Hội nghị khoa học- Bệnh viện Đại học Y Dược TpHCM (1-2/11/2019)

Xu hướng mới trong điều trị bệnh tim mạch hiện nay

ASPIRIN

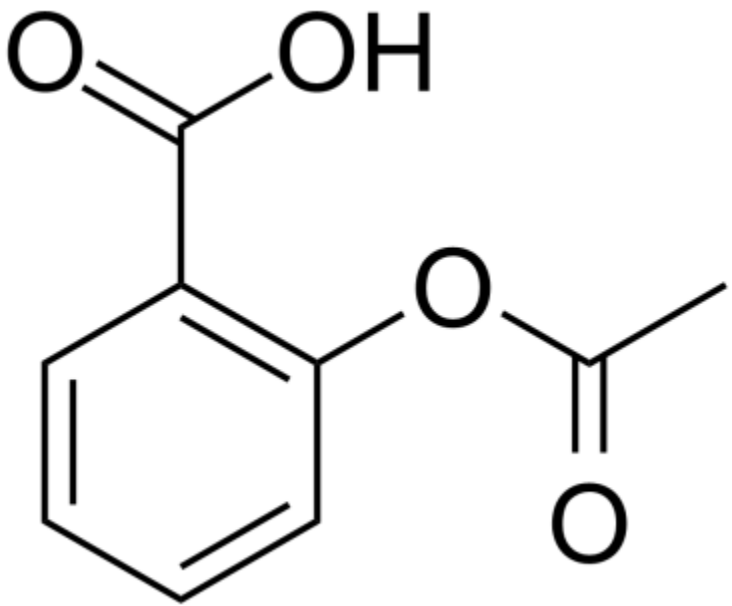
phòng ngừa biến cố tim mạch

Dinh Duc Huy, MD, FSCAI

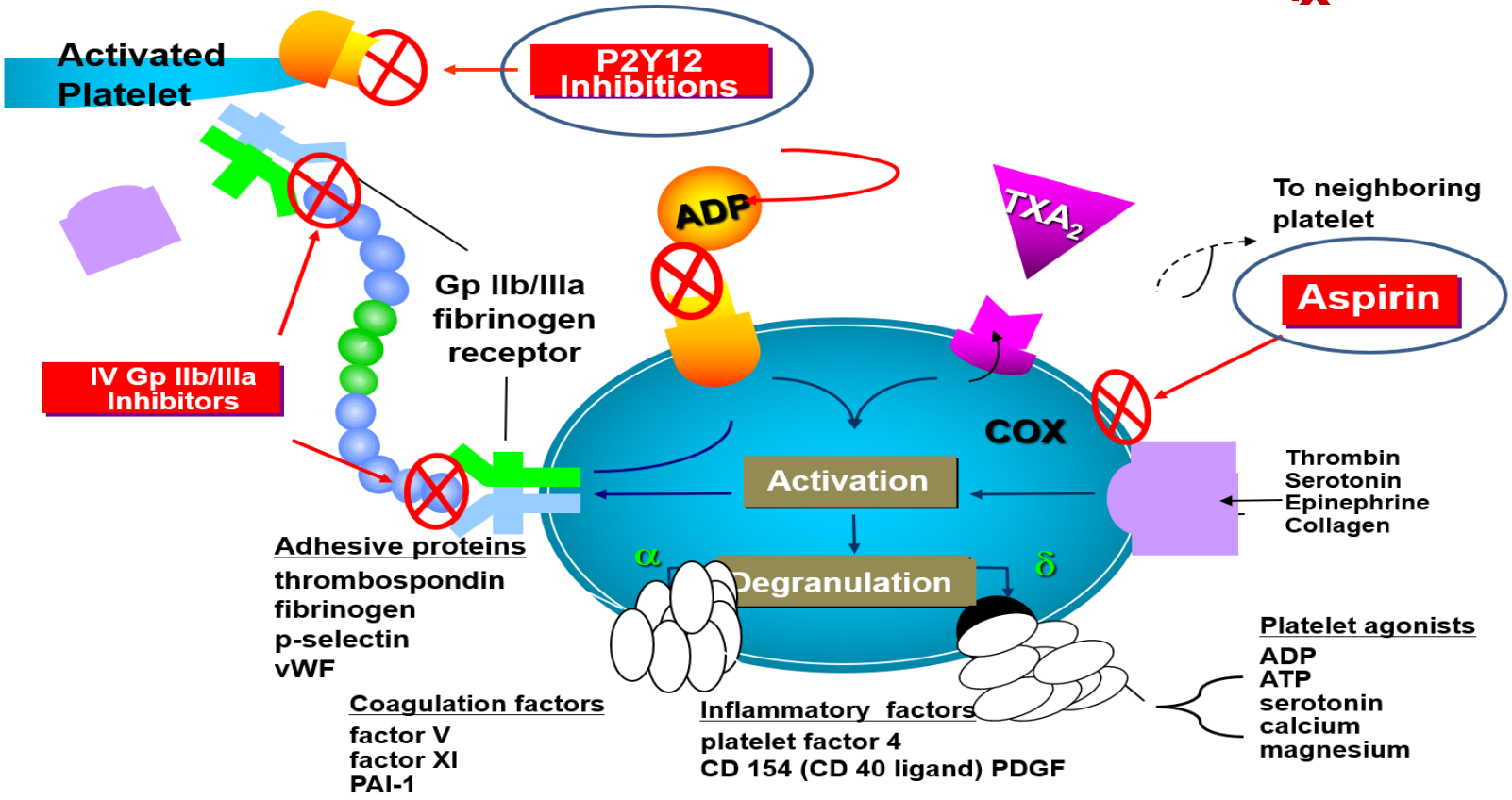
Tam Duc Heart Hospital

Aspirin = acetylsalicylic acid

Liều thấp: 75- 80- 81- 100 mg



Vị trí tác động của thuốc kháng tiểu

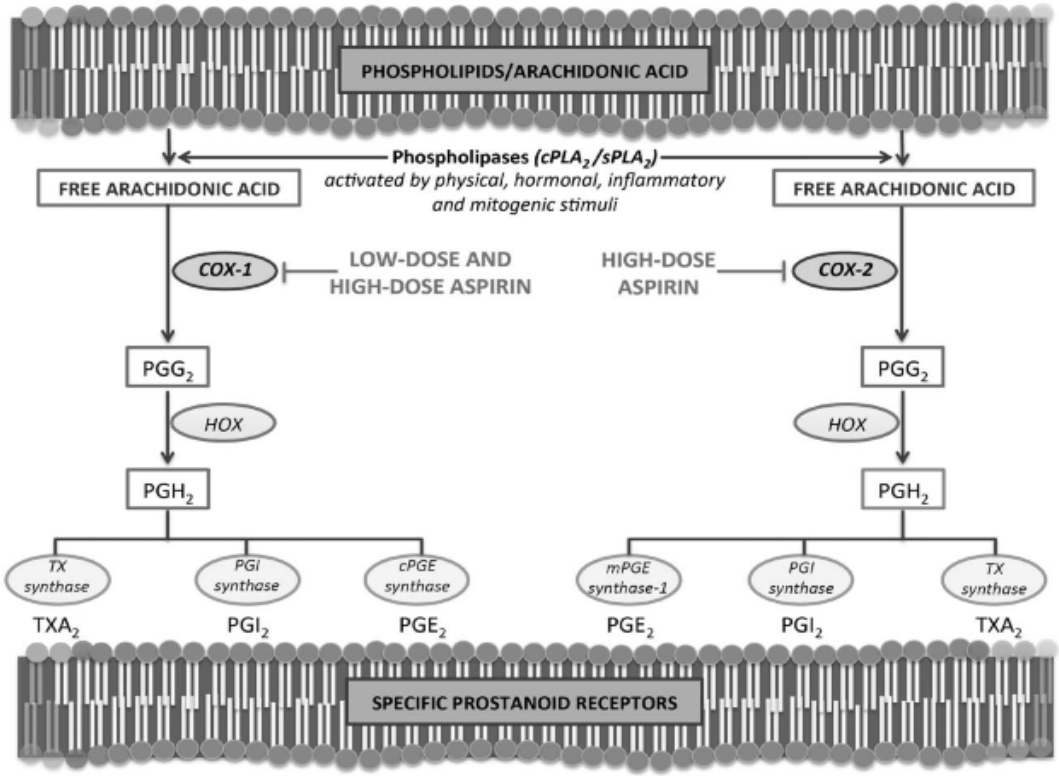


