ATHERO-THROMBOTIC RR

Speaker: Omar Hamoui (Lebanon)

Moderator: Fahad Al Nouri (KSA)

Educational objective: Describe the association of increased thrombotic RR with ASCVD, including the role of dual antiplatelet therapy, single antiplatelet or dual antiplatelet therapy plus low-dose NOAC in reducing RR

2020 MIDDLE EAST SUMMIT ON RESIDUAL CARDIOVASCULAR RISK

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Which of the following statements are true?

Select all that apply

A. Secondary prevention after MACE can prevent up to 45% of CV-related post-MI deaths
B. Antithrombotic prophylaxis is recommended in all patients with established ASCVD
C. In select patients, the use of antiplatelet therapy and/or oral anticoagulants can reduce RR
D. Oral anticoagulant therapy is preferred to oral antiplatelets as primary and secondary prevention

Disclosures

Omar Hamoui

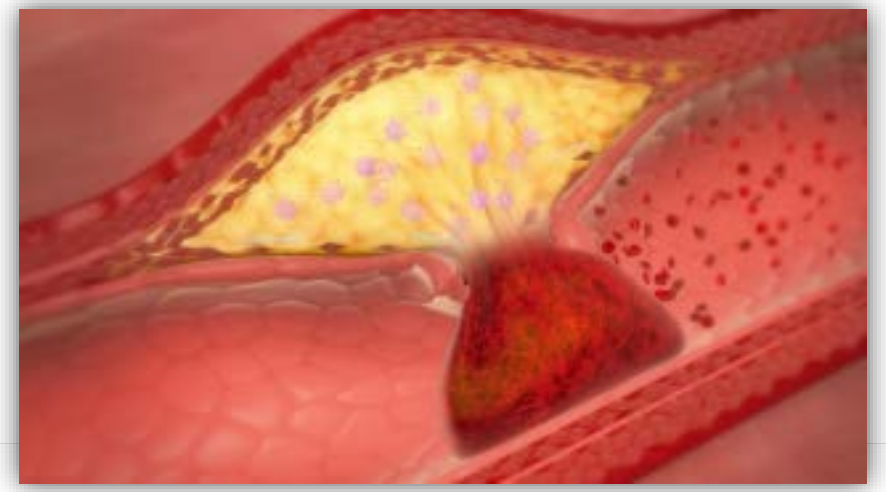
- Honoraria for educational activities: >10 companies

Fahad Al Nouri

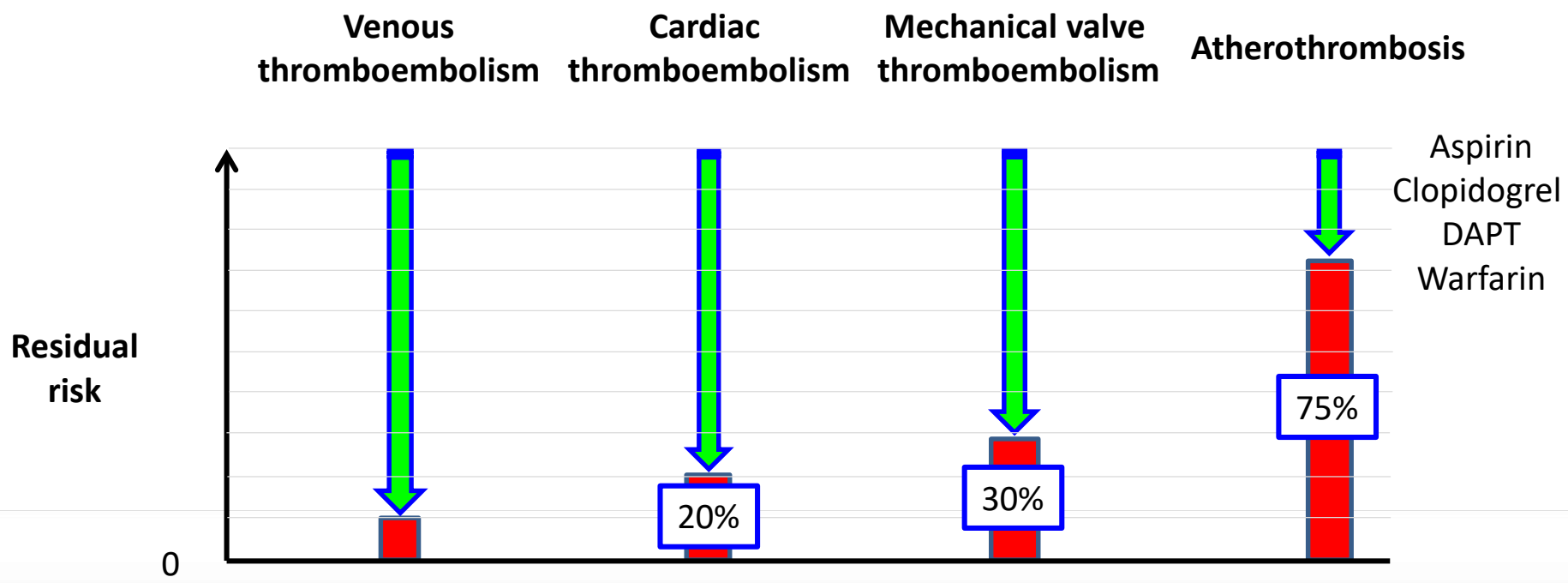
- Advisory Boards: Amgen, Amryt
- Lecturing: Amgen
- Research Grant: Amgen

Athero-thrombotic residual risk

Omar Hamoui, MD
Interventional Cardiology
Clemenceau Medical Center,
Beirut, Lebanon



Efficacy of antithrombotic therapy in patients with atherothrombosis is limited



US and European data demonstrate high residual risk despite use of proven 20 prevention therapies

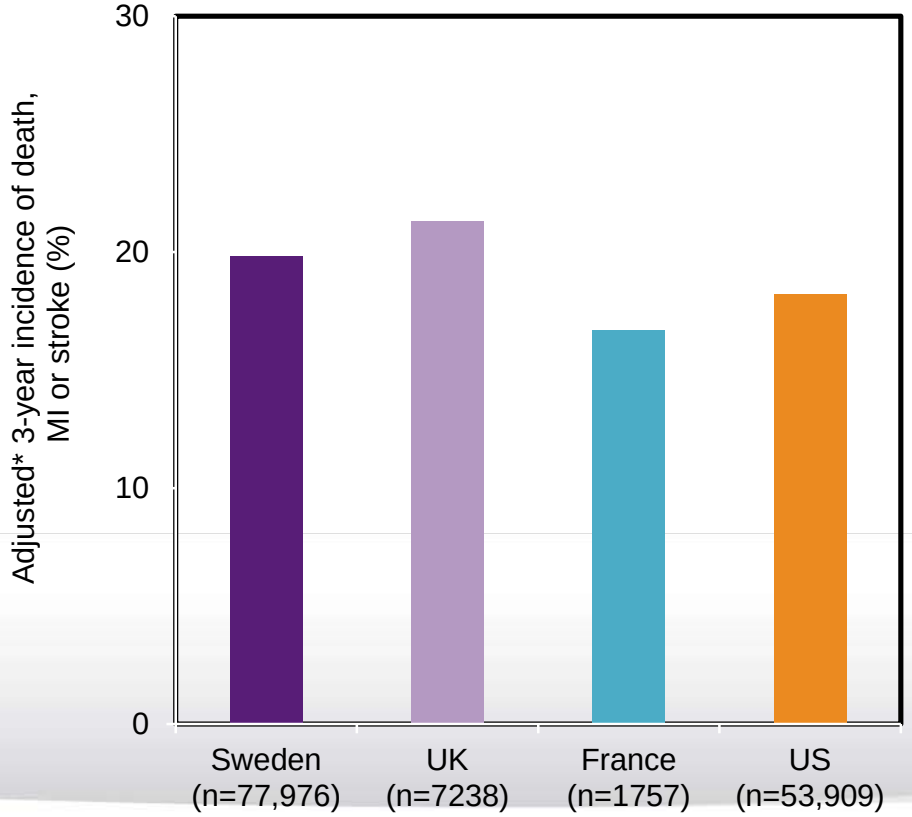
- Rapsomaniki, et al. 2016
- Administrative and insurance databases
- Sweden, USA, England, France
- **N=114,364**
- Mean age 78 years
- At least 1 year post-MI (survivors)

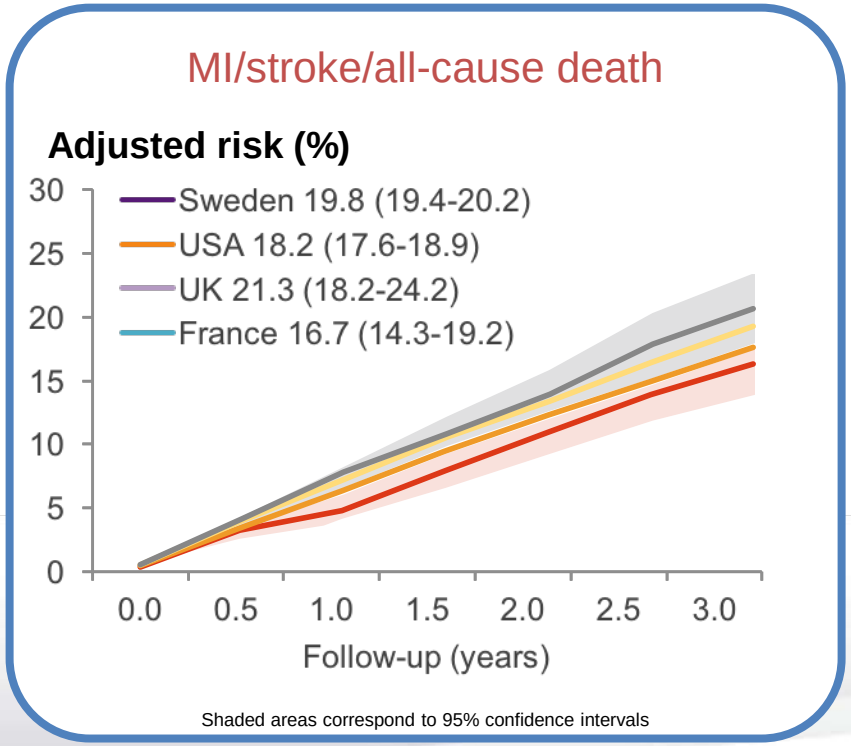
Rapsomaniki E, et al. Eur Heart J Qual Care Clin Outcomes 2016; 2: 172–183.

Mortality, stroke or MI in patients followed from 1 year after MI (age >65)

~1 in 5 pts who are event free for the first year post-MI, will suffer an MI, stroke or death within 3 years

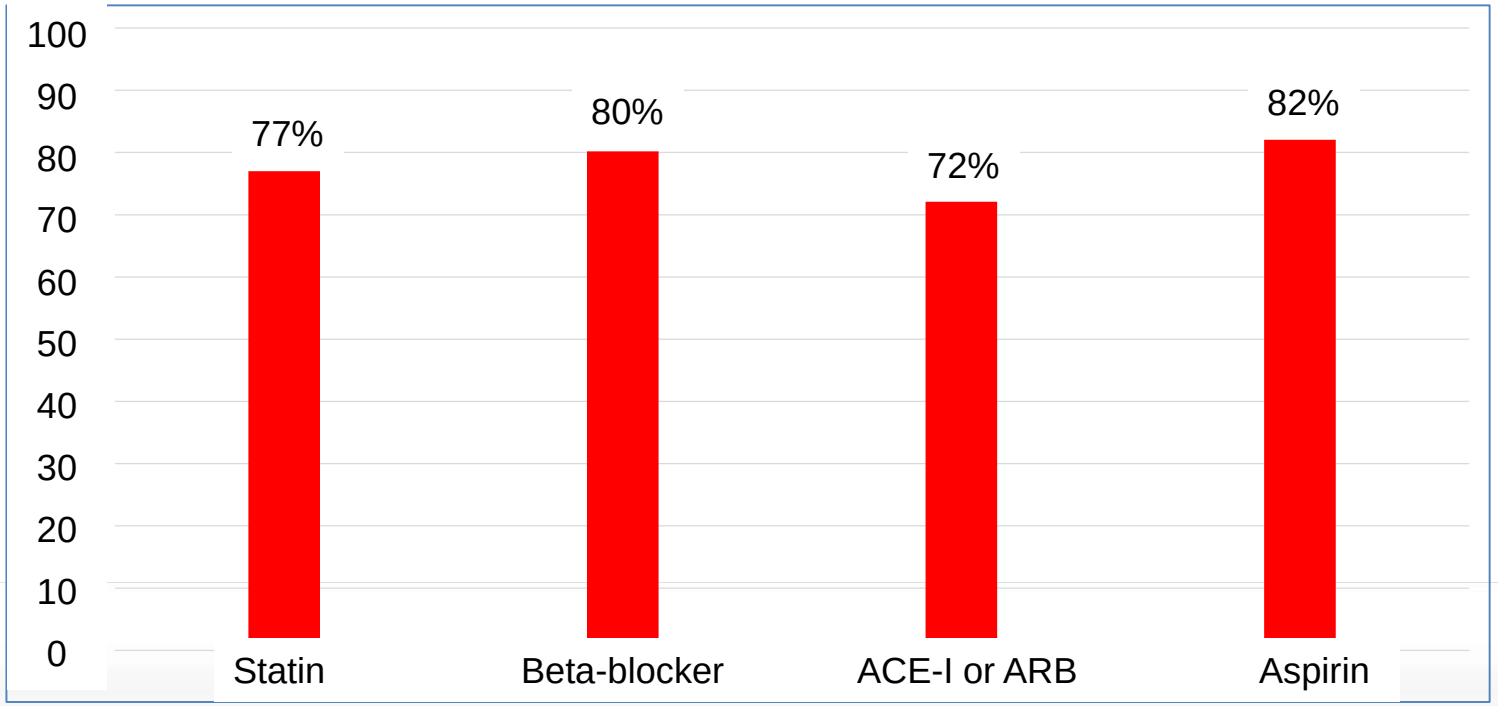
APOLLO 4-country analysis: adjusted incidence





MI, myocardial infarction.
*Adjusted for differences in study populations; MI, myocardial infarction. Shaded areas / figures in brackets [95% CI]
1. Rapsomaniki E et al. ESC Late Breaking Registry presentation 2014.

Widespread use of proven therapies



Rapsomaniki E, et al. Eur Heart J Qual Care Clin Outcomes 2016; 2: 172–183.

High event rates despite proven therapies

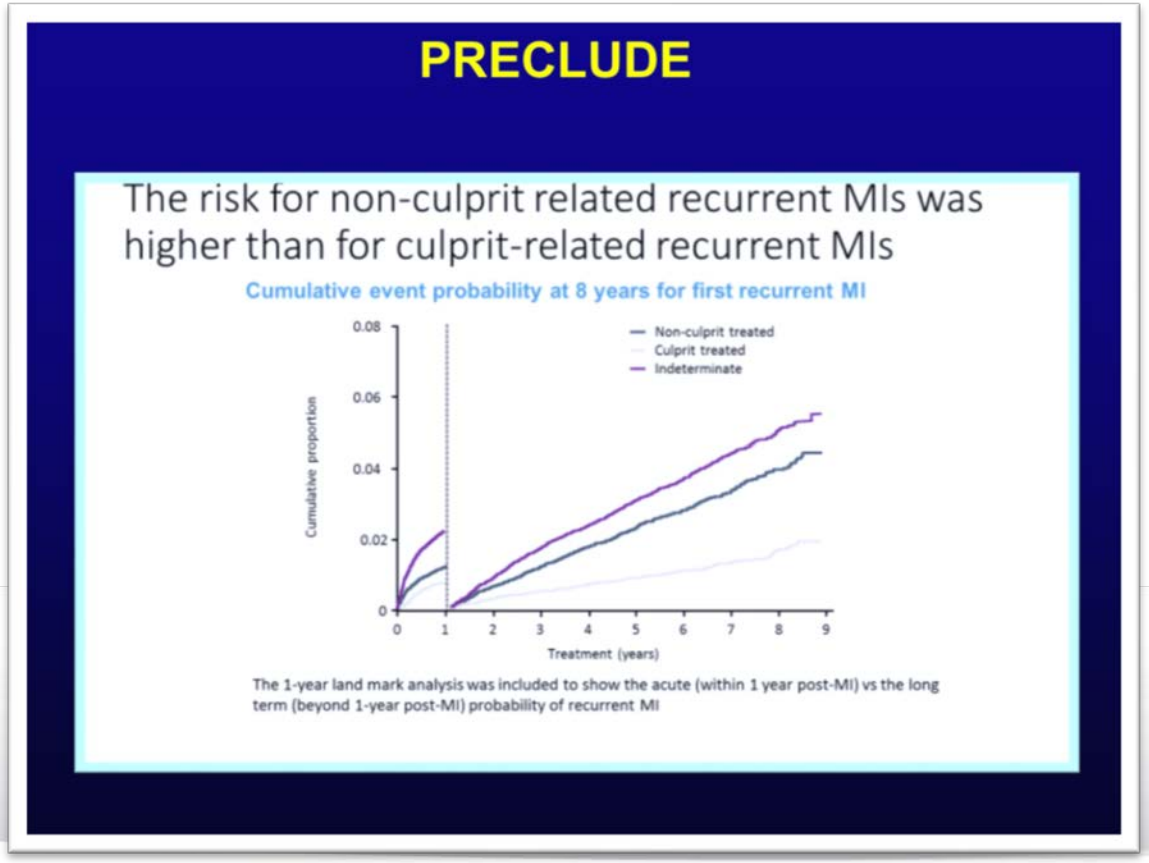
Country	Death, stroke, MI % per year*	Death % per year*
Sweden	11.4%	**9.0%**
USA	12.1%	**10.1%**
England	10.8%	**6.5%**
France	8.7%	**7.4%**

*Crude rates (unadjusted for baseline characteristics)

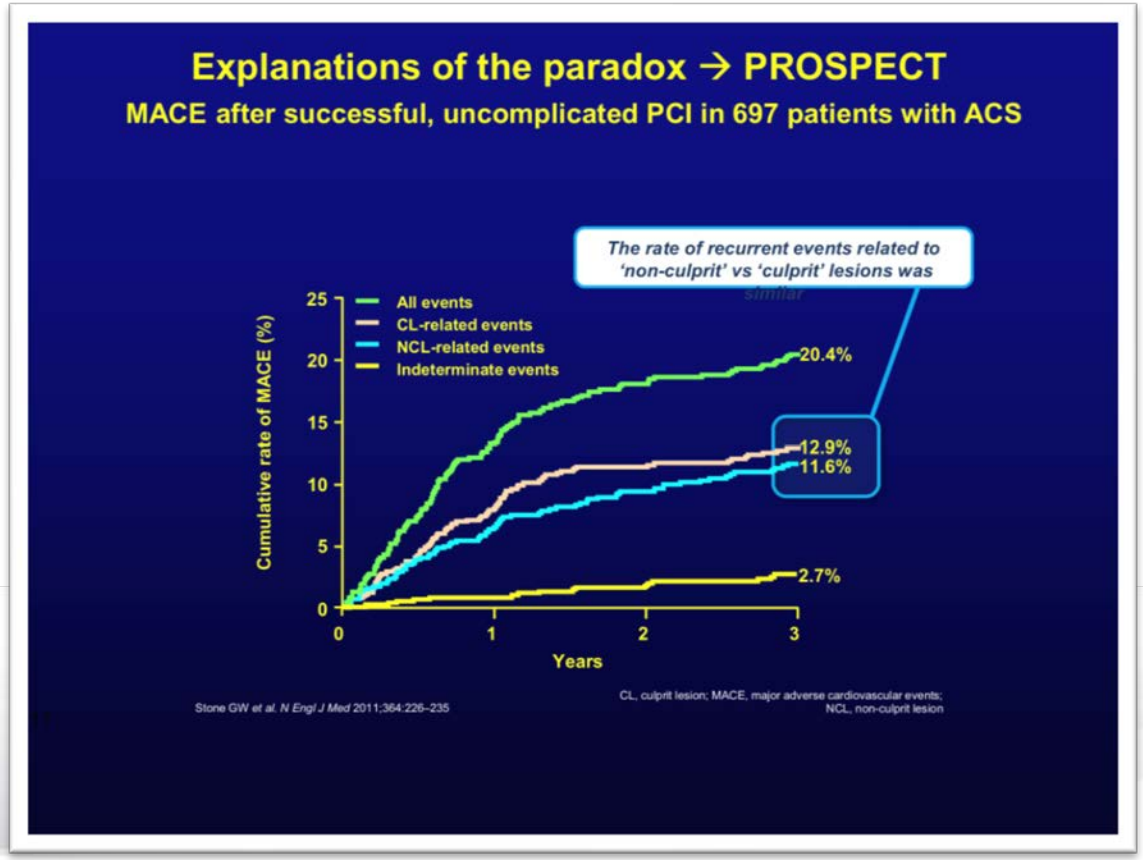
Rapsomaniki E, et al. Eur Heart J Qual Care Clin Outcomes 2016; 2: 172–183.

Recurrent events: Non-culprit vs. culprit vessel

PRECLUDE trial



PROSPECT trial



Despite treatment, patients with CVD continue to be at risk – Potential targets of therapy

ACS, acute coronary syndrome; DAPT, dual anti-platelet therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2.

Bonaca MP et al. Am Heart J 2014;167:437–444; Sahebkar A, Watts GF. Clin Ther 2013;35(8):1082–1098; Thompson PL et al. Clin Ther 2013;35(8):1099–1107; Katz P et al. Diab Vasc Dis Res 2014;11(6):395–409.

