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دانشگاه علوم پزشکی بابل

Antiplatelet Therapy in Acute Coronary Syndrome

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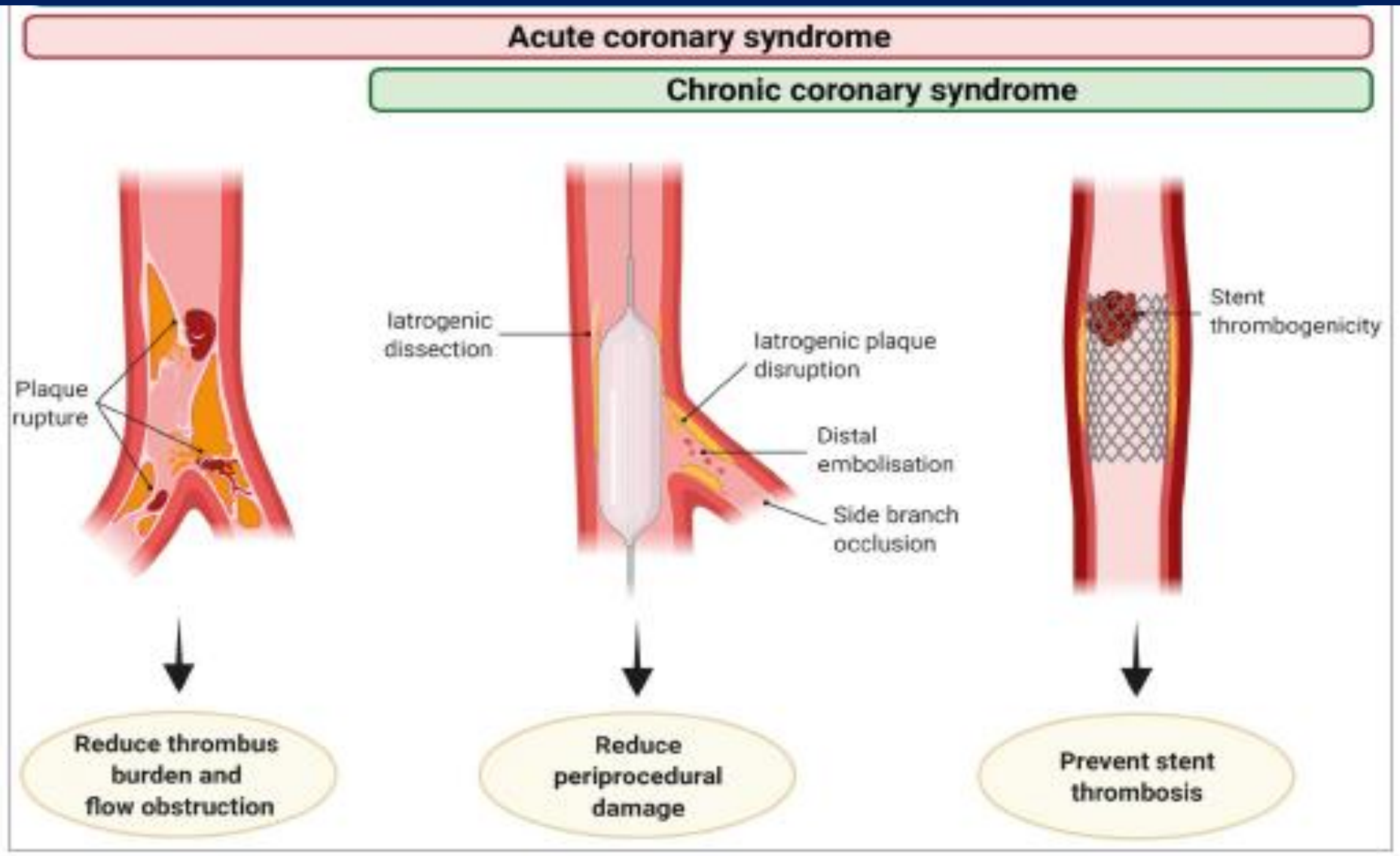
Venotica
Ticagrelor

Rationale for using antiplatelet

1) **ACS patients:**
   - Thrombos formation (Plaque rupture or erosion)
   - Symptomatic event.
2) **CCS patients:**
   - Disease progression (plaque healing phenomenon)
3) **Periprocedural :**
   - Dissections or plaque ruptures, embolisation or side branch occlusions.
4) **Stent thrombosis.**

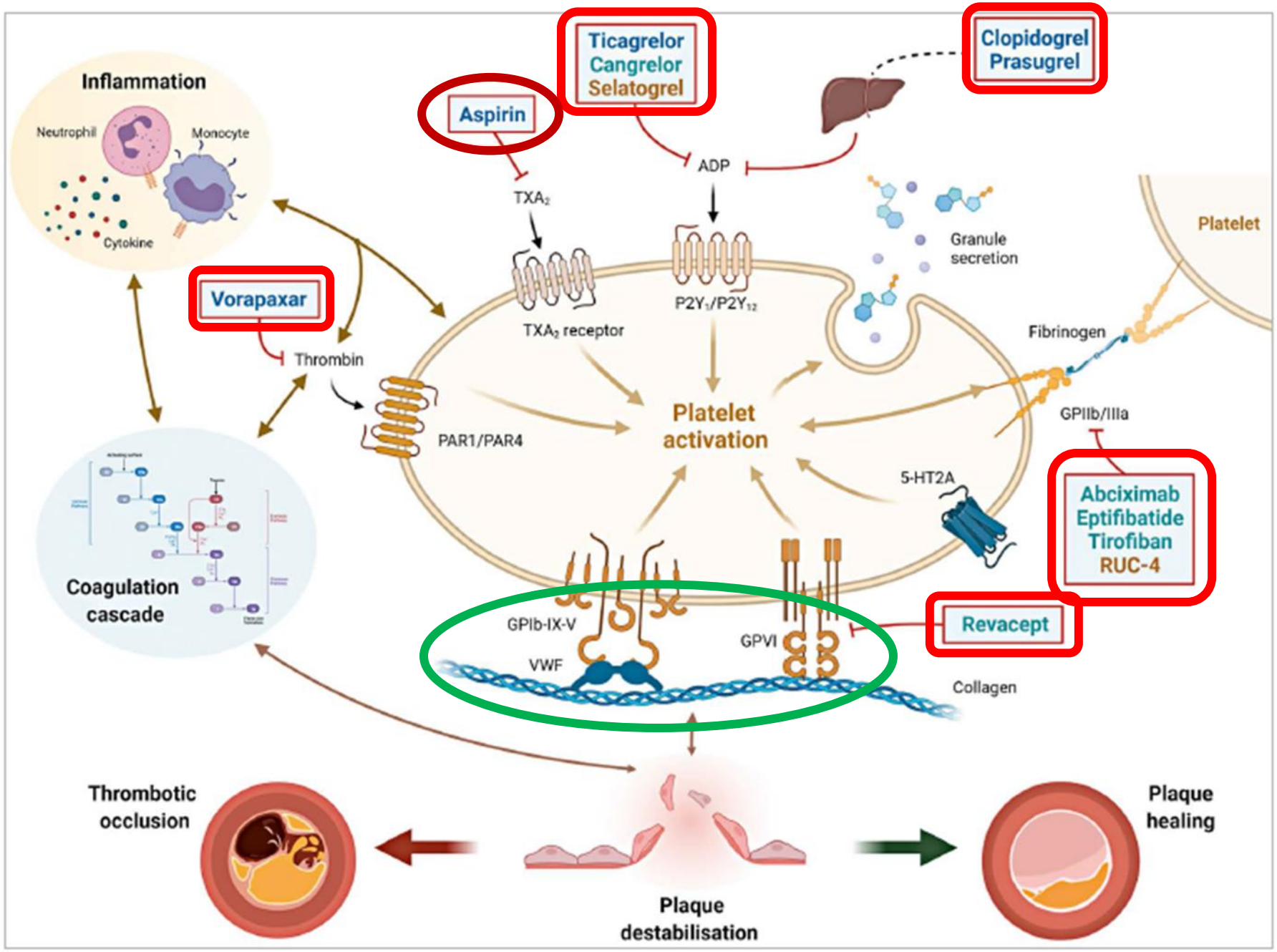
- **Antiplatelet therapy is key to reducing local thrombotic complications and systemic ischaemic events but it is inevitably associated with increased bleeding.**

Rationale for using antiplatelet



Platelets activation pathway

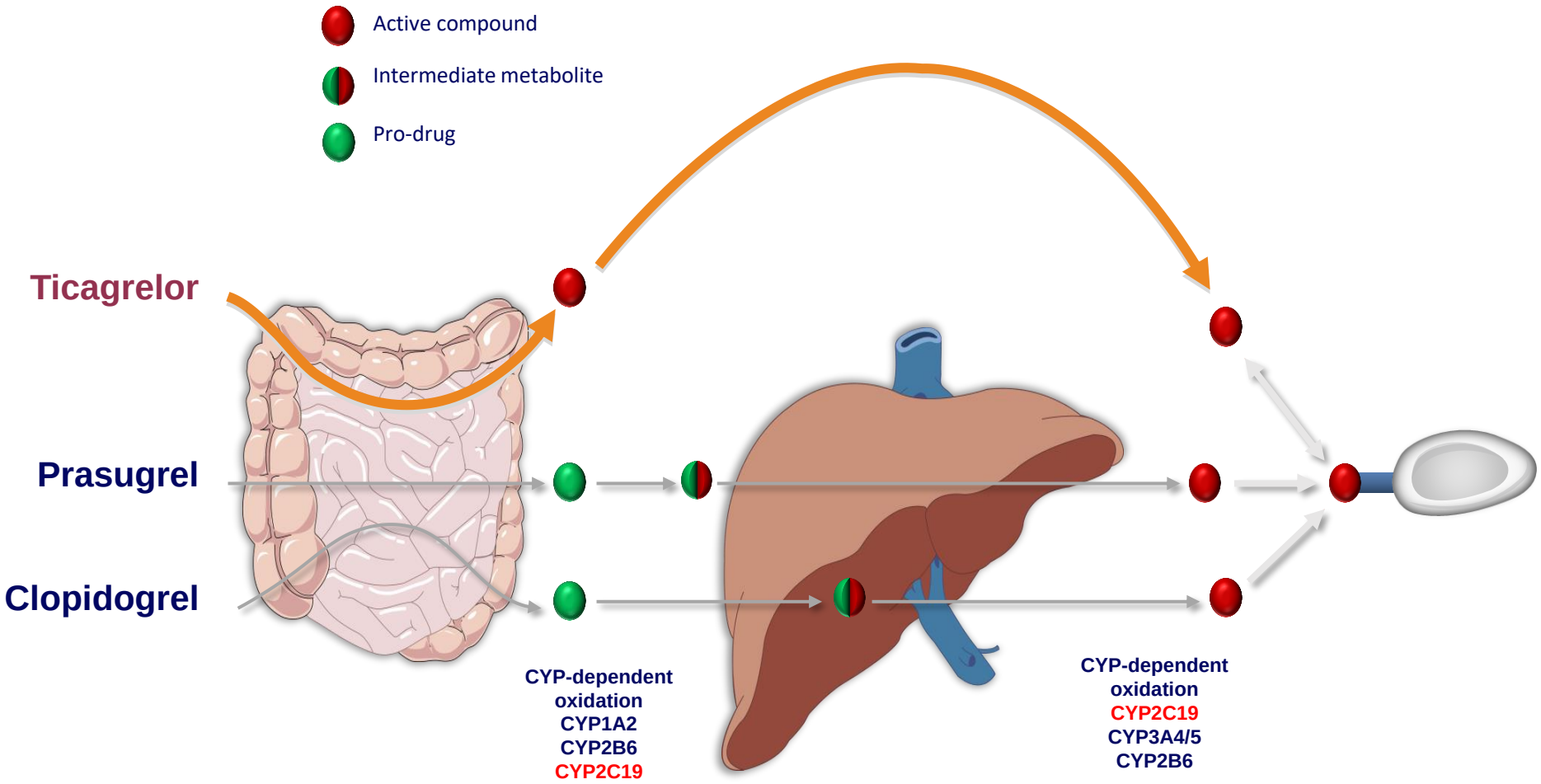
Platelets play a key role in thrombus formation and their initial tethering is mediated by the interaction between the complex glycoprotein (GP) Ib-IX-V and Von Willebrand factor and by collagen receptors present on the platelet surface such as GPVI.


