Recent advances in the treatment of acute coronary syndromes

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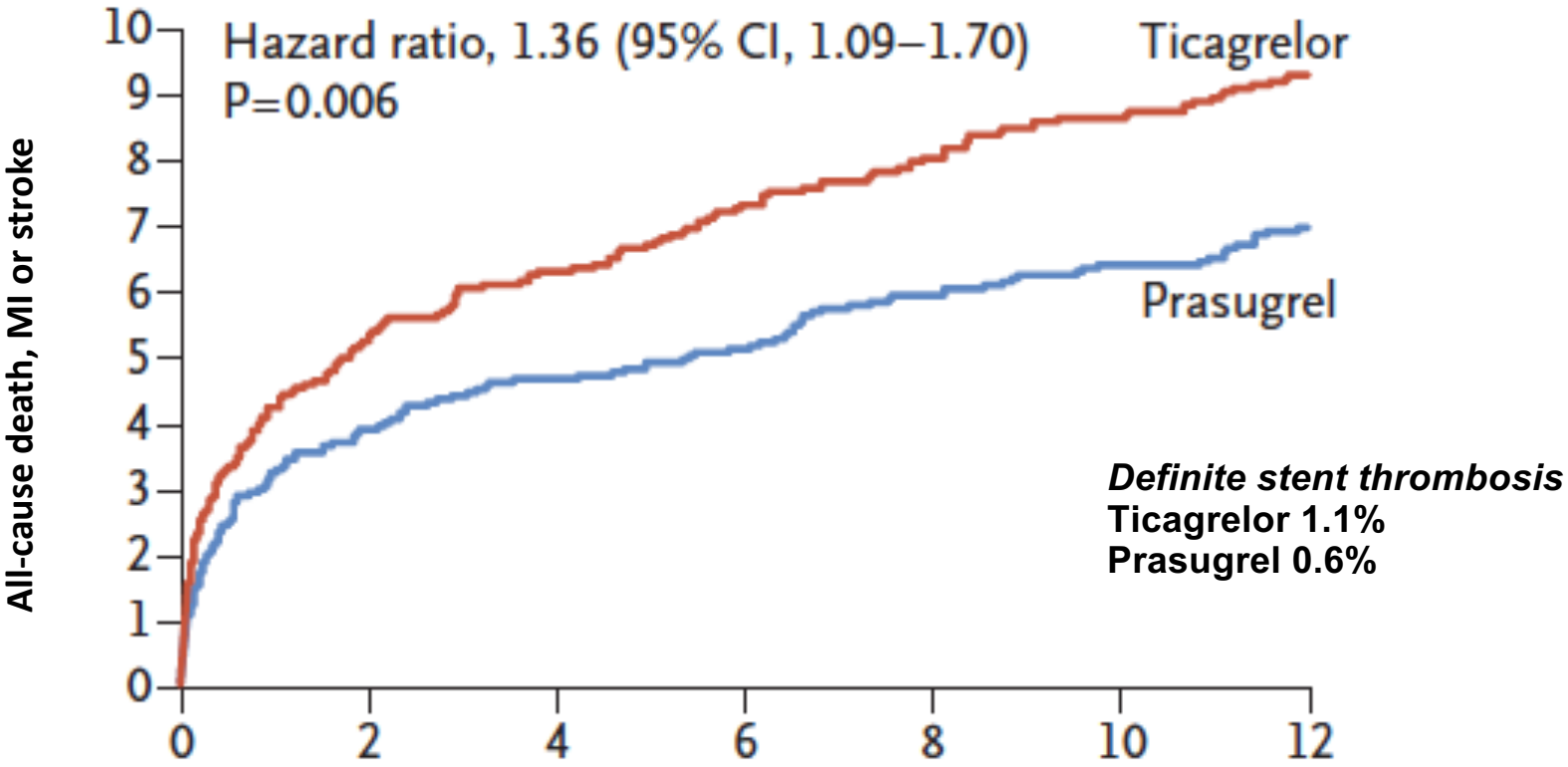
Advances in revascularisation

- Update on antiplatelet therapy
- New PCI techniques

ISAR REACT 5 study



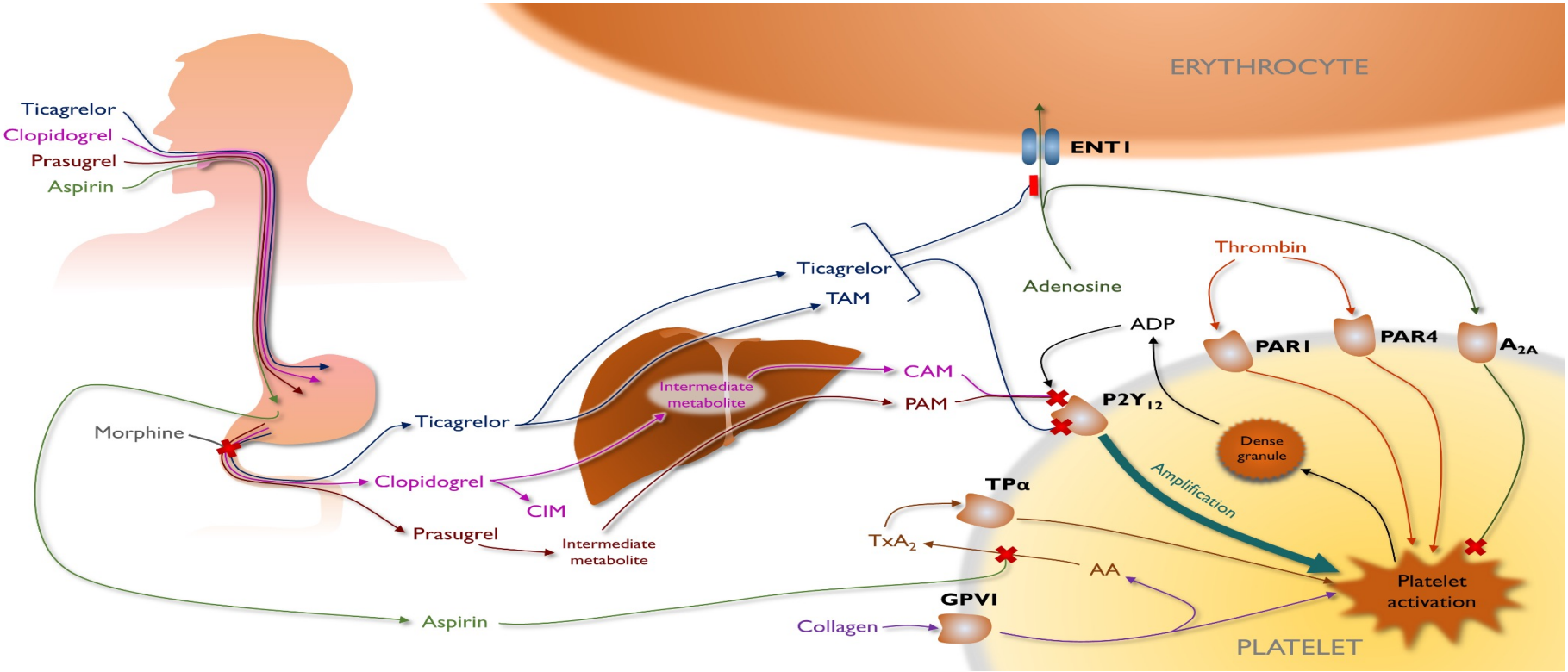
Definite stent thrombosis
Ticagrelor 1.1%
Prasugrel 0.6%

Schupke S et al. New Eng J Med 2019

Actions of aspirin and oral $P2Y_{12}$ inhibitors

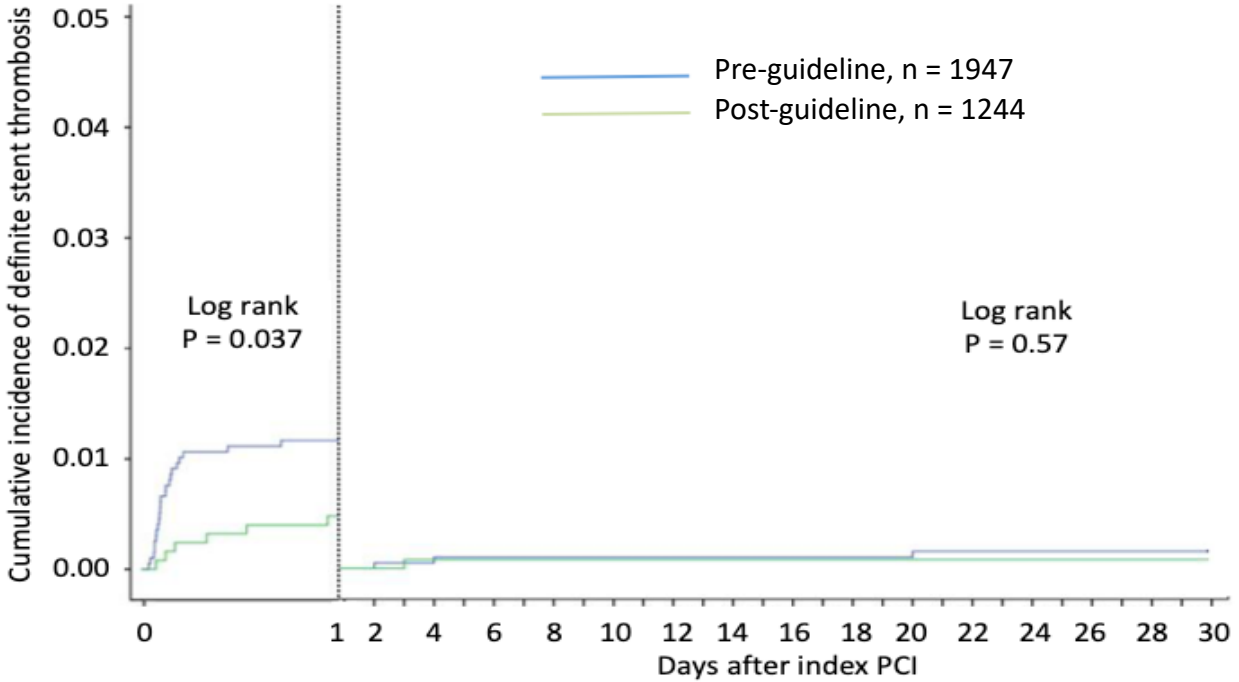
Aspirin is absorbed from the upper GI tract

