CVD SECONDARY PREVENTION

PRIMARY HEALTH TAS EDUCATION INTERFACE 2021

LEARNING OUTCOMES

Identify guideline-based recommendations for managing cardiovascular risk factors in a high risk / secondary prevention setting

Develop strategies to implement best practice cardiovascular risk management within the primary care setting

ESC
European Society of Cardiology

European Heart Journal (2021) **42**, 1289–1367
doi:10.1093/eurheartj/ehaa575

ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

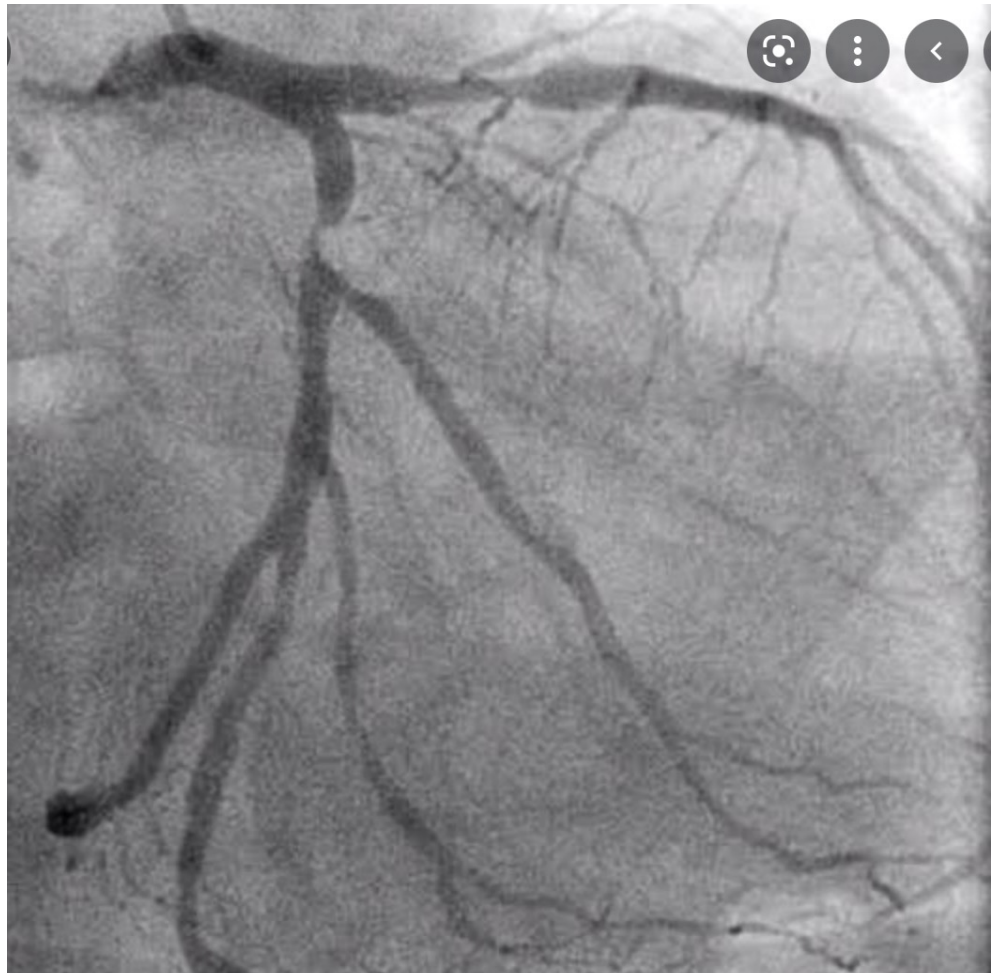
SECONDARY PREVENTION

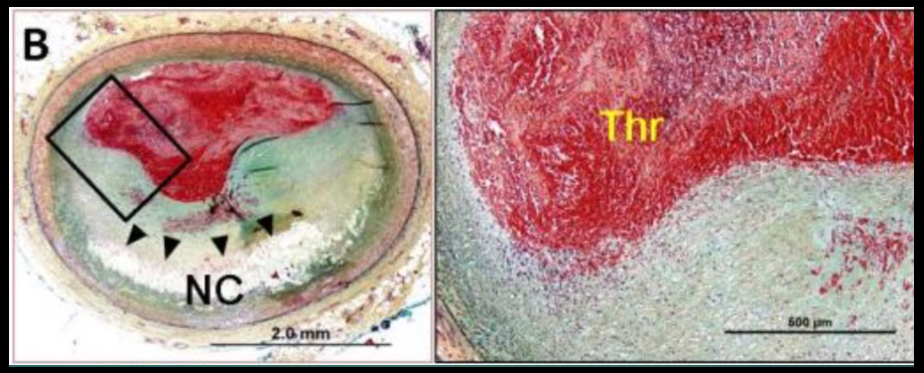
Reduce impact of disease that has already occurred

CORONARY DISEASE PATHOGENESIS

- Presentations
  - Asymptomatic coronary disease
  - Stable angina
  - Acute Coronary Syndrome (ACS)
    - STEMI
    - NSTEMI / NSTEACS
    - Unstable Angina

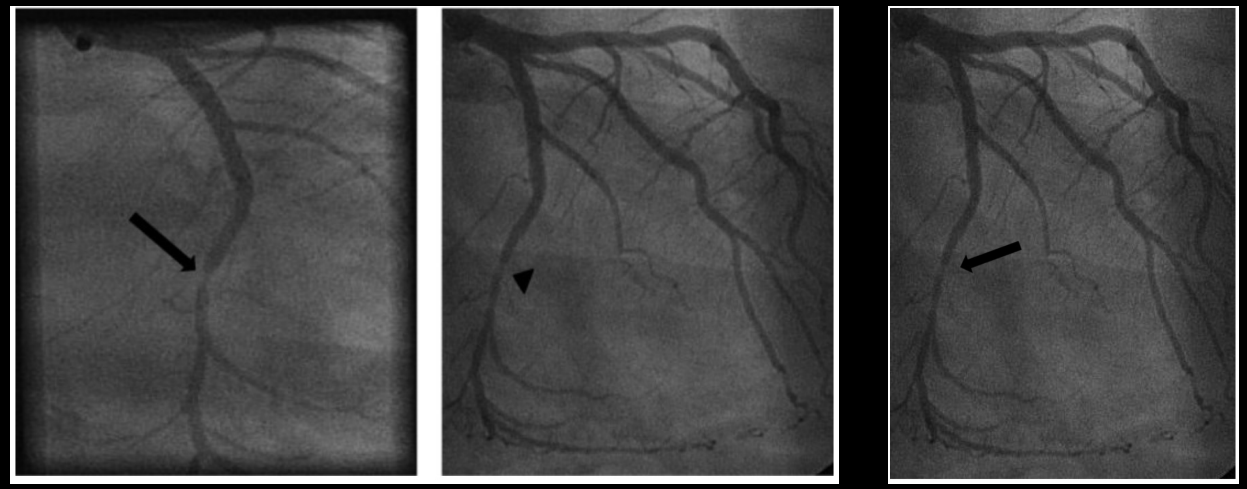
- Traditional understanding
  - Fixed stenosis
  - Progression
  - Occlusion +/- thrombus





Arbab-Zadeh A, et al, Circulation 2012;125(9):1147-1156

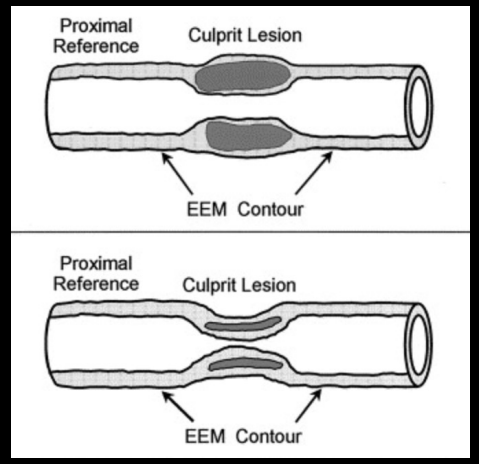
- But
  - ACS often abrupt
  - Plaques often not flow limiting in STEMI

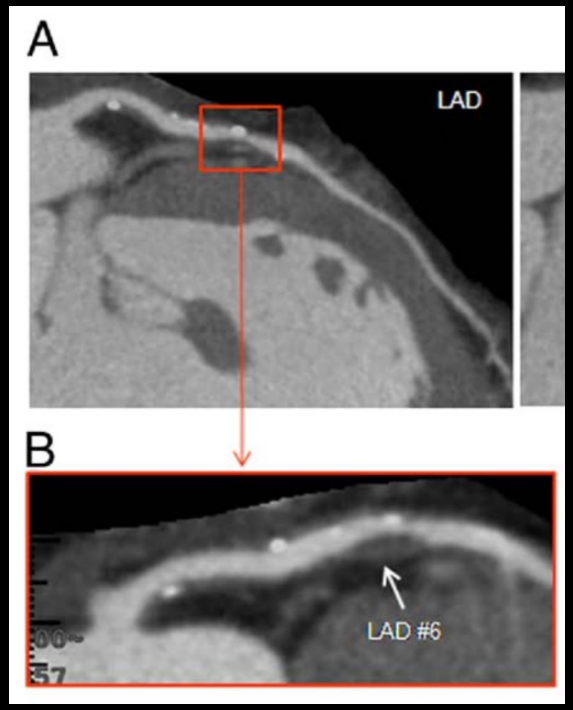


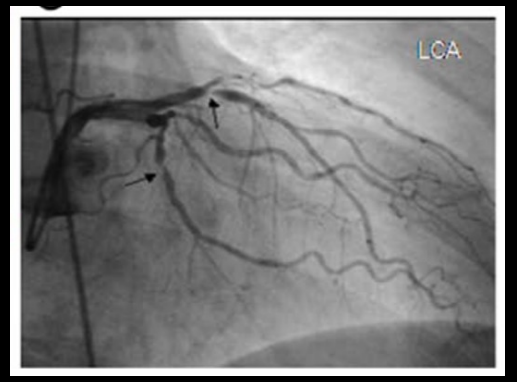
Stone GW et al, N Engl J Med 2011;364:226-35

Jamil G et al, *BMJ Case Rep* 2013.
doi:10.1136/bcr-2013-009002

- "Vulnerable plaque"
  - CT angiography
    - Minimal calcification
    - Positive re-modelling

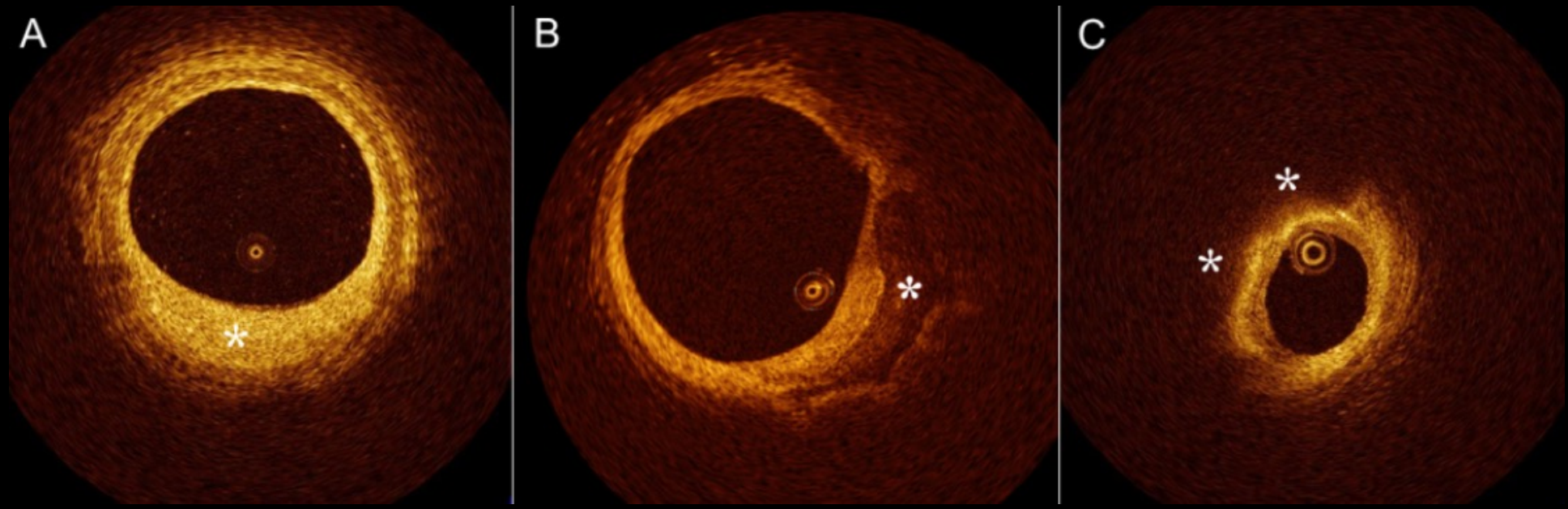






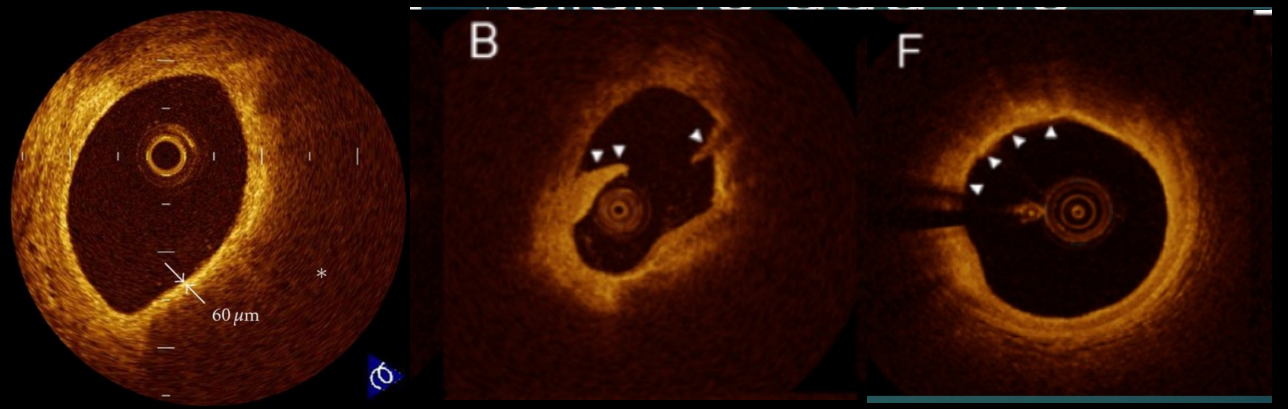
Motoyama S et al., J Am Coll Cardiol 2009;54:49-57

- Optical Coherence Tomography (OCT)



Hasegawa T & K Shimada, "Coronary Artery Disease - Assessment, Surgery, Prevention", 2015

- OCT: Vulnerable plaque features



Yoshinori M et al, *J Am Coll Cardiol Img* 2011;4:638-46

Takarada S et al. *Atherosclerosis* 2009;202(2):491-7

- Therapeutic implications
  - Revascularization (PCI) of stenotic lesions (stable angina)
    - Symptom improvement
    - No consistent ↓ clinical events
  - Medical therapy (statins esp)
    - Minimal effect on degree of stenosis
    - Qualitative vs quantitative aspects of atheroma
    - >> plaque stabilization
    - ↓ MACE (1° and 2°)

MECHANISMS OF ADVERSE EVENTS

- Scar related
  - Pump failure
  - Arrhythmia
- Coronary related
  - Stent failure
  - Second acute plaque
  - New coronary lesion