Schafer AI. Am J Med. 1996;101:199-209

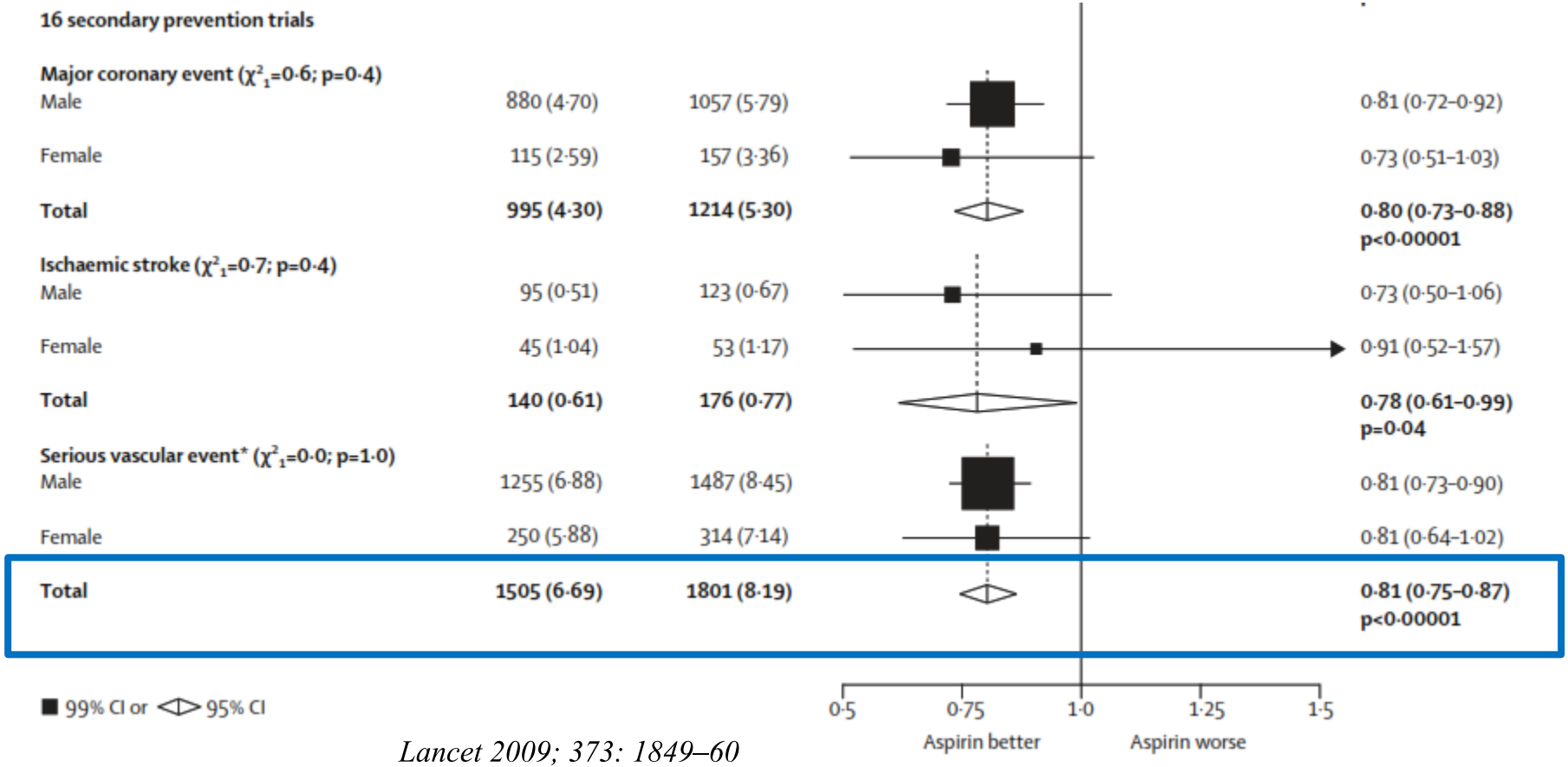
Cơ chế tác động của Aspirin

- **Low dose aspirin** selectively & irreversibly inhibits COX-1 in the arachidonic acid pathway, subsequently blocking the production of TXA2, a platelet agonist, thereby reducing thrombus formation

- The gastrointestinal adverse effects of aspirin and NSAIDs (erosive gastritis and bleeding) are mainly a result of COX-1 inhibition



