State of the Art Antithrombotic Therapies for Coronary and Peripheral Atherosclerosis

A Personalized Approach to Antithrombotics

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Question: In one word, what is your biggest challenge with thrombosis and antithrombotic therapies?

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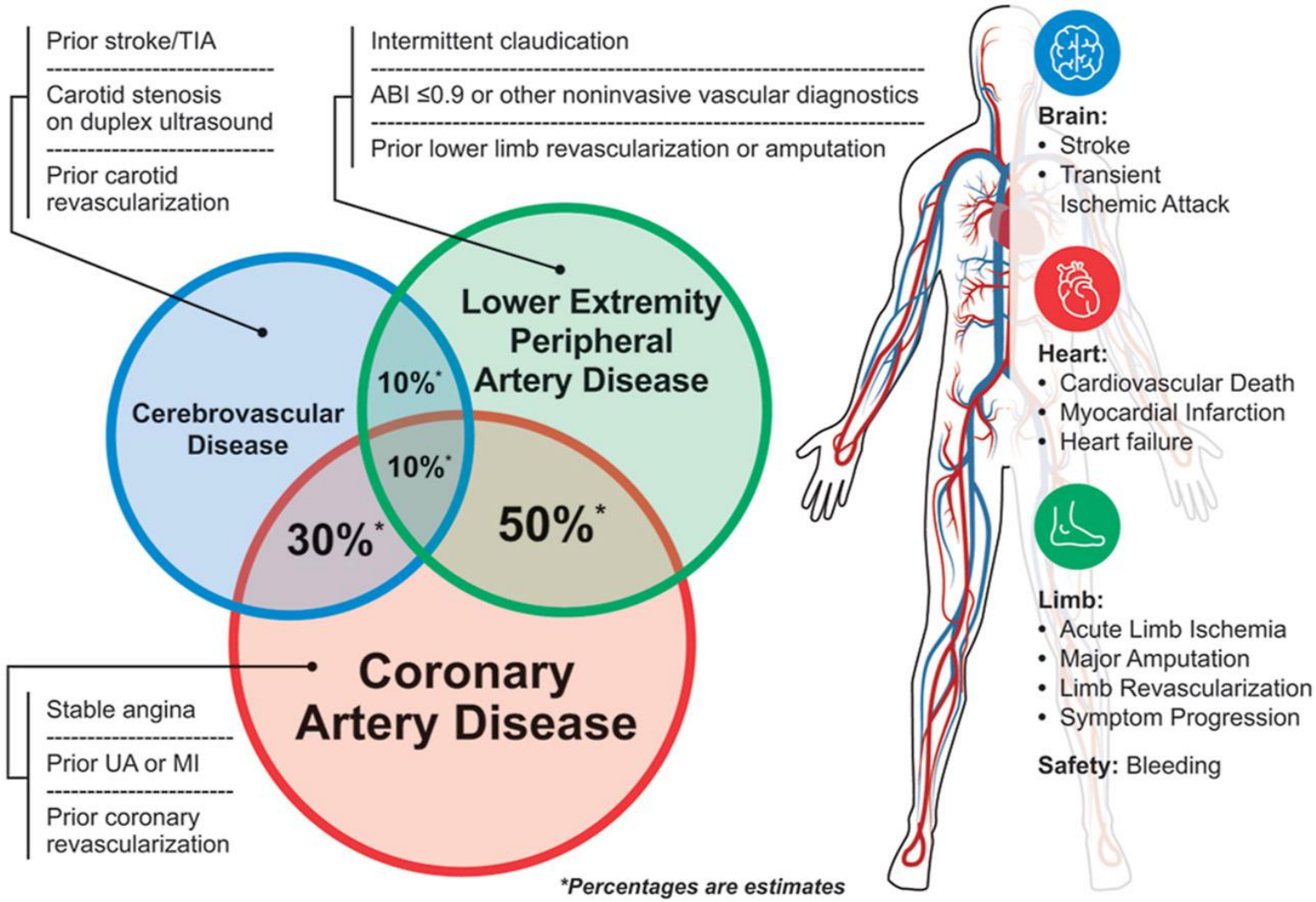
Poll: In one word, what is your biggest challenge with thrombosis and antithrombotic therapies?

State of the Art Antithrombotic Therapies

1. Aspirin-Free Strategies
2. De-escalation Strategies
3. Native Disease Dual Therapy
4. Peripheral Arterial Disease

Atherosclerosis: A Polyvascular Disease



Weissler EH et al., Atherosclerosis. 2020 Dec;315:10-17.

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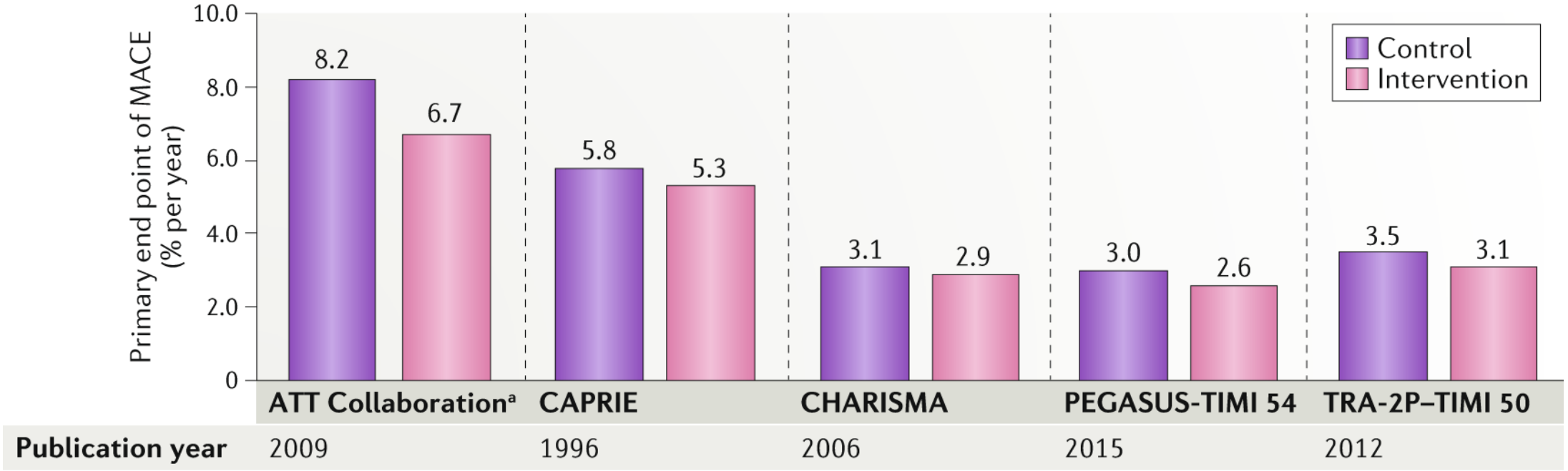
Yearly Residual Risk of CV Events in Patients with CAD Receiving Medical Therapy

~3% MACE risk per year



Capodanno D et al. Nature Reviews Cardiology volume 17, pages242–257 (2020)

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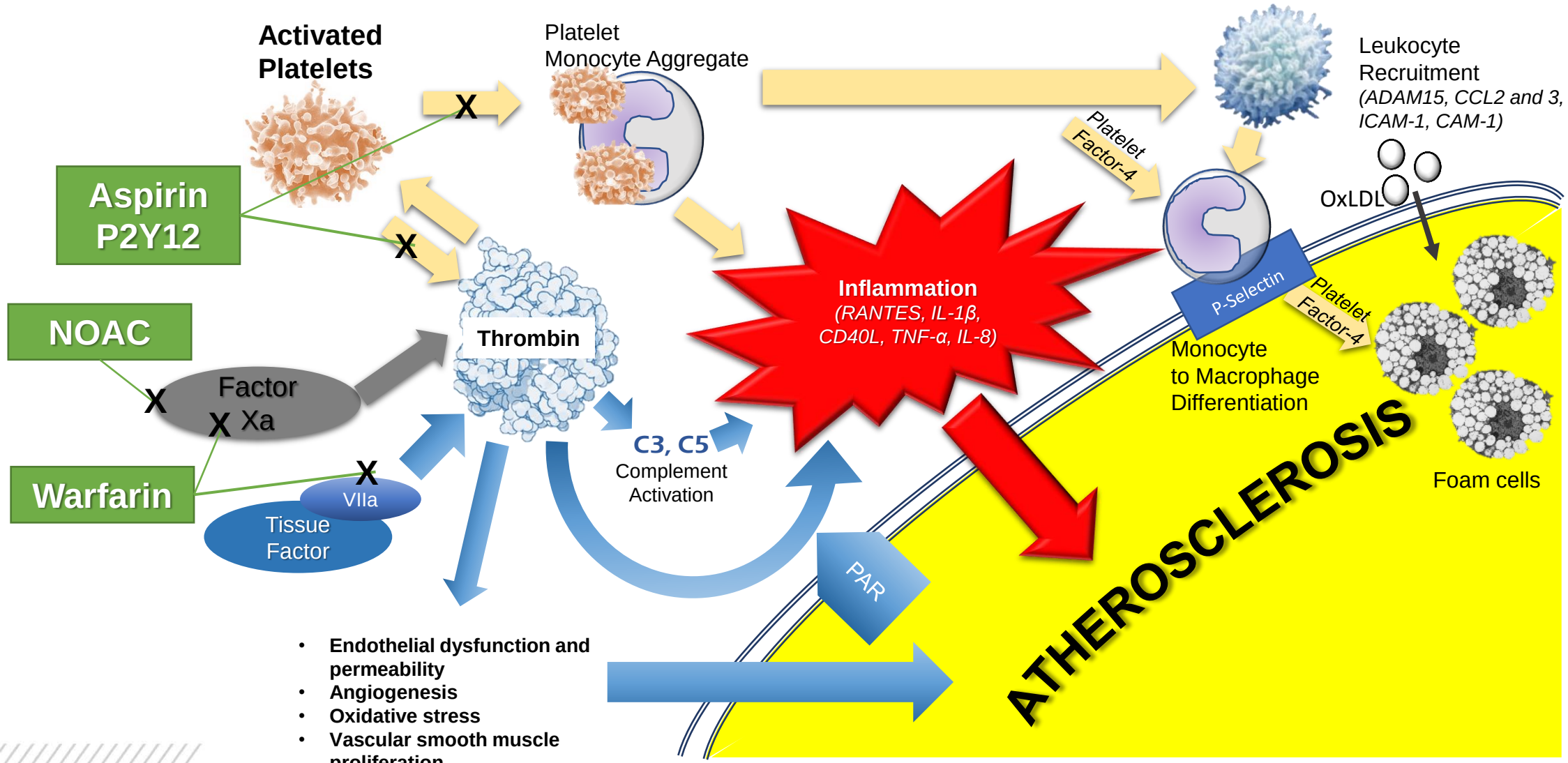
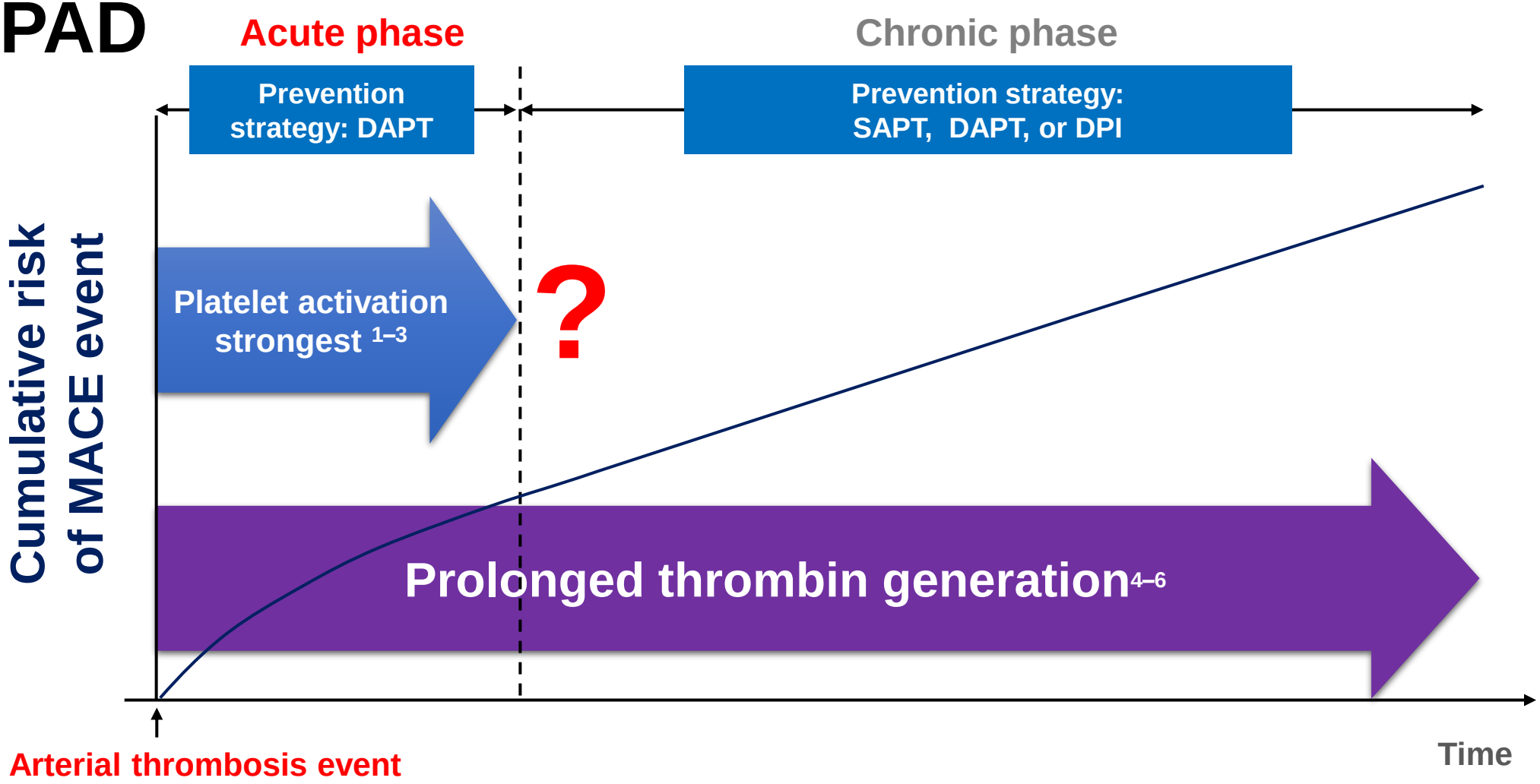
Thrombin and Platelets Promote Atherosclerosis



Thrombosis Generation in Acute and Chronic CAD/PAD



Mackman N. Nature 2008;451:914–918; 2. Franchi F and Angiolillo DJ. Nat Rev Cardiol 2015;12:30–47; 3. Trip MD et al, N Engl J Med 1990;322:1549–1554
Cohen M and Iyer D. Cardiovasc Ther 2014;32:224–232; 5. Merlini PA et al, Circulation 1994;90:61–68; 6. Ardissino D et al, Blood 2003;102:2731–2735

