Università degli Studi di Palermo
Facoltà di Medicina e Chirurgia
Scuola di Specializzazione in
Malattie dell'Apparato Cardiovascolare
Direttore: Prof. Salvatore Novo

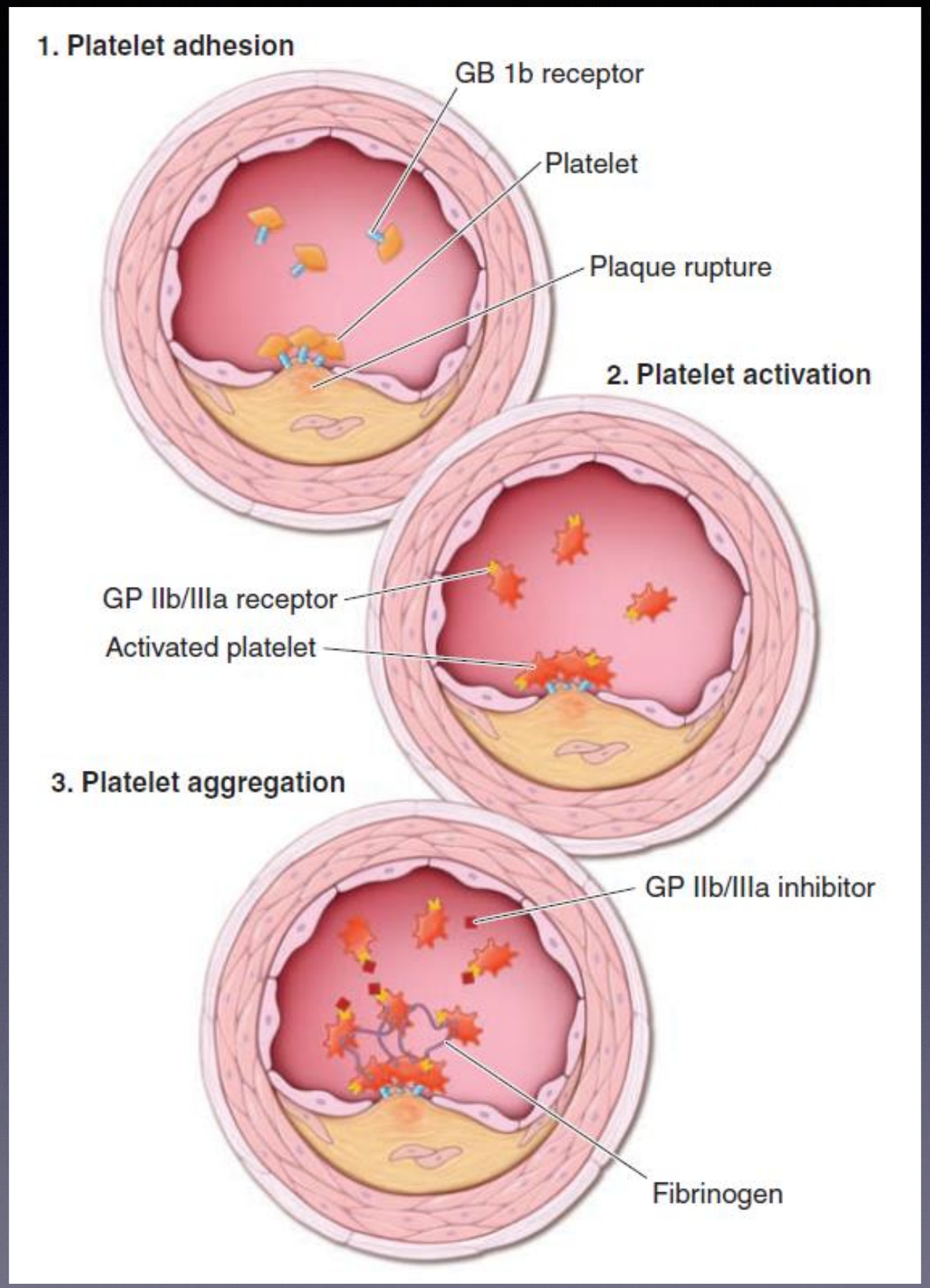
LA DOPPIA TERAPIA ANTIAGGREGANTE PIASTRINICA (DAPT)

Le novità delle Linee Guida ESC 2017

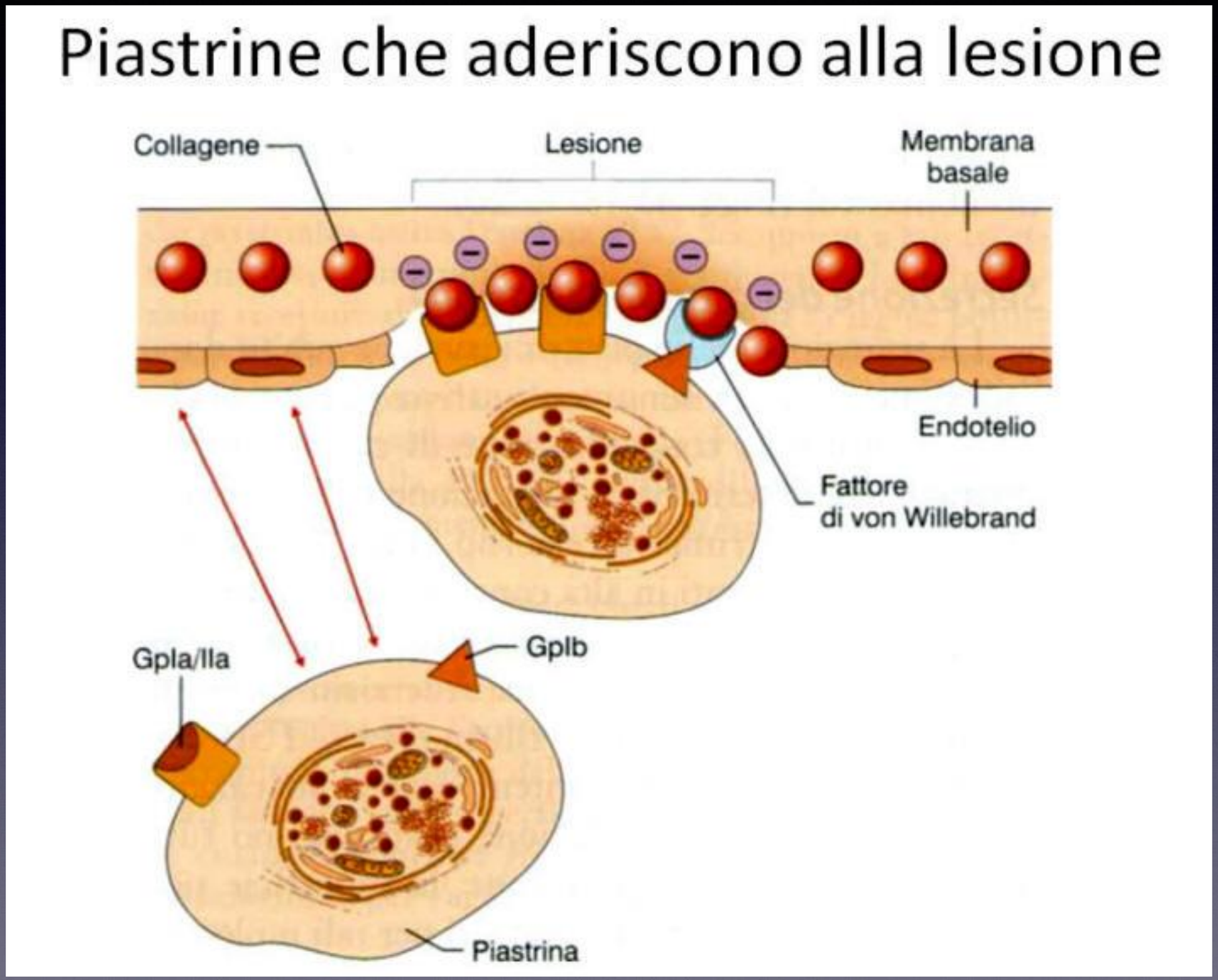
Dott.ssa Marianna Rubino
Dott. Antonino Saladino

Tutor
Prof.ssa Giuseppina Novo

Aggregazione piastrinica



Aggregazione piastrinica



Aggregazione piastrinica

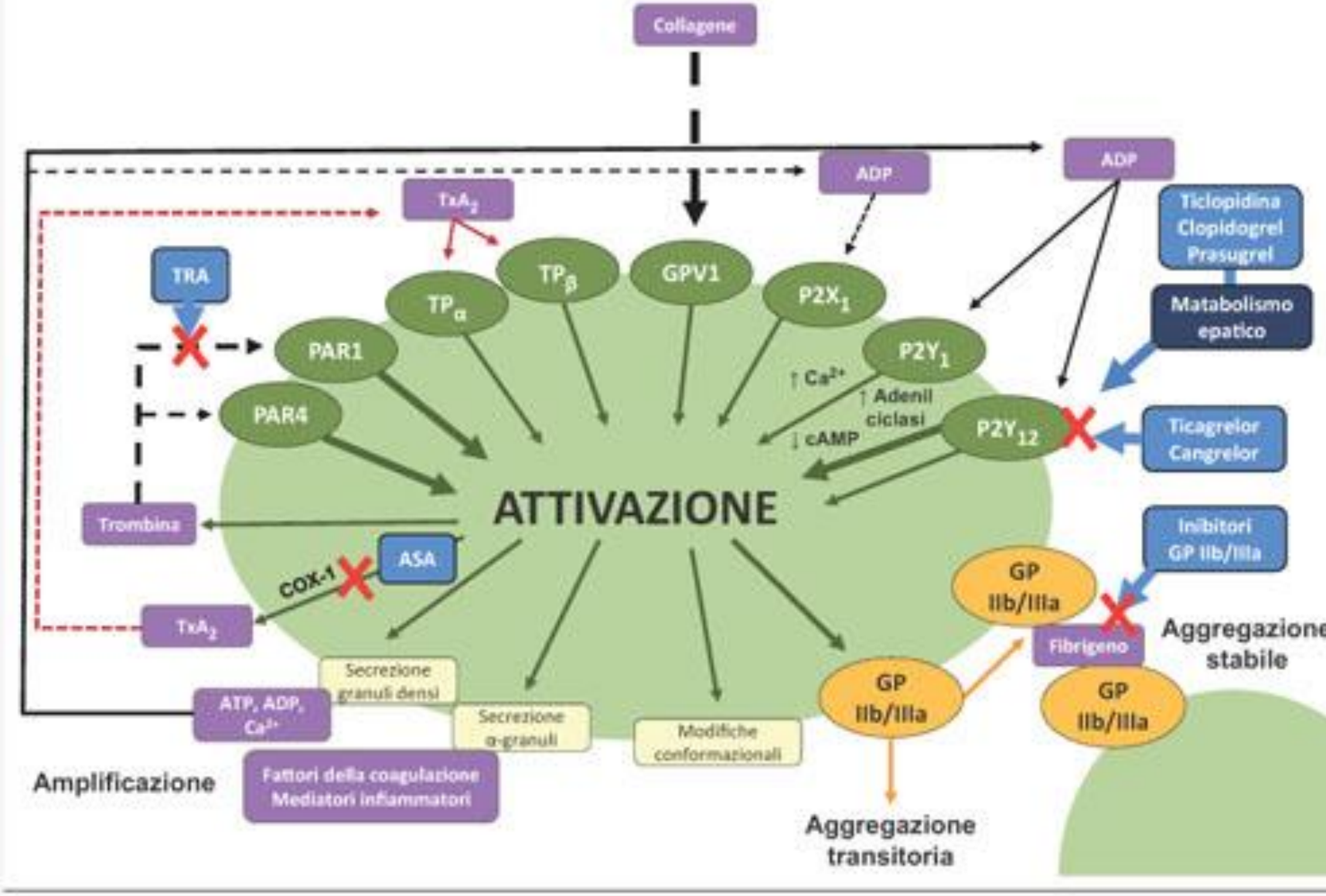


Figura 1. Possibili meccanismi di attivazione piastrinica e modalità d'azione dei principali antiaggreganti piastrinici. ASA, aspirina; COX-1, ciclossigenasi-1; GP, glicoproteina; TRA, antagonisti del recettore della trombina; TxA_2, trombossano A_2.