Aspirin- phòng ngừa thứ phát



Lancet 2009; 373: 1849–60

Aspirin- Antithrombotic Trialists' Collaboration

- 16 secondary prevention RCTs
  (6 post MI & 10 post TIA/ Stroke)
- 17000 individuals at high-risk
- 43000 person-years
- 3306 serious vascular events
- long-term aspirin versus control

- significantly reduction in risk of serious vascular events

  6.7% versus 8.2% per year, P<0.0001
- reductions in total stroke

  2.08% versus 2.54% per year, P=0.002
- reductions in coronary events

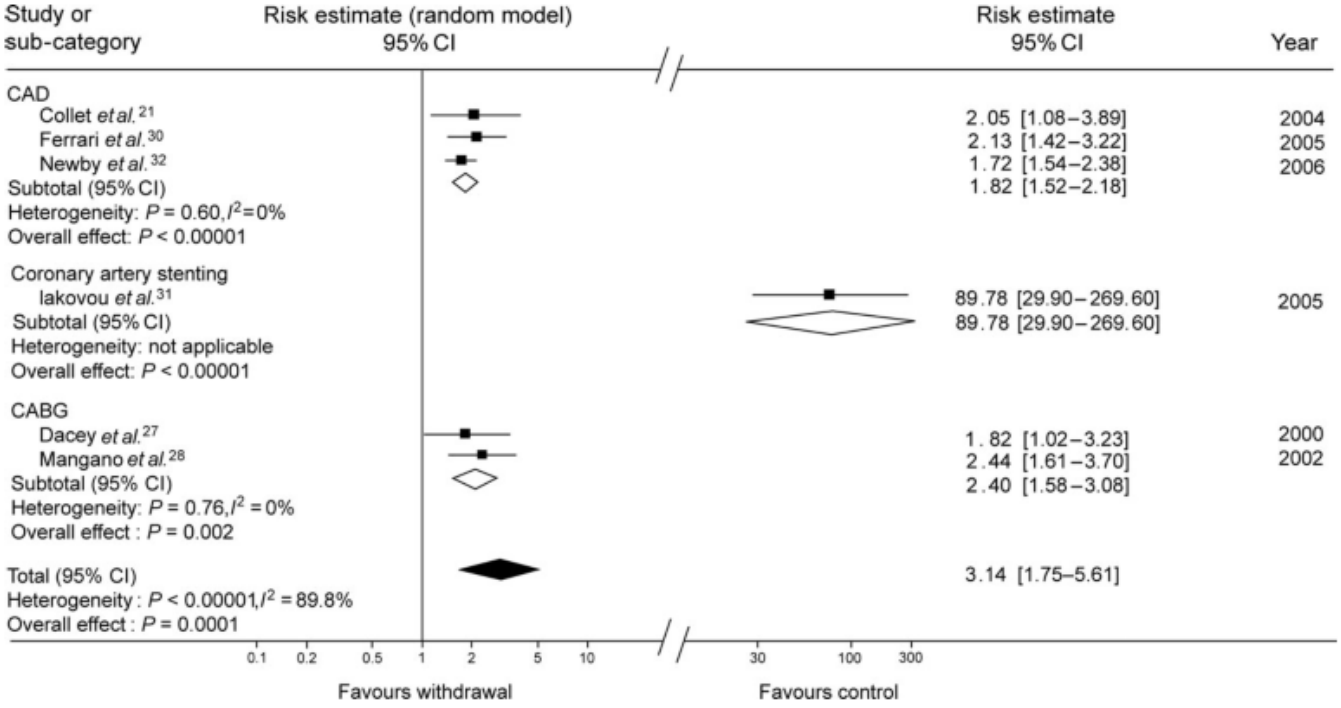
  4.3% versus 5.3% per year, P<0.0001
- non-significant increase in intracranial hemorrhage

Lancet 2009; 373: 1849–60

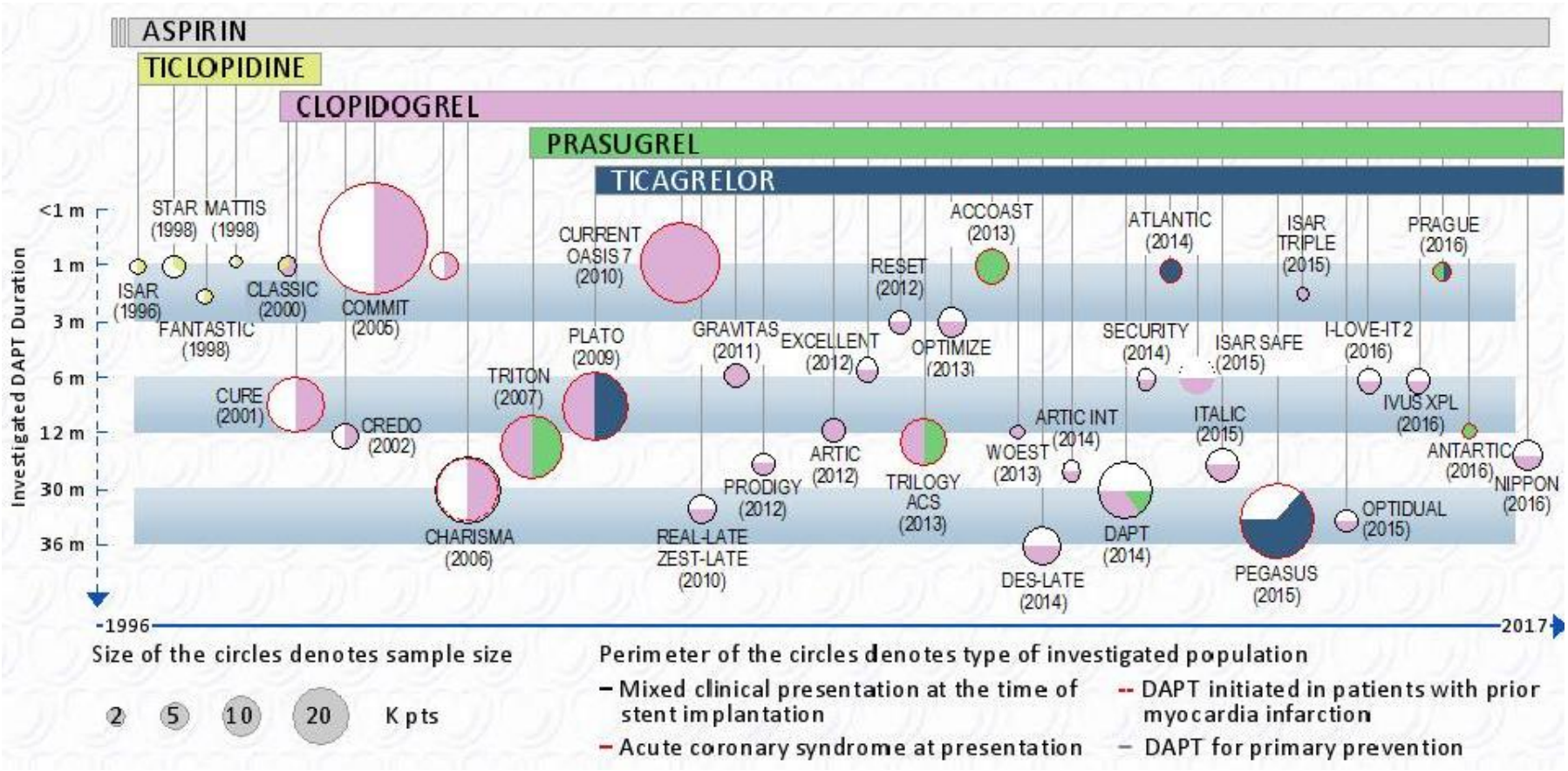
European Heart Journal (2006) 27, 2667–2674
doi:10.1093/eurheartj/ehl334