Absorption of all 3 oral $P2Y_{12}$ inhibitors is delayed by opiates such as morphine



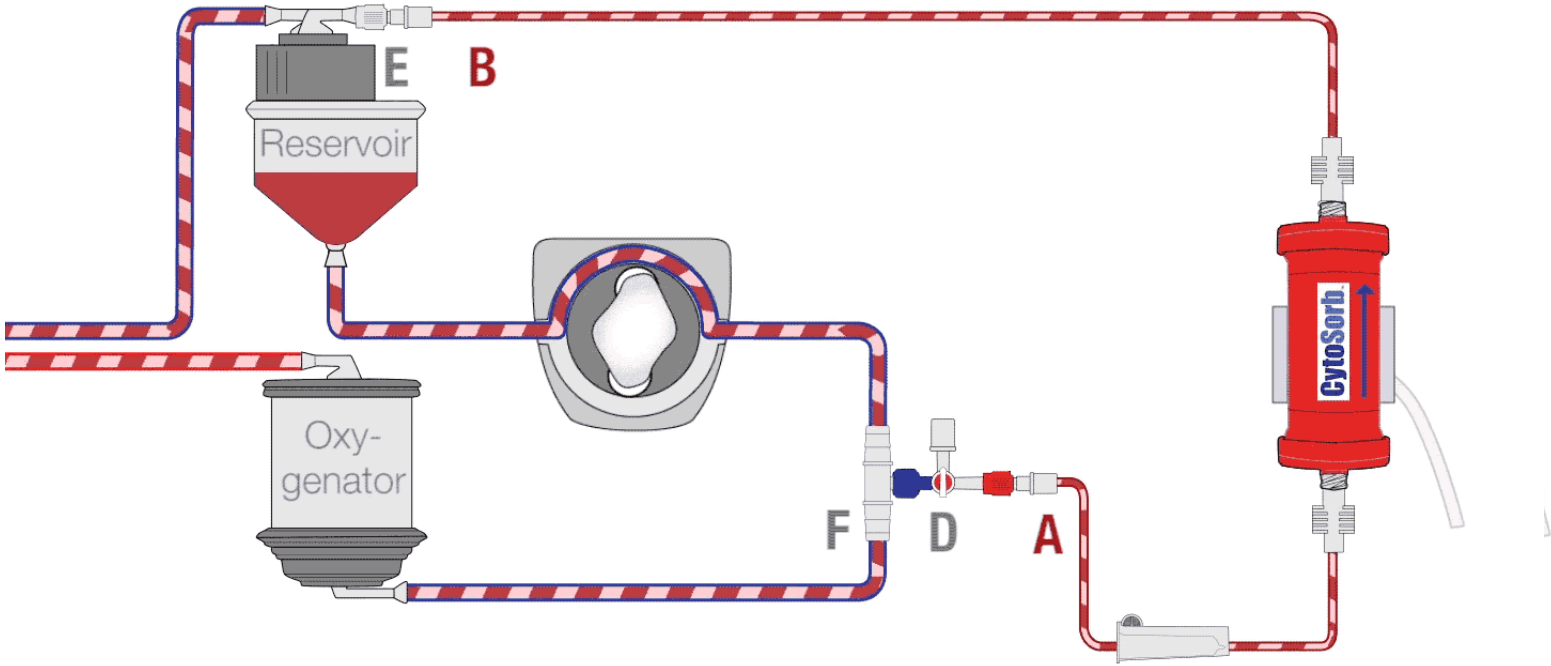
Storey RF & Parker WAE. Circulation 2016; 134:793-6

Impact of local guideline for use of 6-hour parenteral antithrombotic regimen on definite stent thrombosis in morphine-treated primary PCI patients

