Don’t Forget About Dual Pathway Inhibition: When DOAC Should NOT Be Standard Treatment

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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, Astra-Zeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Daiichi-Sankyo, Eli Lilly, Faraday, Haemonetics, Janssen, Merck, Novartis, Novo Nordisk, PhaseBio, PLx Pharma, Pfizer, Sanofi and Vectura;
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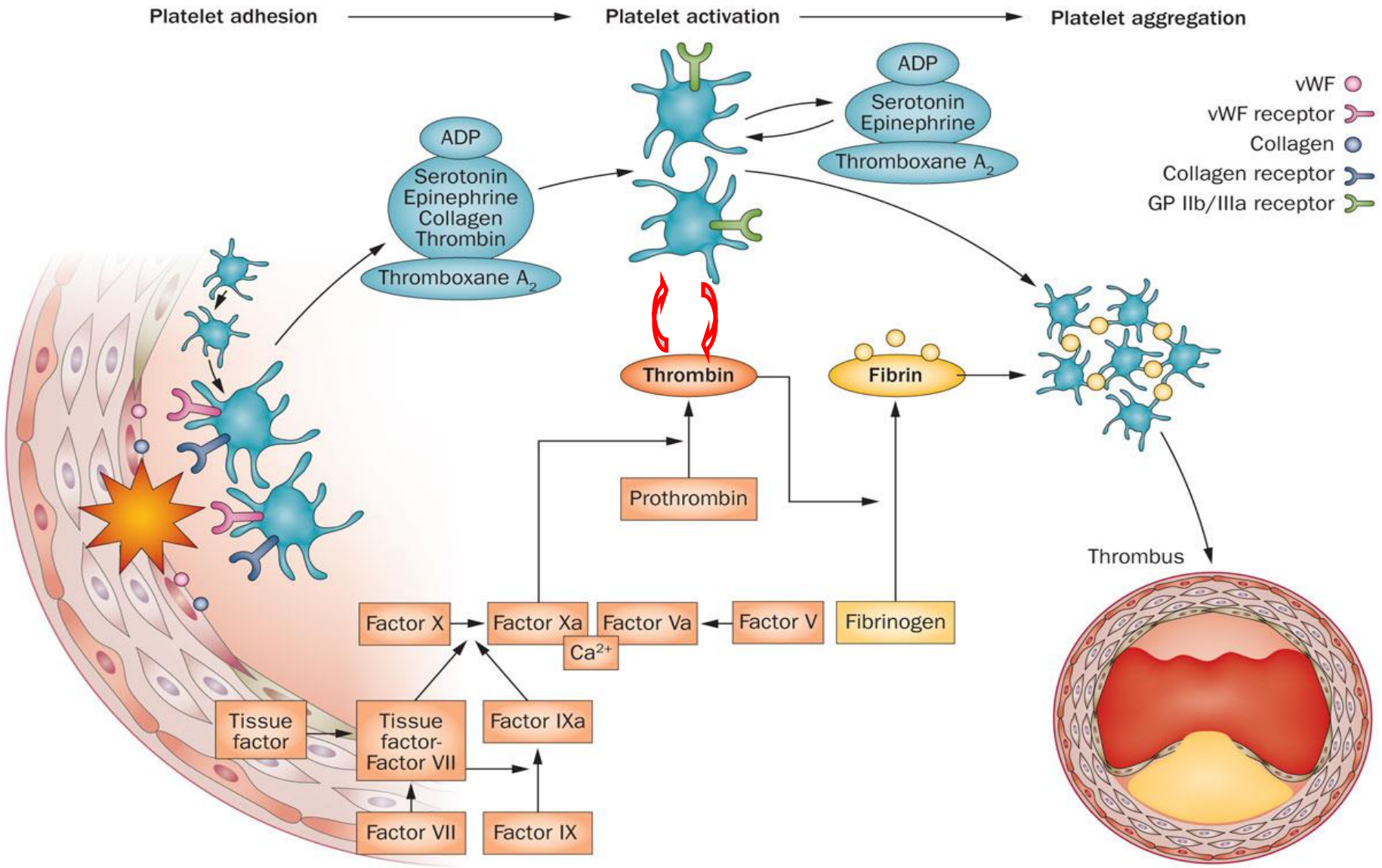
c) Federal agency: NIH