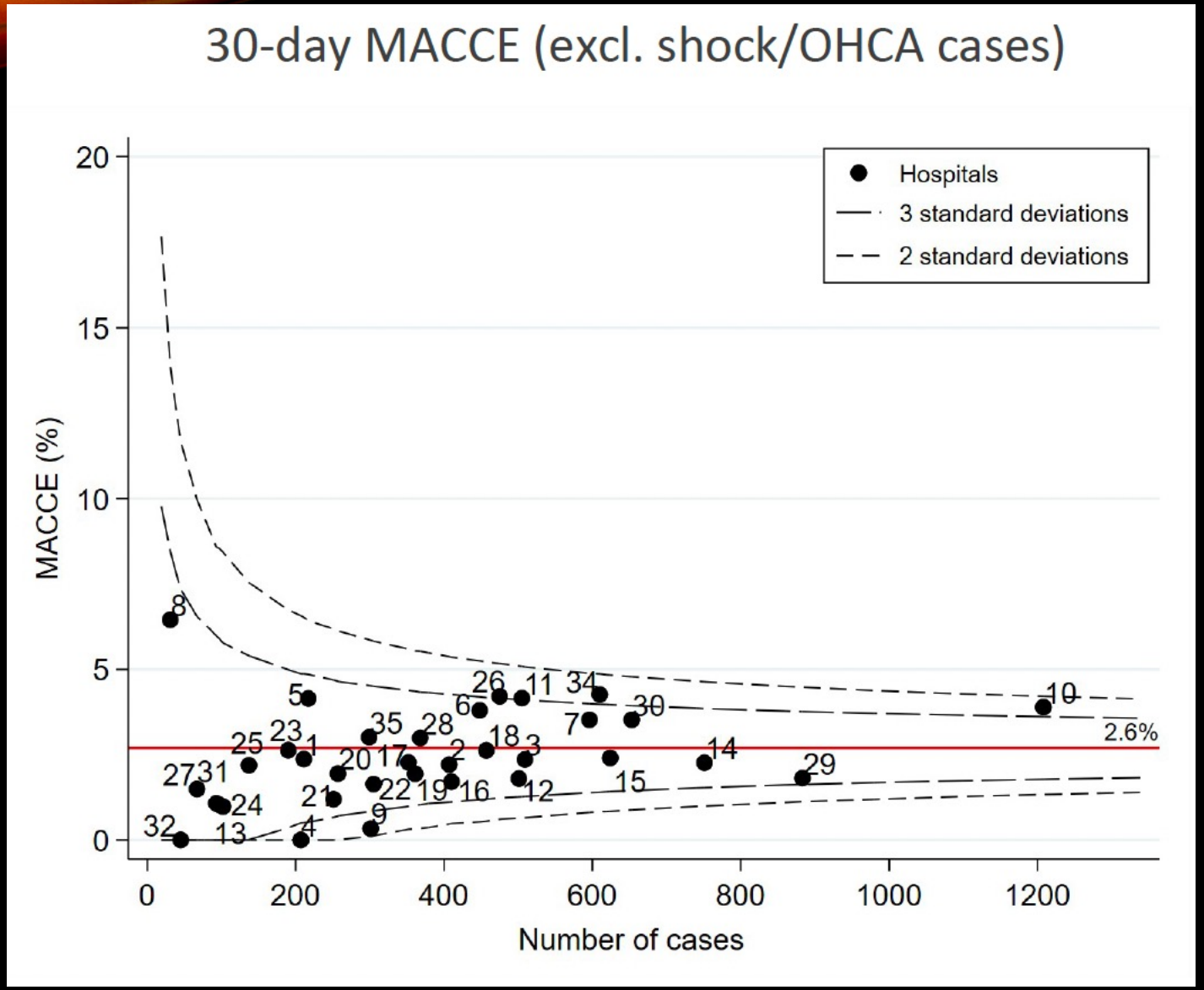

30-day MACCE (excl. shock/OHCA cases)
Hospitals
3 standard deviations
2 standard deviations
MACCE (%)
Number of cases
2.6%
0
5
10
15
20
0
200
400
600
800
1000
1200

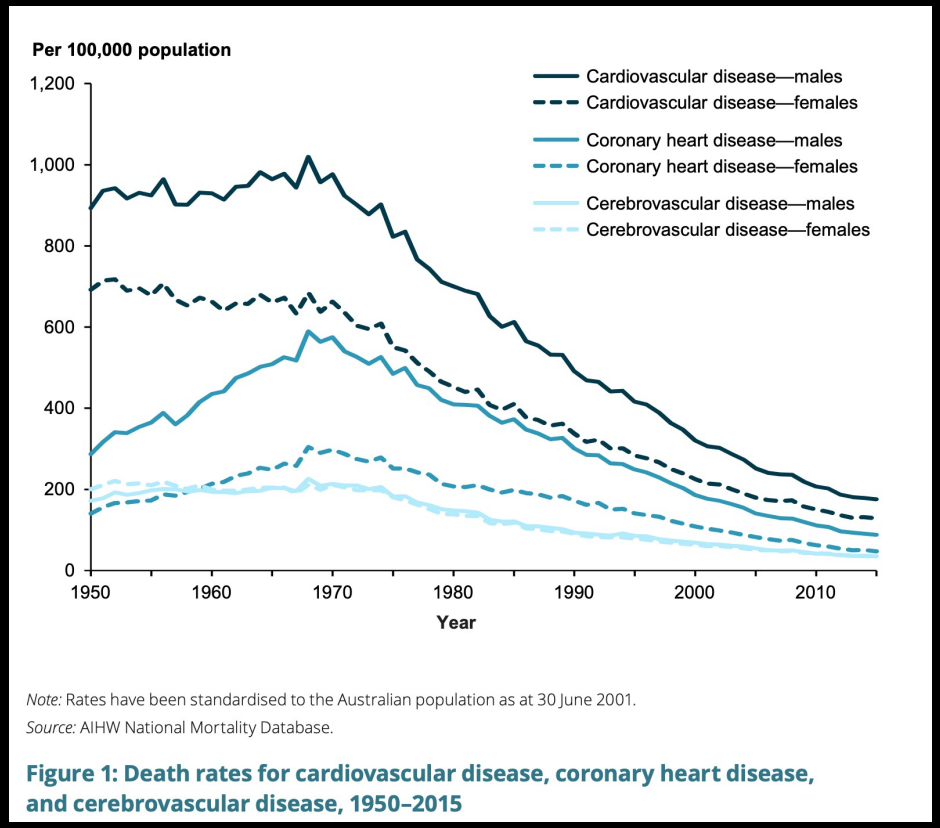
Table 3. Major Efficacy End Points at 12 Months.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82–1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42–1.44)	0.42
Other arterial thrombotic event	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34–1.08)	0.09
Death from vascular causes, MI, stroke — no./total no. (%)				
Invasive treatment planned§	569/6732 (8.9)	668/6676 (10.6)	0.84 (0.75–0.94)	0.003‡
Event rate, days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77–1.00)	0.045
Event rate, days 31–360¶	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70–0.91)	<0.001
Stent thrombosis — no. of patients who received a stent/total no. (%)				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62–0.95)	0.01

Wallentin et al, *New Engl J Med* 2009;361:1045-57

- Improved survival
  - Procedural intervention
  - ↓ disease progression
    - >> risk factor modification

  - Rate of decline slowing
  - Emerging epidemics of diabetes and obesity



Note: Rates have been standardised to the Australian population as at 30 June 2001.

Source: AIHW National Mortality Database.

Figure 1: Death rates for cardiovascular disease, coronary heart disease, and cerebrovascular disease, 1950–2015

Australian Institute of Health and Welfare. Trends in cardiovascular deaths. 2017

SECONDARY PREVENTION STRATEGIES

- Formal cardiac rehabilitation
- Lifestyle
  - Mediterranean diet
  - Regular physical activity
  - Smoking cessation
- Pharmacological
  - Thinners
    - Aspirin
    - P2Y12 inhibitors (clopidogrel, ticagrelor, prasugrel)
    - DOACs
  - LDL lowering
    - Statins, ezetimibe, PCSK9 inhibitors
  - Diabetes management
    - Metformin, SGLT2 inhibitors
  - Other
    - (ACE-I, ARB, beta blockers, spiractin)

Multidisciplinary exercise-based cardiac rehabilitation is recommended as an effective means for patients with CAD to achieve a healthy lifestyle and manage risk factors in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.[487,497,501]	I	A
Involvement of multidisciplinary healthcare professionals (cardiologists, general practitioners, nurses, dieticians, physiotherapists, psychologists, pharmacists) is recommended in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life.[492,499,502,503]	I	A

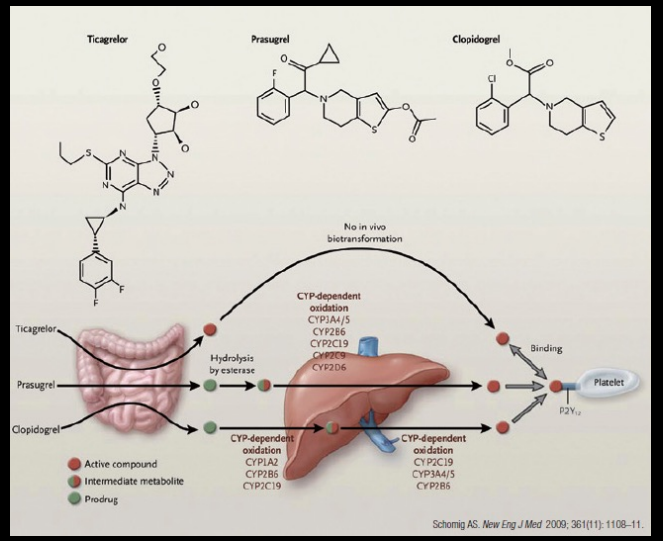
- Traditional cardiac rehab
- Cardihab
- COACH programme

THINNERS

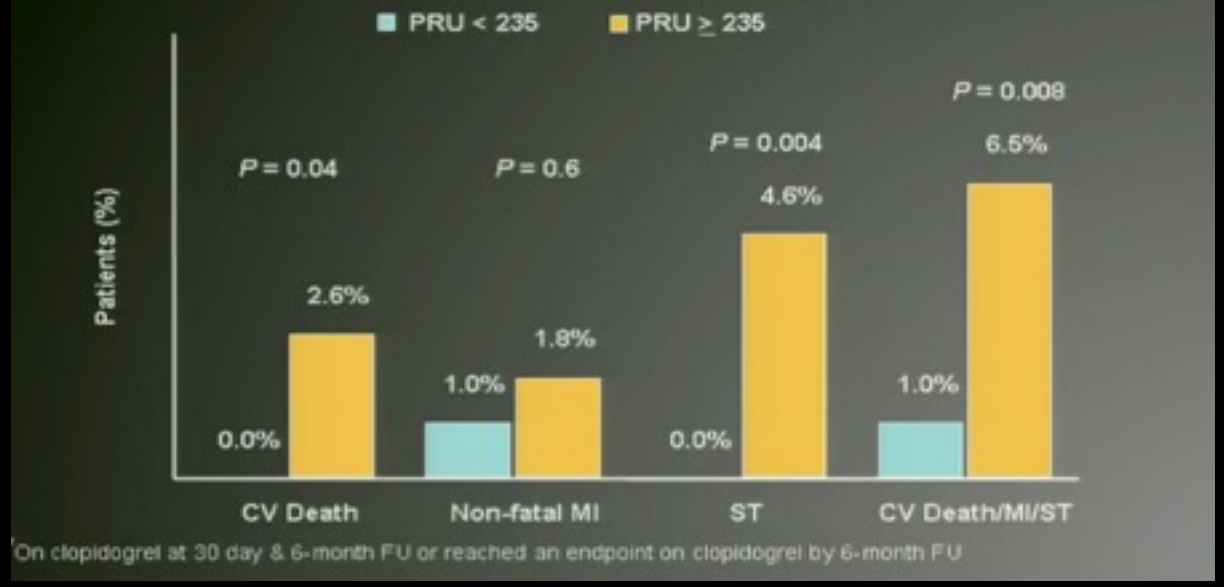
- Aspirin
  - Secondary prevention ☺
  - Primary prevention ☹
- P2Y12 inhibitors
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
- DOACs

ORAL ANTI-PLATELET AGENTS

- Clopidogrel
  - Demonstrated benefit across ACS spectrum
  - Standard of care in ACS and post PCI

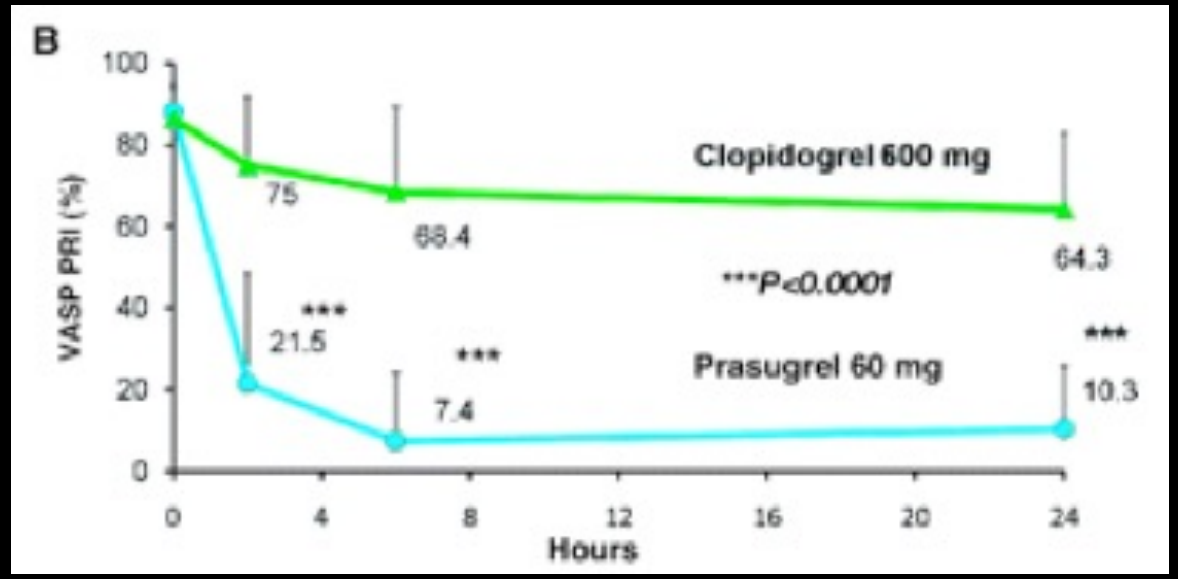


Out-of-hospital 6-Month Outcomes Post-PCI in Patients on Consistent Clopidogrel Therapy at 6 Months Stratified by Reactivity



On clopidogrel at 30 day & 6-month FU or reached an endpoint on clopidogrel by 6-month FU