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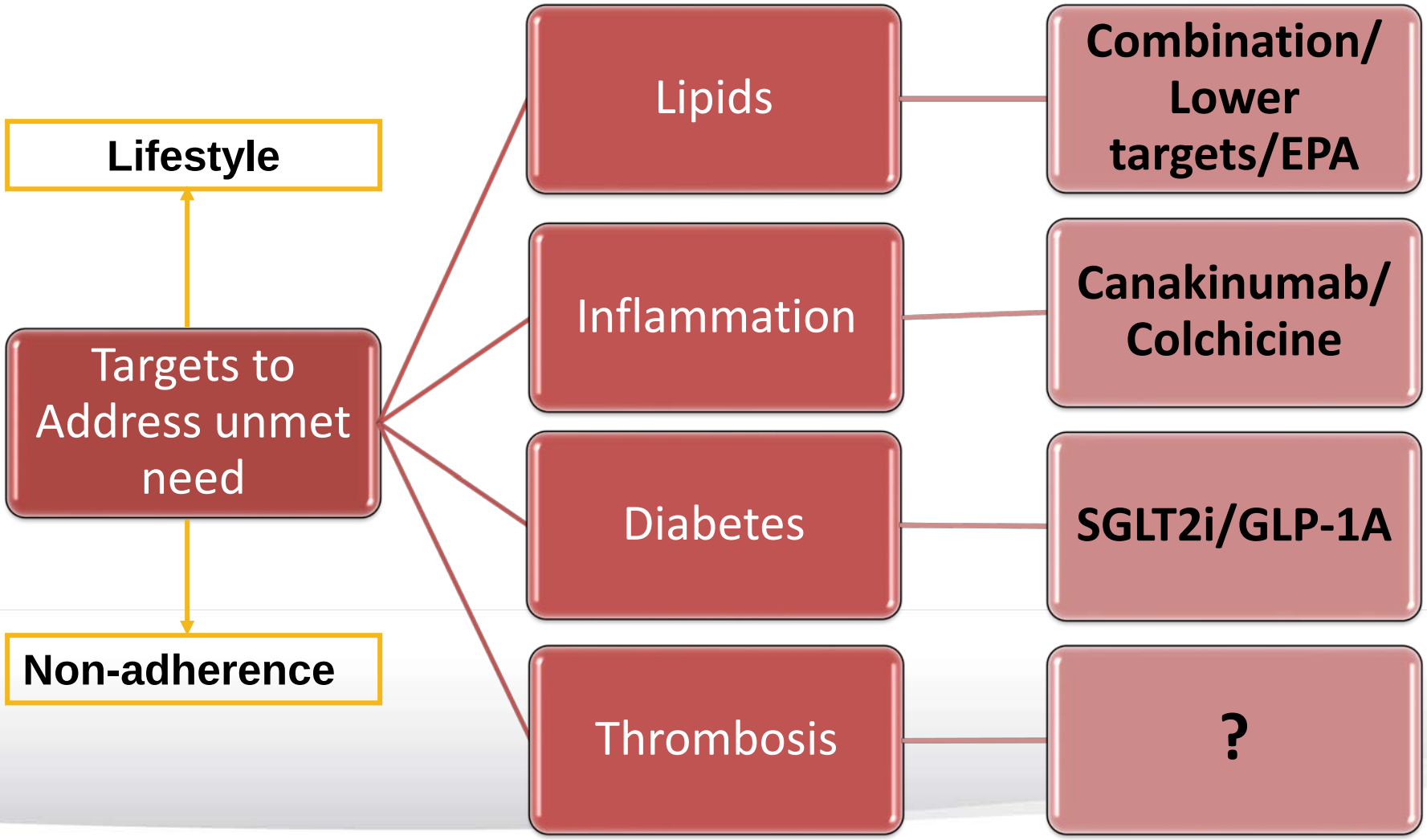

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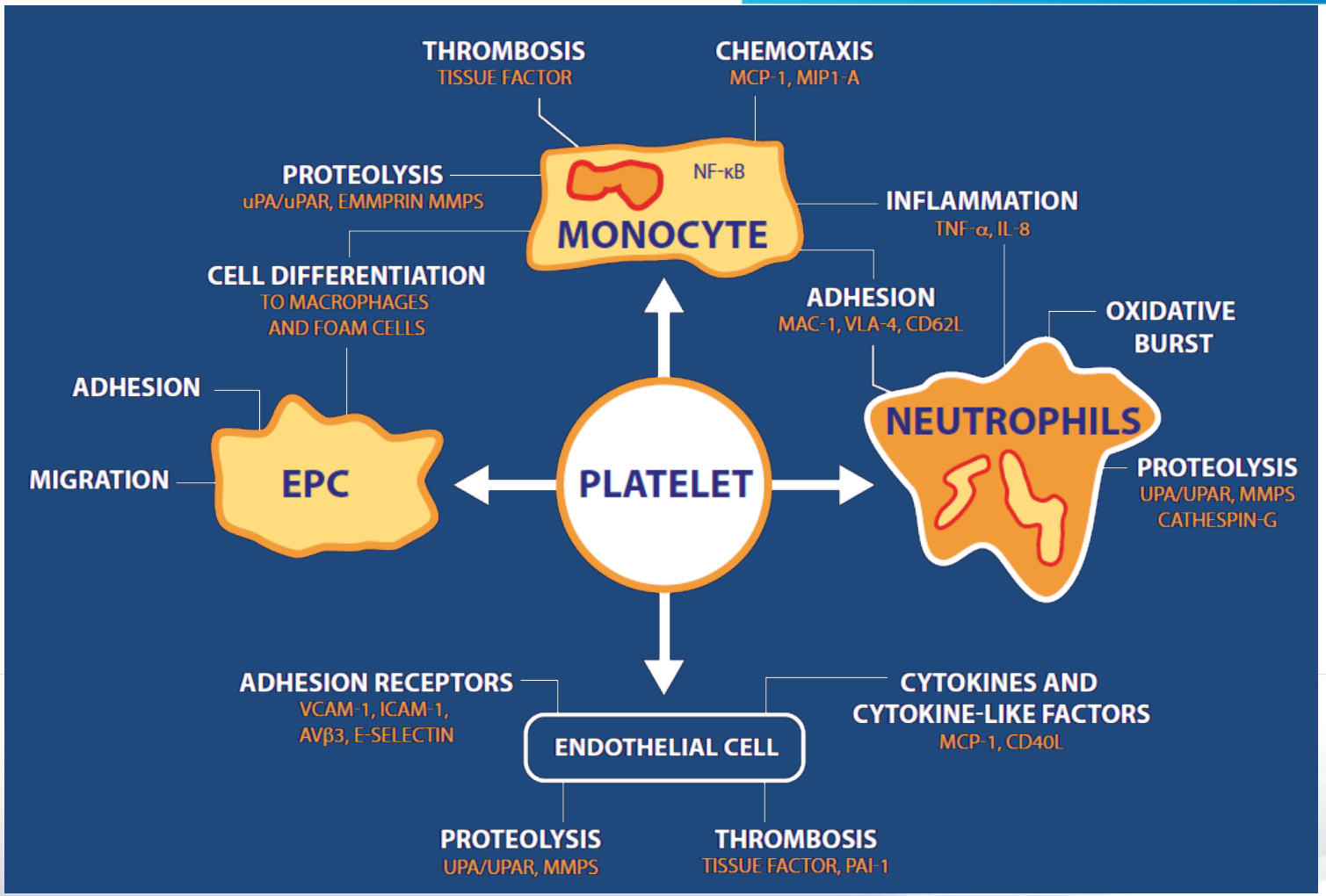
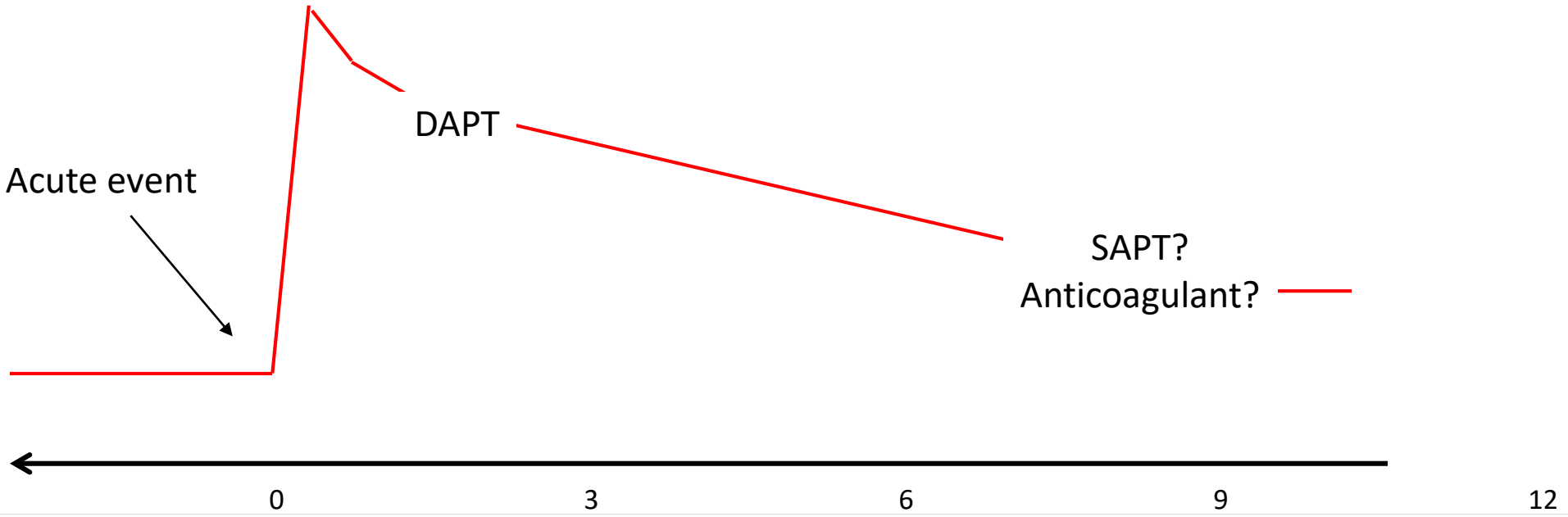
Platelets also have the ability to modulate athero-thrombosis via interaction with other vascular cells

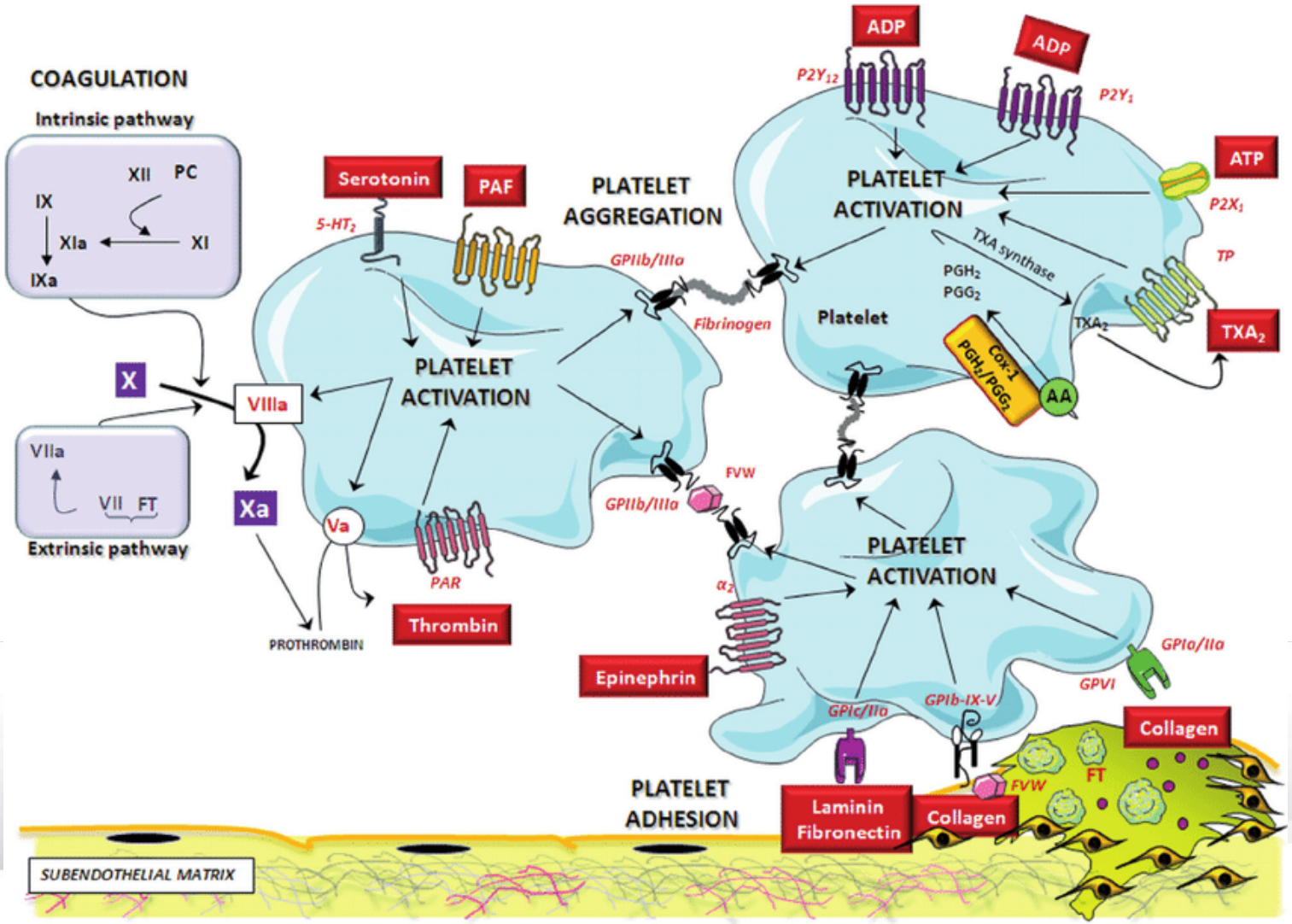


EMMPRIN, extracellular matrix metalloproteinase inducer; EPC, endothelial progenitor cell; ICAM-1, intercellular adhesion molecule-1; IL-8, interleukin-8; MAC-1, macrophage-1; MCP-1, macrophage chemoattractant protein-1; MIPI-A, mantle cell lymphoma international prognostic index; MMPS, matrix metalloproteinases; NF-κB, nuclear factor-kappa B; PAI-1, plasminogen activator inhibitor-1; TNF-⍰, tumor necrosis factor-alpha; uPA, urokinase; uPAR, urokinase receptor; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late antigen-4..Gawaz M. Eur Heart J Suppl 2008:10(Suppl 1);14–17.

Theoretical time course of platelet activation after an acute event

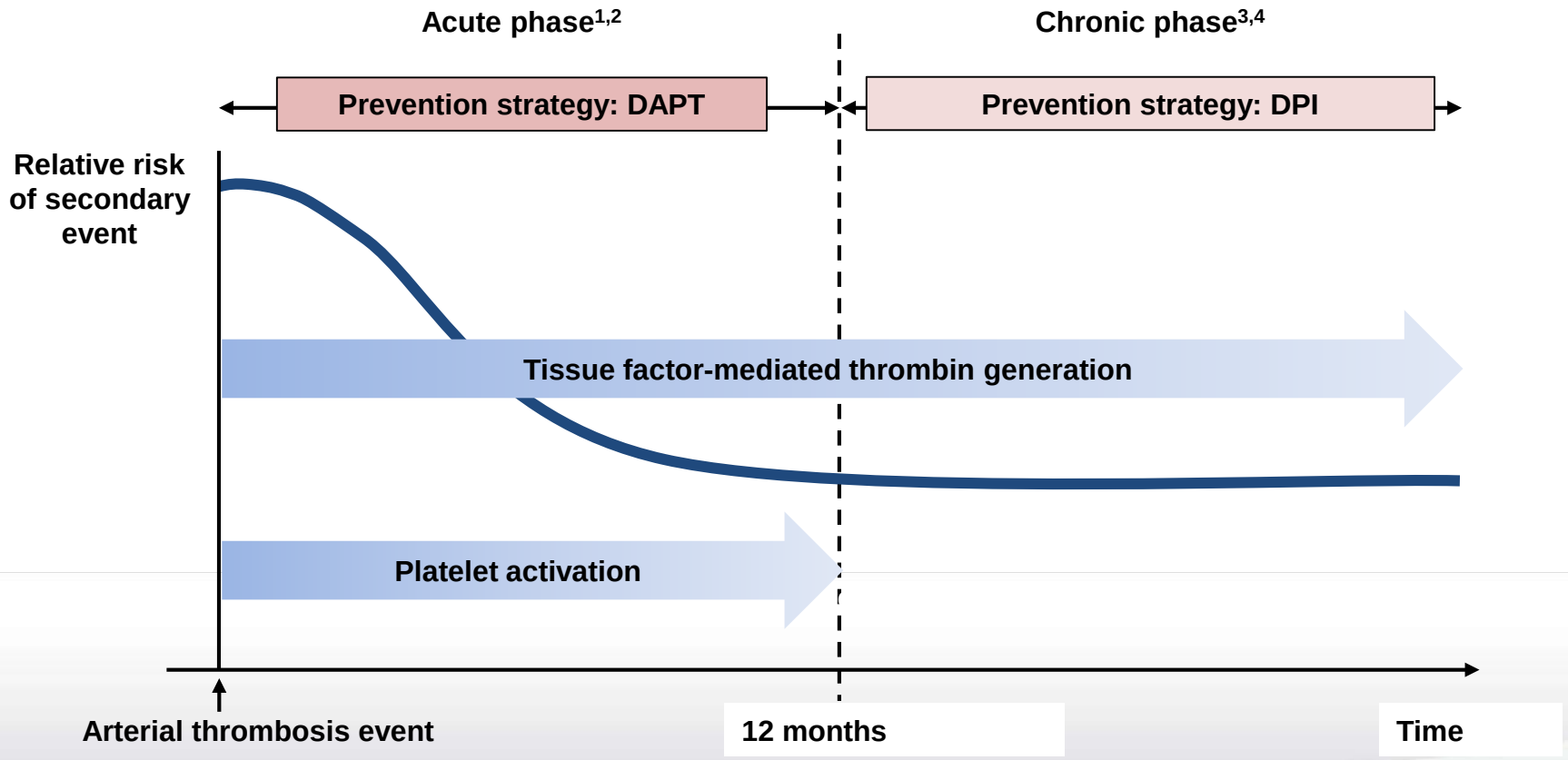


Atherothrombosis: Platelets, coagulation and vessels



European Heart Journal: Acute Cardiovascular Care 1(1):60-74 · April 2012

Thrombin generation persists beyond the acute phase into the chronic phase



1. Franchi F, Angiolillo DJ. Nat Rev Cardiol 2015;12:30–47; 2. Roffi M et al. Eur Heart J 2016;37:267–315; 3. Cohen M, Iyer D. Cardiovasc Ther 2014;32:224–232;
4. Eikelboom JW et al. N Engl J Med 2017;377(14):1319–1330.

WARFARIN
(1948)

HEPARIN
(1916)

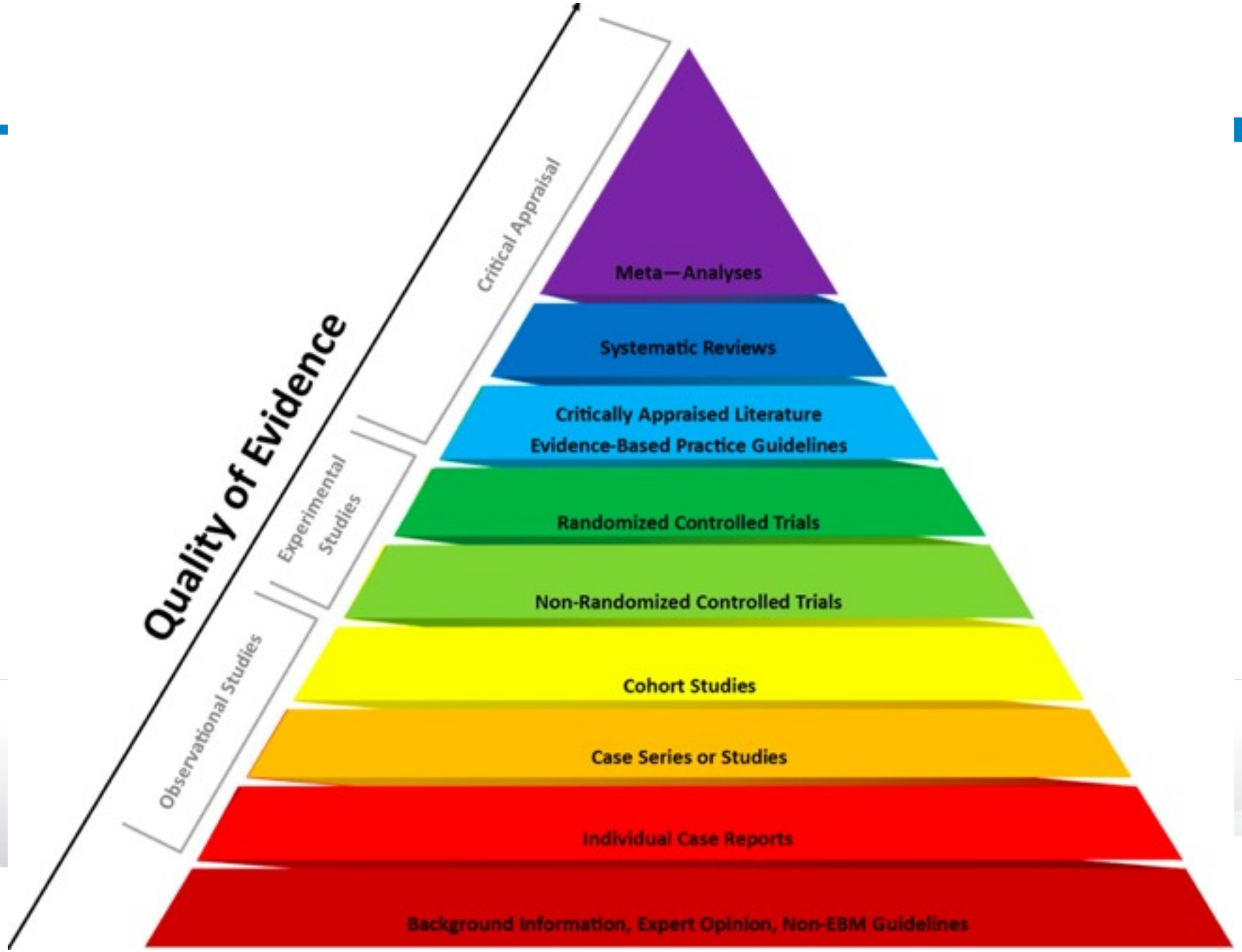
ASPIRIN
(1897)

Anti-platelets 2020

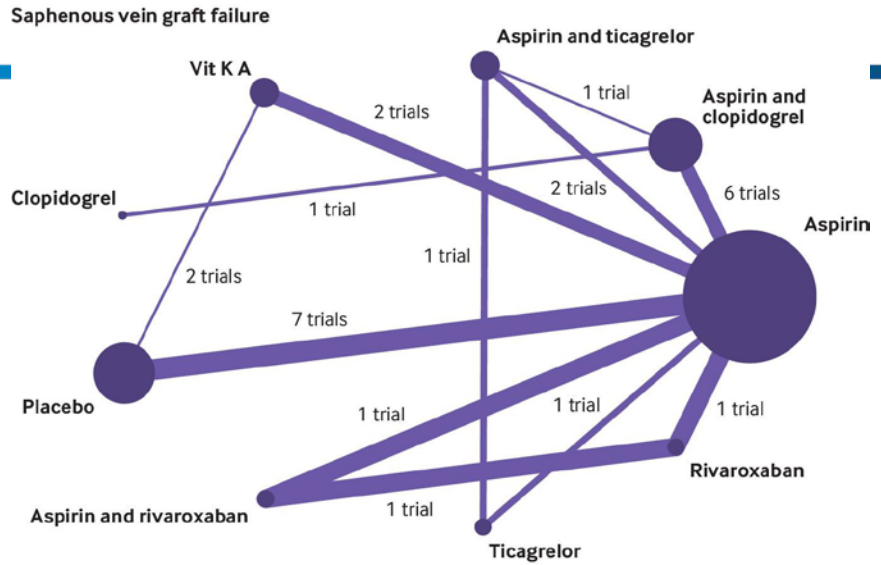
- **Irreversible cyclooxygenase inhibitors**
  - Aspirin
  - Triflusal (Disgren)
- **Adenosine diphosphate (ADP) receptor inhibitors**
  - Cangrelor (Kengreal)
  - Clopidogrel (Plavix)
  - Prasugrel (Effient)
  - Ticagrelor (Brilinta)
  - Ticlopidine (Ticlid)
- **Phosphodiesterase inhibitors**
  - Cilostazol (Pletaal)
- **Protease-activated receptor-1 (PAR-1) antagonists**
  - Vorapaxar (Zontivity)
- **Glycoprotein IIB/IIIA inhibitors** (intravenous use only)
  - Abciximab (ReoPro)
  - Eptifibatide (Integrilin)
  - Tirofiban (Aggrastat)
- **Adenosine reuptake inhibitors**
  - Dipyridamole (Persantine)
- **Thromboxane inhibitors**
  - Terutroban

Anti-coagulants 2020

- **Coumarins (vitamin K antagonists)**
  - Warfarin (Coumadin) – Acenocoumarol – Phenprocoumon – Atromentin – Phenindione
- **Heparin and derivative substances**
  - Heparin – Unfractionated heparin (UFH) – Low molecular weight heparin (LMWH)
  - Ultra-low-molecular weight heparin (ULMWH)
- **Synthetic pentasaccharide inhibitors of factor Xa**
  - Fondaparinux – Idraparinux – Idrabiotaparinux
- **Direct thrombin inhibitors**
  - Bivalent Drugs
    - Hirudin – Lepirudin – Bivalirudin
  - Monovalent Drugs
    - Argatroban – Dabigatran
- **Directly acting oral anticoagulants/NOACs**
  - Direct factor IIa inhibitors
    - Dabigatran
  - Direct factor Xa inhibitors
    - Rivaroxaban – Apixaban – Edoxaban – Betrixaban
    - Darexaban – Letaxaban – Eribaxaban

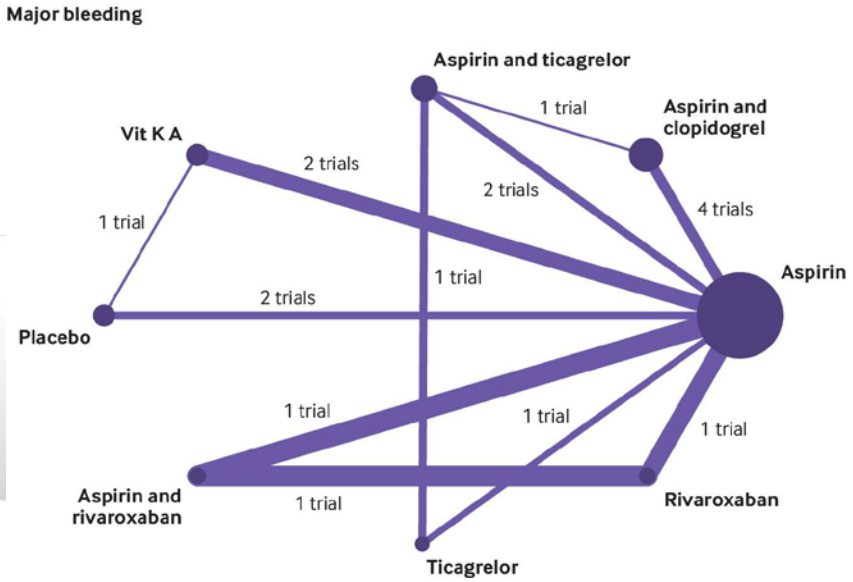

Quality of Evidence
Critical Appraisal
Experimental Studies
Observational Studies
Meta—Analyses
Systematic Reviews
Critically Appraised Literature
Evidence-Based Practice Guidelines
Randomized Controlled Trials
Non-Randomized Controlled Trials
Cohort Studies
Case Series or Studies
Individual Case Reports
Background Information, Expert Opinion, Non-EBM Guidelines

Network of treatment comparisons for saphenous vein graft failure (primary efficacy outcome) and major bleeding (primary safety outcome).



