JAMA | Original Investigation

Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events

A Systematic Review and Meta-analysis

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Key Points

Question What is the association of aspirin use with cardiovascular events and bleeding events in individuals without cardiovascular disease?

Findings In this meta-analysis of 13 trials with 164 225 participants without cardiovascular disease, aspirin use was associated with a lower risk of cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (hazard ratio [HR], 0.89; absolute risk reduction, 0.38%) and an increased risk of major bleeding (HR, 1.43; absolute risk increase, 0.47%).

Meaning In individuals without cardiovascular disease, the use of aspirin was associated with a lower risk of cardiovascular events and an increased risk of major bleeding.

Table. Baseline Characteristics of Included Studies[a]

Source	Aspirin Dose, mg	Comparator	Trial Design	Study Population	Country	Study Period	Total Randomized	Male Participants, No. (%)	Age at Entry, Mean (SD), y	Diabetes, No. (%)	Current Smokers	Hypertension	SBP, Mean (SD), mm H	Total Cholesterol, Mean (SD), mmol/L	BMI	10-y Risk of Primary Outcome, % (95% CI)[b]	Overall Risk of Bias
British Doctors Study,[19] 1988	500 or 300 daily	No aspirin	Randomized, open-label, end point blind	Male physicians	United Kingdom	1978-1984	5139	5139 (100)	61 (7)	101 (2)	661 (13)	508 (10)	136 (17)	NR	24.4 (2.5)	13.9 (11.7-16.4)	High
Physicians' Health Study,[20] 1989	325 alternate day	Placebo	Randomized, double-blind	Male physicians aged 40-84 y	United States	1982-1988	22071	22071 (100)	53 (10)	533 (2)	2438 (11)	5297 (24)	126 (12)	5.5 (1.2)	24.9 (3.0)	6.7 (6.0-7.4)	Low
Hypertension Optimal Treatment,[20] 1998	75 daily	Placebo	Randomized, double-blind; factorial design with hypertension treatment targets	Individuals with hypertension aged 50-80 y	26 Countries across Europe, North and South America, and Asia	1992-1997	18790	9959 (53)	61 (7)	1503 (8)	2988 (16)	18 790 (100)	170 (14)	6.0 (1.1)	28.4 (4.7)	10.7 (9.7-11.9)	Low
Thrombosis Prevention Trial,[22] 1998	75 daily	Placebo	Randomized, double-blind; factorial design with warfarin	Men aged 45-69 y in the top 20%-25% of CV risk score	United Kingdom	1984-1997	5085[c]	5085 (100)	57 (7)	102 (2)	2100 (41)	814 (16)	139 (18)	6.4 (1.0)	27.4 (3.6)	15.9 (14.0-18.0)	Low
Primary Prevention Project,[23] 2001	100 daily	No aspirin	Randomized, open-label, blind end point; factorial design with vitamin E	Individuals with ≥1 CV risk factor	Italy	1994-1998	4495	1912 (42)	64 (7.6)	742 (17)	667 (15)	3065 (68)	145.2 (16.0)	6.1 (1.2)	27.6 (4.7)	8.1 (6.2-10.3)	High
Women's Health Study,[24] 2005	100 alternate day	Placebo	Randomized, double-blind; factorial design with vitamin E	Female health professionals ≥45 y	United States	1992-2004	39876	0 (0)	54 (7.1)	1037 (3)	5224 (13)	10 328 (26)	NR	5.2 (1.0)	26.1 (5.2)	2.6 (2.4-2.8)	Low
Prevention of Arterial Disease and	100 daily	Placebo	Randomized, double-blind; factorial	Individuals with diabetes, ABPI <0.99	United Kingdom	1997-2006	1276	563 (44)	60 (10)	1276 (100)	NR	NR	145 (21)	5.5 (NR)	29.2 (NR)	NA	Low

