ANTITROMBOTICKÁ LÉČBA. PŘICHÁZÍ STÁLE INFORMACE…

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Karlovy Vary, 2022

NOVINKY V PROTIDESTIČKOVÉ LÉČBĚ ICHS

LÉKY

Efektivita

→ Preference Prasu- před Ticagrelorem

→ „Bridge“ do plné účnnosti p.o. iP2Y$_{12}$

Bezpečnost

→ Antidota

POSTUPY

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 2609–2610
doi:10.1093/eurheartj/ehaa880

DISCUSSION FORUM

Prasugrel over ticagrelor in non-ST-elevation acute coronary syndromes: is it justified?

Perhaps the most surpri update is the recommendation on antithrombotic treatment a out persistent ST-segmer

some criticisms on the reliability c REACT 5 trial due to its open-lab double-blinded TRIT phone follow-up in 8

requires once-daily dosing. Although the reported percentages of patients who followed the instructions for the two study drugs were close to perfect (more than 99% for both study drugs), underestimation of the phenomenon of non-adherence to the recommended therapy was likely considering that the atients were

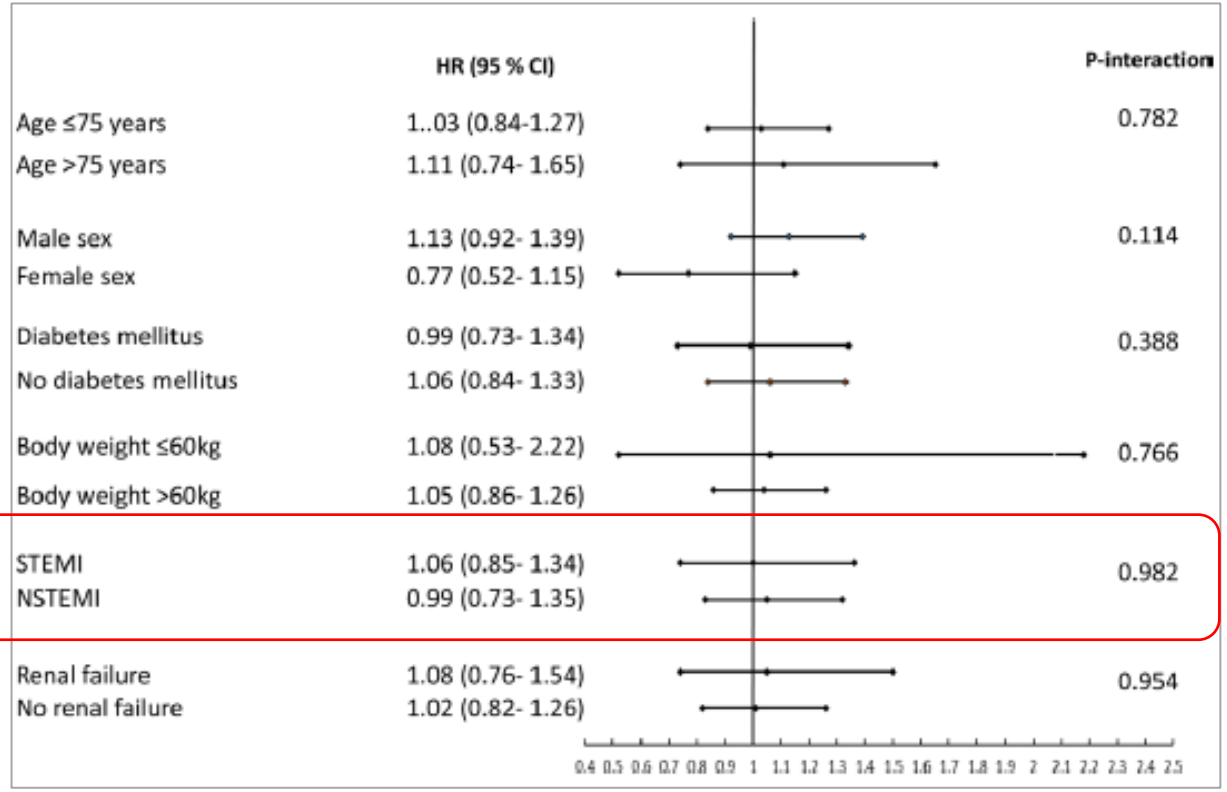
With clear limitations of the ISAR-REACT 5 trial, we feel that it may be premature to recommend in this broadly referenced guideline for prasugrel in favour of ticagrelor among patients with ACS presenting without persistent ST-segment elevation who would undergo PCI. Indeed, we believe that the findings of ISAR-REACT 5

	TICAGRELOR	PRASUGREL
Active form	Parent drug active, also active metabolite	Parent is a prodrug, hepatic conversion to active metabolite
Plasma half-life of active form(s)	8–12 hours	Distribution half-life (most relevant to pharmacodynamic effect): 30 min Elimination half-life: 7 hours
Mode of binding to $P2Y_{12}$ receptor	Reversible, allosteric binding site	Irreversible, blocks ADP binding site
Standard loading dose	180 mg, onset of action within 30–60 min	60 mg, onset of action within 30–60 min
Platelet inhibition after standard loading doses	IPA ~65% at 2 hours*	IPA ~65% at 2 hours †
Maintenance dose	90 mg two times per day in the first year after ACS; 60 mg two times per day after the first year	10 mg once a day; 5 mg once a day if body weight is <60 kg or age is ≥75 years
Platelet inhibition after maintenance dose	90 mg: IPA ~66%*	10 mg: IPA ~58%† 5 mg (at mean body weight 85 kg): IPA ~35%†
Absorption	Intestinal, delayed by opiates	Intestinal, delayed by opiates
Drug interactions	Strong CYP3A inducers reduce effect, strong CYP3A inhibitors reduce elimination	Minor CYP interactions
Pharmacogenetics	Minor genetic effects on drug levels	Minor genetic effects on hepatic metabolism
Time to recover near-normal platelet reactivity after cessation	4–5 days	7 days
Methods of reversal	Cytosorb haemadsorption during cardiopulmonary bypass, antibody antidote (in development)	Platelet transfusion

the SWEDEHEART registry, all patients with **MI treated with PCI** and discharged on prasugrel or ticagrelor from 2010 to 2016

	Prasugrel	Ticagrelor	
Patients, n	2073	35 917	
	Events, n (%)		**HR (95% CI)**
MACCE			
Crude	127 (6.1)	2196 (6.1)	1.00 (0.84 to 1.20)
MV analysis			1.03 (0.86 to 1.24)
IPTW weighting			1.11 (0.87 to 1.40)
PSM cohort*	127 (6.1)	122 (5.9)	1.04 (0.81 to 1.33)

In the unadjusted model (crude) only treatment was included as covariate. In the multivariable model 34 additional covariates were included. Using the same covariates, the individual propensity score, reflecting the probability to be treated with prasugrel, and propensity score weights (IPTW) were calculated. IPTW Cox regression models were constructed.
*Propensity matching resulted in a population of 4142 patients (PSM cohort), 2071 in each group.



Heart 2021;107:1145–1151

Comparative efficacy and safety of ticagrelor vs. prasugrel in patients undergoing PCI for NSTE-ACS. Results of the prospective ALKK-Registry.

Authors:
U Zeymer[1], M Hochadel[2], V Schaechinger[3], R Zahn[1], [1]Klinikum Ludwigshafen - Ludwigshafen - Germany , [2]Stiftung Institut fuer Herzinfarktforschung - Ludwigshafen - Germany , [3]Fulda Heart-Thorax- Cli

Topic(s):
Pharmacotherapy

Background. Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor has become standard of care for patients with NSTE-ACS. Guidelines recommend prasugrel and ticagrelor over clopidogrel. In the l ticagrelor in NSTE-ACS patients. We evaluated the outcome of patients undergoing PCI for NSTE-ACS in a large number of patients in real life and compared patients treated with prasugrel and ticagrelor.
Methods. We used the data of the prospective German ALKK-PCI registry and included patients treated with prasugrel or ticagrelor and undergoing PCI for NSTE-ACS treated in 42 centers. Baseline varia therapies and in-hospital outcomes were centrally collected and analysed. Patients with cardiogenic shock were excluded.
Results. Between 2011 and 2020 a total of 7888 patients < 75 years without prior stroke undergoing PCI for NSTE-ACS were included. Of these 4905 (62.2 %) patients were treated with ticagrelor and 29 Baseline characteristics, procedural features and in-hospital outcomes are given in the table.
Conclusion. In clinical practice in patients with NSTE-ACS undergoing PCI ticagrelor was used more often than prasugrel. Ticagrelor treated patients were older and had more comorbidities. Despite this high hospital mortality and the short-term safety profile were comparable in both groups.

