Antithrombotics in CAD/PAD:

Latest data and clinical implications

A Practical Approach

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Presenter Disclosure Information

Name: Dominick J Angiolillo

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Received payment as an individual for:
a) Consulting fee or honorarium from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company.
b) Honorarium for participation in review activities (DSMB member) from CeloNova.
c) Honorarium from the American Board of Internal Medicine (Interventional Cardiology Subspecialty Exam Writing Committee Member)

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a) Grant support industry: Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, and Renal Guard Solutions.
b) Grant in gift: Spartan; Scott R. MacKenzie Foundation
c) Federal agency: NIH

Case Presentation - 1

- You are seeing a 62 yo White female in your outpatient clinic.
- The patient recently relocated to Hong Kong after living most of her life in Florida.
- She brings her medical records from her last hospitalization and her past medical history can be summarized as follows:
  - She has multiple cardiovascular risk factors, including
    - Diabetes mellitus: treated with metformin for the past 3 years and her last HbA1C was 6.4%.
    - Hypertension: for 15 years on treatment with lisinopril and amlodipine with relatively good blood pressure control (home reading varying from 125-135 / 70-80 mmHg).
    - Smoker: 1 PPD for many years; stop 3 years ago.
    - CKD: GFR of 55 ml/min.

Case Presentation - 2

- She reports having a “stent” placed in her left lower extremity 5 years ago due to claudication. Her symptoms have improved, but not completely subsided.
- She reports having a TIA 3 years ago. Ever since this event she has been more compliant with her medications as she realized that she could have had a “real” stroke.
- Approximately 12 months ago she experienced a NSTEMI and underwent PCI of the mid RCA. She has a stent card that shows a newer generation DES (3.5 x 18 mm) was used.
- Her records also indicate that she has a 50-60% stenosis in her mid-LAD. An FFR done at the time of her PCI was indicative of non hemodynamically significant stenosis (0.95 baseline - 0.87 after adenosine).
- She has been on DAPT with aspirin 81 mg + ticagrelor 90 mg bid (in addition to high-dose statin, amlodipine, lisinopril, and metformin).

Case Presentation - 3

- Since her NSTEMI she has been mostly asymptomatic for angina. She complains of occasional atypical chest pain. She also reports occasional fatigue and shortness of breath which she attributes to deconditioning.
- Her EF at discharge was 45-50% and was found to be 50-55% at a follow-up 2D-echo performed 6 months after her NSTEMI. At the time she also underwent a stress test which was negative for signs and symptoms of ischemia.
- She has followed up regularly with a Cardiologist in Florida who strongly recommended that she establish herself with a new Cardiologist in Hong Kong and it was important that she be seen at 1 year as decisions needed to be made with regards to her “blood thinning medications”.
- She also shows you her most recent labs: CBC is within normal limits, GFR is 55 ml/min, HbA1C is 6.4%, and LDL is 68.

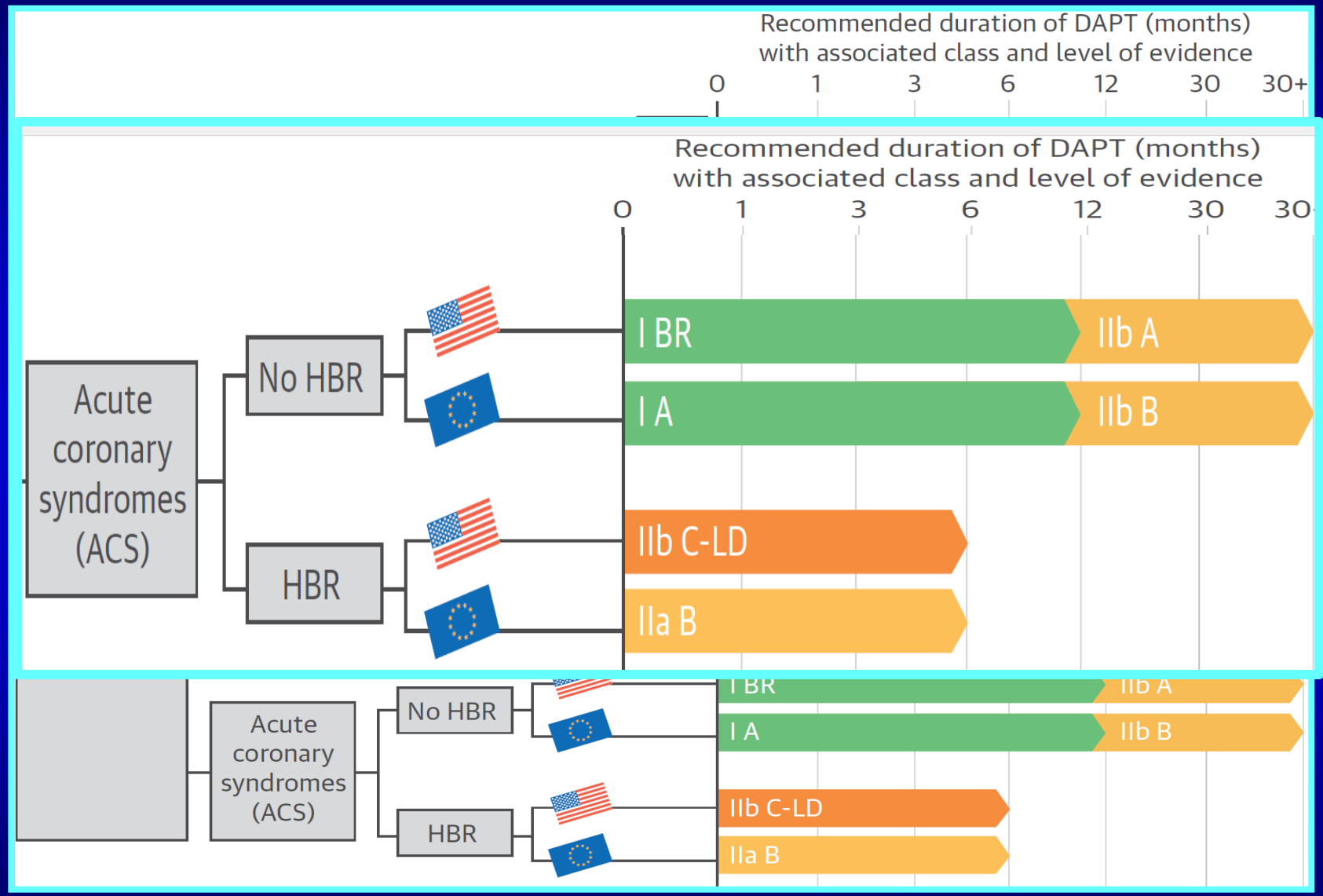
High risk CAD/PAD case

Which antithrombotic regimen do you choose?

- **Stop ticagrelor and maintain aspirin monotherapy?**

- **Maintain dual antithrombotic therapy?**

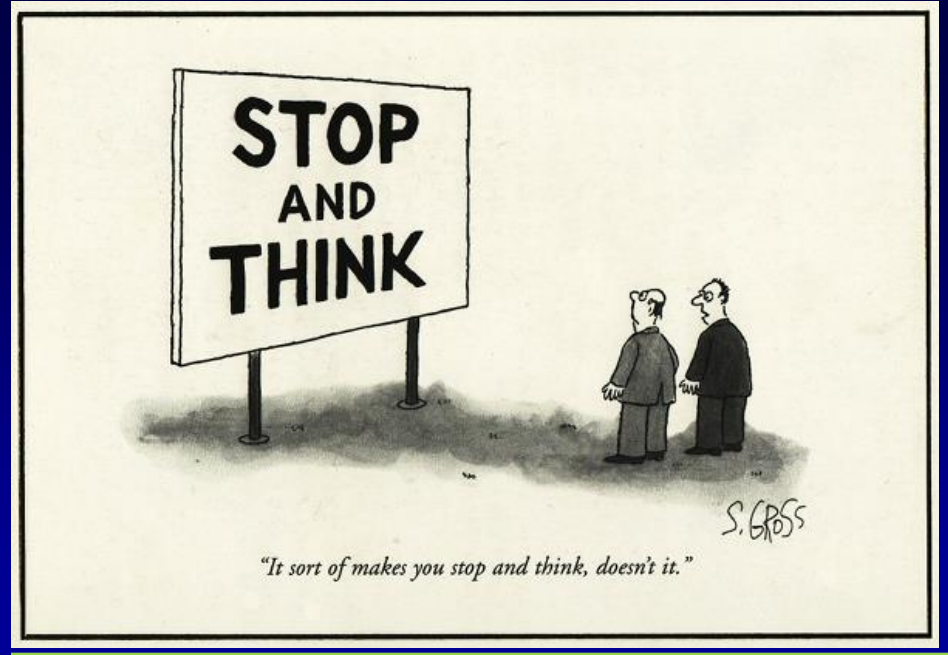
Summary of recommendations for DAPT following PCI



Capodanno D and Angiolillo DJ. JACC 2018; 72 (23): 103-19.

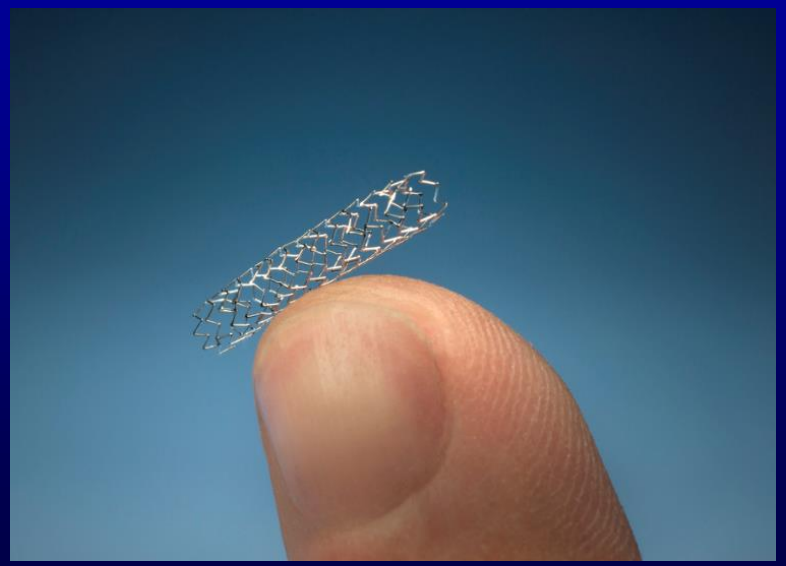
Trials of DAPT duration consistently support short length if new generation DES are used (no excess risk of stent related complications, such as stent thrombosis)

Why and In Whom Prolong Dual Antithrombotic Therapy?



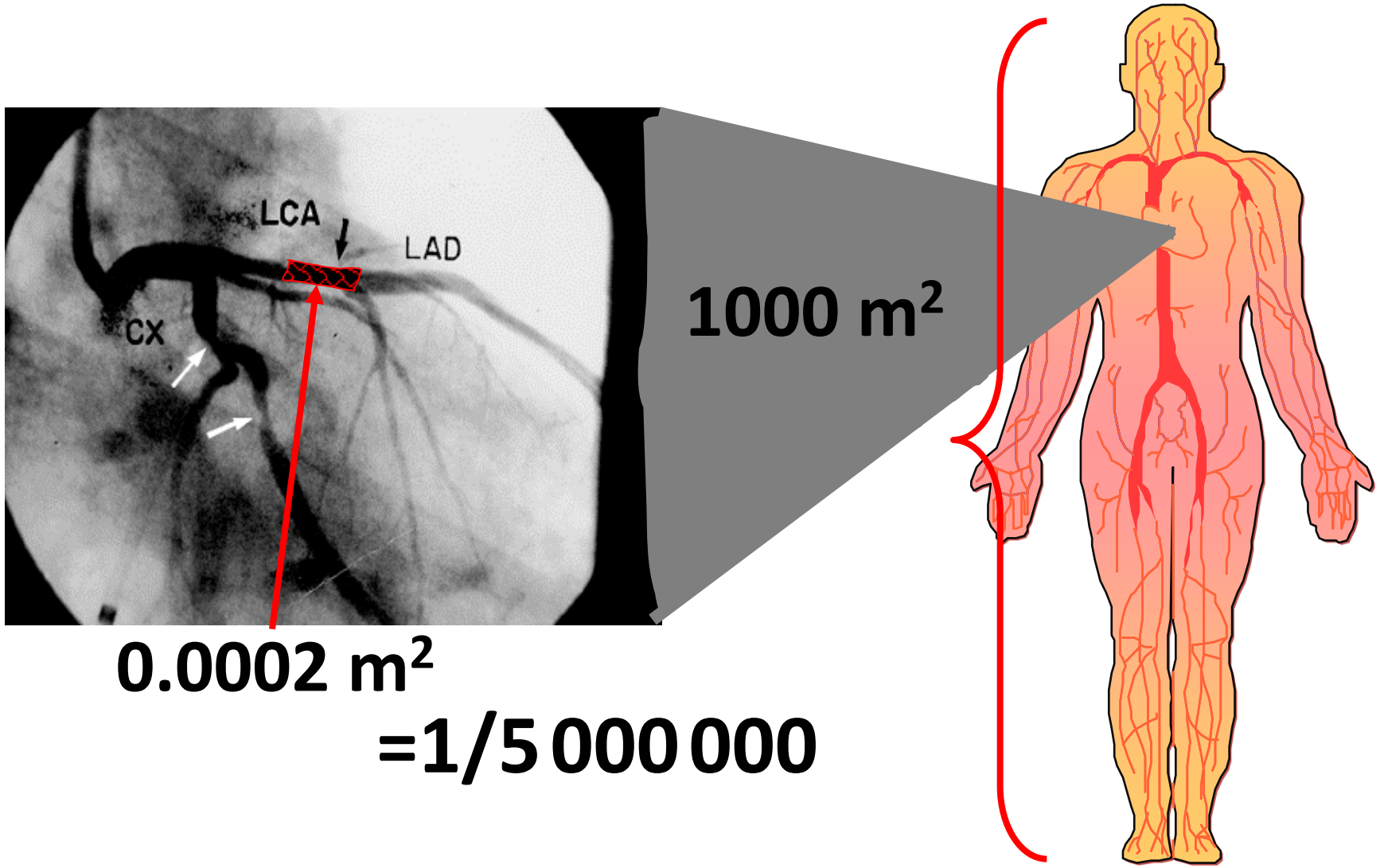
What are we treating?