Patient A

Clinical Presentation

- 62 yo female presents for routine follow up after NSTEMI 3 mo ago
- Feels fine, no chest pain
- Some red bloody stools in past month

PMH:

- NSTEMI (3 mo)
  - Troponin I peak 0.45 ng/mL
  - Mid LAD 80% -> Synergy 3.0x12 mm stent, TIMI 3 flow. No other CAD
- Hypertension x 25 years
- Type II diabetes x 4 years
- Ulcerative colitis x 20 years

Medications:

- Aspirin, Ticagrelor, statin, ARB, Beta-blocker, SGLT2-inhibitor 81 mg daily, Mesalamine 2.4 g daily

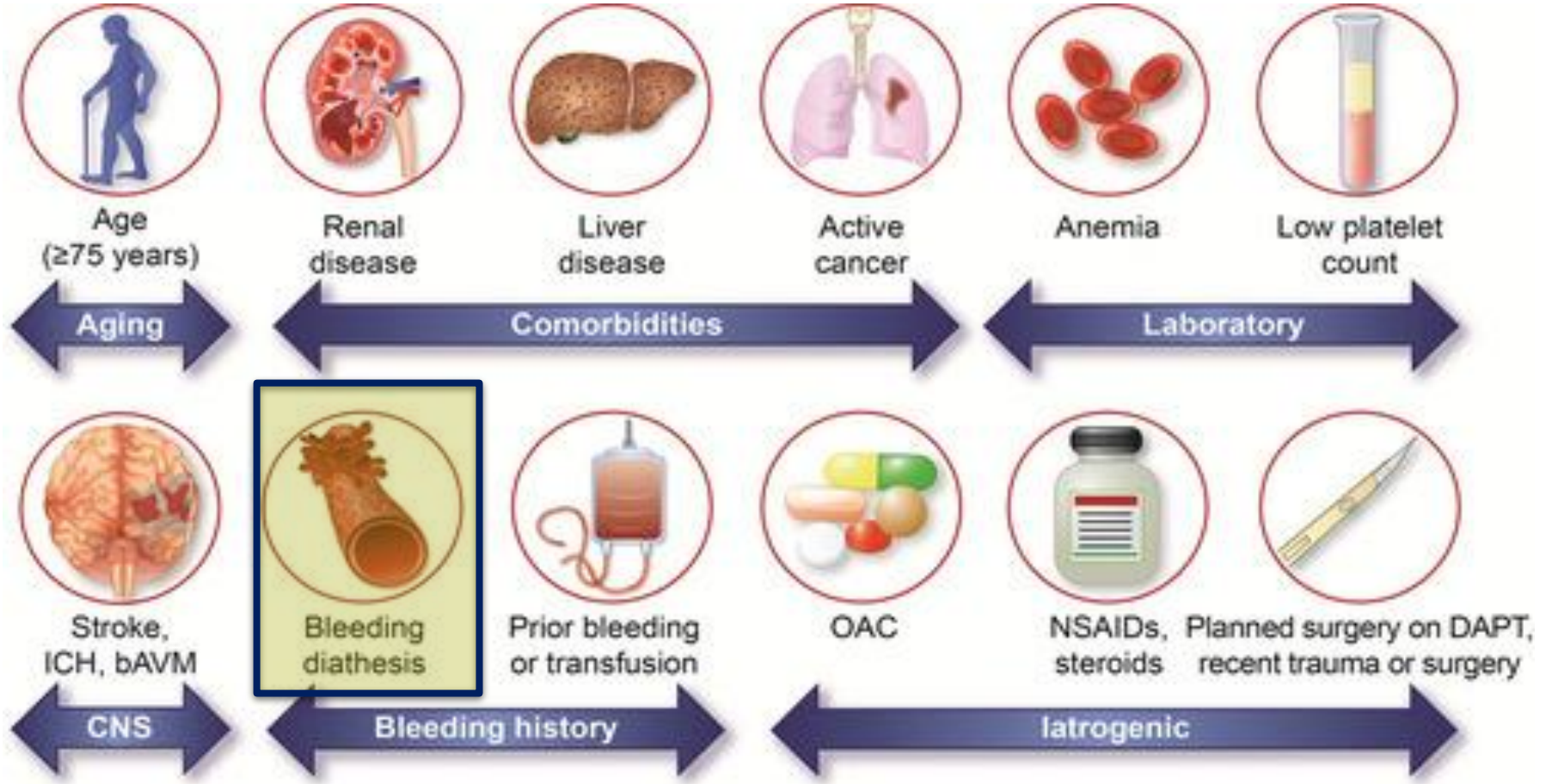
Physical Examination:

- BP 124/79 mmHg, HR 58 bpm, RR 12, BMI 29
- Unremarkable examination

Laboratory Studies:

- Hg 9.2 g/dL (prev 12.1 g/dL)
- Cr 0.8 mg/dL

High Bleeding Risk at PCI



Academic Research Consortium for High Bleeding Risk. Urban P, Mehran R, et al. Circulation. 2019;140:240–261

Live Content Slide

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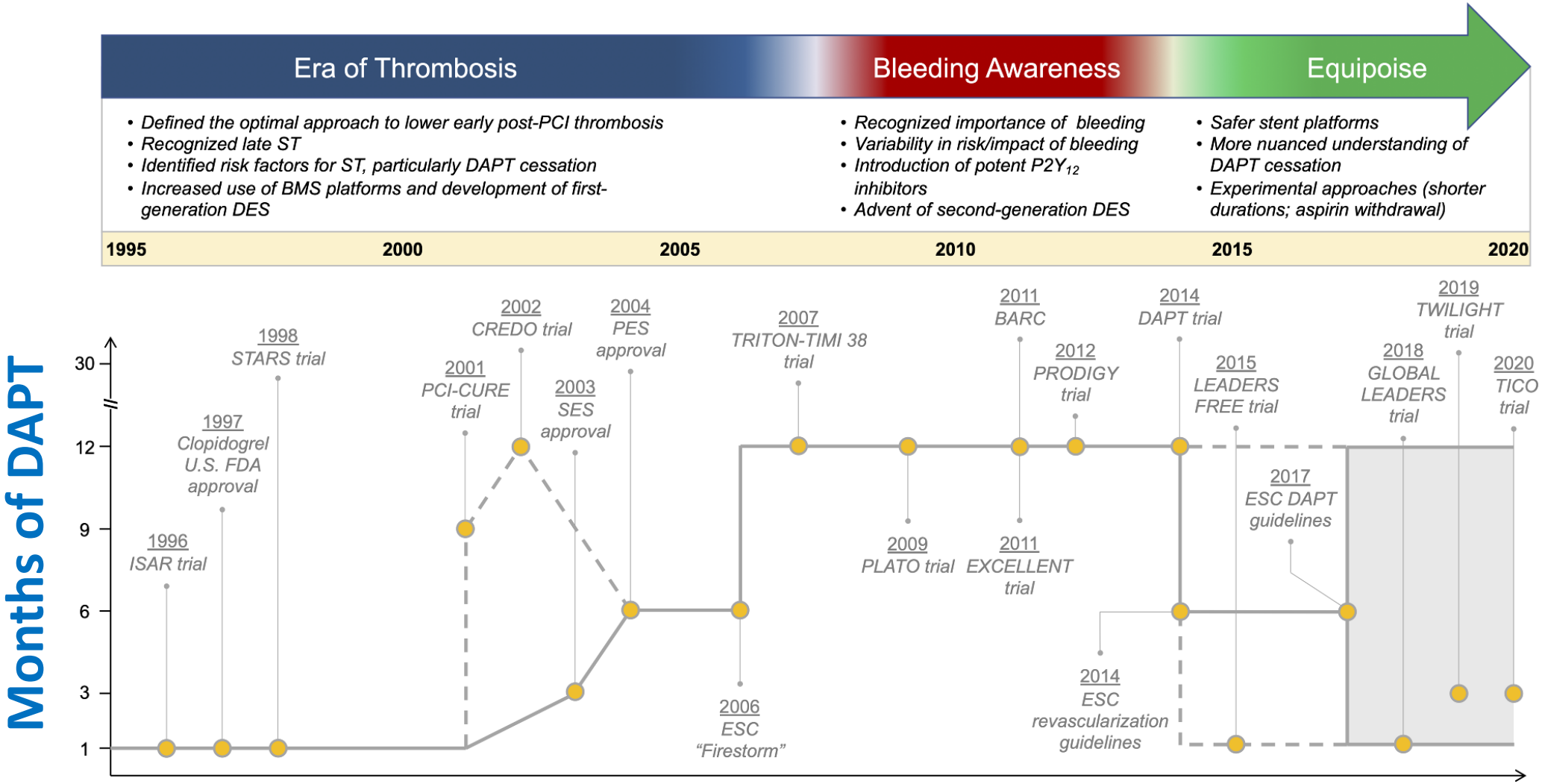
Poll: Question: Which of the following DAPT strategies is the best for our patient?

Evolving Duration of Antiplatelet Therapy After PCI



Cao D et al., Eur Heart J. 2020 Dec 26;ehaa824.

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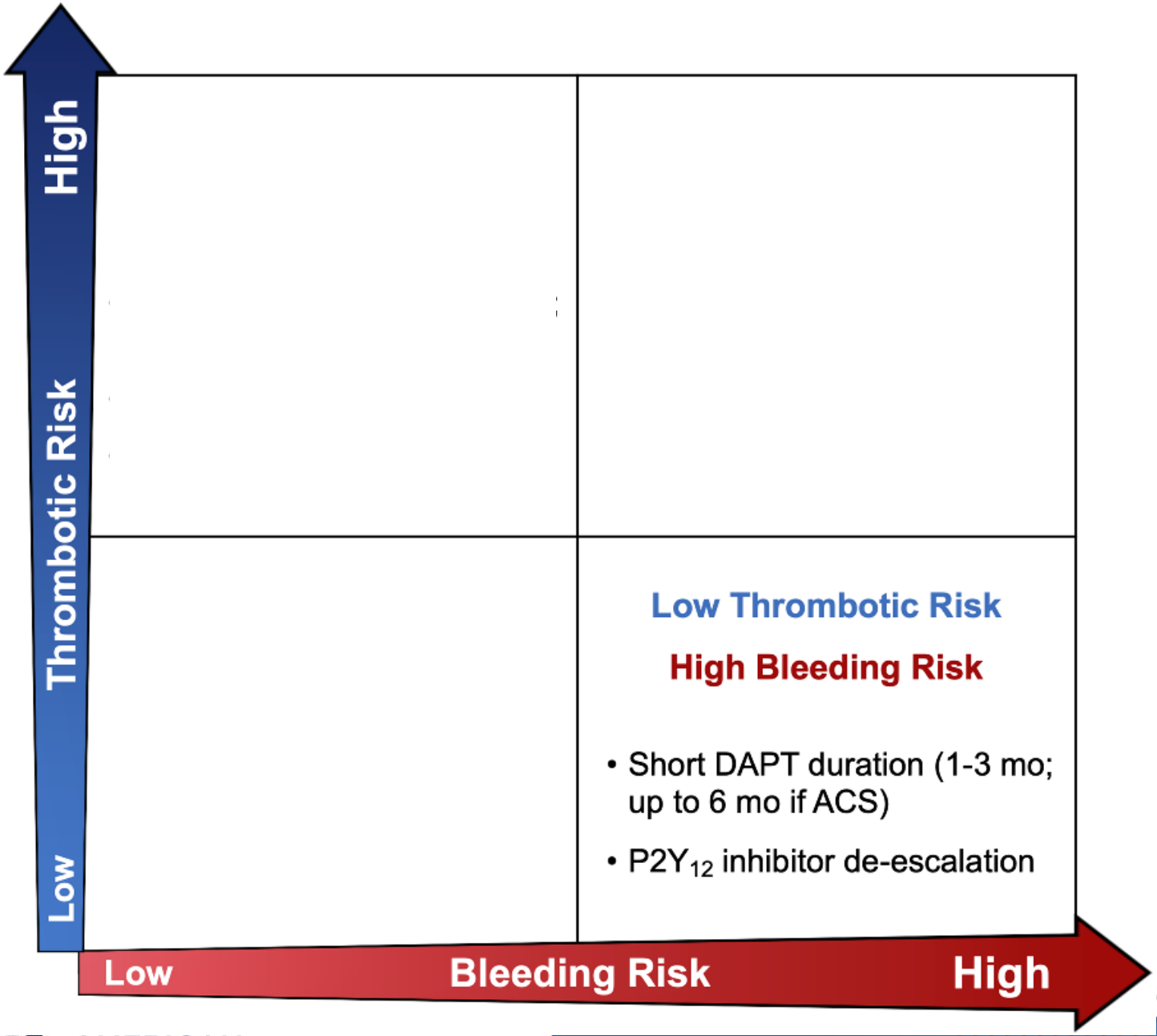
Balance of MACE and Bleeding Risk

Personalized Antithrombotic Therapy



Cao D et al., Eur Heart J. 2020 Dec 26;ehaa824.

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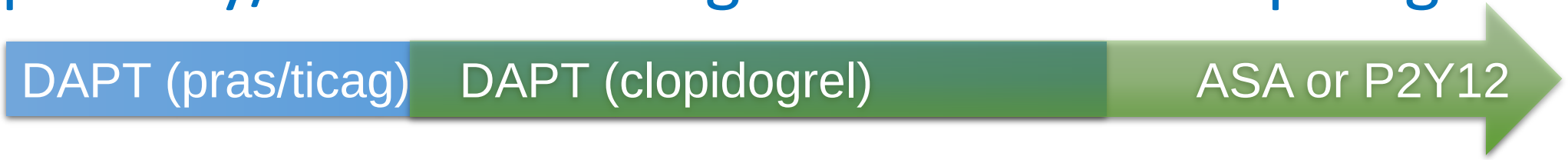
Definitions

Which do you chose?