Saphenous vein graft failure

Placebo	0.64 (0.19 to 2.16)	**0.56 (0.42 to 0.76)**	**0.56 (0.37 to 0.86)**	**0.45 (0.26 to 0.79)**	**0.48 (0.30 to 0.77)**	**0.28 (0.16 to 0.48)**	**0.60 (0.38 to 0.98)**	**0.34 (0.21 to 0.54)**
	Clopidogrel	0.88 (0.27 to 2.84)	0.88 (0.26 to 2.98)	0.70 (0.20 to 2.47)	0.75 (0.22 to 2.55)	0.44 (0.13 to 1.52)	0.93 (0.27 to 3.16)	0.52 (0.17 to 1.60)
		Aspirin	1.00 (0.71 to 1.41)	0.80 (0.49 to 1.29)	0.85 (0.59 to 1.23)	**0.50 (0.31 to 0.79)**	1.06 (0.75 to 1.50)	**0.60 (0.42 to 0.86)**
			Vitamin K antagonists	0.80 (0.44 to 1.44)	0.85 (0.51 to 1.41)	**0.50 (0.28 to 0.88)**	1.06 (0.65 to 1.73)	**0.60 (0.36 to 0.98)**
				Ticagrelor	1.07 (0.58 to 1.95)	0.62 (0.37 to 1.05)	1.33 (0.73 to 2.40)	0.75 (0.42 to 1.35)
					Rivaroxaban	0.58 (0.32 to 1.05)	1.25 (0.87 to 1.78)	0.70 (0.42 to 1.18)
						Aspirin + Ticagrelor	**2.13 (1.20 to 3.85)**	1.20 (0.69 to 2.09)
							Aspirin + Rivaroxaban	**0.56 (0.34 to 0.93)**
								Aspirin + Clopidogrel

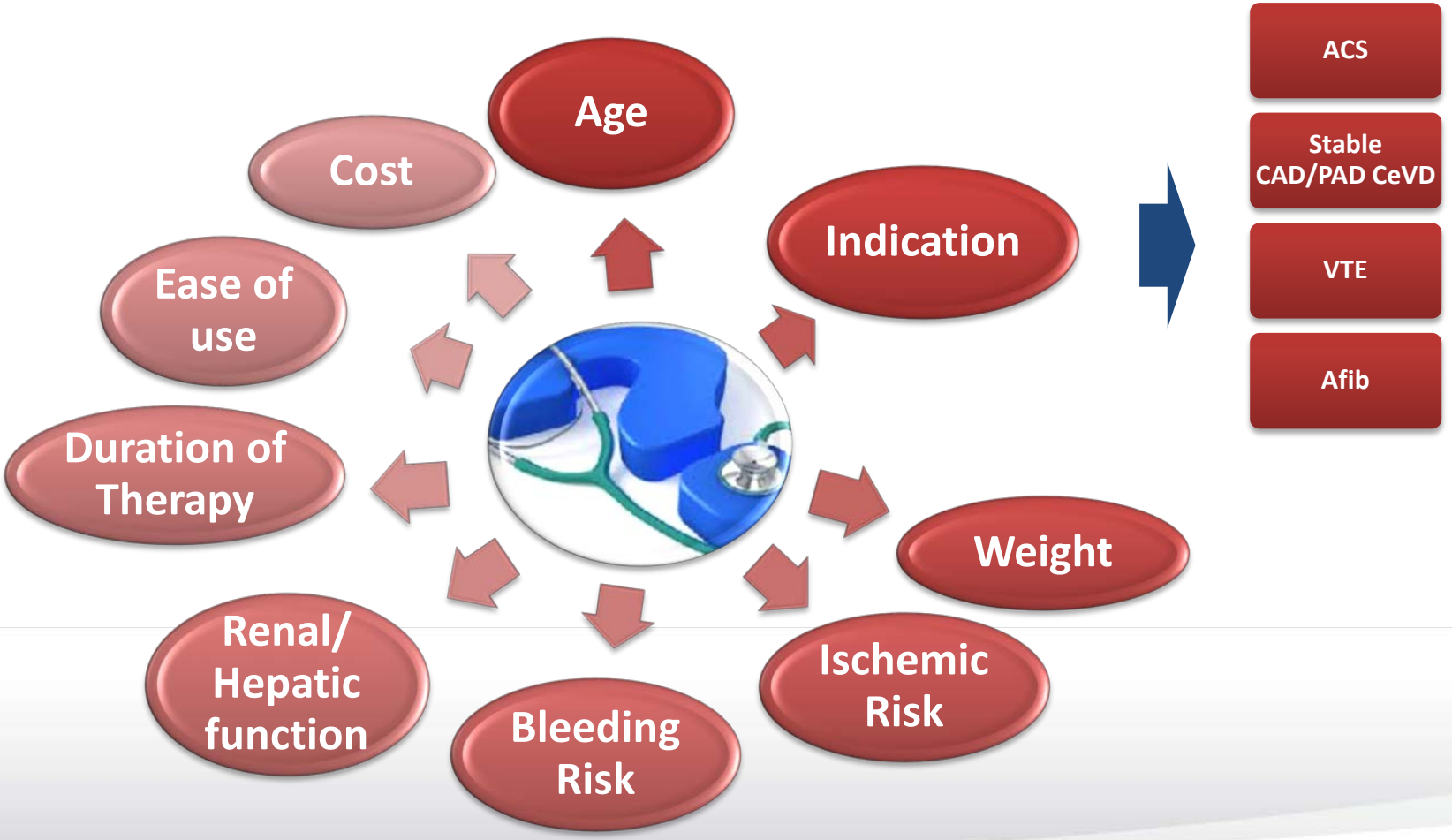


Major bleeding

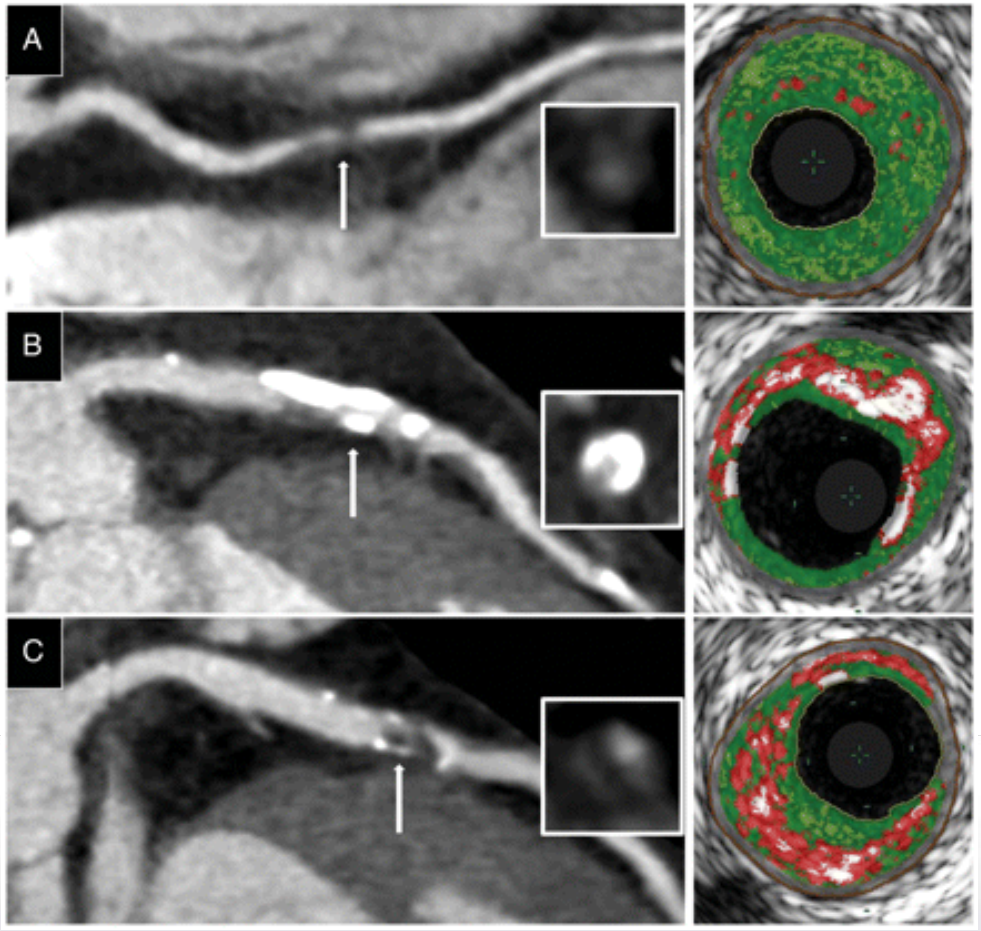
Placebo	2.98 (0.31 to 28.2)	5.31 (0.56 to 50.2)	4.86 (0.20 to 119)	4.45 (0.42 to 47.0)	2.96 (0.28 to 31.8)	5.74 (0.31 to 106)	2.53 (0.21 to 30.0)
	Aspirin	1.78 (0.95 to 3.34)	1.63 (0.17 to 15.9)	1.50 (0.73 to 3.04)	0.99 (0.46 to 2.14)	1.93 (0.30 to 12.4)	0.85 (0.30 to 2.37)
		Vitamin K antagonists	0.91 (0.09 to 9.69)	0.84 (0.32 to 2.16)	0.56 (0.21 to 1.50)	1.08 (0.15 to 7.69)	0.48 (0.14 to 1.59)
			Ticagrelor	0.92 (0.08 to 9.93)	0.61 (0.06 to 6.71)	1.18 (0.24 to 5.91)	0.52 (0.05 to 5.39)
				Rivaroxaban	0.66 (0.33 to 1.33)	1.29 (0.18 to 9.42)	0.57 (0.16 to 1.98)
					Aspirin + Rivaroxaban	1.94 (0.26 to 14.5)	0.86 (0.24 to 3.08)
						Aspirin + Ticagrelor	0.44 (0.07 to 2.97)
							Aspirin + Clopidogrel

Karla Solo et al. BMJ 2019;367:bmj.l5476

Challenge of selecting the anti-thrombotic strategy



Coronary plaques



Non-calcified

Calcified plaque

Partially calcified plaque

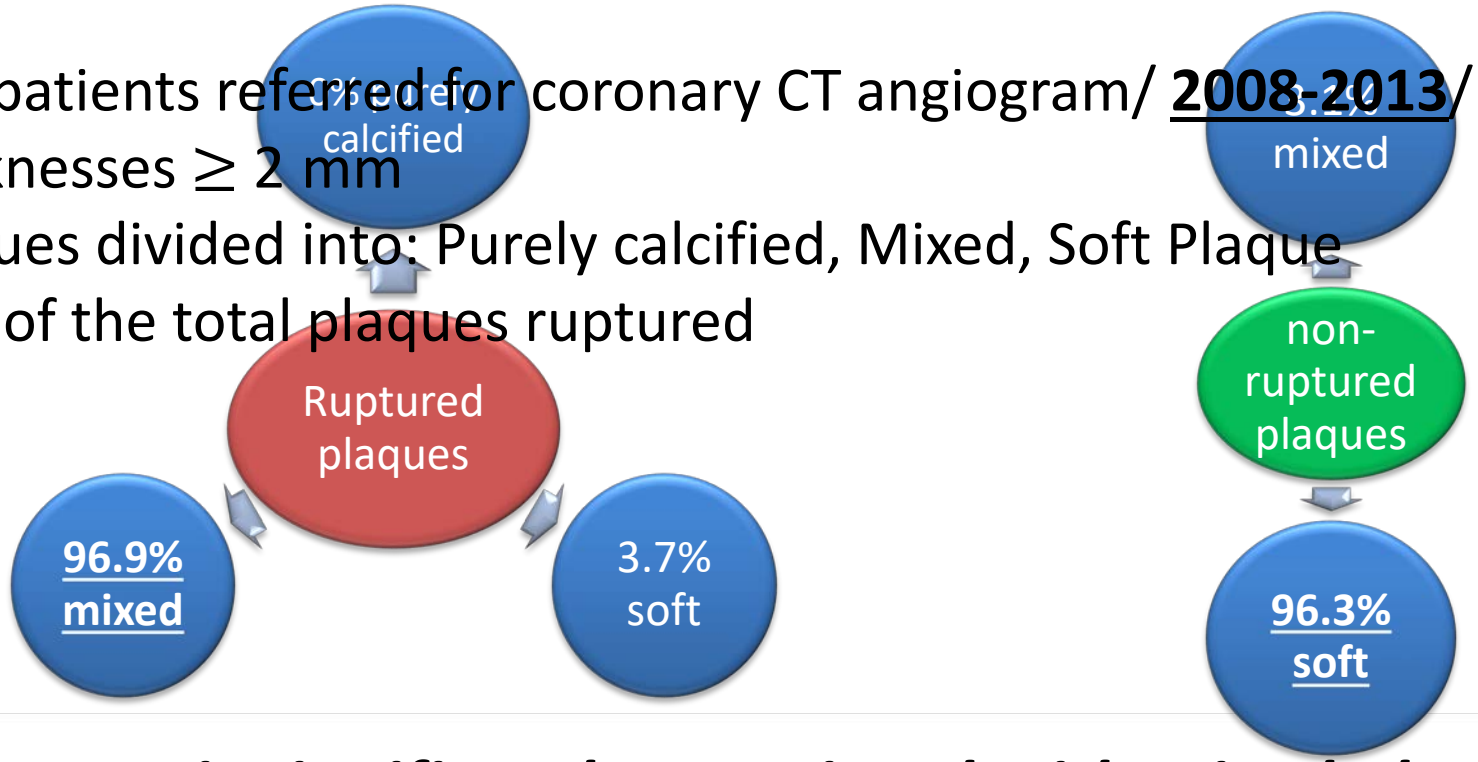
Eur H J CV Img 2012;13:205-218.

Which plaques rupture?

500 patients referred for coronary CT angiogram/ **2008-2013**/ plaque thicknesses ≥ 2 mm

Plaques divided into: Purely calcified, Mixed, Soft Plaque

52% of the total plaques ruptured

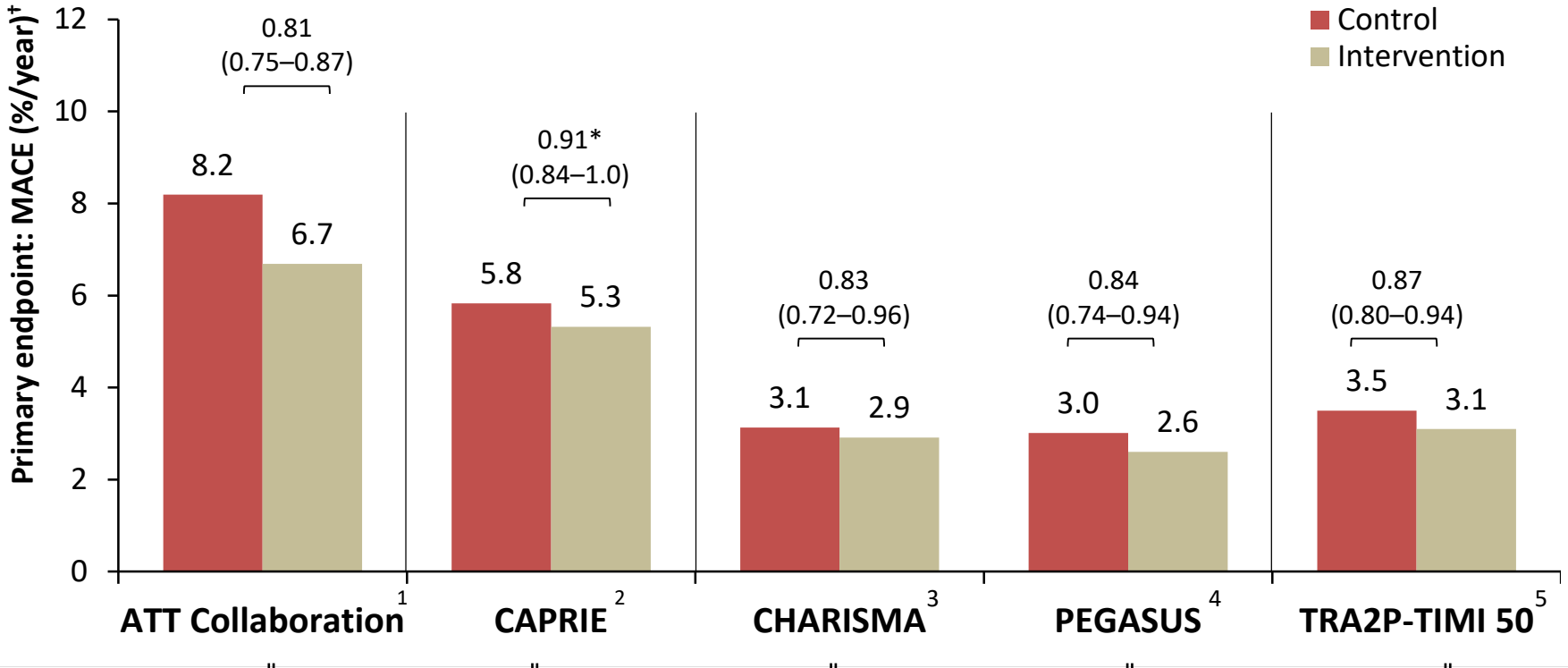


Plaque rupture is significantly associated with mixed plaques containing soft and calcific areas rather than purely soft plaques.

Ramanan et al. Medicine 2015;12:115-122.

ANTI-THROMBOTICS LANDMARK TRIALS IN CHRONIC STABLE PATIENTS

Patients with chronic CAD or PAD remain at risk of vascular events despite currently available medical therapy



% Use of key therapies in intervention arm	ATT Collaboration 1	CAPRIE 2	CHARISMA 3	PEGASUS 4	TRA2P-TIMI 50 5
	Control ‖ Aspirin	Aspirin ‖ Clopidogrel	Placebo + Aspirin ‖ Clopidogrel + Aspirin	Placebo + Aspirin ‖ Ticagrelor + Aspirin	Vorapaxar + Placebo + Aspirin ± Thienopyridine
ACEI/ARB	*Meta-analysis of 16 trials*	*NR*	*up to 85.3*	*80.4*	*73.5*
Statin/ lipid-lowering		*NR*	*77.1–89.3*	*92.4*	*91.0*

*Estimate calculated from reported relative risk reductions; †Estimate calculated from reported overall % across 28 months of median follow up for CHARISMA; and from reported 3-year Kaplan-Meier event rates for PEGASUS & TRA2P-TIMI50.

1. ATT Collaboration. *Lancet* 2009;373:1849–1860; 2. CAPRIE Steering Committee. *Lancet* 1996;348:1329–1339; 3. Bhatt DL *et al. J Am Coll Cardiol* 2007;49:1982–1988; 4. Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800; 5. Morrow DA *et al. N Engl J Med* 2012;366:1404–1413.

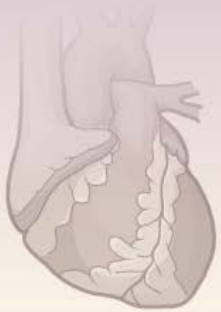
THEMIS trial

The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor in Stable Coronary Disease and Diabetes

MULTICENTER, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

19,220
Patients with type 2 diabetes and stable coronary artery disease



	Ticagrelor 60 mg twice daily + low-dose aspirin 75–150 mg once daily		Placebo + low-dose aspirin 75–150 mg once daily
	N=9619		N=9601
Cardiovascular death, MI, or stroke (median follow-up, 39.9 mo)	7.7% (N=736)	P=0.04	8.5% (N=818)
TIMI major bleeding	2.2% (N=206)	P<0.001	1.0% (N=100)

Ticagrelor + aspirin decreased ischemic cardiovascular events but increased major bleeding

P.G. Steg et al. 10.1056/NEJMoa1908077

Available antithrombotic treatments provide only *modest reductions* in CV events risk

DAPT versus aspirin: 13–17% relative risk reduction in CV events

RRR with current treatments[1–4]

- Clopidogrel superior to aspirin in symptomatic CV disease (8.7% RRR)[3]
- Clopidogrel + aspirin superior to aspirin alone in symptomatic CV disease (17% RRR)[4]
- Ticagrelor + aspirin superior to aspirin alone post-MI (15–16% RRR)[5]
- Vorapaxar combined with clopidogrel + aspirin superior to clopidogrel + aspirin (13% RRR)[6]

Issues with current treatments[1–4]

- Clopidogrel, ticagrelor and vorapaxar increased bleeding in combination with aspirin but

variable stroke benefit
and
no mortality benefit

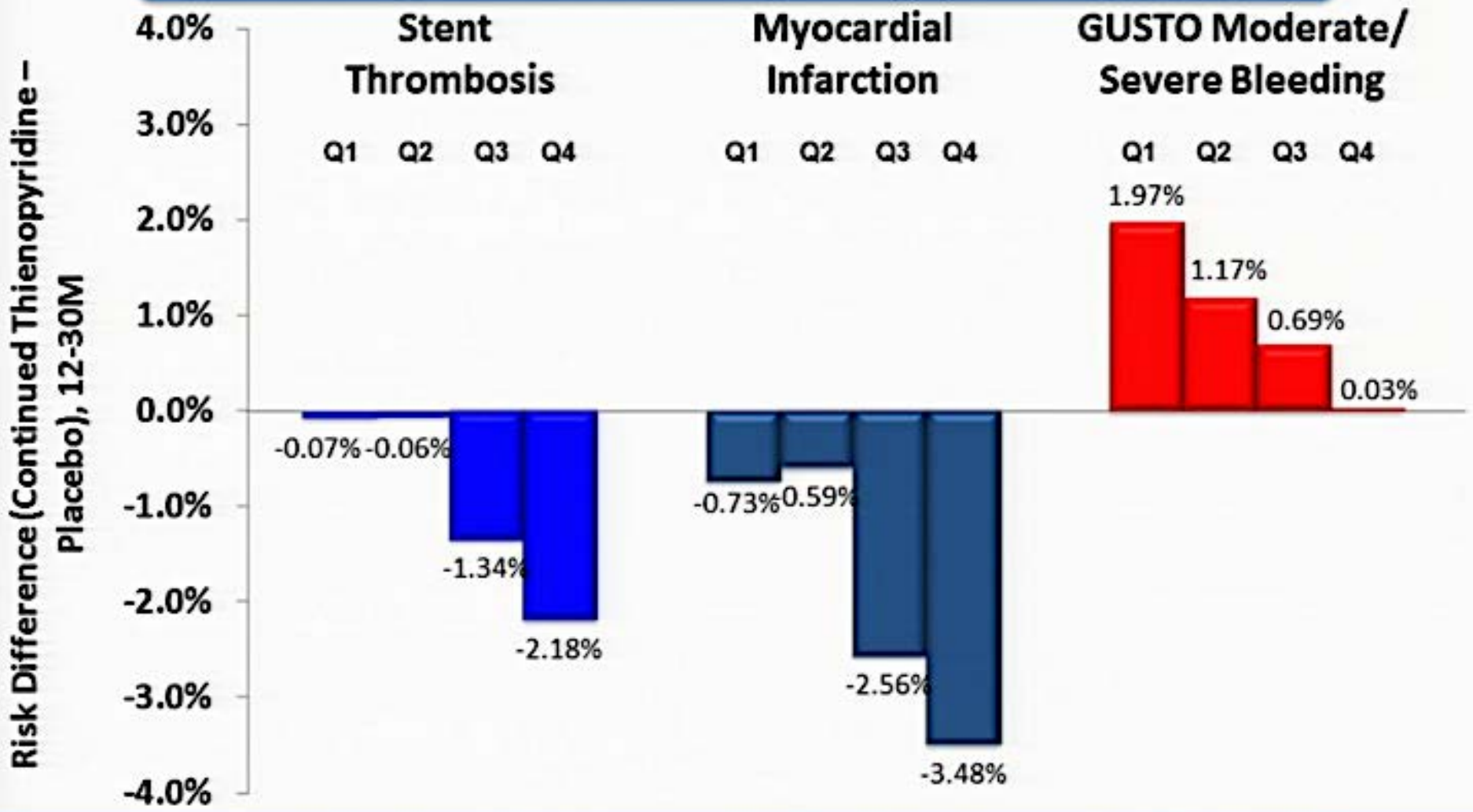
DAPT, dual antiplatelet therapy; RRR, relative risk reduction.