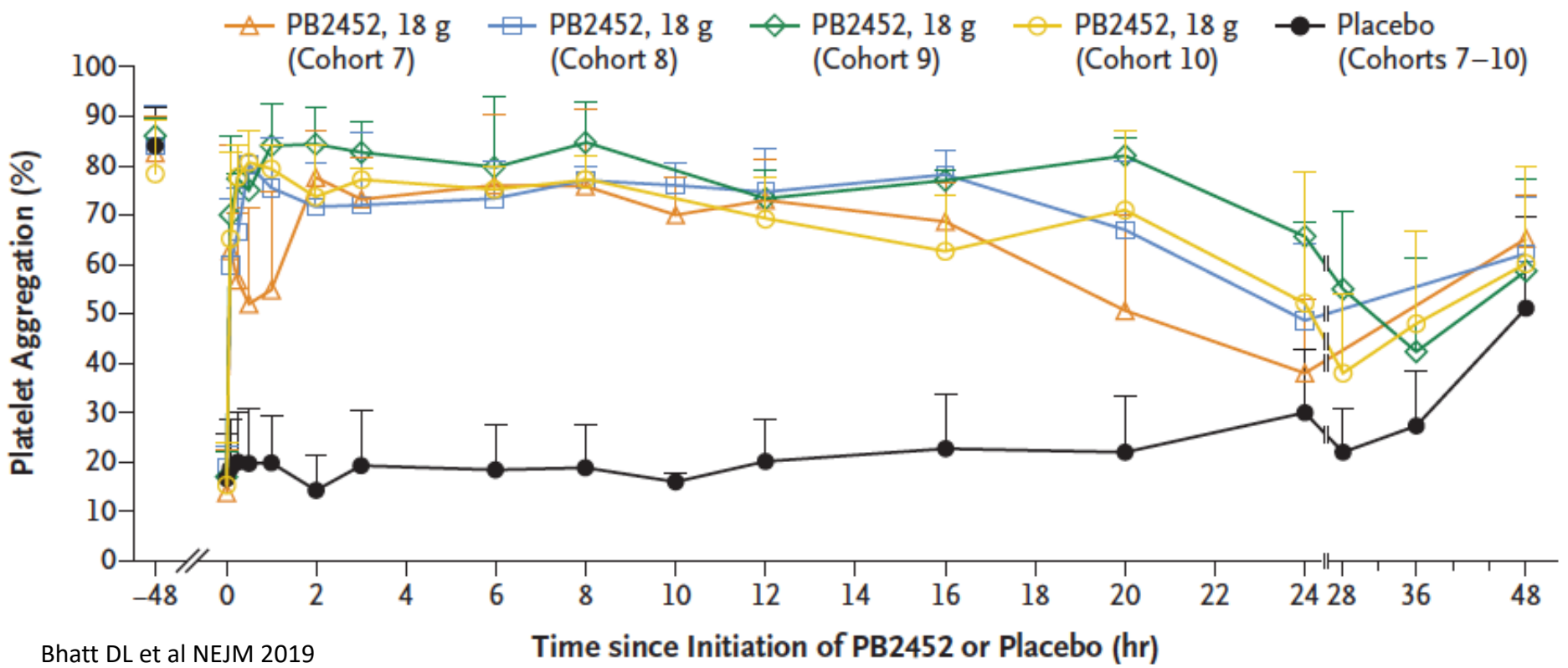


Zwart B, Storey RF et al. Platelets 2019 online 11 Sept 2019

CytoSorb device for ticagrelor removal during CPB surgery



Ticagrelor reversal antibody bentracimab

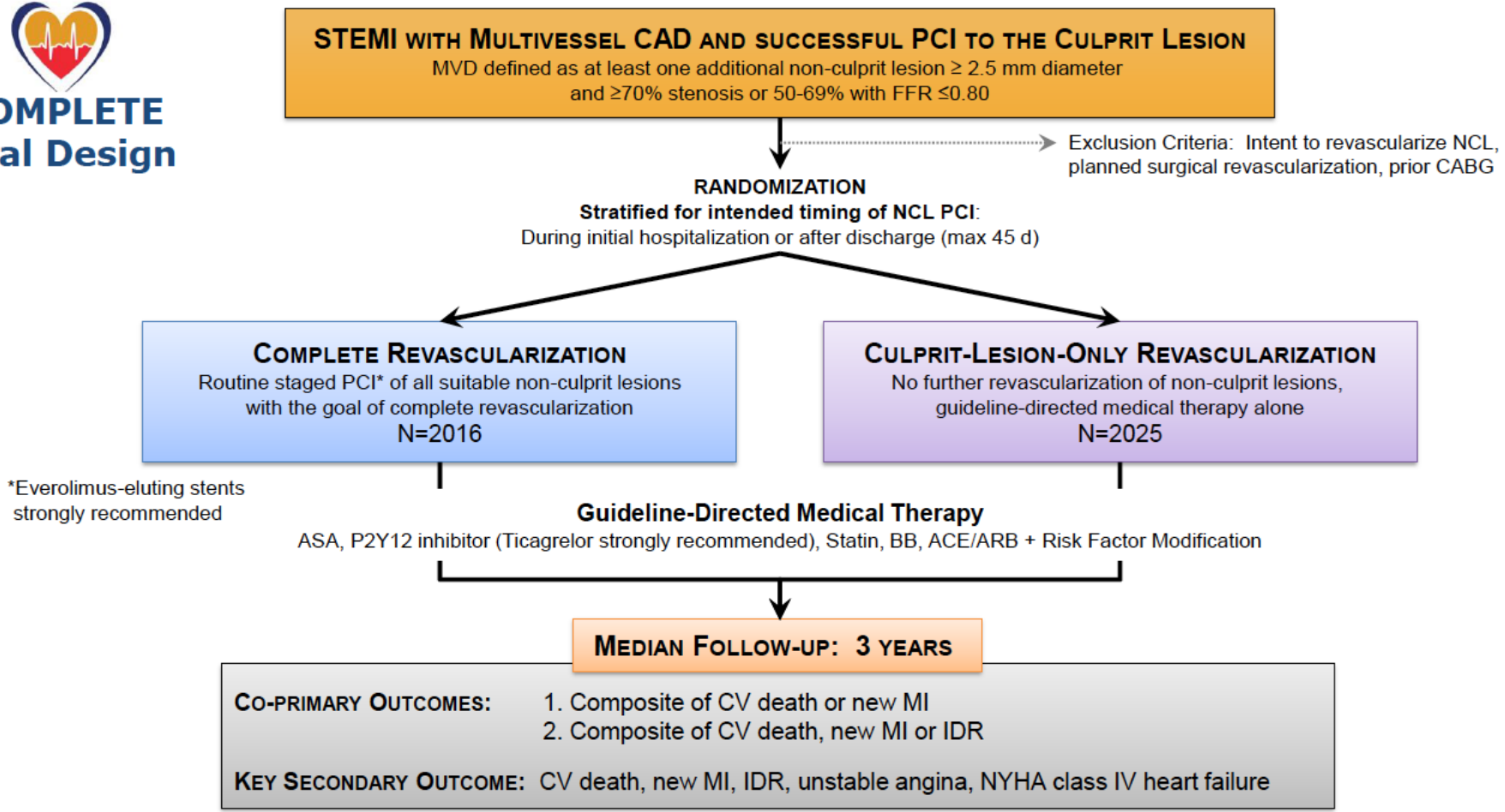


Bhatt DL et al NEJM 2019

Advances in revascularisation

- Update on antiplatelet therapy
- New PCI techniques

COMPLETE Trial Design

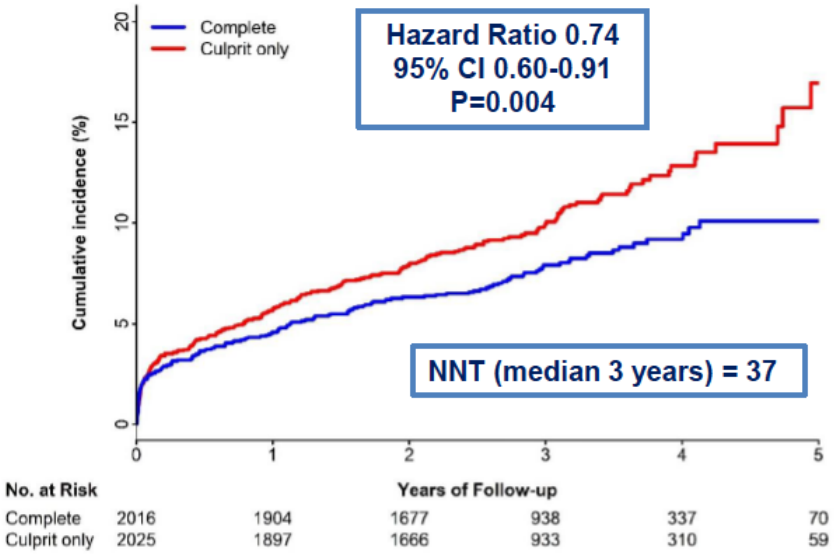


Mehta SR et al. *Am Heart J* 2019; 215:157-166.

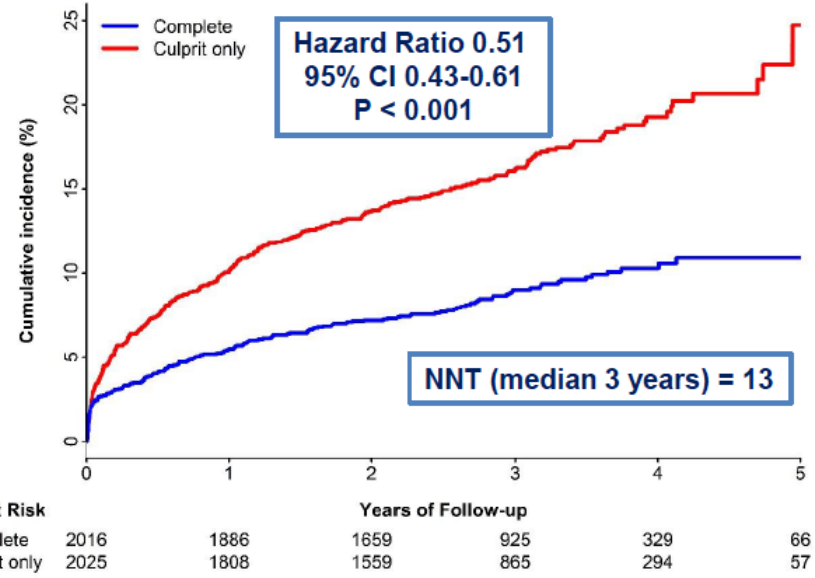
COMPLETE TRIAL

Co-Primary Outcomes

Co-primary #1: CV Death or New MI

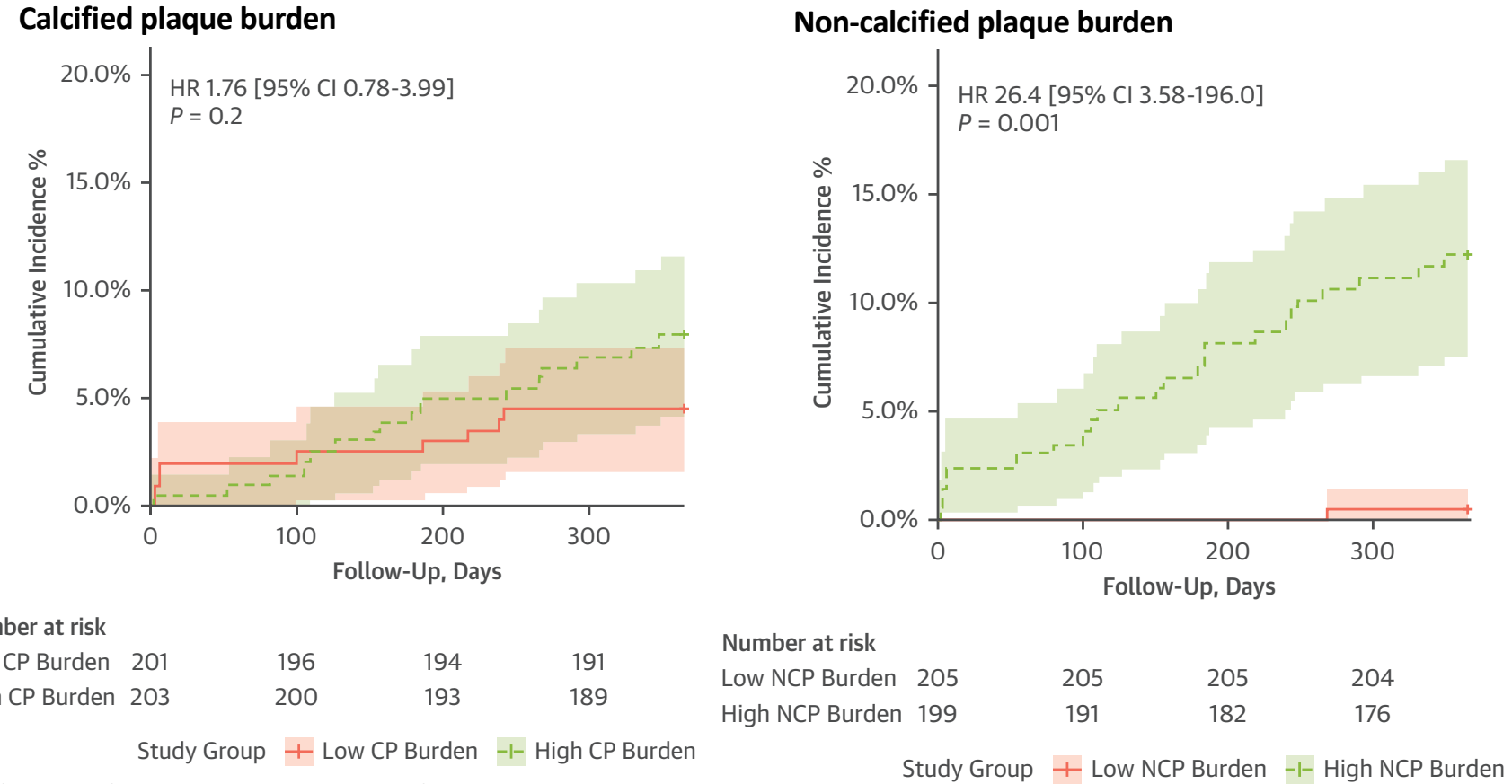


Co-primary #2: CV Death, New MI, or IDR



Mehta SR, Wood DA, Storey RF, Cairns JA et al. *New Eng J Med* e-pub 1 September 2019

All-cause death or type 1 or 4b MI according to CT-defined plaque burden in ACS patients



Meah M et al. JACC Imaging 2022 online

Refinements in treating heavily calcified coronary lesions

Rotablator

Intracoronary lithotripsy
(Shockwave)

Advances in treating chronic total occlusions

Common modifiable and relatively unmodifiable CVD risk factors

Modifiable Risk Factors*	Relatively Fixed Risk Factors†
• Hypertension • Current cigarette smoking, secondhand smoking • Diabetes mellitus • Dyslipidaemia/hypercholesterolaemia • Overweight/obesity • Physical inactivity/low fitness • Unhealthy diet	• CKD • Family history • Increased age • Low socioeconomic/educational status • Male sex • Obstructive sleep apnea • Psychosocial stress

*Factors that can be changed and, if changed, may reduce CVD risk.

†Factors that are difficult to change (CKD, low socioeconomic/educational status, obstructive sleep apnea, cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce CVD risk (psychosocial stress).

