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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Aspirin With or Without Statin in Individuals Without Atherosclerotic Cardiovascular Disease Across Risk Categories

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ABSTRACT

BACKGROUND The effects of aspirin in adults without atherosclerotic cardiovascular disease (ASCVD), stratified by statin use across different ASCVD risks, remain uncertain.

OBJECTIVES The purpose of this study was to examine the effects of aspirin in adults without ASCVD, stratified by statin use across different ASCVD risks.

METHODS We searched databases through March 2022 and selected randomized controlled trials of aspirin without ASCVD and follow-up of ≥1 year. We used random-effects models and estimated relative and absolute risks for cardiovascular outcomes, major bleeding, and mortality over 5 years. We calculated absolute risk differences assuming constant relative risks (RRs) across statin use and ASCVD risks. The Cholesterol Treatment Trialists Collaboration, and the ASCEND (A Study of Cardiovascular Events in Diabetes) trial were used to estimate baseline risks.

RESULTS In 16 trials [171,215 individuals; median age, 64 (Q1-Q3: 60-65) years], aspirin vs control reduced myocardial infarction (MI) [RR: 0.85 (95% CI: 0.77-0.95)] but increased major bleeding [RR: 1.48 (95% CI: 1.32-1.66)]. Aspirin did not reduce mortality. Statin vs no statin was associated with lower bleeding and MI risk; the bleeding and MI risk were proportional to ASCVD risk. For every 10,000 adults, aspirin reduced MI (*very low risk*: 3 events as monotherapy or 1 event with statin; *very high risk*: 49 events as monotherapy or 37 events with statin) and increased major bleeding (*very low risk:* 21 events as monotherapy or 20 events with statin; *very high risk:* 98 events as monotherapy or 94 events with statin) proportional to baseline ASCVD risk.

CONCLUSIONS In adults without ASCVD, concomitant statin appeared to significantly reduce absolute risk reduction for MI associated with aspirin without influencing bleeding risk. The anticipated absolute risk of major bleeding with aspirin exceeds absolute MI benefits for every level of ASCVD risk. (JACC Adv 2023;2:100197) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

ATP = Adult Treatment Panel

CI = confidence interval

CTTC = Cholesterol Treatment Trialist's Collaboration

LDL-C = low-density lipoprotein-cholesterol

MI = myocardial infarction

RR = relative risk

USPSTF = United States Preventive Services Task Force

The role of aspirin in the primary prevention of atherosclerotic cardiovascular disease (ASCVD) remains controversial. In 2019, the American College of Cardiology/American Heart Association recommended considering prophylactic low-dose aspirin only among asymptomatic individuals at high risk of ASCVD events, low bleeding risk, and age <70 years (IIb).[1] In 2021, the European Society of Cardiology primary prevention guidelines endorsed a similar recommendation.[2] More recently, the updated United States Preventive Services Task Force (USPSTF) 2022 guidelines recommended individualizing low-dose aspirin only among adults aged 40 to 59 years, if their 10-year ASCVD risk is ≥10% and they have low bleeding risk (Class C). In contrast, the guidelines recommend against the use of aspirin among adults ≥60 years (Class D). These recommendations stem from a USPSTF meta-analysis of 11 randomized controlled trials demonstrating a significant reduction in major ASCVD events with aspirin at the cost of higher rates of major bleeding.

Statin is used as first-line therapy for the primary prevention of ASCVD due to cardiovascular benefits.[3] Most randomized evidence favoring aspirin in primary prevention was conducted in the pre-statin era,[4] whereas statin therapy use was more frequent at baseline in recent trials. For instance, the proportion of participants on a statin in ASPREE (Aspirin in Reducing Events in the Elderly),[5-7] ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events),[8] and ASCEND (A Study of Cardiovascular Events in Diabetes)[9] trials were 65%, 43%, and 75%, respectively. Since statin therapy would mitigate baseline ASCVD risk,[10] lower cardiovascular effects of aspirin in post-statin era trials might be attributable to the higher use of statin therapy.[11] Furthermore, given a much more favorable risk-benefit profile, most patients considered for ASCVD risk reduction in current clinical practice would be expected to be on baseline statin therapy before entertaining a decision on possible aspirin initiation.

Prior studies[4,11,12] did not explore the potential impact of statin therapy on the net risk/benefit ratio of aspirin therapy. Therefore, this meta-analysis investigated the relative and absolute effects of aspirin in adults without ASCVD, stratified by statin use across different ASCVD risks.

METHODS

We performed this trial-level meta-analysis according to the Cochrane Collaboration guidelines and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[13,14]

DATA SOURCES, SEARCHES, AND STUDY SELECTION. We performed a comprehensive literature search without language restriction using Medline, EMBASE, and the CENTRAL databases through March 2022 using broad search terms ("aspirin", "salicylic acid", "salicylates", "primary prevention", "myocardial infarction", "stroke", "transient ischemic attack", "bleeding" and "mortality") (Supplemental Table 1).

The prespecified inclusion criteria were: 1) randomized controlled trials comparing aspirin (at least 75 mg every other day) vs placebo or no aspirin in adults (≥18 years) without known ASCVD but who may carry ASCVD risk factors; and 2) follow-up of at least 1 year. We excluded trials where nonaspirin antithrombotic medications (eg, warfarin) were coadministered. We included the ETDRS (Early Treatment Diabetic Retinopathy Study),[15] which included <10% of patients with established ASCVD because a minority of patients were unlikely to influence the outcomes. However, we assessed the influence of the trial on estimates in the leave-out sensitivity analysis. We removed duplicates and screened the remaining articles at the title and abstract level and then at the full-text level (Supplemental Figure 1). Two authors (S.U.K. and A.N.L.) independently conducted the study search and selection process and resolved conflicts by discussion and mutual consensus.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT. Two reviewers (S.U.K and A.N.L.) independently abstracted the data onto the data collection sheets,

