Aspirin in Primary Prevention of Atherosclerotic Cardiovascular Diseases (ASCVD)

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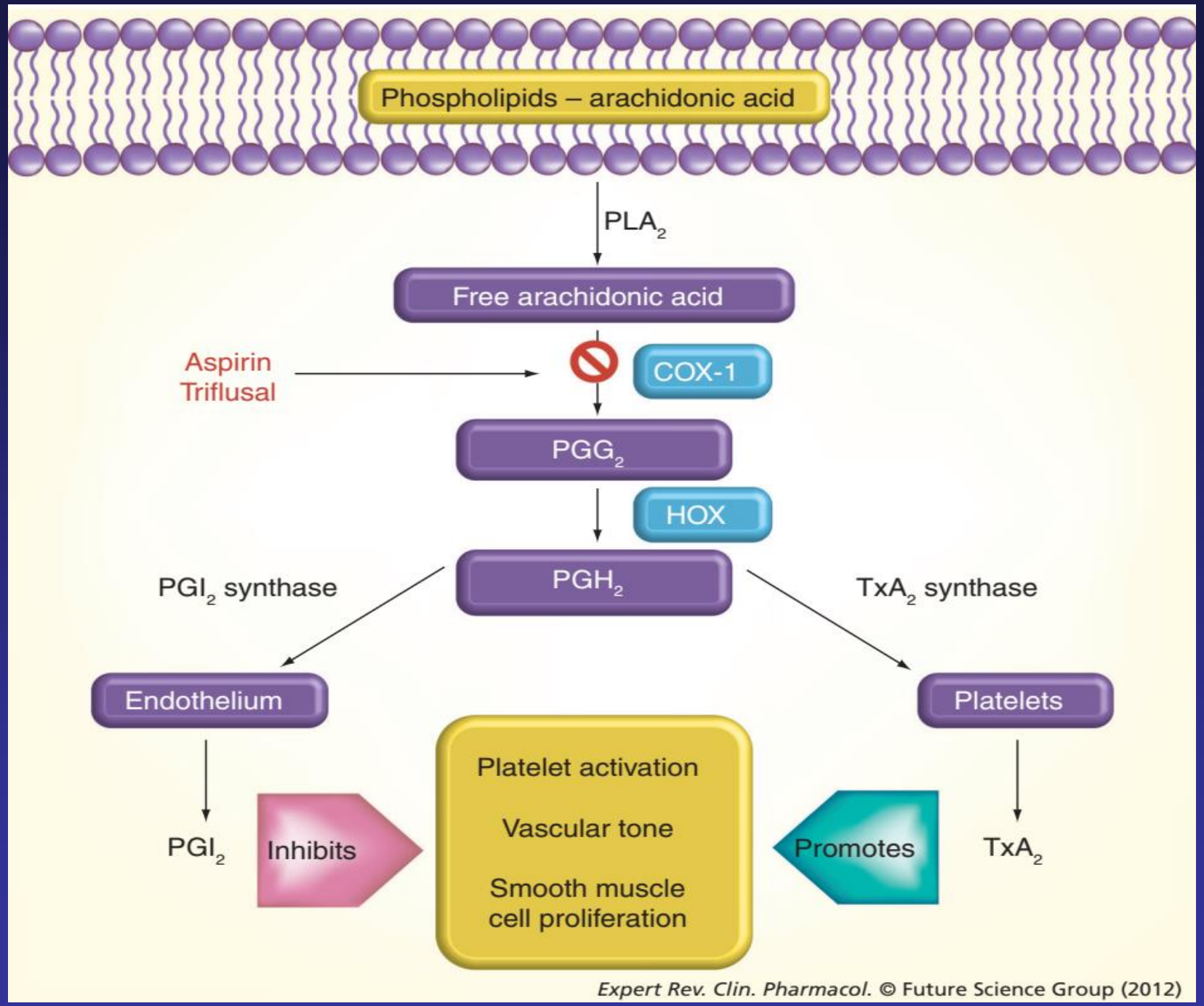
Objectives

- Discuss benefits vs. harm of aspirin in primary prevention of ASCVD
- Describe recent clinical evidences of aspirin in primary prevention of ASCVD
- Discuss current international guidelines on aspirin in primary prevention of ASCVD

Aspirin (ASA)