Atherothrombosis: Basic Concepts

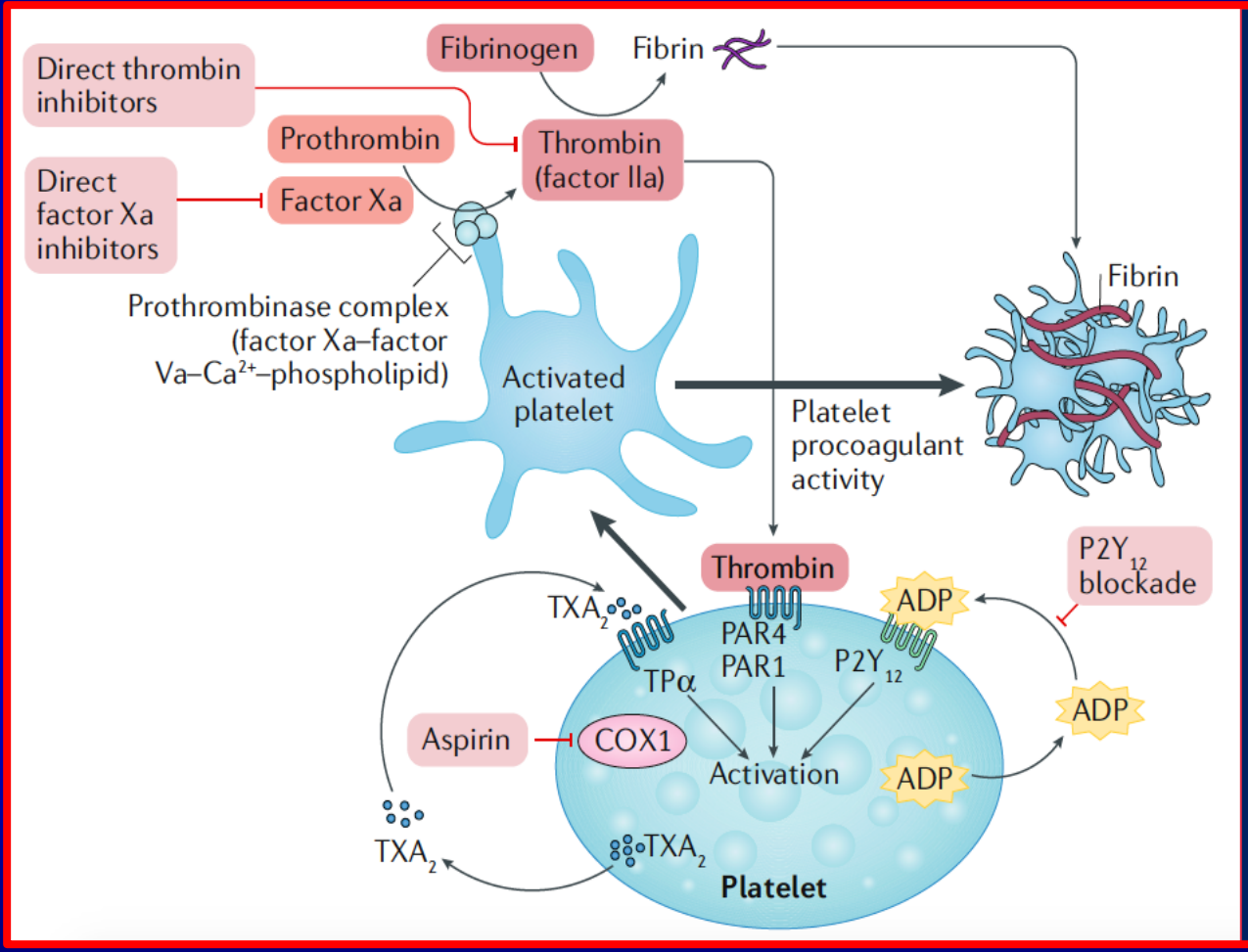
Mechanism of Thrombus Formation

Two key elements: cellular (platelets) and plasma (coagulation factors)