Vulnerable Stent vs Patient ??



20-25% risk of "falling" again in the next 5 years

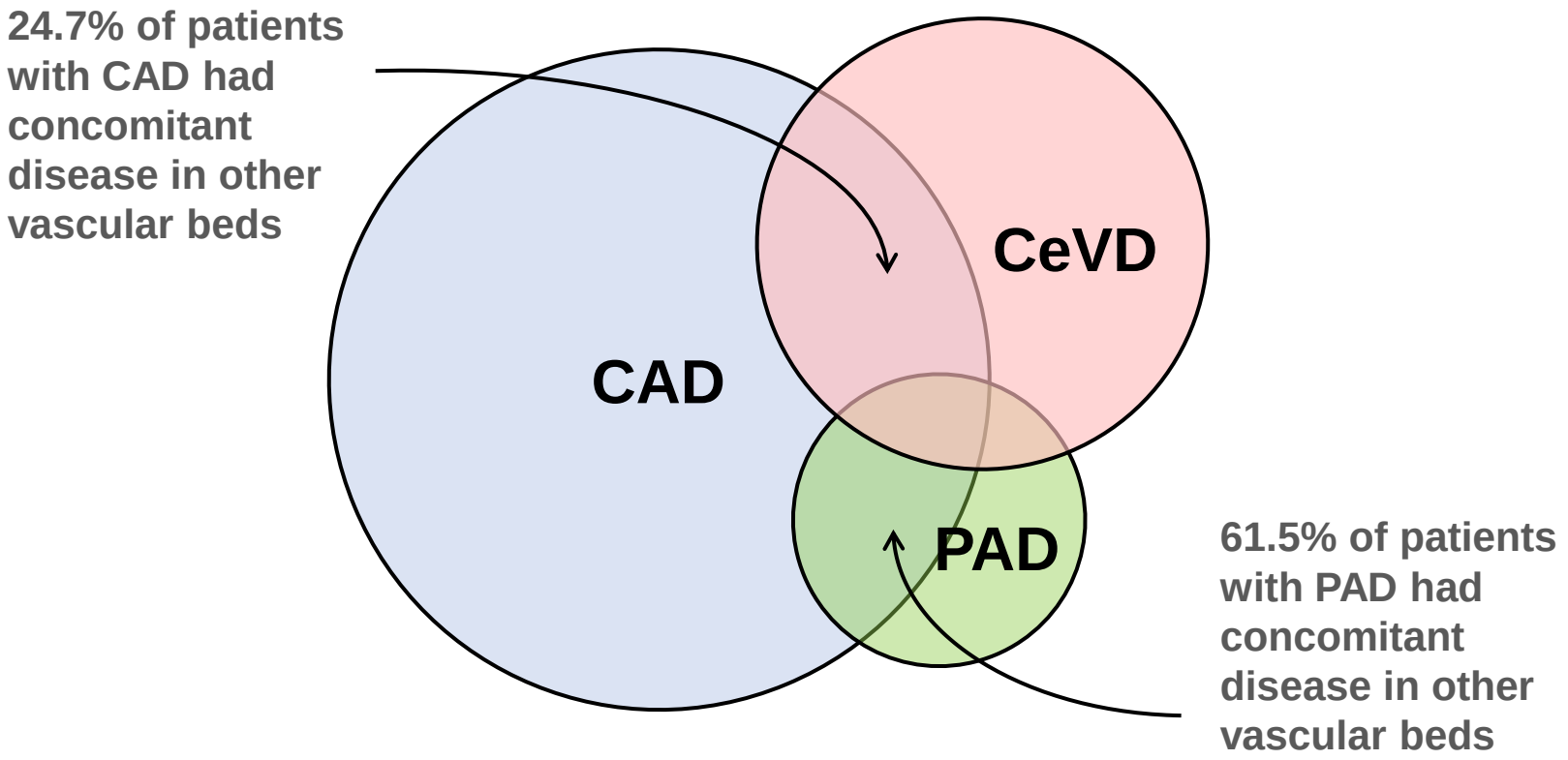
How Much of the Patient Are We Treating?



Courtesy of Steven Steinhubl

Atherosclerosis is a Polyvascular Disease

REACH: More than 3 in 5 patients with PAD have atherothrombotic disease in other arterial territories



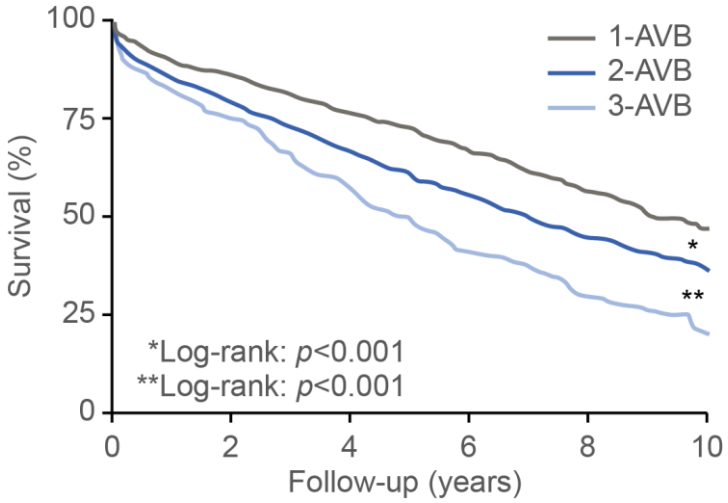
Percentages are calculated from the total population included in the REACH Registry. N=67,888

Bhatt DL *et al*, *JAMA* 2006;295:180–189

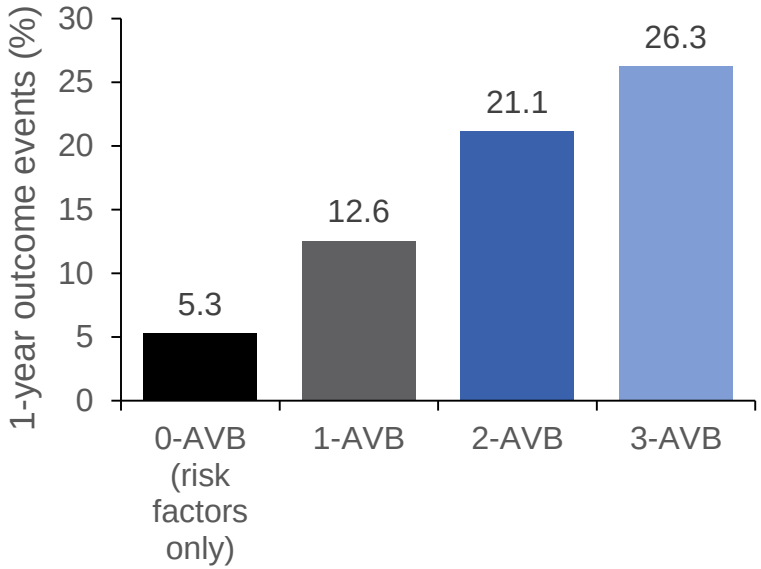
Patients with Polyvascular Disease Have Even Higher Risk of Morbidity and Mortality

- Patients with PAD or CAD often have polyvascular disease[1,2,4]
- Polyvascular disease is associated with an increased risk of morbidity and mortality[2–4]

Long-term all cause mortality in patients with PAD stratified according to number of affected vascular beds (AVB)[2]



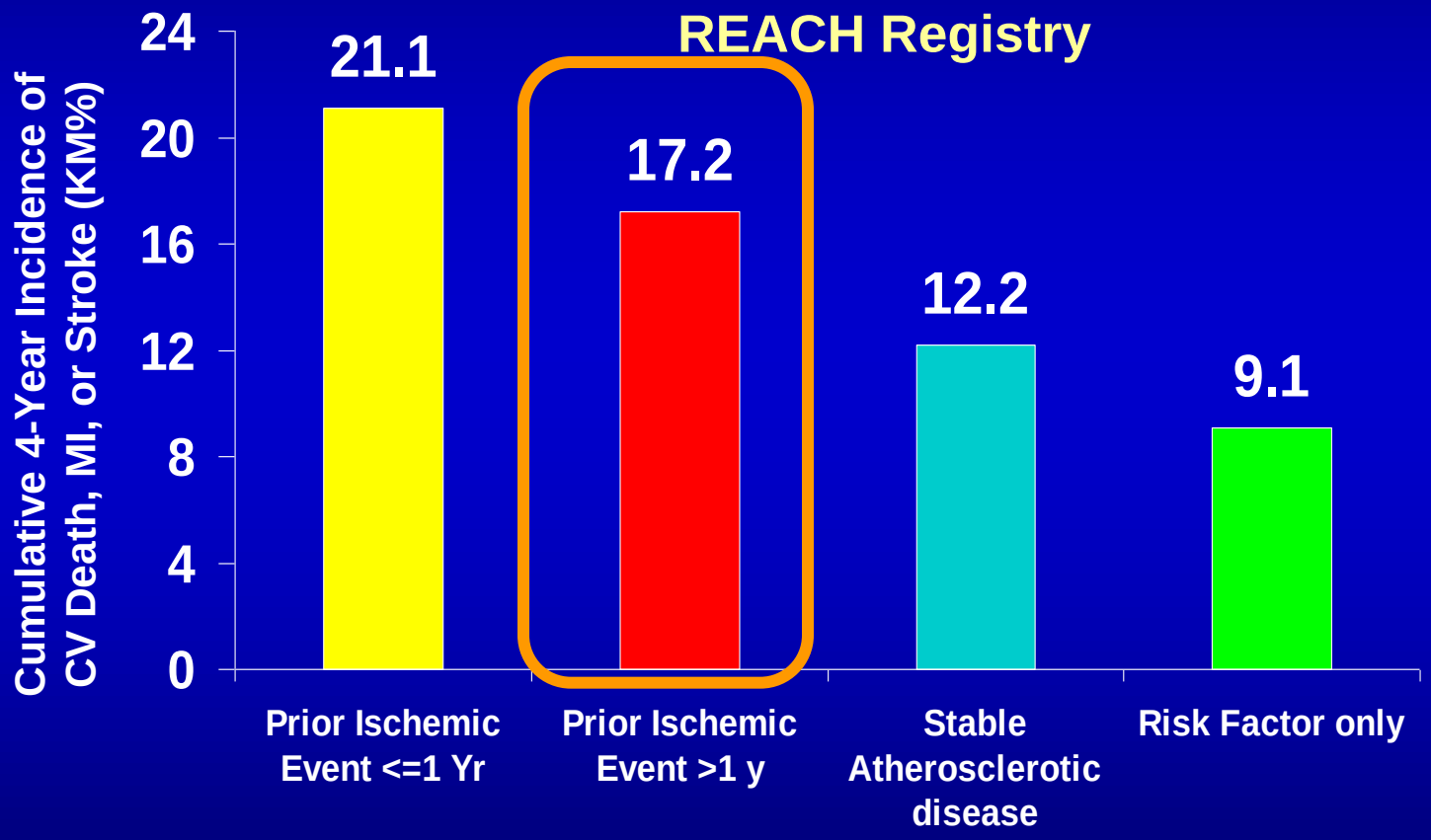
CV death, MI, stroke or hospitalization for atherothrombotic events according to number of affected vascular beds (AVB)[4]



1. Bhatt DL *et al*, *JAMA* 2006;295:180–189; 2. van Kuijk P *et al*, *Eur Heart J* 2010;32:992–999; 3. Alberts MJ *et al*, *Eur Heart J* 2009;30:2318–2326;
4. Steg P *et al*, *JAMA* 2007;297:1197–1206

Patients With a History of Prior Ischemic Events Had a High Risk of CV Events at 4 Years

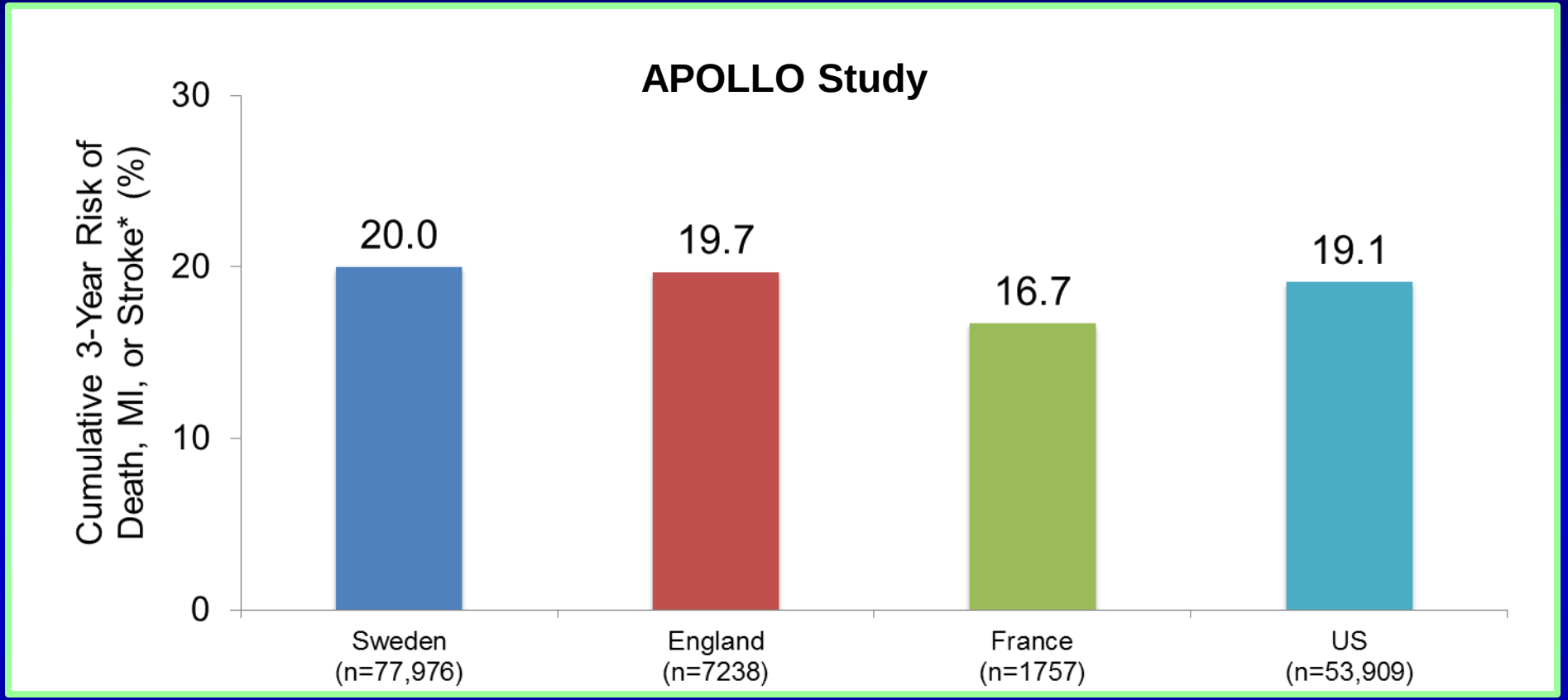
International, prospective, observational study of 45,227 patients ≥45 years of age at risk for or with atherothrombosis. The cohort was enrolled from 29 countries and followed annually for 4 years from 2003 to 2008



REACH=Reduction of Atherothrombosis for Continued Health.