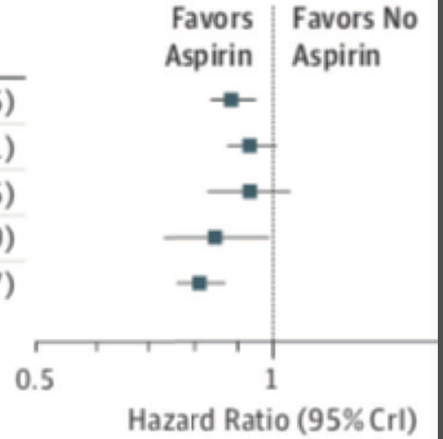
Source	Aspirin Dose, mg	Comparator	Trial Design	Study Population	Country	Study Period	Total Randomized	Male Participants, No. (%)	Age at Entry, Mean (SD), y	Diabetes, No. (%)	Current Smokers	Hypertension	SBP, Mean (SD), mm H	Cholesterol, Mean (SD), mmol/L	BMI	10-y Risk of Primary Outcome, % (95% CI)[b]	Overall Risk of Bias
Aspirin for Asymptomatic Atherosclerosis,[27] 2010	100 daily	Placebo	Randomized, double-blind	Individuals aged 50-75 y with ABPI ≤0.95	United Kingdom	1998-2008	3350	954 (28)	62 (6.7)	88 (3)	1085 (32)	NR	147.5 (22)	6.2 (1.1)	NR	12.8 (11.0-14.8)	Low
Japanese Primary Prevention Project,[26] 2014	100 daily	No aspirin	Randomized, open label, blind end point	Individuals aged 60-85y, with hypertension, dyslipidemia, or diabetes	Japan	2005-2012	14 464	6123 (42)	71 (6.2)	4903 (34)	1893 (13)	12 278 (85)	137.2 (15.7)	5.3 (0.8)	24.2 (3.5)	5.7 (4.9-6.5)	High
A Study of Cardiovascular Events in Diabetes (ASCEND),[5] 2018	100 daily	Placebo	Randomized, double-blind; factorial design with n-3 fatty acid	Individuals with diabetes aged ≥40 y	United Kingdom	2005-2017	15 480	9684 (63)	63 (9.2)	15 480 (100)	1279 (8)	9533 (62)	136.2 (15.3)	4.2 (0.9)	30.7 (6.3)	10.2 (9.4-11.1)	Low
Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE),[6] 2018	100 daily	Placebo	Randomized, double-blind	Males with ≥2 and females with ≥3 CV risk factors. Aimed to recruit patients with 10-y CV risk of 10%-20%	Germany, Italy, Ireland, Poland, Spain, United Kingdom, and United States	2007-2016	12 546	8838 (70)	64 (7.1)	0 (0)	3594 (29)	7866 (63)	143.8 (90-199)[d]	NR	28.4 (4.3)	6.9 (6.1-7.9)	Low
Aspirin in Reducing Events in the Elderly (ASPREE),[13,18] 2018	100 daily	Placebo	Randomized, double-blind	Black or Hispanic individuals in the United States aged ≥65 y and other individuals aged ≥70 y	Australia and United States	2010-2014	19 114	8331 (44)	74 (NR)[d]	2057 (11)	735 (4)	14 283 (74)	139.2 (16.5)	5.3 (1.0)	28.1 (4.7)	8.3 (7.4-9.1)	Low

Abbreviations: ABPI, ankle-brachial pressure index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CV, cardiovascular; NA, not applicable; NR, not reported in study

[b] 10-Year risk of the primary cardiovascular outcome was calculated by multiplying the annualized event rate for the primary cardiovascular outcome in the control group by 10 years.

Figure 1. Cardiovascular and Bleeding Outcomes in all Participants

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Composite CV outcome	11	2911	79717	3072	78 147	0.38 (0.20 to 0.55)	0.89 (0.84-0.95)
All-cause mortality	13	3622	81623	3588	80 057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)
CV mortality	13	995	81623	997	80 057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)
Myocardial infarction	13	1469	81623	1599	80 057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)
Ischemic stroke	10	831	65316	942	63 752	0.16 (0.06 to 0.30)	0.81 (0.76-0.87)



Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Major bleeding	11	1195	74715	834	73 143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)
Intracranial bleeding	12	349	80985	257	79 419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)
Major GI bleeding	10	593	70336	380	70 465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)

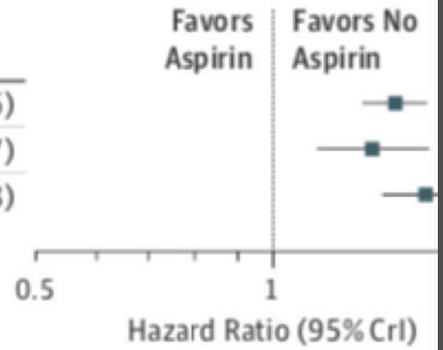
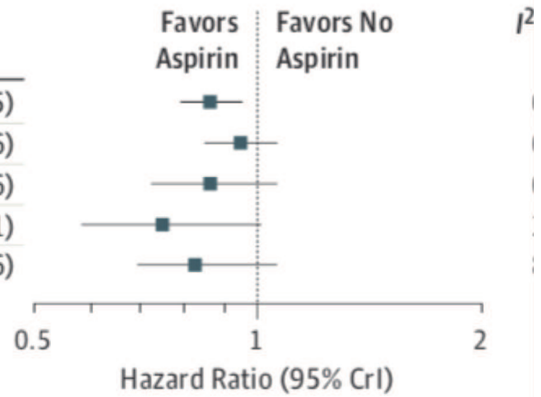