De Luca L. et al: Documento ANMCO/SICE GISE sulla terapia antiaggregante nelle sindromi coronariche acute G.Ital Cardiol 2013 vol 14 (12):839-866

Antiaggreganti

- FANS: acido acetilsalicilico
- TIENOPIRIDINE: Ticlopidina, Clopidogrel, Prasugrel
- BENZOPIRIMIDINE: Ticagrelor
- Analoghi dell'ATP: Cangrelor
- Inibitori di GpIIbIIIa

Acido acetilsalicilico

- Acido semplice ad assorbimento intestinale (picco di concentrazione plasmatica 1-2 ore)
- Idrolizzato rapidamente ad acido acetico e salicilato da esterasi tissutali.
- Emivita varia a seconda del dosaggio (per 600 mg è di circa 3 -5 ore)
- Escrezione urinaria

Meccanismo d'azione

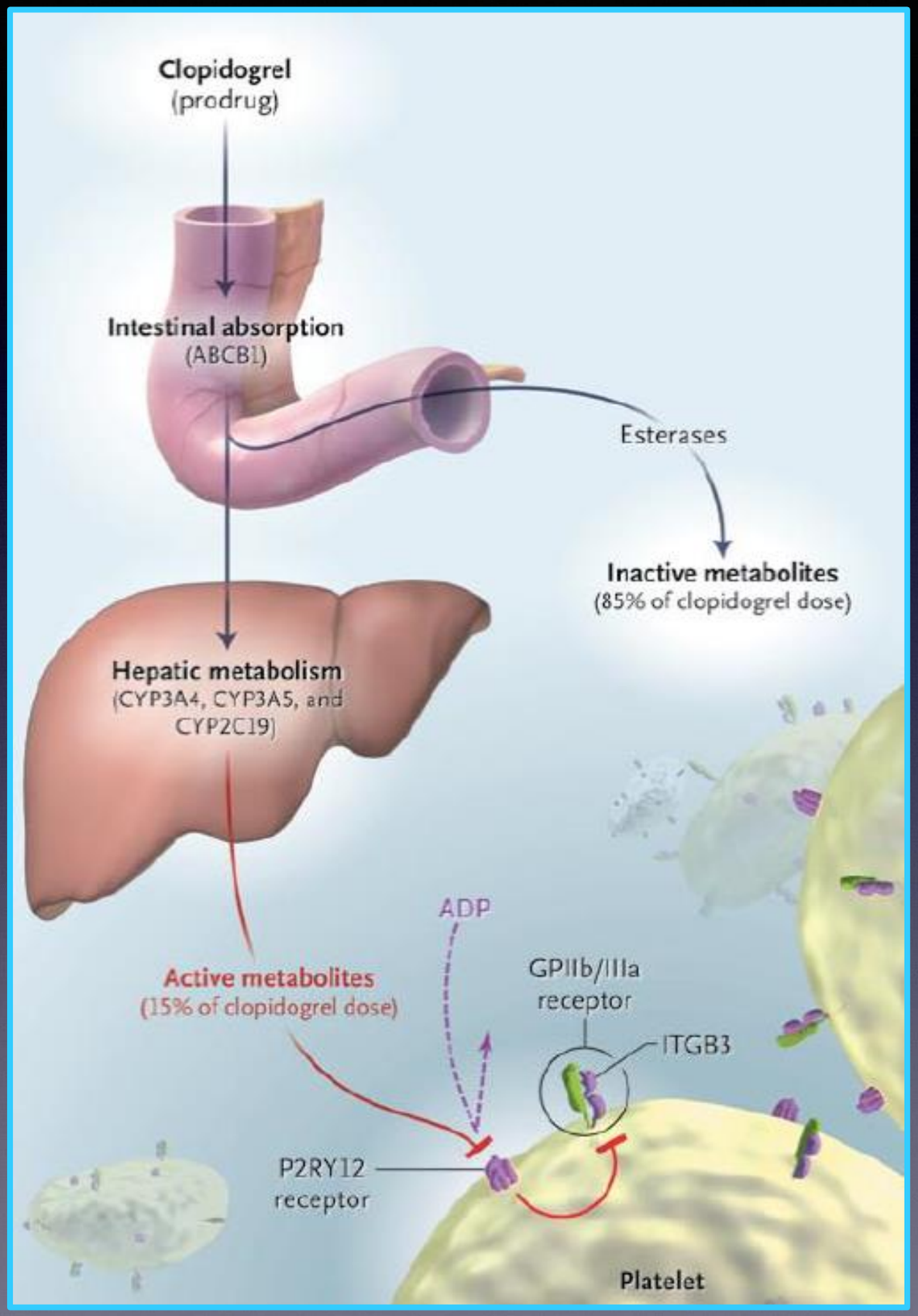
- Inibitore non selettivo ed irreversibile delle COX (acetilazione di un residuo serinico in posizione 529), con il conseguente blocco della produzione di trombossano A2, potente vasocostrittore e attivatore piastrinico

- Effetto persistente sulle piastrine, 8-10 giorni

Ticlopidina

- Profarmaco Tienopiridinico insieme a clopidogrel e prasugrel
- Metabolizzato dal CYP3A4
- Emivita:30-50 ore
- Dosi 250 mg bid
- Inibizione selettiva ed irreversibile recettore P2Y12
- Effetti collaterali: neutropenia (3%), porpora trombotica trombocitopenica (0,02%), rush cutaneo, diarrea

Clopidogrel



- Profarmaco Tienopiridinico insieme a ticlopidina e prasugrel
- Inibizione irreverisibile del recettore P2Y12 espresso sulla superficie piastrinica
- Assorbimento intestinale (50% dose totale)
- Bassa biodisponibilità (circa 15% dopo ossidazione da parte del CY3A4 e CYP2B6)
- Emivita:7-9 ore
- Escrezione urinaria e fecale fino a 5 giorni dall'ultima somministrazione

The FAST-MI Investigators, N Engl J Med 2009;360:363-375

Studio CURE

- Studio randomizzato in doppio cieco eseguito su 12.562 pazienti con diagnosi di SCA-NSTEMI che ha paragonato dose di carico di 300 mg di clopidogrel seguita da dose di mantenimento di 75 mg/die per un anno vs placebo.

The CURE study N Engl J Med 2001;345:494-502

Studio CURE

Table V. Incidence of major outcome measures

Outcome	Placebo (n = 6303)	Clopidogrel (n = 6259)	Relative risk (95% CI)	P
Primary outcome	719 (11.4%)	582 (9.3%)	0.80 (0.72-0.90)	<.001
Co-primary outcome	1187 (18.8%)	1035 (16.5%)	0.86 (0.79-0.94)	<.001
CV death	345 (5.5%)	318 (5.1%)	0.93 (0.79-1.08)	
MI	419 (6.7%)	324 (5.2%)	0.77 (0.67-0.89)	
Stroke	87 (1.4%)	75 (1.2%)	0.86 (0.63-1.18)	
Refractory ischemia	587 (9.3%)	544 (8.7%)	0.93 (0.82-1.04)	
Non-CV death	45 (0.7%)	41 (0.7%)	0.91 (0.60-1.39)	

Table VI. Incidence of bleeding complications

Outcome	Placebo (n = 6303)	Clopidogrel (n = 6259)	Relative risk (95% CI)	P
Major bleeding	169 (2.7%)	231 (3.7%)	1.38 (1.13-1.67)	.001
Life threatening	112 (1.8%)	135 (2.2%)	1.21 (0.95-1.56)	.13
Minor bleeding	153 (2.4%)	322 (5.1%)	2.12 (1.75-2.56)	<.001
All bleeding	317 (5.0%)	533 (8.5%)	1.69 (1.48-1.94)	<.001

Resistenza al Clopidogrel

Reduced clopidogrel bioavailability
- Failure to prescribe
- Poor compliance
- Inadequate dose (perhaps in ACS or stenting)
- Enhanced metabolism
- Interaction with other medications involving the cytochrome P-450 CYP3A4 system

Baseline individual variability
- Increased baseline platelet reactivity
- Increased body mass index
- Diabetes or insulin resistance
- Up-regulation of other platelet pathways in setting of stress
- Variations in metabolism by cytochrome P-450 CYP3A4

Clopidogrel resistance

Genetic variation
- Polymorphisms of the *P2Y12* gene
- Polymorphisms of the P-450 *CYP3A* gene

Accelerated platelet turnover
- Increased platelet production by the bone marrow in response to stress
- Introducing new platelets unexposed to clopidogrel

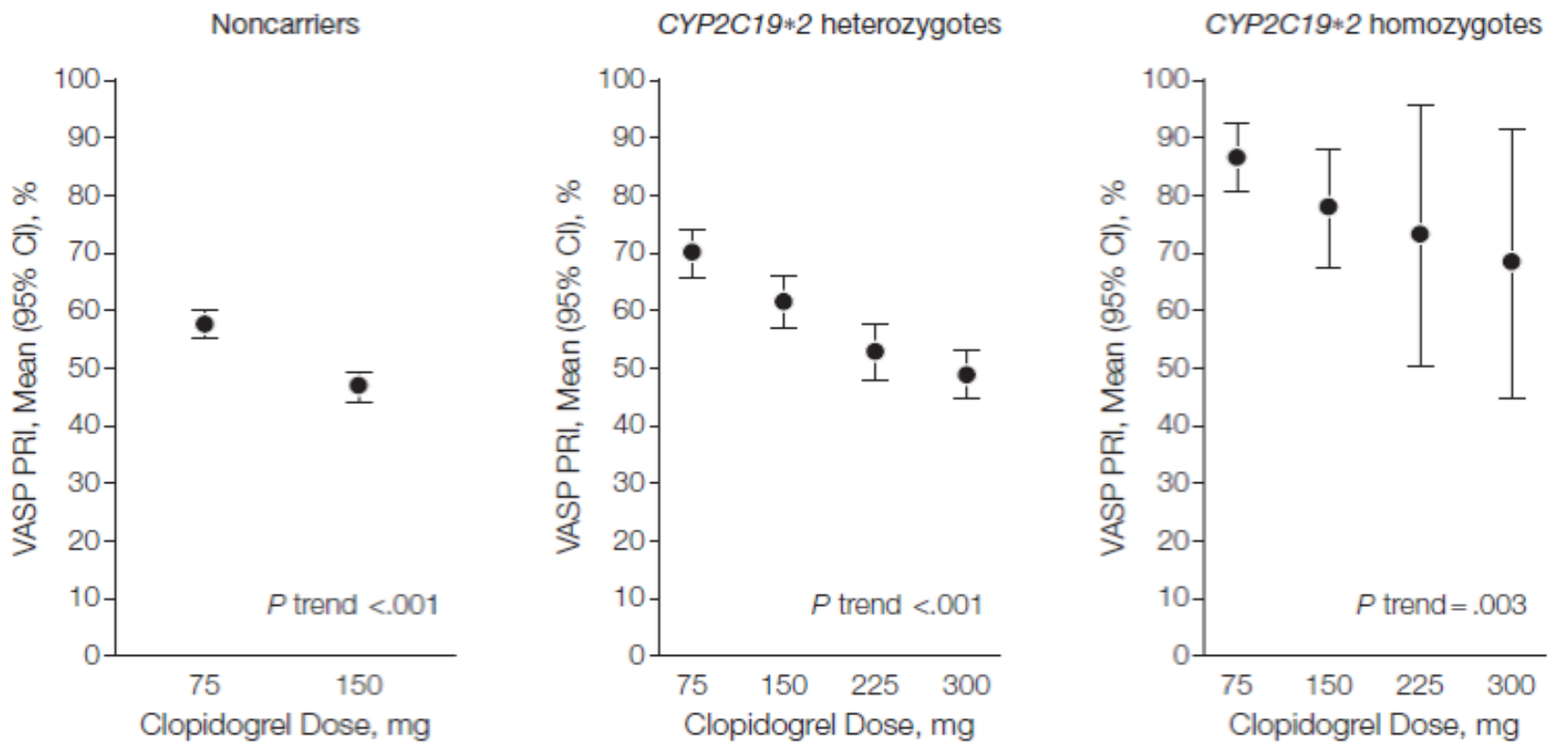
De Luca L. et al: Documento ANMCO/SICE GISE sulla terapia antiaggregante nelle sindromi coronariche acute G.Ital Cardiol 2013 vol 14 (12):839-866

