Queen Mary Hospital

Hong Kong College of Cardiology ASM 2019

Is there still a role for aspirin in primary prevention?

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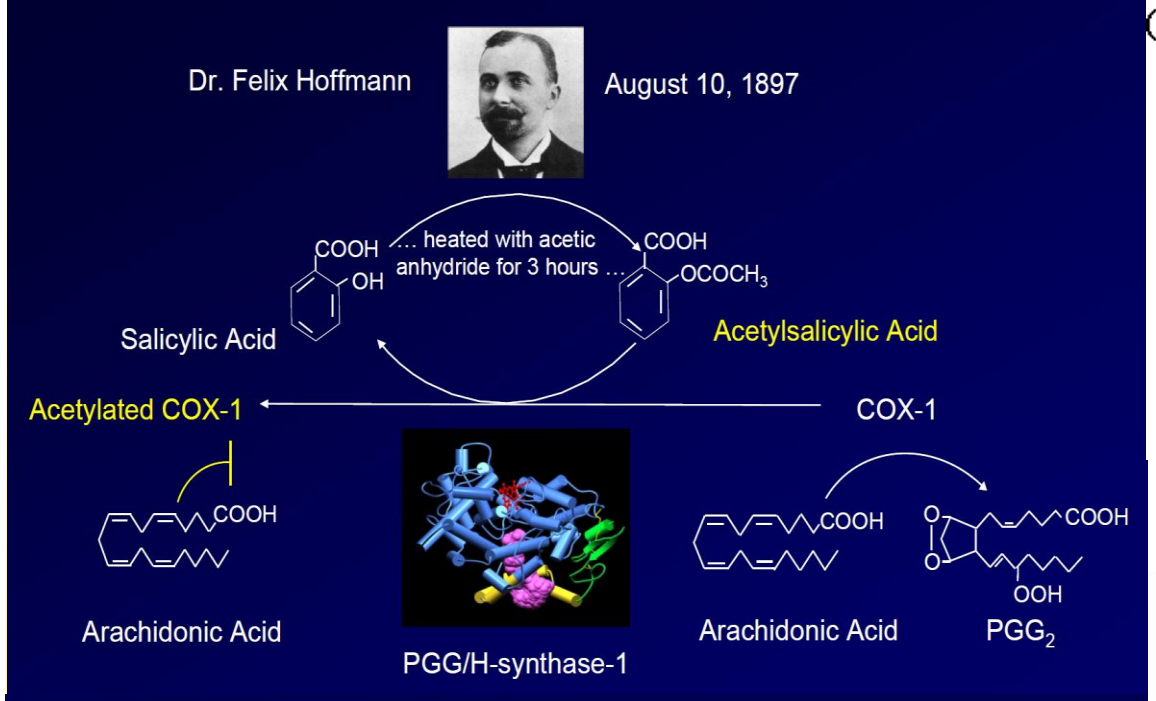
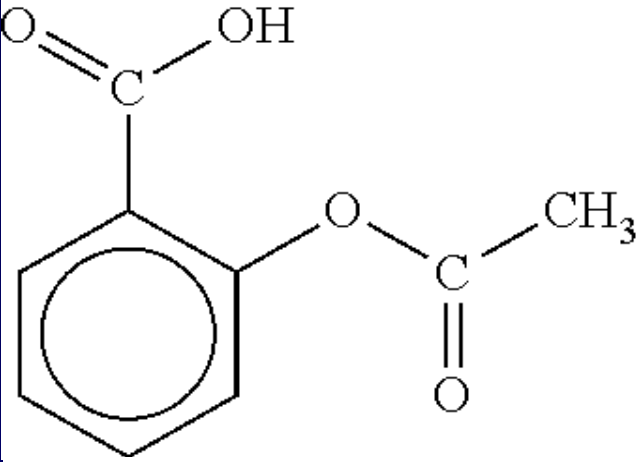
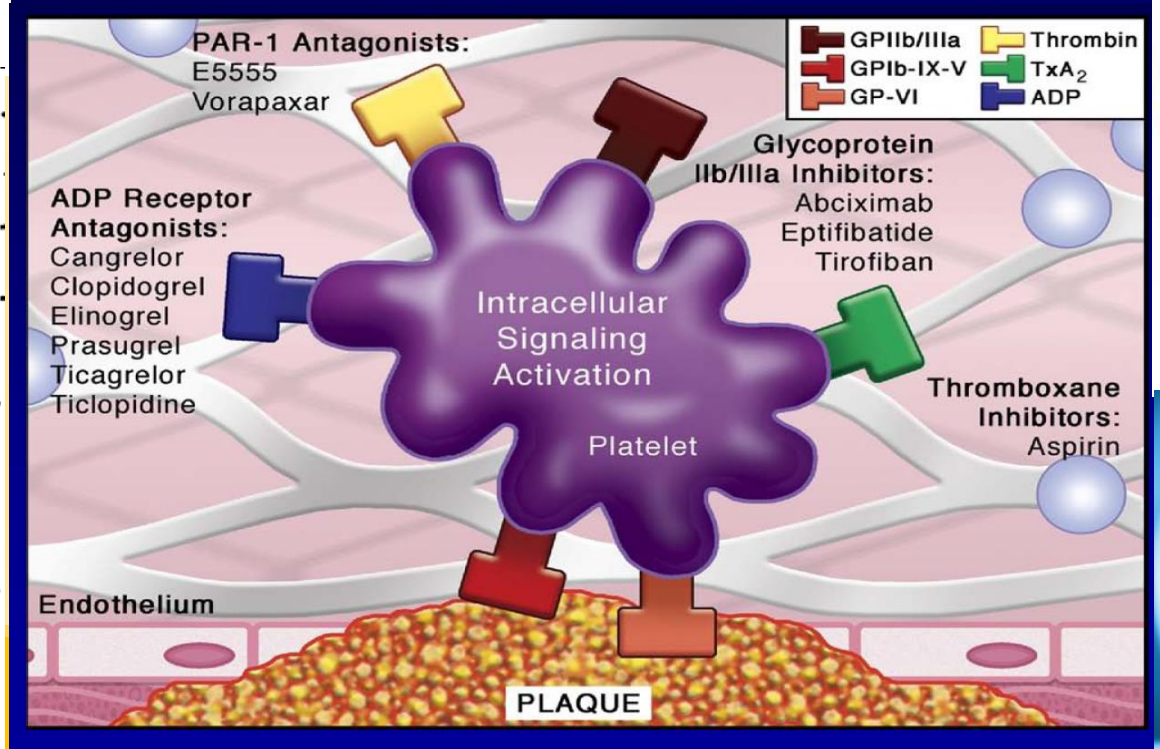


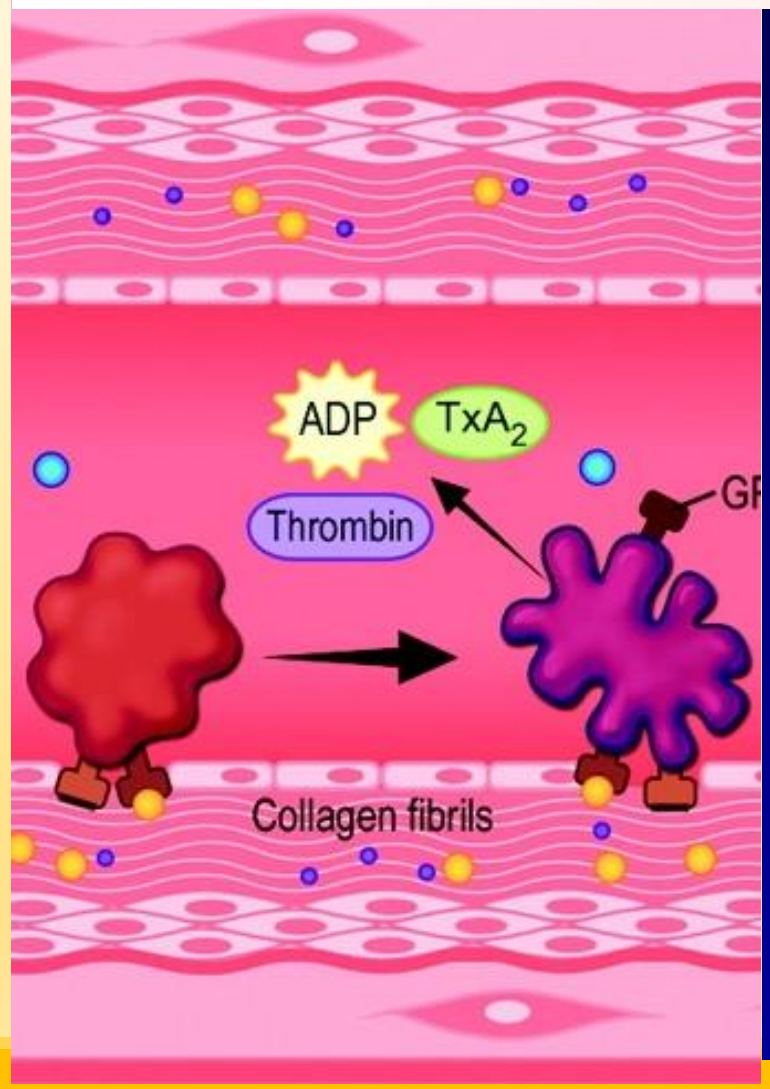


"An aspirin a day will help prevent a heart attack if you have it for lunch instead of a cheeseburger."



Rationale of using Aspirin in CAD

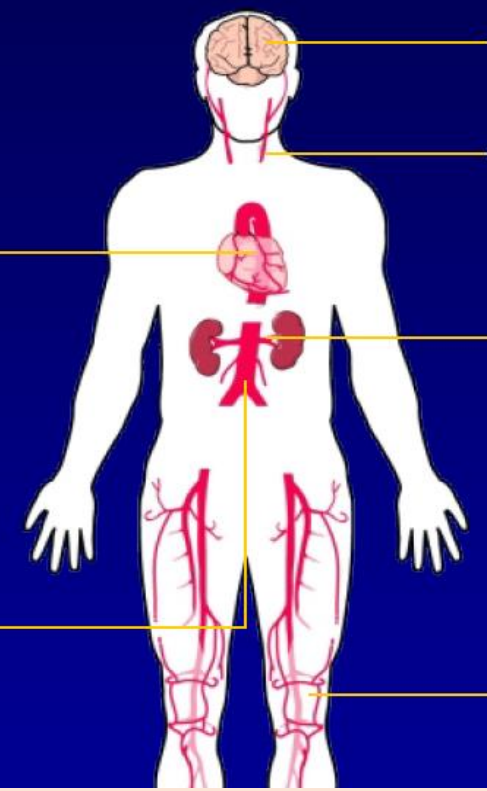
Atherothrombosis



Acute coronary syndromes
- STEMI
- NSTEMI
- Unstable angina

Stable CAD
Atrial Fibrillation
Angioplasty
Bare metal stent
Drug eluting stent
CABG

Abdominal aortic aneurysm (AAA)



Stroke
TIA
Intracranial stenosis

Carotid artery stenosis
CEA
Carotid stenting

Renal artery stenosis
Renal artery stenting

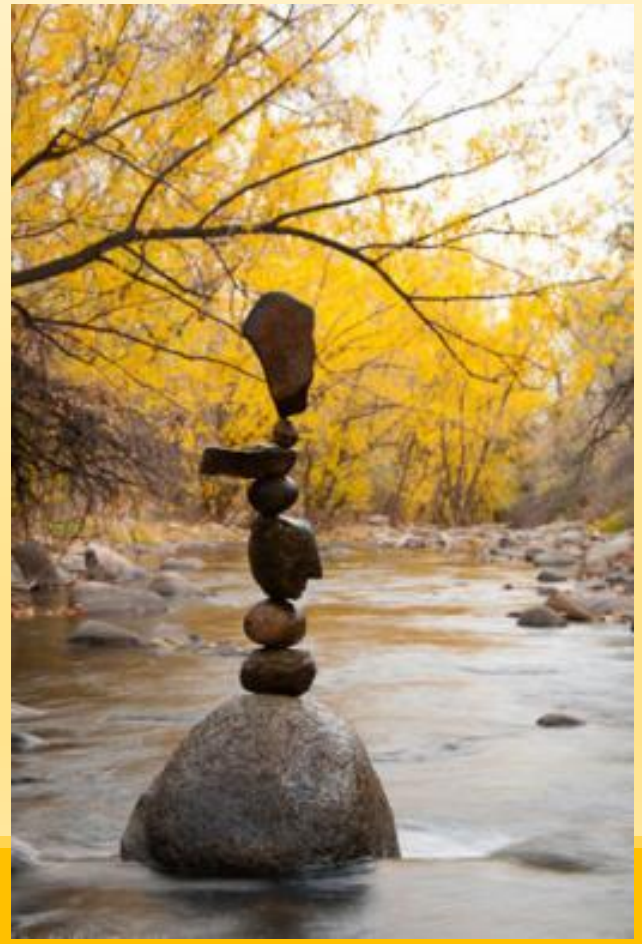
Peripheral arterial disease
Acute limb ischemia
Claudication
Amputation
Endovascular stenting
Peripheral bypass
ABI

Aspirin inhibits platelets, reduces chance of thrombosis

Meadows TA et al Circ Res. 2007;100:1261-1275.