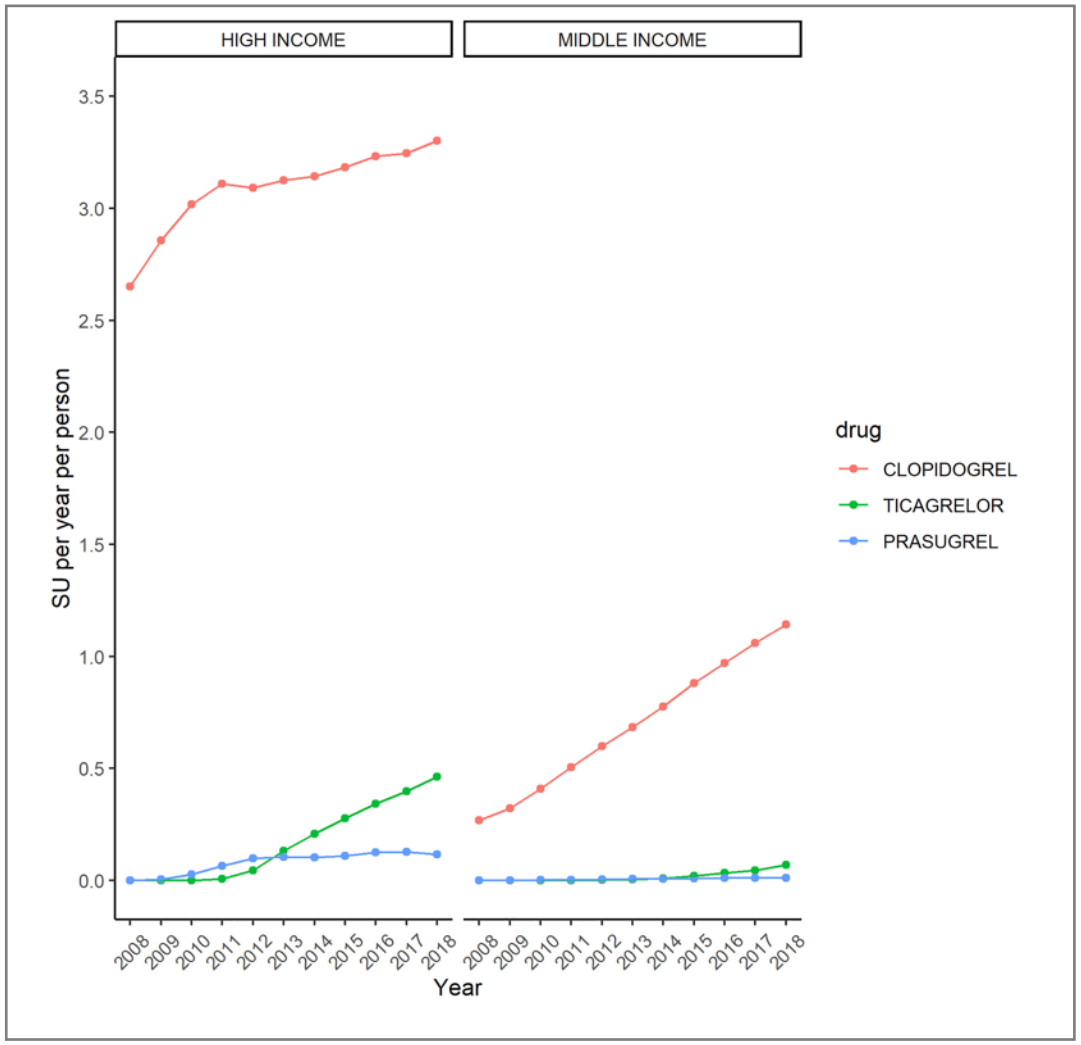
	Ticagrelor (n=4905)	Prasugrel (n=2983)	p-value
Mean Age (years)	61.7	59.5	< 0.001
Women	22.0 %	18.3 %	< 0.001
Peripheral artery disease	7.3 %	4.3 %	< 0.001
Renal insufficiency	12.9 %	9.4 %	< 0.001
Diabetes mellitus	26.3 %	23.9 %	0.02
Ejection fraction < 40%	14.9 %	9.7 %	< 0.001
Left-main coronary artery disease	4.6 %	3.8 %	0.1
3-vessle coronary artery disease	32.9 %	31.0 %	0.07
Immediate multivessel PCI	10.1 %	7.9 %	< 0.001
TIMI 3 flow after PCI	93.6 %	93.1 %	0.8
GP IIb/IIIa-Inhibitors	10.0 %	15.6 %	< 0.001
Non-fatal Stroke	0.2 %	0.1 %	0.6
Bleeding	1.8 %	2.1 %	0.09
In-hospital mortality	1.2 %	1.1 %	0.8
MACCE	1.4 %	1.2 %	0.3

ESC 2022

Preference Prasu- před Ticagrelorem u NSTE ACS

- Je adhrence k doporučením reálná?

Global trends in $P2Y_{12}$ sales stratified by income level from 2008 to 2018



Am Heart J Plus: Cardiology Research and Practice 2021

ČR

Rok	Unikátní pacienti léčení TIKAGRELOR	Unikátní pacienti léčení PRASUGREL
2011		13
2012	261	175
2013	1 347	394
2014	1 956	876
2015	2 274	1 021
2016	2 992	1 030
2017	4 938	911
2018	7 533	690
2019	9 614	599
2020	10 138	566
2021*	10 409	612

* data konce roku 2021 dosud zčásti nedohlášena

Data UZIS

A 2022 joint consensus initiative

EAPCI
European Association of Percutaneous Cardiovascular Interventions

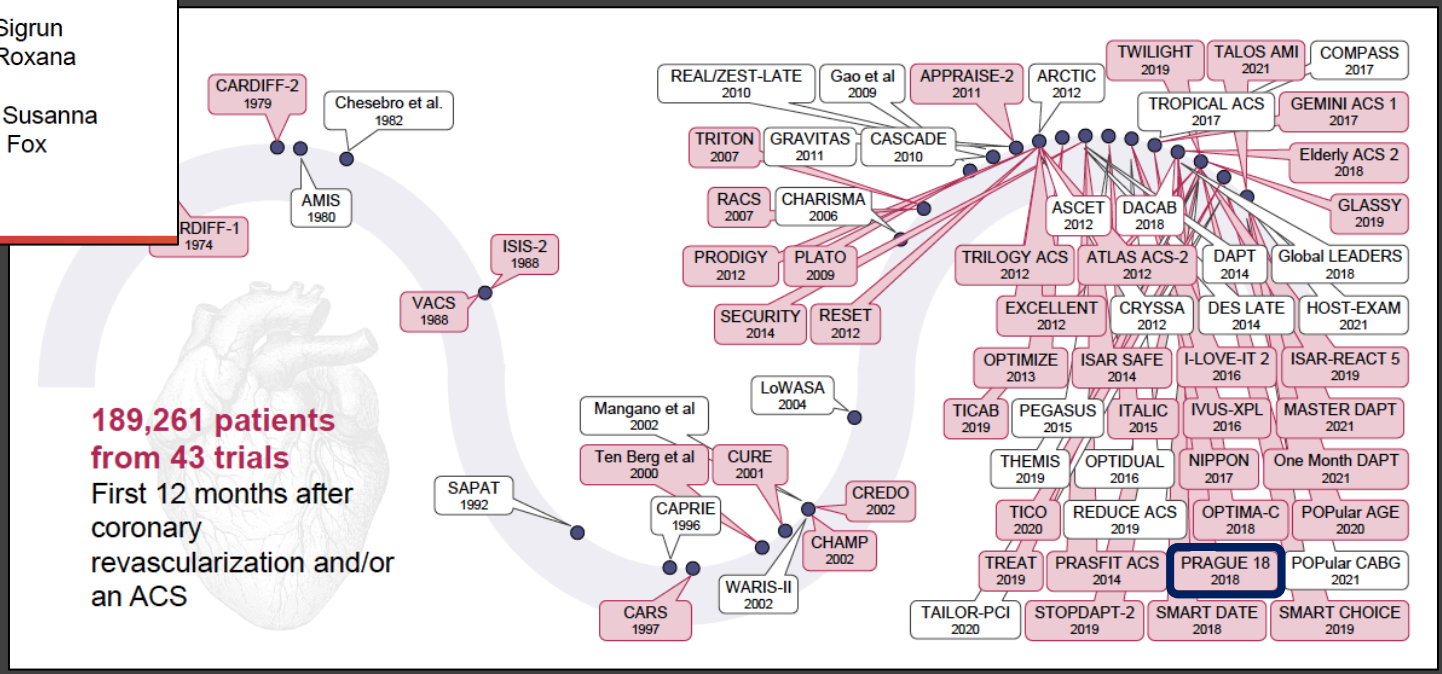
ACVC
Association for Acute CardioVascular Care

EAPC
European Association of Preventive Cardiology

Antithrombotic treatment strategies in patients with established coronary artery disease

2022 joint consensus statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Association for Acute Cardiovascular CardioVascular Care (ACVC) and European Association of Preventive Cardiology (EAPC)

