Does an Aspirin a Day Really Keep the Doctor away

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Disclosure

Presenter disclosure

- **Relationships with financial interests:**
  - **Grants/Research Support:** Bayer, Boehringer Ingelheim, Accorda Therapuetics, Servier, Allergan, Ipsen. CIHR
  - **Speakers Bureau/Honoraria:** Bayer, Servier, Allergan, Novartis
  - **Consulting Fees:** Servier, Bayer, Ipsen, Amgen, Allergan, Novartis, Merz
  - **Other:** N/A

Potential for conflict(s) of interest:

- **Consultant:** Bayer, Servier, Allergan, Dysport

Introduction

- Three major trials (ASPREE, ASCEND, ARRIVE) released in 2018 finding that the risks of serious bleeding outweighed the benefit of reduced heart conditions, stroke and vascular events in healthy people.
- These findings confirmed through several meta-analyses published since the trials released
- Heart & Stroke led an extensive review of the literature and developed recommendations to respond to this new evidence

ASPREE 2018

ARRIVE 2018

ASCEND 2018

GUIDELINE CPD

Canadian Stroke Best Practice Recommendations, seventh edition: acetylsalicylic acid for prevention of vascular events

Theodore Wein MD, M. Patrice Lindsay RN PhD, David J. Gladstone MD PhD, Alexandre Poppe MD CM, Alan Bell MD, Leanne K. Casaubon MD MSc, Norine Foley MSc, Shelagh B. Coutts MD MBChB, Jafna Cox MD, James Douketis MD, Thalia Field MD MHSc, Laura Gioia MD MSc, Jeffrey Habert MD, Eddy Lang MD MDCM, Shamir R. Mehta MD MSc, Christine Papoushek PharmD, William Semchuk PharmD MSc, Mikul Sharma MD MSc, Jacob A. Udell MD MPH, Stephanie Lawrence BA Dip. J., Anita Mountain MD, Gord Gubitz MD, Dar Dowlatshahi MD PhD, Anne Simard MHSc BJ, Andrea de Jong RN MN, Eric E. Smith MD MPH; for the Heart and Stroke Foundation of Canada in collaboration with the Canadian Stroke Consortium

CMAJ 2020 March 23;192:E302-11.

How many Canadians take ASA?

Number of People in Canada in 2019
20 years of age or older
= 29,460,338

5,008,257
- Advised to take ASA by a health professional (17%)

2,904,789
- Following HCP advice and taking ASA (58% of above group)

2,445,208
- Taking ASA on their own (8%)

4,713,654
- Would choose to take ASA even knowing the risks (16%)

5,349,997
People in Canada currently taking ASA (1 in 6)

New Recommendations:

Secondary prevention

- A*cetylsalicylic acid* (ASA) is strongly recommended for **secondary prevention** in individuals with symptomatic cardiovascular, cerebrovascular or peripheral arterial disease [Evidence Level A].

New Recommendations:

Primary prevention

- The use of ASA is not recommended for **primary prevention** of a first vascular event [Evidence Level A].
  - This recommendation pertains to individuals with vascular risk factors who have **not** had a vascular event [Evidence Level A] and for healthy older individuals without vascular risk factors [Evidence Level B].
  - The net benefit of ASA in individuals with asymptomatic atherosclerosis is uncertain [Evidence Level B].

Shared decision-making

- Health professionals (such as physicians [primary care or subspecialty], nurses and nurse practitioners, pharmacists, physician assistants) should engage patients and caregivers in discussions regarding the use of ASA for primary prevention of vascular disease.

- An individual's risk, benefit, values and preferences should be considered in order to make an informed decision to initiate, continue or discontinue ASA for primary prevention of vascular disease [Evidence Level B].

History of Salicylate

- Medicines made from Willow Bark is reported on clay tablets from Sumer and also found on the Ebers Papyrus from ancient Egypt

- Hippocrates referred to the use of salicylic tea to reduce fevers around 400 BC

- Willow bark extract became recognized for its specific effects on fever, pain and inflammation in the mid-eighteenth century

- In 1853, chemist Charles Frederic Gerrhardt treated sodium salicylate with acetyl chloride to produce acetylsalicylic acid for the first time


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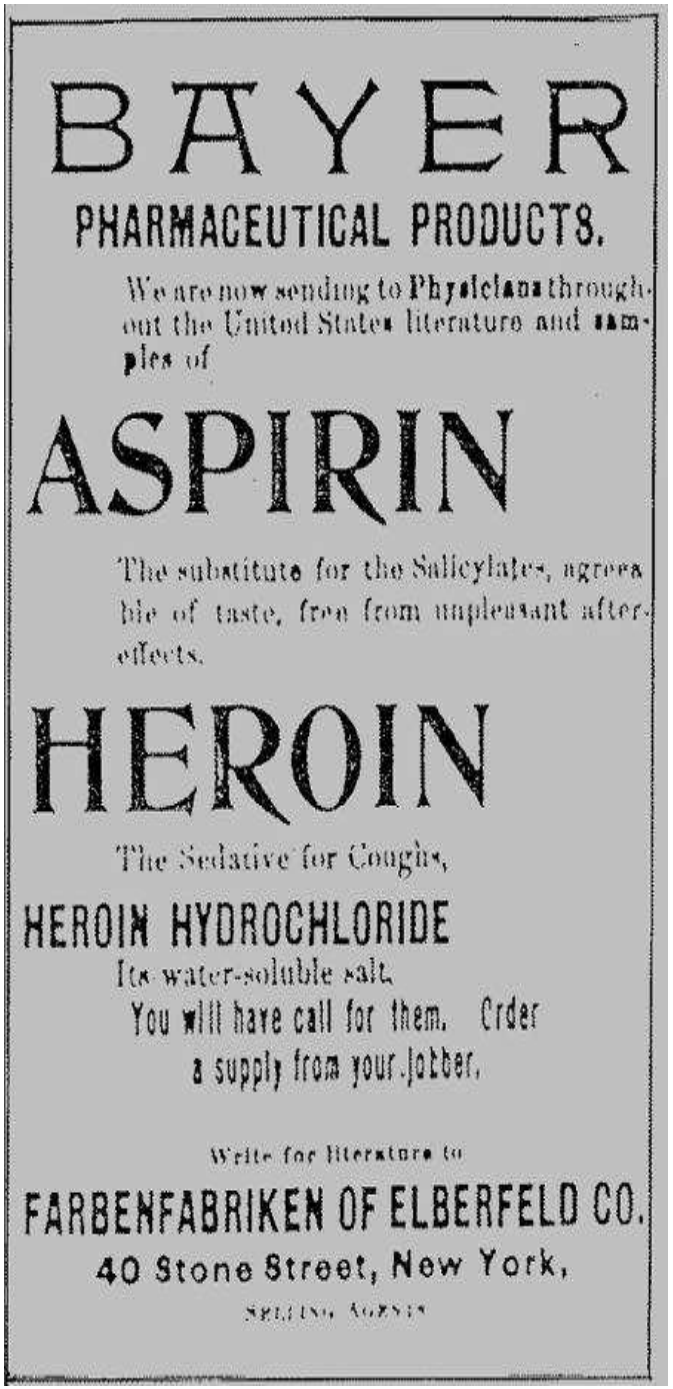

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History of Salicylate

- Aspirin is one of the most widely used medications globally, with an estimated 40,000 tonnes (44,000 tons) (50 to 120 billion pills) consumed each year