Inflammation
Neutrophil
Monocyte
Cytokine
Ticagrelor
Cangrelor
Selatogrel
Clopidogrel
Prasugrel
Aspirin
ADP
TXA2
Granule secretion
Platelet
Vorapaxar
TXA2 receptor
P2Y1/P2Y12
Fibrinogen
Thrombin
PAR1/PAR4
Platelet activation
GPIIb/IIIa
5-HT2A
Abciximab
Eptifibatide
Tirofiban
RUC-4
Coagulation cascade
GPIb-IX-V
GPVI
Revacept
VWF
Collagen
Thrombotic occlusion
Plaque destabilisation
Plaque healing

Routine oral antiplatelet

- **Aspirin**
  - Irreversible inhibitor of platelet cyclooxygenase (COX)-1 and traditionally has been a backbone treatment for patients with atherosclerotic disease.
- **Ticlopidine**,
  - Irreversible platelet inhibitor
  - First-generation thienopyridine,
- **Clopidogrel**,
  - Irreversible inhibitor of of P2Y12 receptor
  - Second-generation thienopyridine,
- **Prasugrel**,
  - Irreversible inhibitor of of P2Y12 receptor
  - Third-generation thienopyridine,
- **Ticagrelor**,
  - Firstin-class cyclopentyl**triazolopyrimidine**, characterised by potent and predictable antiplatelet effects resulting in greater antithrombotic efficacy compared to clopidogrel in the setting of ACS, albeit at the expense of increased bleeding.

Pharmacological Comparison of Clopidogrel and Ticagrelor



So, Ticagrelor is more reliable

Impaired drug metabolism

MOLECULAR MEDICINE REPORTS 17: 4195-4202, 2018

Prevalence of the CYP2C19*2 (681 G>A), *3 (636 G>A) and *17 (-806 C>T) alleles among an Iranian population of different ethnicities

A, CYP2C19*2

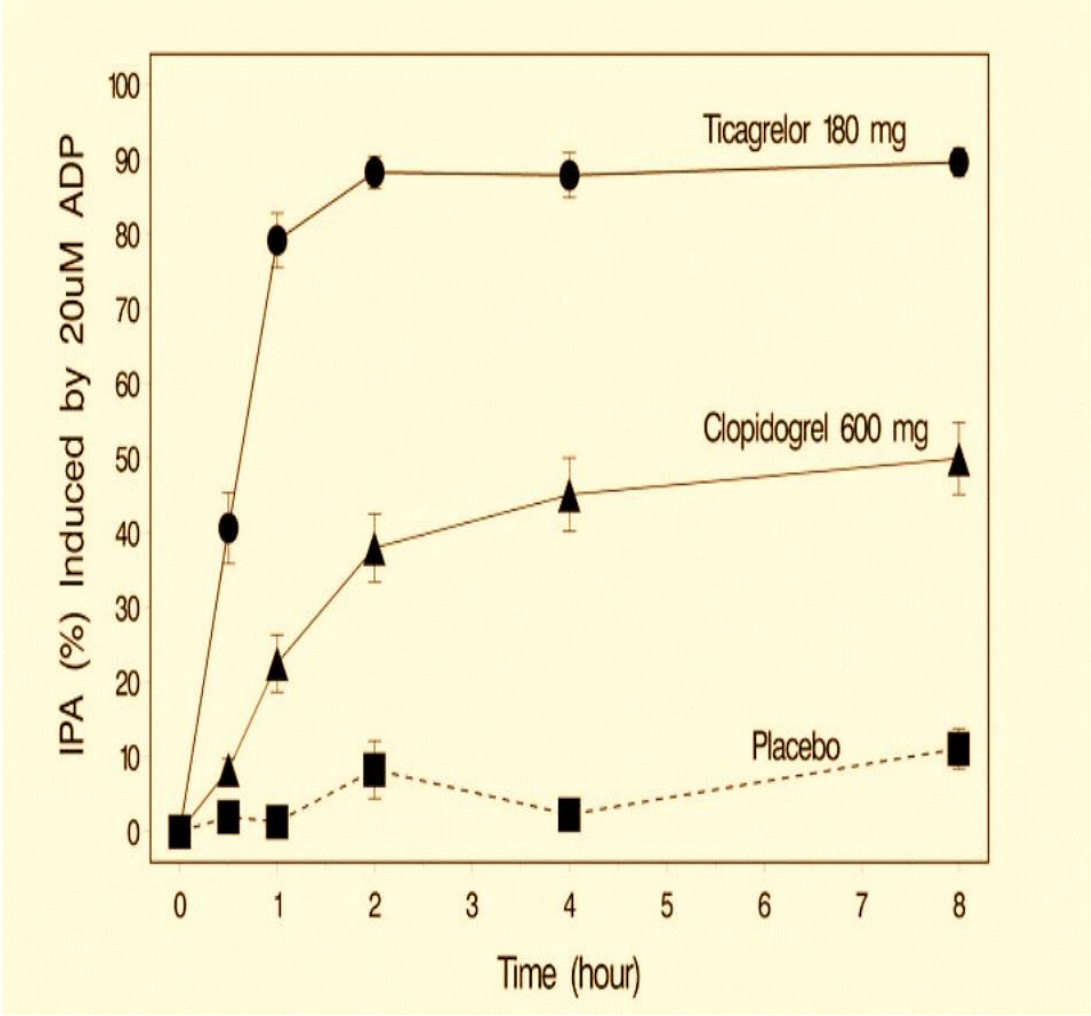
Ethnicity	CYP2C19*2 allele frequency (%)	Genotype frequency (%)			χ^2	P-value
		G/G	G/A	A/A		
Fars	15.3	72.8 (66.1-79.4)	23.9 (17.2-30.6)	3.3 (1.1-6.1)	137.4	<0.001[a]
Turk	25.0	58.2 (49.1-67.3)	33.6 (24.5-42.7)	8.2 (3.6-13.6)	41.2	<0.001[a]
Caspian	9.6	83.6 (74-91.8)	13.7 (5.5-21.9)	2.7 (0.0 -6.8)	84.1	<0.001[a]
Lure	35.0	41.3 (31.3-52.5)	47.5 (37.5-58.8)	11.3 (5.0 -18.8)	18.0	<0.001[a]
Kurd	26.3	55.8 (46.3-66.3)	35.8 (25.3-45.3)	8.4 (3.2-14.7)	32.2	<0.001[a]
Total population	21.4	63.6 (59.9-67.7)	30.1 (26-33.8)	6.3 (4.5-8.6)	269.0	<0.001[a]

Common variants of the CYP2C19 gene are associated with impaired drug metabolism.
CYP2C19*2 and CYP2C19*3 were identified in individuals who exhibited a reduced capability for metabolizing the pro_drugs, and variant CYP2C19*17 is associated with ultra-rapid metabolism of CYP2C19 substrates .

Pharmacokinetic and pharmacodynamics of antiplatelet

	Oral administration			i.v. administration
	Clopidogrel	**Prasugrel**	**Ticagrelor**	**Cangrelor**
Drug class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Adenosine triphosphate analogue
Reversibility	Irreversible	Irreversible	Reversible	Reversible
Bioactivation	Yes (pro-drug, CYP dependent, 2 steps)	Yes (pro-drug, CYP dependent, 1 step)	No[a]	No
(Pretreatment)-Dose	600 mg LD, 75 mg MD	60 mg LD, 10 (5) mg MD	180 mg LD, 2 × 90 (60) mg MD	30 µg/kg i.v. bolus, 4 µg/kg/min i.v. infusion for PCI
Onset of effect	Delayed: 2–6 h	Rapid: 0.5–4 h	Rapid: 0.5–2 h	Immediate: 2 min
Offset of effect	3–10 days	5–10 days	3–4 days	30–60 min
Delay to surgery	5 days	7 days	5 days	No significant delay
Kidney failure	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Dialysis or CrCl <15 mL/min	Limited data	Limited data	Limited data	Limited data