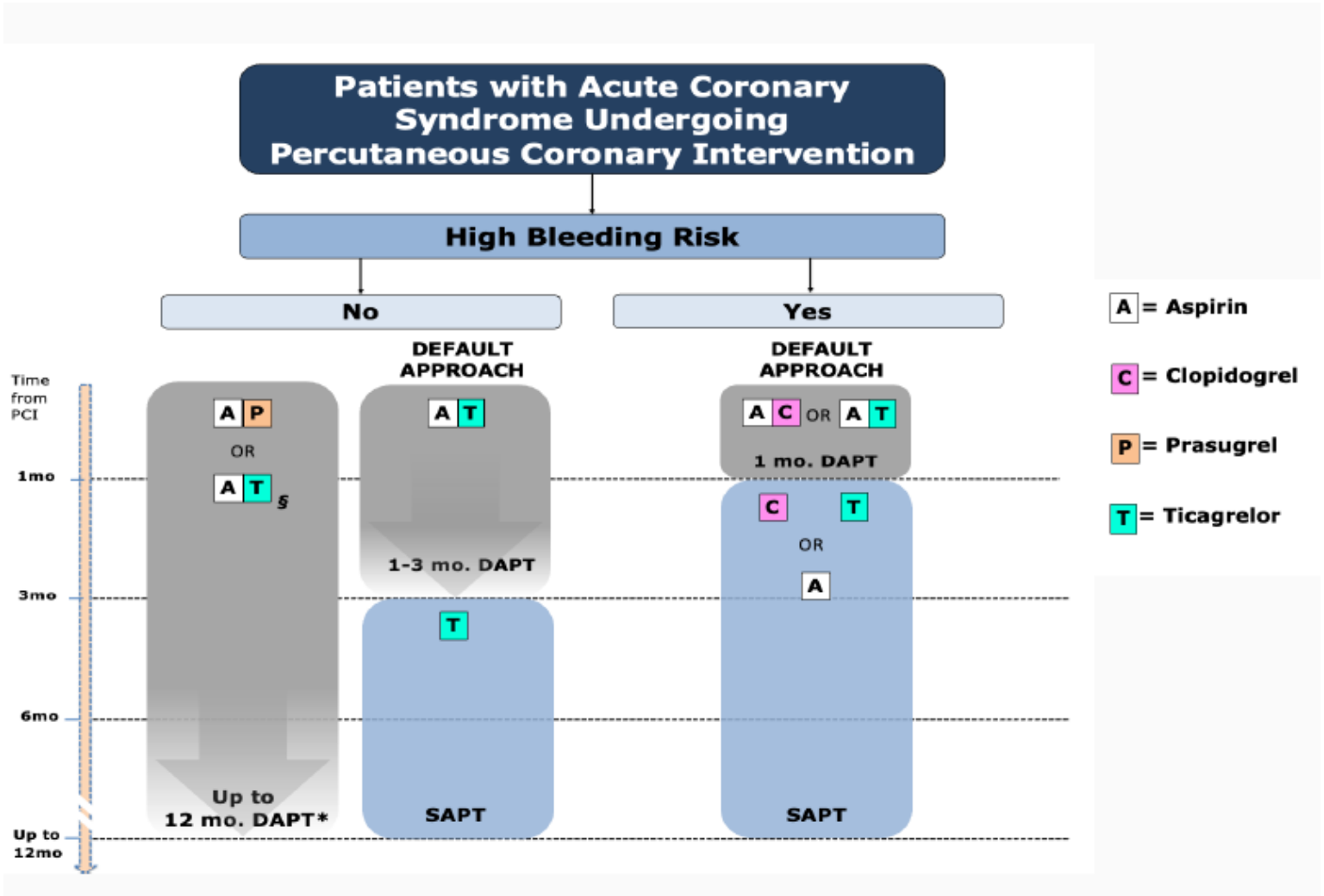
Marco Valgimigli, Victor Aboyans, Dominick Angiolillo, Dan Atar, Davide Capodanno, Sigrun Halvorsen, Stefan James, Peter Jüni, Vijay Kunadian, Antonio Landi, Sergio Leonardi, Roxana Mehran,
Gilles Montalescot, Eliano Pio Navarese, Josef Niebauer, Angelo Oliva, Raffaele Piccolo, Susanna Price, Robert F Storey, Heinz Völler, Pascal Vranckx, Stephan Windecker, Keith A.A. Fox



189,261 patients from 43 trials

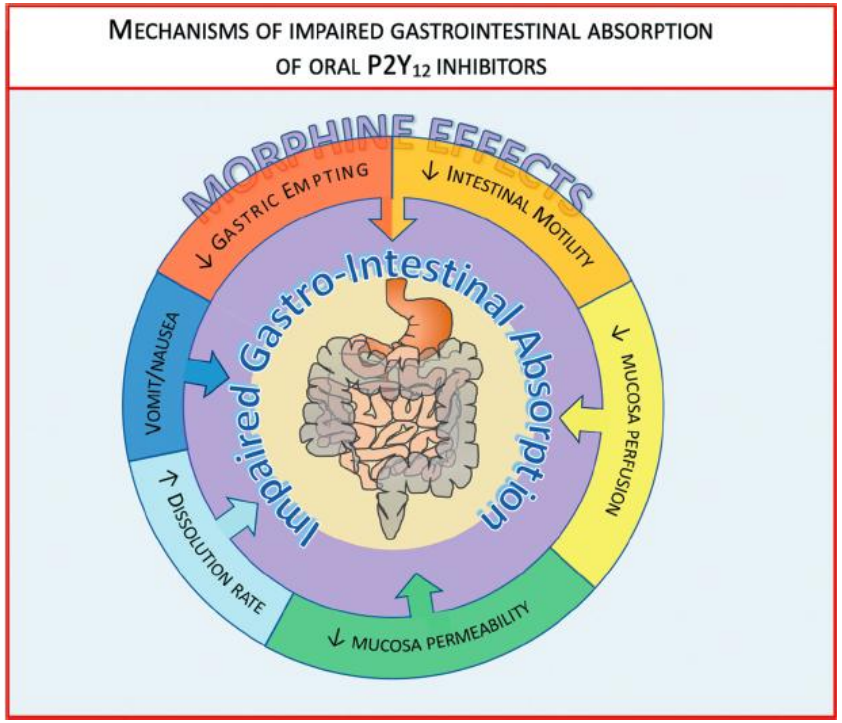
First 12 months after coronary revascularization and/or an ACS

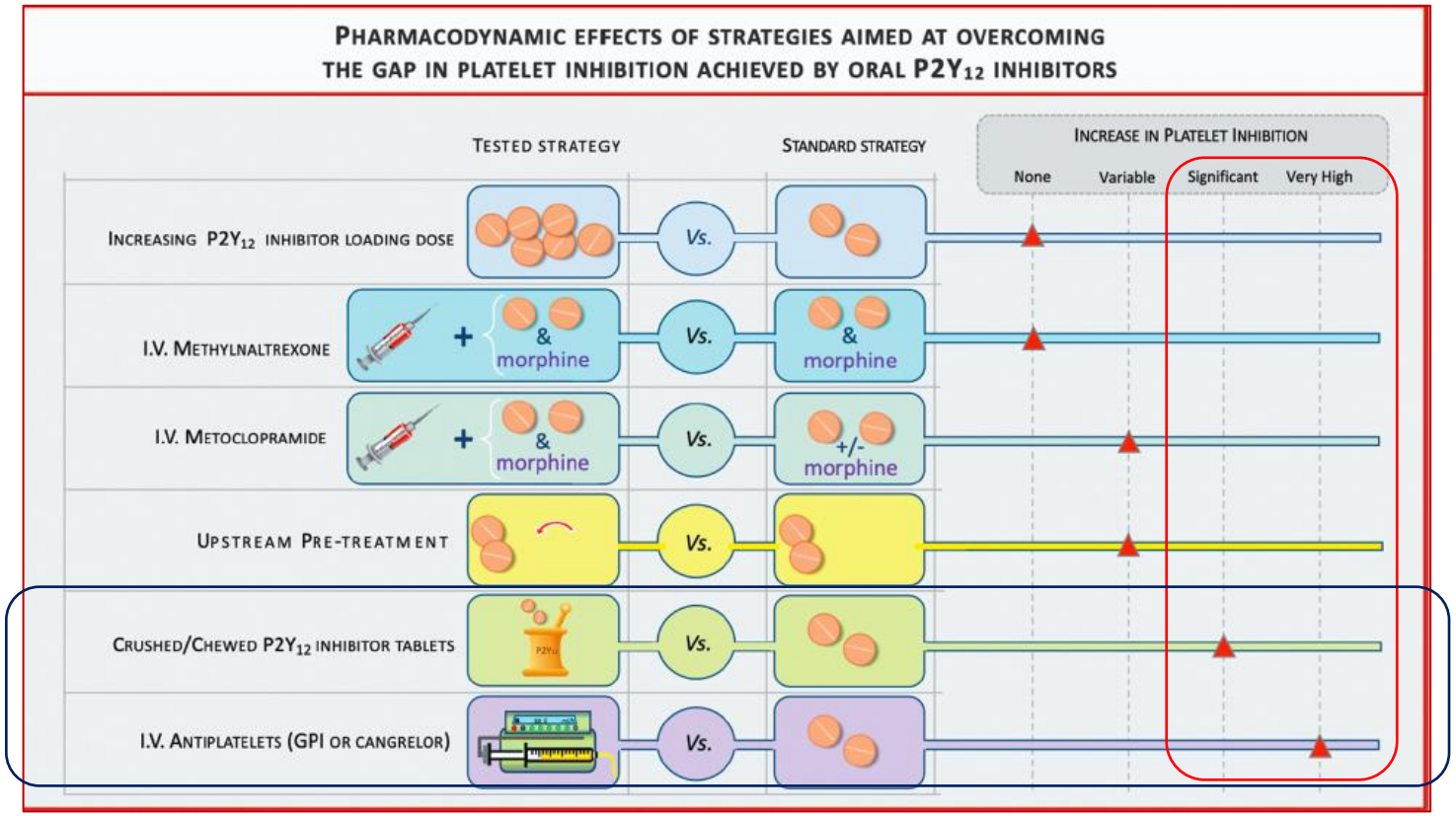
ESC 2022


Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention
High Bleeding Risk
No
Yes
DEFAULT APPROACH
DEFAULT APPROACH
Time from PCI
1mo
3mo
6mo
Up to 12mo
A P
OR
A T §
A T
1-3 mo. DAPT
T
Up to 12 mo. DAPT*
SAPT
A C OR A T
1 mo. DAPT
C T
OR
A
SAPT
A = Aspirin
C = Clopidogrel
P = Prasugrel
T = Ticagrelor