- It is on the World Health Organization's List of Essential Medicines

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

J Michael Gaziano, Carlos Brotons, Rosa Coppolecchia, Claudio Cricelli, Harald Darius, Philip B Gorelick, George Howard, Thomas A Pearson, Peter M Rothwell, Luis Miguel Ruilope, Michal Tendera, Gianni Tognoni; the ARRIVE Executive Committee

Lancet 2018; 392: 1036–46

Inclusion Criteria

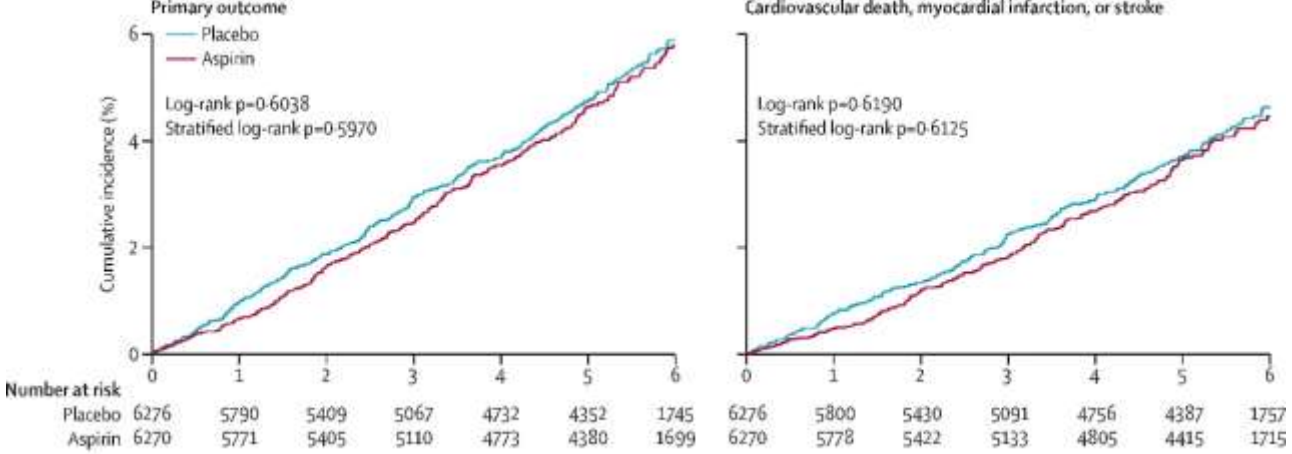
- Men > 55 years
  - 2 – 4 risk factors (smoking, DL, HTN, +ve FH)
- Women > 60 years
  - 3 or > risk factors (smoking, DL, HTN, +ve FH)
- No history of vascular event
- Randomized to ASA 100mg or placebo

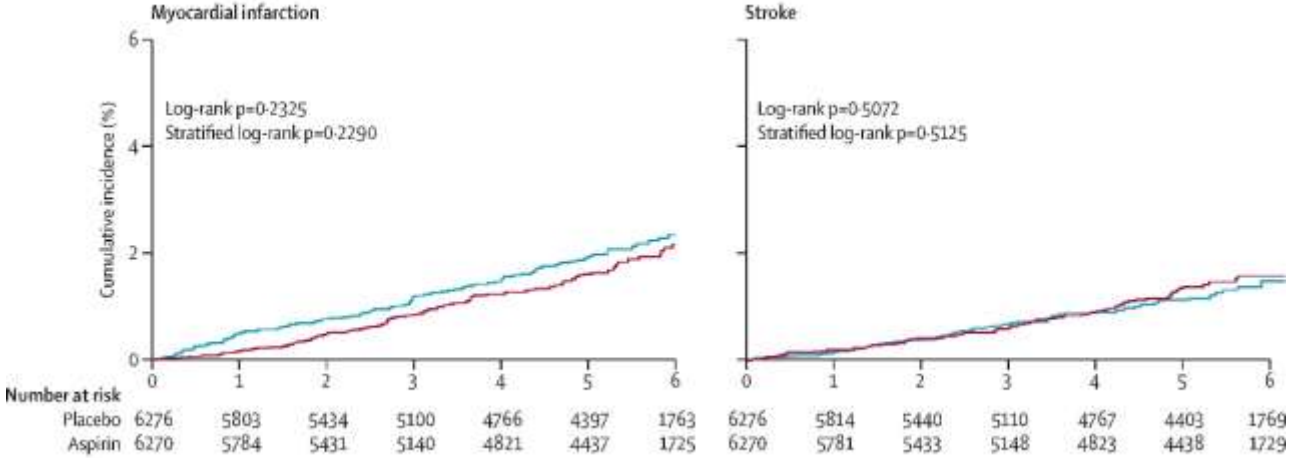
Results

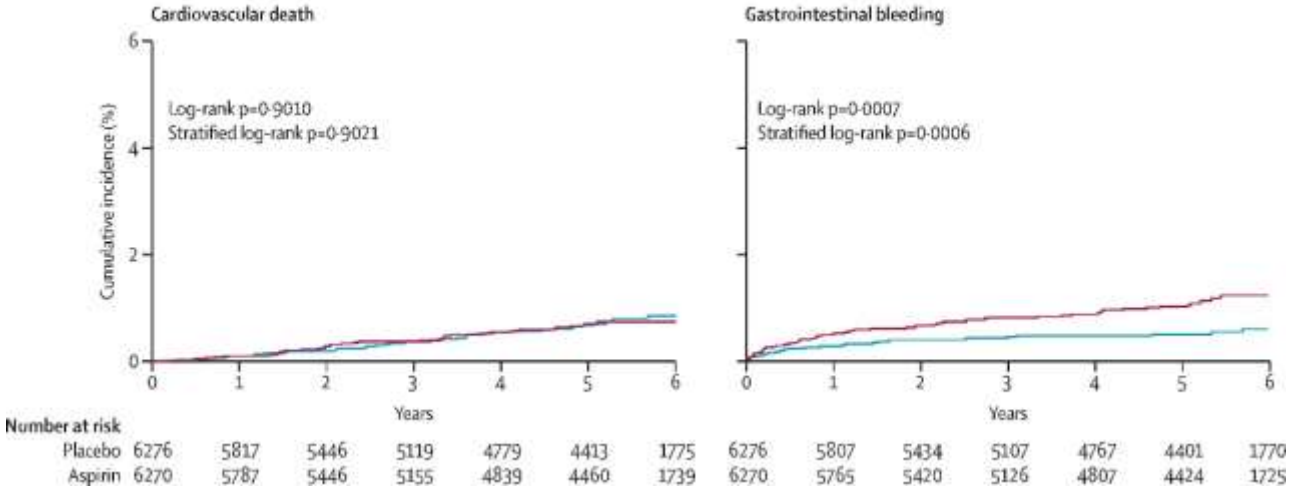
- Primary outcome: Composite vascular event
  - (cardiovascular death, myocardial infarction, unstable angina, stroke, TIA)

- 12,546 patients, mean age 64 years

- After 5.1 years
  - No reduction in the primary outcome or component
  - Increased adverse events in the ASA group
    - GI Bleeds HR 2.11 95% CI 1.36-3.28; p=0.0007
    - 0.97% vs 0.46% over 5 years


