Is There Any Clinical Benefit of Aspirin in Primary Prevention? Insight from ASCEND, ARRIVE, and ASPREE?

Gyeongsang National University Changwon Hospital
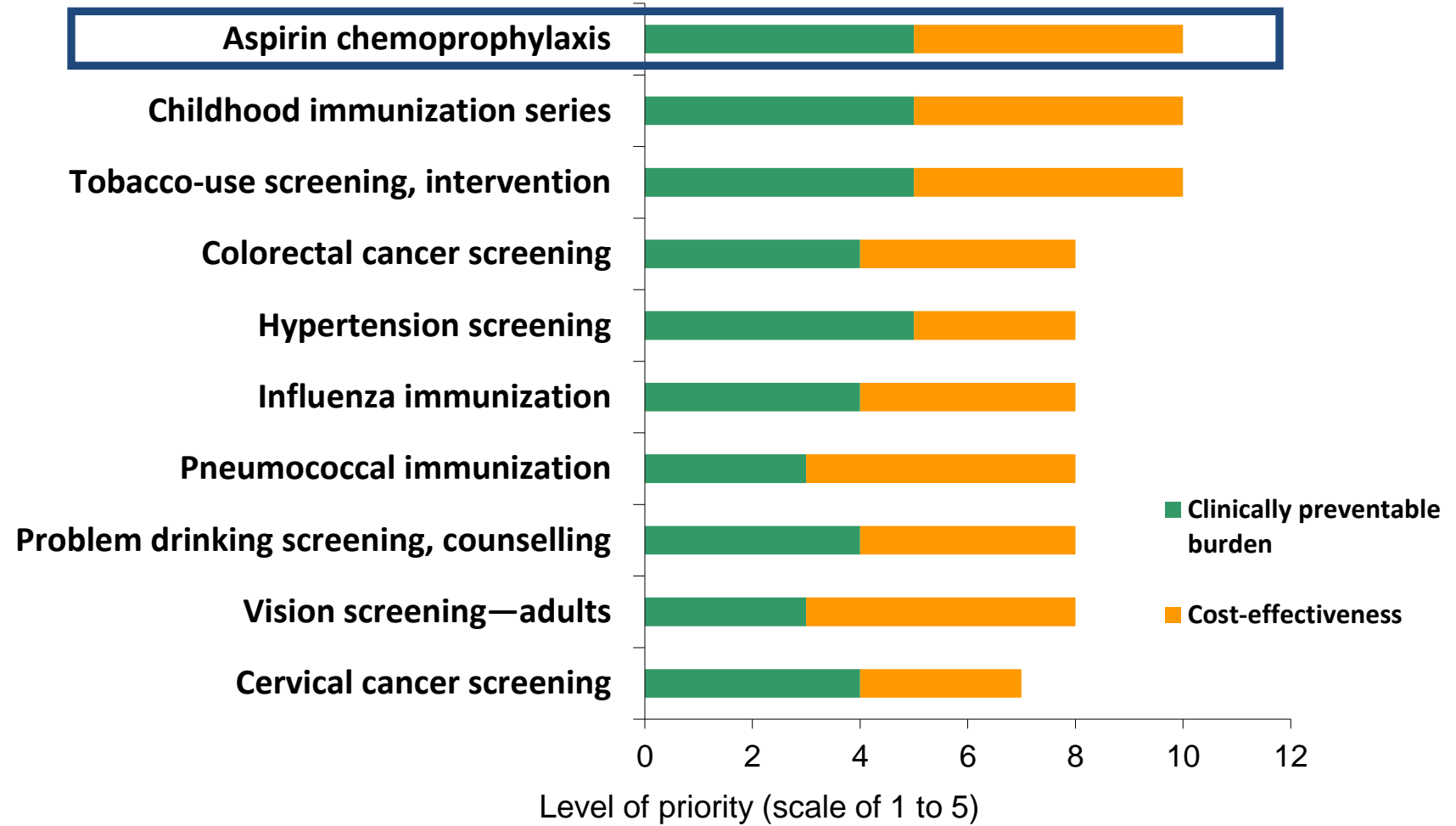
Yongwhi Park

Disclosure

- Nothing for this presentation.

Risk Factors in People Without CVD

Risk Factor	Major Coronary Event	Probable Ischemic Stroke	Hemorrhagic Stroke	Major Extracranial Bleed
Age (per decade)	1.84 (1.74–1.95)	2.46 (2.27–2.65)	1.59 (1.33–1.90)	2.15 (1.93–2.39)
Male*	2.43 (1.94–3.04)	1.44 (1.14–1.82)	1.11 (0.52–2.34)	1.99 (1.45–2.73)
Diabetes mellitus	2.66 (2.28–3.12)	2.06 (1.67–2.54)	1.74 (0.95–3.17)	1.55 (1.13–2.14)
Current smoker	2.05 (1.85–2.28)	2.00 (1.72–2.31)	2.18 (1.57–3.02)	1.56 (1.25–1.94)
Mean blood pressure (per 20 mm Hg)†	1.73 (1.59–1.89)	2.00 (1.77–2.26)	2.18 (1.65–2.87)	1.32 (1.09–1.58)
Cholesterol (per 1 mmol/l)	1.18 (1.12–1.24)	1.02 (0.95–1.09)	0.90 (0.77–1.07)	0.99 (0.90–1.08)
Body mass index (per 5 kg/m²)	1.09 (1.03–1.15)	1.06 (0.98–1.14)	0.85 (0.71–1.02)	1.24 (1.13–1.35)

*Analyses are stratified by trial. The relevance of male sex can therefore be assessed only in the 2 trials that included both men and women, so the 95% CIs for it are wide, particularly for stroke. †Mean of systolic and diastolic blood pressure. Associations with measured values are not corrected for the effects of regression dilution. Reproduced with permission from the Antithrombotic Trialists' (ATT) Collaboration (34).

Effective clinical preventive services

Level of priority (scale of 1 to 5)

- Clinically preventable burden
- Cost-effectiveness

Maciosek MV. Am J Prev Med. 2006;31:52-60.

Aspirin primary prevention trials

| Trial	Design	Main inclusion criteria	Patients (n)	M/F ratio	Duration (yr)
BDT[1]	PC, aspirin 500 mg/day	Healthy male physicians	5139	100/0	6
PHS[2]	PC, aspirin 325 mg/qod	Healthy male physicians	22 071	100/0	5.2
TPT[3]	PC, warfarin, aspirin 75 mg/day	Men at risk of IHD	5499	100/0	6.8
HOT[4]	PC, aspirin 75 mg/day	Hypertension	18 790	53/47	3.8
PPP[5]	Open, aspirin 100 mg/day, vitamin E 300 mg/day	CV risk factors	4495	43/57	3.6
WHS[6]	PC, aspirin 100 mg/day	Women ≥45 years, no CVD	39 876	0/100	10.1
JPAD[7]	PC, aspirin 81–100 mg/day	Type 2 diabetes	2539	55/45	4.4
POPADAD[8]	PC, aspirin 100 mg/day	DM or asymptomatic PAD	1276	44/56	6.7
AAAT[9]	PC, aspirin 100 mg/day	Low ankle brachial index	3350	28/72	8.2

CV cardiovascular; IHD, ischaemic heart disease; PAD, peripheral artery disease; PC, placebo-controlled.
1. Peto R, et al. BMJ 1988;296:313−6; 2. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989;321129−35;
3. The Medical Research Council's General Practice Research Framework. Lancet 1998;351:233−41; 4. Hansson L, et al. Lancet 1998;351:1755−62;
5. Sacco M, et al. Diabetes Care 2003;26:3264−72; 6. Ridker PM, et al. N Engl J Med 2005;352:1293−304;
7. Ogawa H, et al. JAMA 2008;300:2134−41;
8. Belch J, et al. BMJ 2008;337:a1840; 9. Fowkes FG, et al. JAMA 2010;303:841–8.

IHD in participants with aspirin

Study or Subgroup	Aspirin Events	Total	Placebo/ No treatment Events	Total	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
1.2.1 Cardiovascular events							
BDT	289	3429	147	1710	0.98 [0.81, 1.19]	1988	
PHS	320	11037	388	11034	0.82 [0.71, 0.95]	1989	
HOT	315	9399	368	9391	0.86 [0.74, 0.99]	1998	
TPT	112	1268	147	1272	0.76 [0.61, 0.97]	1998	
PPP	47	2226	71	2269	0.67 [0.47, 0.97]	2001	
WHS	477	19934	522	19942	0.91 [0.81, 1.03]	2005	
POPADAD	127	638	132	638	0.96 [0.77, 1.20]	2008	
JPAD	40	1262	46	1277	0.88 [0.58, 1.33]	2008	
AAA	134	1675	136	1675	0.99 [0.78, 1.24]	2010	
Subtotal (95% CI)		**50868**		**49208**	**0.88 [0.83, 0.94]**		
Total events	1861		1957				

Heterogeneity: Tau² = 0.00; Chi² = 7.56, df = 8 (P = 0.48); I² = 0%

Test for overall effect: Z = 3.96 (P < 0.0001)