- **Short DAPT** – DAPT discontinuation to platelet monotherapy at 1 or 3 months with chronic angina, up to 6 months with ACS

- **De-escalation** – DAPT change to lower potency/lower bleeding risk P2Y12 of clopidogrel



State of the Art Antithrombotic Therapies

1. **Aspirin-Free Strategies**
2. De-escalation Strategies
3. Native Disease Dual Therapy
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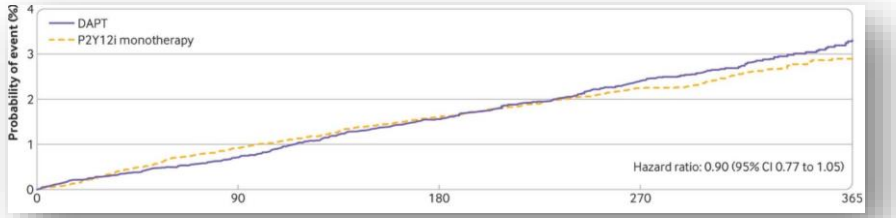
Similar MACE for P2Y12 Monotherapy After Short DAPT

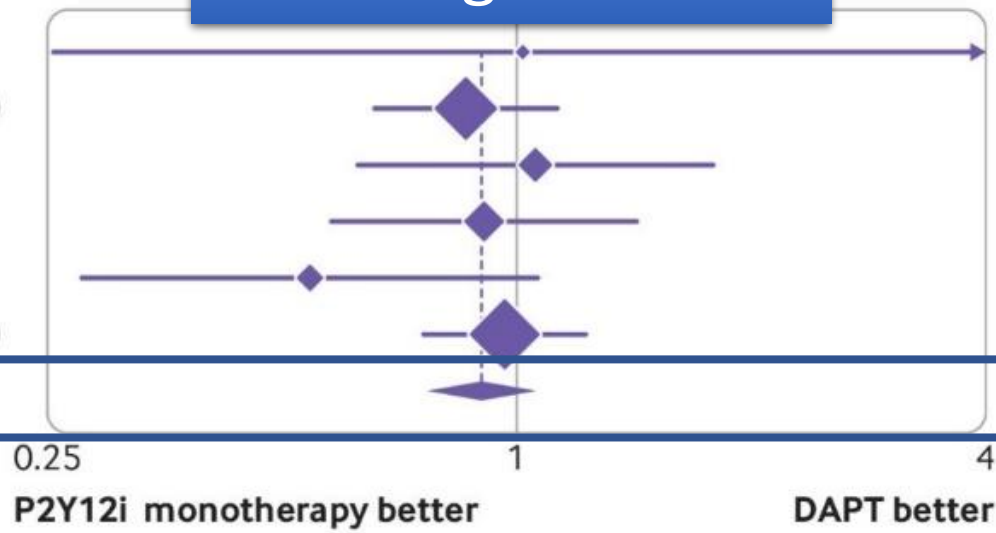
An IPD meta-analysis of 24,096 patients

Primary endpoint of all cause death, MI, or stroke



No change in MACE

Study ID	P2Y12i monotherapy (%)	DAPT (%)	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	4/166 (2.4)	4/168 (2.4)	1.26	1.02 (0.25 to 4.06)
GLASSY (n=7509)	96/3753 (2.6)	112/3756 (3.0)	32.50	0.86 (0.65 to 1.13)
SMART-CHOICE (n=2926)	28/1455 (2.0)	27/1471 (1.9)	8.64	1.05 (0.62 to 1.79)
STOPDAPT-2 (n=3003)	36/1496 (2.4)	40/1507 (2.7)	11.91	0.91 (0.58 to 1.43)
TICO (n=3004)	13/1499 (0.9)	24/1505 (1.6)	5.30	0.54 (0.28 to 1.07)
TWILIGHT (n=6532)	126/3265 (3.9)	131/3267 (4.1)	40.38	0.96 (0.76 to 1.23)
Overall: I^2=0.0%; P=0.71			100.00	0.90 (0.77 to 1.05)



Valgimigli M and Mehran R et.al., BMJ 2021;373:n1332.

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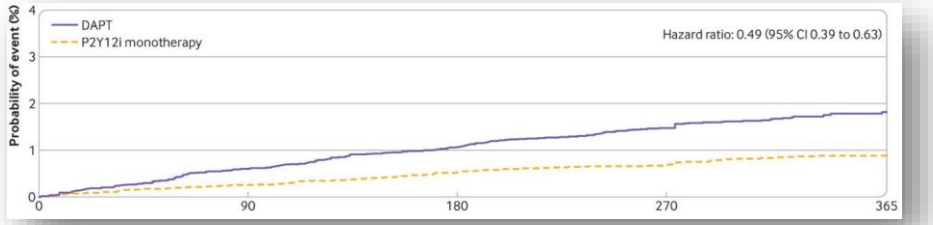
Lower Bleeding for P2Y12 Monotherapy After Short DAPT

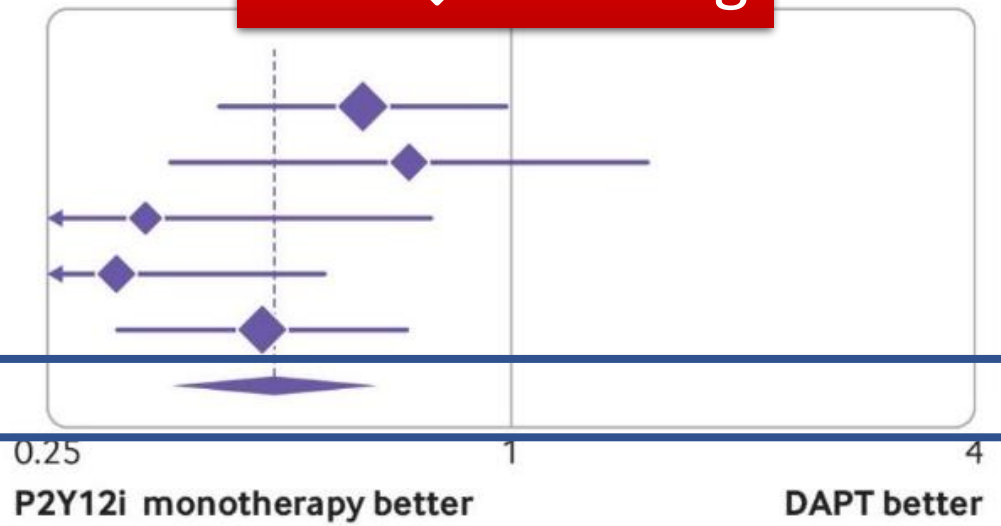
An IPD meta-analysis of 24,096 patients



BARC type 3 or type 5 bleeding

51% ↓ bleeding

Study ID	P2Y12i monotherapy (%)	DAPT (%)	Relative risk	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	-	-		-	-
GLASSY (n=7509)	34/3753 (0.9)	53/3756 (1.4)		28.85	0.64 (0.42 to 0.99)
SMART-CHOICE (n=2926)	13/1455 (1.0)	18/1471 (1.4)		14.32	0.74 (0.36 to 1.50)
STOPDAPT-2 (n=3003)	7/1496 (0.5)	21/1507 (1.4)		10.63	0.33 (0.14 to 0.79)
TICO (n=3004)	13/1499 (0.9)	42/1505 (2.8)		17.68	0.31 (0.17 to 0.57)
TWILIGHT (n=6532)	30/3265 (0.9)	63/3267 (2.0)		28.53	0.47 (0.31 to 0.73)
Overall: I^2=29.3%; P=0.23				100.00	0.49 (0.36 to 0.67)



Valgimigli M and Mehran R et.al., BMJ, 2021;373:n1332.

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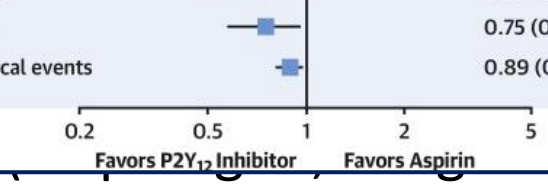
Post-DAPT: PANTHER Meta-Analysis P2Y12 vs ASA

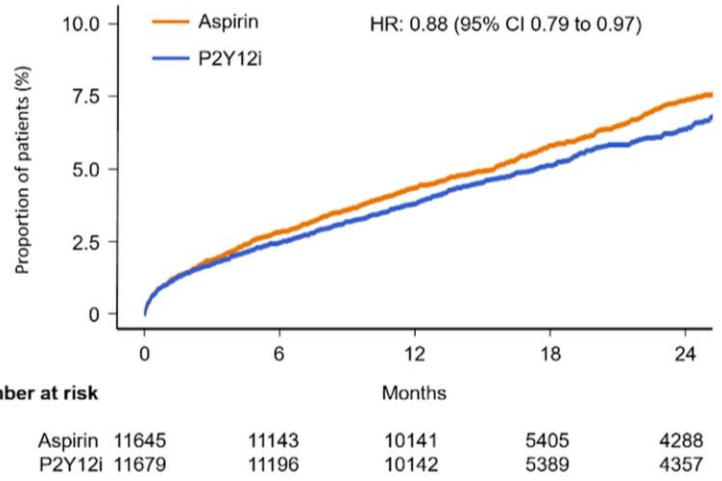
P2Y12 inhibitor versus aspirin monotherapy in patients with coronary artery disease

Clinical Outcomes	$P2Y_{12}$ Inhibitor Monotherapy (N = 12,178) Log HR (95% CI)	Aspirin Monotherapy (N = 12,147) HR (95% CI)	*P* Value
Cardiovascular death, MI, or stroke		0.88 (0.79-0.97)	0.012
All-cause death		1.04 (0.91-1.20)	0.560
Cardiovascular death		1.02 (0.86-1.20)	0.820
Myocardial infarction		0.77 (0.66-0.90)	< 0.001
Any stroke		0.84 (0.70-1.02)	0.076
Ischemic stroke		0.93 (0.75-1.13)	0.450
Hemorrhagic stroke		0.43 (0.23-0.83)	0.012
Definite/probable ST		0.46 (0.23-0.92)	0.028
Major bleeding		0.87 (0.70-1.09)	0.229
Major GI bleeding		0.67 (0.43-1.06)	0.089
Any GI bleeding		0.75 (0.57-0.97)	0.027
Net adverse clinical events		0.89 (0.81-0.98)	0.020

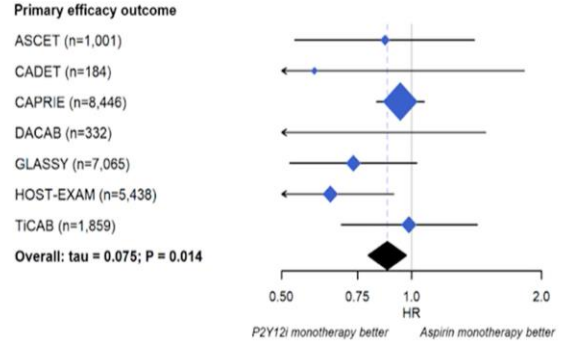


Primary Efficacy Outcome: CV death, MI, stroke

CV death, MI or stroke: 5.5% vs. 6.3%; HR 0.88, 95% CI 0.79 to 0.97, P=0.014; NNTB: 123



12% ↓MACE



Gragnano F, et al. JACC 2023;82:89-105

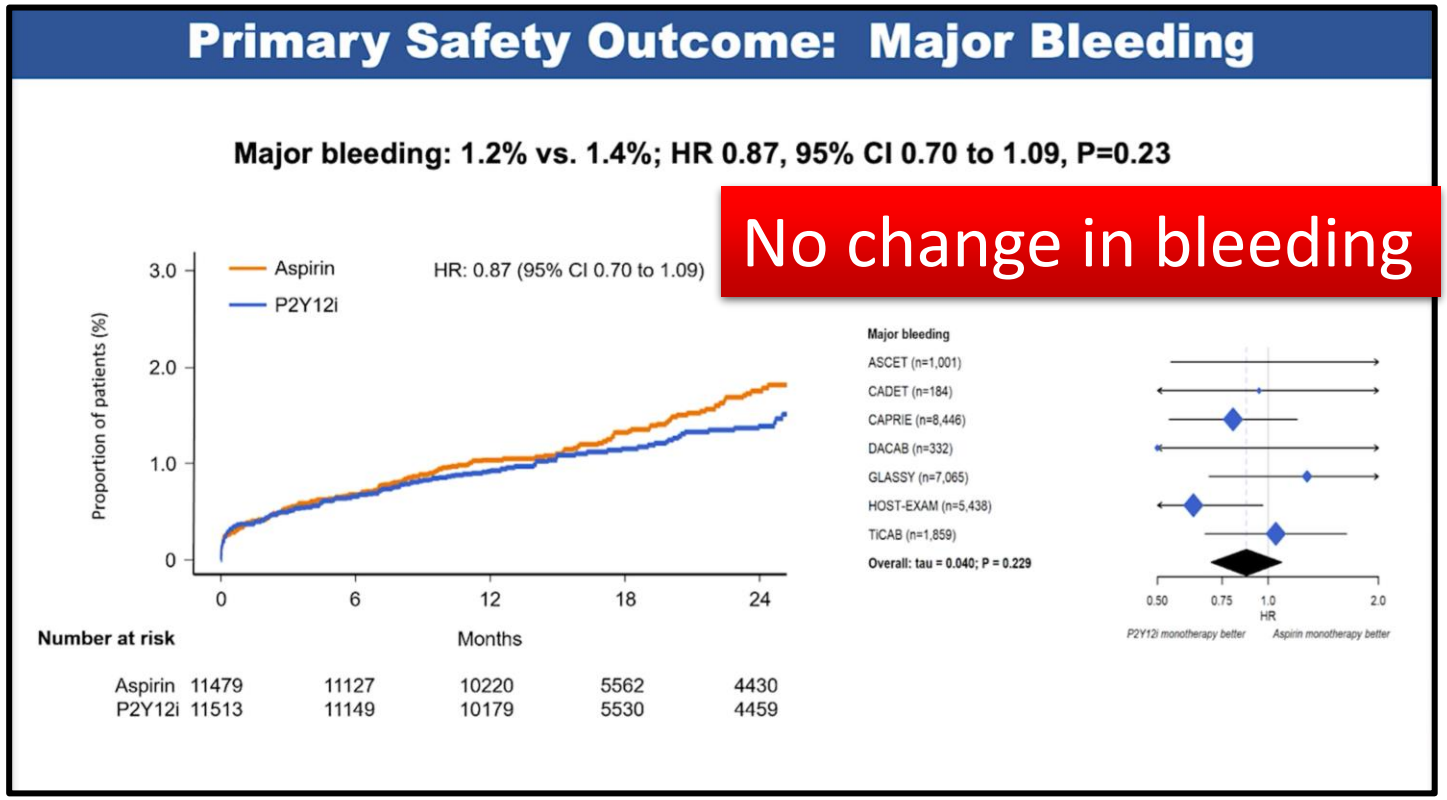
Post-DAPT: PANTHER Meta-Analysis P2Y12 vs ASA

P2Y12 inhibitor versus aspirin monotherapy in patients with coronary artery disease

Meta-analysis of 7 RCT's of patients with CAD, Post-DAPT phase

Mixed clinical contexts (ACS, post-PCI)

Any ASA vs. P2Y12 (clopidogrel, ticagelor)



Gragnano F, et al. JACC 2023;82:89-105

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State of the Art Antithrombotic Therapies