Primary outcome
Placebo
Aspirin
Log-rank p=0·6038
Stratified log-rank p=0·5970
Cumulative incidence (%)
Cardiovascular death, myocardial infarction, or stroke
Log-rank p=0·6190
Stratified log-rank p=0·6125
Number at risk
Placebo 6276 5790 5409 5067 4732 4352 1745 6276 5800 5430 5091 4756 4387 1757
Aspirin 6270 5771 5405 5110 4773 4380 1699 6270 5778 5422 5133 4805 4415 1715


Myocardial infarction
Log-rank p=0·2325
Stratified log-rank p=0·2290
Cumulative incidence (%)
Stroke
Log-rank p=0·5072
Stratified log-rank p=0·5125
Number at risk
Placebo 6276 5803 5434 5100 4766 4397 1763 6276 5814 5440 5110 4767 4403 1769
Aspirin 6270 5784 5431 5140 4821 4437 1725 6270 5781 5433 5148 4823 4438 1729


Cardiovascular death
Log-rank p=0·9010
Stratified log-rank p=0·9021
Cumulative incidence (%)
Gastrointestinal bleeding
Log-rank p=0·0007
Stratified log-rank p=0·0006
Years
Number at risk
Placebo 6276 5817 5446 5119 4779 4413 1775 6276 5807 5434 5107 4767 4401 1770
Aspirin 6270 5787 5446 5155 4839 4460 1739 6270 5765 5420 5126 4807 4424 1725

ASPREE

ORIGINAL ARTICLE

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

J.J. McNeil, R. Wolfe, R.L. Woods, A.M. Tonkin, G.A. Donnan, M.R. Nelson, C.M. Reid, J.E. Lockery, B. Kirpach, E. Storey, R.C. Shah, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, C.I. Johnston, J. Ryan, B. Radziszewska, M. Jelinek, M. Malik, C.B. Eaton, D. Brauer, G. Cloud, E.M. Wood, S.E. Mahady,

N Engl J Med 2018;379:1509-18.

Inclusion Criteria

- African American or Hispanic men or women over 64 years of age

- Caucasian men or women over 69 years of age
- No history of vascular event

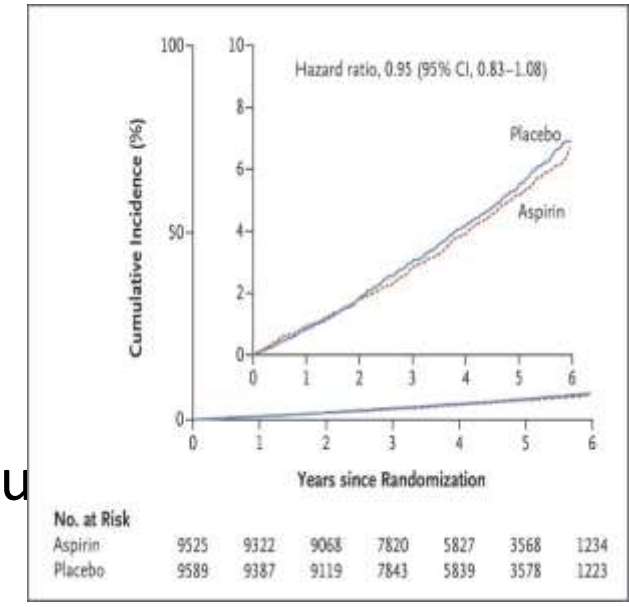
- Randomized to ASA 100mg or placebo

Results

- Primary outcome: Composite vascular event
  - (major hemorrhage and cardiovascular disease (defined as fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure)

- 19,114 patients, mean age 74 years

- After 4.7 years
  - No reduction in the primary outcome
  - Increased hemorrhagic events in the ASA grou
    - 1.38; 95% CI 1.18 to 1.62; P<0.001
    - 0.86% vs 0.62% over 4.7 years



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

N Engl J Med 2018;379:1529-39.

Inclusion Criteria

- Men and women > 39 years of age
- With type 1 or 2 diabetes
- No history of vascular events
- Randomized to ASA 100mg or placebo

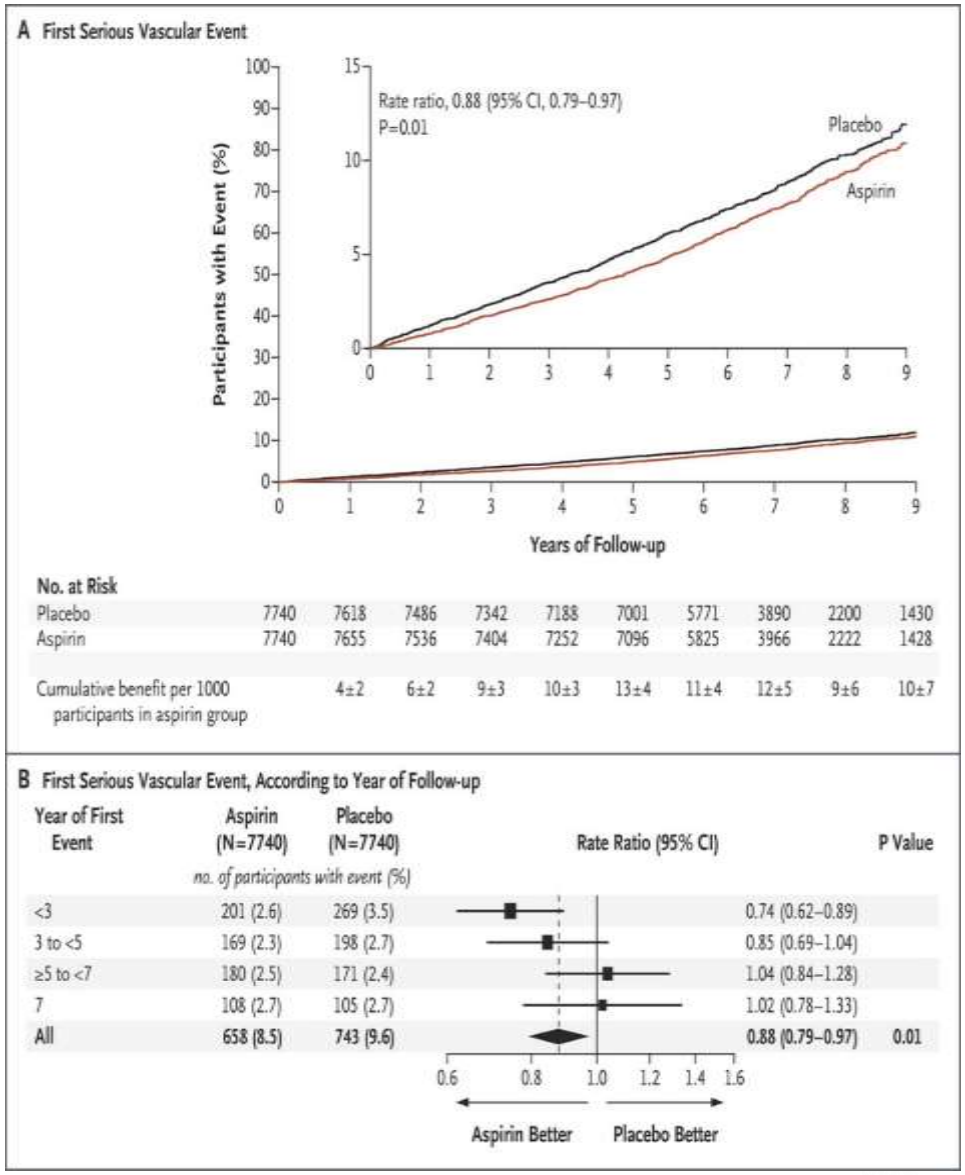
Results

- **Primary outcome: Composite vascular event**
  - **MI, Stroke or TIA, or death from any vascular cause, excluding any confirmed intracranial hemorrhage**

- **15,480 patients, mean age 63 years**

- **After 7.4 years**
  - **Primary outcome: 8.5%(ASA) vs 9.6%(Placebo)**
    - **0.88; 95% CI, 0.79 to 0.97; P=0.01**
  - **Risk of major bleeding: 4.1%(ASA)vs 3.2%(Placebo)**
    - **1.29; 95% CI, 1.09 to 1.52; P=0.003**

First Serious Vascular Event during Follow-up.