ESC 2022

Limitace p.o. antitrombotik

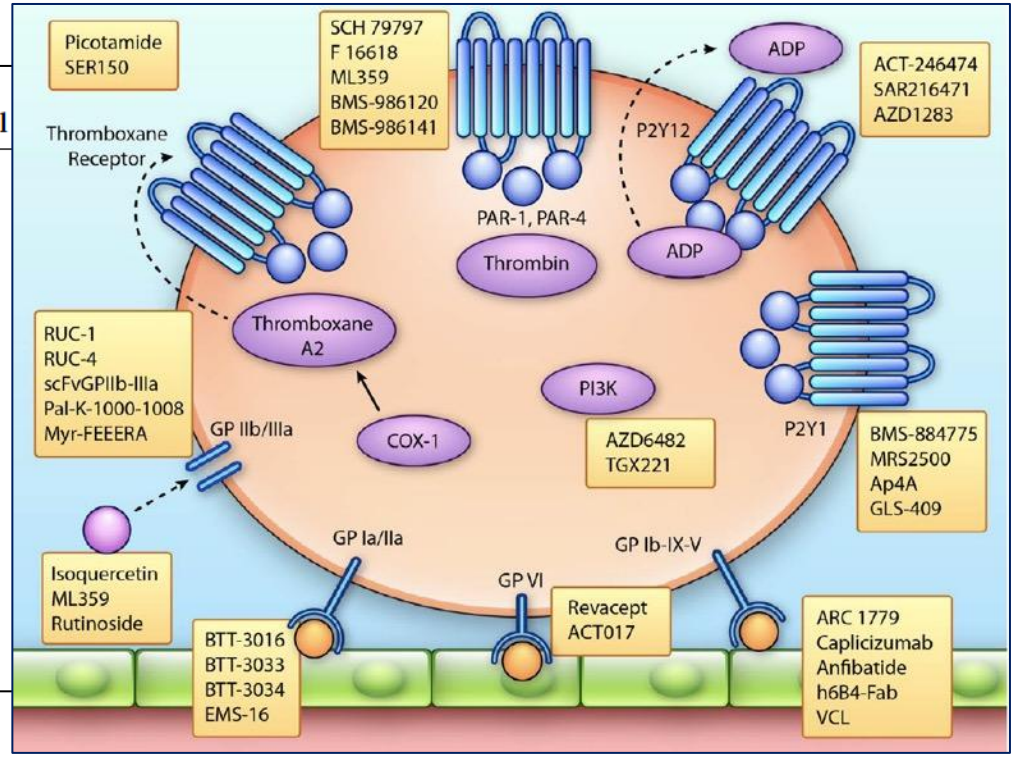




Expert Review of Cardiovascular Therapy 2021

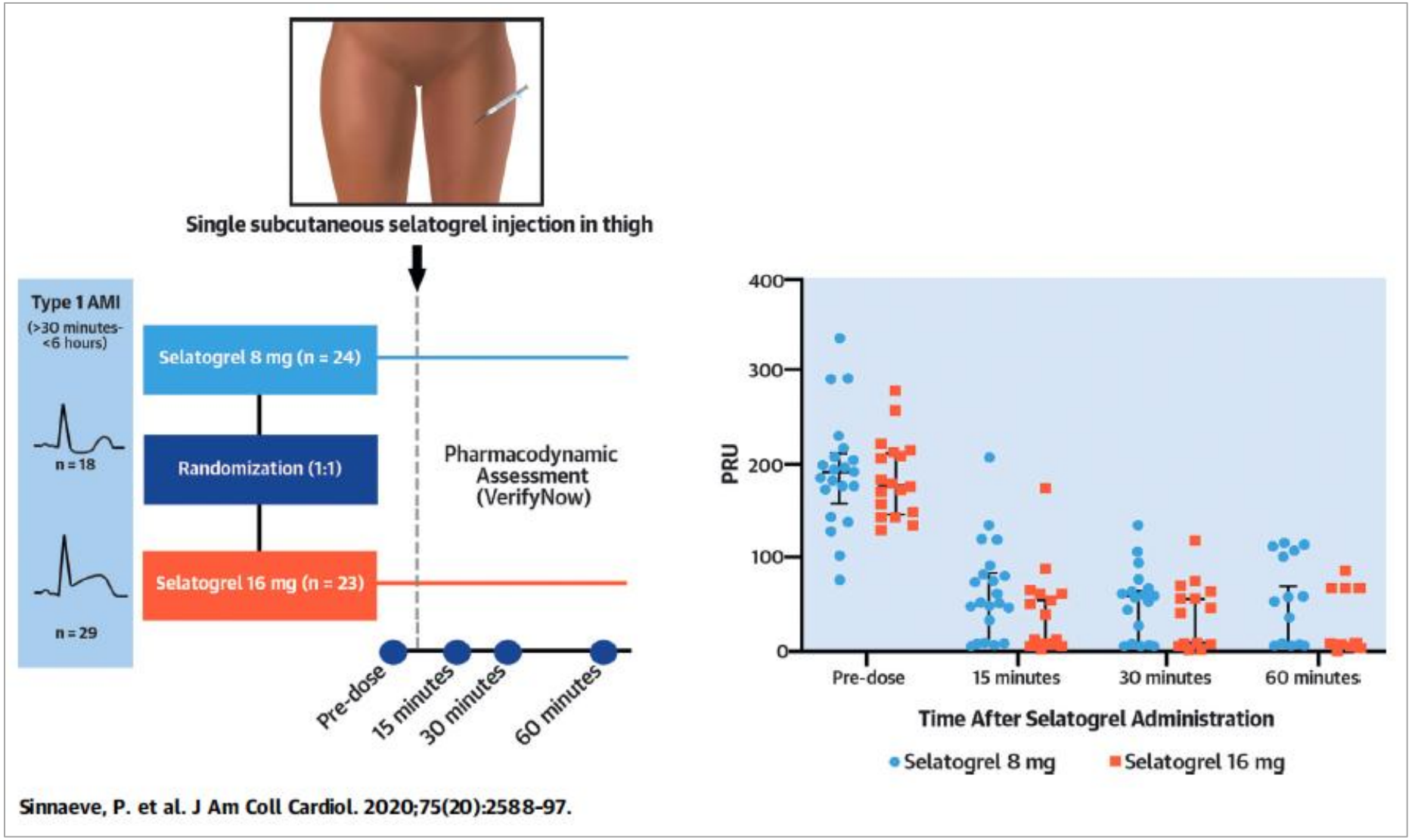
Nové protidestičkové léky v klinickém hodnocení

Name	Company	Type	Route of Administration	Target	Completed Clinical Trial
PZ-128	Tufts Medical Center	Pepducin	IV	PAR1	Phase I
BMS-986120	Bristol-Myers Squibb	Small molecule	oral	PAR4	Phase I
BMS-986141	Bristol-Myers Squibb	Small molecule	oral	PAR4	Phase I Phase II
Revacept	Advance Cor	Fusion protein	IV	GPVI ligand	Phase I Phase II
ACT017	Acticor Biotech	Antibody	IV	GPVI	Phase I
ARC1779	Archemix	DNA aptamer	IV	VWF	Phase I Phase II
AZD6482	AstraZeneca	Small molecule	IV	PI3Kβ	Phase I Phase I
Isoquercetin	Beth Israel NHLBI	Small molecule Small molecule	oral oral	PDI PDI	Phase I Phase II/III



Int J Mol Sci. 2021, 22. 13079, ATVB 2019, 39.

Subcutaneous Selatogrel Inhibits Platelet Aggregation in Patients With Acute Myocardial Infarction



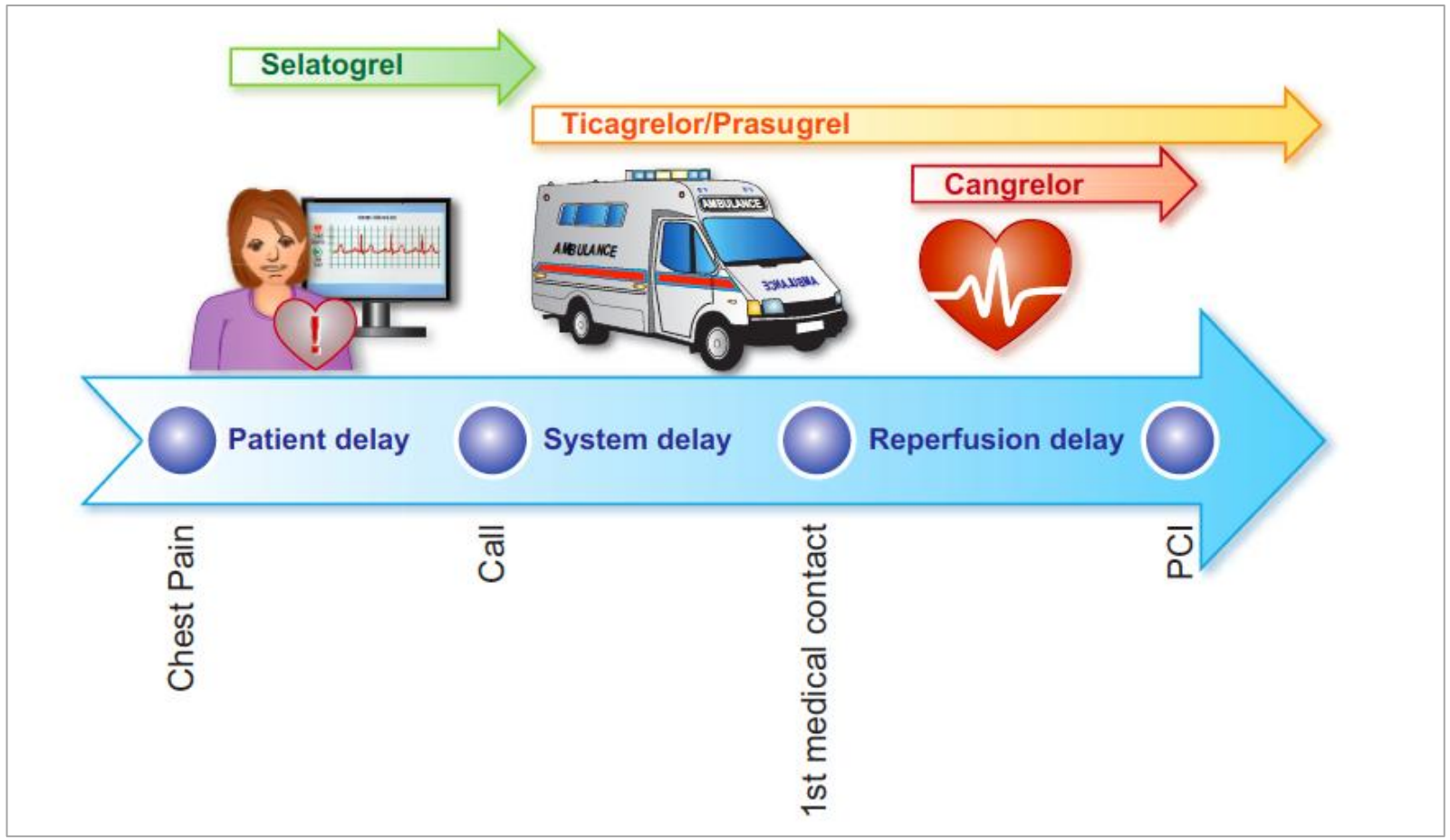
Sinnaeve, P. et al. J Am Coll Cardiol. 2020;75(20):2588-97.