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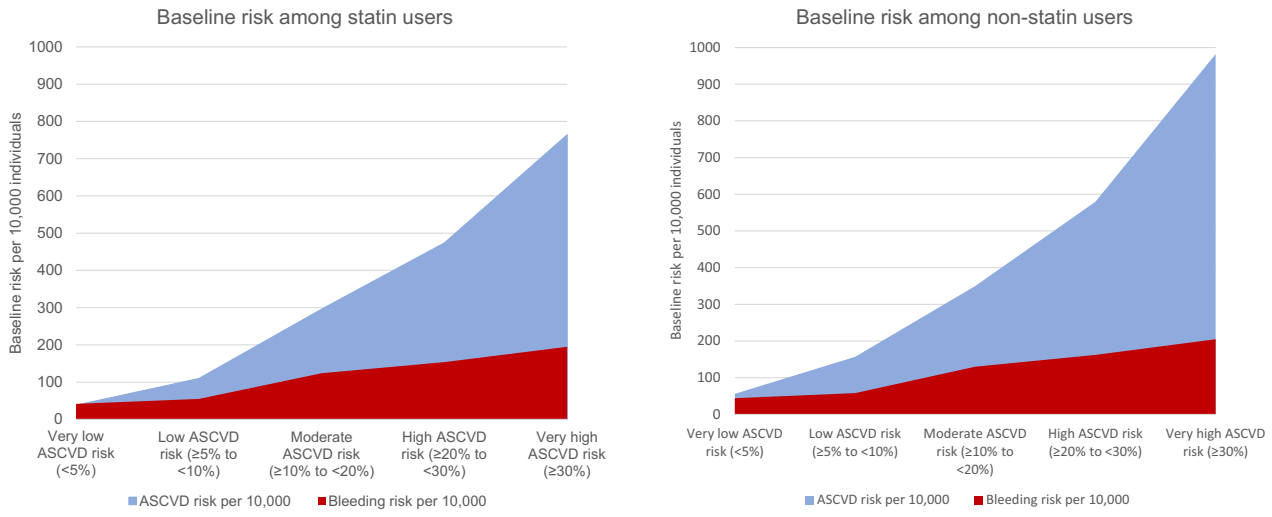
FIGURE 1 **Baseline Risk per 10,000 Individuals Among Statin vs Nonstatin Users for ASCVD and Bleeding in the Primary Prevention Setting**



Atherosclerotic cardiovascular disease (ASCVD) and bleeding events caused per 10,000 individuals with or without statin per 5 years are plotted across ASCVD risk categories derived from Cholesterol Treatment Trialist Collaboration and ASCEND (A Study of Cardiovascular Events in Diabetes) trial.

appraised the data accuracy, performed a risk of bias assessment, and resolved discrepancies by discussing or referring to the original publication. We abstracted the data on characteristics of trials and participants (age, sex, comorbidities, and follow-up duration), point estimates, number of events, and sample sizes. We abstracted data on the intention to treat principle.

We used a Cochrane risk of bias assessment tool for assessing the risk of bias in randomized controlled trials.[16] We assessed the risk of bias at the study level across the following domains: bias due to the randomization process; bias due to deviation from the intended intervention; bias due to missing outcome data; bias in the measurement of the outcomes; bias in the selection of the reported results, including divergence from the registered protocol; and bias owing to early termination for benefit (Supplemental Table 2).

OUTCOMES OF INTEREST. We primarily focused on myocardial infarction (MI) (fatal and nonfatal MI) and major bleeding (bleeding requiring transfusion or hospitalization or leading to death). Other key endpoints were stroke (fatal and nonfatal), all-cause and cardiovascular mortality. Additional outcomes were nonfatal MI, nonfatal ischemic stroke, intracranial hemorrhage, and gastrointestinal bleeding. Outcomes were extracted at the maximum follow-up duration.

DATA SYNTHESIS AND SUMMARY MEASURES. We performed a frequentist pairwise meta-analysis for all patients, regardless of aspirin dosages. We measured risk ratios (RRs) with 95% CIs. We calculated anticipated absolute effects for all outcomes from RRs utilizing baseline ASCVD risk among patients with or without statin therapy. We estimated absolute risk differences assuming constant RRs[17] across different baseline statin therapies (dose and duration) and ASCVD risk categories.

CLINICAL SCENARIOS FOR BASELINE ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK ESTIMATION. For baseline ASCVD risk, we used the Cholesterol Treatment Trialist's Collaboration's (CTTC) framework, which defined 5 baseline major vascular events risk categories at 5-year: *very low risk* (major vascular event: <5%), *low risk* (≥5% to <10%), *moderate risk* (≥10% to <20%), *high risk* (≥20% to <30%), and very high risk (≥30%) among patients without ASCVD.[18] For any major bleeding, we used ASCVD risk-stratified event rates for aspirin therapy reported in the ASCEND trial.[9] **Figure 1** illustrates baseline risk per 10,000 persons for ASCVD and bleeding across ASCVD risk categories. Finally, using CTTC calculations, we theoretically predicted absolute risk reduction in MI with aspirin, for each 40 mg/dL on statin treatment reduction in low-density lipoprotein-cholesterol

(LDL-C) from the corresponding baseline LDL-C.[19,20] Further details are provided in the Supplemental Appendix and Supplemental Figure 1.

STATISTICAL ANALYSIS. We pooled outcomes using a random-effects model. We applied the DerSimonian and Laird method for the estimation of τ.[21] We used I^2 statistics to measure the extent of unexplained statistical heterogeneity: I ≥ 50% was considered a high degree of between-study statistical heterogeneity (Supplemental Table 3).[22] We assessed publication bias using a funnel plot and Egger's regression test (Supplemental Figure 3, Supplemental Table 4).