The ASCEND Study Collaborative Group. N Engl J Med 2018;379:1529-1539.

Conclusion

- **Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events.**

- **The absolute benefits were largely counterbalanced by the bleeding hazard.**

Research

JAMA Neurology | Original Investigation

Frequency of Intracranial Hemorrhage With Low-Dose Aspirin in Individuals Without Symptomatic Cardiovascular Disease

A Systematic Review and Meta-analysis

Wen-Yi Huang, MD, PhD; Jeffrey L. Saver, MD; Yi-Ling Wu, DrPH; Chun-Jen Lin, MD, PhD; Meng Lee, MD; Bruce Ovbiagele, MD, FRCP

JAMA Neurol. 2019;76(8):906-914

Huang 2019

- 13 RCTs n=134,446
- Primary prevention (age 43-74)
- Primary Outcome ICH

Results

- Low-dose aspirin, compared with control, was associated with an increased risk of any intracranial bleeding
  - 8 trials; relative risk, 1.37; 95% CI, 1.13-1.66
  - 2 additional intracranial hemorrhages in 1000 people

- Greatest relative risk for subdural or extradural hemorrhages
  - 4 trials; relative risk, 1.53; 95% CI, 1.08-2.1

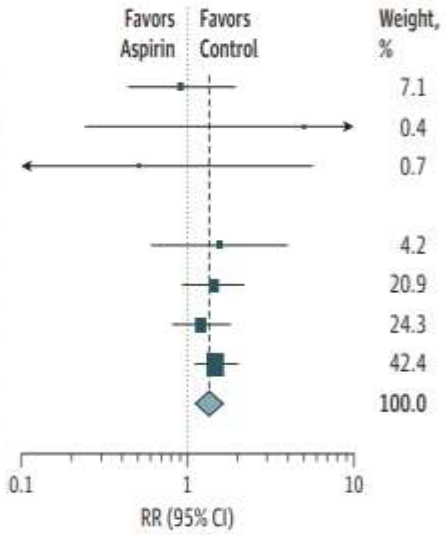
Figure 1. Relative Risk (RR) for Intracranial Hemorrhage (Aspirin vs Placebo or No Aspirin)

A Any intracranial hemorrhage

Study or Subgroup	Aspirin No. of Events	Aspirin No. of Patients	Placebo No. of Events	Placebo No. of Patients	RR (95% CI)
Hansson et al (HOT),[32] 1998	14	9399	15	9391	0.93 (0.45-1.93)
de Gaetano (PPP),[29] 2001	2	2226	0	2269	5.10 (0.24-106.10)
Landolfi et al (ECLAP),[34] 2004	1	253	2	265	0.52 (0.05-5.74)
Erkan et al (APLASA),[30] 2007	0	48	0	50	Not estimable
Fowkes et al (AAA),[31] 2010	11	1675	7	1675	1.57 (0.61-4.04)
Ikeda et al (JPPP),[33] 2014	52	7220	36	7244	1.45 (0.95-2.21)
Bowman et al (ASCEND),[14] 2018	55	7740	45	7740	1.22 (0.83-1.81)
McNeil et al (ASPREE),[15] 2018	107	9525	72	9589	1.50 (1.11-2.01)
Total (95% CI)		**38086**		**38223**	**1.37 (1.13-1.66)**
Total events	242		177		

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 3.22$; $P = .78$; $I^2 = 0\%$

Overall effect: $z = 3.17$; $P = .002$

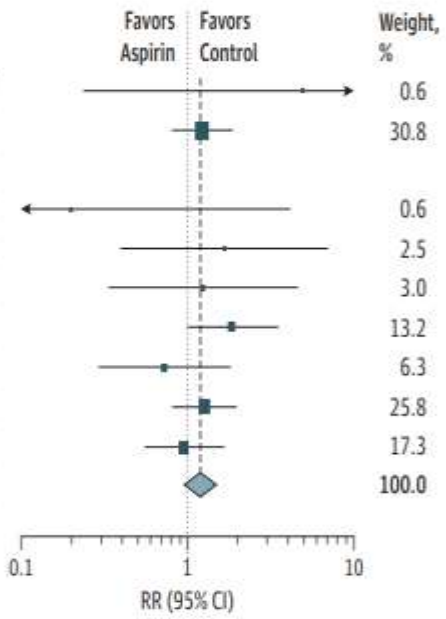


B Intracerebral hemorrhage

Thrombosis Prevention Trial,[25] 1998	2	1268	0	1272	5.02 (0.24-104.37)
Ridker et al (WHS),[37] 2005	51	19934	41	19942	1.24 (0.83-1.88)
Erkan et al (APLASA),[30] 2007	0	48	0	50	Not estimable
Belch et al (POPADAD),[26] 2008	0	318	2	318	0.20 (0.01-4.15)
Ogawa et al (JPAD),[35] 2008	5	1262	3	1277	1.69 (0.40-7.04)
Fowkes et al (AAA),[31] 2010	5	1675	4	1675	1.25 (0.34-4.65)
Ikeda et al (JPPP),[33] 2014	28	7220	15	7244	1.87 (1.00-3.50)
Gaziano et al (ARRIVE),[13] 2018	8	6270	11	6276	0.73 (0.29-1.81)
McNeil et al (ASPREE),[15] 2018	43	9525	34	9589	1.27 (0.81-1.99)
Bowman et al (ASCEND),[14] 2018	25	7740	26	7740	0.96 (0.56-1.66)
Total (95% CI)		**55260**		**55383**	**1.23 (0.98-1.54)**
Total events	167		136		

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 6.20$; $P = .62$; $I^2 = 0\%$

Overall effect: $z = 1.77$; $P = .08$

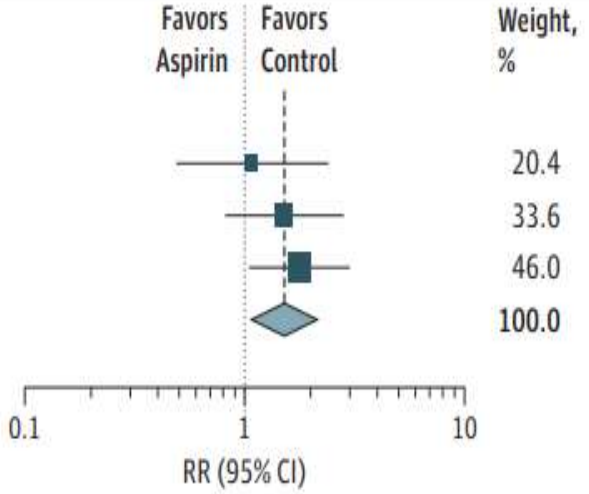


C Subdural or extradural hemorrhage

Erkan et al (APLASA),[30] 2007	0	48	0	50	Not estimable
Ikeda et al (JPPP),[33] 2014	13	7220	12	7244	1.09 (0.50-2.38)
Bowman et al (ASCEND),[14] 2018	26	7740	17	7740	1.53 (0.83-2.82)
McNeil et al (ASPREE),[15] 2018	39	9525	22	9589	1.78 (1.06-3.01)
Total (95% CI)		**24533**		**24623**	**1.53 (1.08-2.18)**
Total events	78		51		