Anti-platelet and bleeding

As with all anti-platelet agents, reducing ischemia means increasing bleeding risks



Art of balance

Ischemia

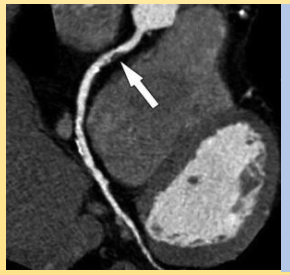
VS

Bleeding

Using Aspirin: benefit vs risk

Acute phase of event
Eg MI, stroke

Post event
Eg post MI, PCI, CABG



Evidence of atherosclerosis
Eg +ve CTA, mild CAD, carotid IMT

High risk of CVD
Eg DM, high ASCVD score

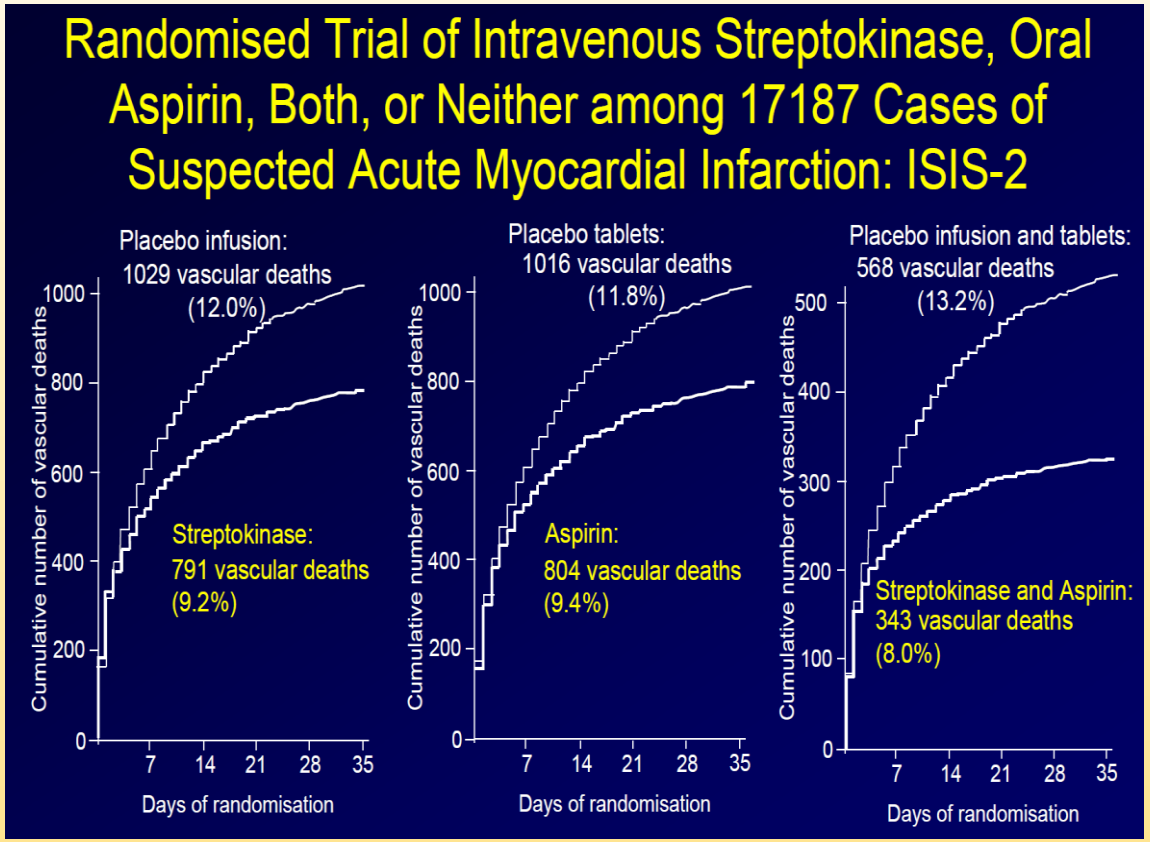
Risk of death

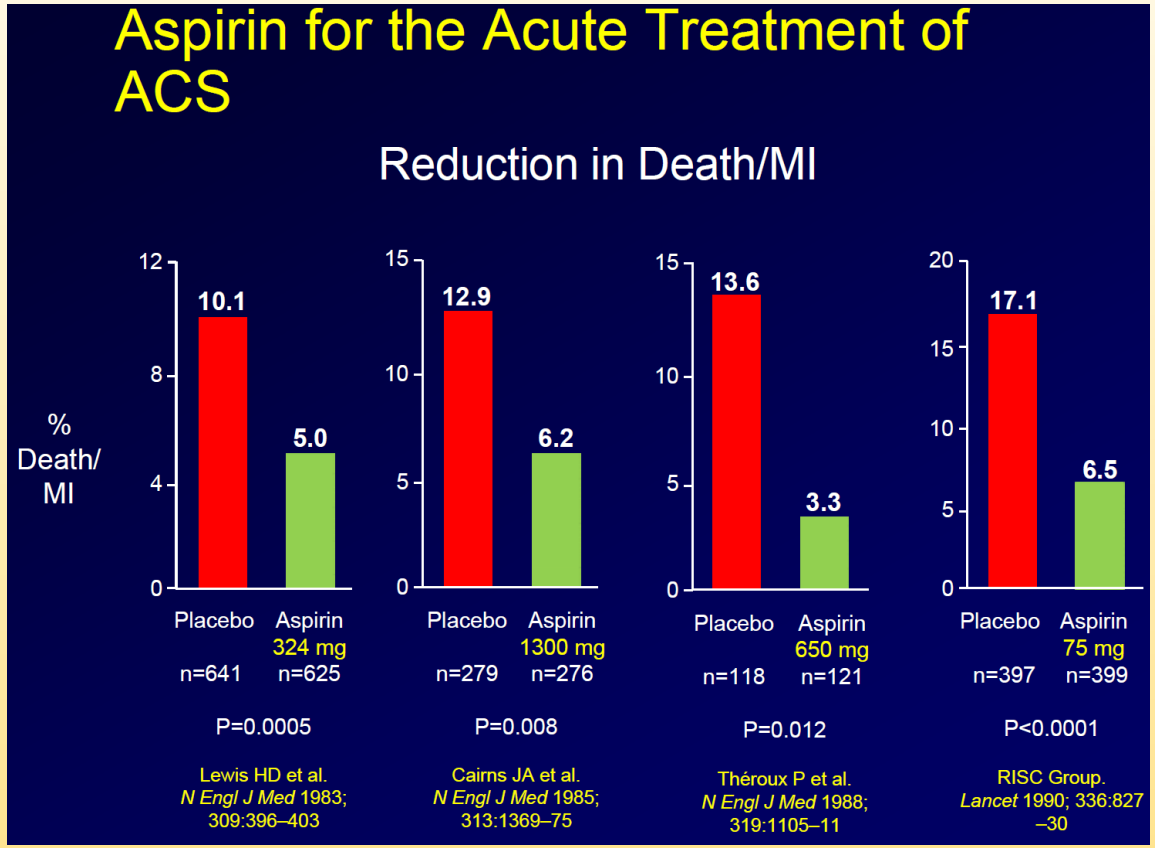
Secondary prevention

‘1.5’ prevention

Primary prevention

Aspirin in secondary prevention





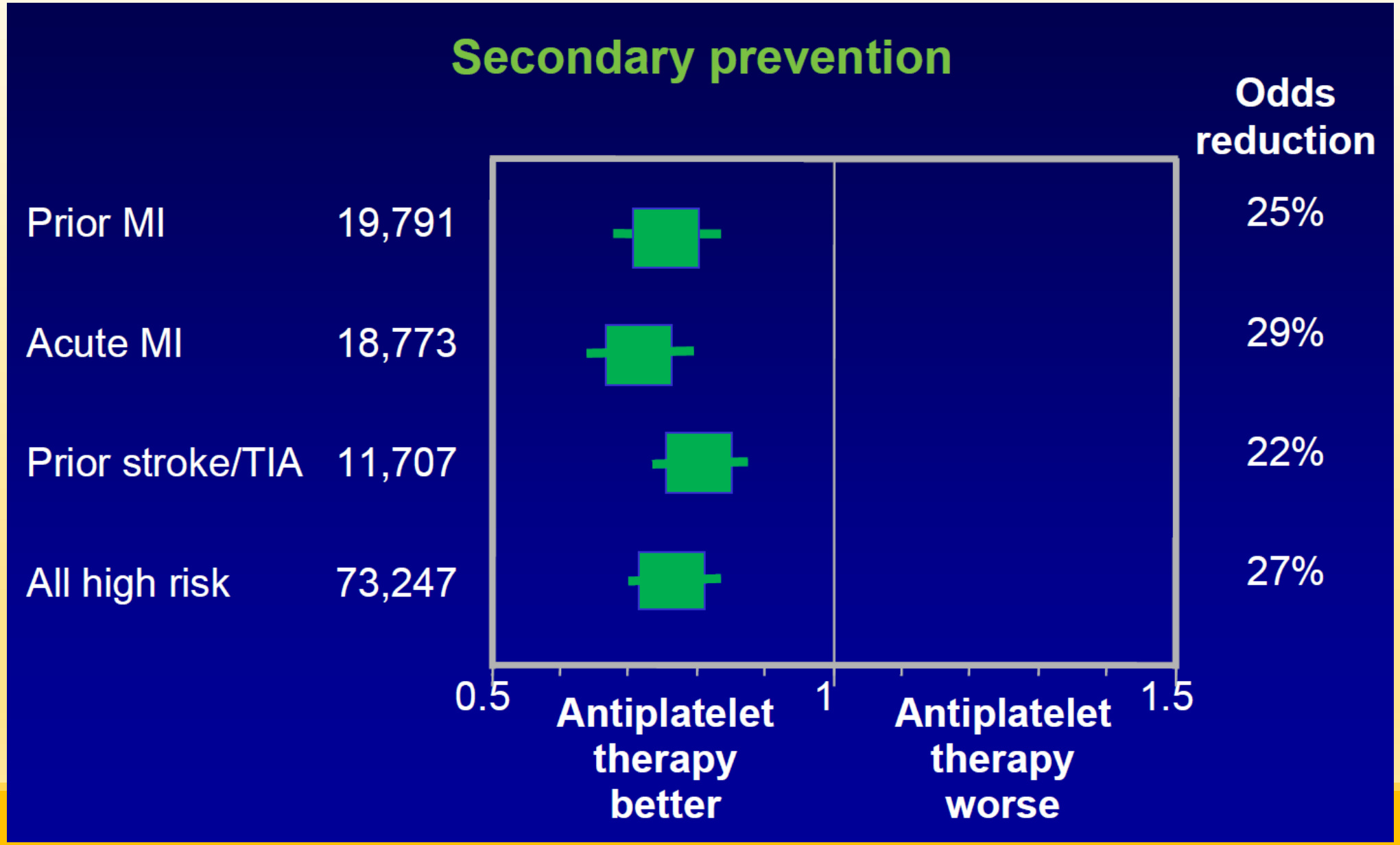
Aspirin and streptokinase superior in acute STEMI

Aspirin beneficial in NSTE-ACS

Aspirin's role undeniable in acute event

ISIS2 Collaborative Group, Lancet 1988; II:349360.

Antiplatelet Trialists' Collaboration



ATC. BMJ 1994

Antiplatelet Therapy

Treatment with aspirin 75 to 162 mg daily should be **continued indefinitely** in the absence of contraindications in patients with SIHD.

Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD.

Aspirin and Primary prevention

Physicians' Health Study	
Subjects randomized	22,071
Follow-up, y	5 (mean)
Patient population	Apparently healthy male physicians
Age range	40-84
Female sex, %	0
ASA dosage	325 mg every other day

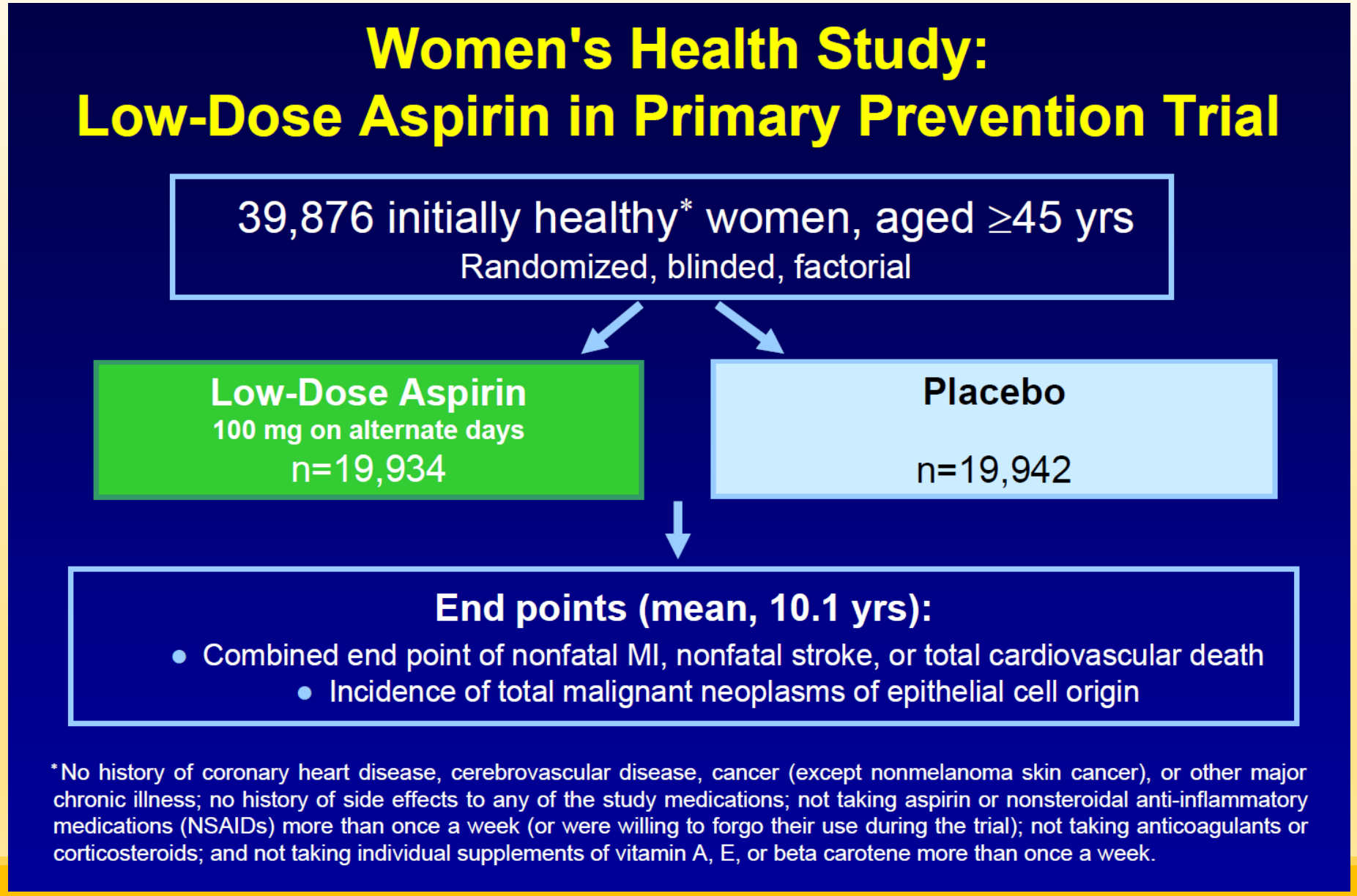
44% reduction in risk of a first MI, p<0.001