A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease

nonadherence or withdrawal of aspirin was associated with a 3x-increased risk of MACE



Aspirin + P2Y12i: giảm thêm biến cố thứ phát



Kháng KTTC kép: Aspirin+ ? & bao lâu

- Aspirin + Clopidogrel > Aspirin (CURE 2001)
- Aspirin + Prasugrel > Aspirin + Clopidogrel (TRITON-TIMI 58 2009)
- Aspirin + Ticagrelor > Aspirin + Clopidogrel (PLATO 2009)

- Hội chứng mạch vành mạn + PCI DAPT 06 tháng
- Hội chứng mạch vành cấp DAPT 12 tháng
- Sau DAPT **Aspirin đơn trị liệu**

TWILIGHT study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

After 3 months of treatment with ticagrelor plus aspirin, patients who had not had a major bleeding event or ischemic event continued to take ticagrelor and were randomly assigned to receive **aspirin or placebo for 1 year**

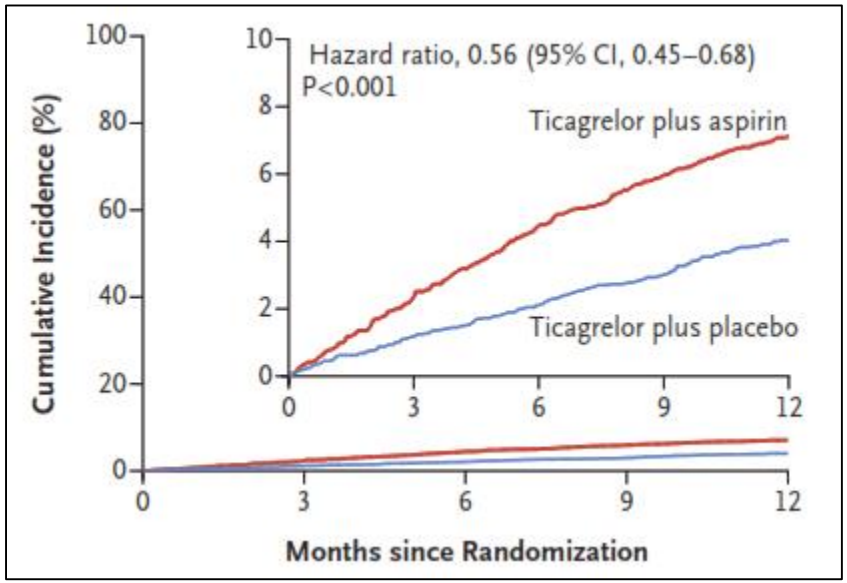
Mehran et al. NEJM online September 26, 2019

TWILIGHT: Giảm xuất huyết nặng khi ngưng Aspirin

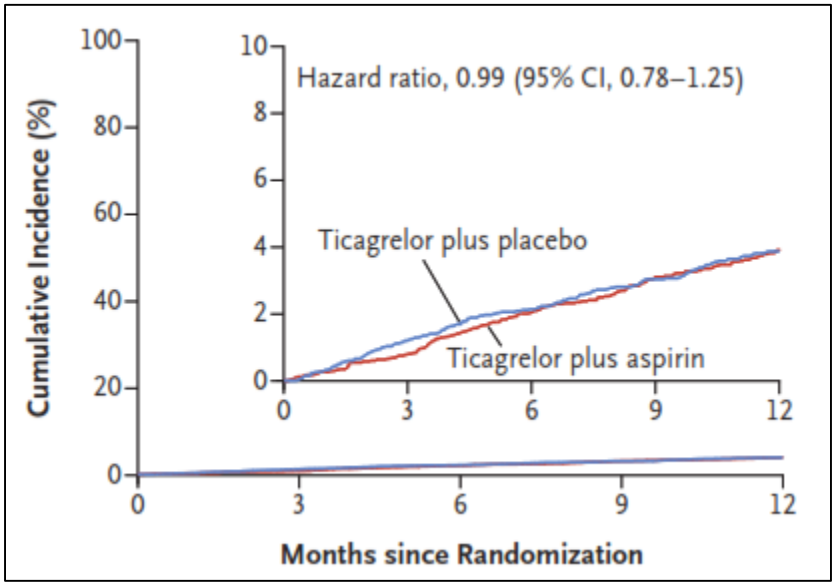
Variable	Ticagrelor plus Placebo (N=3555)	Ticagrelor plus Aspirin (N=3564)	Hazard Ratio (95% CI)†	P Value
	no. of patients (%)‡			
Bleeding end points				
Primary end point: BARC type 2, 3, or 5§	141 (4.0)	250 (7.1)	0.56 (0.45–0.68)	<0.001¶
BARC type 3 or 5§	34 (1.0)	69 (2.0)	0.49 (0.33–0.74)	
TIMI minor or major	141 (4.0)	250 (7.1)	0.56 (0.45–0.68)	
GUSTO moderate or severe	26 (0.7)	49 (1.4)	0.53 (0.33–0.85)	
ISTH major	39 (1.1)	72 (2.1)	0.54 (0.37–0.80)	