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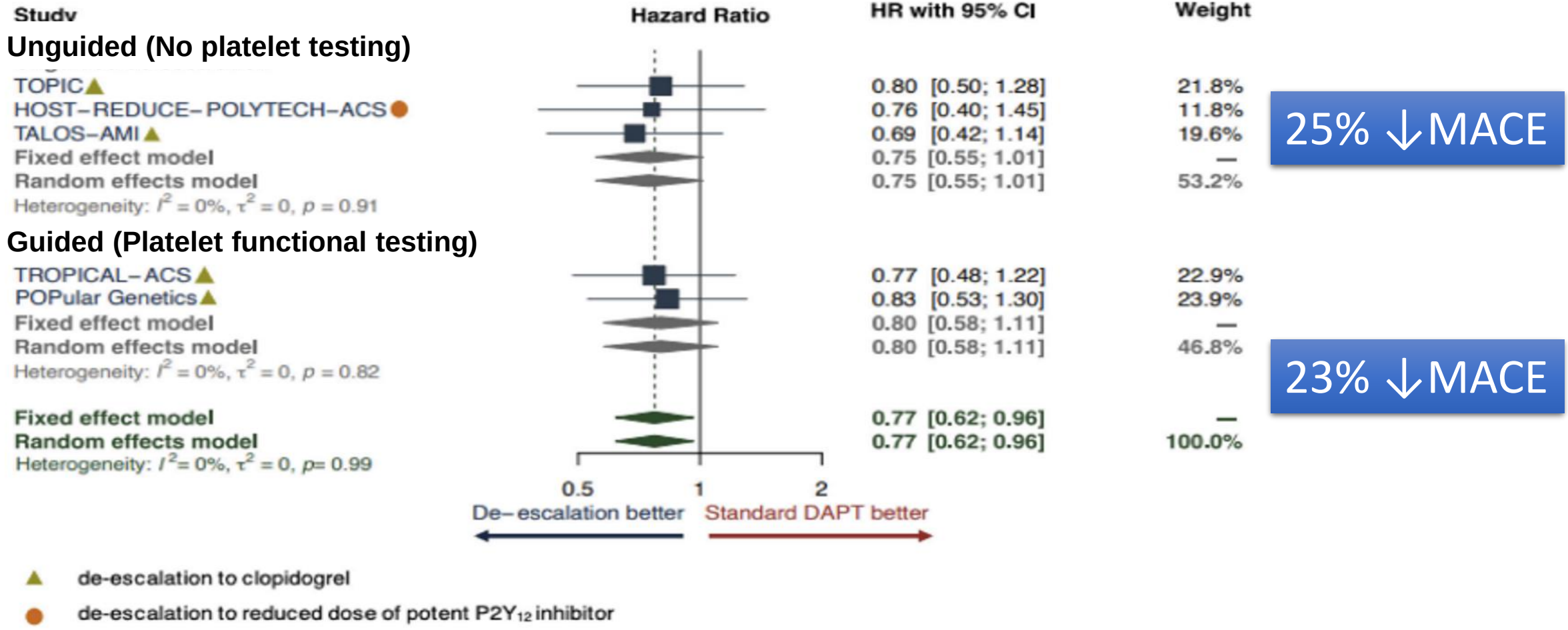
De-Escalation from Potent P2Y12 Inhibitors Post-ACS: Meta-Analysis

DAPT (pras/ticag) → DAPT (clopidogrel) → ASA or P2Y12

MACE



25% ↓MACE

23% ↓MACE

▲ de-escalation to clopidogrel

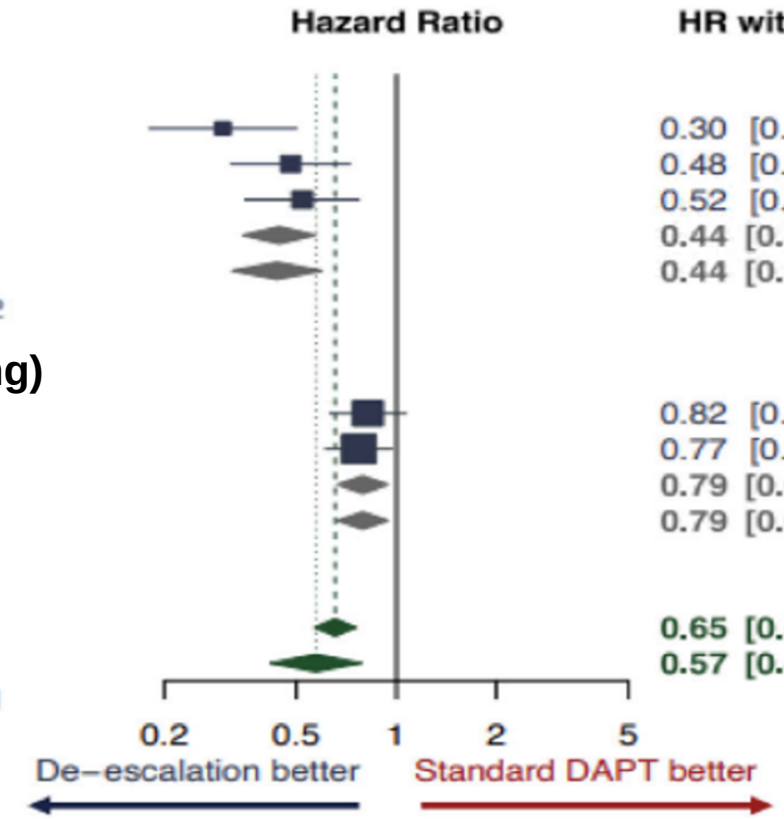
● de-escalation to reduced dose of potent $P2Y_{12}$ inhibitor

Tavenier AH, Dangas G et al., EHJ CVP, 2021

De-Escalation from Potent P2Y12 Inhibitors Post-ACS: Meta-Analysis

DAPT (pras/ticag) → DAPT (clopidogrel) → ASA or P2Y12

BARC 2-5 Bleeding



56% ↓ bleeding

43% ↓ bleeding

▲ de-escalation to clopidogrel

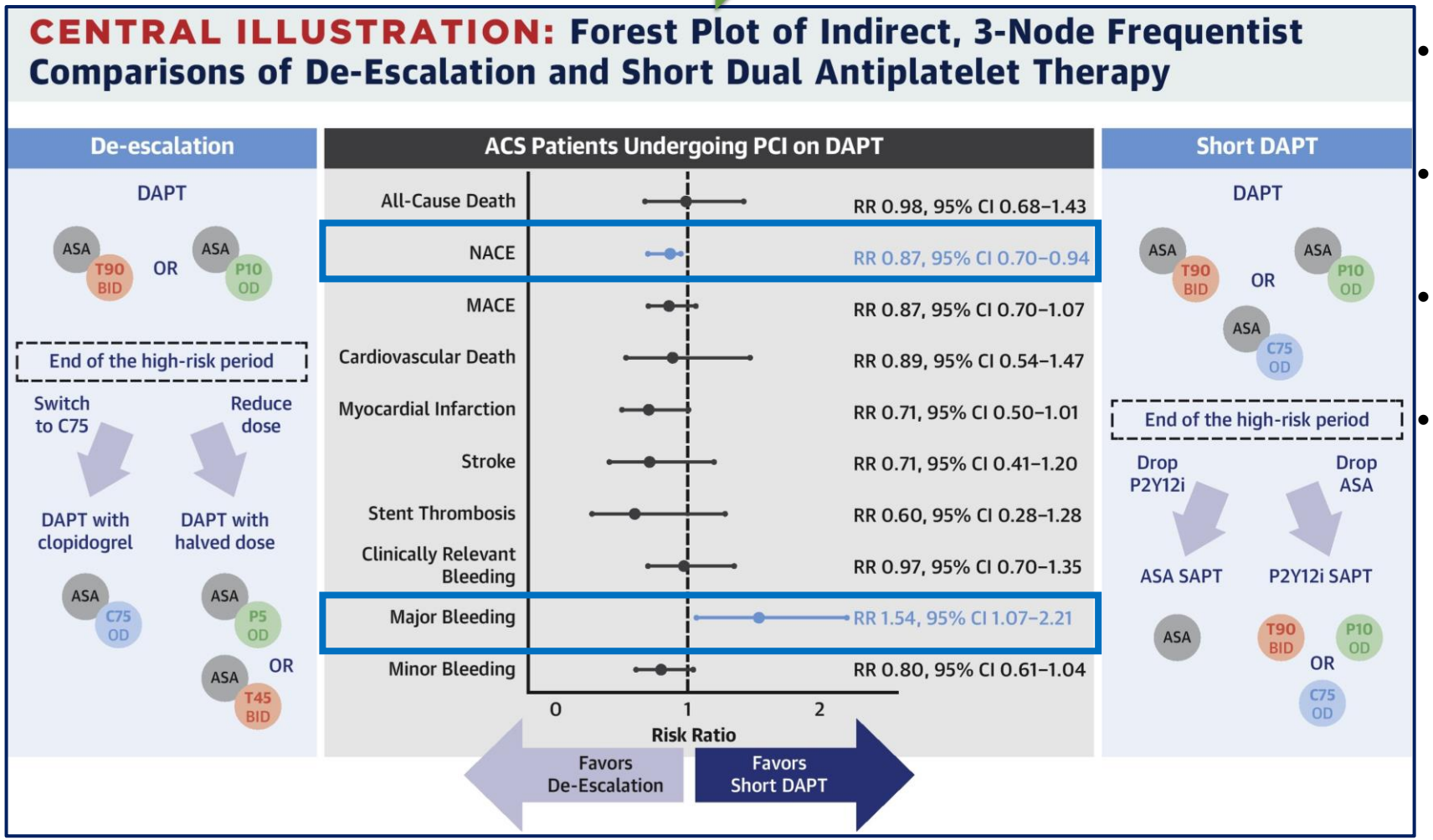
● de-escalation to reduced dose of potent $P2Y_{12}$ inhibitor

Tavenier AH, Dangas G et al., EHJ CVP, 2021

De-Escalation or Short DAPT?

DAPT (pras/ticag) → DAPT (clopidogrel) ASA or P2Y12

DAPT → P2Y12



- 29 RCT studies, 50,602 patients
- Both reduce bleeding, negligible effect on MACE
- De-escalation – lower NACE
- Short DAPT - lower major bleeding

Individualize treatment for each patient based on NACE/MACE risk and bleeding

NACE = net adverse cardiovascular events

Laudani C, et al. J Am Coll Cardiol Intervent 2022;15:268–277

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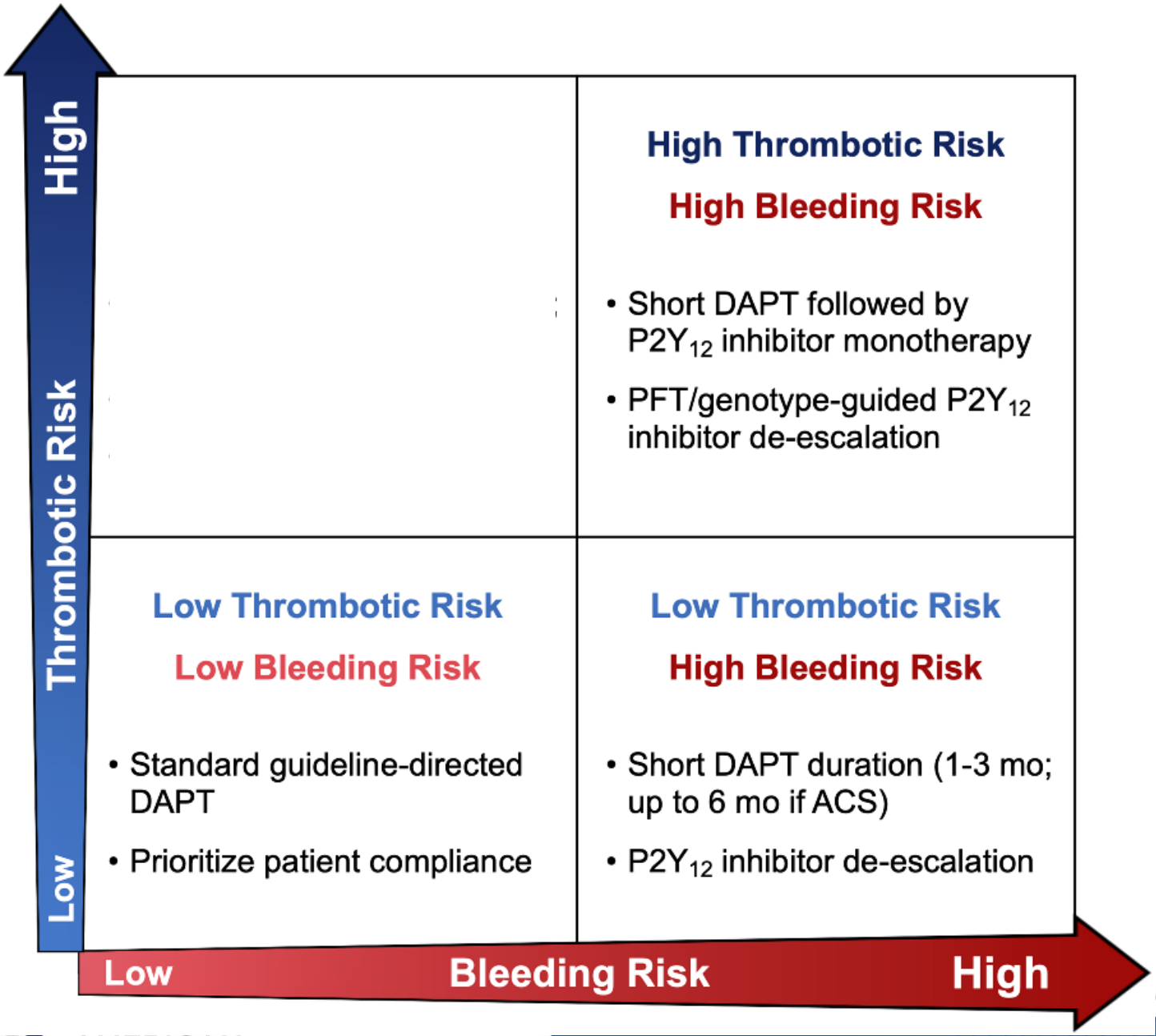
Which do you chose?

You are all correct!

…well, most of you

Balance of MACE and Bleeding Risk

Personalized Antithrombotic Therapy



Cao D et al., Eur Heart J. 2020 Dec 26;ehaa824.