We performed subgroup analyses according to age, diabetes mellitus, aspirin dosage, sample size, follow-up duration, and year of publication in reference to the Adult Treatment Panel (ATP) III guidelines (Supplemental Table 6). Sensitivity analyses comprised a leave-one-out meta-analysis (Supplemental Table 4). For all analyses, statistical significance was set at 5%. Comprehensive meta-analysis V 3.0 (Biostat) and MAGICapp (www.magicapp.org) were used for all analyses.

CERTAINTY OF THE EVIDENCE. Two authors (S.U.K. and A.N.L.) rated the certainty of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach (https://gdt.gradepro.org/app/),[23] as high, moderate, low, or very low (Supplemental Table 7).

RESULTS

STUDY SEARCH AND TRIAL CHARACTERISTICS. Of 4,687 citations, 2,062 were reviewed after removing duplicates, and 525 were reviewed after exclusion at the title and abstract level screening. Furthermore, 509 full-text articles were removed based on a priori selection criteria (Supplemental Figure 2). Finally, 16 trials (171,215 individuals) were included in the analysis (**Table 1**). Four trials[9,15,30,33] were conducted exclusively in patients with diabetes. All but 3 trials[15,24,25] employed a low dose of aspirin (ie, ≤100 mg/d). The median age of participants was 64 (Q1-Q3: 60-65) years, and the median proportion of women was 46% (Q1-Q3: 32%-57%). The overall median proportion of statin was 35% (Q1-Q3: 16%-65%). The median proportions of statin in trials before and after the ATP III guidelines (2001) were 10% (Q1-Q3: 7%-13%) and 43% (Q1-Q3: 31%-69%), respectively. The weighted median follow-up duration was 5 (Q1-Q3: 4-8) years. All trials had a low risk of bias.

MI AND MAJOR BLEEDING. Sixteen trials (171,215 participants) reported MI, and 12 trials (163,578 participants) reported major bleeding. Compared with control, aspirin [RR: 0.85 (95% CI: 0.77-0.95); $P < 0.001$; $I^2 = 57\%$) (**Figure 2A**] was associated with lower rates of MI but a higher risk of major bleeding [RR: 1.48 (95% CI: 1.32-1.66); $P < 0.001$; $I^2 = 19\%$) (**Figure 2B**].

In patients with *very low ASCVD risk (<5%)*, aspirin was likely to have a slight reduction in MI as monotherapy [3 fewer (95% CI: 4-1 fewer) per 10,000] or with statin therapy [1 fewer (2-0 fewer) per 10,000] (moderate certainty) (**Figure 3**), but a modest increase in major bleeding at monotherapy [21 more (14-29 more) per 10,000] or with statin [20 more (13-28 more) per 10,000 (high certainty) (**Central Illustration**). In patients with *low (≥5% to <10%) to moderate (≥10% to <20%) ASCVD risk*, aspirin as monotherapy (10-17 fewer per 10,000) or with statin (6-13 fewer per 10,000) was likely to have a modest reduction in MI (moderate certainty), but a considerable increase in major bleeding as monotherapy (28-62 more per 10,000) or with statin (26-60 more per 10,000) (high certainty). However, in patients with *high (≥20% to <30%) to very high (≥30%) ASCVD risk,* aspirin as monotherapy (27-49 fewer per 10,000) or with statin (20-37 fewer per 10,000) was likely to have a more considerable reduction in MI, but at the expense of a significant increase in major bleeding as monotherapy (78-98 more per 10,000) or with statin therapy (74-94 more per 10,000) (moderate certainty).

STROKE, ALL-CAUSE AND CARDIOVASCULAR MORTALITY. A total of 16 trials (171,215 participants) reported stroke, 14 trials (169,015 participants) reported all-cause mortality, and 15 trials (171,554 participants) reported cardiovascular mortality. Aspirin was not associated with reducing stroke (RR: 0.96 [95% CI: 0.88-1.04]; $P = 0.29$; $I^2 = 21\%$) (Supplemental Figure 4), all-cause mortality (RR: 0.97 [95% CI: 0.93-1.01]; $P = 0.10$; $I^2 = 0\%$) (Supplemental Figure 5), or cardiovascular mortality (RR: 0.93 [95% CI: 0.87-1.01]; $P = 0.07$; $I^2 = 0\%$) (Supplemental Figure 6). In absolute terms, aspirin as monotherapy or in combination with statin did not reduce stroke, all-cause or cardiovascular mortality (moderate to high certainty) (**Table 2**).

ADDITIONAL ENDPOINTS. Compared with control, aspirin was associated with a lower risk of nonfatal MI (RR: 0.82 [95% CI: 0.72-0.94]; $P \leq 0.001$; $I^2 = 58\%$) (Supplemental Figure 7). While aspirin was not associated with reducing nonfatal stroke (RR: 0.90 [95% CI: 0.79-1.01]; $P = 0.08$; $I^2 = 0\%$) (Supplemental Figure 8), aspirin was associated with a higher risk of intracranial hemorrhage (RR: 1.32 [95% CI: 1.12-1.55]; $P \leq 0.001$; $I^2 = 0\%$) (Supplemental Figure 9) and

