Can we use aspirin to prevent cardiovascular events in apparently healthy adult individuals?

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A heavily debated topic

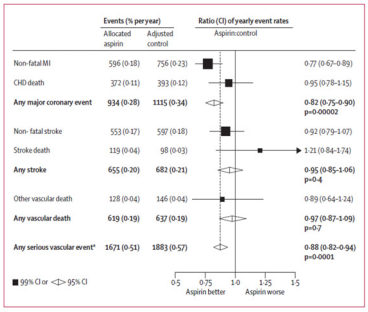
: aspirin for primary prevention of cardiovascular events in patients without prior history of atherosclerotic cardiovascular disease

- The European Association for Cardiovascular Prevention & Rehabilitation (EACPR)[1]: **against its use**
- U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement[2]: **high-risk patients (with high cardiovascular risk)**
- American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research; American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association[3]: **high-risk patients (with diabetes)**

1. Eur Heart J 2016;37:2315–2381.
2. Ann Intern Med 2016;164:836–845.
3. Circulation 2015;132:691–718.

Current Practice

- With these conflicting recommendations, aspirin is still widely used among healthy individuals without established atherosclerosis in the hope of preventing myocardial infarction (MI) and death.
- The recommendation for aspirin use in primary prevention was largely based on a pooled analysis of six randomized trials that showed a reduction in ischemic events with aspirin.[1]



1. Lancet 2009;373:1849–1860.

Uncertainty remains

regarding whether there is a favorable balance of benefit to harm for aspirin in the setting of primary prevention

- The benefit of aspirin for patients with history of an acute ischemic event (i.e. MI or ischemic stroke) is better established: secondary prevention.
- In primary prevention, for example, 21.8% reported taking aspirin for primary prevention, with only a slight decline from previous years in the United States.

1. Prev Med Rep 2017;5:183–186.

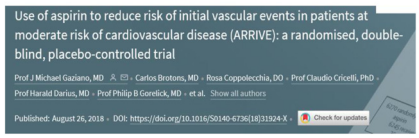
Recent Meta-Analysis Studies

- The first study: aspirin reduced all-cause mortality, MI, and ischemic stroke, with an increased risk of major bleeding.[1]
- The second study: aspirin reduced non-fatal MI, with little or no effect on cardiovascular or all-cause mortality, compared with control in primary prevention.[2]
- However, these analyses included several trials of patients with known atherosclerosis and peripheral vascular disease.[3,4]
  1) This heterogeneity in the patient population selection might have impacted the findings of these meta-analyses.
  2) The benefit of aspirin in these meta-analyses has been attributed to relatively few studies.

1. Am J Med 2011;124:621–629.
2. Ann Intern Med 2016;164:804–813.
3. JAMA 2010;303:841–848.
4. BMJ 2008;337:a1840.

Recent large-scale randomized trials

: a reappraisal of the current evidence based is warranted.



Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

Prof J Michael Gaziano, MD • Carlos Brotons, MD • Rosa Coppolecchia, DO • Prof Claudio Cricelli, PhD • Prof Harald Darius, MD • Prof Philip B Gorelick, MD • et al. Show all authors

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ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

October 18, 2018

N Engl J Med 2018; 379:1529-1539

DOI: 10.1056/NEJMoa1804988

ORIGINAL ARTICLE

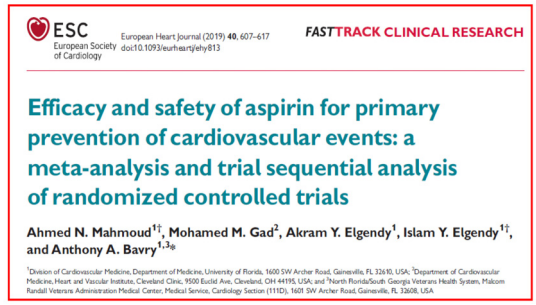
Effect of Aspirin on All-Cause Mortality in the Healthy Elderly

John J. McNeil, M.B., B.S., Ph.D., Mark R. Nelson, M.B., B.S., Ph.D., Robyn L. Woods, Ph.D., Jessica E. Lockery, M.B., B.S., Rory Wolfe, Ph.D., Christopher M. Reid, Ph.D., M.P.H., Brenda Kirpach, C.C.R.A., Raj C. Shah, M.D., Diane G. Ives, M.P.H., Eladon Storey, M.B., B.S., D.Phil., Joanne Ryan, Ph.D., Andrew M. Tonkin, M.B., B.S., M.D., et al., for the ASPREE Investigator Group*