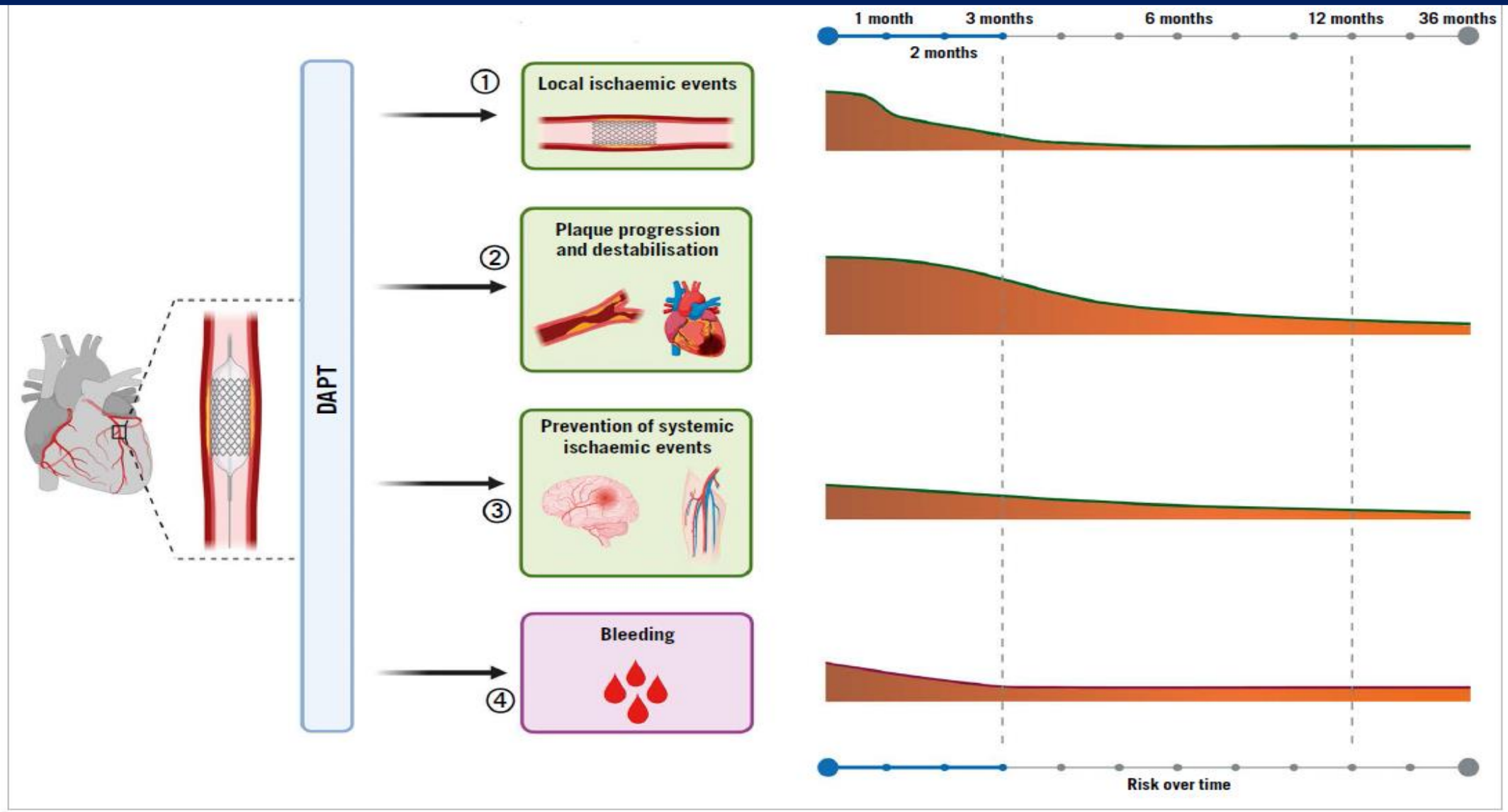
P2Y12I Potency



- ✓ More Potent
- ✓ Faster Onset

IPA: Mean inhibition of platelet activity

Time course of benefit and risk of antiplatelet therapy after PCI.

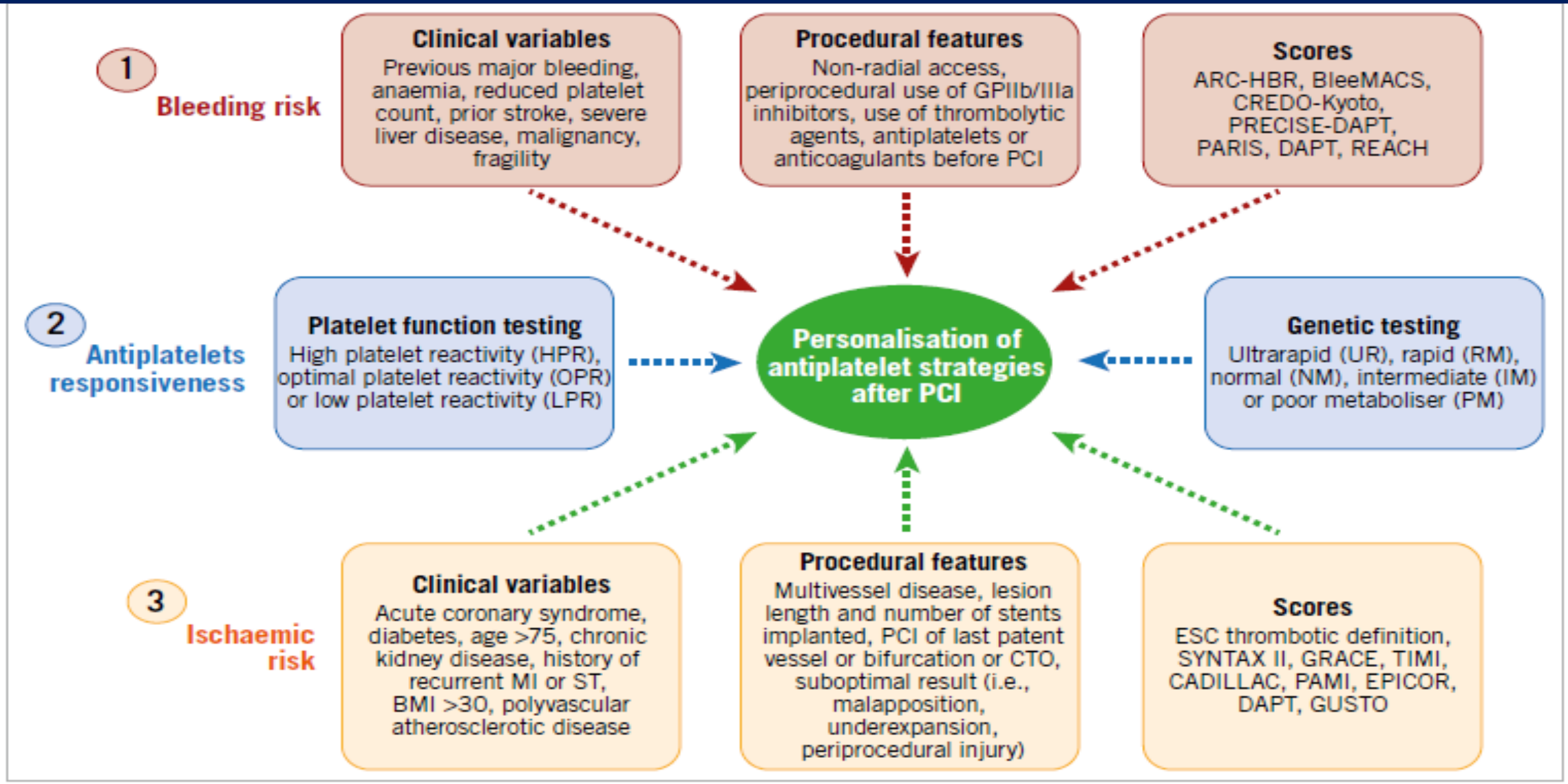


Bleeding and ischemic risk assessment

Academic Research Consortium high bleeding risk definition		European Society of Cardiology ischaemic risk definition	
Major criteria	**Minor criteria**	**High thrombotic risk**	**Moderate thrombotic risk**
At least 1 criterion	**At least 2 criteria**	**Complex CAD and at least 1 criterion**	**Non-complex CAD and at least 1 criterion**
		Risk enhancers	
Anticipated use of long-term oral anticoagulation	Age ≥75 years	Diabetes mellitus requiring medication	Diabetes mellitus requiring medication
Severe or end-stage CKD (eGFR <30 mL/min/1.73 m^2)	Moderate CKD (eGFR 30 to 59 mL/min/1.73 m^2)	History of recurrent MI	History of recurrent MI
Haemoglobin <11 g/dL	Haemoglobin 11 to 12.9 g/dL for men and 11 to 11.9 g/dL for women	Any multivessel CAD	Polyvascular disease (CAD plus PAD)
Spontaneous bleeding requiring hospitalisation or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalisation or transfusion within the past 12 months not meeting the major criterion	Polyvascular disease (CAD plus PAD)	CKD with eGFR 15-59 mL/min/1.73 m^2
Moderate or severe baseline thrombocytopaenia (platelet count <100×10^9/L)	Long-term use of oral NSAIDs or steroids	Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD	–
Chronic bleeding diathesis	Any ischaemic stroke at any time not meeting the major criterion	Concomitant systemic inflammatory disease (e.g., human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis)	–

Liver cirrhosis with portal hypertension	–	CKD with eGFR 15-59 mL/min/1.73 m^2	–
Active malignancy (excluding non-melanoma skin cancer) within the past 12 months	–	*Technical aspects*	
Previous spontaneous ICH (at any time)	–	At least 3 stents implanted	–
Previous traumatic ICH within the past 12 months	–	At least 3 lesions treated	–
Presence of a bAVM	–	Total stent length >60 mm	–
Moderate or severe ischaemic stroke within the past 6 months	–	History of complex revascularisation (left main, bifurcation stenting with >2 stents implanted, chronic total occlusion, stenting of last patent vessel)	–
Non-deferrable major surgery on DAPT	–	History of stent thrombosis on antiplatelet treatment	–
Recent major surgery or major trauma within 30 days before PCI	–	–	–

Bleeding and ischemic risk assessment



ESC European Society of Cardiology

European Heart Journal (2018) **39**, 213–254
doi:10.1093/eurheartj/ehx419

ESC GUIDELINES

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Marco Valgimigli* (Chairperson) (Switzerland), Héctor Bueno (Spain), Robert A. Byrne (Germany), Jean-Philippe Collet (France), Francesco Costa (Italy), Anders Jeppsson[1] (Sweden), Peter Jüni (Canada), Adnan Kastrati (Germany), Philippe Kolh (Belgium), Laura Mauri (USA), Gilles Montalescot (France), Franz-Josef Neumann (Germany), Mate Petricevic[1] (Croatia), Marco Roffi (Switzerland), Philippe Gabriel Steg (France), Stephan Windecker (Switzerland), and Jose Luis Zamorano (Spain)

ESC
European Society of Cardiology
European Heart Journal (2018) **39**, 119–177
doi:10.1093/eurheartj/ehx393

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Borja Ibanez* (Chairperson) (Spain), Stefan James* (Chairperson) (Sweden), Stefan Agewall (Norway), Manuel J. Antunes (Portugal), Chiara Bucciarelli-Ducci (UK), Héctor Bueno (Spain), Alida L. P. Caforio (Italy), Filippo Crea (Italy), John A. Goudevenos (Greece), Sigrun Halvorsen (Norway), Gerhard Hindricks (Germany), Adnan Kastrati (Germany), Mattie J. Lenzen (The Netherlands), Eva Prescott (Denmark), Marco Roffi (Switzerland), Marco Valgimigli (Switzerland), Christoph Varenhorst (Sweden), Pascal Vranckx (Belgium), Petr Widimský (Czech Republic)