TABLE 1 Baseline Characteristics of the Trial

Study First Author, Year	Participants	Aspirin Dose	Age, y	Women, %	HTN, %	DM, %	HbA1C, %	Smoking, %	Statin, %	DLD, %	Follow-Up, y
BMD Peto, 1988[24]	5,139	500 mg QD	64	0	10	2	-	31	-	-	6.0
PHS Physician's Health Study, 1989[25]	22,071	325 mg QD	54	0	9[a]	2[a]	-	11[a]	-	-	5.0
ETDRS Early Treatment Diabetic Retinopathy Report, 1992[15]	3,711	650 mg QD	32	44	44	100	-	44	-	30	5.0
HOT Hanson, 1998[26]	18,790	75 mg QD	61	47	100	8	-	16	-	-	3.8
TPT The Medical Research Council's General Practice Research Framework, 1998[27]	2,540	75 mg QD	58	0	26	2	-	41	-	-	10.0
PPP Rongaclioni, 2001[28]	4,495	100 mg QD	65	58	68	17	-	15	16	39	3.7
WHS Ridker, 2005[29]	39,876	100 mg QOD	55	100	26	3	-	13	-	29	10.1
POPADAD Jill, 2008[30]	1,276	100 mg QD	60	56	-	100	8	32	-	-	6.7
AAA Fowkes, 2010[31]	3,350	100 mg QD	62	72	-	3	-	33	4	-	8.2
JPPP Ikeda, 2014[32]	14,464	100 mg QD	71	58	85	34	6.1	13	72	72	5.0
JPAD Saito, 2016[33]	2,539	81 mg QD or 100 mg QD	66	44	58	100	7.5	21	26	54	10.3
ARRIVE Gaziano, 2018[8]	12,546	100 mg QD	64	30	65	0	-	29	43	58	5.0
ASCEND ASCEND Study Collaborative, 2018[9]	15,480	100 mg QD	63	37	62	100	-	8	75	-	7.4
ASPREE, McNeil, 2018[5-7]	19,114	100 mg QD	74	56	74	11	-	4	35	65	4.7
AASER Goicoechea, 2018[34]	111	100 mg QD	67	33	91	32	6	-	65	-	5.4
TIPS-3 Yusuf, 2020[35]	5,713	75 mg QD	64	53	84	36	-	9	0	-	4.6

All values are reports as aspirin/control or placebo. [a]Data for mean or median value for the whole population.

AAA = Aspirin for Asymptomatic Atherosclerosis; AASER = Acido Acetil Salicilico en la Enfermedad Renal; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors Trial; DLD = dyslipidemia; DM = diabetes mellitus; ETDRS = Early Treatment Diabetic Retinopathy; HbA1C = glycosylated hemoglobin; HOT = Hypertension Optimal Treatment; HTN = hypertension; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; QD = every day; QOD = every other day; TIPS-3 = The International Polycap Study 3; WHS = Woman Health Study.

gastrointestinal bleeding (RR: 1.51 [95% CI: 1.33-1.72]; $P \leq 0.001$; $I^2 = 0\%$) (Supplemental Figure 10).

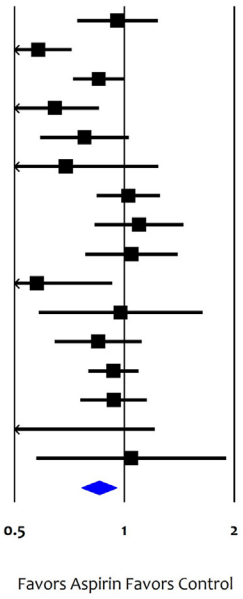
SUBGROUP ANALYSIS AND SENSITIVITY ANALYSIS. Subgroup analysis showed that aspirin ≤100/d was associated with a lower risk of stroke (RR: 0.91 [95% CI: 0.84-0.98]) compared with those using >100 mg/d (RR: 1.19 [95% CI: 1.00-1.42]) (P for interaction < 0.001) (Supplemental Table 5). In addition, trials published before the year 2001 demonstrated a higher reduction in MI (RR: 0.74 [95% CI: 0.62-0.87]) than those published after the year 2001 (RR: 0.95 [95% CI: 0.86-1.05]) (P for interaction = 0.03). Besides, there was no significant interaction across other subgroups. Leave-one-out sensitivity analyses showed concordant results (Supplemental Table 6).

EFFECT OF ASPIRIN ON MI WITH RESPECT TO LDL-C LOWERING BY STATIN. In primary prevention trials, statin therapy has been shown to reduce the relative risk of major vascular events by 25% for every 38.7 mg/dL (1 mmol/L) reduction in LDL-C.[36] However, absolute risk reduction per LDL-C lowering is also a function of baseline LDL-C.[20] In a hypothetical exercise, we plotted the expected absolute risk reduction in MI with aspirin therapy for each 40 mg/dL lowering in LDL-C from a corresponding baseline LDL-C, generated by statin therapy (**Figure 4**). Assuming a person has a baseline LDL-C of 160 mg/dL, a 40 mg/dL reduction in LDL-C by statin therapy would reduce 27 MIs per 10,000 (ie, ~73 per 10,000 events with statin vs ~100 events per 10,000 without statin). Aspirin use would lead

FIGURE 2 Forest Plots Comparing Aspirin vs Control for Myocardial Infarction and Any Major Bleeding