- Prasugrel
  - Single step P450 dependent activation



Wiviott SD, et al. *Circulation* 2007;116:2923-2932

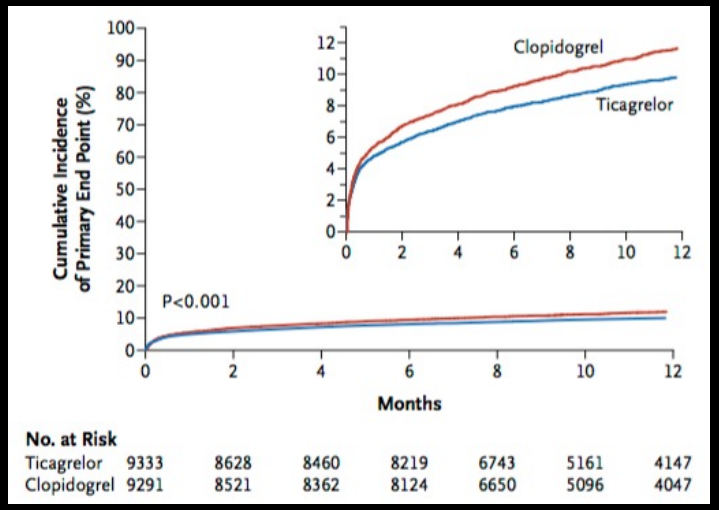
- TRITON-TIMI 38
  - 13608 ACS → PCI
  - Prasugrel vs clopidogrel
  - MACE: 9.9% vs 12.1% (HR 0.81; 0.73-0.90, p<0.001)
  - Major bleeding: 2.4 vs 1.8% (HR 1.32; 1.03-1.68, p=0.03)
    - Fatal bleeding 0.4 vs 0.1% (p=0.002)
    - Life threatening bleeding 1.4 vs 0.9% (p=0.01)

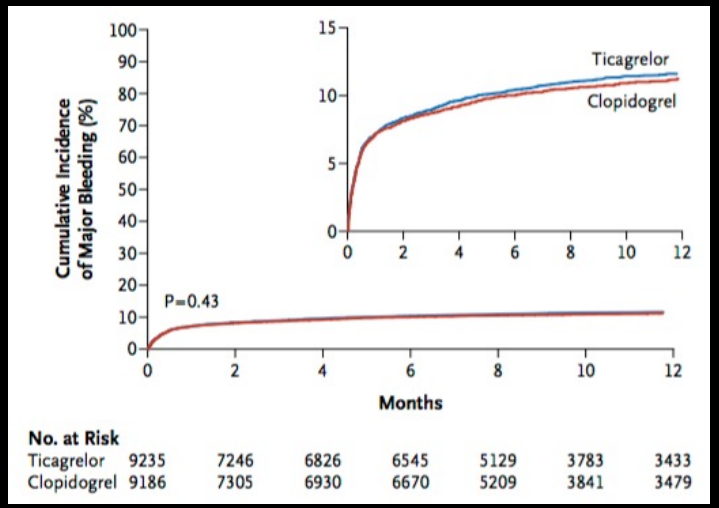
Wiviott SD, et al. *N Engl J Med* 2007;357:2001-2015

- Subgroup analysis
  - Age >= 75
    - No benefit: HR 0.99 (0.81-1.21, p=0.92)
  - Body weight < 60kg
    - No benefit: HR 1.03 (0.69-1.53, p=ns)
  - Prior stroke or TIA
    - Net harm: HR 1.54 (1.02-2.32, p=0.04)
  - Diabetes – primary endpoint
    - 12.2 vs 17% (HR 0.70, p<0.001)

- Ticagrelor
  - Reversible oral ADP antagonist
  - Rapid absorption of active agent

- PLATO
  - 18,624 patients ACS
  - Ticagrelor 180/90bd vs clopidogrel 300/75
- Vascular death / MI / stroke
  - 9.8 vs 11.7% (HR 0.84; 0.77-0.92, p<0.001)
- All-cause mortality
  - 4.5 vs 5.9% (p<0.001)
- Major bleeding
  - 11.6 vs 11.2% (p-0.43)





Wallentin L, et al. *N Engl J Med* 2009;361:1045-1057

- Dyspnoea, ~ 5%
  - ? 20%

• Ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d.).[170]	I	B
• Clopidogrel (300–600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.[182,183]	I	C

In patients with NSTE-ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ receptor inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding.[170,171,225]	I	A

Prolonging antithrombotic treatment duration		
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 9 and 11* for options).[162,212,213,214,223]	IIa	A
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderately increased risk of ischaemic events and without increased risk of major or life-threatening bleeding (see *Tables 9 and 11* for options).[162,212,213,214,223]	IIb	A

DOACS

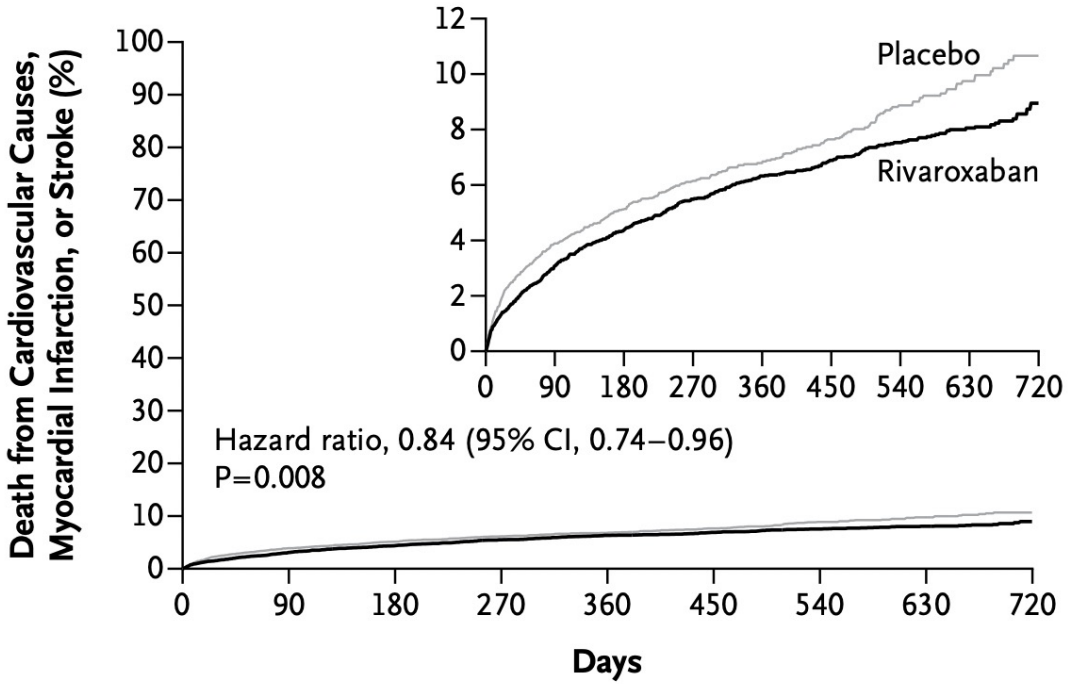
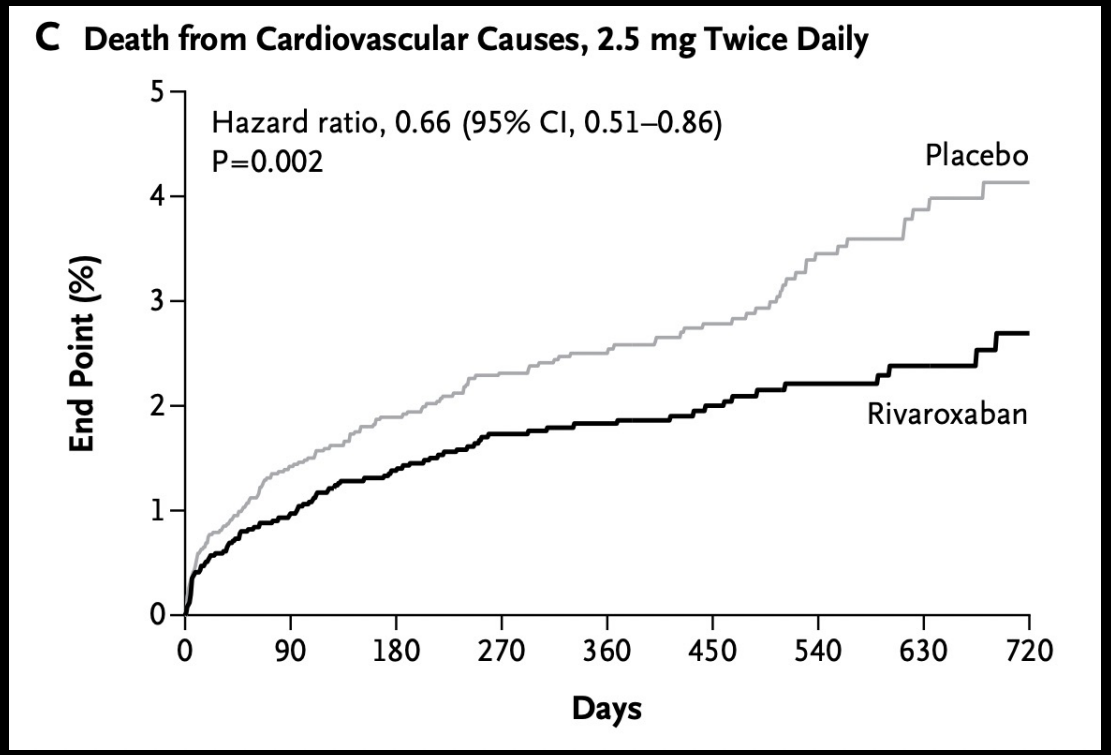


Figure 1. Cumulative Incidence of the Primary Efficacy End Point.

The primary efficacy end point consists of death from cardiovascular causes, myocardial infarction, or stroke. According to these results, the composite end point would be prevented in 1 patient if 56 patients were treated for 2 years with rivaroxaban. The P value is for the modified intention-to-treat analyses. P=0.002 for the intention-to-treat analysis.



ATLAS ACS: Mega JL et al, *New Engl J Med* 2012;366:9-19

Table 2. Kaplan–Meier Estimates and Hazard Ratios for Efficacy and Safety End Points.*

End Point	Rivaroxaban			Placebo (N=5113)	Rivaroxaban 2.5 mg Twice Daily vs. Placebo		
	2.5 mg Twice Daily (N=5114)	5 mg Twice Daily (N=5115)	Combined (N=10,229)		Hazard Ratio (95% CI)	P Value	
						mITT	ITT
Efficacy							
			number (percent)				
Death from cardiovascular causes, myocardial infarction, or stroke — primary end point	313 (9.1)	313 (8.8)	626 (8.9)	376 (10.7)	0.84 (0.72–0.97)	0.02	0.007
Death from cardiovascular causes	94 (2.7)	132 (4.0)	226 (3.3)	143 (4.1)	0.66 (0.51–0.86)	0.002	0.005
Myocardial infarction	205 (6.1)	179 (4.9)	384 (5.5)	229 (6.6)	0.90 (0.75–1.09)	0.27	0.09
Stroke							
Any	46 (1.4)	54 (1.7)	100 (1.6)	41 (1.2)	1.13 (0.74–1.73)	0.56	0.47
Ischemic	30 (1.0)	35 (0.9)	65 (0.9)	34 (1.0)	0.89 (0.55–1.45)	0.64	0.82
Death from any cause, myocardial infarction, or stroke — secondary end point	320 (9.3)	321 (9.1)	641 (9.2)	386 (11.0)	0.83 (0.72–0.97)	0.02	0.004
Death from any cause	103 (2.9)	142 (4.4)	245 (3.7)	153 (4.5)	0.68 (0.53–0.87)	0.002	0.004
Stent thrombosis	47 (2.2)	51 (2.3)	98 (2.3)	72 (2.9)	0.65 (0.45–0.94)	0.02	0.02
	(N=5115)	(N=5110)	(N=10,225)	(N=5125)			
Safety							
TIMI major bleeding not associated with CABG	65 (1.8)	82 (2.4)	147 (2.1)	19 (0.6)	3.46 (2.08–5.77)	<0.001	
TIMI minor bleeding	32 (0.9)	49 (1.6)	81 (1.3)	20 (0.5)	1.62 (0.92–2.82)	0.09	
TIMI bleeding requiring medical attention	492 (12.9)	637 (16.2)	1129 (14.5)	282 (7.5)	1.79 (1.55–2.07)	<0.001	
Intracranial hemorrhage	14 (0.4)	18 (0.7)	32 (0.6)	5 (0.2)	2.83 (1.02–7.86)	0.04	
Fatal bleeding	6 (0.1)	15 (0.4)	21 (0.3)	9 (0.2)	0.67 (0.24–1.89)	0.45	

* Event rates are reported as Kaplan–Meier estimates through 24 months and so are not presented as numerical percentages. Data for efficacy end points correspond to the modified intention-to-treat (mITT) analysis with P values presented for both mITT and ITT analyses. Before the unblinding of study results, 184 patients were excluded from the efficacy analysis because of violations in Good Clinical Practice guidelines at three sites. Myocardial infarction and stroke categories include fatal and nonfatal events. Stroke includes ischemic, hemorrhagic, and stroke of uncertain cause. Stent thrombosis (definite, probable, or possible) analyses were conducted among patients who had received a stent prior to randomization. Data for safety end points correspond to the safety analysis. TIMI denotes Thrombolysis in Myocardial Infarction.

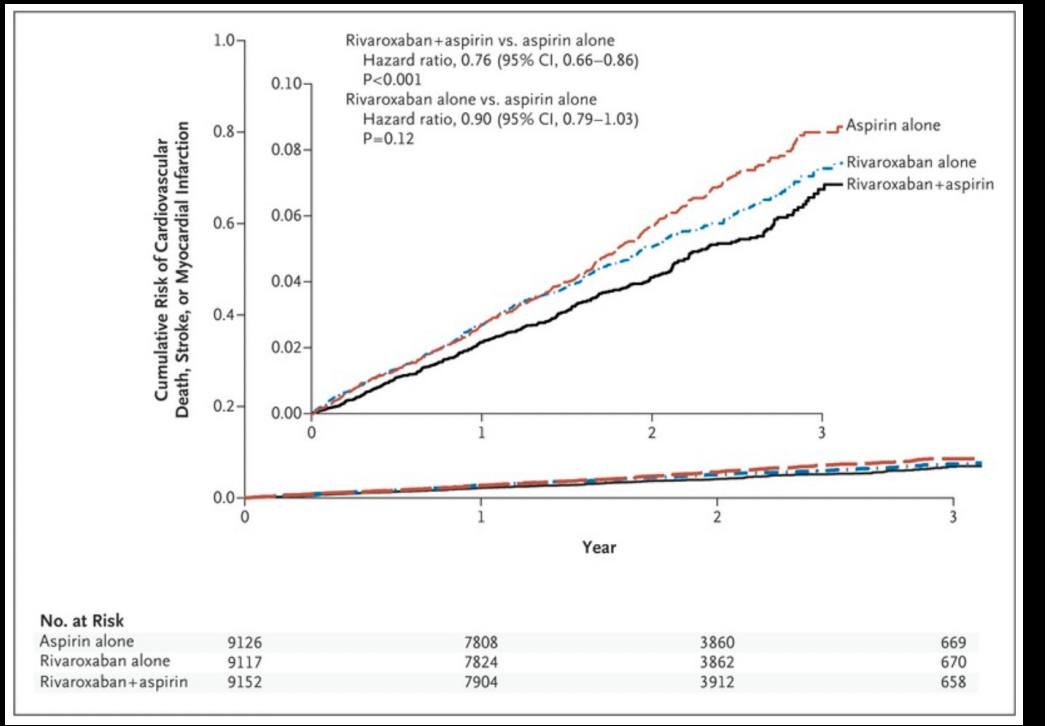


Table 3. Bleeding Events and Net Clinical Benefit.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Major and minor bleeding							
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06
Other major bleeding†	210 (2.3)	164 (1.8)	112 (1.2)	1.88 (1.49–2.36)	<0.001	1.47 (1.16–1.87)	0.001
Fatal bleeding or symptomatic ICH	36 (0.4)	46 (0.5)	29 (0.3)	1.23 (0.76–2.01)	0.40	1.59 (1.00–2.53)	0.05
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	91 (1.0)	58 (0.6)	1.34 (0.95–1.88)	0.09	1.58 (1.13–2.19)	0.006
Major bleeding according to ISTH criteria	206 (2.3)	175 (1.9)	116 (1.3)	1.78 (1.41–2.23)	<0.001	1.52 (1.20–1.92)	<0.001
Transfusion within 48 hr after bleeding	87 (1.0)	66 (0.7)	44 (0.5)	1.97 (1.37–2.83)	<0.001	1.50 (1.03–2.20)	0.03
Minor bleeding	838 (9.2)	741 (8.1)	503 (5.5)	1.70 (1.52–1.90)	<0.001	1.50 (1.34–1.68)	<0.001
Site of major bleeding							
Gastrointestinal	140 (1.5)	91 (1.0)	65 (0.7)	2.15 (1.60–2.89)	<0.001	1.40 (1.02–1.93)	0.04
Intracranial	28 (0.3)	43 (0.5)	24 (0.3)	1.16 (0.67–2.00)	0.60	1.80 (1.09–2.96)	0.02
Skin or injection site	28 (0.3)	28 (0.3)	12 (0.1)	2.31 (1.18–4.54)	0.01	2.34 (1.19–4.60)	0.01
Urinary	13 (0.1)	30 (0.3)	21 (0.2)	0.61 (0.31–1.23)	0.16	1.43 (0.82–2.50)	0.20
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)	<0.001	0.94 (0.84–1.07)	0.36