Resistenza al Clopidogrel

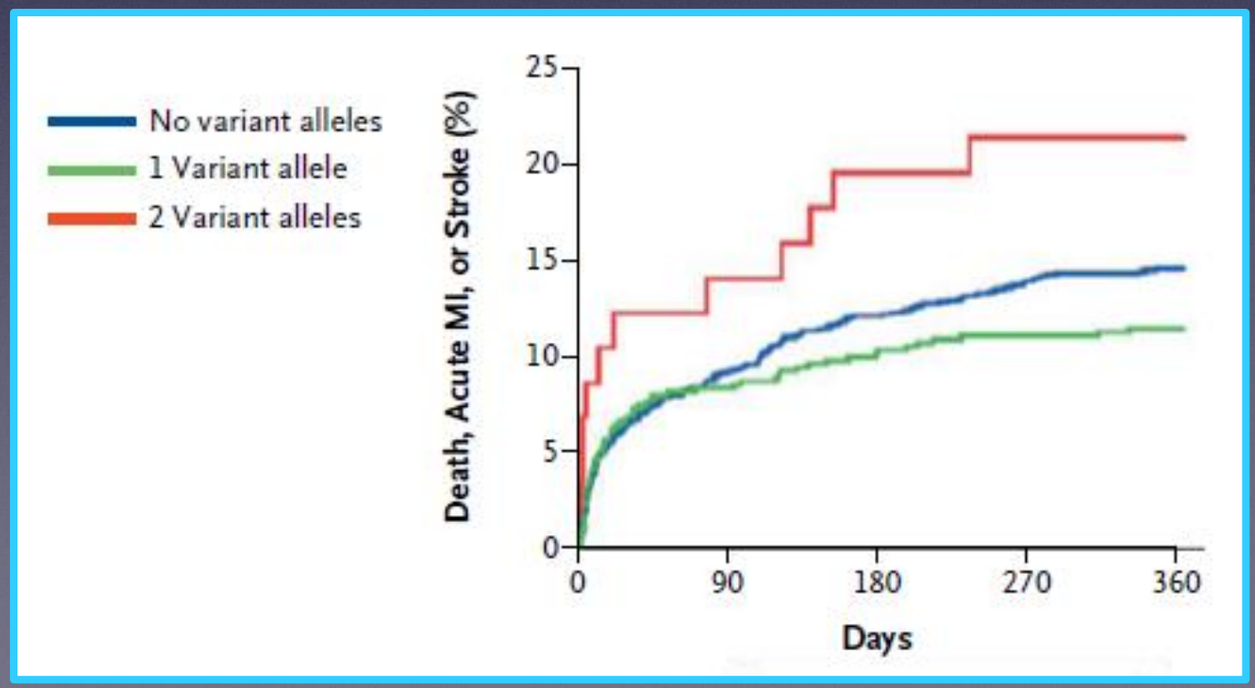
PRI: platelets reactivity index
Normal: >69%

Dosing Clopidogrel Based on *CYP2C19* Genotype and the Effect on Platelet Reactivity in Patients With Stable Cardiovascular Disease

Figure 2. On-Treatment Platelet Reactivity Across Genotype and Clopidogrel Daily Dose



The ELEVATE-TIMI 56 Investigators, JAMA 2011;306:2221-2228



The FAST-MI Investigators, N Engl J Med 2009;360:363-375

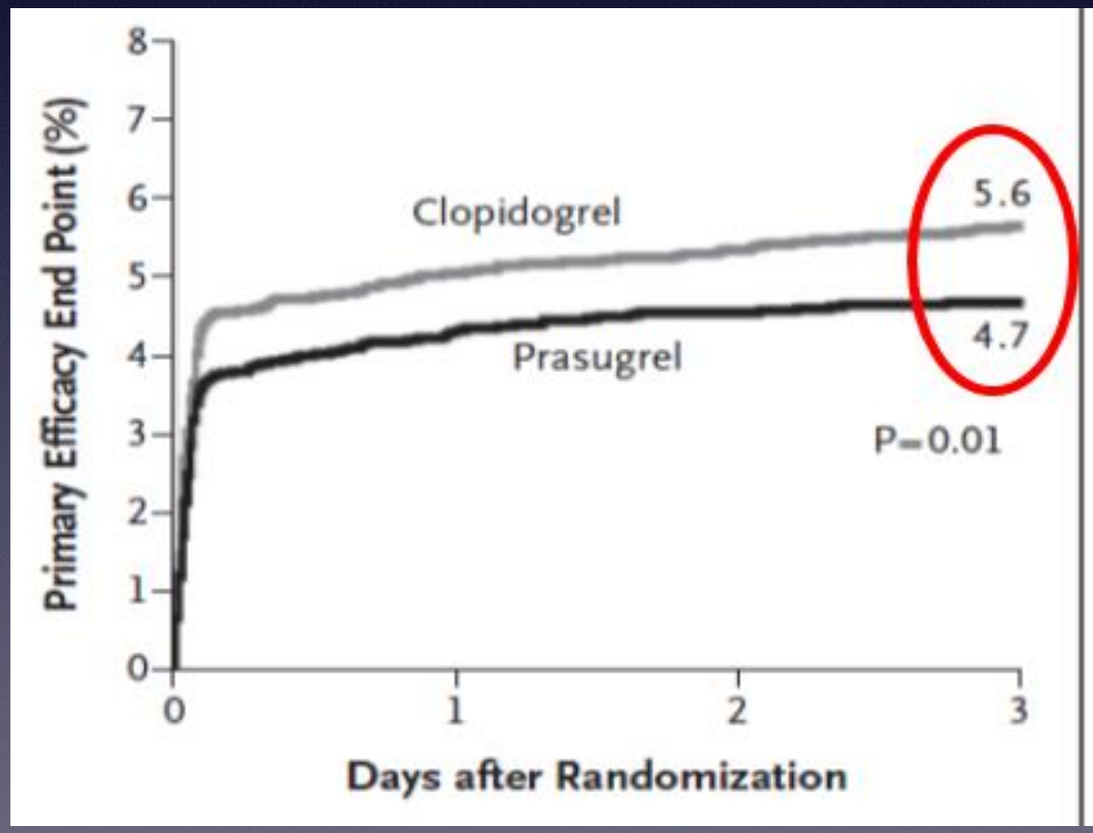
Prasugrel

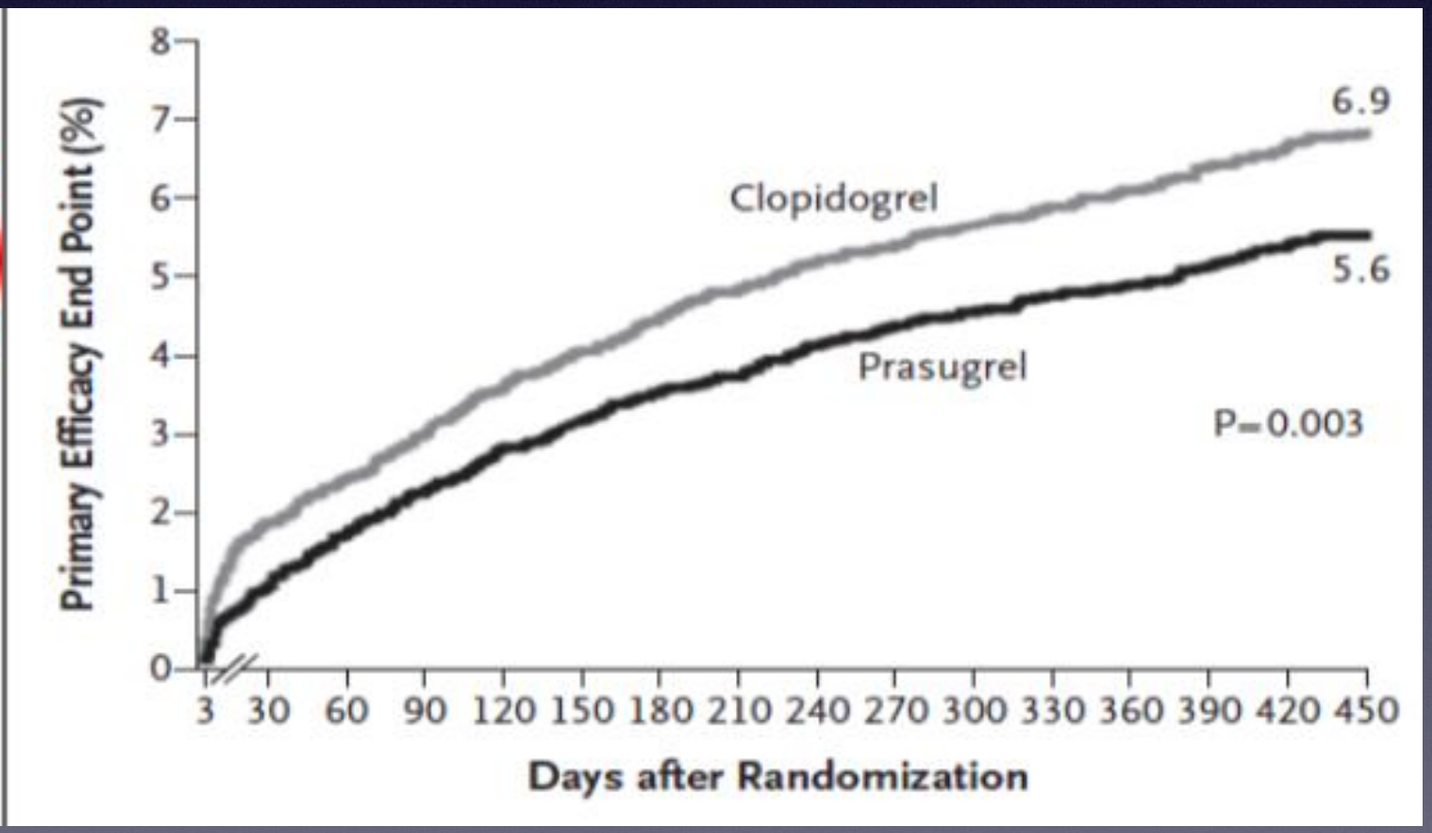
- Profarmaco Tienopiridinico insieme a ticlopidina e clopidogrel
- Assorbimento intestinale e attivazione da parte del CYP3A4
- Antagonista selettivo e irreverbile del P2Y12
- Rapida azione: picco plasmatico 30 minuti (in vitro)
- Emivita:4 ore
- Inibizione piastrinica 5-9 volte più potente rispetto al clopidogrel
- Escrezione urinaria e fecale fino a 2 giorni dall'ultima somministrazione

De Luca L. et al: Documento ANMCO/SICE GISE sulla terapia antiaggregante nelle sindromi coronariche acute G.Ital Cardiol 2013 vol 14 (12):839-866

Studio TRITON TIMI 38

Studio randomizzato in doppio cieco, multicentrico 13608 pazienti con SCA-NSTEMI e STEMI da sottoporre a PCI e randomizzati a ricevere clopidogrel (300 mg di carico seguiti da 75 mg/die di mantenimento)o prasugrel (60 mg di carico seguiti da 10 mg/die di mantenimento)





