Cardiovascular risk and diabetes. Are the methods of risk prediction satisfactory? Eur J Cardiovasc Prev Rehabil 2004 Dec;11(6):521-8. PMID: 15580065.
122. Empana JP, Ducimetiere P, Arveiler D, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. Eur Heart J 2003 Nov;24(21):1903-11. PMID: 14585248.
123. Cooper JA, Miller GJ, Humphries SE. A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the

Second Northwick Park Heart Study. Atherosclerosis 2005 Jul;181(1):93-100. PMID: 15939059.
124. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007 Feb;93(2):172-6. PMID: 17090561.
125. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ 2007 Jul 21;335(7611):136. PMID: 17615182.
126. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991 Mar;22(3):312-8. PMID: 2003301.
127. D'Agostino RB, Wolf PA, Belanger AJ, et al. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke 1994 Jan;25(1):40-3. PMID: 8266381.
128. Truelsen T, Lindenstrom E, Boysen G. Comparison of probability of stroke between the Copenhagen City Heart Study and the Framingham Study. Stroke 1994 Apr;25(4):802-7. PMID: 8160224.
129. Teramoto T, Shimada K, Uchiyama S, et al. Rationale, design, and baseline data of the Japanese Primary Prevention Project (JPPP)-a randomized, open-label, controlled trial of aspirin versus no aspirin in patients with multiple risk factors for vascular events. Am Heart J 2010 Mar;159(3):361-9. PMID: 20211296.
130. Bayer. ARRIVE: A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE). http://clinicaltrials gov/ct2/show/record/NCT00501059?term=ARRIVE&rank=2 2013 PMID: None.
131. Guidelines and Protocols Advisory Committee. Cardiovascular disease - primary prevention. Victoria: BC Ministry of Health; 2008.
132. Guidelines and Protocols Advisory Committee. Diabetes Care. Victoria: BC Ministry of Health; 2010.
133. World Health Organization. Pocket Guidelines for Assessment and Management of Cardiovascular Risk. Geneva: 2007.
134. Hayden M, Pignone M, Phillips C, et al. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002 Jan 15;136(2):161-72. PMID: 11790072.
135. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2009 Mar 17;150(6):405-10. PMID: 19293073.
136. Calonge N, Lefevre M. USPSTF Response to the ATT Collaboration Meta-Analysis. U.S. Preventive Services Task Force; 2009.

Figure 1. Analytic Framework



Abbreviations: CVD = cardiovacular disease; MI = myocardial infarction.

Figure 2. Forest Plot of All-Cause Mortality, Sorted by Length of Followup

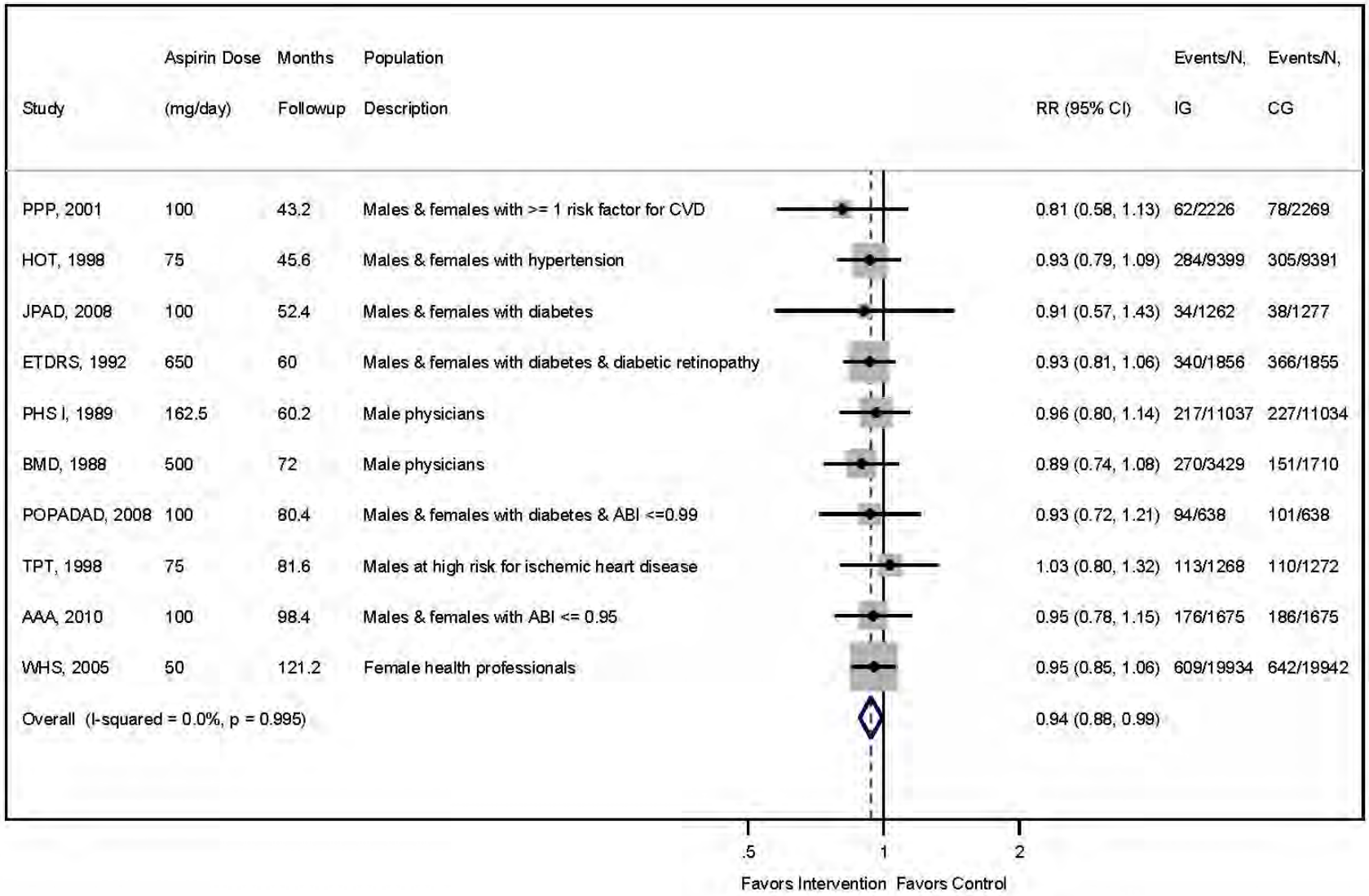


Figure 3. Forest Plot of Total MI/Coronary Events (Fatal and Nonfatal), Sorted by Length of Followup

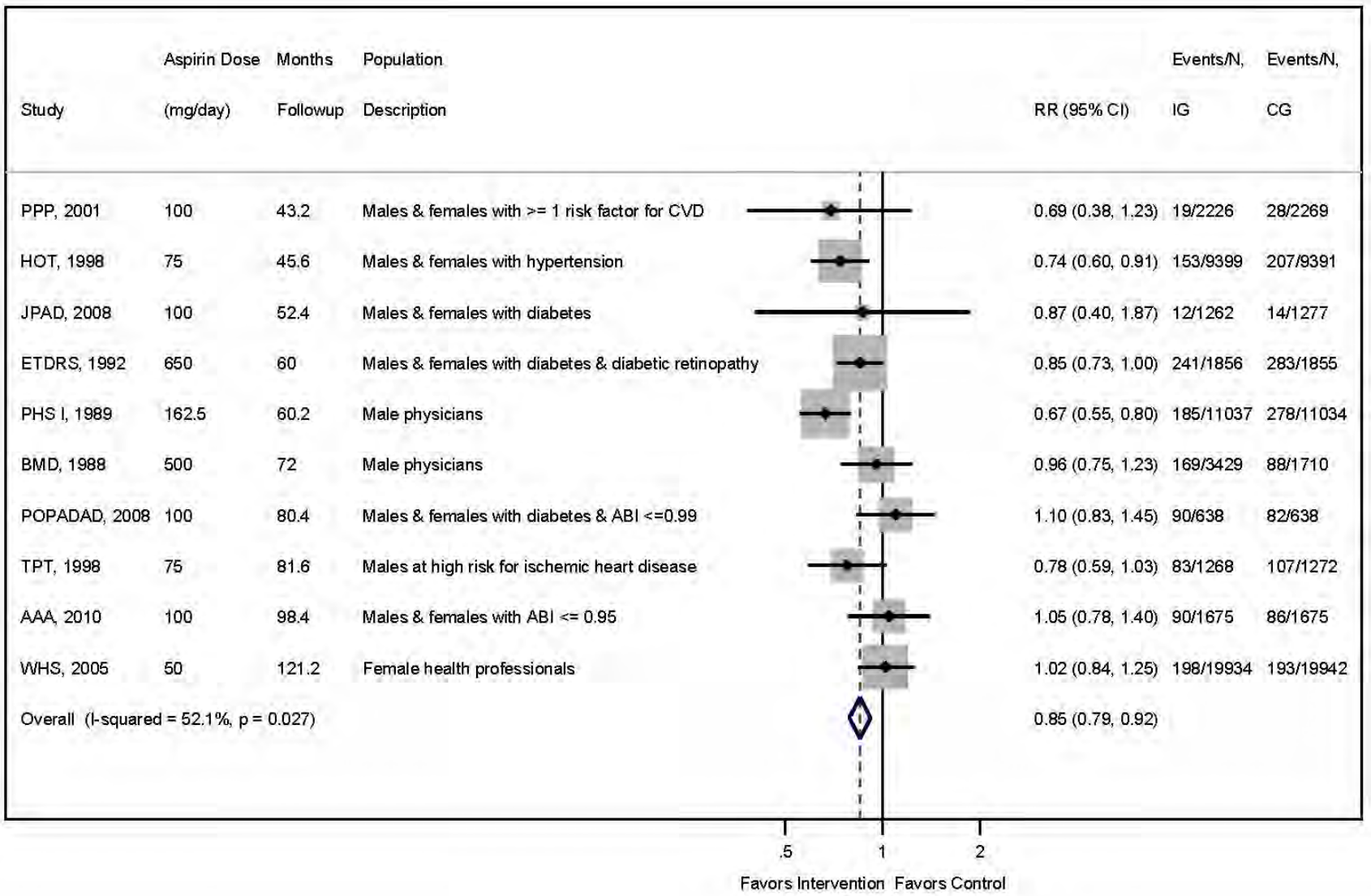


Figure 4. Forest Plot of Fatal MI/Coronary Events, Sorted by Length of Followup

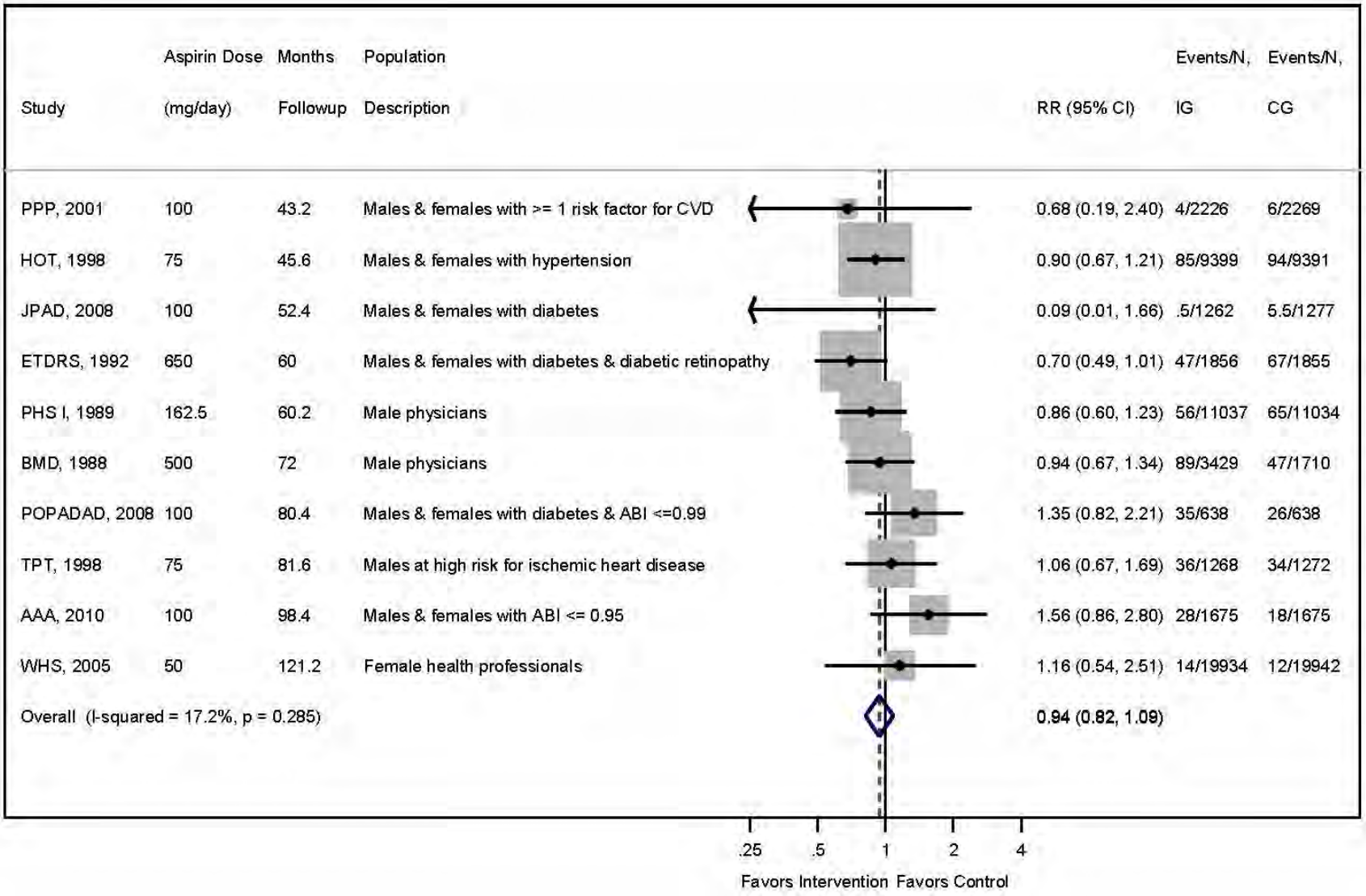


Figure 5. Forest Plot of Nonfatal MI/Coronary Events, Sorted by Length of Followup

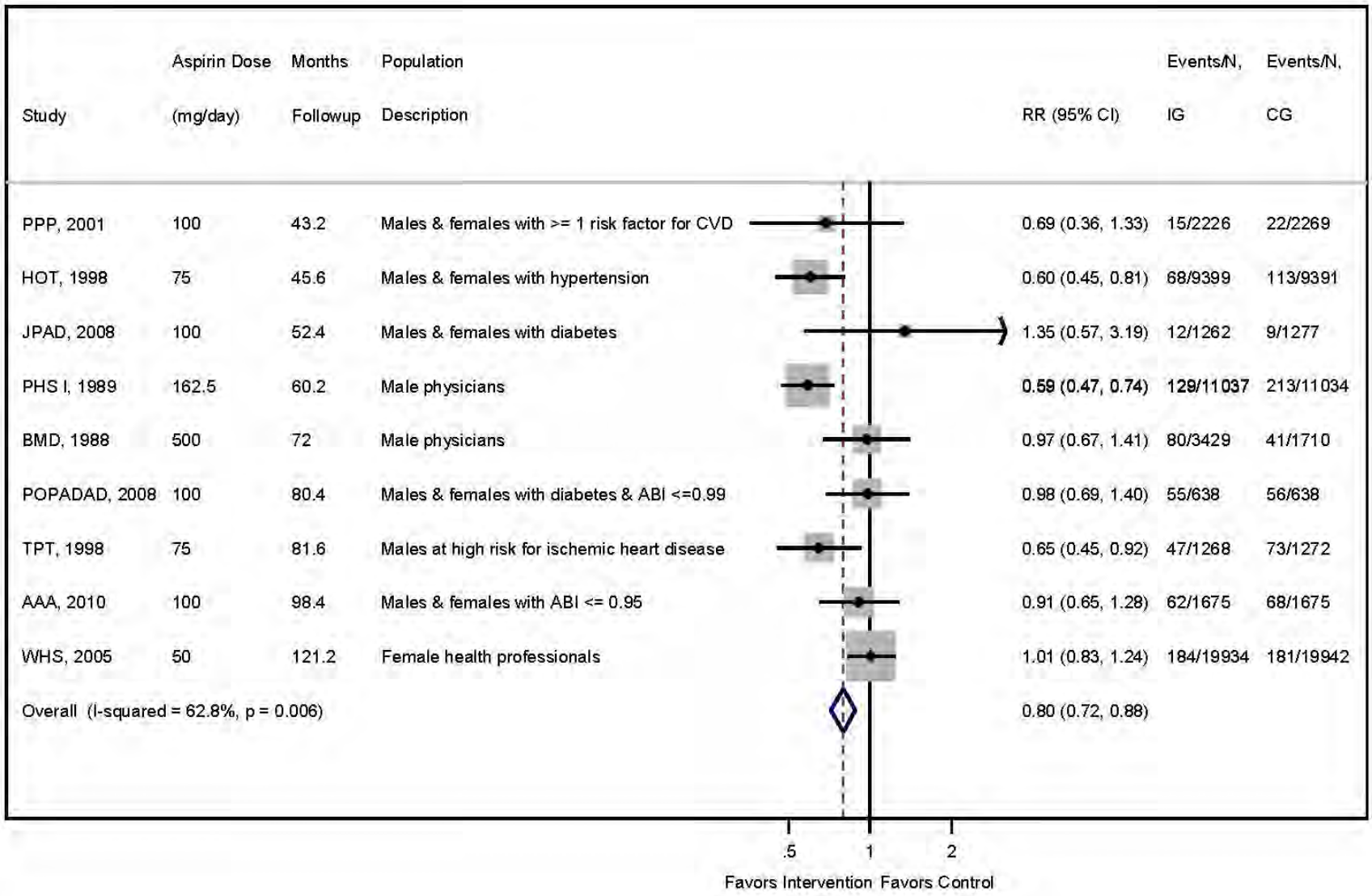


Figure 6. Forest Plot of Total Stroke Events (Fatal and Nonfatal), Sorted by Length of Followup

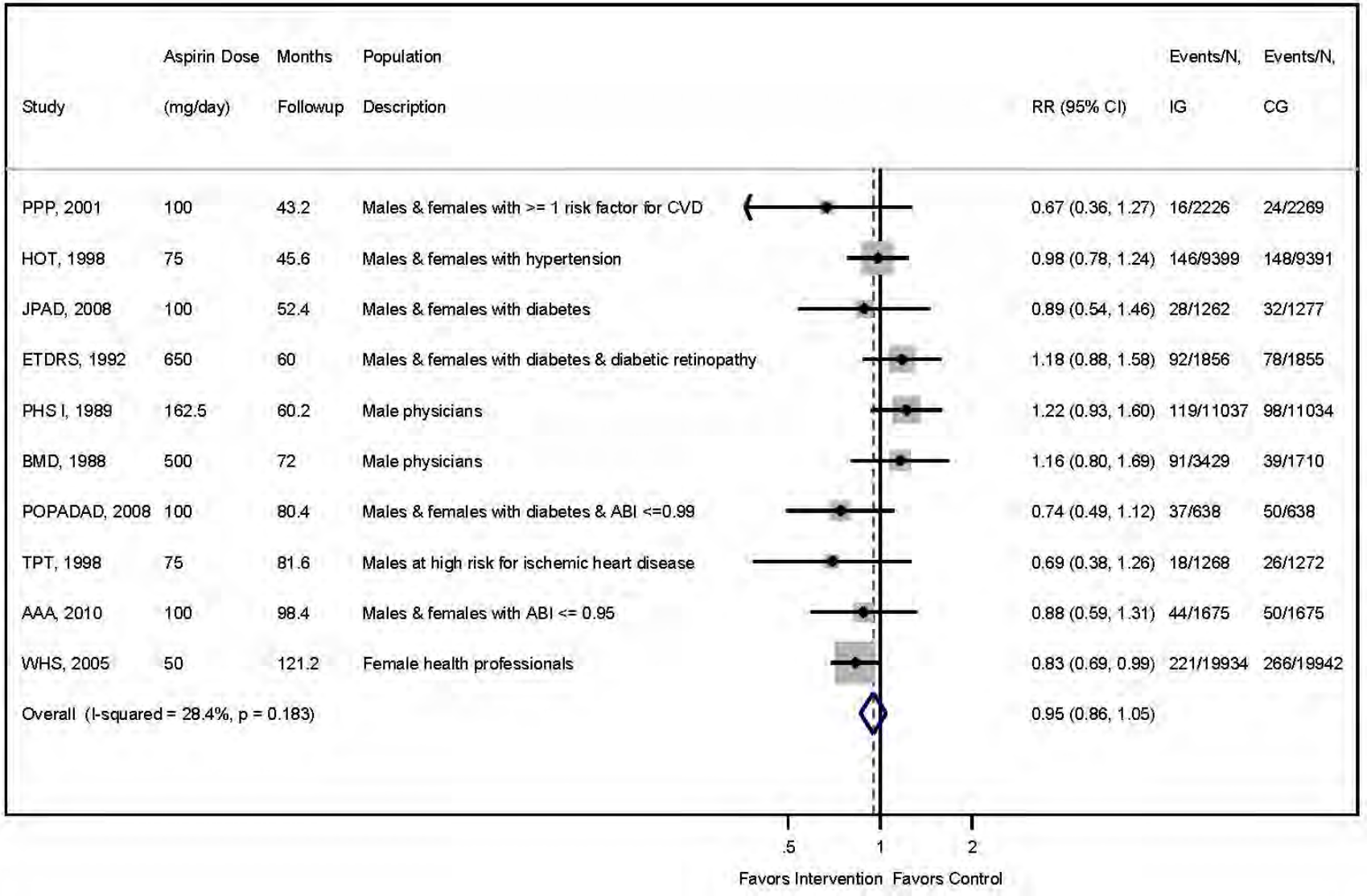


Figure 7. Forest Plot of Fatal Stroke Events, Sorted by Length of Followup

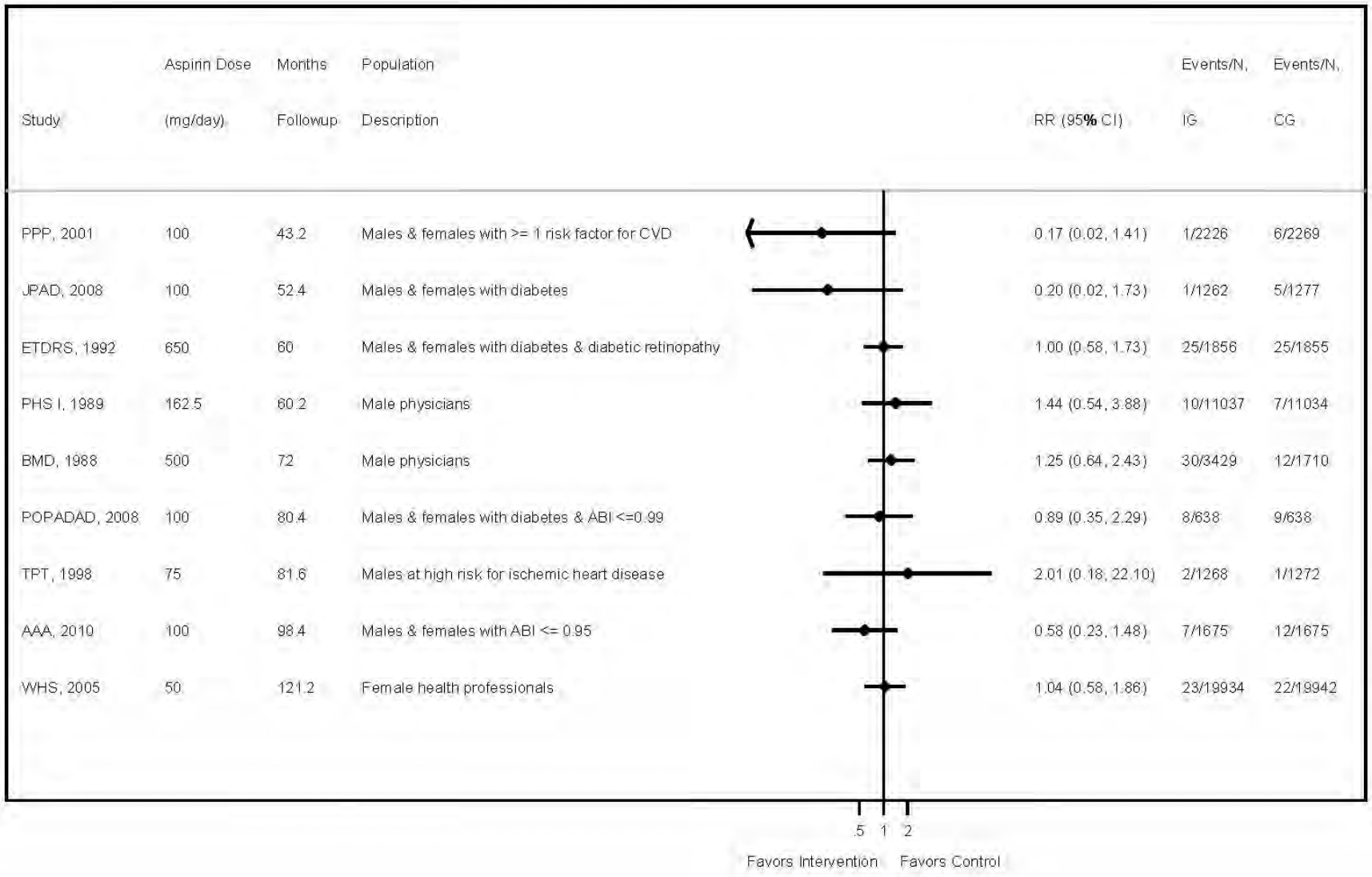


Figure 8. Forest Plot of Nonfatal Stroke Events, Sorted by Length of Followup

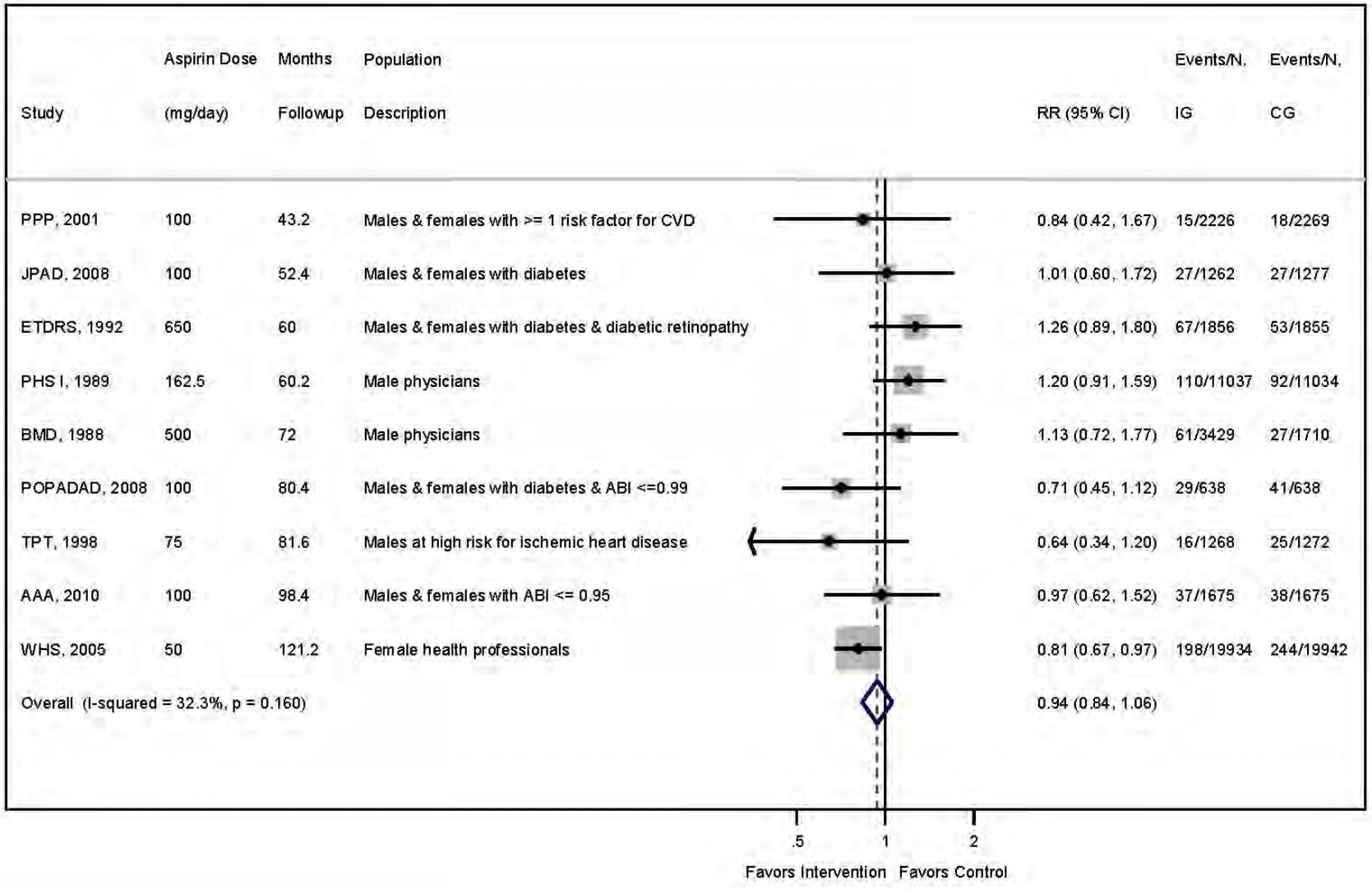


Figure 9. Forest Plot of Total Ischemic Stroke Events (Fatal and Nonfatal), Sorted by Length of Followup

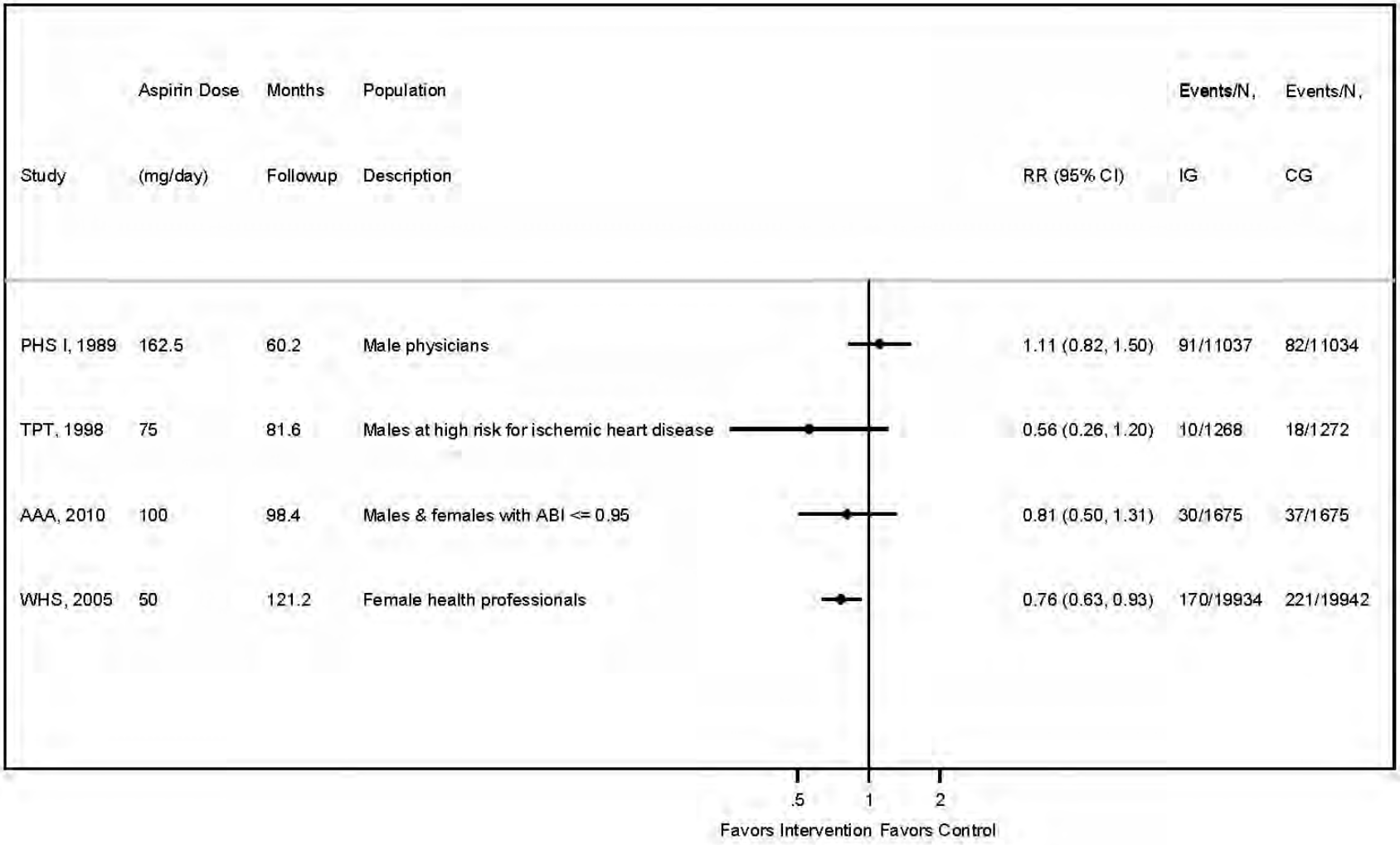


Figure 10. Forest Plot of Fatal Ischemic Stroke Events, Sorted by Length of Followup