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

RIVAROXABAN

Source: General Schedule

Body System: BLOOD AND BLOOD FORMING ORGANS > ANTITHROMBOTIC AGENTS > ANTITHROMBOTIC AGENTS

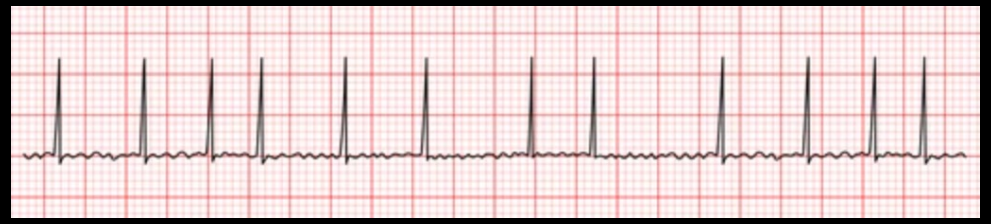
▸ Note

▸ ⚠ Authority Required (STREAMLINED)

Code & Prescriber	Medicinal Product Pack (Name, form & strength and pack size)	Max qty packs	Max qty units	No. of repeats	DPMQ	Max Safety Net	General Patient Charge
12192Q (MP) (NP)	RIVAROXABAN rivaroxaban 2.5 mg tablet, 60 (PI, CMI)	1	60	5	$85.44	$41.30	$41.30
	Available brands						
	Xarelto						

In ACS patients with no prior stroke/transient ischaemic attack who are at high ischaemic risk and low bleeding risk and are receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.[224]

IIb	B



AF → Stroke

ACS → Recurrent infarction

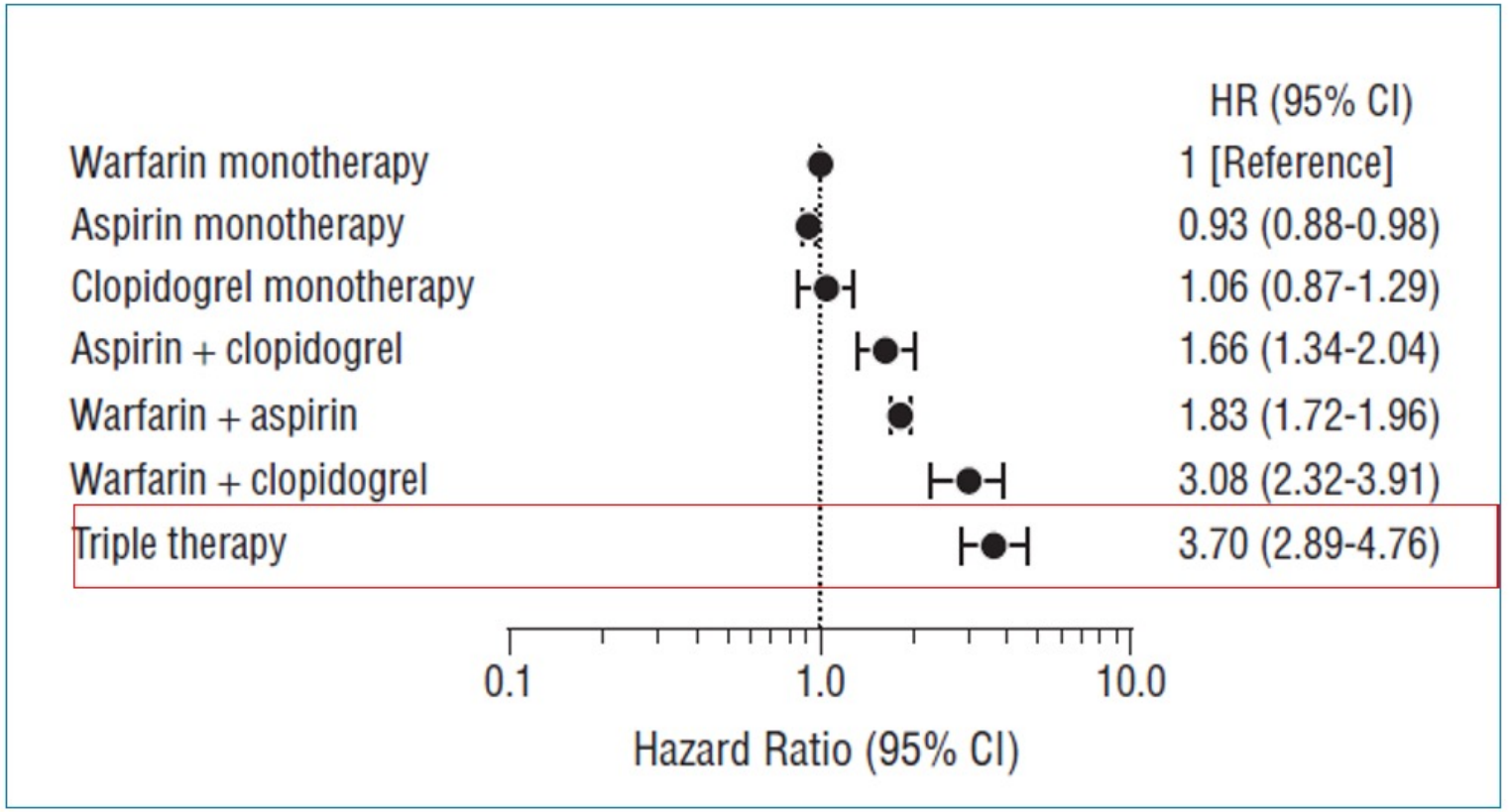
PCI → Stent thrombosis

MANAGEMENT OF RISK

AF → Stroke	→ Anticoagulation
ACS → Recurrent infarction	→ DAPT
PCI → Stent thrombosis	→ DAPT

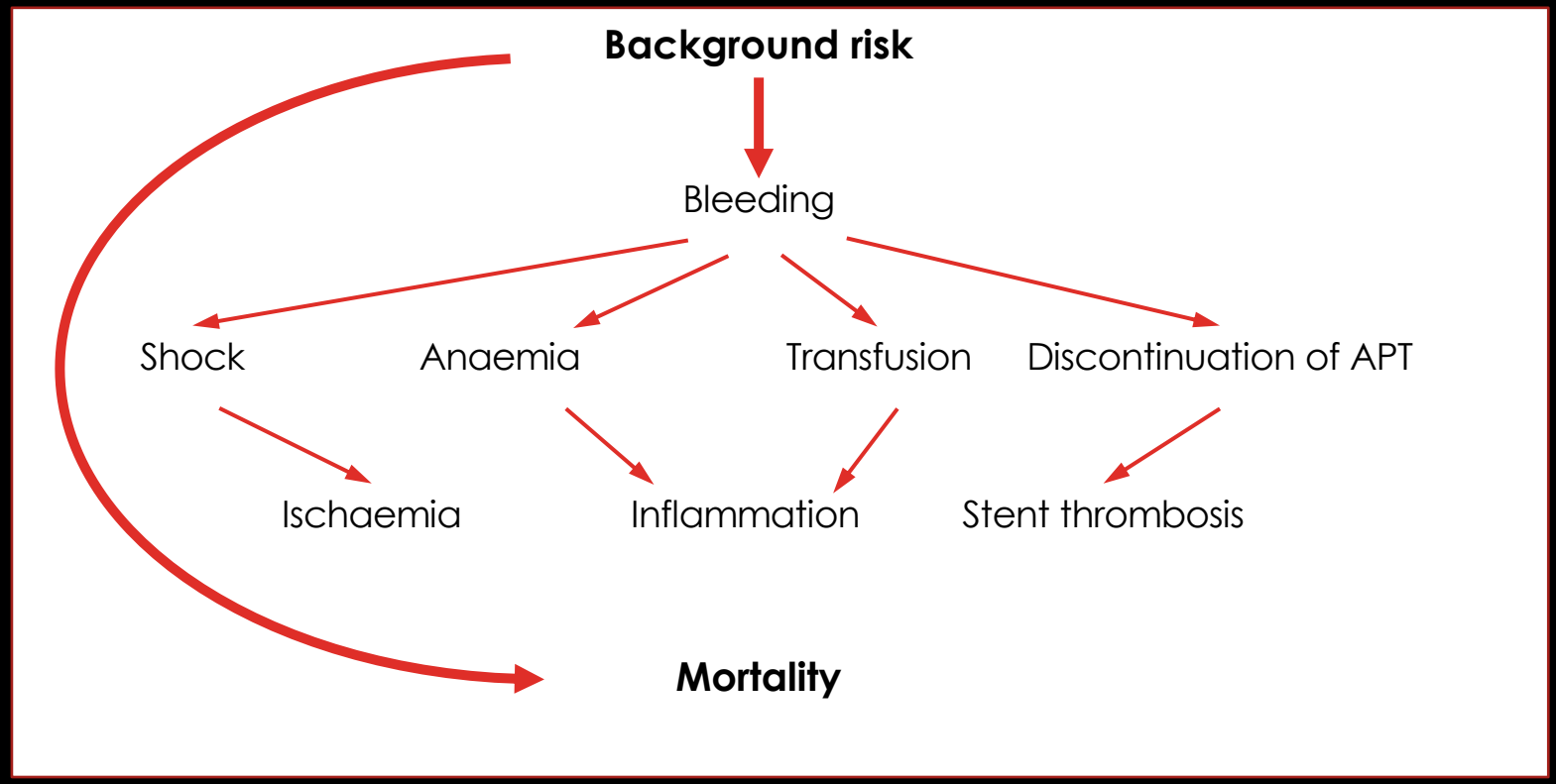
→ "Triple therapy"

HR for Risk of Bleeding



Arch Intern Med. 2010;170(16):1433-41

IMPLICATIONS OF BLEEDING IN ACS



- Bleeding increases early and late mortality: Absolute risk ↑11%, 95% CI 8-14%

Adapted from Steg et al. 2011, Hypothetical mechanism linking bleeding and mortality.
APT, antiplatelet therapy; ACS, acute coronary syndrome.

1. Steg PG et al. Eur Heart J 2011

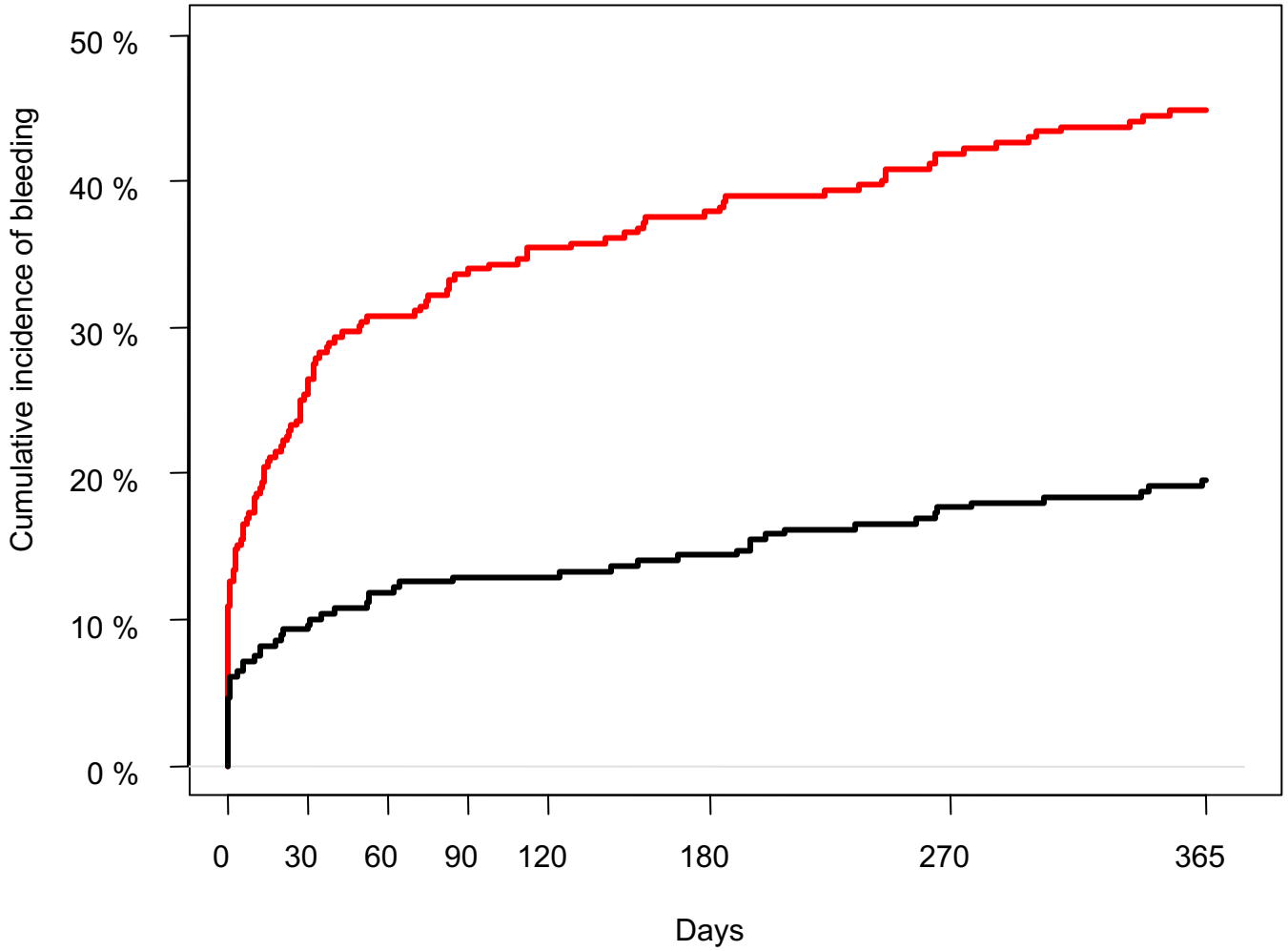
TRIPLE THERAPY

- ? Warfarin & aspirin & clopidogrel
- ? DOAC
- ? Ticagrelor

- Is aspirin a necessary component of triple therapy?