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

The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Jean-Philippe Collet * (Chairperson) (France), Holger Thiele * (Chairperson) (Germany), Emanuele Barbato (Italy), Olivier Barthélémy (France), Johann Bauersachs (Germany), Deepak L. Bhatt (United States of America), Paul Dendale (Belgium), Maria Dorobantu (Romania), Thor Edvardsen (Norway), Thierry Folliguet (France), Chris P. Gale (United Kingdom), Martine Gilard (France), Alexander Jobs (Germany), Peter Jüni (Canada), Ekaterini Lambrinou (Cyprus), Basil S. Lewis (Israel), Julinda Mehilli (Germany), Emanuele Meliga (Italy), Béla Merkely (Hungary), Christian Mueller (Switzerland), Marco Roffi (Switzerland), Frans H. Rutten (Netherlands), Dirk Sibbing (Germany), George C.M. Siontis (Switzerland)

Circulation

ACC/AHA/SCAI CLINICAL PRACTICE GUIDELINE

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Writing Committee Members*

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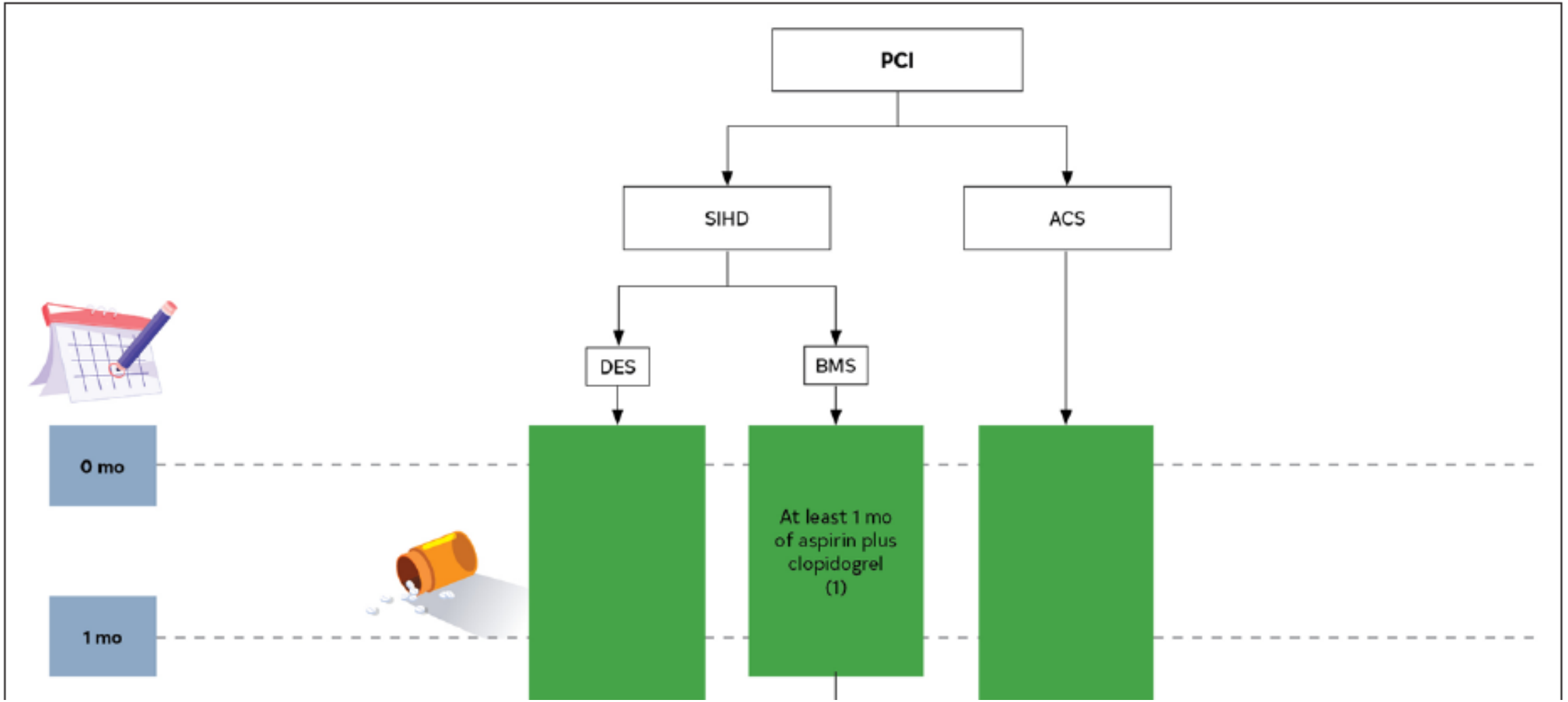
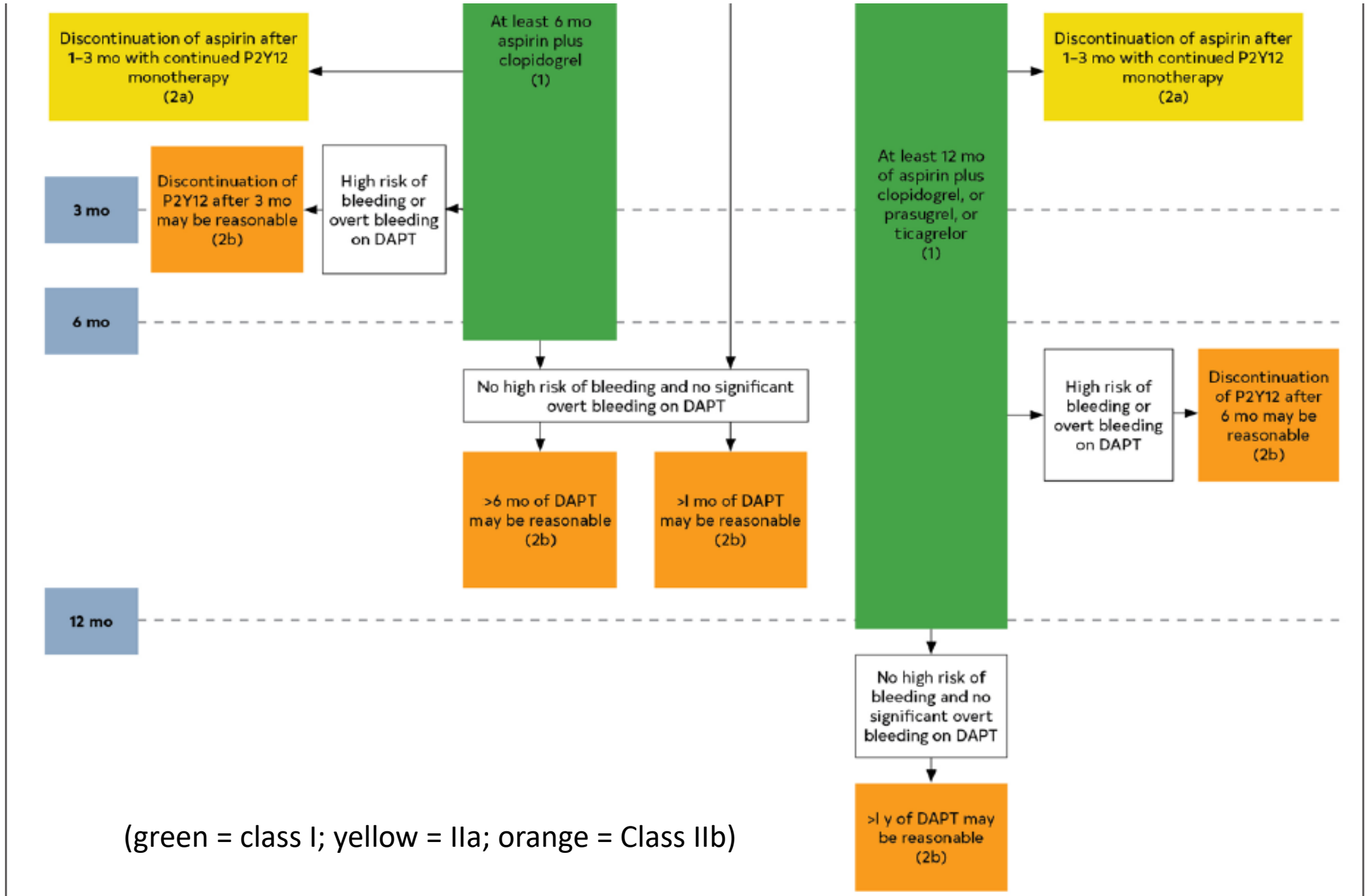
Current Guidelines of the ESC recommendations for oral antiplatelet agents

	Before PCI	During PCI	After PCI
Stable 	Aspirin — I A Clopidogrel (high probability of PCI) — IIb C	Clopidogrel — I A Prasugrel or ticagrelor over Clopidogrel (high ischaemic risk) — IIb C	DAPT for 6 months — I A Extended DAPT (high ischaemic and low bleeding risk) — IIa A 3-month DAPT→ aspirin (high bleeding risk) — IIa A 1-month DAPT→ aspirin (high bleeding risk) — IIb C
NSTE-ACS 	Aspirin — I A Routine $P2Y_{12}$ inhibitor — III A	Prasugrel — I A Ticagrelor — I A Clopidogrel — I C Prasugrel over ticagrelor — IIa B	DAPT for 12 months — I A Extended DAPT or DPI (high ischaemic risk) — IIa A 1-month DAPT→ clopidogrel (very high bleeding risk) — IIa B 3-month DAPT→ aspirin (high bleeding risk) — IIa B 3-month DAPT with ticagrelor→ ticagrelor — IIa B Extended DAPT or DPI (moderate ischaemic risk) — IIb A Guided de-escalation — IIb A
STE-ACS 	Aspirin — I B Potent $P2Y_{12}$ inhibitor — I A		DAPT for 12 months — I A 6-month DAPT→ aspirin (high bleeding risk) — IIa B Extended DAPT or DPI (high ischaemic/low bleeding risk) — IIb B Guided de-escalation — IIb A