Phospholipids – arachidonic acid
PLA2
Free arachidonic acid
Aspirin
Triflusal
COX-1
PGG2
HOX
PGH2
PGI2 synthase
TxA2 synthase
Endothelium
Platelets
PGI2
Inhibits
Platelet activation
Vascular tone
Smooth muscle cell proliferation
Promotes
TxA2
Expert Rev. Clin. Pharmacol. © Future Science Group (2012)

ASA Benefits vs. Harm in ASCVD Prevention

- ASA reduces CV morbidity and mortality in patients with ASCVD (secondary prevention) and possibly in prevention of colorectal cancer
- In primary prevention, benefits of ASA much lower than secondary prevention
- ASA use associated with major bleeding e.g. GI bleed
- Previously AHA recommend ASA for primary prevention of ASCVD in patients with 10-year risk >10%

Recent RCTs of ASA for Primary Prevention of ASCVD

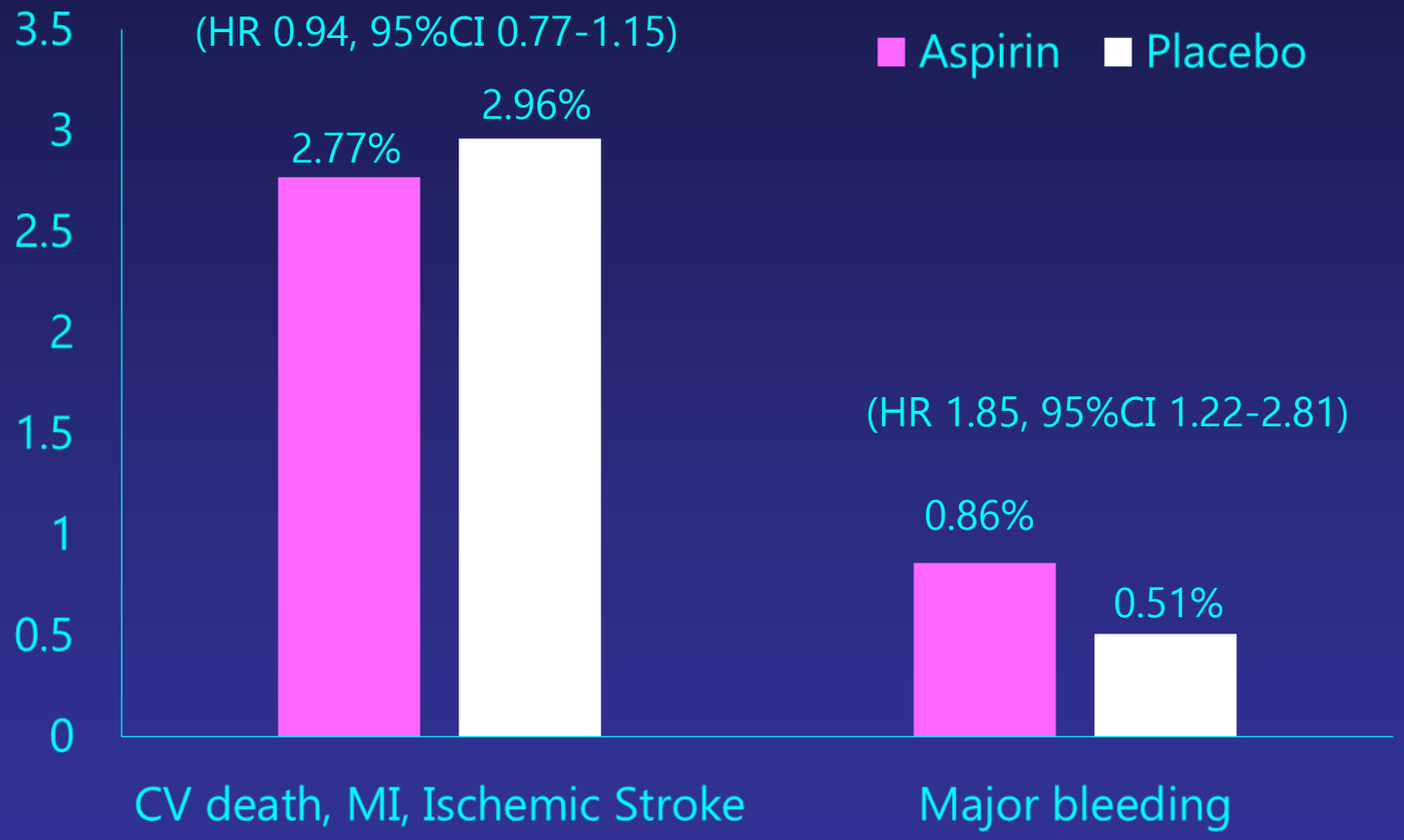
- JPPP
- Population: Japanese elderly (mean age 70 y) with at least 1 risk factor of ASCVD (HTN, dyslipidemia, DM, family history of premature CVD)
- N = 14,464
- Intervention and comparator: ASA 100 mg vs. placebo
- Follow-up time: 5 year (early termination)