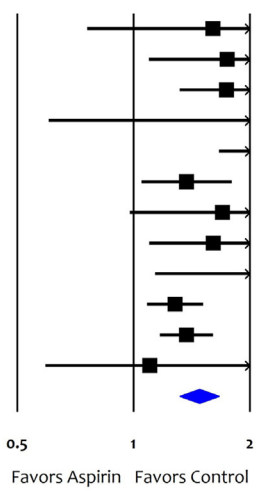
A

Study name	Year Published	Events / Total		Statistics for each study				Relative weight
		Aspirin	Control	Risk ratio	Lower limit	Upper limit	p-Value	
BMD	1988	169 / 3429	88 / 1710	0.96	0.75	1.23	0.74	7.47
PHS	1989	139 / 11037	239 / 11034	0.58	0.47	0.72	0.00	8.58
ETDRS	1992	241 / 1856	283 / 1855	0.85	0.73	1.00	0.05	9.87
HOT	1998	82 / 9399	127 / 9391	0.65	0.49	0.85	0.00	6.89
TPT	1998	83 / 1268	107 / 1272	0.78	0.59	1.03	0.07	6.89
PPP	2001	19 / 2226	28 / 2269	0.69	0.39	1.23	0.21	2.71
WHS	2005	198 / 19934	193 / 19942	1.03	0.84	1.25	0.80	8.85
POPADAD	2008	90 / 638	82 / 638	1.10	0.83	1.45	0.51	6.84
AAA	2010	90 / 1675	86 / 1675	1.05	0.78	1.40	0.76	6.63
JPPP	2014	27 / 7220	47 / 7244	0.58	0.36	0.92	0.02	3.68
JPAD2	2017	28 / 1262	29 / 1277	0.98	0.58	1.63	0.93	3.26
ARRIVE	2018	95 / 6270	112 / 6276	0.85	0.65	1.11	0.24	7.00
ASCEND	2018	296 / 7740	317 / 7740	0.93	0.80	1.09	0.39	9.98
ASPREE	2018	171 / 9525	184 / 9589	0.94	0.76	1.15	0.53	8.61
AASER	2018	0 / 50	8 / 61	0.07	0.00	1.21	0.07	0.14
TIPS-3	2020	22 / 2860	21 / 2853	1.05	0.58	1.90	0.88	2.59
		1750 / 86389	1951 / 84826	0.85	0.77	0.95	0.00	



B

Study name	Year Published	Events / Total		Statistics for each study				Relative weight
		Aspirin	Control	Risk ratio	Lower limit	Upper limit	p-Value	
BMD	1988	29 / 3429	9 / 1710	1.61	0.76	3.39	0.21	2.26
PHS	1989	49 / 11037	28 / 11034	1.75	1.10	2.78	0.02	5.40
HOT	1998	136 / 9399	78 / 9391	1.74	1.32	2.30	0.00	12.41
TPT	1998	8 / 1268	4 / 1272	2.01	0.61	6.65	0.25	0.90
PPP	2001	24 / 2226	6 / 2269	4.08	1.67	9.96	0.00	1.60
WHS	2005	129 / 19934	94 / 19942	1.37	1.05	1.79	0.02	13.21
AAA	2010	34 / 1675	20 / 1675	1.70	0.98	2.94	0.06	4.00
JPPP	2014	69 / 7220	43 / 7244	1.61	1.10	2.35	0.01	7.60
ARRIVE	2018	19 / 6270	7 / 6276	2.72	1.14	6.46	0.02	1.69
ASCEND	2018	314 / 7740	245 / 7740	1.28	1.09	1.51	0.00	23.30
ASPREE	2018	361 / 9525	265 / 9589	1.37	1.17	1.60	0.00	24.42
TIPS-3	2020	21 / 2860	19 / 2853	1.10	0.59	2.05	0.76	3.20
		1193 / 82583	818 / 80995	1.48	1.32	1.66	0.00	



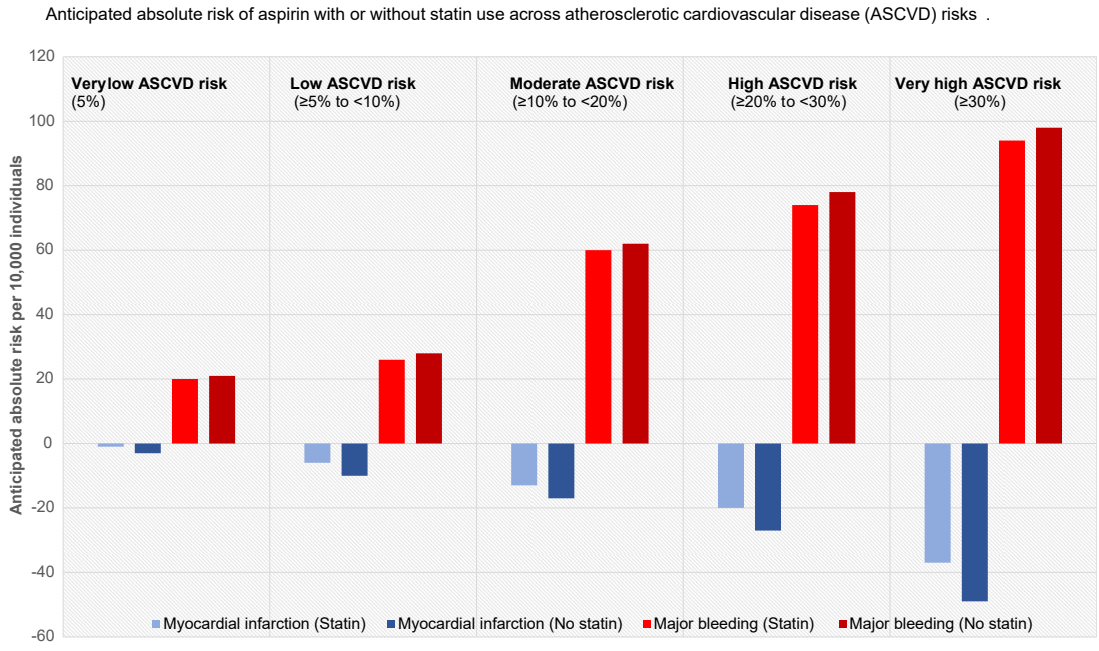
Forest plot comparing aspirin vs control for **(A)** myocardial infarction and **(B)** any major bleeding.

to ~11 fewer MIs per 10,000 with statin and ~15 fewer per 10,000 without statin. For each subsequent 40 mg/dL lowering in LDL-C by statin therapy up to baseline LDL-C of 40 mg/dL, aspirin would likely reduce 9, 8, and 7 MIs per 10,000 persons, respectively.