1. CAPRIE Steering Committee, *Lancet* 1996;348:1329–1339; 2. Bhatt DL *et al*, *J Am Coll Cardiol* 2007;49:1982–1988;
3. Bonaca MP *et al*, *N Engl J Med* 2015;372:1791–1800; 4 Morrow DA e*t al*, *N Engl J Med* 2012; 366:1404–1413.

Continued Thienopyridine vs. Placebo Treatment Effect by DAPT Score Quartile (N = 11,648)

DAPT STUDY

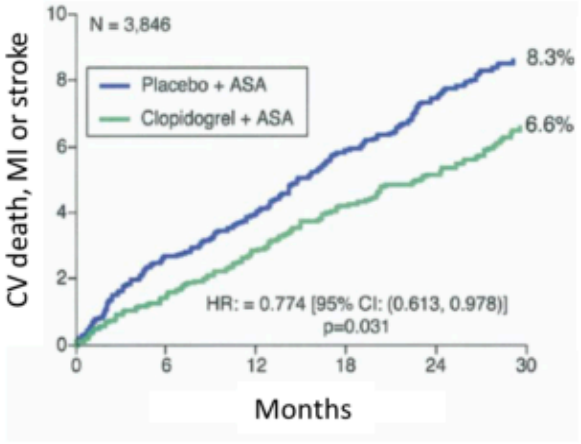
Q1 = DAPT Score -2 to 0
Q2 = DAPT Score 1
Q3 = DAPT Score 2
Q4 = DAPT Score > 2



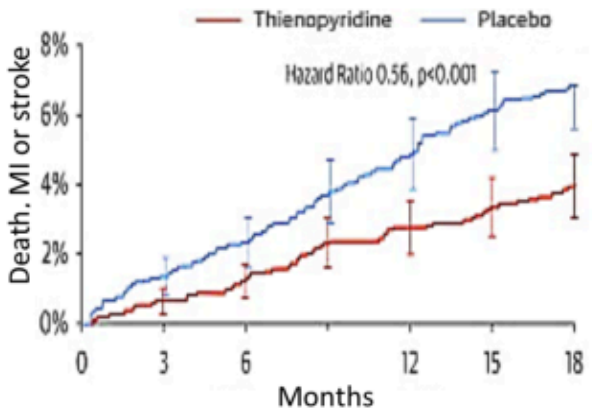
The paradox of DAPT duration

DAPT > 1 year after myocardial infarction

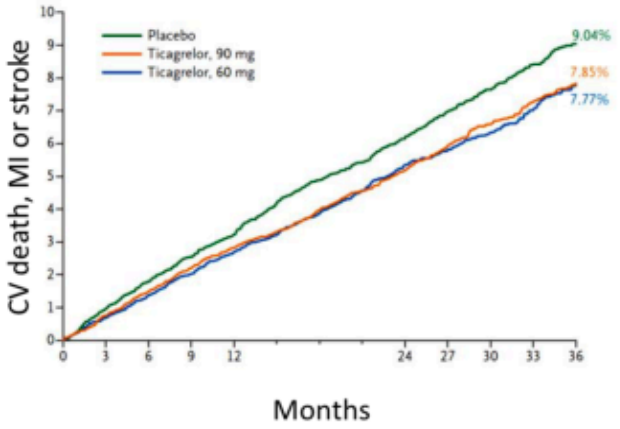
CHARISMA (prior MI subgroup)



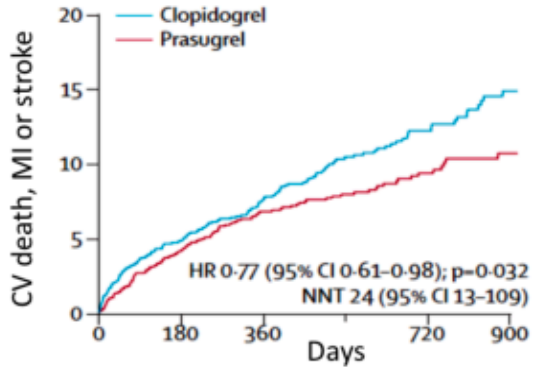
DAPT (prior MI subgroup)



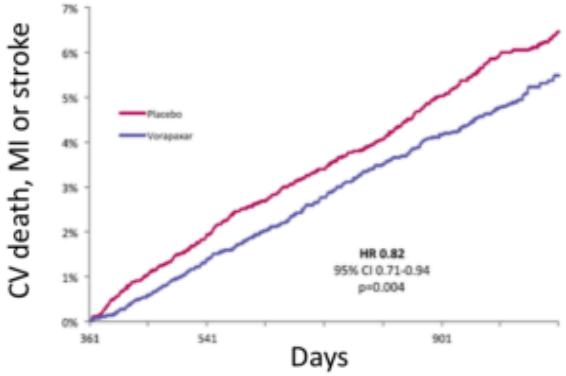
PEGASUS-TIMI 54 trial (prior MI)



TRILOGY (prior angiogram subgroup)



TRA-2P (prior MI subgroup)



Montalescot G and Sabatine M. EHJ 2015

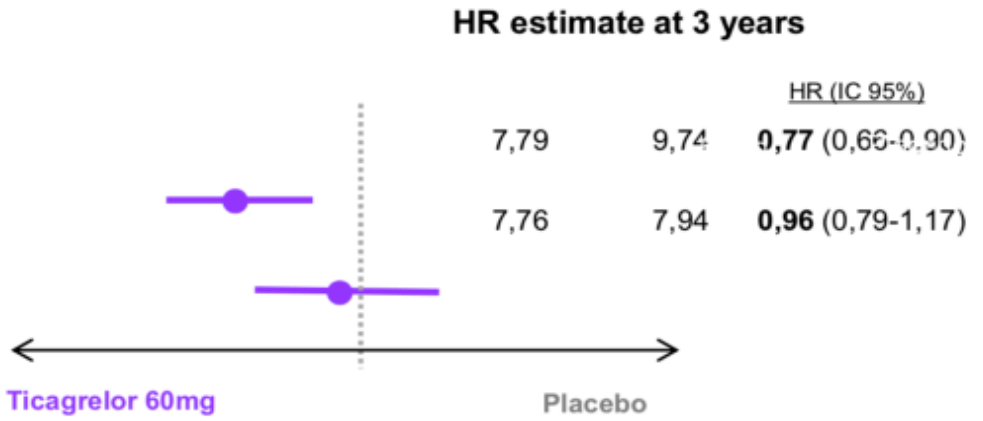
Time since last MI: PEGASUS subgroup analysis

Delay since last MI

- CV death, MI, Stroke

< 2 years (Recent)

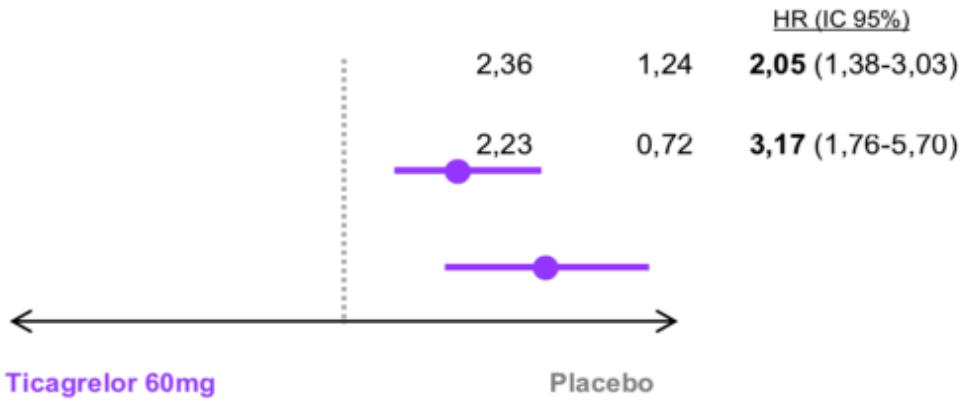
≥ 2 years



- TIMI major bleeding

< 2 years (Recent)

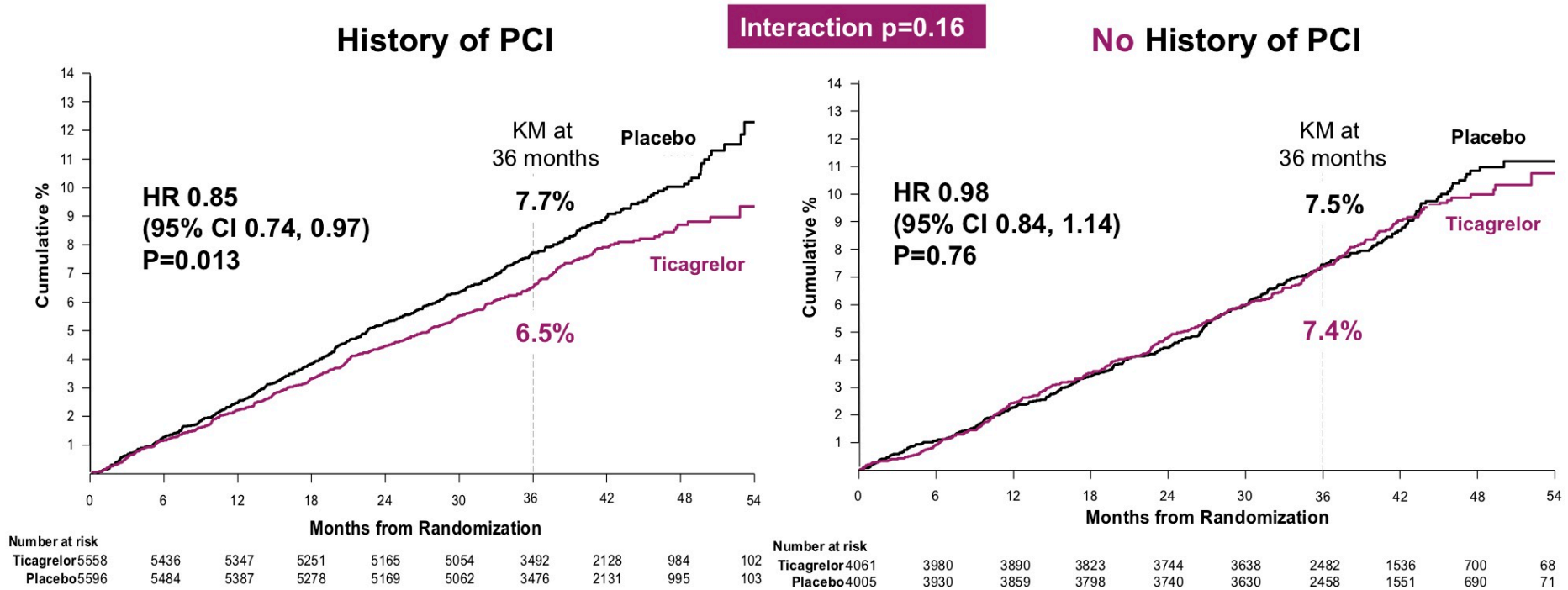
≥ 2 years



Bonaca M, *et al*. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800. Supplementary Appendix.

Primary Efficacy Endpoint

CV death/MI/stroke (ITT)

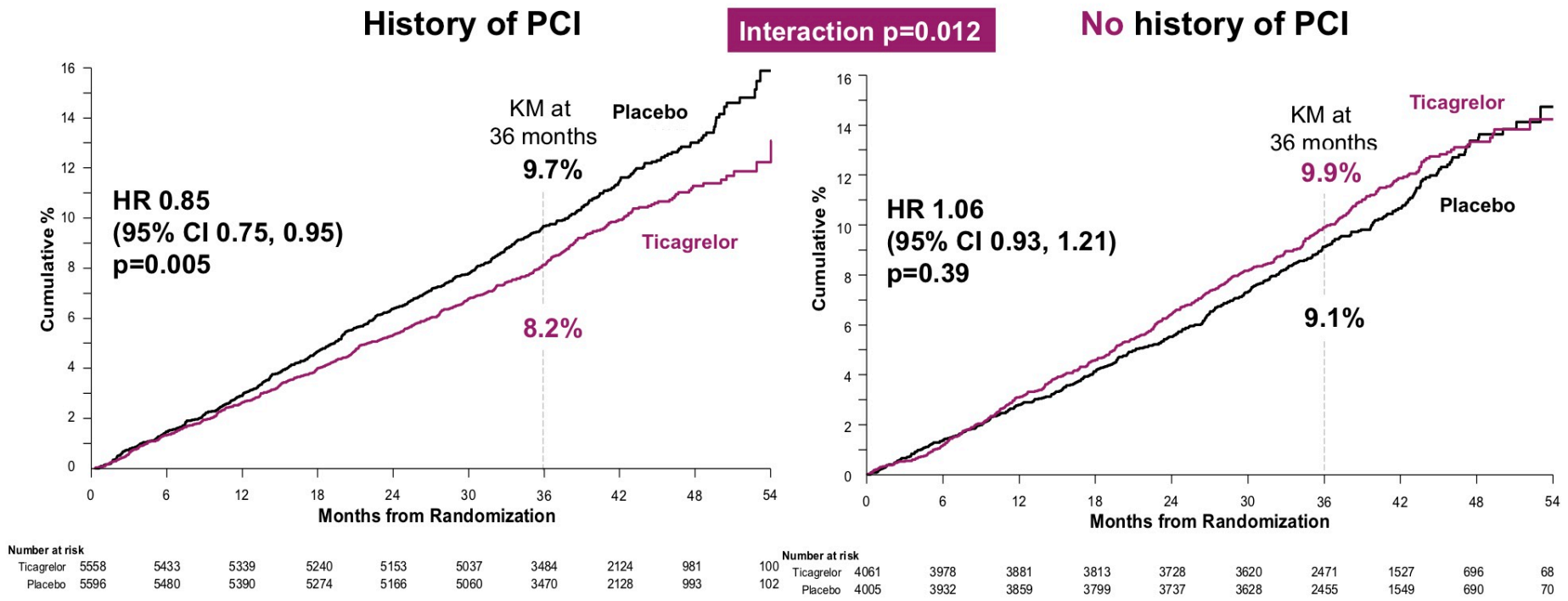


CI=Confidence Interval; CV=cardiovascular; HR=hazard ratio; KM=Kaplan-Meier; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention

Bhatt DL, Steg PG, et al. *Lancet* 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31887-2.

Net Clinical Benefit

All cause death, MI, stroke, fatal bleed, or ICH (ITT)*



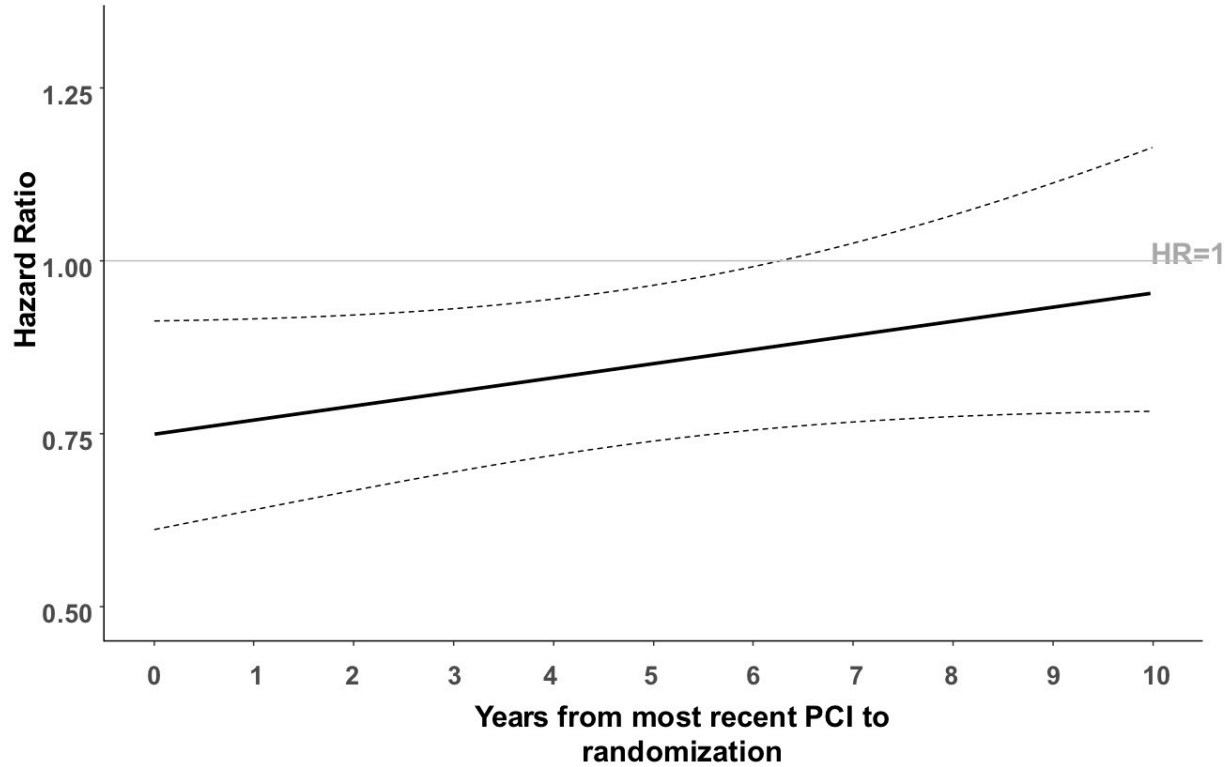
*Prespecified definition of net clinical benefit.

CI=confidence interval; HR=hazard ratio; ICH=intracranial hemorrhage; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention

Bhatt DL, Steg PG, et al. *Lancet* 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31887-2.

Benefit of Ticagrelor vs Placebo

as a Function of Time between PCI and randomization



Dotted lines signify 95% confidence interval; HR=hazard ratio; PCI=percutaneous coronary intervention

Bhatt DL, Steg PG, et al. *Lancet* 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31887-2.

Saphenous vein graft failure after coronary artery bypass graft surgery

- **Up to 30-40% in the first year**

Cooper GJ, Underwood MJ, Deverall PB. Arterial and venous conduits for coronary artery bypass. A current review. Eur J Cardiothorac Surg1996;10:129-40. doi:10.1016/S1010-7940(96)80135-7 pmid:8664004

Alexander JH, Hafley G, Harrington RA, et al.,

PREVENT IV Investigators. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. JAMA2005;294:2446-54. doi:10.1001/jama.294.19.2446 pmid:16287955

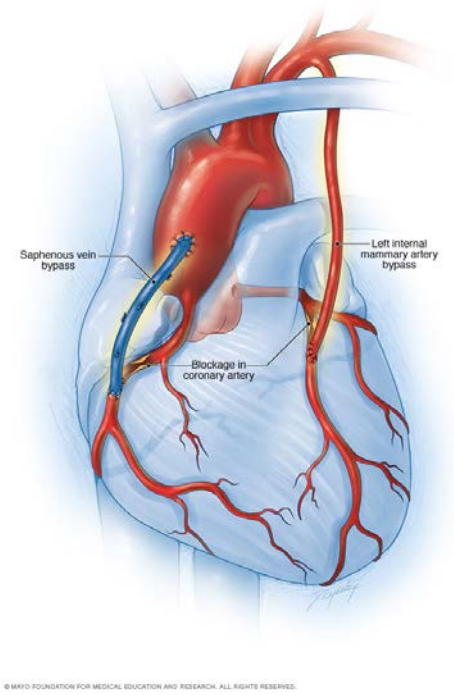
- **Up to 70% beyond 10 years**

Cooper GJ, Underwood MJ, Deverall PB. Arterial and venous conduits for coronary artery bypass. A current review. Eur J Cardiothorac Surg1996;10:129-40.

Campeau L. Failure of saphenous vein coronary artery bypass grafts and its potential prevention. Curr Opin Cardiol1987;2:990-5

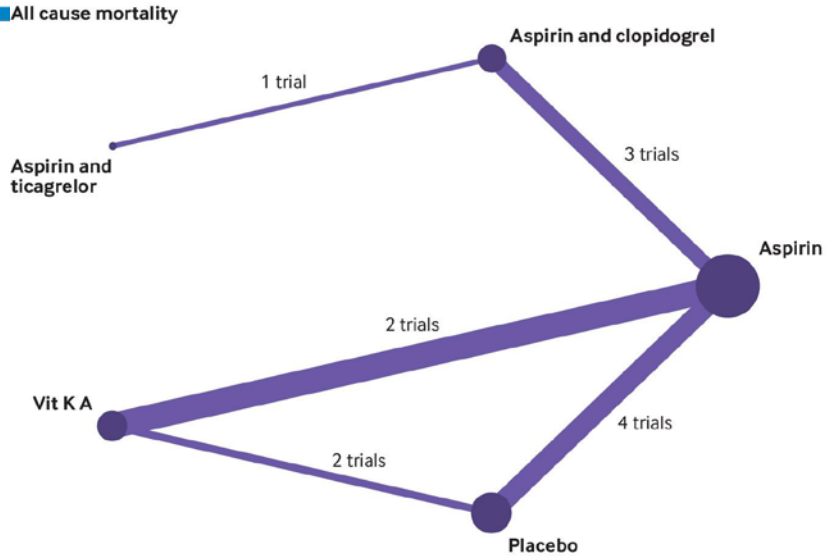
Goldman S, Zadina K, Moritz T, et al., VA Cooperative Study Group #207/297/364. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. J Am Coll Cardiol2004;44:2149-56.

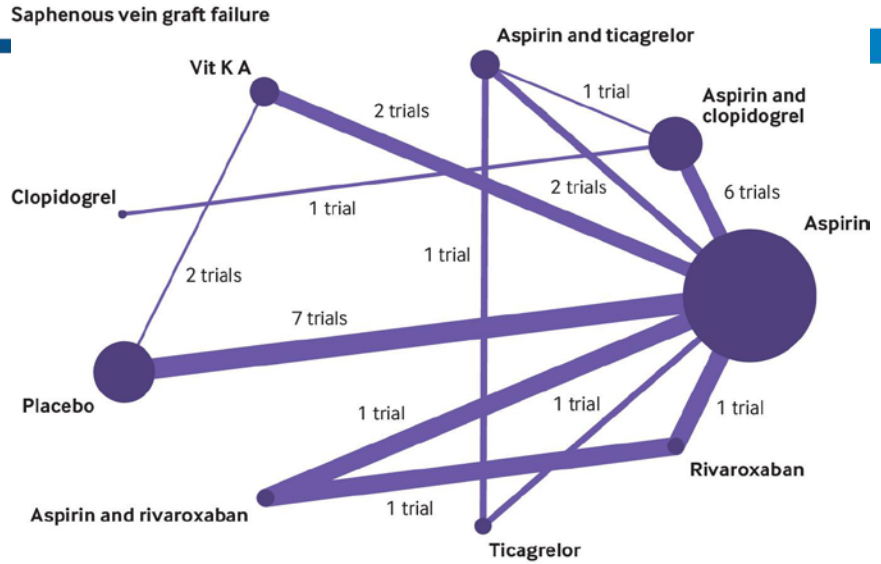
deVries MR, Simons KH, Jukema JW, Braun J, Quax PH Vein graft failure: from pathophysiology to clinical outcomes. Nat Rev Cardiol2016;13:45170.