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 3141–3143
doi:10.1093/eurheartj/ehz862

EDITORIAL

Do we need a new $P2Y_{12}$ receptor antagonist?

Jean-Sébastien Hulot [1,2] **and Gilles Montalescot** [3]*



Selatogrel in AMI (phase 3)

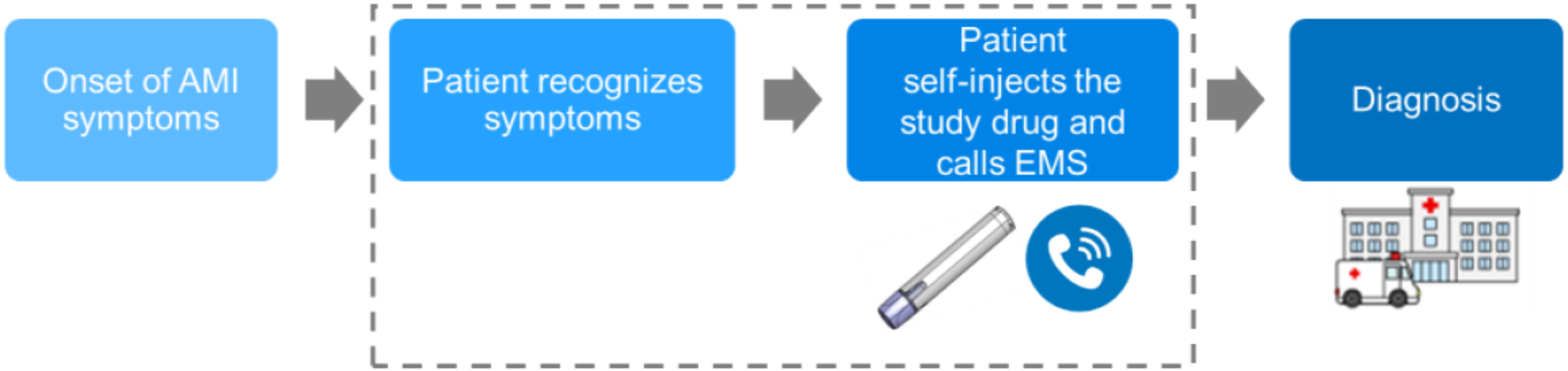
Selatogrel Outcome Study in suspected Acute Myocardial Infarction

SOS AMI

Population:
Patients with an history of AMI at risk of recurrent AMI.

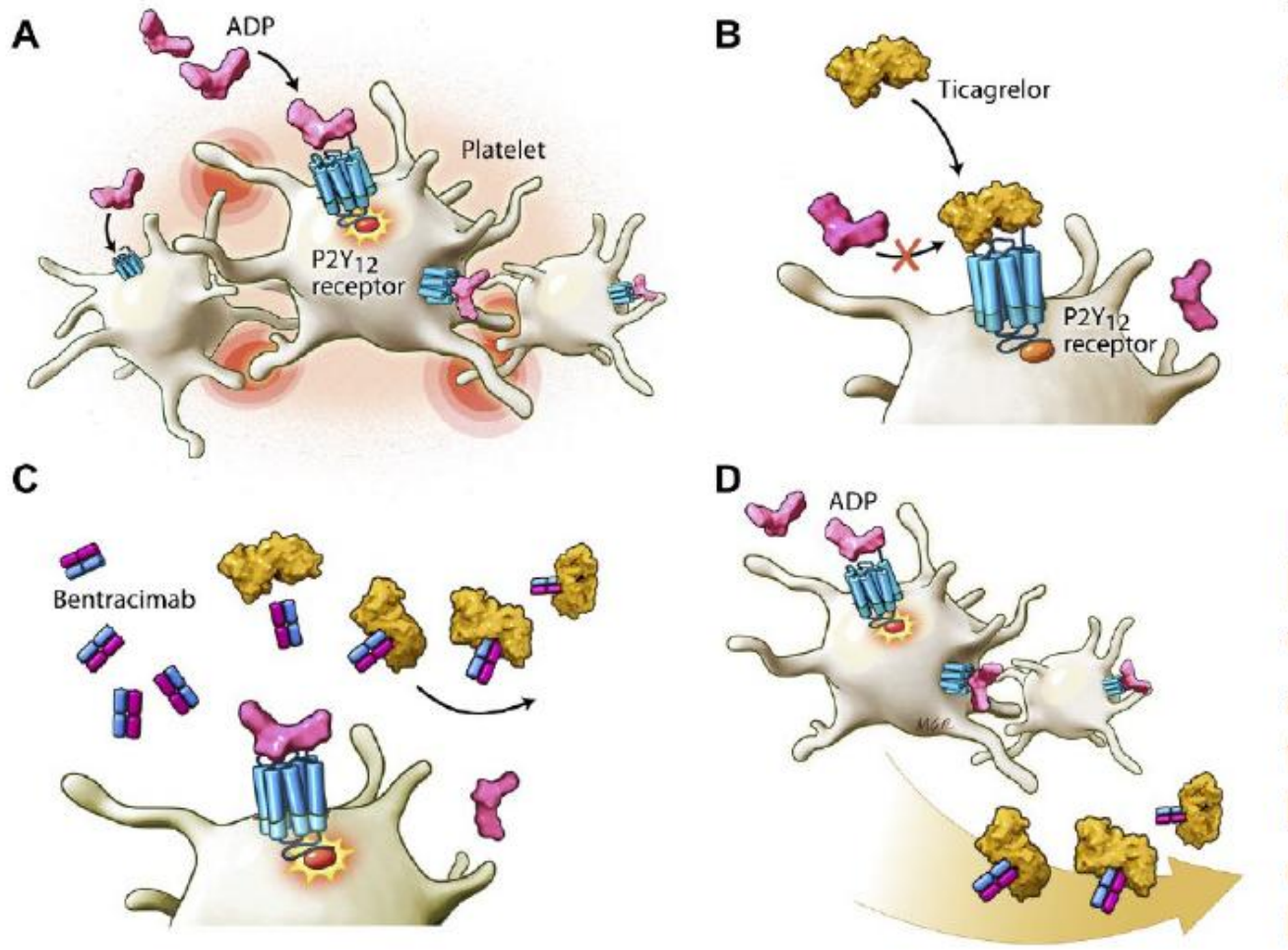
Training:
Participants will be trained on when and how to self-administer study treatment.

Study treatment:
Study drug (selatogrel or placebo) self-administered by patient using a ready-to use integrated drug delivery device.



ClinicalTrials.gov Identifier: NCT04957719

Bezpečnost



1. **Immediate and sustained ticagrelor reversal with bolus + prolonged infusion** of 18 g bentracimab.
2. Significant reversal was observed 5 minutes after initiation of bentracimab infusion.
3. Duration of reversal was infusion-time dependent, lasting 20-24 hours with a 16-hour infusion.

J Am Coll Cardiol. 2021;78:1372-1384

NOVINKY V PROTIDESTIČKOVÉ LÉČBĚ ICHS

LÉKY

Efektivita

→ Preference Prasu- před Ticagrelorem

→ „Bridge“ do plné účnnosti p.o. iP2Y$_{12}$

Bezpečnost

→ Antidota

POSTUPY

Efektivita a bezpečnost

→ Intenzita dlouhodobé léčby

Je Aspirin potřebný jako součást DAPT a esenciální lék pro SAP dlouhodobě po PCI?