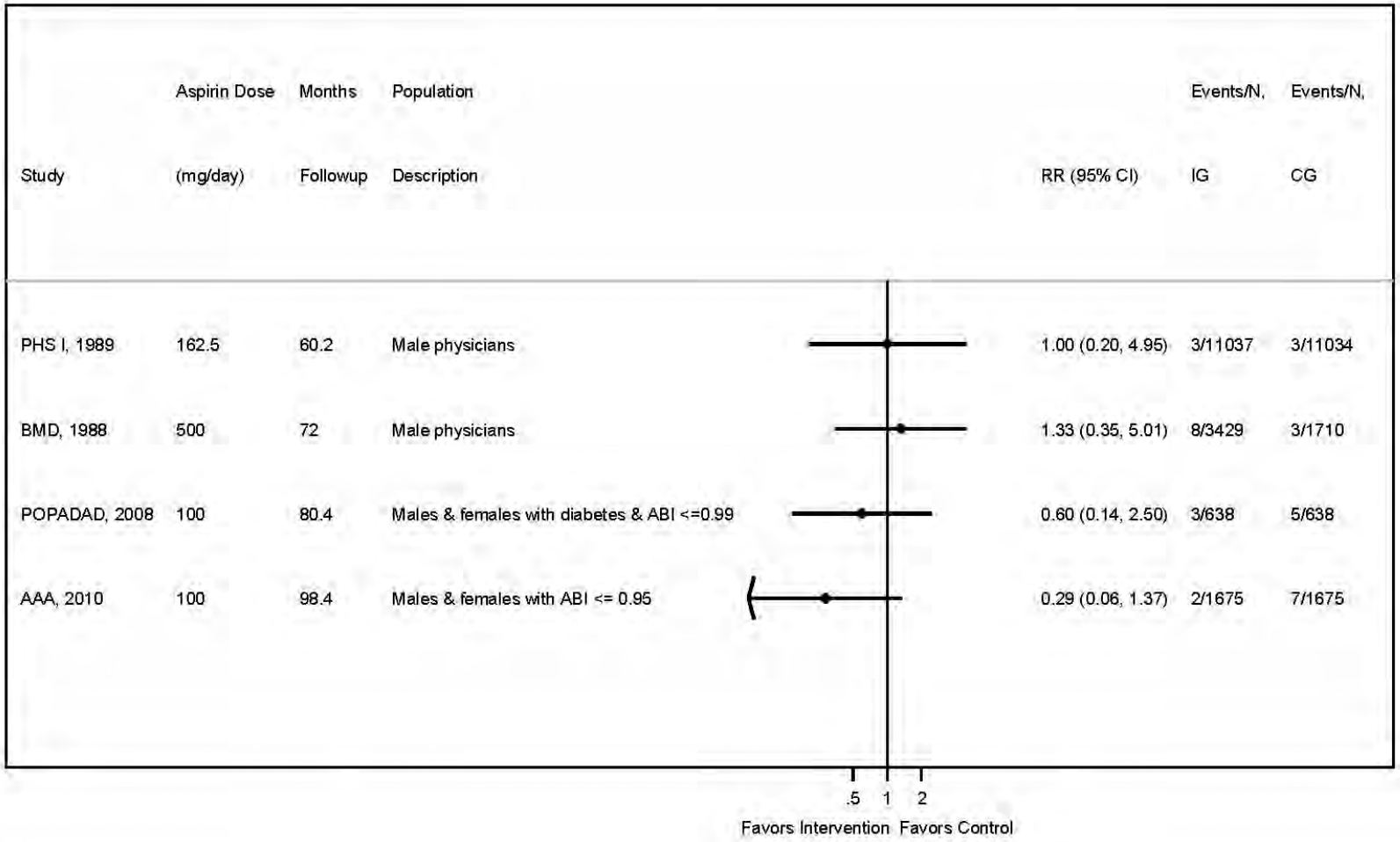


Figure 11. Forest Plot of Nonfatal Ischemic Stroke Events, Sorted by Length of Followup

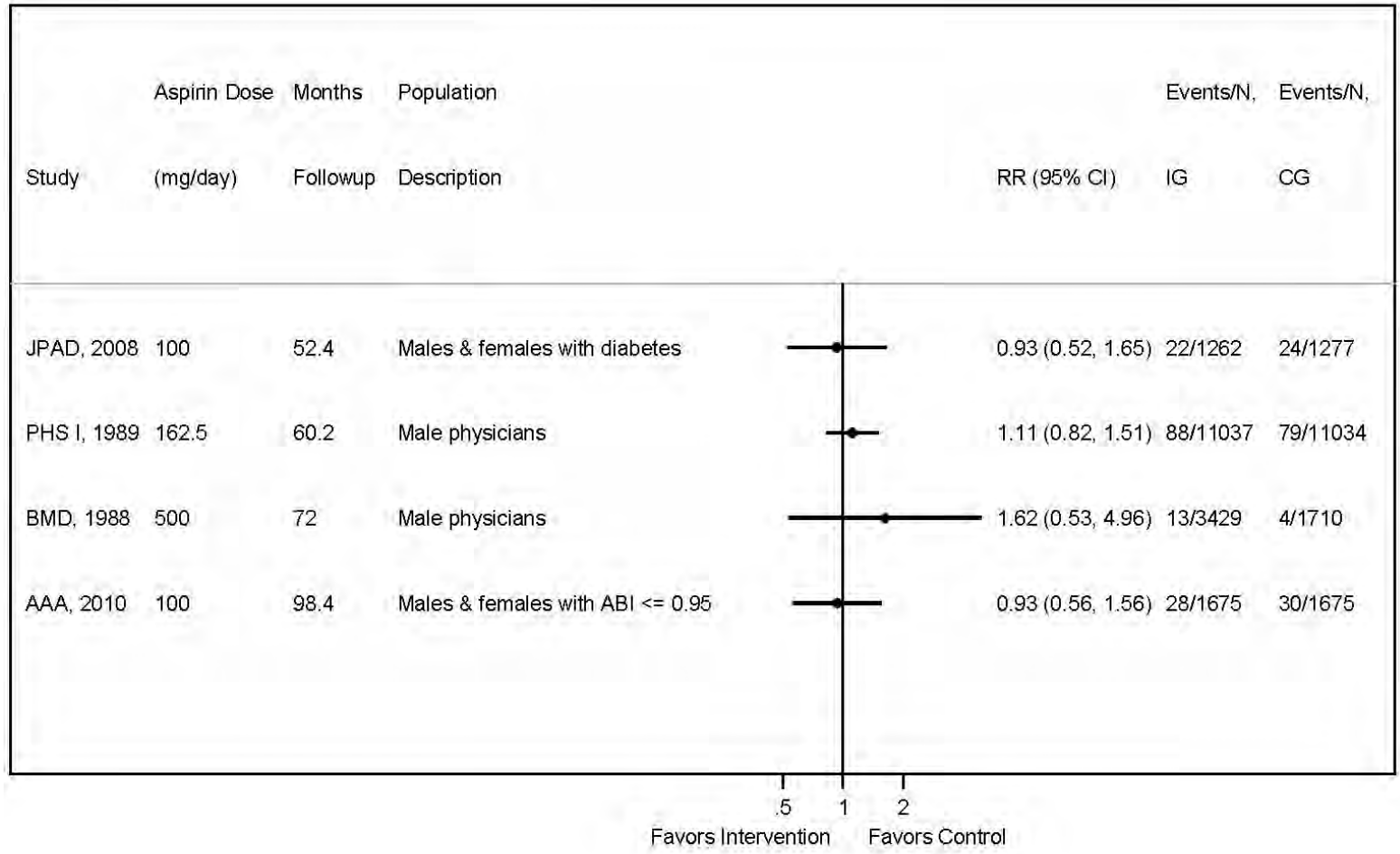


Figure 12. Forest Plot of Fatal MI/Coronary Events Combined With Fatal Stroke Events, Sorted by Length of Followup

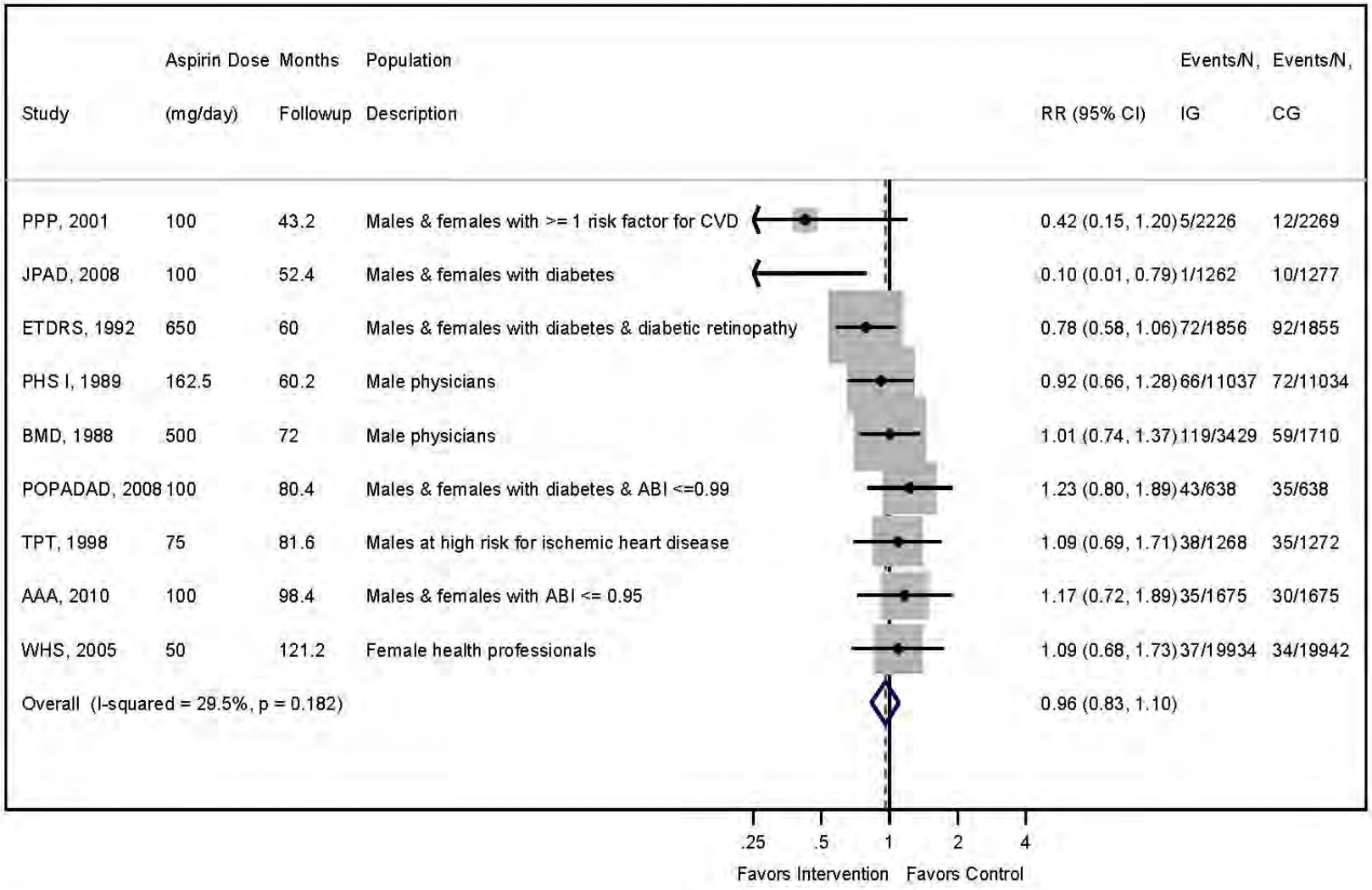


Figure 13. Forest Plot of Fatal MI/Coronary Events Combined With Fatal Stroke Events and CVD Mortality, Sorted by Length of Followup

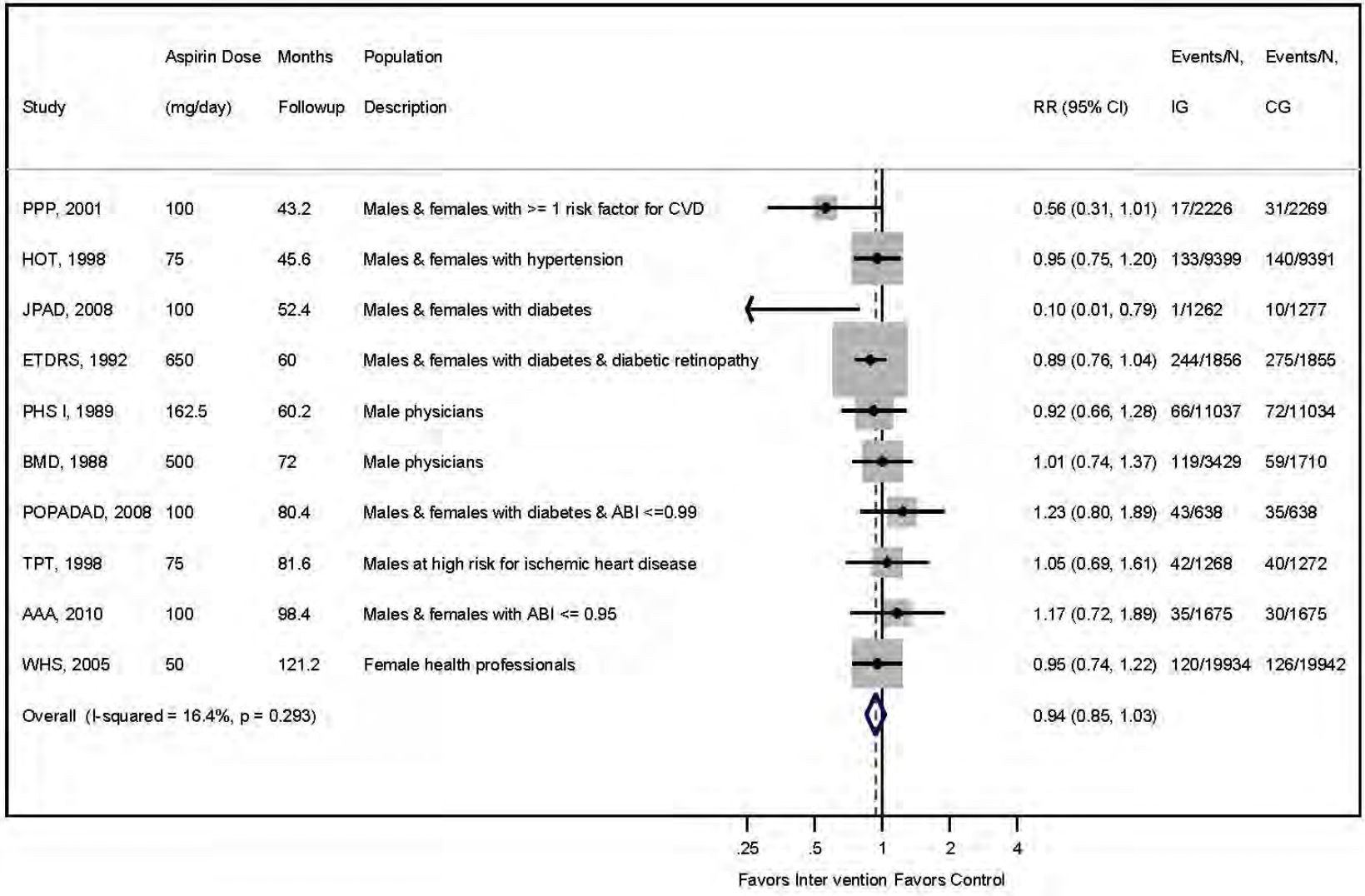


Figure 14. Forest Plot of Nonfatal MI/Coronary Events Combined With Nonfatal Stroke Events, Sorted by Length of Followup

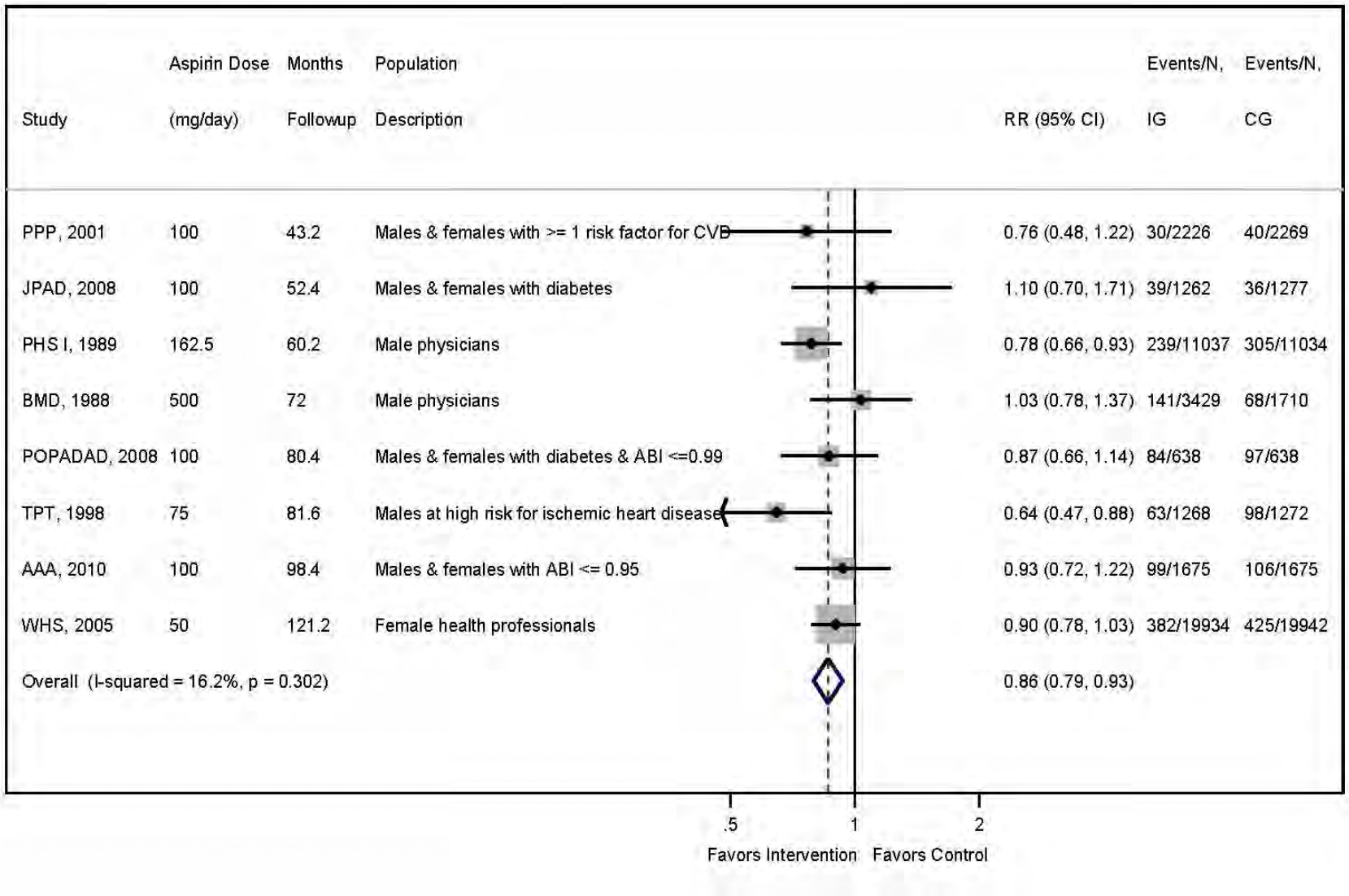


Figure 15. Forest Plot of Total MI/Coronary Events (Fatal and Nonfatal) Combined With Total Stroke Events (Fatal and Nonfatal) and CVD Mortality, Sorted by Length of Followup

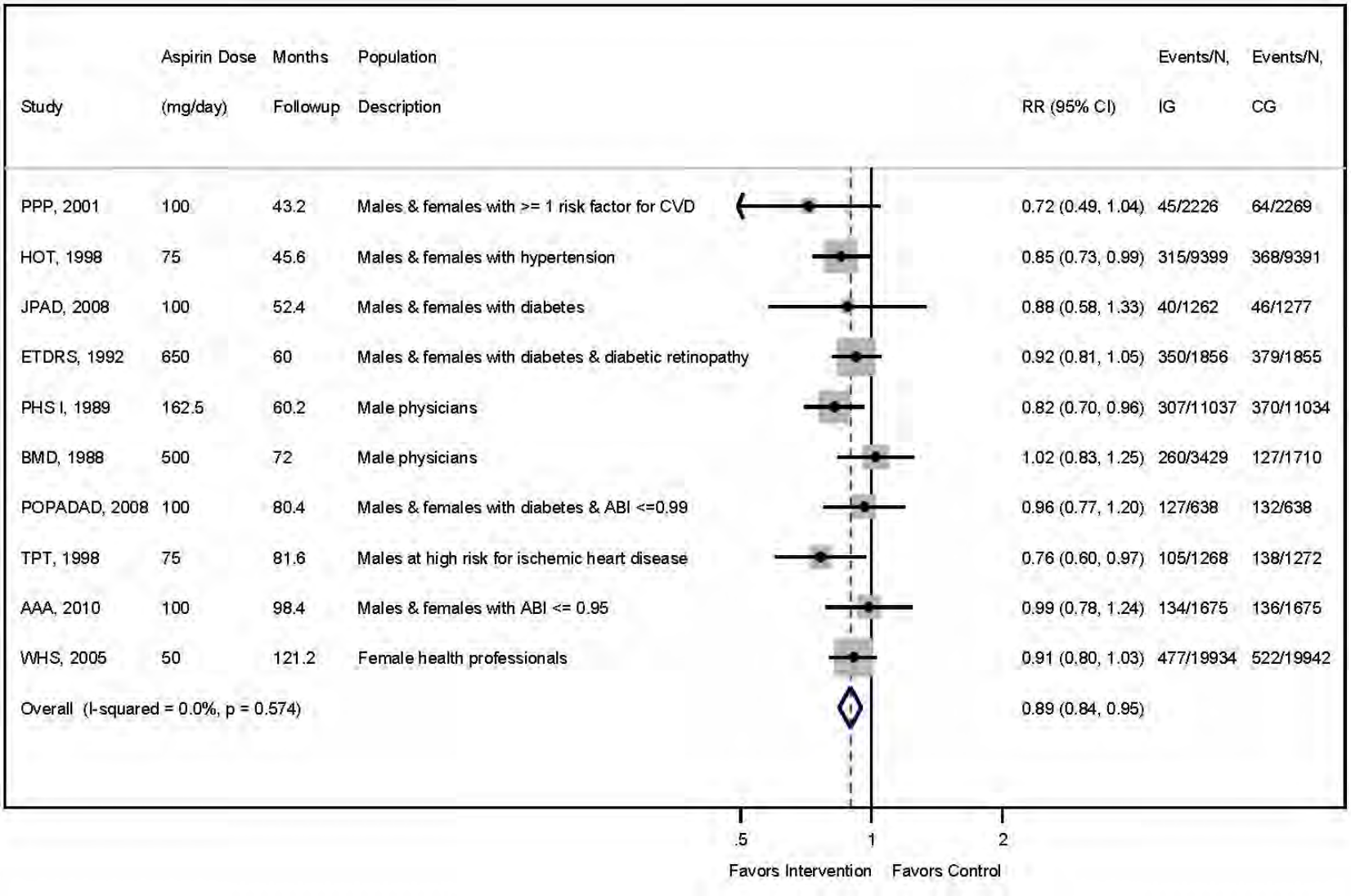


Figure 16. Forest Plot of Total Hemorrhagic Stroke Events (Fatal and Nonfatal), Sorted by Length of Followup

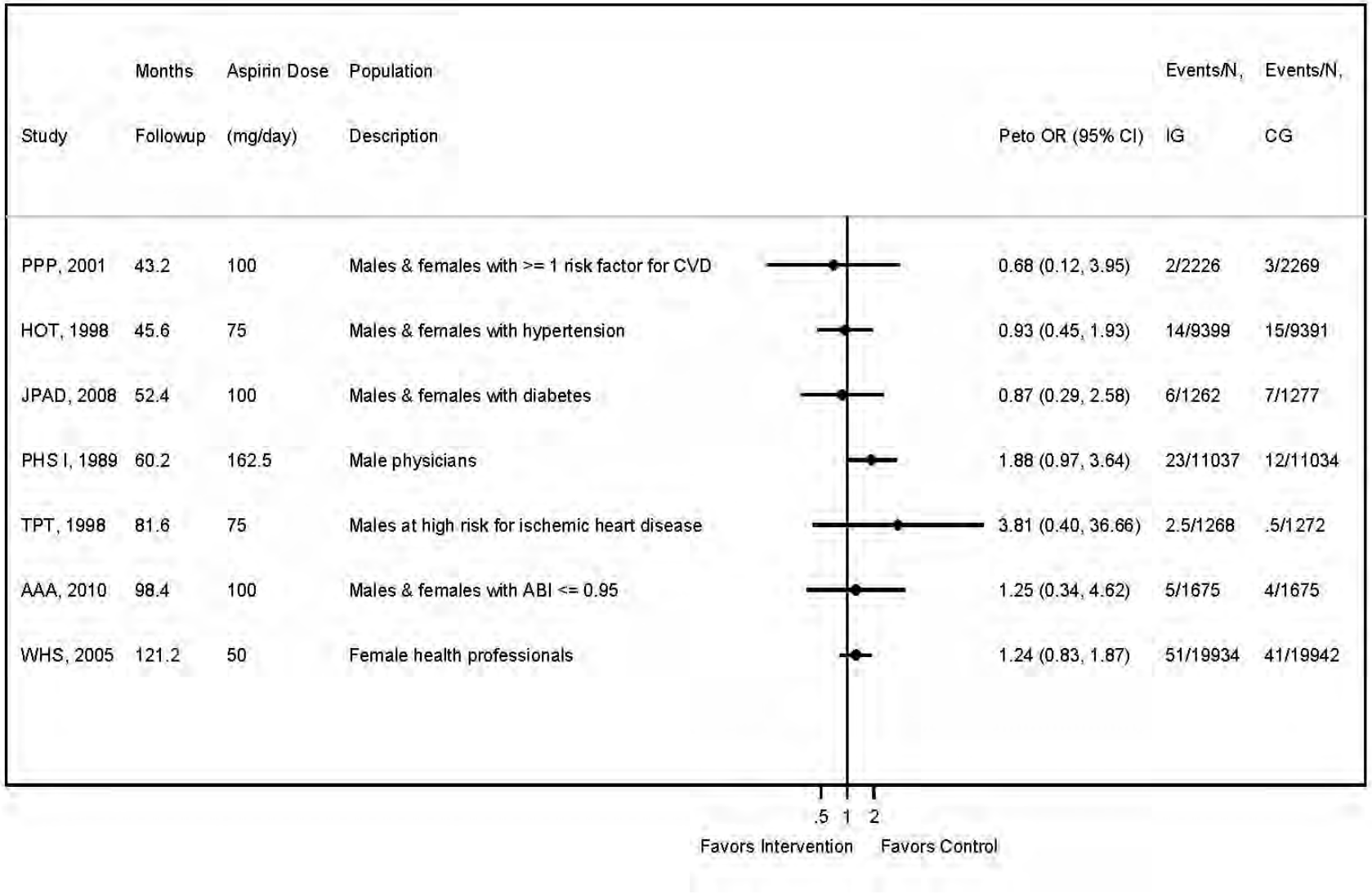


Figure 17. Forest Plot of Fatal Hemorrhagic Stroke Events, Sorted by Length of Followup

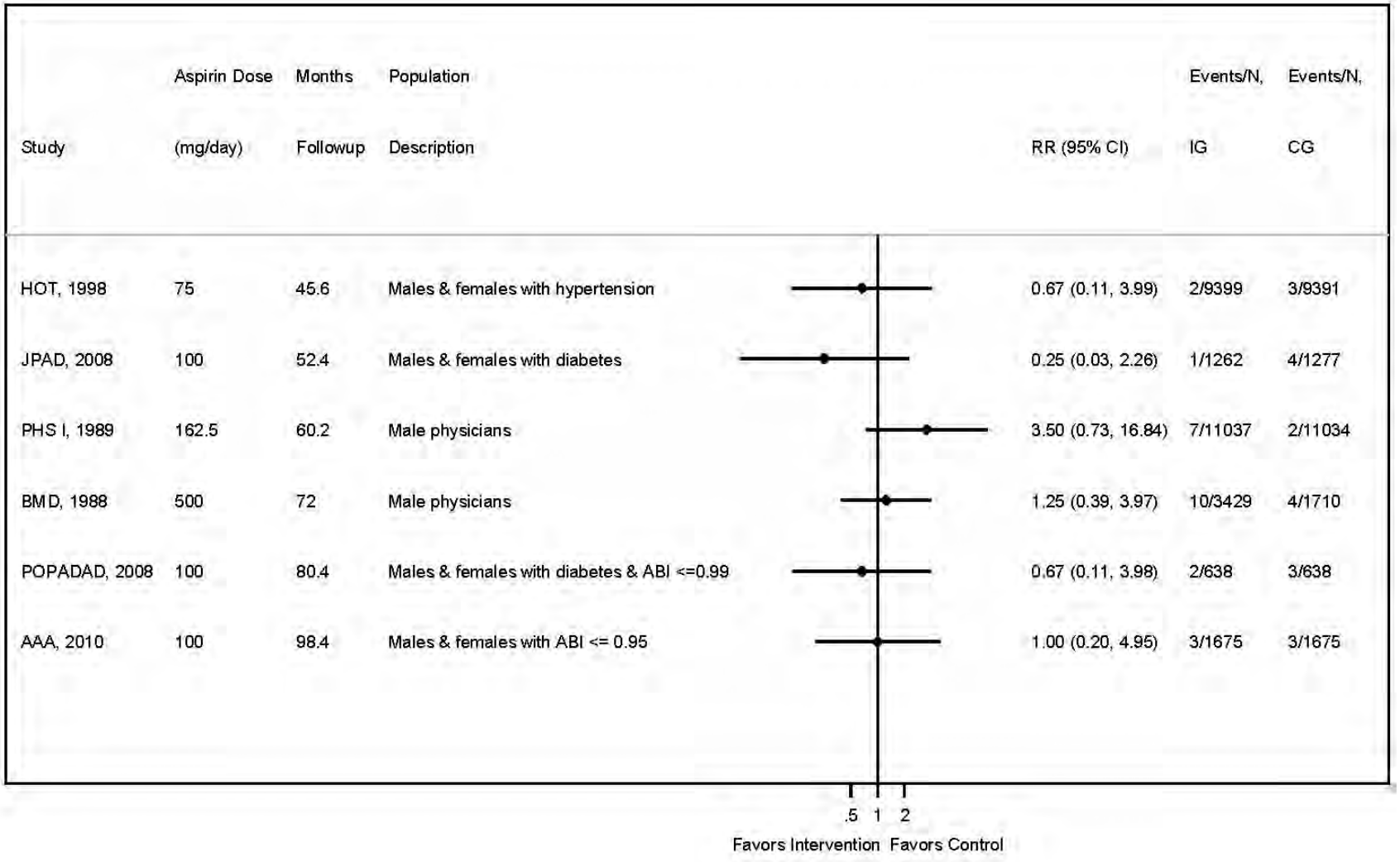


Figure 18. Forest Plot of Nonfatal Hemorrhagic Stroke Events, Sorted by Length of Followup