Use of DAPT for patients after PCI

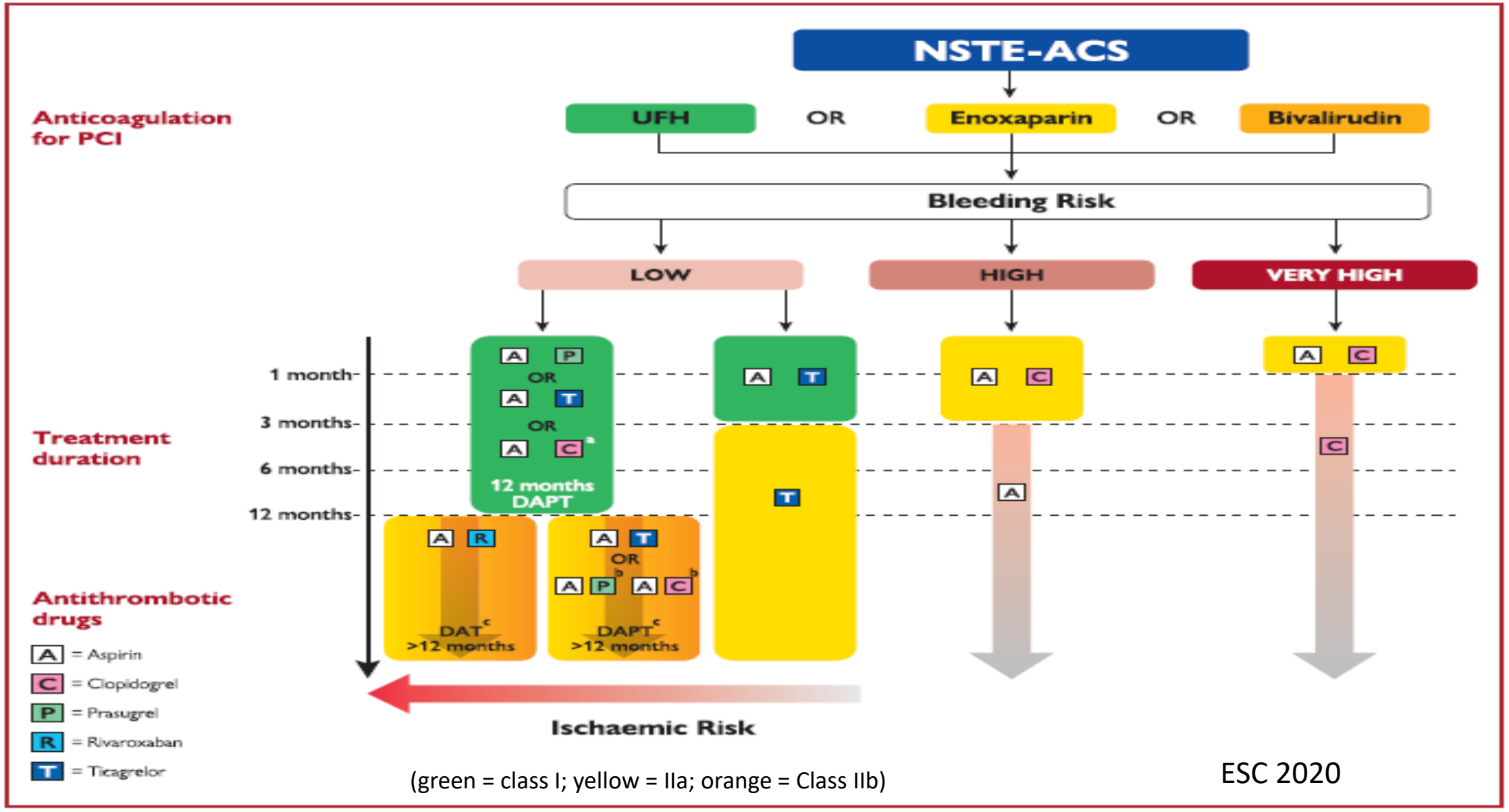
2021 ACC/AHA/SCAI Guideline





(green = class I; yellow = IIa; orange = Class IIb)

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization



(green = class I; yellow = IIa; orange = Class IIb)

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In patients with NSTE-ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT >_25 or ARC-HBR criteria met), discontinuation of P2Y12 receptor inhibitor therapy after 3 - 6 months should be considered.
In patients at very high risk of bleeding, defined as a recent bleeding episode in the past month or planned, not deferrable surgery in the near future, 1 month of aspirin and clopidogrel should be considered.

Recommendations for antithrombotic treatment in non-STE ACS patients without AF undergoing PCI

Recommendations	Class[a]	Level[b]
Antiplatelet treatment		
Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.), and at a MD of 75–100 mg o.d. for long-term treatment.[179–181]	I	A
A $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, and maintained over 12 months unless there are contraindications or an excessive risk of bleeding.[170,171,182] Options are:	I	A
• Prasugrel in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg/d as standard dose, 5 mg/d for patients aged ≥75 years or with a body weight <60 kg).[171]	I	B
• 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
Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI.[174]	IIa	B
GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI.[184–187]	IIb	A
Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have an HBR.	IIb	C
Treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.[188,189]	III	A
It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned.[174,177,178,190,191]	III	A

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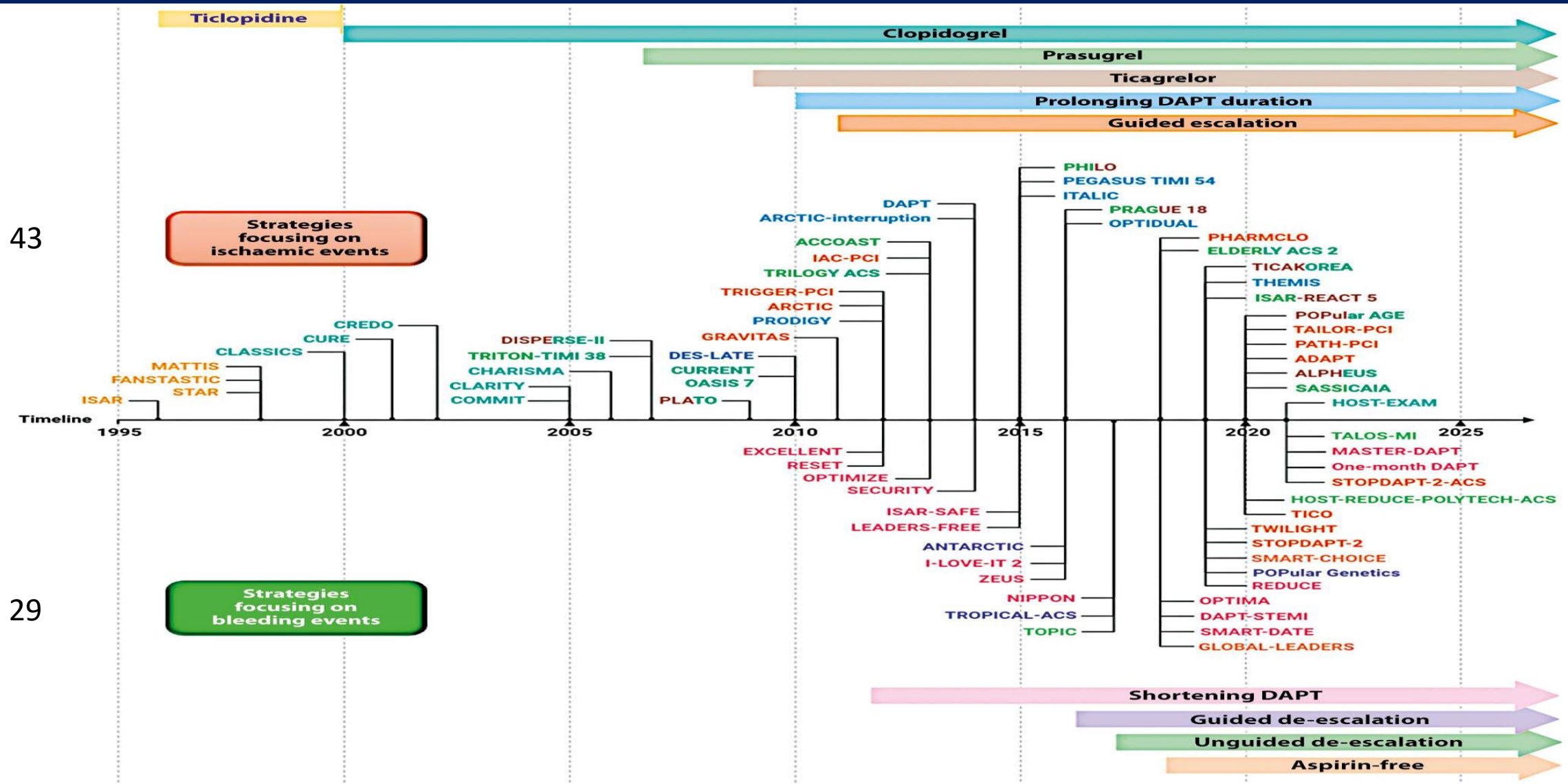
Timeline of RCT on antiplatelet therapy focusing on strategies aiming at reducing ischemic (upper) or bleeding (lower) events.



Escalation of p2y12 inhibitors

- From a clinical standpoint, an escalation strategy is aimed at reducing ischaemic events without a trade-off in bleeding.
- A recent meta-analysis found a strategy of a guided escalation of antiplatelet therapy to be associated with a 26% reduction of composite ischaemic events and no difference in bleeding as compared to standard selection of antiplatelet therapy among patients undergoing PCI.

Prolonging DAPT duration

- Overall, these above-mentioned trials led to the most recent changes in guideline recommendations for long-term intensified antithrombotic regimens by means of DAPT or DPI among high and moderate ischemic risk patients in the absence of high bleeding risk.
- The guidelines, however, do not provide recommendations for choosing between the 2 strategies (DAPT vs DPI) nor as to which P2Y12 inhibitor to consider if a DAPT strategy is chosen.

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
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

2020 ESC Guidelines for the management of acute coronary syndromes

Randomised controlled trials testing antiplatelet strategies aiming at reducing ischemic events among patients undergoing percutaneous coronary intervention.

Study name	Year of publica-tion	Number of patients enrolled	Clinical presentation (%)		Treatment arms and population	Primary endpoint definition	Primary endpoint met?	Follow-up duration
			ACS	CCS				
Potent $P2Y_{12}$ inhibiting therapy								
TRITON TIMI 38	2007	13,608	100	0	Prasugrel versus clopidogrel among ACS	CV death, MI or stroke	Yes	14 months
PLATO	2009	18,624	100	0	Ticagrelor versus clopidogrel among ACS	CV death, MI or stroke	Yes	12 months
PHILO	2015	801	100	0	Ticagrelor versus clopidogrel among ACS	Any major bleeding CV death, MI or stroke	No	12 months
PRAGUE-18	2016	1,230	100	0	Ticagrelor versus prasugrel among STEMI patients	All-death, reinfarction, urgent target vessel revascularisa-tion, stroke and serious bleeding requiring transfusion or prolonging hospitalisation at 7 days	No	12 months
ELDERLY ACS 2	2018	1,443	100	0	Reduced dose of prasugrel (5 mg die) versus clopidogrel among ACS	All death, MI, disabling stroke and rehospitalisation for CV causes or bleeding	No	12 months
TICAKOREA	2019	800	100	0	Ticagrelor versus clopidogrel among ACS	Major or minor PLATO bleeding	Yes	12 months
ISAR-REACT 5	2019	4,018	100	0	Ticagrelor versus prasugrel among ACS	CV death, MI or stroke	Yes	12 months
POPular AGE	2020	1,002	100	0	Ticagrelor versus clopidogrel among elderly (>70 years) ACS	Major or minor PLATO bleeding All-cause death, myocardial infarction, stroke, major and minor PLATO bleeding	No	12 months
SASSICAIA	2020	781	0	100	Prasugrel versus clopidogrel among patients undergoing elective PCI	All death, any MI, definite/ probable ST, stroke and urgent vessel revascularisation	No	30 days
ALPHEUS	2020	1,910	0	100	Ticagrelor versus clopidogrel among patients undergoing high-risk PCI	PCI-related type 4 (a or b) MI or major myocardial injury Major bleeding	No	48 hours 30 days