Primary Endpoint: Total number of TIMI bleeding events

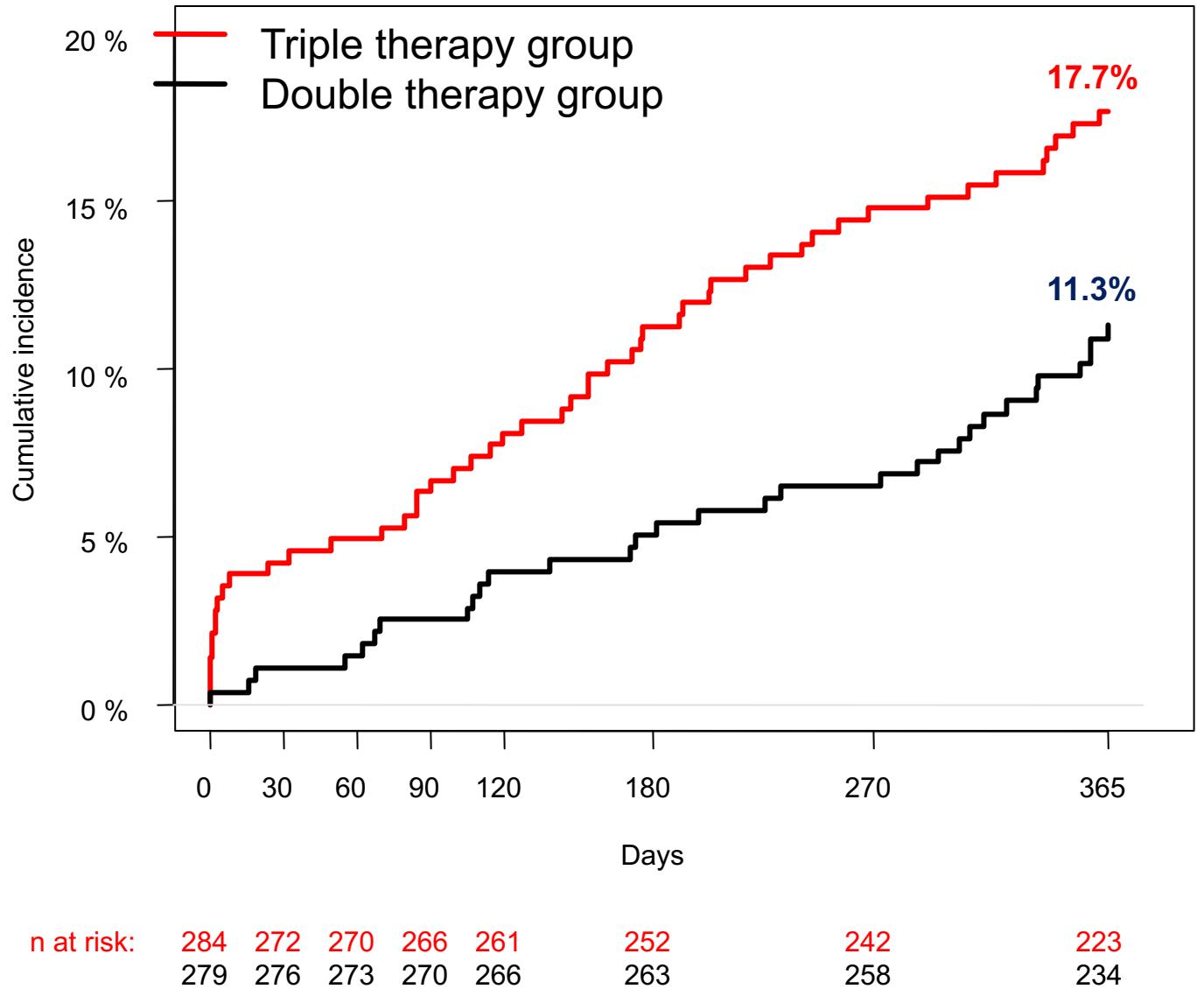
WOEST



Dewilde WJM, et al. *Lancet* 2013;381(9872):1107-1115

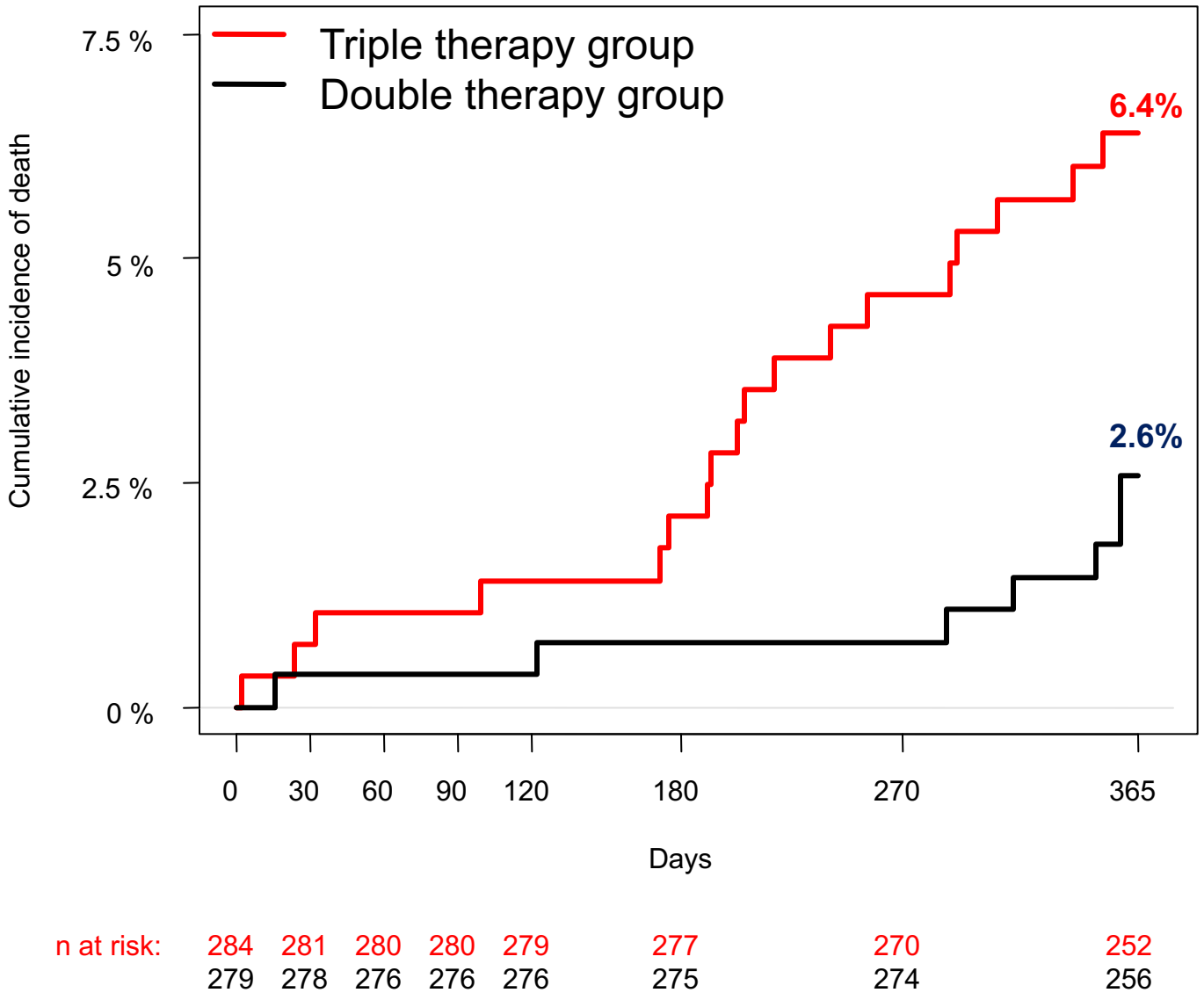
Secondary Endpoint (Death, MI,TVR, Stroke, ST)

WOEST



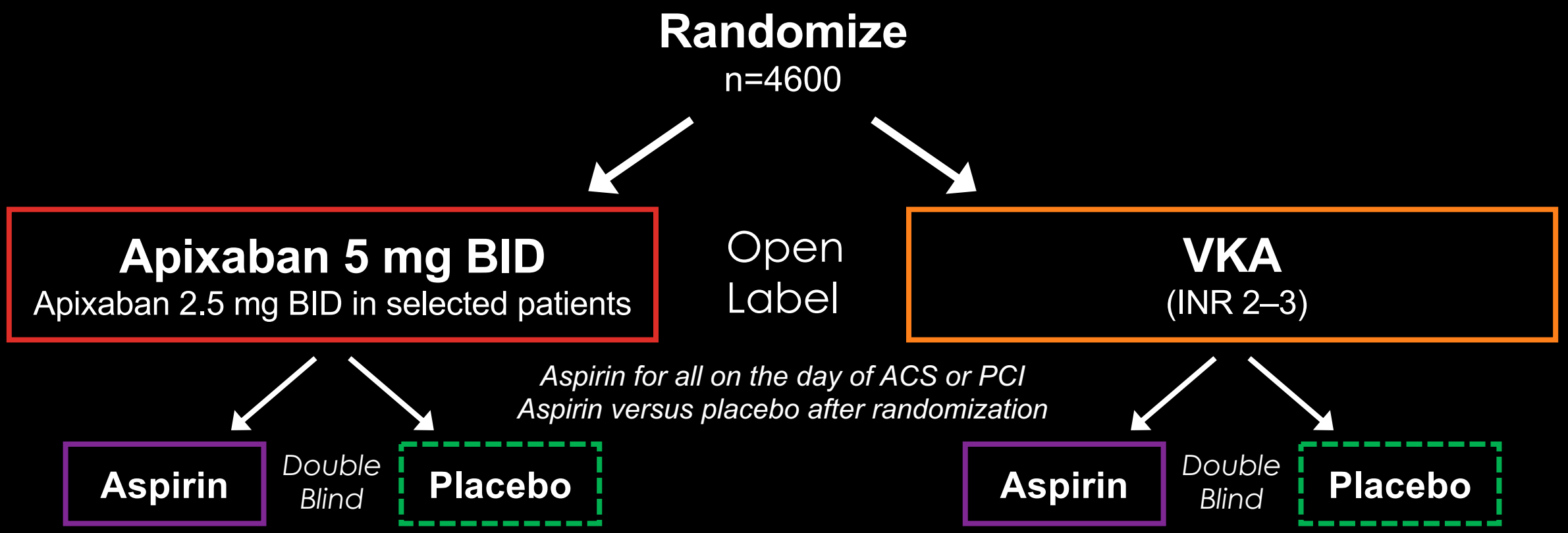
WOEST

All-Cause Mortality



- PIONEER AF-PCI: rivaroxaban
- REDUAL-PCI: dabigatran
- AUGUSTUS: apixaban

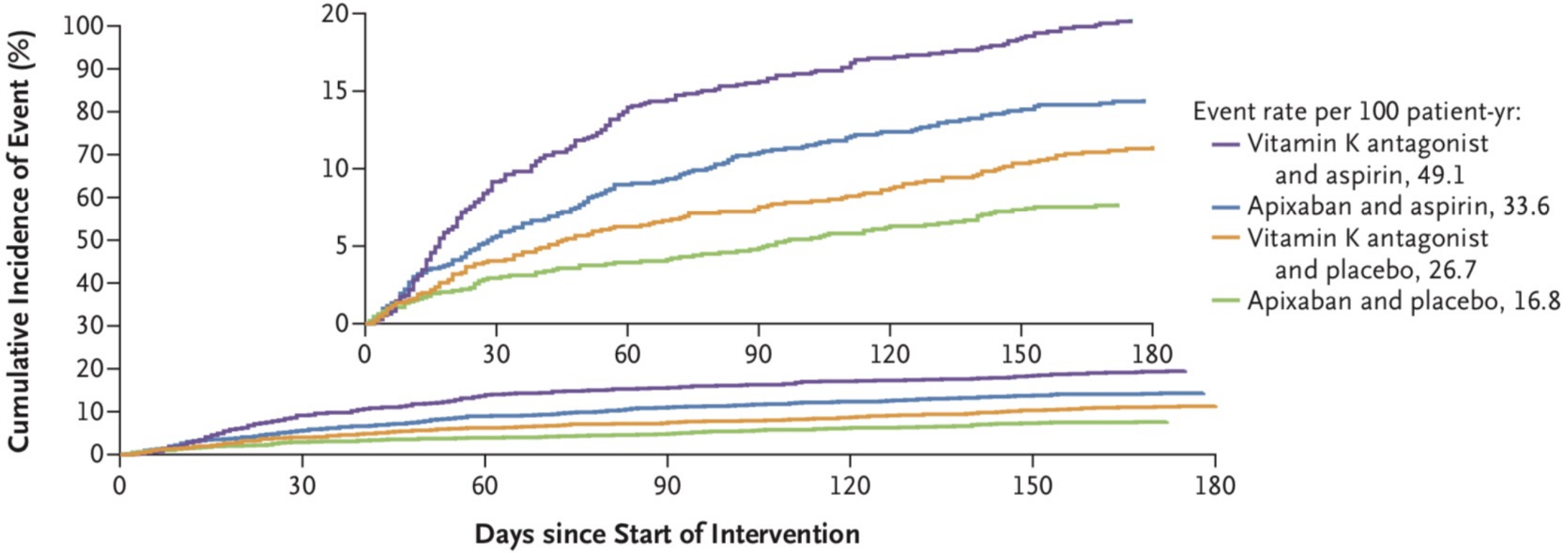
AUGUSTUS



Primary outcome: ISTH major / CRNM bleeding
Secondary outcome(s): death / hospitalization, death / ischemic events

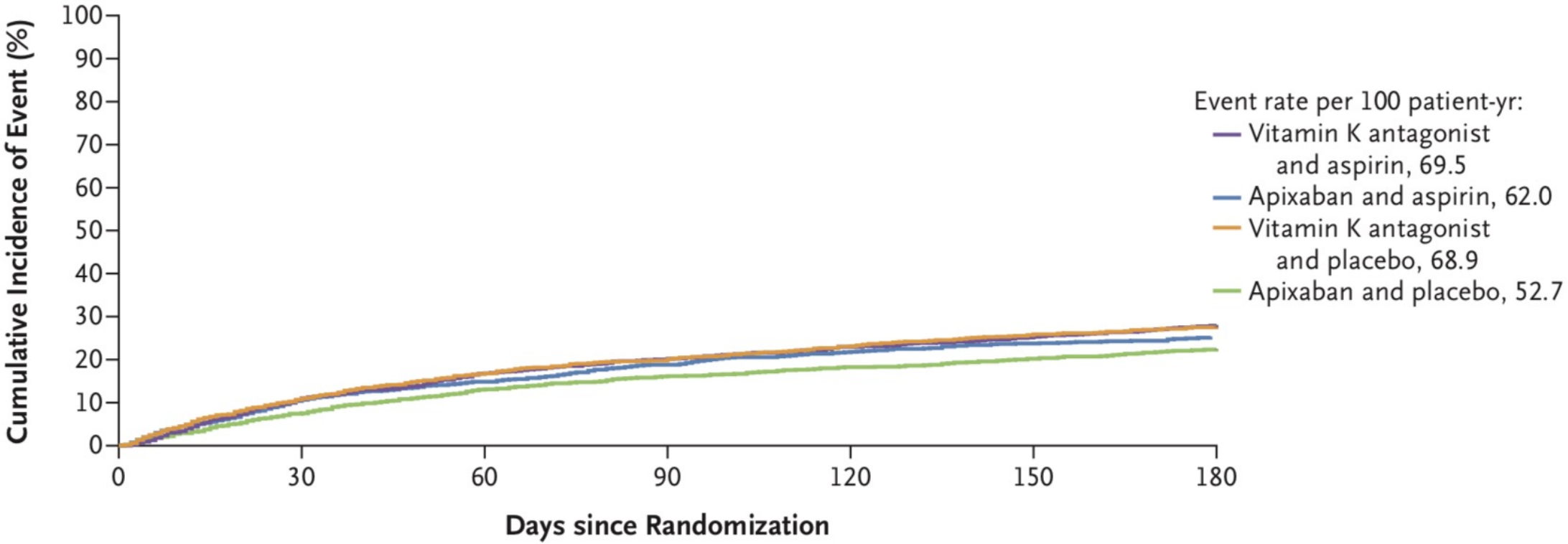
Lopes RD, et al. Am Heart J. 2018;200:17-23.