Reduction in the risk of MI was apparent only among those >50 years

No benefit on all cause mortality, CV death and stroke

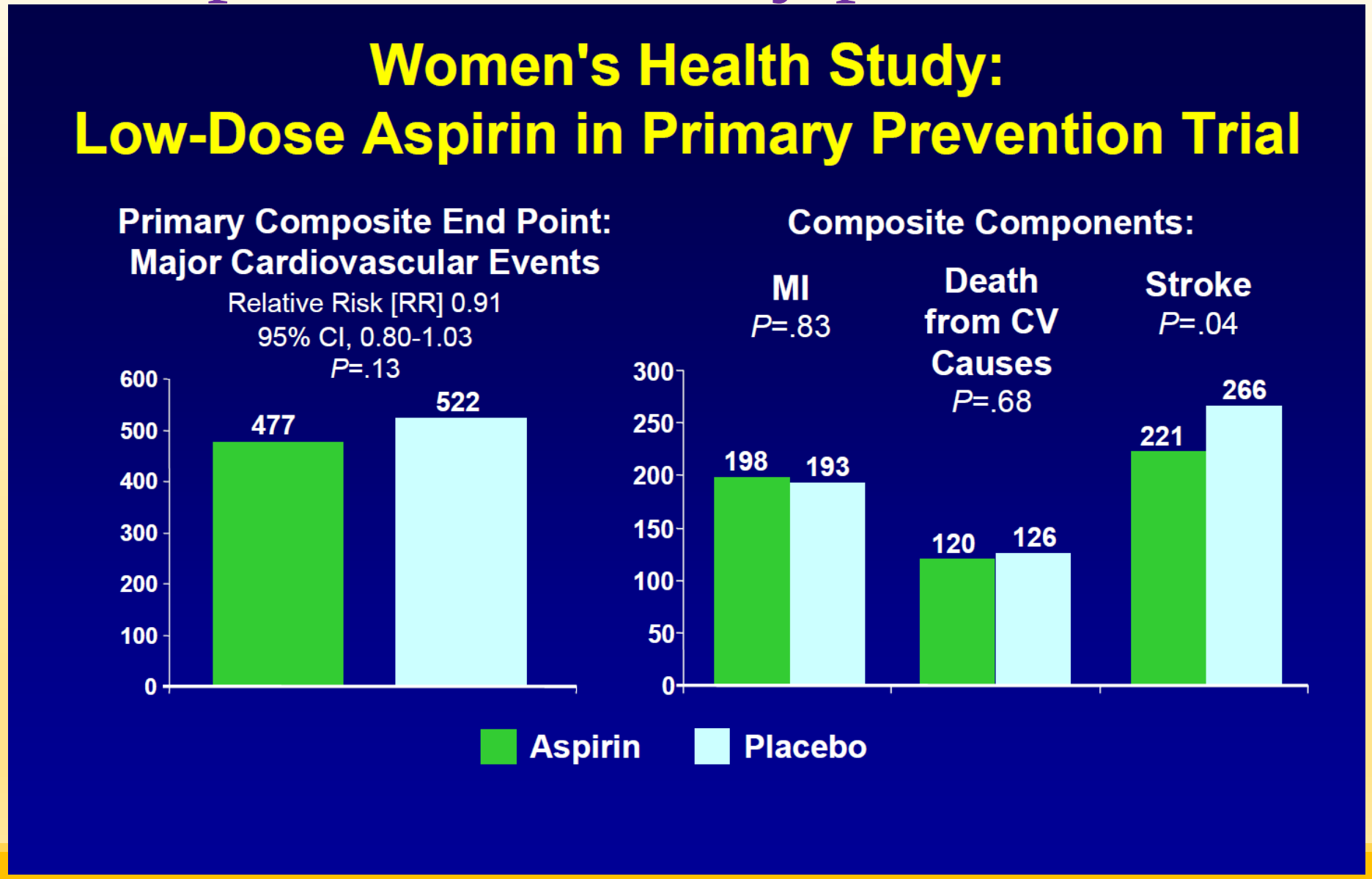
Steering Committee of the Physicians' Health Study Research Group. N Engl J Med. 1989

Aspirin and Primary prevention



Ridker PM, et al. N Engl J Med. 2005

Aspirin and Primary prevention



Ridker PM, et al. N Engl J Med. 2005

Aspirin and Primary prevention

Fatal/non-fatal MI

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
BDT	170	3429	88	1710	12.8%	0.96 [0.75, 1.24]	1988
PHS	139	11037	239	11034	14.4%	0.58 [0.47, 0.72]	1989
TPT	154	2545	190	2540	14.4%	0.81 [0.66, 0.99]	1998
HOT	157	9399	184	9391	14.2%	0.85 [0.69, 1.05]	1998
PPP	19	2226	28	2269	5.1%	0.69 [0.39, 1.23]	2001
WHS	198	19934	193	19942	14.7%	1.03 [0.84, 1.25]	2005
JPAD	12	1262	14	1277	3.2%	0.87 [0.40, 1.87]	2008
POPADAD	76	638	69	638	10.9%	1.10 [0.81, 1.50]	2008
AAA	68	1675	70	1675	10.3%	0.97 [0.70, 1.35]	2010
Total (95% CI)		**52145**		**50476**	**100.0%**	**0.86 [0.74, 1.00]**	
Total events	993		1075				

Heterogeneity: Tau² = 0.03; Chi² = 21.45, df = 8 (*P* = .006); I² = 63%

Test for overall effect: Z = 1.92 (*P* = .06)

Risk Ratio M-H, Random, 95% CI

0.2 0.5 1 2 5

All cause mortality

A

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
BDT	270	3429	151	1710	10.4%	0.89 [0.74, 1.08]	1988
PHS	217	11037	227	11034	11.1%	0.96 [0.79, 1.15]	1989
TPT	216	2545	205	2540	11.2%	1.05 [0.88, 1.26]	1998
HOT	284	9399	305	9391	14.9%	0.93 [0.79, 1.09]	1998
PPP	62	2226	78	2269	3.5%	0.81 [0.58, 1.13]	2001
WHS	609	19934	642	19942	31.6%	0.95 [0.85, 1.06]	2005
POPADAD	94	638	101	638	5.6%	0.93 [0.72, 1.21]	2008
JPAD	34	1262	38	1277	1.8%	0.91 [0.57, 1.43]	2008
AAA	176	1675	186	1675	9.9%	0.95 [0.78, 1.15]	2010
Total (95% CI)		**52145**		**50476**	**100.0%**	**0.94 [0.89, 1.00]**	
Total events	1962		1933				

Heterogeneity: Tau² = 0.00; Chi² = 2.61, df = 8 (*P* = .96); I² = 0%

Test for overall effect: Z = 1.83 (*P* = .07)

Risk Ratio M-H, Random, 95% CI

0.5 0.7 1 1.5 2

CV death

B

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
BDT	148	3429	79	1710	15.7%	0.93 [0.72, 1.22]	1988
PHS	81	11037	83	11034	13.6%	0.98 [0.72, 1.32]	1989
HOT	133	9399	140	9391	17.8%	0.95 [0.75, 1.20]	1998
TPT	101	2545	81	2540	14.6%	1.24 [0.93, 1.66]	1998
PPP	17	2226	31	2269	5.2%	0.56 [0.31, 1.01]	2001
WHS	120	19934	126	19942	16.9%	0.95 [0.74, 1.22]	2005
JPAD	1	1262	10	1277	0.5%	0.10 [0.01, 0.79]	2008
POPADAD	43	638	35	638	8.5%	1.23 [0.80, 1.89]	2008
AAA	35	1675	30	1675	7.2%	1.17 [0.72, 1.89]	2010
Total (95% CI)		**52145**		**50476**	**100.0%**	**0.99 [0.85, 1.14]**	
Total events	679		615				

Heterogeneity: Tau² = 0.02; Chi² = 12.63, df = 8 (*P* = .13); I² = 37%

Test for overall effect: Z = 0.17 (*P* = .86)

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Meta-analysis:

'Aspirin prevent MI'

Heterogenous study results

Most benefit derived from Physican Health Study

Berger JS. Am Heart J 2011

AHA/ADA Scientific Statement

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

Recommendations

1. **Low-dose aspirin (75–162 mg/d) is reasonable among those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding (*ACC/AHA Class IIa; Level of Evidence B*) (*ADA Level of Evidence C*).**
2. **Low-dose aspirin is reasonable in adults with diabetes mellitus at intermediate risk (10-year CVD risk, 5%–10%) (*ACC/AHA Class IIb; Level of Evidence C*) (*ADA Level of Evidence E*).**

Class IIa

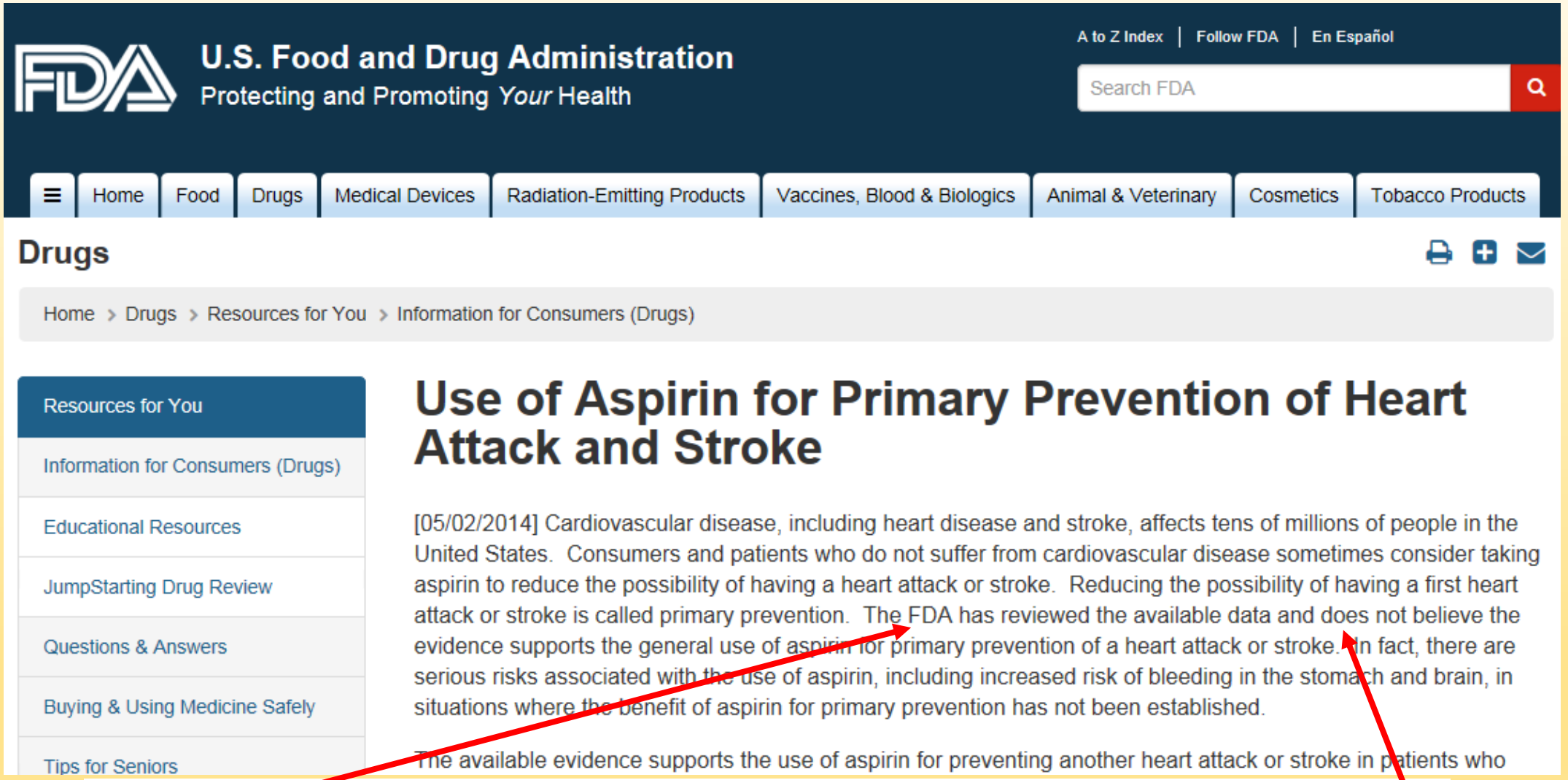
Class IIb

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

Aspirin or clopidogrel cannot be recommended in individuals without cardiovascular or cerebrovascular disease due to the increased risk of major bleeding.	III	B

Circulation. 2015; EHJ 2012

What does FDA say?



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Use of Aspirin for Primary Prevention of Heart Attack and Stroke

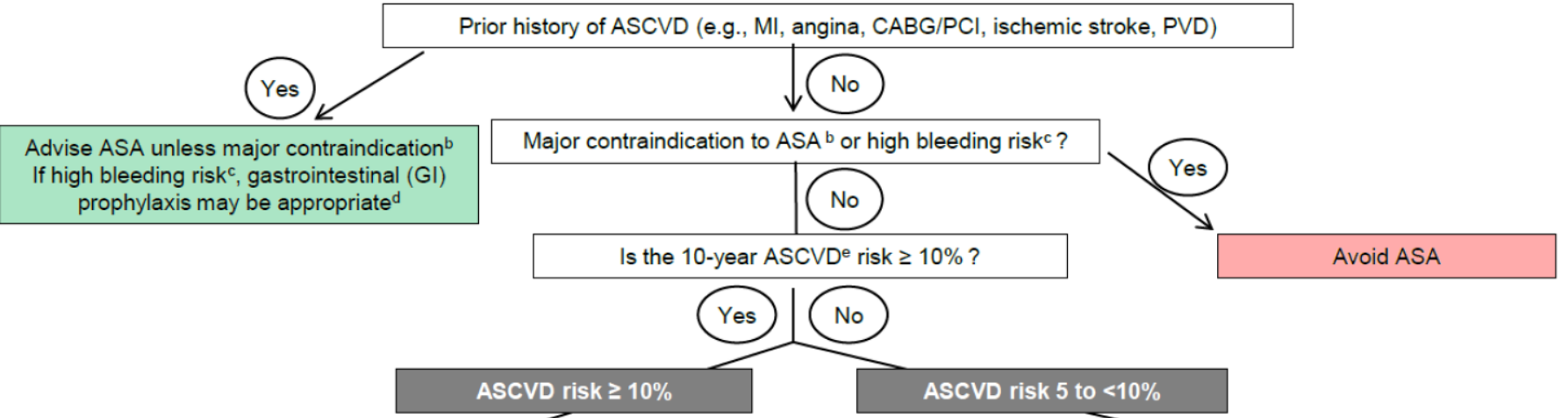
[05/02/2014] Cardiovascular disease, including heart disease and stroke, affects tens of millions of people in the United States. Consumers and patients who do not suffer from cardiovascular disease sometimes consider taking aspirin to reduce the possibility of having a heart attack or stroke. Reducing the possibility of having a first heart attack or stroke is called primary prevention. The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke. In fact, there are serious risks associated with the use of aspirin, including increased risk of bleeding in the stomach and brain, in situations where the benefit of aspirin for primary prevention has not been established.

The available evidence supports the use of aspirin for preventing another heart attack or stroke in patients who

attack or stroke is called primary prevention. The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke. In fact, there are serious risks associated with the use of aspirin, including increased risk of bleeding in the stomach and brain, in situations where the benefit of aspirin for primary prevention has not been established.