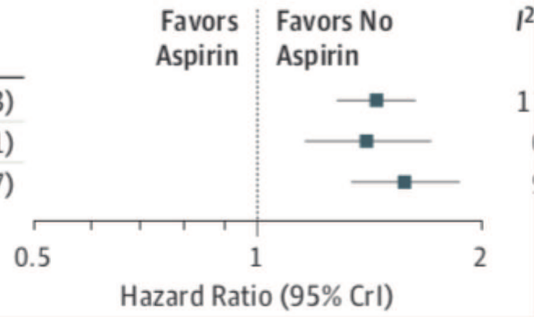
Figure 2. Cardiovascular and Bleeding Outcomes for Studies With Participants at High and Low Risk for the Primary CV Outcome and Participants With Diabetes

A Participants with low CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Composite CV outcome	6	1559	56212	1753	56354	0.34 (0.14 to 0.52)	0.87 (0.79-0.95)
All-cause mortality	6	1903	56212	1905	56354	0.01 (-0.27 to 0.27)	0.95 (0.85-1.06)
CV mortality	6	405	56212	448	56354	0.07 (-0.03 to 0.16)	0.87 (0.72-1.06)
Myocardial infarction	6	649	56212	793	56354	0.27 (0.00 to 0.49)	0.75 (0.58-1.01)
Ischemic stroke	5	508	49942	593	50078	0.16 (0.02 to 0.29)	0.83 (0.69-1.06)

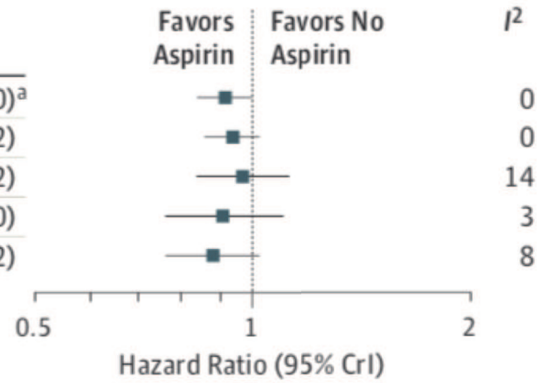


Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Major bleeding	5	665	49942	465	50078	0.40 (0.25 to 0.57)	1.45 (1.28-1.63)
Intracranial bleeding	6	245	56212	175	56354	0.13 (0.05 to 0.22)	1.41 (1.16-1.71)
Major GI bleeding	5	359	48992	228	49110	0.27 (0.15 to 0.40)	1.58 (1.34-1.87)

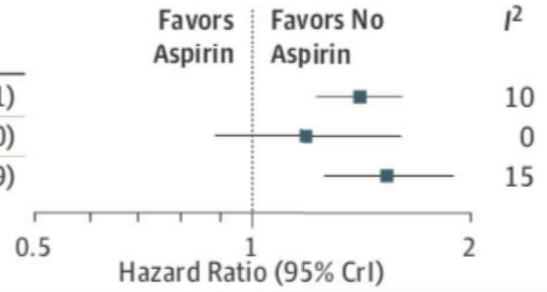


B Participants with high CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Composite CV outcome[c]	6	1352	23 505	1319	21 793	0.51 (0.06 to 0.93)	0.92 (0.84-1.00)[a]
All-cause mortality	7	1719	25 411	1683	23 703	0.43 (-0.02 to 0.84)	0.94 (0.86-1.02)
CV mortality	7	590	25 411	549	23 703	0.04 (-0.27 to 0.32)	0.97 (0.84-1.12)
Myocardial infarction[c]	8	820	25 411	806	23 703	0.32 (-0.16 to 0.74)	0.91 (0.76-1.10)
Ischemic stroke[c]	6	323	15 374	350	13 674	0.28 (-0.12 to 0.63)	0.88 (0.76-1.02)

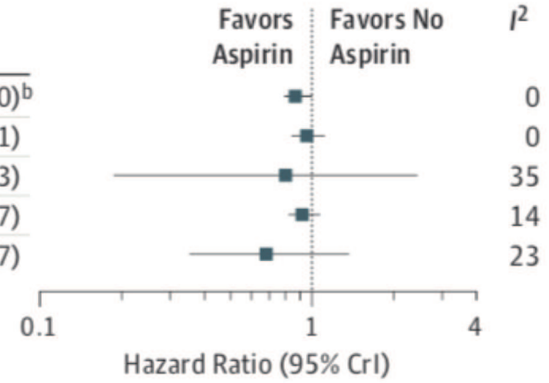


Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Major bleeding	6	530	24 773	369	23 065	0.64 (0.35 to 0.97)	1.41 (1.23-1.61)
Intracranial bleeding	6	104	24 773	82	23 065	0.07 (-0.04 to 0.21)	1.19 (0.89-1.60)
Major GI bleeding	5	34	19 452	30	19 444	0.39 (0.16 to 0.69)	1.54 (1.26-1.89)