Lancet 2009; 373: 1849-60.
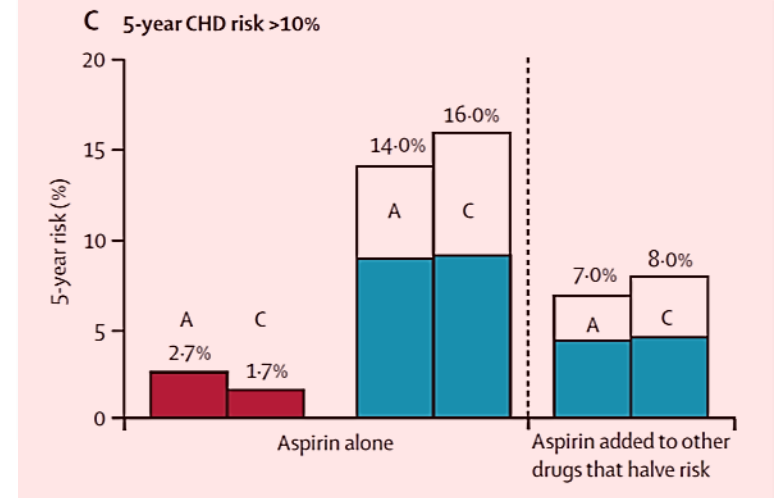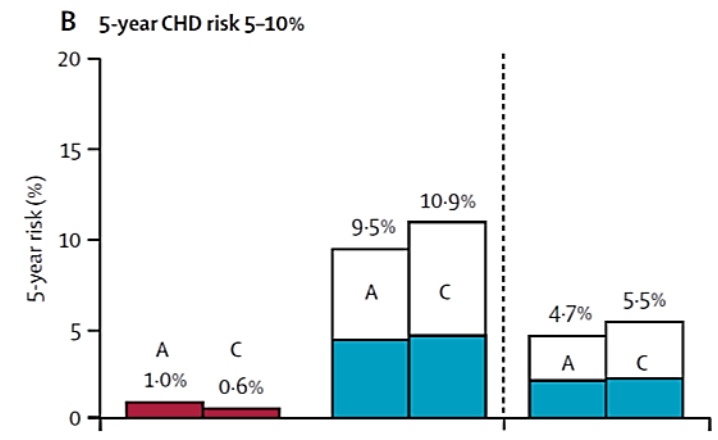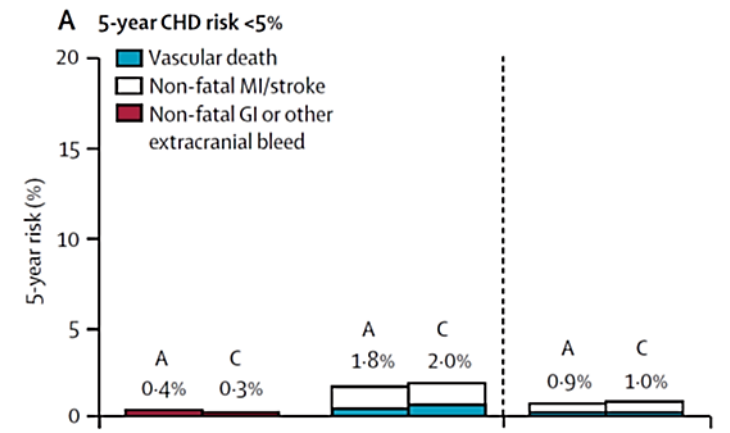
Relative Risk Estimates for ASCVD Risk Reduction

Therapy	Estimated RR for ASCVD Events (95% CI)	Quality of Evidence*	Comment
Aspirin	0.90 (0.85–0.96)	High	Increased risk for major bleeding (RR, 1.54; 95% CI, 1.30–1.82)
Blood pressure-lowering†	CHD: 0.84 (0.79–0.90) overall; 0.79 (0.72–0.86) per 10 mm Hg reduction in SBP	High High	Adverse effects poorly reported
	Stroke: 0.64 (0.56–0.73) overall; 0.54 (0.45–0.65) per 10 mm Hg reduction in SBP	High	
Cholesterol-lowering (statin)	0.75 (0.70–0.81) overall; 0.75 (0.70–0.80) per 1 mmol/L (38.7 mg/dL) reduction in LDL-cholesterol	High	No increased risk for adverse effects overall (RR, 1.00; 95% CI, 0.97–1.03)
Smoking cessation‡	0.73 overall; 0.85 at 1 y (>6–18 mo follow up); 0.73 at 2 y (>18–30 mo); 0.62 at 3 y (>30–42 mo); 0.53 at 4 y (>42 mo)	Not graded	Adverse effects poorly reported

Guidelines on the Use of Aspirin in Primary Prevention

Organization (yr)	Recommendation	Class (LoE)
ESC (2016)	**Not recommended** in individuals without CVD due to the increased risk of major bleeding.	III (B)
ADA (2018)	**may be** considered as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased CV risk. **age >50 years** who have at least one additional major risk factor (**family history of premature ASCVD, HTN, dyslipidemia, smoking, or albuminuria**) and are not at increased risk of bleeding.	C
USPSTF (2016)	**Initiate in adults 50 to 59 years of age with a ≥10% 10-year CVD risk**	**B**
	Individual judgment in adults 60 to 69 years of age with a ≥10% 10-year CVD risk	C
	No recommendation in adults <50 years or ≥70 years of age	I

EHJ 2016;37:2315–81.
Diabetes Care 2018;41(Supplement 1):S86-S104.

Aspirin for primary prevention of CVD

- Diabetes.

- Population at high CVD risk.

- Population at 50-59 years of age.

Male, 57 years.

No symptom.

DM.
HTN.
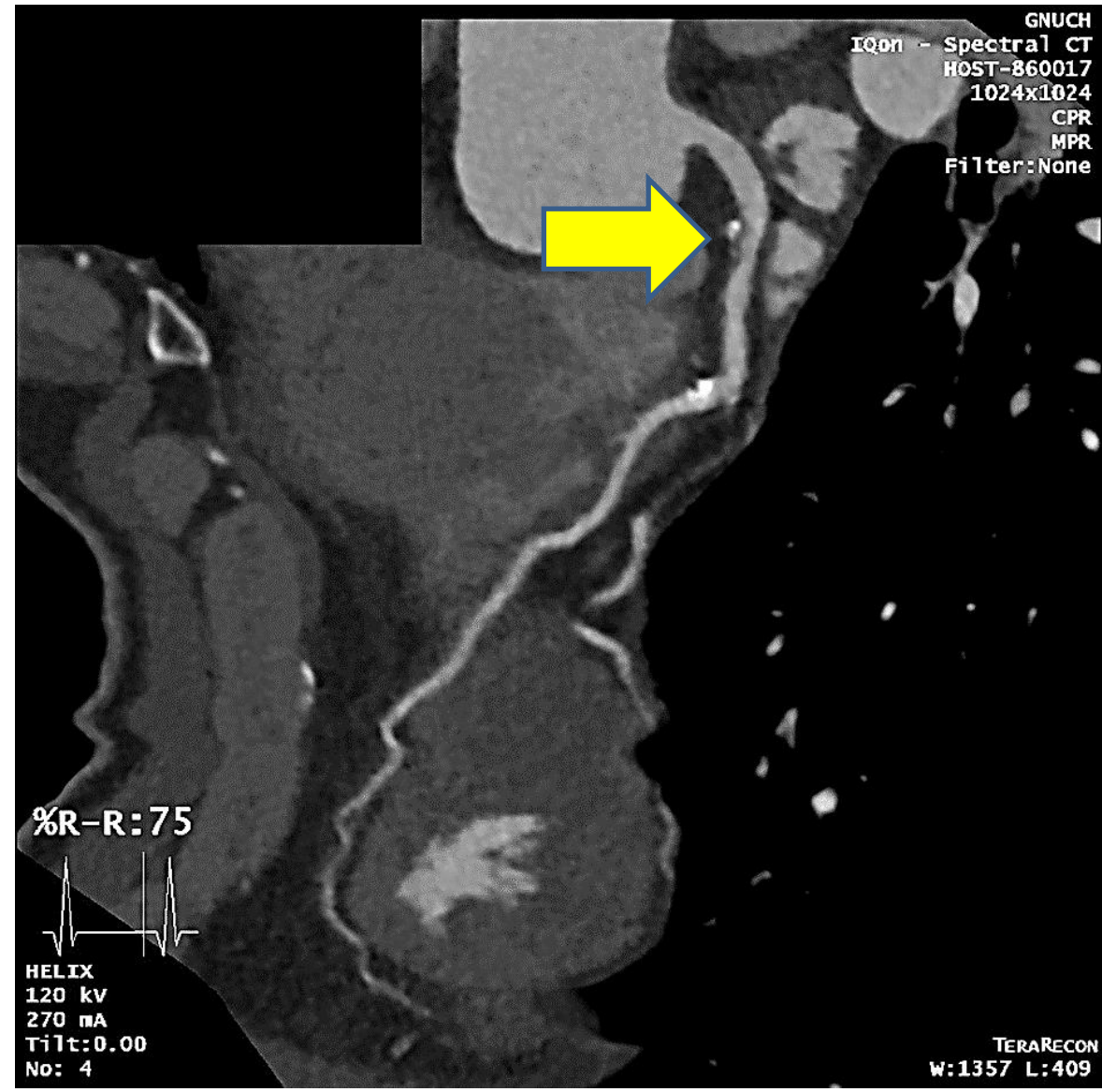Hyperlipidemia.

Hs-CRP: 3.3mg/L
Non-smoker.
10-yr ASCVD risk=8.0%.

ASA in DM: ASCEND

Gyeongsang National University Changwon Hospital

ASCEND in patients with DM

- Men and women ≥ 40 years.
- Diabetes mellitus without CV disease.
- 15,480 UK patients.
- Follow-up: Mean 7.4 years.
- Serious vascular events: nonfatal MI, nonfatal stroke (excluding confirmed intracranial hemorrhage) or TIA, or death from any vascular cause (excluding confirmed intracranial hemorrhage).
- Major bleeding: intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or any other serious bleeding (i.e., a bleeding event that resulted in hospitalization or transfusion or that was fatal).

Effect of aspirin on Serious Vascular Events*

*nonfatal MI, nonfatal stroke (excluding confirmed intracranial hemorrhage) or TIA, or death from any vascular cause (excluding confirmed intracranial hemorrhage)

N Engl J Med. 2018;379:1529-1539.