Franchi, F. & Angiolillo, D. J. *Nat. Rev. Cardiol. 2015;12:30-47*

Emerging Concepts: Dual-Pathway Inhibition (DPI)

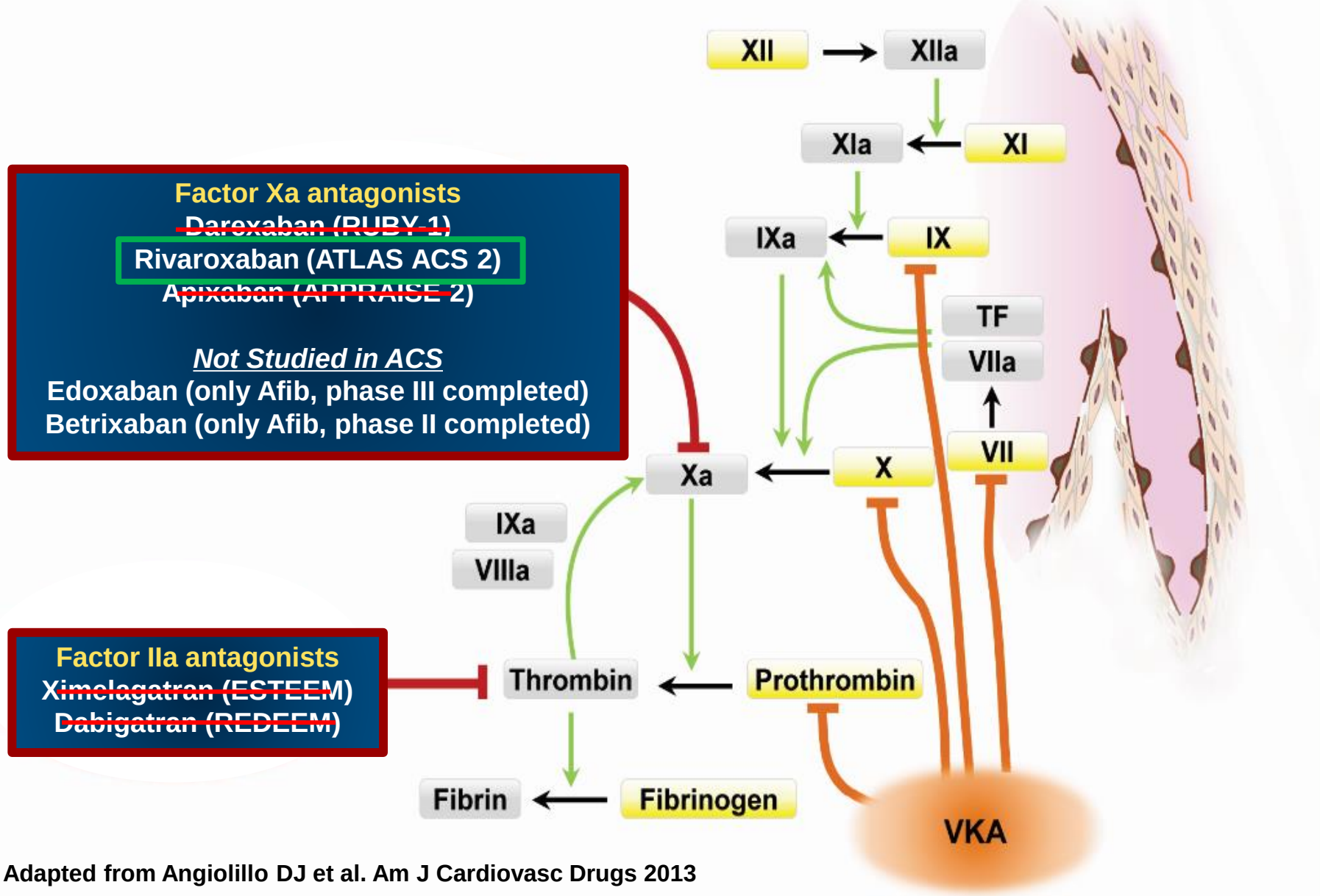


Synergy of oral anticoagulant and antiplatelet therapy

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

Novel Oral Anticoagulants in ACS



