CLINICAL RESEARCH STUDY

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A Meta-Analysis of Aspirin for the Primary Prevention of Cardiovascular Diseases in the Context of Contemporary Preventive Strategies

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ABSTRACT

BACKGROUND: The role of aspirin for primary prevention of cardiovascular diseases remains controversial, particularly in the context of contemporary aggressive preventive strategies.

METHODS: Relevant randomized clinical trials were included, and risk ratios (RRs) were calculated using random-effects models. Additional moderator analyses were performed to compare the pooled treatment effects from recent trials (those reported after the guidelines of the National Cholesterol Education Program Third Adult Treatment Panel were published in 2001; thus, conducted on the background of contemporary preventive strategies) to the results of older trials.

RESULTS: Data from 14 randomized controlled trials involving 164,751 patients were included. Aspirin use decreased myocardial infarction risk by 16% compared with placebo (RR 0.84; 95% confidence interval [CI], 0.75-0.94); however, in the moderator analyses, aspirin was not associated with a decreased risk of myocardial infarction in recent trials, but was in older trials (*P*-interaction = .02). Overall, aspirin use significantly increased the occurrence of major bleeding (RR 1.49; 95% CI, 1.32-1.69) and hemorrhagic stroke (RR 1.25; 95% CI, 1.01-1.54). In moderator analyses, the risk of major bleeding (*P*-interaction = .12) or hemorrhagic stroke (*P*-interaction = .44) with aspirin was not significantly different between the older and new trials. Differences between aspirin and placebo in the risks for all-cause stroke, cardiac death, and all-cause mortality were not found.

CONCLUSIONS: In the context of contemporary primary prevention guidelines, the effect of aspirin on myocardial infarction risk was significantly attenuated, whereas its major bleeding and hemorrhagic stroke complications were retained. Therefore, in contemporary practice, routine use of aspirin for the primary prevention of cardiovascular events may have a net harmful effect.

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KEYWORDS: Aspirin; Cardiovascular diseases; Primary prevention

INTRODUCTION

In patients with known cardiovascular diseases, aspirin is the cornerstone therapy based on robust evidence that it provides a net benefit in secondary prevention.[1,2] However, in primary prevention, its net balance between benefit and harm is unclear, given the most current evidence. Current guidelines also conflict, some recommending aspirin for primary prevention, and others not.[1,3–5] Individual randomized clinical trials (RCTs) have reached conflicting conclusions,[6–16] but meta-analyses of those RCTs suggest that aspirin is effective in the primary prevention of cardiovascular diseases, a result predominantly driven by a small decrease in the risk of myocardial infarction.[17–19] Prior meta-analyses have been criticized because they included older trials that enrolled patient populations with higher smoking rates and lower use of risk-

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modifying medications such as antihypertensive agents and statins.[17,20,21]

Since those trials, major advances have been made in cardiovascular diseases prevention strategies, including statins for primary prevention.[22–24] Following some early RCTs supporting the use of statins for primary prevention,[22,23] the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) published clinical guidelines in 2001, recommending intensive cholesterol-lowering therapy in clinical practice.[25] Those guidelines led to a significant increase in statin use among US adults as early as 2003, resulting in a substantive improvement in population low-density lipoprotein levels.[26] Therefore, it is unclear whether aspirin is effective for primary prevention of cardiovascular events in contemporary clinical practice. Recent RCTs have investigated the current role of aspirin in primary prevention on the background of contemporary preventive strategies.[27–30] Therefore, an updated meta-analysis of RCTs was performed to evaluate the safety and efficacy of aspirin for the primary prevention of cardiovascular diseases. Additionally, a moderator analysis was performed using data from only those trials reported after the publication of the NCEP-ATP III guidelines to investigate the safety and efficacy of aspirin for primary prevention of cardiovascular disease in the context of contemporary preventive strategies.

CLINICAL SIGNIFICANCE

- For primary prevention, aspirin decreases the risk of myocardial infarction at the expense of increased risks for major bleeding and hemorrhagic stroke.
- However, with contemporary aggressive preventive strategies, the effect of aspirin on myocardial infarction risk seems to be significantly attenuated, whereas its harmful effects on bleeding remain.
- Based on current evidence, routine aspirin use for the primary prevention of cardiovascular diseases may have a net harmful effect.

METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses.[31]

Data Sources and Searches

Computerized literature searches of the PubMed, Embase, and Cochrane databases, and clinical trial registries were conducted (without language restrictions) to locate relevant studies, and relevant articles were cross-referenced. Searches were performed using various combinations of the following terms: "aspirin," "cardiovascular disease," "cardiovascular events," "primary," "prevention," and "clinical trial."