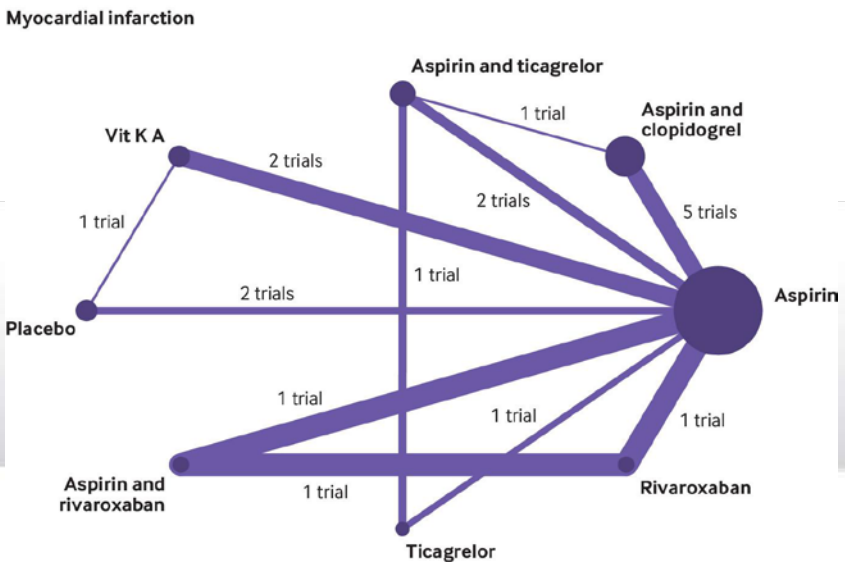


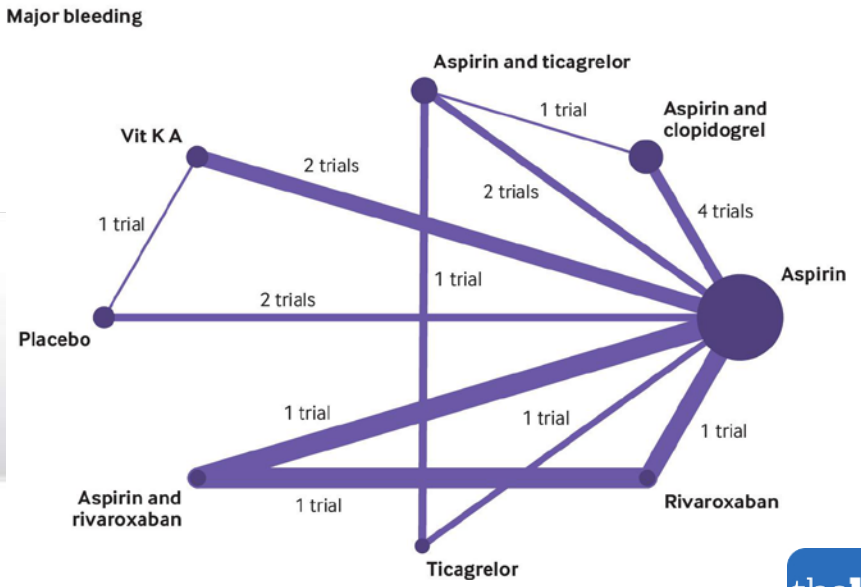
Network of treatment comparisons for secondary outcomes all cause mortality and myocardial infarction.

Network of treatment comparisons for saphenous vein graft failure (primary efficacy outcome) and major bleeding (primary safety outcome).









Karla Solo et al. BMJ 2019;367:bmj.l5476.

Network meta-analysis and certainty of evidence for saphenous vein graft failure (primary efficacy outcome) and major bleeding (primary safety outcome).

Saphenous vein graft failure

Placebo	0.64 (0.19 to 2.16)	**0.56 (0.42 to 0.76)**	**0.56 (0.37 to 0.86)**	**0.45 (0.26 to 0.79)**	**0.48 (0.30 to 0.77)**	**0.28 (0.16 to 0.48)**	**0.60 (0.38 to 0.98)**	**0.34 (0.21 to 0.54)**
	Clopidogrel	0.88 (0.27 to 2.84)	0.88 (0.26 to 2.98)	0.70 (0.20 to 2.47)	0.75 (0.22 to 2.55)	0.44 (0.13 to 1.52)	0.93 (0.27 to 3.16)	0.52 (0.17 to 1.60)
		Aspirin	1.00 (0.71 to 1.41)	0.80 (0.49 to 1.29)	0.85 (0.59 to 1.23)	**0.50 (0.31 to 0.79)**	1.06 (0.75 to 1.50)	**0.60 (0.42 to 0.86)**
			Vitamin K antagonists	0.80 (0.44 to 1.44)	0.85 (0.51 to 1.41)	**0.50 (0.28 to 0.88)**	1.06 (0.65 to 1.73)	**0.60 (0.36 to 0.98)**
				Ticagrelor	1.07 (0.58 to 1.95)	0.62 (0.37 to 1.05)	1.33 (0.73 to 2.40)	0.75 (0.42 to 1.35)
					Rivaroxaban	0.58 (0.32 to 1.05)	1.25 (0.87 to 1.78)	0.70 (0.42 to 1.18)
						Aspirin + Ticagrelor	**2.13 (1.20 to 3.85)**	1.20 (0.69 to 2.09)
							Aspirin + Rivaroxaban	**0.56 (0.34 to 0.93)**
								Aspirin + Clopidogrel

Major bleeding

Placebo	2.98 (0.31 to 28.2)	5.31 (0.56 to 50.2)	4.86 (0.20 to 119)	4.45 (0.42 to 47.0)	2.96 (0.28 to 31.8)	5.74 (0.31 to 106)	2.53 (0.21 to 30.0)
	Aspirin	1.78 (0.95 to 3.34)	1.63 (0.17 to 15.9)	1.50 (0.73 to 3.04)	0.99 (0.46 to 2.14)	1.93 (0.30 to 12.4)	0.85 (0.30 to 2.37)
		Vitamin K antagonists	0.91 (0.09 to 9.69)	0.84 (0.32 to 2.16)	0.56 (0.21 to 1.50)	1.08 (0.15 to 7.69)	0.48 (0.14 to 1.59)
			Ticagrelor	0.92 (0.08 to 9.93)	0.61 (0.06 to 6.71)	1.18 (0.24 to 5.91)	0.52 (0.05 to 5.39)
				Rivaroxaban	0.66 (0.33 to 1.33)	1.29 (0.18 to 9.42)	0.57 (0.16 to 1.98)
					Aspirin + Rivaroxaban	1.94 (0.26 to 14.5)	0.86 (0.24 to 3.08)
						Aspirin + Ticagrelor	0.44 (0.07 to 2.97)
							Aspirin + Clopidogrel

Network meta-analysis and certainty of evidence for secondary outcomes all cause mortality and myocardial infarction.

All cause mortality

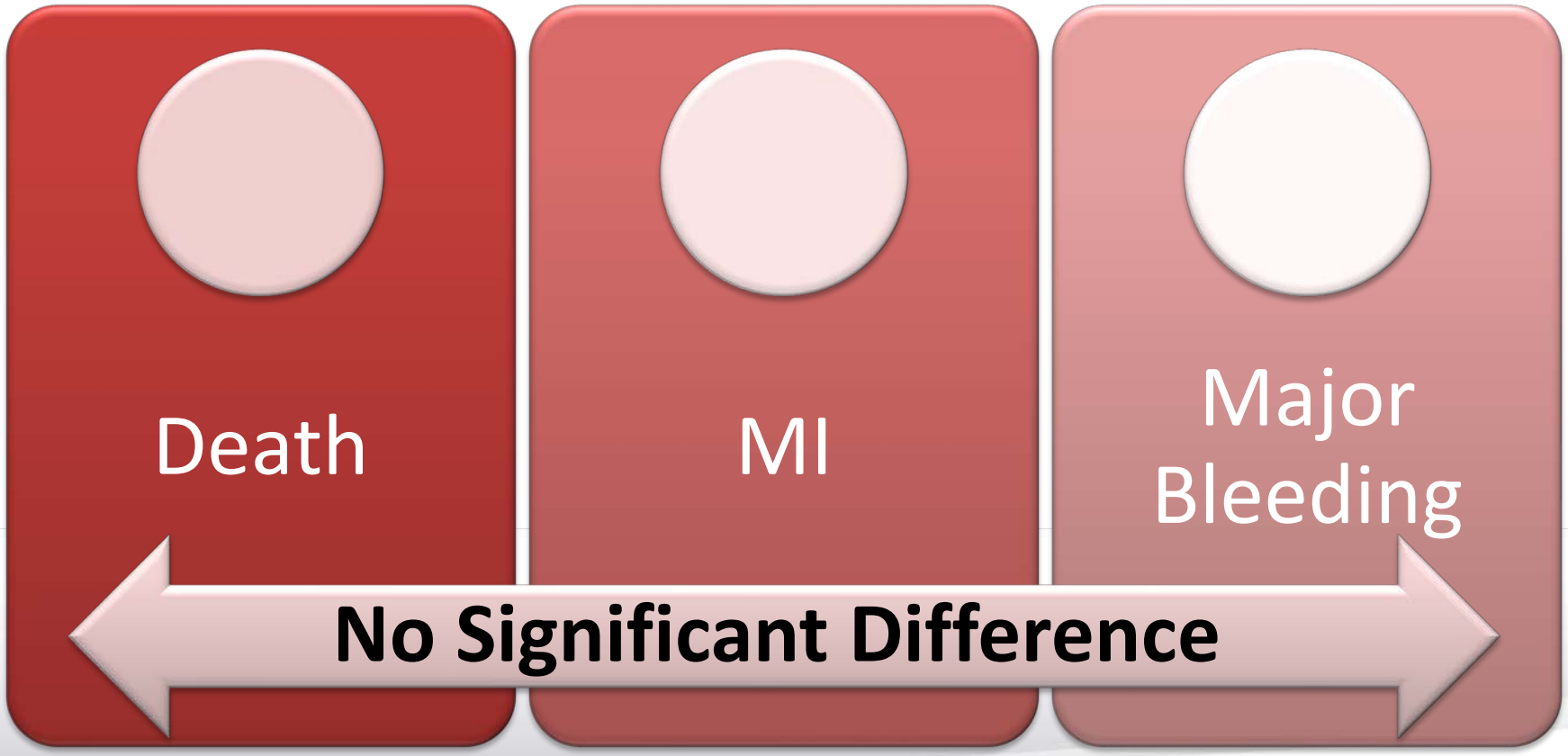
Placebo	1.77 (0.52 to 5.99)	1.04 (0.23 to 4.72)	1.24 (0.01 to 114)	1.24 (0.13 to 11.5)
	Aspirin	0.59 (0.19 to 1.87)	0.70 (0.01 to 54.3)	0.70 (0.11 to 4.50)
		Vitamin K antagonists	1.19 (0.01 to 107)	1.19 (0.13 to 10.6)
			Aspirin + Ticagrelor	1.00 (0.02 to 51.1)
				Aspirin + Clopidogrel

Myocardial infarction

Placebo	0.49 (0.11 to 2.11)	0.45 (0.10 to 2.00)	0.33 (0.03 to 3.28)	0.47 (0.08 to 2.84)	0.34 (0.04 to 2.84)	0.25 (0.04 to 1.73)	0.34 (0.06 to 2.05)
	Aspirin	0.92 (0.52 to 1.63)	0.68 (0.12 to 3.97)	0.96 (0.33 to 2.75)	0.70 (0.15 to 3.22)	0.52 (0.15 to 1.80)	0.71 (0.26 to 1.96)
		Vitamin K antagonists	0.74 (0.12 to 4.71)	1.04 (0.31 to 3.45)	0.76 (0.15 to 3.88)	0.57 (0.15 to 2.21)	0.77 (0.24 to 2.46)
			Ticagrelor	1.40 (0.18 to 10.93)	1.03 (0.16 to 6.80)	0.77 (0.09 to 6.58)	1.04 (0.14 to 7.68)
				Rivaroxaban	0.74 (0.12 to 4.68)	0.55 (0.16 to 1.88)	0.74 (0.17 to 3.20)
					Aspirin + Ticagrelor	0.74 (0.10 to 5.27)	1.00 (0.18 to 5.74)
						Aspirin + Rivaroxaban	1.35 (0.27 to 6.70)
							Aspirin + Clopidogrel

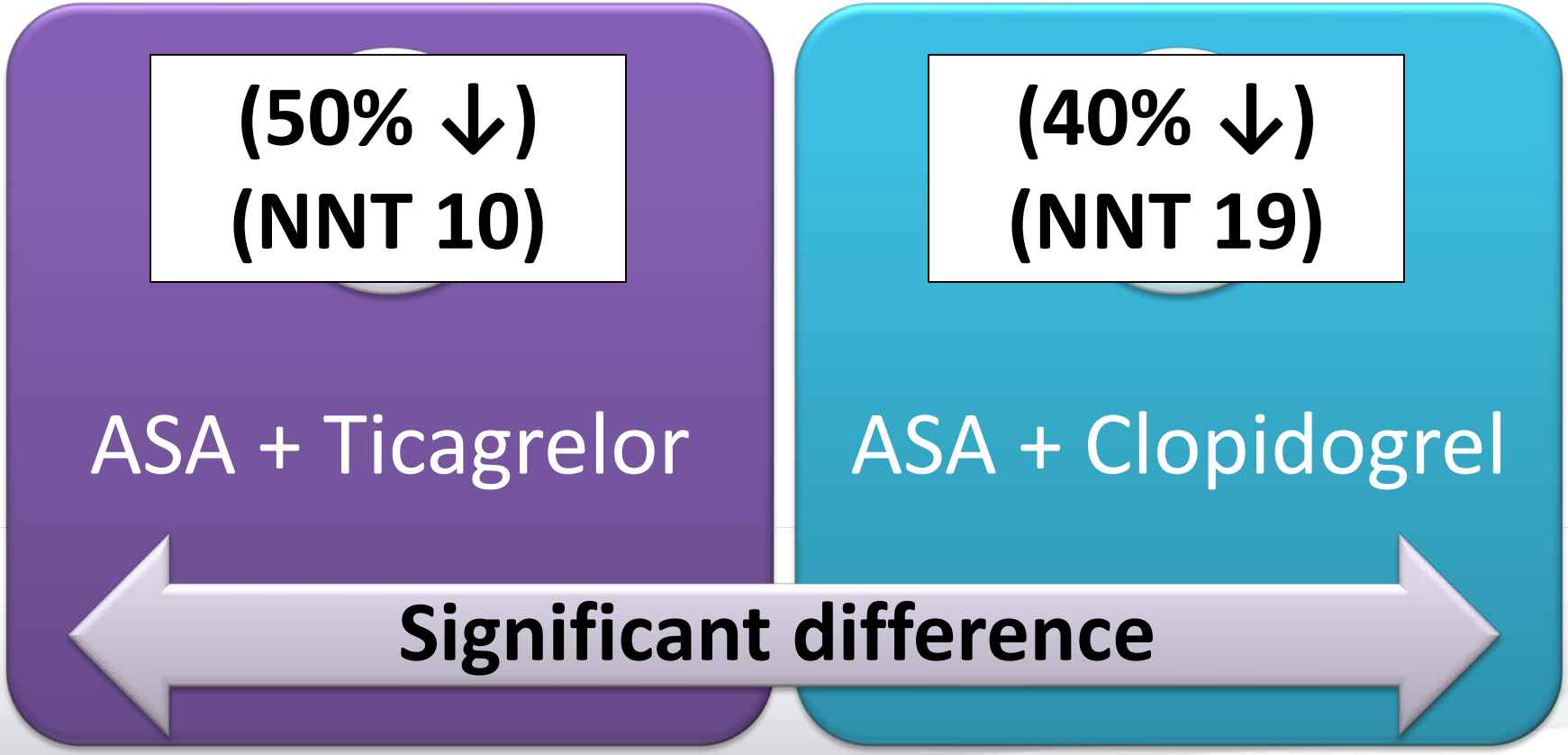
Karla Solo et al. BMJ 2019;367:bmj.l5476.

Different antithrombotic therapies post CABG



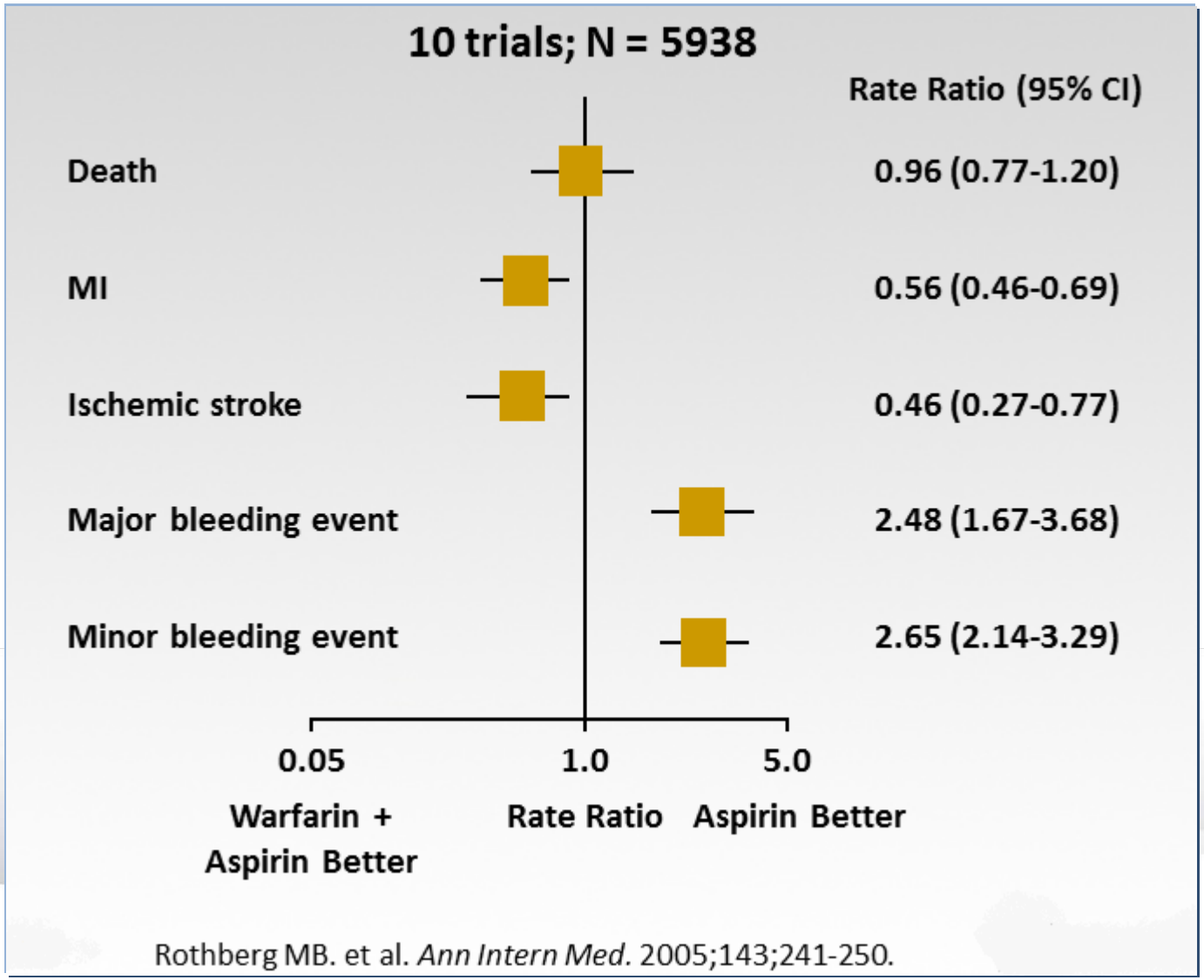
Different antithrombotic therapies post CABG

Graft failure



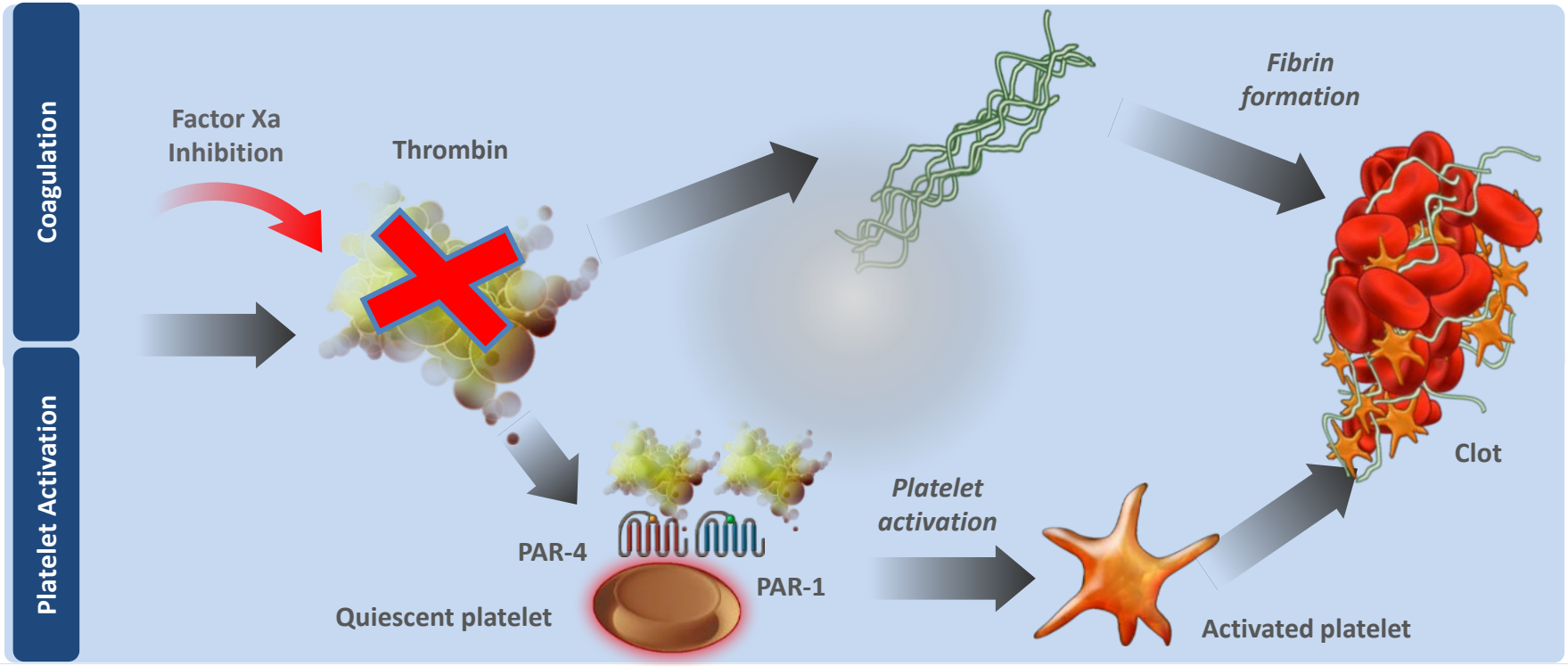
ANTIPLATELET PLUS ANTICOAGULANT COMBINATION

Secondary prevention with warfarin and aspirin vs aspirin alone after ACS



Rothberg MB. et al. *Ann Intern Med.* 2005;143;241-250.

Dual pathway inhibition targets both platelet activation and persistent thrombin generation in chronic CAD and PAD

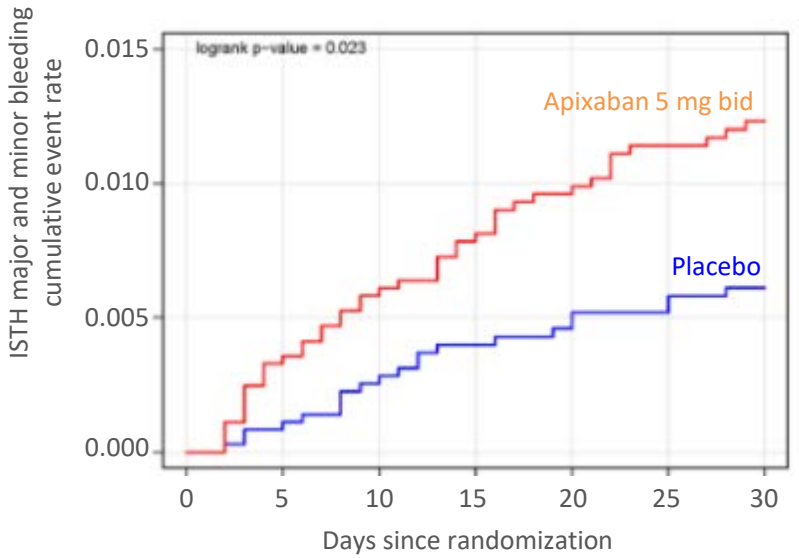


Factor Xa inhibition affects not only fibrin formation, but also platelet activation

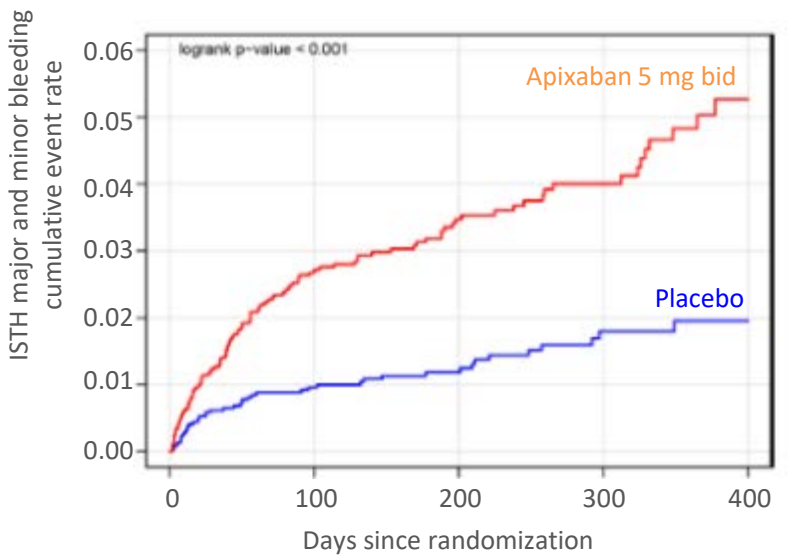
Adapted from Angiolillo DJ et al. Eur Heart J 2010;31:17–28.