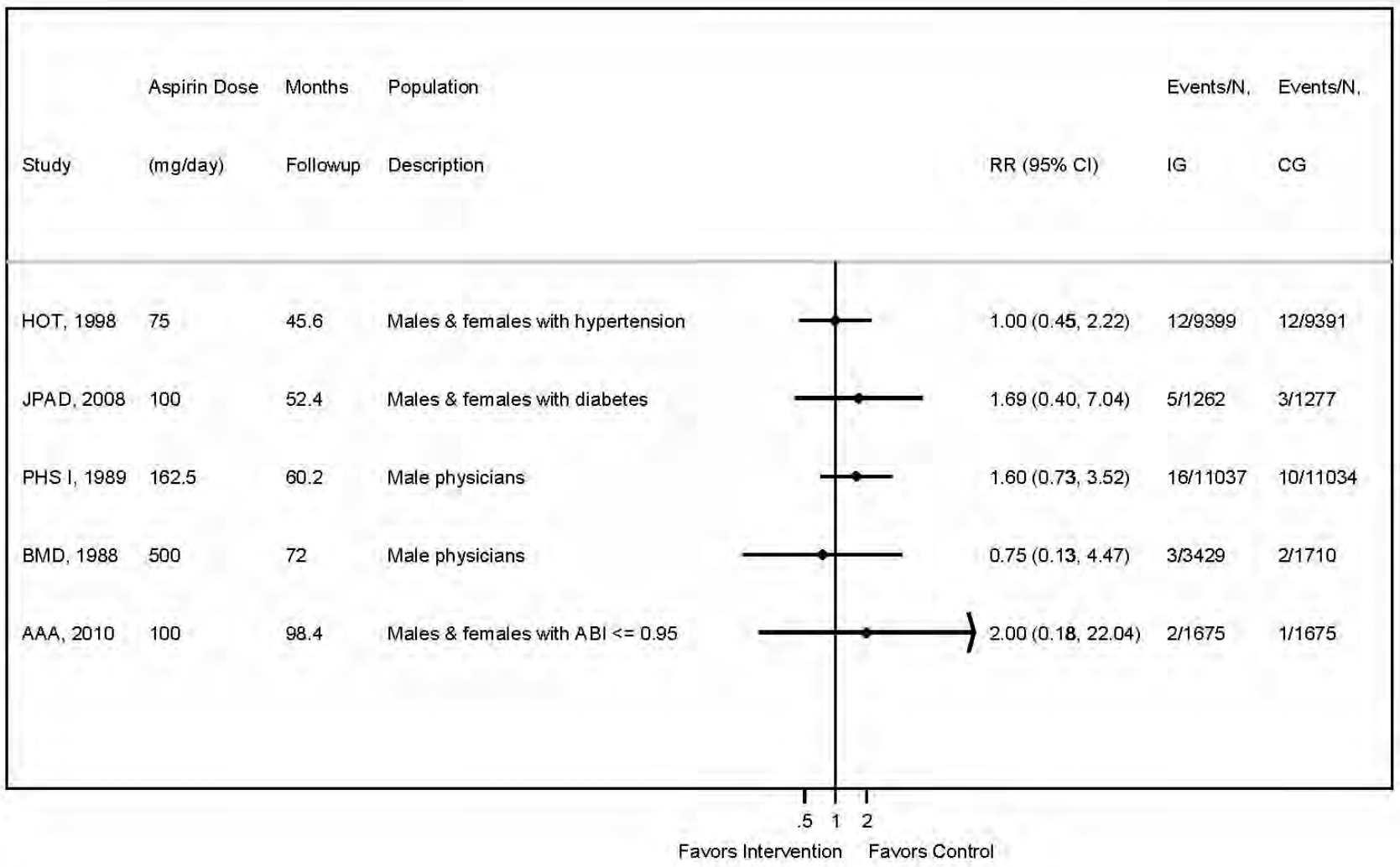


Figure 19. Forest Plot of Major GI Bleeding, Sorted by Length of Followup

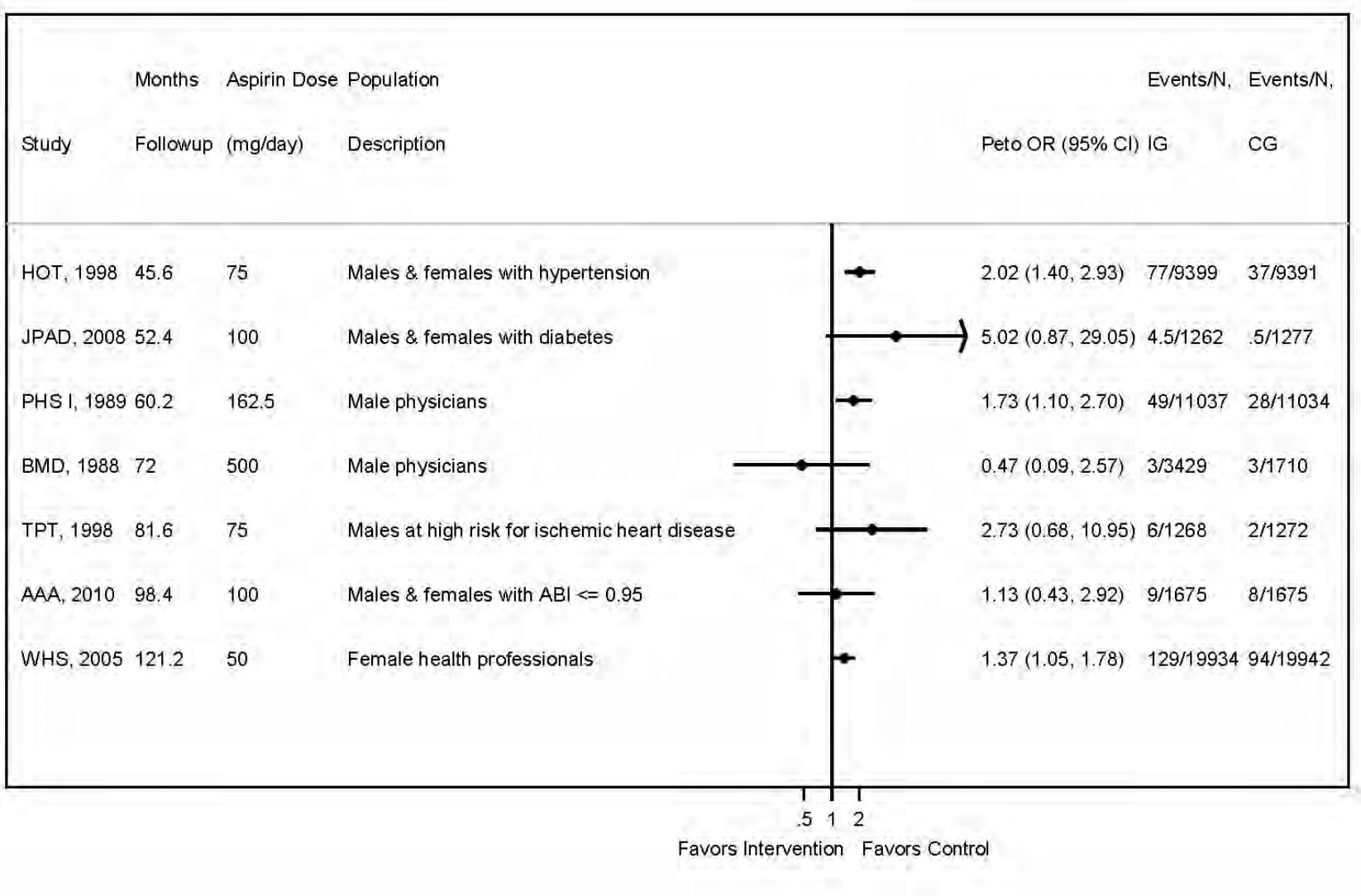


Figure 20. Forest Plot of Intracranial Bleeding, Sorted by Length of Followup

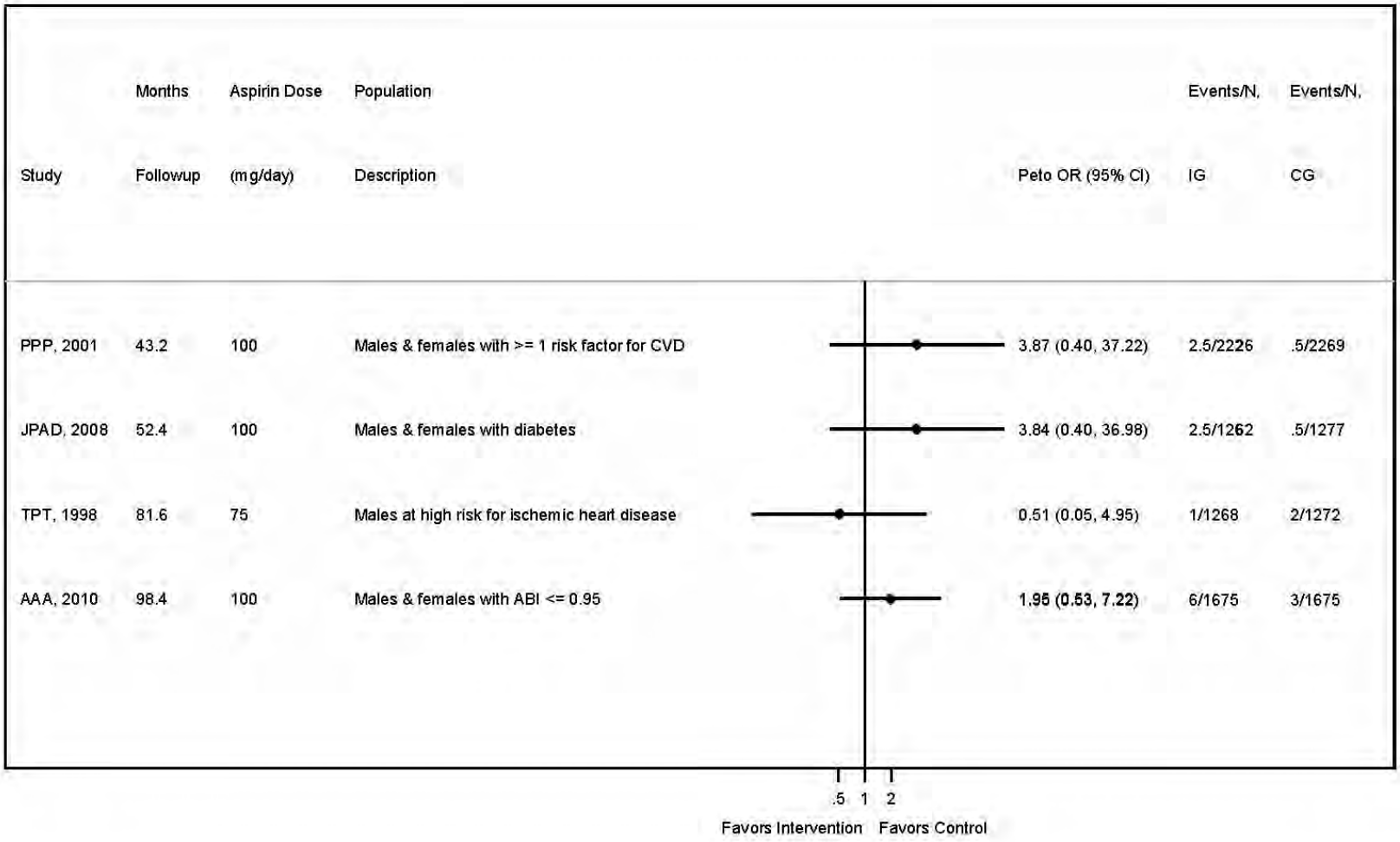


Table 1. Baseline Participant Characteristics of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

	BMD, 1988[57]	PHS I, 1989[53]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Quality	Fair	Good	Fair	Fair	Fair	Fair	Good	Fair	Fair	Fair
Country	UK	US	US	26 countries[¶]	UK	Italy	US	Japan	Scotland	UK
N Randomized	5,139	22,071	3,711	18,790	2,540	4,495	39,876	2,539	1,276	3,350
Age, years (mean)	<60: 46.8% 60-69: 39.0% 70-79: 14.1%	40-49: 41.0%* 50-59: 33.8%* 60-69: 18.5%* 70-84: 6.7%*	<30: 16.9* 30-49: 31.5* ≥50: 51.7*	61.5*	57.5*	64.4	54.6	64.5	60.3	62.0
% Female	0	0	43.5*	47.0*	0	58.0	100.0	45.4	55.9	72
Hypertension										
% HTN	9.9	NR	44.4*[†]	100	NR	68.0	25.9	58.0	NR	NR
SBP/DBP, mm Hg (mean)	135.8/NR	SBP: <109: 3.2* 110-129: 52.6* 130-149: 39.7* ≥150: 4.5* DBP: ≤69: 5.9* 70-79: 31.4* 80-89: 52.4* ≥90: 10.4*	SBP ≥130.0: 66.0%* DBP ≥85.0: 39.1%*	170.0/105.0	139.0/NR*	145.2/85.4	<120/<75: 32.6% 120-29/75-84: 32.0% 130-39/85-89: 19.4% ≥140/≥90: 16.0%	135.0/76.5	145/79.0*	147.5/84.0
% Treated for HTN	NR	NR	NR	100.0	1,421 participants treated during part or all of the trial	66.0	NR	Ca channel blocker: 34.5 ARB: 21.0 ACE: 14.7 β blocker: 6.4 α blocker: 3.6	NR	Diuretic: 15.2 Nitrate/Ca channel blocker: 6.4 ACE/ARB: 6.2 β blocker: 9.8
Cholesterol										
TC, mg/dL (mean)	NR	<159: 10.0* 160-209: 39.1* 210-259: 36.4* ≥260: 14.6*	NR	235.5*	247.1*	235.5*	NR	201.0	212.4*[#]	238.5
LDL, mg/dL (mean)	NR	NR	NR	NR	NR	150.6*	NR	NR	119.7*[#]	NR
HDL, mg/dL (mean)	NR	NR	NR	NR	NR	54.1*	NR	55	46.3*[#]	NR
% Treated for Cholesterol	NR	NR	NR	NR	NR	16.0	NR	25.6	NR	4.0
Diabetes										
% with Diabetes	2.0	2.4*	100.0	8.0*	NR	17.0	2.6	100.0	100.0	3.0
FPG, mg/dL	NR	NR	NR	NR	NR	109.9*	NR	147.0	NR	NR
HbA1c, %	NR	NR	≥10: 42.0%*	NR	NR	NR	NR	7.05	8.0	NR

Table 1. Baseline Participant Characteristics of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

	BMD, 1988[57]	PHS I, 1989[53]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
PAD										
% with Abnormal ABI (≤0.99)	NR	NR	9.4*‡	NR	NR	NR	NR	NR	100.0	100.0
ABI (mean)	NR	NR	NR	NR	NR	NR	NR	NR	0.9*#	0.86
% Current Smokers	≥21 cigarettes per day: 6.1	11.0*	≥6 cigarettes per day: 44.2*	15.9*	41.3*	15.0	13.1	21.2	31.1	33.0
Mean BMI (kg/m^2)	NR	≤23.0: 25.7* 23.0-24.4: 24.1* 24.4-26.3: 25.1* ≥26.4: 25.0*	≥120% of desirable weight: 41.5*	28.4*	27.4*	27.6	26.0	24.0	29.2*#	NR
CVD Risk	NR	NR	NR	NR	All participants 20% or 25% of risk score§	≥3 CVD risk factors: 29%	Framingham 10-year CHD risk, %: <5.0%: 84.5 5.0-9.9%: 11.5 ≥10.0%: 4.0	NR	NR	NR
% Prior CVD	Heart disease (excluding MI): 6.2 Other vascular disease: 3.6 TIA: 2.6	0	MI: 5.6* TIA: 1.5* CAD: 7.7* CHF: 2.8* Stroke: 1.8*	MI: 1.5* Other CHD: 5.9* Stroke: 1.2*	0	0	0	0	0	0
Annual Risk of Cardiovascular Events (%) ‖	1.54	0.67	4.08	1.19	1.53	0.76	0.26	0.82	2.53	0.99

* Data calculated.
† Elevated BP (SBP ≥160 mm Hg or DBP ≥95 mm Hg) or on HTN medications.
‡ Intermittent claudication.
§ According to risk assessment tool derived from Northwick Park Heart Study variables.
‖ Data are from Berger 2011 meta-analysis; calculated as percent with cardiovascular events in control group/years followup.
¶ 26 countries in Europe, North and South America, and Asia.
# Median.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMD = British Doctor's Trial; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular disease; DBP = diastolic blood pressure; ETDRS = Early Treatment Diabetic Retinopathy; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HOT = Hypertension Optimal Treatment; HTN = hypertension; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; LDL = low-density lipoprotein; MI = myocardial infarction; N = number; NR = not reported; PAD = peripheral arterial disease; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; SBP = systolic blood pressure; TC = total cholesterol; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK = United Kingdom; US = United States; WHS = Women's Health Study.

Table 2. Methodological and Intervention Characteristics of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

	BMD, 1988[57]	PHS I, 1989[53]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Quality	Fair	Good	Fair	Fair	Fair	Fair	Good	Fair	Fair	Fair
Country	UK	US	US	26 countries[§]	UK	Italy	US	Japan	UK	UK
N Randomized	5,139	22,071	3,711	18,790	2,540	4,495	39,876	2,539	1,276	3,350
Study Design	RCT	2x2 RCT, Beta-carotene	2x2 RCT, Early or delayed photocoagulation	3x2 RCT, HTN treatment goals	2x2 RCT, Warfarin	2x2 RCT, Vitamin E	2x2 RCT, Vitamin E	RCT	2x2 RCT, Antioxidant	RCT
Inclusion	Male physicians	Male physicians ages 40-84 years	Men & women ages 18-70 years with diabetes & diabetic retinopathy	Men & women ages 50-80 years with HTN	Men ages 45-69 years at the top 20% or 25% of CVD risk score	Men & women age ≥50 years with at least 1 CVD risk factor	Female health professionals age ≥45 years	Men & women ages 30-85 years with diabetes	Men & women age ≥40 years with diabetes & asymptomatic PAD (ABI ≤0.99	Men & women ages 50-75 years with ABI of ≤0.95
ASA Dose & Formulation	500 mg daily, unspecified*	325 mg QOD, tablet, not enteric coated[†]	650 mg daily, tablet, not enteric coated	75 mg daily, unspecified	75 mg daily, controlled release capsule	100 mg daily, enteric coated tablet	100 mg QOD, tablet, not enteric coated	100 mg daily, tablet, not enteric coated[‡]	100 mg daily, tablet, not enteric coated	100 mg daily, tablet, enteric coated
ASA Duration & Mean Followup	6 years	5 years	5 years	3.8 years	6.8 years[‖]	3.6 years	10.1 years	4.37 years[‖]	6.7 years[‖]	8.2 years
Primary Endpoint	Mortality from stroke, MI, or other vascular conditions	CVD mortality	All-cause mortality	Composite of major CV events: fatal and nonfatal MI, fatal and nonfatal stroke, and death due to CVD	All IHD: coronary death and fatal and nonfatal MI Fatal IHD: coronary death and fatal MI	Composite outcome: cumulative rate of CV death, nonfatal MI, and nonfatal stroke	Composite outcome: major CV event, defined as a nonfatal MI, nonfatal stroke, or CVD death	Composite of any atherosclerotic event: sudden death; death from coronary, cerebrovascular, or aortic causes; nonfatal acute MI; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease	2 composite end points: 1) death from CHD or stroke, nonfatal MI or stroke, above ankle amputation for critical limb ischemia; 2) death from CHD or stroke	Composite outcome: initial (earliest) fatal or nonfatal coronary event or stroke or revascular-ization

Table 2. Methodological and Intervention Characteristics of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

	BMD, 1988[57]	PHS I, 1989[53]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Secondary Endpoints	Nonfatal vascular and nonvascular events: MI, CVA, TIA, bleeding, other vascular conditions and nonfatal malignant neoplasms, respiratory events, cataracts, migraines, musculoskel-etal disorders	MI events (fatal and nonfatal), strokes (fatal and nonfatal), all-cause mortality	Cause-specific mortality, CV events (fatal and nonfatal MI, stroke), amputations, kidney disease or failure	Fatal and nonfatal MI or stroke, CVD mortality, total mortality, death from kidney failure, change in eGFR, major and minor hemorrhage	Stroke (thrombotic and hemorrhagic)	CV death, total death, nonfatal MI, total CV events: CV deaths, total deaths, total CV events (defined as nonfatal MI, nonfatal stroke, angina, TIA, PAD, revasculari-zation procedures)	MI, stroke, CVD mortality, all-cause mortality	Each primary end point and combinations of primary end points and death from any cause; adverse events: reported GI events, any hemorrhagic events other than CVA	All-cause mortality, nonfatal MI, and occurrence of other vascular events	1) All initial vascular events, defined as a composite outcome: primary end point event or angina, intermittent claudication, or TIA; 2) all-cause mortality
Adherence & Crossover	At 1 year, 19.5% of IG stopped ASA, and at 5 years, 24.8% stopped ASA	At 5 years, 85.7% in IG was still taking ASA or platelet-active drug; 14.2% of CG reported taking ASA or other antiplatelets	At 1 year, 8.2% of IG was not taking drug; at 5 years, 89% of IG was taking ASA (70%) or other platelet-affecting drug (19%). In CG, 71% was taking only placebo and 18% was taking known platelet-affecting drug.	NR	According to tablet counts, about 2% of tablets were missed at followup visits; serum salicylate was measured in a subsample, with 6.8% in IG indicating no recent ASA use	At 1 year, 19.2% of IG was no longer taking ASA; at the end of surveillance, 19.3% was no longer taking ASA	Compliance was defined as use on at least 120 days per year: Year 1: 88% Year 5: 76% Year 10: 67% Trial average: 73%	At trial end, 90.3% of participants were taking ASA	At 1 year, 14% of participants stopped taking trial drugs; at 5 years, 50% (cumulative) of patients withdrew from trial therapy¶	At 5 years, those taking ASA did so for 88% of person-years throughout trial

* Patients had the option to select either 500 or 300 mg per day of either effervescent aspirin or an enteric coated tablet.
† General tablet formulation unspecified; however, 624 participants 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.
¶ Unclear how adherence information was ascertained.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; ASA = aspirin; BMD = British Doctor's Trial; CHD = coronary heart disease; CG = control group; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; eGFR = epidermal growth factor receptor; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment; HTN = hypertension; IHD = ischemic heart disease; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI = myocardial infarction; N = number; NR = not reported; PAD = peripheral arterial disease; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; QOD = every other day; RCT = randomized, controlled trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK = United Kingdom; US = United States; WHS = Women's Health Study.

Table 3. Summary of Composite and Mortality Outcomes of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

		BMD, 1988[57]	PHS I, 1989[53]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Quality		Fair	Good	Fair	Fair	Fair	Fair	Good	Fair	Fair	Fair
Mean Followup		6 years	6 years	5 years	3.8 years	6.8 years**	3.6 years	10.1 years	4.4 years**	6.7 years**	8.2 years
Primary Composite CVD Outcome Reported in Trials¶	IG events/ n (%)	NR	307/11,037 (2.8%)	350/1,856 (18.9%)	315/9,399 (3.4%)	83/1,268 (6.5%)	45/2,226 (2.0%)	477/19,934 (2.4%)	68/1,262 (5.4%)	116/638 (18.2%)	181/1,675 (10.8%)
	CG events/ n (%)	NR	370/11,034 (3.4%)	379/1,855 (20.4%)	368/9,391 (3.9%)	107/1,272 (8.4%)	64/2,269 (2.8%)	522/19,942 (2.6%)	86/1,277 (6.7%)	117/638 (18.3%)	176/1,675 (10.5%)
	IG vs. CG	NR	Adj RR‡ (95% CI): 0.82 (0.70 to 0.96), p=0.01	Adj RR§ (99% CI): 0.90 (0.74 to 1.09), Z test: -1.21	RR (95% CI): 0.85 (0.73 to 0.99), p=0.03	NR	RR (95% CI): 0.71 (0.48 to 1.04), p=0.04	AdjRR‖ (95% CI): 0.91 (0.80 to 1.03), p=0.13	HR (95% CI): 0.80 (0.58 to 1.10), p=0.16	HR (95% CI): 0.98 (0.76 to 1.26), p=0.86	Adj HR† (95% CI): 1.00 (0.81 to 1.23)
Composite Fatal MI/ Coronary Events + Stroke + CVD Death	IG events/ n (%)	119/3,429 (3.5%)*	66/11,037 (0.6%)*	244/1,856 (13.1%)	133/9,399 (1.4%)	42/1,268 (3.3%)*	17/2,226 (0.8%)	120/19,934 (0.6%)*	1/1,262 (0.1%)	43/638 (6.7%)	35/1,675 (2.1%)*
	CG events/ n (%)	59/1,710 (3.4%)*	72/11,034 (0.7%)*	275/1,855 (14.8%)	140/9,391 (1.5%)	40/1,272 (3.1%)*	31/2,269 (1.4%)	126/19,942 (0.6%)*	10/1,277 (0.8%)	35/638 (5.5%)	30/1,675 (1.8%)*
	IG vs. CG	RR (95% CI): 1.01 (0.74 to 1.37)*	RR (95% CI): 0.92 (0.66 to 1.28)	Adj RR§ (99% CI): 0.87 (0.69 to 1.09), Z test: -1.47	RR (95% CI): 0.95 (0.75 to 1.20), p=0.65	RR (95% CI): 1.05 (0.69 to 1.61)*	Adj RR (95% CI): 0.56 (0.31 to 0.99), p=0.049	RR (95% CI): 0.95 (0.74 to 1.22)*	HR (95% CI): 0.10 (0.01 to 0.79), p=0.003	HR (95% CI): 1.23 (0.79 to 1.93), p=0.36	RR (95% CI): 1.17 (0.72 to 1.89)*
Composite Nonfatal MI/ Coronary Events + Stroke	IG events/ n (%)	141/3,429 (4.1%)*	239/11,037 (2.2%)*	NR	NR	63/1,268 (5.0%)*	30/2,226 (1.3%)*	382/19,934 (1.9%)*	39/1,262 (3.1%)*	84/638 (13.2%)*	99/1,675 (5.9%)*
	CG events/ n (%)	68/1,710 (4.0%)*	305/11,034 (2.8%)*	NR	NR	98/1,272 (7.7%)*	40/2,269 (1.8%)*	425/19,942 (2.1%)*	36/1,277 (2.8%)*	97/638 (15.2%)*	106/1,675 (6.3%)*
	IG vs. CG	RR (95% CI): 1.03 (0.78 to 1.37)*	RR (95% CI): 0.78 (0.66 to 0.93)*	NR	NR	RR (95% CI): 0.64 (0.47 to 0.88)*	RR (95% CI): 0.76 (0.48 to 1.22)*	RR (95% CI): 0.90 (0.78 to 1.03)*	RR (95% CI): 1.10 (0.70 to 1.71)*	RR (95% CI): 0.87 (0.66 to 1.14)*	RR (95% CI): 0.93 (0.72 to 1.22)*
All-Cause Mortality	IG events/ n (%)	270/3,429 (7.9%)*	217/11,037 (2.0%)	340/1,856 (18.3%)	284/9,399 (3.0%)	113/1,268 (8.9%)	62/2,226 (2.8%)	609/19,934 (3.1%)	34/1,262 (2.7%)	94/638 (14.7%)	176/1,675 (10.5%)
	CG events/ n (%)	151/1,710 (8.8%)*	227/11,034 (2.1%)	366/1,855 (19.7%)	305/9,391 (3.2%)	110/1,272 (8.6%)	78/2,269 (3.4%)	642/19,942 (3.2%)	38/1,277 (3.0%)	101/638 (15.8%)	186/1,675 (11.1%)
	IG vs. CG	RR (95% CI): 0.89 (0.74 to 1.08)* p=NS	Adj RR‡ (95% CI): 0.96 (0.8 to 1.14), p=0.64	Adj RR§ (99% CI): 0.91 (0.75 to 1.11), Z test: -1.10	RR (95% CI): 0.93 (0.79 to 1.09), p=0.36	RR (95% CI): 1.03 (0.80 to 1.32)*	RR (95% CI): 0.81 (0.58 to 1.13)	Adj RR‖ (95% CI): 0.95 (0.85 to 1.06), p=0.32	HR (95% CI): 0.90 (0.57 to 1.14), p=0.67	HR (95% CI): 0.93 (0.71 to 1.24), p=0.63	HR (95% CI): 0.95 (0.77 to 1.16)

Table 3. Summary of Composite and Mortality Outcomes of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

		BMD, 1988[57]	PHS I, 1989[53]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Mortality From Other Causes	IG events/ n (%)	NR	NR	87/1,856 (4.7%)	NR	NR	45/2,226 (2.0%)	NR	18/1,262 (1.4%)*	NR	NR
	CG events/ n (%)	NR	NR	85/1,855 (4.6%)	NR	NR	47/2,269 (2.0%)	NR	9/1,277 (0.7%)*	NR	NR
	IG vs. CG	NR	NR	Z test: 0.15	NR	NR	RR (95% CI): 0.98 (0.65 to 1.46)	NR	NR	NR	NR

* Calculated.
† Adjusted for baseline age, ankle-brachial index, cholesterol, systolic blood pressure, smoking, and socioeconomic status.
‡ RR adjusted for age and assignment to beta-carotene.
§ Adjusted for age >30 years; age >50 years; male; nonwhite; type I diabetes; type 2 diabetes; and clinical center. P-values reported only for unadjusted RRs, adjusted RRs abstracted above.
‖ RR adjusted for age and treatment assignment.
¶ See Table 2 for definitions of composites reported in trials.
** Median.

Abbreviations: AAA = Aspiring for Asymptomatic Atherosclerosis Trial; Adj = adjusted; BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; HR = hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; MI = myocardial infarction; n = population; NR = not reported; NS = not significant; PHS = Physician's 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 4. Primary Meta-Analysis Results

Outcome	k	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Primary Outcomes					
Death from MI/coronary events, stroke, other CVD	10	0.94 (0.85 to 1.03)	16.4	0.93 (0.84 to 1.03)	31.3
Nonfatal stroke	9	0.94 (0.84 to 1.06)	32.3	0.94 (0.84 to 1.06)	31.8
Nonfatal MI/coronary events	9	0.80 (0.72 to 0.88)	62.8	0.79 (0.71 to 0.88)	61.4
All-cause mortality	10	0.94 (0.88 to 0.99)	0	0.93 (0.88 to 0.99)	0
Secondary Outcomes					
Total stroke	10	0.95 (0.86 to 1.05)	28.4	0.95 (0.86 to 1.05)	28.6
Total MI/coronary events	10	0.85 (0.79 to 0.92)	52.1	0.84 (0.78 to 0.91)	51.4
Fatal MI/coronary events	10	0.94 (0.82 to 1.09)	15.5	0.93 (0.81 to 1.08)	17.4
Fatal MI/coronary events plus fatal stroke	9	0.96 (0.83 to 1.10)	29.5	0.94 (0.82 to 1.09)	41.8
Nonfatal MI/coronary events plus nonfatal stroke	8	0.86 (0.79 to 0.93)	16.2	0.86 (0.79 to 0.93)	16.9
MI/coronary events and stroke (fatal plus nonfatal) plus CVD death	10	0.89 (0.84 to 0.95)	0	0.88 (0.83 to 0.94)	0
Any reported CVD composite	9	0.89 (0.84 to 0.94)	0	0.88 (0.82 to 0.94)	0

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; k = number of studies; OR = odds ratio; MI = myocardial infarction; RR = relative risk.

Table 5. Summary of MI/Coronary Event Outcomes of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

		BMD, 1988[57]	PHS I, 1989[53¶]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Quality		Fair	Good	Fair	Fair	Fair	Fair	Good	Fair	Fair	Fair
Mean Followup		6 years	6 years	5 years	3.8 years	6.8 years†	3.6 years	10.1 years	4.37 years†	6.7 years†	8.2 years
Total MI/ Coronary Events	IG events/ n (%)	169/3,429 (4.9%)*	139/11,037 (1.2%)	241/1,856 (13.0%)	153/9,399 (1.6%)*	83/1,268 (6.5%)*	19/2,226 (0.8%)	198/19,934 (1.0%)	12/1,262 (1.0%)*	90/638 (14.1%)*	90/1,675 (5.4%)*
	CG events/ n (%)	88/1,710 (5.1%)*	239/11,034 (2.2%)	283/1,855 (15.3%)	207/9,391 (2.2%)*	107/1,272 (8.4%)*	28/2,269 (1.2%)	193/19,942 (1.0%)	14/1,277 (1.1%)*	82/638 (12.9%)*	86/1,675 (5.1%)*
	IG vs. CG	RR (95% CI): 0.96 (0.75 to 1.23)*	Adj RR‡ (95% CI): 0.56 (0.45 to 0.70), p<0.00001	Adj RR§ (99% CI): 0.82 (0.65 to 1.03), Z test: -1.99	RR (95% CI): 0.74 (0.60 to 0.91)*	RR (95% CI): 0.78 (0.59 to 1.03)*	RR (95% CI): 0.69 (0.38 to 1.23)	Adj RR‖ (95% CI): 1.02 (0.84 to 1.25), p=0.83	RR (95% CI): 0.87 (0.40 to 1.87)*	RR (95% CI): 1.10 (0.83 to 1.45)*	RR (95% CI): 1.05 (0.78 to 1.40)*
Fatal MI/ Coronary Events	IG events/ n (%)	89/3,429 (2.6%)*	56/11,037 (0.5%)*	47/1,856 (2.5%)	85/9,399 (0.9%)*	36/1,268 (2.8%)	4/2,226 (0.2%)*	14/19,934 (0.1%)	0/1,262 (0%)	35/638 (5.5%)	28/1,675 (1.7%)
	CG events/ n (%)	47/1,710 (2.7%)*	65/11,034 (0.6%)*	67/1,855 (3.6%)	94/9,391 (1.0%)*	34/1,272 (2.7%)	6/2,269 (0.3%)*	12/19,942 (0.1%)	5/1,277 (0.4%)	26/638 (4.1%)	18/1,675 (1.1%)
	IG vs. CG	RR (95% CI): 0.94 (0.67 to 1.34)*, p=NS	RR (95% CI): 0.86 (0.60 to 1.23)*	RR (95% CI): 0.70 (0.49 to 1.01)* Z test: -1.91	RR (95% CI): 0.90 (0.67 to 1.21)*	RR (95% CI): 1.06 (0.67 to 1.69)*	RR (95% CI): 0.68 (0.19 to 2.40)*	Adj RR‖ (95% CI): 1.16 (0.54 to 2.51), p=0.70	RR (95% CI): 0.10 (0.01 to 1.85)*	HR (95% CI): 1.35 (0.81 to 2.25), p=0.24	RR (95% CI): 1.56 (0.86 to 2.80)*
Nonfatal MI/ Coronary Events	IG events/ n (%)	80/3,429 (2.3%)*	129/11,037 (1.2%)	NR	68/9,399 (0.7%)*	47/1,268 (3.7%)	15/2,226 (0.7%)	184/19,934 (0.9%)	12/1,262 (1.0%)	55/638 (8.6%)	62/1,675 (3.7%)
	CG events/ n (%)	41/1,710 (2.4%)*	213/11,034 (1.9%)	NR	113/9,391 (1.2%)*	73/1,272 (5.7%)	22/2,269 (1.0%)	181/19,942 (0.9%)	9/1,277 (0.7%)	56/638 (8.8%)	68/1,675 (4.1%)
	IG vs. CG	RR (95% CI): 0.97 (0.67 to 1.41)*, p=NS	Adj RR‡ (95% CI): 0.59 (0.47 to 0.74), p<0.00001	NR	RR (95% CI): 0.60 (0.45 to 0.81)*	RR (95% CI): 0.65 (0.45 to 0.92)*	RR (95% CI): 0.69 (0.36 to 1.33)	Adj RR‖ (95% CI): 1.01 (0.83 to 1.24), p=0.90	HR (95% CI): 1.34 (0.57 to 3.19), p=0.50	HR (95% CI): 0.98 (0.68 to 1.43), p=0.93	RR (95% CI): 0.91 (0.65 to 1.28)*

* Calculated.
† Median.
‡ RR adjusted for age and assignment to beta-carotene.
§ Adjusted for age >30 years; age >50 years; male; nonwhite; type 1 diabetes; type 2 diabetes; and clinical center. P-values reported only for unadjusted RRs, adjusted RRs abstracted above.
‖ RR adjusted for age and treatment assignment.
¶ Fatal and nonfatal events may not add up to total events because of first-event analyses in some outcomes.

Abbreviations: AAA = Aspiring for Asymptomatic Atherosclerosis Trial; Adj = adjusted; BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; HR = hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; MI = myocardial infarction; n = population; NR = not reported; NS = not significant; PHS = Physician 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 Healthy Study.