Study Selection

Randomized clinical trials were included if patients without established cardiovascular disease were enrolled and aspirin therapy was compared with placebo or no therapy for the prevention of cardiovascular diseases. No restrictions based on study design, follow-up, or language were applied. Two independent reviewers screened the studies at the title and abstract level, and full-text articles were retrieved if inclusion criteria were met.

Data Extraction and Study Quality

Two investigators independently extracted data pertaining to study characteristics, design, and outcomes. The efficacy endpoints were myocardial infarction, all-cause stroke, ischemic stroke, cardiovascular mortality, and all-cause mortality. The safety outcomes were major bleeding and hemorrhagic stroke. Individual study definitions were used for the endpoints. The potential risk of bias in each RCT was appraised using Cochrane Collaboration guidelines (random sequence generation and random allocation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; and selective outcome reporting bias).[32]

Data Synthesis and Analysis

A standard pairwise meta-analysis was performed using the Comprehensive Meta-Analysis system, version 3 (Comprehensive Meta-Analysis; Biostat Inc., Englewood, NJ). Pooled risk ratios (RRs) were calculated using random-effects models because this is the most conservative methodology to account for between-trial heterogeneity. To evaluate whether the efficacy of aspirin is modified by contemporary preventive strategies, additional moderator analyses were performed to compare the pooled treatment effects from recent trials (reported after publication of the NCEP-ATP III guidelines) with the results of older trials. Heterogeneity across trials was evaluated using the Cochran Q test and the Higgins I^2 test.[33] When heterogeneity was discovered, a sensitivity analysis was performed by excluding one study at a time and evaluating the impact on the summary results.[34]

RESULTS

Study Selection and Patient Population

Fourteen RCTs including 164,751 patients (48% male) satisfied the inclusion criteria.[6–16,27–30] The search flow diagram is shown in Supplementary Figure 1 (Appendix, available online), and the bias assessment for each RCT is shown in Supplementary Figure 2 (Appendix, available online). The majority of these studies were high-quality trials based on Cochrane Collaboration guidelines (Supplementary Figure 2). Supplementary Table 1 (Appendix, available online) shows the inclusion and exclusion criteria for each trial.

The Table shows the basic characteristics of each individual trial. Four studies, the British Male Doctors Trial (BMD), the

Table Baseline Characteristics of Included Trials

Trial (Publication Year)	Group Size, n		Age, Mean (SD), Years		Mean Follow-Up, Years	Male, n (%)		DM, n (%)		HTN, n (%)		Aspirin Dose, mg*
	Aspirin	Placebo	Aspirin	Placebo		Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	
BMD (1998)	3429	1710	NR	NR	6.0	3429 (100)	1710 (100)	69 (2.0)	32 (1.9)	349 (10.2)	159 (9.3)	500
PHS (1989)	11,037	11,034	NR	NR	5.2	11 037 (100)	11,034 (100)	275 (2.5)	258 (2.3)	NR	NR	325
ETDRS (1992)	1856	1855	NR	NR	5.0	1031 (55.5)	1065 (57.4)	1856 (100)	1855 (100)	840 (45.3)	806 (43.4)	650
TPT (1998)	1268	1272	57.7 (6.7)	57.3 (6.6)	6.8‡	1268 (100)	1272 (100)	NR	NR	NR	NR	75
HOT (1998)	9399	9391	61.5 (7.5)	61.5 (7.5)†	3.8	4981 (53)†	4977 (53)†	752 (8.0)†	751 (8.0)†	9399 (100)	9391 (100)	75
PPP (2001)	2226	2269	64.5 (7.7)	64.3 (7.6)	3.6	949 (43.0)	963 (42.0)	377 (17.0)	365 (16.0)	1527 (69.0)	1538 (68.0)	100
WHS (2005)	19,934	19,942	54.6 (7.0)	54.6 (7.0)	10.1	0 (0.0)	0 (0.0)	538 (2.7)	499 (2.5)	5183 (26.0)	5125 (25.7)	100
JPAD (2008)	1262	1277	65.0 (10.0)	64.0 (10.0)	4.3‡	706 (56.0)	681 (53.0)	1262 (100)	1277 (100)	742 (59)	731 (57)	81-100
POPADAD (2008)	318	318	60.0 (10.1)	60.1 (9.7)	6.7‡	135 (42.5)	138 (43.4)	135 (100)	138 (100)	NR	NR	300
AAAT (2010)	1675	1675	62.2 (6.7)	61.7 (6.6)	8.2	481 (29.0)	473 (28.0)	45 (3.0)	43 (3.0)	NR	NR	100
JPPP (2014)	7220	7244	70.6 (6.2)	70.5 (6.2)	5.0‡	3055 (42.3)	3068 (42.4)	2445 (33.9)	2458 (33.9)	6144 (84.9)	6145 (84.8)	100
ARRIVE (2018)	6270	6276	63.9 (7.1)	63.9 (7.1)	5.0	4419 (70.5)	4419 (70.4)	0 (0.0)	0 (0.0)	3916 (62.5)	3950 (62.9)	100
ASCEND (2018)	7740	7740	63.2 (9.2)	63.3 (9.2)	7.4	4843 (62.6)	4841 (62.5)	7740 (100)	7740 (100)	4766 (61.6)	4767 (61.6)	100
ASPREE (2018)	9525	9589	NR	NR	4.7‡	4152 (44.0)	4179 (44.0)	1027 (11.0)	1030 (11.0)	7065 (74.0)	7148 (75.0)	100

AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle–brachial index; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = The Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors Trial; CVD = cardiovascular disease; DM = diabetes mellitus; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; HTN = Hypertension; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; 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; RCT = randomized controlled trial; SD = standard deviation; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

*Daily dose except in PHS (dosed every other day).

†For the entire study population; subgroup data not reported.

‡Median.

Primary Prevention Project, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes, and the Japanese Primary Prevention Project were open-label trials in which aspirin was compared with no therapy (no placebo).[6,10,12,15] The remainder were double-blind, placebo-controlled trials. These trials included a broad spectrum of patients. Three trials, the BMD, the Physician's Health Study (PHS), and the Thrombosis Prevention Trial exclusively enrolled male patients.[6,7,16] The Women's Health Study exclusively enrolled female patients.[11] Three trials, the BMD, the PHS, and the Women's Health Study exclusively enrolled health professionals.[6,7,11] Four trials, the Early Treatment Diabetic Retinopathy, Thrombosis Prevention Trial, Prevention of Progression of Arterial Disease and Diabetes, and A Study of Cardiovascular Events in Diabetes were conducted using only diabetic patients.[8,13,16,28] The mean duration of follow-up ranged from 3.8 years to 10.1 years, primarily around 5 years. The Aspirin in Reducing Events in the Elderly trial exclusively enrolled older patients (aged more than 65 years).[29,30] Mean age ranged from 54.6 years to 70.5 years in all other trials. The majority of trial participants were from the United States and United Kingdom, but 2 trials exclusively used Japanese patients.[12,15] The aspirin dose was 75 to 500 mg daily, but was typically 100 mg.

Efficacy Outcomes

Myocardial infarction. Myocardial infarction occurred in 2.1% of those in the aspirin group, compared with 2.3% in the placebo group. Aspirin use decreased myocardial infarction risk by 16% (RR 0.84; 95% CI, 0.75-0.94) compared