→ Monoterapie Ticagrelorem 3 měsíce po PCI u pacientů bez MACE s vysokým ischemickým a krvácivým rizikem (studie TWILIGT -subanalýza)

→ Ukončení DAPT u pacientů s vysokým rizikem krvácení po 1 měsíci bez MACE po PCI (MASTER DAPT)

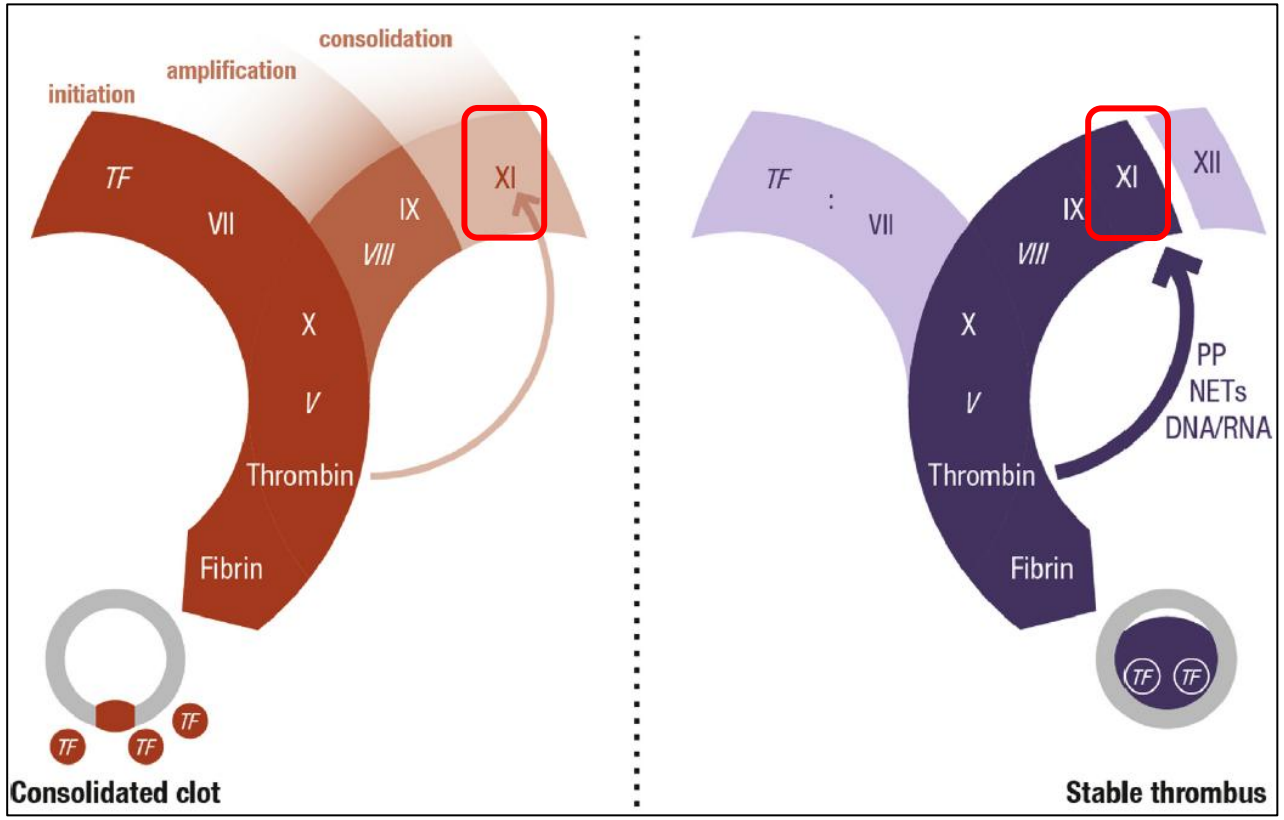
→ Clopidogrel místo ASA 6-8 měsíců po PCI dlouhodobě (studie HOST EXAM)

NOVINKY V ANTITROMBINOVÉ(ANTIKOAGULAČNÍ) LÉČBĚ

LÉKY

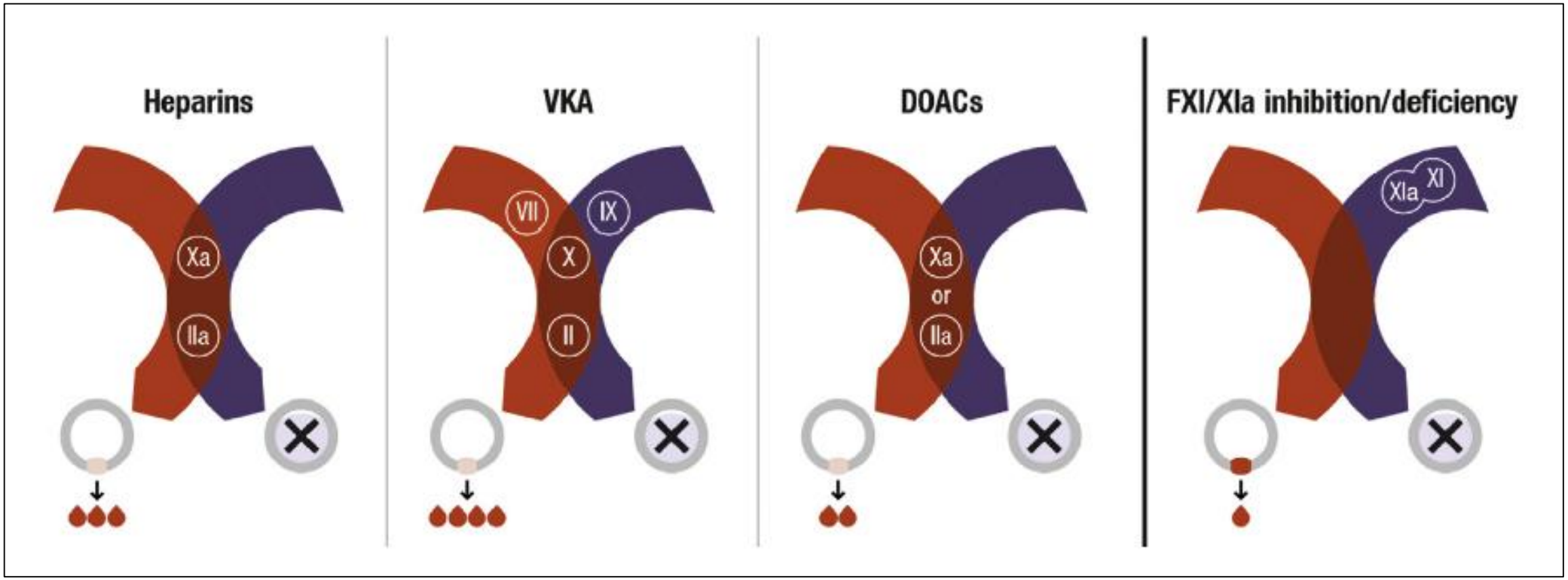
Efektivita/ Bezpečnost

→ Inhibitory f. XI

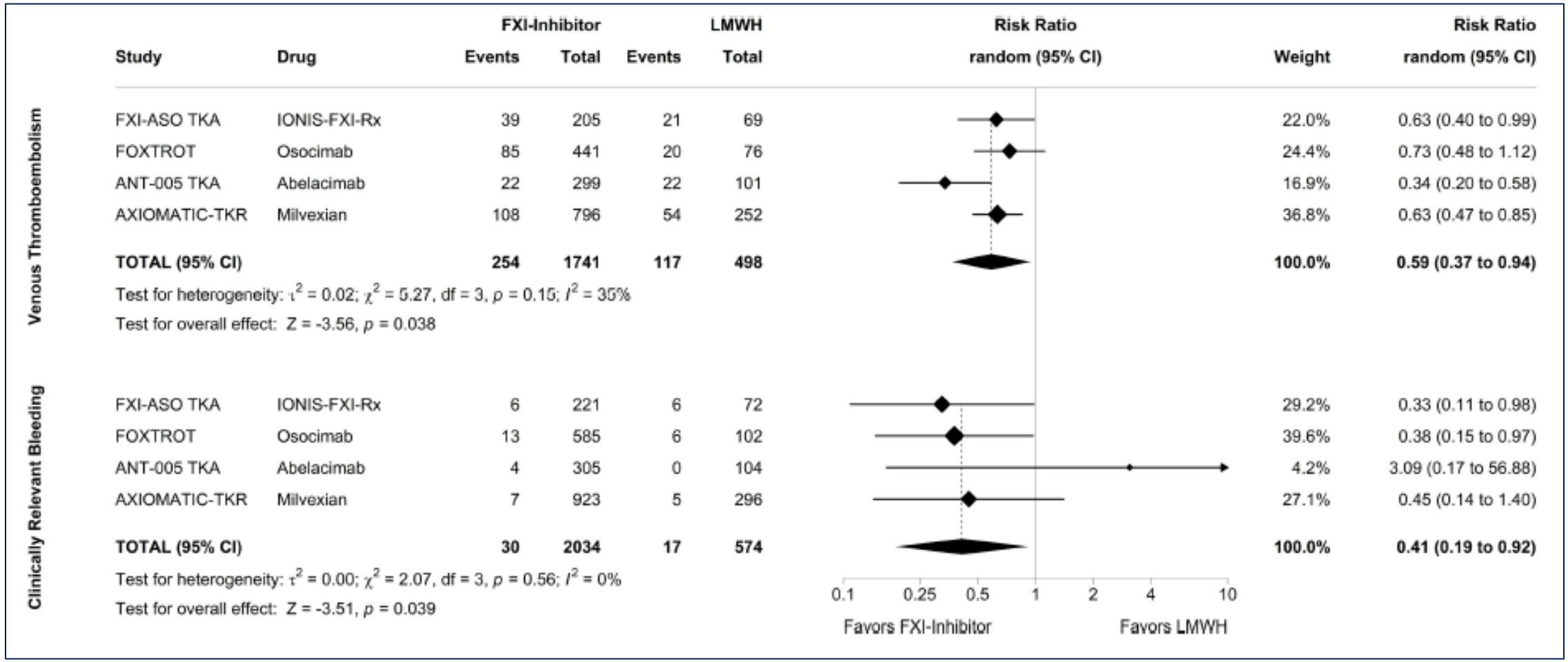


J Am Coll Cardiol 2021;78:625–631

Factor XI Inhibition to Uncouple Thrombosis From Hemostasis



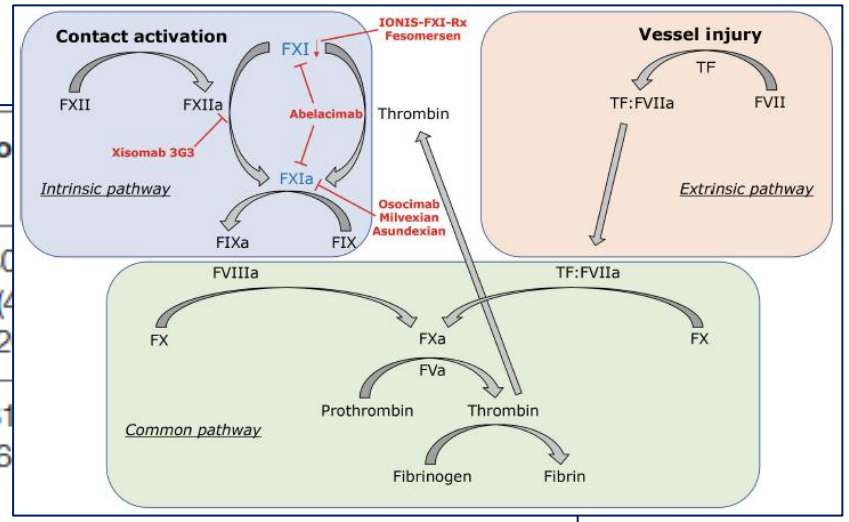
J Am Coll Cardiol 2021;78:625–631



Front Cardiovasc Med 2022;9:903029.