C **Primary Outcome, According to Intervention Combination**



Lopes RD et al. *New Engl J Med* 2019;DOI:10.1056/NEJMoa181783

C Death or Hospitalization, According to Intervention Combination



Lopes RD et al. *New Engl J Med* 2019;DOI:10.1056/NEJMoa181783

ISCHEMIC OUTCOMES: APIXABAN VS WARFARIN

Endpoint	Apixaban (N=2306)	VKA (N=2308)	HR (95% CI)
Death / Ischemic Events (%)	6.7	7.1	0.93 (0.75–1.16)
Death (%)	3.3	3.2	1.03 (0.75–1.42)
CV Death (%)	2.5	2.3	1.05 (0.72–1.52)
Stroke (%)	**0.6**	**1.1**	**0.50 (0.26–0.97)**
Myocardial Infarction (%)	3.1	3.5	0.89 (0.65–1.23)
Definite or Probable Stent Thrombosis (%)	0.6	0.8	0.77 (0.38–1.56)
Urgent Revascularization (%)	1.7	1.9	0.90 (0.59–1.38)
Hospitalization (%)	**22.5**	**26.3**	**0.83 (0.74–0.93)**

ISCHEMIC OUTCOMES: ASPIRIN VS PLACEBO

Endpoint	Aspirin (N=2307)	Placebo (N=2307)	HR (95% CI)
Death / Ischemic Events (%)	6.5	7.3	0.89 (0.71–1.11)
Death (%)	3.1	3.4	0.91 (0.66–1.26)
CV Death (%)	2.3	2.5	0.92 (0.63–1.33)
Stroke (%)	0.9	0.8	1.06 (0.56–1.98)
Myocardial Infarction (%)	2.9	3.6	0.81 (0.59–1.12)
Definite or Probable Stent Thrombosis (%)	0.5	0.9	0.52 (0.25–1.08)
Urgent Revascularization (%)	1.6	2.0	0.79 (0.51–1.21)
Hospitalization (%)	25.4	23.4	1.10 (0.98–1.24)

META-ANALYSIS OF RCTS

ESC European Society of Cardiology

European Heart Journal (2018) **00**, 1–11
doi:10.1093/eurheartj/ehy162

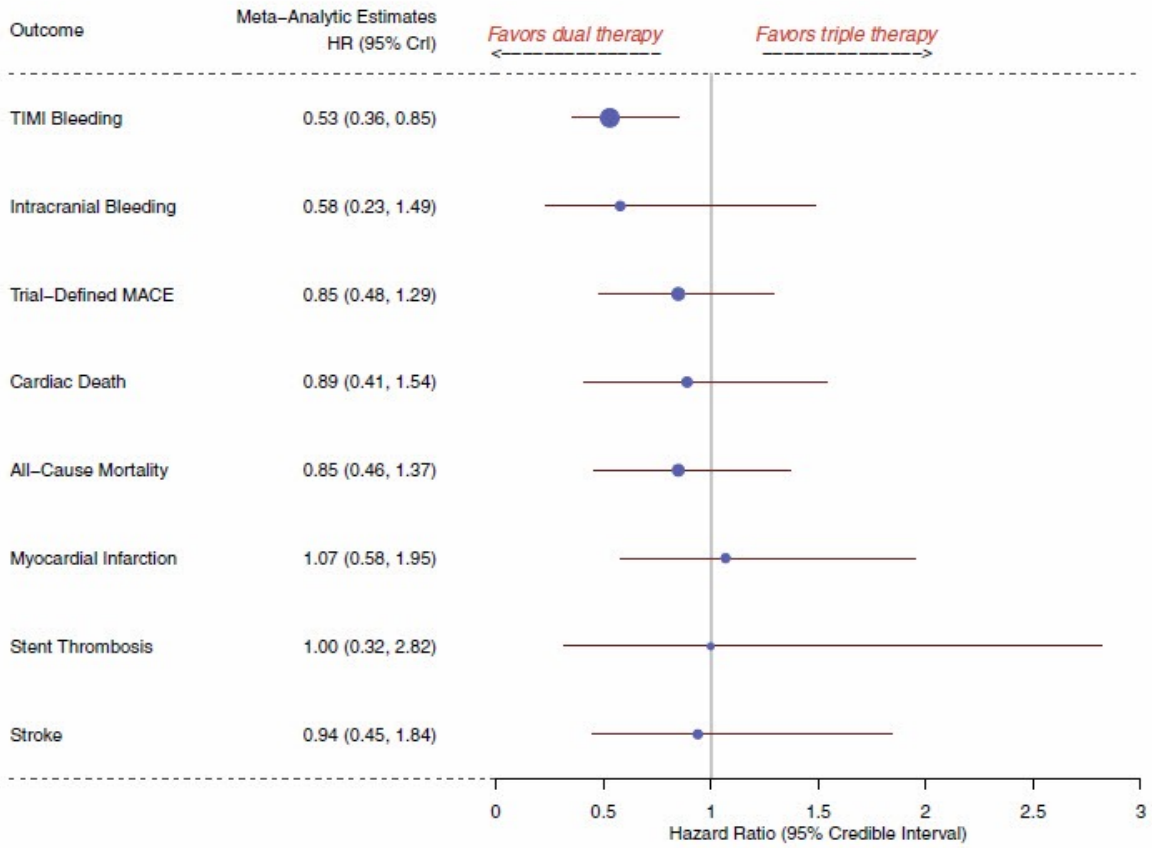
META-ANALYSIS

Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials

Harsh B. Golwala[1], Christopher P. Cannon[1,2], Ph. Gabriel Steg[3], Gheorghe Doros[2,4], Arman Qamar[1], Stephen G. Ellis[5], Jonas Oldgren[6], Jurrien M. ten Berg[7], Takeshi Kimura[8], Stefan H. Hohnloser[9], Gregory Y. H. Lip[10], and Deepak L. Bhatt[1]*

Golwala et al, EHJ 2018; (in press; online)

CTS



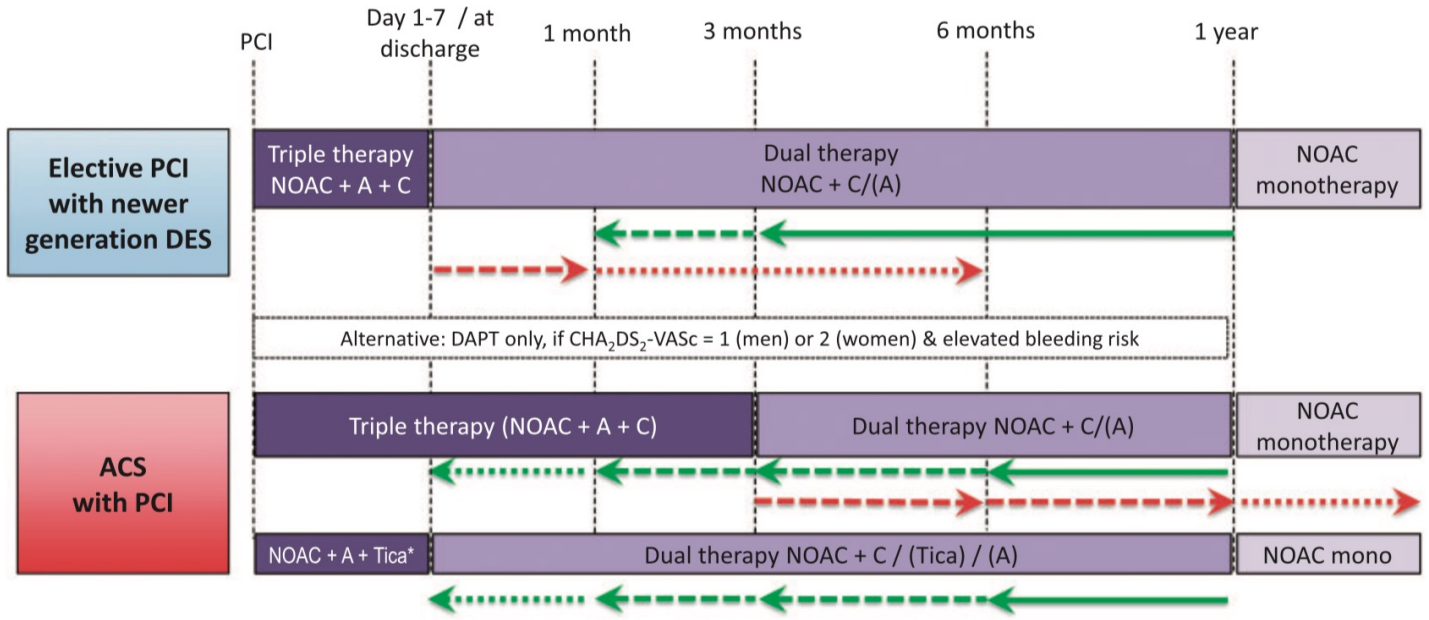
Take home figure Summary of bleeding and ischaemic risks for dual versus triple antithrombotic therapy.

Golwala et al, EHJ 2018; (in press; online)

Conclusion Compared with TAT, DAT shows a reduction in TIMI major or minor bleeding by 47% with comparable outcomes of MACE. Our findings support the concept that DAT may be a better option than TAT in many patients with AF following PCI.

When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A

Benussi S, et al, 2016. *Eur Heart J* 2016; 37:2893-2962



Factors to shorten combination therapy

- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE ≥140 if ACS)

Factors to lengthen combination therapy

- First-generation DES
- High atherothrombotic risk (scores as above ; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

LDL LOWERING

- Statins
- Ezetimibe
- PCSK9 inhibitors

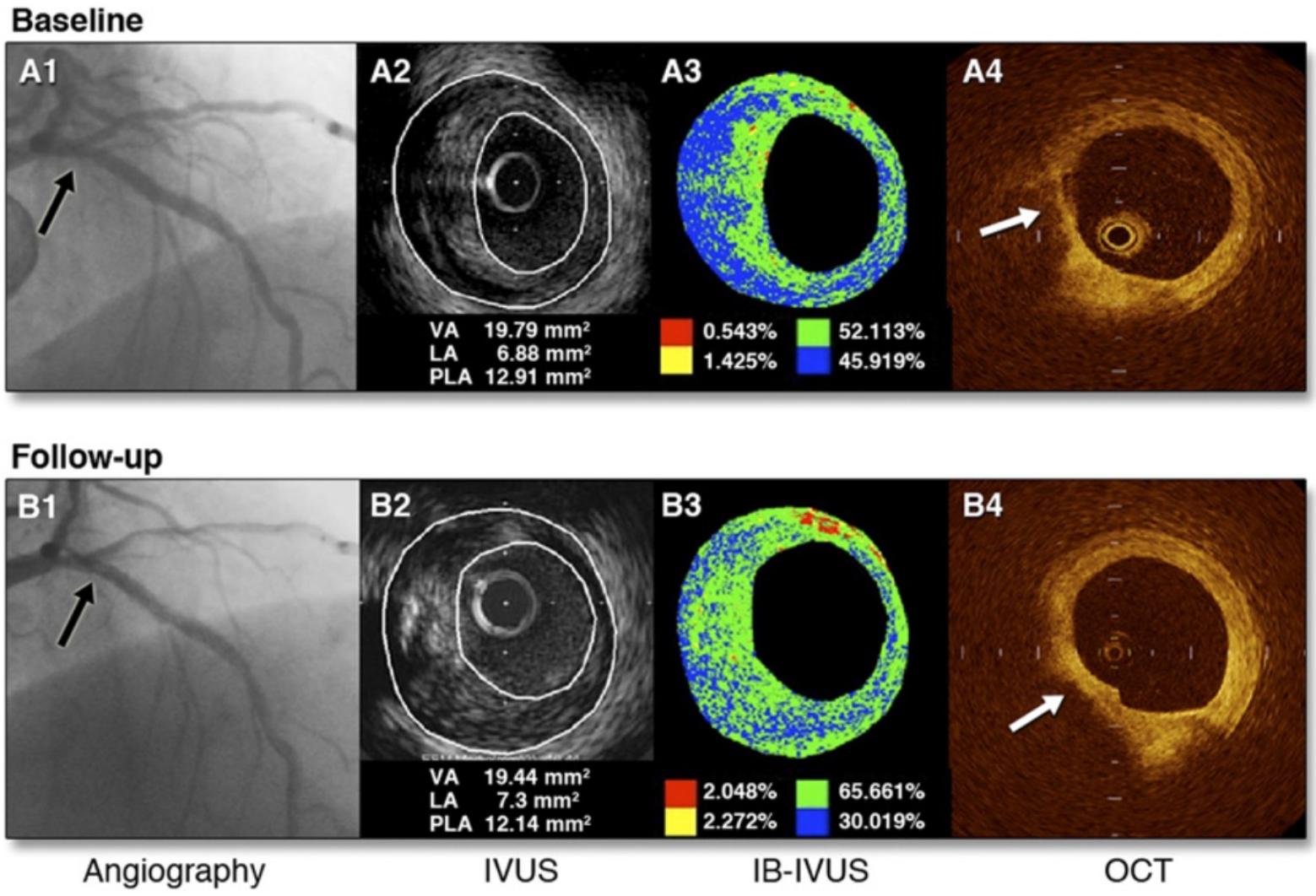
- Fibrates (fenofibrate in combination; x gemfibrozil)