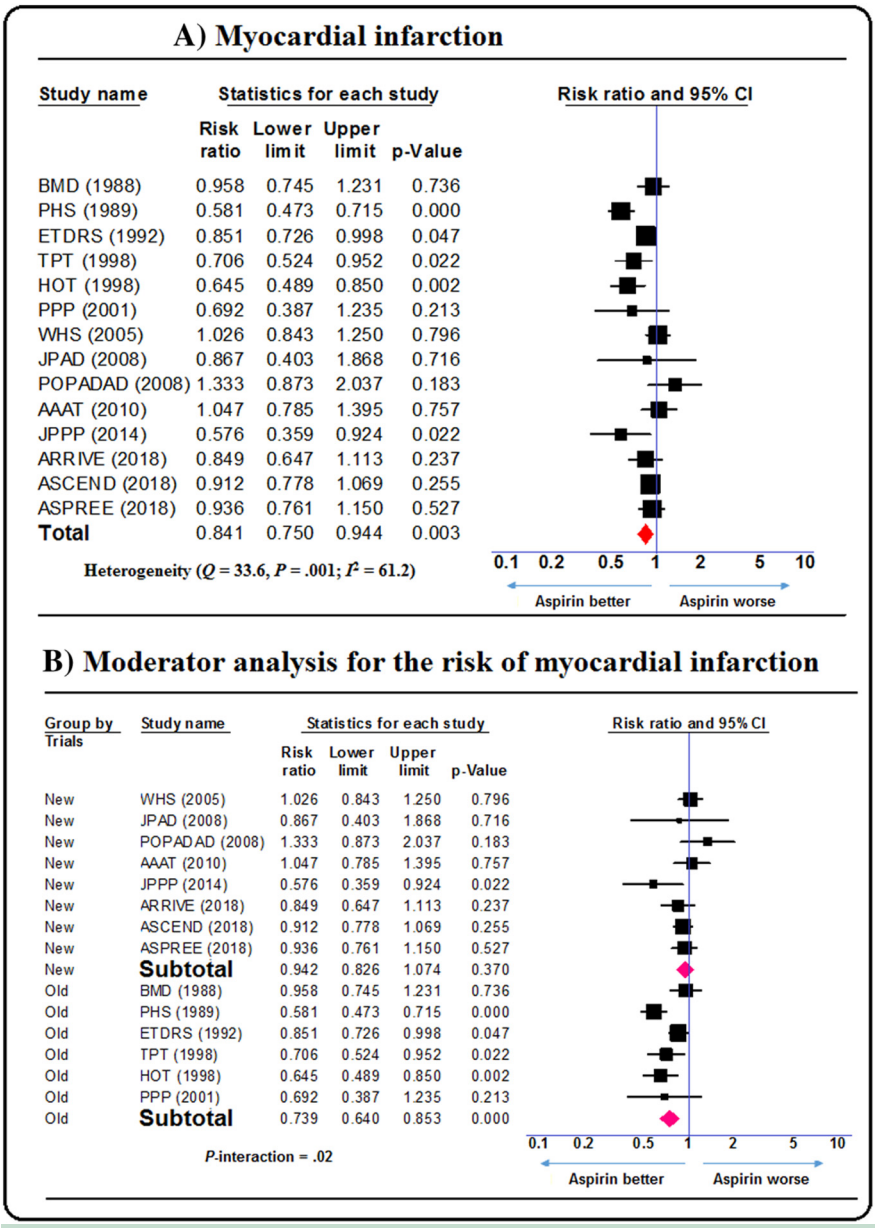

Figure 1 Myocardial infarction. **(A)** Individual and pooled risk ratios (RRs) for myocardial infarction. **(B)** Moderator analysis with separate pooled estimates for the risk of myocardial infarction in recent trials vs older trials. The RR estimate from each study is indicated with a square. The size of the square represents the weight of the corresponding study in the meta-analysis. CI = confidence interval; MI = myocardial infarction; RR = risk ratio. Study names are as in the Table.

with placebo (Figure 1A). However, moderate heterogeneity was found between trials ($Q = 33.6$, $P = .001$; $I^2 = 61.2$). A sensitivity analysis suggests that the heterogeneity originated from the PHS trial.[7] During sensitivity analyses, removing the PHS trial eliminated heterogeneity without affecting summary results. On the other hand, removing any other study did not eliminate heterogeneity.

Among the trials included in this meta-analysis, 8 were reported after publication of the NCEP-ATP III guidelines. Moderator analysis, including data from only the 8 most recent trials, showed that aspirin did not decrease myocardial infarction risk (RR 0.94; 95% CI, 0.83-1.07; Figure 1B). On the other hand, when using data that include the 6 older trials, the protective effect of aspirin on myocardial infarction was more robust (RR 0.74; 95% CI, 0.64-0.85; Figure 1B). The *P* value for interaction was .02.

Cerebrovascular events. All-cause stroke occurred in 1.7% of those in the aspirin group, compared with 1.8% in the placebo group. Differences in the risk for all-cause stroke between the 2 groups were insignificant (RR 0.95; 95% CI, 0.87-1.04; Figure 2A). Statistically significant heterogeneity was not found between the trials for a stroke outcome.