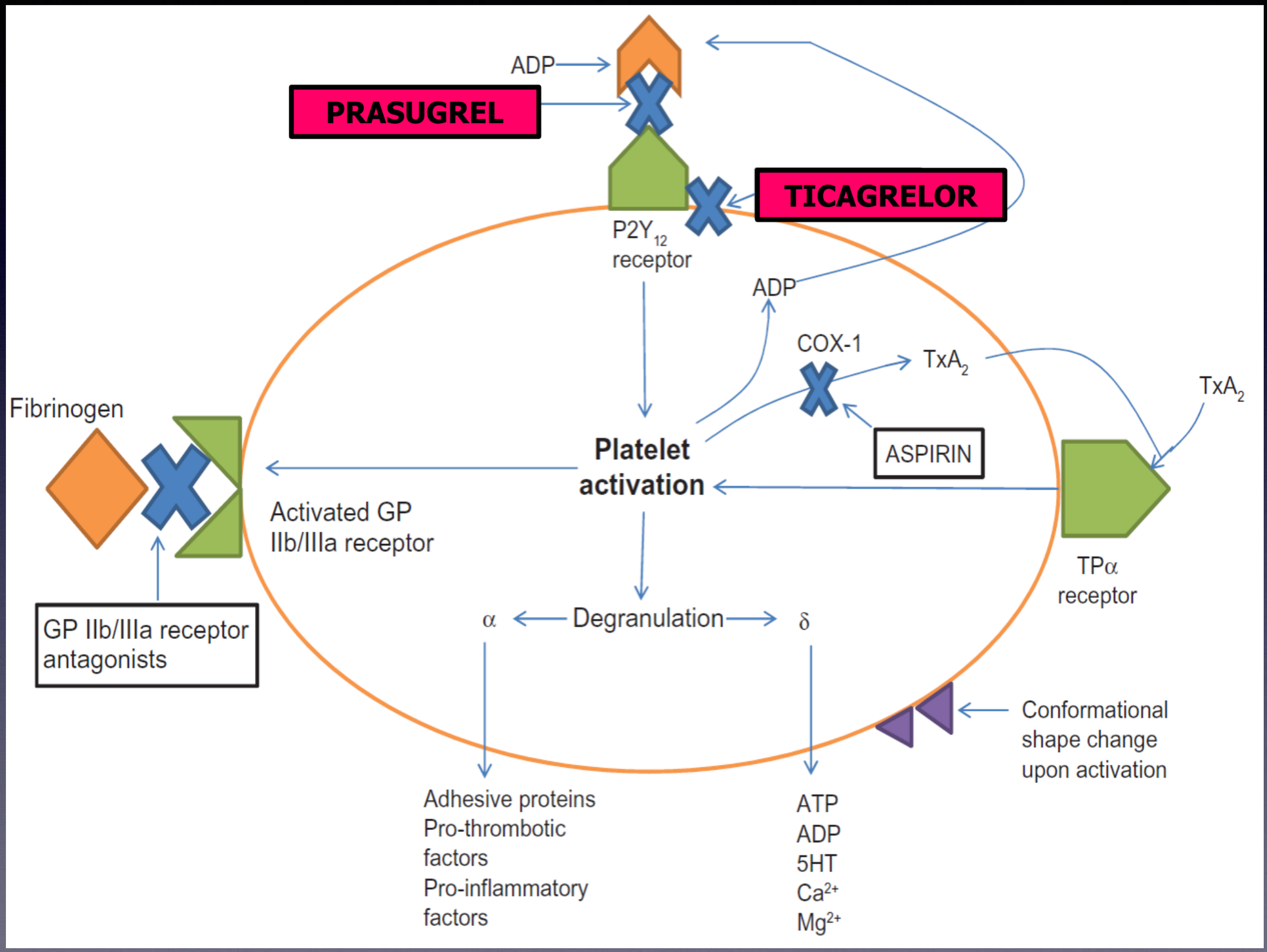
The TRITON-TIMI 38 Investigators, *N Engl J Med* 2007;357:2001-2015

Ticagrelor

- Ciclopentiltriazolopirimidina
- Non è un profarmaco
- Emivita:6-12 ore
- Antagonista selettivo e reversibile del P2Y12
- Inibitore del reuptake dell'adenosina
- Inibizione piastrinica di circa il 90% rispetto al 20% del clopidogrel

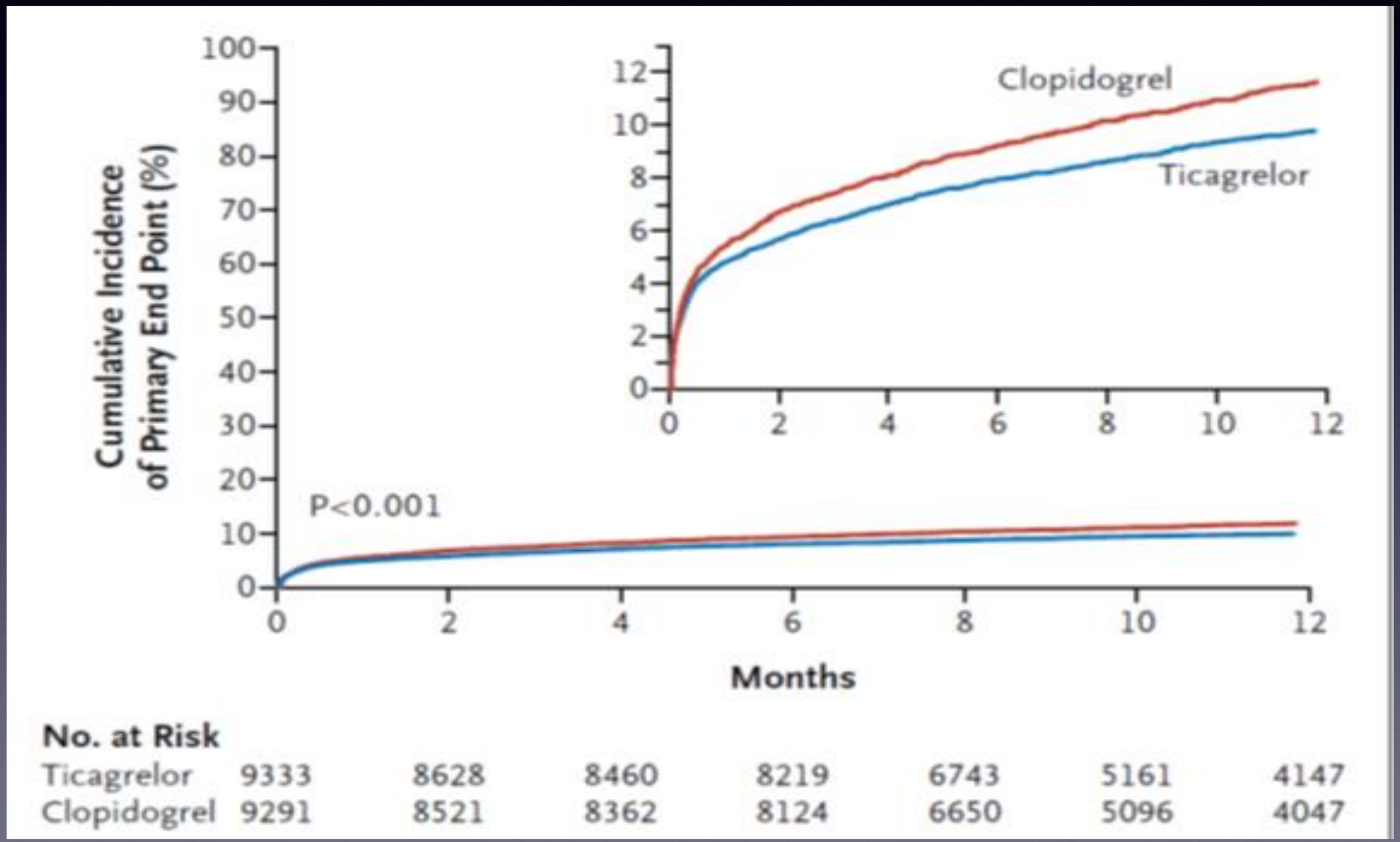
De Luca L. et al: Documento ANMCO/SICE GISE sulla terapia antiaggregante nelle sindromi coronariche acute G.Ital Cardiol 2013 vol 14 (12):839-866

Farmaci antiaggreganti
Farmacodinamica



STUDIO PLATO

18624 pazienti randomizzati in doppio cieco a ricevere ticagrelor (180 mg Dose di carico +90 m



No. at Risk

Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

The PLATO Investigators, *Circulation* 2010;1222131-2141

Effetti avversi Ticagrelor

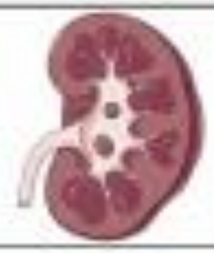
- Aumentato rischio di sanguinamenti maggiori (2,8% vs 2,2%)
- dispnea (13,8 vs 7,8%)
- pause ventricolari > 3 sec e bradicardia
- iperuricemia
- aumento della creatininemia

Controindicazioni:

- IRC V STADIO NFK (eGFR < 15 mL/min/1.73 m2)

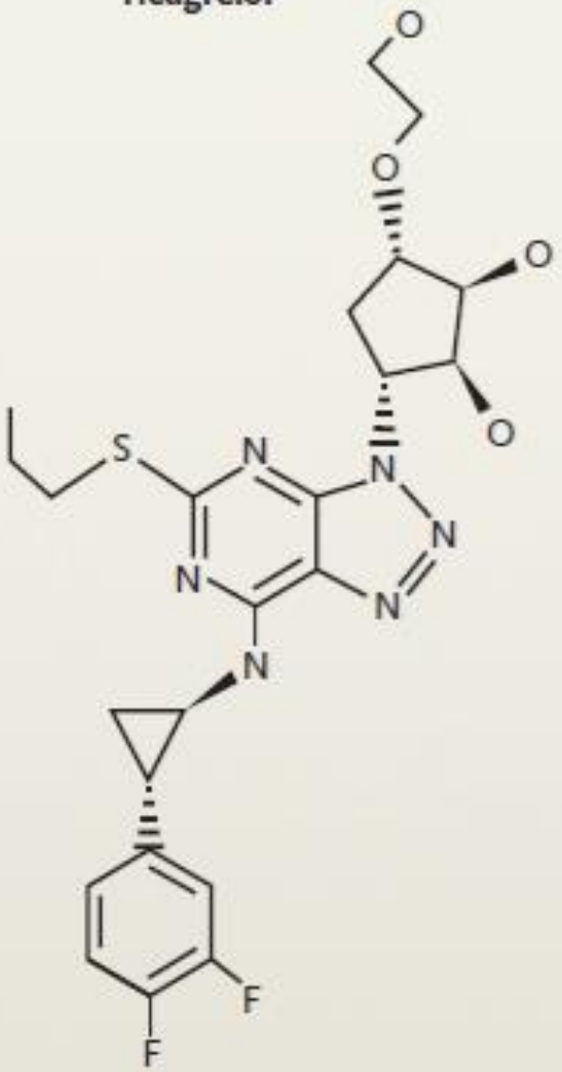
The PLATO Investigators, *Circulation* 2010;1222131-2141

Ticagrelor ed effetti Adenosina-mediati

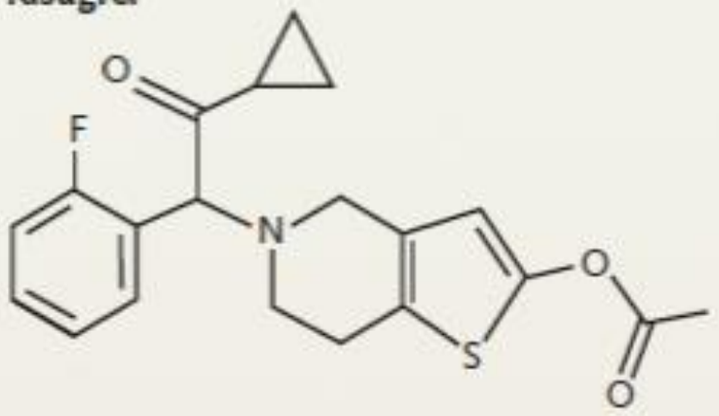
Ticagrelor		Adenosine
↑ Adenosine-induced increases in coronary blood flow (dogs and humans) ↑ Endothelial function (ACS patients)		↑ Vasodilation ↑ Endothelial progenitor cell migration
↓ Incidence of MACE (ACS patients) ↓ CV and all cause mortality (ACS patients) ↑ Incidence of ventricular pauses (ACS patients) ↓ Infarct size (animal models)		↓ Ischemia/reperfusion injury Induces pharmacological preconditioning ↓ Electrical conduction
↑ Adenosine-induced platelet inhibition (in vitro) ↓ Mortality (ACS patients with pulmonary infection)		↑ Platelet inhibition Modulates inflammation
↑ Creatinine levels (ACS patients)		↓ Glomerular filtration
↑ Incidence of dyspnea (ACS patients) ↑ Adenosine-induced dyspnea (healthy subjects)		↑ Incidence of dyspnea