Effect of aspirin on major bleed*

*intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or any other serious bleeding (i.e., a bleeding event that resulted in hospitalization or transfusion or that was fatal)
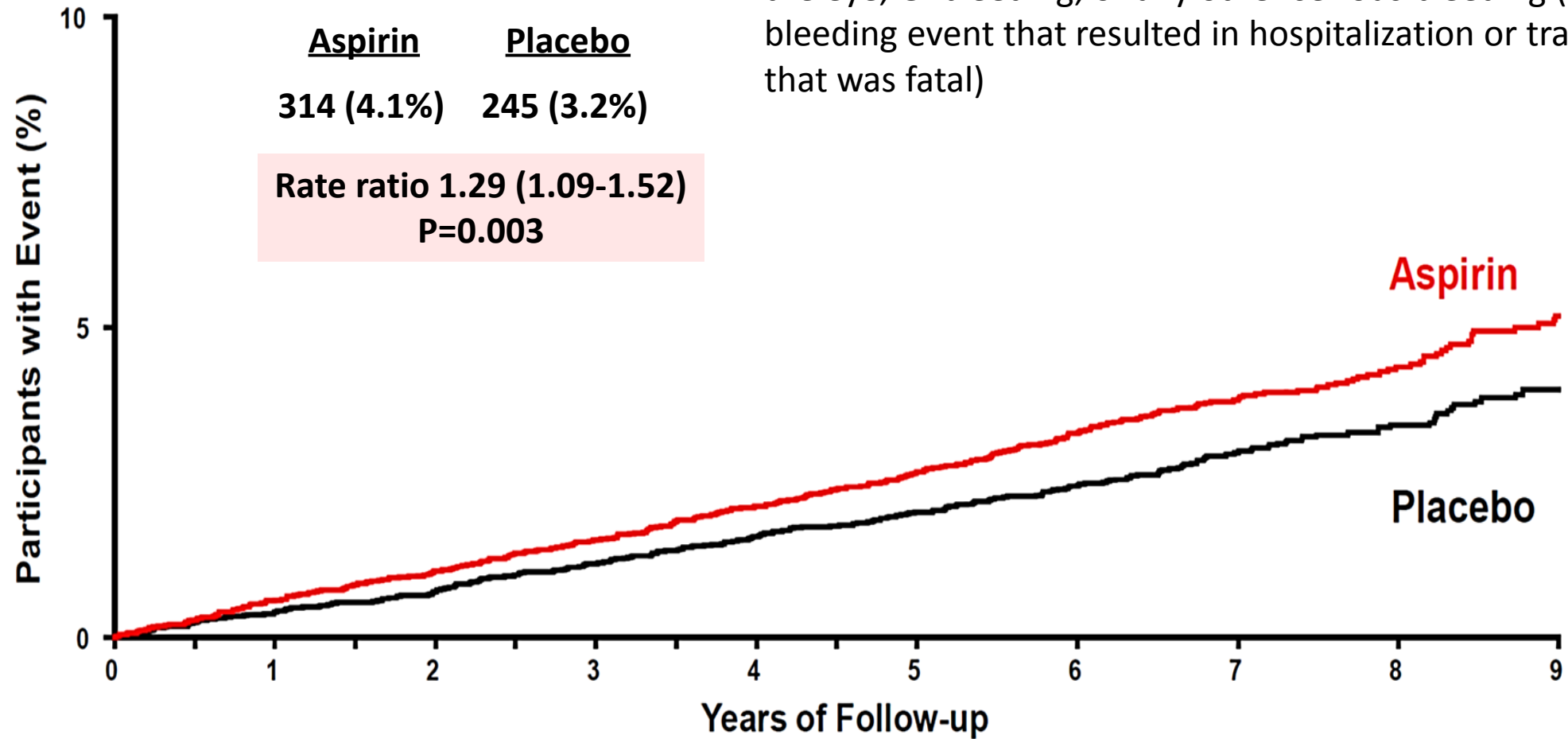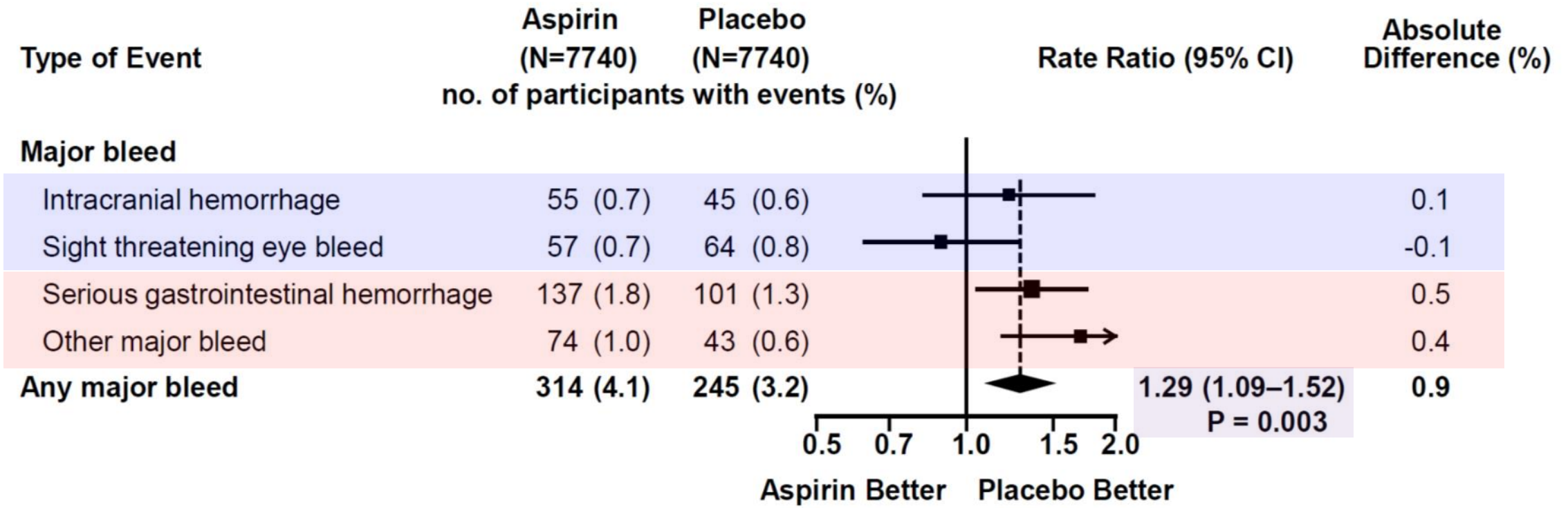
	Aspirin	Placebo
	314 (4.1%)	245 (3.2%)

Rate ratio 1.29 (1.09-1.52)
P=0.003

N Engl J Med. 2018;379:1529-1539.

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

0.5 0.7 1.0 1.5 2.0
Aspirin Better   Placebo Better

N Engl J Med. 2018;379:1529-1539.

Components of the efficacy outcome + revascularization

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)		
	no. of participants with events (%)				
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	

0.6   0.8   1.0   1.2

Aspirin Better   Placebo Better

N Engl J Med. 2018;379:1529-1539.

Effects of ASA in different types of participants
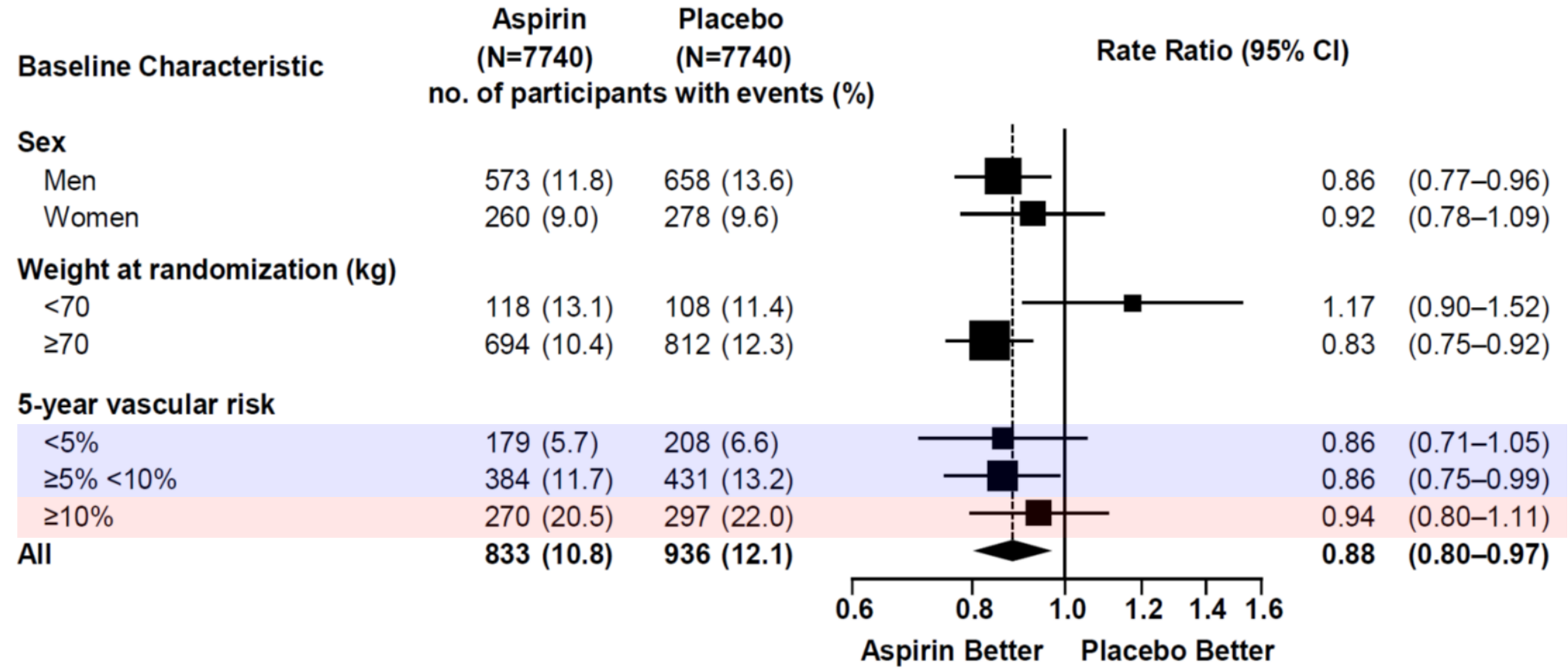
Baseline Characteristic	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	
	no. of participants with events (%)			
Sex				
Men	573 (11.8)	658 (13.6)	0.86	(0.77–0.96)
Women	260 (9.0)	278 (9.6)	0.92	(0.78–1.09)
Weight at randomization (kg)				
<70	118 (13.1)	108 (11.4)	1.17	(0.90–1.52)
≥70	694 (10.4)	812 (12.3)	0.83	(0.75–0.92)
5-year vascular risk				
<5%	179 (5.7)	208 (6.6)	0.86	(0.71–1.05)
≥5% <10%	384 (11.7)	431 (13.2)	0.86	(0.75–0.99)
≥10%	270 (20.5)	297 (22.0)	0.94	(0.80–1.11)
All	**833 (10.8)**	**936 (12.1)**	**0.88**	**(0.80–0.97)**