October 18, 2018

N Engl J Med 2018; 379:1519-1528

DOI: 10.1056/NEJMoa1803955



ESC European Society of Cardiology

European Heart Journal (2019) 40, 607–617

doi:10.1093/eurheartj/ehy813

FASTTRACK CLINICAL RESEARCH

Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials

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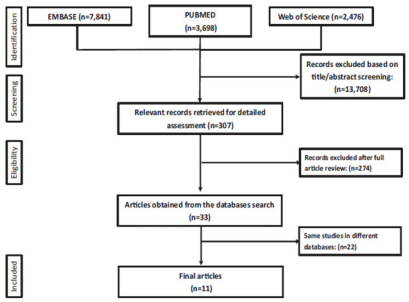
- Perform an updated meta-analysis and trial sequential analysis of randomized trials to evaluate the efficacy and safety of aspirin (ASA) among patients without prior known history of atherosclerotic cardiovascular disease.



- Data sources: Pubmed, MEDLINE, Web of Science, and Embase (from inception till 25 September 2018 for randomized trials comparing aspirin with placebo or no aspirin control)

- Inclusion criteria:

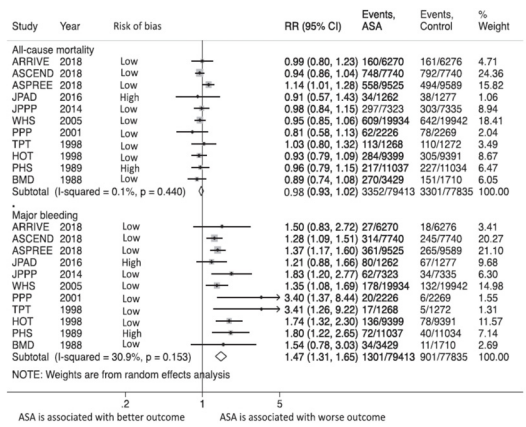
1) Randomized trial
2) Comparing aspirin vs. placebo/no aspirin control
3) In adult patients without prior history of atherosclerosis (including peripheral arterial disease, coronary artery disease, prior MI, prior stroke or TIA, prior percutaneous coronary intervention, prior coronary artery bypass grafting)
4) including ≥ 500 patients

Table 1 Study baseline characteristics

Trial	ARRIVE[12]	ASCEND[13]	ASPREE[14]	JPAD[15]	JPPP[16]	WHS[19]	PPP[20]	TPT[21]	HOT[17]	PHS[18]	BMD[22]
Year	2018	2018	2018	2016	2014	2005	2001	1998	1998	1989	1988
Patient population	Patients with moderate cardiovascular risk	Diabetic patients without known cardiovascular disease	People without cardiovascular disease, dementia, or disability	Diabetic patients	Patients with hypertension, dyslipidaemia, or diabetes	Female health professionals	Patients over 50 years	Men at increased cardiovascular risk	Hypertensive patients	Male physicians	Male physicians
Control arm	Placebo	Placebo	Placebo	No ASA	No ASA	Placebo	No ASA	Placebo	Placebo	Placebo	No ASA
Follow-up (years)	5	7.4	4.7	10.3	6.5	10.1	3.6	6.8	3.8	5	6
Lost to follow-up (%)	3/3	1/1	2/2	38/34	10/11	1/3	1/1	—	3[a]	—	0/0
10-Year MACE[b] in control arm (%)	5.7	10.8	7.8	12.9	5.9	2.6	7.8	—	10.5	6.7	—
Enrolment range (mid enrolment year)	2007–2016 (2012)	2005–2011 (2008)	2010–2014 (2012)	2003–2005 (2005)	2005–2007 (2006)	1992–1995 (1993)	1994–1998 (1996)	1984–1989 (1987)	1992–1996 (1994)	1981–1987 (1984)	1978–1979 (1978)
Risk of bias	Low	Low	Low	High	Low	Low	Low	Low	Low	High	Low
Number of patients	6270/6276	7740/7740	9525/9589	1262/1277	7323/7335	19 934/19 942	2226/2269	1268/1272	9399/9391	11 037/11 034	3429/1710
Mean age (years)	63.9/63.9	63.2/63.3	50% ≥74 years	65/64	70.6/70.5	54.6/54.6	64.4/64.4	57.7/57.3	61.5/61.5	55% >50 years	53% ≥60 years
Females (%)	30/30	37/38	56/56	43/46	58/58	100/100	57/58	0/0	47/47	0/0	0/0
Hypertension (%)	63/63	62/62	74/75	59/57	85/85	26/26	69/68	139/139[c]	170/170[c]	39/39	9/10
Smoking (%)	29/29	8/8	4/4	23/19	13/13	13/13	15/15	41/42	16/16	11/11	31/32
Daily dose of aspirin (mg/day)	100	100	100	81/100	100	100[d]	100	75	75	325[d]	500 (or 300)