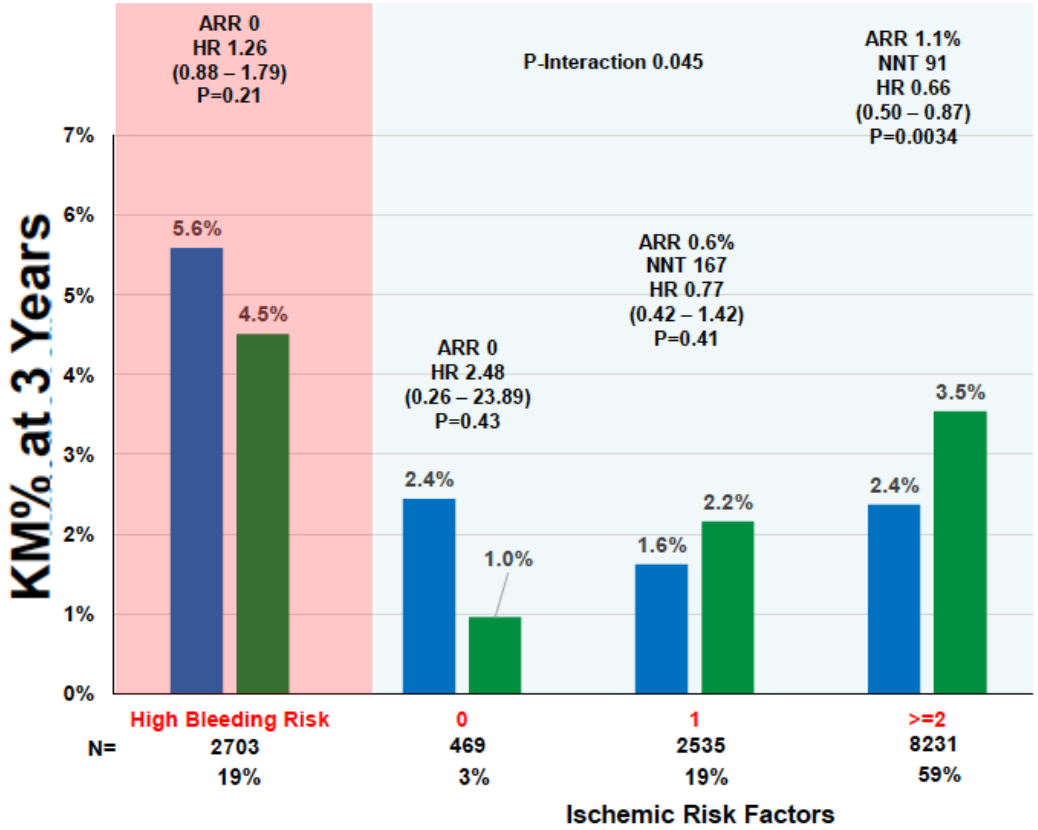
CKD indicates chronic kidney disease; and CVD, cardiovascular disease.

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA
Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Targets in post-MI management

- Thrombosis and bleeding risk
- Lipids
- Blood pressure
- Glycaemic control

PEGASUS TIMI 54: Long-term CV death reduction with ticagrelor 60mg bd according to risk factors for bleeding and ischaemic events



Ticagrelor
Placebo

Bleeding Risk Factors
Low Hgb *or* Prior Hosp for Bleeding

Ischemic Risk Factors
Recent ADP & Recent MI (<2 yrs)
Multivessel coronary disease
Diabetes Mellitus
Peripheral artery disease
Chronic kidney disease
Multiple prior MIs

Bonaca M et al. Poster presented at American Heart Association annual scientific sessions, November 2018

2019 ESC Guidelines on the diagnosis and management of chronic coronary syndromes

Recommendations	Class	Level
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with high risk of ischaemic events[a] and without high bleeding risk.[b]	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 ischaemic events[c] and without high bleeding risk.[b]	IIb	A

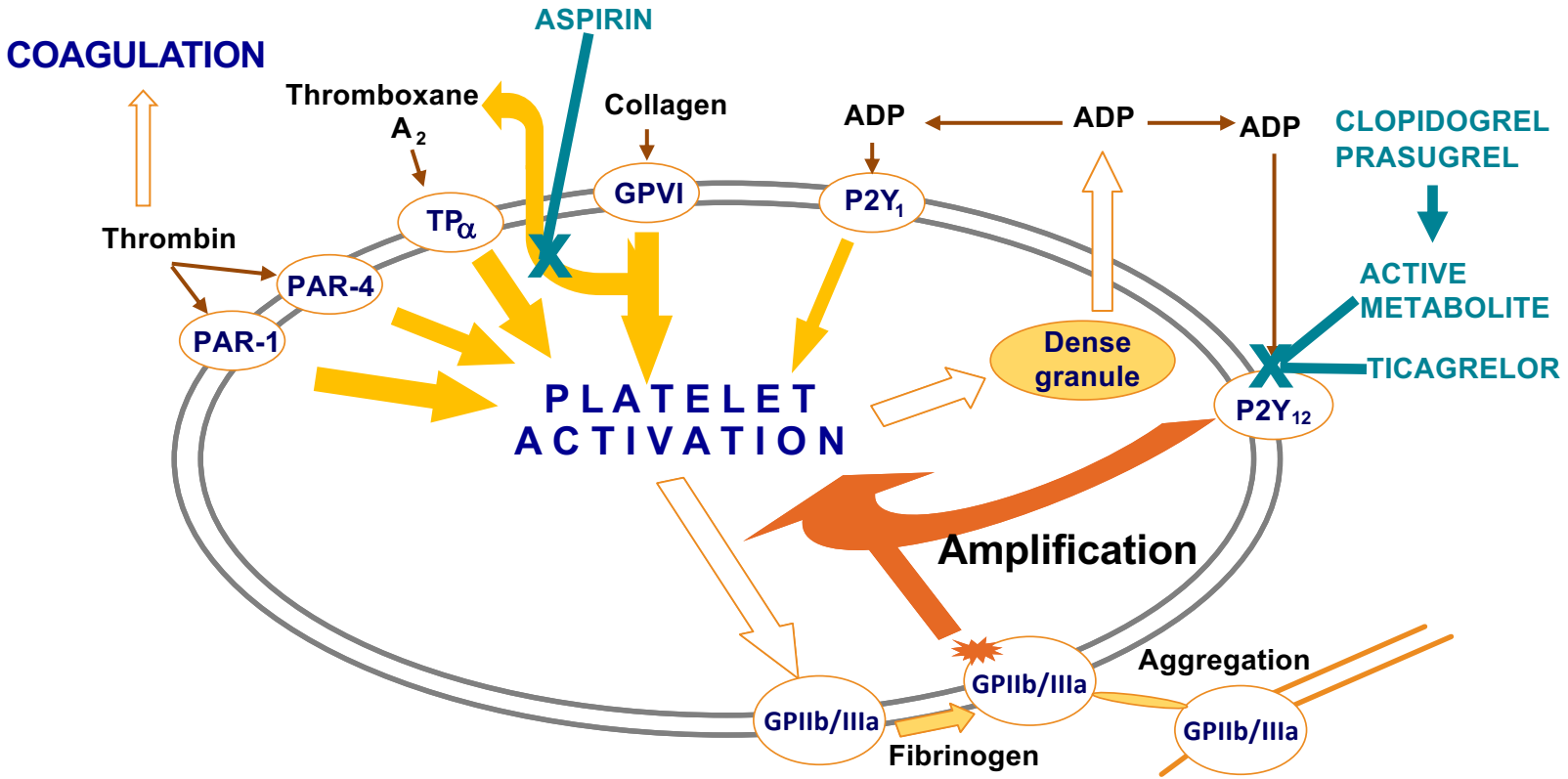
[a] **Diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15-59 mL/min/1.73 m^2.**

[b] **Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.**

[c] At least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15-59 mL/min/1.73 m2

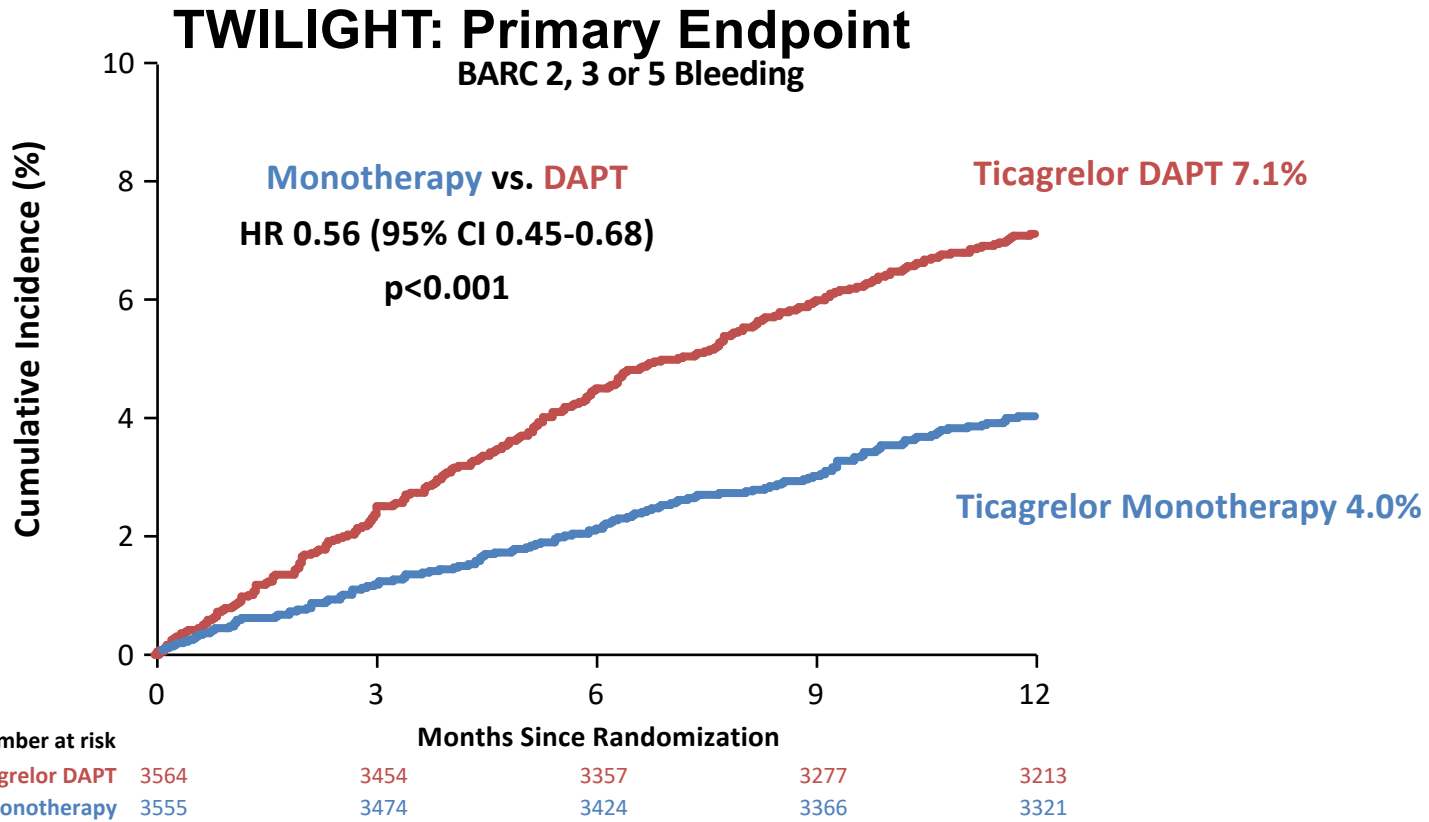
www.escardio.org/guidelines

Oral Antiplatelet Drug Mechanisms of Action



Storey RF. *Curr Pharm Des* 2006

Dropping aspirin 3 months post PCI reduces bleeding…..