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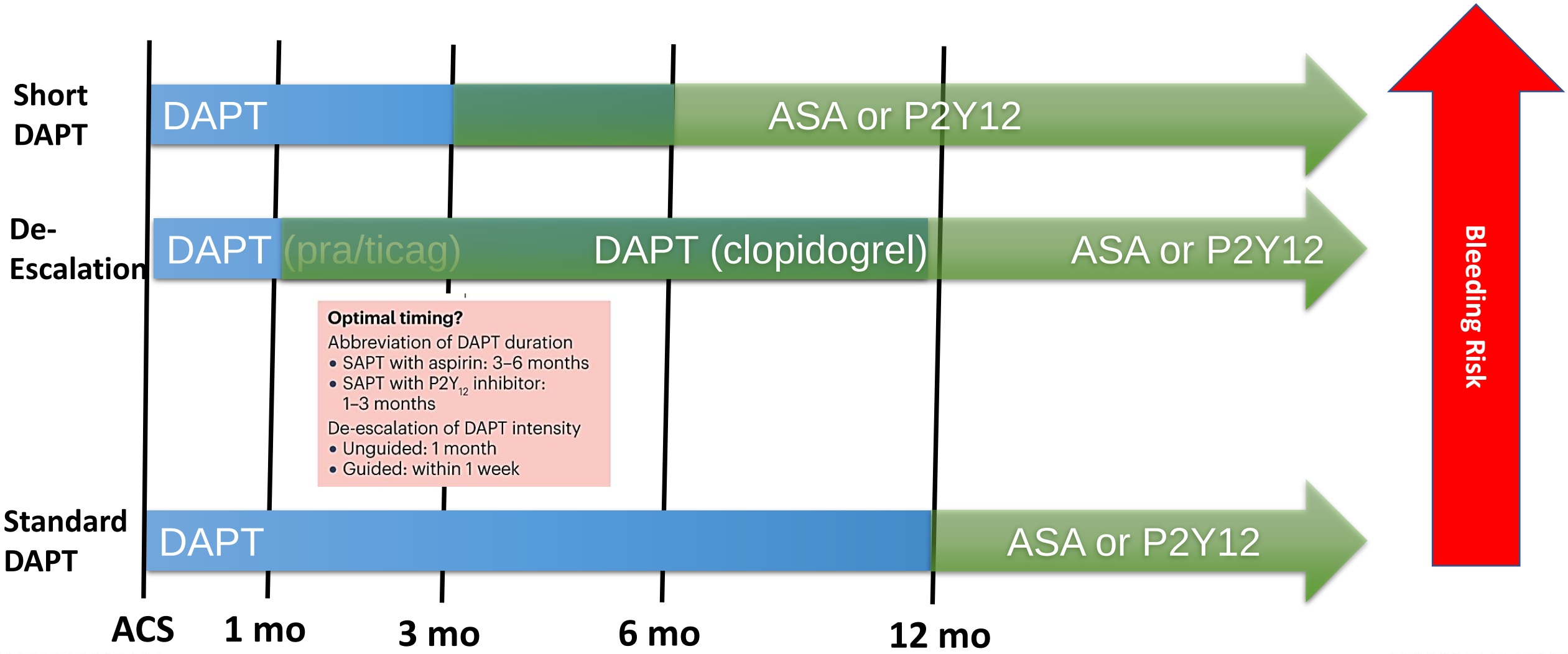
Potential DAPT Strategies



Adapted from Gorog, D.A. Nat Rev Cardiol 2023. https://doi.org/10.1038/s41569-023-00901-2

PATIENT C:

Clinical Presentation

- 58 yo male presents for transfer of care
- No chest pain, exercises 5x/week

PMH:

- CAD – Angina, LAD and RCA stent (2015) – off prasugrel for 3 years
  - Anteroapical akinesis on echo
- Hypertension
- Dyslipidemia
- Family history of early CAD

Medications:

- Aspirin 81 mg daily
- Rosuvastatin 20 mg daily
- Losartan 100 mg daily
- Tramadol 250 mg prn pain

Physical Examination:

- BP 138/88 mmHg, HR 75 bpm, RR 12
- Right carotid bruit

Carotid Ultrasound:

- Right internal: 50-70%, Left internal: 1-25%. No other significant disease.

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Poll: Question: What is the best next step for the patient?

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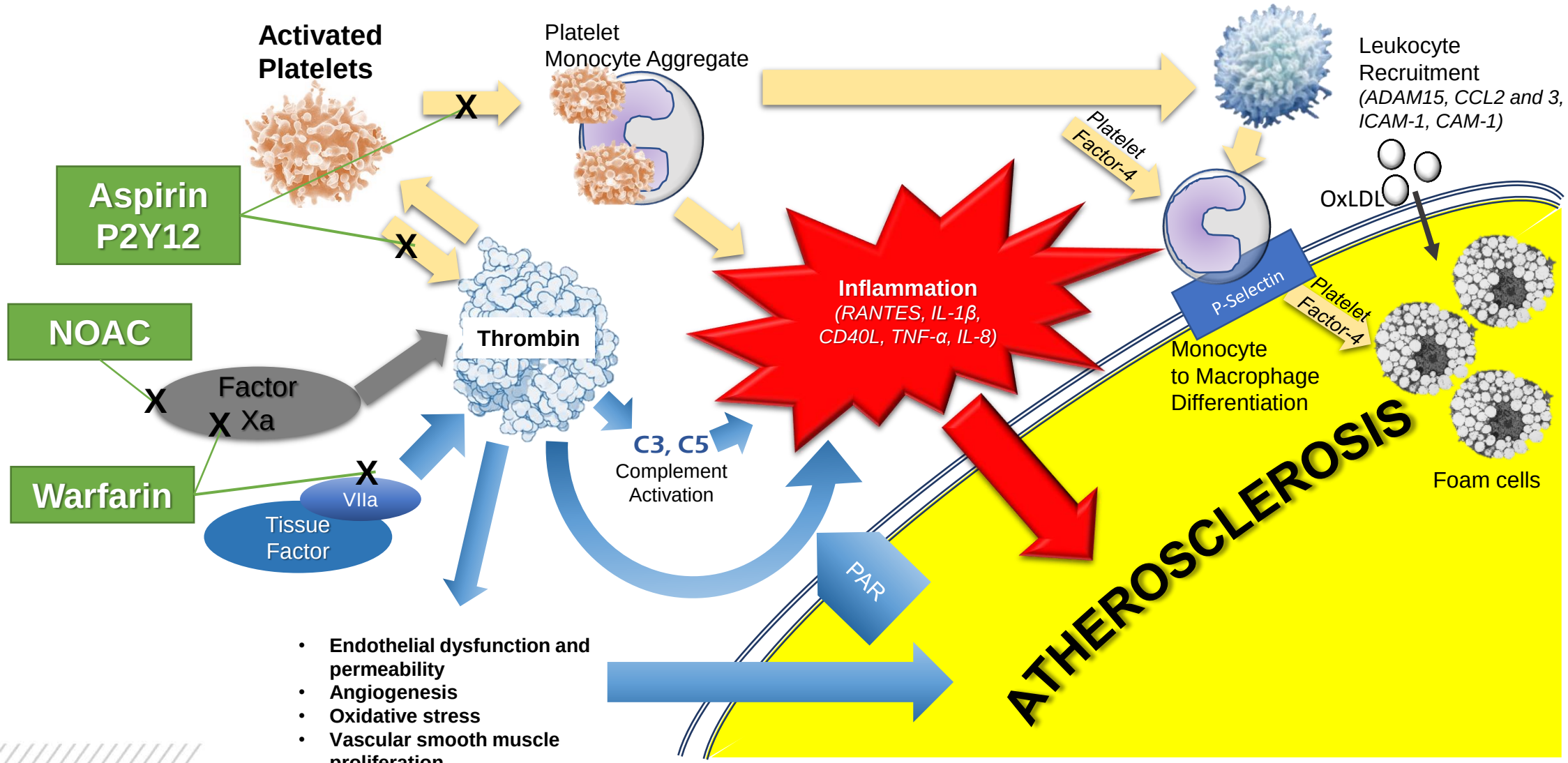
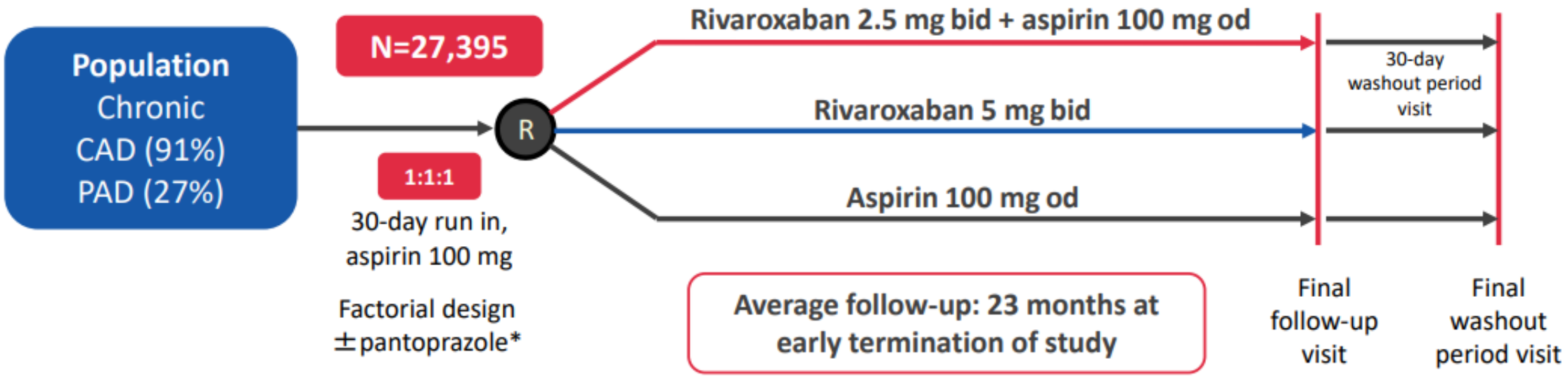
Thrombin and Platelets Promote Atherosclerosis



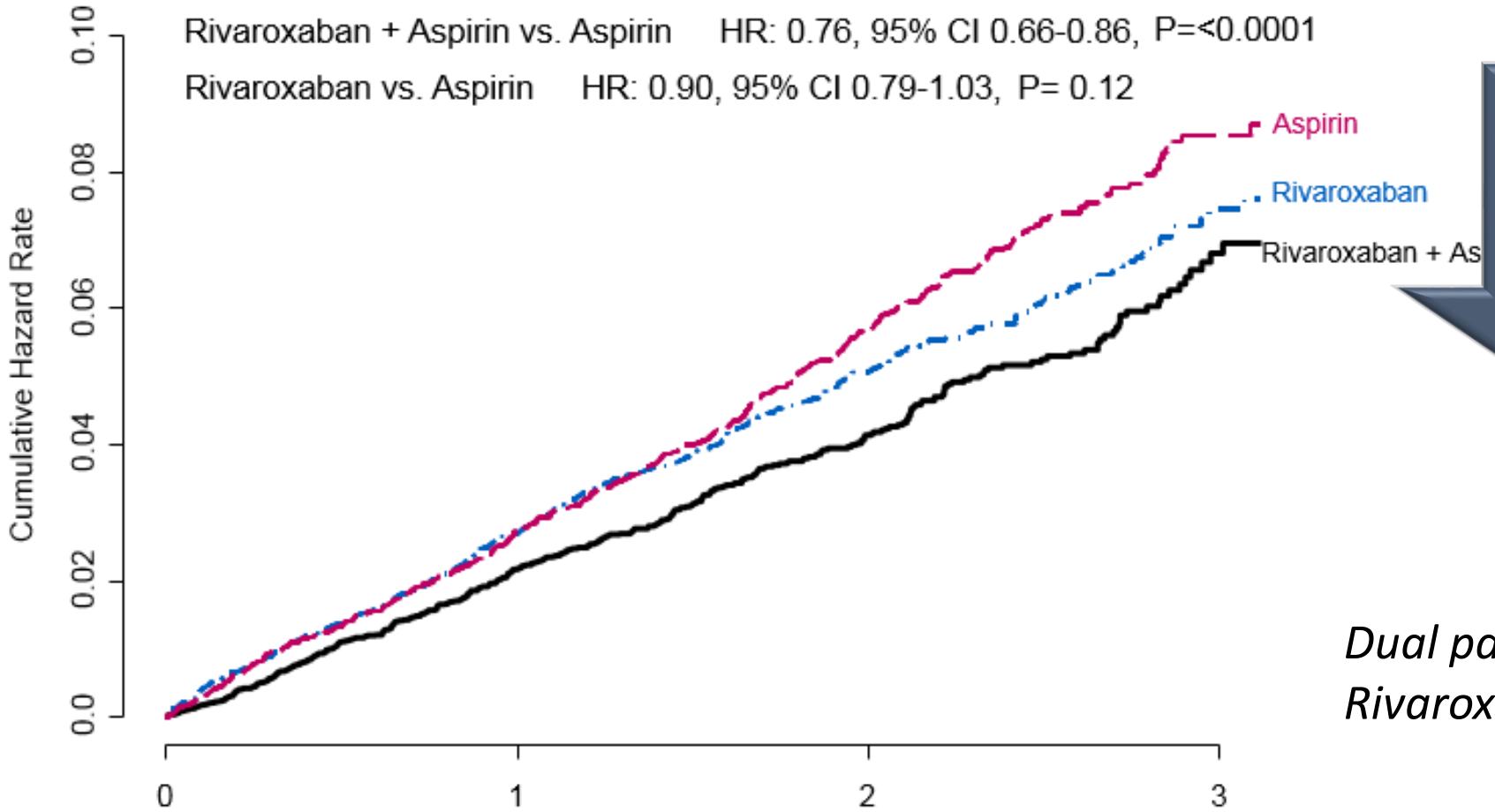
Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease: COMPASS Trial