Prolonging DAPT duration								
DES-LATE	2010	2,701	63	37	12 months versus 24 months DAPT	CV death or MI	No	2 years
PRODIGY	2012	2,013	74	26	6 months versus 24 months DAPT 30 days after PCI	All death, myocardial infarction or cerebrovascular accident	No	2 years
DAPT	2014	9,960	46	54	12 months versus 30 months DAPT	Stent thrombosis All death, MI, or stroke Moderate and severe bleeding	Yes	33 months
ARCTIC-interruption	2014	1,259	0	100	12 months versus 18 months DAPT	All death, myocardial infarction, stent thrombosis, stroke and urgent revascularisation	No	17 months
ITALIC	2015	2,301	23	76	6 months versus 24 months DAPT	All death, MI, urgent target vessel revascularisation, stroke and major bleeding	No	12 months
PEGASUS-TIMI 54	2015	21,162	0	100	Ticagrelor 90 mg or ticagrelor 60 mg versus placebo 1 to 3 years after MI	CV death, MI or stroke and TIMI major bleeding	Yes	33 months
OPTIDUAL	2016	1,799	35	65	12 months versus 48 months DAPT	All death, MI, stroke or major bleeding	No	33 months
THEMIS	2019	19,220	0	100	Ticagrelor plus aspirin versus placebo plus aspirin among stable patients with DM	CV death, MI or stroke	No	40 months

Study name	Year of publication	Number of patients enrolled	Clinical presentation (%)		Treatment arms and population	Primary endpoint definition	Primary endpoint met?	Follow-up duration
			ACS	CCS				
GRAVITAS	2011	2,214	45	55	High-dose (150 mg) versus standard-dose clopidogrel (75 mg daily) among clopidogrel non-responders defined by PFT	CV death, MI or ST	No	6 months
ARCTIC	2012	2,440	0	100	High-dose (150 mg) prasugrel versus standard-dose clopidogrel (75 mg daily) among clopidogrel non-responders defined by PFT	All death, MI, ST, stroke and urgent revascularisation	No	12 months
TRIGGER-PCI	2012	423	0	100	Prasugrel versus clopidogrel among clopidogrel non-responders defined by PFT	CV death or MI	No	6 months
PHARMCLO	2018	888	97	3	Prasugrel or ticagrelor among clopidogrel non-responders defined by genetic testing versus standard therapy	CV death, MI, stroke and BARC bleeding 3-5	Yes	12 months
PATH-PCI	2019	2,285	0	100	Ticagrelor among clopidogrel non-responders defined by PFT versus standard therapy	CV death, MI, stroke, ST, urgent revascularisation and BARC bleeding 3-5	Yes	6 months
TAILOR-PCI	2020	5,302	69	31	Prasugrel or ticagrelor among clopidogrel non-responders defined by genetic testing versus standard therapy	CV death, MI, stroke, ST and severe recurrent ischaemia	No	12 months
ADAPT	2020	504	50	50	Prasugrel or ticagrelor among clopidogrel non-responders defined by genetic testing versus standard therapy	CV death, MI, stroke, urgent need for revascularisation and ST	No	16 months

Strategies focused on reducing bleeding events

- These strategies include:
  - Shortening DAPT,
  - The use of P2Y12 monotherapy
  - De-escalation of P2Y12 inhibitors
- Overall, results of the individual studies, as well as pooled analyses of RCTs, showed the early withdrawal of $P2Y_{12}$ inhibitor reduced bleeding, including major bleeding without any significant increase of thrombotic events.
- Overall, shortened DAPT durations should be reserved for HBR patients for whom the benefits are more likely to outweigh the risks.

De-escalation of p2y12 inhibitors

- De-escalation of P2Y12 inhibiting therapy consists in switching from more potent (i.e., prasugrel or ticagrelor) to less potent (i.e., clopidogrel) agents, and aims at reducing bleeding without any trade-off in ischaemic events.
- Accordingly, the strategy of de escalation typically applies to the setting of ACS, in which more potent P2Y12 inhibitors are recommended as the standard of care.
- **De-escalation can be guided or un-guided**
- An unguided approach consists in de-escalation without the aid of platelet function or genetic testing.
- A guided approach allows for de-escalation early after PCI.
- An unguided de-escalation **early after PCI** has been associated with an increase in thrombotic complication.
- Accordingly, waiting for the highest risk period of thrombotic complications post-PCI to elapse **(e.g., 1 month)** prior to de-escalation, represents a safer time frame for considering unguided deescalation.

Guided de-escalation

- A recent meta-analysis overcoming such limitations found that a strategy of guided de-escalation of antiplatelet therapy is associated with a 19% reduction of any bleeding, driven by a reduction of minor bleeding, without any trade-off in efficacy among patients undergoing PCI.
- Finally, a network meta-analysis focusing on ACS has shown that, compared with routine selection of potent P2Y12 inhibiting therapy (prasugrel or ticagrelora guided selection of P2Y12 inhibiting therapy is associated with the most favorable balance between safety and efficacy.

Unguided de-escalation

- It is important to note that in these trials the de-escalatio of P2Y12 inhibitors was performed 1 month after PCI – the period in which the risk of ischemic events is highest – while among trials using a guided de-escalation this was performed earlier (0-14 days) after PCI.
- A recent meta-analysis has shown that both guided and unguided de-escalation reduce bleeding without any trade-off in ischemic events.

Shortening antithrombotic treatment duration		
After stent implantation with high risk of bleeding (e.g. PRECISE-DAPT ≥25 or ARC-HBR criteria met), discontinuation of $P2Y_{12}$ receptor inhibitor therapy after 3 months should be considered.[154,226]	IIa	B
After stent implantation in patients undergoing a strategy of DAPT, stopping aspirin after 3—6 months should be considered, depending on the balance between the ischaemic and bleeding risk.[208,209,227]	IIa	A
De-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on patient's risk profile and availability of respective assays.[218,220,221]	IIb	A

2020 ESC Guidelines for the management of acute coronary syndromes

Randomised controlled trials testing antiplatelet strategies aiming at reducing bleeding events among patients undergoing PCI

Study name	Year of publication	Number of patients enrolled	Clinical presentation (%)		Treatment arms and population	Primary endpoint definition	Primary endpoint met?	Follow-up duration (months)
			ACS	CCS				
Shortening DAPT								
EXCELLENT	2012	1,443	51	49	6 versus 12 months DAPT	CV death, MI and ischaemia-driven target vessel revascularisation	Yes	12
RESET	2012	2,148	54	46	3 versus 12 months DAPT	CV death, MI, ST, target vessel revascularisation and bleeding	Yes	12
OPTIMIZE	2013	3,211	32	68	3 versus 12 months DAPT	All death, MI, stroke and major bleeding	Yes	12
SECURITY	2014	1,404	39	61	6 versus 12 months DAPT	CV death, MI, stroke, definite or probable ST and BARC bleeding 3-5	Yes	12
ISAR-SAFE	2015	4,005	39	61	6 versus 12 months DAPT	All death, MI, ST, stroke and TIMI major bleeding	Yes	9
I-LOVE-IT 2	2016	1,829	85	15	3 versus 12 months DAPT	CV death, target vessel MI or clinically-indicated target lesion revascularisation	Yes	18
NIPPON	2017	3,773	32	68	6 versus 12 months DAPT	All death, MI, stroke and major bleeding	Yes	36
DAPT-STEMI	2018	1,100	100	0	6 versus 12 months DAPT	All death, MI, any revascularisation, stroke, and TIMI major bleeding	Yes	18
SMART-DATE	2018	2,712	100	0	6 versus 12 months DAPT	All death, MI or stroke	Yes	18
OPTIMA-C	2018	1,368	51	49	6 versus 12 months DAPT	All death, MI or ischaemia-driven target lesion revascularisation	Yes	12

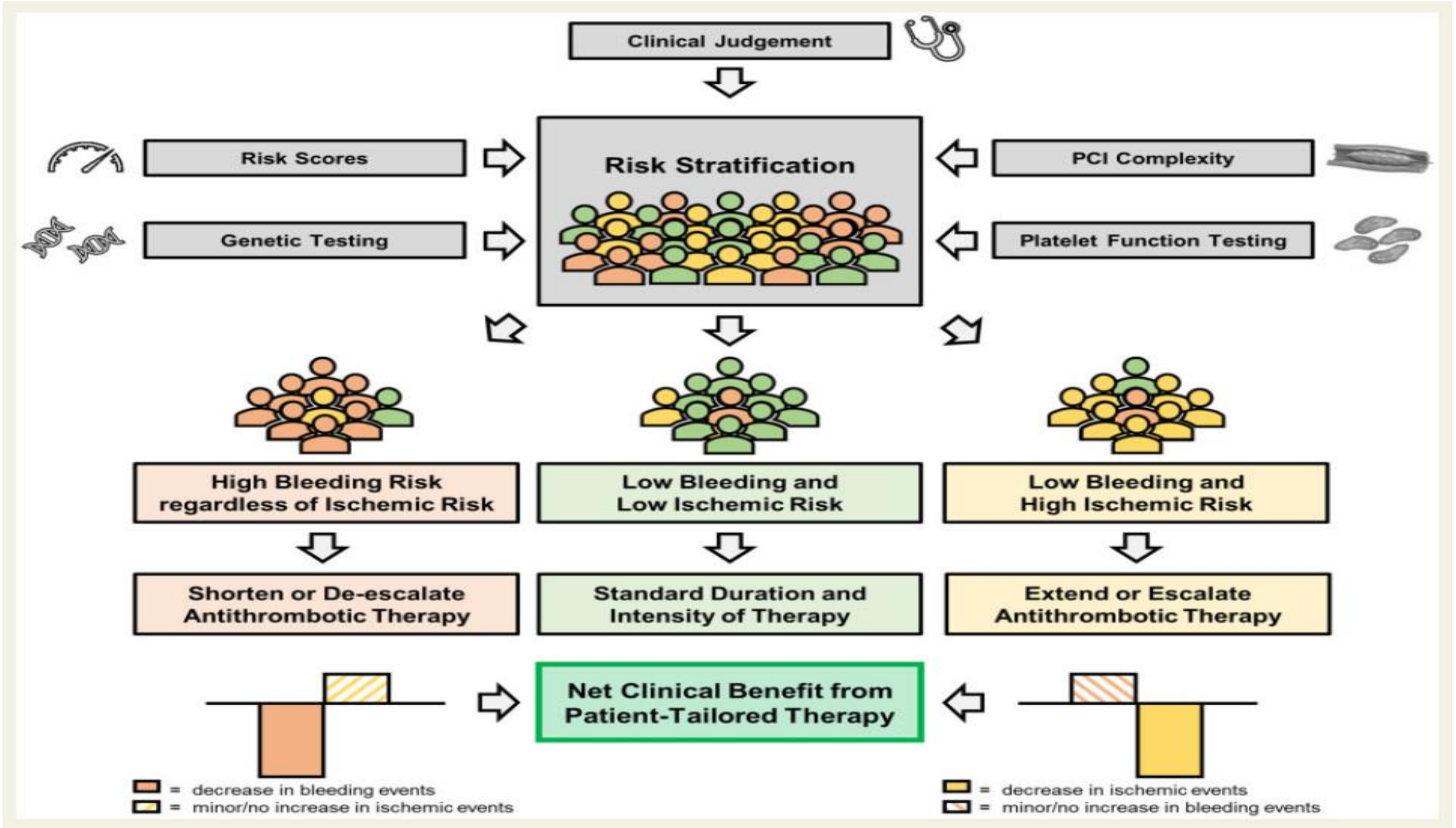
Randomised controlled trials testing antiplatelet strategies aiming at reducing bleeding events among patients undergoing PCI