Drug	Type	Mechanism	Administration route	Studies (NCT)	Populatio		
IONIS-FXI$_{Rx}$	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT01713361 NCT02553889 NCT03358030	TKA (30 ESKD (4 ESKD (2		
Osocimab	Monoclonal antibody to FXIa	Binds and inhibits FXIa	Intravenous, subcutaneous (monthly)	NCT03276143 NCT04523220	TKA (81 ESKD (6		
Abelacimab	Monoclonal antibody to FXI/FXIa	Binds and inhibits FXI and FXIa	Subcutaneous (monthly)	EudraCT 2019-003756-37 NCT04755283 NCT05171049 NCT05171075	TKA (412) AF (1,200) CAT (1,655) CAT (1,020)	Enoxaparin Rivaroxaban Apixaban Dalteparin	Published Ongoing Ongoing Ongoing
Milvexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT03891524 NCT03766581	TKA (1,242) Stroke (2,366)	Enoxaparin Placebo	Published Ongoing
Xisomab 3G3	Monoclonal antibody to FXI	Binds FXI and blocks activation by FXIIa	Intravenous (single dose)	NCT03612856 NCT04465760	ESKD (24) CRT (50)	Placebo None	Published Ongoing
Fesomersen	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT04534114	ESKD (305)	Placebo	Ongoing
Asundexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT04218266 NCT04304534 NCT04304508	AF (753) AMI (1,592) Stroke (1,790)	Apixaban Placebo Placebo	Published Completed Ongoing

AF, atrial fibrillation; CAT, cancer-associated thrombosis; CRT, catheter-related thrombosis in cancer patients; ESKD, end-stage kidney disease; TKA, total knee arthroplasty.



Inhibitors of factor XI: game changers of anti-thrombotic therapy?

Eugene Braunwald *

New findings

Up to 28 August 2022, clinical observations of FXI inhibitors were limited largely to normal subjects, to patients undergoing knee arthroplasty, a procedure with a high incidence of VTE, and to patients with atrial fibrillation. On this date, three Phase 2 dose-ranging placebo-controlled trials on patients with arterial disease were presented at the meeting of the European Society of Cardiology.

In the PACIFIC AMI trial,[12] Rao *et al.*[13] compared asundexian with placebo in patients with a recent acute myocardial infarction receiving dual antiplatelet therapy. While FXI was markedly inhibited without a significant increase in bleeding, no change in recurrent ischaemic events was observed. The PACIFIC-STROKE trial was carried out in patients with a recent non-cardioembolic ischaemic stroke on dual antiplatelet therapy. The highest dose of asundexian was associated with a non-significant trend of excessive bleeding without reduction of the primary endpoint, i.e. ischaemic stroke or covert infarct on magnetic resonance imaging. The AXIOMATIC-SSP trial compared milvexian[11] with placebo in patients with a recent ischaemic stroke or transient ischaemic event receiving antiplatelet therapy. Again, there was a trend of excessive bleeding, but no clear reduction of the primary endpoint—overt ischaemic stroke or covert brain infarct.

EHJ 2022

2020 ESC NSTE-ACS Guidelines

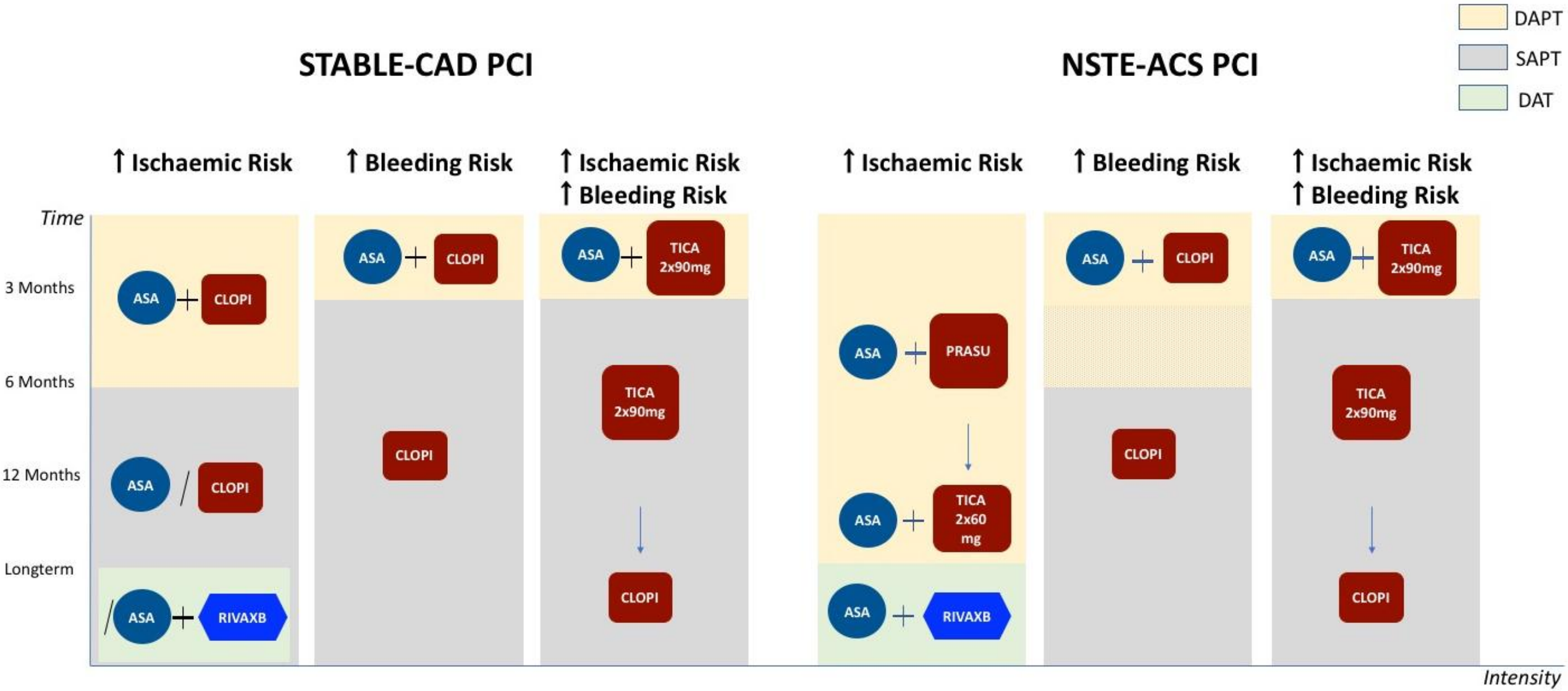
After stent implantation in patients undergoing a strategy of DAPT, stopping aspirin after 3–6 months should be considered, depending on the balance between the ischaemic and bleeding risk.[208,209,227]	IIa	A

2021 ACC/AHA/SCAI Guidelines

Recommendation for Dual Antiplatelet Therapy in Patients After PCI
Referenced studies that support the recommendation are summarized in Online Data Supplement 44.

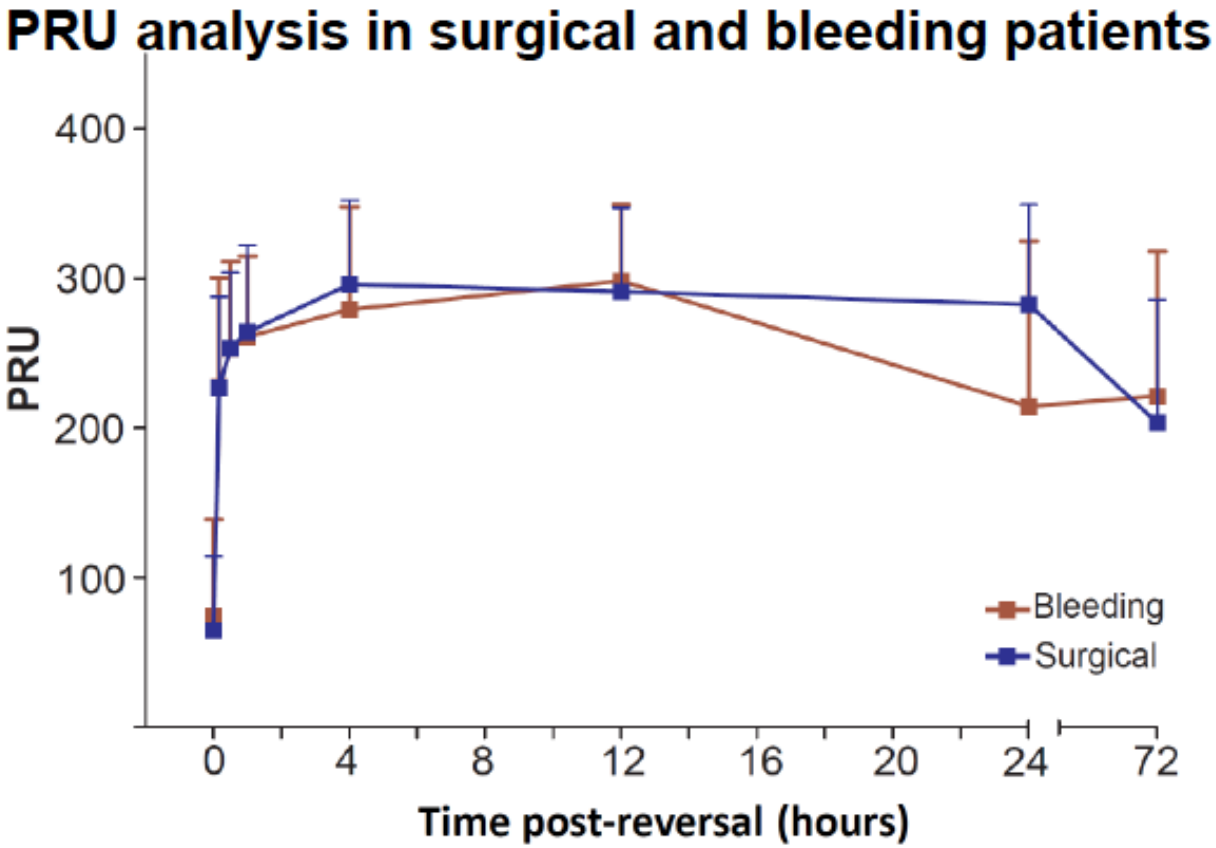
COR	LOE	RECOMMENDATION
2a	A	1. In selected patients undergoing PCI, shorter-duration DAPT (1-3 months) is reasonable, with subsequent transition to P2Y12 inhibitor monotherapy to reduce the risk of bleeding events (1-4).