JAMA 2014;312:2510-20.

JPPP Trial: Baseline Characteristics

Characteristics	Aspirin (N=7220) n (%)	Placebo (N=7244) n (%)
Male	3055 (42.3)	3068 (42.4)
Age >70 y	3968 (55.2)	3985 (55.0)
BMI≥25	2644 (36.6)	2604 (35.9)
Current smoker	959 (13.3)	934 (12.9)
FH of premature CV disease	1981 (27.4)	1982 (27.4)
DM	2445 (33.9)	2458 (33.9)
HTN	6133 (84.9)	6145 (84.8)
Dyslipidemia	5198 (72.0)	5200 (71.8)
Average BP (mm Hg)	137.1/77.7	137.2/77.6
Average LDL-C (mg/dL)	119.2±30.5	119.8±30.3

JPPP: Results



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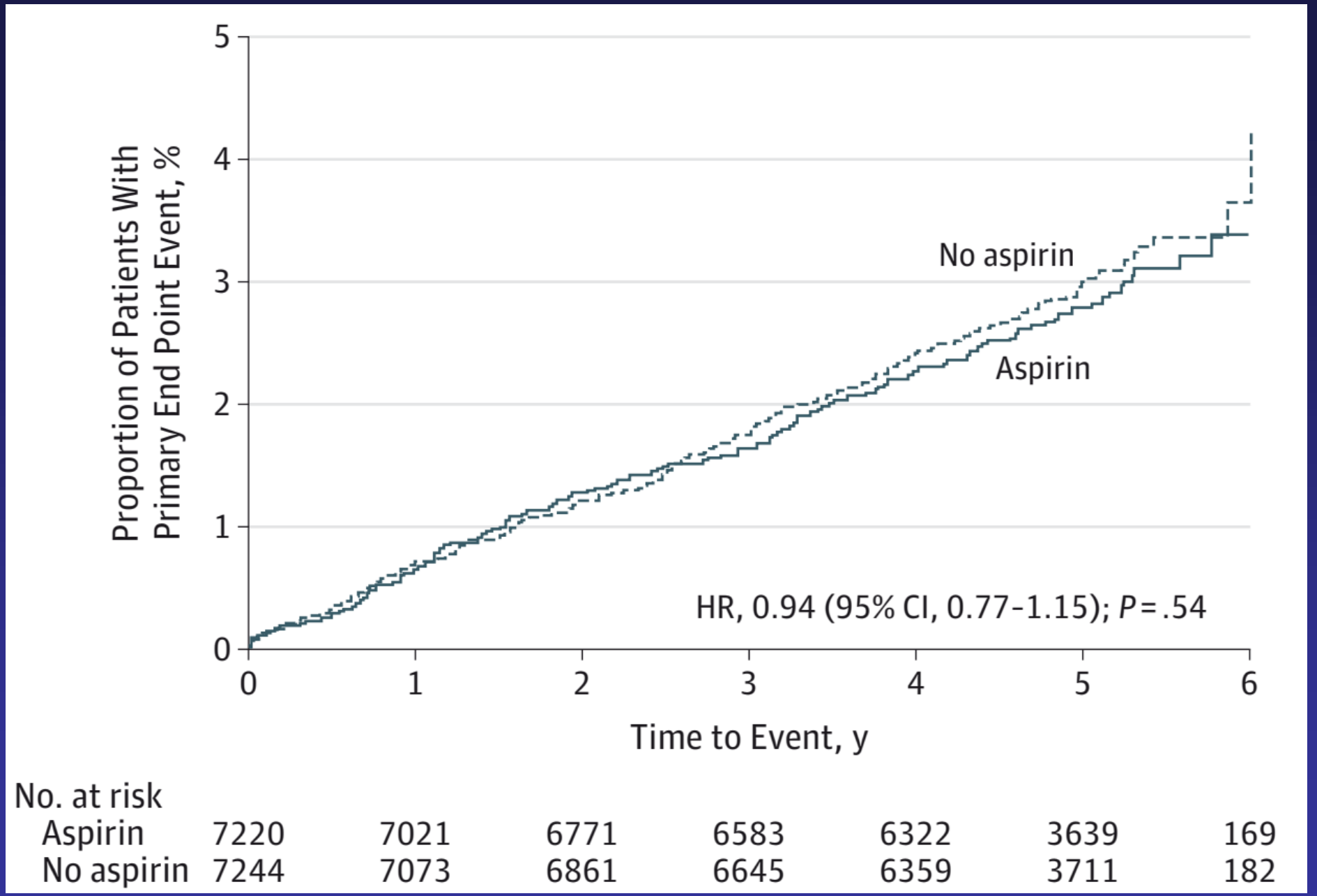