Cattaneo et al: Adenosine-Mediated effects of Ticagrelor, JACC 2014: 63-2503-9

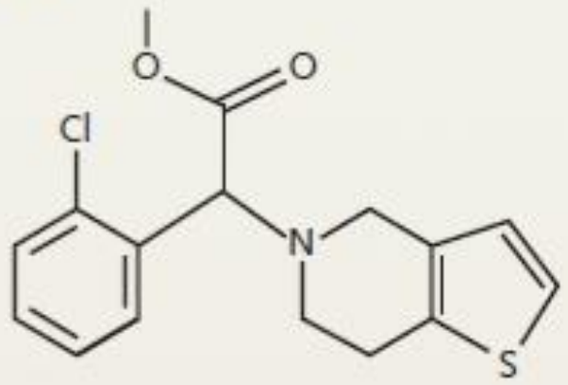
Ticagrelor

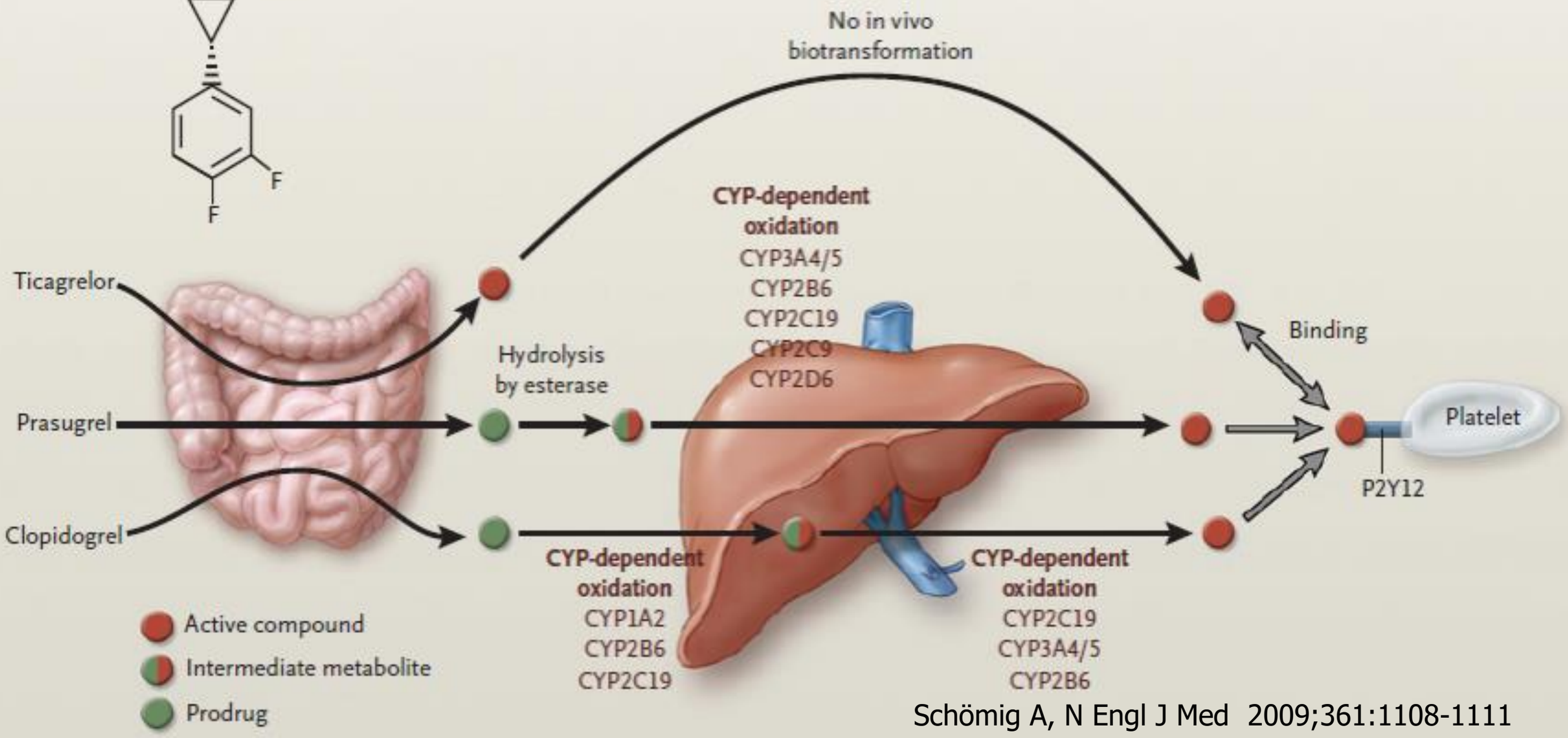


Prasugrel



Clopidogrel





Schömig A, N Engl J Med 2009;361:1108-1111

Cangrelor

- Analogo dell'ATP che lega reversibilmente e con alta affinità il recettore P2Y12
- Emivita < 10 minuti
- Somministrazione endovenosa
- Possibile somministrazione come bridging therapy per CABG

Cangrelor may be considered in $P2Y_{12}$ inhibitor–naive patients undergoing PCI.	IIb	A

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation, 2015

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg orally then 75 mg a day	60 mg orally then 10 mg a day	180 mg orally then 90 mg twice a day	30 μg/kg bolus and 4 μg/kg/min infusion
Dosing in CKD				
• Stage 3 (eGFR 30–59 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 4 (eGFR 15–29 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 5 (eGFR <15 mL/min/1.73m^2)	Use only for selected indications (e.g. stent thrombosis prevention)	Not recommended	Not recommended	No dose adjustment
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with predictable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading dose effect[a]	2–6 hours[b]	30 min[b]	30 min[b]	2 min
Duration of effect	3–10 days	7–10 days	3–5 days	1–2 hours
Withdrawal before surgery	5 days[c]	7 days[c]	5 days[c]	1 hour
Plasma half-life of active $P2Y_{12}$ inhibitor[d]	30–60 min	30–60 min[e]	6–12 hours	5–10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes ('inactive' metabolite only)

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation, 2015

Inibitori GpIIbIIIa

- Bloccanti complesso GpIIb/IIIa- blocco fase finale dell'attivazione piastrinica (formazione dei ponti interpiastrinici e con il fibrinogeno)

- ABCIXIMAB anticorpo monoclonale, emivita plasmatica 10-30', permane in circolo fino a 15 giorni dopo la somministrazione
  BOLO:0,25 mg/Kg seguito da infusione di max 24 h di 0,125 mcg/Kg/min

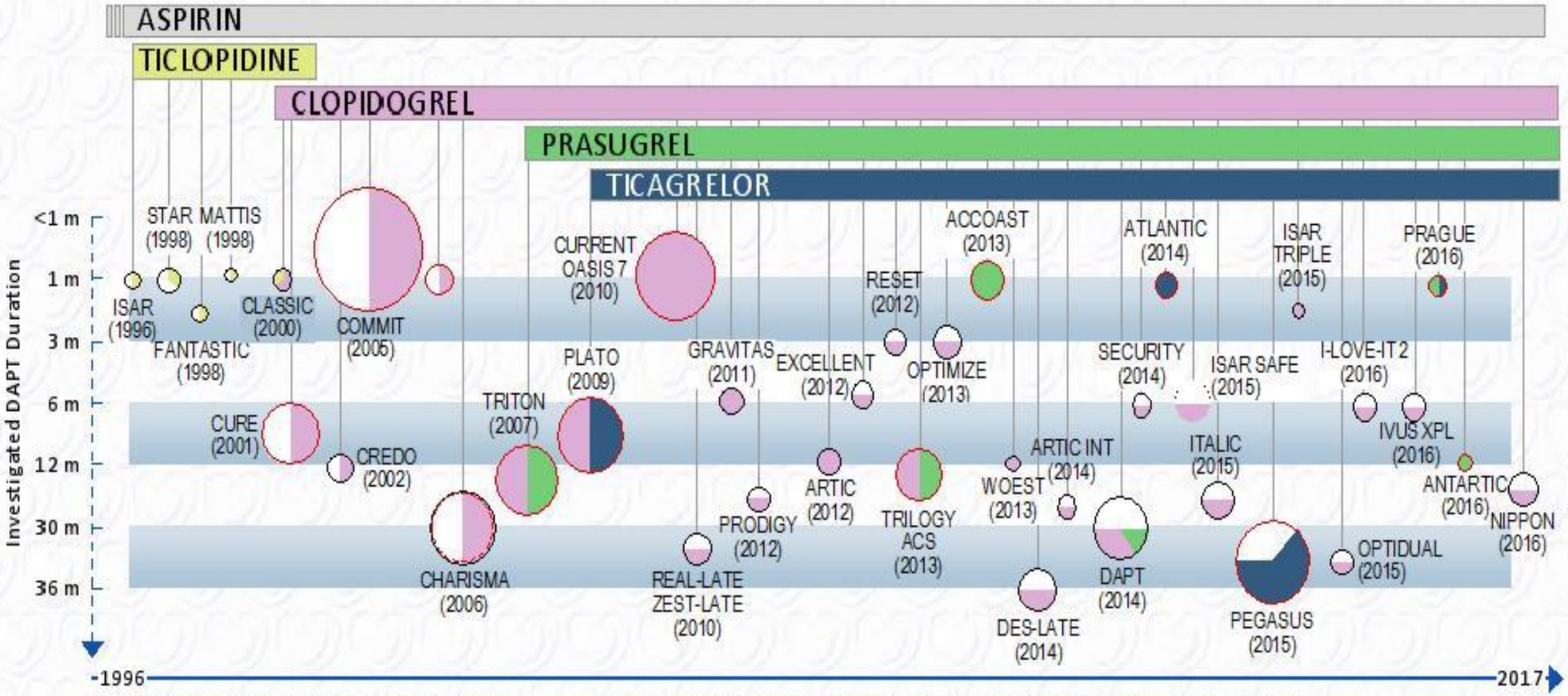
- EPTIFIBATIDE eptapeptide ciclico sintetico, emivita plasmatica 1-2 h
  BOLO:180mcg/Kg seguito da infusione di max 72 h di 2 mcg/Kg/min

- TIROFIBAN peptido-mimetico non peptidico
  stemi: infusione 0,4mcg/Kg/min per 30 min, 0,1mcg/Kg/min fino a 48 min

Opie: Farmaci per il cuore VIII edizione, 374 cap.9

History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease

ESC European Society of Cardiology



Size of the circles denotes sample size

2 5 10 20 K pts

Perimeter of the circles denotes type of investigated population

- Mixed clinical presentation at the time of stent implantation
- Acute coronary syndrome at presentation
- DAPT initiated in patients with prior myocardia infarction
- DAPT for primary prevention

6

www.escardio.org/guidelines 2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

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

$P2Y_{12}$ inhibitor selection and timing

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contra-indications.	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high-risk of life-threatening bleeding or other contra-indications.	I	B

www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

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

$P2Y_{12}$ inhibitor selection and timing *(continued)*

ESC European Society of Cardiology

Recommendations	Class	Level
Pre-treatment with a $P2Y_{12}$ inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI.	I	A
In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
In patients with stable CAD pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C

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(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

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

$P2Y_{12}$ inhibitor selection and timing *(continued)*

ESC European Society of Cardiology

Recommendations	Class	Level
Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC.	I	A
Clopidogrel (300 mg loading dose in patients ≤75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis.	I	A

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

$P2Y_{12}$ inhibitor selection and timing *(continued)*

ESC European Society of Cardiology

Recommendations	Class	Level
Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischaemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT) risks.	IIb	C
In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel.	III	B

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Measures to minimize bleeding while on dual antiplatelet therapy

ESC European Society of Cardiology

Recommendations	Class	Level
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.	I	A
In patients treated with DAPT, a daily aspirin dose of 75–100 mg is recommended.	I	A
A PPI in combination with DAPT is recommended.	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A