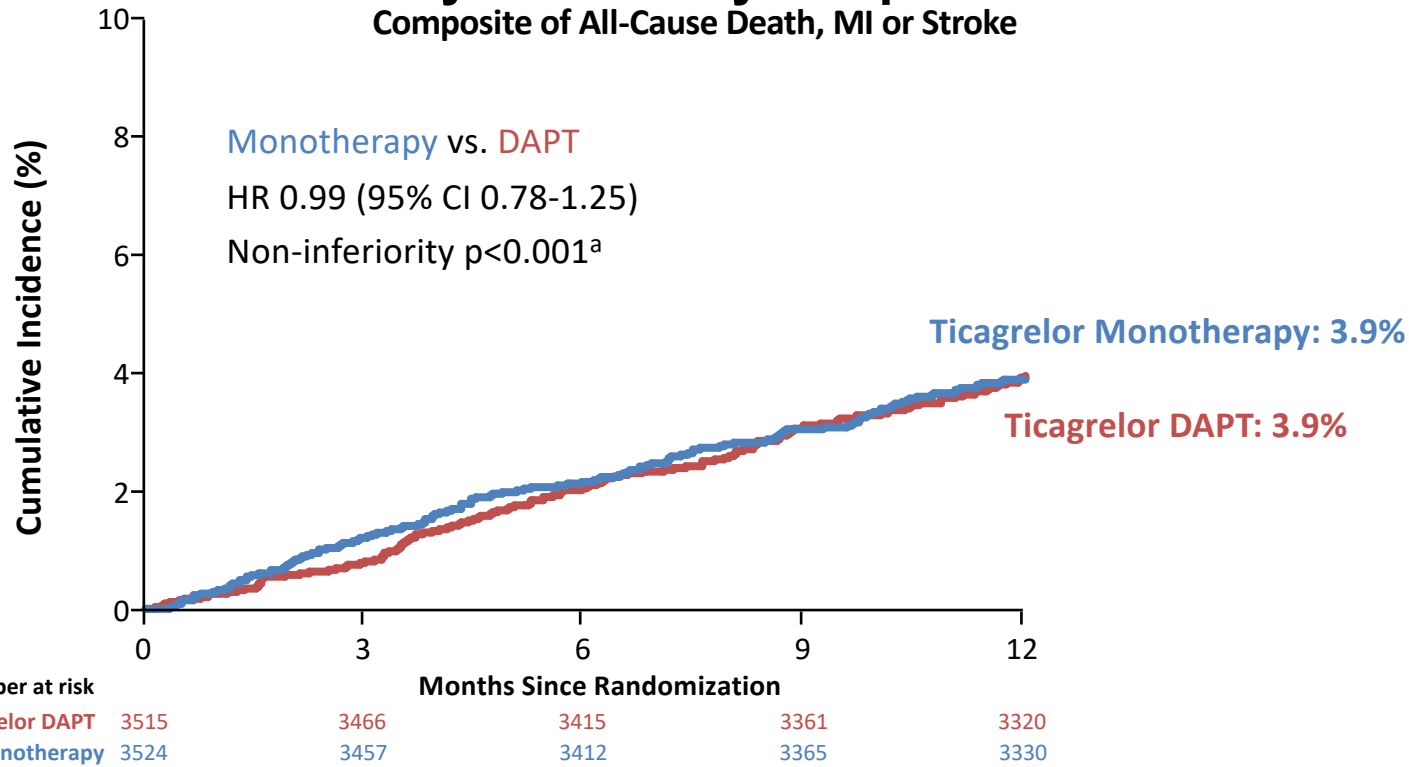


Note: The primary endpoint analysis was performed in the ITT cohort, including those who were successfully randomized at the 3-month visit.[2]

1. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

….without penalty in ischaemic events?

TWILIGHT: Key Secondary Endpoint



Note: The key secondary endpoint was performed in the per protocol cohort, including those who were randomized and completed all study-related contacts without any major protocol deviations.[2]

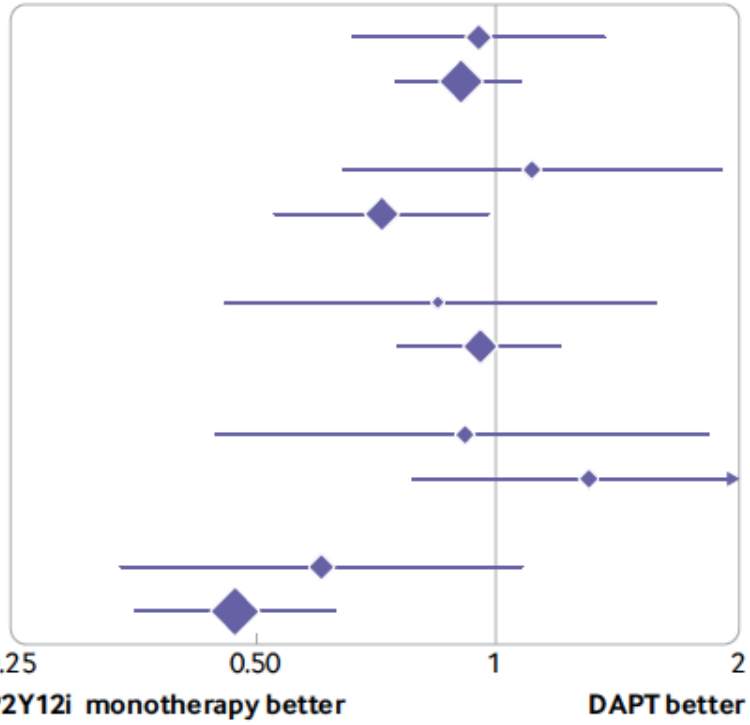
[a]Non-inferiority was tested at a one-sided alpha level of 0.025 using 1.6% as the absolute upper limit of the 95% CI.[2]

1. Mehran R et al. Online ahead of print. *N Engl J Med*. 2019; 2. Baber U et al. *Am Heart J.* 2016;182:125-134.

Meta-analysis of DAPT vs $P2Y_{12}$ inhibitor monotherapy studies

Primary outcome: All-cause death, myocardial infarction or stroke

	P2Y12i monotherapy (%) (n=11 634)	DAPT (%) (n=11 674)	Hazard ratio (95% CI)	P value for interaction	Hazard ratio (95% CI)
Primary outcome					
Clopidogrel	60/2618 (2.5)	65/2650 (2.7)		0.16	0.94 (0.66 to 1.33)
Newer P2Y12i	243/9016 (2.9)	273/9024 (3.4)			0.89 (0.75 to 1.06)
All cause mortality					
Clopidogrel	29/2618 (1.2)	27/2650 (1.1)		0.16	1.09 (0.65 to 1.84)
Newer P2Y12i	78/9016 (0.9)	110/9024 (1.4)			0.71 (0.53 to 0.95)
Myocardial infarction					
Clopidogrel	19/2618 (0.8)	23/2650 (1.0)		0.23	0.84 (0.46 to 1.54)
Newer P2Y12i	148/9016 (1.8)	158/9024 (1.9)			0.94 (0.75 to 1.17)
Stroke					
Clopidogrel	15/2618 (0.6)	17/2650 (0.7)		0.40	0.90 (0.45 to 1.79)
Newer P2Y12i	36/9016 (0.5)	28/9024 (0.3)			1.29 (0.79 to 2.11)
BARC 3 or 5					
Clopidogrel	19/2618 (0.8)	32/2650 (1.3)		0.41	0.60 (0.34 to 1.06)
Newer P2Y12i	78/9016 (0.9)	165/9024 (1.9)			0.47 (0.36 to 0.62)