Adapted from Angiolillo DJ et al. Am J Cardiovasc Drugs 2013

Long-term secondary prevention

New antithrombotic strategies: Dual Pathway Inhibition (DPI)

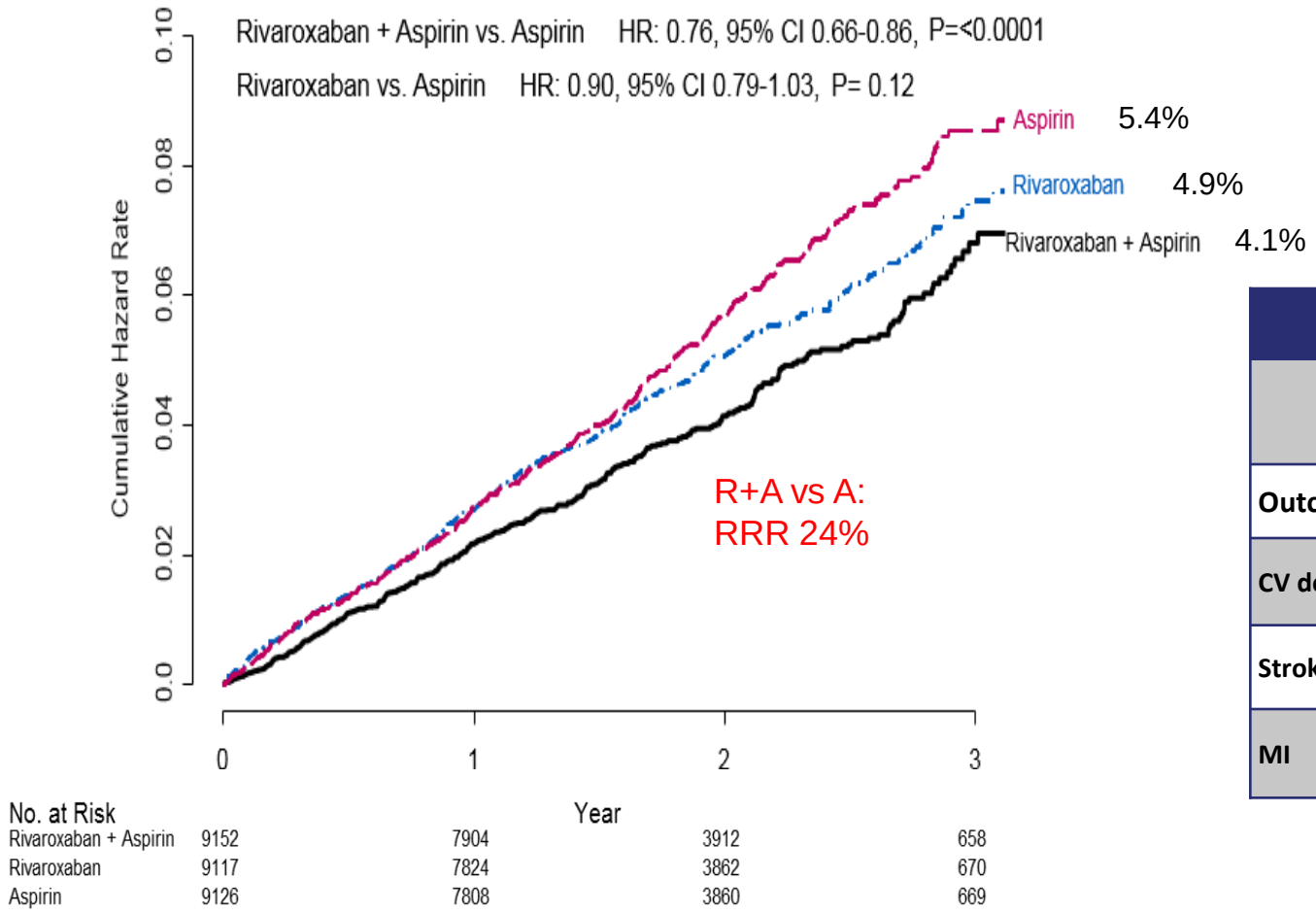
Aspirin mono-therapy is the standard of care for secondary prevention in patients with vascular disease manifestations (stable CAD and PAD).