No. at risk							
Aspirin	7220	7021	6771	6583	6322	3639	169
No aspirin	7244	7073	6861	6645	6359	3711	182

JAMA 2014;312:2510-20.

Recent RCTs of ASA for Primary Prevention of ASCVD

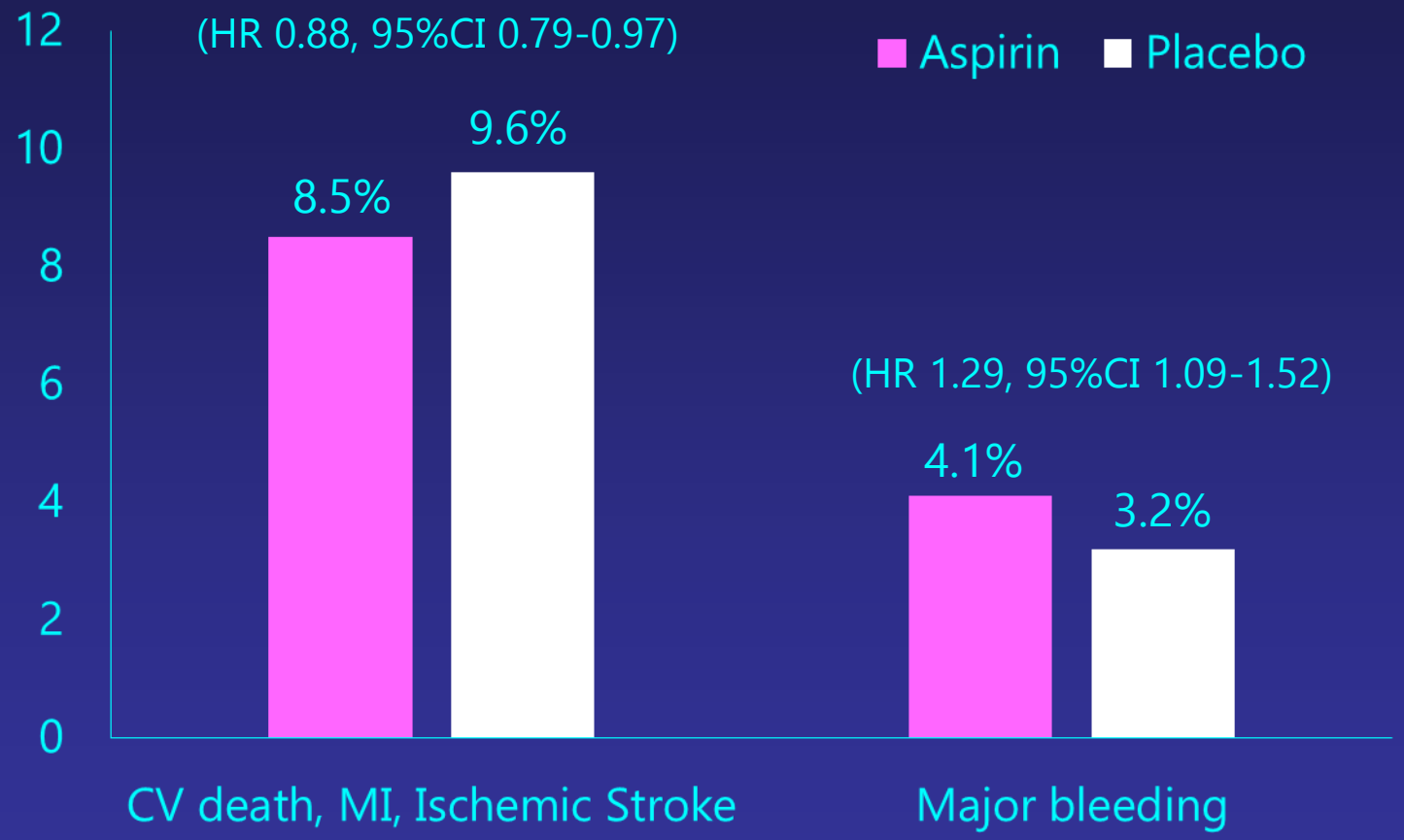
- ASCEND
- Population: Diabetics with no previous diagnosis of ASCVD, N = 15, 480
- Intervention and comparator: ASA 100 mg vs. placebo
- F/U time 7.4 year