Table 6. Summary of Stroke Outcomes of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

		BMD, 1988[57]	PHS I, 1989[53#]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Quality		Fair	Good	Fair	Fair	Fair	Fair	Good	Fair	Fair	Fair
Mean Followup		6 years	6 years	5 years	3.8 years	6.8 years†	3.6 years	10.1 years	4.37 years†	6.7 years†	8.2 years
Total Stroke	IG events/ n (%)	91/3,429 (2.7%)*	119/11,037 (1.1%)	92/1,856 (5.0%)	146/9,399 (1.6%)	18/1,268 (1.4%)	16/2,226 (0.7%)	221/19,934 (1.1%)	28/1,262 (2.2%)	37/638 (5.8%)*	44/1,675 (2.6%)*
	CG events/ n (%)	39/1,710 (2.3%)*	98/11,034 (0.9%)	78/1,855 (4.2%)	148/9,391 (1.6%)	26/1,272 (2.0%)	24/2,269 (1.1%)	266/19,942 (1.3%)	32/1,277 (2.5%)	50/638 (7.8%)*	50/1,675 (3.0%)*
	IG vs. CG	RR (95% CI): 1.16 (0.80 to 1.69)*	Adj RR‡ (95% CI): 1.22 (0.93 to 1.60), p=0.15	Adj RR§ (99% CI): 1.17 (0.79 to 1.74), Z test: 1.10	RR (95% CI): 0.98 (0.78 to 1.24), p=0.88	RR (95% CI): 0.69 (0.38 to 1.26)*	RR (95% CI): 0.67 (0.36 to 1.27)	Adj RR‖ (95% CI): 0.83 (0.69 to 0.99), p=0.04	HR (95% CI): 0.84 (0.53 to 1.32), p=0.44	RR (95% CI): 0.74 (0.49 to 1.12)*	RR (95% CI): 0.88 (0.59 to 1.31)*
Fatal Stroke	IG events/ n (%)	30/3,429 (0.9%)*	10/11,037 (0.1%)*	25/1,856 (1.3%)	NR	2/1,268 (0.2%)	1/2,226 (0.04%)*	23/19,934 (0.1%)	1/1,262 (0.1%)	8/638 (1.3%)	7/1,675 (0.4%)
	CG events/ n (%)	12/1,710 (0.7%)*	7/11,034 (0.01%)*	25/1,855 (1.3%)	NR	1/1,272 (0.1%)	6/2,269 (0.3%)*	22/19,942 (0.1%)	5/1,277 (0.4%)	9/638 (1.4%)	12/1,675 (0.7%)
	IG vs. CG	RR (95% CI): 1.25 (0.64 to 2.43)*	RR (95% CI): 1.44 (0.54 to 3.88)*	RR (95% CI): 1.00 (0.58 to 1.73)* Z test: 0.00	NR	RR (95% CI): 2.01 (0.18 to 22.10)*	RR (95% CI): 0.17 (0.02 to 1.41)*	Adj RR‖ (95% CI): 1.04 (0.58 to 1.86), p=0.90	HR (95% CI): 0.20 (0.024 to 1.74), p=0.15	HR (95% CI): 0.89 (0.34 to 2.30), p=0.80	RR (95% CI): 0.58 (0.23 to 1.48)*
Nonfatal Stroke	IG events/ n (%)	61/3,429 (1.8%)*	110/11,037 (1.0%)	67/1,856 (3.6%)*	NR	16/1,268 (1.3%)*	15/2,226 (0.7%)	198/19,934 (1.0%)	27/1,262 (2.1%)*	29/638 (4.6%)	37/1,675 (2.2%)
	CG events/ n (%)	27/1,710 (1.6%)*	92/11,034 (0.8%)	53/1,855 (2.9%)*	NR	25/1,272 (2.0%)*	18/2,269 (0.8%)	244/19,942 (1.2%)	27/1,277 (2.1%)*	41/638 (6.4%)	38/1,675 (2.3%)
	IG vs. CG	RR (95% CI): 1.13 (0.72 to 1.77), p=NS	Adj RR‡ (95% CI): 1.20 (0.91 to 1.59), p=0.20	RR (95% CI): 1.26 (0.89 to 1.80)*	NR	RR (95% CI): 0.64 (0.34 to 1.20)*	RR (95% CI): 0.84 (0.42 to 1.67)	Adj RR‖ (95% CI): 0.81 (0.67 to 0.97), p=0.02	RR (95% CI): 1.01 (0.60 to 1.72)*	HR (95% CI): 0.71 (0.44 to 1.14), p=0.15	RR (95% CI): 0.97 (0.62 to 1.52)*
Total Ischemic Stroke	IG events/ n (%)	NR	91/11,037 (0.8%)	NR	NR	10/1,268 (0.8%)	NR	170/19,934 (0.8%)	NR	NR	30/1,675 (1.8%)*
	CG events/ n (%)	NR	82/11,034 (0.7%)	NR	NR	18/1,272 (1.4%)	NR	221/19,942 (1.1%)	NR	NR	37/1,675 (2.2%)*
	IG vs. CG	NR	Adj RR‡ (95% CI): 1.11 (0.82 to 1.50), p=0.50	NR	NR	RR (95% CI): 0.56 (0.26 to 1.20)*	NR	Adj RR‖ (95% CI): 0.76 (0.63 to 0.93), p=0.009	NR	NR	RR (95% CI): 0.81 (0.50 to 1.31)*

Table 6. Summary of Stroke Outcomes of Included Trials for Aspirin for Primary Prevention of Cardiovascular Events

		BMD, 1988[57]	PHS I, 1989[53#]	ETDRS, 1992[55]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Fatal Ischemic Stroke	IG events/ n (%)	8/3,429 (0.2%)*	3/11,037 (0.03%)	NR	NR	NR	NR	NR	NR	3/638 (0.5%)	2/1,675 (0.1%)
	CG events/ n (%)	3/1,710 (0.2%)*	3/11,034 (0.03%)	NR	NR	NR	NR	NR	NR	5/638 (0.8%)	7/1,675 (0.4%)
	IG vs. CG	RR (95% CI): 1.33 (0.35 to 5.01)*	RR (95% CI): 1.00 (0.20 to 4.95)*	NR	NR	NR	NR	NR	NR	RR (95% CI): 0.60 (0.14 to 2.50)*	RR (95% CI): 0.29 (0.06 to 1.37)*
Nonfatal Ischemic Stroke	IG events/ n (%)	13/3,429 (0.4%)*	88/11,037 (0.8%)*	NR	NR	NR	NR	NR	22/1,262 (1.7%)	NR	28/1,675 (1.7%)
	CG events/ n (%)	4/1,710 (0.2%)*	79/11,034 (0.7%)*	NR	NR	NR	NR	NR	24/1,277 (1.9%)	NR	30/1,675 (1.8%)
	IG vs. CG	RR (95% CI): 1.62 (0.53 to 4.96)*	RR (95% CI): 1.11 (0.82 to 1.51)*	NR	NR	NR	NR	NR	HR (95% CI): 0.93 (0.52 to 1.66), p=0.80	NR	RR (95% CI): 0.93 (0.56 to 1.56)*

* Calculated.
† Median.
‡ RR adjusted for age and assignment to beta-carotene.
§ Adjusted for age >30 years; age >50 years; male; nonwhite; type 1 diabetes; type 2 diabetes; and clinical center. P-values reported only for unadjusted RRs, adjusted RRs abstracted above.
‖ RR adjusted for age and treatment assignment.
¶ Adjusted for baseline age, ankle-brachial index, cholesterol, systolic blood pressure, smoking, socioeconomic status, and sex.
# Fatal and nonfatal events may not add up to total events because of first-event analyses in some outcomes.

Abbreviations: AAA = Aspiring for Asymptomatic Atherosclerosis Trial; Adj = adjusted; BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; HR = hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; n = population; NR = not reported; NS = not significant; PHS = Physician's 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 7. Results of Dose Sensitivity Analyses for Total Stroke

Outcome	k	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Total stroke low dose (<325 mg)	8	0.90 (0.81 to 1.01)	18.3	0.91 (0.81 to 1.01)	19.5
Total stroke high dose (≥325 mg)	2	1.18 (0.93 to 1.49)	0	1.18 (0.93 to 1.49)	0
Total stroke low dose (≤100 mg)	7	0.85 (0.76 to 0.96)	0	0.86 (0.76 to 0.96)	0
Total stroke high dose (>100 mg)	3	1.19 (1.00 to 1.42)	0	1.19 (1.00 to 1.43)	0

Abbreviations: CI = confidence interval; OR = odds ratio; RR = relative risk.

Table 8. Age Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding*

Study Reference Quality Rating Mean Followup	Type of Analysis P-Value for Interaction	Age, years	Fatal MI/ Coronary Events + Fatal Stroke Events/ Participants (%) RR (95% CI)	Fatal MI/Coronary Events + Fatal Stroke + CVD Death (Not Specified) Events/ Participants (%) RR (95% CI)	Fatal MI/Coronary Events + Fatal Stroke + CVD Death (Not Specified) + Nonfatal MI/Coronary Events + Nonfatal Stroke Events/Participants (%) RR (95% CI)	Other CVD Composite Reported in the Trial Events/Participants (%) RR (95% CI)	All-Cause Mortality Events/ Participants (%) RR (95% CI)	Major GI Bleeding, Events/ Participants (%) RR (95% CI)
AAA Fowkes, 2010[45] Fair 8.2 years	A priori p-value for interaction: NR	<62	NR	NR	NR	Primary composite outcome: (Initial fatal or nonfatal coronary event or stroke or revascularization) Events/per 1,000 p-y (95% CI): IG: 57/8.6 (6.5 to 11.2) CG: 70/10.2 (8.0 to 12.9) HR: 0.85 (95% CI: 0.60 to 1.20)	NR	NR
		≥62	NR	NR	NR	IG: 124/18.8 (15.6 to 22.4) CG: 106/16.6 (13.6 to 20.1) HR: 1.13 (95% CI, 0.87 to 1.47)	NR	NR
HOT Kjeldsen, 2000[60] Fair 38 years	Specification unclear p-value for interaction: NR	<65	NR	IG: 2.1/1,000 p-y CG: 2.6/1,000 p-y 0.80 (0.55 to 1.16)	IG: 6.5/1,000 p-y CG: 8.2/1,000 p-y 0.79 (0.64 to 0.98)	NR	IG: 4.9/1,000 p-y CG: 5.5/1,000 p-y 0.90 (0.70 to 1.15)	Fatal bleeding (mainly GI and cerebral): IG: 0.2/1,000 p-y CG: 0.2/1,000 p-y NR Nonfatal major bleeding (requiring hospitalization, including GI, cerebral, and nasal): IG: 3.0/1,000 p-y CG: 1.7/1,000 p-y NR
		≥65	NR	IG: 7.4/1,000 p-y CG: 6.8/1,000 p-y 1.08 (0.79 to 1.48)	IG: 14.4/1,000 p-y CG: 15.6/1,000 p-y 0.92 (0.74 to 1.15)	NR	IG: 14.7/1,000 p-y CG: 15.3/1,000 p-y 0.96 (0.77 to 1.19)	Fatal bleeding: IG: 0.3/1,000 p-y CG: 0.4/1,000 p-y NR Nonfatal major bleeding: IG: 4.3/1,000 p-y CG: 2.6/1,000 p-y NR

Table 8. Age Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding*

Study Reference Quality Rating Mean Followup	Type of Analysis P-Value for Interaction	Age, years	Fatal MI/ Coronary Events + Fatal Stroke Events/ Participants (%) RR (95% CI)	Fatal MI/Coronary Events + Fatal Stroke + CVD Death (Not Specified) Events/ Participants (%) RR (95% CI)	Fatal MI/Coronary Events + Fatal Stroke + CVD Death (Not Specified) + Nonfatal MI/Coronary Events + Nonfatal Stroke Events/Participants (%) RR (95% CI)	Other CVD Composite Reported in the Trial Events/Participants (%) RR (95% CI)	All-Cause Mortality Events/ Participants (%) RR (95% CI)	Major GI Bleeding, Events/ Participants (%) RR (95% CI)
JPAD Ogawa, 2008[43] Fair 4.4 years†	A priori p-value for interaction: 0.27 for primary composite outcome	<65	NR	NR	NR	Primary composite outcome: (sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute MI; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease) IG: 23/543 (4.2%) CG: 27/633 (4.3%) 0.99 (0.58 to 1.71)‖	NR	NR
		≥65	NR	NR	NR	IG: 45/719 (6.3%) CG: 59/644 (9.2%) 0.68 (0.47 to 0.99)‖	NR	NR
PHS I Physician's Health Study, 1989[53] Good 5 years	Specification unclear p-value for interaction: NR	40-84	NR	Authors state that there was no consistent effect of age on CVD mortality; data not shown	NR	NR	NR	NR
POPADAD Belch, 2008[44] Fair 6.7 years†	Specification unclear p-value for interaction: 0.44 for primary composite; 0.77 for death from CHD or stroke	<60	IG: 10/297 (3.4%) CG: 10/315 (3.2%) 1.06 (0.45 to 2.51)‖	NR	NR	Primary composite outcome: (death from CHD or stroke, nonfatal MI or stroke, or above ankle amputation for critical limb ischemia) IG: 38/297 (12.8%) CG: 36/315 (11.4%) 1.12 (0.73 to 1.72)‖	NR	NR
		≥60	IG: 33/341 (9.7%) CG: 25/323 (7.7%) 1.25 (0.76 to 2.06)‖	NR	NR	IG: 78/341 (22.9%) CG: 81/323 (25.1%) 0.91 (0.70 to 1.20)‖	NR	NR

Table 8. Age Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding*

Study Reference Quality Rating Mean Followup	Type of Analysis P-Value for Interaction	Age, years	Fatal MI/ Coronary Events + Fatal Stroke Events/ Participants (%) RR (95% CI)	Fatal MI/Coronary Events + Fatal Stroke + CVD Death (Not Specified) Events/ Participants (%) RR (95% CI)	Fatal MI/Coronary Events + Fatal Stroke + CVD Death (Not Specified) + Nonfatal MI/Coronary Events + Nonfatal Stroke Events/Participants (%) RR (95% CI)	Other CVD Composite Reported in the Trial Events/Participants (%) RR (95% CI)	All-Cause Mortality Events/ Participants (%) RR (95% CI)	Major GI Bleeding, Events/ Participants (%) RR (95% CI)
WHS Ridker, 2005[58] Good 10.1 years	A priori p-value for interaction: 0.05 for total CV events	45-54	NR	NR	IG: 163/12,210 (1.3%)‡ CG: 161/12,224 (1.3%)‡ 1.01 (0.81 to 1.26)§	NR	NR	NR
		55-64	NR	NR	IG: 183/5,751 (3.2%)‡ CG: 186/5,743 (3.2%)‡ 0.98 (0.80 to 1.20)§	NR	NR	NR
		≥65	NR	NR	IG: 131/1,983 (6.6%)‡ CG: 175/1,984 (8.8%)‡ 0.74 (0.59 to 0.92)§	NR	NR	NR

Within study comparisons listed first.
* Nonfatal composite outcome not reported by age for any trial.
† Median.
‡ All denominator Ns (and event %) in each group back-calculated from Table 1 in Rexrode 2000 (Ns for IG and CG by age category not reported). Back-calculation results in a discrepancy of 10 participants in the IG and 9 participants in the CG, likely due to rounding.
§ Adjusted for age and treatment assignment to vitamin E and beta carotene.
‖ Calculated.

Abbreviations: CG = control group; CI = confidence interval; CHD = coronary heart disease; CVD = cardiovascular disease; GI = gastrointestinal; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; MI = myocardial infarction; NR = not reported; PHS = Physician Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y= person-years; RR = relative risk; TIA = transient ischemic attack; WHS = Women's Health Study.

Table 9. Age Subgroup: Total, Fatal, and Nonfatal MI/Coronary Events

Study Reference Quality Rating Mean Followup	Type of Analysis P-Value For Interaction	Age, years	All MI Events/Participants (%) RR (95% CI)	Fatal MI Events/Participants (%) RR (95% CI)	Nonfatal MI Events/Participants (%) RR (95% CI)
HOT Kjeldsen, 2000[60] Fair 3.8 years	Specification unclear p-value for interaction: NR	<65	IG: 2.2/1,000 p-y CG: 3.4/1,000 p-y 0.66 (0.47 to 0.93)	NR	NR
		≥65	IG: 2.5/1,000 p-y CG: 4.1/1,000 p-y 0.62 (0.38 to 0.98)	NR	NR
PHS I Physician's Health Study, 1989[53] Good 5 years	Specification unclear p-value for interaction: reported as p-value for trend in relative risk, 0.02 for total MI	40-49	IG: 27/4,527 (0.6%) CG: 24/4,524 (0.5%) 1.12 (0.65 to 1.94)§	NR	NR
		50-59	IG: 51/3,725 (1.4%) CG: 87/3,725 (2.3%) 0.59 (0.42 to 0.83)§	NR	NR
		60-69	IG: 39/2,045 (1.9%) CG: 84/2,045 (4.1%) 0.46 (0.32 to 0.68)*§	NR	NR
		70-84	IG: 22/740 (3.0%) CG: 44/740 (6.0%) 0.50 (0.30 to 0.83)*§	NR	NR
WHS Ridker, 2005[58] Good 10.1 years	A priori p-value for interaction: 0.03 for total MI	45-54	IG: 69/12,210 (0.6%)† CG: 56/12,224 (0.5%)† 1.23 (0.87 to 1.75)‡	NR	NR
		55-64	IG: 88/5,751 (1.5%)† CG: 75/5,743 (1.3%)† 1.17 (0.86 to 1.59)‡	NR	NR
		≥65	IG: 41/1,983 (2.1)† CG: 62/1,984 (3.1)† 0.66 (0.44 to 0.97)‡	NR	NR

Within study comparisons listed first.
* Adjusted for treatment assignment to beta carotene.
† All denominator Ns (and event %) in each group back-calculated from Table 1 in Rexrode 2000 (Ns for IG and CG by age category not reported). Back-calculation results in a discrepancy of 10 participants in the IG and 9 participants in the CG, likely due to rounding.
‡ Adjusted for age and treatment assignment to vitamin E and beta carotene.
§ Calculated.

Abbreviations: CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; MI = myocardial infarction; NR = not reported; PHS = Physician Health Study; p-y = person-years; RR = relative risk; TIA = transient ischemic attack; WHS = Women's Health Study.

Table 10. Age Subgroup: Total, Fatal, and Nonfatal Stroke

Study Reference Quality Rating Mean Followup	Type of Analysis P-Value for Interaction	Age, years	All Stroke Events/Participants (%) RR (95% CI)	Fatal Stroke Events/Participants (%) RR (95% CI)	Nonfatal Stroke Events/Participants (%) RR (95% CI)
HOT Kjeldsen, 2000[60] Fair 3.8 years	Specification unclear p-value for interaction: NR	<65	IG: 3.0/1,000 p-y CG: 2.7/1,000 p-y 1.14 (0.82 to 1.60)	NR	NR
		≥65	IG: 6.6/1,000 p-y CG: 7.5/1,000 p-y 0.87 (0.64 to 1.19)	NR	NR
TPT TPT Authors, 1998[54] Meade, 2000[66] Fair 6.8 years*	Specification unclear p-value for interaction: 0.85	45-49	IG: 0/1,447 (0.0%)† CG: 1/1,502 (0.7%)† NR	NR	NR
		50-54	IG: 3/1,905 (1.6%)† CG: 0/1,899 (0.0%)† NR	NR	NR
		55-59	IG: 4/1,663 (2.4%) CG: 11/1,812 (6.1%) 0.40 (NR)‡	NR	NR
		60-64	IG: 7/1,811 (3.9%) CG: 9/1,756 (5.1%) 0.99 (NR)‡	NR	NR
		65-69	IG: 4/1,279 (3.1%) CG: 5/1,102 (4.5%) 0.59 (NR)‡	NR	NR
WHS Ridker, 2005[58] Good 10.1 years	A priori p-value for interaction: NR	45-54	IG: 77/12,210 (0.6%)§ CG: 90/12,224 (0.7%)§ 0.85 (0.63 to 1.16)‖	NR	NR
		55-64	IG: 76/5,751 (1.3%)§ CG: 90/5,743 (1.6%)§ 0.84 (0.62 to 1.14)‖	NR	NR
		≥65	IG: 68/1,983 (3.4%)§ CG: 86/1,984 (4.3%)§ 0.78 (0.57 to 1.08)‖	NR	NR

Within study comparisons listed first.
* Median
† Events/p-y at entry (rates per 1,000 p-y).
‡ Adjusted for factors used in risk scoring procedure (history of smoking, family history of premature coronary heart disease, body mass index, total cholesterol, plasma fibrinogen, plasma factor VII coagulant).
§ All denominator Ns (and event %) in each group back-calculated from Table 1 in Rexrode 2000 (Ns for IG and CG by age category not reported). Back-calculation results in a discrepancy of 10 participants in the IG and 9 participants in the CG, likely due to rounding.
‖ Adjusted for age and treatment assignment to vitamin E and beta carotene.

Abbreviations: CG = control group; HOT = Hypertension Optimal Treatment Study; IG = intervention group; p-y = person-years; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

Table 11. Sex Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
AAA Fowkes, 2010[45] Fair 8.2 years	A priori	Fatal MI/coronary events + fFatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	NR	NR	NR
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Other CVD composite reported in the trial	Primary composite outcome: initial (earliest) fatal or nonfatal coronary event or stroke or revascularization IG: 96/481 (20.0%) CG: 83/473 (17.5%) 1.14 (0.87 to 1.48)[#]	Primary composite outcome: initial (earliest) fatal or nonfatal coronary event or stroke or revascularization IG: 85/1,194 (7.1%) CG: 93/1,202 (7.7%) 0.92 (0.69 to 1.22)[#]	NR
		All-cause mortality	NR	NR	NR
		Major GI bleeding	NR	NR	NR
ETDRS ETDRS, 1992[55] Fair 5 years	Specification unclear	Fatal MI/coronary events + fatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	IG: 8.6*/1,031 CG: 10.2*/1,065 0.83 (99% CI, 0.61 to 1.14)†	IG: 10.1*/825 CG: 12.5*/790 0.92 (99% CI, 0.66 to 1.28)†	NR
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	Primary composite outcome: CV death, nonfatal MI, or stroke IG: 13.5*/1,031 CG: 16.5*/1,065 0.81 (99% CI, 0.63 to 1.05)†	Primary composite outcome: CV death, nonfatal MI, or stroke IG: 14.6*/825 CG: 16.8*/790 1.00 (99% CI, 0.75 to 1.34)†	NR
		Other CVD composite reported in the trial	Composite outcome: all deaths, nonfatal MI, or stroke IG: 16.8*/1,031 CG: 19.8*/1,065 0.88 (99% CI, 0.70 to 1.11)†	Composite outcome: all deaths, nonfatal MI, or stroke IG: 16.2*/825 CG: 20.2*/790 0.97 (99% CI, 0.75 to 1.26)†	NR
		All-cause mortality	IG: 12.4*/1,031 CG: 13.8*/1,065 0.94 (99% CI, 0.73 to 1.22)†	IG: 11.6*/825 CG: 16.2*/790 0.88 (99% CI, 0.65 to 1.17)†	NR
		Major GI bleeding	NR	NR	NR

Table 11. Sex Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
HOT Kjeldsen, 2000[60] Fair 3.8 years	Specification unclear	Fatal MI/coronary events + fatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	IG: 4.4/1,000 p-y CG: 5.0/1,000 p-y 0.89 (0.66 to 1.19)	IG: 3.0/1,000 p-y CG: 2.8/1,000 p-y 1.06 (0.72 to 1.59)	NR
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	Primary composite outcome: major CV events consisting of MI, stroke, and death due to CVD IG: 11.2/1,000 p-y CG: 12.8/1,000 p-y 0.87 (0.72 to 1.05)	Primary composite outcome: major CV events consisting of MI, stroke, and death due to CVD IG: 6.5/1,000 p-y CG: 8.0/1,000 p-y 0.81 (0.63 to 1.04)	NR
		Other CVD composite reported in the trial	NR	NR	NR
		All-cause mortality	IG: 9.2/1,000 p-y CG: 11.1/1,000 p-y 0.83 (0.68 to 1.02)	IG: 6.6/1,000 p-y CG: 5.9/1,000 p-y 1.12 (0.86 to 1.47)	NR
		Major GI bleeding	Fatal bleeding (mainly GI and cerebral) IG: 0.3/1,000 p-y CG: 0.2/1,000 p-y RR NR; p=NS Nonfatal major bleeding (requiring hospitalization and including GI, cerebral, and nasal) IG: 4.1/1,000 p-y CG: 2.5/1,000 p-y RR NR; p=0.010	Fatal bleeding (mainly GI and cerebral) IG: 0.1/1,000 p-y CG: 0.2/1,000 p-y RR NR; p=NS Nonfatal major bleeding (requiring hospitalization and including GI, cerebral, and nasal) IG: 2.7/1,000 p-y CG: 1.3/1,000 p-y RR NR; p=0.006	NR
JPAD Ogawa, 2008[43] Fair 4.4 years‡	A priori	Fatal MI/coronary events + fatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	NR	NR	NR
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR

Table 11. Sex Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
		Other CVD composite reported in the trial	Primary composite outcome: sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute MI; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease IG: 40/706 (5.7%) CG: 51/681 (7.5%) 0.76 (0.51 to 1.13)#	Primary composite outcome: sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute MI; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease IG: 28/556 (5.0%) CG: 35/596 (5.9%) 0.86 (0.53 to 1.39)#	NR
		All-cause mortality	NR	NR	NR
		Major GI bleeding	NR	NR	NR
POPADAD Belch, 2008[44] Fair 6.7 years‡	Specification unclear	Fatal MI/coronary events + fatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	IG: 26/286 (9.1%) CG: 19/277 (6.9%) 1.32 (0.75 to 2.34)#	IG: 17/352 (4.8%) CG: 16/361 (4.4%) 1.09 (0.56 to 2.12)#	0.68
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Other CVD composite reported in the trial	Primary composite outcome: death from CHD or stroke, nonfatal MI or stroke, or above ankle amputation for critical limb ischemia IG: 68/286 (23.8%) CG: 62/277 (22.4%) 1.06 (0.78 to 1.44)#	Primary composite outcome: death from CHD or stroke, nonfatal MI or stroke, or above ankle amputation for critical limb ischemia IG: 48/352 (13.6%) CG: 55/361 (15.2%) 0.90 (0.63 to 1.28)#	0.54
		All-cause mortality	NR	NR	NR
		Major GI bleeding	NR	NR	NR
PPP Berger, 2006[61] Fair 3.6 years	Specification unclear	Fatal MI/coronary events + fatal stroke	NR	NR	NR
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	IG: 11/949 (1.2%) CG: 16/963 (1.7%) 0.70 (0.32 to 1.50)#	IG: 6/1,277 (0.5%) CG: 15/1,306 (1.1%) 0.41 (0.16 to 1.05)#	NR
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR

Table 11. Sex Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	Primary composite outcome: major CV events (CV mortality, nonfatal MI, nonfatal stroke) IG: 28/949 (3.0%) CG: 38/963 (3.9%) 0.75 (0.46 to 1.21)[#]	Primary composite outcome: major CV events (CV mortality, nonfatal MI, nonfatal stroke) IG: 17/1,277 (1.3%) CG: 26/1,306 (2.0%) 0.67 (0.36 to 1.23)[#]	NR
		Other CVD composite reported in the trial	Same as total CVD event composite	Same as total CVD event composite	NR
		All-cause mortality	IG: 42/949 (4.4%) CG: 44/963 (4.6%) 0.97 (0.64 to 1.46)[#]	IG: 20/1,277 (1.6%) CG: 34/1,306 (2.6%) 0.60 (0.35 to 1.04)[#]	NR
		Major GI bleeding	Major bleeding (not defined): IG: 15/949 (1.6%) CG: 4/963 (0.4%) 3.80 (1.27 to 11.42)[#]	Major bleeding (not defined): IG: 9/1,277 (0.7%) CG: 2/1,306 (0.2%) 4.60 (1.00 to 21.26)[#]	NR
BMD Peto, 1988[57] Fair 6 years	N/A; trial in males only	Fatal MI/coronary events + fatal stroke	IG: 119/3,429 (3.5%)[#] CG: 59/1,710 (3.5%)[#] 1.01 (0.74 to 1.37)[#]	NA	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	Same as clean fatal composite	NA	NA
		Nonfatal MI/coronary events + nonfatal stroke	IG: 141/3,429 (4.1%)[#] CG: 68/1,710 (4.0%)[#] 1.03 (0.78 to 1.37)[#]	NA	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	IG: 260/3,429 (7.6%)[#] CG: 127/1,710 (7.4%)[#] 1.02 (0.83 to 1.25)[#]	NA	NA
		Other CVD composite reported in the trial	NR	NA	NA
		All-cause mortality	IG: 270/3,429 (7.9%)[#] CG: 151/1,710 (8.8%)[#] 0.89 (0.74 to 1.08)[#]	NA	NA
		Major GI bleeding	Fatal gastric hemorrhage, fatal hemorrhagic peptic ulcer, fatal perforated peptic ulcer IG: 3/3,429 (0.1%)[#] CG: 3/1,710 (0.2%)[#] 0.50 (0.10 to 2.47)[#]	NA	NA

Table 11. Sex Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
PHS I Physician's Health Study, 1989[53] Good 5 years	N/A; trial in males only	Fatal MI/coronary events + fatal stroke	IG: 66/11,037 (0.6%)[#] CG: 72/11,034 (0.7%)[#] 0.92 (0.66 to 1.28)[#]	NA	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	Same as clean fatal composite	NA	NA
		Nonfatal MI/coronary events + nonfatal stroke	IG: 239/11,037 (2.2%)[#] CG: 305/11,034 (2.8%)[#] 0.78 (0.66 to 0.93)[#]	NA	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	Primary composite outcome (nonfatal MI, nonfatal stroke, death from CV cause) IG: 307/11,037 (2.8%) CG: 370/11,034 (3.4%) 0.82 (0.70 to 0.96)§	NA	NA
		Other CVD composite reported in the trial	Same as total CVD event composite	NA	NA
		All-cause mortality	IG: 217/11,037 (2.0%) CG: 227/11,034 (2.1%) 0.96 (0.80 to 1.14)§	NA	NA
		Major GI bleeding	IG: 49/11,037 (0.4%)[#‖] CG: 28/11,034 (0.3%)[#‖] 1.75 (1.10 to 2.78)[#]	NA	NA
TPT TPT Authors, 1998[54] Fair 6.8 years‡	N/A; trial in males only	Fatal MI/coronary events + fatal stroke	IG: 38/1,268 (3.0%) CG: 35/1,272 (2.8%) 1.09 (0.69 to 1.71)[#]	NA	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	IG: 42/1,268 (3.3%)[#] CG: 40/1,272 (3.1%)[#] 1.05 (0.69 to 1.61)[#]	NA	NA
		Nonfatal MI/coronary events + nonfatal stroke	IG: 63/1,268 (5.0%)[#] CG: 98/1,272 (7.7%)[#] 0.64 (0.47 to 0.88)[#]	NA	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	IG: 105/1,268 (8.3%)[#] CG: 138/1,272 (10.8%)[#] 0.76 (0.60 to 0.97)[#]	NA	NA
		Other CVD composite reported in the trial	Primary composite outcome: sum of fatal and nonfatal IHD events (coronary death and fatal and nonfatal MI) IG: 83/1,268 (6.5%)	NA	NA

Table 11. Sex Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
			CG: 107/1,272 (8.4%) 0.78 (0.59 to 1.03)#		
		All-cause mortality	IG: 113/1,268 (8.9%) CG: 110/1,272 (8.6%) 1.03 (0.80 to 1.32)#	NA	NA
		Major GI bleeding	IG: 6/1,268 (0.5%)# CG: 2/1,272 (0.2%)# 3.01 (0.61 to 14.88)#	NA	
WHS Ridker, 2005[58] Rexrode, 2000[69] Good 10.1 years	N/A; trial in females only	Fatal MI/coronary events + fatal stroke	NA	IG: 37/19,934 (0.2%)# CG: 34/19,942 (0.2%)# 1.09 (0.68 to 1.73)#	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified)	NA	IG: 120/19,934 (0.6%) CG: 126/19,942 (0.6%) 0.95 (0.74 to 1.22)¶	NA
		Nonfatal MI/coronary events + nonfatal stroke	NA	IG: 382/19,934 (1.9%)# CG: 425/19,942 (2.1%)# 0.90 (0.78 to 1.03)#	NA
		Fatal MI/coronary events + fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	NA	Primary composite outcome: nonfatal MI, nonfatal stroke, or CVD death IG: 477/19,934 (2.4%) CG: 522/19,942 (2.6%) 0.91 (0.80 to 1.03)¶	NA
		Other CVD composite reported in the trial	NA	Same as total CVD event composite	NA
		All-cause mortality	NA	IG: 609/19,934 (3.1%) CG: 642/19,942 (3.2%) 0.95 (0.85 to 1.06)¶	NA
		Major GI bleeding	NA	IG: 129/19,934 (0.6%)#‖ CG: 94/19,942 (0.5%)#‖ 1.37 (1.05 to 1.79)#	NA

Within study comparisons listed first.
* 5-year life table rates.
† Adjusted for age, nonwhite race, diabetes type, and clinical center.
‡ Median.
§ Adjusted for age and assignment to beta carotene.
‖ Death from GI hemorrhage plus bleeding requiring transfusion.
¶ Adjusted for age and treatment assignment to vitamin E and beta carotene.
# Calculated.

Table 11. Sex Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Abbreviations: AAA = Aspiring for Asymptomatic Atherosclerosis Trial; BMD = British Medical Doctor's Study; CG = control group; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy Study; GI = gastrointestinal; HOT = Hypertension Optimal Treatment Study; IG = intervention group; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; MI = myocardial infarction; N/A = not applicable; NR = not reported; PHS = Physician Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; p-y= person-years; RR = relative risk; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

Table 12. Sex Subgroup: Total, Fatal, and Nonfatal MI/Coronary Events

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
ETDRS ETDRS, 1992[55] Fair 5 years	Specification unclear	Total MI/Coronary Events	IG: 8.6*/1,031 CG: 12.0*/1,065 (99% CI): 0.74 (0.54 to 1.00)†	IG: 9.8*/825 CG: 12.6*/790 (99% CI): 0.91 (0.65 to 1.28)†	NR
		Fatal MI/Coronary Events	NR	NR	NR
		Nonfatal MI/Coronary Events	NR	NR	NR
HOT Kjeldsen, 2000[60] Fair 3.8 years	Specification unclear	Total MI/Coronary Events	IG: 2.9/1,000 p-y CG: 5.0/1,000 p-y 0.58 (0.41 to 0.81)	IG: 1.7/1,000 p-y CG: 2.1/1,000 p-y 0.81 (0.49 to 1.31)	NR
		Fatal MI/Coronary Events	NR	NR	NR
		Nonfatal MI/Coronary Events	NR	NR	NR
PPP Berger, 2006[61] Fair 3.6 years	Specification unclear	Total MI/Coronary Events	IG: 11/949 (1.2%) CG: 22/963 (2.3%) 0.51 (0.25 to 1.04)**	IG: 8/1,277 (0.6%) CG: 6/1,306 (0.4%) 1.36 (0.47 to 3.92)**	NR
		Fatal MI/Coronary Events	NR	NR	NR
		Nonfatal MI/Coronary Events	NR	NR	NR
BMD Peto, 1988[57] Fair 6 years	N/A; trial in males only	Total MI/Coronary Events	IG: 169/3,429‡ (4.9%)** CG: 88/1,710‡ (5.1%)** 0.96 (0.75 to 1.23)**	NA	NA
		Fatal MI/Coronary Events	IG: 89/3,429 (2.6%) CG: 47/1,710 (2.7%) 0.94 (0.67 to 1.34)**	NA	NA
		Nonfatal MI/Coronary Events	IG: 80/3,429§ (2.3%) CG: 41/1,710§ (2.4%) 0.97 (0.67 to 1.41)**	NA	NA
PHS I Physician's Health Study, 1989[53] Good 5 years	N/A; trial in males only	Total MI/Coronary Events	IG: 185/11,037 (1.7%)** CG: 278/11,034 (2.5%)** 0.67 (0.55 to 0.80)**	NA	NA
		Fatal MI/Coronary Events	IG: 56/11,037 (0.5%)** CG: 65/11,034 (0.6%)** 0.86 (0.60 to 1.23)**	NA	NA
		Nonfatal MI/Coronary Events	IG: 129/11,037 (1.2%) CG: 213/11,034 (1.9%) 0.59 (0.47 to 0.74)‖	NA	NA
TPT TPT Authors, 1998[54] Fair 6.8 years¶	N/A; trial in males only	Total MI/Coronary Events	IG: 83/1,268 (6.5%) CG: 107/1,272 (8.4%) 0.78 (0.59 to 1.03)**	NA	NA
		Fatal MI/Coronary Events	IG: 36/1,268 (2.8%) CG: 34/1,272 (2.7%) 1.06 (0.67 to 1.69)**	NA	NA
		Nonfatal MI/Coronary Events	IG: 47/1,268 (3.7%) CG: 73/1,272 (5.7%) 0.65 (0.45 to 0.92)**	NA	NA

Table 12. Sex Subgroup: Total, Fatal, and Nonfatal MI/Coronary Events

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
WHS Ridker, 2005[58] Good 10.1 years	N/A; trial in females only	Total MI/Coronary Events	NA	IG: 198/19,934 (1.0%) CG: 193/19,942 (1.0%) 1.02 (0.84 to 1.25)#	NA
		Fatal MI/Coronary Events	NA	IG: 14/19,934 (0.07%) CG: 12/19,942 (0.06%) 1.16 (0.54 to 2.51)#	NA
		Nonfatal MI/Coronary Events	NA	IG: 184/19,934 (0.9%) CG: 181/19,942 (0.9%) 1.01 (0.83 to 1.24)#	NA

Within study comparisons listed first.
* 5-year life table rates.
† Adjusted for age, sex, race/ethnicity, diabetes type, and clinical center.
‡ Fatal MI plus confirmed nonfatal MI.
§ Confirmed nonfatal MI; possible MI also reported.
‖ Adjusted for age and assignment to beta carotene.
¶ Median.
# Adjusted for age and treatment assignment to vitamin E and beta carotene.
** Calculated.