Aspirin-Guide: *A personalized approach and mobile app for shared decision making*

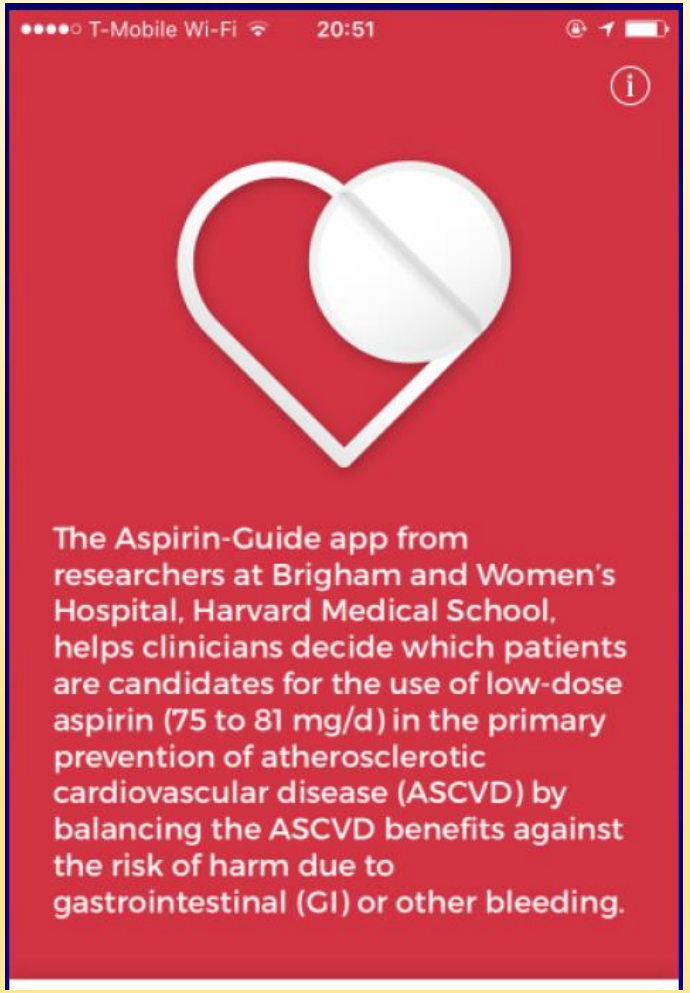
eFigure. Practical Algorithm for Shared Decision Making in the Use of Low-Dose Aspirin (ASA, 75 to 81 mg/d) in Primary Prevention of ASCVD[a]



Assess Age, Sex, Potential Benefit (NNT), Potential Harm (NNH)[f]			
NNT to prevent one ASCVD event on aspirin versus NNH to cause one excess bleeding event caused by aspirin[f]		Age (Yrs)[g]	
		Men 50-69	Women 50-69
	NNT ≤ NNH (benefit ≥ harm)	Advise ASA[g]	Advise ASA[g]
	NNT > NNH (benefit < harm)	Avoid ASA[i]	Avoid ASA[i]

Assess Age, Sex, Potential Benefit (NNT), Potential Harm (NNH)[f]			
NNT to prevent one ASCVD event on aspirin versus NNH to cause one excess bleeding event caused by aspirin[f]		Age (Yrs)[g]	
		Men <50 Women <65	Men ≥50 Women ≥65
	NNT ≤ NNH (benefit ≥ harm)	Avoid ASA[g,i]	Consider ASA[g,h]
	NNT > NNH (benefit < harm)		Avoid ASA[i]

[g] USPSTF guidelines consider insufficient data for aspirin use in individuals <50 or ≥ 70 years; detailed clinical assessment recommended for individuals <50 or ≥ 70 years.
[h] Based on randomized clinical trial sex-specific subgroup analyses. In both sexes, avoid ASA if the 10-year ASCVD risk score is <5%.
[i] Could consider ASA + GI prophylaxis if NNT ≤ NNH, when recalculated on GI prophylaxis in patients with elevated GI bleeding risk.



www.aspiringuide.com

Aspirin and Primary prevention in 2019

Traditional CV risk factors

ASCVD Risk scores

DM

Bleeding risk factors

Risk scores

History of bleeding

Alternative treatment for CVD prevention

Eg statins, PCSK9 inh, SGLT-2 inhibitors, GLP-1

Alternative treatment to reduce bleeding risk

Eg PPI, HP eradication, endoscopic therapies

ARRIVE study

THE LANCET

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

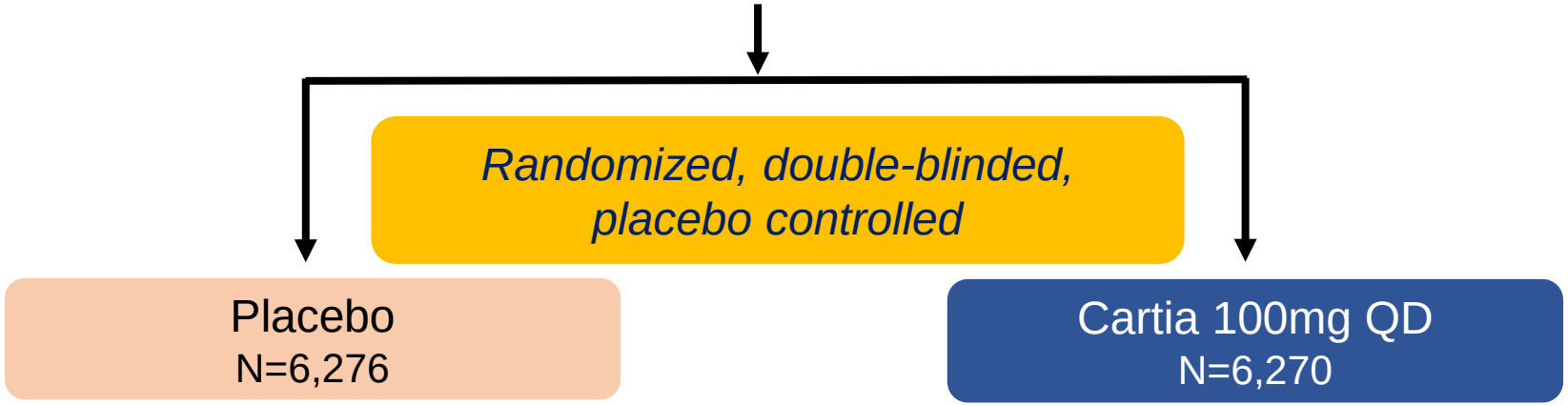
J Michael Gaziano, Carlos Brotons, Rosa Coppolecchia, Claudio Cricelli, Harald Darius, Philip B Gorelick, George Howard, Thomas A Pearson, Peter M Rothwell, Luis Miguel Ruilope, Michal Tendera, Gianni Tognoni; the ARRIVE Executive Committee

Lancet 2018

ARRIVE study:
Study Design

Primary prevention in high CV risk

- Male ≥55, 2/more CV risk factors; Female ≥60, 3/more CV risk factors
- Calculated cardiovascular risk (10-year risk of CHD of 10–20%)
- No Diabetes
- No history of vascular event
- No history of serious bleeding



Primary endpoint:

Composite outcome consisting of time to first occurrence of confirmed myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischaemic attack

ARRIVE study:
Study Population

Primary prevention in high CV risk

(Intent-to-Treat Population)

	Placebo Arm (n= 6276)	Aspirin Arm (n= 6270)
Age at Randomization (year)		
Mean	63.9	63.9
SD	7.05	7.10
Median	63.0	63.0
Min – Max	50 - 97	50 - 91
		25.89%
		52.70%
		21.42%
		29.52%
		70.48%
White, %	97.9	97.8
Current antihypertensive medication, %	65.3	64.4
Elevated total cholesterol, %	58.3	58.2
Mean Framingham 10-year CHD risk score	14.1%	13.9%
Mean ACC/AHA 10-year ASCVD risk score	17.4%	17.3%

Note: Percentages based on number of subjects randomized to the indicated treatment group

Actual event rate lower than expected (calculated)

Reflecting the effective contemporary CV medications

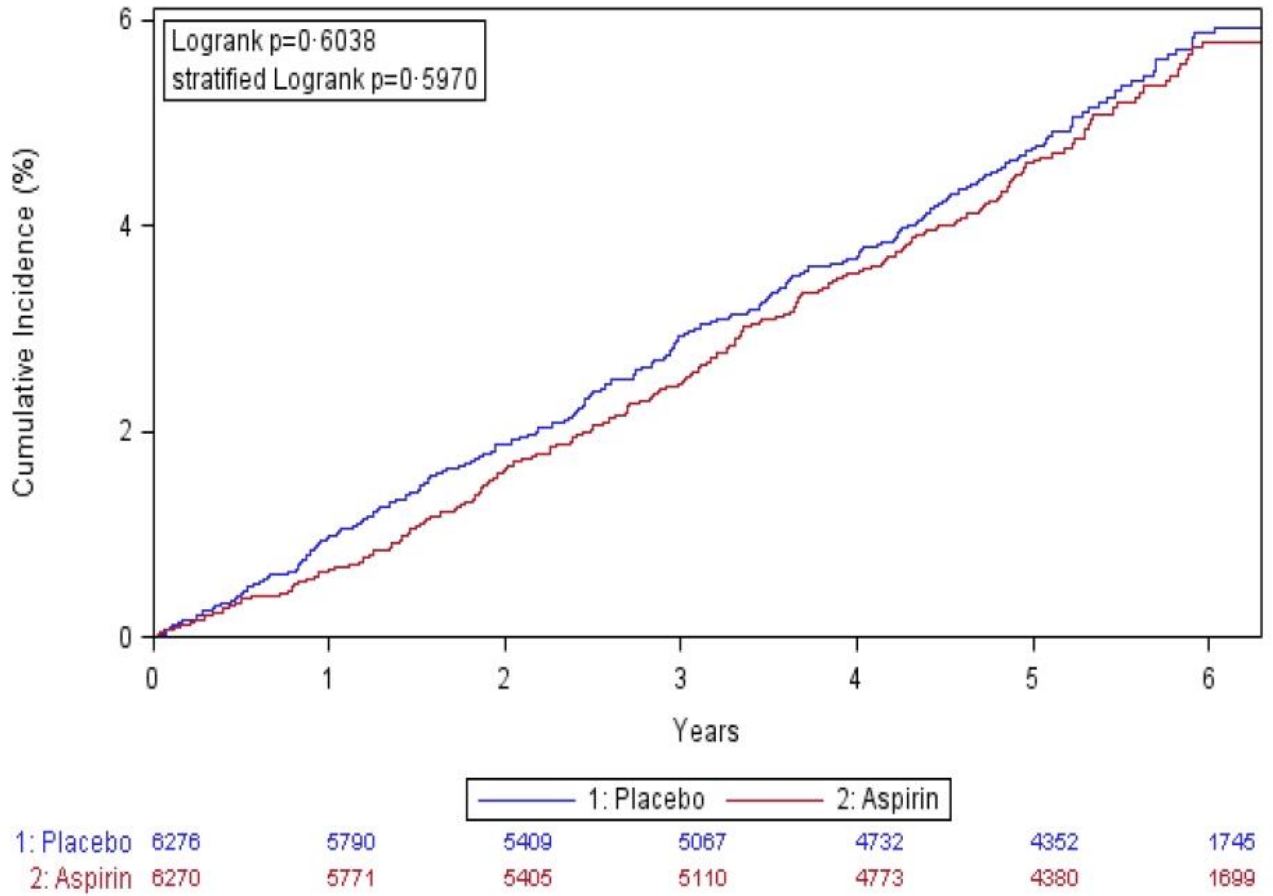
Observed ASCVD event rate normalized to 10 years **8.43%** **8.80%**

ARRIVE study:
Efficacy Outcome

Primary prevention in high CV risk

Primary Efficacy Endpoint: CVD Death, MI, UA, Stroke or TIA

Time to First Occurrence of CV Death, MI, UA, Stroke or TIA (Intent-to-Treat population)



HR (95% CI)*
0.96 (0.81;1.13)

p-Value*
0.6038

*Comparison: Aspirin vs Placebo

ARRIVE study:
Safety Outcome

Primary prevention in high CV risk

Gastrointestinal Bleeding
(Intent-to-Treat Population)

Gastrointestinal Bleeding Adjudication	Placebo Arm (n=6276)	Aspirin Arm (n=6270)
Time to First GI Bleeding		
Patients with events, n (%)	29 (0.46%)	61 (0.97%)
Hazard Ratio (95% CI)*	2.11 [1.36;3.28]	
p-Value*	0.0007	
Severity of adjudicated first GI Bleeding		
Mild, n (%)	22 (0.35%)	42 (0.67%)
Moderate, n (%)	5 (0.08%)	15 (0.24%)
Severe, n (%)	2 (0.03%)	4 (0.06%)

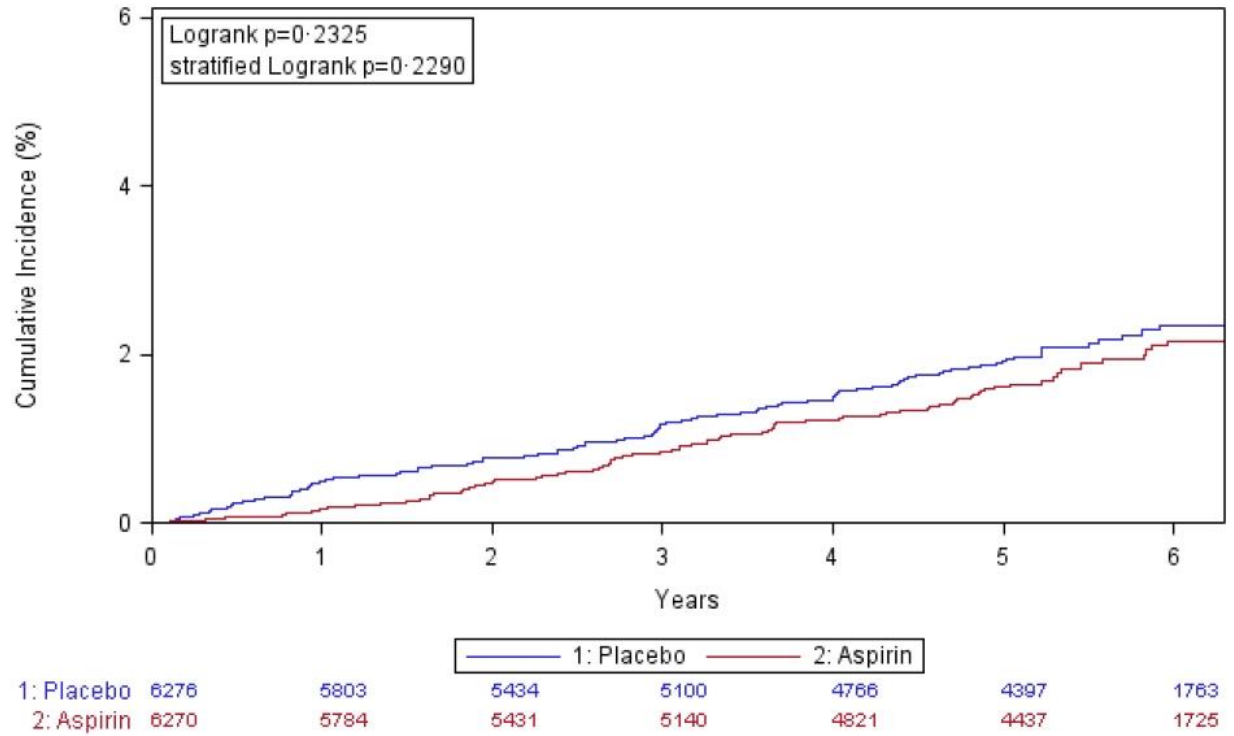
*Comparison: Aspirin vs Placebo; p-Value from log-rank test of time to first event
Note: Percentages based on number of subjects randomized to the indicated treatment group

ARRIVE study:
Efficacy Outcome

Primary prevention in high CV risk

Cumulative Incidence Curve for Time to Fatal or Non-Fatal MI (Intent-to-Treat Population)

Time to first occurrence of Fatal or Non-Fatal MI (Intent-to-Treat population)



HR (95% CI)*
0.85 (0.64;11)