Study name	Year of publication	Number of patients enrolled	Clinical presentation (%)		Treatment arms and population	Primary endpoint definition	Primary endpoint met?	Follow-up duration (months)
			ACS	CCS				
Shortening DAPT								
One-Month DAPT	2021	3,020	39	61	1 versus 6-12 months DAPT in non-complex PCI	CV death, MI, target vessel revascularisation, stroke and major bleeding	Yes	12
MASTER DAPT	2021	4,434	49	51	1 versus 5 months DAPT among HBR patients	All death, MI, stroke, or major bleeding All death, MI, stroke Major or clinically relevant non-major bleeding	Yes	11
$P2Y_{12}$ monotherapy								
GLOBAL-LEADERS	2018	15,968	47	53	Ticagrelor monotherapy for 23 months versus DAPT with ticagrelor for 12 months	All death or MI	Yes	24
TWILIGHT	2019	7,119	64	36	Ticagrelor monotherapy after 3 months of DAPT versus standard DAPT in uneventful patients with high-risk PCI	BARC bleeding type 2, 3, or 5 and all-cause death or MI and stroke	Yes	15
SMART-CHOICE	2019	2,993	58	42	$P2Y_{12}$ inhibitor monotherapy after 3 months of DAPT versus standard DAPT	All death, MI or stroke	Yes	12
STOPDAPT-2	2019	3,045	38	62	Clopidogrel monotherapy after 1 month of DAPT versus standard DAPT	CV death, MI, stroke, ST and TIMI major or minor bleeding	Yes	12
TICO	2020	3,056	100	0	Ticagrelor monotherapy after 3 months of DAPT versus standard DAPT	TIMI major bleeding, all-cause death, MI, ST, stroke and target vessel revascularisation	Yes	12
STOPDAPT-2-ACS	2021	4,169	100	0	Clopidogrel monotherapy after 1 month of DAPT versus standard DAPT among ACS	CV death, MI, stroke, ST and TIMI major or minor bleeding	No	12

Randomised controlled trials testing antiplatelet strategies aiming at reducing bleeding events among patients undergoing PCI

Study name	Year of publication	Number of patients enrolled	Clinical presentation (%)		Treatment arms and population	Primary endpoint definition	Primary endpoint met?	Follow-up duration (months)
			ACS	CCS				
Guided de-escalation								
ANTARTIC	2016	877	100	0	PFT-guided de-escalation versus standard DAPT	CV death, MI, stroke, ST, urgent revascularisation and BARC 2-5 bleeding	No	12
TROPICAL-ACS	2017	2,610	100	0	PFT-guided de-escalation versus standard DAPT	CV death, MI, stroke and BARC 2-5 bleeding	Yes	12
POPular Genetics	2019	2,488	100	0	Genotype-guided de-escalation versus standard DAPT	All death, MI, definite ST, stroke, or PLATO major bleeding and PLATO major or minor bleeding	Yes	12
Unguided de-escalation								
TOPIC	2017	646	100	0	Clopidogrel-based DAPT versus standard DAPT	CV death, urgent revascularisation, stroke and BARC 2-5 bleeding	Yes	12
HOST-REDUCE-POLYTHEC-ACS	2020	3,429	100	0	Prasugrel 5 mg-based DAPT versus prasugrel 10 mg-based DAPT	All death, MI, ST, repeat revascularisation, stroke and BARC 2-5 bleeding	Yes	12
TALOS-MI	2021	2,697	100	0	Clopidogrel-based DAPT versus ticagrelor-based DAPT	CV death, MI, stroke and BARC 2-5 bleeding	Yes	12

ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CCS: chronic coronary syndrome; CRNM: clinically relevant non-major; CV: cardiovascular; DAPT: dual antiplatelet therapy; HBR: high bleeding risk; ISTH: International Society on Thrombosis and Haemostasis; MI: myocardial infarction; PFT: platelet function test; PLATO: Platelet Inhibition and Patient Outcomes; ST: stent thrombosis; TIMI: Thrombolysis in Myocardial Infarction; VKA: vitamin K antagonists



European Heart Journal (2021) 42, 1038–1046

Switching
Hospital Admission

Switching between oral $P2Y_{12}$ inhibitors

Recommendations	Class[a]	Level[b]
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose[c] of clopidogrel, unless contraindications to ticagrelor exist.[20]	I	B
Additional switching between oral $P2Y_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.	IIb	C

- **ALL ACS Patients**
- **Early after hospital admission**
- **Irrespective of timing and loading dose of clopidogrel**
- **Unless ticagrelor contraindication**

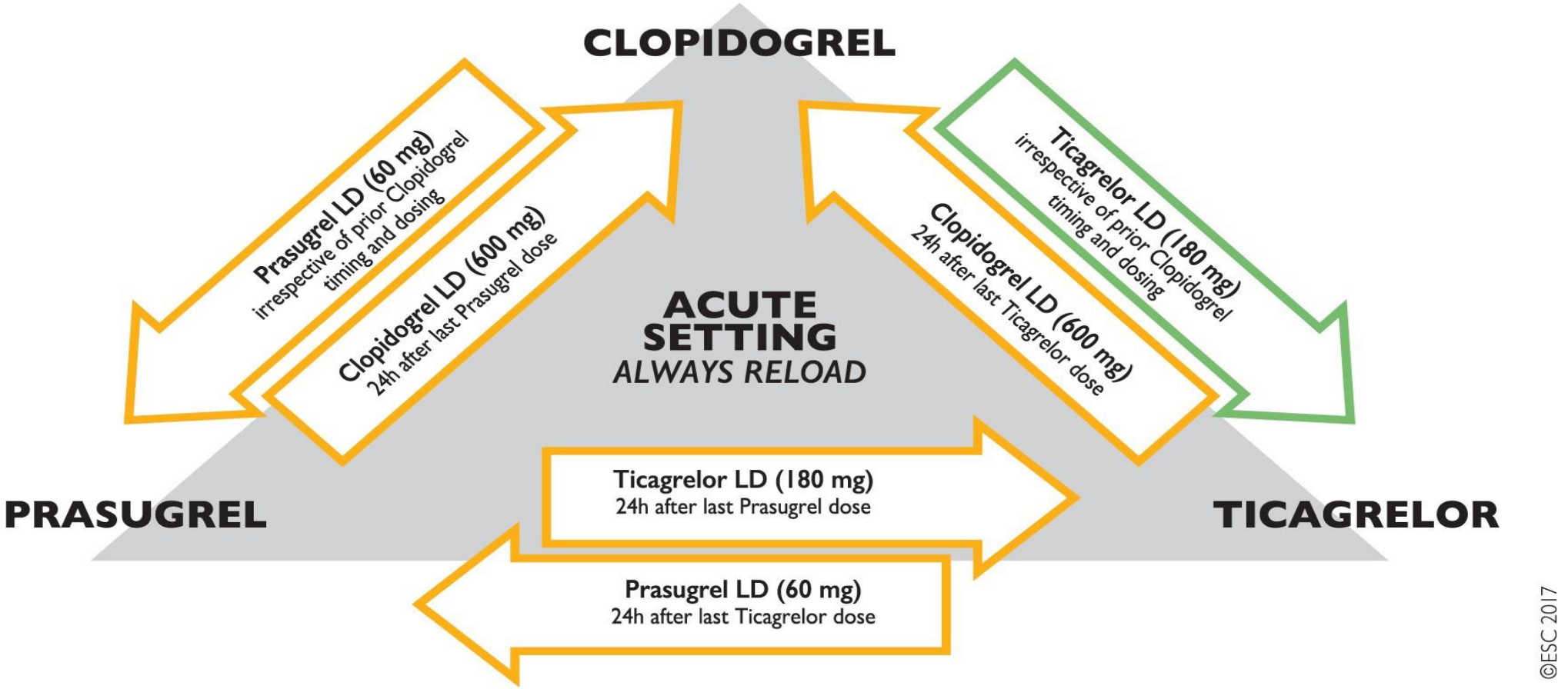
2017 ESC focused update on dual antiplatelet therapy in CAD

Pre-intervention

Prehospital administration of **ticagrelor**:

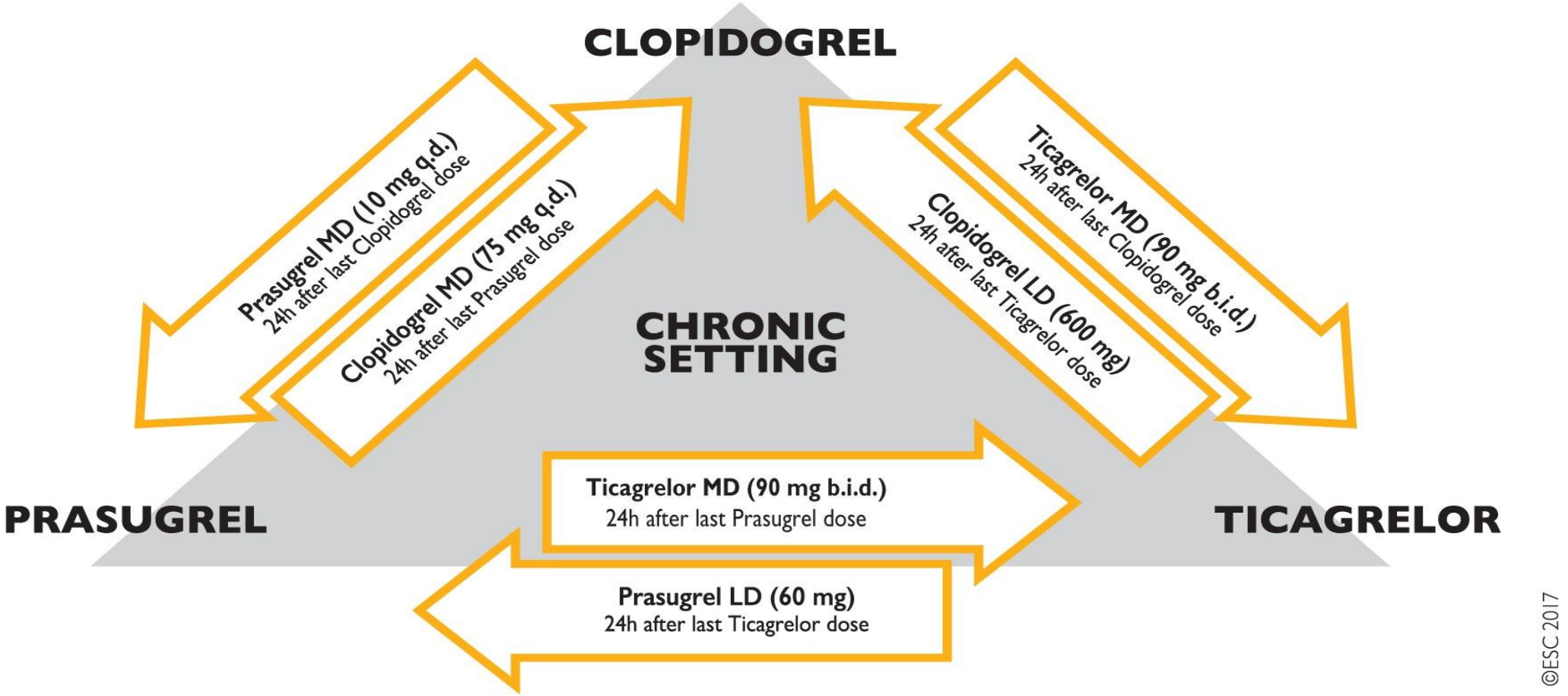
- Did not improve the primary endpoint of coronary reperfusion
- but did **reduce** the secondary endpoint of **stent thrombosis** without any additional bleeding compared to in-hospital administration in patients with STEMI undergoing primary PCI in the ATLANTIC trial 2014.

Switching between oral P2Y12 inhibitors in the acute setting



Eur Heart J, Volume 39, Issue 3, 14 January 2018, Pages 213–260, https://doi.org/10.1093/eurheartj/ehx419

Switching between oral P2Y12 inhibitors in the chronic setting



Eur Heart J, Volume 39, Issue 3, 14 January 2018, Pages 213–260, https://doi.org/10.1093/eurheartj/ehx419

Crushing Antiplatelet

If the pt experince be intubated, what do you do?

All type of antiplatlets can be crushed
(same as all DOAC except Dabigatran)

But :

Chewable aspirin may be faster than soluble aspirin at decreasing the amount of time to achieve platelet inhibition.

Soluble aspirin is faster than whole solid aspirin, which is faster than ***enteric-coated*** aspirin.

NEWS - INTERVENTIONAL | TCT 2020

No Reperfusion Benefit From Crushed Prasugrel Prior to PCI: COMPARE CRUSH

The findings contrast with observations that early dosing with crushed pills improves platelet inhibition over integral tablets.

By L.A. McKeown | October 14, 2020

Giving ***crushed prasugrel tablets in the ambulance to STEMI patients with planned primary PCI*** does ***not improve*** reperfusion rates compared with giving the tablets whole, according to results of the COMPARE CRUSH trial.

No Differences in Clinical Endpoints

Clinical Trials

Ticagrelor Provides This Opportunity to Discontinue Aspirin

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 1038–1046
doi:10.1093/eurheartj/ehaa1097

STATE OF THE ART REVIEW
Interventional cardiology

Patient-tailored antithrombotic therapy following percutaneous coronary intervention

Niels M.R. van der Sangen [1], Rik Rozemeijer [2], Dean R.P.P Chan Pin Yin [3], Marco Valgimigli [4,5], Stephan Windecker [5], Stefan K. James [6], Sergio Buccheri [6], Jurriën M. ten Berg [3,7], José P.S. Henriques [1], Michiel Voskuil [2], and Wouter J. Kikkert [1,8,*]

De-escalation and Escalation

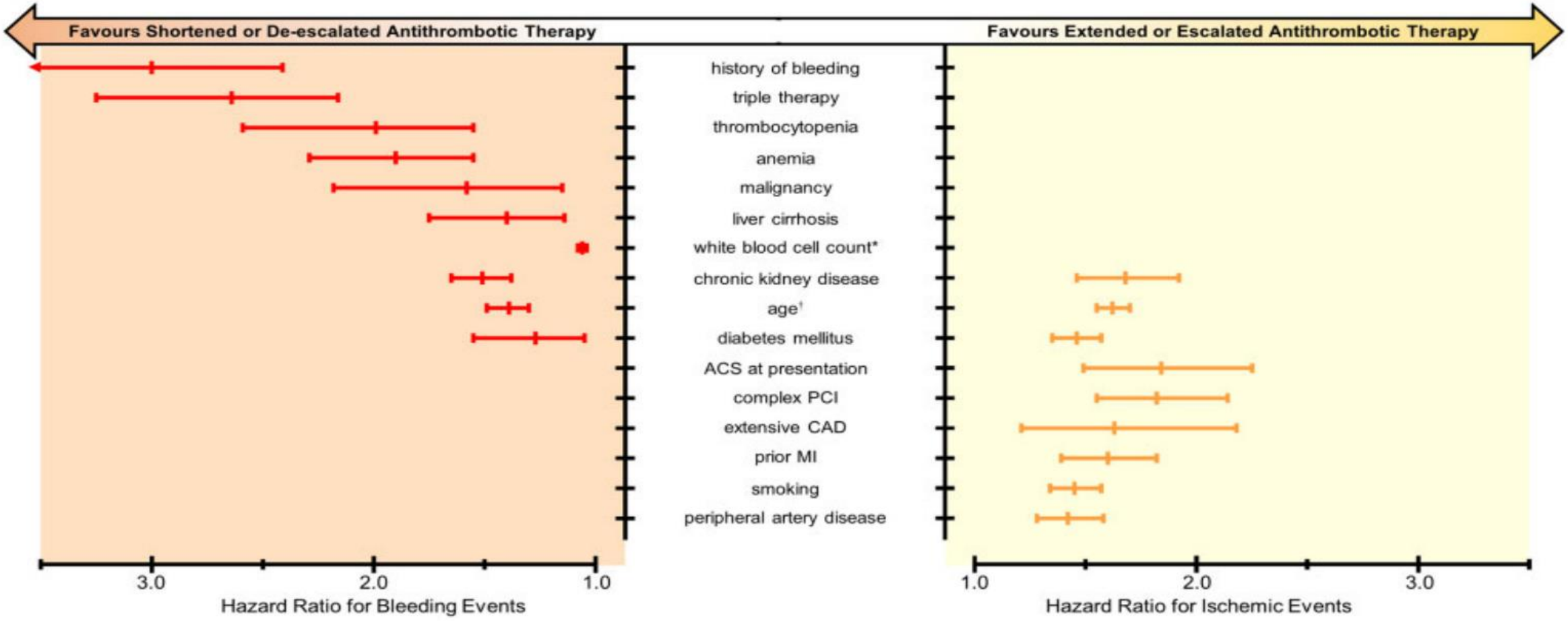


Figure 1 Clinical risk factors associated with increased risk of bleeding and/or ischaemic events. *Age per 10 years; †white blood cell count 10^3 cells/μL. ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction.

Short dual antiplatelet therapy followed by aspirin monotherapy

To date, 12 RCTs have evaluated short DAPT.

The vast majority of these trials demonstrated that short DAPT was non-inferior compared to standard DAPT in terms of the primary ischaemic endpoint, while some trials also showed a significant reduction in bleeding complications.

In most studies, patients had a relatively low risk of recurrent ischemia (mostly patients with CCS or low-risk ACS).

The investigated short DAPT varied from 3 to 6 months and in the majority of studies clopidogrel was used.

Importantly, the SMART-DATE trial, which only included ACS patients, did show a higher risk of MI with 6 months DAPT (Clopidogrel and Aspirin) as compared to 12 months.

Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy

In recent years, **the status of aspirin as the mainstay of antithrombotic therapy** has been challenged. **Aspirin** use is associated with an **increased risk of bleeding** (in particular gastrointestinal bleeding), especially in the **elderly** and those who concurrently use other **antithrombotic** agents.

The advent of potent P2Y12 inhibitors, i.e. ticagrelor and prasugrel, has raised questions as to whether the additional antithrombotic benefit of aspirin outweighs the increase in bleeding complications. Especially since the antithrombotic potency of ticagrelor alone seems to be **comparable** to that of ticagrelor and aspirin with respect to ex vivo blood thrombogenicity.

In addition, contemporary pharmacological therapies for cardiovascular risk factors, such as hypertension, dyslipidemia, and impaired glucose metabolism, have led to **reductions in an individual's cardiovascular risk**. These therapies were not available at the time of the pivotal studies evaluating aspirin in the setting of secondary prevention.

Therefore, relative benefits of adding aspirin might translate into smaller absolute risk reductions in current clinical practice as compared to previous clinical trials. Together, these observations have supported the hypothesis that P2Y12 inhibitor monotherapy (after a short course DAPT) might be superior to standard 12 months DAPT.

Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy

In fact, even complete omission of aspirin after PCI is now a topic of investigation.

To date, five RCTs have investigated the efficacy and safety of aspirin discontinuation (i.e. P2Y12 inhibitor monotherapy) after a short course of DAPT in patients undergoing PCI with new generation DES.

Importantly, three of these trials were underpowered to test non-inferiority of short DAPT compared to standard DAPT with regard to ischaemic events. Four trials applied an openlabel design and randomized patients at the time of PCI (instead of at DAPT discontinuation).

In the pivotal, placebo-controlled, double-blind TWILIGHT trial, 3 months DAPT followed by ticagrelor monotherapy up to 15 months was associated with a significant reduction in BARC types 2, 3, and 5 bleeding compared to 15 months DAPT (with ticagrelor).

Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy

To Conclude:

Based on the available evidence, **P2Y12 inhibitor monotherapy** after an initial short course DAPT should be considered as an alternative to standard DAPT in patients without high ischaemic risk undergoing PCI.

Ticagrelor should be the agent of choice for ACS patients, due to its **superiority to clopidogrel** and its predominant use in trials evaluating P2Y12 inhibitor monotherapy

دانشگاه علوم پزشکی بابل

Thanks for Your Attention

Arvand Pharmed