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

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

COMPASS Primary Outcome: MACE



R+A vs. A

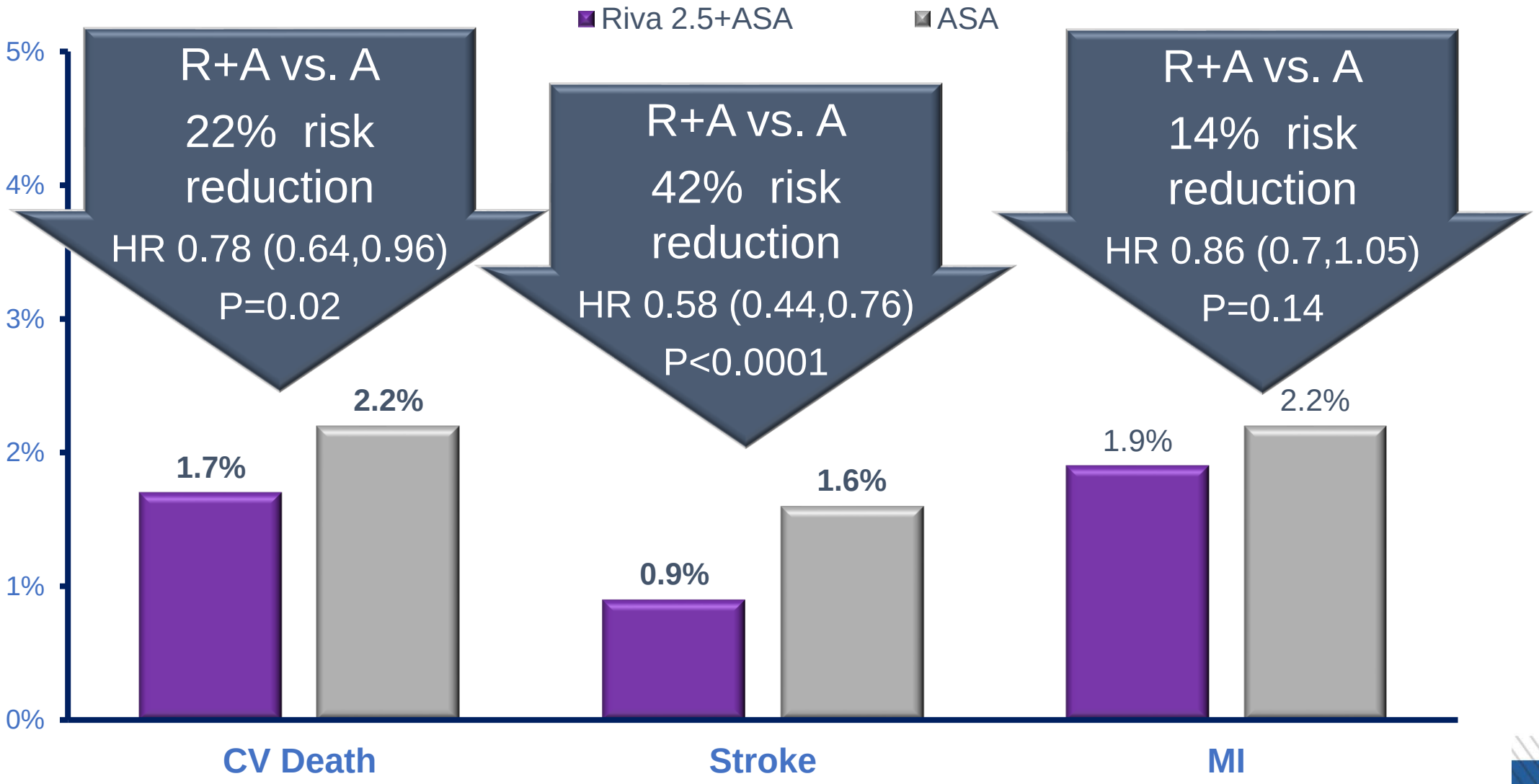
24% risk reduction

HR=0.76 (0.66,0.86)

NNT=77

Dual pathway inhibtion (DPI): Rivaroxaban 2.5 BID + ASA QD

Compass: Primary MACE Components



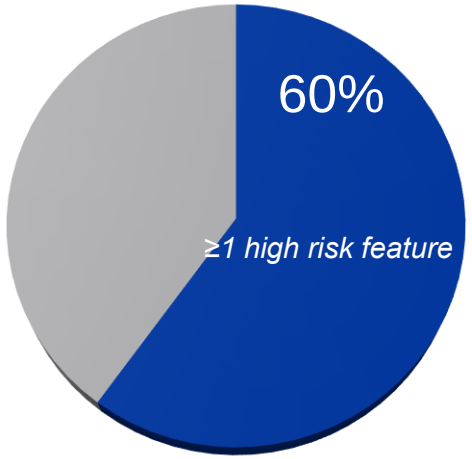
Eikelboom JW, et al. N Engl J Med 2017;377:1319-1330

High Risk Populations in COMPASS:
When to Accelerate

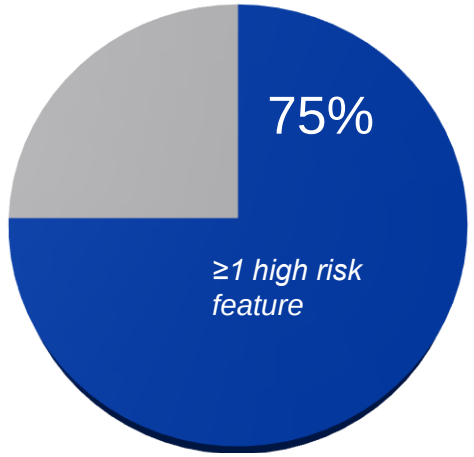
High Risk Features

- ✓ ≥2 vascular beds
- ✓ History of heart failure (HFpEF)
- ✓ Low eGFR < 60 ml/min
- ✓ Diabetes

Patients with high-risk features accounted for:



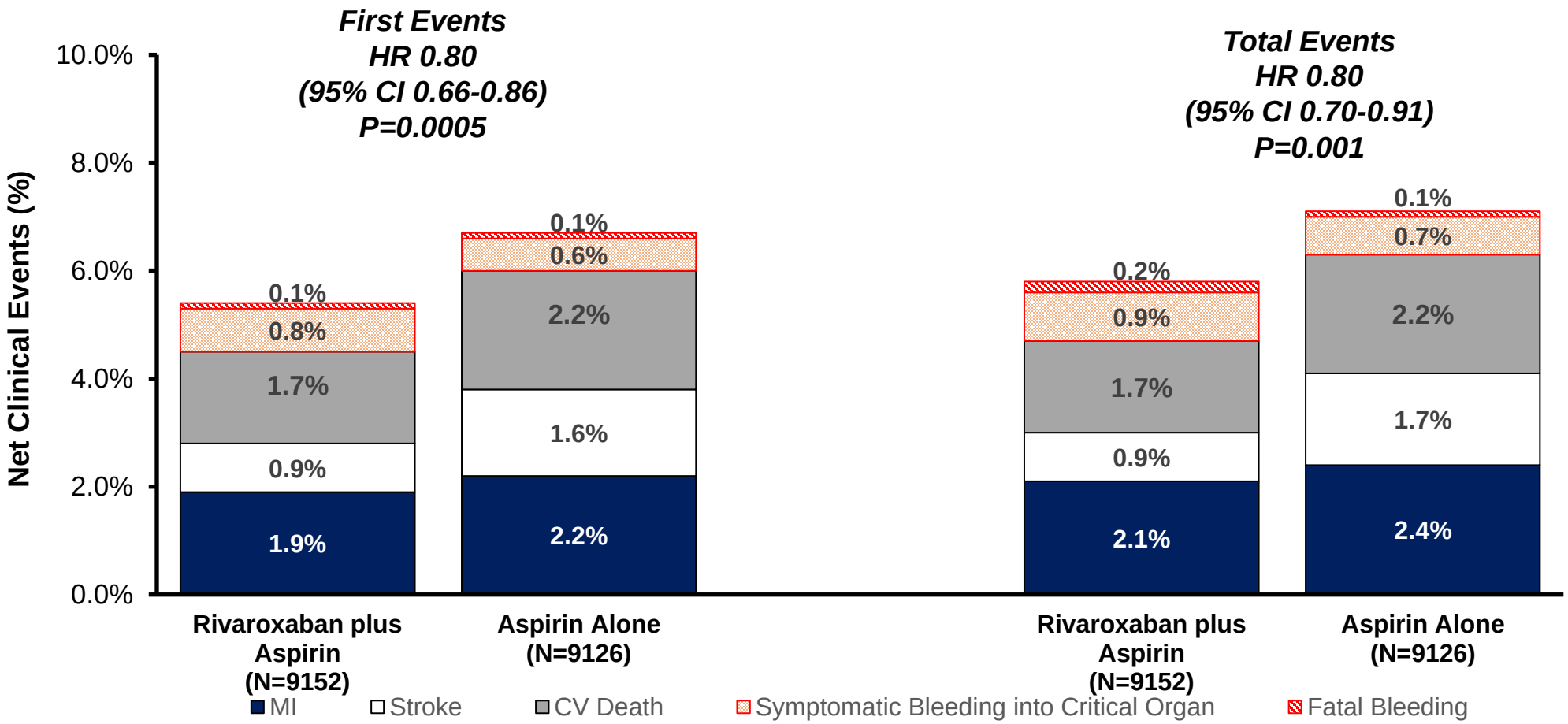
…total patients



…primary events

Anand SS, et al. JACC 2019:73:3271-3280. Fox KAA et al, J Am Coll Cardiol 2019;73:2243-2250. Branch KR, et al, Circulation 2019;13;140(7):529-537.

Net Clinical Benefit: First and Total Events



Branch KR, et al. Am Heart J 2023;258:60-68.

High Residual Risk: *Risk Factors*

High Ischemic Risk (*ESC 2019*)

Diffuse multivessel CAD with ≥1 of the following:

- Peripheral arterial disease (PAD)
- Recurrent myocardial infarction
- Diabetes mellitus, *medicated*
- Renal disease (*eGFR 15-59 ml/min/1.73m^2*)

Very High Ischemic Risk (*AHA/ACC 2018*)
Recurrent MACE or MACE + ≥1 HRF's

Major MACE:

- Recent ACS (<12 mo)
- Prior MI or stroke
- Symptomatic PAD

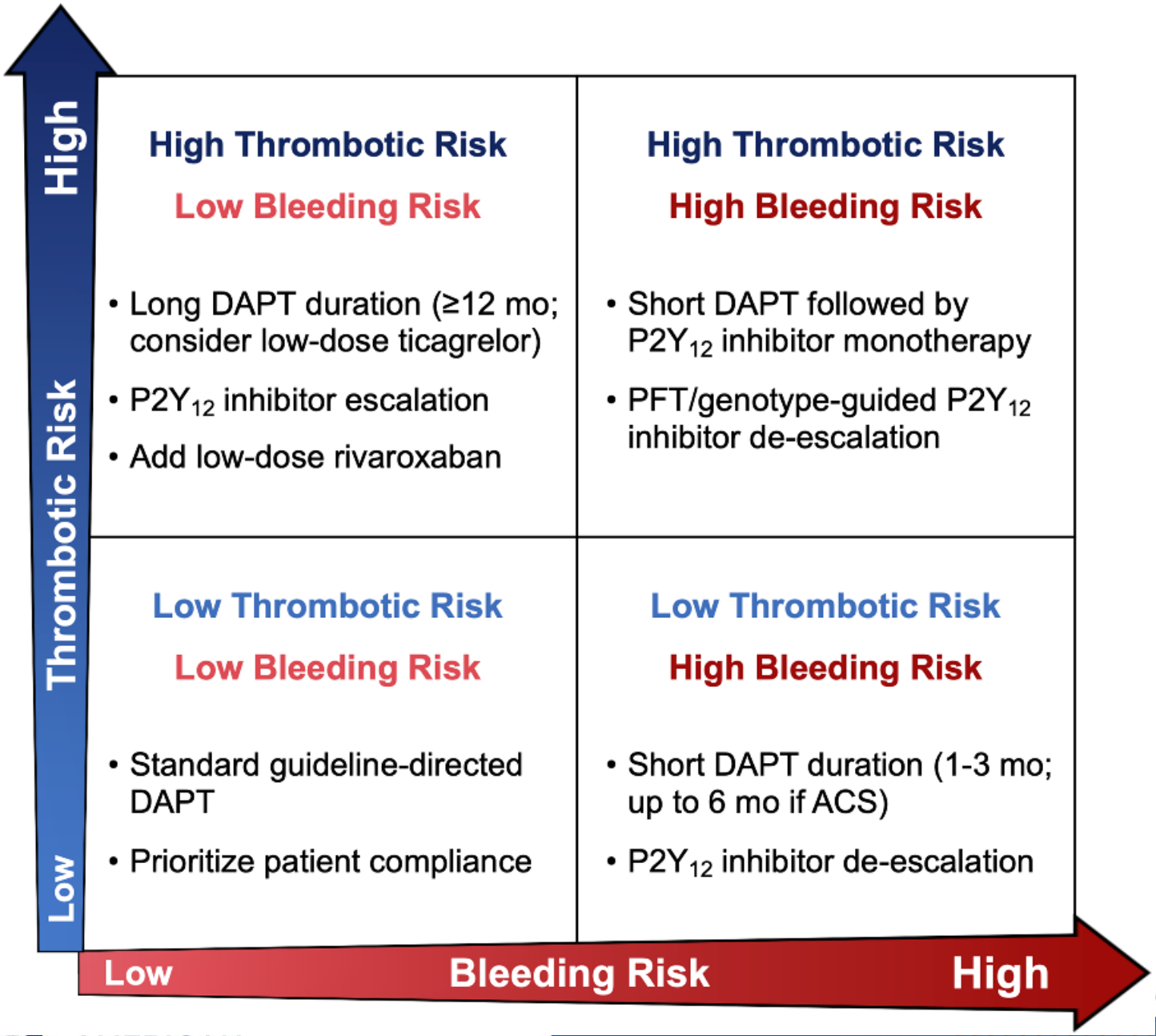
High Risk Factors (HRF):

- Age >65 yrs
- Diabetes mellitus
- Hypertension
- Renal disease (*eGFR 15-59 ml/min/1.73m^2*)
- Heterozygous familial hypercholesterolemia
- Prior coronary revascularization
- Smoking
- LDL >100 mg/dL on maximal meds
- Heart failure

Knuuti, et al. Eur Heart J 2020;41;407-7. Grundy SM, et al. J Am Coll Cardiol 2019;73:3168-209..

Key Points to Remember

Personalized Antithrombotic Therapy



Cao D et al., Eur Heart J. 2020 Dec 26;ehaa824.

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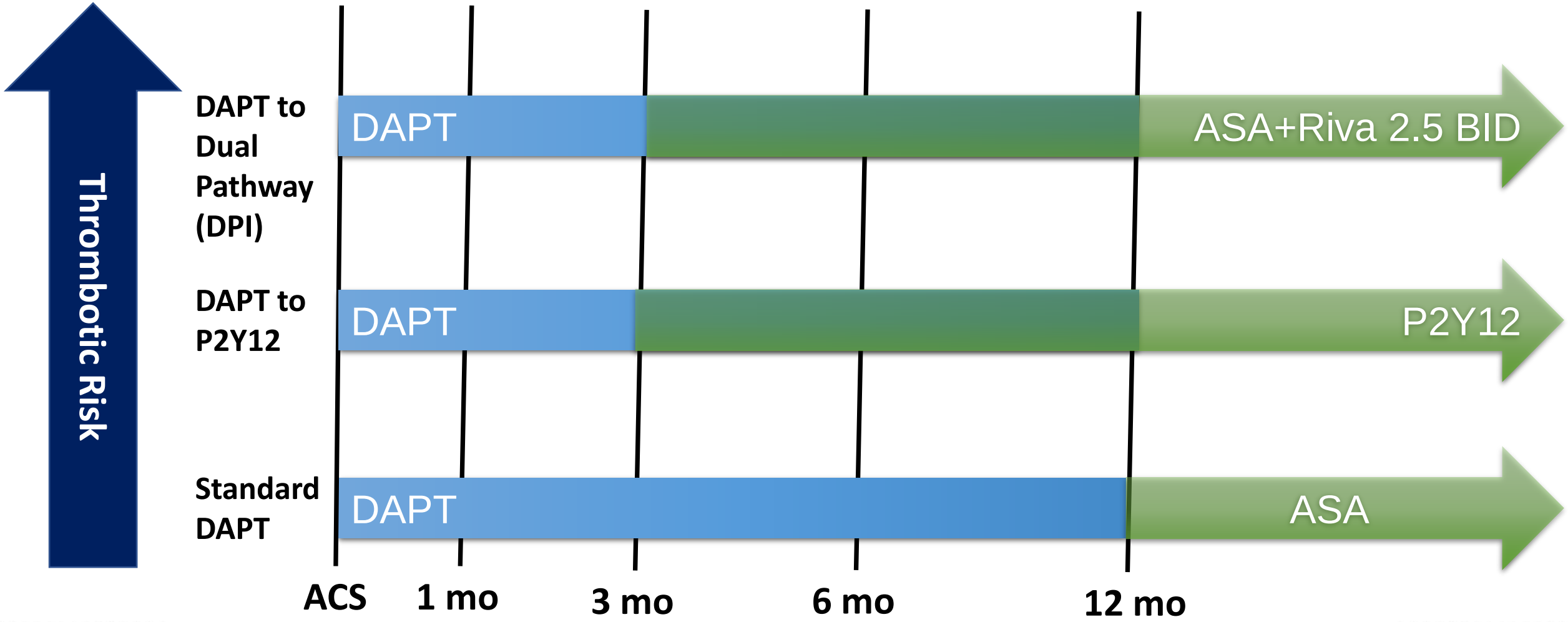
Potential DAPT and DPI Strategies

Not High Bleeding Risk



Adapted from Gorog, D.A. Nat Rev Cardiol 2023. https://doi.org/10.1038/s41569-023-00901-2

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State of the Art Antithrombotic Therapies

1. Aspirin-Free Strategies
2. De-escalation Strategies
3. Native Disease Dual Therapy
4. **Peripheral Arterial Disease**

PATIENT D:

72 yo male presents for CV follow-up for dyslipidemia, HTN

- Complains of leg discomfort, inability to keep up with grandkids

What patient characteristics would suggest SAPT as most appropriate therapy?