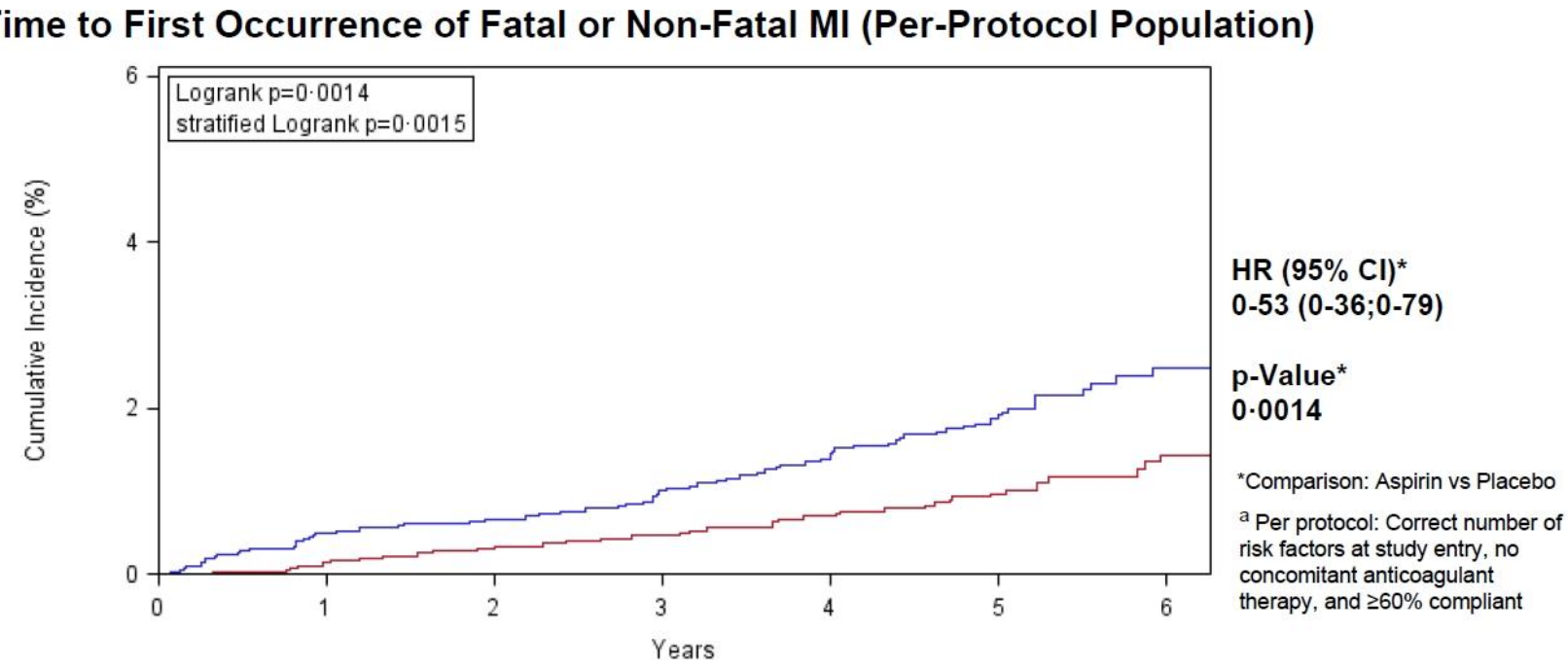
p-Value*
0.2325

*Comparison: Aspirin vs Placebo

ARRIVE study:
Efficacy Outcome

Primary prevention in high CV risk

Cumulative Incidence Curve for Time to Fatal or Non-Fatal MI (Per-Protocol Population [a])



Per-Protocol analysis (N=7,702): only select subjects with reasonably good drug compliance

ARRIVE study:
Conclusions

Primary prevention in high CV risk

- With contemporary treatment, actual CV event rate seemed to decrease
- It is difficult to conduct primary prevention trials as patient compliance is fair in long run
- Aspirin seemed can reduce risk of MI if compliance is good, with increased risk of GI bleeding

ASPREE study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Aspirin on Disability-free Survival in the Healthy Elderly

J.J. McNeil, R.L. Woods, M.R. Nelson, C.M. Reid, B. Kirpach, R. Wolfe, E. Storey, R.C. Shah, J.E. Lockery, A.M. Tonkin, A.B. Newman, 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, G.A. Donnan, P. Gibbs, C.I. Johnston, J. Ryan, B. Radziszewska, R. Grimm, and A.M. Murray, for the ASPREE Investigator Group*

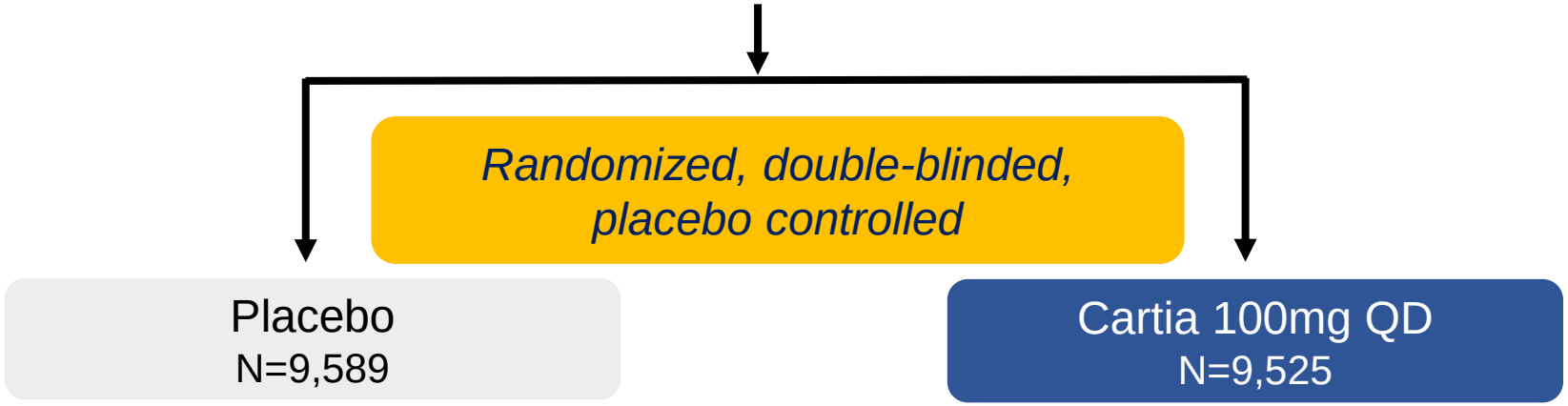
Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

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, S. Satterfield,* R. Grimm, and A.M. Murray, for the ASPREE Investigator Group†

ASPREE study:
Study Design

Primary prevention in Elderly

- Age ≥70
- No history of cardiovascular, cerebrovascular disease
- No history of chronic illness which limit life expectancy
- No history of serious bleeding



Median FU: 4.7 years

Primary endpoint: survival free from dementia or persistent physical disability
Key secondary endpoints: major hemorrhage and cardiovascular disease (defined as fatal CHD, nonfatal MI, fatal or nonfatal stroke, or hospitalization for heart failure)

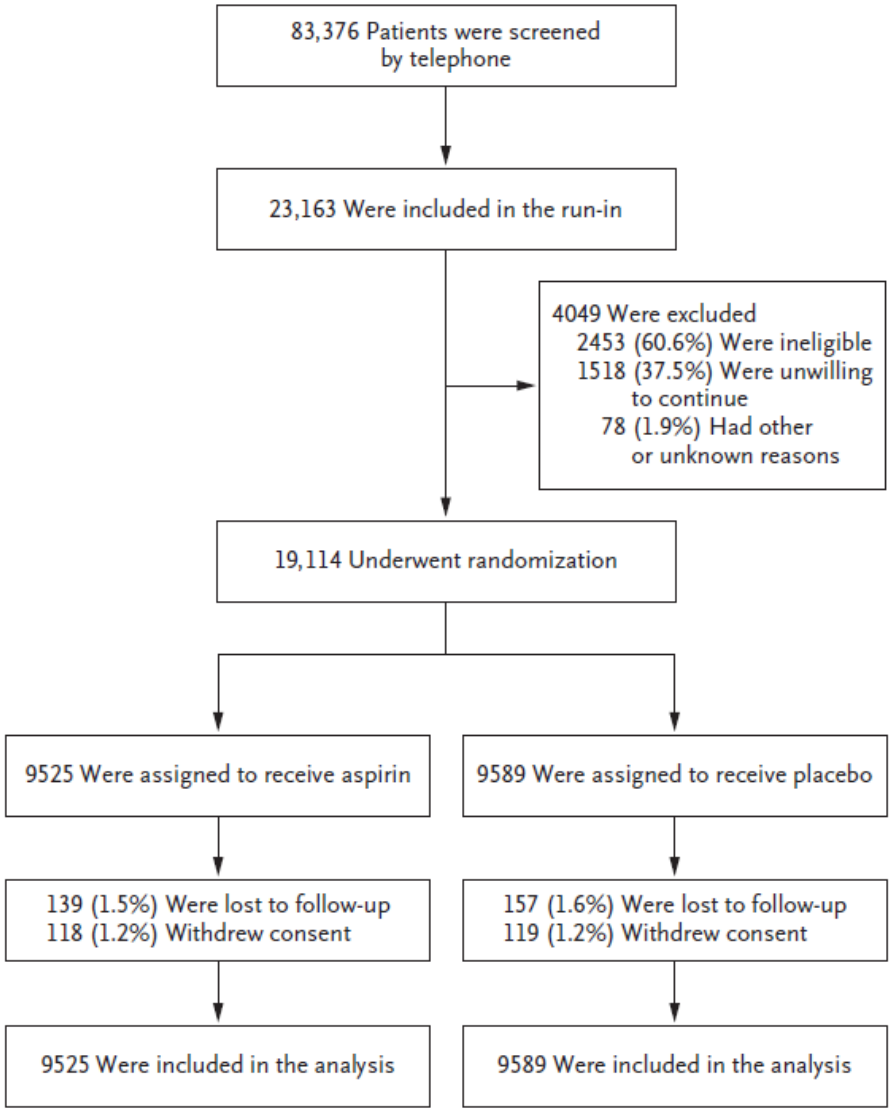
ASPREE study:
Study population

Primary prevention in Elderly

Table 1. **Demographic Characteristics, Cardiovascular Risk Factors, and Treatment of the Participants at Randomization.***

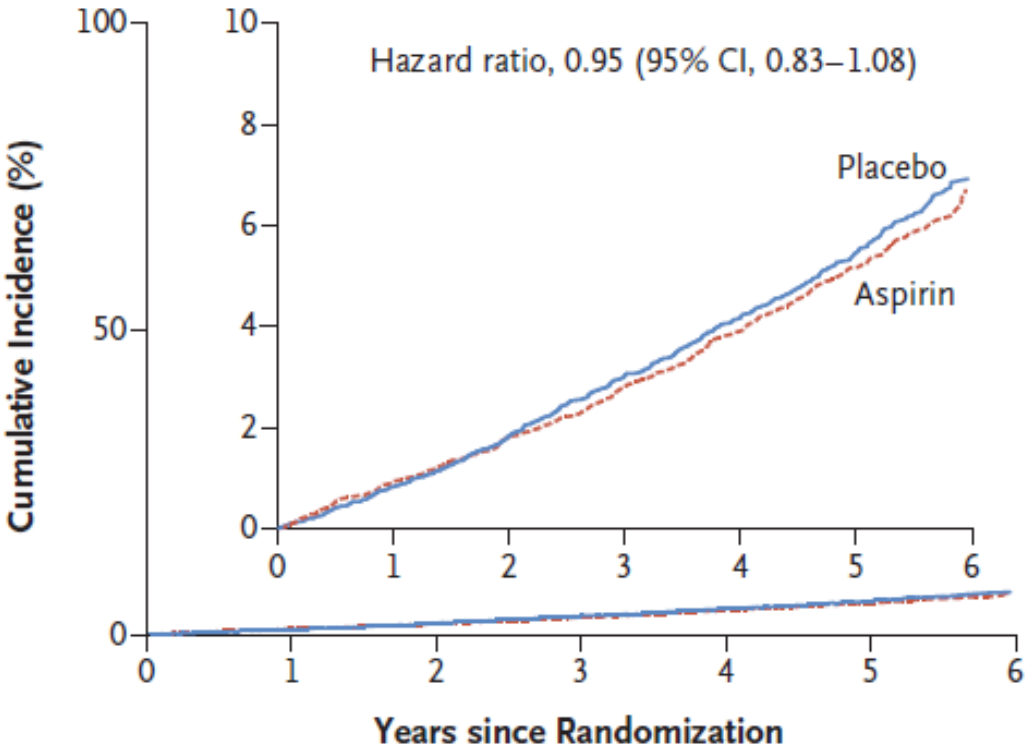
Variable	Aspirin (N=9525)	Placebo (N=9589)
	no. (%)	
Male sex	4152 (44)	4179 (44)
Age ≥74 yr	4806 (50)	4766 (50)
Black race†	451 (5)	450 (5)
Obese‡	2820 (30)	2857 (30)
Smoking		
Current	352 (4)	383 (4)
Former	3909 (41)	3890 (41)
Never	5264 (55)	5316 (55)
Diabetes§	1027 (11)	1030 (11)
Hypertension¶	7065 (74)	7148 (75)
Dyslipidemia‖	6159 (65)	6308 (66)
Chronic kidney disease**	2456 (26)	2464 (26)
Number of cardiovascular risk factors††		
0 or 1	2935 (31)	2885 (30)
2	3968 (42)	4049 (42)
3 or 4	2622 (28)	2655 (28)
Previous regular aspirin use‡‡	1053 (11)	1041 (11)
Statin use at trial entry§§	3244 (34)	3226 (34)
Use of nonsteroidal antiinflammatory drug at trial entry	1371 (14)	1342 (14)
Use of H_2-receptor blocker at trial entry	189 (2)	183 (2)
Use of proton-pump inhibitor at trial entry	2340 (25)	2374 (25)

~10% DM



ASPREE study:
Efficacy Outcome

Primary prevention in Elderly



No significant benefit in CV event

Table 2. Cardiovascular Events.*

End Point	Overall (N=19,114)	Aspirin (N=9525)		Placebo (N=9589)		Hazard Ratio (95% CI)
	no. of participants with event	*no. of participants with event*	*rate per 1000 person-yr*	*no. of participants with event*	*rate per 1000 person-yr*	
Cardiovascular disease†	922	448	10.7	474	11.3	0.95 (0.83–1.08)
Major adverse cardiovascular event‡	701	329	7.8	372	8.8	0.89 (0.77–1.03)
Fatal cardiovascular disease§	159	78	1.8	81	1.9	0.97 (0.71–1.33)
Hospitalization for heart failure	171	88	2.1	83	1.9	1.07 (0.79–1.44)
Fatal or nonfatal myocardial infarction	355	171	4.0	184	4.3	0.93 (0.76–1.15)
Fatal or nonfatal ischemic stroke¶	315	148	3.5	167	3.9	0.89 (0.71–1.11)

ASPREE study:
Safety Outcome

Primary prevention in Elderly

Table 3. Major Hemorrhagic Events.*

End Point	Overall (N=19,114)	Aspirin (N=9525)		Placebo (N=9589)		Hazard Ratio (95% CI)	P Value
	no. of participants with event	*no. of participants with event*	*rate per 1000 person-yr*	*no. of participants with event*	*rate per 1000 person-yr*		
Major hemorrhage†	626	361	8.6	265	6.2	1.38 (1.18–1.62)	<0.001
Intracranial bleeding							
Any	179	107	2.5	72	1.7	1.50 (1.11–2.02)	—
Hemorrhagic stroke	77	43	1.0	34	0.8	1.27 (0.81–2.00)	—
Subdural or extradural hemorrhage	61	39	0.9	22	0.5	1.79 (1.06–3.02)	—
Subarachnoid hemorrhage‡	32	18	0.4	14	0.3	1.30 (0.64–2.60)	—
Extracranial bleeding							
Upper gastrointestinal bleeding	137	89	2.1	48	1.1	1.87 (1.32–2.66)	—
Lower gastrointestinal bleeding	127	73	1.7	54	1.3	1.36 (0.96–1.94)	—
Bleeding at another site§	189	101	2.4	88	2.1	1.16 (0.87–1.54)	—
Fatal bleeding							
Fatal major hemorrhage¶	52	28	0.7	24	0.6	1.18 (0.68–2.03)	—
Fatal hemorrhagic stroke	26	13	0.3	13	0.3	1.01 (0.47–2.17)	—