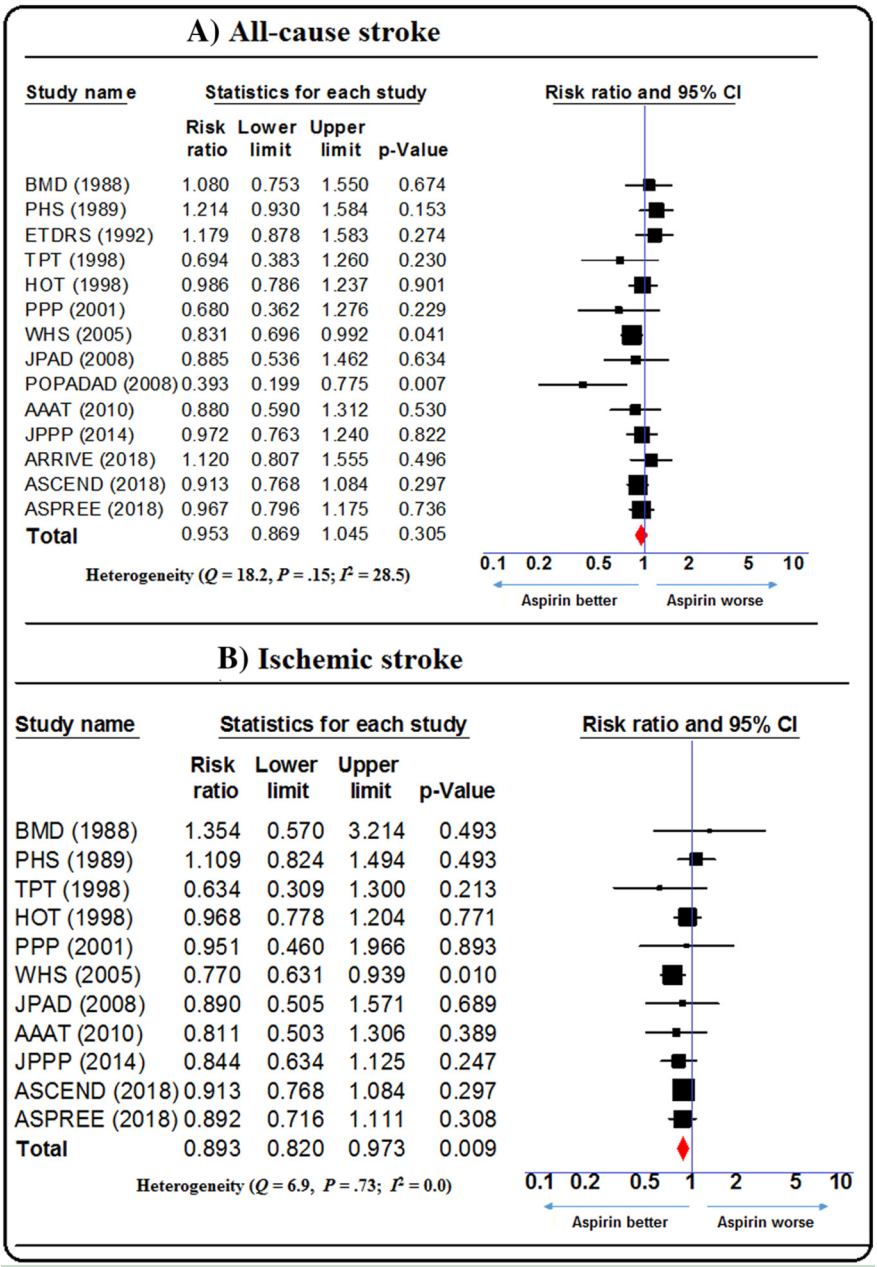

Figure 2 Cerebrovascular events. Individual and pooled risk ratio (RRs) for **(A)** all-cause stroke and **(B)** ischemic stroke. The RR estimate from each study is indicated with a square. The size of the square represents the weight of the corresponding study in the meta-analysis. Study names are as in the Table.

Data for ischemic stroke were available from 11 trials. Aspirin use decreased ischemic stroke risk by 11% (RR 0.89; 95% CI, 0.82-0.97) compared with placebo (Figure 2B). Statistically significant heterogeneity between trials was not found. In the moderator analyses, no differences were found between the older and newer trials for the risks of all-cause stroke *(P*-interaction = .12) or ischemic stroke (*P*-interaction = .12).

Mortality. All-cause mortality was 4.7%, and cardiovascular mortality was 1.5% in the aspirin group, compared with 4.8% and 1.5%, respectively, in the placebo group. Aspirin did not significantly decrease all-cause mortality (RR 0.96; 95% CI, 0.92-1.01) or cardiovascular mortality (RR 0.93; 95% CI, 0.86-1.00) compared with placebo (Figure 3). Statistically significant heterogeneity between trials was not found for these outcomes. In addition, in the moderator analyses, the effects of aspirin on all-cause mortality *(P*-interaction = .19) and cardiac mortality *(P*-interaction = .77) were not significantly different between the older and recent trials.

Safety Outcomes

Major bleeding. Major bleeding rates were reported from 11 trials. Major bleeding occurred in 1.5% in the aspirin group, compared with 1.1% in the placebo group. Aspirin use increased major bleeding risk by 49% (RR 1.49; 95%