Abbreviations: BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; IG = intervention group; MI = myocardial infarction; N/A = not applicable; NR = not reported; PHS = Physician Health Study; PPP = Primary Prevention Project; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Healthy Study.

Table 13. Sex Subgroup: Total, Fatal, and Nonfatal Stroke

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
ETDRS ETDRS, 1992[55] Fair 5 years	Specification unclear	All Stroke	IG: 4.4/1,031* CG: 3.9/1,065* (99% CI): 1.07 (0.63 to 1.83)	IG: 4.6/825* CG: 3.8/790* (99% CI): 1.31 (0.71 to 2.39)	NR
		Fatal Stroke	NR	NR	NR
		Nonfatal Stroke	NR	NR	NR
HOT Kjeldsen, 2000[60] Fair 3.8 years	Specification unclear	All Stroke	IG: 5.0/1,000 p-y CG: 4.3/1,000 p-y 1.16 (0.86 to 1.56)	IG: 3.2/1,000 p-y CG: 4.0/1,000 p-y 0.78 (0.54 to 1.12)	NR
		Fatal Stroke	NR	NR	NR
		Nonfatal Stroke	NR	NR	NR
PPP Berger, 2006[61] Fair 3.6 years	Specification unclear	All Stroke	IG: 10/949 (1.0%) CG: 13/963 (1.3%) 0.78 (0.34 to 1.77)††	IG: 6/1,277 (0.5%) CG: 11/1,306 (0.8%) 0.56 (0.21 to 1.50)††	NR
		Fatal Stroke	NR	NR	NR
		Nonfatal Stroke	NR	NR	NR
BMD Peto, 1988[57] Fair 6 years	N/A; trial in males only	All Stroke	IG: 91/3,429 (2.7%)‡†† CG: 39/1,710 (2.3%)‡†† 1.16 (0.80 to 1.69)††	NA	NA
		Fatal Stroke	IG: 30/3,429 (0.9%)†† CG: 12/1,710 (0.7%)†† 1.25 (0.64 to 2.43)††	NA	NA
		Nonfatal Stroke	IG: 61/3,429 (1.8%)§ CG: 27/1,710 (1.6%)§ 1.13 (0.72 to 1.77)††	NA	NA
PHS I Physician's Health Study, 1989[53] Good 5 years	N/A; trial in males only	All Stroke	IG: 119/11,037 (1.1%)††‖ CG: 98/11,034 (0.9%)††‖ 1.22 (0.93 to 1.60)¶	NA	NA
		Fatal Stroke	IG: 10/11,037 (0.09%) CG: 7/11,034 (0.06%) 1.44 (0.54 to 3.88)¶	NA	NA
		Nonfatal Stroke	IG: 110/11,037 (1.0%) CG: 92/11,034 (0.8%) 1.20 (0.91 to 1.59)¶	NA	NA
TPT TPT Authors, 1998[54] Fair 6.8 years#	N/A; trial in males only	All Stroke	IG: 18/1,268 (1.4%) CG: 26/1,272 (2.0%) 0.69 (0.38 to 1.26)††	NA	NA
		Fatal Stroke	IG: 2/1,268 (0.2%) CG: 1/1,272 (0.1%) 2.01 (0.18 to 22.10)††	NA	NA
		Nonfatal Stroke	IG: 16/1,268 (1.3%) CG: 25/1,272 (2.0%) 0.64 (0.34 to 1.20)††	NA	NA

Table 13. Sex Subgroup: Total, Fatal, and Nonfatal Stroke

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
WHS Ridker, 2005[58] Good 10.1 years	N/A; trial in females only	All Stroke	NA	IG: 221/19,934 (1.1%) CG: 266/19,942 (1.3%) 0.83 (0.69 to 0.99)**	NA
		Fatal Stroke	NA	IG: 23/19,934 (0.1%) CG: 22/19,942 (0.1%) 1.04 (0.58 to 1.86)**	NA
		Nonfatal Stroke	NA	IG: 198/19,934 (1.0%) CG: 244/19,942 (1.2%) 0.81 (0.67 to 0.97)**	NA

Within study comparisons listed first.
*5-year life table rates.
†Adjusted for age, sex, race/ethnicity, diabetes type, and clinical center.
‡Fatal stroke plus confirmed nonfatal stroke.
§Confirmed nonfatal stroke; possible stroke also reported.
ǁFirst stroke event.
¶Adjusted for age and assignment to beta carotene.
#Median.
**Adjusted for age and treatment assignment to vitamin E and beta carotene.
††Calculated.

Abbreviations: BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; IG = intervention group; NR = not reported; PHS = Physician's Health Study; PPP = Primary Prevention Project; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

Table 14. Diabetes Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
AAA Fowkes, 2010[45] Fair 8.2 years	Post hoc Diagnostic criteria: self-reported DM	Fatal MI/coronary events + Fatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified)	NR	NR	NR
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Other CVD composite reported in the trial	NR	Primary composite outcome: (initial fatal or nonfatal coronary event or stroke or revascularization) per 1,000 p-y (95% CI) IG: 13.7 (11.7 to 15.9) CG: 12.8 (10.9 to 14.9) HR: 1.07 (0.87 to 1.33)	NR
		All-cause mortality	NR	NR	NR
		Major GI bleeding	NR	NR	NR
HOT Zanchetti, 2007[62] Fair 3.8 years	Specification unclear Diagnostic criteria: NR	Fatal MI/coronary events + Fatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified)	IG: 23/752 (3.0%) CG: 26/749 (3.5%) 0.89 (0.51 to 1.57)	IG: 110/8,647 (1.3%) CG: 114/8,642 (1.3%) 0.96 (0.74 to 1.25)	NS (value NR)
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	IG: 47/752 (6.2%) CG: 54/749 (7.2%) 0.87 (0.59 to 1.28)	IG: 268/8,647 (3.1%) CG: 314/8,642 (3.6%) 0.85 (0.72 to 1.00)	NS (value NR)
		Other CVD composite reported in the trial	Same as total CVD event composite	Same as total CVD event composite	NR
		All-cause mortality	IG: 40/752 (5.3%) CG: 36/749 (4.8%) 1.12 (0.72 to 1.76)	IG: 244/8,647 (2.8%) CG: 269/8,642 (3.1%) 0.90 (0.76 to 1.07)	NS (value NR)
		Major GI bleeding	NR	NR	NR

Table 14. Diabetes Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
PPP* Sacco, 2003[63] Fair 3.7 years	Post hoc Diagnostic criteria: fasting venous plasma glucose ≥7.8 mmol/L on at leas 2 separate occasions or treatment with antidiabetes drugs	Fatal MI/coronary events + Fatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified)	IG: 10/519 (1.9%) CG: 8/512 (1.6%) 1.23 (0.49 to 3.10)	IG: 8/1,875† (0.4%) CG: 25/1,889† (1.3%) 0.32 (0.14 to 0.72)	0.3
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	Primary composite outcome (CV death, nonfatal MI, and nonfatal stroke) IG: 20/519 (3.9%) CG: 22/512 (4.3%) 0.90 (0.50 to 1.62)	Primary composite outcome (CV death, nonfatal MI, and nonfatal stroke) IG: 30/1,875† (1.6%) CG: 51/1,889† (2.7%) 0.59 (0.37 to 0.94)	NR
		Other CVD composite reported in the trial	All CV events or diseases (CV death, nonfatal MI, nonfatal stroke, angina, TIA, PAD, and revascularization) IG: 53/519 (10.2%) CG: 59/512 (11.5%) 0.89 (0.62 to 1.26)	All CV events or diseases (CV death, nonfatal MI, nonfatal stroke, angina, TIA, PAD, and revascularization) IG: 98/1,875† (5.3%) CG: 142/1,889† (7.5%) 0.69 (0.53 to 0.90)	NR
		All-cause mortality	IG: 25/519 (4.8%) CG: 20/512 (3.9%) 1.23 (0.69 to 2.19)	IG: 42/1,875† (2.3%) CG: 61/1,889† (3.2%) 0.70 (0.47 to 1.04)	NR
		Major GI bleeding	NR	NR	NR
WHS Ridker, 2005[58] Rexrode, 2000[69] Good 10.1 years	A priori Diagnostic criteria: assumption is self-reported history of diabetes from the enrollment questionnaire	Fatal MI/coronary events + Fatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke+ CVD death (not specified)	NR	NR	NR
		Nonfatal MI/coronary events + nonfatal stroke	NR	NR	NR
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	IG: 58/528‡ (11.0%) CG: 62/499‡ (12.4%) 0.9 (0.63 to 1.29)§	IG: 418/19,406‡ (2.2%) CG: 460/19,443‡ (2.4%) 0.9 (0.79 to 1.03)§	NR
		Other CVD composite reported in the trial	Same as total CVD event composite	Same as total CVD event composite	NR
		All-cause mortality	NR	NR	NR
		Major GI bleeding	NR	NR	NR

Table 14. Diabetes Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
ETDRS ETDRS, 1992[55] Fair 5 years	NA (trial in DM only) Diagnostic criteria: clinical diagnosis of type 1 or 2 DM (additionally, mus have diabetic retinopathy)	Fatal MI/coronary events + Fatal stroke	IG: 72/1,856 (3.9%) CG: 92/1,855 (5.0%) 0.78 (0.58 to 1.06)**	NA	NA
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified)	IG: 244/1,856 (13.1%) CG: 275/1,855 (14.8%) 0.89 (0.76 to 1.04)**	NA	NA
		Nonfatal MI/coronary events + nonfatal stroke	NR	NA	NA
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	IG: 350/1,856 (18.9%) CG: 379/1,855 (20.4%) 0.92 (0.81 to 1.05)**	NA	NA
		Other CVD composite reported in the trial	Same as total CVD event composite	NA	NA
		All-cause mortality	IG: 340/1,856 (18.3%) CG: 366/1,855 (19.7%) 0.93 (0.81 to 1.06)**	NA	NA
		Major GI bleeding	NR	NA	NA
JPAD Ogawa, 2008[43] Fair 4.4 yearsǁ	NA (trial in DM only) Diagnostic criteria: diagnosis of type 2 DM	Fatal MI/coronary events + Fatal stroke	IG: 1/1,262 (0.08%) CG: 10/1,277 (0.8%) 0.10 (0.01 to 0.79)**	NA	NA
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified)	IG: 1/1,262 (0.08%) CG: 10/1,277 (0.8%) 0.10 (0.01 to 0.79)**	NA	NA
		Nonfatal MI/coronary events + nonfatal stroke	IG: 39/1,262 (3.1%)** CG: 36/1,277 (2.8%)** 1.10 (0.70 to 1.71)**	NA	NA
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	IG: 40/1,262 (3.2%)** CG: 46/1,277 (3.6%)** 0.88 (0.58 to 1.33)**	NA	NA
		Other CVD composite reported in the trial	Primary composite outcome (sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute MI; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease) IG: 68/1,262 (5.4%)	NA	NA

Table 14. Diabetes Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
			CG: 86/1,277 (6.7%) 0.80 (0.59 to 1.09)**		
		All-cause mortality	IG: 34/1,262 (2.7%) CG: 38/1,277 (3.0%) 0.91 (0.57 to 1.43)**	NA	NA
		Major GI bleeding	IG 4/1,262¶ (0.3%) CG 0/1,277¶ (0%) 8.10 (0.43 to 152.96)**	NA	NA
POPADAD Belch, 2008[44] Fair 6.7 yearsǁ	NA (trial in DM only) Diagnostic criteria: type 1 or 2 diabetes, not further specified	Fatal MI/coronary events + Fatal stroke	IG: 43/638 (6.7%) CG: 35/638 (5.5%) 1.23 (0.80 to 1.89)**	NA	NA
		Fatal MI/coronary events + Fatal stroke + CVD death (not specified)	IG: 43/638 (6.7%) CG: 35/638 (5.5%) 1.23 (0.80 to 1.89)**	NA	NA
		Nonfatal MI/coronary events + nonfatal stroke	IG: 84/638 (13.2%)** CG: 97/638 (15.2%)** 0.87 (0.66 to 1.14)**	NA	NA
		Fatal MI/coronary events + Fatal stroke+ CVD death (not specified) + nonfatal MI/coronary events + nonfatal stroke	IG: 127/638 (19.9%)** CG: 132/638 (20.7%)** 0.96 (0.77 to 1.20)**	NA	NA
		Other CVD composite reported in the trial	Primary composite outcome (death from CHD or stroke, nonfatal MI or stroke, or above ankle amputation for critical limb ischemia) IG: 116/638 (18.2%) CG: 117/638 (18.3%) 0.99 (0.79 to 1.25)**	NA	NA
		All-cause mortality	IG: 94/638 (14.7%) CG: 101/638 (15.8%) 0.93 (0.72 to 1.21)**	NA	NA
		Major GI bleeding	NR#	NA	NA

Within study comparisons listed first.
*There are an additional 289 patients with DM in this publication compared with Roncaglioni 2001 because "in parallel with the main trial, we also involved 14 DM clinics with the aim of recruiting additional sample of DM patients."
†N for patients with no DM in IG and CG back-calculated from % with event reported in Figure 2 (Ns are not reported in the article), resulting in a discrepancy of 11 participants, likely due to rounding. Back-calculation was performed using primary endpoint; resulting Ns are different depending on which outcome was used.
‡All denominator Ns in each group back-calculated from Table 3 in Rexrode 2000 (Ns for IG and CG for those with and without DM not reported). Back-calculation results in a discrepancy of 24 participants, likely due to rounding.
§RRs adjusted for age and treatment assignment to vitamin E and beta carotene.
ǁMedian.

Table 14. Diabetes Subgroup: Composite CVD Outcomes, All-Cause Mortality, and Major GI Bleeding

¶Severe GI bleeding requiring transfusion.
#Severity of reported GI bleeding events unknown; thus, we did not classify as major.
**Calculated

Abbreviations: AAA = Aspiring for Asymptomatic Atherosclerosis Trial; BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; MI = myocardial infarction; N/A = not applicable; NR = not reported; PAD = peripheral artery disease; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; TIA = transient ischemic attack; WHS = Women's Health Study.

Table 15. Diabetes Subgroup: Total, Fatal, and Nonfatal MI/Coronary Events

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
HOT Zanchetti, 2007[62] Fair 3.8 years	Specification unclear Diagnostic criteria: NR	Total MI/Coronary Events	IG: 11/752 (1.5%) CG: 18/749 (2.4%) 0.61 (0.29 to 1.29)	IG: 71/8,647 (0.8%) CG: 109/8,642 (1.3%) 0.65 (0.48 to 0.87)	NS (value NR)
		Fatal MI/Coronary Events	NR	NR	NR
		Nonfatal MI/Coronary Events	NR	NR	NR
PHS I Physician's Health Study, 1989[53] Good 5 years	Specification unclear Diagnostic criteria: NR	Total MI/Coronary Events	IG: 11/275 (4.0%) CG: 26/258 (10.1%) 0.40 (0.20 to 0.79) [c]	IG: 128/10,750 (1.2%) CG: 213/10,763 (2.0%) 0.60 (0.48 to 0.75) [c]	0.22†
		Fatal MI/Coronary Events	NR	NR	NR
		Nonfatal MI/Coronary Events	NR	NR	NR
PPP‡ Sacco, 2003[63] Fair 3.7 years	Post hoc Diagnostic criteria: fasting venous plasma glucose ≥7.8 mmol/L on at least 2 separate occasions or treated with antidiabetes drug	Total MI/Coronary Events	IG: 5/519 (1.0%) CG: 10/512 (2.0) 0.49 (0.17 to 1.40)	IG: 15/1,875§ (0.8%) CG: 22/1,889§ (1.2%) 0.69 (0.36 to 1.35)	NR
		Fatal MI/Coronary Events	NR	NR	NR
		Nonfatal MI/Coronary Events	NR	NR	NR
WHS Ridker, 2005[58] Rexrode, 2000[69] Good 10.1 years	A priori Diagnostic criteria: Assumed self-reported history of diabetes from the enrollment questionnaire	Total MI/Coronary Events	IG: 36/528‖ (6.8%) CG: 24/499‖ (4.8%) 1.48 (0.88 to 2.49)¶	IG: 162/19,406‖ (0.8%) CG: 169/19,443‖ (0.9%) 0.96 (0.77 to 1.18)¶	NR
		Fatal MI/Coronary Events	NR	NR	NR
		Nonfatal MI/Coronary Events	NR	NR	NR
ETDRS ETDRS, 1992[55] Fair 5 years	NA (trial in DM only) Diagnostic criteria: clinical diagnosis of type 1 or 2 DM (additionally, must have diabetic retinopathy)	Total MI/Coronary Events	IG: 241/1,856 (13.0%) CG: 283/1,855 (15.3%) 0.85 (0.73 to 1.00)††	NA	NA
		Fatal MI/Coronary Events	IG: 47/1,856 (2.5%)# CG: 67/1,855 (3.6%)# 0.70 (0.49 to 1.01)††	NA	NA
		Nonfatal MI/Coronary Events	NR	NA	NA
JPAD Ogawa, 2008[43] Fair 4.4 years**	NA (trial in DM only) Diagnostic criteria: diagnosis of type 2 DM, not further	Total MI/Coronary Events	IG: 12/1,262 (1.0%) CG: 14/1,277 (1.1%) 0.87 (0.40 to 1.87)††	NA	NA
		Fatal MI/Coronary Events	IG: 0/1,262 (0%) CG: 5/1,277 (0.4%)	NA	NA

Table 15. Diabetes Subgroup: Total, Fatal, and Nonfatal MI/Coronary Events

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
	specified		0.10 (0.01 to 1.85)††		
		Nonfatal MI/Coronary Events	IG: 12/1,262 (1.0%) CG: 9/1,277 (0.7%) 1.35 (0.57 to 3.19)††	NA	NA
POPADAD Belch, 2008[44] Fair 6.7 years**	NA (trial in DM only) Diagnostic criteria: type 1 or 2 diabetes, not further specified	Total MI/Coronary Events	IG: 90/638 (14.1%) CG: 82/638 (12.8%) 1.10 (0.83 to 1.45)††	NA	NA
		Fatal MI/Coronary Events	IG: 35/638 (5.5%) CG: 26/638 (4.1%) 1.35 (0.81 to 2.25)††	NA	NA
		Nonfatal MI/Coronary Events	IG: 55/638 (8.6%) CG: 56/638 (8.8%) 0.98 (0.69 to 1.40)††	NA	NA

Within study comparisons listed first.
†P-value of trend in relative risk.
‡There are an additional 289 patients with DM in this publication compared with Roncaglioni 2001 because "in parallel with the main trial, we also involved 14 DM clinics with the aim of recruiting additional sample of DM patients."
§N for patients with no DM in IG and CG back-calculated from % with event reported in Figure 2 (these Ns are not reported in the article), resulting in a discrepancy of 11 participants, likely due to rounding. Back-calculation was performed using primary endpoint; resulting Ns are different depending on the outcome.
‖All denominator Ns in each group back-calculated from Table 3 in Rexrode 2000 (Ns for IG and CG for those with and without DM not reported). Back-calculation results in a discrepancy of 24 participants, likely due to rounding.
¶Adjusted for age and treatment assignment to vitamin E and beta carotene.
#Sudden coronary death.
**Median.
††Calculated.

Abbreviations: CG = control group; CI = confidence interval; DM = diabetes mellitus; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; MI = myocardial infarction; NA = not applicable; NR = not reported; PHS = Physicians Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; WHS = Women's Health Study.

Table 16. Diabetes Subgroup: Total, Fatal, and Nonfatal Stroke

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
HOT Zanchetti, 2007[62] Fair 3.8 years	Specification unclear Diagnostic criteria: NR	Total Stroke	IG: 20/752 (2.6%) CG: 22/749 (2.9%) 0.91 (0.50 to 1.67)	IG: 126/8,647 (1.4%) CG: 126/8,642 (1.4%) 1.00 (0.78 to 1.27)	NS (value NR)
		Fatal Stroke	NR	NR	NR
		Nonfatal Stroke	NR	NR	NR
PPP* Sacco, 2003[63] Fair 3.7 years	Post hoc Diagnostic criteria: fasting venous plasma glucose ≥7.8 mmol/L on at least 2 separate occasions or treated with antidiabetes drugs	Total Stroke	IG: 9/519 (1.7%) CG: 10/512 (2.0%) 0.89 (0.36 to 2.17)	IG: 11/1,875† (0.6%) CG: 19/1,889† (0.1%) 0.59 (0.28 to 1.25)	NR
		Fatal Stroke	NR	NR	NR
		Nonfatal Stroke	NR	NR	NR
WHS Ridker, 2005[58] Rexrode, 2000[69] Good 10.1 years	A priori Diagnostic criteria: assumed self-reported history of diabetes from the enrollment questionnaire	Total Stroke	IG: 15/528‡ (2.8%) CG: 31/499‡ (6.2%) 0.46 (0.25 to 0.85)§	IG: 206/19,406‡ (1.1%) CG: 235/19,443‡ (1.2%) 0.87 (0.72 to 1.05)§	NR
		Fatal Stroke	NR	NR	NR
		Nonfatal Stroke	NR	NR	NR
ETDRS ETDRS, 1992[55] Fair 5 years	NA (trial in DM only) Diagnostic criteria: clinical diagnosis of type 1 or 2 DM (additionally, must have diabetic retinopathy)	Total Stroke	IG: 92/1,856 (5.0%) CG: 78/1,855 (4.2%) 1.18 (0.88 to 1.58)¶	NA	NA
		Fatal Stroke	IG: 25/1,856 (1.3%) CG: 25/1,855 (1.3%) 1.00 (0.58 to 1.73)¶	NA	NA
		Nonfatal Stroke	IG: 67/1,856 (3.6%) CG: 53/1,855 (2.8%) 1.26 (0.89 to 1.80)¶	NA	NA
JPAD Ogawa, 2008[43] Fair 4.4 yearsǁ	NA (trial in DM only) Diagnostic criteria: diagnosis of type 2 DM, not further specified	Total Stroke	IG: 28/1,262 (2.2%) CG: 32/1,277 (2.5%) 0.89 (0.54 to 1.46)¶	NA	NA
		Fatal Stroke	IG: 1/1,262 (0.08%) CG: 5/1,277 (0.4%) 0.20 (0.02 to 1.73)¶	NA	NA
		Nonfatal Stroke	IG: 27/1,262 (2.1%) CG: 27/1,277 (2.1%) 1.01 (0.60 to 1.72)¶	NA	NA
POPADAD Belch, 2008[44] Fair 6.7 yearsǁ	NA (trial in DM only) Diagnostic criteria: type 1 or 2 diabetes, not further specified	Total Stroke	IG: 37/638 (5.8%) CG: 50/638 (7.8%) 0.74 (0.49 to 1.12)¶	NA	NA
		Fatal Stroke	IG: 8/638 (1.3%) CG: 9/638 (1.4%) 0.89 (0.35 to 2.29)¶	NA	NA

Table 16. Diabetes Subgroup: Total, Fatal, and Nonfatal Stroke

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
		Nonfatal Stroke	IG: 29/638 (4.6%) CG: 41/638 (6.4%) 0.71 (0.45 to 1.12)¶	NA	NA

Within study comparisons listed first.
*There are an additional 289 patients with DM in this publication compared with Roncaglioni 2001 because "in parallel with the main trial, we also involved 14 DM clinics with the aim of recruiting additional sample of DM patients."
†N for patients with no DM in IG and CG back-calculated from % with event reported in Figure 2 (these Ns are not reported in the article), resulting in a discrepancy of 11 participants, likely due to rounding. Back-calculation was performed using primary endpoint; resulting Ns are different depending on the outcome.
‡Note: All denominator Ns in each group back-calculated from Table 3 in Rexrode 2000 (Ns for IG and CG for those with and without DM not reported). Back-calculation results in a discrepancy of 24 participants, likely due to rounding.
§Adjusted for age and treatment assignment to vitamin E and beta carotene.
‖Median.
¶Calculated.

Abbreviations: CG = control group; CI = confidence interval; DM = diabetes mellitus; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; MI = myocardial infarction; NA = not applicable; NR = not reported; NS = not significant; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; WHS = Women's Health Study.

Table 17. Sensitivity Analysis Results: All Included Trials* and Trials With Doses <325 mg†

Primary Outcome	k	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Death from MI/coronary events, stroke, other CVD	10	0.94 (0.85 to 1.03)	16.4	0.93 (0.84 to 1.03)	31.3
	8	0.96 (0.84 to 1.09)	30.0	0.94 (0.83 to 1.07)	43.1
Nonfatal stroke	9	0.94 (0.84 to 1.06)	32.3	0.94 (0.84 to 1.06)	31.8
	7	0.89 (0.78 to 1.01)	23.2	0.89 (0.78 to 1.02)	23.1
Nonfatal MI/coronary events	9	0.80 (0.72 to 0.88)	62.8	0.79 (0.71 to 0.88)	61.4
	8	0.78 (0.70 to 0.87)	65.5	0.78 (0.70 to 0.86)	64.0
All-cause mortality	10	0.94 (0.88 to 0.99)	0	0.93 (0.88 to 0.99)	0
	8	0.94 (0.88 to 1.01)	0	0.94 (0.88 to 1.01)	0

*Top row for each of the primary outcomes.
†Bottom row for each of the primary outcomes.

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; MI = myocardial infarction; OR = odds ratio; RR = relative risk.

Table 18. Sensitivity Analysis Results: All Included Trials* and Trials With Doses ≤100 mg†

Primary Outcome	k	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Death from MI/coronary events, stroke, other CVD	10	0.94 (0.85 to 1.03)	16.4	0.93 (0.84 to 1.03)	31.3
	7	0.96 (0.84 to 1.11)	39.5	0.95 (0.83 to 1.09)	51.1
Nonfatal stroke	9	0.94 (0.84 to 1.06)	32.3	0.94 (0.84 to 1.06)	31.8
	6	0.82 (0.71 to 0.95)	0	0.82 (0.71 to 0.95)	0
Nonfatal MI/coronary events	9	0.80 (0.72 to 0.88)	62.8	0.79 (0.71 to 0.88)	61.4
	7	0.85 (0.75 to 0.97)	52.1	0.85 (0.74 to 0.96)	52.5
All-cause mortality	10	0.94 (0.88 to 0.99)	0	0.93 (0.88 to 0.99)	0
	7	0.94 (0.88 to 1.01)	0	0.94 (0.87 to 1.01)	0

*Top row for each of the primary outcomes.
†Bottom row for each of the primary outcomes.

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; MI = myocardial infarction; OR = odds ratio; RR = relative risk.

Table 19. Harms of Aspirin for the Primary Prevention of Cardiovascular Events in Included Trials

		BMD, 1988[57]	PHS I, 1989[53]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Quality		Fair	Good	Fair	Fair	Fair	Good	Fair	Fair	Fair
Mean Followup		6 years	5 years	3.8 years	6.8 years*	3.6 years	10.1 years	4.4 years*	6.7 years*	8.2 years
Major GI Bleeding†	IG events/ n (%)	3/3,429 (0.1%)‡	49/11,037 (0.4%)‡	77/9,399 (0.8%)‡	6/1,268 (0.5%)‡	NR	129/19,934 (0.6%)‡	4/1,262 (0.3)‡	NR	9/1,675 (0.5%)‡
	CG events/ n (%)	3/1,710 (0.2%)‡	28/11,034 (0.3%)‡	37/9,391 (0.4%)‡	2/1,272 (0.2%)‡	NR	94/19,942 (0.5%)‡	0/1,277 (0.0)‡	NR	8/1,675 (0.5%)‡
	IG vs. CG	RR (95% CI): 0.50 (0.10 to 2.47)‡	RR (95% CI): 1.75 (1.10 to 2.78)‡	RR (95% CI): 2.08 (1.41 to 3.07)‡	RR (95% CI): 3.01 (0.61 to 14.88)‡	NR	RR (95% CI): 1.37 (1.05 to 1.79)‡	RR (95% CI): 8.10 (0.43 to 152.96)‡	NR	RR (95% CI): 1.13 (0.44 to 2.91)‡
Fatal GI Bleeding	IG events/ n (%)	3/3,429 (0.1%)‡	1/11,037 (0.01%)	5/9,399 (0.05%)	0/1,286 (0%)	NR	2/19,934 (0.01%)	NR	NR	NR
	CG events/ n (%)	3/1,710 (0.2%)‡	0/11,034 (0.0%)	3/9,391 (0.03%)	1/1,272 (0.08%)	NR	3/19,942 (0.02%)	NR	NR	NR
	IG vs. CG	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total Hemorrhagic Stroke	IG events/ n (%)	NR	23/11,037 (0.2%)	14/9,399 (0.1%)‡	2/1,268 (0.2%)	2/2,226 (0.1%)	51/19,934 (0.2%)	6/1,262 (0.5%)‡	NR	5/1,675 (0.3%)‡
	CG events/ n (%)	NR	12/11,034 (0.1%)	15/9,391 (0.2%)‡	0/1,272 (0.0%)	3/2,269 (0.1%)	41/19,942 (0.2%)	7/1,277 (0.5%)‡	NR	4/1,675 (0.2%)‡
	IG vs. CG	NR	AdjRR§ (95% CI): 2.14 (0.96 to 4.77), p=0.06	RR (95% CI): 0.93 (0.45 to 1.93)‡	RR (95% CI): 4.01 (0.18 to 88.90)‡	RR (95% CI): 0.68 (0.11 to 4.06)‡	AdjRR‖ (95% CI): 1.24 (0.82 to 1.87), p=0.31	RR (95% CI): 0.87 (0.29 to 2.57)‡	NR	RR (95% CI): 1.25 (0.34 to 4.65)‡
Fatal Hemorrhagic Stroke	IG events/ n (%)	10/3,429 (0.3%)	7/11,037 (0.1%)‡	2/9,399 (0.02%)	NR	NR	NR	1/1,262 (0.1%)	2/638 (0.3%)	3/1,675 (0.2%)
	CG events/ n (%)	4/1,710 (0.2%)	2/11,034 (0.0%)‡	3/9,391 (0.03%)	NR	NR	NR	4/1,277 (0.3%)	3/638 (0.5%)	3/1,675 (0.2%)
	IG vs. CG	RR (95% CI): 1.25 (0.39 to 3.97)‡	RR (95% CI): 3.50 (0.73 to 16.84)‡, p=NS	RR (95% CI): 0.67 (0.11 to 3.99)‡	NR	NR	NR	RR (95% CI): 0.25 (0.03 to 2.26)‡	RR (95% CI): 0.67 (0.11 to 3.98)‡	RR (95% CI): 1.00 (0.20 to 4.95)‡
Nonfatal Hemorrhagic Stroke	IG events/ n (%)	3/3,429 (0.1%)	16/11,037 (0.1%)‡	12/9,399 (0.1%)	NR	NR	NR	5/1,262 (0.4%)	NR	2/1,675 (0.1%)
	CG events/ n (%)	2/1,710 (0.1%)	10/11,034 (0.1%)‡	12/9,391 (0.1%)	NR	NR	NR	3/1,277 (0.2%)	NR	1/1,675 (0.1%)
	IG vs. CG	RR (95% CI): 0.75 (0.13 to 4.47)‡, p=NS	RR (95% CI): 1.60 (0.73 to 3.52)‡	RR (95% CI): 1.00 (0.45 to 2.22)‡	NR	NR	NR	HR (95% CI): 1.68 (0.40 to 7.04), p=0.48	NR	RR (95% CI): 2.00 (0.18 to 22.04)‡

Table 19. Harms of Aspirin for the Primary Prevention of Cardiovascular Events in Included Trials

		BMD, 1988[57]	PHS I, 1989[53]	HOT, 1998[56]	TPT, 1998[54]	PPP, 2001[59]	WHS, 2005[58]	JPAD, 2008[43]	POPADAD, 2008[44]	AAA, 2010[45]
Intracranial Bleeding	IG events/ n (%)	NR	NR	NR	1/1,268 (0.1%)‡¶	2/2,226 (0.1%)#	NR	2/1,262 (0.2%)‡**	NR	6/1,675 (0.4%)‡††
	CG events/ n (%)	NR	NR	NR	2/1,272 (0.2%)‡¶	0/2,269 (0.0%)#	NR	0/1,277 (0.0%)‡**	NR	3/1,675 (0.2%)‡††
	IG vs. CG	NR	NR	NR	RR (95% CI): 0.50 (0.05 to 5.52)‡¶	RR (95% CI): 4.08 (0.18 to 90.37)‡#	NR	RR (95% CI): 4.05 (0.18 to 89.67)‡	NR	RR (95% CI): 2.00 (0.50 to 7.98)‡

*Median.
†Major GI bleeding defined as GI bleeding requiring transfusion, hospitalization, or leading to death. If a trial reported transfusions and death from GI bleeding separately, we added these events together. If a trial only reported deaths from GI bleeding, we used that number for major GI bleeding. If a trial reported GI bleeding without any mention of severity, we did not include it.
‡Calculated.
§RR adjusted for age and assignment to beta carotene.
‖RR adjusted for age and assignment to vitamin E.
¶Defined as subarachnoid stroke/subdural hemorrhage.
#Defined as intracranial (not parenchymal).
**Defined as chronic subdural hematoma.
††Defined as fatal or nonfatal subarachanoid/subdural hemorrhage.