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 1.07$; $P = .59$; $I^2 = 0\%$

Overall effect: $z = 2.36$; $P = .02$



D Subarachnoid hemorrhage

Thrombosis Prevention Trial,[25] 1998	1	1268	2	1272	0.50 (0.05-5.52)
Erkan et al (APLASA),[30] 2007	0	48	0	50	Not estimable
Ikeda et al (JPPP),[33] 2014	10	7220	8	7244	1.25 (0.50-3.18)
Bowman et al (ASCEND),[14] 2018	7	7740	8	7740	0.88 (0.32-2.41)
McNeil et al (ASPREE),[15] 2018	18	9525	14	9589	1.29 (0.64-2.60)
Total (95% CI)		**25801**		**25895**	**1.13 (0.70-1.83)**
Total events	36		32		

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 0.88$; $P = .83$; $I^2 = 0\%$

Overall effect: $z = 0.51$; $P = .61$

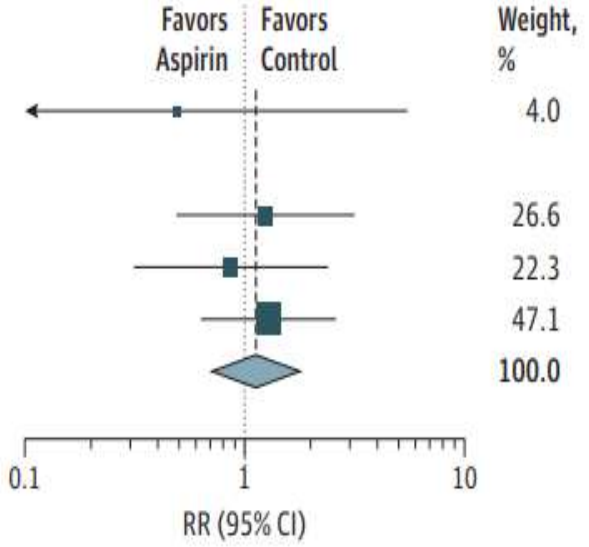
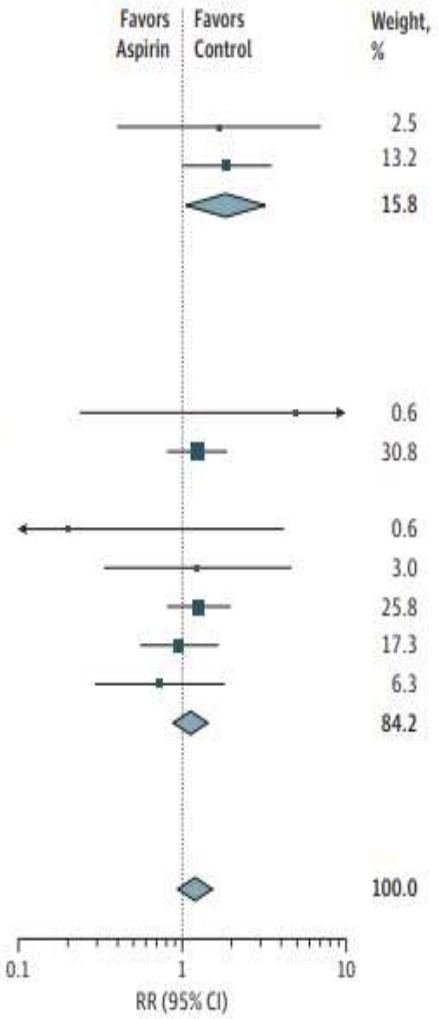


Figure 2. Subgroup Analysis of Intracerebral Hemorrhage (Aspirin vs Placebo or No Aspirin)

A Asian and non-Asian patients

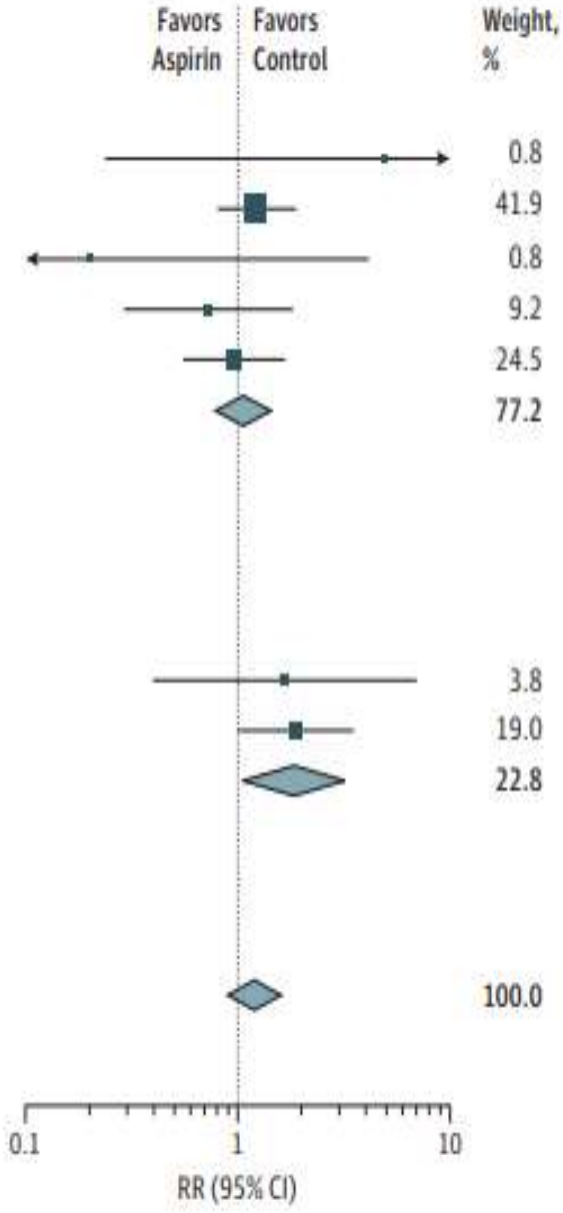
Study or Subgroup	Aspirin No. of Events	Aspirin No. of Patients	Placebo No. of Events	Placebo No. of Patients	RR (95% CI)	Weight, %
Asian Patients						
Ogawa et al (JPAD),[35] 2008	5	1262	3	1277	1.69 (0.40-7.04)	2.5
Ikeda et al (JPPP),[33] 2014	28	7220	15	7244	1.87 (1.00-3.50)	13.2
Subtotal (95% CI)		**8482**		**8521**	**1.84 (1.04-3.27)**	**15.8**
Total events	33		18			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.02$; $P = .90$; $I^2 = 0\%$						
Overall effect: $z = 2.09$; $P = .04$						
Non-Asian Patients						
Thrombosis Prevention Trial,[25] 1998	2	1268	0	1272	5.02 (0.24-104.37)	0.6
Ridker et al (WHS),[37] 2005	51	19934	41	19942	1.24 (0.83-1.88)	30.8
Erkan et al (APLASA),[30] 2007	0	48	0	45	Not estimable	
Belch et al (POPADAD),[26] 2008	0	318	2	318	0.20 (0.01-4.15)	0.6
Fowkes et al (AAA),[31] 2010	5	1675	4	1675	1.25 (0.34-4.65)	3.0
McNeil et al (ASPREE),[15] 2018	43	9525	34	9589	1.27 (0.81-1.99)	25.8
Bowman et al (ASCEND),[15] 2018	25	7740	26	7740	0.96 (0.56-1.66)	17.3
Gaziano et al (ARRIVE),[13] 2018	8	6270	11	6276	0.73 (0.29-1.81)	6.3
Subtotal (95% CI)		**46778**		**46857**	**1.14 (0.89-1.46)**	**84.2**
Total events	134		118			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 3.91$; $P = .69$; $I^2 = 0\%$						
Overall effect: $z = 1.03$; $P = .30$						
Total (95% CI)		**55260**		**55378**	**1.23 (0.98-1.54)**	**100.0**
Total events	167		136			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 6.20$; $P = .62$; $I^2 = 0\%$						
Overall effect: $z = 1.77$; $P = .08$						
Subgroup differences: $\chi^2_1 = 2.27$; $P = .13$; $I^2 = 56.0\%$						