Valgimigli M et al. Brit Med J 2021; 373:n1332

HOST-EXAM study

Clopidogrel vs aspirin monotherapy from 6-18 months after PCI

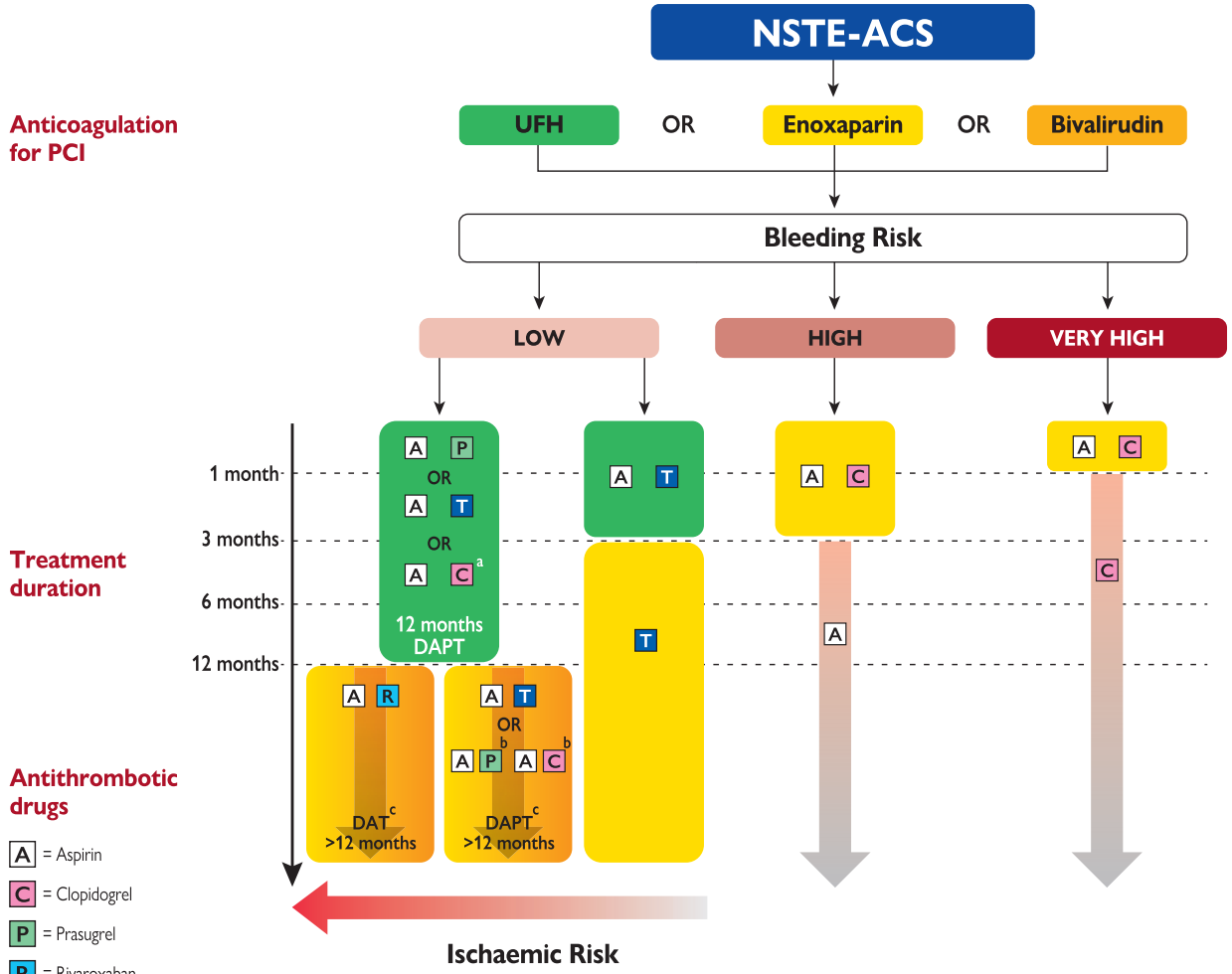
	Clopidogrel N = 2710	Aspirin N = 2728	HR (95% CI)	P value
Primary composite endpoint†	5.7%	7.7%	0.73 (0.59-0.90)	0.003
Thrombotic composite endpoint‡	3.7%	5.5%	0.68 (0.52-0.87)	0.003
Any bleeding (BARC type 2-5)	2.3%	3.3%	0.70 (0.51-0.98)	0.036
All-cause death	1.9%	1.3%	1.43 (0.93-2.19)	0.101
Cardiac death	0.7%	0.5%	1.37 (0.69-2.73)	0.374
Non-cardiac death	1.2%	0.8%	1.47 (0.85-2.52)	0.167

† Composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to ACS, and major bleeding events (BARC type ≥3)

‡ Cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to ACS, and definite or probable stent thrombosis

Koo B-K et al. Lancet 2021; 397: 2487-96

2020 ESC NSTE-ACS guidelines



[a]Clopidogrel during 12 months DAPT if patient is not eligible for treatment with prasugrel or ticagrelor or in a setting of DAPT de-escalation with a switch to clopidogrel (class IIb).

[b]Clopidogrel or prasugrel if patient is not eligible for treatment with ticagrelor.

[c]Class IIa indication in patients at high risk for ischaemic events and without increased risk of major bleeding = prior history of intracranial haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, renal failure requiring dialysis, or with eGFR <15 mL/ min/1.73 m^2

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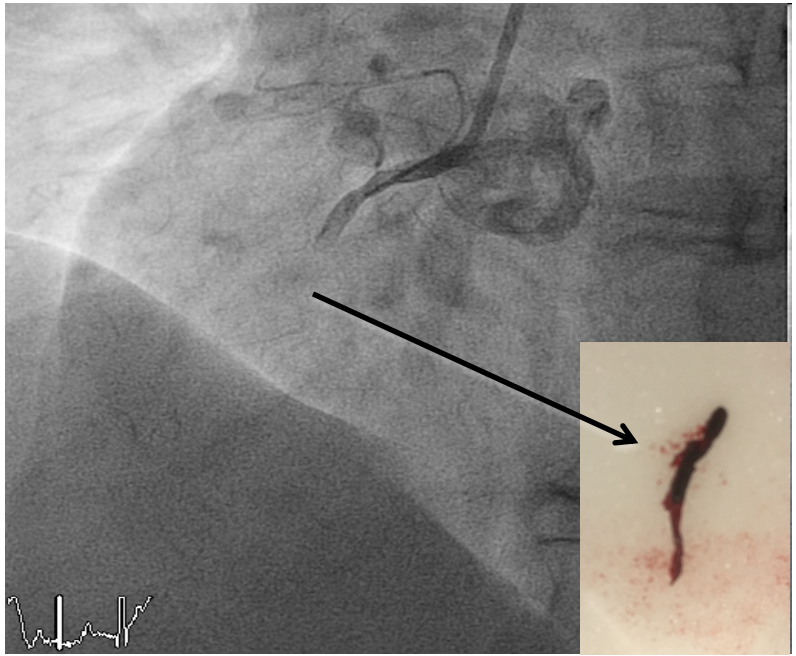
The challenge of AF and ACS

How do you treat coronary thrombosis

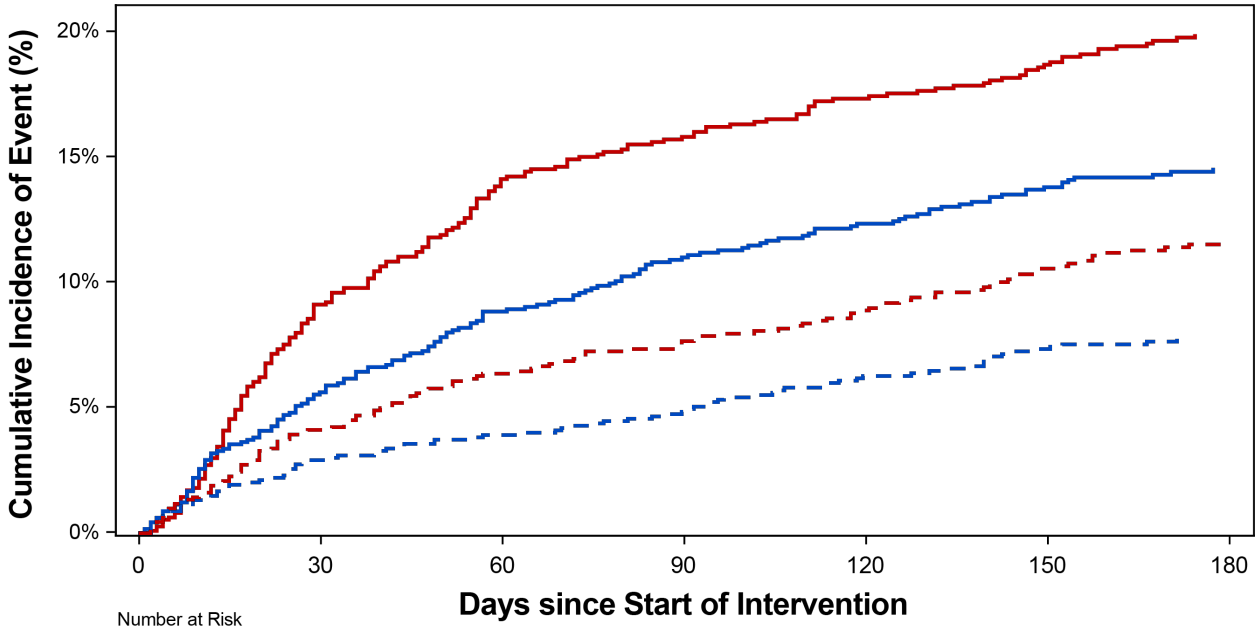


….and prevent cardiac thromboembolism?

ACS: acute coronary syndrome; AF: atrial fibrillation.