Bhatt DL et al. *JAMA.* 2010;304:1350-1357.

Patients Free of MI for 1 Year Continued to Be at Risk for CV Events Over the Next 3 Years



Retrospective 4-country analysis of patients who survived without a further MI for 1 year following hospitalization for MI in 2002 to 2011. Results are based on data from national linked electronic health records and disease registries as well as administrative data

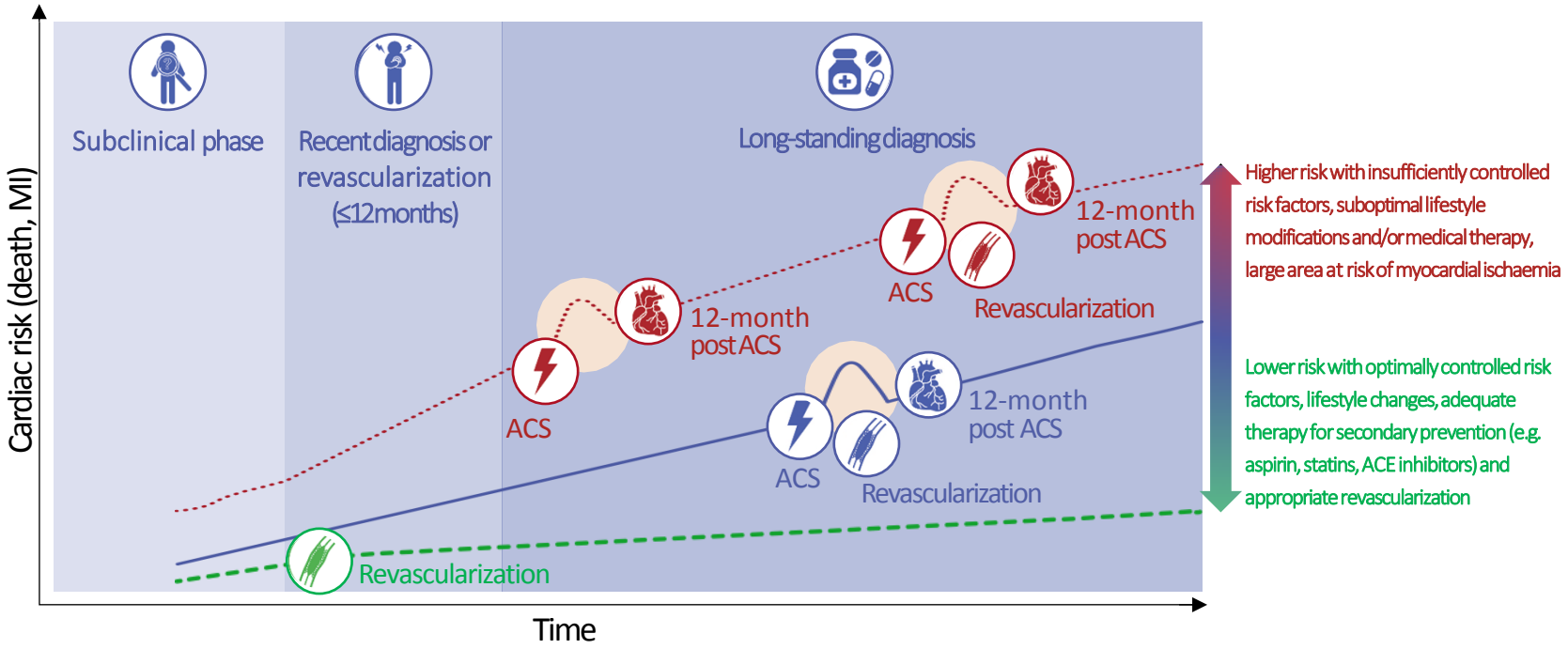
*Adjusted for differences in study populations.

Rapsomaniki E et al. Presented at: European Society of Cardiology Meeting; August 30-September 3, 2014; Barcelona, Spain.

Natural history of CCS: A dynamic process

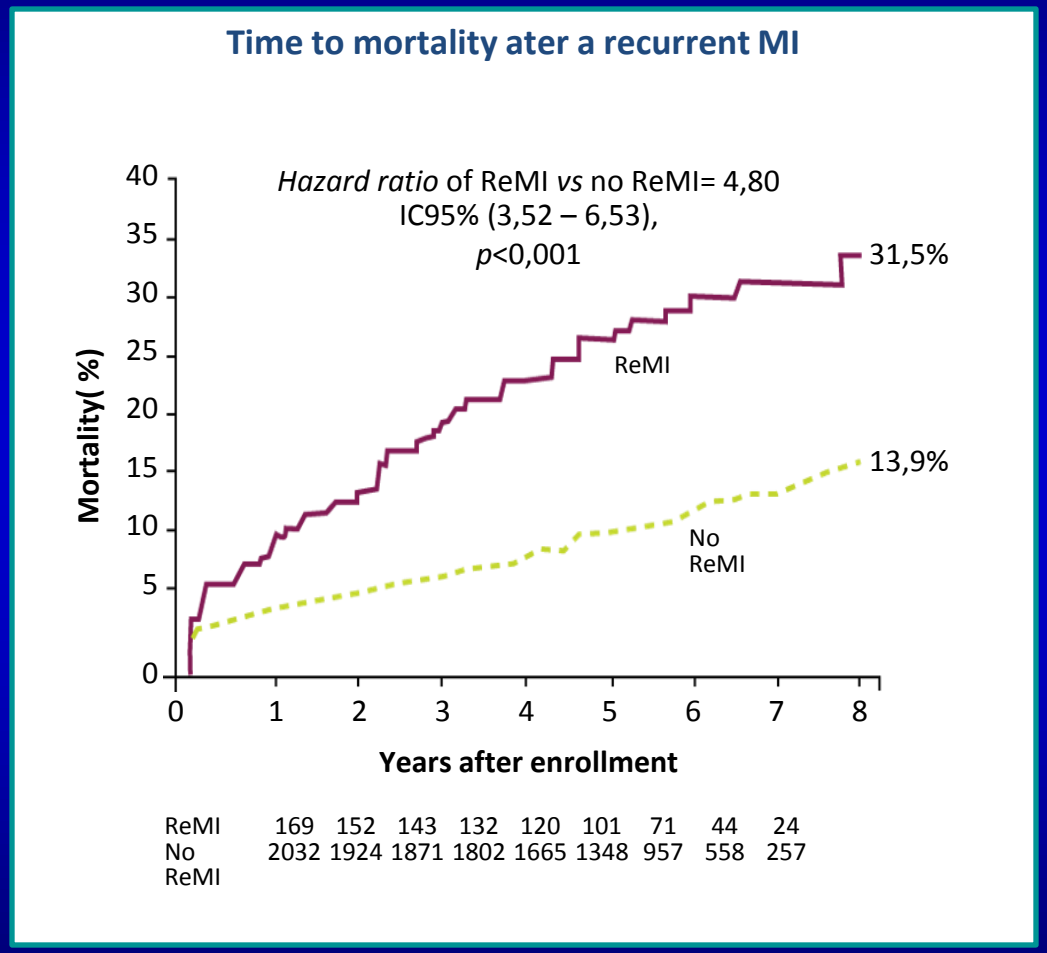
Patients with Chronic CAD Are not Necessarily Stable

- **Natural history of CAD according to the 2019 CCS guidelines[1]**



Knuuti J, et al. Eur Heart J 2019

Impact of recurrent MI on long-term mortality



Recurrent MI 28 days after index event:

- Recurrent MI ocurred in 8% of patients at 7 years
- Nearly 5-fold increase in moratlity rate

Mendis S et al. *Int J Epidemiol.* 2011;40:139-146;; Adlbrecht C et al. *Int J Cardiol.* 2014;174(1):90-95.

UNIVERSITY OF FLORIDA
The Cardiovascular Center at SHANDS Jacksonville

Antithrombotic therapy in patients with CCS and sinus rhythm – ESC 2019 guideline

Dual antithrombotic therapy

Recommendations	Class	Level
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic 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 ischaemic events and without high bleeding risk	IIb	A

High risk of ischemic events include diffuse multivessel CAD with at least one of the following: DM requiring medication, recurrent MI, PAD, or CKD with eGFR 15-59 mL/min/1.73 m^2.

Moderate risk of ischemic events include at least one of the following: multivessel/diffuse CAD, DM requiring medication, recurrent MI, PAD, HF or, CKD with eGFR 15-59 mL/min/1.73 m^2.

High bleeding risk include prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent GI 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.

Knuuti J, et al. Eur Heart J 2019

High risk CAD/PAD case

Which antithrombotic regimen do you choose?

- **Stop ticagrelor and maintain aspirin monotherapy?**

- **Maintain dual antithrombotic therapy?**

First Question That Should be Asked

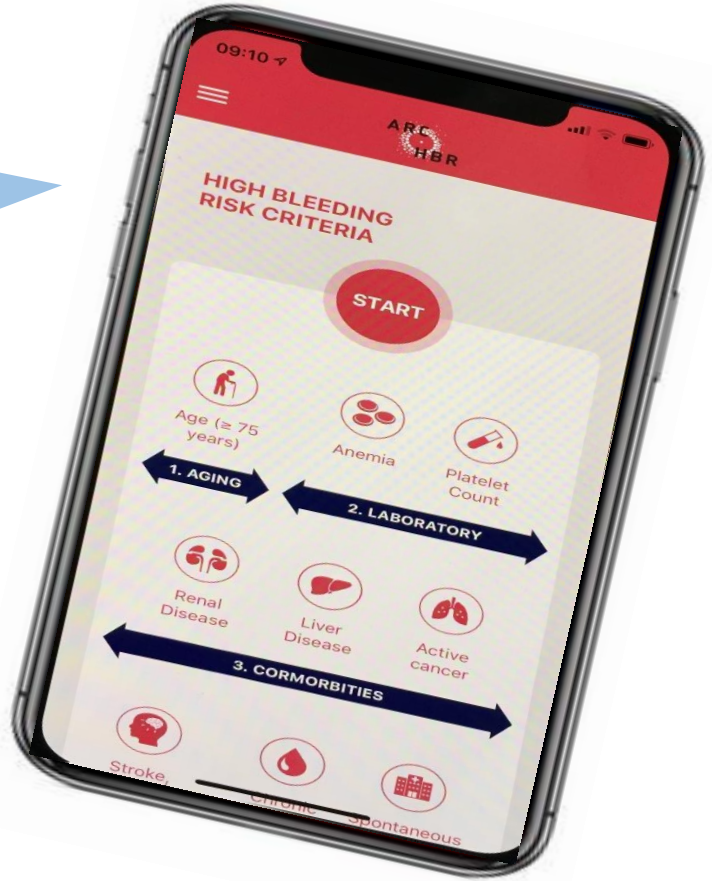
- **Is the patient at high risk for bleeding?**

Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent GI 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

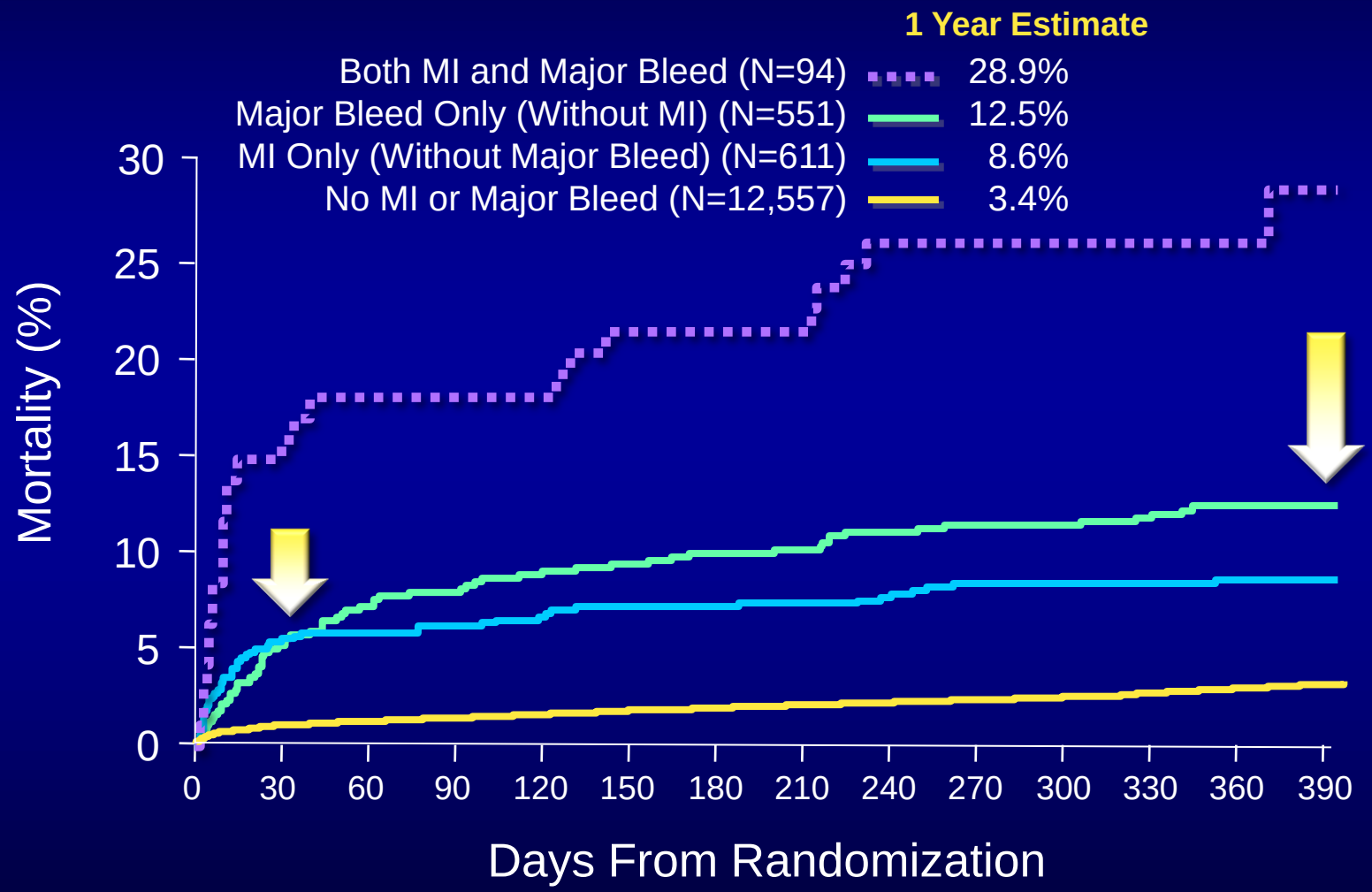
ARC HBR

ARC HBR

ARC HBR



Impact of MI and Major Bleeding (Non-CABG) in the First 30 Days on Risk of Death Over 1 Year



CABG=coronary artery bypass graft; MI=myocardial infarction.