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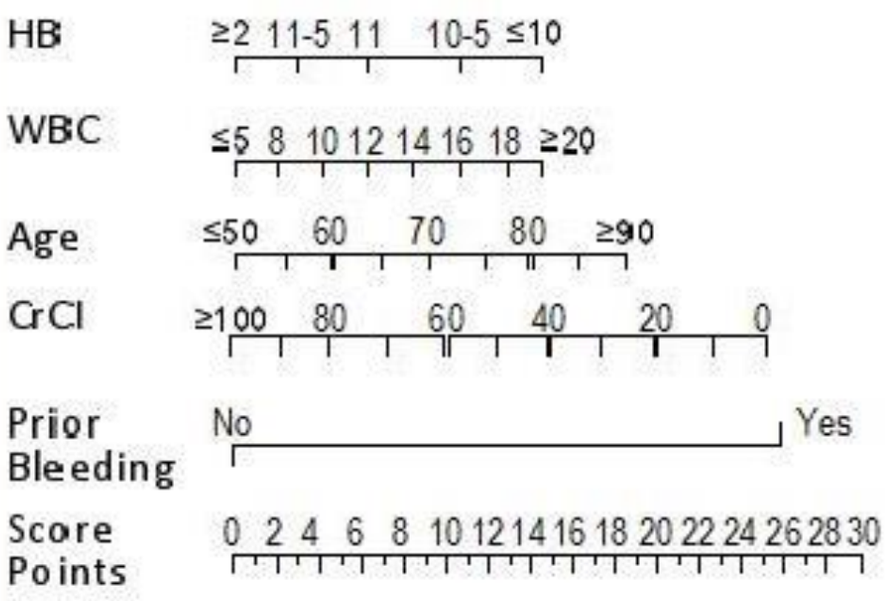
ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

Timing

Stratificazione del rischio ischemico ed emorragico

- **Alto rischio emorragico** (PRECISE DAPT ≥ 25)
- **Basso rischio emorragico** (PRECISE DAPT<25)
- **Alto rischio ischemico** DAPT score >2 o Pegasus like

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

	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 −2 pt −1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	−2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

Recommendations	Class	Level
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.	IIb	A

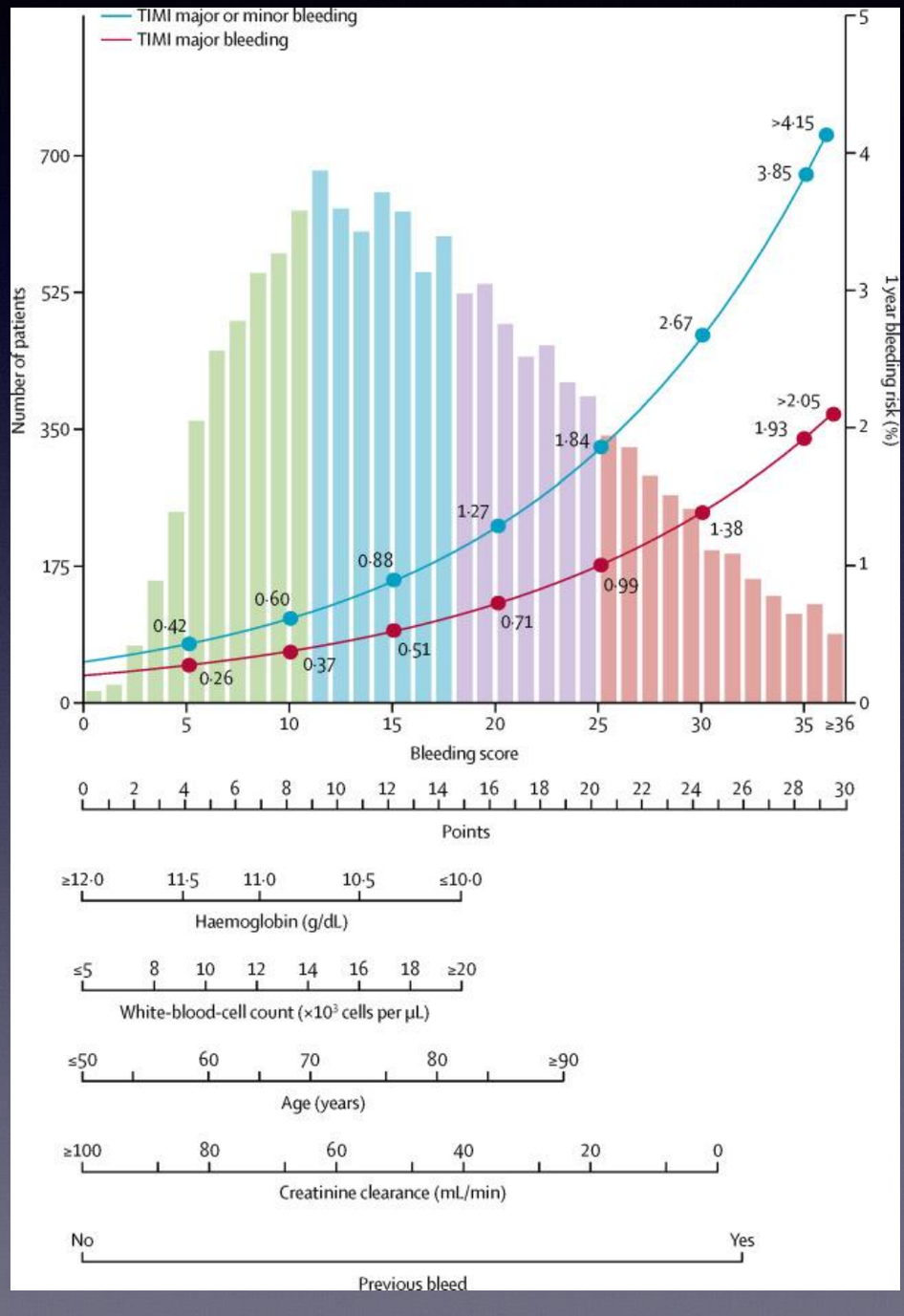
ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

PRECISE DAPT score

- 14963 pazienti trattati con DAPT dopo stenting coronarico randomizzati in DAPT per un timing variabile e valutazione sanguinanti
- Terapia a breve (3-6 mesi) o a lungo termine (12-24 mesi)
- IL PRECISE-DAPT score include cinque elementi (età del paziente, clearance della creatinina, emoglobina, conta dei globuli bianchi e precedente sanguinamento spontaneo)
- Sanguinamenti significativamente aumentato nei pazienti ad alto rischio (punteggio ≥25)

SCORE ≥ 25 -> SHORT DAPT

SCORE<25 -> STANDARD/LONG DAPT



Costa F et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRE

www.precisedaptscore.com

Haemoglobin ⓘ unit

10 g/dl mmol/L

Age (years)

80

White blood cells ⓘ unit

20 u/mcL 10^9/L

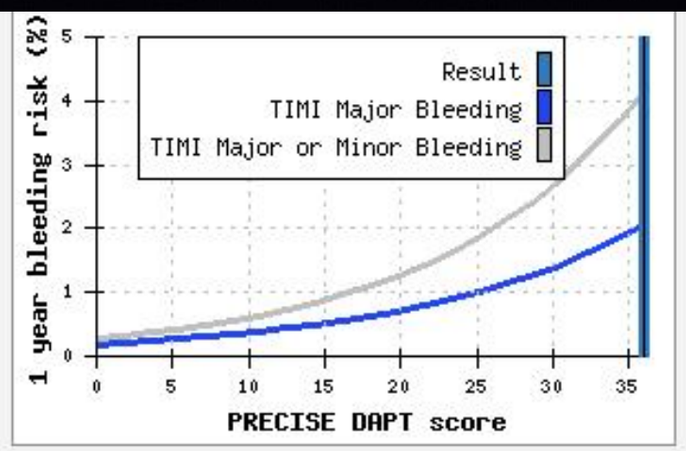
Creatinine Clearance (ml/min) ⓘ

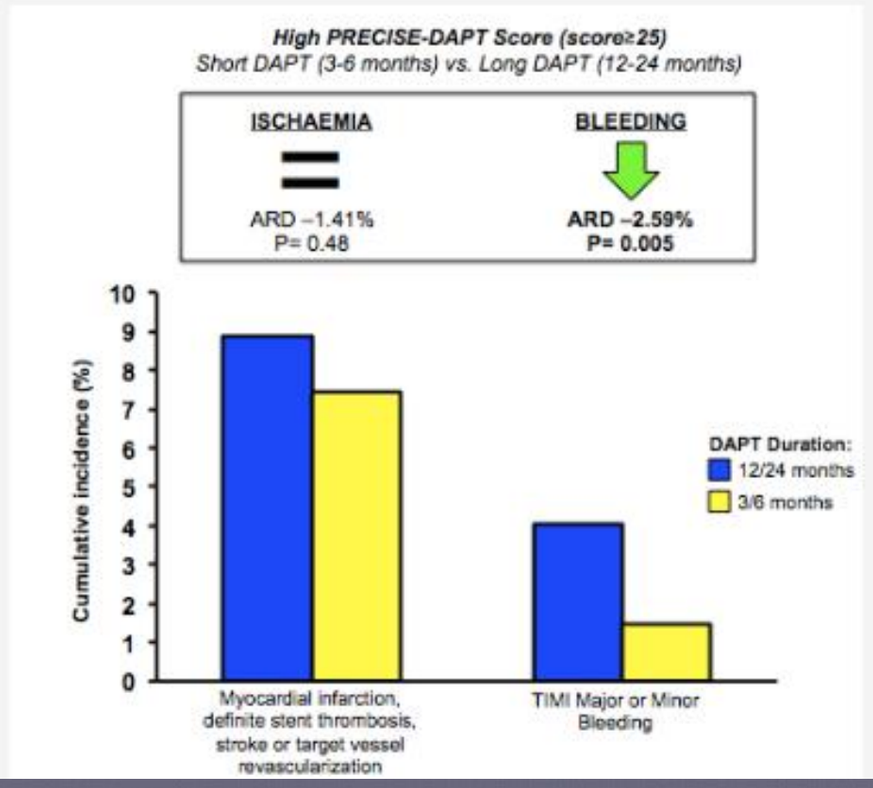
20

Prior Bleeding ⓘ ☑

CALCULATE

RESET





RESULT:

Cluster of risk:

High

Score Calculated

75

12 months risk of TIMI major or minor Bleeding

> 4.14%

12 months risk of TIMI Major Bleeding

> 2.06%

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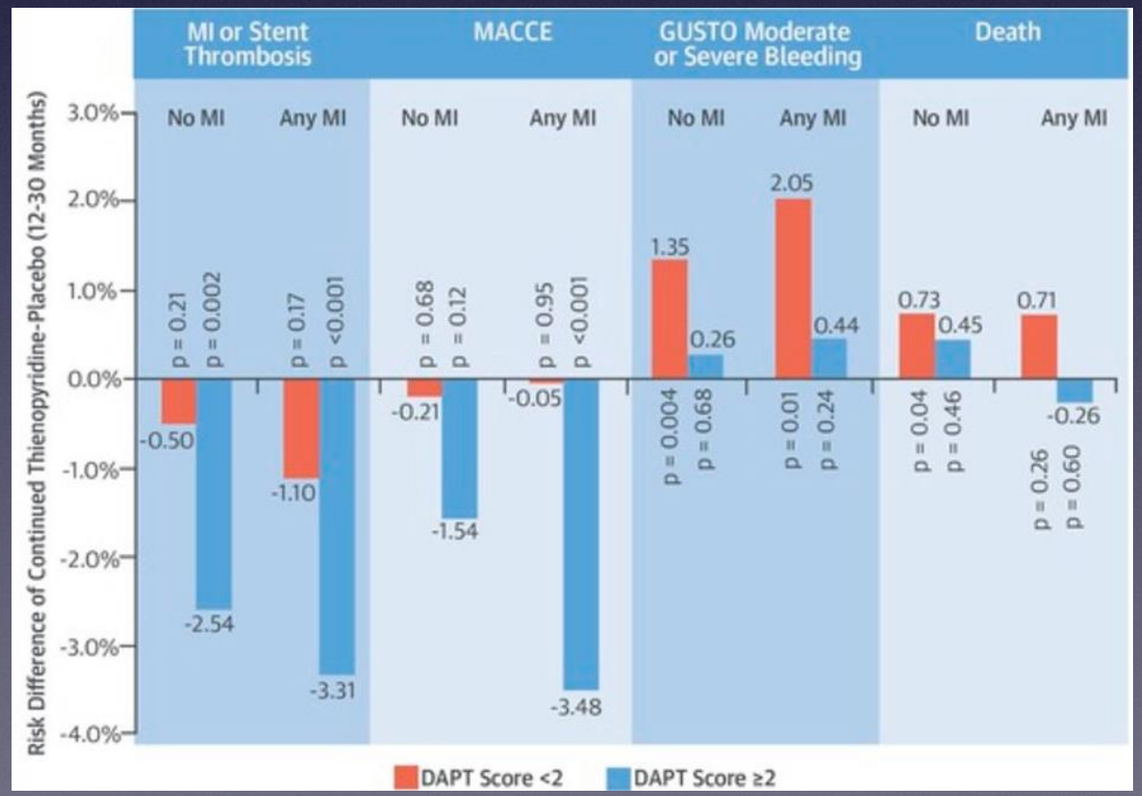
DAPT score