B PMI

B BMI

Study or Subgroup	Aspirin No. of Events	Aspirin No. of Patients	Placebo No. of Events	Placebo No. of Patients	RR (95% CI)	Weight, %
Patients With BMI ≥25						
Thrombosis Prevention Trial,[25] 1998	2	1268	0	1272	5.02 (0.24-104.37)	0.8
Ridker et al (WHS),[37] 2005	51	19934	41	19942	1.24 (0.83-1.88)	41.9
Belch et al (POPADAD),[26] 2008	0	318	2	318	0.20 (0.01-4.15)	0.8
Gaziano et al (ARRIVE),[13] 2018	8	6270	11	6276	0.73 (0.29-1.81)	9.2
Bowman et al (ASCEND),[14] 2018	25	7740	26	7740	0.96 (0.56-1.66)	24.5
Subtotal (95% CI)		**35530**		**35548**	**1.08 (0.79-1.46)**	**77.2**
Total events	86		80			
Heterogeneity: $\tau^2=0.00$; $\chi^2_4=3.52$; $P=.47$; $I^2=0\%$						
Overall effect: $z=0.47$; $P=.64$						
Patients With BMI <25						
Ogawa et al (JPAD),[35] 2008	5	1262	3	1277	1.69 (0.40-7.04)	3.8
Ikeda et al (JPPP),[33] 2014	28	7220	15	7244	1.87 (1.00-3.50)	19.0
Subtotal (95% CI)		**8482**		**8521**	**1.84 (1.04-3.27)**	**22.8**
Total events	33		18			
Heterogeneity: $\tau^2=0.00$; $\chi^2_1=0.02$; $P=.90$; $I^2=0\%$						
Overall effect: $z=2.09$; $P=.04$						
Total (95% CI)		**44012**		**44069**	**1.21 (0.92-1.60)**	**100.0**
Total events	119		98			
Heterogeneity: $\tau^2=0.00$; $\chi^2_6=6.16$; $P=.41$; $I^2=3\%$						
Overall effect: $z=1.35$; $P=.18$						
Subgroup differences: $\chi^2_1=2.62$; $P=.11$; $I^2=61.9\%$						



Authors Conclusion

- **The use of low-dose aspirin for primary prevention of cardiovascular events in individuals without symptomatic cardiovascular disease was associated with an increased risk of overall intracranial hemorrhages**

- **The risk of intracerebral hemorrhage was particularly elevated in Asian populations and in populations with lower mean BMI**

- **Because the benefits of low-dose aspirin for primary prevention of cardiovascular events are not well established, and the outcomes of intracranial hemorrhage are often catastrophic, these findings suggest caution regarding using low-dose aspirin in individuals without symptomatic cardiovascular disease**

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 607–617
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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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See page 618 for the editorial comment on this article (doi: 10.1093/eurheartj/ehy872)

Aims The role of aspirin in the primary prevention setting is continuously evolving. Recent randomized trials have challenged the role of aspirin in the primary prevention setting.

Methods and results Electronic databases were searched for randomized trials that compared aspirin vs. placebo (or control) in subjects without established atherosclerotic disease. The primary efficacy outcome was all-cause mortality, while the primary safety outcome was major bleeding. Summary estimates were reported using a DerSimonian and Laird random effects model. A total of 11 trials with 157 248 subjects were included. At a mean follow-up of 6.6 years, aspirin was not associated with a lower incidence of all-cause mortality [risk ratio (RR) 0.98, 95% confidence interval (CI) 0.93–1.02; $P = 0.30$]; however, aspirin was associated with an increased incidence of major bleeding (RR 1.47, 95% CI 1.31–1.65; $P < 0.0001$) and intracranial haemorrhage (RR 1.33, 95% CI 1.13–1.58; $P = 0.001$). A similar effect on all-cause mortality and major bleeding was demonstrated in diabetic and high cardiovascular risk patients (i.e. 10-year risk >7.5%). Aspirin was associated with a lower incidence of myocardial infarction (RR 0.82, 95% CI 0.71–0.94; $P = 0.006$); however, this outcome was characterized by considerable heterogeneity ($I^2 = 67\%$), and this effect was no longer evident upon limiting the analysis to the more recent trials. Trial sequential analysis confirmed the lack of benefit of aspirin for all-cause mortality up to a relative risk reduction of 5%.

Conclusion Among adults without established cardiovascular disease, aspirin was not associated with a reduction in the incidence of all-cause mortality; however, it was associated with an increased incidence of major bleeding. The routine use of aspirin for primary prevention needs to be reconsidered.

Keywords Prevention • Aspirin • Cardiovascular • Mortality • Meta-analysis

Mahmoud 2019

- **11 RCTs (n=157248): with known atherosclerotic disease. (average age 61)**
- **Primary efficacy outcome was all cause mortality**
- **Primary Safety outcome was major bleeding**
- **Mean Follow up 6.6 year**

Results

- Aspirin was not associated with a lower incidence of all-cause mortality
  - (RR) 0.98, 95% confidence interval (CI) 0.93–1.02; P = 0.30
- Aspirin was associated with an increased incidence of major bleeding
  - (RR 1.47, 95% CI 1.31–1.65; P < 0.0001)
- Aspirin was associated with an increased incidence of intracranial haemorrhage
  - (RR 1.33, 95% CI 1.13–1.58; P = 0.001)