Mehran R, et al. *Eur Heart J.* 2009;30(12):1457-1466.

Possible Mechanisms Linking Hemorrhagic Complications to Mortality

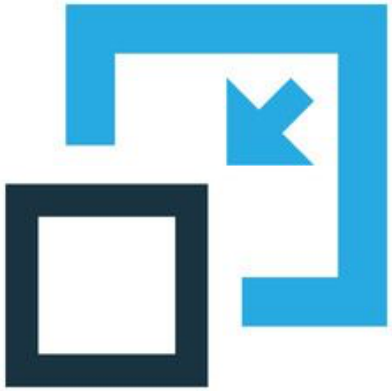
1. Fatal hemorrhage (e.g. intracranial bleed)
2. Vol. depletion ⇨ Hypotension, ischemia, arrhythmias
3. Complications from procedures to manage bleeding
4. Discontinuation of lifesaving medications (antiplatelet agents, beta blockers, statins)
5. Blood transfusions depleted in NO ⇨ systemic vasoconstriction, inflammation, apoptosis
6. Unmeasured confounders (e.g. *“Sick people bleed, and sick people die”*)

ONGOING DIRECTIONS IN TAILORING ANTITHROMBOTIC PHARMACOTHERAPY FOR HBR PATIENTS

STRATEGIES TO REDUCE THE RISK OF BLEEDING AFTER PCI

Shortening DAPT

11 TRIALS OF SHORT
VS. STANDARD DAPT



De-escalation

TOPIC
TROPICAL ACS
POPular Genetics ESC 2019

Aspirin withdrawal

GLOBAL LEADERS
GLASSY ACC 2019
SMART-CHOICE ACC 2019
STOPDAPT-2 ACC 2019
TWILIGHT TCT 2019

AF + PCI

WOEST
PIONEER- AF-PCI
RE-DUAL PCI
AUGUSTUS ACC 2019
ENTRUST ESC 2019

High risk CAD/PAD case

In an HBR patient…….

Which antithrombotic regimen do you choose?

- **Stop ticagrelor and maintain aspirin monotherapy**

- ~~**Maintain dual antithrombotic therapy**~~

High risk CAD case

In a patient without HBR and at high ischemic risk

Which antithrombotic regimen do you choose?

- ~~Stop ticagrelor and maintain aspirin monotherapy~~

- **Maintain dual antithrombotic therapy**

If no HBR, the Second Question That Should be Asked

- **Is the patient at high risk for ischemic events?**

High risk of ischemic events include diffuse multivessel CAD with at least one of the following: DM requiring medication, recurrent MI, PAD, or CKD with eGFR 15-59 mL/min/1.73 m^2.

Moderate risk of ischemic events include at least one of the following: multivessel/diffuse CAD, DM requiring medication, recurrent MI, PAD, HF or, CKD with eGFR 15-59 mL/min/1.73 m^2.

Antithrombotic therapy in patients with CCS and sinus rhythm

Event prevention

Drug option	Dose	Indication	Additional cautions
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year	
Prasugrel	10 mg o.d. or 5 mg o.d. if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15-29 mL/min
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	

Treatment options for dual antithrombotic therapy in combination with aspirin 75-100 mg daily are reported for patients who have a high or moderate risk of ischaemic events, and do not have a high bleeding risk.

Knuuti J, et al. Eur Heart J 2019

Limitations about CCS guidelines

CCS guidelines provides recommendation on when to use and which are the available dual antithrombotic therapy options (i.e,, DAPT with aspirin plus different P2Y12 inhibitors or DPI with aspirin plus vascular dose rivaroxaban) but does not provide recommendations on which option to choose.

Which is the best option for our patient and why?

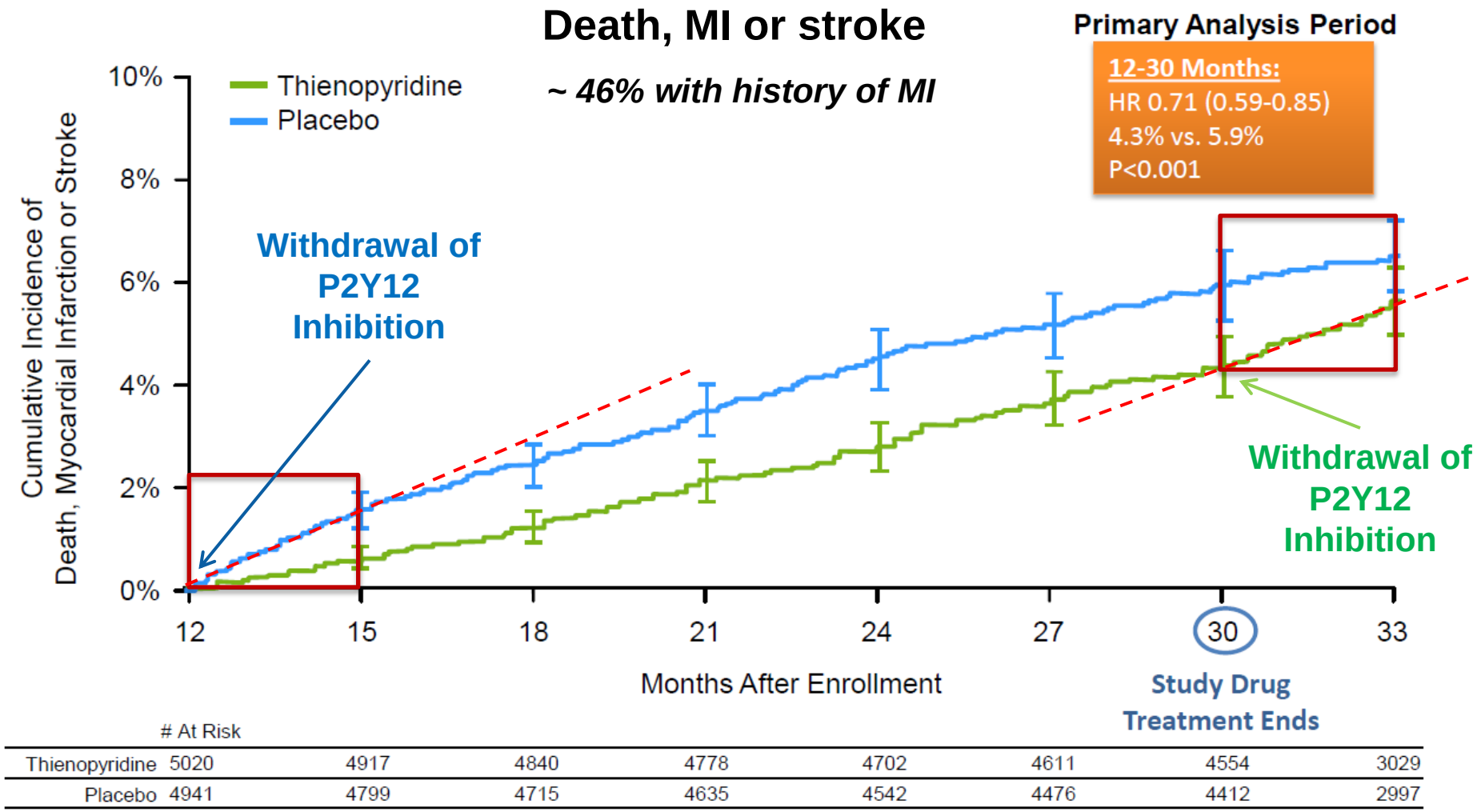
DAPT with aspirin and clopidogrel 75 mg – PROBABLY NOT

Reasons in favor: generic (useful in patients with limited access to branded medications); benefit from DAPT trial mostly in patients with prior MI; DAPT score: ≥ 2

Reasons against: benefit shown from a subgroup analysis of prior MI patients; clopidogrel not very efficacious (more “resistance”) in DM and CKD (particularly if combined)