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 (2.5 mg bid "vascular protection dose") in adjunct to aspirin (DPI) reduce ischemic events?

Primary Endpoint: CV Death, Stroke, MI

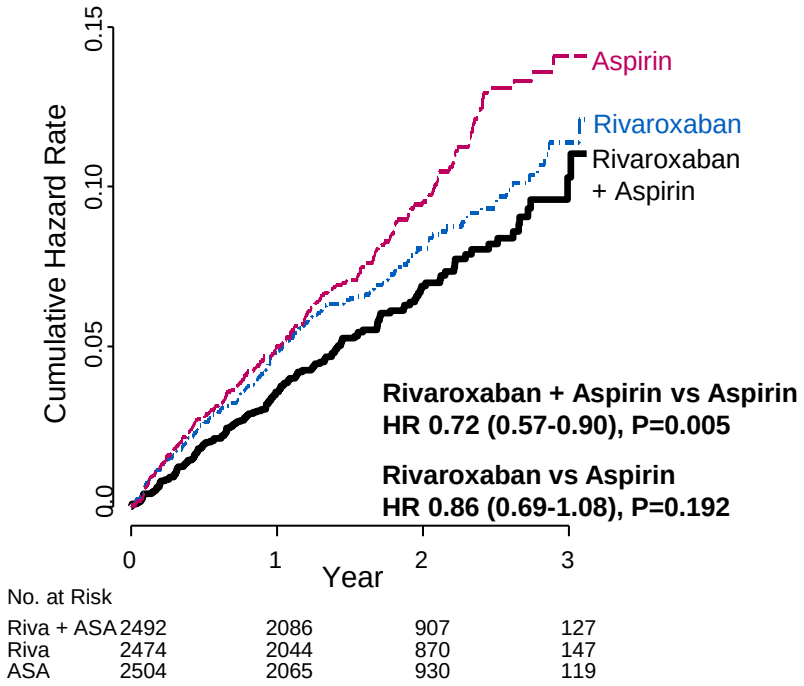


Primary Endpoint Components				
	R + A N=9152	A N=9126	Rivaroxaban + Aspirin vs Aspirin	
Outcome	**N (%)**	**N (%)**	**HR (95% CI)**	**P**
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

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

COMPASS-PAD: MACE and Limb Outcome

Primary Outcome: CV death, MI, or stroke



Major adverse limb event (MALE) & 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**