N Engl J Med 2018;379:1529-39

ASCEND Trial: Baseline Characteristics

Characteristics	Aspirin (N=7740) n (%)	Placebo (N=7740) n (%)
Male	4843 (62.6)	4841 (62.5)
Age >70 y	1822 (23.5)	1821 (23.5)
White race	7467 (96.5)	7468 (96.5)
Current smoker	639 (8.3)	640 (8.3)
DM	7282 (94.1)	7287 (94.1)
Duration of DM (median)	7 (3-13)	7 (3-13)
HTN	4766 (61.6)	4767 (61.6)
Vascular risk		
Low vascular risk	3128 (40.4)	3136 (40.5)
Moderate vascular risk	3294 (42.6)	3254 (42.0)
High vascular risk	1318 (17.0)	1350 (17.4)

ASCEND: Results



GI cancer =2.0% in both groups

Modified from N Engl J Med 2018;379:1529-39

Recent RCTs of ASA for Primary Prevention of ASCVD

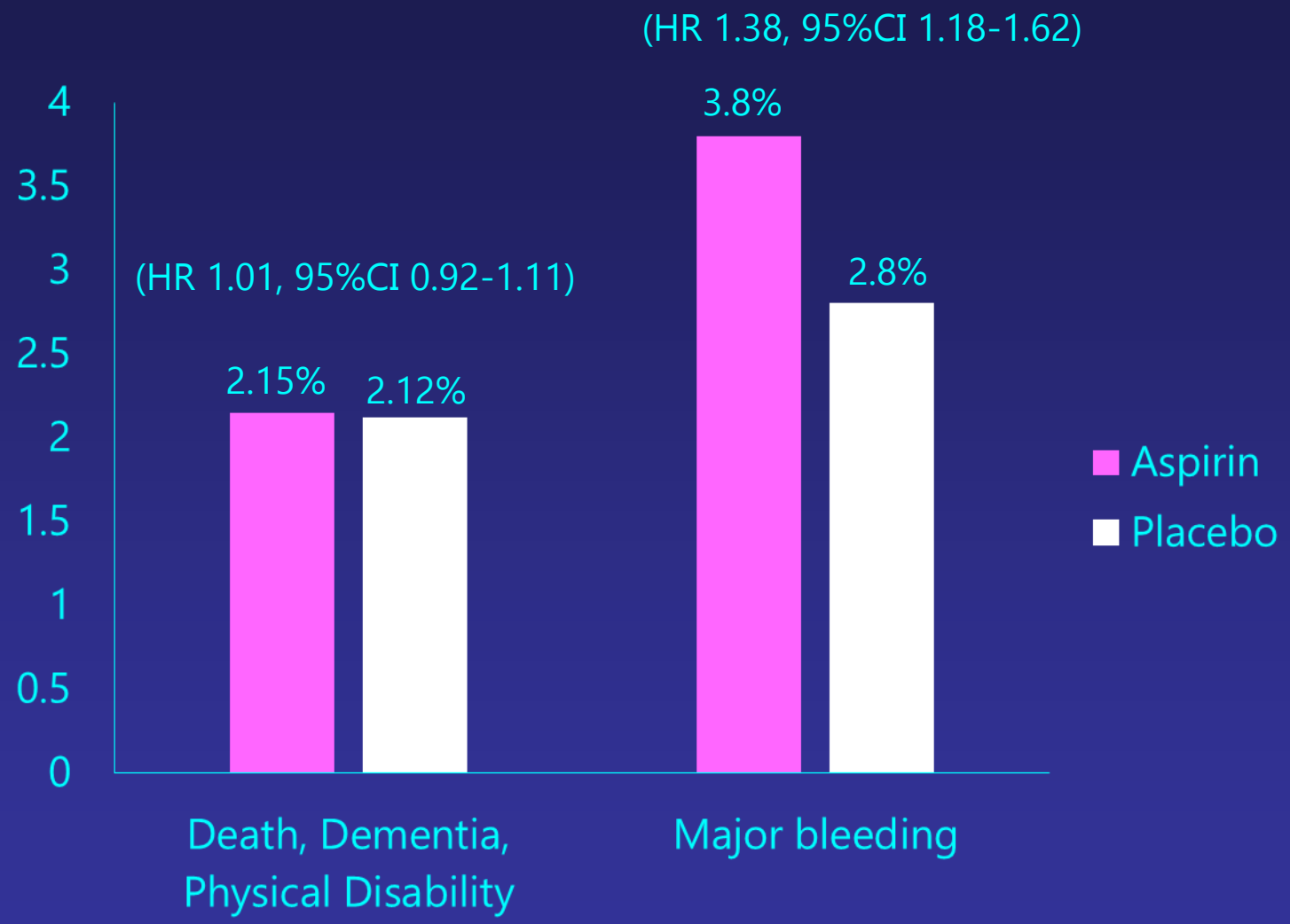
- ASPREE
- Population: Elderly (>70 y) living in community, in good health , N =19,114
- Intervention and comparator: ASA 100 mg vs. placebo
- F/U time: 4.7 year (early termination)