APPRAISE-2: Apixaban increased risk of bleeding and was not associated with an efficacy benefit

ISTH major and minor bleeding increased in the short- and long-term in patients with ACS[1]



Number at risk							
Placebo	3642	3565	3452	3371	3293	3249	3183
Apixaban	3673	3591	3485	3401	3325	3257	3185



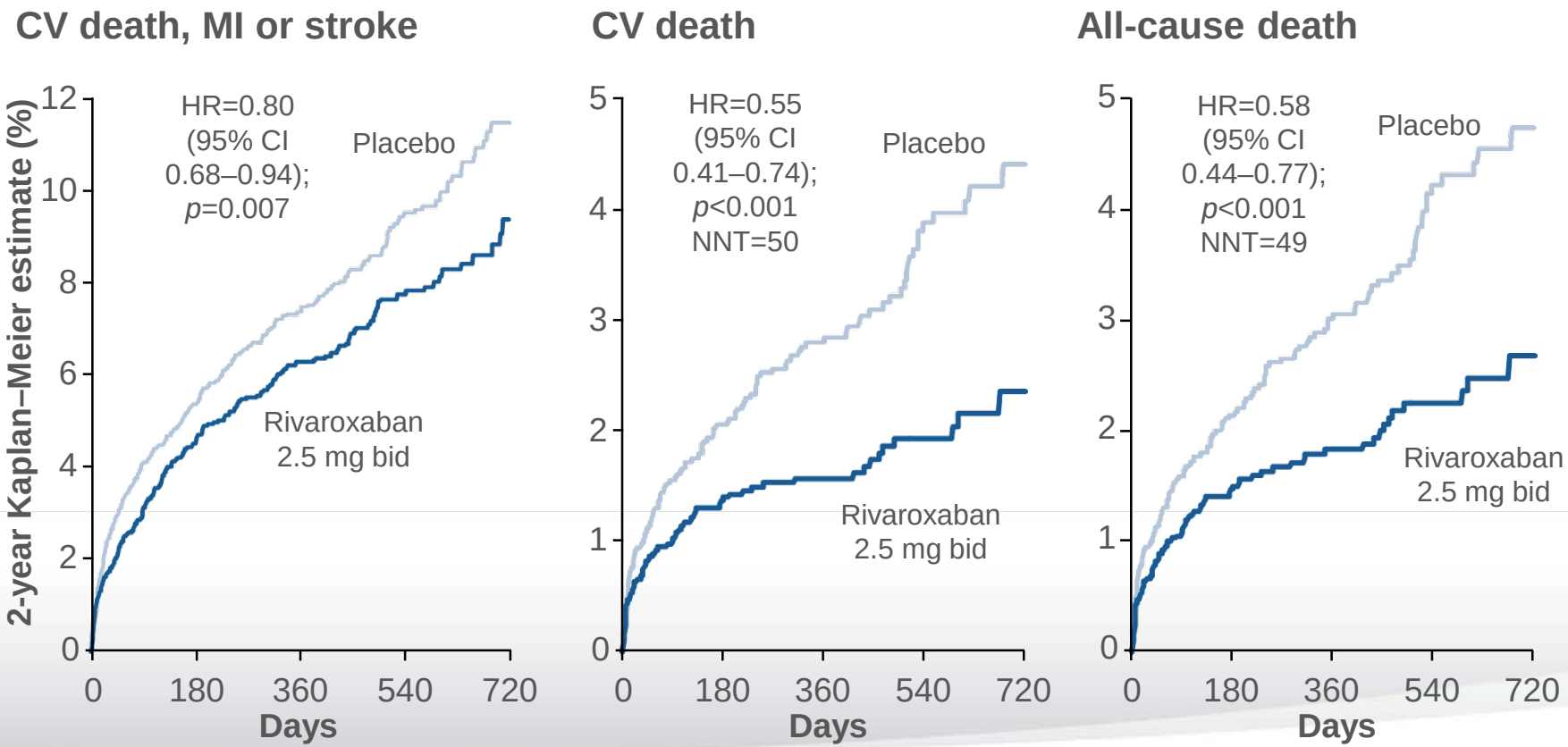
Number at risk					
Placebo	3642	2528	1668	907	333
Apixaban	3673	2442	1587	883	301

- No reduction in cardiovascular death, myocardial infarction or ischemic stroke was associated with apixaban 5 mg bid compared with placebo (HR=0.95; 95% CI 0.80–1.11)[2]

1. Khan R et al, Heart 2015;101:1475–1484; 2. Alexander JH et al, N Engl J Med 2011;365:699–708.

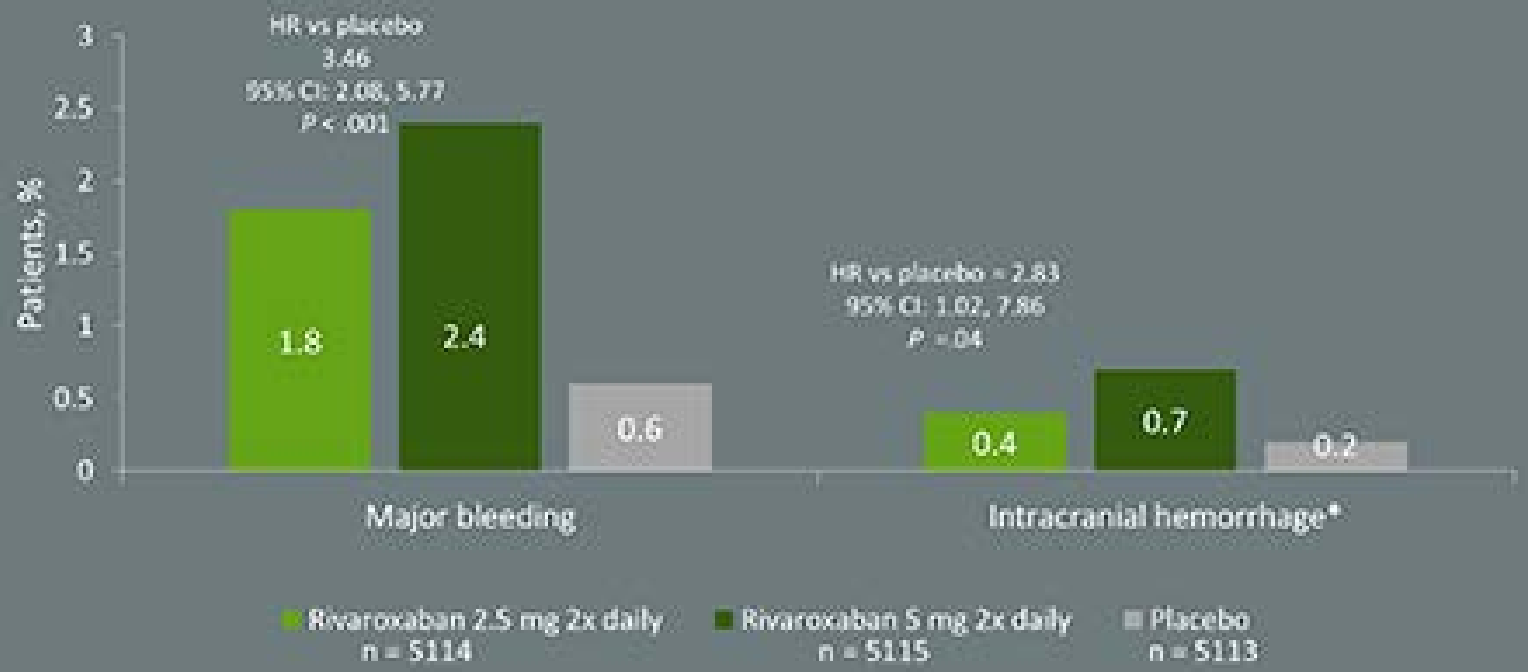
ATLAS ACS 2 TIMI 51: Rivaroxaban vascular dose reduced CV events and death in patients with ACS

Patients with elevated cardiac biomarkers and no prior stroke/transient ischemic attack



CI, confidence interval; HR, hazard ratio; NNT, number needed to treat.
Patients also received antiplatelet standard of care: ASA + thienopyridine (~93%) or ASA alone (~7%).
Mega JL et al, Eur Heart J 2014;35(Suppl.):992. Abstract P5518 (poster presentation).

ATLAS ACS 2–TIMI 51



*0.6% for the 2 rivaroxaban groups combined ($P = .009$ vs placebo).

Mega JL, et al. *N Engl J Med*. 2012;366:9-18.

Why study rivaroxaban in the chronic CAD and PAD setting: Current clinical evidence

- Rivaroxaban vascular dose has been shown to reduce the risk of atherothrombotic events, including death, in patients with ACS (ATLAS ACS 2 TIMI 51)[2]

- Rivaroxaban vascular dose 2.5 mg bid with single antiplatelet has an acceptable safety profile in patients with CAD (ATLAS ACS TIMI 46, ATLAS ACS 2 TIMI 51 and GEMINI ACS 1)[2-4]

2. Mega JL et al, N Engl J Med 2012;366:9–19; 3. Mega JL et al, Lancet 2009;374:29–38;
4. Ohman EM et al, Lancet 2017;389:1799–1808

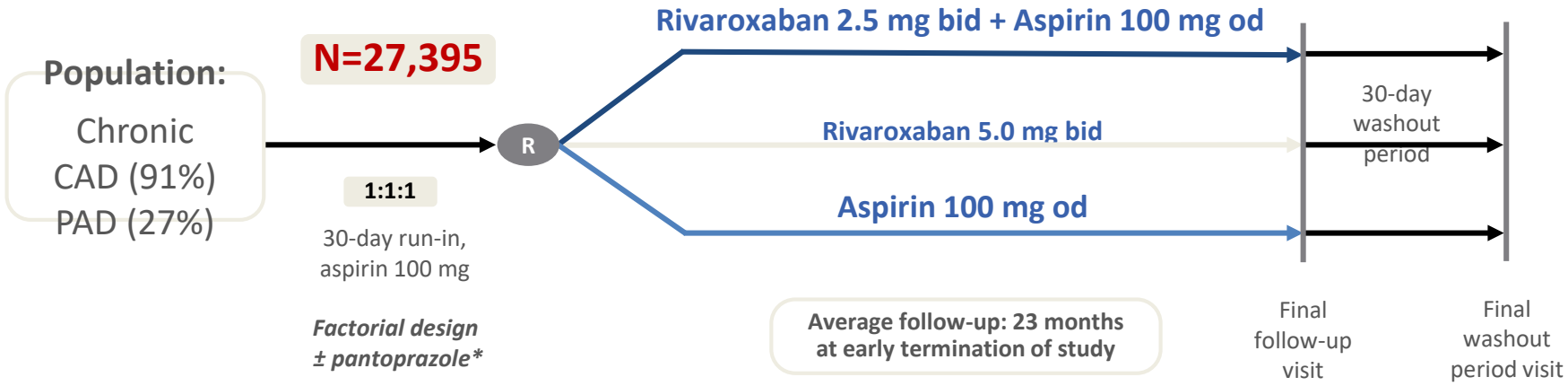
COMPASS trial

Cardiovascular outcomes for people using anticoagulation strategies

A dual pathway approach targeting chronic patients with CAD or PAD was investigated in COMPASS

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD

2,200 participants with a primary outcome event



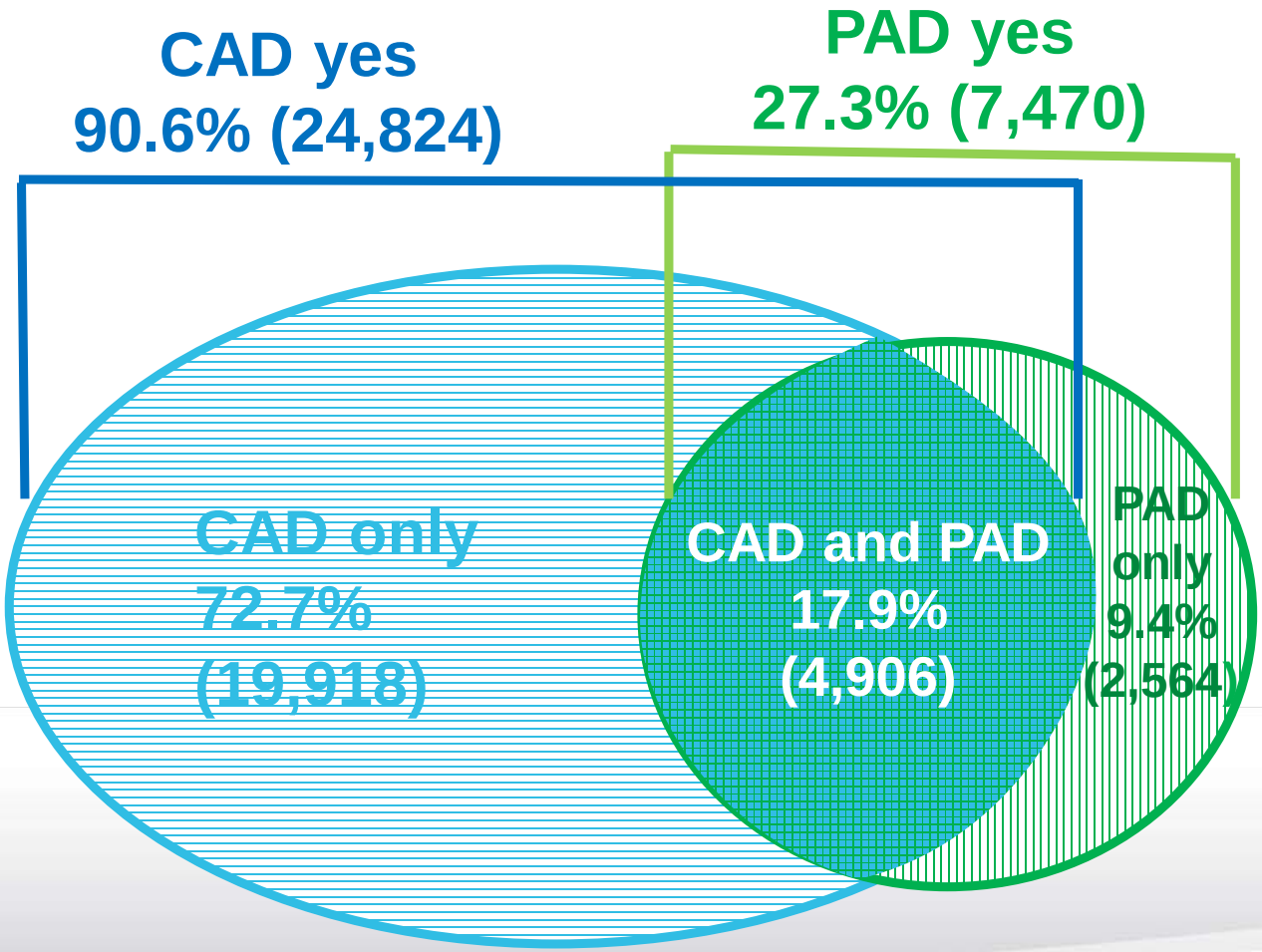
Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al. N Engl J Med* 2017;377(14):1319-30;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

COMPASS

CAD and PAD subgroups



Eikelboom JW, et al. N Engl J Med 2017; 377: 1319-1330.

Inclusion and exclusion criteria ensure that patients are chronic CAD and PAD patients

Key inclusion criteria*

- **PAD**
- **CAD with ≥1 of:**
  - Age ≥65 years
  - Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
    - Current smoker
    - Diabetes mellitus
    - Renal dysfunction (eGFR<60 ml/min)
    - Heart failure
    - Non-lacunar ischemic stroke ≥1 month ago

Key exclusion criteria‡

- Stroke ≤1 month or any haemorrhagic or lacunar stroke
- Severe HF with known ejection fraction <30% or NYHA class III or IV symptoms
- **Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy**
- eGFR <15 ml/min

#Including but not limited to; ‡any other exclusion criteria in conjunction with the local Product Information and any other contraindication listed in the local labelling for rivaroxaban or the comparator have to be considered.

www.clinicaltrials.gov/ct2/show/NCT01776424 [accessed 21 Mar 2017];
Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035.

COMPASS

COMPASS enrolled over 24,000 patients with advanced, chronic CAD

CAD definition	Number of patients (% of CAD population)[1]
All patients with CAD	24,824
Prior MI	17,028 (69%)
<1 year	1238 (5%)
1–<2 years	2341 (9%)
2–<5 years	**4893 (20%)**
≥5 years	**8520 (34%)**
Multivessel coronary disease*	15,469 (62%)
Prior PCI	14,862 (60%)
Prior CABG	7845 (32%)
Patients randomized immediately post-CABG	1448 (6%)

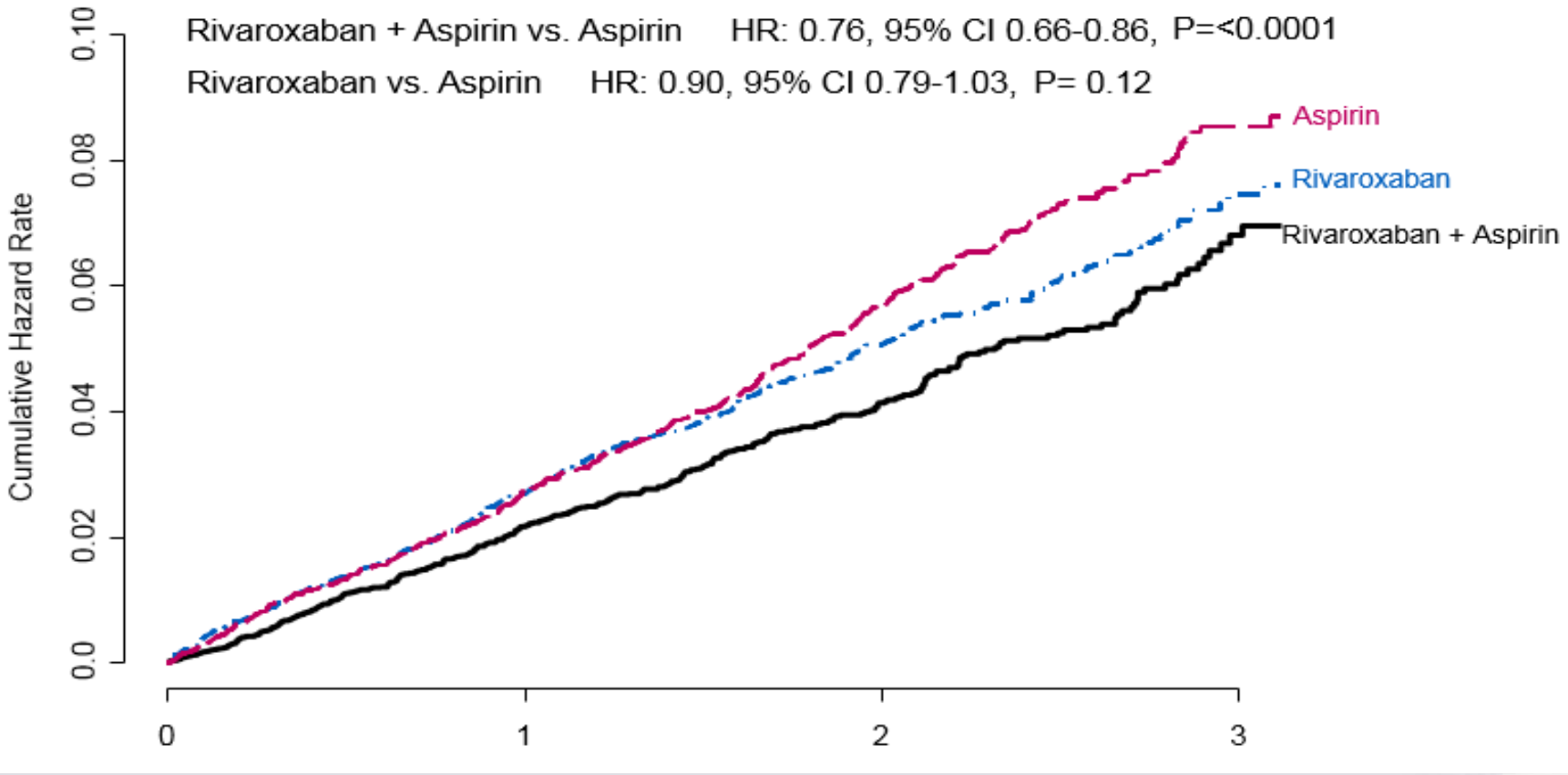
Half of all previous MIs occurred ≥5 years prior to enrolment in COMPASS[1]

*Refers to stenosis of ≥50% in 2 or more coronary arteries, confirmed using invasive coronary angiography, or non-invasive imaging or stress studies suggestive of significant ischemia in ≥2 coronary territories; or in 1 coronary territory if at least 1 other territory has been revascularized.[2]

1. Connolly SJ *et al*, *Lancet* 2018;391(10117):205-18; 2. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035.

COMPASS

Dual pathway inhibition with rivaroxaban vascular dose 2.5 mg bid + aspirin reduced CV death, stroke and MI



RRR

24%

COMPASS

*Rates as at mean follow up of 23 months.

Eikelboom JW *et al. N Engl J Med* 2017;377(14):1319-30.

Consistent benefit of rivaroxaban 2.5 mg bid + aspirin supported by secondary outcomes, including all-cause mortality

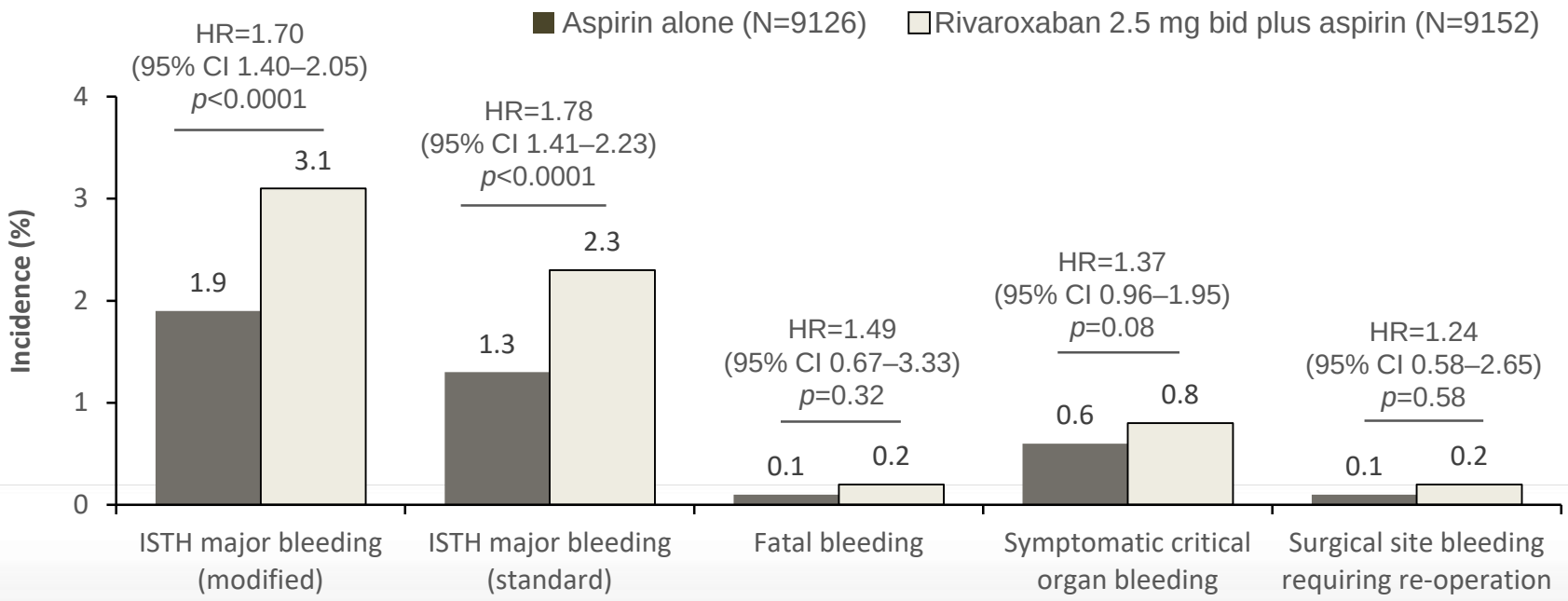
Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
CHD death, ischemic stroke, MI, ALI	329 (3.6%)	450 (4.9%)	**0.72 (0.63–0.83)**	<0.001
CV death, ischemic stroke, MI, ALI	389 (4.3%)	516 (5.7%)	**0.74 (0.65–0.85)**	<0.001
Mortality (all-cause)	313 (3.4%)	378 (4.1%)	**0.82 (0.71–0.96)**	0.01

CHD coronary heart disease death: death due to acute MI, sudden death, or CV procedure.