Abbreviations: AAA = Aspiring for Asymptomatic Atherosclerosis Trial; Adj = adjusted; BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; HR = hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; n = population; NR = not reported; NS = not significant; PHS = Physician's 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 20. Sex Subgroup: Total, Fatal, and Nonfatal Stroke by Stroke Type

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
PPP Berger, 2006[58] Fair 3.6 years	Specification unclear	All Ischemic Stroke	IG: 8/949 (0.8%) CG: 7/963 (0.7%) 1.16 (0.42 to 3.18)**	IG: 6/1,277 (0.5%) CG: 9/1,306 (0.7%) 0.68 (0.24 to1.91)**	NR
		Fatal Ischemic Stroke	NR	NR	NR
		Nonfatal Ischemic Stroke	NR	NR	NR
		All Hemorrhagic Stroke	IG: 2/949 (0.2%) CG: 1/963 (0.1%) 2.03 (0.18 to 22.34)**	IG: 0/1,277 (0%) CG: 2/1,306 (0.2%) 0.20 (0.01 to 4.26)**	NR
		Fatal Hemorrhagic Stroke	NR	NR	NR
		Nonfatal Hemorrhagic Stroke	NR	NR	NR
		Total Stroke of Unknown Type	NR	NR	NR
		Fatal Stroke of Unknown Type	NR	NR	NR
		Nonfatal Stroke of Unknown Type	NR	NR	NR
BMD Peto, 1988[57] Fair 6 years	NA; trial in males only	All Ischemic Stroke	NR*	NA	NA
		Fatal Ischemic Stroke	IG: 8/3,429 (0.2%) CG: 3/1,710 (0.2%) 1.33 (0.35 to 5.01)**	NA	NA
		Nonfatal Ischemic Stroke	IG: 13/3,429 (0.4%)† CG: 4/1,710 (0.2%)† 1.62 (0.53 to 4.96)**	NA	NA
		All Hemorrhagic Stroke	NR†	NA	NA
		Fatal Hemorrhagic Stroke	IG: 10/3,429 (0.3%) CG: 4/1,710 (0.2%) 1.25 (0.39 to 3.97)	NA	NA
		Nonfatal Hemorrhagic Stroke	IG: 3/3,429 (0.1%)‡ CG: 2/1,710 (0.1%)‡ 0.75 (0.13 to 4.47) [c]	NA	NA
		Total Stroke of Unknown Type	IG: 57/3,429 (1.7%)** CG: 26/1,710 (1.5%)** 1.09 (0.69 to 1.73)**	NA	NA
		Fatal Stroke of Unknown Type	IG: 12/3,429 (0.4%) CG: 5/1,710 (0.3%) 1.20 (0.42 to 3.39)**	NA	NA
		Nonfatal Stroke of Unknown Type	IG: 45/3,429 (1.3%) CG: 21/1,710 (1.2%) 1.07 (0.64 to 1.79)**	NA	NA
PHS I Physician's Health Study, 1989[53] Good 5 years	NA; trial in males only	All Ischemic Stroke	IG: 91/11,037 (0.8%) CG: 82/11,034 (0.7%) 1.11 (0.82 to 1.50)§	NA	NA
		Fatal Ischemic Stroke	IG: 3/11,037 (0.03%) CG: 3/11,034 (0.03%) 1.00 (0.20 to 4.95)**	NA	NA

Table 20. Sex Subgroup: Total, Fatal, and Nonfatal Stroke by Stroke Type

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
		Nonfatal Ischemic Stroke	IG: 88/11,037 (0.8%)** CG: 79/11,034 (0.7%)** 1.11 (0.82 to 1.51)**	NA	NA
		All Hemorrhagic Stroke	IG: 23/11,037 (0.2%) CG: 12/11,034 (0.1%) 2.14 (0.96 to 4.77)§	NA	NA
		Fatal Hemorrhagic Stroke	IG: 7/11,037 (0.06%) CG: 2/11,034 (0.02%) 3.50 (0.73 to 16.84)**	NA	NA
		Nonfatal Hemorrhagic Stroke	IG: 16/11,037 (0.1%) CG: 10/11,034 (0.1%) 1.60 (0.73 to 3.52)**	NA	NA
		Total Stroke of Unknown Type	IG: 5/11,037 (0.04%) CG: 4/11,034 (0.04%) 1.25 (0.34 to 4.65)**	NA	NA
		Fatal Stroke of Unknown Type	IG: 0/11,037 (0%) CG: 2/11,034 (0.02%) 0.20 (0.01 to 4.16)**	NA	NA
		Nonfatal Stroke of Unknown Type	IG: 5/11,037 (0.04%)** CG: 2/11,034 (0.02%)** 2.50 (0.48 to 12.88)**	NA	NA
TPT TPT Authors, 1998[54] Fair 6.8 years‖	NA; trial in males only	All Ischemic Stroke	IG: 10/1,268 (0.8%) CG: 18/1,272 (1.4%) 0.56 (0.26 to 1.20)**	NA	NA
		Fatal Ischemic Stroke	NR	NA	NA
		Nonfatal Ischemic Stroke	NR	NA	NA
		All Hemorrhagic Stroke	IG: 2/1,268 (0.2%)¶ CG: 0/1,272 (0%)¶ 4.01 (0.18 to 88.90)**	NA	NA
		Fatal Hemorrhagic Stroke	NR	NA	NA
		Nonfatal Hemorrhagic Stroke	NR	NA	
		Total Stroke of Unknown Type	IG: 5/1,268 (0.4%) CG: 6/1,272 (0.5%) 0.84 (0.26 to 2.73)**	NA	NA
		Fatal Stroke of Unknown Type	NR	NA	NA
		Nonfatal Stroke of Unknown Type	NR	NA	NA
WHS Ridker, 2005[58] Good 10.1 years	NA; trial in females only	All Ischemic Stroke	NA	IG: 170/19,934 (0.8%) CG: 221/19,942 (1.1%) 0.76 (0.63 to 0.93)#	NA
		Fatal Ischemic Stroke	NA	NR	NA
		Nonfatal Ischemic Stroke	NA	NR	NA

Table 20. Sex Subgroup: Total, Fatal, and Nonfatal Stroke by Stroke Type

Study Reference Quality Rating Mean Followup	Type of Analysis	Outcome	Men Events/Participants (%) RR (95% CI)	Women Events/Participants (%) RR (95% CI)	P-Value for Interaction
		All Hemorrhagic Stroke	NA	IG: 51/19,934 (0.2%) CG: 41/19,942 (0.2%) 1.24 (0.82 to 1.87)#	NA
		Fatal Hemorrhagic Stroke	NA	NR	NA
		Nonfatal Hemorrhagic Stroke	NA	NR	NA
		Total Stroke of Unknown Type	NA	NR	NA
		Fatal Stroke of Unknown Type	NA	NR	NA
		Nonfatal Stroke of Unknown Type	NA	NR	NA

Within study comparisons listed first.
* Not calculated from fatal plus nonfatal due to a large proportion of strokes of unknown type.
† Classified as probably ischemic.
‡ Classified as probably hemorrhagic.
§ Adjusted for age and assignment to beta carotene.
‖ Median.
¶ There were additional cases of subarachnoid stroke; 1 in the IG and 2 in the CG.
# Adjusted for age and treatment assignment to vitamin E and beta carotene.
** Calculated.

Abbreviations: BMD = British Medical Doctor's Study; CG = control group; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; NA = not applicable; NR = not reported; NS = not significant; PHS = Physician's Health Study; PPP = Primary Prevention Project; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

Table 21. Diabetes Subgroup: Total, Fatal, and Nonfatal Stroke by Stroke Type

Study Reference Quality Rating Mean Followup	Type of Analysis Diabetes Diagnostic Criteria	Outcome	Diabetes Events/Participants (%) RR (95% CI)	No Diabetes Events/Participants (%) RR (95% CI)	P-Value for Interaction
WHS Ridker, 2005[58] Rexrode, 2000[69] Good 10.1 years	A priori Diagnostic criteria: assumed self-reported history of diabetes from the enrollment questionnaire	All Ischemic Stroke	IG: 13/528* (2.5%) CG: 29/499* (5.8%) 0.42 (0.22 to 0.82)†	IG: 157/19,406* (0.8%) CG: 192/19,443* (1.0%) 0.81 (0.66 to 1.00)†	NR
		Fatal Ischemic Stroke	NR	NR	NR
		Nonfatal Ischemic Stroke	NR	NR	NR
		All Hemorrhagic Stroke	NR‡	NR‡	NR
		Fatal Hemorrhagic Stroke	NR	NR	NR
		Nonfatal Hemorrhagic Stroke	NR	NR	NR
		Total Stroke of Unknown Type	NR	NR	NR
		Fatal Stroke of Unknown Type	NR	NR	NR
		Nonfatal Stroke of Unknown Type	NR	NR	NR
JPAD Ogawa, 2008[43] Fair 4.4 years§	NA (trial in DM only) Diagnostic criteria: diagnosis of type 2 DM, not further specified	All Ischemic Stroke	NR	NA	NA
		Fatal Ischemic Stroke	NR	NA	NA
		Nonfatal Ischemic Stroke	IG: 22/1,262 (1.7%) CG: 24/1,277 (1.9%) 0.93 (0.52 to 1.65)¶	NA	NA
		All Hemorrhagic Stroke	IG: 6/1,262 (0.5%)‖ CG: 7/1,277(0.5%)‖ 0.87 (0.29 to 2.57)¶	NA	NA
		Fatal Hemorrhagic Stroke	IG: 1/1,262 (0.1%) CG: 4/1,277 (0.3%) 0.25 (0.03 to 2.26)¶	NA	NA
		Nonfatal Hemorrhagic Stroke	IG: 5/1,262 (0.4%) CG: 3/1,277 (0.2%) 1.69 (0.40 to 7.04)¶	NA	NA
		Total Stroke of Unknown Type	NR	NA	NA
		Fatal Stroke of Unknown Type	NR	NA	NA
		Nonfatal Stroke of Unknown Type	NR	NA	NA
POPADAD Belch, 2008[44] Fair 6.7 years§	NA (trial in DM only) Diagnostic criteria: type 1 or 2 diabetes, not further specified	All Ischemic Stroke	NR	NA	NA
		Fatal Ischemic Stroke	IG: 3/638 (0.5%) CG: 5/638 (0.8%) 0.60 (0.14 to 2.50)¶	NA	NA
		Nonfatal Ischemic Stroke	NR	NA	NA
		All Hemorrhagic Stroke	NR	NA	NA
		Fatal Hemorrhagic Stroke	IG: 2/638 (0.3%) CG: 3/638 (0.5%) 0.67 (0.11 to 3.98)¶	NA	NA
		Nonfatal Hemorrhagic Stroke	NR	NA	NA
		Total Stroke of Unknown Type	NR	NA	NA
		Fatal Stroke of Unknown Type	NR	NA	NA
		Nonfatal Stroke of Unknown Type	NR	NA	NA

Table 21. Diabetes Subgroup: Total, Fatal, and Nonfatal Stroke by Stroke Type

Within study comparisons listed first.
*All denominator Ns in each group back-calculated from Table 3 in Rexrode 2000 (Ns for IG and CG for those with and without DM not reported). Back-calculation results in a discrepancy of 24 participants, likely due to rounding.
†Adjusted for age and treatment assignment to vitamin E and beta carotene.
‡Cannot calculate based on number of ischemic strokes because there were 4 strokes of unknown type in the placebo group (not clear whether occurring in participants with or without DM).
§Median.
‖There were an additional 2 cases of chronic subdural hematoma in the aspirin group (0 in the placebo group).
¶Calculated.

Abbreviations: CG = control group; CI = confidence interval; DM = diabetes mellitus; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; NA = not applicable; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk; WHS = Women's Health Study.

Table 22. Summary of Evidence

Population	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 1 (Health Outcomes)								
Adults without known CVD	K=10 n=103,787 10 RCTs	Aspirin 50-650 mg/day does not have an effect on: total stroke (k=10), nonfatal stroke (k=9), CVD death (k=10), fatal MI + fatal stroke (k=9), or all-cause mortality (k=10). Aspirin 50-650 mg/day reduces the risk of major CVD events (total MI, total stroke, CVD death) by 11% (k=10; RR, 0.89 [95% CI, 0.84 to 0.95]; I^2=0%), which appears to be largely driven by a 20% reduction in nonfatal MI (k=9; RR, 0.80 [0.72 to 0.88]; I^2=62.8%).	By outcome: *Major CVD events:* Consistent. Reasonably precise. *Nonfatal MI:* Reasonably consistent. Imprecise. *Nonfatal stroke:* Inconsistent. Imprecise. *Fatal MI:* Inconsistent. Imprecise. *Fatal stroke:* Inconsistent. Imprecise. *All-cause mortality:* Consistent. Imprecise.	Undetected.	Fair	Substantial heterogeneity in populations, trial designs, aspirin dosing, and trial durations. Trials were mostly 4-6 years with 1 trial as long as 10 years. Trials powered for composite CVD outcomes of varying severity (fatal and nonfatal outcomes with some trials, including angina, revascularization in composite CVD outcome). The few studies that adjusted for any confounders did so inadequately.	MODERATE for reduction in CVD events. MODERATE for reduction in nonfatal MI. LOW for benefit vs. harm for nonfatal stroke. LOW for no effect in CVD death. LOW for individual outcomes of fatal MI and fatal stroke due to imprecision and inconsistency. MODERATE for no statistically different effect in all-cause mortality at 5-10 years.	Primary prevention populations including those with co-morbidities.

Table 22. Summary of Evidence

Population	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 1a (Subpopulations)								
A priori sub-populations of adults without known CVD	Age: k=7; n=90,442, 7 RCTs Sex: k=10; n=103,787, 10 RCTs Diabetes: k=8; n=96,108, 8 RCTs HTN: k=5; n=85,816, 5 RCTs CVD risk: k=3; n=61,206, 3 RCTs Lipid levels: k=4; n=67,026, 4 RCTs ABI: k=2; n=4,626, 2 RCTs Smoking: k=3; n=64,486, 3 RCTs Race/ethnicity: k=0	Aspirin consistently achieves a greater RR reduction in total MI in older age groups (age ≥65 years). The RR reduction for various CVD outcomes appears to be the same for men and women. Aspirin's effect on CVD outcomes is not modified in patients with diabetes selected for disease status only. There is insufficient evidence to make any conclusions about treatment modification for aspirin in any of the following subpopulations: CVD risk, lipid level, blood pressure level, ABI, smoking status, and race/ethnicity.	By subpopulation for specified CVD outcomes: *Age*: Reasonably consistent for total MI in trials, but not confirmed in IPD MA. Inconsistent for stroke, composite CVD outcome*. Insufficient for all-cause mortality (1 trial). Imprecise for MI, stroke, all-cause mortality, and composite CVD outcome*. *Sex*: Consistent, with major limitations and lack of adjustment for confounders for MI, thereby limiting credibility; inconsistent for stroke outcomes, all-cause mortality, and CVD composite outcome*. Imprecise for MI, stroke, all-cause mortality, and CVD composite outcomes*. *Diabetes*: Inconsistent and	Undetected, but possible due to limited reporting (i.e., unclear if a priori vs. posthoc subgroup analyses for many trials).	Age, sex, DM: Fair ABI/ lipids/ smoking/ CVD risk/HTN/ race/ ethnicity: Poor	Trials were not powered for subgroup analyses. Subgroup analyses rarely reported interaction testing, never adequately controlled for confounders, and commonly did not specify timing of subgroup specification, lending it to potential bias. Moreover, few studies had direct evidence from within-study comparisons.	LOW to MODERATE for greater RR reduction for total MI in older adults (age ≥65 vs. <65 years). MODERATE that aspirin's effect on CVD-related outcomes is the same by sex. MODERATE that aspirin's effect on CVD composite outcomes* and total MI is not modified based on diabetes disease status only. LOW that aspirin's effect on stroke and all-cause mortality is not modified based on diabetes disease status. INSUFFICIENT for any treatment modification in other subpopulations: CVD risk, lipid level, blood pressure levels, ABI, smoking status, race/ethnicity.	Sub-population specific applicability

Table 22. Summary of Evidence

Population	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
			imprecise for all-cause mortality and stroke. Reasonably consistent and imprecise for MI. Consistent and imprecise for composite CVD*. *ABI/lipids/ smoking/CVD risk/HTN*: Inconsistent. Imprecise for all CVD related outcomes. *Race/ethnicity*: N/A					
Key Question 1b (Dose, Formulation Duration)								
Adults without known CVD	Dose: ≤100 mg: k=7; n=72,866; 7 RCTs; >100 mg: k=3; n=30,921; 3 RCTs Formulation: k=10; n=103,787; 10 RCTs Duration: k=10; n=103,787; 10 RCTS, specifically k=8 for time-to-event reporting; n=76,577; 8 RCTs	Aspirin at doses ≤100 mg/day reduces total stroke by 15% (k=7; RR, 0.85 [95% CI, 0.76 to 0.96]; I^2=0%), driven by a reduction in nonfatal stroke (k=6; RR, 0.82 [95% CI, 0.71 to 0.95]; I^2=0%). Aspirin at doses ≤100 mg/day reduces nonfatal MI by 15% (k=7; RR, 0.85 [95% CI, 0.75 to 0.97]; I^2=52.1%), with some between-study variability. Aspirin doses of <325 mg/day reduces nonfatal MI by 22% (k=8; RR, 0.78 [95% CI, 0.70 to 0.87]; I^2=65.5), with between-study variability, but doesn't affect nonfatal stroke (k=7; RR,	*Dose:* ≤100 and <325 mg/day for MI and stroke outcomes: Reasonably consistent. Imprecise. *Formulation:* Inconsistent. Imprecise. *Duration:* Consistent. Imprecise.	Undetected.	Fair	Heterogeneous dosing schedules and formulations. Time-to-event data reported in 8 trials for various outcomes. Trial durations mostly 4-6 years, with 1 trial of 10 years; no trial with aspirin administration longer than 10 years.	MODERATE that lower dose of aspirin (≤100 mg/day) reduces nonfatal MI and nonfatal stroke. MODERATE that aspirin's CVD-related treatment benefit (largely from nonfatal MI) begins within the first 5 years (likely years 1-2). INSUFFICIENT for any treatment modification by formulation.	Primary prevention populations, including those with co-morbidities.

Table 22. Summary of Evidence

Population	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
		0.89 [95% CI, 0.78 to 1.01]; I^2=23.2%) or total stroke (k=8; RR, 0.90 [95% CI, 0.81 to 1.01]; I^2=18.3%). No conclusions can be made regarding benefit modification based on aspirin formulation. CVD benefit (largely from nonfatal MI) begins within the first 5 years of use (likely the first 1-2 years) and available evidence suggests there is no diminishing benefit through the first 4 to 5 years, with limited data for longer durations.						
Key Question 2 (Health Outcomes)								
Adults without known CVD	k=9 n=100,076 9 RCTs Major GI bleeding: k=7; n=94,305; 7 RCTs Total hemorrhagic stroke: k=7; n=93,661; 7 RCTs ARMD: k=2; n=61,947; 2 RCTs	Qualitative synthesis shows that major GI bleeding and hemorrhagic stroke are more common in aspirin group; however, precise estimates of this increased risk are not possible. *Major GI bleeding*: 7 trials report this rare event (≤0.8%) and RRs were >1 in all but 1 trial, ranging from 1.13 to 8.10 in those 6 trials. An IPD MA showed a 50% increase in major GI and other extracranial bleeding (RR, 1.54 [95% CI, 1.30 to 1.82]).	By outcome *Major GI bleeding:* Consistent. Imprecise. *Hemorrhagic stroke:* Inconsistent. Imprecise. *ARMD:* Reasonably consistent. Imprecise.	Undetected.	Fair	Trial design, dose, duration, population heterogeneity and rare events limit ability to pool data. No trial reported ascertainment methods for GI bleeding. Major GI bleeding rare (≤0.8%). Total hemorrhagic stroke rare (≤0.5%).	MODERATE that there is an increase in major GI bleeding with aspirin, but estimates are imprecise. Based on 2 RCTs with >10 events in the control group in the general population (WHS, PHS), the RR estimate likely lies between 1.37 and 1.75. LOW for aspirin's effect on hemorrhagic stroke due to rare events. MODERATE that	Primary prevention populations including those with co-morbidities.

Table 22. Summary of Evidence

Population	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
		Total hemorrhagic stroke: 7 trials report this rare outcome (event rates, 0% to 0.5%) and showed nonstatistically significant mixed results, with RRs ranging from 0.68 to 4.01. 3 out of 7 trials had RRs <1 and 4 remaining trials show RRs of 1.24 to 2.14. PHS and WHS were the largest RCTs with consistent, nonsignificant trend toward harm, with adjRRs of 1.24 and 2.14. An IPD MA reported a nonstatistically significant trend of a higher incidence of hemorrhagic stroke in the aspirin group compared to the control group (RR, 1.32 [95% CI, 0.91 to 1.91]). *ARMD*: 2 large RCTs report no difference in ARMD with vision loss in the aspirin group compared to the control group (PHS adjRR, 0.78 [95% CI, 0.46 to 1.32]; WHS adjRR, 0.82 [95% CI, 0.64 to 1.06]).					there is no difference in ARMD with vision loss with aspirin use.	
Key Question 2a (Subpopulations)								
A priori sub-populations of adults without known CVD	*Major GI bleeding:* Age: k=1; n=18,790; 1 RCT Sex: k=6; n=92,911; 6	Few trials report GI bleeding or hemorrhagic stroke by subgroup. Due to the rare occurrence of harm events in the entire populations studied, it is not possible to make	By outcome: *Major GI bleeding*: Age, DM, HTN, CVD risk, lipids, ABI, smoking,	Undetected.	Poor	The most subgroup evidence for aspirin's bleeding risks exists for sex-specific subgroups, but rare events make numbers too unstable for	INSUFFICIENT evidence that there is any modification in harm risk by subpopulation.	Primary prevention populations including those with co-morbidities.

Table 22. Summary of Evidence

Population	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
	RCTs DM: k=1; n=2,539; 1 RCT HTN: k=1; n=18,790; 1 RCT 10-yr CVD risk: k=1; n=18,790; 1 RCT Lipids, ABI, smoking, race/ethnicity: k=0 *Hemorrhagic stroke:* Age: k=0 Sex: k=5; n=74,121; 5 RCTs DM: k=2; n=3,815; 2 RCTs HTN, lipids, ABI, CVD risk, smoking: k=0 DM: k=2; n=61,947 *ARMD:* Age, sex, smoking, alcohol, HTN, lipids, ABI, CVD risk, race/ ethnicity: k=0	conclusions regarding possible differential harms profile among subpopulations. Sex: Only 2 RCTs allow within trial comparisons showing major GI bleeding is more common in men vs. women, but no interaction testing done. Interaction testing in 2 RCTs reporting ARMD with or without vision loss by subgroup (unclear if analysis a priori) found no effect modifications for any subgroup, except 1 RCT showed HTN status altered the treatment effect, with hypertensive men having a statistically significant 65% reduction in ARMD (RR, 0.35 [95% CI, 0.15 to 0.83]; p =0.04 for interaction; no correction for multiple testing).	race/ ethnicity: N/A (0-1 trial) Sex: Inconsistent. Imprecise. *Hemorrhagic stroke:* Age, DM, HTN, lipids, ABI, CVD risk, smoking, race/ethnicity: N/A (0 trials) Sex: Inconsistent. Imprecise. *ARMD:* Sex, age, smoking, alcohol, HTN, lipids, DM: Reasonably consistent (2 trials). Imprecise.			conclusions. Zero to one trial for bleeding harms (major GI bleeding or hemorrhagic stroke) in any given subgroup (except sex).		

Table 22. Summary of Evidence

Population	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 2b (Dose, Formulation Duration)								
Adults without known CVD	*Major GI bleeding:* Dose: k=7; n=94,305; 7 RCTs Duration: k=7; n=94,305; 7 RCTs Formulation: k=7; n=94,305; 7 RCTs *Hemorrhagic stroke:* Dose: k=7; n=93,661; 7 RCTs Duration: k=7; n=93,661; 7 RCTs Formulation: k=7; n=93,661; 7 RCTs *ARMD:* k=2; n=61,947; 2 RCTs	In all RCTs, the bleeding events were rare, making it difficult to make generalizable conclusions regarding the relationship between aspirin dose, duration, formulation, and bleeding events.	By outcome: *Major GI bleeding:* Dose, duration, formulation: Inconsistent. Imprecise. *Hemorrhagic stroke:* Dose, duration, formulation: Inconsistent. Imprecise. *ARMD:* Dose, duration, formulation: Inconsistent. Imprecise.	Undetected.	Poor	Given the lack of precision in estimating major GI bleeding and hemorrhagic stroke harms when examining all trials, little can be said about how dose, duration, and formulation alter these harms. Given that only 2 RCTs examined ARMD, it is not possible to make conclusions regarding the impact of dose, duration, or formulation.	INSUFFICIENT that dose, duration, or formulation alters relative risks for bleeding harms.	Primary prevention populations including those with co-morbidities.

*Composite CVD outcome=Total MI + total stroke + CVD mortality.

Abbreviations: ABI = ankle brachial index; ARMD = age-related macular degeneration; CI = confidence interval; CVD = cardiovascular disease; DM = diabetes mellitus; GI = gastrointestinal; HTN = hypertension; IPD MA = individual participant data meta-analysis; MI = myocardial infarction; NA = not applicable; PHS = Physicians' Health Study; RCT = randomized, controlled trial; RR = relative risk; WHS = Women's Health Study.

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
ACC/AHA Pooled Cohort Equation, 2013[14]	4 equations, sex- and race-specific Other covariates: • Age • Treated or untreated SBP • TC • HDL-C • Current smoking • Diabetes	10-year risk for first hard ASCVD event (nonfatal MI, CHD death, fatal or nonfatal stroke)	**Source:** 4 NHLBI-sponsored longitudinal community-based cohort studies (ARIC, CHS, CARDIA, Framingham/Framingham Offspring); derivation cohort restricted to those 40-79, African American or White, no previous MI, stroke, HF, coronary revascularization, AF. ARIC, CARDIA, CHS contribute African American participants. White participants are from the same cohorts plus Framingham/Framingham-Offspring. **Time period:** **ARIC[114]:** Baseline examinations conducted between 1986 and 1989 **CARDIA[115]:** Recruitment conducted 1984-1985 **CHS[116]:** Baseline examinations conducted in 1989 **Framingham[6]:** Data collected 1968-1971 for original cohort; 1971-1975 or 1984-1987 for Offspring cohort **Recruitment:** **ARIC:** Random selection of approximately 4,000 subjects from each of 4 communities **CARDIA:** Random selection from phone/address lists in 3 sites and random selection from health plan participant rosters in 1 site **CHS:** Random sampling of Medicare eligibility lists **Framingham:** Random sample of 2/3 of the adult population **N:** White women: 11,240 White men: 9,098 African American women: 2,641 African American men: 1,647 **Age, years:** range for all, 40-79 White women: 56.8 White men: 56.2 African American women: 55.3 African American men: 55.4 **Risk characteristics:** *BP meds:*	Munter, 2014: REGARDS cohort, a community-based cohort of adults 45 years or older in the US. Analyses restricted to participants 45-79 without CHD, stroke, HF, or AF; 5 year F/U. Additional analyses also further restricted to participants without diabetes, LDL 70-189 mg/dL and not taking statins (population considered for statin initiation under ATP IV guidelines). Analyses also made with Medicare-linked data for additional outcome ascertainment. When all participants were analyzed, calibration was poor for all groups and the C-index was above 0.7 for women and whites only. When analyses were restricted to those without diabetes, LDL 70-189 mg/dL and not taking statins, calibration was improved with Hosmer-Lemeshow χ^2 less than 20.0 for all sex and race groups; discrimination was above 0.7 for women and whites only. Calibration additionally improved when additional events were ascertained through Medicare-linked data. Comparison of observed to predicted events shows marked overprediction in the >=10% risk category. ACC/AHA, 2013: MESA cohort, restricted to those 40 to 79 years of age, free of MI, stroke, CHF, coronary revascularization, or AF and with complete data; 6 year F/U. Calibration poor for white and black men, calibration χ^2 <20 for white women and black women (14.56 and 18.51); discrimination >0.7 for white women and men and black women. Overprediction in most race-sex groups and risk categories except for in white women, where observed events were greater than those predicted in risk categories <5% and 7.5 to <10% and observed and predicted events were closely matched in the 5% to <7.5% category.	No equations for Hispanics or Asians; lack of large external datasets with needed covariate data to validate in these subpopulations. Archimedes external validation of Hispanics with data from MESA showed overprediction in women but not men; for ALLHAT, overprediction for men and women (observed to predicted ratios of 1.38 and 1.47, respectively). Not enough event data to validate in Asians. Almost always large overprediction in >=10% risk group. General trend of overprediction in other risk groups, but some external validation cohorts show underprediction or well-matched observed to predicted events in the <5% group. Small numbers events in validation cohorts, particularly in lower risk groups.

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
			White women: 18.5% White men: 16.9% African American women: 40.8% African American men: 31.2% *TC, mg/dL:* White women: 220.5 White men: 210.7 African American women: 214.8 African American men: 208.4 *HDL, mg/dL:* White women: 58.2 White men: 44.4 African American women: 58.6 African American men: 51.0 *Smoking:* White women: 24.9% White men: 25.5% African American women: 22.7% African American men: 35.5% *Diabetes:* White women: 6.3% White men: 8.8% African American women: 17.4% African American men: 15.9% *Incident ASCVD events:* White women: 902 (8.0%) White men: 1,259 (13.8%) African American women: 290 (11.0%) African American men: 238 (14.4%) All demographic characteristics calculated as weighted averages from Table 2 in Supplement	ACC/AHA, 2013: Contemporary Cohort (ARIC visit 4; Framingham cycle 22 or 23; Framingham offspring cycle 5 or 6), restricted to those 40 to 79 years of age, free of MI, stroke, CHF, coronary revascularization, or AF and with complete data. Calibration χ^2 <20 only for black women and men. Discrimination (C-index) >0.7 for all race-sex groups except white men (0.6843). When examining observed vs predicted events, overprediction greater in >10% risk group compared with lower risk groups for all race-sex groups except for black men, where overprediction was greatest in 5 to 7.5% risk group. Kavousi, 2014: Rotterdam study, a prospective cohort study of adults 55 or older in the Netherlands, excludes individuals on statins at baseline, those with CVD, and those with LDL >190 mg/dL. This analysis also compared ATP III Framingham and SCORE models. χ^2 statistics NR but calibration qualitatively described as poor for all 3 models examined; all models overestimated risk in men and women across all risk categories. Ridker, Cook, 2013: Women's Health Study, Physician's Health Study, Women's Health Initiative Observational Study. Systematic overestimation of observed risks by 75-150% in all three cohorts.	