Data are presented as aspirin/control and percentages are approximated to the nearest integer.
MACE, major adverse cardiovascular events.
[a]Percentage is of the total cohort.
[b]MACE was defined as composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, whenever possible.
[c]Mean systolic blood pressure in both arms.
[d]Every other day doses.

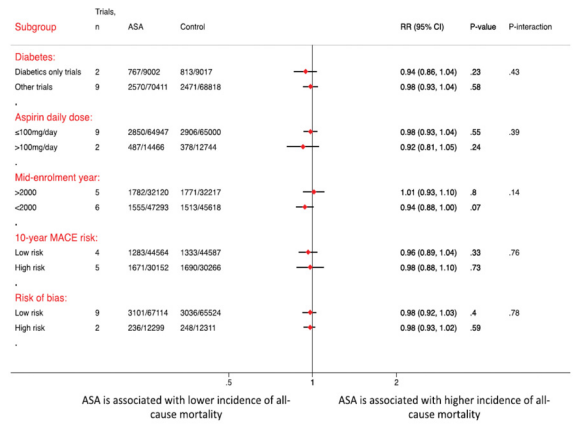
Primary efficacy (all-cause mortality) and safety (major bleeding) outcomes.



Study	Year	Risk of bias	RR (95% CI)	Events, ASA	Events, Control	% Weight
All-cause mortality						
ARRIVE	2018	Low	0.99 (0.80, 1.23)	160/6270	161/6276	4.71
ASCEND	2018	Low	0.94 (0.86, 1.04)	748/7740	792/7740	24.36
ASPREE	2018	Low	1.14 (1.01, 1.28)	558/9525	494/9589	15.82
JPAD	2016	High	0.91 (0.57, 1.43)	34/1262	38/1277	1.06
JPPP	2014	Low	0.98 (0.84, 1.15)	297/7323	303/7335	8.94
WHS	2005	Low	0.95 (0.85, 1.06)	609/19934	642/19942	18.41
PPP	2001	Low	0.81 (0.58, 1.13)	62/2226	78/2269	2.04
TPT	1998	Low	1.03 (0.80, 1.32)	113/1268	110/1272	3.49
HOT	1998	Low	0.93 (0.79, 1.09)	284/9399	305/9391	8.67
PHS	1989	High	0.96 (0.79, 1.15)	217/11037	227/11034	6.47
BMD	1988	Low	0.89 (0.74, 1.08)	270/3429	151/1710	6.05
Subtotal	(I-squared = 0.1%, p = 0.440)		0.98 (0.93, 1.02)	3352/79413	3301/77835	100.00
Major bleeding						
ARRIVE	2018	Low	1.50 (0.83, 2.72)	27/6270	18/6276	3.41
ASCEND	2018	Low	1.28 (1.09, 1.51)	314/7740	245/7740	20.27
ASPREE	2018	Low	1.37 (1.17, 1.60)	361/9525	265/9589	21.10
JPAD	2016	High	1.21 (0.88, 1.66)	80/1262	67/1277	9.68
JPPP	2014	Low	1.83 (1.20, 2.77)	62/7323	34/7335	6.30
WHS	2005	Low	1.35 (1.08, 1.69)	178/19934	132/19942	14.98
PPP	2001	Low	3.40 (1.37, 8.44)	20/2226	6/2269	1.55
TPT	1998	Low	3.41 (1.26, 9.22)	17/1268	5/1272	1.31
HOT	1998	Low	1.74 (1.32, 2.30)	136/9399	78/9391	11.57
PHS	1989	High	1.80 (1.22, 2.65)	72/11037	40/11034	7.14
BMD	1988	Low	1.54 (0.78, 3.03)	34/3429	11/1710	2.69
Subtotal	(I-squared = 30.9%, p = 0.153)		1.47 (1.31, 1.65)	1301/79413	901/77835	100.00