DAPT: Withdrawal of Thienopyridine 12 Months after Coronary Stenting

DAPT STUDY

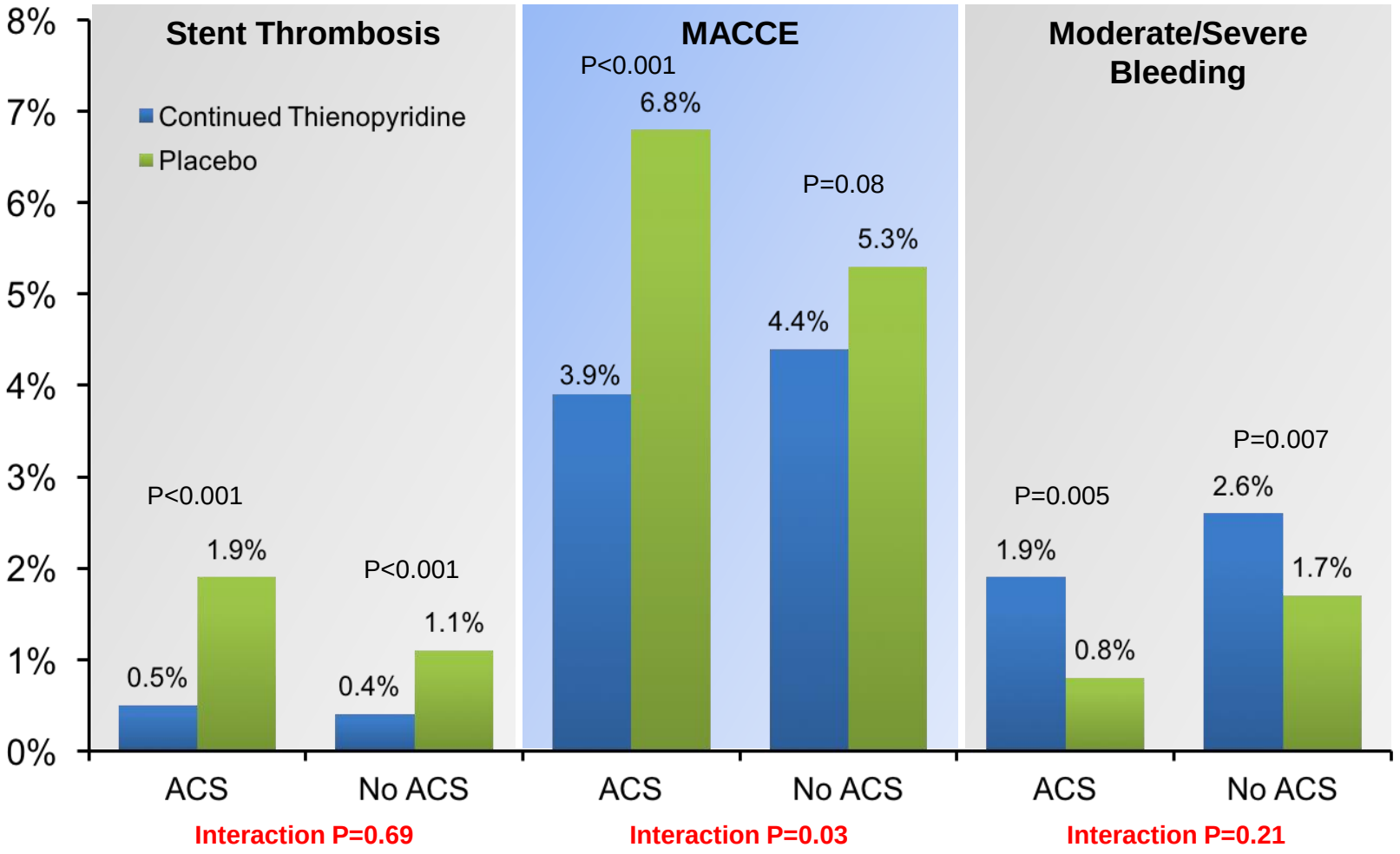


# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

Mauri et al. NEJM 2014

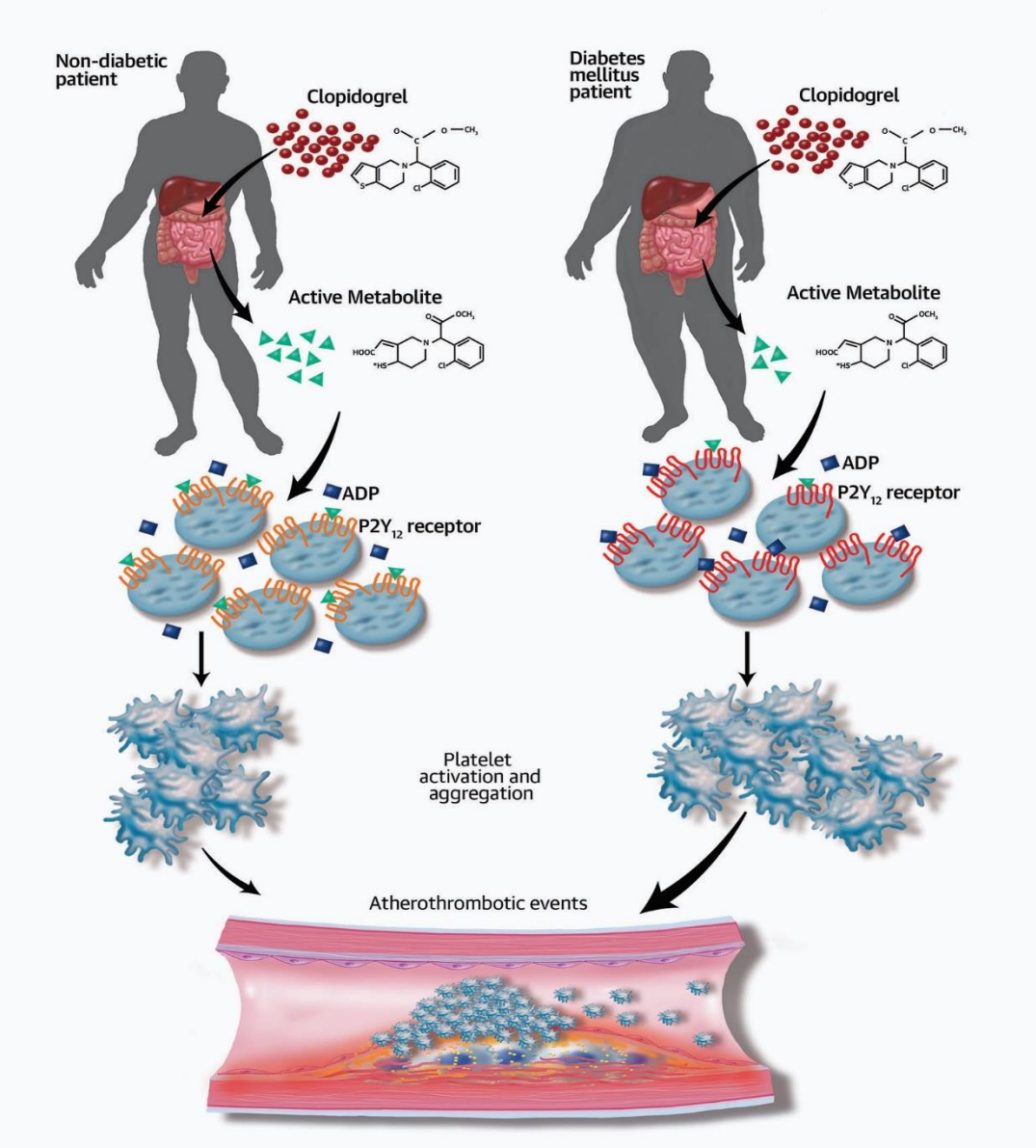
DAPT Trial: Treatment Effect According to ACS Status at 12-30 Months: Primary Endpoints

All Randomized Subjects (N=11648)



Yeh RW et al J Am Coll Cardiol.2015;65:2211-21.

Mechanistic Insights on Impaired Clopidogrel-Induced Antiplatelet Effects in Diabetes Mellitus: Results of an In Vitro and Ex Vivo PD/ PK Investigations



Among DM patients, impaired P2Y12 inhibition mediated by clopidogrel is largely attributable to attenuation of clopidogrel's PK profile, characterized by lower plasma levels of active metabolite compared with non-DM patients and only modestly attributed to upregulation of the P2Y12 signaling pathway.

Angiolillo DJ et al. J Am Coll Cardiol. 2014;64:1005-14.

Which is the best option for our patient and why?

DAPT with aspirin and ticagrelor 60 mg – POSSIBLY (but not the best evidence based option)

Reason against: despite PEGASUS being the best evidence for prolonging DAPT post-MI, patients with prior CVA were excluded from the trial. Hence the safety in of prolonged ticagrelor therapy in prior CVA is unknown.

Reason for considering: still commonly used in practice (there is no contraindication for prior ischemic stroke) particularly in patients with diffuse CAD burden/coronary stenting for which DAPT is known to be efficacious.

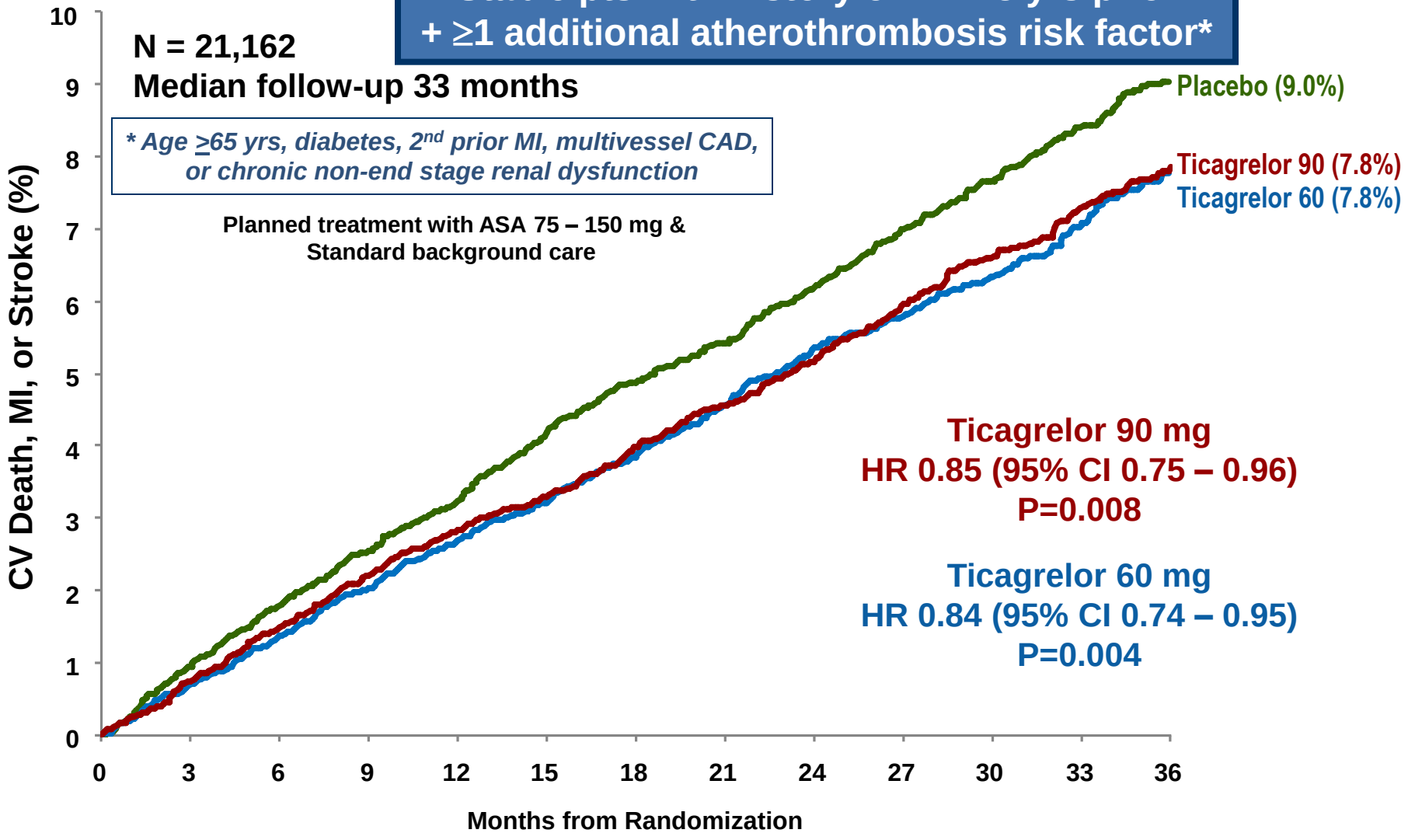
Primary Endpoint

Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*

N = 21,162
Median follow-up 33 months

** Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction*

Planned treatment with ASA 75 – 150 mg & Standard background care

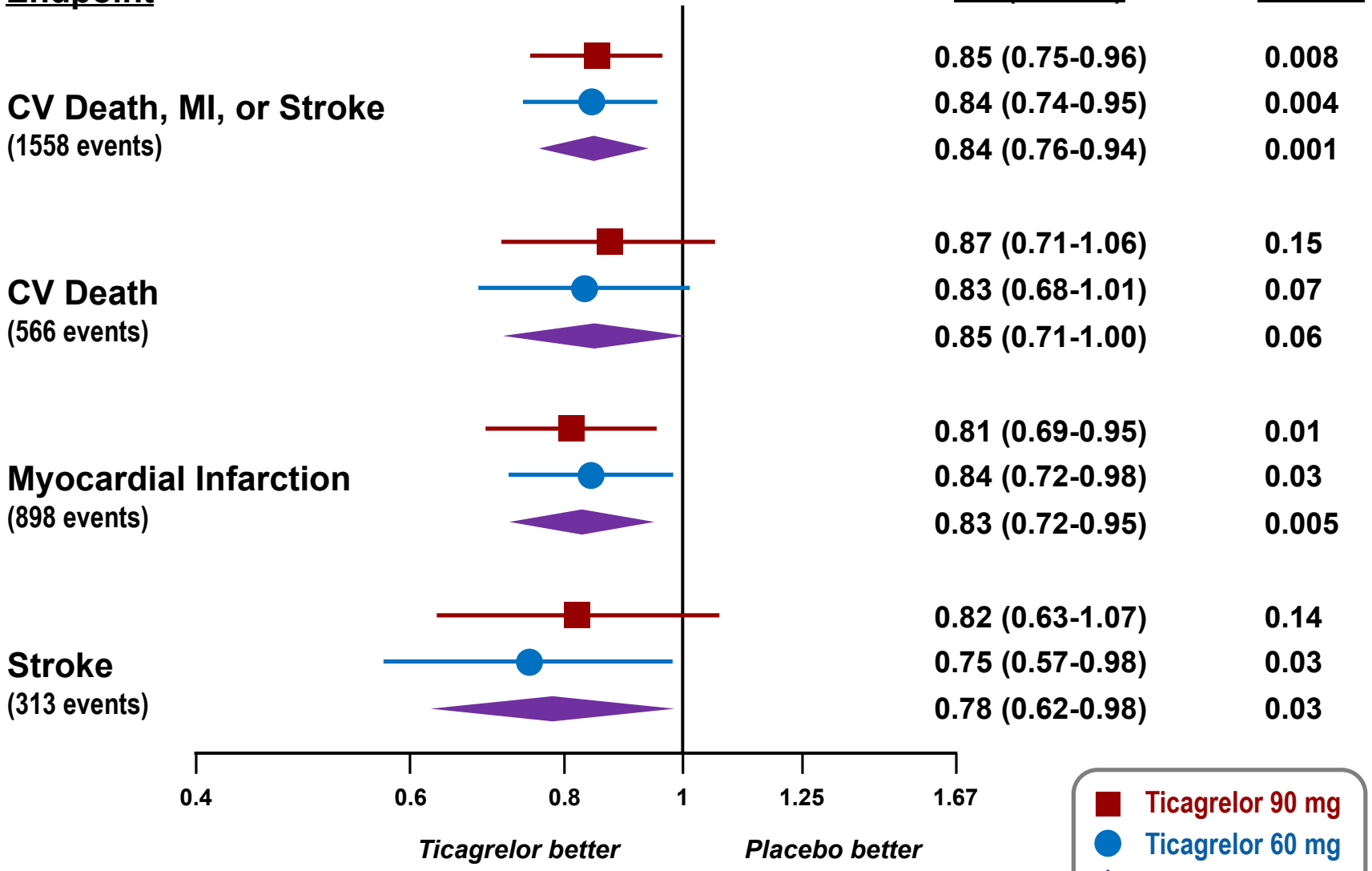


Ticagrelor 90 mg
HR 0.85 (95% CI 0.75 – 0.96)
P=0.008

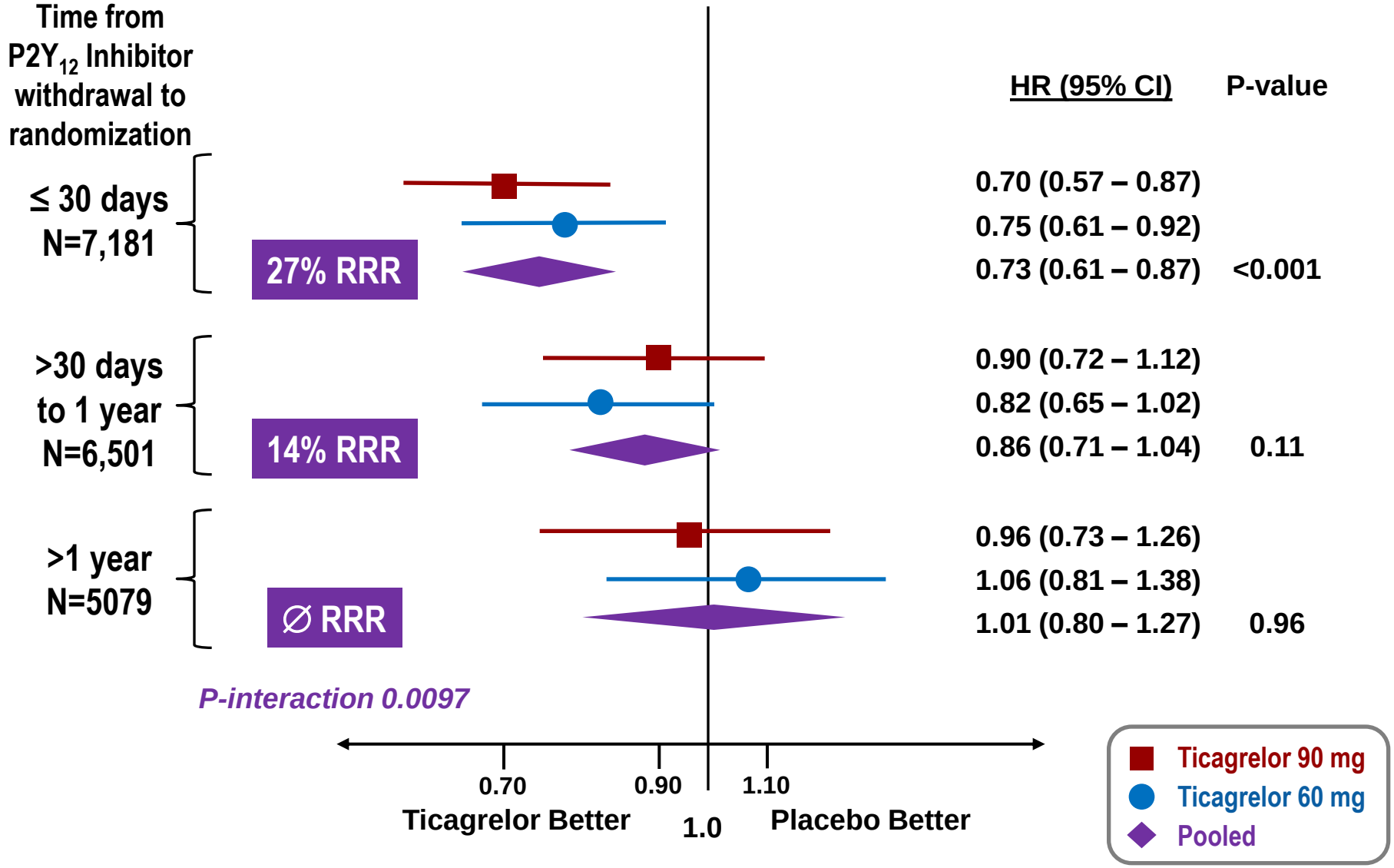
Ticagrelor 60 mg
HR 0.84 (95% CI 0.74 – 0.95)
P=0.004