- X Niacin
- Bempedoic acid

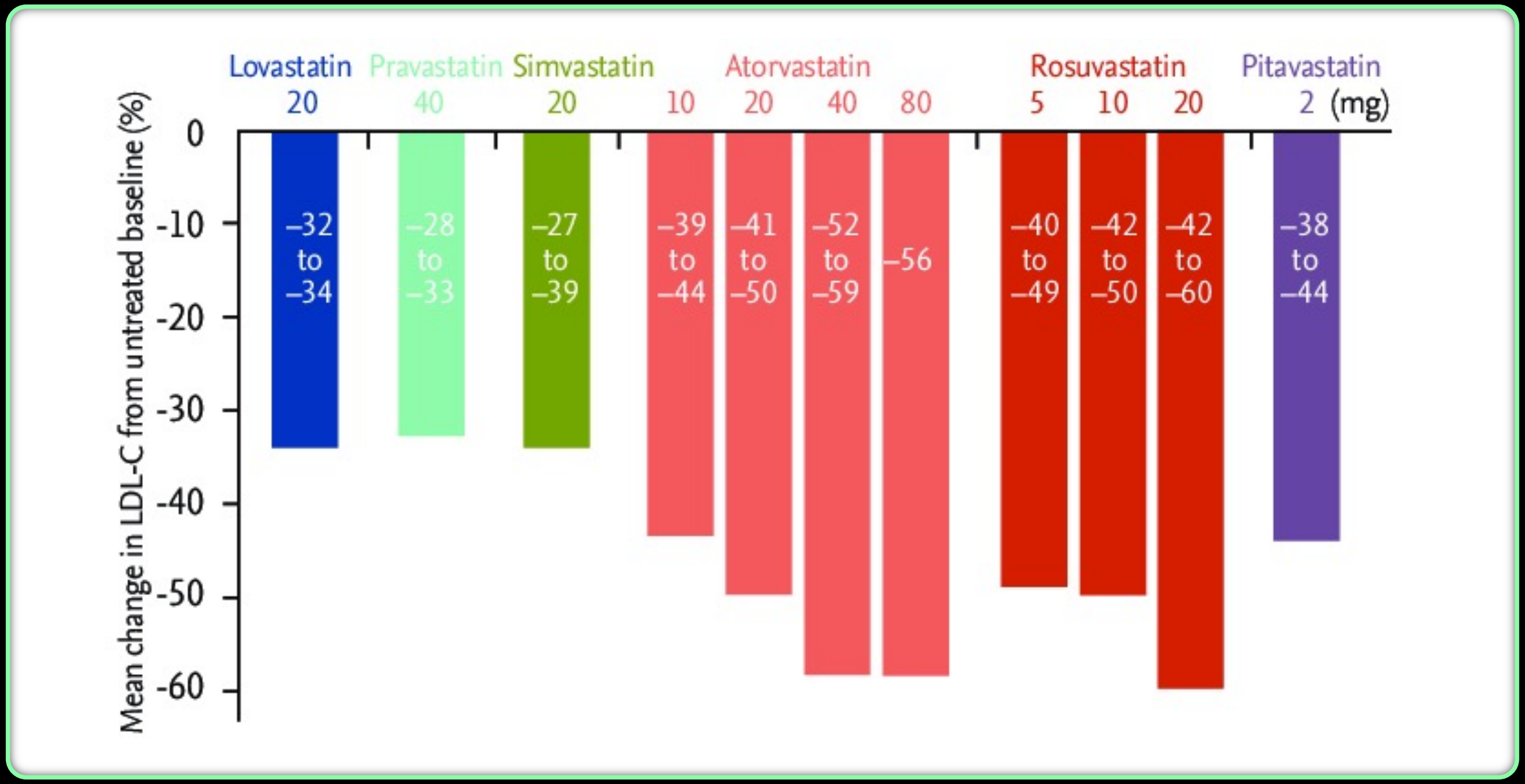
- Familial hypercholesterolemia
  - Events before 55 (men), 60 (women)
  - LDL > 5mmol/L
  - TC > 7.5mmol/L
  - Dutch Lipid Score >= 6

Criteria		Score	Patient Score
Family history			
First degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years) OR First degree relative with known LDL-cholesterol above the 95th percentile for age and gender		**1**	
First degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged <18 years with LDL-cholesterol above the 95th percentile for age and gender		**2**	
Clinical history			
Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)		**2**	
Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)		**1**	
Physical examination			
Tendinous xanthomata		**6**	
Arcus cornealis before 45 years of age		**4**	
Investigation			
LDL-cholesterol (mmol/L)	LDL-C ≥8.5	**8**	
NB. This is the **untreated** LDL-cholesterol concentration. See supporting documentation for method of calculation.	LDL-C 6.5–8.4	**5**	
	LDL-C 5.0–6.4	**3**	
	LDL-C 4.0–4.9	**1**	
		Patient total	

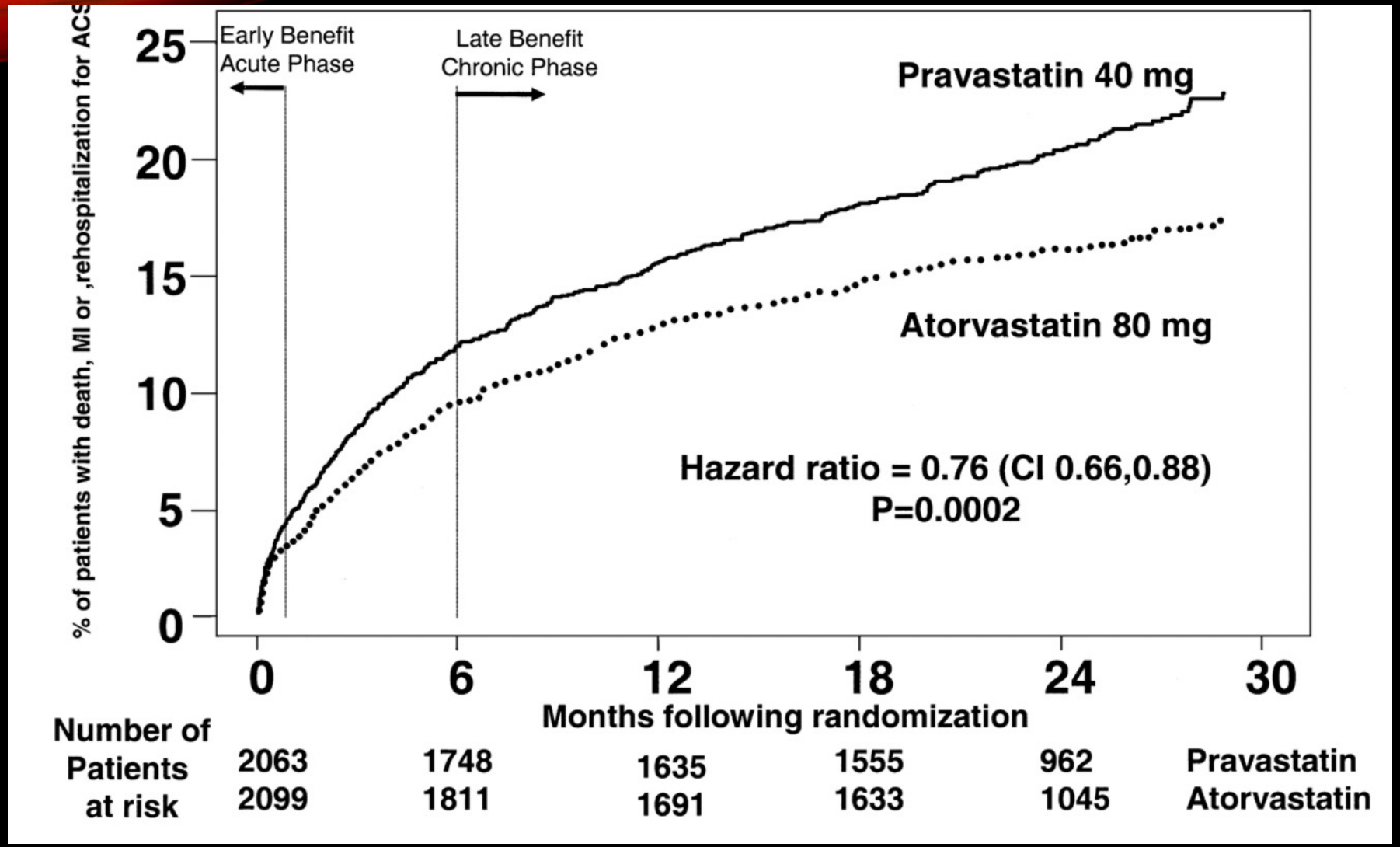
Diagnosis	Total
Definite FH	**>8**
Probable FH	**6-8**
Possible FH	**3-5**
Unlikely FH	**<3**



Hattori et al. JACC Cardiovasc Imaging 2012;5:169-77



Rhee E & HC Kim, *The Korean Journal of Internal Medicine* 2019;34(4):723-771



Ray KK, et al. *J Am Coll Cardiol* 2005;46(8):1405-1410

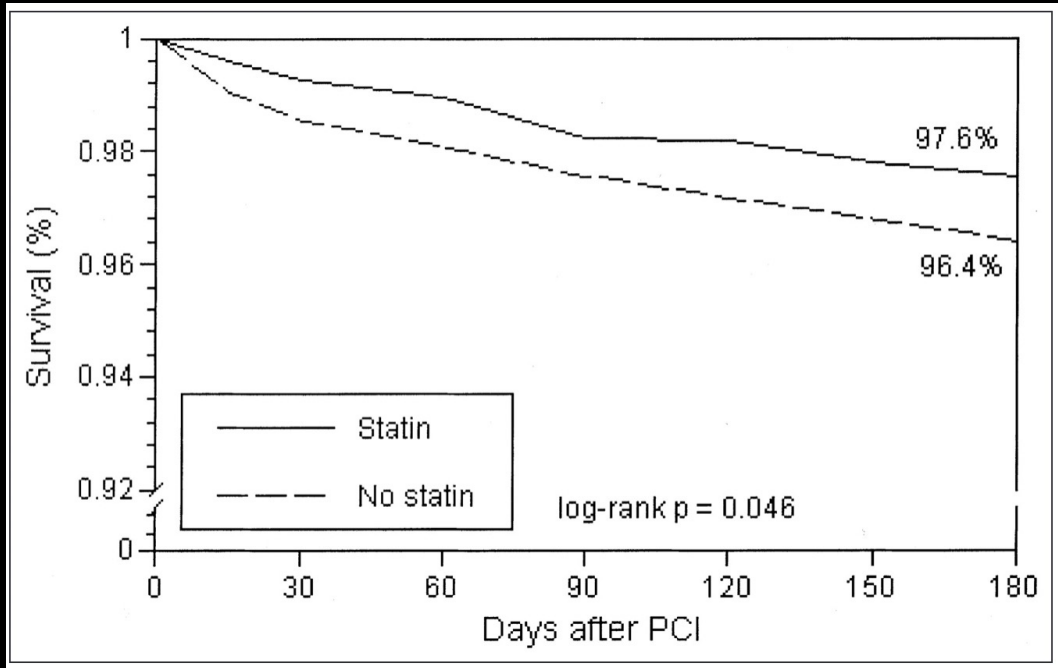


Figure 1. Kaplan-Meier estimates of survival according statin therapy before PCI.

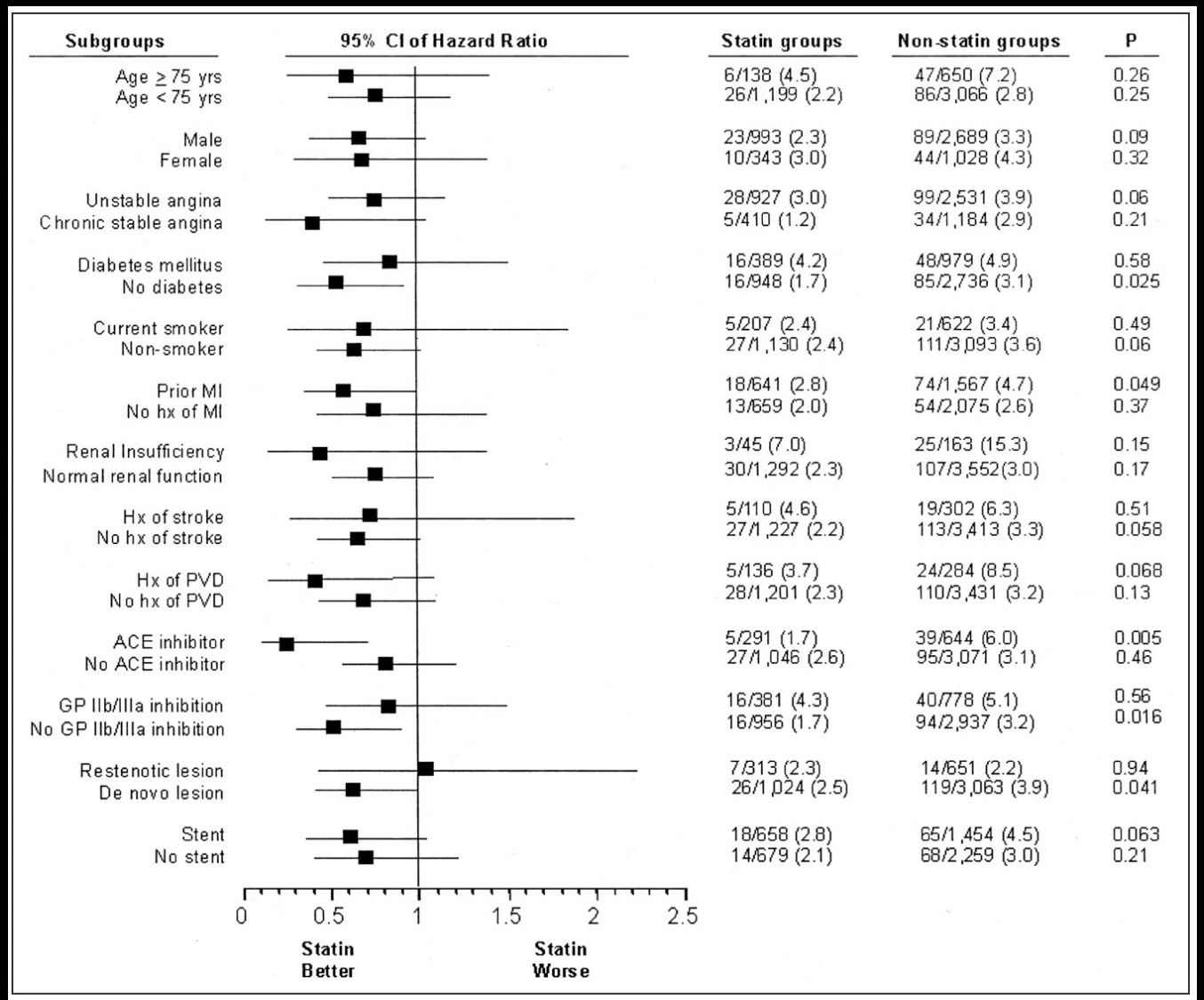


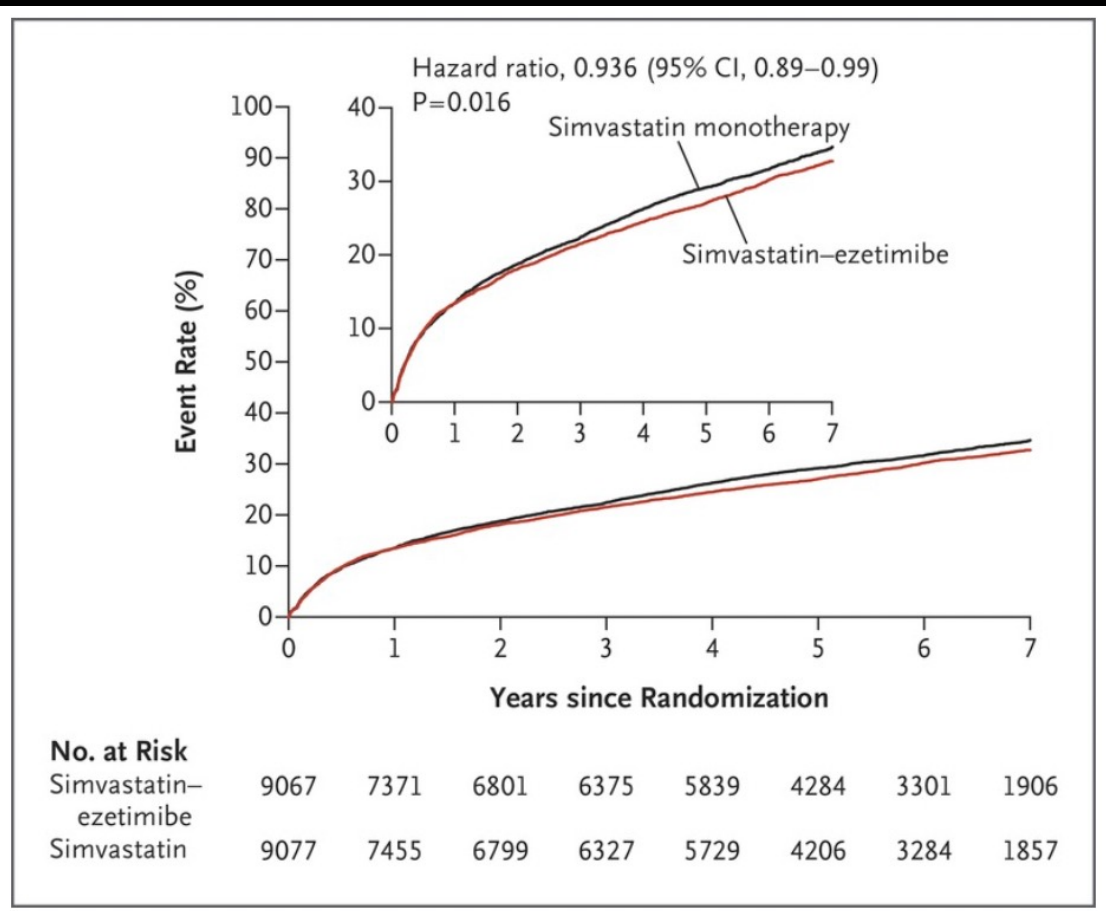
Figure 2. Six-month mortality comparison between treatments stratified by subgroups. GP indicates glycoprotein.