Eikelboom JW et al. N Engl J Med 2017; DOI: 10.1056/NEJMoa1709118.

Addition of rivaroxaban 2.5 mg bid to aspirin increased major bleeding but not fatal or critical organ bleeding

Incidence rates of major bleeding per category



Eikelboom JW *et al*, *J Am Coll Cardiol* 2019 [in press]

Net clinical benefit: 20% RRR with rivaroxaban 2.5 mg bid + aspirin versus aspirin

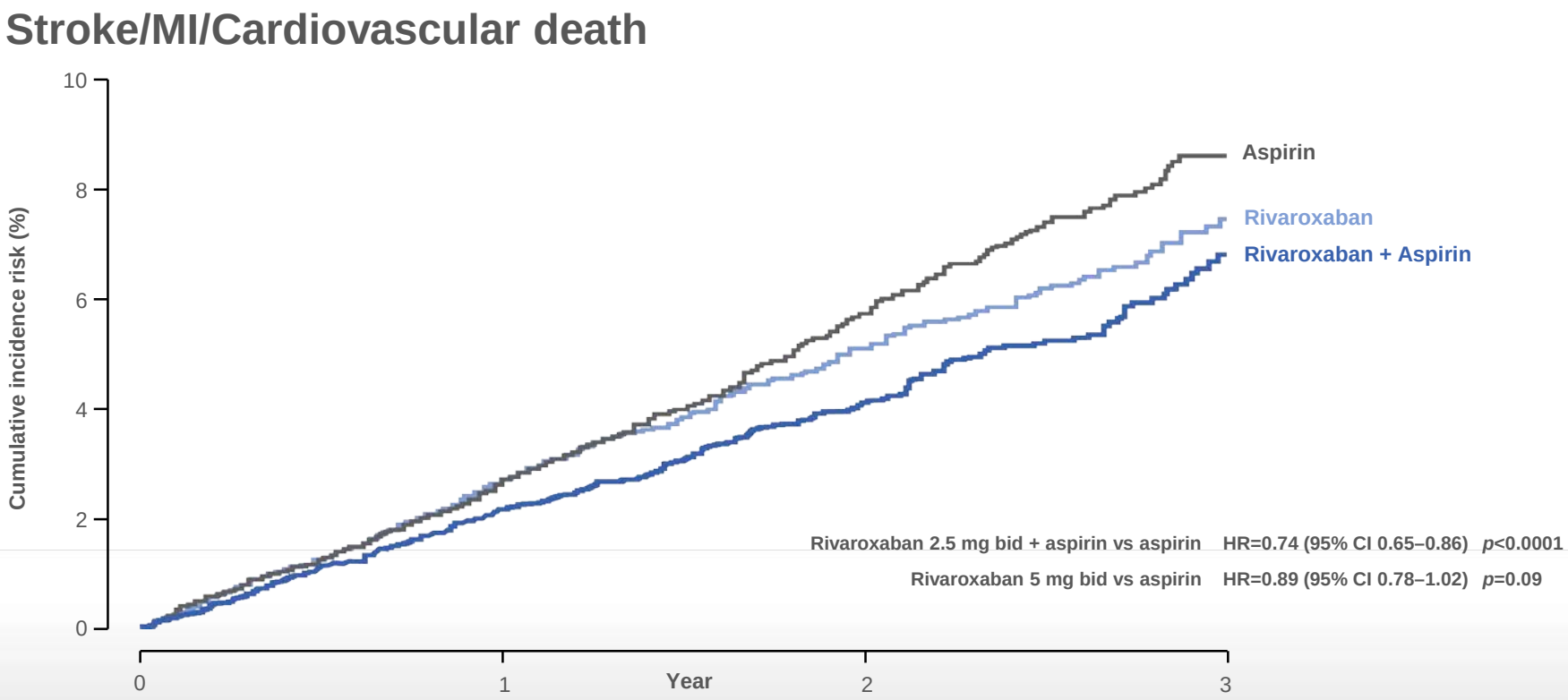
- **Definition:** composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ
  - **In other words, net clinical benefit represented the composite of fatal and non-fatal events of irreversible harm**

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
Net clinical benefit	431 (4.7%)	534 (5.9%)	**0.80** (0.70–0.91)	<0.001

Eikelboom JW *et al. N Engl J Med* 2017;377(14):1319-30

COMPASS

Dual pathway inhibition with rivaroxaban 2.5 mg bid + aspirin significantly reduced MACE by 26% versus aspirin in CAD patients



Connolly SJ *et al*, *Lancet* 2018;391(10117):205-18.

COMPASS

22% reduction in risk of the composite net clinical benefit outcome with rivaroxaban vascular dose 2.5 mg bid + aspirin vs aspirin

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin N=8313	Rivaroxaban 5 mg bid N=8250	Aspirin N=8261	Rivaroxaban 2.5 mg bid + aspirin vs aspirin		Rivaroxaban 5 mg bid vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Net clinical benefit (CV death, stroke, MI, fatal or critical organ bleeding)	392 (5)	462 (6)	494 (6)	**0.78 (0.69–0.90)**	**0.0003**	0.94 (0.82–1.06)	0.31
All-cause mortality	262 (3)	316 (4)	339 (4)	**0.77 (0.65–0.90)**	**0.0012**	0.93 (0.80–1.09)	0.37
CV death	139 (2)	175 (2)	184 (2)	0.75 (0.60–0.93)	0.010	0.95 (0.77–1.17)	0.63
Non-CV death	123 (2)	141 (2)	155 (2)	0.79 (0.62–1.00)	0.048	0.91 (0.73–1.15)	0.43

- For every 1000 patients **with CAD** treated with rivaroxaban plus aspirin, 13 MACE events would be prevented and 2 fatal or critical organ bleeds would be caused over a mean 23-month period

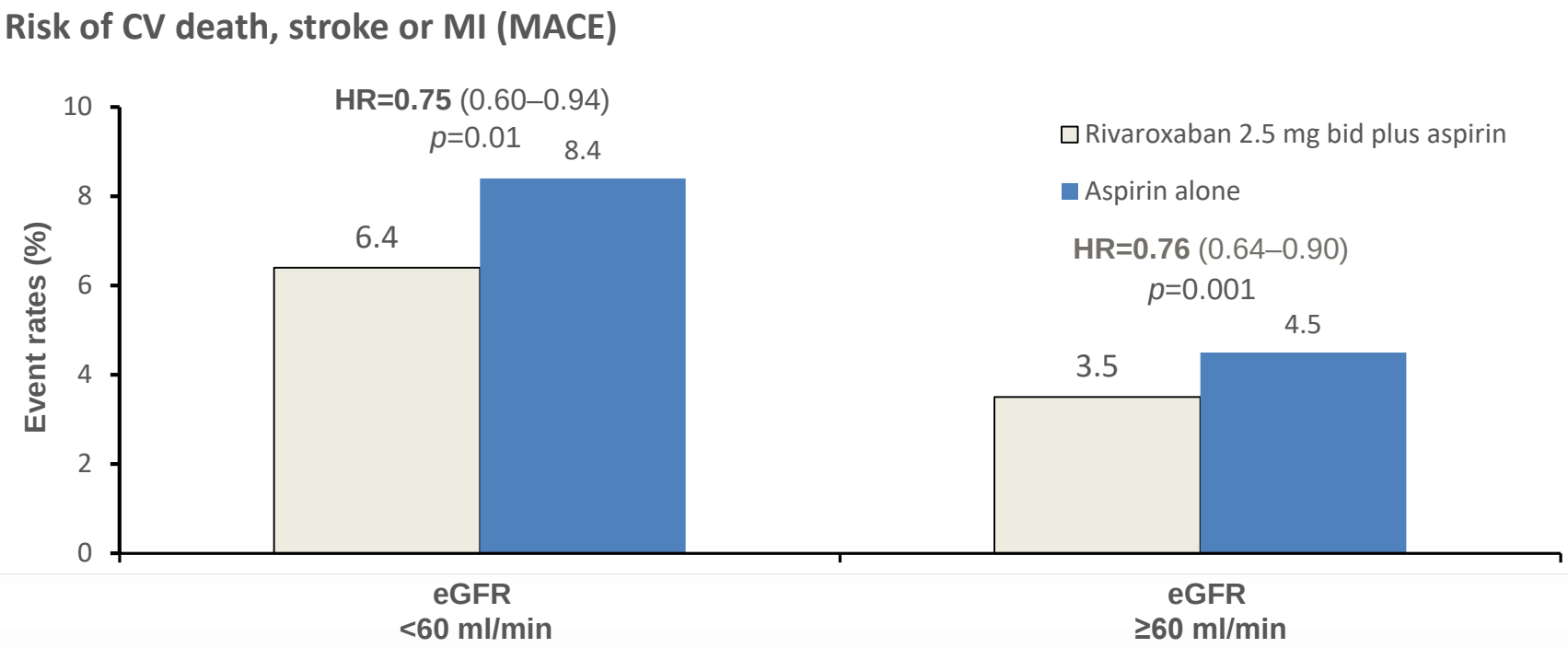
Rivaroxaban was associated with improved outcomes in a broad population of patients with CAD

- Dual pathway inhibition with Rivaroxaban vascular dose 2.5 mg BID plus aspirin significantly reduced the risk of MACE by 26%
  - Stroke 44% (significant)
  - MI 14% (non-significant)
  - CV Death 25% (significant)
- Overall bleeding rates were low, with an expected increase in major bleeding with the dual pathway inhibition versus aspirin alone. Notably there was no significant increase in critical organ bleeding including intracranial or fatal bleeding
- There was a significant reduction in all three secondary outcomes including a reduction in all-cause mortality by 23%

Connolly SJ *et al*, *Lancet* 2018;391(10117):205-18.

COMPASS

Consistently lower risk of MACE in patients taking rivaroxaban 2.5 mg bid plus aspirin compared with aspirin alone, irrespective of renal function



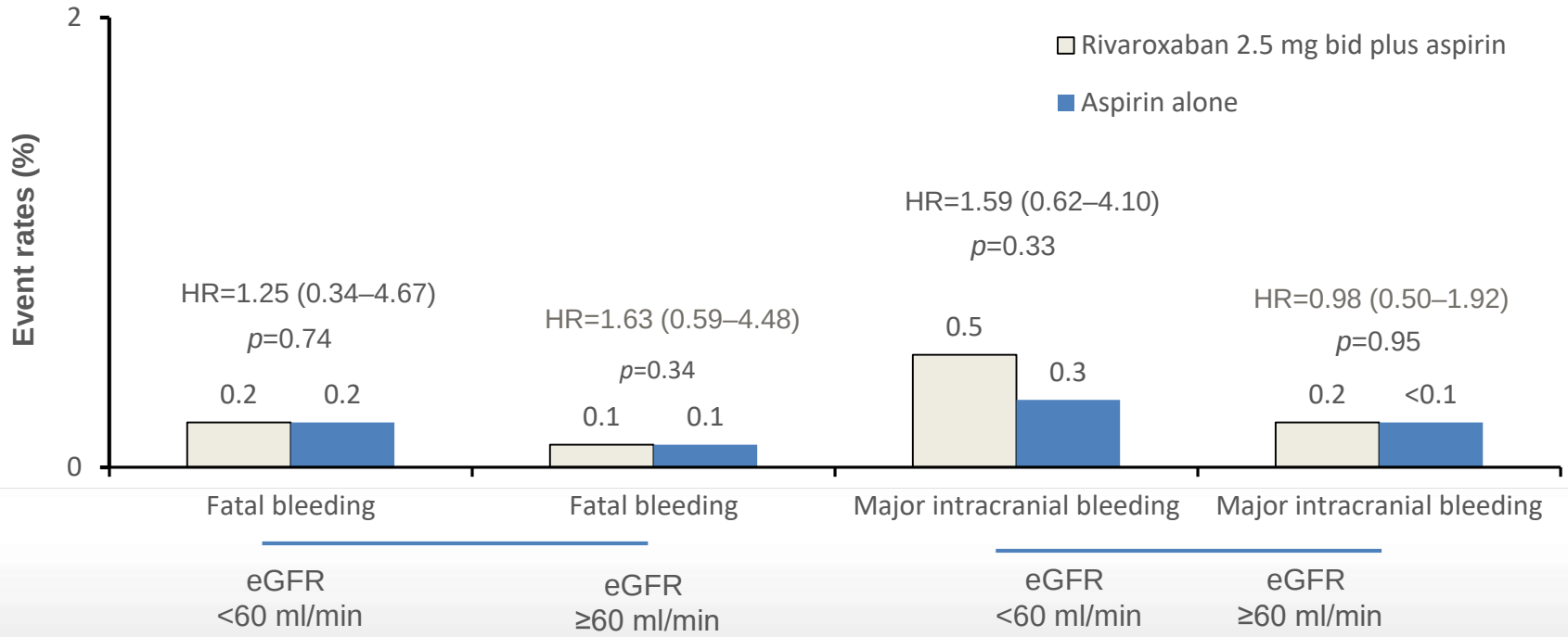
Hazard ratios are presented in HR (95% CI).

Fox KAA *et al*, *JACC* 2019;73:2243–2250.

COMPASS

Safety data for moderate renal impairment are consistent with overall data

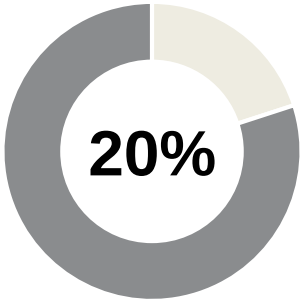
Risk of major bleeding: severe bleeding events of interest



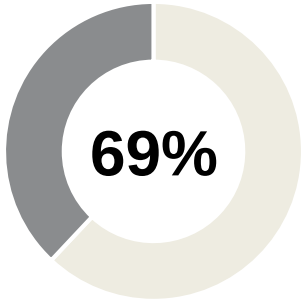
Hazard ratios are presented in HR (95% CI).
Fox KAA *et al*, *JACC* 2019;73:2243–2250.

COMPASS

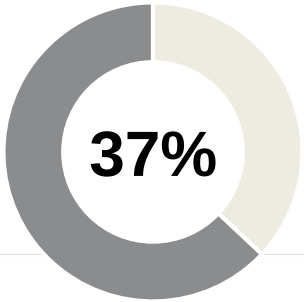
CAD patients with high-risk comorbidities represented in COMPASS



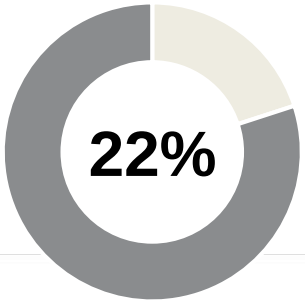
CAD and PAD[1]



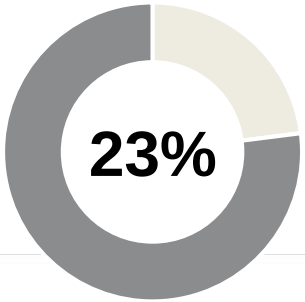
Previous MI[1]



Diabetes[1]



Renal impairment*†[2]

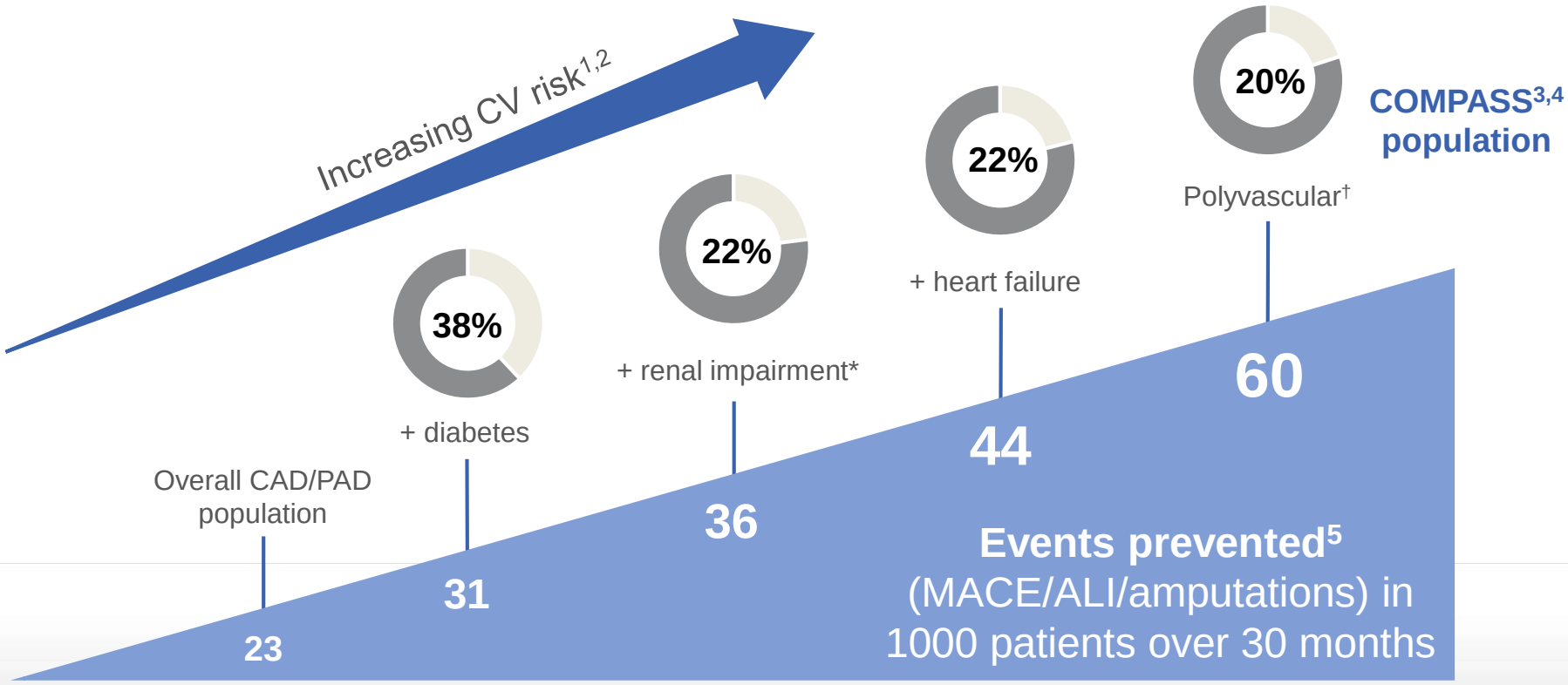


Heart failure[1]

*eGFR: 30−59 mL/min; †Patients with CAD/PAD.

1. Connolly SJ et al. *Lancet* 2018;391:205–218; 2. Eikelboom JW et al. *N Engl J Med* 2017;377:1319−1330.

Patients at higher CV risk benefit more from rivaroxaban vascular dose plus aspirin



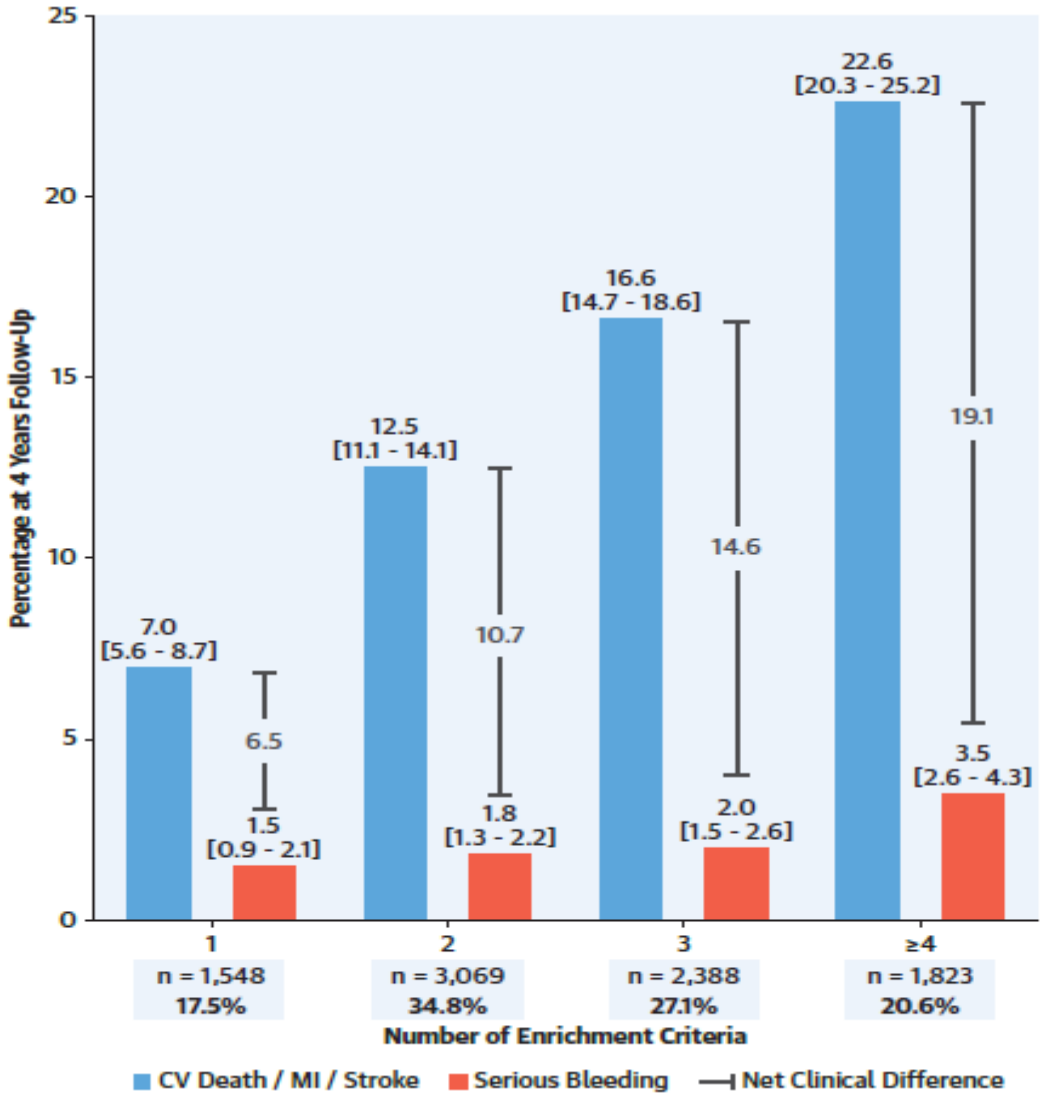
*eGFR: <60 mL/min; †≥2 vascular beds.

1. Dumaine RL et al. *Am Heart J* 2009;158:141–148.e1; 2. Bhatt DL et al. *JAMA* 2010;304:1350–1357; 3. Eikelboom JW et al. *N Engl J Med* 2017;377(14):1319–1330;
4. Connolly SJ et al. *Lancet* 2018;391:205–218; 5. Anand SS et al. *J Am Coll Cardiol* 2019;73:3271−3280.