- 9961 pazienti trattati con DAPT per 12 mesi dopo stenting coronarico, i quali non avevano mostrato aventi avversi
- Terapia prolungata (DAPT per altri 18 mesi) vs PLACEBO.
- Valutazione eventi ischemici(MACE- morte, IM, ictus, trombosi intrastent) e sanguinanti maggiori

DAPT Score Calculation	
Variable	Points
Age (Years)	
≥75	-2
65 - <75	-1
<65	0
Current Cigarette Smoker	1
Diabetes Mellitus	1
MI at Presentation	1
Prior PCI or Prior MI	1
Paclitaxel-eluting Stent	1
Stent Diameter <3mm	1
CHF or LVEF <30%	2
Vein Graft PCI	2

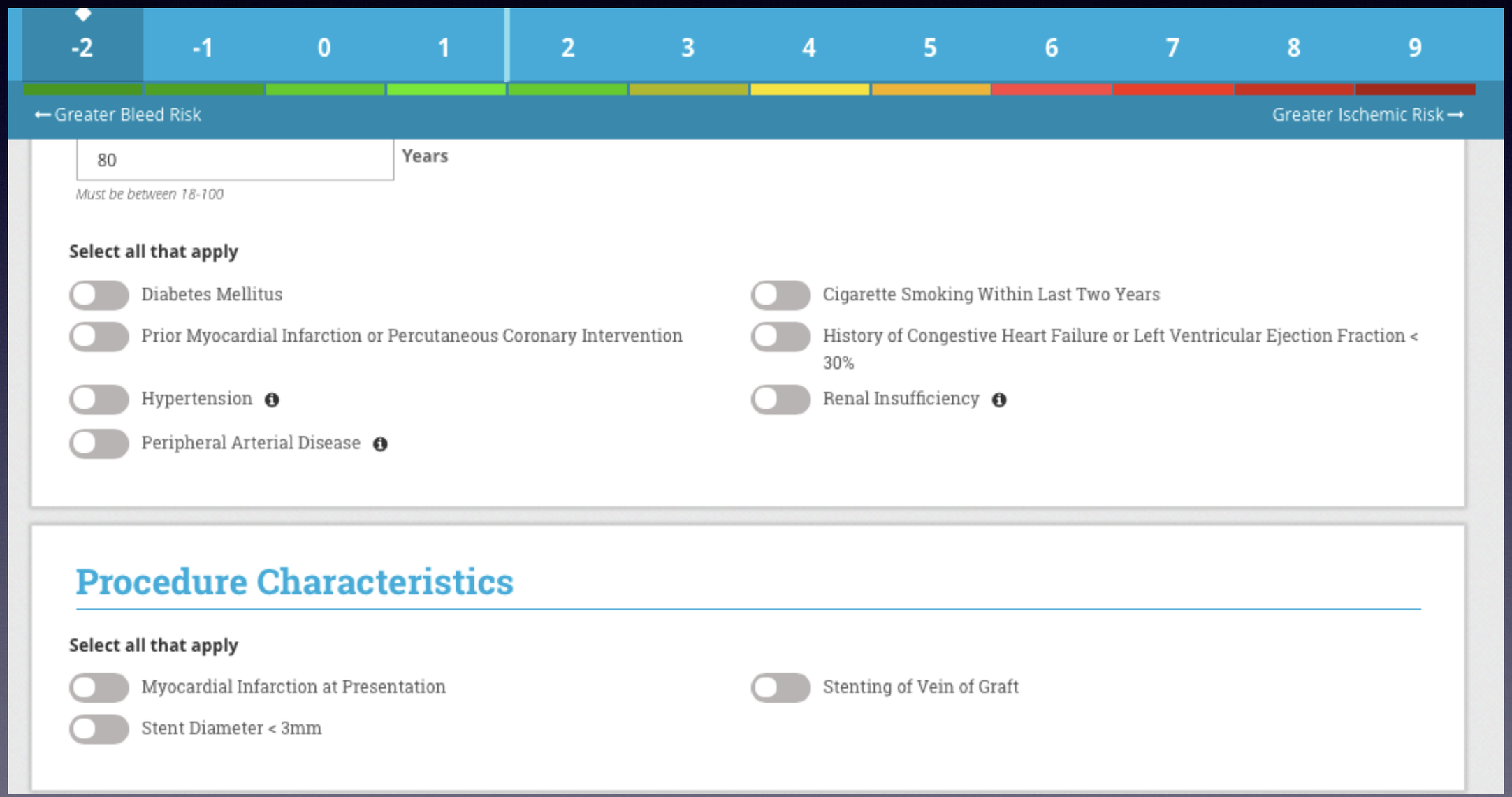


SCORE>2 -> Prolonged DAPT

SCORE<2 -> STANDARD DAPT

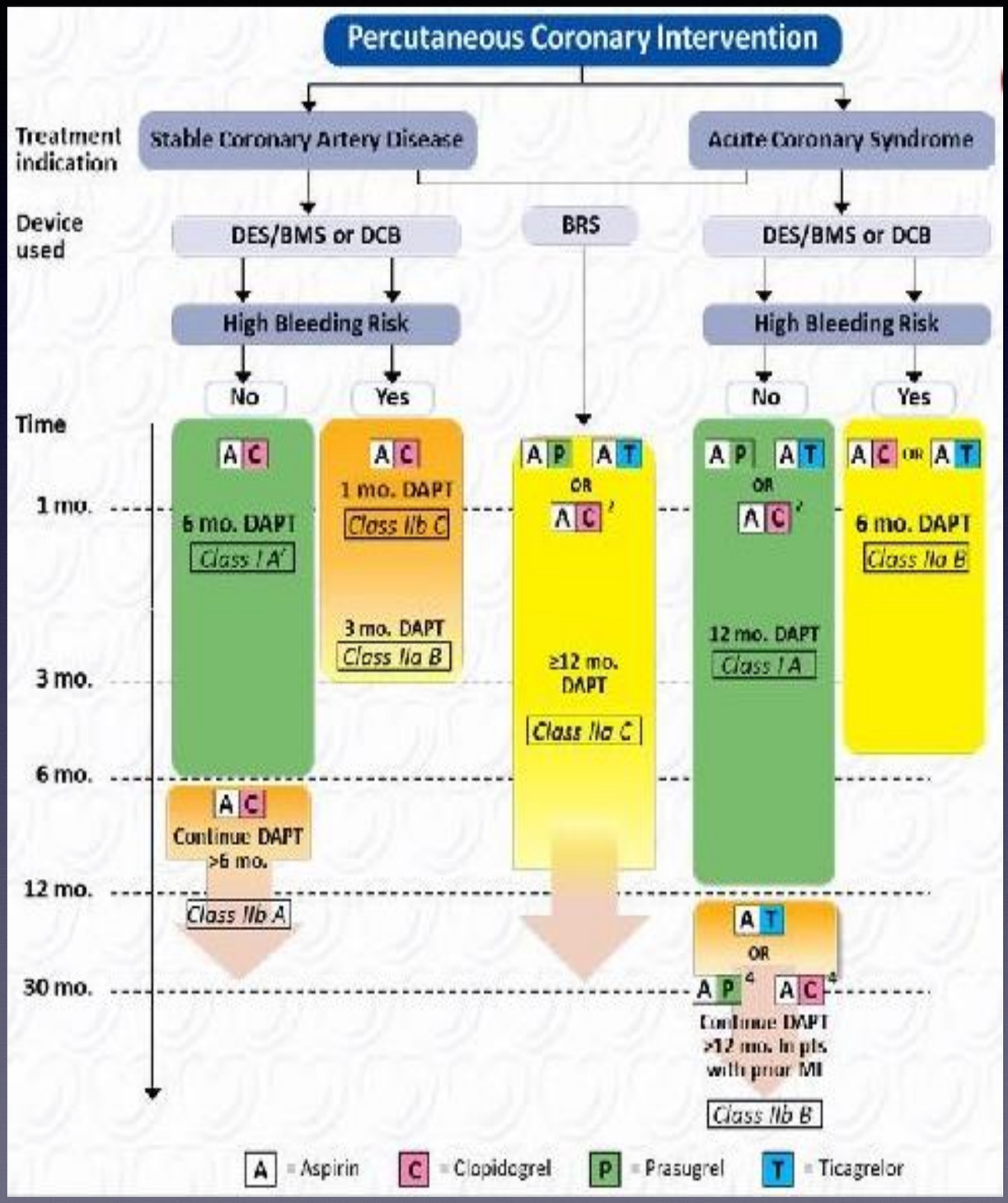
Yeh RW et al, Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1year after percutaneous coronary intervention. JAMA 20

www.daptstudy.org



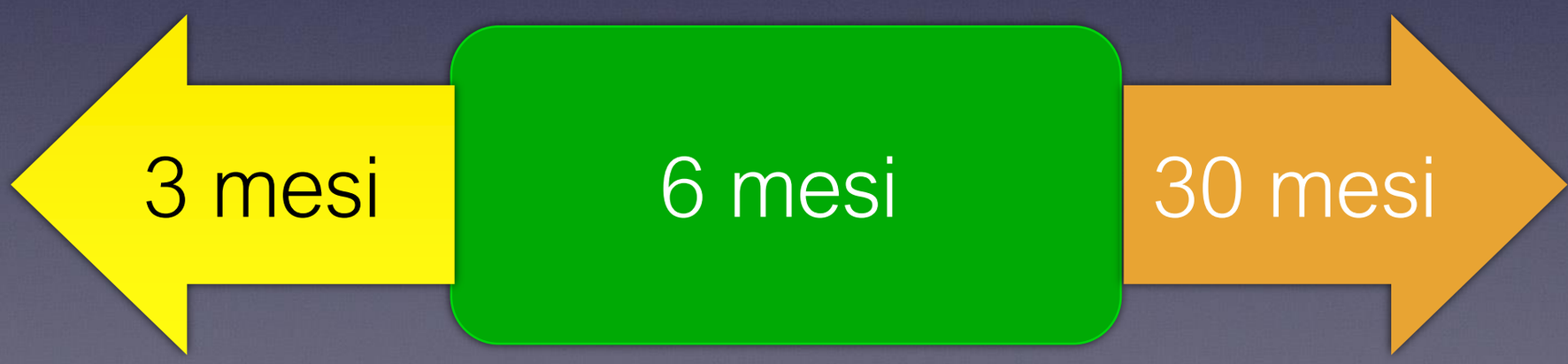
Yeh RW et al, Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1year after percutaneous coronary intervention. JAMA 201