Bonaca MP et al. NEJM 2015

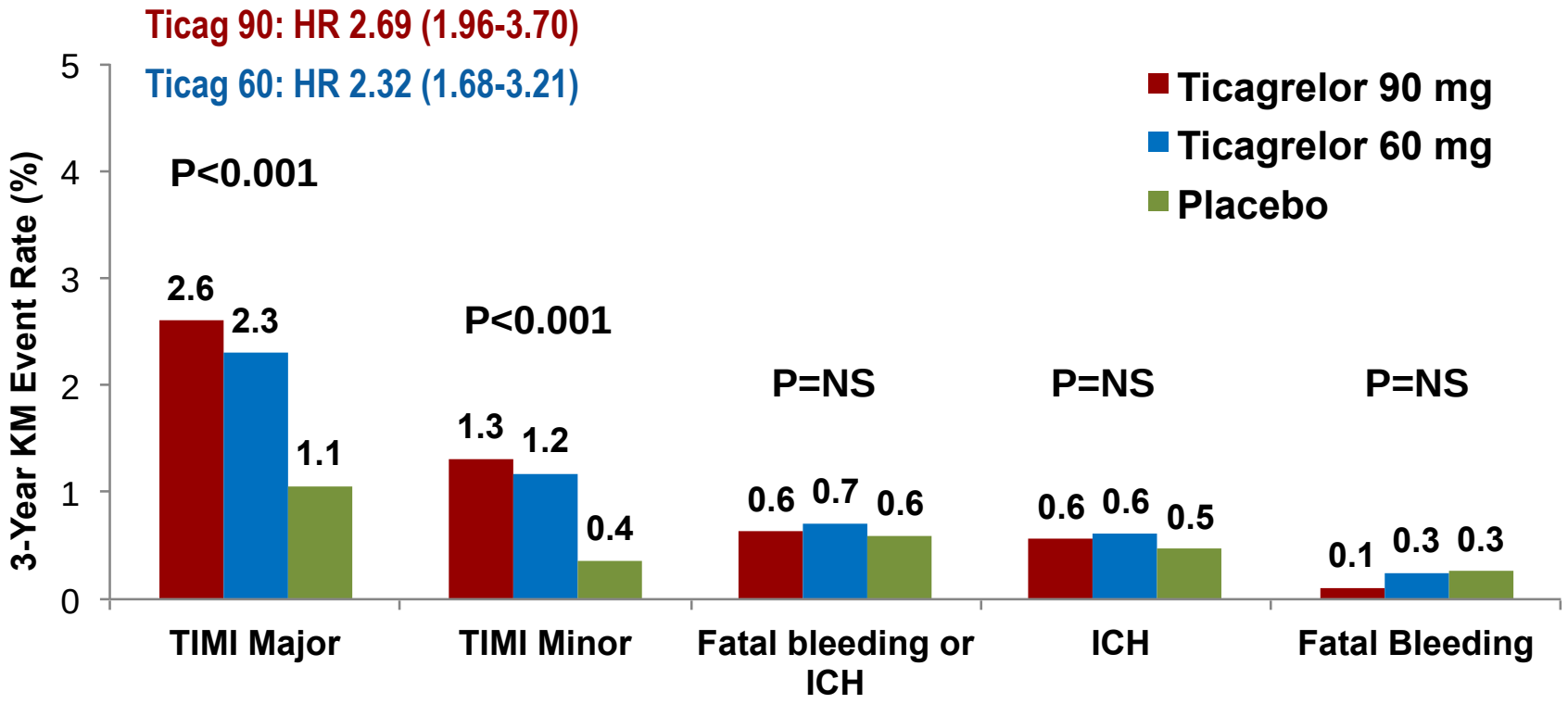
Components of Primary Endpoint



Reduction in MACE with Ticagrelor by Time from $P2Y_{12}$ Inhibitor Withdrawal



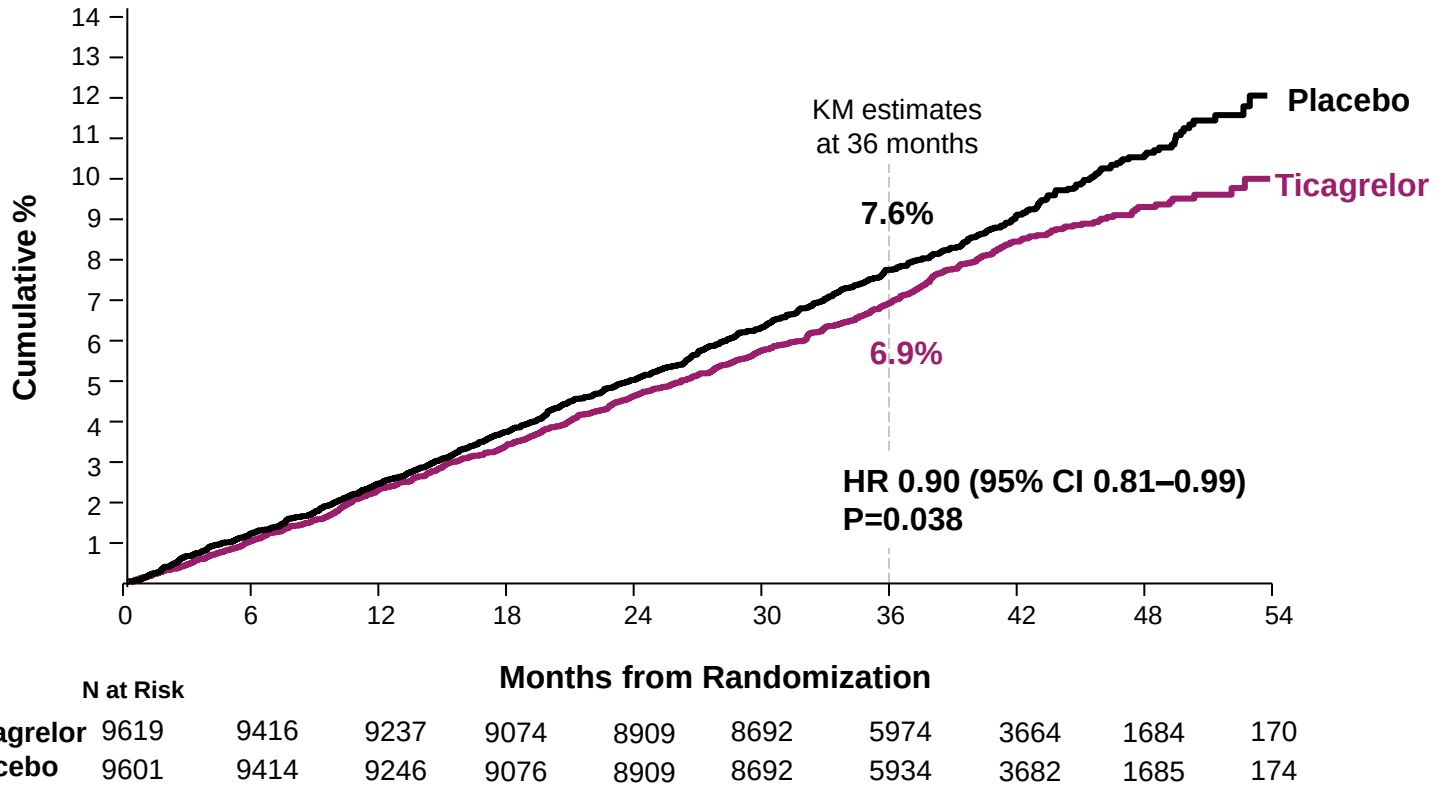
Bleeding



For every 10,000 patients treated with ticagrelor 60mg bid, 42 primary endpoint events are prevented at the expense of 31 major bleeding events, with <1% of these fatal or ICH.

Bonaca MP et al. NEJM 2015

THEMIS
Primary Composite Endpoint
Cardiovascular death/MI/stroke



N at Risk										
Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; N=number of patients

Steg PG, Bhatt DL, et al. NEJM 2019 DOI: 10.1056/NEJMoa1908077.

THEMIS
Bleeding Outcomes

	Ticagrelor (N=9562)		Placebo (N=9531)			
	Patients with events (%)	Event rate/ 100 patient years)	Patients with events (%)	Event rate/ 100 patient years)	Hazard Ratio (95% CI)	p-value
TIMI major bleeding	206 (2.2%)	0.89	100 (1.0%)	0.38	2.32 (1.82–2.94)	<0.001
TIMI major or minor bleeding	285 (3.0%)	1.23	129 (1.4%)	0.49	2.49 (2.02–3.07)	<0.001
TIMI major, minor, or requiring medical attention	1072 (11.2%)	4.61	485 (5.1%)	1.85	2.51 (2.26–2.80)	<0.001
PLATO major bleeding	310 (3.2%)	1.33	145 (1.5%)	0.55	2.41 (1.98–2.93)	<0.001
BARC bleeding						
5 (fatal bleeding)	17 (0.2%)	0.07	10 (0.1%)	0.04	1.90 (0.87–4.15)	0.11
5 or 4	17 (0.2%)	0.07	11 (0.1%)	0.04	1.73 (0.81–3.69)	0.16
5, 4 or 3	341 (3.6%)	1.47	163 (1.7%)	0.62	2.36 (1.96–2.84)	<0.001
Intracranial hemorrhage	70 (0.7%)	0.30	46 (0.5%)	0.18	1.71 (1.18–2.48)	0.005
Spontaneous	28 (0.3%)	0.12	27 (0.3%)	0.10	1.17 (0.69–1.98)	0.57
Procedural	1 (0.0%)	0.00	3 (0.0%)	0.01		
Traumatic	41 (0.4%)	0.18	16 (0.2%)	0.06	2.87 (1.61–5.12)	<0.001

Includes events with onset from randomization up to 7 days after last dose. BARC bleeding was defined according to a score of 3 to 5 as follows: type 3, bleeding with a decrease in the hemoglobin of more than 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; type 4, CABG-related bleeding; and type 5, fatal bleeding. Traumatic ICH: 27 (66%) on ticagrelor and 6 (38%) on placebo reported as subdural bleeding by investigators.

BARC=Bleeding Academic Research Consortium, CABG=coronary artery bypass grafting; CI=confidence interval; N=number of patients; PLATO=PLATelet inhibition and patient outcomes; TIMI=Thrombolysis in Myocardial Infarction

Which is the best option for our patient and why?

DAPT with aspirin and rivaroxaban 2.5 mg – YES

Reason: This the COMPASS-like patient!