What patient characteristics would suggest dual pathway inhibition as most appropriate therapy?

Factors to consider:

- Physical exam
- Comorbidities
- Testing data
- Bleeding risk
- Other medications
- Clinical setting

In one-word, what patient characteristics would suggest SAPT as most appropriate therapy?

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: In one-word, what patient characteristic would suggest SAPT as most appropriate therapy?

In one word, what patient characteristics would suggest dual pathway inhibitions as most appropriate therapy?

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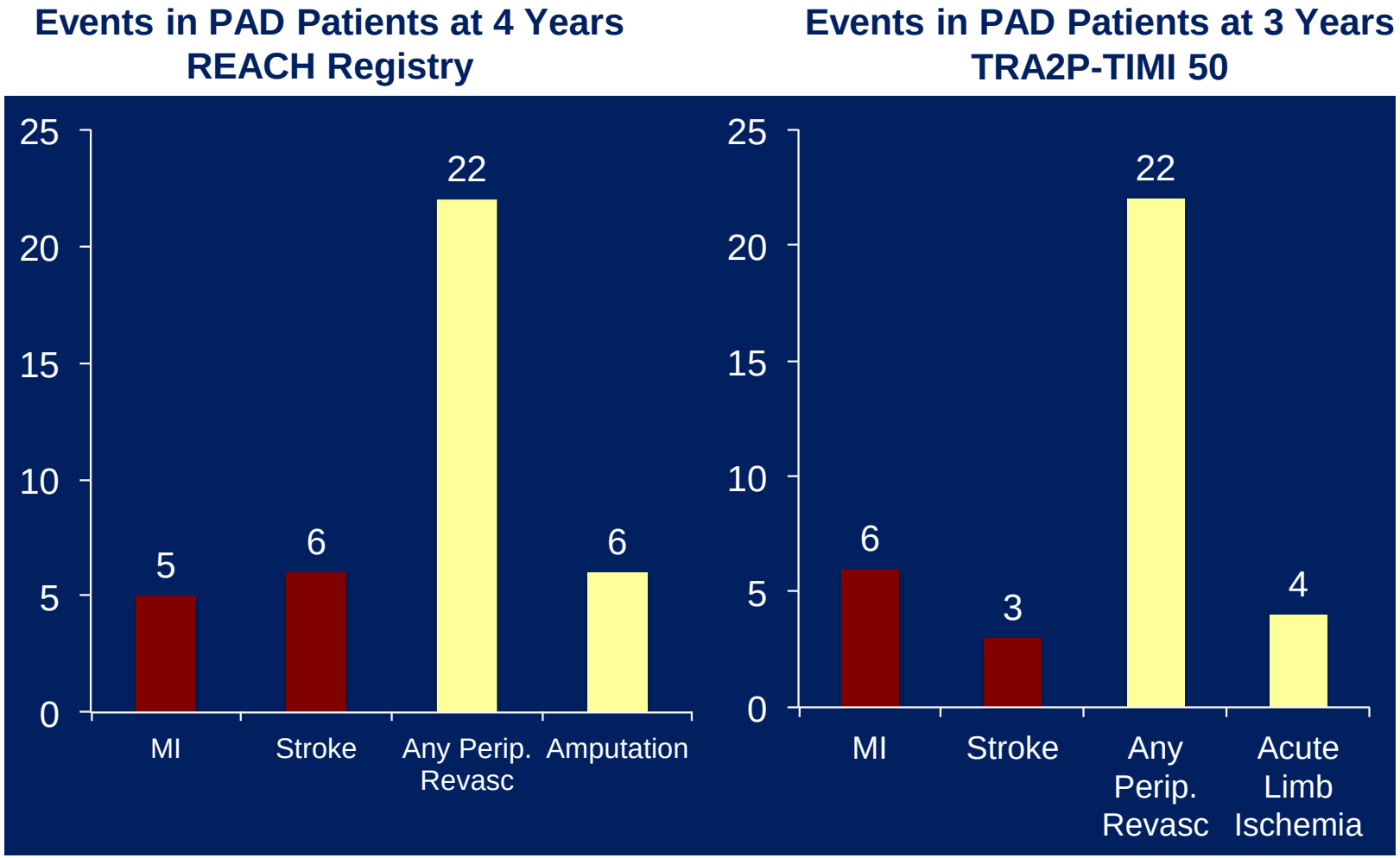
Poll: In one word, what patient characteristic would suggest dual pathway inhibitions as most appropriate therapy?

Burden of PAD

- >200 million with PAD globally
- Incidence is increasing with key risk factors of age, obesity and diabetes
- Key morbidity is limb symptoms (claudication → critical limb ischemia)

Kumbhani et al. EHJ 2014. Bonaca et al. Circulation 2013. Fowkes *et al. Lancet* 2017;14:156-170

Burden of Risk in PAD is Driven by Limb Events



- **Limb revascularization procedure → most common outcome**
- **Limb tissue loss events (e.g. amputation and ALI) are as common as MI and stroke**

Kumbhani et al. EHJ 2014. Bonaca et al. Circulation 2013. Fowkes *et al. Lancet* 2017;14:156-170

ACC / AHA PAD Guidelines 2016 – No Class 1 Recommendations for MALE

- Similar to 2005 Guideline
- **Recommendations for therapy to reduce MACE** based on presence of claudication (not MACE risk factors)

For "Symptomatic PAD"

COR LOE	Therapy	Comment
I A	**Monotherapy** ASA 75-325 mg or **Clopidogrel**	CAPRIE showed clopidogrel superior to ASA
IIb B-R	**DAPT** ASA+ Clopidogrel	Refer to the DAPT guideline for CAD
IIb B-R	**DAPT or TAPT** **Vorapaxar** (plus ASA and/or clopidogrel)	Benefit for MACE and ALI but increase in bleeding so overall benefit uncertain

US FDA approved for PAD in BLUE

MALE = major adverse limb events

Gerhard-Herman et al. Circulation 2016

Are current guidelines good enough?

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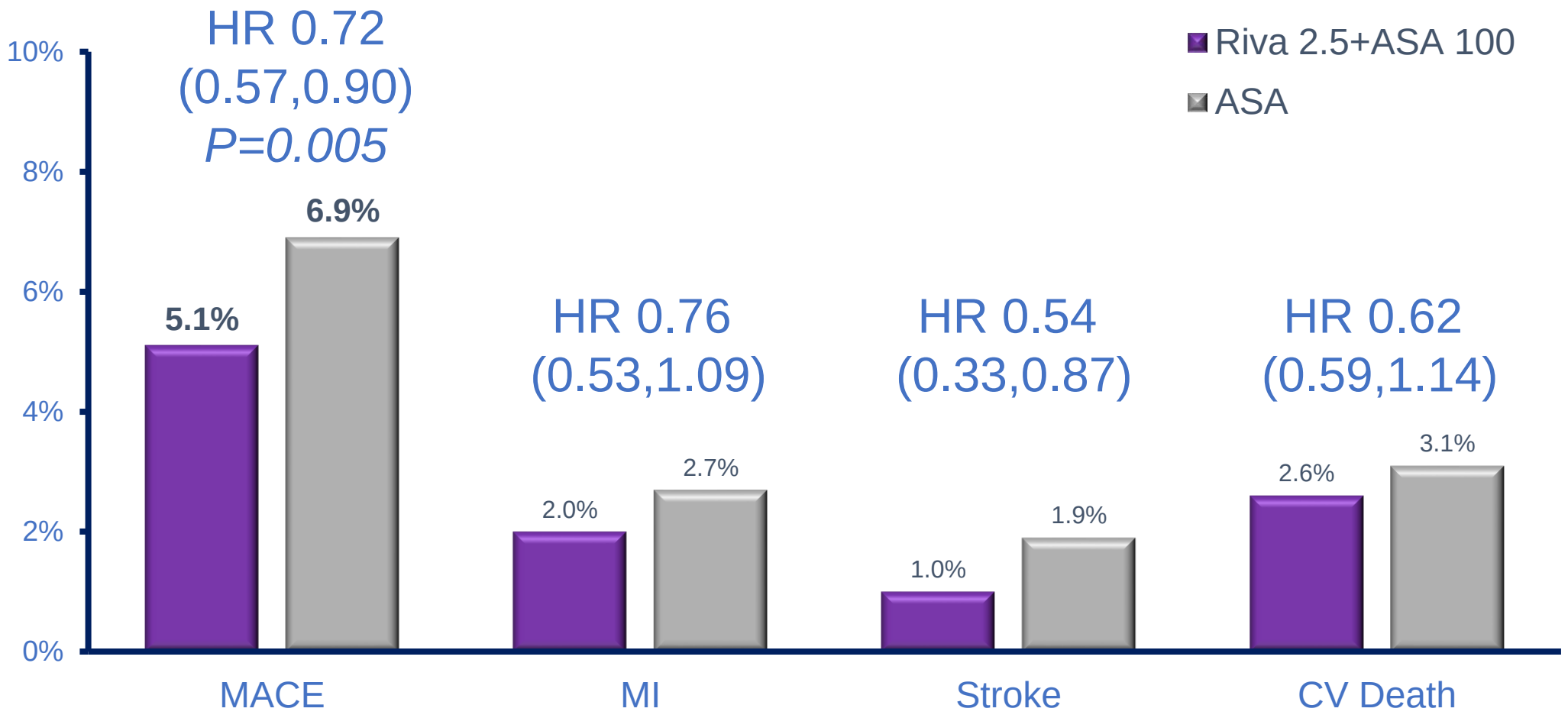
Poll: Patient D Question 2: Which treatment could best lower this patient's risk of major cardiovascular outcome and peripheral artery outcomes?

COMPASS PAD: Primary Outcome and Components

PAD N=7470 (27%)

-Symptomatic lower extremity disease, revascularization, amputation
-Carotid stenosis ≥50%



Riva 5mg BID alone (p=0.19)

Anand et al, Lancet 2018;391(10117):219-229

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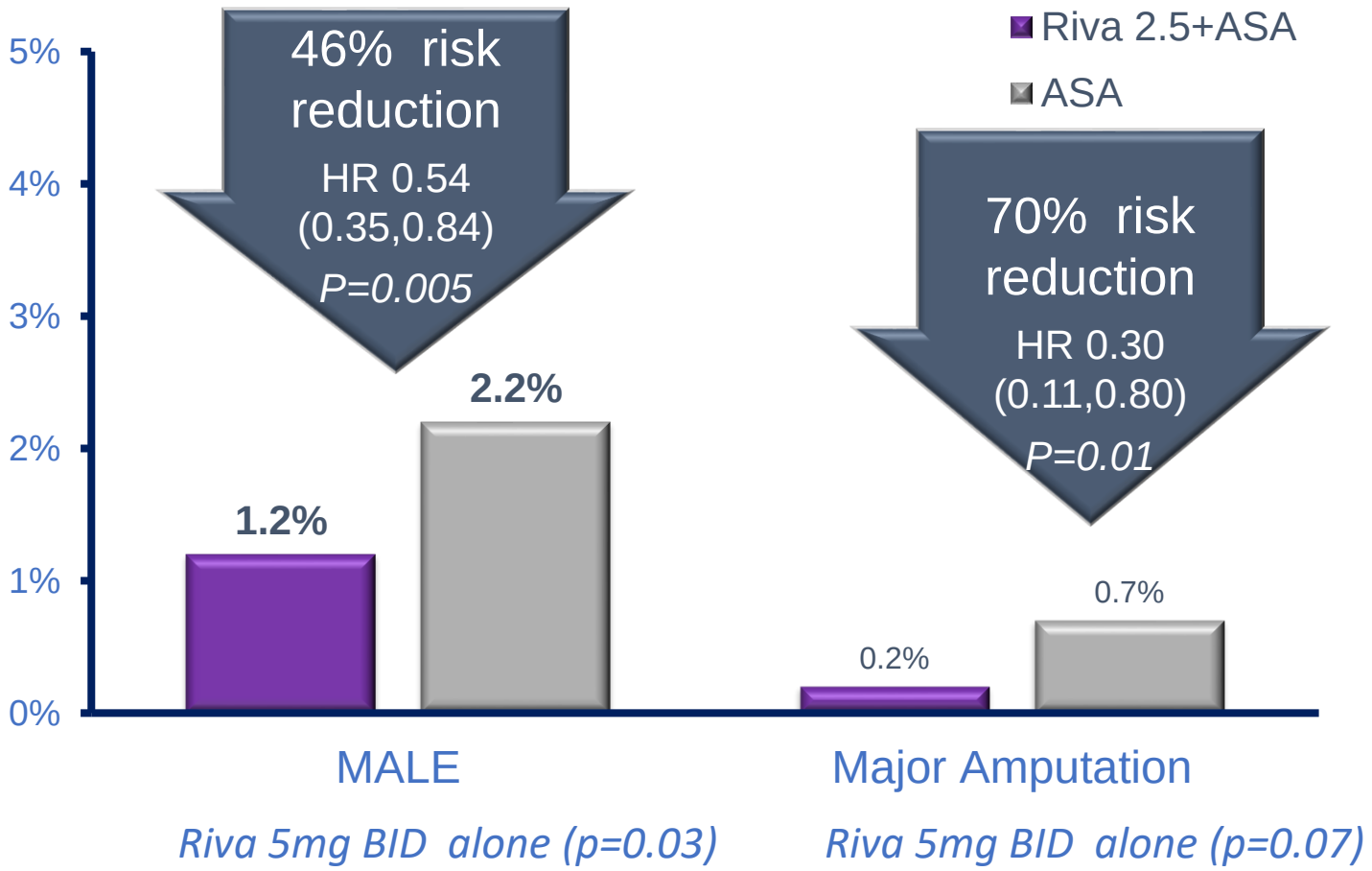
COMPASS PAD: MALE, or Major Amputation