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
Framingham CHD – Wilson, 1998[8] ATP III modification of Wilson, 2002[15]	Wilson; sex-specific equations with the following covariates: • Age • TC • HDL • BP • Diabetes • Smoking ATP III modification of Wilson; sex-specific equations with the following covariates: • Age • TC • HDL • SBP • Treatment for HTN • Smoking	10-year risk of CHD (angina pectoris, 'recognized and unrecognized' MI, coronary insufficiency, sudden death); score sheets provide comparison with hard CHD (total CHD without angina pectoris) ATP III version of Wilson: 10-year risk for hard CHD (MI and CHD death)	**Source:** Community-based cohort of adults free of CHD and 30-74 years old; Framingham, MA **Time period:** Data collected 1971-1974; 12 years F/U **Recruitment:** Random sample of 2/3 of the adult population in the community **N:** 5,345 [11th exam of original Framingham cohort or 1st exam of Framingham offspring cohort] **% male/female*:** 46.4/53.6 **Age:** range, 30-74 Mean, men: 48.3 Mean, women: 49.6 **Risk characteristics:** *BP >140/90 mm Hg:* Men: 36% Women: 29% *TC >240 mg/dL, %:* Men: 23 Women: 29 *HDL <45 mg/dL, %:* Men: 55 Women: 19 *Smoking, %:* Men: 40 Women: 38 *Diabetes, %:* Men: 5 Women: 4 *Incident CHD events over 12 years F/U:* Men: 383 (15.4%) Women: 227 (7.9%) **Race/ethnicity:** Predominately white (% NR)	External validation reported for a wide range of cohorts in the US, Europe and Australia, including community-based and occupational cohorts as well as among individuals with family history of CVD[101] Landmark validation paper in multiethnic populations used 6 non-Framingham cohorts (D'Agostino 2001[117]) • ARIC: 1987-1988 data; prospective cohort of 14,178 Black and White men and women ages 44-66; 26.5% Black • PHS: 1982 data; Prospective nested case-control study of 901 White male physicians ages 40-74 • HHP: 1980-1982 data; prospective cohort of 2,755 Japanese American men ages 51-81 • PR: 1965-1968 data; prospective cohort of 8,713 Hispanic men ages 35-74 • SHS: 1989-1991 data; prospective cohort of 3,782 Native American men and women ages 45-75 • CHS: 1989-1990 data; prospective cohort of 2,557 white men and women ages 65-74	Tendency to over-estimate CHD risk in groups with low observed risk and under-predict risk in high-risk groups (diabetes, strong family history of premature CVD, regions with high incidence and SES deprived groups). Predicted to observed ratios for CHD range from underprediction of 0.43 in a study of people with a family history of CHD to overprediction of 2.87 in an occupational sample of women from Germany[101] Among 6 nonFramingham US cohorts, the risk score is able to discriminate between subjects who develop CHD and those who do not reasonably well for white and black men and women, but overestimates risk for Japanese American men, Hispanic men, and Native American women[117] No validation in populations <30 and >80 years (only validated in 1 cohort that includes subjects 80 years and above; most validation cohorts have an upper age range of 64 or 74)

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
Framingham -Anderson, 1991[16,25]	• Sex • Age • SBP • Smoking • TC/HDL-C • Diabetes • ECG-LVH	1. MI (including silent and unrecognized) 2. CHD death 3. CHD (MI and CHD death, angina pectoris, coronary insufficiency) 4. Stroke (including transient ischemia) 5. CVD (1-4 plus CHF and PVD) 6. CVD death	**Source:** Community-based cohort of adults free of CHD and 30-74 years old; Framingham, MA **Time period:** Data collected 1968-1975; 12 years F/U **Recruitment:** Random sample of 2/3 of the adult population in the community **N:** 5,573 [Original Framingham cohort examinations 10-12 and first examination of offspring cohort] **% male/female:** 46.5/53.5 **Age:** range 30-74 **Risk characteristics:** *Median BP, mm Hg:* Men: 128/82 Women: 123/79 *Median TC, mg/dL:* Men: 210 Women: 212 *Median HDL-C, mg/dL:* Men: 43 Women: 56 *Smoking, %:* Men: 41 Women: 39 *Diabetes, %:* Men: 7 Women: 5 *ECG-LVH, %:* Men: 1 Women: 0.5 *Incident CHD events over 12 years F/U:* Men: 385 (15%) Women: 241 (8%) **Race/ethnicity:** Predominately white (% NR)	External validation reported for a wide range of cohorts in the US, Europe and New Zealand, including community-based and occupational cohorts as well as among participants of antihypertensive and lipid lowering intervention RCTs[101,102] The number and location and external validation cohorts vary by the outcome investigated. **CHD:** Most number of external validation studies are for this outcome, including US-based cohorts. Trend for underprediction in higher risk populations and overprediction in lower risk populations. Calibration reasonably accurate when baseline 10-year risk is 8 to 16%.[102] **CVD:** External validation cohorts from Australia, New Zealand, UK, and Europe; additionally LIFE study which included US-participants in LIFE study, with limited reporting from poster presentation. Predicted to observed ratios for CVD range from underprediction of 0.67 in UK subjects with diabetes to overprediction of 2.60 in high risk hypertensives; two validations in Australia and New Zealand show concordance between predicted and observed events[102] **Stroke:** Predicted risk of stroke close to actual risk for overall population; underprediction in higher-risk countries (Italy, Spain, Netherlands) and overprediction in lower-risk countries (France, Scandinavia). External validation for this outcome limited to 1 study of treated hypertensives in Europe/Israel[118]	Limited US-based external validation for CVD outcome; no US-based external validation for stroke outcome Historically dated derivation cohort (data collection 1968-1975) Predominately white source population Criticism about universally accepted criteria for LVH by ECG

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
Framingham CVD, 2008[6]	Sex-specific equations with the following covariates: • Age • TC • HDL • SBP • Antihyperten-sive medication use • Smoking • Diabetes	10-year risk of CVD (composite of CHD (coronary death, MI, coronary insufficiency, and angina), cerebrovascular events (ischemic stroke, hemorrhagic stroke, and TIA), peripheral artery disease (intermittent claudication), and heart failure)	**Source:** Community-based cohort of adults free of CVD and 30-74 years old; Framingham, MA **Time period:** Data collected 1968-1971 for original cohort; 1971-1975 or 1984-1987 for Offspring cohort depending on 1st or 3rd exam; 12 years F/U **Recruitment:** Random sample of 2/3 of the adult population **N:** 8,491 [11th exam of original Framingham cohort or 1st or 3rd exam of Framingham offspring cohort] **% male/female:** 46.7/53.3 **Age:** range, 30-74 Mean, men: 48.5 Mean, women: 49.1 **Risk characteristics:** *Mean TC, mg/dL:* Men: 212.5 Women: 215.1 *Mean HDL-C, mg/dL:* Men: 44.9 Women: 57.6 *Mean SBP, mm Hg:* Men: 129.7 Women: 125.8 *BP treatment, %:* Men: 10.13 Women: 11.76 *Smoking, %:* Men: 35.22 Women: 34.23 *Diabetes, %:* Men: 6.5 Women: 3.76 *Incident CVD events over 12 years F/U:* Men: 718 (18.09%) Women: 456 (10.08%) **Race/ethnicity:** Predominately white (% NR)	Not externally validated	Not limited to "hard' outcomes

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
ARIC, 2003[17]	• Sex • Race • Age • Cigarette smoking • TC • HDL • SBP • Antihypertensive medication use • Diabetes *Note: The risk factors above are described by the "Basic + Age model." Additional models with nontraditional risk factors are included in Chambless et al 2003 and Folsom et al 2003*	10-year risk for CHD event (validated definite or probable hospitalized MI, definite CHD death, unrecognized MI defined by ARIC ECG readings, or coronary revascularization	**Source:** Cohort of adults 45-64 years old and free of CVD from four U.S. communities (Minneapolis suburbs, MN; Forsyth County, NC; Washington County, MD; and black residents from Jackson, MS) **Time period:** Baseline examinations conducted between 1987 and 1989; F/U is ongoing. The present analysis includes F/U through 1998 (median 10.2 years) **Recruitment:** Random selection of approximately 4,000 subjects from each of 4 communities **N:** 14,054 **% male/female:** 43.2/56.8 **Age:** range, 45-64 **Risk characteristics:** *Mean TC, mg/dL:* Men: 211 Women: 218 *Mean HDL-C, mg/dL:* Men: 44 Women: 57 *Hypertension (>140/90 mm Hg or on meds), %:* Men: 35 Women: 35 *Smoking, %:* Men: 28 Women: 25 *Diabetes, n (%):*[119] Men: 639 (10.5%) Women: 861 (10.8%) *Incident CHD events over 10.2 years F/U:* Black women: 113 (4.9%) White women: 232 (4.1%) Black men: 133 (9.5%) White men: 586 (12.5%) **Race/ethnicity, %:** Black: 26.3 White: 73.7	Not externally validated[23]†	Model includes race, but race options are limited to Black and White Not inclusive of ages <45 or >65 years

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
SCORE, 2003[18]	• Age • Sex • Smoking • TC or TC/HDL ratio • SBP • Smoking • High and low risk regions of Europe	10-year risk of fatal CV event (MI, stroke, aortic aneurysm)	**Source:** Pooled data set of population-based and occupational cohort studies from 12 European countries **Time period:** Earliest recruitment period was 1967-1972 for the Paris Prospective Study; latest recruitment period of 1977-1991 for Glostrup Population Studies **Recruitment:** Varied based on cohort; recruitment included random sample, complete population, birth cohort and occupational cohort **N:** 205,178 **% male/female:** 57.1/42.9 **Age:** age range heterogeneous by cohort; model fit limited to ages 45-64 **Risk characteristics:** *Range of mean TC across cohorts, mg/dL:*[§] Men: 216.6 (Italy) to 251.4 (Finland) Women: 212.7 (Italy) to 251.4 (Scotland) *Range of mean HDL-C across cohorts, mg/dL:* Men: 44.5 (UK) to 53.0 (Scotland) Women: 54.2 (Spain) to 65.0 (Scotland) *Range of mean SBP across cohorts, mm Hg:* Men: 129 (Denmark) to 149 (Sweden) Women: 120 (Spain) to 140 (Finland) *Range of prevalence across cohorts, %:* Men: 39 (Germany) to 68 (France) Women: 12 (Spain) to 47 (Denmark) *Range of cumulative CVD death rate by age 65, %:* Men: 2.81 (Spain) to 12.80 (Finland) Women: 0.94 (Spain) to 2.66 (Finland)	Externally validated in European cohorts (11 evaluation studies)[23] Not validated in US; validation results mixed in European cohort, including overestimation in Norway and Austria and underestimation in South Asians residing in the UK, a population with a higher burden of diabetes (21% prevalence in sample)	No nonfatal events Diabetes not included as a risk factor because it was not uniformly collected in source cohort, but patients with diabetes included in source cohort; one validation study suggests underprediction in subjects with a high burden of diabetes[120] Risk functions are based on single risk factor measurements and not 'usual' levels Not validated in US

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
Reynolds, women, 2007[19]	• Age • SBP • Smoking • TC • HDL-C • hsCRP • Parental history of MI <60 years • HbA1c if diabetic	10-year risk of CV events (MI, ischemic stroke, coronary revascularization, CV death)	**Source:** Women's Health Study, a nationwide cohort of healthy US women (health professionals) 45 years and older and free of CVD and cancer at study entry; 2/3 of participants assigned to model derivation data set and 1/3 assigned to validation data set **Time period:** 1992-2004; mean 10.2 years F/U **Recruitment:** Female health professionals (76% RNs) **N:** 16,400 in derivation cohort **% male/female:** 0/100 **Age, median (IQR):** 52 (48-58) **Risk characteristics:** *Median TC, IQR, mg/dL*: 208 (183-235) *Median HDL-C,IQR, mg/dL:* 51.9 (43.1-62.5) *Median LDL-C, IQR, mg/dL:* 121.0 (100.1-144.1) *Lipid-lowering therapy, %:* 3.2 *History of hypertension, %:* 24.8 *Menopausal, %:* 54.4 *Current smoking, %:* 11.6 *Diabetes, %:* 2.7 *Parental history of MI, %:* 12.9 *Incident CVD events over 10.2 years F/U:* 504 events (3.1%) **Race/ethnicity, %** White: 95.2 Black: 1.9 Hispanic: 1.0 Asian: 1.4 Other: 0.5	Validated in same population from which it was derived **Source:** Women's Health Study, a nationwide cohort of healthy US women (health professionals) 45 years and older and free of CVD and cancer at study entry; 2/3 of participants assigned to model derivation data set and 1/3 assigned to validation data set **Time period:** 1992-2004; mean 10.2 years F/U **Recruitment:** Female health professionals (76% RNs) **N:** 8,158 in validation cohort **% male/female:** 0/100 **Age, median (IQR):** 52 (49-59) **Risk characteristics:** *Median TC, mg/dL:* 208 (184-235) *Median HDL-C, mg/dL:* 52.2 (43.4-62.5) *Median LDL-C, mg/dL:* 121.3 (100.9-143.8) *Lipid-lowering therapy, %:* 3.2 *History of hypertension, %:* 25.3 *Menopausal, %:* 54.3 *Current smoking, %:* 11.4 *Diabetes, %:* 2.9 *Parental history of MI, %:* 12.7 *Incident CVD events over10.2 years F/U:* 262 events (3.2%) **Race/ethnicity, %** White: 95.3 Black: 1.9 Hispanic: 1.0 Asian: 1.5 Other: 0.3	Not externally validated outside of source cohort Primarily white 100% of sample is health professionals; health behaviors and SES may not be generalizable Data on BP, obesity, and family history based on self-report

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
Reynolds, men, 2008[20]	• Age • SBP • Smoking • TC • HDL-C • hsCRP • Parental history of MI <60 years	10-year risk of CV events (MI, stroke, coronary revascularization, CV death)	**Source:** Physicians Health Study II, nationwide cohort of healthy male physicians 50-80 years of age and free of CVD, DM, and cancer at study entry **Time period:** 1995-2008; median 10.8 years F/U **Recruitment:** Male physicians **N:** 10,724 **% male/female:** 100/0 **Age, median (IQR):** 63 (57-70) **Risk characteristics:** *Mean TC, IQR, mg/dL:* 203 (180-227) *Mean HDL-C,IQR, mg/dL:* 42.5 (24.4-52.4) *Median SBP, IQR, mm Hg:* 128 (120-135) *Lipid-lowering therapy, %:* 17.3 *Antihypertensive therapy, %:* 24.2 *Current smoking, %:* 3.2 *Parental history of MI before age 60, %:* 10.8 *Incident CVD events over 10.8 years F/U:* 1294 events (12.1%) **Race/ethnicity:** Primarily white (% NR in risk score paper)	Not externally validated	Primarily white source population 100% of sample is health professionals; health behaviors, access to health care, and SES may not be generalizable Data on BP, obesity, and family history based on self-report Uncertain applicability in men <50
QRISK2, 2008[21]	• Self-assigned ethnicity • Age • Sex • Smoking status • SBP • Ratio of TC/HDL-C • BMI • Family history of CHD in first degree relative <60 years • Townsend deprivation score	10-year risk of CHD (angina and MI), stroke, or TIA	**Source:** UK primary care database; subjects aged 35-74 years and free of cardiovascular or cerebrovascular disease and not taking statins at baseline; 2/3 of participants randomly allocated to derivation dataset and 1/3 assigned to validation data set **Time period:** 1993-2008, mean F/U 7.3 years for women and 6.9 years for men **Recruitment:** Patients registered at primary care practices in the UK **N:** 1,535,583 **% male/female:** 49.6/50.4 **Age:** range, 35-74 Median (IQR), men: 48 (40-58) Median (IQR), women: 49 (41-60)	Validated in same population from which it was derived **Source:** UK primary care database; subjects aged 35-74 years and free of cardiovascular or cerebrovascular disease and not taking statins at baseline; 2/3 of participants randomly allocated to derivation dataset and 1/3 assigned to validation data set **Time period:** 1993-2008, mean F/U 7.3 years for women and 6.9 years for men **Recruitment:** Patients registered at primary care practices in the UK **N:** 750,232 **% male/female:** 49.9/50.1	Not externally validated Only 3% from ethnic minority groups Recording of family history of CHD may not be systematic Townsend deprivation score is specific to UK

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
	• Treated HTN • Rheumatoid arthritis • Chronic kidney disease • Diabetes • Atrial fibrillation		**Risk characteristics:** *Treated hypertension, %:* Men: 5.59 Women: 7.12 *Current smoking, %:* Men: 27.4 Women: 22.8 *Diabetes, %:* Men: 2.24 Women: 1.70 *Atrial fibrillation, %:* Men: 0.25 Women: 0.35 *Chronic kidney disease, %:* Men: 0.15 Women: 0.16 *Incident CVD events:* Men: 55,667 events (7.3%) over 6.9 years mean F/U Women: 41,042 events (5.3%) over 7.3 years mean F/U **White race/ethnicity, %:** Men: 97.5 Women: 97.3	**Age:** range, 35-74 Median (IQR), men: 47 (40-57) Median (IQR), women: 49 (41-59) **Risk characteristics:** *Treated hypertension, %:* Men: 5.36 Women: 6.91 *Current smoking, %:* Men: 28.0 Women: 23.6 *Diabetes, %:* Men: 2.18 Women: 1.65 *Atrial fibrillation, %:* Men: 0.58 Women: 0.33 *Chronic kidney disease, %:* Men: 0.13 Women: 0.17 *Incident CVD events:* Reported as similar to derivation data set but data not shown **White race/ethnicity, %:** Men: 97.0 Women: 96.7	
PROCAM, 2002[22]	• Age • LDL-C • HDL-C • TG • Smoking • Diabetes • Family history of MI <60 years • SBP	10-year risk of a major coronary event (sudden cardiac death, definite fatal or nonfatal MI)	**Source:** Sample of men from prospective cohort study of Germans 35-65 without history of MI, stroke, angina, or ECG evidence of ischemic heart disease **Time period:** recruitment from1979-1985 and 10 years F/U **Recruitment:** Occupational sample from 52 companies and government agencies **N:** 5,389 **% male/female:** 100/0 **Age, mean (SD):** 46.7 (7.5) **Risk characteristics:** *Mean LDL-C (SD), mg/dL:* 148.5 (37.6) *Mean HDL-C (SD), mg/dL:* 45.7 (11.9) *Mean SBP (SD), mm Hg:* 131.4 (18.4)	Externally validated in several European cohorts[23] In external validation among a cohort of 798 subjects with diabetes in the UK, ages 35-74 and free of CVD, renal failure and family history of dyslipidemia, PROCAM showed poor discrimination and statistically significant underprediction of risk for CHD [O/E ratio 2.05 (95% CI, 1.82-2.31)][121] In external validation among a cohort of 9,758 men ages 50-59 living in Belfast and France and free of CHD, there was clear overestimation of events both in France, a lower risk population, and in the higher risk Belfast population[122]	Excludes women Not applicable to patients >65 Tendency for underprediction in diabetics and overprediction in healthy European populations

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
			Mean TG (SD), mg/dL: 126.2 (65.9) *Smoking, %:* 31.1 *Family history of MI before age 60, %:* 16.1 *Diabetes, %:* 6.7 *Incident CHD events over 10 years F/U:* 325 events (6.03%) **Race/ethnicity:** NR	In an external validation cohort of 2,732 healthy Caucasian men ages 50-64 years in UK general practices, statistically significant overestimation of risk for CHD [O/E ratio 0.46 (95% CI, 0.40-0.52)][123]	
ASSIGN, 2007[124]	• TC • HDL-C • SBP • Smoking • Cigarettes per day • Family history • Diabetes • Index of social status/ deprivation	10-year risk for CV death, hospitalization for CHD or cerebrovascular disease, coronary artery interventions (CABG or PTCA)	**Source:** Nationally representative Scottish database of participants 30-74 who were free of CHD, stroke, or TIA [Scottish Heart Health Extended Cohort (SHHEC)]. **Recruitment:** SHHEC included data from two overlapping studies: Scottish Heart Health Study, a random sample of men and women 40-59 years in Scotland and the Scottish MONICA Project, which included participants 25-74 from Edinburgh and north Glasgow. **Time period:** Scottish Heart Health Study: 1984-1987; MONICA: Edinburgh and north Glasgow in 1986, north Glasgow in 1989 and 1995, ages 25–64 and 1992, ages 25–74; F/U ranged 10-21 years **N:** 13,297 **% male/female:** 49.2/50.8 **Age, mean (SE):** Men: 48.9 (0.1) Women: 48.8 (0.1) **Risk characteristics:** *Mean TC (SE), mg/dL[§]:* Men: 240.91 (0.39) Women: 247.87 (0.77) *Mean HDL-C (SE), mg/dL:* Men: 52.20 (0.00) Women: 63.03 (0.39) *Mean SBP (SE), mm Hg:* Men: 133.8 (0.2) Women: 130.1 (0.3) *Smoking, %:* Men: 41.5	When applied to UK general practice database of subjects 35-75 years of age, ASSIGN overpredicted risk by 36%. This UK database had a lower prevalence of risk factors (i.e., smoking, family history) and incident CVD than the ASSIGN source database.[125]	Social deprivation index specific to Scotland High prevalence of smoking and family history in source cohort

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
			Women: 40.5 *Among smokers, cigarettes per day, mean (SE):* Men: 19.2 (0.2) Women: 15.9 (0.2) *Family history of heart disease before age 60, %:* Men: 26.4 Women: 32.6 *Diabetes, %:* Men: 1.5 Women: 1.3 *Incident CVD events over 10 years F/U:* Men: 743 (11.4%) Women: 422 (6.2%) **Race/ethnicity:** NR		
Framingham Stroke-Wolf, 1991 with 1994 update [126,127]	Sex-specific equations with the following covariates: • Age • SBP • AntiHTN therapy • Diabetes • Smoking • Prior CVD (CHD, cardiac failure, intermittent claudication) • AF • LVH-ECG	Stroke (including atherothrombotic brain infarction, TIA, cerebral embolus, intracerebral hemorrhage, subarachnoid hemorrhage)	**Source:** Community-based cohort of adults age 55-84 and free of stroke; Framingham, MA **Time period:** Data collection period 1965-1967[‖]; 10 years F/U **Recruitment:** Random sample of 2/3 of the adult population in the community **N:** 5,734 [Framingham examination cycles 9 and 14] **% male/female:** 41/59 **Age, mean years:** Men: 65.4 Women: 66.1 **Risk characteristics:** *Mean BP, mm Hg:* Men: 139.3 Women: 142.8 *Antihypertensive therapy, %* Men: 16.1 Women: 25.0 *Smoking, %* Men: 33.8 Women: 26.4 *Diabetes, %* Men: 10.6 Women: 7.9	Copenhagen City Heart Study, a prospective study of 19,698 men and women aged 20 years or older. The Copenhagen population included a much higher proportion of smokers and patients with LVH compared with the Framingham source cohort, and a lower proportion of individuals with diabetes or being treated with antiHTN therapy. The observed frequency of stroke was compatible with probability intervals based on the prediction model.[128]	Derivation cohort includes participants with prior CVD (22.2% of men and 14.2% of women) Not externally validated in US population Historically dated derivation cohort (data collection 1965-1967 Predominately white source population

Appendix A. CHD/CVD Risk Score Characteristics Table

Risk Score	Risk Factors Included in the Model	Outcomes and Time Horizon	Population Derived/ Source Cohort	Validation Cohorts	Limitations
			CVD, % Men: 22.2 Women: 14.2 *AF, %* Men: 2.8 Women: 2.2 *LVH-ECG, %* Men: 3.5 Women 2.9 *Incident stroke events over 10 years F/U* Men: 213 (9.0%) Women: 259 (7.7%) **Race/ethnicity:** Predominately white (% NR)		

*Demographic characteristics of the source cohort reported in D'Agostino 2001
†A table of externally validated methods is available in Matheny, 2011, Table 5 (page 51)
‡Risk characteristics for TC through smoking reported at the ARIC website: http://www2.cscc.unc.edu/aric/system/files/CohortCharacteristics.pdf. Reported for the full cohort of 15,792 (not the model derivation cohort of 14,054).
§Units converted from source paper
‖Reported in Beswick, 2008[102]

Abbreviations: ACC/AHA= American College of Cardiology/American Heart Association; AF= Atrial Fibrillation; ALLHAT= Anti=hypertensive and Lipid Lowering Treatment to Prevent Heart Attack; ARIC= Atherosclerosis Risk in Communities; ASCVD= Atherosclerotic Cardiovascular Disease; ATP= Adult Treatment Panel; BMI= Body Mass Index; BP= Blood Pressure; CABG= Coronary Artery Bypass Grafting; CARDIA= Coronary Artery Risk Development in Young Adults; CHD= Coronary Heart Disease; CHS= Cardiovascular Health Study; CVD= Cardiovascular Disease; ECG= Electrocardiogram; F/U= Followup; HbA1c= Hemoglobin A1c; HDL= High Density Lipoprotein; HDL-C= High Density Lipoprotein Cholesterol; HF= Heart Failure; HHP= Honolulu Heart Program; hsCRP= High Sensitivity C-Reactive Protein; HTN= Hypertension; IQR= Interquartile Range; LDL= Low Density Lipoprotein; LIFE= Life Style Interventions and Independence for Elders; LVH= Left Ventricular Hypertrophy; mg/dL= Milligrams per Deciliter; MA= Massachusetts; MD= Maryland; MESA= Multi Ethnic Study of Atherosclerosis; MI= Myocardial Infarction; mm Hg= Millimeter of Mercury; MN= Minnesota; MONICA= Multinational Monitoring; MS= Mississippi; NC= North Carolina; NHLBI= National Heart Lung and Blood Institute; NR= Not Reported; O/E= Observed to Expected; PHS= Physicians Health Study; PRHHP= Puerto Rican Heart Health Program; PROCAM= Prospective Cardiovascular Muenster Study; PTCA= Percutaneous Transluminal Coronary Angioplasty; PVD= Peripheral Vascular Disease; REGARDS= Reasons for Geographic and Racial Differences in Stroke; RCT= Randomized Controlled Trial; RN= Registered Nurse; SBP= Systolic Blood Pressure; SCORE= Systematic Coronary Risk Evaluation; SD=Standard Deviation; SE= Standard Error; SES= Socio=economic Status; SHS= Strong Heart Study; SHHEC= Scottish Heart Health Extended Cohort; TC= Total Cholesterol; TG= Triglycerides; TIA= Transient Ischemic Attack; US= United States; UK= United Kingdom

Systematic Reviews Literature Search Strategy

BMJ Clinical Evidence - searched on 4/26/2013
Most specific results found when search limited to "aspirin" and filtered by "systematic reviews". Large set of results retrieved; all were secondary prevention references.

Cochrane Database of Systematic Reviews search strategy- searched on 4/29/13
#1 Aspirin or "acetylsalicylic acid" or Salicylate*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols)
#2 coronary or angina or "cardiac arrest" or "cardiac death" or myocardial or heart near attack* or "heart arrest":ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols)
#3 Cardiovascular next Disease* or Heart next Disease*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols)
#4 vascular next disease* or stroke or brain next infarction* or "brain stem" near infarction*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols)
#5 "Lateral Medullary Syndrome" or Cerebral near infarction* or Dementia near Multi-Infarct*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols)
#6 Cerebrovascular next disease* or Cerebrovascular next disorder*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols)
#7 #2 or #3 or #4 or #5 or #6 from 2008 to 2013, in Cochrane Reviews
#8 #1 and #7 from 2008 to 2013, in Cochrane Reviews

Database of Abstracts of Reviews of Effects search strategy- searched on 4/29/13
1 (aspirin) OR (acetylsalicylic ADJ acid) OR (salicylate*) IN DARE FROM 2008 TO 2013
2 (coronary) OR (angina) OR (cardiac adj arrest) OR (cardiac adj death) OR (myocardial) IN DARE FROM 2008 TO 2013
3 (heart adj attack*) OR (heart adj arrest) OR (Cardiovascular adj Disease*) OR (Heart adj Disease*) OR (vascular adj disease*) IN DARE FROM 2008 TO 2013
4 (stroke) OR (brain adj infarction*) OR (brain near infarction*) OR (Lateral adj Medullary) OR (Cerebral near infarction*) IN DARE FROM 2008 TO 2013
5 (Dementia next Multi-Infarct*) OR (Cerebrovascular adj disease*) OR (Cerebrovascular adj disorder*) IN DARE FROM 2008 TO 2013
6 #2 OR #3 OR #4 OR #5
7 #1 AND #6

National Institute for Health and Clinical Excellence search strategy for "Guidance" Reports - searched on 4/26/2013
53 results for "aspirin" limited to "Guidance reports". Results retrieved all were secondary prevention references.

PubMed search strategy - searched on 4/29/13
#24 #14 OR #23 Filters: Publication date from 2008/01/01; English
#23 #19 AND prevent*[tiab] AND (publisher[sb] OR in process[sb] OR pubmednotmedline[sb]) Filters: Publication date from 2008/01/01; English

#22 #19 AND prevent*[tiab] AND (publisher[sb] OR in process[sb] OR pubmednotmedline[sb]) Filters: English
#21 #19 AND prevent*[tiab] AND (publisher[sb] OR in process[sb] OR pubmednotmedline[sb])
#20 #19 AND prevent*[tiab]
#19 #17 AND #18 AND systematic[sb]
#18 Aspirin[tiab] OR "acetylsalicylic acid"[tiab] OR Salicylate*[tiab]
#17 #15 OR #16
#16 stroke[tiab] OR cerebrovascular disease*[tiab] OR cerebrovascular disorder*[tiab]
#15 cardiovascular disease*[tiab] OR heart disease*[tiab] OR "myocardial infarction"[tiab] OR "heart arrest"[tiab] OR "myocardial ischemia"[tiab] OR "myocardial ischaemia"[tiab] OR "coronary artery disease"[tiab] OR heart attack*[tiab]
#14 #10 AND #11 AND systematic[sb] Filters: Publication date from 2008/01/01; English
#13 #10 AND #11 AND systematic[sb] Filters: English
#12 #10 AND #11
#11 "prevention and control" [Subheading] OR prevent*[tiab]
#10 #8 AND #9
#9 "Aspirin"[Mesh] OR "Salicylates"[Mesh:NoExp]
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7 "Dementia, Multi-Infarct"[Mesh] OR "Infarction, Anterior Cerebral Artery"[Mesh] OR "Infarction, Middle Cerebral Artery"[Mesh] OR "Infarction, Posterior Cerebral Artery"[Mesh] OR "Stroke, Lacunar"[Mesh]
#6 "Vascular Diseases"[Mesh:NoExp] OR "Stroke"[Mesh:NoExp] OR "Brain Infarction"[Mesh:NoExp] OR "Brain Stem Infarctions"[Mesh:NoExp] OR "Lateral Medullary Syndrome"[Mesh] OR "Cerebral Infarction"[Mesh:NoExp]
#5 "No-Reflow Phenomenon"[Mesh] OR "Shock, Cardiogenic"[Mesh] OR "Myocardial Reperfusion Injury"[Mesh] OR "Myocardial Stunning"[Mesh]
#4 "Coronary Thrombosis"[Mesh] OR "Myocardial Infarction"[Mesh:NoExp] OR "Anterior Wall Myocardial Infarction"[Mesh] OR "Inferior Wall Myocardial Infarction"[Mesh] OR "Myocardial Stunning"[Mesh]
#3 "Coronary Disease"[Mesh:NoExp] OR "Coronary Artery Disease"[Mesh] OR "Coronary Occlusion"[Mesh] OR "Coronary Stenosis"[Mesh:NoExp] OR "Coronary Restenosis"[Mesh]
#2 "Myocardial Ischemia"[Mesh:NoExp] OR "Acute Coronary Syndrome"[Mesh:NoExp] OR "Angina Pectoris"[Mesh:NoExp] OR "Angina, Stable"[Mesh] OR "Angina, Unstable"[Mesh:NoExp] OR "Angina Pectoris, Variant"[Mesh] OR "Microvascular Angina"[Mesh]
#1 "Cardiovascular Diseases"[Mesh:NoExp] OR "Heart Diseases"[Mesh:NoExp] OR "Heart Arrest"[Mesh:NoExp]OR "Death, Sudden, Cardiac"[Mesh] OR "Out-of-Hospital Cardiac Arrest"[Mesh]

Search Strategies to Identify Relevant Literature for Key Questions 1 and 2

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
ti = word in title
ab = word in abstract

PUBMED- *[publisher supplied references only]*

#5	Search #3 AND #4 AND publisher[sb] Filters: Publication date from 2008/01/01 to 2013/12/31
#4	Search Aspirin[tiab] OR "acetylsalicylic acid"[tiab] OR Salicylate*[tiab]
#3	Search #1 OR #2
#2	Search stroke[tiab] OR cerebrovascular disease*[tiab] OR cerebrovascular disorder*[tiab] OR brain infarction*[tiab] OR cerebral infarction*[tiab] OR artery infarction*[tiab] OR “coronary thrombosis”[tiab] OR “coronary occlusion”[tiab] OR “cardiogenic shock”[tiab] OR “myocardial reperfusion”[tiab] OR “myocardial stunning”[tiab] OR “lateral medullary syndrome”[tiab]
#1	Search cardiovascular disease*[tiab] OR heart disease*[tiab] OR coronary disease*[tiab] OR vascular disease*[tiab] OR "myocardial infarction"[tiab] OR “cardiac arrest”[tiab] OR "heart arrest"[tiab] OR heart attack*[tiab] OR "myocardial ischemia"[tiab] OR "myocardial ischaemia"[tiab] OR "coronary artery disease"[tiab] OR “acute coronary syndrome”[tiab] OR angina[tiab] OR “coronary restenosis”[tiab] OR “coronary stenosis”[tiab]

MEDLINE

Database: Ovid MEDLINE(R) without Revisions <1996 to August Week 4 2013>, Ovid MEDLINE(R) Daily Update <September 04, 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 04, 2013>
Search Strategy:
---

1 Cardiovascular Diseases/ (69908)
2 Heart Diseases/ (22607)
3 Heart Arrest/ (11085)
4 Death, Sudden, Cardiac/ (9037)
5 Out-of-Hospital Cardiac Arrest/ (636)
6 Myocardial Ischemia/ (25293)
7 Acute Coronary Syndrome/ (6366)

8 Angina Pectoris/ (8885)
9 Angina, Stable/ (251)
10 Angina, Unstable/ (5786)
11 Angina Pectoris, Variant/ (442)
12 Microvascular Angina/ (681)
13 Coronary Disease/ (43610)
14 Coronary Artery Disease/ (31368)
15 Coronary Occlusion/ (1006)
16 Coronary Stenosis/ (7518)
17 Coronary Restenosis/ (5975)
18 Coronary Thrombosis/ (4237)
19 Myocardial Infarction/ (65360)
20 Anterior Wall Myocardial Infarction/ (160)
21 Inferior Wall Myocardial Infarction/ (96)
22 No-Reflow Phenomenon/ (197)
23 Shock, Cardiogenic/ (2740)
24 Myocardial Reperfusion Injury/ (7999)
25 Myocardial Stunning/ (1700)
26 Vascular Diseases/ (9327)
27 Stroke/ (52363)
28 Brain Infarction/ (2974)
29 Brain Stem Infarctions/ (515)
30 Lateral Medullary Syndrome/ (255)
31 Cerebral Infarction/ (10099)
32 Infarction, Anterior Cerebral Artery/ (161)
33 Infarction, Middle Cerebral Artery/ (4996)
34 Infarction, Posterior Cerebral Artery/ (198)
35 Stroke, Lacunar/ (108)
36 cardiovascular disease$.ti,ab. (77289)
37 heart disease$.ti,ab. (71714)
38 myocardial infarction.ti,ab. (79396)
39 heart arrest.ti,ab. (170)
40 myocardial ischemia.ti,ab. (11761)
41 myocardial ischaemia.ti,ab. (2176)
42 coronary artery disease.ti,ab. (40330)
43 heart attack$.ti,ab. (2841)
44 stroke.ti,ab. (105225)
45 cerebrovascular disease$.ti,ab. (8757)
46 cerebrovascular disorder$.ti,ab. (698)
47 cardiac arrest.ti,ab. (12605)
48 acute coronary syndrome.ti,ab. (9561)
49 angina pectoris.ti,ab. (6476)
50 stable angina.ti,ab. (3827)
51 unstable angina.ti,ab. (7250)
52 microvascular angina.ti,ab. (111)
53 coronary occlusion.ti,ab. (2109)

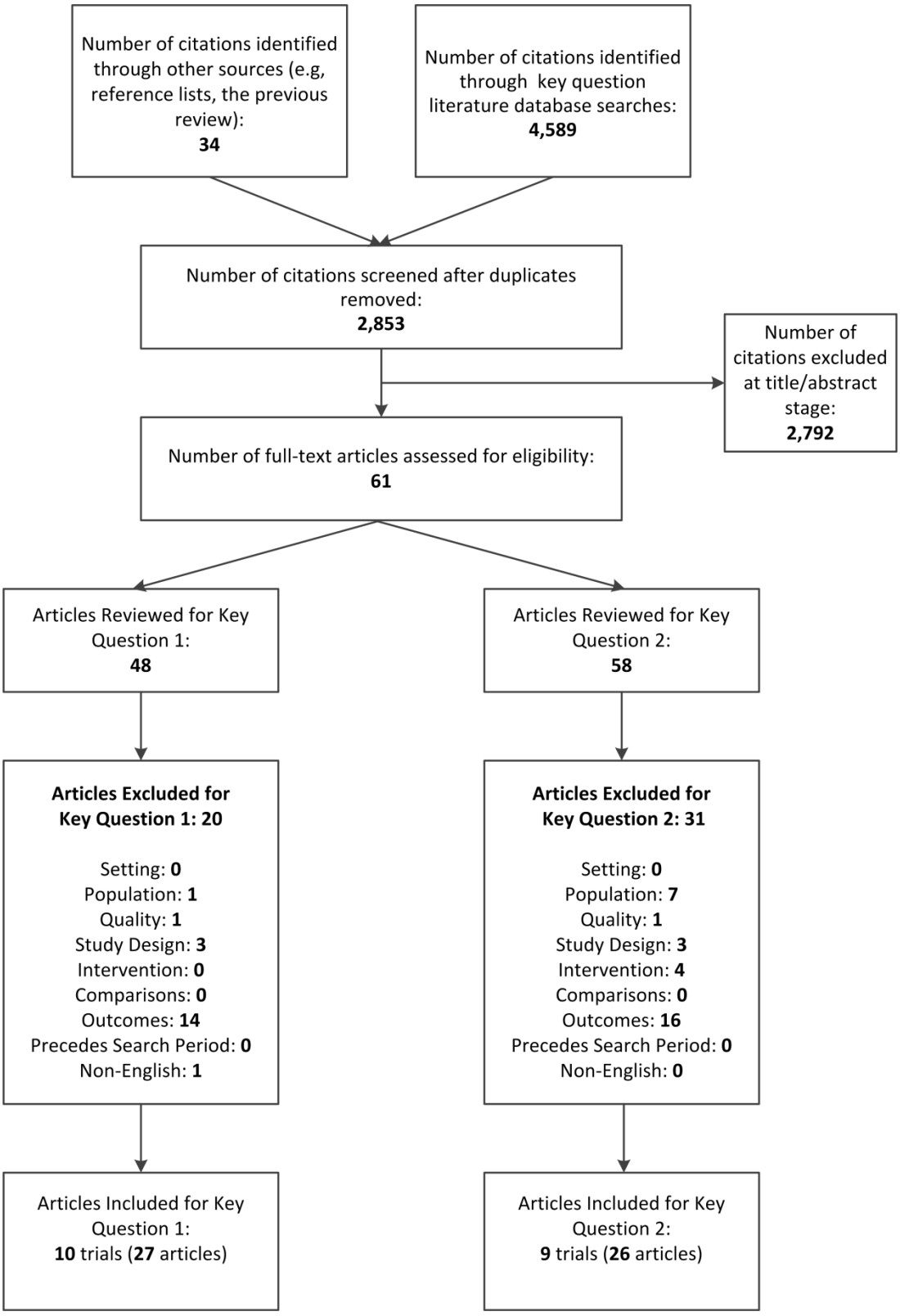
54 coronary disease.ti,ab. (6101)
55 coronary thrombosis.ti,ab. (668)
56 coronary stenosis.ti,ab. (2187)
57 coronary restenosis.ti,ab. (335)
58 myocardial stunning.ti,ab. (752)
59 no-reflow phenomenon.ti,ab. (504)
60 cardiogenic shock.ti,ab. (4318)
61 myocardial reperfusion.ti,ab. (971)
62 vascular disease$.ti,ab. (20623)
63 brain infarction$.ti,ab. (1306)
64 brain stem infarction$.ti,ab. (100)
65 artery infarction$.ti,ab. (413)
66 cerebral infarction$.ti,ab. (6165)
67 lateral medullary syndrome.ti,ab. (76)
68 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 (512035)
69 Aspirin/ (17711)
70 Salicylates/ (2783)
71 aspirin.ti,ab. (22553)
72 acetylsalicylic acid.ti,ab. (3367)
73 salicylate$.ti,ab. (3850)
74 69 or 70 or 71 or 72 or 73 (34949)
75 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (161447)
76 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (466852)
77 Random$.ti,ab. (528273)
78 control groups/ or double-blind method/ or single-blind method/ (91598)
79 clinical trial$.ti,ab. (162642)
80 controlled trial$.ti,ab. (93370)
81 75 or 76 or 77 or 78 or 79 or 80 (966067)
82 68 and 74 and 81 (5025)
83 limit 82 to (english language and yr="2008 -Current") (1603)
84 remove duplicates from 83 (1603)