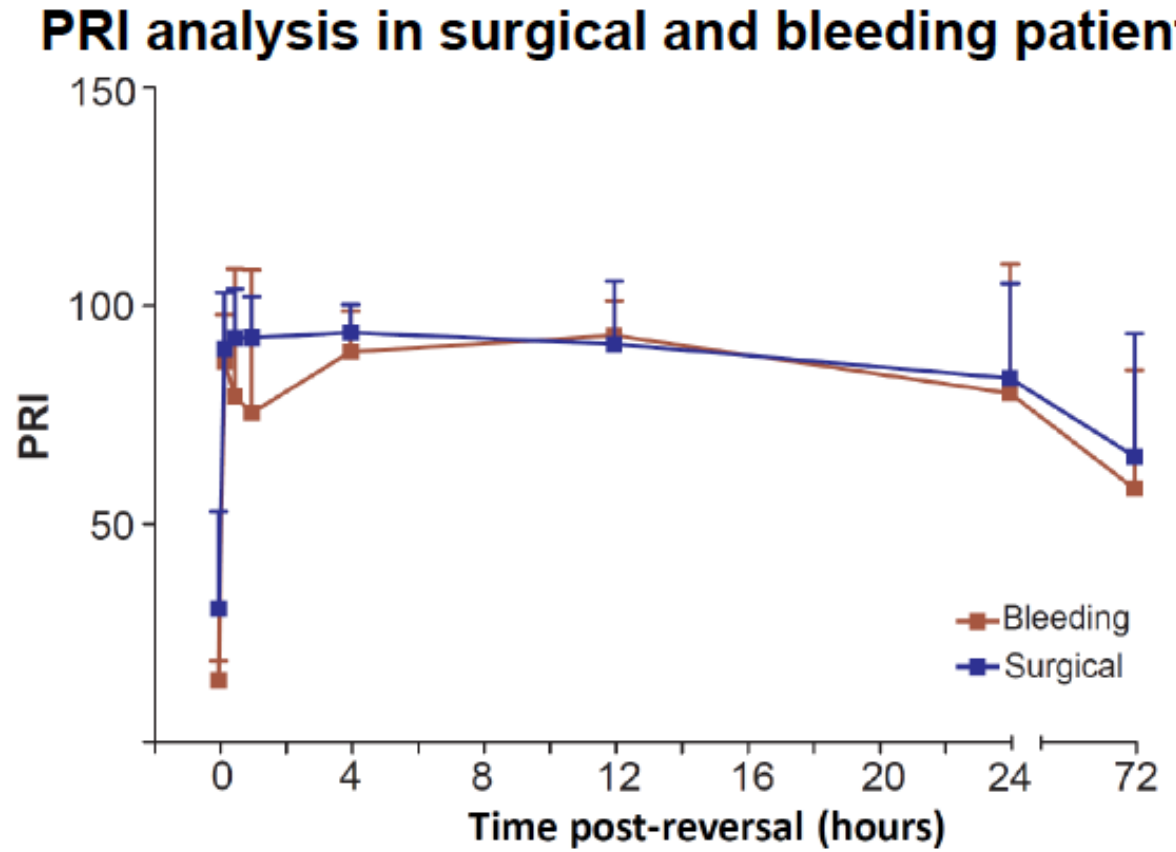
Lawton JS, et.al. Circulation. 2022 Jan 18;145(3):e18-e114;
Collet JP et al. Eur Heart J. 2021 Apr 7;42(14):1289-1367



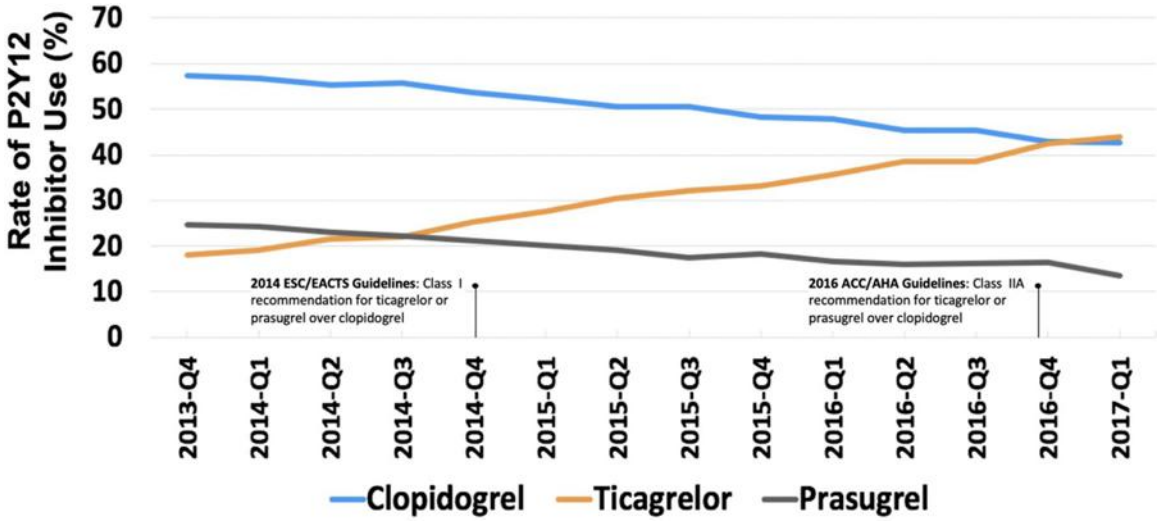
Motovska Z, Montalescot G, Eur Heart J 2021

REVERSE-IT: Reversal in Surgical and Bleeding Pts



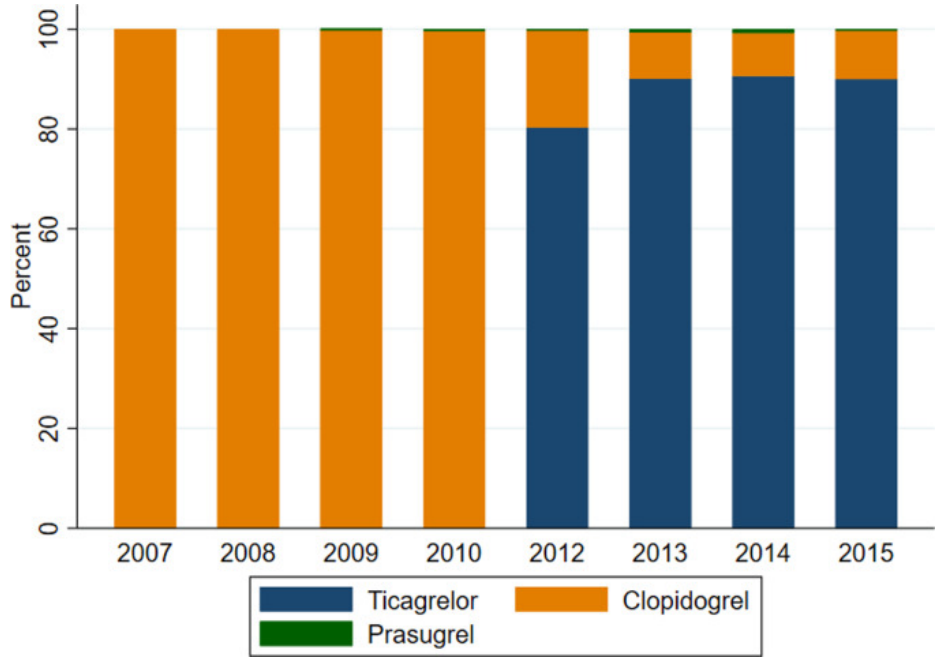


No Platelet Rebound Activity



National rates of P2Y12 inhibitor use at STEMI hospital discharge

Circulation: Cardiovas Quality Outcomes. 2020;13:e006275



The Lancet Regional Health – Europe, 2022; 14: 100301

Contraindication	clopidogrel	prasugrel	ticagrelor
Active bleeding			
Severe liver disorders			
History of ischaemic stroke	Within 7 days		
History of TIA			
History of intracranial haemorrhage			
Use of oral anticoagulants			
Age ≥ 75 years			
Body weight < 60 kg			

TIA — transient ischaemic attack; blue — can be used; grey — is not recommended; black — should not be used

Kardiologia Polska 2017; 75, 4: 399–408

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