DISCUSSION

In this meta-analysis of 171,215 individuals without established ASCVD, aspirin reduced MI at the expense of higher rates of major bleeding. Aspirin was not associated with total or cardiovascular

FIGURE 3 **Anticipated Absolute Risk Differences per 10,000 Individuals for Aspirin on Myocardial Infarction and Major Bleeding in Patients Without Cardiovascular Disease Across Different Atherosclerotic Cardiovascular Risk Categories, Stratified by Statin**



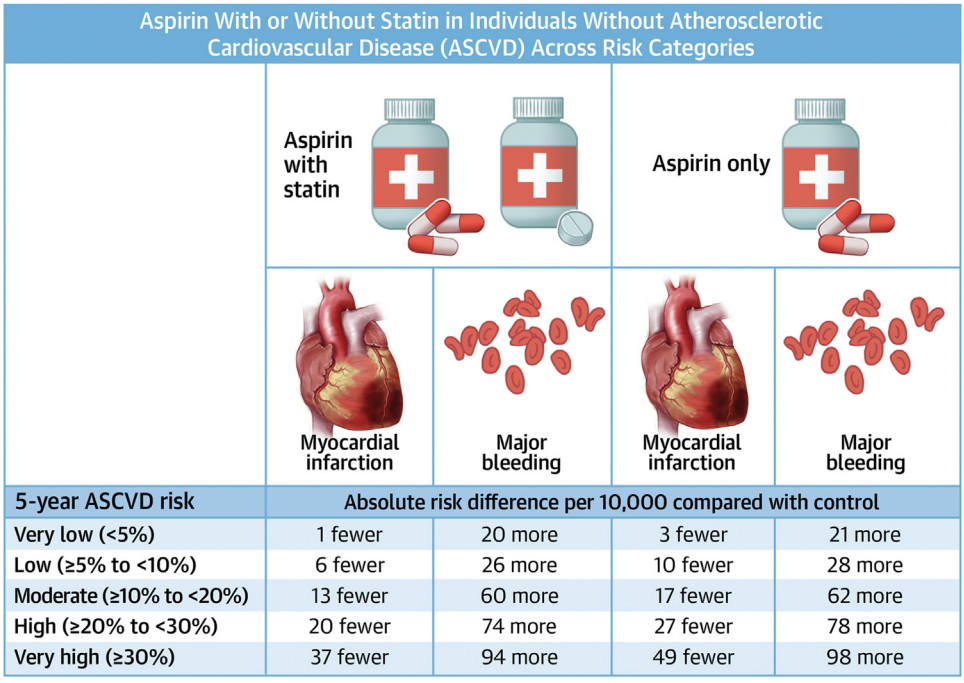
survival benefits. The absolute effects of aspirin on MI and major bleeding were proportional to baseline ASCVD risk. Individuals with the highest ASCVD risk appeared to gain maximum reductions in MI, although at the expense of higher major bleeding events, while those with moderate to low ASCVD risk achieved small absolute reductions in MI, also at the cost of major bleeding events. The magnitude of absolute risk reduction in cardiovascular outcomes by aspirin was diminished by statin therapy. In contrast, statin use did not influence the bleeding risk of aspirin.

The 2022 USPSTF report documented more considerable relative risk reductions in major vascular events and MI in aspirin trials published before ATP III guidelines (2001) than those published after 2001.[4] These findings are consistent with our subgroup analysis and previous report.[4,11] The authors attributed these observations to heterogeneity in the trial populations and in aspirin dosages.[4] However, relative estimates are average treatment effects, whereas absolute reductions are a function of baseline risk and efficacy of the treatment. Since statin therapy has been shown to reduce baseline ASCVD risk,[10] it is conceivable that aspirin would confer lower absolute reductions in cardiovascular outcomes among participants taking a statin.

The Antithrombotic Trialist's (ATT) Collaboration estimated that adding aspirin to a statin-based regimen would have generated an absolute reduction of about half as large as was shown in older primary prevention trials, without influencing bleeding hazards.[37] Consistent with this, we found that background statin therapy attenuates the absolute reduction in MI by at least one-third among participants treated with aspirin, without modifying bleeding risk. The lack of significant interaction of aspirin and statin on the bleeding in the ASCEND and ASPREE trials also supports the finding of no effect modification in bleeding events.[5-7,9] On the same note, since we used data from the ASCEND trial (people with diabetes; mean age of 63 years) for ASCVD risk groups for major bleeding,[9] one may argue that our ASCVD risk stratification may not be reflective of most of the primary prevention population. However, prior data have shown a direct correlation between increased risk of bleeding and ischemic events since they mostly share similar risk factors, with age being a fundamental driver of both.[38,39] Furthermore, our baseline risk estimates across ASCVD risk categories were similar to previous study.[40]

We observed that absolute event reduction in MI among individuals on aspirin would plateau after more intensive lowering in LDL-C by statin therapy

CENTRAL ILLUSTRATION **Aspirin With or Without Statin in Adults Without Cardiovascular Risk**



5-year ASCVD risk	Absolute risk difference per 10,000 compared with control			
Very low (<5%)	1 fewer	20 more	3 fewer	21 more
Low (≥5% to <10%)	6 fewer	26 more	10 fewer	28 more
Moderate (≥10% to <20%)	13 fewer	60 more	17 fewer	62 more
High (≥20% to <30%)	20 fewer	74 more	27 fewer	78 more
Very high (≥30%)	37 fewer	94 more	49 fewer	98 more

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due to a reduction in baseline LDL-C (ie, the baseline risk of participants). Furthermore, our results were restricted to 5 years; therefore, for longer follow-up duration (eg, 10 years), statins may further reduce the baseline risk and attenuate the absolute benefit of aspirin. Finally, our analyses accounted for 1 mmol/L reduction in LDL-C (40 mg/dL) associated with statin therapy. With high-intensity statin therapy, one would expect even higher LDL-C reduction, further reducing any additional absolute event reduction associated with aspirin therapy.