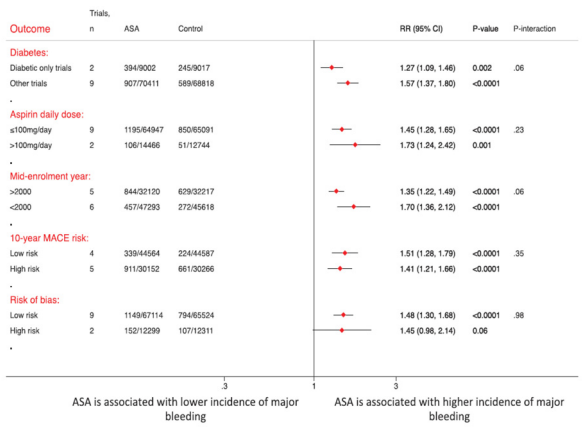
NOTE: Weights are from random effects analysis

Primary efficacy (all-cause mortality) according to various subgroups of interest

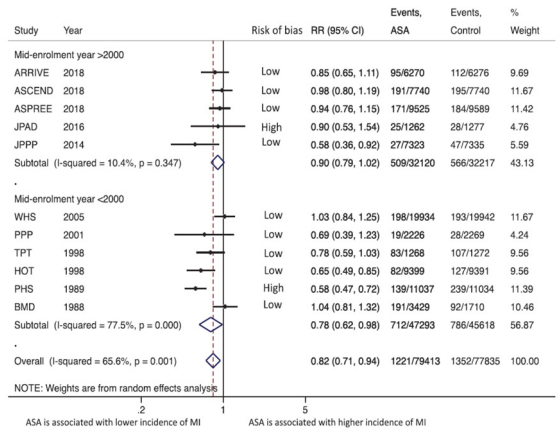


Subgroup	Trials, n	ASA	Control	RR (95% CI)	P-value	P-interaction
Diabetes:						
Diabetics only trials	2	767/9002	813/9017	0.94 (0.86, 1.04)	.23	.43
Other trials	9	2570/70411	2471/68818	0.98 (0.93, 1.04)	.58	
Aspirin daily dose:						
≤100mg/day	9	2850/64947	2906/65000	0.98 (0.93, 1.04)	.55	.39
>100mg/day	2	487/14466	378/12744	0.92 (0.81, 1.05)	.24	
Mid-enrolment year:						
>2000	5	1782/32120	1771/32217	1.01 (0.93, 1.10)	.8	.14
<2000	6	1555/47293	1513/45618	0.94 (0.88, 1.00)	.07	
10-year MACE risk:						
Low risk	4	1283/44564	1333/44587	0.96 (0.89, 1.04)	.33	.76
High risk	5	1671/30152	1690/30266	0.98 (0.88, 1.10)	.73	
Risk of bias:						
Low risk	9	3101/67114	3036/65524	0.98 (0.92, 1.03)	.4	.78
High risk	2	236/12299	248/12311	0.98 (0.93, 1.02)	.59	

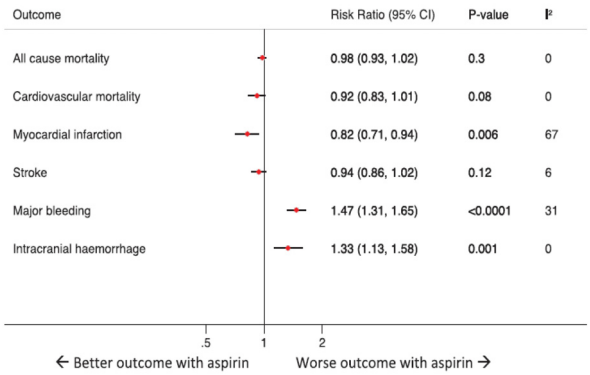
Primary safety (major bleeding) according to various subgroups of interest



MI outcome according to the mid-enrollment year of the included trials



TAKE HOME FIGURE (RR with 95% CI)



Conclusions

- Aspirin use among healthy individuals without known atherosclerosis appears to be associated with increased harm and lack of mortality benefit.
- In this setting, aspirin is possibly associated with a modest reduction in MI risk; however, this comes at a cost of increased major bleeding and including intracranial hemorrhage.
- The routine use of aspirin for primary prevention needs to be reconsidered.

Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Preventive Medication (April 2016)

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD 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.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who 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 are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I