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

COMPASS: Bleeding Outcomes

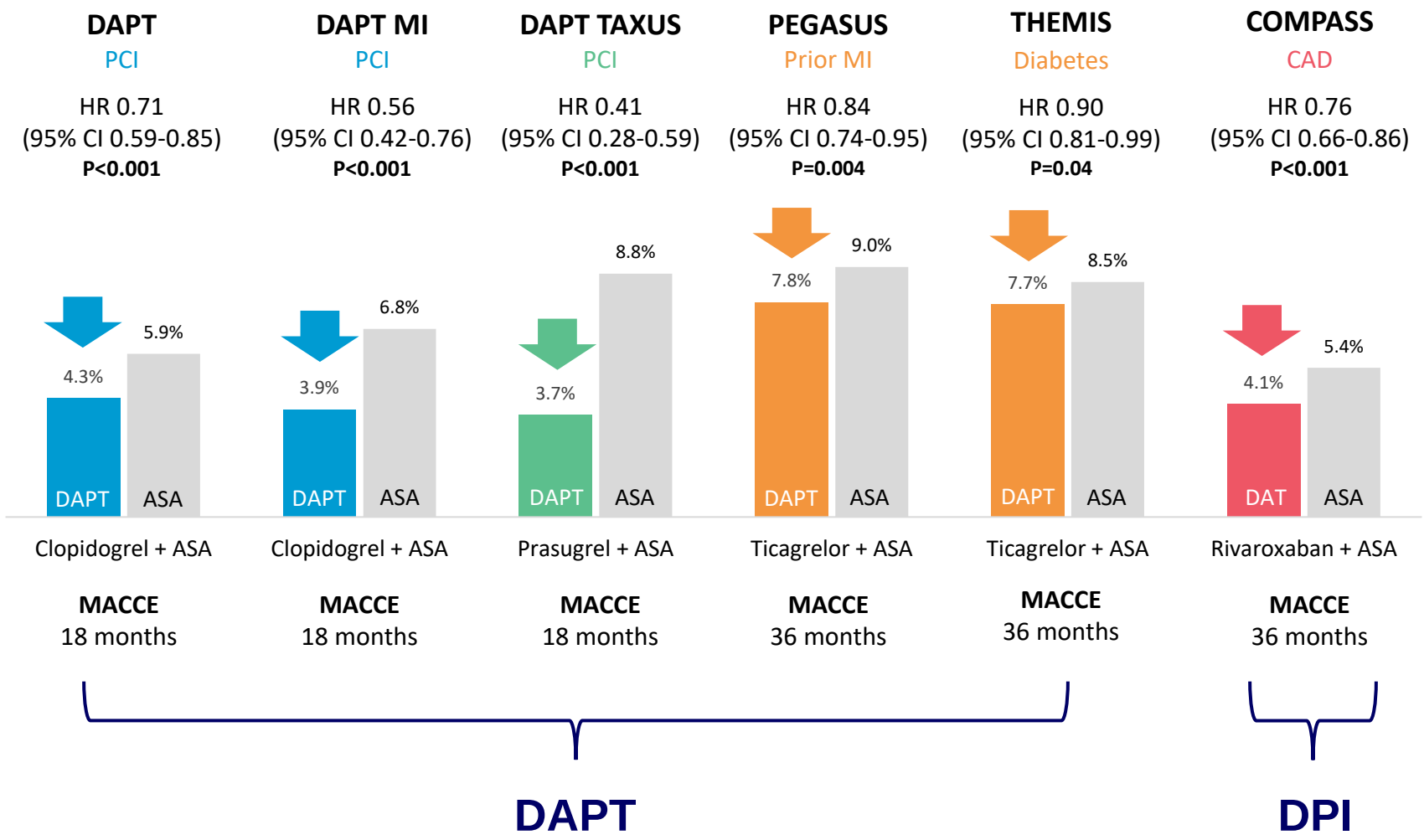
Major bleeding
ISTH major (modified)

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

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

Studies of intensified antithrombotic therapy for long-term secondary prevention in CCS



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.