Aspirin Better   Placebo Better

N Engl J Med. 2018;379:1529-1539.
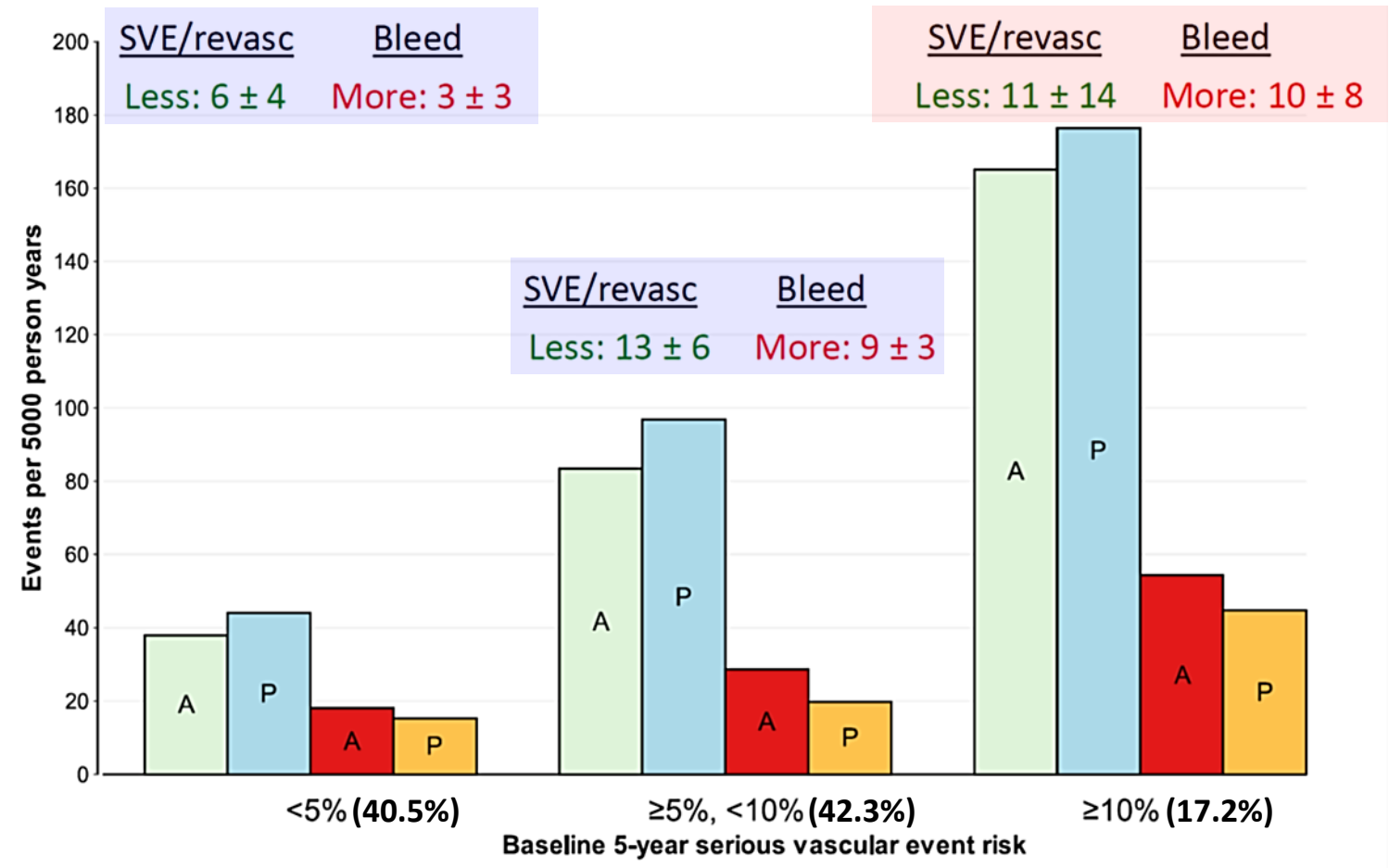
ARRIVE in non-DM patients with moderate CV risk

- 10-year risk of coronary heart disease of 10-20% (10-year CVD risk of approximately 20-30%)*.

- Primary efficacy outcome = MI, stroke, CV death, UA, or TIA.

- Safety outcome = GUSTO criteria.

- Combining data from the PROCAM, Framingham, and SCORE datasets.

- 12,546 population aged ≥55 years (men) or ≥60 years (women).
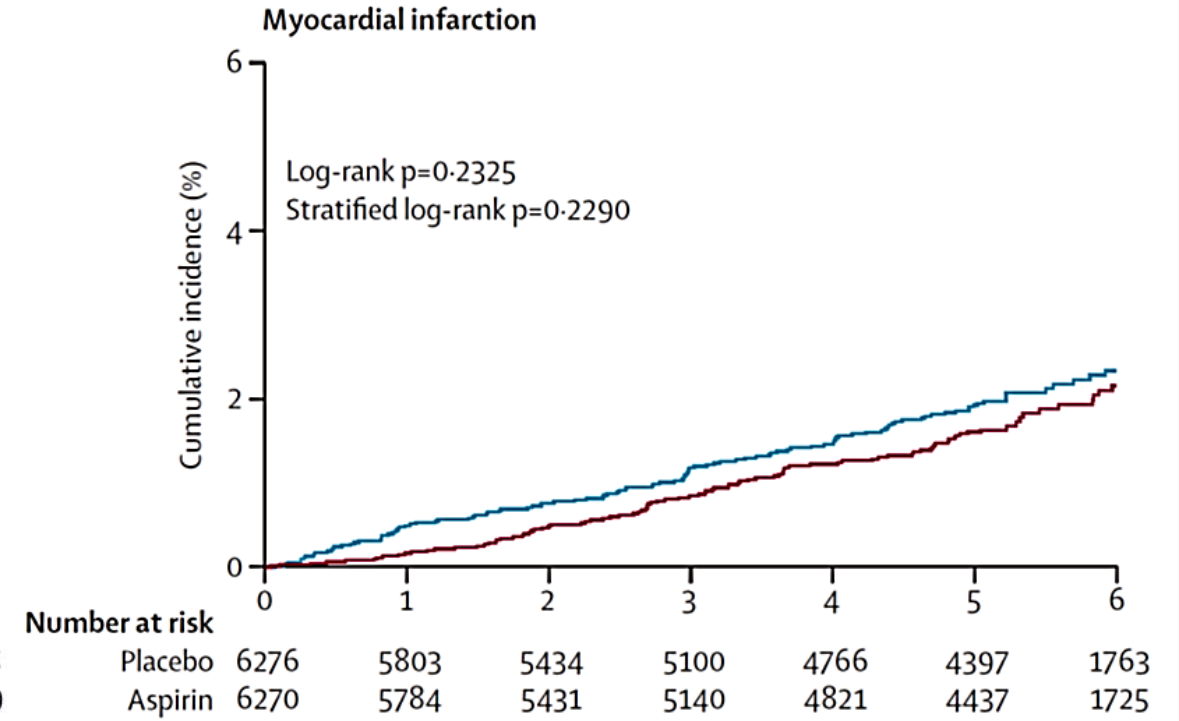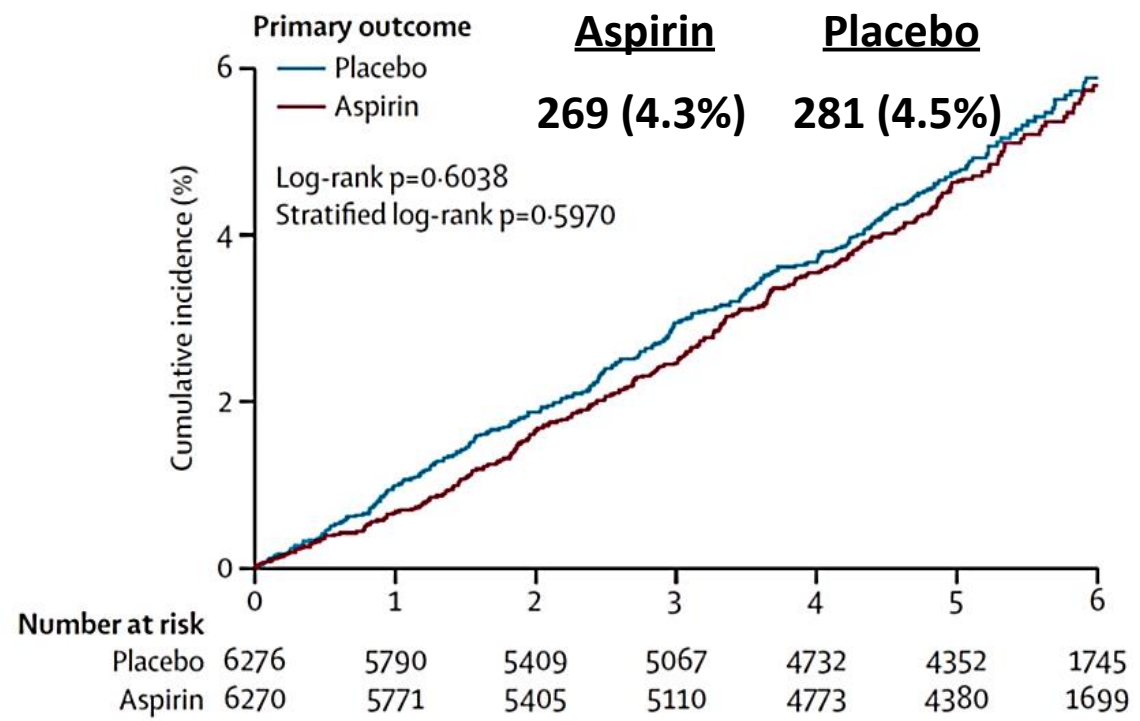
- Follow-up: Mean 60 months.