Increased risk of major bleeding

JPPP study

JAMA The Journal of the American Medical Association

Research

Original Investigation

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors

A Randomized Clinical Trial

Yasuo Ikeda, MD; Kazuyuki Shimada, MD; Tamio Teramoto, MD; Shinichiro Uchiyama, MD; Tsutomu Yamazaki, MD; Shinichi Oikawa, MD; Masahiro Sugawara, MD; Katsuyuki Ando, MD; Mitsuru Murata, MD; Kenji Yokoyama, MD; Naoki Ishizuka, PhD

JAMA 2014

JPPP study:
Study Design

Primary prevention in high CV risk

- Age 60-85
- Hypertension OR hyperlipidemia OR DM
- No history of atherosclerosis, cardiovascular, cerebrovascular disease
- No history of serious bleeding

Randomized, open label

NO aspirin
N=7,244

Cartia 100mg QD
N=7,220

Median FU: 5.02 years

Primary endpoint: composite of death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction

JPPP study:
Study population

Primary prevention in high CV risk

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Patient demographics		
Age, mean (SD), y	70.6 (6.2)	70.5 (6.2)
Age, No. (%)		
<70 y	3234 (44.8)	3259 (45.0)
≥70 y	3986 (55.2)	3985 (55.0)
Men, No. (%)	3055 (42.3)	3068 (42.4)
Waist circumference, mean (SD), cm	85.2 (9.9)	84.7 (10.0)
Weight, mean (SD), kg	58.7 (10.4)	58.6 (10.3)
BMI ≥25, No. (%)	2644 (36.6)	2604 (35.9)
Risk factors for vascular events, No. (%)		
HT	6133 (84.9)	6145 (84.8)
DL	5198 (72.0)	5200 (71.8)
DM	2445 (33.9)	2458 (33.9)
HT and DL	4276 (59.2)	4264 (58.9)
DL and DM	1794 (24.8)	1798 (24.8)
HT and DM	1932 (26.8)	1939 (26.8)
HT, DL, and DM	1446 (20.0)	1442 (19.9)
BMI, mean (SD)	24.2 (3.5)	24.2 (3.4)

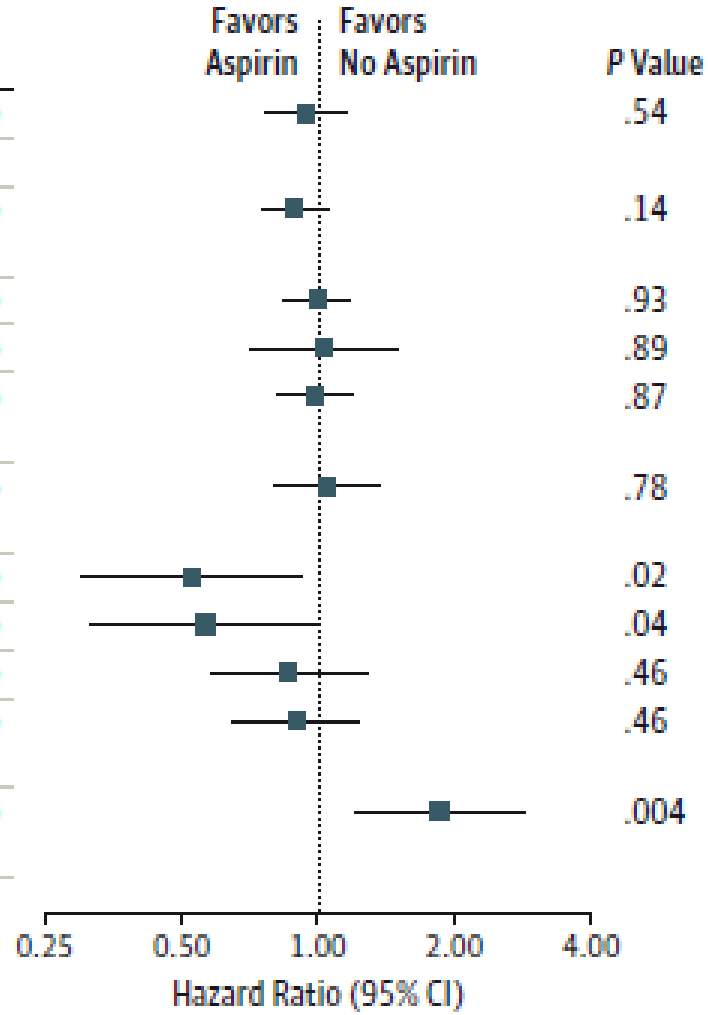
~30% DM

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Blood pressure, mm Hg		
Systolic	137.1 (15.8)	137.2 (15.6)
Diastolic	77.7 (10.4)	77.6 (10.2)
Currently smoking, No. (%)	959 (13.3)	934 (12.9)
Family history of premature CV disease, No. (%)		
No	4058 (56.2)	4086 (56.4)
Yes	1981 (27.4)	1982 (27.4)
Unknown	1181 (16.4)	1176 (16.2)
Laboratory values, mean (SD)		
Cholesterol, mean (SD), mg/dL		
Total	202.9 (32.9)	203.6 (32.5)
Low-density lipoprotein[a]	119.2 (30.5)	119.8 (30.3)
High-density lipoprotein	57.8 (15.8)	58.2 (15.7)
Triglycerides, mean (SD), mg/dL	132.8 (76.0)	131.0 (75.9)
Fasting blood glucose, mean (SD), mg/dL	107.8 (31.2)	107.7 (32.0)
HbA_{1c}, mean (SD), %[b]	6.1 (1.0)	6.0 (1.0)

JPPP study:
Efficacy and safety outcome

Primary prevention in high CV risk

End Point	Aspirin (n = 7220) No. of Events	Aspirin (n = 7220) Event Rate Over 5 Years, % (95% CI)	No Aspirin (n = 7244) No. of Events	No Aspirin (n = 7244) Event Rate Over 5 Years, % (95% CI)	Hazard Ratio (95% CI)	P Value
Primary end point[a]	193	2.77 (2.40-3.20)	207	2.96 (2.58-3.40)	0.94 (0.77-1.15)	.54
Secondary end point						
Any atherosclerotic or cardiovascular event[b]	280	4.00 (3.55-4.50)	319	4.59 (4.11-5.13)	0.89 (0.75-1.04)	.14
Any cause of death	297	4.29 (3.83-4.82)	303	4.11 (3.66-4.62)	0.99 (0.85-1.17)	.93
Death from cardiovascular disease	58	0.86 (0.66-1.12)	57	0.78 (0.60-1.02)	1.03 (0.71-1.48)	.89
Death from causes other than cardiovascular disease	239	3.46 (3.04-3.94)	246	3.36 (2.94-3.83)	0.99 (0.82-1.18)	.87
Nonfatal cerebrovascular disease (ischemic or hemorrhagic)	117	1.65 (1.37-1.99)	114	1.64 (1.36-1.98)	1.04 (0.80-1.34)	.78
Nonfatal myocardial infarction	20	0.30 (0.19-0.47)	38	0.58 (0.42-0.81)	0.53 (0.31-0.91)	.02
Transient ischemic attack	19	0.26 (0.16-0.42)	34	0.49 (0.35-0.69)	0.57 (0.32-0.99)	.04
Angina pectoris	46	0.66 (0.49-0.89)	54	0.81 (0.61-1.07)	0.86 (0.58-1.28)	.46
Arteriosclerotic diseases requiring surgery or intervention	75	1.08 (0.86-1.36)	85	1.24 (0.99-1.55)	0.89 (0.65-1.21)	.46
Serious extracranial hemorrhage requiring transfusion or hospitalization	62	0.86 (0.67-1.11)	34	0.51 (0.37-0.72)	1.85 (1.22-2.81)	.004



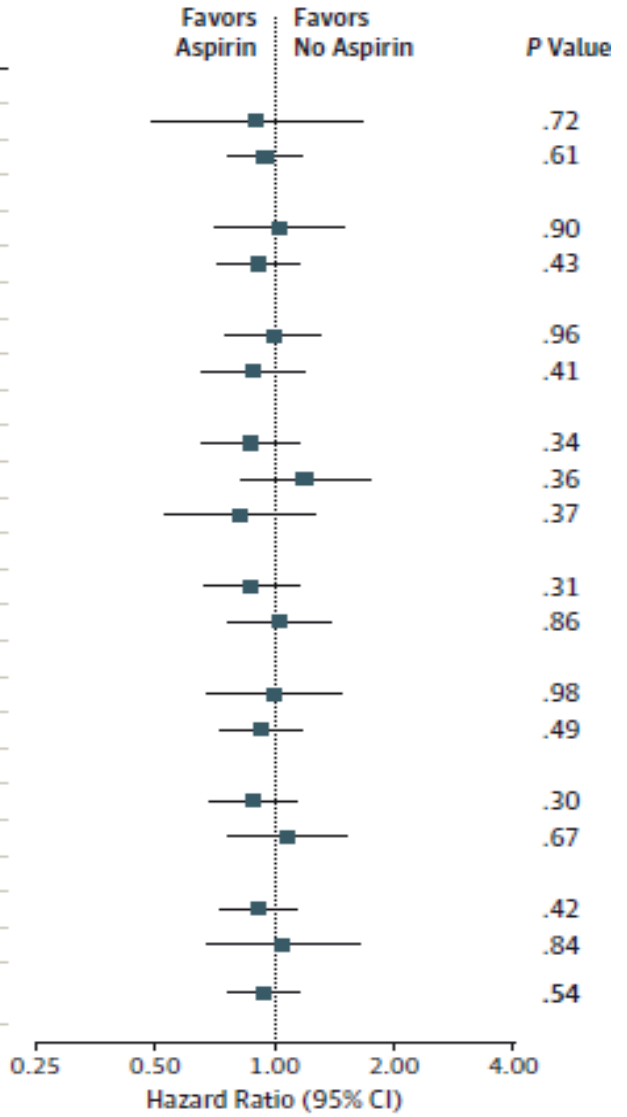
No difference in primary endpoint
Reduction in non-fatal MI

Increase major bleeding

JPPP study:
Study population

Primary prevention in high CV risk

Disease Risk Factor	Aspirin			No Aspirin			Hazard Ratio (95% CI)	*P* Value
	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)		
Hypertension								
No	20	1087	1.74 (1.08-2.80)	23	1099	2.12 (1.40-3.20)	0.90 (0.49-1.63)	.72
Yes	173	6133	2.95 (2.54-3.44)	184	6145	3.11 (2.68-3.60)	0.95 (0.77-1.17)	.61
Dyslipidemia								
No	56	2022	2.89 (2.21-3.78)	56	2044	2.93 (2.26-3.81)	1.02 (0.71-1.48)	.90
Yes	137	5198	2.73 (2.30-3.23)	151	5200	2.97 (2.52-3.50)	0.91 (0.72-1.15)	.43
Diabetes mellitus								
No	107	4775	2.30 (1.89-2.79)	109	4786	2.36 (1.95-2.86)	0.99 (0.76-1.30)	.96
Yes	86	2445	3.70 (2.99-4.58)	98	2458	4.14 (3.38-5.06)	0.89 (0.66-1.18)	.41
Family history[b]								
No	94	4058	2.44 (1.98-3.00)	109	4086	2.72 (2.24-3.30)	0.87 (0.66-1.15)	.34
Yes	61	1981	3.13 (2.42-4.03)	52	1982	2.83 (2.16-3.72)	1.19 (0.82-1.72)	.36
Unknown	38	1181	3.33 (2.41-4.59)	46	1176	4.01 (2.98-5.37)	0.82 (0.54-1.26)	.37
Sex								
Men	99	3055	3.42 (2.80-4.18)	114	3068	3.85 (3.19-4.65)	0.87 (0.67-1.14)	.31
Women	94	4165	2.30 (1.87-2.83)	93	4176	2.32 (1.88-2.85)	1.03 (0.77-1.37)	.86
Age, y								
<70	52	3234	1.67 (1.27-2.21)	53	3259	1.73 (1.31-2.28)	1.00 (0.68-1.46)	.98
≥70	141	3986	3.67 (3.10-4.34)	154	3985	3.98 (3.39-4.67)	0.92 (0.73-1.16)	.49
BMI								
<25	122	4576	2.75 (2.29-3.29)	141	4640	3.21 (2.71-3.79)	0.88 (0.69-1.12)	.30
≥25	71	2644	2.82 (2.22-3.57)	66	2604	2.53 (1.97-3.25)	1.08 (0.77-1.50)	.67
Smoker								
No	150	6261	2.48 (2.10-2.92)	167	6310	2.71 (2.32-3.17)	0.91 (0.73-1.14)	.42
Yes	43	959	4.76 (3.51-6.43)	40	934	4.69 (3.43-6.40)	1.05 (0.68-1.61)	.84
Overall	**193**	**7220**	**2.77 (2.40-3.20)**	**207**	**7244**	**2.96 (2.58-3.40)**	**0.94 (0.77-1.15)**	**.54**



ASCEND study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

ASCEND study:
Study Design

Primary prevention in DM

- Age ≥40
- Diabetes Mellitus
- No history of cardiovascular disease

Randomized, double-blinded, placebo controlled

Placebo
N=7,740

Cartia 100mg QD
N=7,740

Median FU: 7.4 years

Primary endpoint: first Serious Vascular Event (SVE), which was defined as a composite of nonfatal myocardial infarction, nonfatal stroke or transient ischemic attack, or death from any vascular cause.