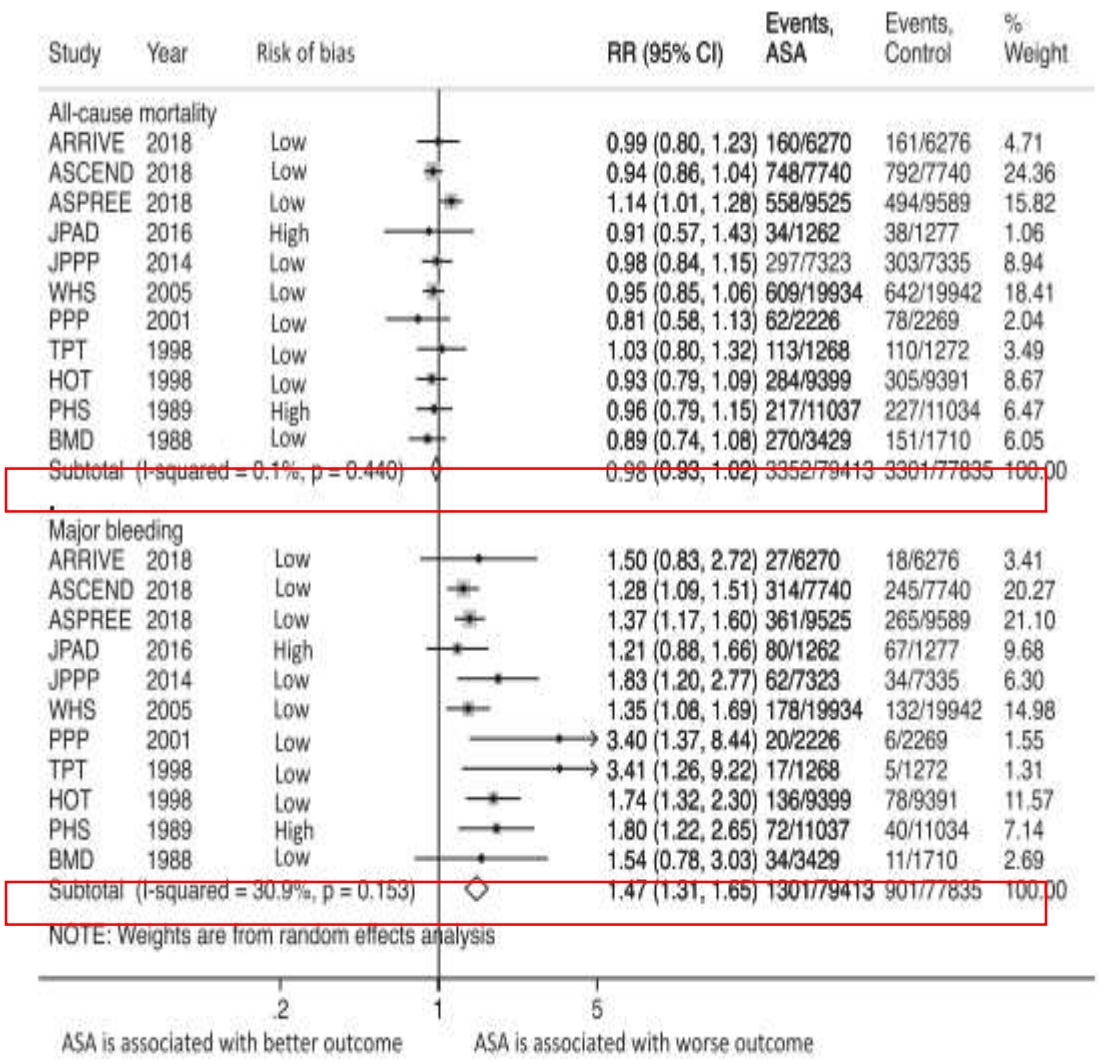


Figure 2 Summary plot for primary efficacy (all-cause mortality) and safety (major bleeding) outcomes. The relative size of the data markers indicates the weight of the sample size from each study. ASA, aspirin; CI, confidence interval; RR, risk ratio.

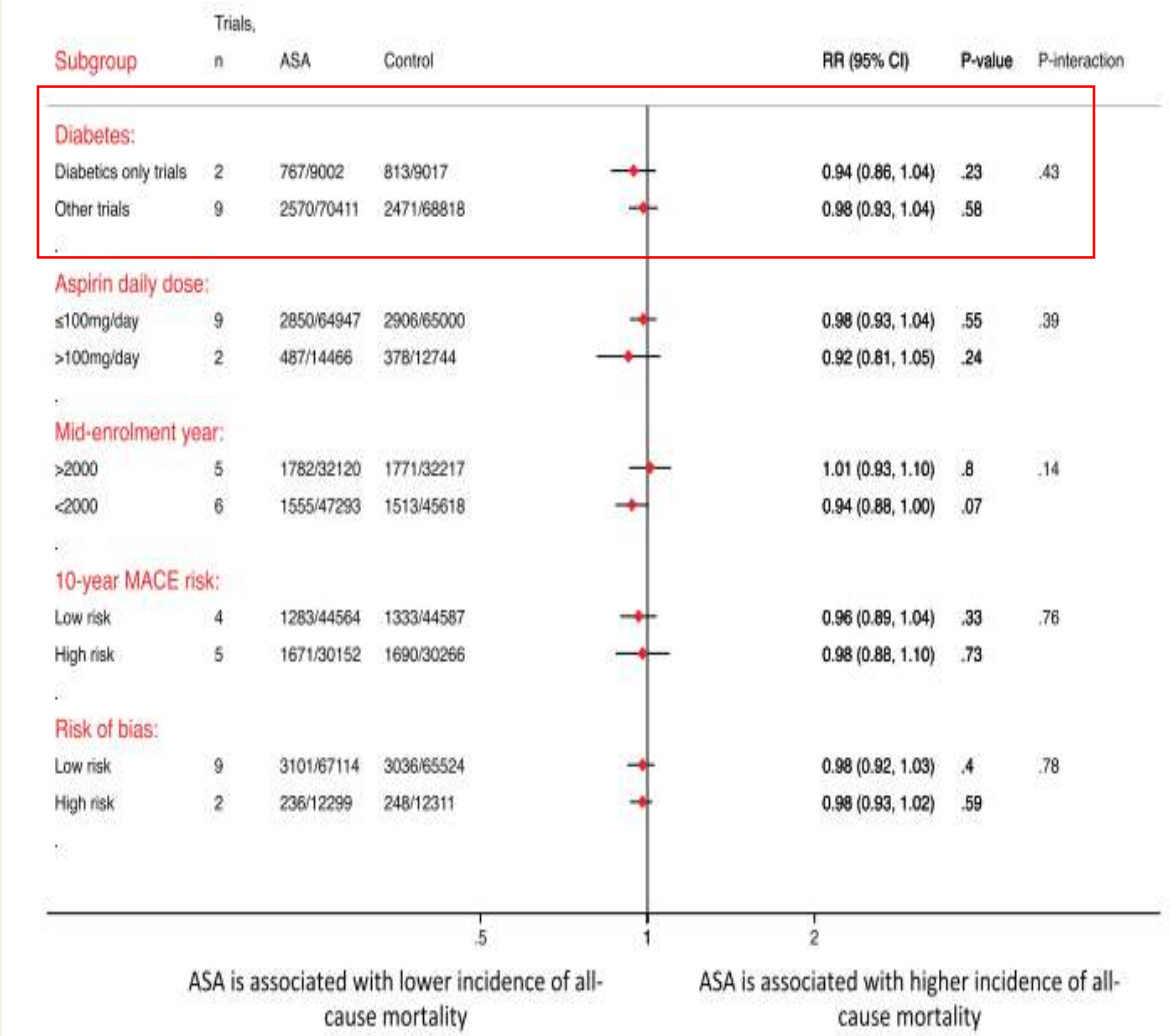
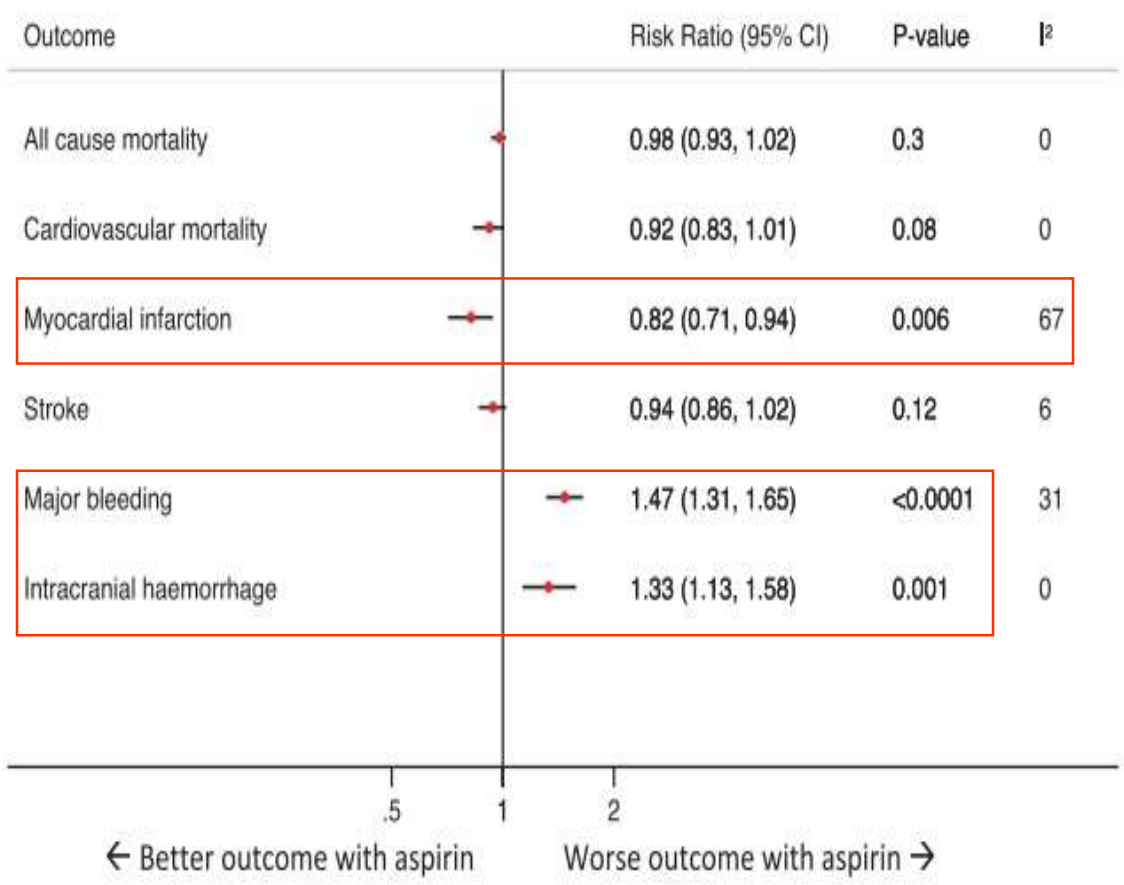