*Combining data from the PROCAM, Framingham, and SCORE datasets.

Trial outcomes (Intention-to-treat)

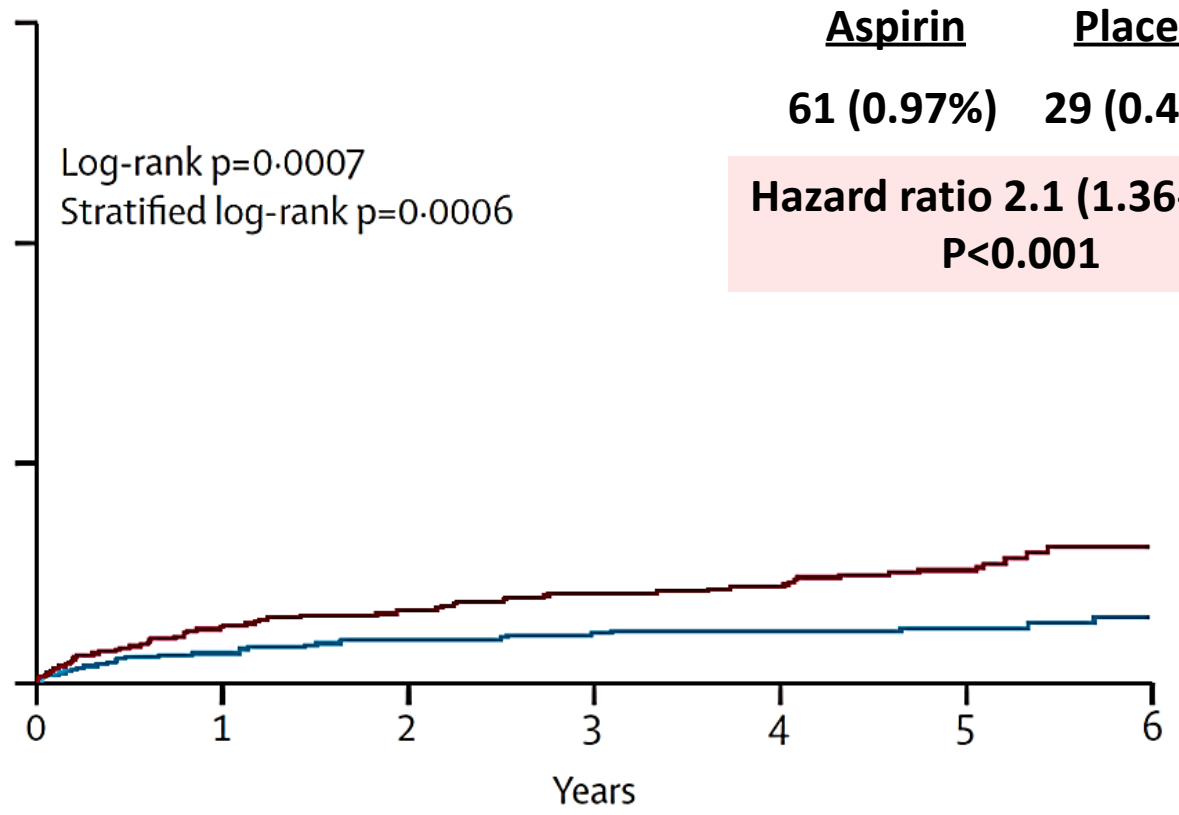**Lower event rate and compliance than expected.**

Primary assumption of event rates: 11.4% vs. 13.4%
Amendment: Event rate = 2.48% → 1.5%/year

	Aspirin	Placebo
	269 (4.3%)	281 (4.5%)

Primary outcome
- Placebo
- Aspirin

Log-rank p=0·6038
Stratified log-rank p=0·5970

Cumulative incidence (%)

Number at risk
Placebo 6276 5790 5409 5067 4732 4352 1745
Aspirin 6270 5771 5405 5110 4773 4380 1699

Myocardial infarction

Log-rank p=0·2325
Stratified log-rank p=0·2290

Cumulative incidence (%)

Number at risk
Placebo 6276 5803 5434 5100 4766 4397 1763
Aspirin 6270 5784 5431 5140 4821 4437 1725

Lancet 2018; 392: 1036-46.

Safety outcome

Gastrointestinal bleeding

	Aspirin	Placebo
	61 (0.97%)	29 (0.46%)

Hazard ratio 2.1 (1.36-3.28)
P<0.001

Log-rank p=0·0007
Stratified log-rank p=0·0006

0	1	2	3	4	5	6
6276	5807	5434	5107	4767	4401	1770
6270	5765	5420	5126	4807	4424	1725

Years

Lancet 2018; 392: 1036-46.

Trial outcomes (Per-protocol)

Primary Outcome

GI bleeding

	Aspirin	Placebo
	129 (3.4%)	164 (4.2%)

HR 0.81 (0.64-1.02)
P=0.0756

Logrank p=0·0756
stratified Logrank p=0·0818

Logrank p=0·0278
stratified Logrank p=0·0270

Cumulative Incidence (%)

Years
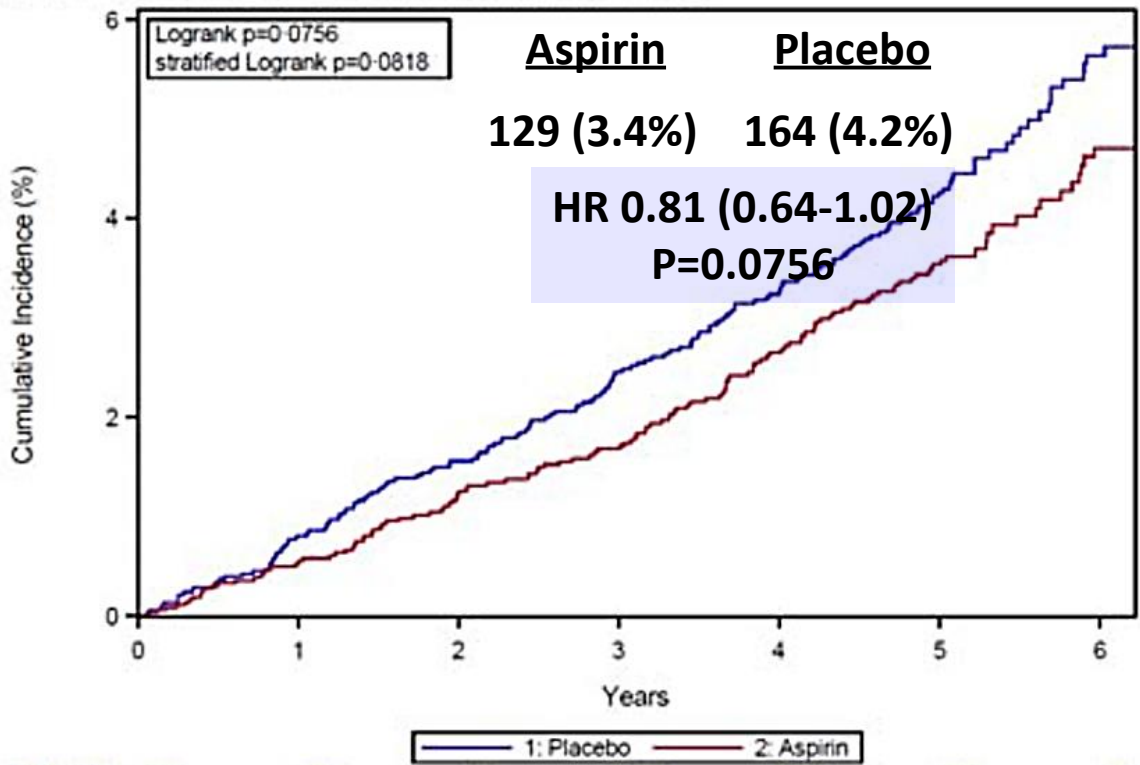
1: Placebo   2: Aspirin

1: Placebo	3912	3645	3412	3210	3010	2801	113(
2: Aspirin	3790	3564	3314	3145	2928	2711	107(
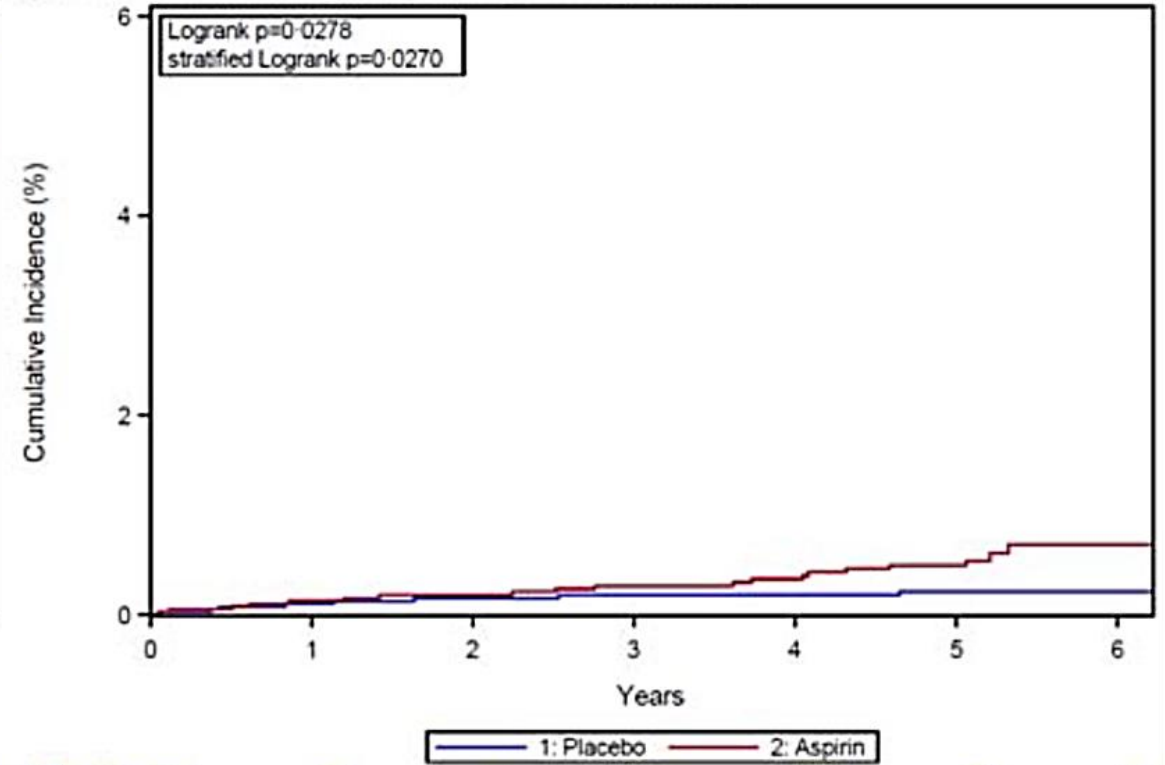
|						
1: Placebo	3912	3652	3418	3221	3020	2819	115(
2: Aspirin	3790	3564	3318	3145	2935	2723	106(

Lancet 2018; 392: 1036-46.