Primary safety endpoint: first occurrence of any major bleeding event

ASCEND study:
Study Population

Primary prevention in DM

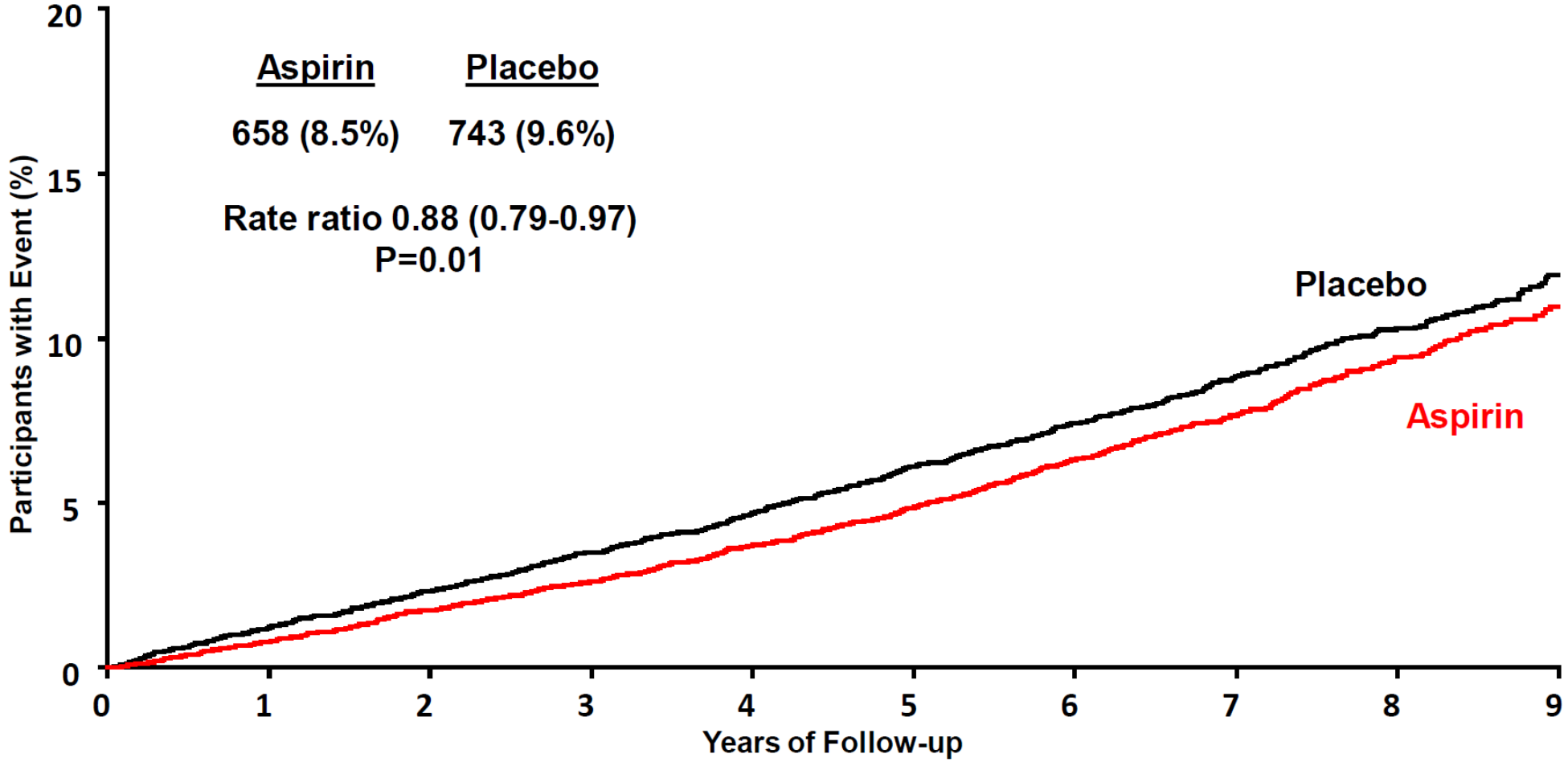
Baseline demographics (N=15,480)

Characteristic	Aspirin	Placebo
Age, years	63	63
Male	63%	63%
Type 2 diabetes	94%	94%
Diabetes duration, median years	7	7
Hypertension	62%	62%
Statin use	76%	75%
Body Mass Index, kg/m^2	31	31
Glycated haemoglobin, mmol/mol	55 (7.2%)	55 (7.2%)

ASCEND study:
Efficacy outcome

Primary prevention in DM

Effect of aspirin on Serious Vascular Events

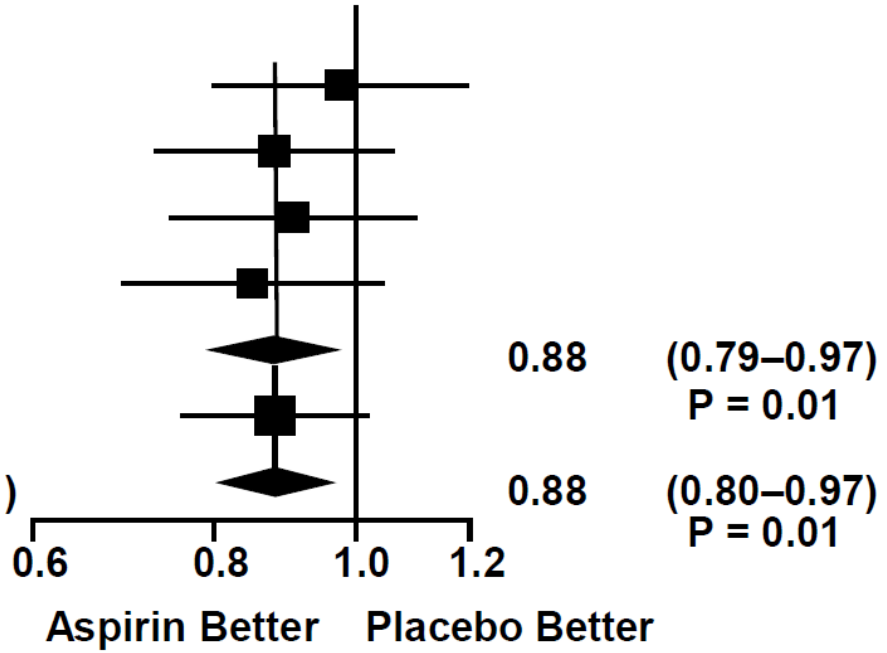


ASCEND study:
Efficacy outcome

Primary prevention in DM

Components of the primary efficacy outcome plus revascularization

Type of Event	Aspirin (N=7740) no. of participants with events	(%)	Placebo (N=7740) no. of participants with events	(%)	Rate Ratio (95% CI)	
Vascular outcomes						
Non-fatal myocardial infarction	191	(2.5)	195	(2.5)		
Non-fatal presumed ischaemic stroke	202	(2.6)	229	(3.0)		
Vascular death excl. intracranial haemorrhage	197	(2.5)	217	(2.8)		
Transient ischaemic attack (TIA)	168	(2.2)	197	(2.5)		
Any serious vascular event	**658**	**(8.5)**	**743**	**(9.6)**	**0.88**	**(0.79–0.97) P = 0.01**
Any arterial revascularization	340	(4.4)	384	(5.0)		
Any serious vascular event or revascularization	**833**	**(10.8)**	**936**	**(12.1)**	**0.88**	**(0.80–0.97) P = 0.01**

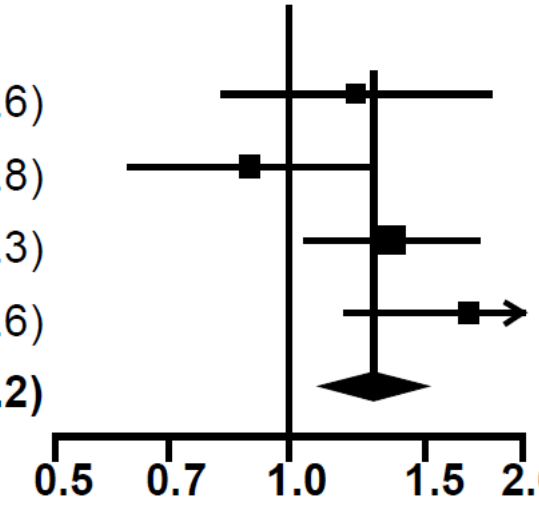


ASCEND study:
Safety outcome

Primary prevention in DM

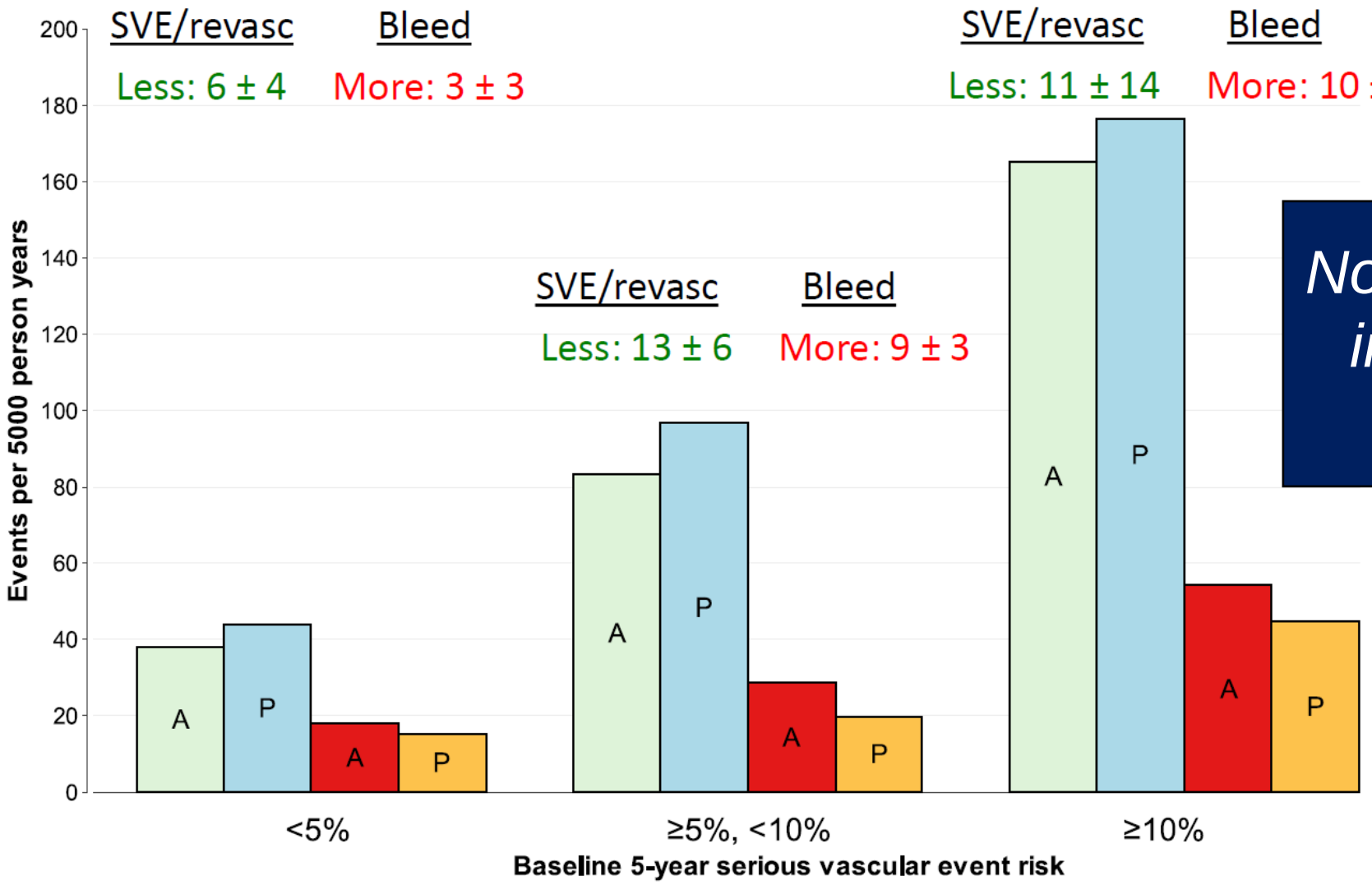
Effect of aspirin on major bleed

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	Absolute Difference (%)
	no. of participants with events (%)			
Major bleed				
Intracranial hemorrhage	55 (0.7)	45 (0.6)		0.1
Sight threatening eye bleed	57 (0.7)	64 (0.8)		-0.1
Serious gastrointestinal hemorrhage	137 (1.8)	101 (1.3)		0.5
Other major bleed	74 (1.0)	43 (0.6)		0.4
Any major bleed	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)** P = 0.003	**0.9**



ASCEND study:
Risk benefit ratio

Primary prevention in DM



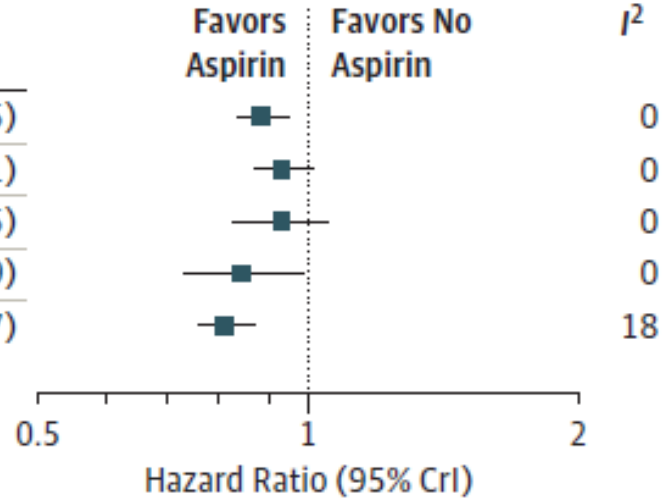
No significant difference in risk-benefit ratio in different subgroup

Meta-analysis in 2019

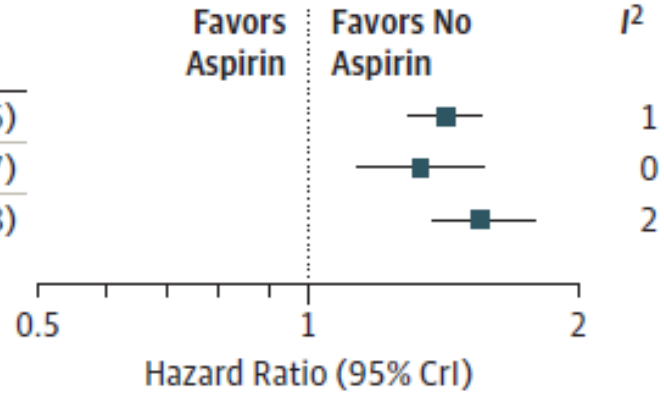
13 trials randomizing 164,225 participants with 1,050,511 participant-years of follow-up

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	11	2911	79717	3072	78147	0.38 (0.20 to 0.55)	0.89 (0.84-0.95)	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	0.16 (0.06 to 0.30)	0.81 (0.76-0.87)	18



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



Probably reduces CV event
Increases major bleeding

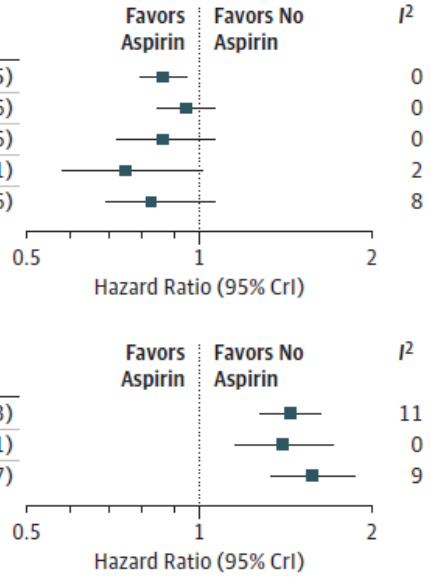
Zheng et al. JAMA. 2019;321(3):277-287

Meta-analysis in 2019

A Participants with low CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome	6	1559	56212	1753	56354	0.34 (0.14 to 0.52)	0.87 (0.79-0.95)	0
All-cause mortality	6	1903	56212	1905	56354	0.01 (-0.27 to 0.27)	0.95 (0.85-1.06)	0
CV mortality	6	405	56212	448	56354	0.07 (-0.03 to 0.16)	0.87 (0.72-1.06)	0
Myocardial infarction	6	649	56212	793	56354	0.27 (0.00 to 0.49)	0.75 (0.58-1.01)	2
Ischemic stroke	5	508	49942	593	50078	0.16 (0.02 to 0.29)	0.83 (0.69-1.06)	8