Benefits of COMPASS regimen according to number of enrichment criteria

Enrichment Criteria for Eligibility to COMPASS

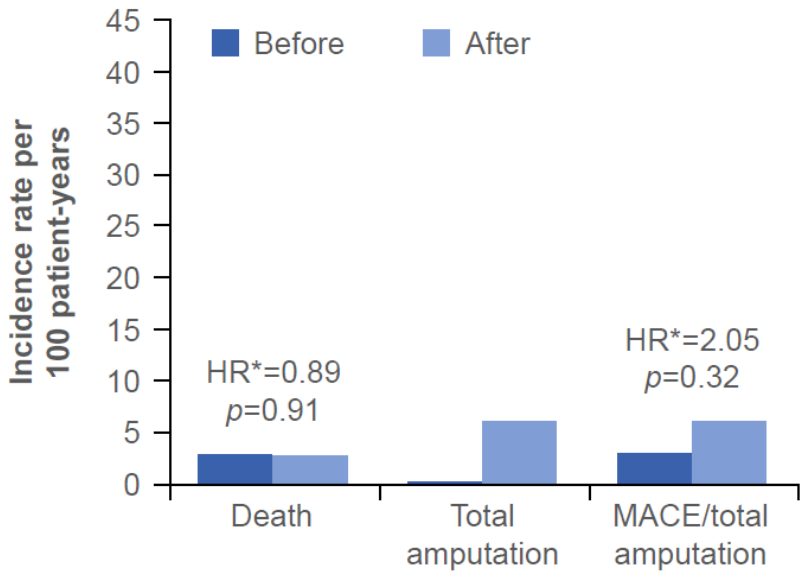
- Age >65 Years Old
- Asymptomatic Carotid Stenosis >70%
- Diabetes
- Heart Failure
- Chronic Kidney Disease (eGFR <60 mL / min)
- History of Ischemic Stroke
- Peripheral Artery Disease
- Current Smoking Status



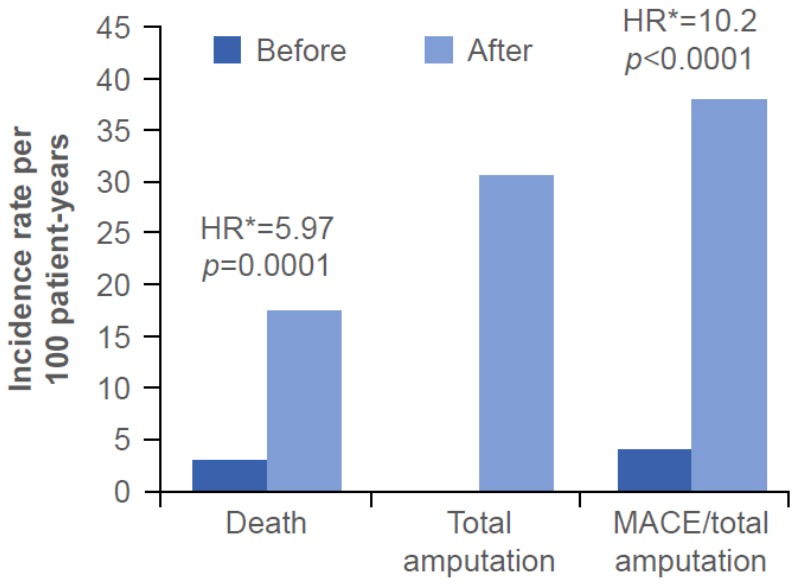
Darmon A, et al. J Am Coll Cardiol 2019; 73: 3281-91.

COMPASS regimen improves outcomes after MALE

Prognosis of MALE in patients randomized to receive rivaroxaban 2.5 mg bid plus aspirin 100 mg

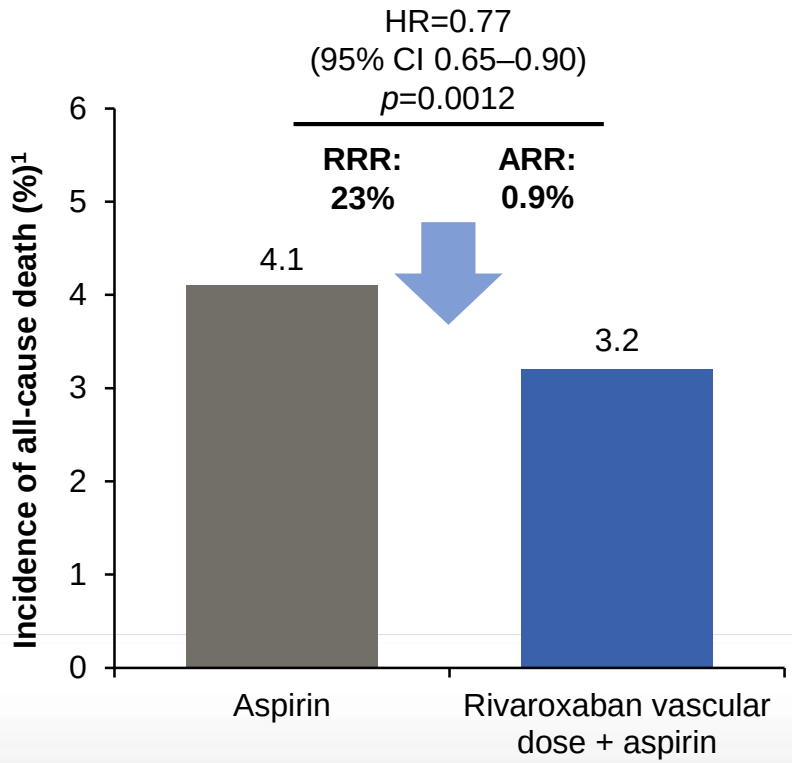


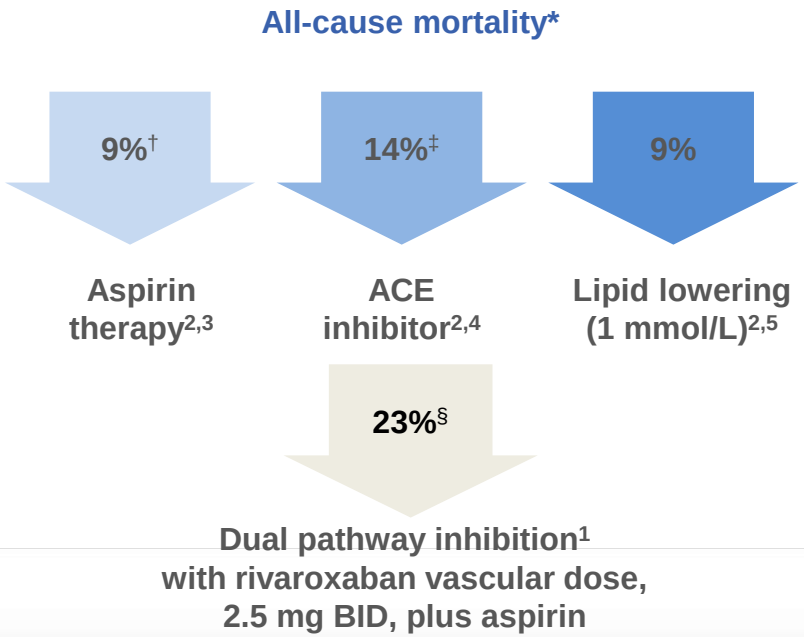
Prognosis of MALE in patients randomized to receive aspirin 100 mg alone



Anand SS, et al. J Am Coll Cardiol 2018;71:2306-15.

COMPASS is the first antithrombotic in a chronic CAD population to show a mortality benefit





*Relative risk reductions calculated from annualized rates; †Vascular mortality reduction in secondary prevention trials. Non-significant; ‡Evaluated at 4−5 years follow-up. 13% mortality reduction for 10 mmHg lowering of systolic blood pressure; §Subgroup analysis of patients with CAD.

1. Connolly SJ et al. *Lancet* 2018;391:205–218; 2. Fox KAA et al. *Eur Heart J* 2018; doi:10.1093/eurheartj/ehy347; 3. ATT Collaboration. *Lancet* 2009; 373:1849–1860; 4. Dagenais GR et al. *Lancet* 2006;368:581–588; 5. CTT Collaboration. *Lancet* 2015;385:1397–1405.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 7, 2015 VOL. 372 NO. 19

Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Overall outcomes

PEGASUS Ticagrelor 60 mg bid	Trial	COMPASS Rivaroxaban 2.5 mg bid
16%	Primary endpoint	24%
17% NS	CV Death	22%
16%	MI	14% NS
25%	Stroke	42%
-	VTE	39%
35%	MALE	46%
132%	Major bleeding	70%
11% NS	Mortality	18%

Outcomes in post-MI patients

DAPT meta-analysis post MI[1]	Trial	COMPASS post MI[2]
22%	Primary endpoint	26%
15%	CV death	32%
30%	MI	15% (NS)
19%	Stroke	39%
73%	Major bleeding	61%
8% (NS)	Mortality	27%

CV, cardiovascular; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NS, not significant.

1. Udell JA, et al. Eur Heart J 2016; 37:390–9; 2. Connolly SJ, et al. Unpublished data.

COMPASS regimen is the first long-term antithrombotic since ASA to reduce mortality

	ASA[1] (ATTC)	Clopidogrel[2] (CAPRIE)	ASA + clopidogrel[3] (CHARISMA)	ASA + ticagrelor[4] (PEGASUS)	ASA + Rivaroxaban[5] (COMPASS)
MACE	–19%	–9%	–7%*	–16%	**–24%**
Stroke	+18%*	NA	-21%§	–25%	**–42%**
MI	–20%†	NA	-6%§*	–16%	**–14%***
Bleeding	+69%	-25%	+25-62%¶	+132%	**+70%**
Death	**–10%**	**–2%***	**–1%***	**–11%***	**–18%**

*Not significant. †Major coronary event. ‡Gastrointestinal bleeding. §Non-fatal. ¶severe and moderate GUSTO bleeding, respectively.

1. Antithrombotic Trialists' Collaboration. Lancet 2009; 2: 172–183. 2. CAPRIE Investigators. Lancet 1996; 348: 1329-39;
3. Bhatt DL, et al. N Engl J Med 2006 Apr 20;354(16):1706-17; 4. Bonaca MP, et al. N Engl J Med 2015; 372: 1791-800;
5. Eikelboom JW, et al. N Engl J Med 2017; 377:1319–30.

New guidelines recommend a second antithrombotic for selected pts with chronic coronary syndromes

2019 guidelines for the management of CCS

Recommendations	Class	Evidence level
Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention should be considered in patients with a **high risk of ischemic events** and without high bleeding risk	**IIa**	**A**
Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk of ischemic events** and without high bleeding risk	**IIb**	A

High ischemic risk defined as:

- Diffuse multivessel CAD with **at least 1** of the following:
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - CKD with eGFR 15–59 ml/min/1.73 m^2

Moderate ischemic risk defined as:

- **At least 1** of the following:
  - Multivessel/diffuse CAD
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - HF
  - CKD with eGFR 15–59 ml/min/1.73 m^2

Knuuti J *et al, Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz42.

Single vs. dual anti-platelet therapy

- ✓ Potent P2Y12 inhibition not only blocks platelet activation via P2Y12 dependent pathways, but it also may block thromboxane A2-dependent pathways—the same pathways targeted by aspirin
- ✓ Adding aspirin on a background of potent P2Y12 inhibition may not lead to further inhibition of platelet activation

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ORIGINAL ARTICLE | Open Access

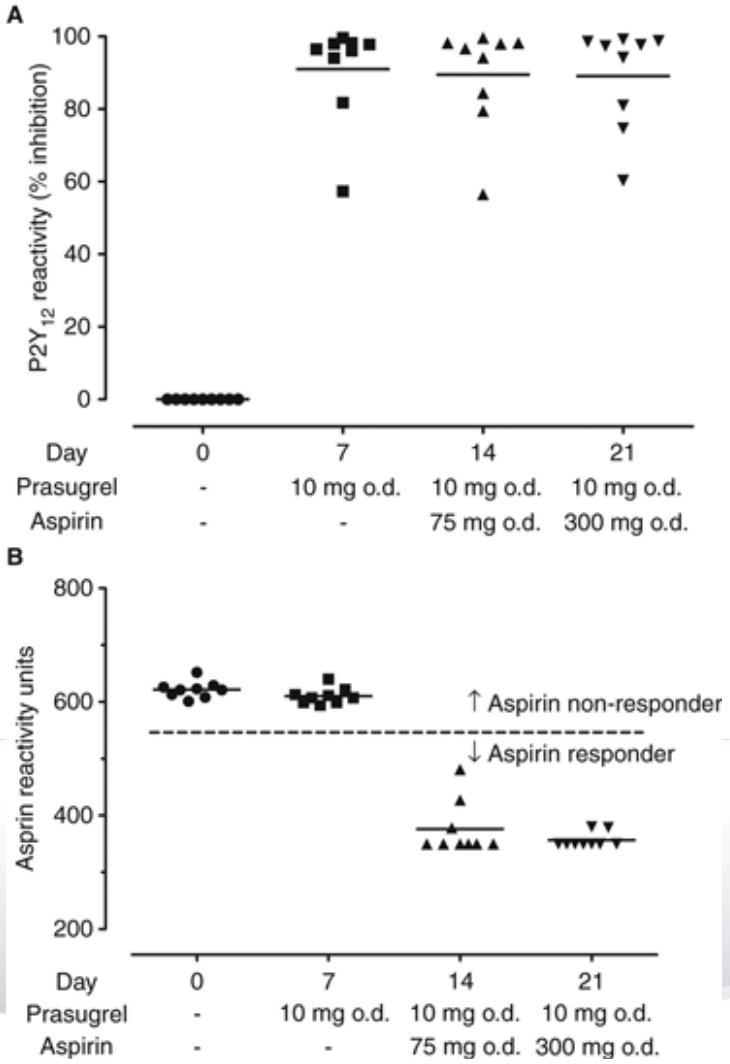
Aspirin has little additional anti-platelet effect in healthy volunteers receiving prasugrel

P. D. M. LEADBEATER, N. S. KIRKBY, S. THOMAS, A.-R. DHANJI, A. T. TUCKER, G. L. MILNE, J. A. MITCHELL, T. D. WARNER

First published:21 July 2011 | https://doi.org/10.1111/j.1538-7836.2011.04450.x |
Citations: 17

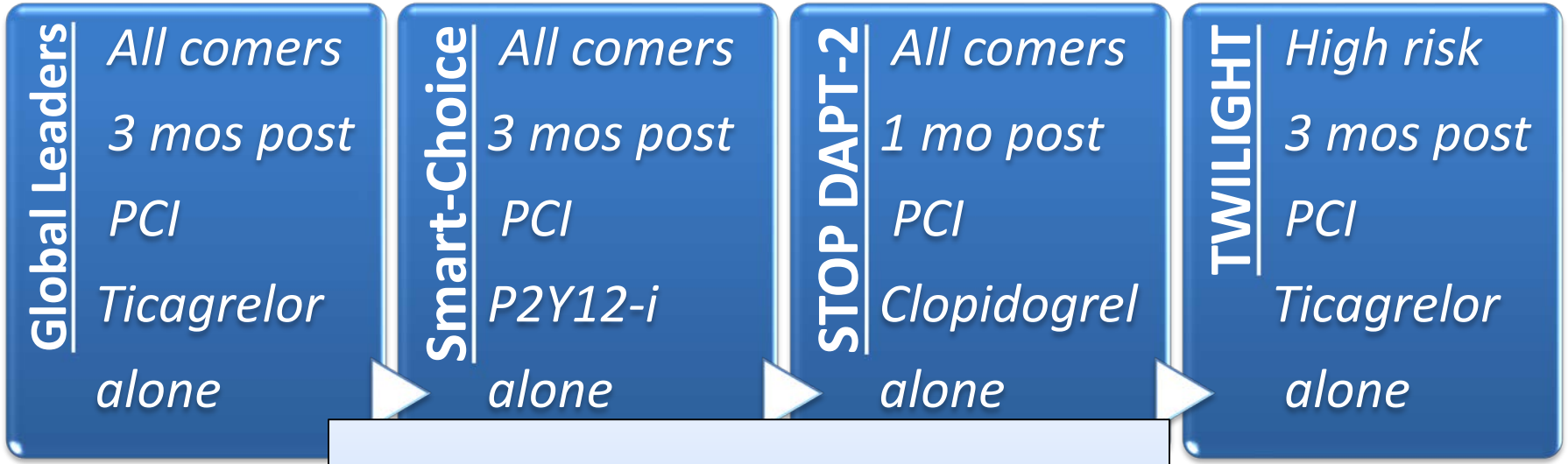
✉ Tim D. Warner, The William Harvey Research Institute, Barts & the London School of Medicine & Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK.

Aspirin has little additional anti-platelet effect in healthy volunteers receiving prasugrel



Journal of Thrombosis and Haemostasis, Volume: 9, Issue: 10, Pages: 2050-2056, First published: 21 July 2011, DOI: (10.1111/j.1538-7836.2011.04450.x).

Trials dropping aspirin in secondary prevention



Marco Valgimigli,
ACC 2018
Published:10/28/2019

MACE ↔

Major Bleeding ↓

Dharam J. Kumbhani,
TCT 2019
Published:09/26/2019

~ 30, 000 Patients

Unanswered questions

- We know that **clopidogrel** has very significant interpatient variability. Would a strategy of clopidogrel monotherapy alone (dropping aspirin) be sufficient if you didn't know whether that patient was a clopidogrel responder?
- Also, would you continue P2Y12 inhibitor monotherapy indefinitely? Or would there be some point along the way where you would switch back to aspirin?

Aspirin in primary prevention

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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

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

Donna K. Arnett, Roger S. Blumenthal, Michelle A. Albert, Andrew B. Buroker, Zachary D. Goldberger, Ellen J. Hahn, Cheryl Dennison Himmelfarb, Amit Khera, Donald Lloyd-Jones, J. William McEvoy, Erin D. Michos, Michael D. Miedema, Daniel Muñoz, Sidney C. Smith Jr., Salim S. Virani, Kim A. Williams Sr., Joseph Yeboah and Boback Ziaeian

4.6 Aspirin Use

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).**

Aspirin in primary prevention metanalysis

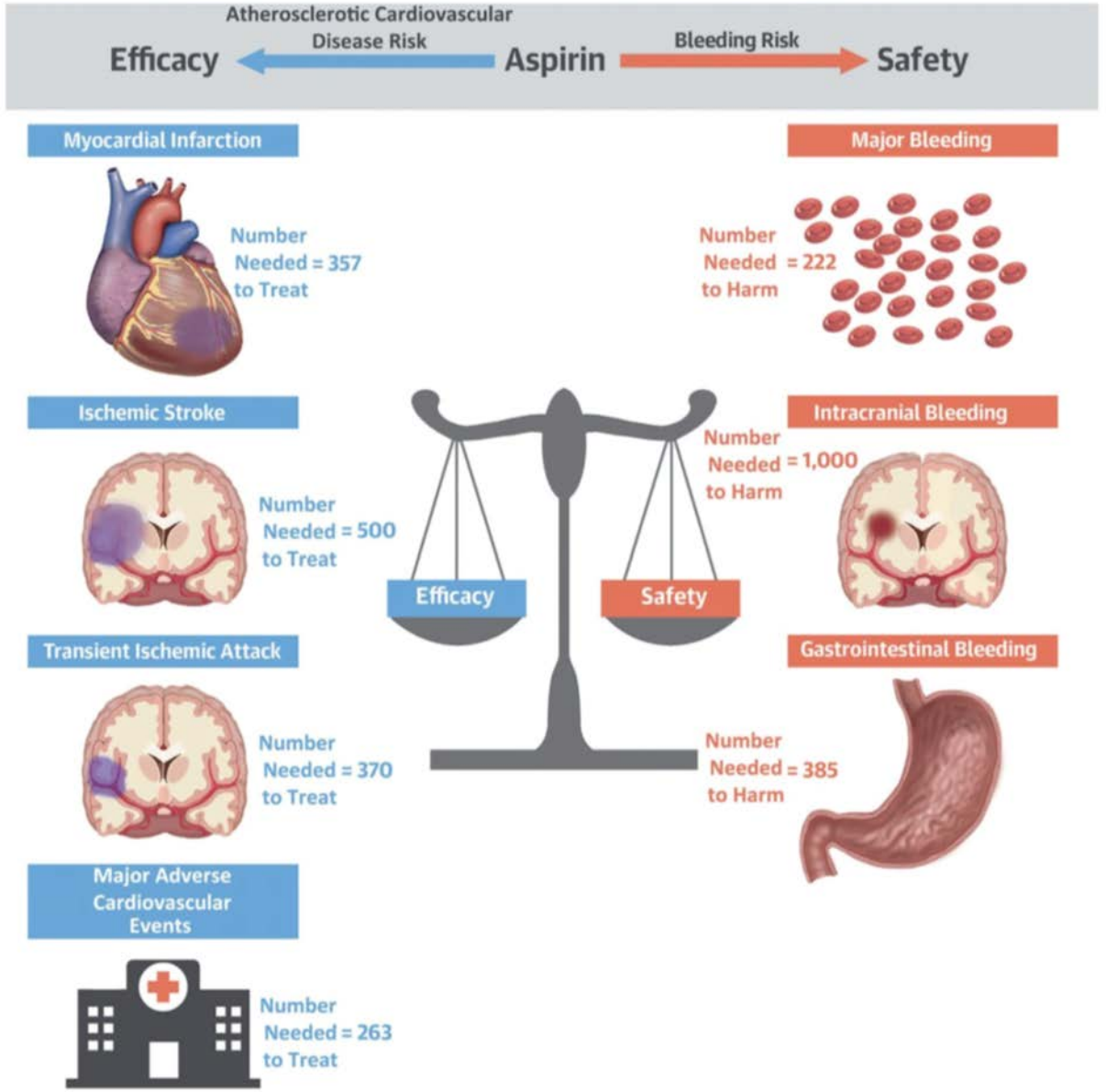
15 randomized controlled trials 165,502 participants

- **Similar all-cause death (RR: 0.97)**
- **Similar CV death (RR: 0.93)**
- **Similar non-CV death (RR: 0.98)**
- **Lower risk of nonfatal MI (RR: 0.82)**
- **Lower TIA (RR: 0.79)**
- **Lower ischemic stroke (RR 0.87)**
- **Higher major bleeding (RR: 1.5)**
- **Higher intracranial bleeding (RR: 1.32)**
- **Higher major GI bleeding (RR: 1.52)**
- **Similar fatal bleeding (RR: 1.09)**
- **Similar total cancer and cancer-related deaths**

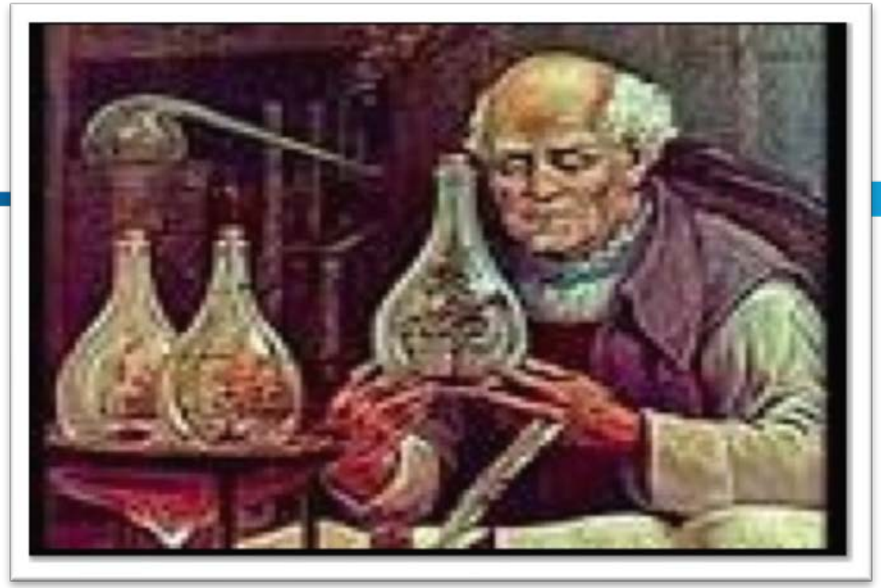
Conclusions Aspirin for primary prevention reduces nonfatal ischemic events but significantly increases nonfatal bleeding events.

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

CENTRAL ILLUSTRATION: Aspirin for Primary Prevention of Cardiovascular Events



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



“All drugs are poisons,
the benefits depends on the dosage”

Paracelsus
Father of Pharmacology, circa 15th Century

Thank you for your attention!