N Engl J Med 2018;379:1519-28

ASPREE Trial: Baseline Characteristics

Characteristics	Aspirin (N=9525) n (%)	Placebo (N=9589) n (%)
Male	4152 (44)	4179 (44)
Age >74 y	4806 (50)	4766 (50)
Obese	2820 (30)	2857 (30)
Current smoker	352 (4)	383 (4)
DM	1027 (11)	1030 (11)
HTN	7065 (74)	7148 (75)
Dyslipidemia	6159 (65)	6308 (66)
CKD	2456 (26)	2464 (26)
Previous ASA use	1053 (11)	1041 (11)
Statins use at entry	2340 (25)	2374 (25)

ASPREE: Results



Modified from N Engl J Med 2018;379:1519-28

Recent RCTs of ASA for Primary Prevention of ASCVD

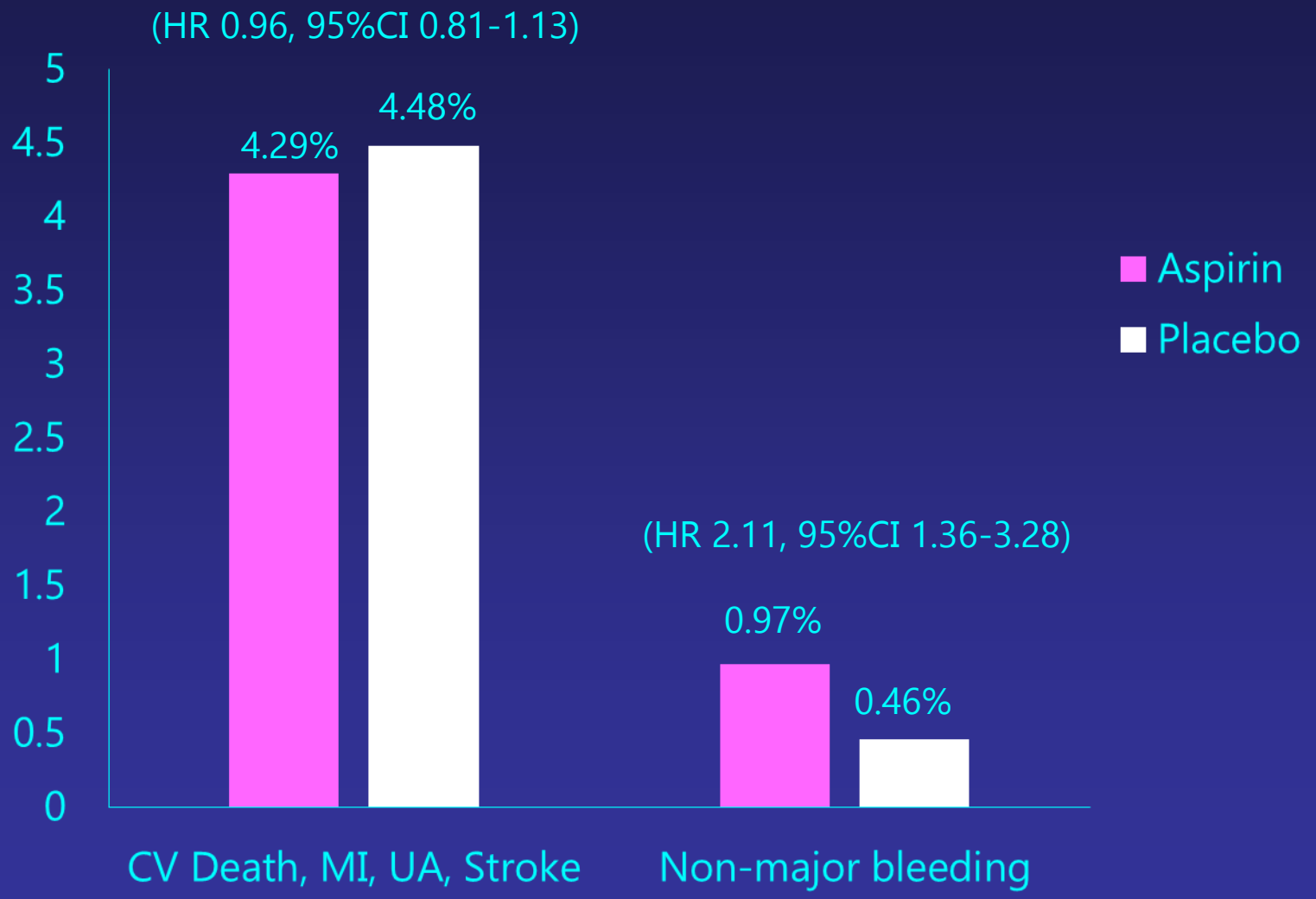
- ARRIVE
- Population: male (>55 y), female (>60 y) with 2-4 ASCVD risk factors (10-20% 10-y ASCVD risk)