***Cochrane Central Register of Controlled Clinical Trials (CENTRAL)* Issue 8 of 12, August 2013**

#1 Aspirin:ti,ab,kw from 2008 to 2013, in Trials
#2 "acetylsalicylic acid":ti,ab,kw from 2008 to 2013, in Trials
#3 Salicylate:ti,ab,kw from 2008 to 2013, in Trials*
#4 #1 or #2 or #3 from 2008 to 2013, in Trials

#5 (coronary or angina or myocardial or "cardiac arrest" or "cardiac death" or "heart arrest"):ti,ab,kw from 2008 to 2013, in Trials
#6 (heart near attack):ti,ab,kw from 2008 to 2013, in Trials*
#7 (Cardiovascular next Disease):ti,ab,kw from 2008 to 2013, in Trials*
#8 (Heart next Disease):ti,ab,kw from 2008 to 2013, in Trials*
#9 (vascular next disease):ti,ab,kw from 2008 to 2013, in Trials*
#10 stroke:ti,ab,kw from 2008 to 2013, in Trials
#11 (brain next infarction):ti,ab,kw from 2008 to 2013, in Trials*
#12 ("brain stem" near infarction):ti,ab,kw from 2008 to 2013, in Trials*
#13 "Lateral Medullary Syndrome":ti,ab,kw from 2008 to 2013, in Trials
#14 (Cerebral near infarction):ti,ab,kw from 2008 to 2013, in Trials*
#15 (Cerebrovascular next disease):ti,ab,kw from 2008 to 2013, in Trials*
#16 (Cerebrovascular next disorder):ti,ab,kw from 2008 to 2013, in Trials*
#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 from 2008 to 2013, in Trials
#18 #4 and #17 from 2008 to 2013, in Trials

Appendix B Figure 1. Literature Flow Diagram



Appendix B Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Aim	Primary prevention of cardiovascular disease: MI, stroke, death from MI or stroke, or all-cause mortality	Secondary and tertiary prevention of MI, stroke, death from MI or stroke, or all-cause mortality
Populations	Adults (age ≥40 years) *without* known CVD	Non-human populations; other selected non-generalizable populations; patients with existing CVD diagnosis or history (heart failure, previous stroke, previous MI, transient ischemic attack, angina, or previous bypass or angioplasty); patients with atrial fibrillation; patients with familial hypercholesterolemia; patients with hypercoagulable disorders; children and young adults (age <40 years)
Interventions	Regular oral aspirin use (minimum of 75 mg every other day)	Non-aspirin anti-thrombotic medications; Studies where there is no information on dose; Interventions limited to irregular or occasional use only; Studies in which aspirin is a co-treatment; Nonoral, nontablet forms of aspirin
Comparisons	Placebo or no treatment	Any active substance or intervention (e.g., non-aspirin medication, dietary supplements, dietary change, weight loss)
Outcomes	KQ1: MI (coronary events, sudden death), stroke, death from MI or stroke, all-cause mortality, or quality of life KQ2: Gastrointestinal bleeding, hemorrhagic stroke, or other serious harms (e.g. age-related macular degeneration)	KQ1: intermediate markers of CVD (e.g. calcium scores, intimal thickness, asymptomatic electrocardiography findings); intermediate markers of platelet function or clotting (e.g. in vitro clotting time, platelet aggregation) KQ2: intermediate markers of platelet function or clotting
Study Designs	KQ 1: RCTs, CCT KQ 2: RCTs, CCTs, observational studies (cohort, case-control)	KQ1: Observational studies (case control, case studies, or case series) KQ 2: Case-control, case studies, or case series
Duration	≥1 year exposure to intervention, ≥1 year followup	< 1 year exposure, <1 year followup
Setting	Trials conducted in countries listed as "high" human development on Human Development Index (over .90): Andorra, Argentina, Australia, Austria, Barbados, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Seychelles, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States	
Study Quality	Good & fair quality according to USPSTF criteria	Poor quality according to USPSTF criteria
Language	English	Non-English studies

Abbreviations: CCT = controlled clinical trial; CVD = cardiovascular disease; KQ = Key Question; MI = myocardial infarction; RCT = randomized controlled trial; USPSTF = US Preventive Services Task Force

Appendix B Table 2. Quality Assessment Criteria

Design	USPSTF quality rating criteria[47]	NICE methodology checklists[48]
Randomized controlled trials (RCTs)	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups is randomized • An adequate concealment method is used • Subjects and investigators are kept 'blind' about treatment allocation • The treatment and control groups are similar at the start of the trial • The only difference between groups is the treatment under investigation • All relevant outcomes are measured in a standard, valid and reliable way • What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? • All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis) • Where the study is carried out at more than one site, results are comparable for all sites

Appendix C. Excluded Studies

Exclusion Code	Definition
E1	**Setting** – not in a high GDI country
E2 **E2a** **E2b** **E2c**	**Population** Patients with existing CVD diagnosis or history Patients with a-fib, familial hypercholesterolemia, or hypercoaguable disorders Children or adults <40 years of age
E3	**Study quality**
E4	**Study design** – not an RCT or CCT(KQ1) or observational(KQ2)
E5 **E5a** **E5b** **E5c** **E5d**	**Intervention** Duration <1 year Dose – aspirin dose <75mg QOD, dose NR, or irregular or occasional use Non-oral or non-tablet forms of aspirin Aspirin as a co-treatment
E6	**Comparisons** – Any active substance or intervention
E7 **E7a**	**Outcomes** Composite outcome includes non-eligible endpoints (e.g., angina or revascularization) and there is no separate reporting of individual outcomes
E8	Precedes search period
E9	Non-English

1. Berger JS. Aspirin as preventive therapy in patients with asymptomatic vascular disease. JAMA 2010 Mar 3;303(9):880-2. PMID: 20197537. **KQ1E4**

2. Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. J Myocardial Ischemia 1992(4):27-9. PMID: None. **KQ1E7, KQ2E7**

3. Bytzer P, Pratt S, Elkin E, et al. Burden of upper gastrointestinal symptoms in patients receiving low-dose acetylsalicylic acid for cardiovascular risk management: a prospective observational study. American Journal of Cardiovascular Drugs 2013 Feb;13(1):27-35. PMID: 23315343. **KQ2E5a.**

4. Cook NR, Hebert PR, Manson JE, et al. Self-selected posttrial aspirin use and subsequent cardiovascular disease and mortality in the physicians's health study. Archives of Internal Medicine 2000 Apr 10;160(7):921-8. PMID: 10761956. **KQ1E7, KQ2E7**

5. Cook NR, Cole SR, Hennekens CH. Use of a Marginal Structural Model to Determine the Effect of Aspirin on Cardiovascular Mortality in the Physicians' Health Study. American Journal of Epidemiology 2002 Jun 1;155(11):1045-53. PMID: 12034583. **KQ1E7, KQ2E7**

6. Critical Leg Ischaemia Prevention Study (CLIPS) Group. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. Journal of Internal Medicine 2007;261:276-84. PMID: None. **KQ1E2a, KQ2E2a**

7. de Jong PT. Aspirin and age-related macular degeneration. Ophthalmology 2010;117(6):1279-80. PMID: 20522343. **KQ2E4**

8. de Jong PT, Chakravarthy U, Rahu M, et al. Associations between aspirin use and aging macula disorder: the European Eye Study. Ophthalmology 2012 Jan;119(1):112-8. PMID: 21920607. **KQ2E5**

9. Dorresteijn JA, Visseren FL, Ridker PM, et al. Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects. European Heart Journal 2011 Dec;32(23):2962-9. **KQ1E7, KQ2E7**

10. ETDRS Investigators. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology 1991 May;98(5 Suppl):741-56. **KQ2E7**

11. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA 1992 Sep 9;268(10):1292-300. **KQ2E7**

12. Fasey N, BRENNAN PJ, Meade TW. Thrombosis prevention trial: follow-up study of practical implications. Br J Gen Pract 2002

Mar;52(476):208-9. PMID: 12030663. **KQ1E7, KQ2E7**

13. Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study: 12-month data on blood pressure and tolerability. With special reference to age and gender. Blood Press 1995 Sep;4(5):313-9. PMID: 8535554. **KQ1E7, KQ2E7**

14. Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study: 24-month data on blood pressure and tolerability. Blood Press 1997 Sep;6(5):313-7. PMID: 9360003. **KQ1E7, KQ2E7**

15. Huang ES, Strate LL, Ho WW, et al. A prospective study of aspirin use and the risk of gastrointestinal bleeding in men. PLoS One 2010;5 PMID: 21209949. **KQ2E2a.**

16. Kurth T, Glynn RJ, Walker AM, et al. Inhibition of Clinical Benefits of Aspirin on First Myocardial Infarction by Nonsteroidal Antiinflammatory Drugs. Circulation 2003 Sep 9;108(10):1191-5. PMID: 12939216. **KQ1E7, KQ2E7**

17. Meade TW, WILKES HC, STIRLING Y, et al. Randomized controlled trial of low dose warfarin in the primary prevention of ischaemic heart disease in men at high risk: design and pilot study. European Heart Journal 1988 Aug 1;9(8):836-43. PMID: 3053176. **KQ1E7, KQ2E7**

18. Okada S, Morimoto T, Ogawa H, et al. Differential effect of low-dose aspirin for primary prevention of atherosclerotic events in diabetes management: a subanalysis of the JPAD trial. Diabetes Care 2011 Jun;34(6):1277-83. PMID: 21515838. **KQ1E7, KQ2E7**

19. Rose PW, Watson EK, Jenkins LS. Aspirin for prevention of cancer and cardiovascular disease. British Journal of General Practice 2011 Jun;61(587):412-5. PMID: 21801534. **KQ1E4**

20. RUDNICKA AR, MT-ISA S, Meade TW. Associations of plasma fibrinogen and factor VII clotting activity with coronary heart disease and stroke: prospective cohort study from the screening phase of the Thrombosis Prevention Trial. Journal of Thrombosis and Haemostasis 2006 Nov 1;4(11):2405-10. PMID: 17002654. **KQ1E7, KQ2E7**

21. Saito Y, Morimoto T, Ogawa H, et al. Low-dose aspirin therapy in patients with type 2 diabetes and reduced glomerular filtration rate: subanalysis from the JPAD trial. Diabetes Care 2011 Feb;34(2):280-5. PMID: 21270185. **KQ1E7, KQ2E7**

22. Scheiman JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). Heart 2011 May;97(10):797-802. PMID: 21415072. **KQ2E2a**

23. Scheiman JM, Herlitz J, Veldhuyzen van Zanten SJ, et al. Esomeprazole for prevention and resolution of upper gastrointestinal symptoms in patients treated with low-dose acetylsalicylic acid for cardiovascular protection: the OBERON trial. Journal of Cardiovascular Pharmacology 2013 Mar;61(3):250-7. PMID: 23188121. **KQ2E2a**

24. Shiotani A, Haruma K, Nishi R, et al. Randomized, double-blind, pilot study of geranylgeranylacetone versus placebo in patients taking low-dose enteric-coated aspirin. Low-dose aspirin-induced small bowel damage. Scandinavian Journal of Gastroenterology 2010 Mar;45(3):292-8. PMID: 19968611. **KQ2E5a**

25. Sirois C, Moisan J, Poirier P, et al. Myocardial infarction and gastro-intestinal bleeding risks associated with aspirin use among elderly individuals with type 2 diabetes. Ann Med 2014 May 2 PMID: 24785356. **KQ2E4.**

26. Soejima H, Ogawa H. [Investigation of the effects of low dose aspirin therapy on primary and secondary prevention of cardiovascular disease]. Nihon rinsho Japanese journal of clinical medicine 2010;68:882-6. PMID: 20446587. **KQ1E9**

27. Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding.[Summary for patients in Ann Intern Med. 2009 Mar 17;150(6):I-22; PMID: 19293067]. Annals of Internal Medicine 2009 Mar 17;150(6):379-86. PMID: 19293071. **KQ2E5d**

28. Sugano K, Matsumoto Y, Itabashi T, et al. Lansoprazole for secondary prevention of gastric

or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. Journal of Gastroenterology 2011 Jun;46(6):724-35. PMID: 21499703. **KQ2E2a**

29. Tagliabue L, Dipaola F, Perego F, et al. Aspirin for the primary prevention of cardiovascular diseases. Intern Emerg Med 2012 Aug;7(4):375-9. PMID: 22669555. **KQ1E4, KQ2E4**

30. Taha AS, McCloskey C, Prasad R, et al. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. Lancet 2009 Jul 11;374(9684):119-25. PMID: 19577798. **KQ2E2a**

31. Uemura N, Sugano K, Hiraishi H, et al. Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study. J Gastroenterol 2013 Jun 12 PMID: 23754512. **KQ2E2a**

32. Welin L, Wilhelmsen L, Bjornberg A, et al. Aspirin increases mortality in diabetic patients without cardiovascular disease: a Swedish record linkage study. Pharmacoepidemiology & Drug Safety 2009 Dec;18(12):1143-9. PMID: 19672841. **KQ1E3, KQ2E3**

33. Zanchetti A, Hansson L, Dahlof B, et al. Effects of individual risk factors on the incidence of cardiovascular events in the treated hypertensive patients of the Hypertension Optimal Treatment Study. HOT Study Group. J Hypertens 2001 Jun;19(6):1149-59. PMID: 11403365. **KQ1E7, KQ2E7**

34. Zanchetti A, Hansson L, Menard J, et al. Risk assessment and treatment benefit in intensively treated hypertensive patients of the hypertension Optimal Treatment (HOT) study. J Hypertens 2001 Apr;19(4):819-25. PMID: 11330886. **KQ1E7, KQ2E7**

Appendix D. Ongoing Studies

Ongoing Trial	ASPREE[94]	ACCEPT-D[92]	ASCEND[91]	JPPP[129]	ARRIVE[130]
Location	US and Australia	Italy	UK	Japan	US and Europe
Sample	Healthy men and women age 70 or older	Men and women age 50 or older with diabetes and on a statin or candidate to start statin treatment	Men and women age 40 or older with diabetes	Men and women age 60-85 years with one or more of the following: HTN, hyperlipidemia, or DM	Men and women age 55 or older (males 55 or older with 2 to 4 risk factors; females 60 or older with 3 or more risk factors)
Estimated enrollment	19,000	5,170	15,000	10,000	NR
Aspirin dose	100 mg (enteric-coated), daily	100 mg daily	100 mg daily	100 mg (enteric-coated), daily	100 mg (enteric-coated), daily
Primary endpoint	Death from any cause or incident dementia or persistent physical disability	Composite of CV death, non-fatal MI, non-fatal stroke, and hospital admission for CV causes	Composite of non-fatal MI, non-fatal stroke or vascular death, excluding confirmed cerebral hemorrhage	Composite of CV death, nonfatal cerebral stroke and nonfatal MI	Time to first occurrence of the composite outcome of MI, stroke or cardiovascular death
Length of Followup (Yrs)	5	5	5-7	4	5
Estimated completion date	August 2016	December 2013*	December 2016	Unknown. Enrollment completed June 2007 with 4 years planned F/U*.	May 2015

*Trial authors were contacted regarding preliminary data for these trials, no response was received.

Abbreviations: ACCEPT-D= Aspirin and Simvistatin Combination for Cardiovascular Events Prevention in Trials in Diabetes; ASCEND= A Study of Cardiovascular Events in Diabetes; ASPREE= Aspirin in Reducing Events in the Elderly; ARRIVE= Aspirin to Reduce Risk of Initial Vascular Events; CV= Cardiovascular; DM= Diabetes Mellitus; F/U= Followup; HTN= Hypertension; JPPP= Japanese Primary Prevention Project; mg= milligram; NR= Not Reported; UK= United Kingdom; US= United States

Appendix E Table 1. Recommendations of Other Organizations

		UK CKS-NICE, 2013[38]	UK JBS3, 2014[39]	SIGN, 2013[40]	Europe ESC, 2012[41]	USPSTF, 2009[35]	AHA, 2011[36]	ADA, 2010[37]	Canada, 2008 and 2010[131,132]	WHO, 2007[133]
Subjects without Diabetes	Age (years)	--	--	--	--	Men 45-79, Women 55-79	--	--	<70	--
	10-year Risk	Weak evidence for aspirin in hypertensives over 50 years with >20% CVD risk or with reduced renal function		--	--	(CHD Risk) Men: 45-59 if ≥4%, 60-69 if ≥9%, 70-79 if ≥12% (Stroke Risk) Women: 55-59 if ≥3%, 60-69 if ≥8%, 70-79 if ≥11%	(CVD Risk) ≥6-10%	--	(CHD Risk) ≥20%	(CVD Risk) ≥30%
	Aspirin regimen	Not recommended	Not stated	Not recommended	Not justified	75 mg/d	81 mg/d or 100 mg every other day	--	81 mg/d	75-100 mg/d
Subjects with Diabetes	Age (years)	--	--	--	--	--	--	--	--	--
	10-year Risk	--	--	--	--	Diabetes a risk factor in risk assessment models	--	(CVD Risk) >10%; those at highest risk include most men ≥50, women ≥60 years with additional risk factors	Decision to prescribe should be based on individual clinical judgment	Specific 10-year risk tables
	Aspirin regimen	--	Not recommended	--	Not recommended	--	Not useful in absence of other CVD	75 to 162 mg	--	--

*Adapted from Matthys, 2014[95]

Abbreviations: ADA= American Diabetes Association; AHA= American Heart Association; CKS-NICE= Clinical Knowledge Summaries-National Institute for Health and Care Excellence; ESC= European Society of Cardiology; JBS= Joint British Societies; SIGN= Scottish Intercollegiate Guidelines Network; USPSTF= United States Preventive Services Task Force; WHO= World Health Organization

Appendix E Table 2. Audit of Subgroup Analyses in Included Trials

A *priori* sub-populations from Work Plan	Study is subpopulation- specific	Study reports a priori subgroup analysis	Study reports post hoc subgroup analysis	Study reports subgroup analysis and the specification of the analysis is unclear
Age		JPAD[43] (<65, ≥65) AAA[45] (<62, ≥62) WHS[58] (45-54, 55-64, ≥ 65)		PHS[53] (40-49, 50-59, 60-69, 70-84) POPADAD[44] (<60, ≥60) HOT[60] (<65, ≥65) TPT[66]- 45-49, 50-54, 55-59, 60-64, 65-69
Sex	BMD[57] – Men PHS[53] – Men TPT[54] - Men WHS[58] - Women	JPAD[43] AAA[45]		POPADAD[44] ETDRS[55] HOT[60] PPP[61]
Smoking Status		JPAD[43] (current or past, nonsmoker) WHS[58] (current, past or never)		PHS (never, past, current)
Race/ Ethnicity	JPAD[43] - Japan			
10-yr CVD Risk	TPT[54] – Top 20% risk (by Northwick Park Heart Study algorithm)	WHS[58] (<5%, 5%-9.9%, >=10%)	WHS[58]	HOT[64] (15-20%, >20%) JPAD[71] (age plus presence of risk factors)
Diabetes	JPAD[43] POPADAD[44] ETDRS[55]	WHS[58]	PPP[63] AAA[45] (without DM only)	PHS[53] HOT[62]
ABI	POPADAD[44] (ABI ≤0.99) AAA[45] (ABI ≤0.95)		AAA[45] (≤0.95, ≤0.90, ≤0.85, ≤0.80)	POPADAD[44] (≤.90, 0.91-0.99)
Elevated BP	HOT[64]	JPAD[65] (HTN, no HTN for composite) WHS[58] (by HTN status and BP level; <120/75, 120-129/75-89, 130-139/85-89, ≥140/90)		HOT[64] (SBP ≥180, 160 to <180, <160; DBP ≥107, 104 to <107, <104) JPAD[65] (attained/unattained BP goal, for stroke) PHS[53] (SBP <109, 110-129, 130-149, ≥150; DBP ≤69, 70-79, 80-89, ≥90) TPT[66] (SBP <130, 130-145, >145)
Risk related conditions: Lipid status		JPAD[43] WHS[58]		PHS[53] TPT[54] (<5.9, 5.9-6.7, >6.7 mmol/L)
Risk related conditions: Kidney function			JPAD[43] HOT[64]	
Risk related conditions: Number of risk factors		WHS[58]		

Abbreviations: AAA = Aspiring for Asymptomatic Atherosclerosis Trial; ABI= Ankle Brachial Index; BMD = British Medical Doctor's Study; BP= Blood Pressure; CVD= Cardiovascular Disease; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix E Table 3. Results of Other Recent Meta-Analyses

Author, Year, k	Statistic and Model	Major CV Events	Total MI	Total Stroke	All-cause Mortality	Major Bleeding
Berger, 2011[75]*, k=9*	Risk Ratio (95% CI) Random effects, model not specified	0.90 (0.85, 0.96)	0.86 (0.74, 1.00)	0.94 (0.84, 1.06)	0.94 (0.89, 1.00) p=0.07	1.62 (1.31, 2.00)†
Seshasai, 2012[72]*, k=9*	Odds Ratio (95% CI) Random effects, model not specified, fixed effects were conducted for comparison	0.90 (0.85, 0.96)	0.86 (0.74, 1.01)	0.94 (0.84, 1.06)	0.94 (0.88, 1.00)	1.70 (1.17, 2.46)‡
Raju, 2011[73] *k=9*	Relative Risk (95% CI) DerSimonian-Laird Random effects	0.88 (0.83, 0.94)	0.83 (0.69, 1.00)	0.93 (0.82, 1.05)	0.94 (0.88, 1.00)	1.66 (1.41, 1.95)†
Bartolucci, 2011[74] *k=9*	Odds Ratio (95% CI) Mantel-Haenszel chi-square	0.865 (0.804, 0.930)	0.854 (0.688, 1.061)	0.919 (0.828, 1.021)	0.945 (0.881, 1.014), p=0.115	NR
ATT Collaboration,2009[33]* *k=6*	Rate Ratio (95% CI) IPD meta-analysis	0.82 (0.75, 0.90) p=0.00002	NR	0.95 (0.85, 1.06) p=0.4	0.95 (0.88, 1.02)	1.54 (1.300, 1.82)§

*Individual patient-level meta-analysis

†"Major bleeding" as defined by trial authors, GI bleeding reported separately

‡ "Nontrivial bleeding" defined as "fatal bleeding from any site; cerebrovascular or retinal bleeding; bleeding from hollow viscous; bleeding requiring hospitalization and/or transfusion; or study-defined major bleeding regardless of source"

§Major extra-cranial bleeding, not defined

Abbreviations: ATT = Antithrombotic Trialists; CI = confidence interval; CV = cardiovascular; IPD = individual participant data; MI = myocardial infarction;

Appendix E Table 4. Timeline of Publications of Aspirin for CVD Prevention With a Focus on Sex-Specific Conclusions

Document	Journal and Date Published	Summary/Conclusions
Evidence Synthesis for the USPSTF, 2002[134] SR of five trials; three of which were in men only	*Annals*, January 15, 2002	Sex-specific data reported for only one of two studies (HOT), showing a smaller and non-significant effect for MI in women (unadj RR=0.81 [0.49-1.31]) compared with men (unadj RR=0.58 [0.41-0.81]). Pre-specification of sex subgroups is unclear and no interaction tests were performed. PPP investigators noted that women derive the same level of benefit for CHD reduction as men, but data not reported. No sex differences seen for stroke or all-cause mortality. Authors' conclusions: unclear whether sex modifies the effect of aspirin.
USPSTF Recommendation, 2002[42]	*Annals*, January 15, 2002	The USPSTF made an A recommendation that clinicians should discuss aspirin chemoprevention in patients at high risk for heart disease. The balance of benefits and harms is most favorable in patients with a 5-year risk ≥ 3% for CHD. Sex-specific recommendations were not made.
WHS, 2005[58]	*NEJM*, March 31, 2005	In this large primary prevention trial of women (N=39,876) with a mean follow-up of 10.1 years, aspirin did not reduce the risk of the primary outcome of composite cardiovascular events (adj RR=0.91 [0.80-1.03]); or the secondary outcomes of total MI, fatal or nonfatal MI, fatal stroke, hemorrhagic stroke, or all-cause mortality. Aspirin did reduce secondary outcomes of nonfatal stroke (adj RR=0.81 [0.67-0.97]) and ischemic stroke (adj RR=0.76 [0.63-0.93]). Pre-specified subgroup analysis with interaction testing showed that in women age ≥65 years, MI was reduced (adj RR=0.66 [0.44-0.97]) as well as composite CVD events (adj RR=0.74 [0.59-0.92]).
Berger, 2006[61] MA of six trials, and includes some unpublished sex-specific outcomes from PPP Sex-specific findings driven by WHS, due to sample sizes.	*JAMA*, January 18, 2006	In men and women aspirin reduced the risk of a composite of cardiovascular events (men:k=5;n=44,114; OR=0.86 [0.78-0.94]; women:k=3;N=51,342; OR=0.88 [0.79-0.99]) in trials with mean followup of 3.7-10 years. The effect of aspirin was judged to be different men and women. Interaction tests and multivariate adjustment for other risk factors were not performed. In women, aspirin reduced the risk of total strokes (k=3; N=51,342; OR=0.83 [0.70-0.97]) and ischemic stroke (k=2; N=42,459; OR=0.76 [0.63-0.93]). In men, it reduced the risk of total MI (k=5;N=44,114; OR 0.68 [0.54-0.86]). Aspirin significantly increased the risk of bleeding to a similar degree in men and women. Authors' conclusions: aspirin reduces the risk of a composite of cardiovascular events in men and women; however, this works through different outcomes - a reduction of ischemic stroke in women and MI in men.
Evidence Synthesis for the USPSTF (AHRQ in-house review), 2009[135] WHS and Berger, 2006 MA	*Annals,* March 17, 2009	Authors' conclusions based on findings from WHS and the Berger, 2006 meta-analysis: aspirin reduces the risk of CVD events in men and women without a history of CVD. Men have reduced risk for MI, and women have reduced risk for ischemic strokes. Aspirin does not seem to affect CVD mortality or all-cause mortality.
USPSTF Recommendation, 2009[135]	*Annals*, March 17, 2009	The USPSTF made the following recommendations: • Encourage men age 45 to 79 years to use aspirin when the potential benefit of a reduction in myocardial infarctions outweighs the potential harm of an increase in gastrointestinal hemorrhage. (A recommendation) • Encourage women age 55 to 79 years to use aspirin when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage. (A recommendation) • Evidence is insufficient to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older. (I statement) • Do not encourage aspirin use for cardiovascular disease prevention in women younger than 55 years and in men younger than 45 years. (D recommendation)

Appendix E Table 4. Timeline of Publications of Aspirin for CVD Prevention With a Focus on Sex-Specific Conclusions

Document	Journal and Date Published	Summary/Conclusions
ATT, 2009[33] Individual patient-level data MA of six primary prevention trials (BMD, TPT, WHS, HOT, PPP, PHS)	*Lancet*, May 30, 2009	This patient level MA of the same 6 studies included in Berger, 2006 showed similar statistical trends by sex as assessed by interaction tests (although slightly different outcomes; for men, major coronary event ratio of annual event rates=0.77 [0.67-0.89] and for women, ischemic stroke annual event rates= 0.77[0.59-0.99]); however interactions tests were not statistically significant after adjustment for multiple comparisons. Multivariate adjustment for other risk factors was not performed. Authors' conclusions: in primary prevention, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against an increase in major bleeds.
USPSTF Response to the ATT Collaboration Meta-Analysis, 2009[136]	*USPSTF Website* May 30, 2009	The Task Force responded that combining data on men and women obscures gender-specific benefits, noting that a gender-specific analysis is most appropriate in this case, given the differing epidemiology of cardiovascular disease in men and women. The Task Force cited the heterogeneity of treatment effect, suggesting that a gender-combined analysis is not appropriate for drawing an overall conclusion. The Task Force also noted that the ATT authors use of a combined outcome of "serious vascular event," defined as myocardial infarction (MI), stroke, or death from a vascular cause (including sudden death, pulmonary embolism, and hemorrhage), further obscures interpretation of findings since it combines widely varying entities across a wide spectrum of severity. Such a combined outcome diluted the observed effects of the reduction of MIs in men and reduction of stroke in women. Finally, the USPSTF disagreed with the suitability of subgroup analysis by CHD risk because CHD risk stratification would not capture the potential benefit of reduction in stroke in women.
POPADAD, 2008[44] **JPAD, 2008**[43] **AAA, 2010**[45]	*BMJ, October 16, 2008* *JAMA, November, 2008* *JAMA, March 3, 2010*	Three new trials published since the previous recommendation were all were conducted in special populations (individuals with diabetes, abnormal ABI, or both). JPAD and AAA included pre-specified subgroup analyses for sex subgroups; interaction testing was not performed but these 2 trials reported no significant sex differences for the primary endpoint of all atherosclerotic events (value of p for interaction only reported as not significant). For JPAD, composite of all atherosclerotic events was reported in men as HR 0.74(0.49-1.12) and in women as HR 0.88(0.53-1.44). For AAA, composite endpoint of fatal/nonfatal MI, fatal/nonfatal stroke+ revascularization was reported in men as HR 1.15 (0.86-1.54) and in women as HR 0.92(0.68-1.23).The pre-specification of sex subgroup analyses in POPADAD is unclear and authors performed interaction testing and reported a p of 0.54 for the heterogeneity of treatment effect; there were no sex specific differences for the outcome of CVD composite or CVD mortality.
Berger, 2011[75] MA, nine trials included (all of the same as our review minus ETDRS, thus 6 primary prevention trials, JPAD, POPAD, AAA)	*American Heart Journal*, July, 2011	This MA of nine trials with mean followup ranging from 3.7 to 10 years showed that aspirin primary prevention reduced the composite of major cardiovascular events (nonfatal MI+nonfatal stroke+CVD death) (k=9; N=102,621; RR=0.90 [0.85-0.96]) but did not reduce total MI, total stroke, ischemic stroke, hemorrhagic stroke or ACM. In a meta-regression, there was no relationship between sex and the effect of aspirin. Authors' conclusions: benefit of aspirin chemoprevention is offset by risk.

Abbreviations: AAA= Aspiring for Asymptomatic Atherosclerosis Trial; ABI= Ankle Brachial Index; ACM= All-Cause Mortality; adj= adjusted; AHRQ= Agency for Healthcare Research and Quality; ATT= Antithrombotic Trialists; BMD= British Medical Doctors Trial; BMJ= British Medical Journal; CHD= Coronary Heart Disease; CVD= Cardiovascular Disease; ETDRS= Early Treatment for Diabetic Retinopathy Study; HOT= Hypertension Optimal Treatment Trial; HR= Hazard Ratio; JAMA= Journal of the American Medical Association; JPAD= Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; k= number of trials; MA= Meta-Analysis; MI= Myocardial Infarction; N= population; n= trial population; NEJM= New England Journal of Medicine; OR= Odds Ratio; PHS= Physician's Health Study; POPADAD= Prevention of Progression of Arterial Disease and Diabetes; PPP= Primary Prevention Project; RR= Relative Risk; SR= Systematic Review; TPT= Thrombosis Prevention Trial; unadj= Unadjusted; USPSTF= United States Preventive Services Task Force; WHS= Women's Health Study

Appendix E Table 5. Availability of Risk Assessment Calculators

Outcome	US-based derivation cohort	Major CVD/CHD/Stroke Risk Assessment Tools*	Externally Validated	Externally Validated in US Population
CVD	*Yes*	Framingham-Anderson, 1991[16,25] Reynolds – Women, 2007[19] Framingham-D'Agostino, 2008[6] Reynolds – Men, 2008[20] ACC/AHA Pooled Cohort Equation, 2013[14]	Framingham-Anderson, 1991[16,25] ACC/AHA Pooled Cohort Equation, 2013[14]	Framingham-Anderson, 1991[16,25]† ACC/AHA Pooled Cohort Equation, 2013[14]
	No	SCORE, 2003[18] ASSIGN, 2007[124]	SCORE, 2003[18] ASSIGN, 2007[124]	
CHD	*Yes*	Framingham-Anderson, 1991[16,25] Framingham-Wilson, 1998‡[8] Framingham-ATP III, 2002[15] ARIC, 2003[17]	Framingham-Anderson, 1991[16,25] Framingham-Wilson, 1998‡[8] Framingham-ATP III, 2002[15]	Framingham-Anderson, 1991[16,25] Framingham-Wilson, 1998‡[8] Framingham-ATP III, 2002[15]
	No	PROCAM, 2002[22] QRISK2, 2008[21]	PROCAM, 2002[22]	
Stroke	*Yes*	Framingham-Anderson, 1991[16,25] Framingham-Wolf, 1991†[126,127]	Framingham-Anderson, 1991[16,25] Framingham-Wolf, 1991†[126,127]	
	No			

*As identified by SRs of risk assessment tools[23,101-103]; does not include tools exclusive to patients with diabetes (DARTS, UKPDS, ARIC-Diabetes, Cardiff, Royal College of Physicians of Edinburgh)
†Included US participants from LIFE study but available only as poster presentation; data not published
‡Cited in 2009 USPSTF aspirin recommendation[35]

Abbreviations: ACC/AHA= American College of Cardiology/American Heart Association; ARIC= Atherosclerosis Risk in Communities; ASCVD= Atherosclerotic Cardiovascular Disease; CHD= Coronary Heart Disease; CVD= Cardiovascular Disease; SCORE= Systematic Coronary Risk Evaluation