AUGUSTUS primary outcome

Major or clinically-relevant non-major bleeding



Number at Risk							
Apixaban and Aspirin	1145	1036	975	937	903	880	485
Apixaban and Placebo	1143	1075	1044	1007	975	947	536
VKA and Aspirin	1123	962	881	838	800	776	467
VKA and Placebo	1126	1007	947	917	883	851	528

VKA + Aspirin (18.7%)

Apixaban + Aspirin (13.8%)

VKA + Placebo (10.9%)

Apixaban + Placebo (7.3%)

Apixaban + Placebo vs. VKA + Aspirin: 11.4% absolute risk reduction (NNT=9)

Lopes RD et al. *N Engl J Med* 2019;doi: 10.1056/NEJMoa1817083

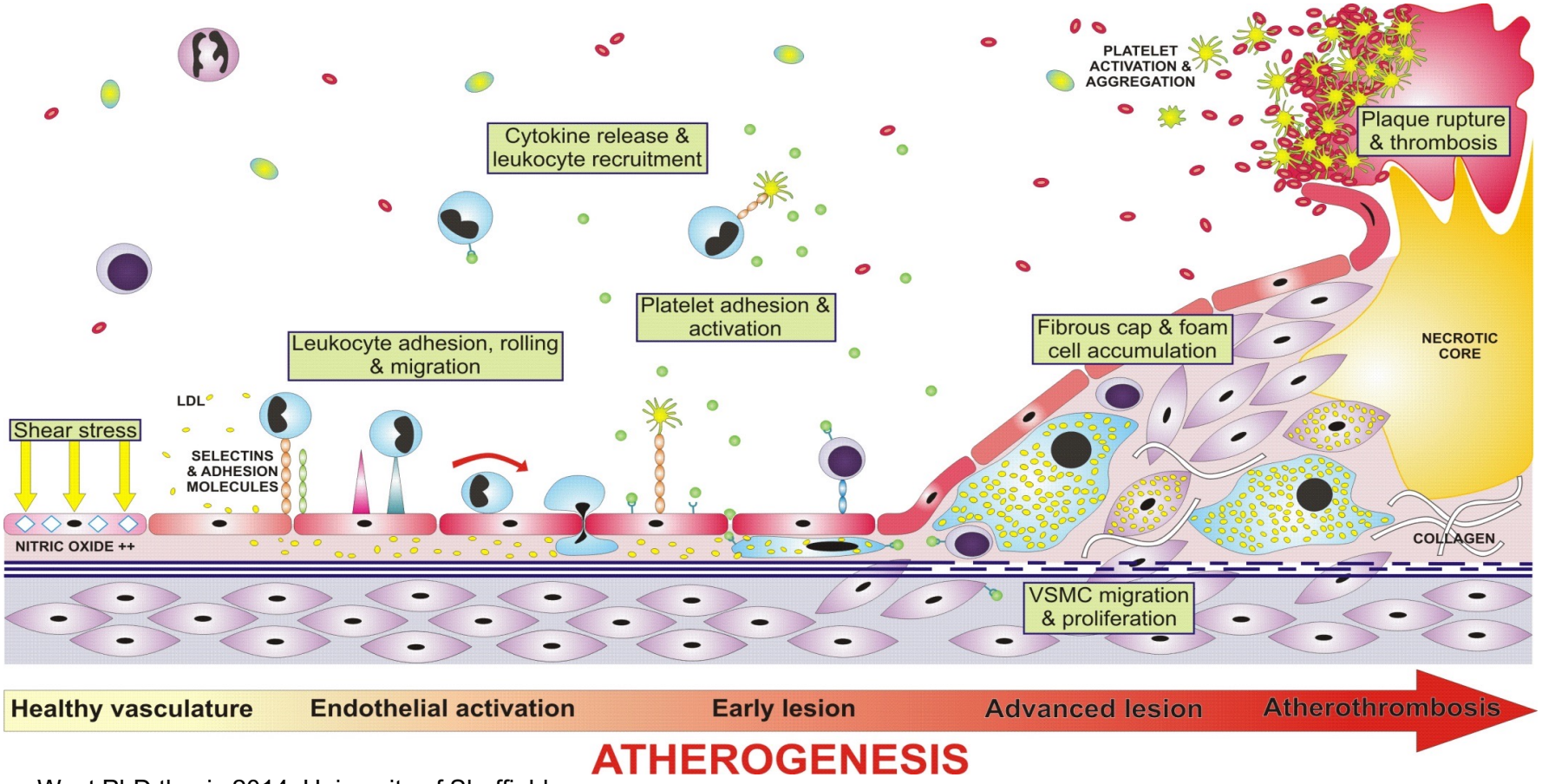
AF and PCI
General principles

- Assess risk of cardiac thromboembolism - DAPT alone may suffice if CHA_2DS_2-VASc is low
- Determine the risk of stent thrombosis based on patient and lesion characteristics and procedural outcome – higher thrombosis risk if stent deployment is suboptimal
- Determine which factors are present that increase the risk of bleeding
- Use NOAC in preference to warfarin unless poor renal function
- Stop aspirin early after PCI if stent thrombosis risk is low or bleeding risk outweighs the stent thrombosis risk
- If using aspirin, clopidogrel and warfarin, minimise duration of combined therapy and *take care over INR control (2.0-2.5)*

Targets in post-MI management

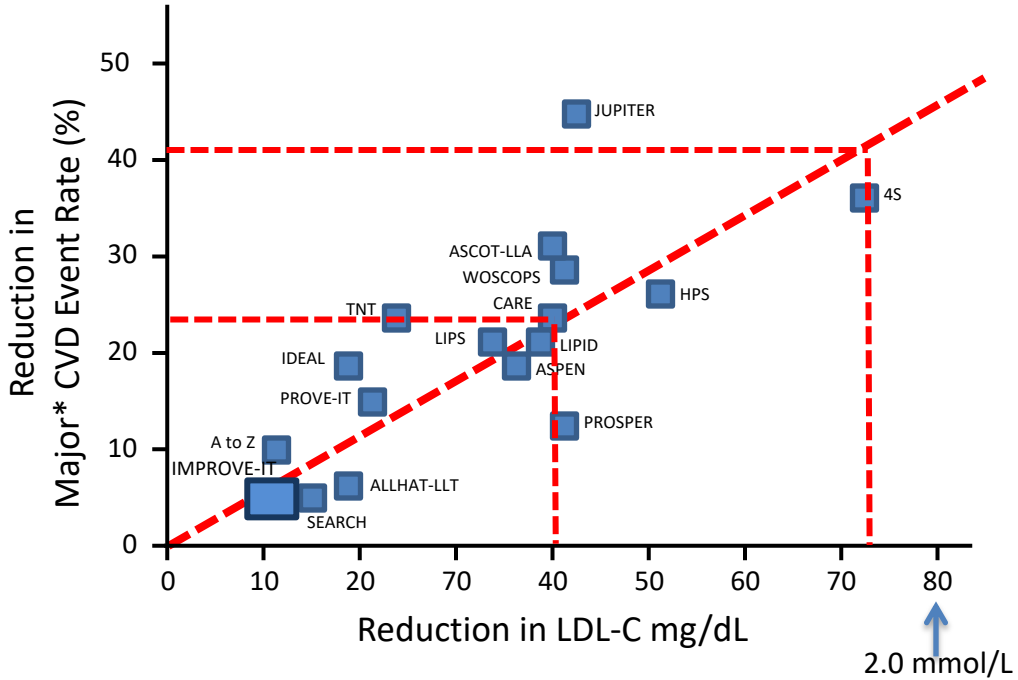
- Thrombosis and bleeding risk
- Lipids
- Blood pressure
- Glycaemic control

Mechanisms in atherothrombosis



Laura West PhD thesis 2014, University of Sheffield

Reduction in CVD events is related to absolute reduction in LDL-C



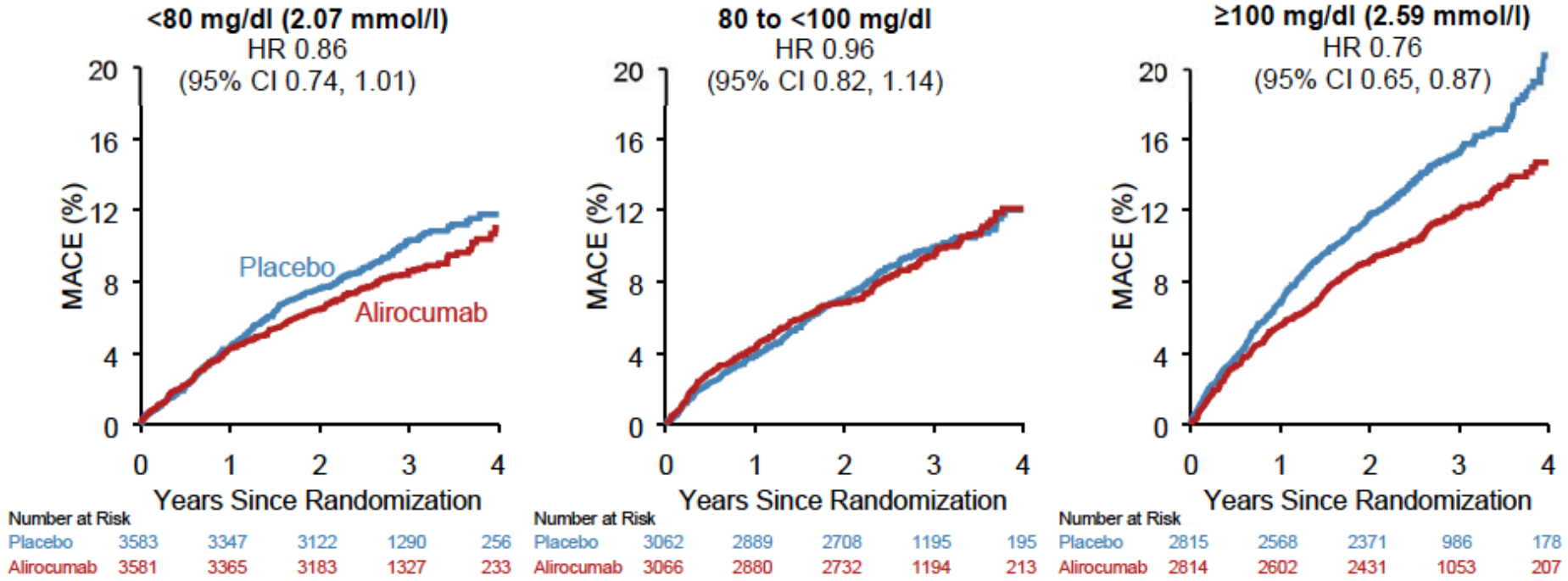
*defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation or stroke.

1 mmol/L = ~40 mg/dL.