- Intervention and comparator: ASA 100 mg vs. placebo
- Follow-up time: 5 years

Lancet 2018;392:1036-46

ARRIVE Trial: Baseline Characteristics

Characteristics	Aspirin (N=6270) n (%)	Placebo (N=6276) n (%)
Male	4419 (70.5)	4419 (70.4)
Mean Age (year)	63.9±7.1	63.9±7.1
White race	6133 (97.8)	6146 (97.9)
Current smoker	1808 (28.8)	1786 (28.5)
High SBP	3916 (62.5)	3950 (62.9)
Taking antihypertensive meds	4038 (64.4)	4097 (65.3)
High LDL-C	2775 (44.3)	2869 (45.7)
Cardiovascular risk		
Framingham 10-year CHD risk (%)	13.9±6.4	14.1±6.4
ACC/AHA 10-year ASCVD risk (%)	17.3±9.8	17.4±9.7

ARRIVE: Results



Modified from Lancet 2018;392:1036-46

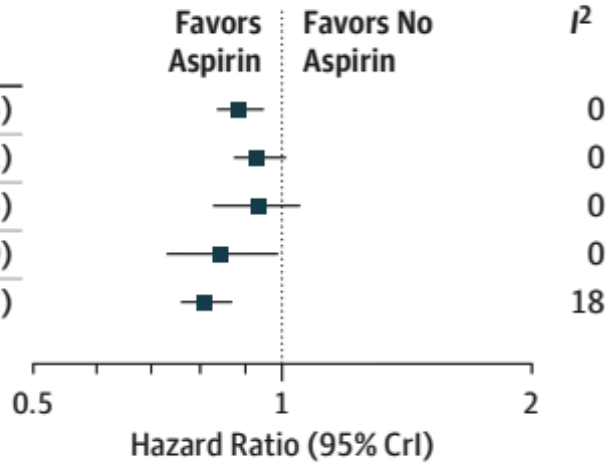
Meta-analysis of ASA for Primary Prevention of ASCVD