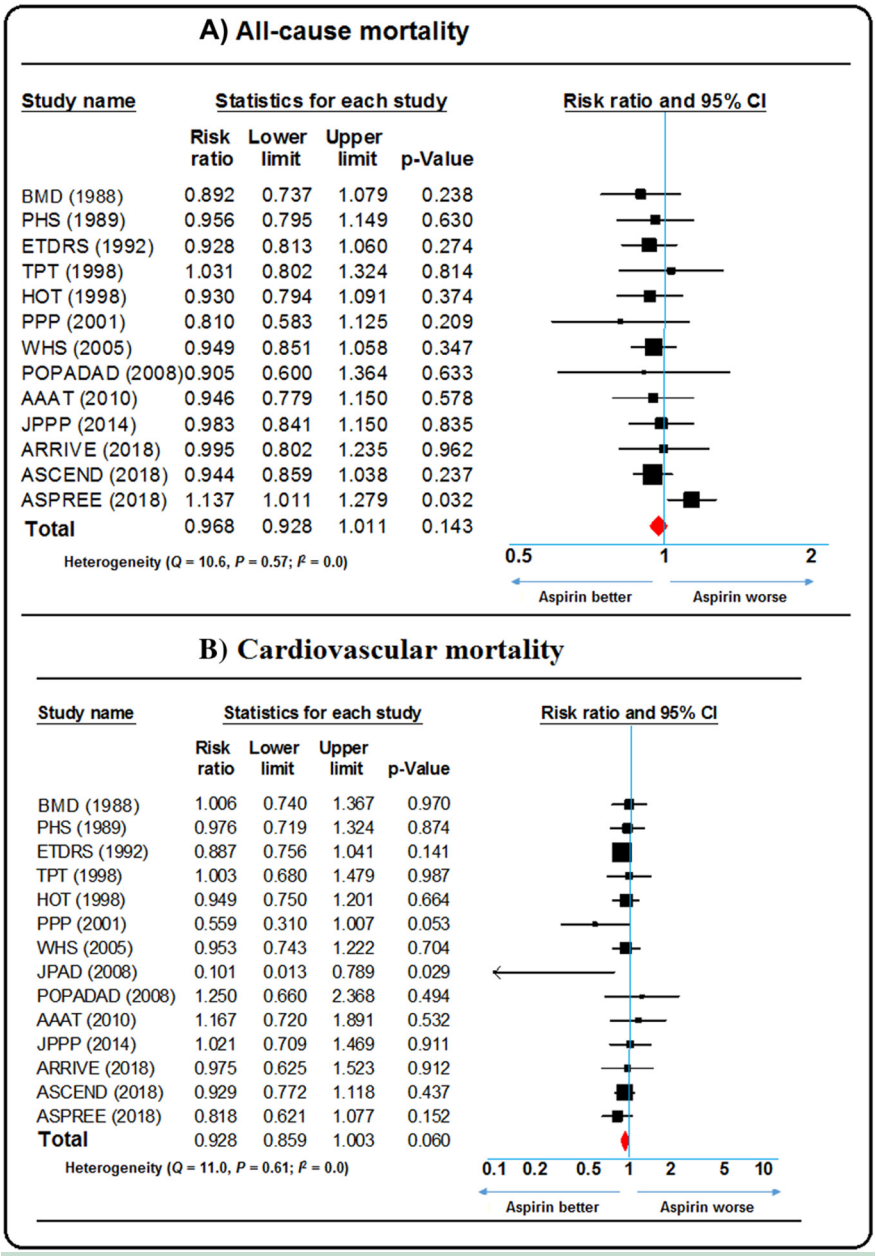

Figure 3 Mortality. Individual and pooled risk ratio (RRs) for **(A)** all-cause mortality and **(B)** cardiovascular mortality. The RR estimate from each study is indicated with a square. The size of the square represents the weight of the corresponding study in the meta-analysis. CI = confidence interval; CV = cardiovascular; RR = risk ratio. Study names are as in the Table.

CI, 1.32-1.69) compared with placebo (Figure 4A). Statistically significant heterogeneity between trials was not found. In the moderator analyses, the increased risk of major bleeding with aspirin use was not significantly different in recent trials than in older trials (*P*-interaction = .12) (Figure 4B).

Hemorrhagic stroke. Data describing hemorrhagic stroke was available from 13 trials. Aspirin significantly increased hemorrhagic stroke risk by 25% (RR 1.25; 95% CI, 1.02-1.51) compared with placebo (Figure 4C). Statistically significant heterogeneity between trials was not found. Again, in the moderator analyses, no differences were found between the older and new trials for the risk of hemorrhagic stroke (*P*-interaction = .44).

DISCUSSION

In this study of 164,751 patients enrolled in 14 RCTs, we compared the efficacy and safety of aspirin use for the primary prevention of cardiovascular diseases. We found that aspirin use in patients without known cardiovascular diseases decreased the risk of myocardial infarction by 16% at the expense of increased risks for major bleeding and hemorrhagic stroke (49%