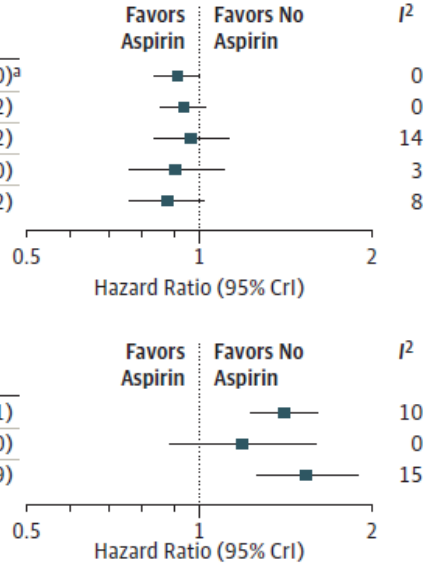
Bleeding Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	5	665	49942	465	50078	0.40 (0.25 to 0.57)	1.45 (1.28-1.63)	11
Intracranial bleeding	6	245	56212	175	56354	0.13 (0.05 to 0.22)	1.41 (1.16-1.71)	0
Major GI bleeding	5	359	48992	228	49110	0.27 (0.15 to 0.40)	1.58 (1.34-1.87)	9



B Participants with high CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome[c]	6	1352	23505	1319	21793	0.51 (0.06 to 0.93)	0.92 (0.84-1.00)[a]	0
All-cause mortality	7	1719	25411	1683	23703	0.43 (-0.02 to 0.84)	0.94 (0.86-1.02)	0
CV mortality	7	590	25411	549	23703	0.04 (-0.27 to 0.32)	0.97 (0.84-1.12)	14
Myocardial infarction[c]	8	820	25411	806	23703	0.32 (-0.16 to 0.74)	0.91 (0.76-1.10)	3
Ischemic stroke[c]	6	323	15374	350	13674	0.28 (-0.12 to 0.63)	0.88 (0.76-1.02)	8

Bleeding Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	6	530	24773	369	23065	0.64 (0.35 to 0.97)	1.41 (1.23-1.61)	10
Intracranial bleeding	6	104	24773	82	23065	0.07 (-0.04 to 0.21)	1.19 (0.89-1.60)	0
Major GI bleeding	5	34	19452	30	19444	0.39 (0.16 to 0.69)	1.54 (1.26-1.89)	15



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

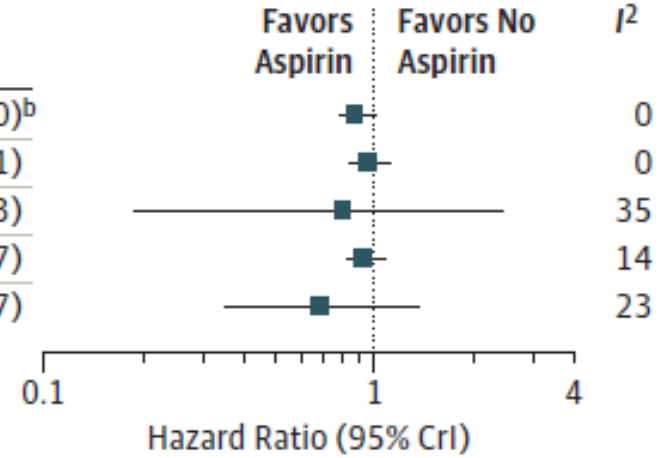
Similar outcome across low OR high CV risk

Increase risk of bleeding

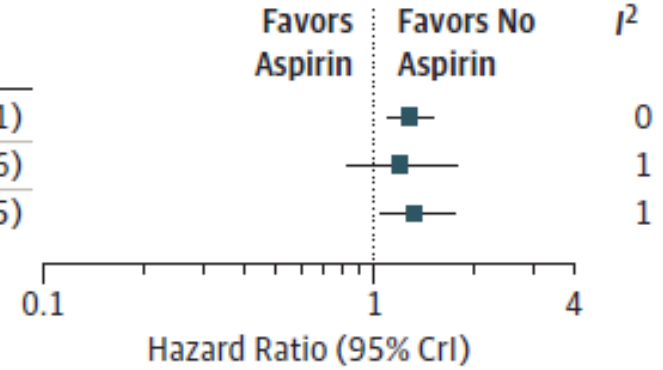
Meta-analysis in 2019

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)



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

Meta-analysis in 2019

13 trials; 134,446 participants

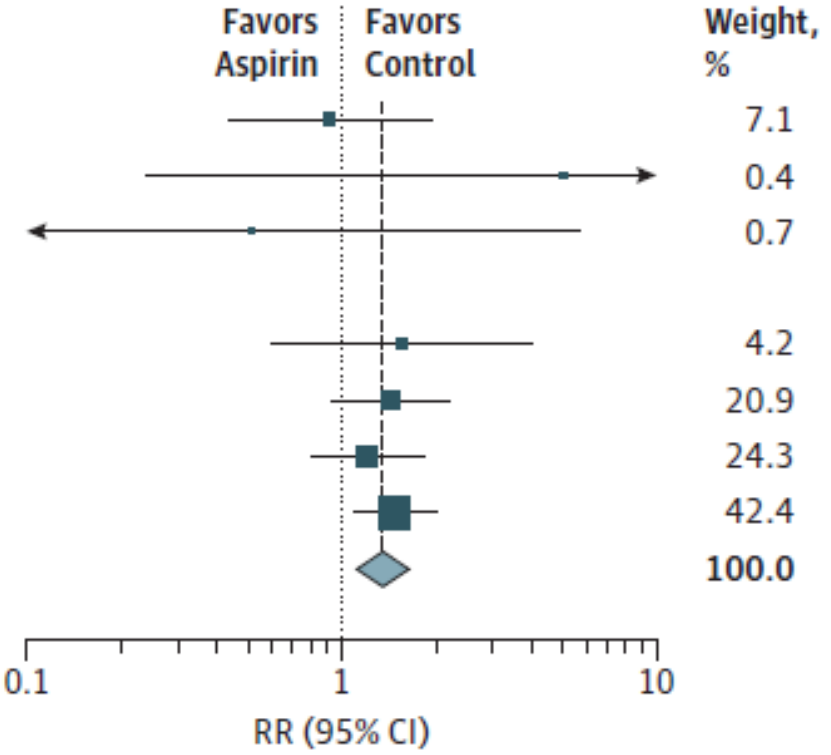
Intracranial hemorrhage

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)	Weight, %
Hansson et al (HOT),[32] 1998	14	9399	15	9391	0.93 (0.45-1.93)	7.1
de Gaetano (PPP),[29] 2001	2	2226	0	2269	5.10 (0.24-106.10)	0.4
Landolfi et al (ECLAP),[34] 2004	1	253	2	265	0.52 (0.05-5.74)	0.7
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)	4.2
Ikeda et al (JPPP),[33] 2014	52	7220	36	7244	1.45 (0.95-2.21)	20.9
Bowman et al (ASCEND),[14] 2018	55	7740	45	7740	1.22 (0.83-1.81)	24.3
McNeil et al (ASPREE),[15] 2018	107	9525	72	9589	1.50 (1.11-2.01)	42.4
Total (95% CI)		**38086**		**38223**	**1.37 (1.13-1.66)**	**100.0**
Total events	242		177			

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

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



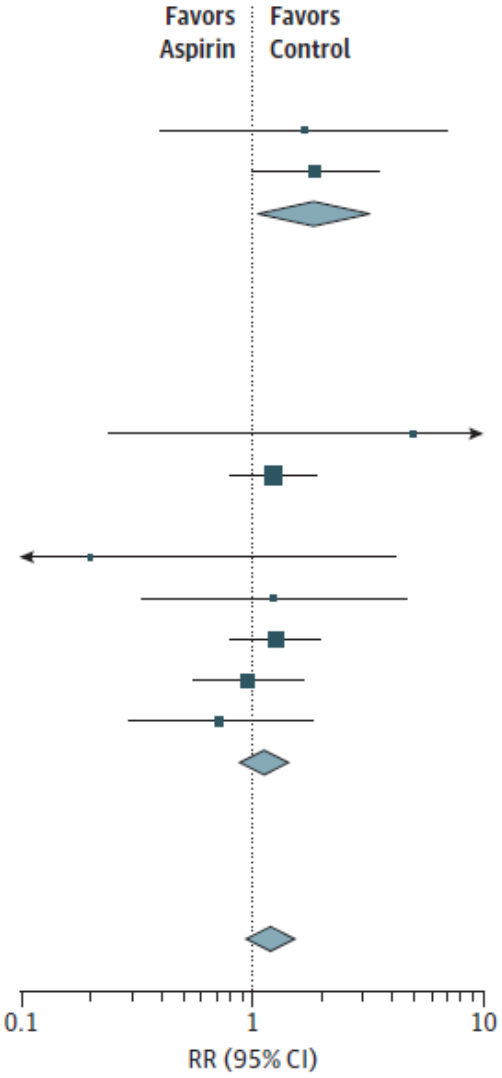
Increases risk of ICH

Huang et al. JAMA. 2019

Meta-analysis in 2019

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: $\chi^2_1=2.27$; $P=.13$; $I^2=56.0\%$						



Intracranial hemorrhage

Asians at higher risk

Huang et al. JAMA. 2019

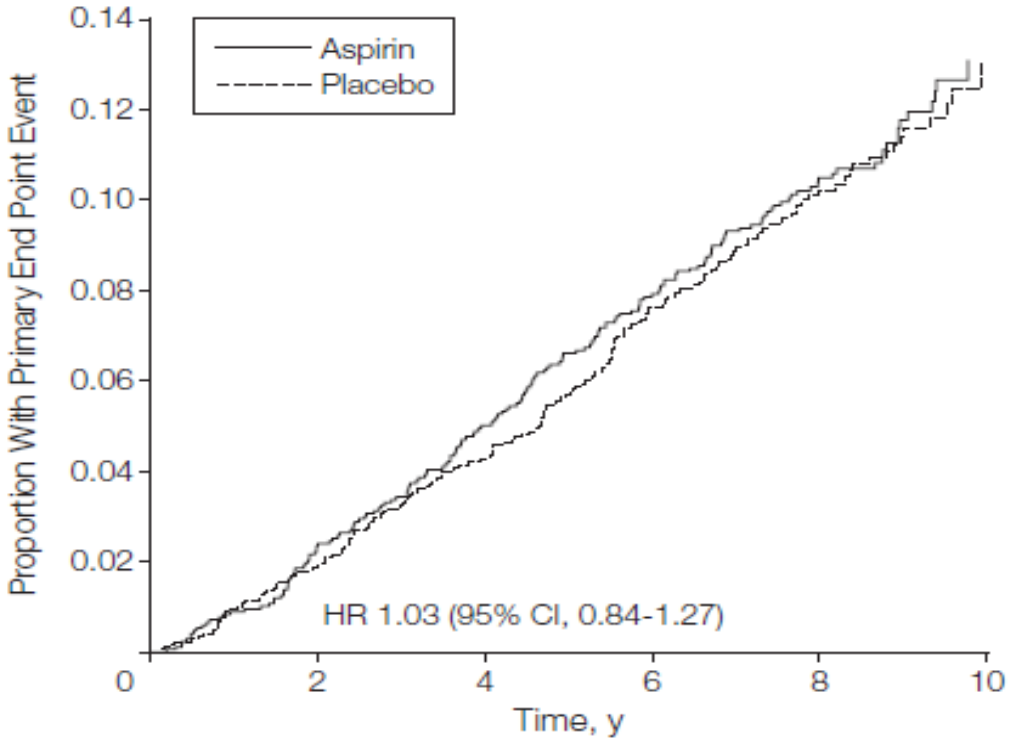
Stable atherosclerosis (‘1.5 prevention’)

Mild CAD on CTA
Mild CAD on CORO
Stable angina
Carotid IMT, mild carotid stenosis
Mild peripheral vascular disease (PVD)

Aspirin for asymptomatic atherosclerosis study

N=3,350, age 50-75
No history of MI or stroke or taking Aspirin

ABI≤0.95
(PVD, asymptomatic atherosclerosis)



Fowkes et al. JAMA. 2010

Stable atherosclerosis ('1.5 prevention')

THEMIS

Design and main eligibility criteria

Type 2 diabetes; men and women ≥ 50 years
≥ 6 months glucose lowering drug treatment
*At high risk for CV events**
No previous MI or stroke
No planned use of ADP receptor antagonist or planned revascularisation

Low-dose ASA background therapy based on individual risk

** At high risk of CV events defined as history of PCI or CABG or angiographic evidence of ≥ 50% lumen stenosis of at least 1 coronary artery*

Ticagrelor | *Placebo*

Event driven study; 1034 CV events required. 2 years mean follow-up. (n=19 000)

Primary endpoint : Composite of CV death, MI or stroke

Secondary endpoint: Composite of all-cause death, MI or stroke; CV death; All-cause death

Primary safety: TIMI Major bleeding

Stable atherosclerosis (‘1.5 prevention’)

News > Medscape Medical News

THEMIS Top-Line Results: Ticagrelor Cuts CV Event Risk in Diabetics With Coronary Disease

N=19,271

DM patients

No MI/stroke

Documented CAD
Details pending

Post PCI vs CABG vs just atherosclerosis

Aspirin + Ticagrelor
Vs
Aspirin

Aspirin in prevention of CV event

Practical considerations

Acute phase of event
Eg MI, stroke

Post event
Eg post MI, PCI, CABG

Aspirin indicated

Stable atherosclerosis

Aspirin if no C/I or low risk of bleeding
(also depends on extent of atherosclerosis)

High CV risk, DM

In the contemporary practice of alternative treatment
Eg Statins, PCSK9
SGLT-2 inh, GLP-1 for DM

Need to discuss with patients benefit and risk of Aspirin

Benefit: probably reduces chance of MI

Risk: risk of bleeding (particularly GIB)

Queen Mary Hospital

Hong Kong College of Cardiology ASM 2019

Thank you

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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	22 071	22 071 (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	18 790	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	39 876	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 Diabetes (POPADAD),[25] 2008	100 daily	Placebo	Randomized, double-blind; factorial design with antioxidant	Individuals with diabetes, ABPI ≤0.99, aged ≥40 y	United Kingdom	1997-2006	1276	563 (44)	60 (10)	1276 (100)	NR	NR	145 (21)	5.5 (NR)	29.2 (NR)	NA	Low
Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes,[28] 2008	81 or 100 daily	No aspirin	Randomized, open-label, blind end point	Individuals with diabetes aged 30-85 y	Japan	2002-2008	2539	1387 (55)	65 (10)	2539 (100)	537 (21)	1473 (58)	135 (15)	5.2 (0.9)	24 (4)	12.5 (9.8-15.9)	High

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
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 60-85 y, 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 publication; SBP, systolic blood pressure.

SI conversion factor: To convert cholesterol data to mg/dL, multiply by 0.0259.

[a] Data are presented as mean (SD) unless otherwise specified.

[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.

[c] 5085 Participants were randomized in a 2x2 factorial design warfarin, aspirin, warfarin and aspirin, or placebo. 2545 Were randomized to warfarin and excluded from analysis.

[d] Data reported as median (range).