- Zheng et al.
- 13 RCTs, N 164,225, primary prevention with at least 1000 participants with no ASCVD, follow-up time at least 12 months
- Intervention and comparator: ASA 100 mg vs. placebo

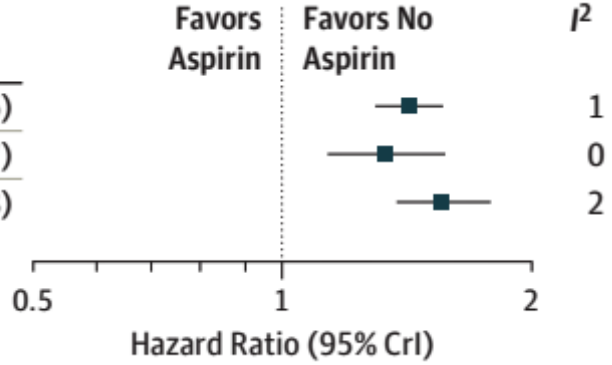
JAMA. 2019;321(3):277-287.

Meta-analysis of ASA for Primary Prevention of ASCVD

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



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Recommendation from Guidelines on ASA for Primary Prevention of ASCVD

- USPSTF 2016
  - Low-dose aspirin to prevent CVD and colorectal cancer in adults aged 50-59 years with ≥10% CVD risk, not high risk for bleeding, life expectancy ≥10 years, and willing to take low-dose aspirin daily for at least 10 years (grade B)
  - 60-69 y with 10-y risk ≥10% → weigh benefit and risk (grade C)
  - ไม่แนะนำถ้าอายุ <50 หรือ >70 ปี

Recommendation from Guidelines on ASA for Primary Prevention of ASCVD

- ESC 2016
  - ASA not recommended for primary prevention (class III recommendation)

Recommendation from Guidelines on ASA for Primary Prevention of ASCVD

- AHA/ACC 2019
  - ASA 75-100 mg for primary prevention in 40-70 y at high risk of ASCVD and low bleeding-risk (class IIb recommendation)
  - Consider risk-enhancing factors
  - ไม่แนะนำ ASA for primary prevention ในคนอายุ >70 ปี
  - ไม่แนะนำ ASA ในผู้ที่มีความเสี่ยงต่อการเกิดภาวะเลือดออกรุนแรง

Risk-Enhancing Factors in CVD Prevention

- FH of premature ASCVD (males, age <55 y; females, age <65 y)
- Primary hypercholesterolemia (LDL-C, 160–189 mg/dL; non–HDL-C 190–219 mg/dL)
- Metabolic syndrome (increased waist circumference; elevated triglycerides, elevated BP, elevated glucose, and low HDL-C
- CKD
- Chronic inflammatory conditions, such as psoriasis, RA, lupus, or HIV/AIDS

Risk-Enhancing Factors in CVD Prevention

- Premature menopause (before age 40 y), Preeclampsia
- High-risk race/ethnicity (e.g., South Asian ancestry)
- Lipids/biomarkers: associated with increased ASCVD risk
  - Persistently elevated hypertriglyceridemia (≥175 mg/dL)
  - Elevated C-reactive protein (≥2.0 mg/L)
  - Elevated Lp(a) (≥50 mg/dL)
  - Elevated apoB (≥130 mg/dL)
  - Ankle-brachial index (<0.9)

Bleeding Risk Assessment

- Validated algorithm for assessing bleeding risk in patients receiving aspirin monotherapy not currently available
- Increased bleeding risk
  - A history of previous GI bleeding or PUD or bleeding at other sites
  - Age >70 years
  - Thrombocytopenia,
  - Coagulopathy
  - CKD
  - Concurrent use of NSAIDs, steroids, oral anticoagulants

Summary

- ASA with some benefit in reducing CV events, associated with increased major bleeding
- Recent evidences do not support routine use of ASA for primary prevention of ASCVD, but may be consider in patients 40-70 years of age at high-risk for ASCVD and low-risk of bleeding
- Bleeding risk increased in patients with age>70 y, history of bleeding, thrombocytopenia, CKD, coagulopathy and concurrent use of certain medications