Cannon CP et al N Engl J Med 2015; 372:2387-2397

ODYSSEY OUTCOMES

Primary endpoint according to baseline LDL-cholesterol



Schwartz GG et al. N Engl J Med 2018; 379:2097-2107

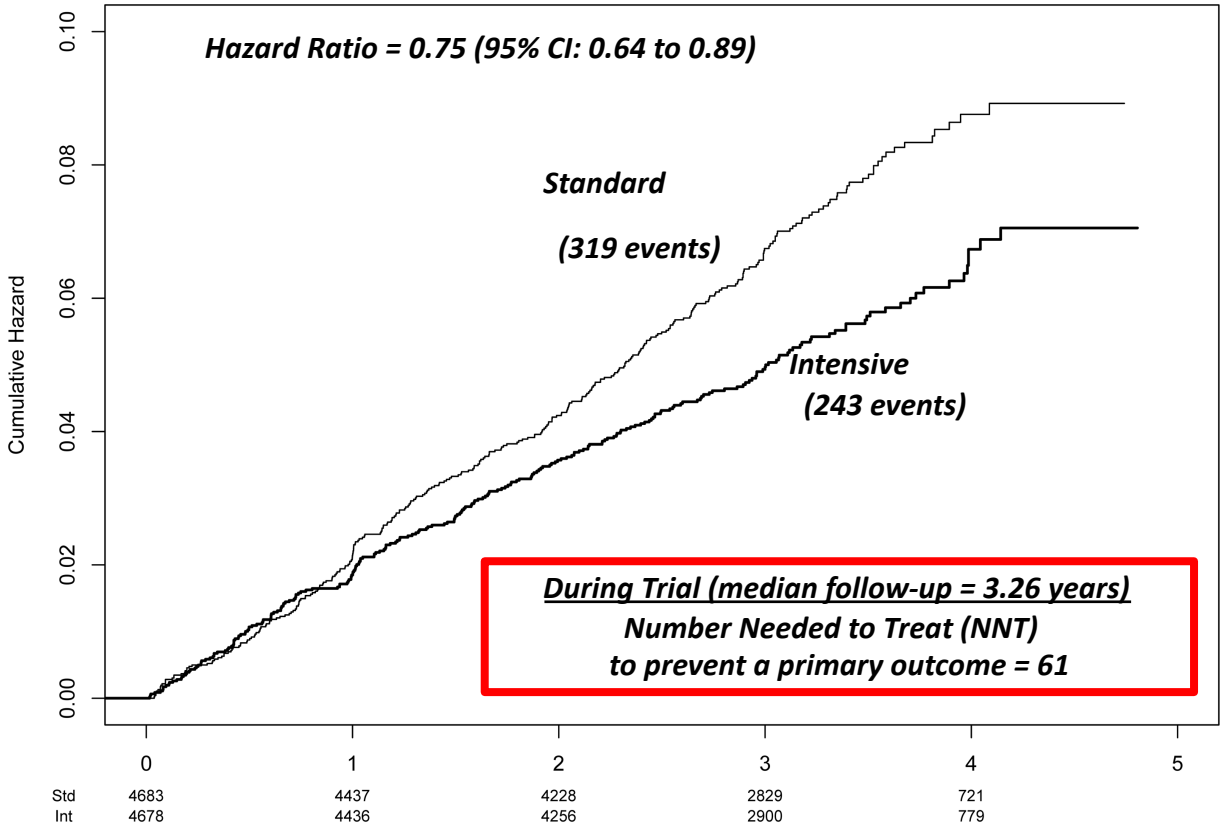
Inclisiran

Bempedoic acid

Targets in post-MI management

- Thrombosis risk
- Lipids
- Blood pressure
- Glycaemic control

SPRINT study primary outcome



Sprint Research Group. NEJM 2015

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Categories of BP in Adults*

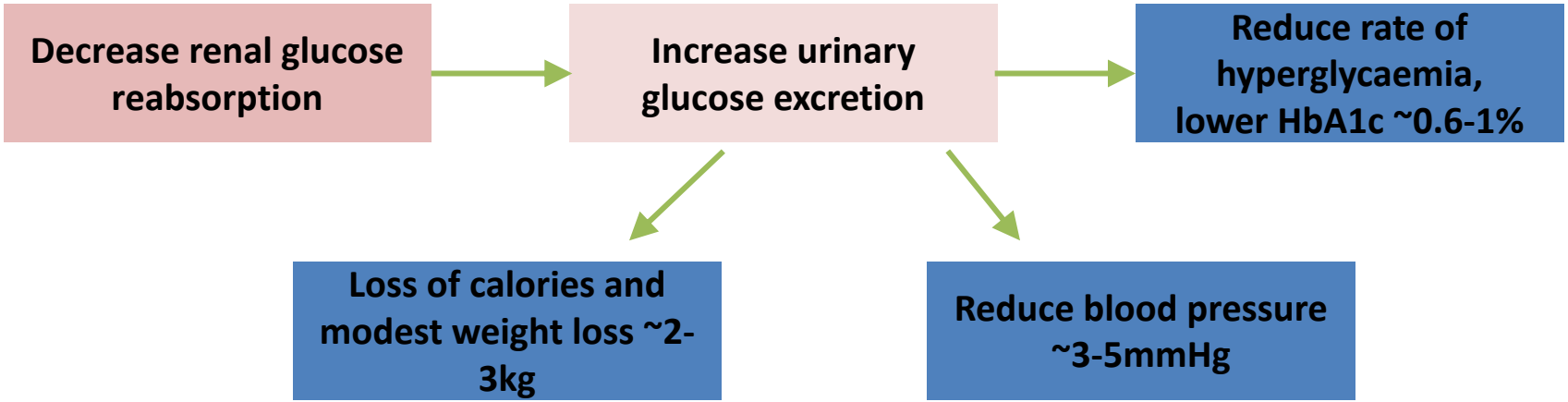
BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

Targets in post-MI management

- Thrombosis risk
- Lipids
- Blood pressure
- Glycaemic control

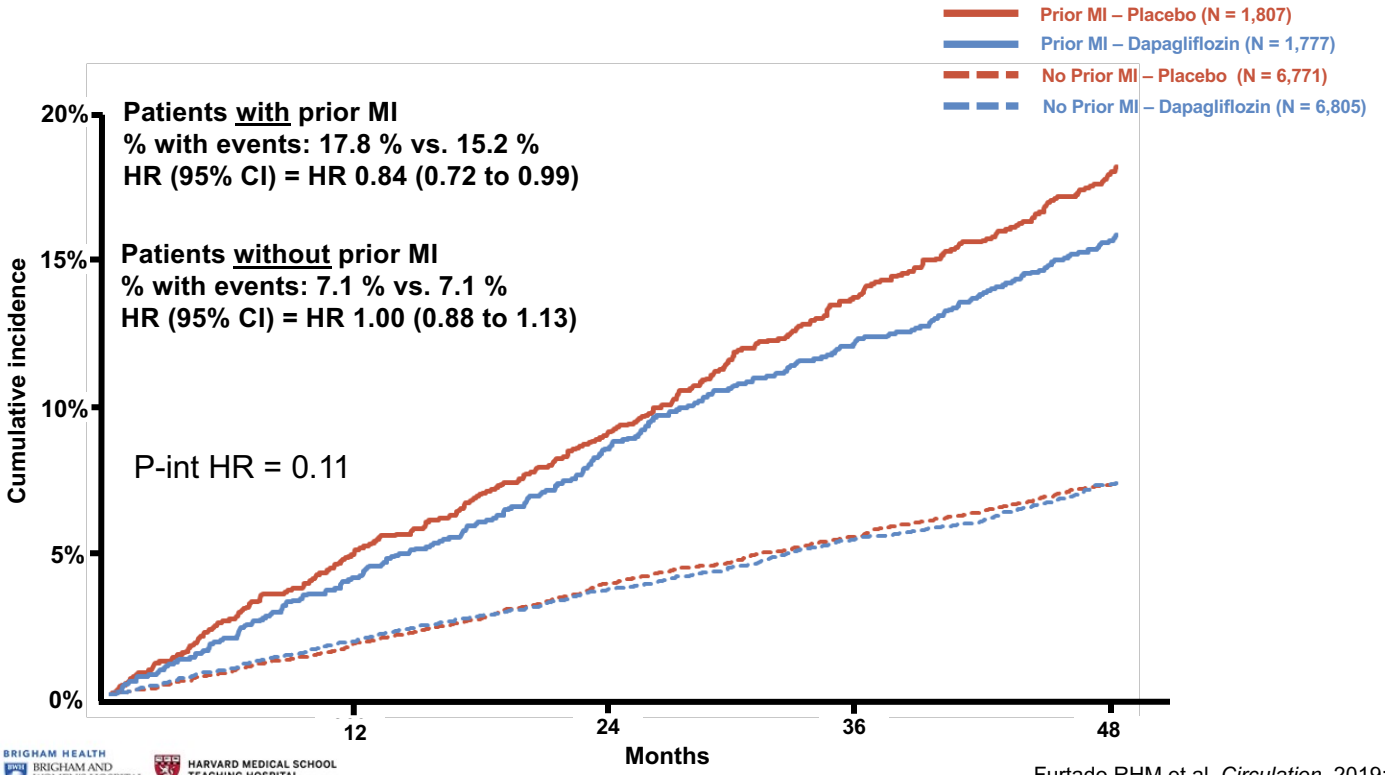
SGLT2 inhibitors in patients with diabetes



Zinman B *et al, N Engl J Med* 2015; 373:2117–2128; Wilding JP et al, Diabetes Obes Metab 2014;16:124-136; Forst T el al, Diabetes Obes Metab 2014; 16:467-477; Valentine V. Clin Diabetes 2012;30: 151-155; Rosenstock J et al. Diabetes Obes Metab 2014;15:1154-1160; Goring S et al, Diabetes Obes Metab 2014; 16:433-442

CV outcomes with dapagliflozin

MACE – CV death, MI or ischemic stroke



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Furtado RHM et al. *Circulation.* 2019;139:2516–2527

Conclusions

- Improvements in PCI techniques have improved outcomes and extended the range of disease that can be effectively treated
- Prasugrel and ticagrelor are both options for first-line antiplatelet therapy in ACS and each has pros and cons
- Long-term DAPT is indicated in patients at high ischaemic risk who don't have high bleeding risk conditions whilst $P2Y_{12}$ inhibitor monotherapy from 3 months post-ACS may be appropriate to lower bleeding risk in those with lower ischaemic risk or high bleeding risk
- LDL-cholesterol: aim low for best risk reduction; new options available
- Blood pressure: manage to target; ambulatory or home BP monitoring appears most reliable
- Diabetes: use of new agents (SGLT-2i, liraglutide) with appropriate counselling can improve clinical outcomes – ongoing studies looking at post-MI SGLT-2i in patients with and without diabetes