MALE = Major Adverse Limb Events

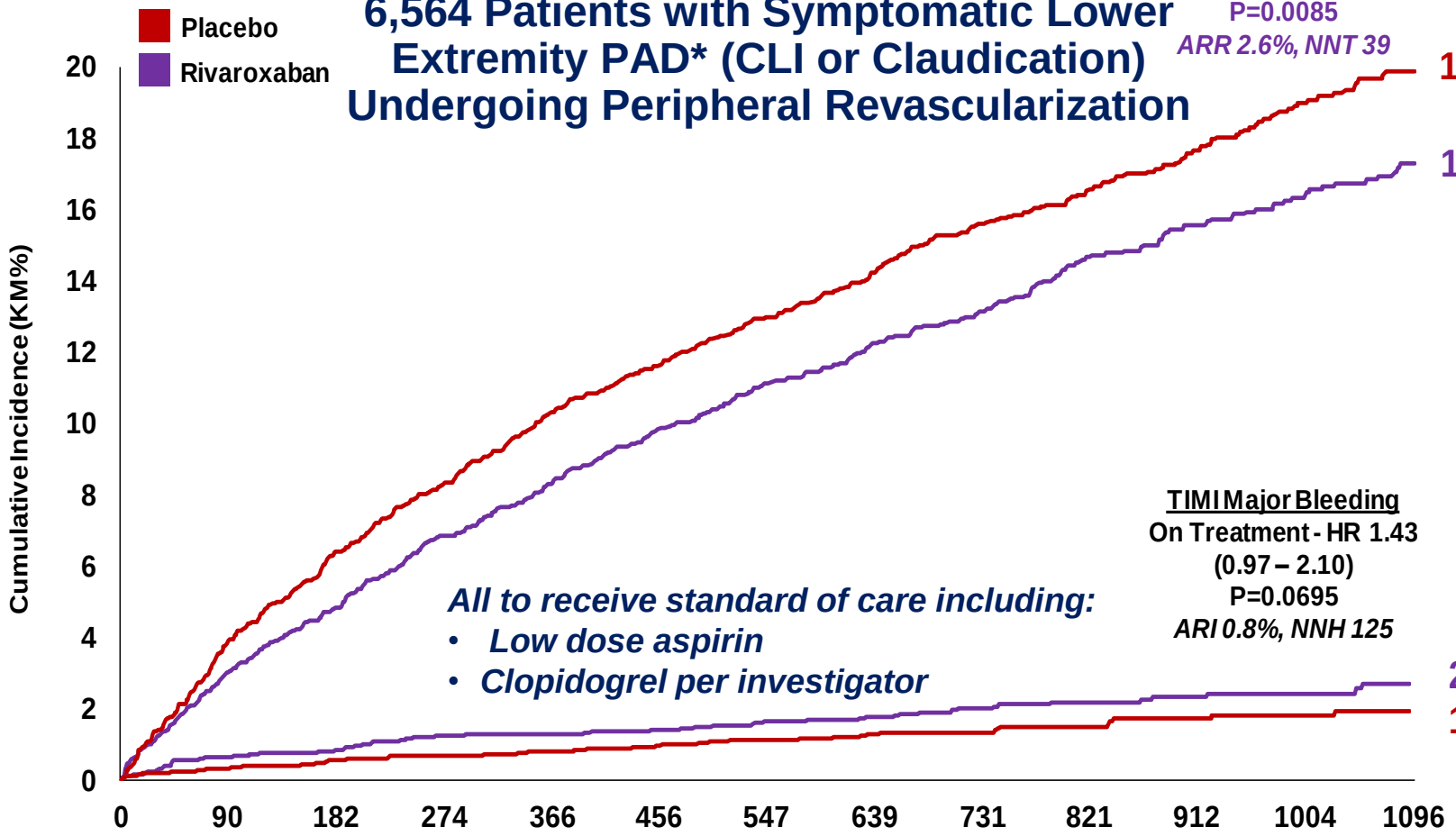


Anand et Lancet 2019

VOYAGER PAD Primary Results

Primary Endpoint*
ITT - HR 0.85
(0.76 – 0.96)
P=0.0085
ARR 2.6%, NNT 39

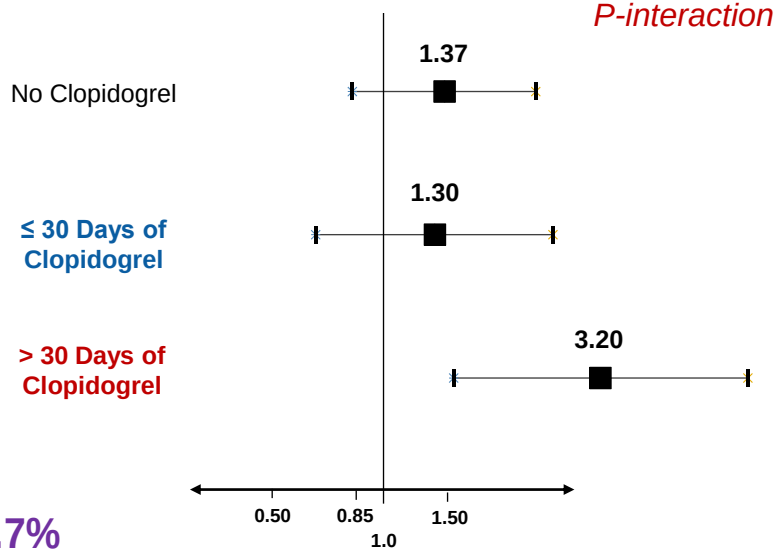
6,564 Patients with Symptomatic Lower Extremity PAD* (CLI or Claudication) Undergoing Peripheral Revascularization



All to receive standard of care including:
- ***Low dose aspirin***
- ***Clopidogrel per investigator***

TIMI Major Bleeding
On Treatment - HR 1.43
(0.97 – 2.10)
P=0.0695
ARI 0.8%, NNH 125

P-interaction 0.069



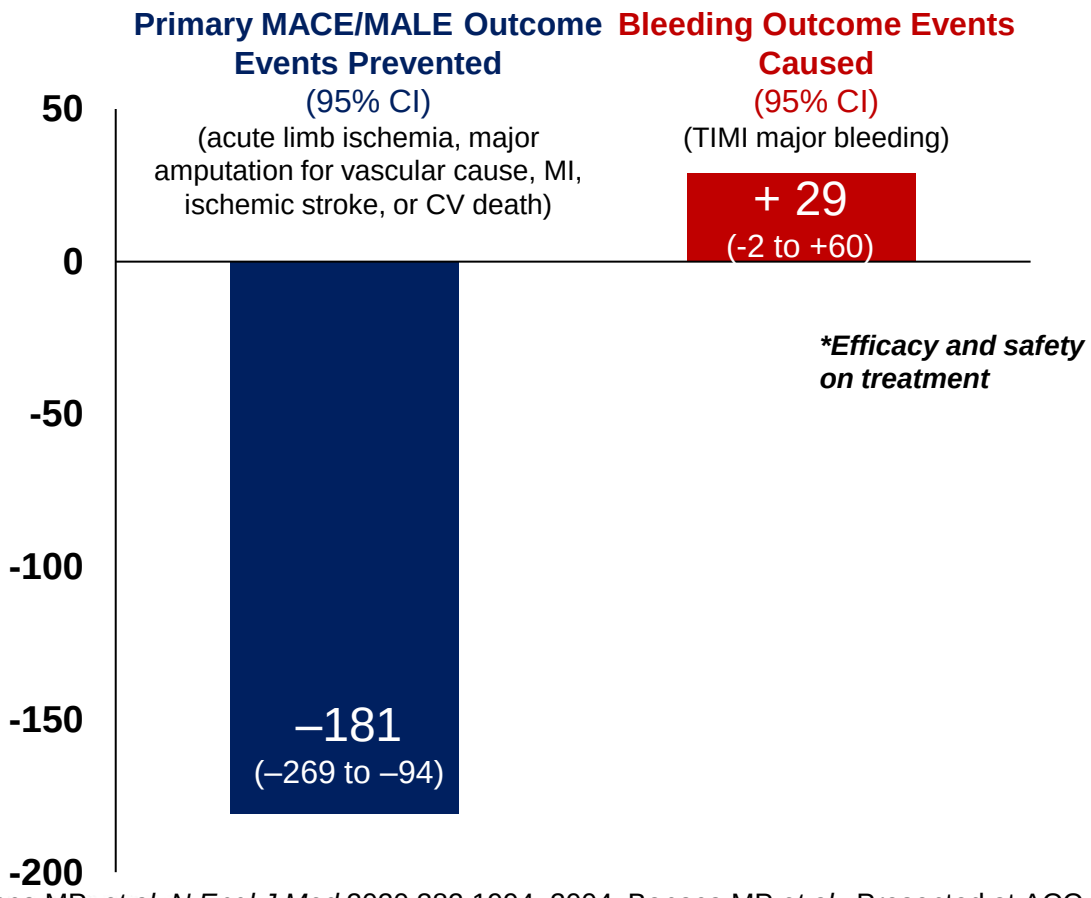
Hiatt WR et al. Circulation 2020

*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death

Bonaca MP, *et al*. *N Engl J Med* 2020;382:1994–2004

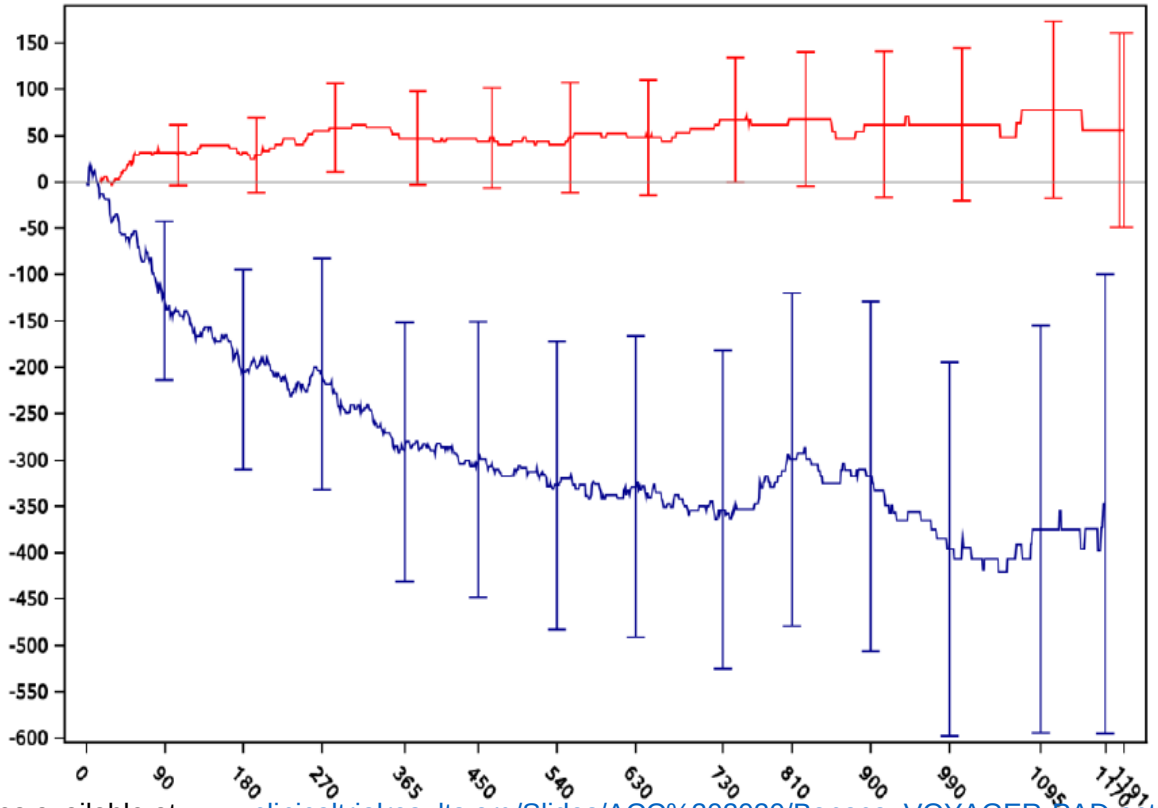
Riva+ ASA: Incremental Risk Benefit, Stable Bleeding Risk

First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year



Efficacy and safety on treatment

First Events Prevented / Caused from Time from Randomization



Bonaca MP, *et al*. *N Engl J Med* 2020;382:1994–2004. Bonaca MP *et al*.. Presented at ACC 2020. Slides available at www.clinicaltrialresults.org/Slides/ACC%202020/Bonaca_VOYAGER-PAD.pptx

PATIENT D:

72 yo male presents for CV follow-up for dyslipidemia, HTN

- Complains of leg discomfort, inability to keep up with grandkids

SAPT as most appropriate therapy?

- **No CLI findings**
- **Few comorbidities**
- **Mild ABI abnormalities**
- **Higher bleeding risk (NSAID use, prior bleed)**

Dual pathway inhibition as most appropriate therapy?

- **CLI or ALI**
- **Polyvascular, CKD, DM2**
- **Moderate-severe ABI abnormalities**
- **Low bleeding risk**
- **Post-procedure**

State of the Art Antithrombotic Therapies

Personalize Approach to Antithrombotics

- ASA: ↓ MACE for CAD and PAD; ↑ bleeding risk
- DAPT post-ACS - duration dependent on bleeding and thrombotic risk
- Shorter DAPT (3-6 mo) in high bleeding risk - ↓ major bleeding, neutral MACE
- DAPT de-escalation to lower potency P2Y12 (clopidogrel) in high bleeding risk - ↓ net adverse clinical events (NACE)

Reduce antithrombotic potency with higher bleeding risk and low (or intermediate) thrombotic risk

State of the Art Antithrombotic Therapies
Personalized Approach to Antithrombotics

- Patients with PAD: ↑ risk of MACE and MALE
  - Thrombin plays significant role in limb ischemia, stroke
- Rivaroxaban 2.5 mg + aspirin 81: ↓ MACE and MALE with favorable net clinical benefit
  - Post-PAD procedure AND chronic disease (PAD, chronic coronary syndrome)
  - Not applicable to other oral anticoagulants

High risk patients (polyvascular disease, eGFR 15-59, DM, HFpEF) benefit from addition of higher potency agents (e.g. DAPT or rivaroxaban) if not at heightened bleeding risk

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