These findings have practical implications. The expected absolute risk of major bleeding exceeds absolute MI benefits by aspirin for every level of ASCVD risk. While aspirin has a significant role in secondary prevention, our analysis suggests that the risk-benefit equilibrium may be tilted toward more harm for primary prevention. Beyond lifestyle modifications, smoking cessation, and exercise, preventive statin therapy has taken over the landscape of clinical practice.[4] Our analyses inform that in adults without ASCVD, adding aspirin to statin is unlikely to achieve additional meaningful cardiovascular benefits but would enhance bleeding hazards, regardless of baseline ASCVD risk.

We compared our review with prior meta-analyses. The 2022 USPSTF review focused on trials with low-dose aspirin and excluded data of TIPS-3 (The International Polycap Study 3).[35] Zheng and Roddick included 13 trials and stratified composite cardiovascular outcome and bleeding risk according to 10-year ASCVD risk (high ≥10%, low <10%).[41] In their study, aspirin yielded a similar magnitude of absolute reduction in composite cardiovascular outcomes (ie, 63 per 1,000) across both high- and low-risk groups. However, similar to our observations, the major bleeding risk was higher (64 per 1,000) in high vs low ASCVD risk (40 per 1,000) participants. Other meta-analyses focused on relative estimates and did not report the absolute effects of aspirin in primary prevention.[11,12] Most of the prior meta-analyses focused on composite major adverse cardiovascular events for the primary endpoint. We avoided using major adverse cardiovascular events due to heterogeneity in individual component cardiovascular outcomes across the trials. Instead, we chose MI (fatal and nonfatal), which appears to be more meaningful to clinicians and patients to assess the net effects of aspirin in primary prevention.

TABLE 2 Anticipated Absolute Risk Differences per 10,000 Individuals of Aspirin on Outcomes in Patients Without Cardiovascular Disease Across Different Atherosclerotic Cardiovascular Risk Categories, Stratified by Statin

5-Year Atherosclerotic Cardiovascular Disease Risks	Relative Risk (95% CI)	Baseline Risk for Statin	Anticipated Absolute Risk Difference With Aspirin Added to Statin per 10,000	Baseline Risk Without Statin	Anticipated Absolute Risk Difference With Aspirin Added to No Statin per 10,000
Very low risk (<5%)					
Myocardial infarction	0.85 (0.77-0.95)	8 per 10,000	1 fewer (2 fewer to 0 fewer)	17 per 10,000	3 fewer (4 fewer to 1 fewer)
Stroke	0.96 (0.88-1.04)	16 per 10,000	1 fewer (2 fewer to 1 more)	20 per 10,000	1 fewer (2 fewer to 1 more)
All-cause mortality	0.97 (0.93-1.01)	52 per 10,000	2 fewer (4 fewer to 1 more)	54 per 10,000	2 fewer (4 fewer to 1 more)
Cardiovascular mortality	0.93 (0.87-1.01)	18 per 10,000	1 fewer (2 fewer to 0 more)	20 per 10,000	1 fewer (3 fewer to 0 more)
Any major bleeding	1.48 (1.32-1.66)	42 per 10,000	20 more (13 more to 28 more)	44 per 10,000	21 more (14 more to 29 more)
Low risk (≥5% to <10%)					
Myocardial infarction	0.85 (0.77-0.95)	41 per 10,000	6 fewer (9 fewer to 2 fewer)	67 per 10,000	10 fewer (15 fewer to 3 fewer)
Stroke	0.96 (0.88-1.04)	34 per 10,000	1 fewer (4 fewer to 1 more)	43 per 10,000	2 fewer (5 fewer to 2 more)
All-cause mortality	0.97 (0.93-1.01)	114 per 10,000	3 fewer (8 fewer to 1 more)	127 per 10,000	4 fewer (9 fewer to 1 more)
Cardiovascular mortality	0.93 (0.87-1.01)	55 per 10,000	4 fewer (7 fewer to 1 more)	59 per 10,000	4 fewer (8 fewer to 1 more)
Any major bleeding	1.48 (1.32-1.66)	55 per 10,000	26 more (18 more to 36 more)	58 per 10,000	28 more (19 more to 38 more)
Moderate risk (≥10% to <20%)					
Myocardial infarction	0.85 (0.77-0.95)	88 per 10,000	13 fewer (20 fewer to 4 fewer)	112 per 10,000	17 fewer (26 fewer to 6 fewer)
Stroke	0.96 (0.88-1.04)	62 per 10,000	2 fewer (7 fewer to 2 more)	71 per 10,000	3 fewer (9 fewer to 3 more)
All-cause mortality	0.97 (0.93-1.01)	204 per 10,000	6 fewer (14 fewer to 2 more)	219 per 10,000	7 fewer (15 fewer to 2 more)
Cardiovascular mortality	0.93 (0.87-1.01)	114 per 10,000	8 fewer (15 fewer to 1 more)	123 per 10,000	9 fewer (16 fewer to 1 more)
Any major bleeding	1.48 (1.32-1.66)	124 per 10,000	60 more (40 more to 82 more)	130 per 10,000	62 more (42 more to 86 more)
High risk (≥20% to <30%)					
Myocardial infarction	0.85 (0.77-0.95)	134 per 10,000	20 fewer (31 fewer to 7 fewer)	177 per 10,000	27 fewer (41 fewer to 9 fewer)
Stroke	0.96 (0.88-1.04)	84 per 10,000	3 fewer (10 fewer to 3 more)	97 per 10,000	4 fewer (12 fewer to 4 more)
All-cause mortality	0.97 (0.93-1.01)	280 per 10,000	8 fewer (20 fewer to 3 more)	304 per 10,000	9 fewer (21 fewer to 3 more)
Cardiovascular mortality	0.93 (0.87-1.01)	167 per 10,000	12 fewer (22 fewer to 2 more)	192 per 10,000	13 fewer (25 fewer to 2 more)
Any major bleeding	1.48 (1.32-1.66)	154 per 10,000	74 more (49 more to 102 more)	162 per 10,000	78 more (52 more to 107 more)
Very high risk (≥30%)					
Myocardial infarction	0.85 (0.77-0.95)	248 per 10,000	37 fewer (57 fewer to 12 fewer)	327 per 10,000	49 fewer (75 fewer to 16 fewer)
Stroke	0.96 (0.88-1.04)	145 per 10,000	6 fewer (17 fewer to 6 more)	168 per 10,000	7 fewer (20 fewer to 7 more)
All-cause mortality	0.97 (0.93-1.01)	522 per 10,000	16 fewer (37 fewer to 5 more)	578 per 10,000	17 fewer (40 fewer to 6 more)
Cardiovascular mortality	0.93 (0.87-1.01)	323 per 10,000	23 fewer (42 fewer to 3 more)	369 per 10,000	26 fewer (48 fewer to 4 more)
Any major bleeding	1.48 (1.32-1.66)	195 per 10,000	94 more (62 more to 129 more)	205 per 10,000	98 more (66 more to 135 more)