Efficacy endpoints in the intention-to-treat and per-protocol populations

	Number of events in the intention-to-treat population			Number of events in the per-protocol population		
	Aspirin (n=6270)	Placebo (n=6276)	Hazard ratio (95% CI); p value	Aspirin (n=3790)	Placebo (n=3912)	Hazard ratio (95% CI); p value
Myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischaemic attack	269 (4·29%)	281 (4·48%)	0·96 (0·81–1·13); p=0·6038	129 (3·40%)	164 (4·19%)	0·81 (0·64–1·02); p=0·0756
Myocardial infarction, stroke, or cardiovascular death	208 (3·32%)	218 (3·47%)	0·95 (0·79–1·15); p=0·6190	103 (2·72%)	135 (3·45%)	0·79 (0·61–1·02); p=0·0661
Myocardial infarction*	95 (1·52%)	112 (1·78%)	0·85 (0·64–1·11); p=0·2325	37 (0·98%)	72 (1·84%)	0·53 (0·36–0·79); p=0·0014
Non-fatal myocardial infarction	88 (1·40%)	98 (1·56%)	0·90 (0·67–1·20); p=0·4562	32 (0·84%)	60 (1·53%)	0·55 (0·36–0·84); p=0·0056
Stroke*	75 (1·20%)	67 (1·07%)	1·12 (0·80–1·55); p=0·5072	40 (1·06%)	37 (0·95%)	1·12 (0·71–1·75); p=0·6291
Cardiovascular death	38 (0·61%)	39 (0·62%)	0·97 (0·62–1·52); p=0·9010	26 (0·69%)	26 (0·66%)	1·03 (0·60–1·77); p=0·9161
Unstable angina	20 (0·32%)	20 (0·32%)	1·00 (0·54–1·86); p=0·9979	8 (0·21%)	11 (0·28%)	0·75 (0·30–1·87); p=0·5380
Transient ischaemic attack	42 (0·67%)	45 (0·72%)	0·93 (0·61–1·42); p=0·7455	19 (0·50%)	19 (0·49%)	1·03 (0·55–1·95); p=0·9181
Any death	160 (2·55%)	161 (2·57%)	0·99 (0·80–1·24); p=0·9459	108 (2·85%)	101 (2·58%)	1·10 (0·84–1·45); p=0·4796

*Fatal or non-fatal.

Lancet 2018; 392: 1036-46.

Primary outcome by prespecified subgroups
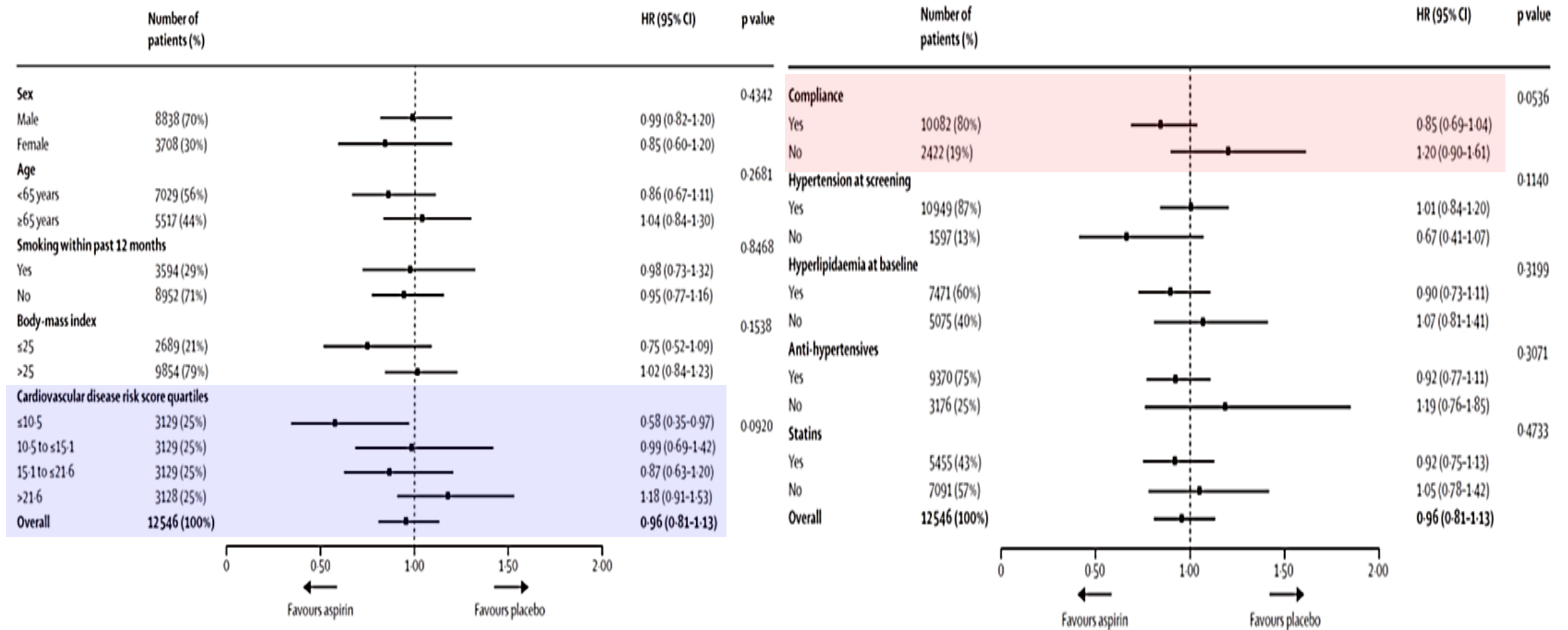
ASA in the elderly: ASPREE

ASPREE in the elderly

- ≥70 years of whites (or ≥65 years of blacks and Hispanics)
- All-cause mortality, disability-free survival, and CV events and bleeding
- 19,114 elderly persons.
- Follow up: a median of 4.7 years.
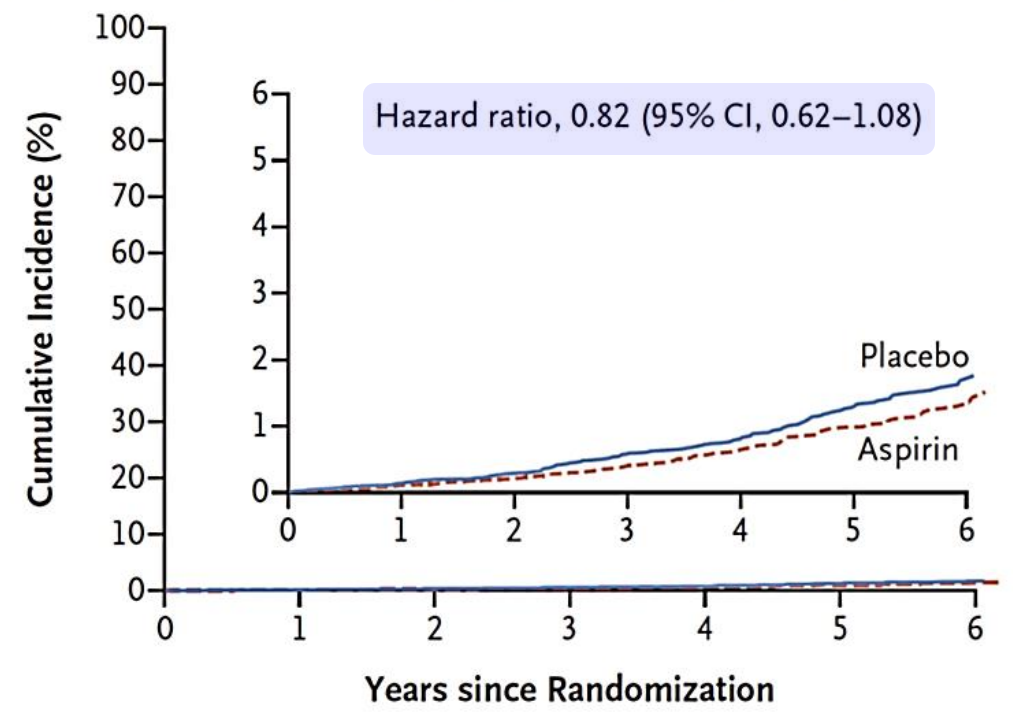- Disability-free survival: survival free from dementia or persistent physical disability.

N Engl J Med. 2018;379:1519-1528; N Engl J Med. 2018;379:1509-1518;
N Engl J Med. 2018;379:1499-1508.