New antithrombotic strategies: Dual Pathway Inhibition (DPI)

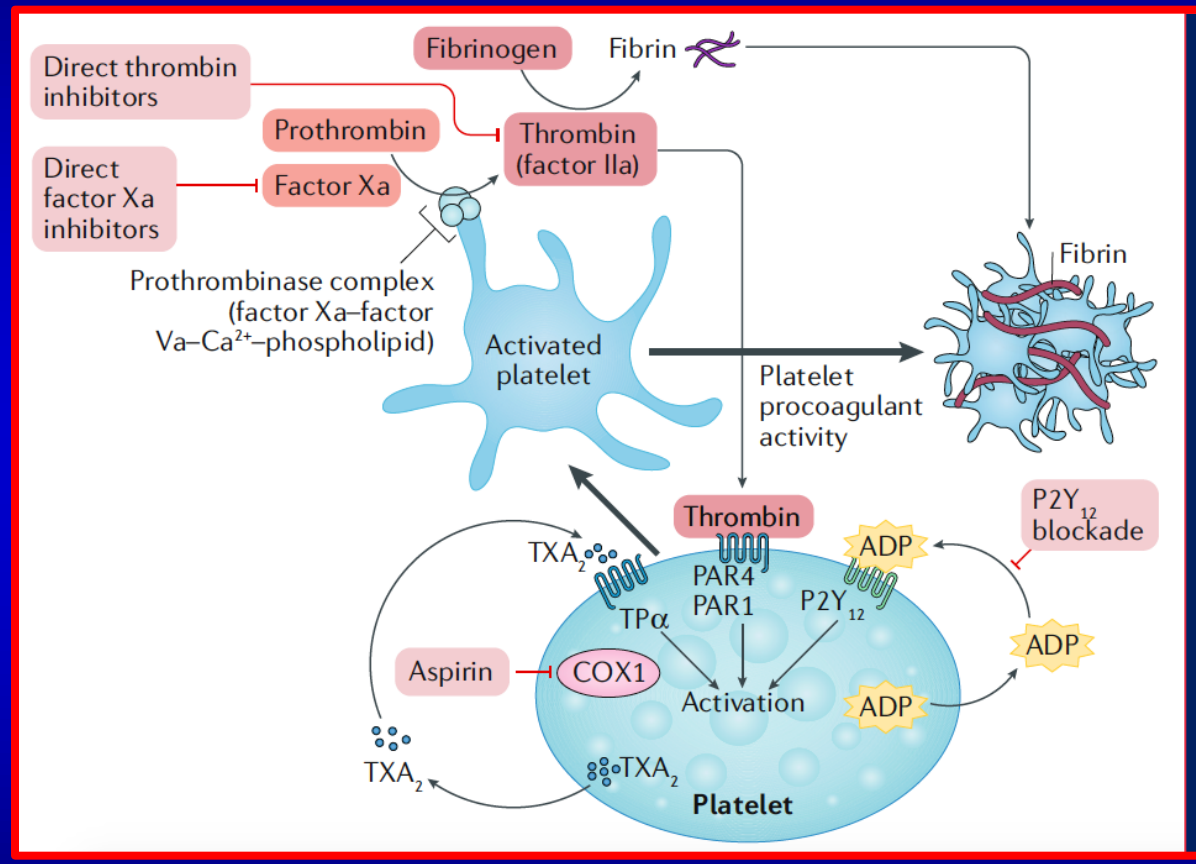
Aspirin mono-therapy is the standard of care for secondary prevention in patients with vascular disease manifestations (stable CAD and PAD).

However, ischemic recurrences persist while on aspirin mono-therapy.

A number of other antiplatelet strategies have failed to reduce ischemic events or mortality compared with aspirin alone.

Can very low dose rivaroxaban ("vascular protection dose") in adjunct to aspirin (DPI) reduce ischemic events / mortality?

Emerging Concepts: Dual-Pathway Inhibition (DPI)



Synergy of oral anticoagulant and antiplatelet therapy

Oral anticoagulant therapy, including direct inhibitors of factor IIa and Xa, and antiplatelet agents, such as acetylsalicylic acid and $P2Y_{12}$ inhibitors, synergistically target two essential components of thrombosis: coagulation and platelet activation.

Capodanno D & Angiolillo DJ. Nat Rev Cardiol. 2018; 15:480-496

COMPASS Design

Secondary prevention in **CAD and PAD patients** with an indication for single antiplatelet therapy

Patients with ***established*** atherosclerotic disease with a ***high risk*** of incident cardiovascular disease

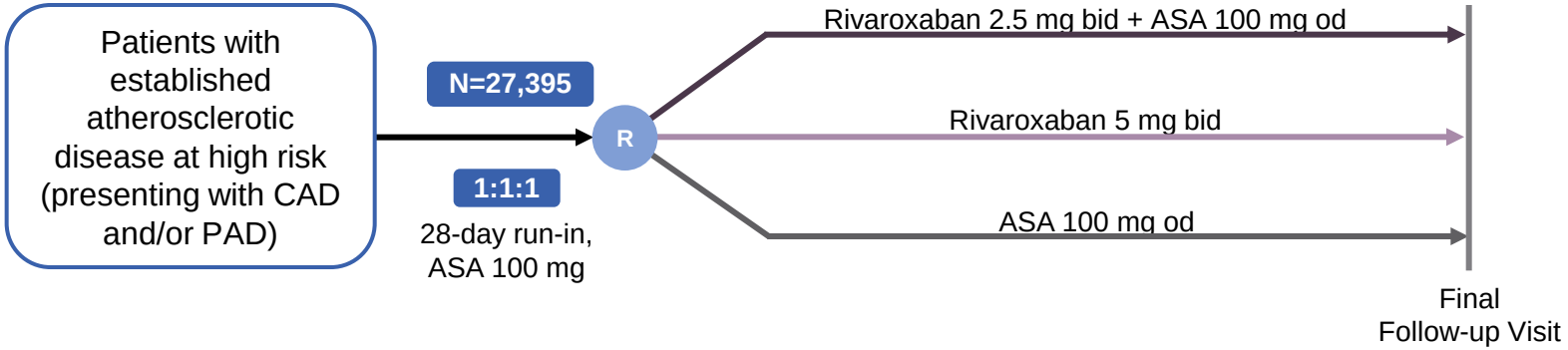
CAD (N=24,824)

- multivessel CAD and/or prior MI
- for patients < 65 years two vascular beds or two additional cardiovascular risk factors

PAD (N=7,470)

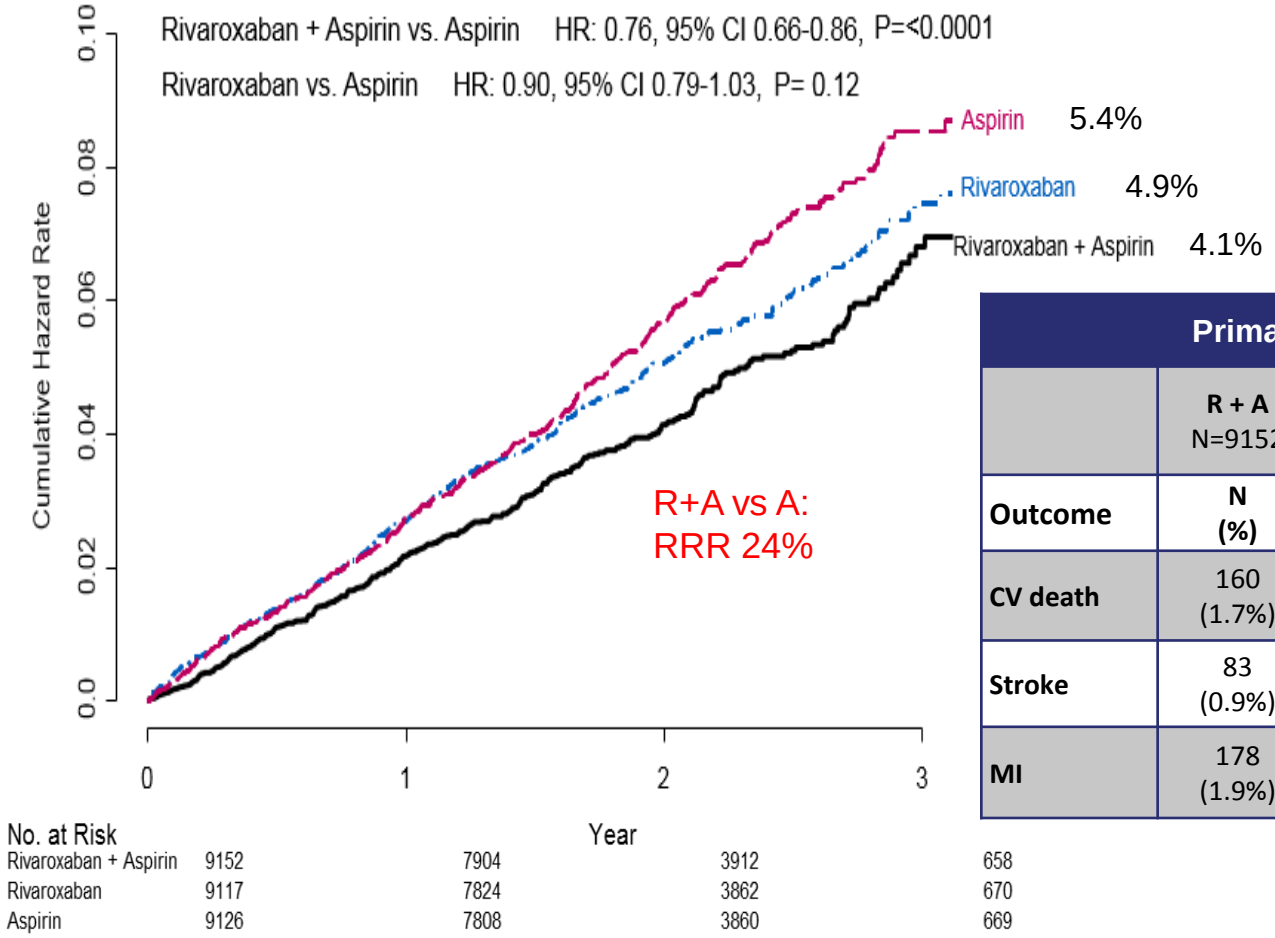
- previous interventions of peripheral bypass surgery or PTCA
- limb or foot amputation
- symptomatic intermittent claudication with ankle/arm blood pressure ratio < 0.90 or significant peripheral artery stenosis
- previous carotid revascularization or asymptomatic carotid artery stenosis ≥ 50%

Primary efficacy outcome: MI, stroke and cardiovascular death



- All patients must have had an indication for ASA according to guidelines
- Patients with an indication for DAPT were excluded as only stable patients were studied

Primary Endpoint: CV Death, Stroke, MI



Primary Endpoint Components				
	R + A N=9152	A N=9126	Rivaroxaban + Aspirin vs Aspirin	
Outcome	**N (%)**	**N (%)**	**HR (95% CI)**	**P**
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

Eikelboom JW et al. *N Eng J Med*. 2017;377:1319-30.

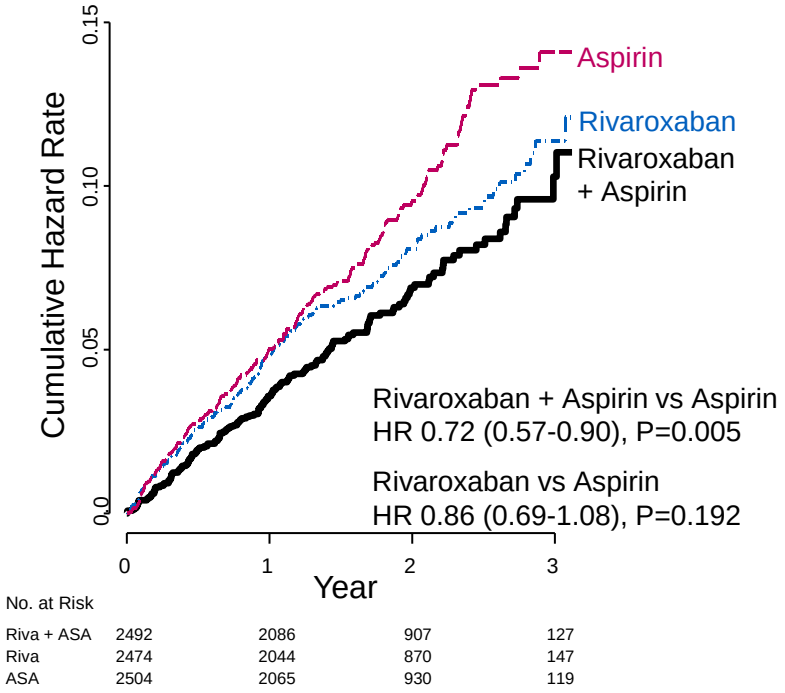
COMPASS: CAD and PAD Subgroups for Primary Outcome

	R + A N=9152	A N=9126	Rivaroxaban + Aspirin vs Aspirin
Outcome	**N (%)**	**N (%)**	**HR (95% CI)**
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

Anand SS et al. *Lancet*. 2017;pii:S0140-6736(17)32409-1.

COMPASS and PAD: MACE and Limb Outcomes

Primary Outcome: CV death, MI, or stroke



Anand SS et al. *Lancet*. 2017;pii:S0140-6736(17)32409-1.

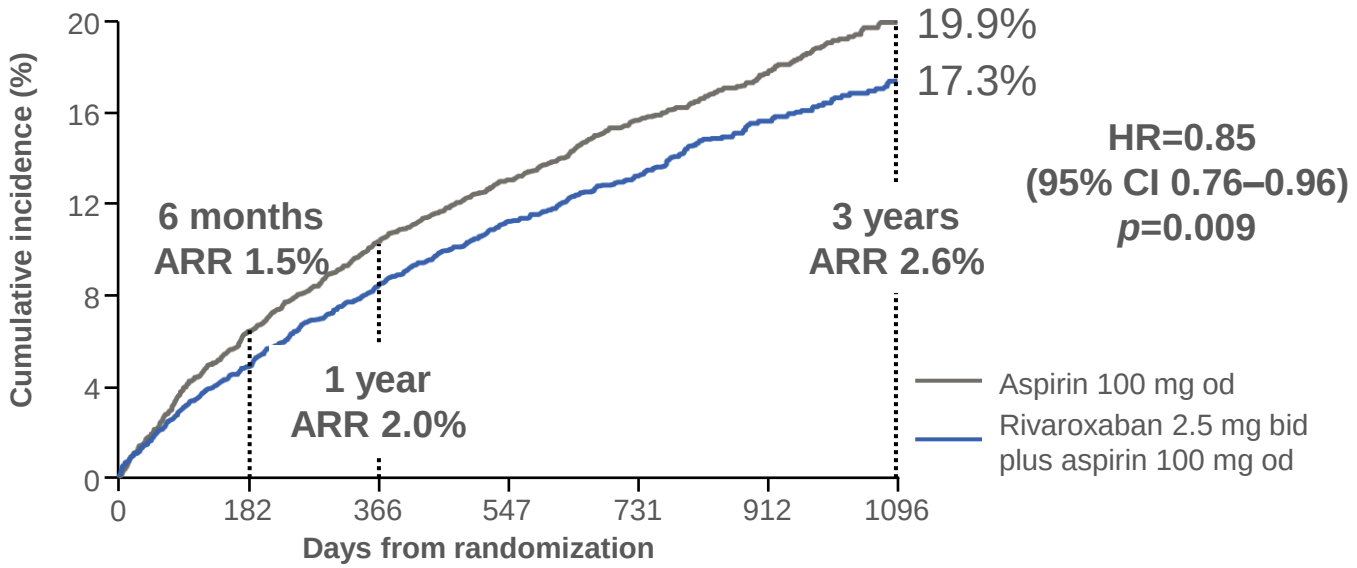
Major adverse limb event (MALE) and Major Amputation