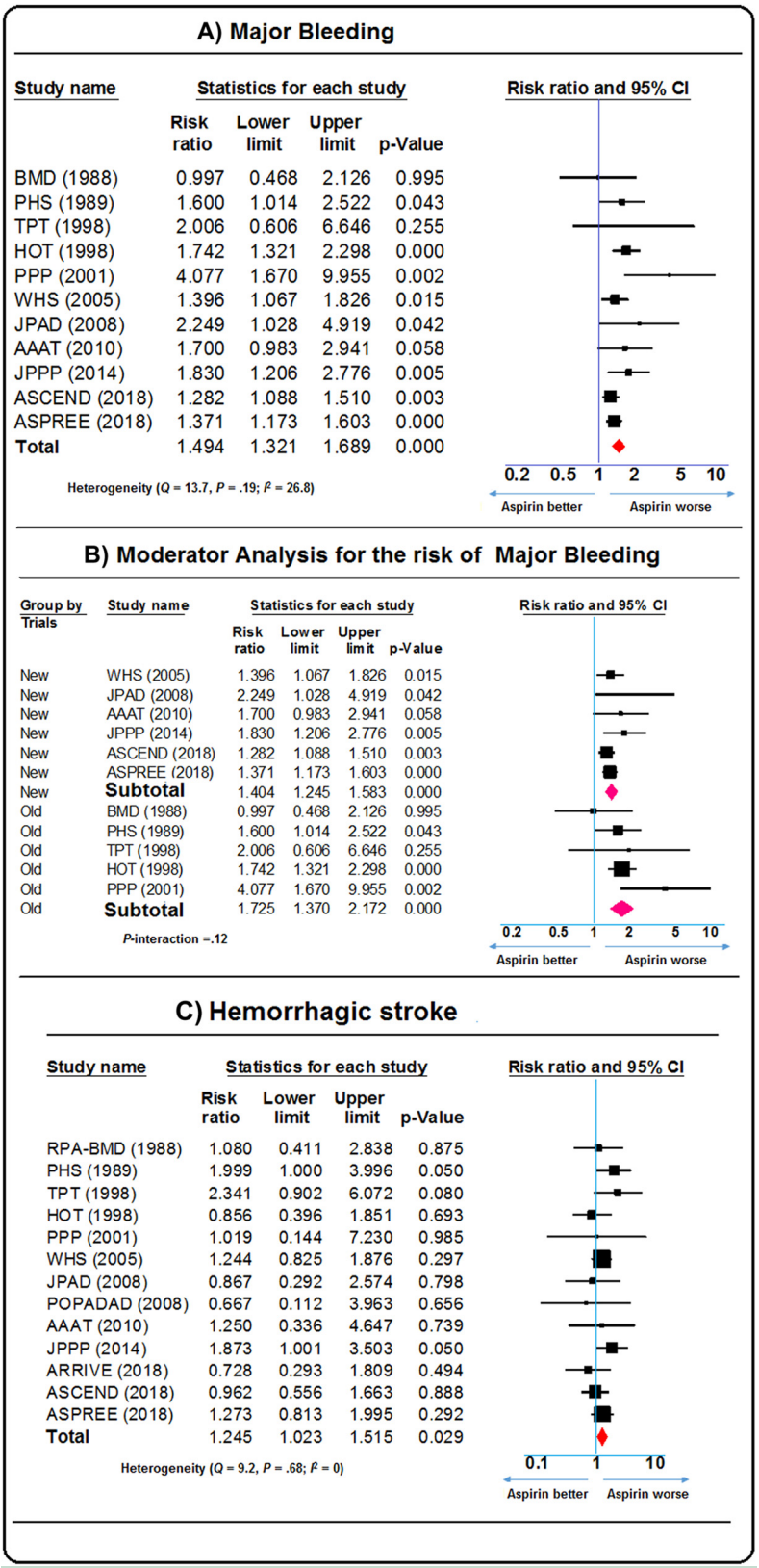

Figure 4 Safety outcomes. **(A)** Individual and pooled risk ratios (RRs) for major bleeding. **(B)** Moderator analysis with separate pooled estimates for the risk of major bleeding in recent trials vs older trials. **(C)** Individual and pooled RRs for hemorrhagic stroke. The RR estimate from each study is indicated with a square. The size of the square represents the weight of the corresponding study in the meta-analysis. Study names are as in the Table.

and 25%, respectively). The risks for all-cause stroke, cardiovascular mortality, and all-cause mortality were not affected. Furthermore, it seems that with aggressive contemporary preventive strategies, aspirin might not even decrease the risk of myocardial infarction, but its harmful effects on bleeding remain.

Current evidence of the net benefit of aspirin therapy for patients with established cardiovascular diseases is robust.[2,20,35] Thus, all guidelines recommend aspirin therapy for secondary prevention.[1,36] However, current evidence and guideline recommendations about the net benefit of aspirin in primary prevention conflict.[3] The 2016 United States Preventive Services Task Force recommends initiating low-dose aspirin use for the primary prevention of cardiovascular diseases in adults aged 50 to 59 years who have a 10% or greater 10-year cardiovascular risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.[3] The decision to initiate low-dose aspirin use for the primary prevention of cardiovascular diseases in adults aged 60 to 69 years who have a 10% or greater 10-year cardiovascular diseases risk should be an individual decision. For patients <50 years of age or older than 70 years, aspirin is not recommended. Similarly, the 2012 guidelines of the American College of Chest Physicians suggest low-dose aspirin (75-100 mg/d) for the primary prevention of cardiovascular diseases in patients aged more than 50 years.[1] On the other hand, the 2016 European Society of Cardiology guidelines recommend against the routine use of aspirin for primary prevention of cardiovascular diseases.[4] Similarly, the US Food and Drug Administration does not recommend aspirin use for the primary prevention of myocardial infarction.[37] According to the 2019 American College of Cardiology/American Heart Association guidelines, use of aspirin for the primary prevention of cardiovascular diseases in patients aged more than 70 years or at high risk of bleeding is harmful (Class III indication).[5] Low-dose aspirin might be considered (Class IIb indication) for the primary prevention of cardiovascular diseases in select high-risk patients aged 40-70 years who are not at increased bleeding risk.[5]