Mehran et al. NEJM online September 26, 2019

TWILIGHT: không tăng biến cố thiếu máu khi ngưng Aspirin



Xuất huyết giảm



Tử vong/ NMCT/ Đột quỵ tương đương

Mehran et al. NEJM online September 26, 2019

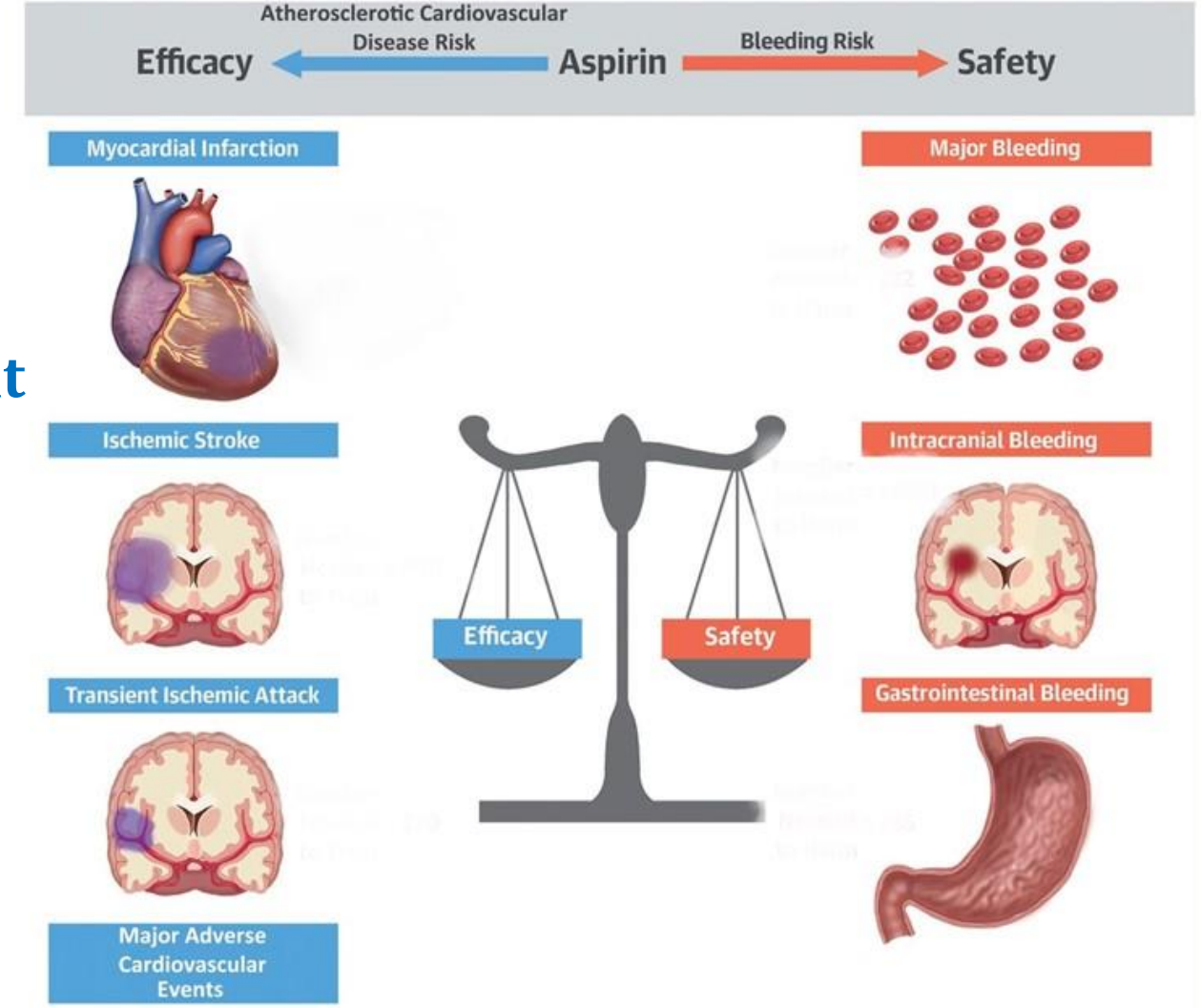
Aspirin

phòng ngừa tiên phát

biến cố tim mạch

versus

Nguy cơ xuất huyết



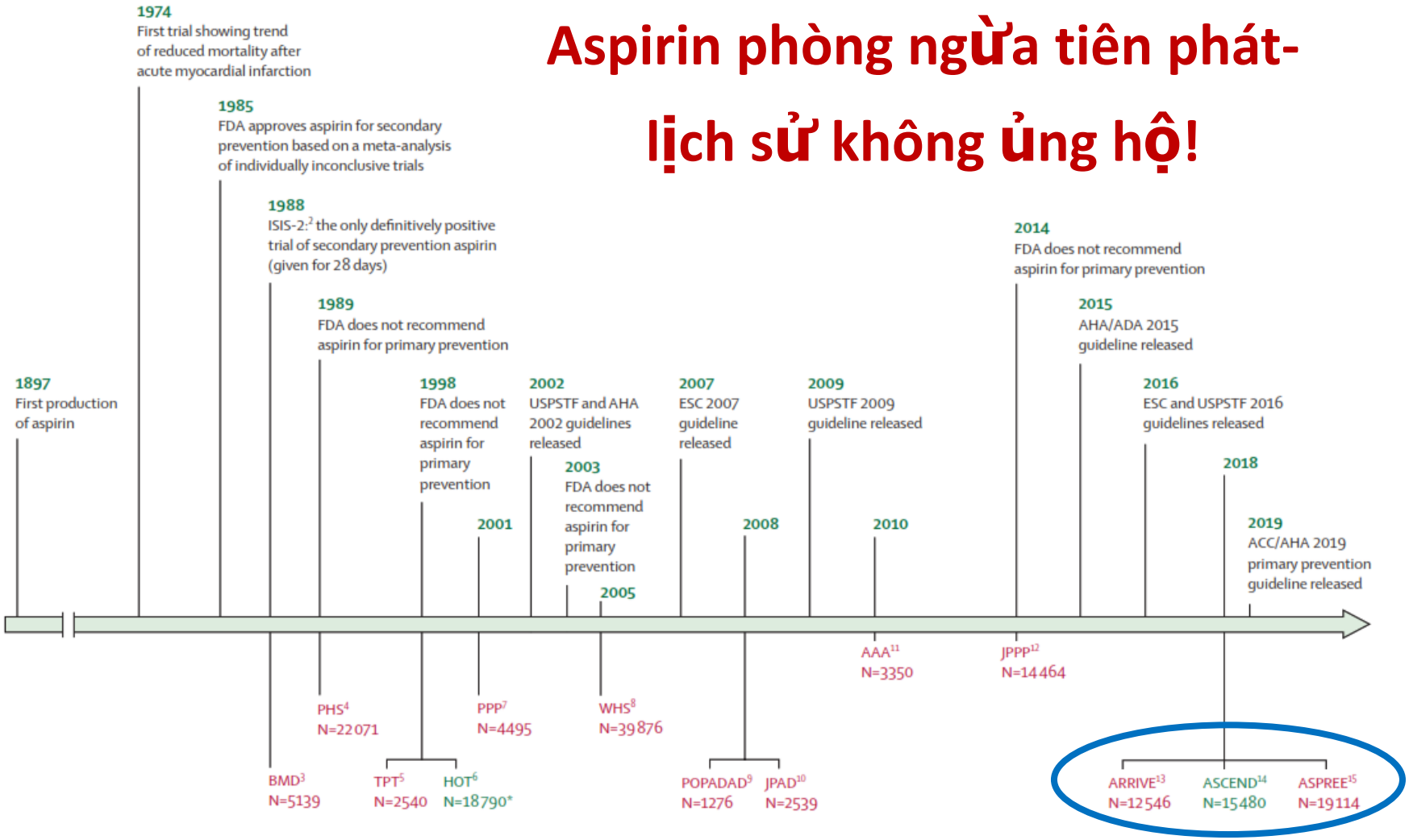
The rise and fall of aspirin in the primary prevention of cardiovascular disease