Mortality (1)

A **Death Related to Cancer**
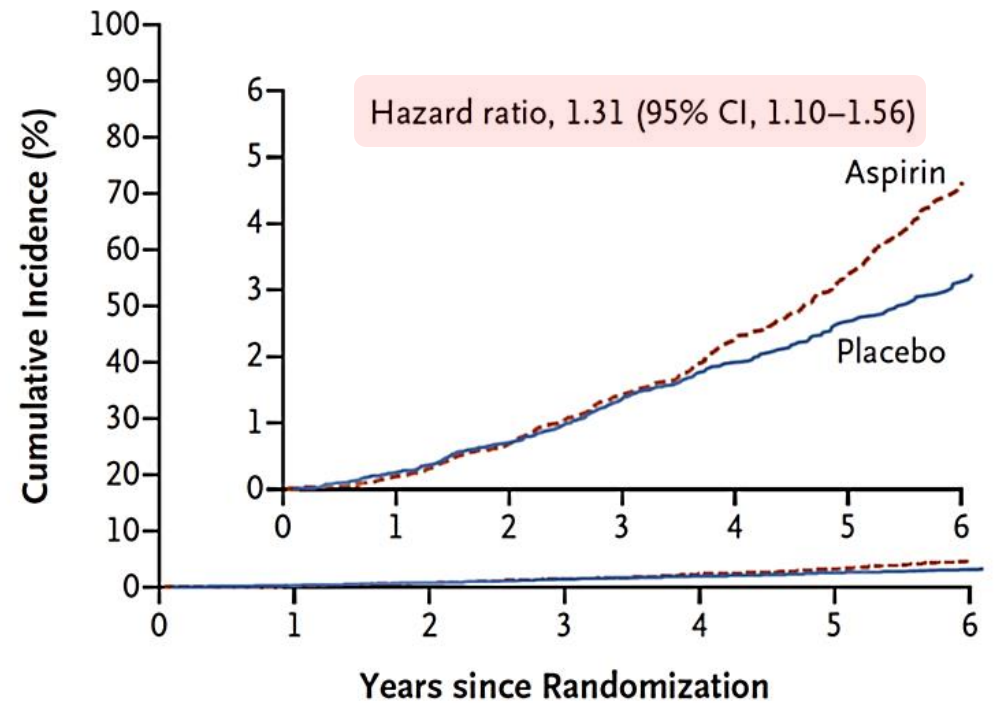
Hazard ratio, 1.31 (95% CI, 1.10–1.56)

B **Death Related to Cardiovascular Disease, Including Ischemic Stroke**

Hazard ratio, 0.82 (95% CI, 0.62–1.08)

No. at Risk

Aspirin	9525	9481	9408	8286	6291	4016	1495
Placebo	9589	9545	9466	8369	6367	4077	1476

No. at Risk

Aspirin	9525	9481	9408	8286	6291	4016	1495
Placebo	9589	9545	9466	8369	6367	4077	1476

Mortality (2)

C Death Related to Major Hemorrhage, Including Hemorrhagic Stroke
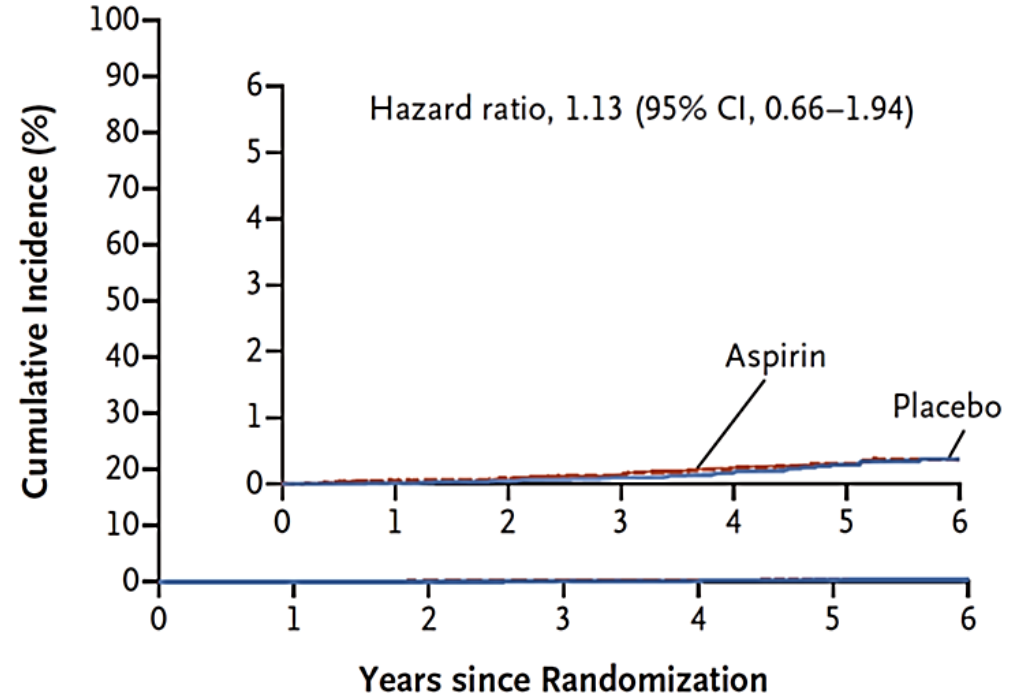
Hazard ratio, 1.13 (95% CI, 0.66–1.94)

Aspirin

Placebo

Cumulative Incidence (%)

Years since Randomization

No. at Risk

Aspirin	9525	9481	9408	8286	6291	4016	1495
Placebo	9589	9545	9466	8369	6367	4077	1476

D Death Related to Other Causes
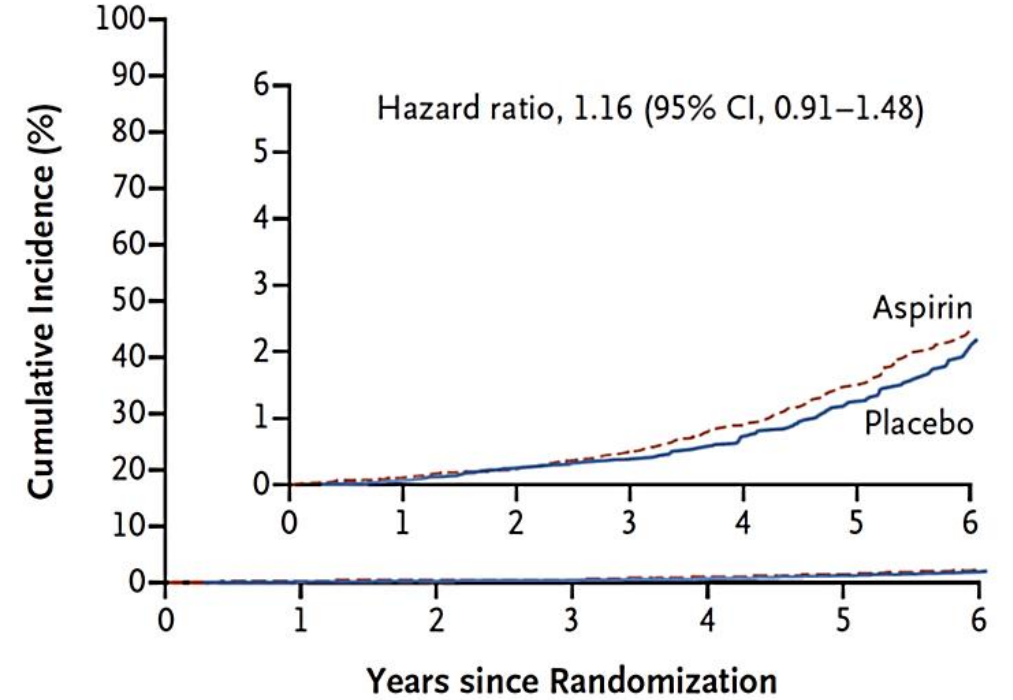
Hazard ratio, 1.16 (95% CI, 0.91–1.48)

Aspirin

Placebo

Cumulative Incidence (%)

Years since Randomization

No. at Risk

Aspirin	9525	9481	9408	8286	6291	4016	1495
Placebo	9589	9545	9466	8369	6367	4077	1476