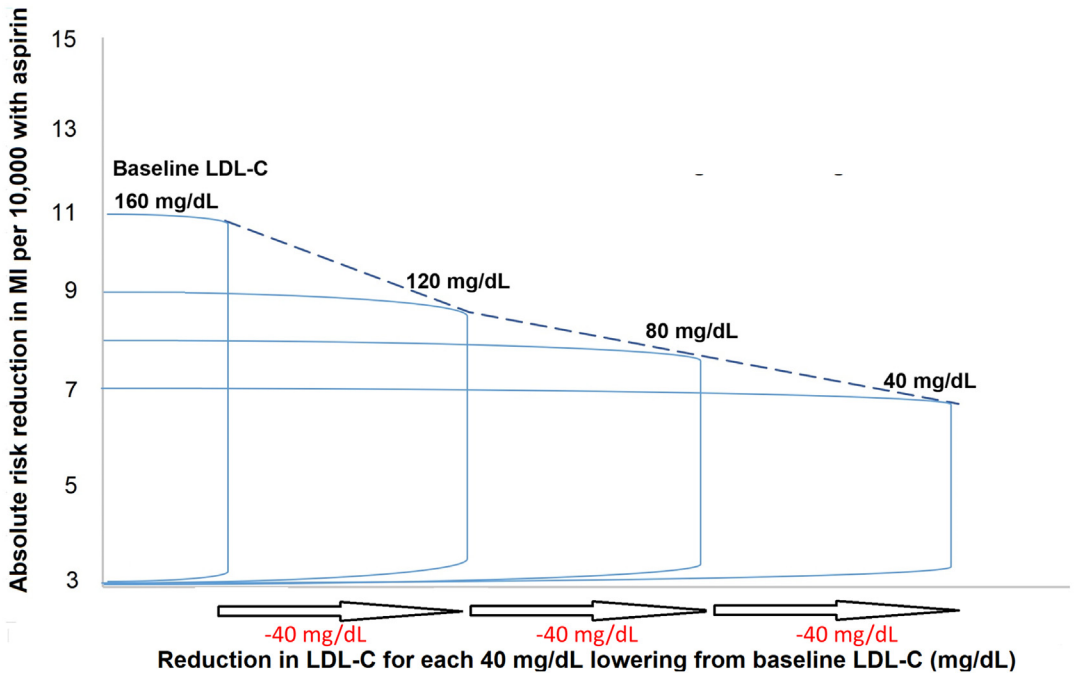
High certainty | Moderate certainty | Low certainty | Very low certainty

STUDY LIMITATIONS. First, this is a meta-analysis of trials with heterogeneous participants, variable outcome definitions, and follow-ups. Second, our prespecified subgroup analyses were conducted at the study level instead of the participant level due to a lack of individual data, which also limited us in estimating individual baseline risk. Third, while relative effects did not vary across the prespecified age strata (<65, ≥65 years), the absolute risk may vary across age groups. Therefore, it remains uncertain whether the benefit-risk ratio of aspirin may be more favorable in younger populations at high absolute risk. Fourth, we could not calculate individual ASCVD risk given the lack of information on the baseline variables of individual participants. One may also argue to present results based on the Pooled Cohort Equation derived classification of low, moderate, or high ASCVD risk categories.[42] However, we used the CTTC estimates due to its more granular stratification of baseline risk at 5 years to match the median follow-up of trials. On the same note, we extrapolated major bleeding risk using ASCEND data, and we assumed that the proportional effects on the severe vascular events and bleeding risk were similar across different levels of ASCVD risk.[9] While different risk calculators may provide contrasting results, they cannot account for all cardiovascular risk factors. Therefore, clinicians must supplement our results with clinical judgment.

CONCLUSIONS

In this meta-analysis, concomitant statin appeared to significantly reduce the absolute risk reduction for MI

FIGURE 4 Diminishing Absolute Risk Reduction in MI by Aspirin for the Same LDL-C Lowering by Statin With Lower Baseline LDL-C



Calculations based on the Cholesterol Treatment Trialist's Collaboration analysis. LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.

associated with aspirin without influencing bleeding risk. The absolute risk of major bleeding exceeds absolute MI benefits for every level of ASCVD risk. These findings may have implications for the use of aspirin in those already on statin therapy for primary ASCVD prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients without ASCVD, the absolute risk of major bleeding exceeds the absolute reduction in MI by aspirin across all ASCVD risks. Concomitant use of statin therapy further diminishes the cardiovascular effects of aspirin without influencing bleeding risk.

TRANSLATIONAL OUTLOOK: For patients without ASCVD who are already on statin therapy, adding aspirin is unlikely to achieve additional meaningful cardiovascular benefits but would enhance bleeding risk.

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KEY WORDS aspirin, meta-analysis, primary prevention, statin

APPENDIX For the supplemental appendix including the Protocol and supplemental figures and tables, please see the online version of this paper.