Inbar Raber, Cian P McCarthy, Muthiah Vaduganathan, Deepak L Bhatt, David A Wood, John G F Cleland, Roger S Blumenthal, John W McEvoy

reappraise the role of aspirin in primary prevention of cardiovascular disease, contextualising data from historical and contemporary trials

Lancet 2019; 393: 2155–67

Aspirin phòng ngừa tiên phát- lịch sử không ủng hộ!

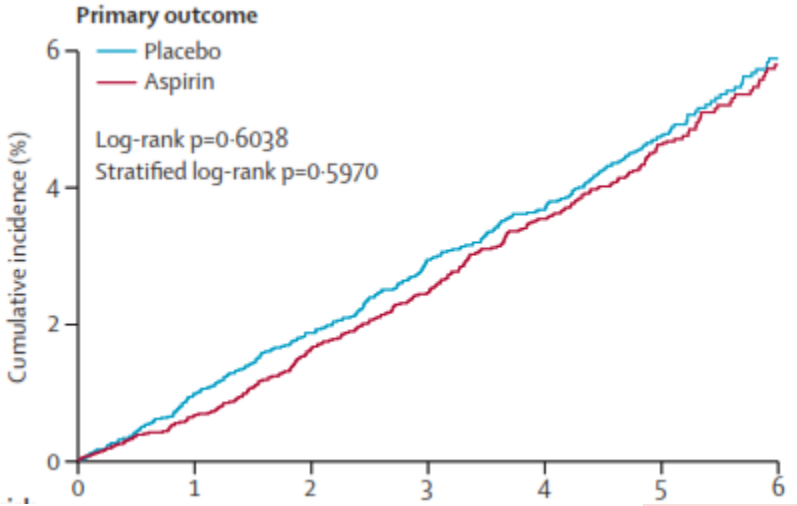


Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

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

- Nam > 55 tuổi, nữ > 60 tuổi
- Nguy cơ tim mạch trung bình (yếu tố nguy cơ)
- Phân nhóm ngẫu nhiên 1:1
- Aspirin 100 mg (n= 6270) vs. Placebo (n= 6276)
- Theo dõi trung vị 60 tháng
- PE: tử vong tim mạch, NMCT, CĐTNKOĐ, đột quỵ/ TIA

Lancet 2018; 392: 1036–46



ARRIVE- Kết quả chính

- Tiêu chính hiệu quả chính:

  ASA 4.29 % vs. Placebo 4.48%; p= 0.6038

- Xuất huyết tiêu hóa

  ASA 0.97% vs. Placebo 0.46%; p= 0.0007

	Number of events in the intention-to-treat population		
	Aspirin (n=6270)	Placebo (n=6276)	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
Myocardial infarction, stroke, or cardiovascular death	208 (3·32%)	218 (3·47%)	0·95 (0·79–1·15); p=0·6190
Myocardial infarction*	95 (1·52%)	112 (1·78%)	0·85 (0·64–1·11); p=0·2325
Non-fatal myocardial infarction	88 (1·40%)	98 (1·56%)	0·90 (0·67–1·20); p=0·4562
Stroke*	75 (1·20%)	67 (1·07%)	1·12 (0·80–1·55); p=0·5072
Cardiovascular death	38 (0·61%)	39 (0·62%)	0·97 (0·62–1·52); p=0·9010
Unstable angina	20 (0·32%)	20 (0·32%)	1·00 (0·54–1·86); p=0·9979
Transient ischaemic attack	42 (0·67%)	45 (0·72%)	0·93 (0·61–1·42); p=0·7455
Any death	160 (2·55%)	161 (2·57%)	0·99 (0·80–1·24); p=0·9459
Mean Framingham 10-year coronary heart disease risk score	13·9% (6·4)	14·1% (6·4)	

ORIGINAL ARTICLE

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

- ≥ 70 tuổi, không bệnh lý tim mạch, sa sút trí tuệ hoặc tàn tật
- Aspirin 100 mg (n= 9525) vs. Placebo (n= 9589)
- Theo dõi 4.7 năm
- Nguy cơ tử vong do bất kỳ nguyên nhân nào là 12.7/ 1000 bệnh nhân-năm ở nhóm Aspirin so với 11.1/ 1000 bệnh nhân-năm ở nhóm Placebo

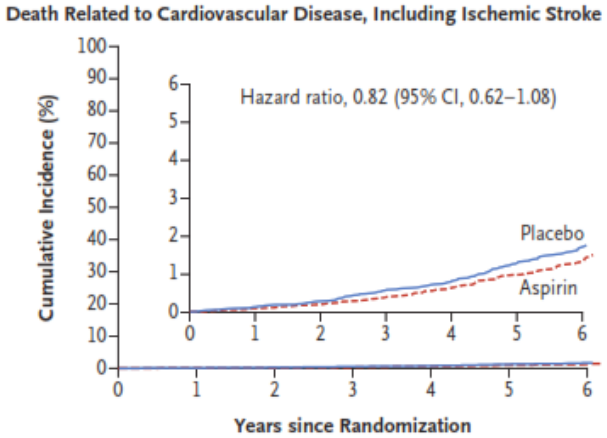
NEJM online, September 16, 2018

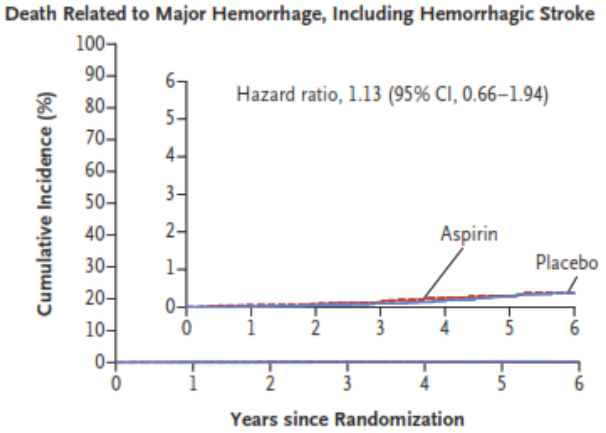
Table 1. Mortality According to the Underlying Cause of Death.*