The first 2 RCTs evaluating the role of aspirin in primary prevention were conducted using male physicians in the United States and United Kingdom, and reached disparate conclusions.[6,7] Since then, 12 additional RCTs have been reported.[8–16,27–30] The primary outcomes of interest in these trials varied, as did their conclusions: some showed a benefit, but others showed potential harm. Similarly, meta-analyses reached conflicting conclusions.[17,18,20] A 2016 meta-analysis by the US Preventive Services Task Force including 11 trials concluded that aspirin does provide a modest benefit for the primary prevention of cardiovascular diseases, driven by lower nonfatal myocardial infarction and nonfatal stroke events.[17] On the other hand, the Antithrombotic Trialists' (ATT's) collaborative meta-analysis of individual participant data from 6 RCTs concluded that, for the primary prevention of cardiovascular diseases, aspirin is of uncertain net value.[20] Since those meta-analyses, 3 new RCTs (conducted on a background of aggressive contemporary preventive strategies) have been reported, rendering the older ones arguably outdated.[27–30]

Our meta-analysis, by including these new RCTs, employs the largest sample size ever reported and shows that aspirin therapy decreases myocardial infarction risk at the expense of increased risks for major bleeding and hemorrhagic stroke without affecting all-cause or cardiovascular mortality. However, the absolute benefit was small because the absolute reduction of myocardial infarction risk was only 0.2%. In addition, moderate heterogeneity was found, driven by the PHS.[7] Several characteristics of the PHS were different compared with others: participants were male patients only, were of higher social economic/educational status (US physicians), received higher aspirin doses, and on alternate days. In addition, it was terminated prematurely (3 years ahead of schedule). Finally, it was one of the oldest studies, performed when risk-modifying medications such as statins were not used. Indeed, moderator analyses using data from the 8 recent trials (conducted on backgrounds of aggressive contemporary preventive strategies) showed that aspirin does not decrease myocardial infarction risk. Therefore, in our meta-analysis and in previous meta-analyses, lower rates of myocardial infarction with aspirin were driven by those older trials when statins and other aggressive measures were not routinely used for primary prevention. In contemporary practice where risk-modifying medications (eg, statins and antihypertensive medications) and other primary prevention measures (eg, smoking cessation counseling) are aggressively used, aspirin therapy may not have a role. This issue has previously been examined by the ATT collaborators in their hypothetical primary and secondary prevention risk models, pointing out that in most of the older trials, aspirin was prescribed to patients not receiving statin therapy, which would have reduced both myocardial infarction and ischemic stroke risks.[20] By adding statins or other measures, if ischemic event risks are reduced by half, adding aspirin would be less beneficial in preventing ischemic events while maintaining bleeding risk. Thus, based on our analysis and the prevention models of the ATT collaborators, aspirin use for primary prevention in contemporary practice might have a net harmful effect.

Limitations

This meta-analysis has several limitations. First, we did not have access to individual participant data; therefore, the data we analyzed were combined from various studies, each with its own protocol, inclusion/exclusion criteria, primary endpoints of interest, and definitions. Specifically, the definition of major bleeding events and cardiovascular mortality (Supplementary Table 2, Appendix, available online) varied across trials. In addition, aspirin dose, follow-up duration, baseline characteristics, cardiovascular risks, and comorbidity varied across trials. Furthermore, some trials were performed decades ago, and since then, major advances have been made in the field of cardiovascular diseases prevention. Therefore, these

findings might not be generalizable to contemporary clinical practice. However, additional sensitivity analysis was performed using data from the recent trials. Finally, a small number of studies in a meta-analysis (as in our subgroup analysis) can introduce bias in the heterogeneity test.[38] Despite these limitations, this is the largest meta-analysis addressing this topic, and it will assist physicians in deciding the net risk/benefit of aspirin therapy for the primary prevention of cardiovascular diseases.

CONCLUSIONS

Based on this meta-analysis, in patients without known cardiovascular diseases, aspirin decreases the risk of myocardial infarction by 16%, at the expense of increasing risks for major bleeding and hemorrhagic stroke (49% and 25%, respectively) without affecting the risks for all-cause stroke, all-cause mortality, or cardiovascular mortality. Furthermore, in contemporary practice, where statins and other measures are used aggressively for primary prevention, aspirin might not even decrease myocardial risk. Therefore, in contemporary practice, the routine use of aspirin for primary prevention may have a net harmful effect, as it will increase hemorrhagic complications without decreasing cardiovascular diseases.

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APPENDIX ASUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2019.05.015.