Chan AW, et al. *Circulation* 2002;105(6):691-696

In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.[438,440,442]	I	A
Lipid levels should be re-evaluated 4–6 weeks after ACS to determine whether a reduction of ≥50% from baseline and goal levels of LDL-C <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.	IIa	C

EZETIMIBE

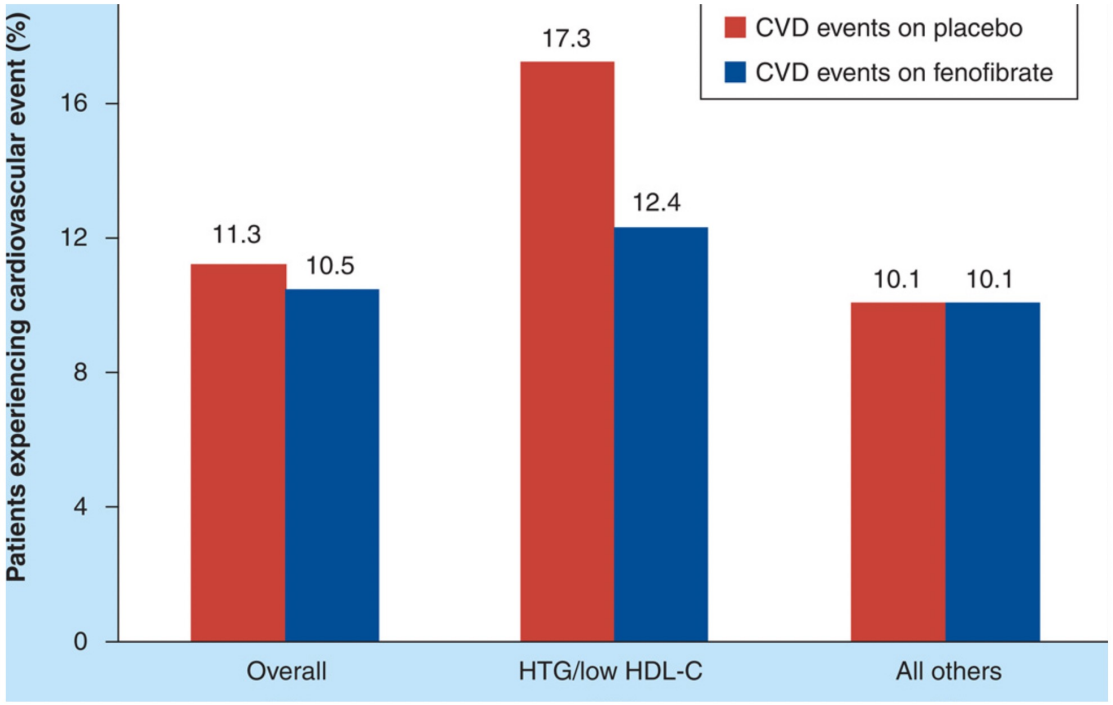
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.[33]	I	B



Kaplan–Meier Curves for the Primary Efficacy End Point.

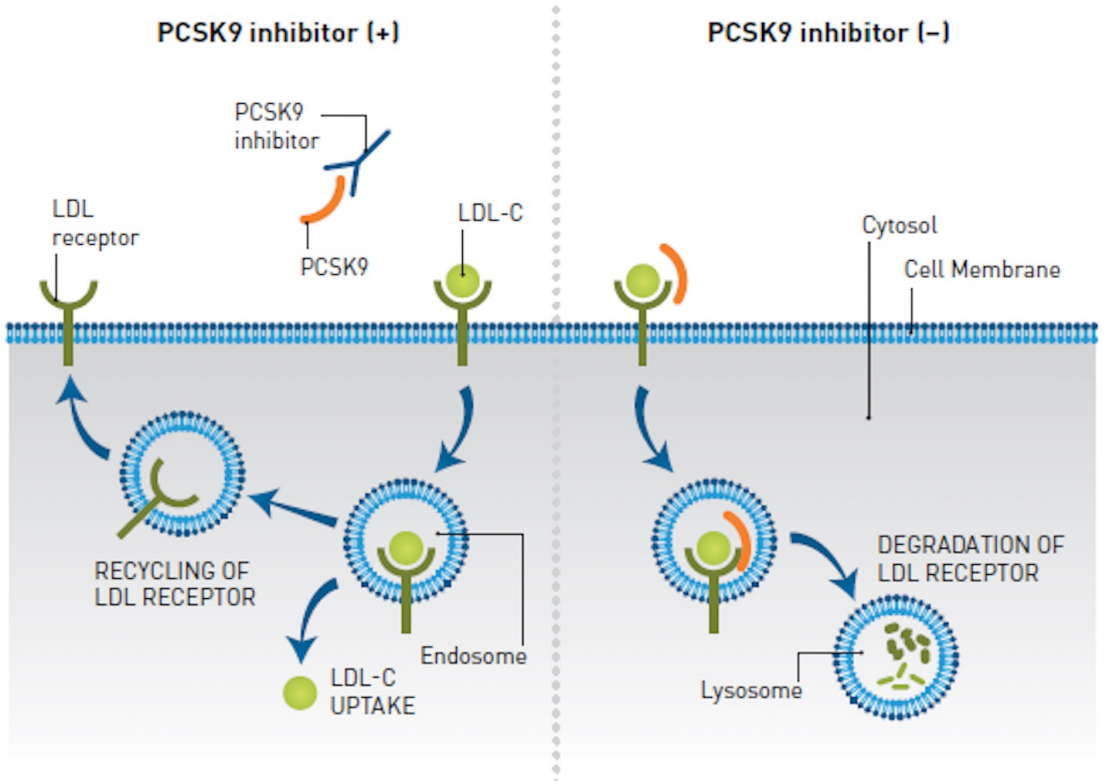
Cannon CP, et al. *New Engl J Med* 2015;372:2387-2397

FIBRATES



Elam M, et al. *Clin Lipidol* 2011;6(1):9-20

PCSK9 INHIBITORS



Ahn CH, Choi SH. *Diabetes Metab J* 2015;39(2):87-94

- Evolocumab (Repatha)
  - FOURIER
    - n=27,564 atherosclerotic CVD
    - Statin +/- evolocumab
    - MACE RRR 15%, 2 years
    - Lowest LDL had lowest MACE
- Alirocumab (Praluent)
  - ODYSSEY Outcomes
    - n=18,924 recent ACS
    - Statin +/- alirocumab
    - MACE RRR 15%; all-cause mortality RRR 15%, 2.8 years
- No significant adverse events
- Earlier initiation probably better

EVOLOCUMAB

Source General Schedule

Body System CARDIOVASCULAR SYSTEM > LIPID MODIFYING AGENTS > LIPID MODIFYING AGENTS, PLAIN

▸ Note

▾ ⚠ Authority Required

Familial heterozygous hypercholesterolaemia

Treatment Phase: Initial treatment

Clinical criteria:

- The treatment must be in conjunction with dietary therapy and exercise,

AND

- The condition must have been confirmed by genetic testing; OR
- The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 6,

AND

- Patient must have an LDL cholesterol level in excess of 2.6 millimoles per litre in the presence of symptomatic atherosclerotic cardiovascular disease; OR
- Patient must have an LDL cholesterol level in excess of 5 millimoles per litre,

AND

- Patient must have been treated with the maximum recommended dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) according to the TGA-approved Product Information or the maximum tolerated dose of atorvastatin or rosuvastatin for at least 12 consecutive weeks in conjunction with dietary therapy and exercise; OR
- Patient must have developed clinically important product-related adverse events necessitating withdrawal of statin treatment to trials of each of atorvastatin and rosuvastatin; OR
- Patient must be contraindicated to treatment with a HMG CoA reductase inhibitor (statin) as defined in the TGA-approved Product Information,

AND

- Patient must have been treated with ezetimibe for at least 12 consecutive weeks in conjunction with a statin (if tolerated), dietary therapy and exercise,

If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended.[119,120]

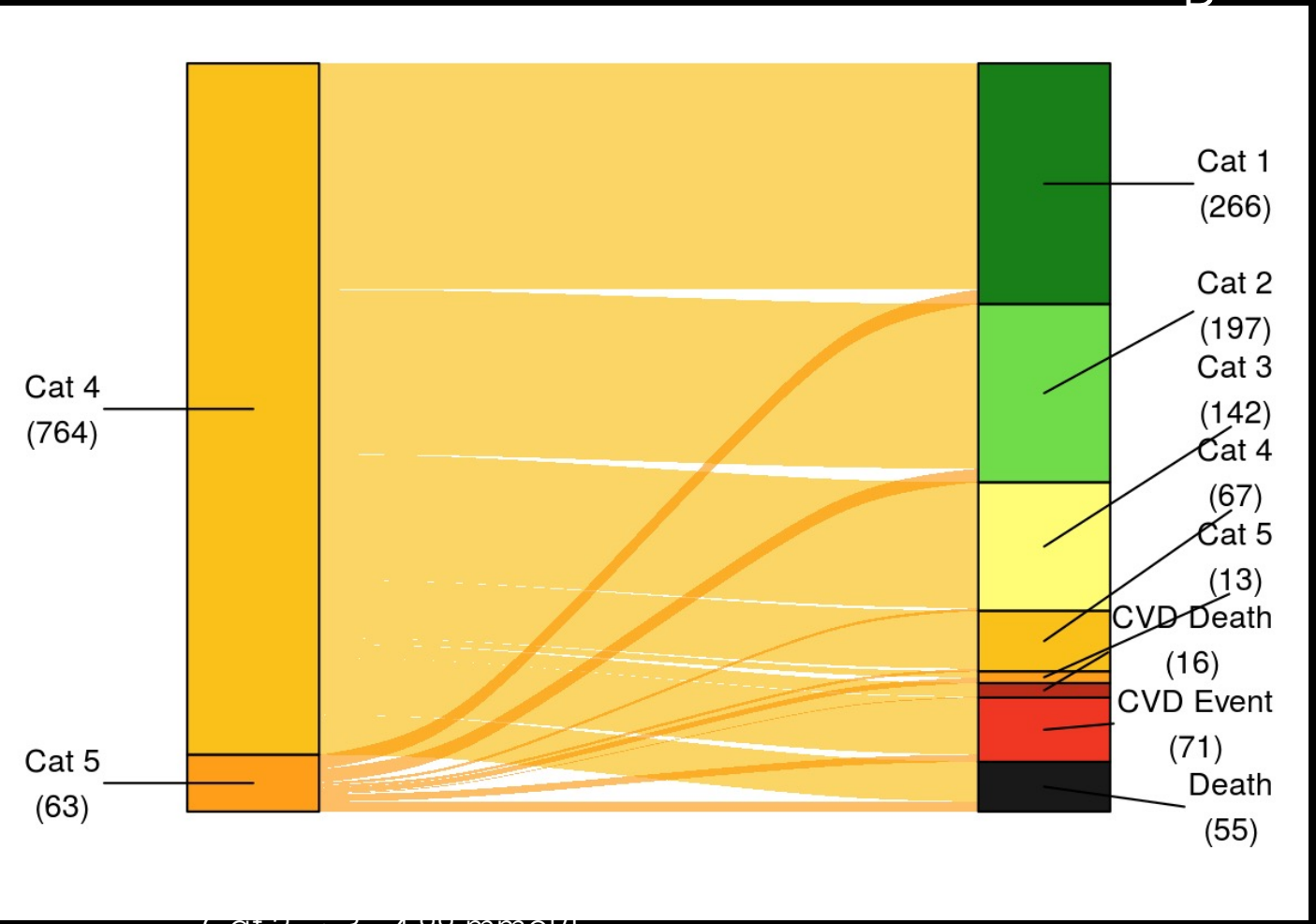
I B

OTHER

- Type 2 diabetes – Metformin, SGLT2 inhibitors, GLP-1 agonists
- ACE-I, ARB
- Beta blockers
- Spiractin
- Entresto
- Devices
  - Cardiac resynchronization
  - Implantable defibrillator

- < 50% of hypertensive patients meeting target BP[1]
- 45% of ACS patients not on optimal LDL therapy at 12 months[2]
- 40% of secondary prevention patients not meeting LDL targets[3]
  - 69% statin monotherapy
  - 6% statin / ezetimibe
  - 6% ezetimibe monotherapy
  - 0.02% PCSK9 inhibitor
- 50% of smokers continue smoking post discharge after ACS or cardiac surgery[4]

[1] Muntner P, et al. *Circulation* 2018;137(2):109-118
[2] Brieger D, et al, *Med J Aust* 2019;210(2):80-86
[3] Carrington MJ, et al. CODE RED: Overturning Australia's cholesterol complacency. May 2020, Baker Heart and Diabetes Institute
[4] Riley H, et al. *Clin Cardiol* 2019;42(12):1189-1194



Cat 2 → 3 - 4.99 mmol/L
Cat 3 → 5 - 6.49 mmol/L
Cat 4 → 6.5 - 8.49 mmol/L
Cat 5 → ≥ 8.5 mmol/L

- (2004 – 2017, n ~ 400,000)
- Ages 18 – 80
- LDL; incident and 5-yr follow up
- LDL > 6.5mmol/L, n = 827

- Alive at 5 years, n = 756
  - LDL < 3mmol/L, n = 266 (35.2)
  - LDL > 6.5mmol/L, n = 80 (10.6)

HOBART PATHOLOGY
LAUNCESTON PATHOLOGY
NORTH WEST PATHOLOGY
Quality is in our DNA

- Secondary prevention (Royal Hobart)
  - Premature ACS event + LDL > 5mmol/L (n=43 of 246 consecutive ACS cases)
  - Most recent lipid measurement (> 12 months)
    - LDL < 1.4mmol/L: 5%
    - LDL < 1.8mmol/L: 13%
    - LDL > 4.0mmol/L: 30%