Cause of Death	Overall (N = 19,114)	Aspirin (N = 9525)	Placebo (N = 9589)	Hazard Ratio (95% CI)
	no. of deaths	*no. of deaths (%)*		
Any	1052	558 (5.9)	494 (5.2)	1.14 (1.01–1.29)
Cancer†	522	295 (3.1)	227 (2.3)	1.31 (1.10–1.56)
Cardiovascular disease, including ischemic stroke‡	203	91 (1.0)	112 (1.2)	0.82 (0.62–1.08)
Major hemorrhage, including hemorrhagic stroke§	53	28 (0.3)	25 (0.3)	1.13 (0.66–1.94)
Other¶	262	140 (1.5)	122 (1.3)	1.16 (0.91–1.48)
Insufficient information‖	12	4 (<0.1)	8 (0.1)	—

ASPREE- Kết quả chính

NEJM online, September 16, 2018





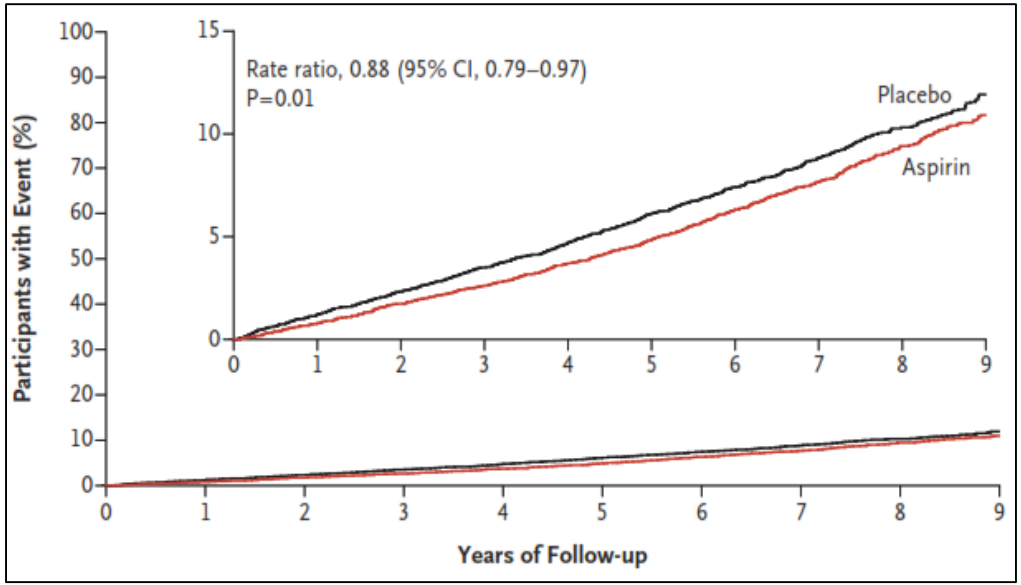
ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

- 15480 bệnh nhân đái tháo đường, không có bệnh tim mạch, phân nhóm ngẫu nhiên 1:1
- Aspirin 100 mg (n= 7740) vs. Placebo (n= 7740)
- Theo dõi 7.4 năm
- Tiêu chí hiệu quả chính: biến cố tim mạch nặng
- Tiêu chí an toàn chính: biến cố xuất huyết nặng

NEJM online, August 26, 2018



ASCEND- Kết quả chính

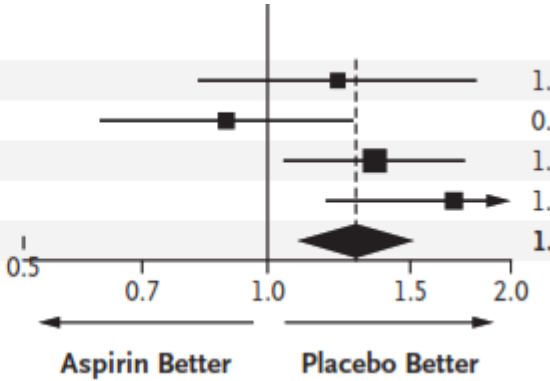
- Tiêu chí hiệu quả chính:

ASA 8.5 % vs. Placebo 9.6%; p= 0.01

- Xuất huyết tiêu nặng

ASA 4.1% vs. Placebo 3.2%; p= 0.003

Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



NEJM online, August 26, 2018

Aspirin for Primary Prevention of Cardiovascular Events

- 15 RCTs
- 165,502 participants
- Aspirin (n= 83,529)
- Control (n= 81,973)