C Participants with diabetes

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Composite CV outcome	7	850	14278	940	14260	0.65 (0.10 to 1.16)	0.89 (0.80-1.00)[b]
All-cause mortality	5	1028	11938	1055	11946	0.24 (-0.49 to 0.91)	0.97 (0.85-1.11)
CV mortality	4	264	10159	279	10167	0.05 (-1.27 to 0.94)	0.82 (0.19-2.43)
Myocardial infarction	8	472	11788	490	11700	0.26 (-0.47 to 0.88)	0.94 (0.83-1.07)
Ischemic stroke	3	275	9535	317	9511	0.83 (-0.50 to 1.70)	0.70 (0.36-1.37)



Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Major bleeding	3	370	10029	287	10047	0.80 (0.29 to 1.39)	1.29 (1.11-1.51)
Intracranial bleeding	2	63	9002	52	9017	0.12 (-0.09 to 0.43)	1.21 (0.84-1.76)
Major GI bleeding	2	142	9002	105	9017	0.41 (0.06 to 0.86)	1.35 (1.05-1.75)

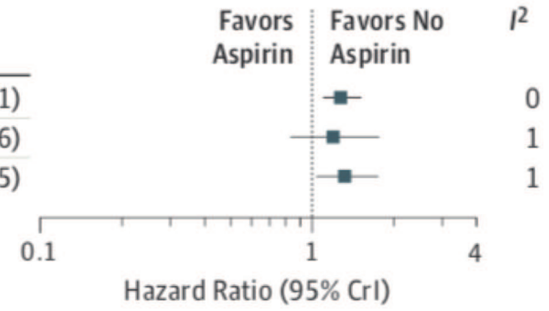
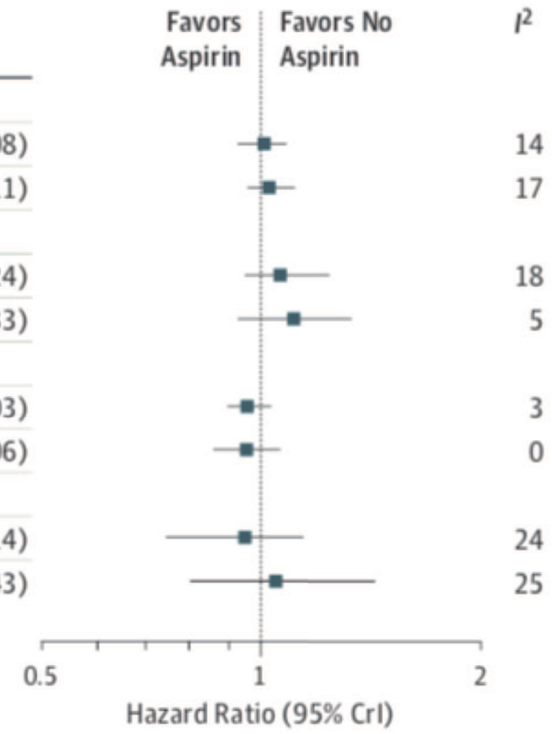


Figure 3. Exploratory Cancer Outcomes

Efficacy	No. of Studies	Aspirin		No Aspirin		Absolute Risk Difference, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
All participants								
Incident cancer	10	4507	63048	4409	61475	0.03 (-0.37 to 0.46)	1.01 (0.93-1.08)	14
Cancer mortality	12	1530	75353	1447	73781	0.05 (-0.11 to 0.23)	1.03 (0.96-1.11)	17
Low CV risk participants								
Incident cancer	4	2837	38905	2730	39044	0.41 (-0.13 to 1.01)	1.06 (0.95-1.24)	18
Cancer mortality	5	823	49942	748	50078	0.16 (-0.06 to 0.42)	1.11 (0.93-1.33)	5
High CV risk participants								
Incident cancer	6	1670	24143	1679	22431	-0.30 (-0.76 to 0.19)	0.96 (0.90-1.03)	3
Cancer mortality	7	707	25411	699	23703	-0.13 (-0.41 to 0.17)	0.96 (0.86-1.06)	0
Participants with diabetes								
Incident cancer	3	1091	9640	1116	9655	-0.68 (-2.09 to 0.95)	0.95 (0.74-1.14)	24
Cancer mortality	4	445	10667	438	10685	0.16 (-0.56 to 1.02)	1.05 (0.80-1.43)	25



Conclusions

In this meta-analysis, the use of aspirin in individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding. This information may inform discussions with patients about aspirin for primary prevention of cardiovascular events and bleeding.