2019 ESC Guidelines for CCS. Eur Heart J. 2019

Dual antithrombotic therapy

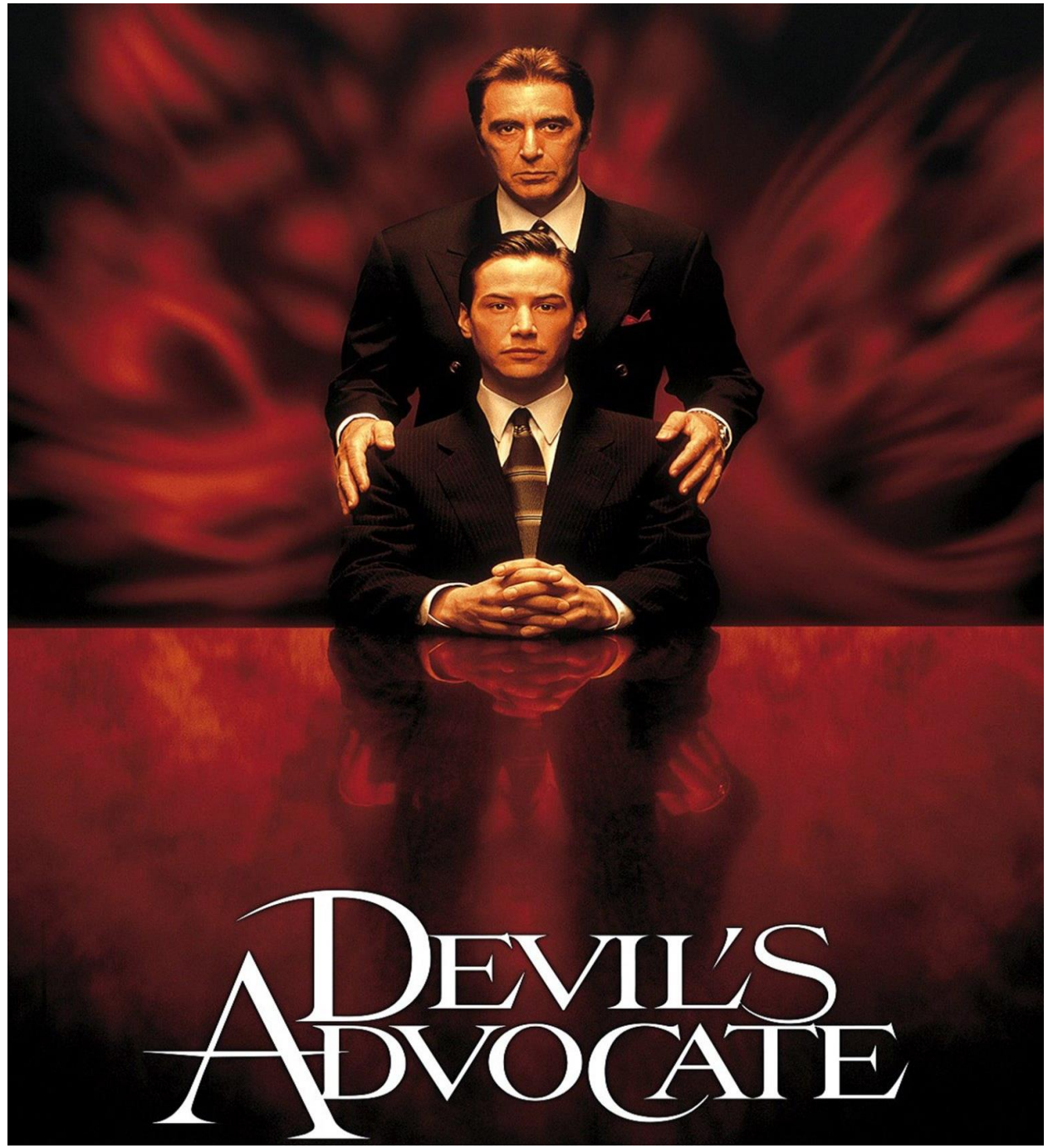
Options for intensified antithrombotic therapy

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.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.