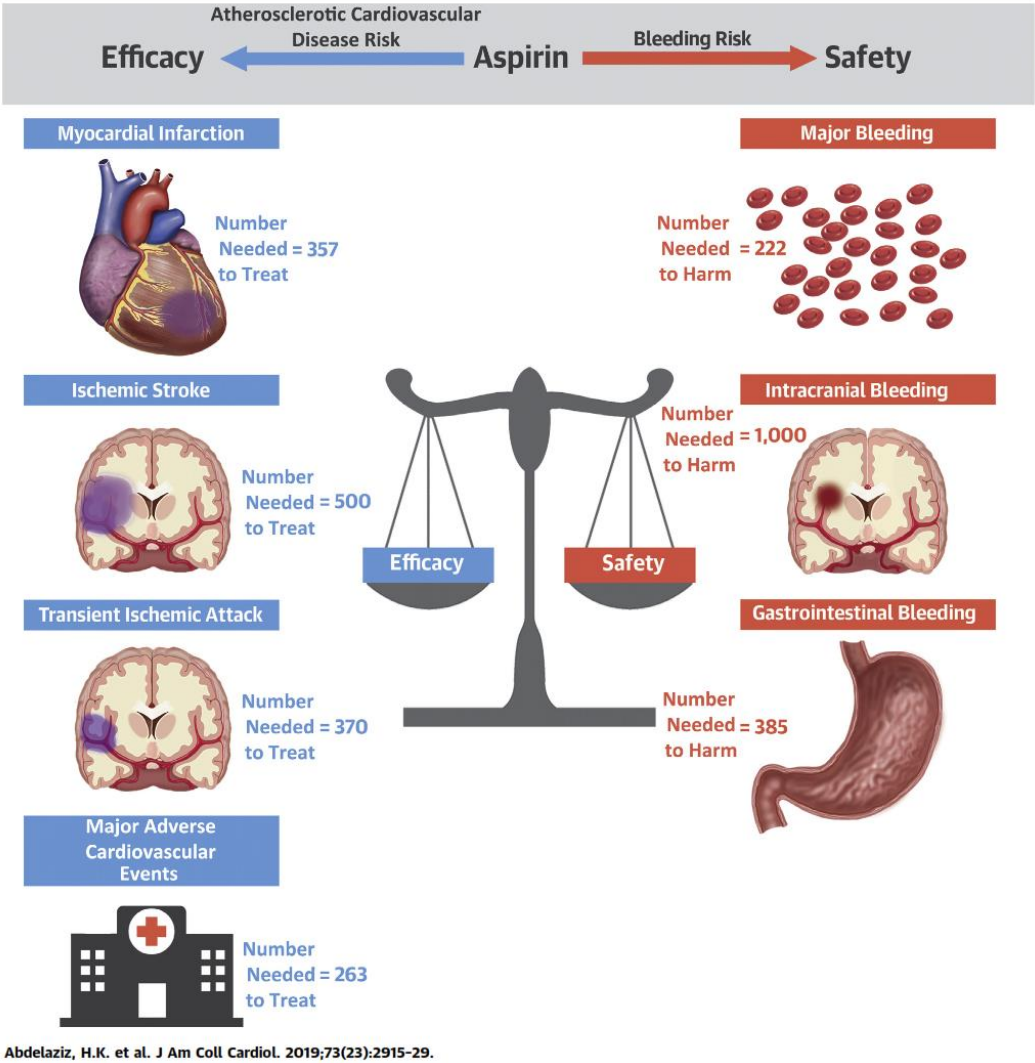
TABLE 1 Baseline Characteristics of the Included Studies

Study (Year)	Country	Aspirin/Control, n	Study Design	Patient Population
ASPREE (2018)	Australia and United States	9,525/9,589	Double-blinded RCT	Age ≥70 yrs (≥65 yrs among blacks and Hispanics in U.S.)
ARRIVE (2018)	Europe and United States	6,270/6,276	Triple-blinded RCT	Male >55 yrs + 2-4 CV risk factors, female >60 yrs +3-4 CV risk factors
ASCEND (2018)	United Kingdom	7,740/7,740	Quadruple-blinded, 2 × 2 RCT, omega-3 fatty acid	Age >40 yrs + DM
AASER (2018)	Spain	50/61	Open-label RCT	CKD Stage 3-4
JPAD 2 (2017)	Japan	1,262/1,277	Open-label RCT	Age 30-85 yrs + DM
JPPP (2014)	Japan	7,220/7,224	Open-label RCT	Age 60-85 yrs + HTN, DM, or dyslipidemia
AAA (2010)	United Kingdom	1,675/1,675	Double-blinded RCT	Age 50-75 yrs + ABI <0.96
POPADAD (2008)	United Kingdom	638/638	Double-blinded, 2 × 2 RCT, antioxidant	Age >40 yrs + DM+ asymptomatic PAD with ABI ≤0.99
WHS (2005)	United States	19,934/19,942	Double-blinded, 2 × 2 RCT, vitamin E	Female health professionals age >45 yrs
PPP (2001)	Italy	2,226/2,269	Open-label 2 × 2 RCT, vitamin E	Age >50 yrs + ≥1 CVD risk factor
HOT (1998)	Europe, Asia, Americas	9,399/9,391	Double-blinded, 3 × 2 RCT, hypertension treatment goals	Age 50-80 yrs + HTN
TPT (1998)	United Kingdom	1,268/1,272	Double-blinded, 2 × 2 RCT, warfarin	Male aged 45-69 yrs at the top 20% or 25% of CVD risk score
ETDRS (1992)	United States	1,856/1,855	Double-blinded RCT	Age 18-70 yrs + DM + diabetic retinopathy
PHS (1989)	United States	11,037/11,034	Double-blinded RCT	Healthy male doctors ages 40-84 yrs
BMD (1988)	United Kingdom	3,429/1,710	Open-label RCT	Healthy male doctors age ≤80 yrs

Abdelaziz et al. J Am Coll Cardiol 2019;73:2915–29

Aspirin for Primary Prevention of Cardiovascular Events

- Aspirin dùng trong phòng ngừa tiên phát:
- giảm nguy cơ biến cố do thiếu máu (NMCT, đột quỵ, TIA, biến cố tim mạch nặng)
- Tăng nguy cơ xuất huyết nặng, XH nội sọ, XH tiêu hóa (không tử vong)
- Lợi ích nhiều hơn khi áp dụng cho bệnh nhân với nguy cơ bệnh tim mạch do xơ vữa 10 năm (ASCVD risk) ≥7.5%



Abdelaziz, H.K. et al. J Am Coll Cardiol. 2019;73(23):2915-29.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

4.6.Aspirin use

Recommendations for Aspirin Use

Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.[S4.6-1–S4.6-8]
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.[S4.6-9]
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.[S4.6-10]

Circulation. 2019;140:e596–e646. DOI:10.1161/CIR.0000000000000678

Một số điểm cần ghi nhớ khi sử dụng Aspirin để phòng ngừa biến cố tim mạch

1. **Liều thấp: 75- 100 mg/ ngày**
2. **Phòng ngừa thứ phát: Hiệu quả, an toàn đã được chứng minh**
   - *Dùng chung với kháng P2Y12 sau đặt stent mạch vành, HCVC*
   - *Đơn trị liệu kháng KTTC với Aspirin lâu dài sau liệu pháp kháng KTTC kép; có thể bị thay thế bằng kháng P2Y12 mới (?)*
3. **Phòng ngừa tiên phát: Hiệu quả còn tranh cãi**
   - *Có thể gây biên cố xuất huyết nặng*
   - *Cá thể hóa, có thể xem xét sử dụng cho bệnh nhân có nguy cơ TM cao*

Cám ơn quý đồng nghiệp!