CV death and bleeding

Cardiovascular Disease   **Major bleeding**
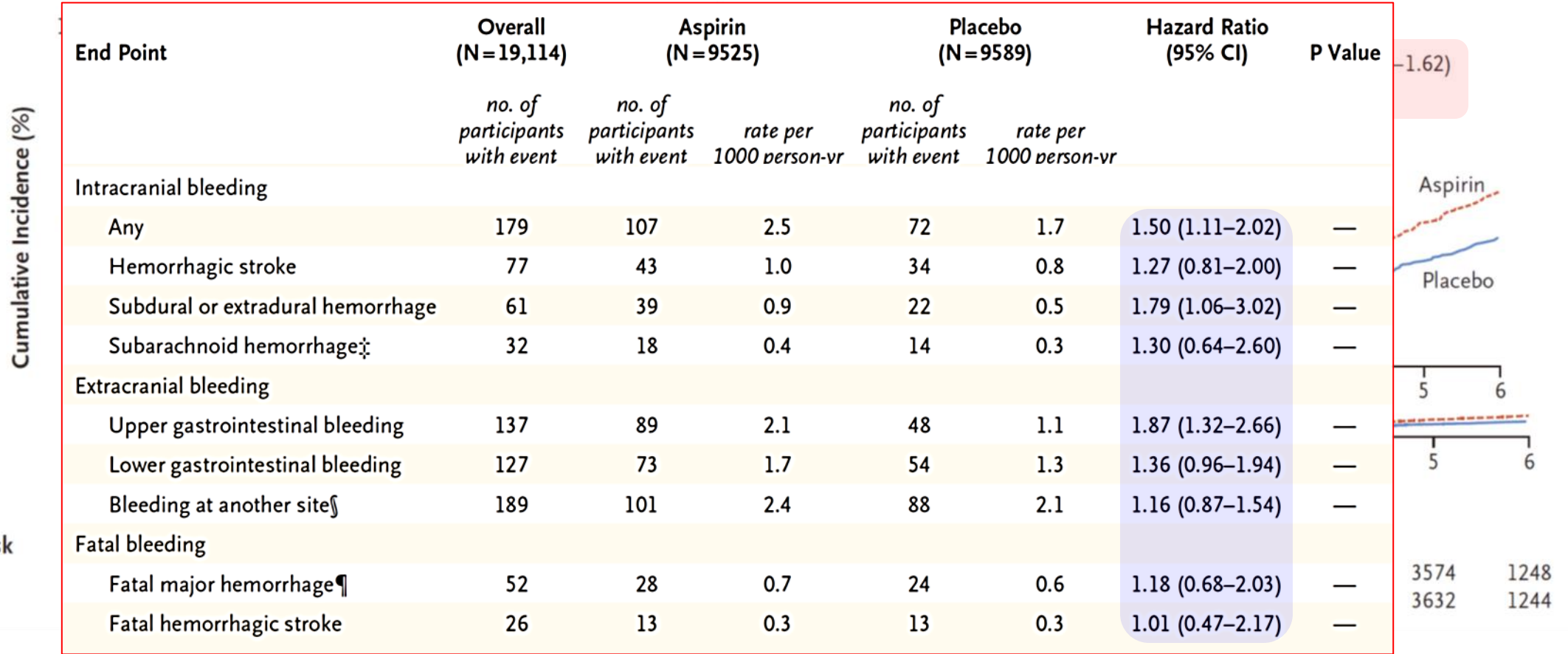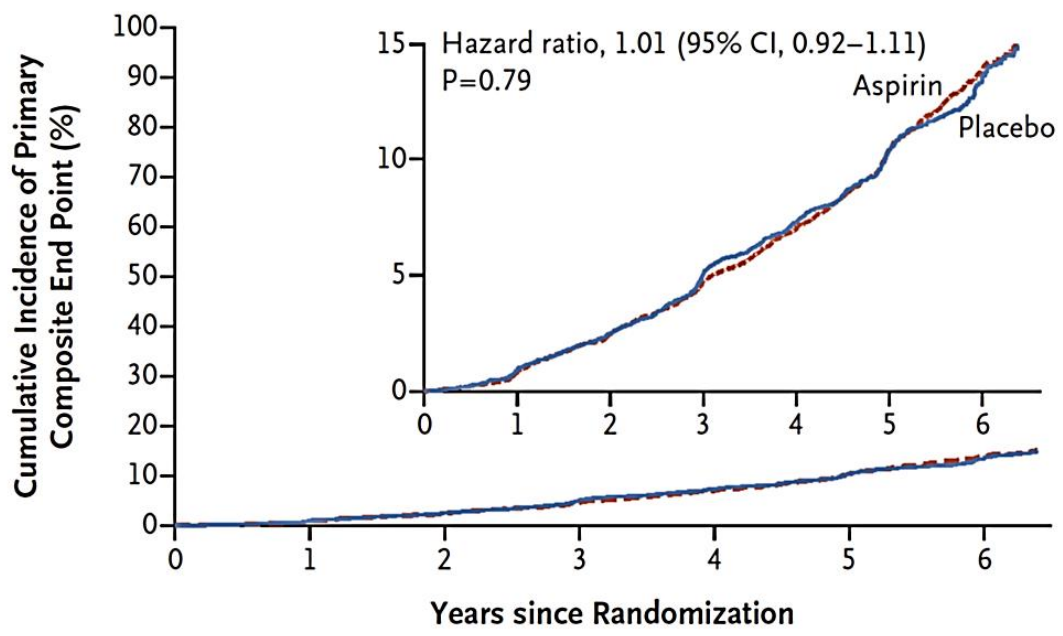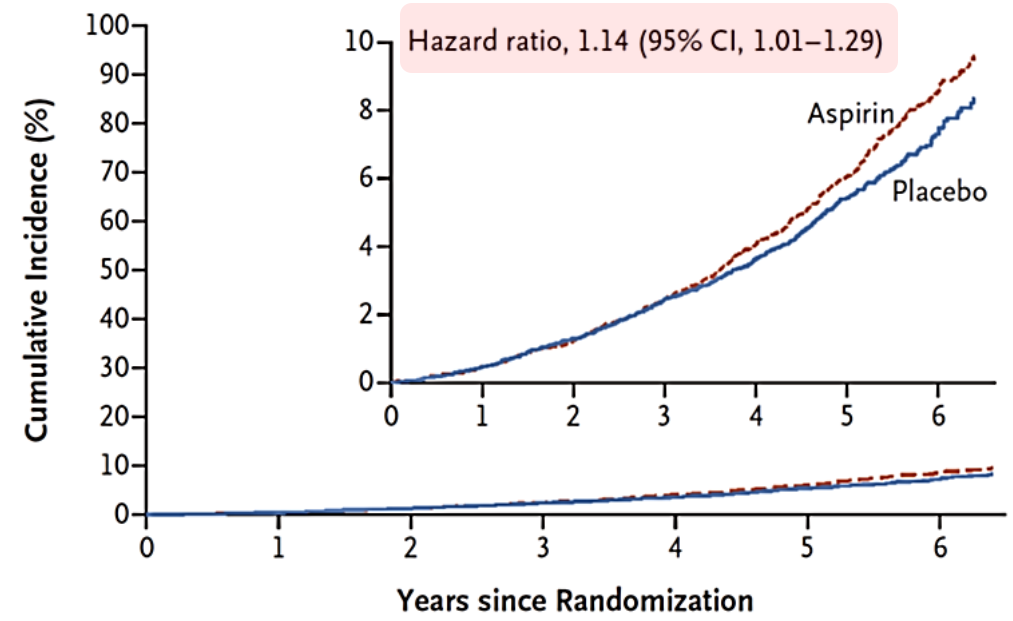
End Point	Overall (N=19,114)	Aspirin (N=9525)		Placebo (N=9589)		Hazard Ratio (95% CI)	P Value
	no. of participants with event	no. of participants with event	rate per 1000 person-yr	no. of participants with event	rate per 1000 person-yr		
Intracranial bleeding							
Any	179	107	2.5	72	1.7	1.50 (1.11–2.02)	—
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)	—

N Engl J Med. 2018;379:1509-1518.

Disability-free survival*

*death from any cause, dementia, or persistent physical disability

N Engl J Med. 2018;379:1499-1508.

Summary

- **ASCEND: ASA prevented CV event in patients with DM. But, the absolute benefits from preventing serious vascular events were largely counterbalanced by the bleeding hazard.**
- **ARRIVE: Low event rate made the study more representative of a low-risk population. However, in a per-protocol analysis, the results were more optimistic.**
- **ASPREE: no benefit with respect to the composite primary end point of death, dementia, or persistent physical disability; no evidence of a CV benefit of aspirin yet the higher risk of major bleeding.**
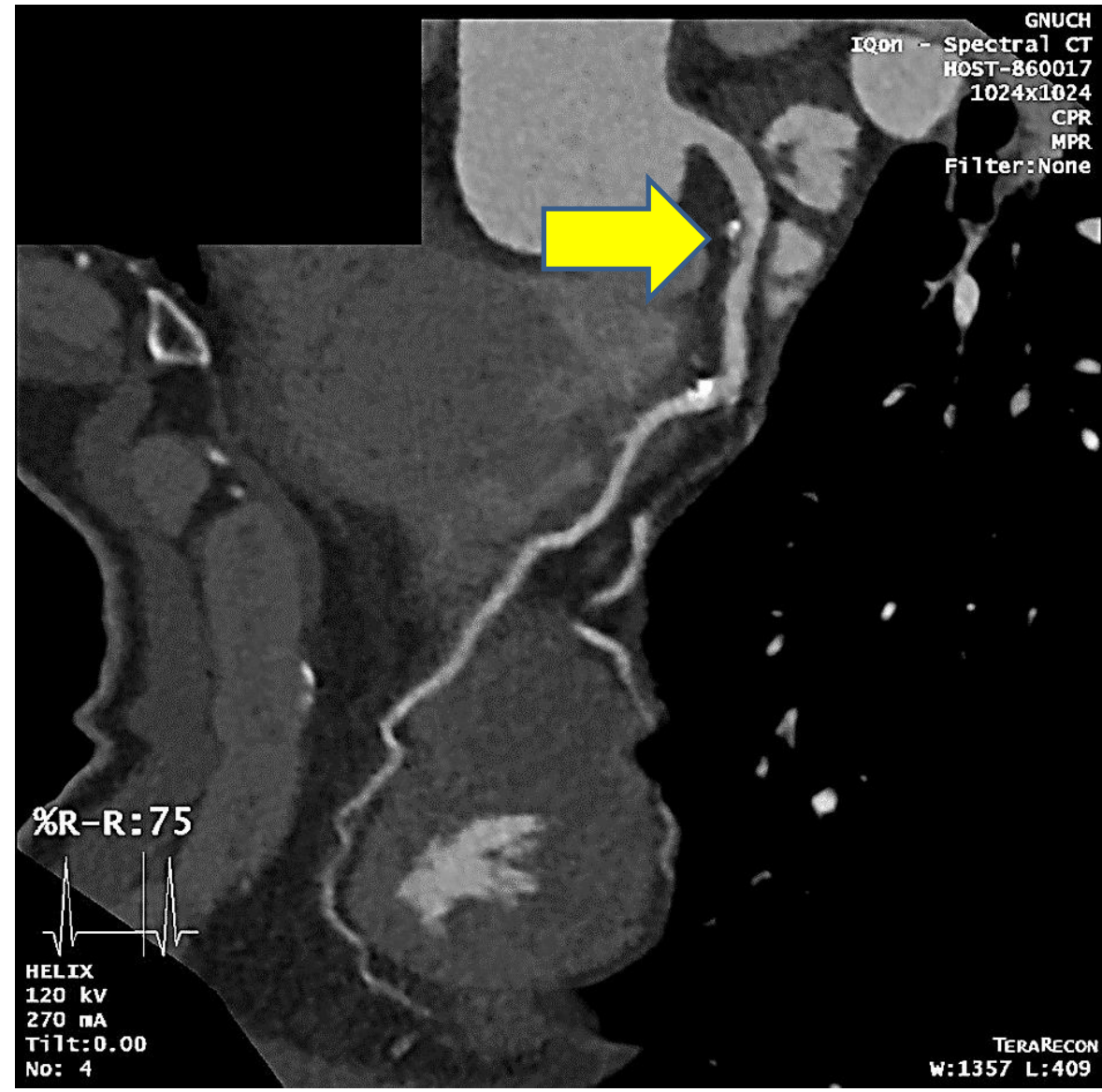
Aspirin?

"To prevent a heart attack, take one aspirin every day. Take it out for a jog, then take it to the gym, then take it for a bike ride…"

Conclusion

- **It's time to say good bye to an old friend!**

Thank You