Caveat: no recommendations of drug selection

2019 ESC Guidelines for CCS. Eur Heart J. 2019


DEVIL'S
ADVOCATE

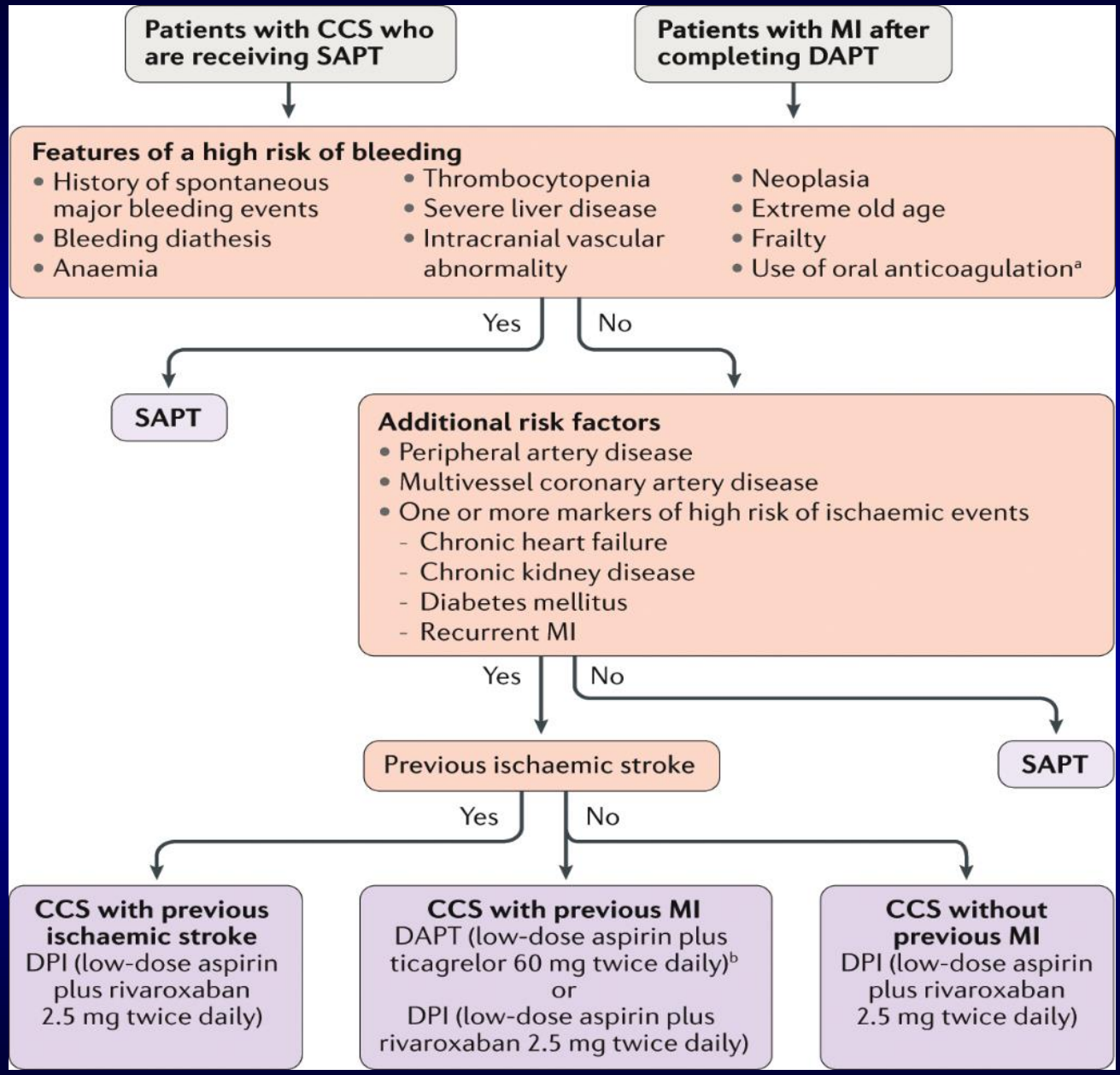
DPI vs DAPT: Practical Considerations

1. In COMPASS, the mean time from MI was 7 years but in real world clinical practice, the decision on whether to continue with intensified antithrombotic therapy (mostly DAPT) is at 1 year post-MI. If a patient is doing fine on aspirin years after an MI, would you start DPI?

2. Patients enrolled in COMPASS were mostly on aspirin, and while there is PD data on switching from DAPT to DPI (SWAP-AC-2), there is no clinical data on such switch at 1 year post-MI.

3. Many patients will require PCI in the future, thus why not just stay on DAPT instead of having to switch back from DPI to DAPT?

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.