	R + A N=2492	A N=2504	Rivaroxaban + Aspirin vs Aspirin	
	N (%)	N (%)	HR (95% CI)	P
MALE	30 (1.2)	56 (2.2)	0.54 (0.35-0.84)	0.005
Major amp.	5 (0.2)	17 (0.7)	0.30 (0.11-0.80)	0.01

- Primary Cardiovascular Outcome (MACE):
  - CV death, Stroke, or MI
- Major Adverse Limb Events (MALE):
  - Severe limb ischemia leading to an intervention (angioplasty, bypass surgery, amputation, thrombolysis)
  - Major amputation above forefoot due to vascular cause

Rivaroxaban Vascular Dose plus Aspirin Significantly Reduced Risk of the Composite Primary Endpoint by 15% Versus Aspirin

Cumulative incidence of ALI, major amputation of vascular aetiology, MI, ischaemic stroke or CV death



Number at risk							
Rivaroxaban plus aspirin	3286	3082	2938	2834	2219	1415	684
Aspirin	3278	3030	2881	2773	2151	1351	642

Bonaca MP *et al*. ACC. Chicago, USA, 28–30 March 2020, Abstract 402-10. Available at https://cpcclinicalresearch.org/wp-content/uploads/2020/03/CPC-VOYAGER-PAD-Primary-Results-Slide-Presentation-by-Marc-P.-Bonaca.pdf [accessed 31 March 2020]

VOYAGER PAD

COMPASS

Major bleeding

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	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
Non fatal 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
Non-fatal other 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

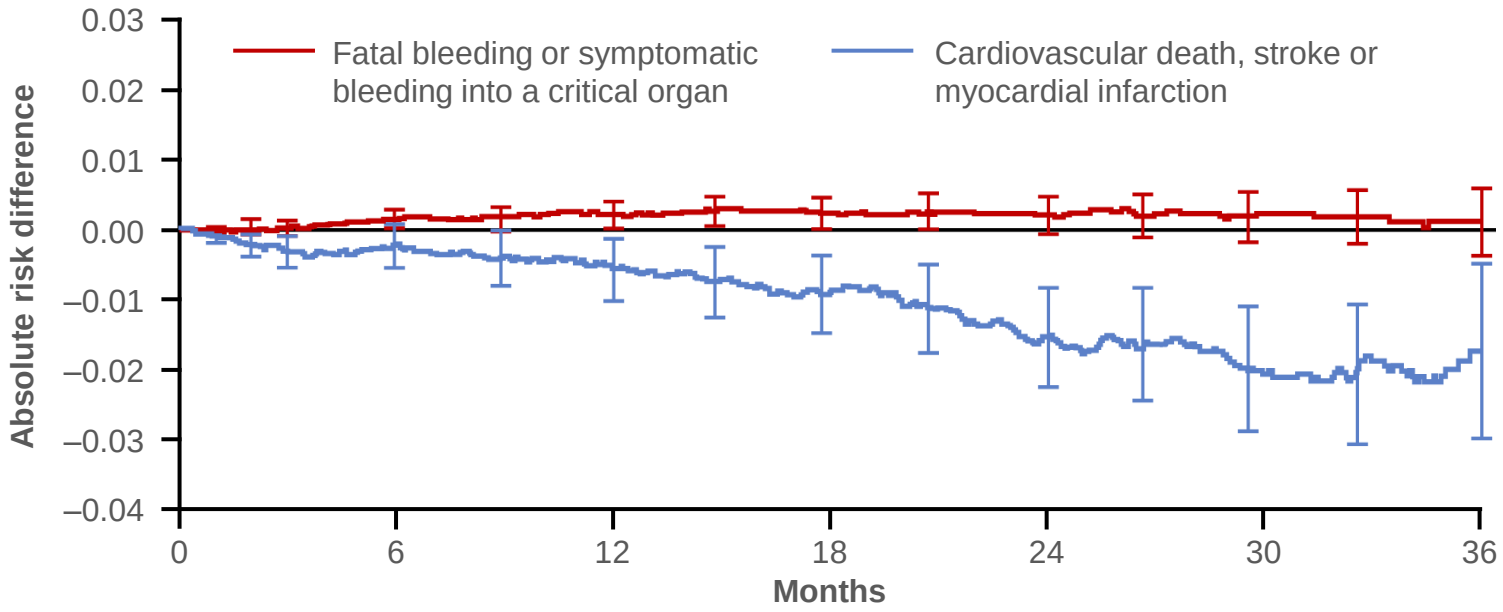
* symptomatic

Net clinical benefit

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

The Balance Between The Increase in Bleeding Events and Reduction in MACE Suggests a Net Clinical Benefit Over Time

Absolute risk differences over time for severe bleeding and MACE



- The increase in major bleeding and GI bleeding with rivaroxaban 2.5 mg bid plus aspirin was confined to the first year after randomization, with no significant excess bleeding thereafter
- In contrast, the benefits of rivaroxaban 2.5 mg bid plus aspirin in preventing CV death, stroke or MI, and mortality were consistent over time

Eikelboom JW *et al*, *J Am Coll Cardiol* 2019;74(12):1519-1528

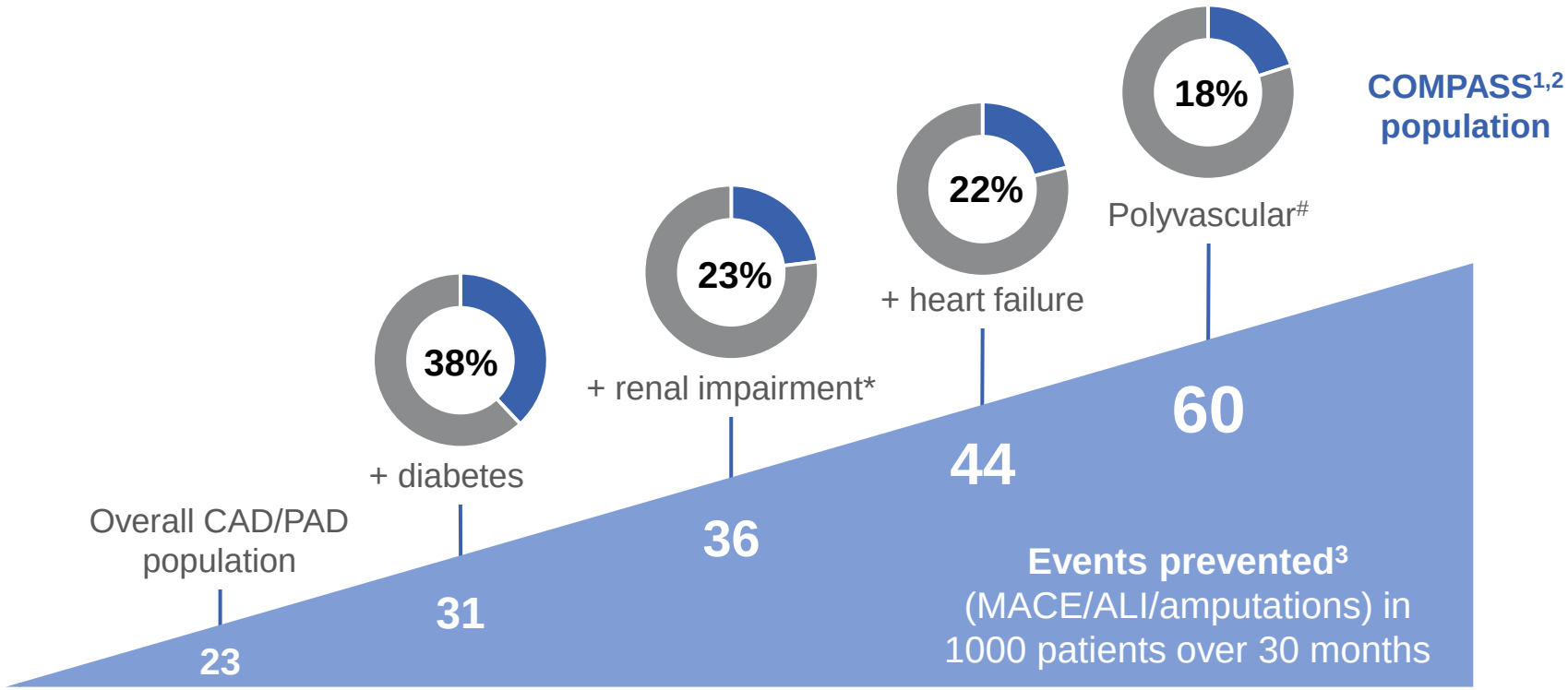
COMPASS

COMPASS in Perspective: Relative Risk of Antithrombotics for Secondary Prevention

	CAPRIE Clopidogrel	CHARISMA Clopidogrel + Aspirin	PEGASUS Ticagrelor 90 + Aspirin	PEGASUS Ticagrelor 60 + Aspirin	COMPASS Rivaroxaban + Aspirin
MACE	↓7%	↓7%	↓15%	↓16%	↓**24%**
Death	↓2%	↓1%	0%	↓11%	↓**18%**
Stroke	-	↓21%*	↓18%	↓25%	↓**42%**
MI	-	↓6%*	↓19%	↓16%	↓**14%**
Major Bleeds	↓27%	↑25% and ↑62%†	↑169%	↑132%	↑**70%**
ICH	↓29%	4%	↑44%	↑33%	↑**10%**

*Non-fatal. †Severe and moderate GUSTO, respectively. CAPRIE Steering Committee. *Lancet*. 1996;348:1329-39. CHARISMA Investigators. *N Engl J Med*. 2006;354:1706-17. PEGASUS-TIMI 54 Steering Committee and Investigators. *N Engl J Med*. 2015;372:1791-800. COMPASS Investigators. *N Engl J Med*. 2017;377:1319-30.

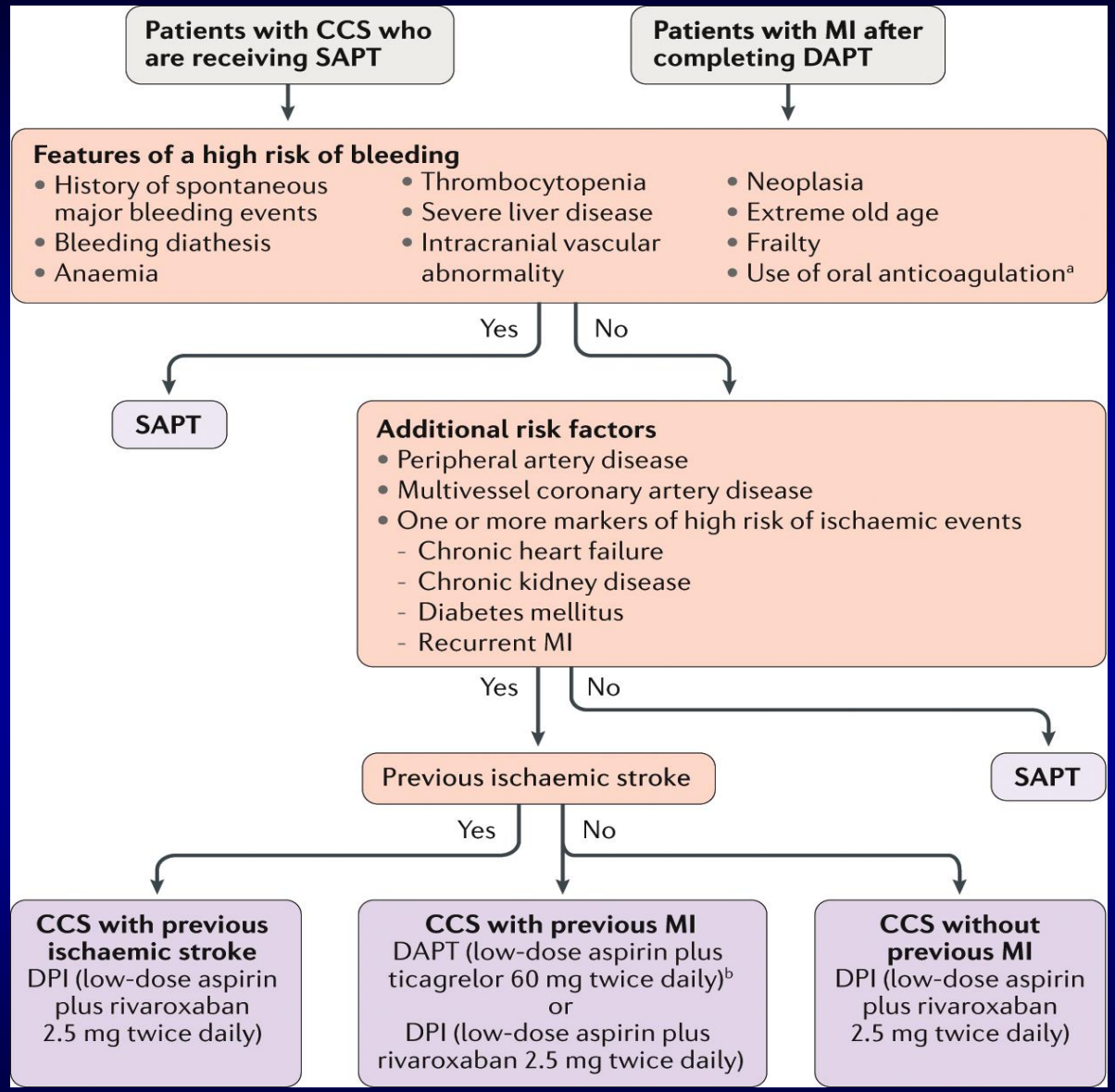
Patients at Higher CV Risk Benefit More from Rivaroxaban Vascular Dose 2.5 mg bid plus Aspirin



*eGFR <60 ml/min; #≥2 vascular beds

1. Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319–1330; 2. Connolly SJ *et al*, *Lancet* 2018;391:205–218; 3. Anand SS *et al*, *J Am Coll Cardiol* 2019;73:3271−3280

Algorithm for the choice of antithrombotic therapy in CCS patients



Capodanno D & Angiolillo DJ. Nat Rev Cardiol. 2020. doi: 10.1038/s41569-019-0314-y.