Figure 3 A forest plot illustrating the risk ratio and 95% confidence intervals of all-cause mortality according to various subgroups of interest. ASA, aspirin; CI, confidence interval; RR, risk ratio.



Take home figure A forest plot illustrating the risk ratios and 95% confidence interval for all outcomes of interest.

Authors Conclusion

- 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 haemorrhage.
- The routine use of aspirin for primary prevention needs to be reconsidered.

Research

JAMA | Original Investigation

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

A Systematic Review and Meta-analysis

Sean L. Zheng, BM, BCh, MA, MRCP; Alistair J. Roddick, BSc

JAMA. 2019;321(3):277-287

Zheng 2019

- 13 RCTs (n=164225): (median age 62)
- 1 050 511 participant years
- 19% diabetic

- The primary cardiovascular outcome was a composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke

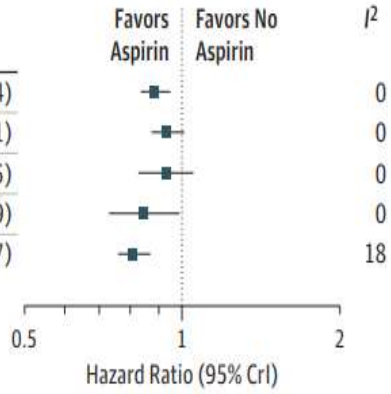
Results

- **Aspirin use was associated with significant reductions in the composite cardiovascular outcome compared with no aspirin**
  - **60.2 per 10 000 participant-years with aspirin and 65.2 per 10 000 participant-years with no aspirin)**
  - **HR, 0.89 95% credible interval, 0.84-0.94**
  - **absolute risk reduction, 0.41% [95% CI, 0.23%-0.59%];** **NNT: 241.**

- **Aspirin use was associated with an increased risk of major bleeding events compared with no aspirin**
  - **23.1 per 10 000 participant-years with aspirin and 16.4 per 10 000 participant-years without**
  - **HR, 1.43 [95% credible interval, 1.30-1.56];**
  - **absolute risk increase, 0.47% [95% CI, 0.34%-0.62%];** **NNH: 210**

Figure 1. Cardiovascular and Bleeding Outcomes in All Participants

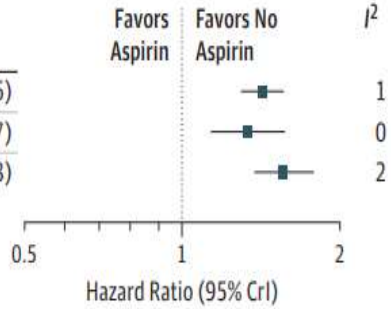
Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Composite CV outcome	13	2911	79717	3342	80057	0.41 (0.23 to 0.59)	0.89 (0.84-0.94)	0
All-cause mortality	13	3622	81623	3588	80057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)	0
CV mortality	13	995	81623	997	80057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)	0
Myocardial infarction	13	1469	81623	1599	80057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)	0
Ischemic stroke	10	831	65316	942	63752	0.19 (0.06 to 0.30)	0.81 (0.76-0.87)	18



NNT, 361

NNT, 540

Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Major bleeding	11	1195	74715	834	73143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)	1
Intracranial bleeding	12	349	80985	257	79419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)	0
Major GI bleeding	10	593	70336	380	70465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)	2



The composite cardiovascular (CV) outcome consisted of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Hazard ratios (HRs) and 95% credible interval variables (CrIs) were calculated using Bayesian meta-analysis of trial-level event counts. The absolute risk reductions and increases were calculated by multiplying the control event risk by the relative risk and 95% CIs derived by frequentist meta-analysis (eFigure 4 in Supplement 2). GI indicates gastrointestinal.

Authors Conclusion

- 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

”Primum non nocere”

Challenges and Gaps in Knowledge

- Those who fall through the cracks
  - Body Weight
  - Gender
  - Hypertension
  - Afib
  - Asymptomatic Carotid Atherosclerotic disease
  - Small Vessel disease on CT or MRI of Brain

- What do we do for them?

Endorsement