Timing


Percutaneous Coronary Intervention
Treatment indication
Stable Coronary Artery Disease
Acute Coronary Syndrome
Device used
DES/BMS or DCB
BRS
DES/BMS or DCB
High Bleeding Risk
High Bleeding Risk
No
Yes
No
Yes
Time
1 mo.
3 mo.
6 mo.
12 mo.
30 mo.
A C
6 mo. DAPT
Class I A
A C
1 mo. DAPT
Class IIb C
3 mo. DAPT
Class IIa B
A P A T
OR
A C
≥12 mo. DAPT
Class IIa C
A P A T
OR
A C
12 mo. DAPT
Class I A
A C OR A T
6 mo. DAPT
Class IIa B
A C
Continue DAPT >6 mo.
Class IIb A
A T
OR
A P
A C
Continue DAPT >12 mo. in pts. with prior MI
Class IIb B
A = Aspirin
C = Clopidogrel
P = Prasugrel
T = Ticagrelor

DAPT in STABLE CAD post PCI+DES o BMS

- Clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type (IA) -EXCELLENT STUDY
- In **High bleeding risk** (e.g. PRECISE-DAPT ≥ 25), DAPT for 3 months **should** be considered (IIA)
- In patients with stable CAD in whom 3 month DAPT poses safety concerns, DAPT for 1 month may be considered (IIB)
- In **Low bleeding but High thrombotic risk**, continuation of DAPT until 30 months **may** be considered (IIB)



BRS IN CAD

- DAPT for at least 12 months should be considered (IIa)
- Higher rate of stent thrombosis . in comparison with conventional DES, especially in the first 30 days after implantation
- No dedicated study

12 mesi

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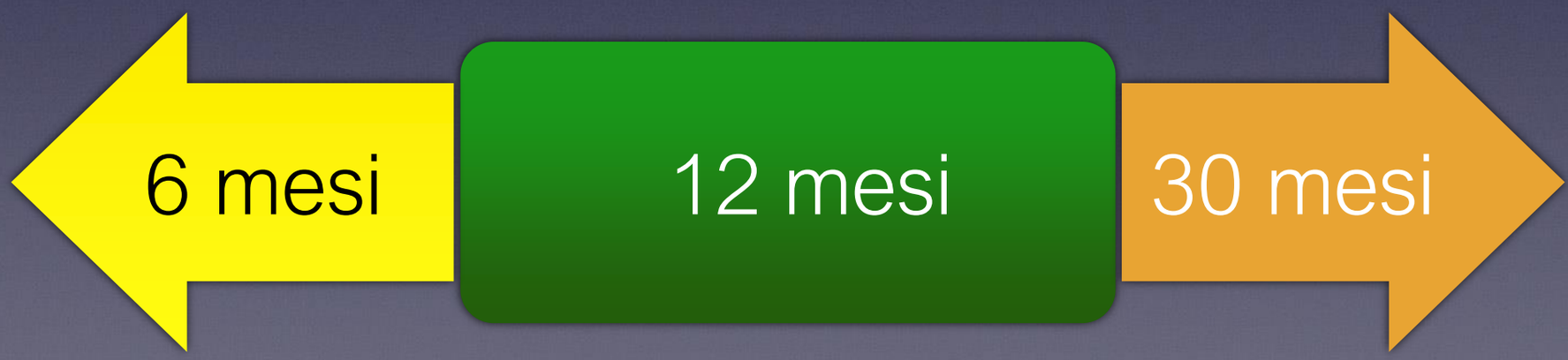
DAPT in SCA

- $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (IA)
- In **High risk of bleeding** discontinuation of $P2Y_{12}$ inhibitor (Clopidogrel) therapy after 6 months **should** be considered (IIa) -RESET study
- In patients with **MI and high ischaemic risk** who have tolerated DAPT without, ticagrelor 60 mg b.i.d. for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.



PEGASUS STUDY
DAPT FOR SECONDARY PREVENTION AFTER MI

21 162 patients with spontaneous MI 1–3 years before

Pazienti PEGASUS like ≥ 50 years old and had at least one addition diabetes mellitus, a second spontaneous MI, multivessel CAD, or chronic renal dysfunction.

3 gruppi Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

placebo

Primary efficacy endpoints -> MACE

Secondary safety endpoints -> TIMI bleedings

Bonaca MP et l. PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. Engl J Med 2015;372:1791–1800.

Trial Schema

PEGASUS TIMI 54

N ~ 21,000

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

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

RANDOMIZE
DOUBLE BLIND

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

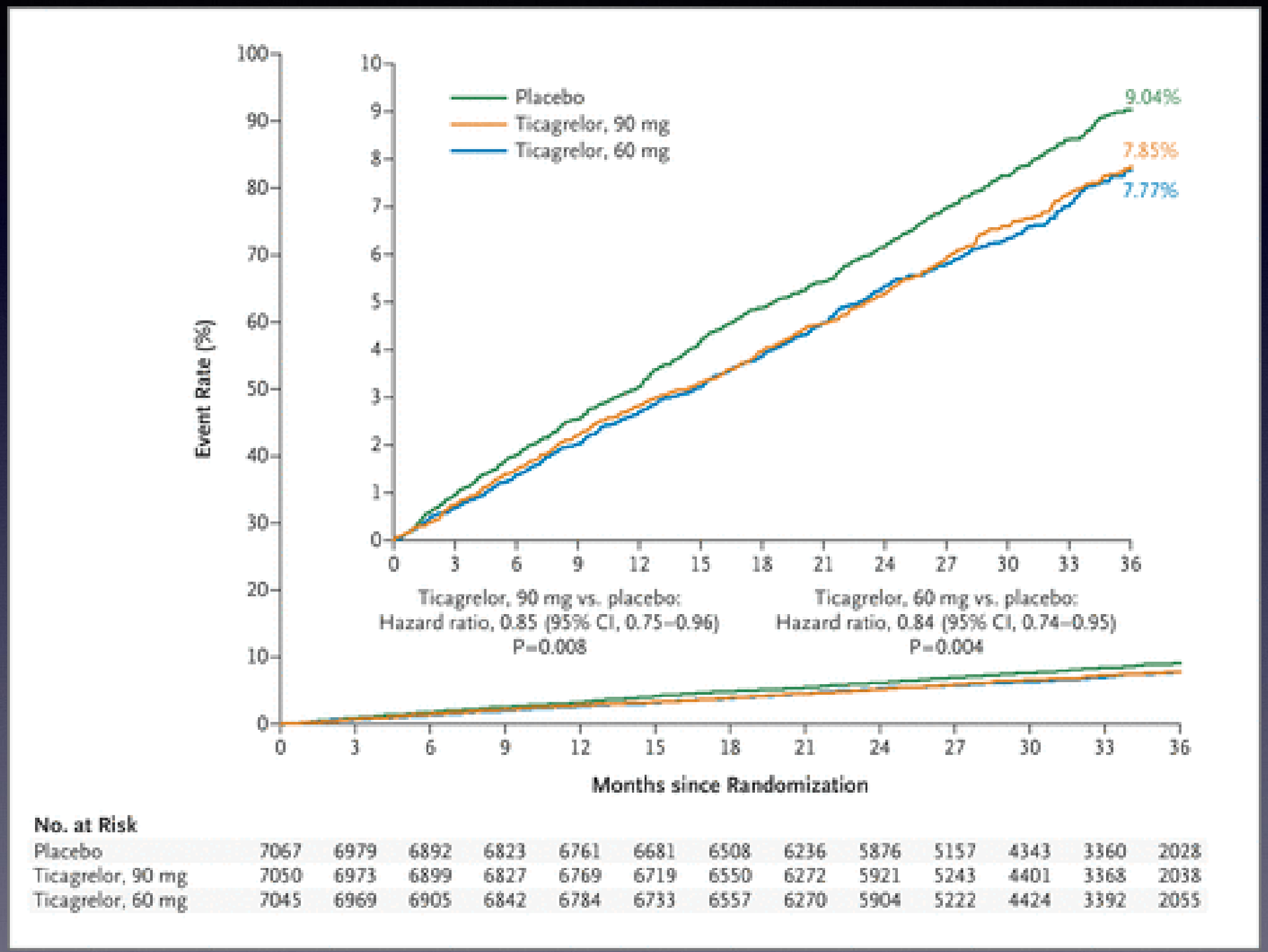
- Ticagrelor 90 mg bid
- Ticagrelor 60 mg bid
- Placebo

Follow-up Visits
Q4 mos for 1st yr, then Q6 mos

Min 12 mos and median 26 mos follow-up
Event-driven trial

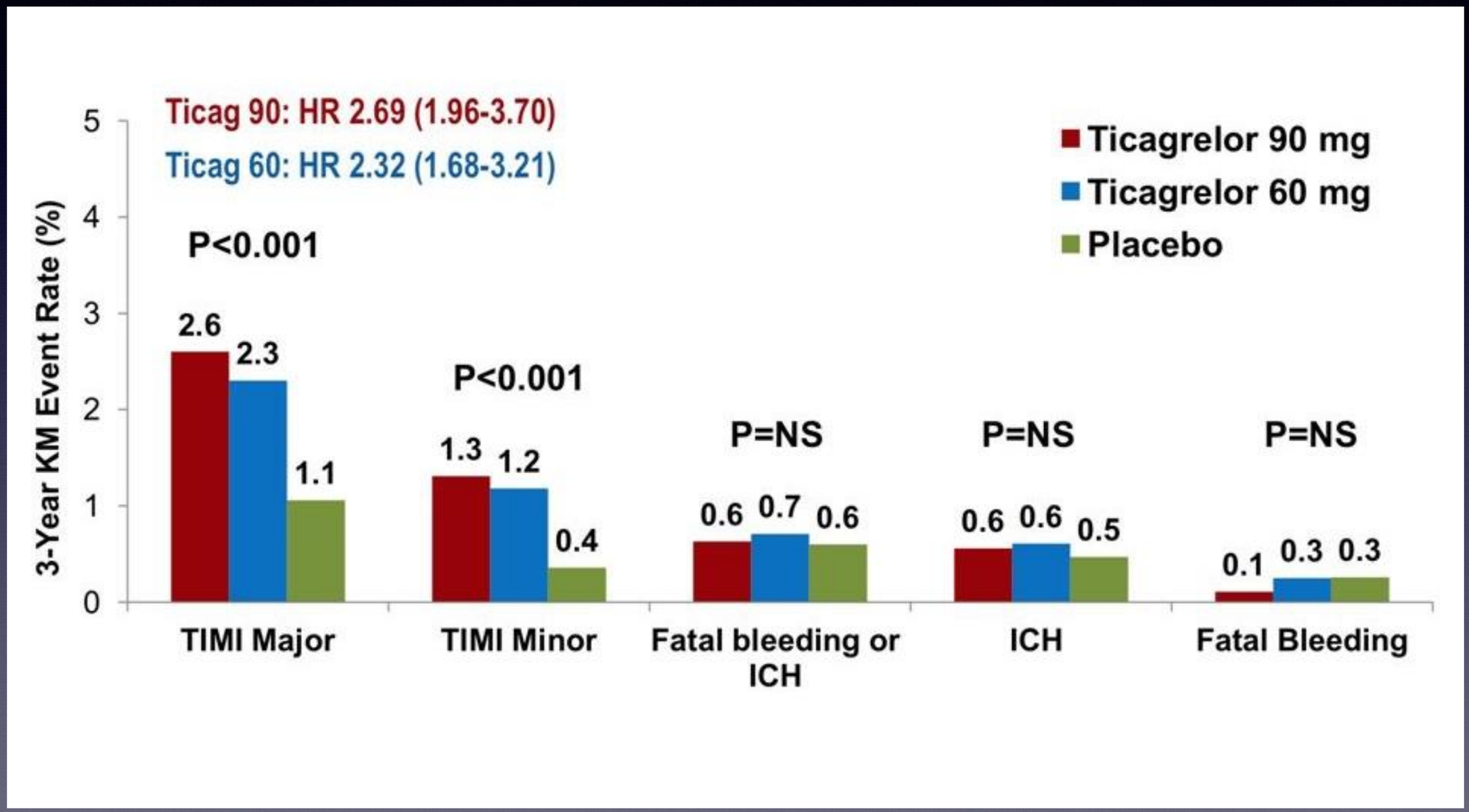
Primary Efficacy Endpoint: CV Death, MI, or Stroke
Primary Safety Endpoint: TIMI Major Bleeding

MACE

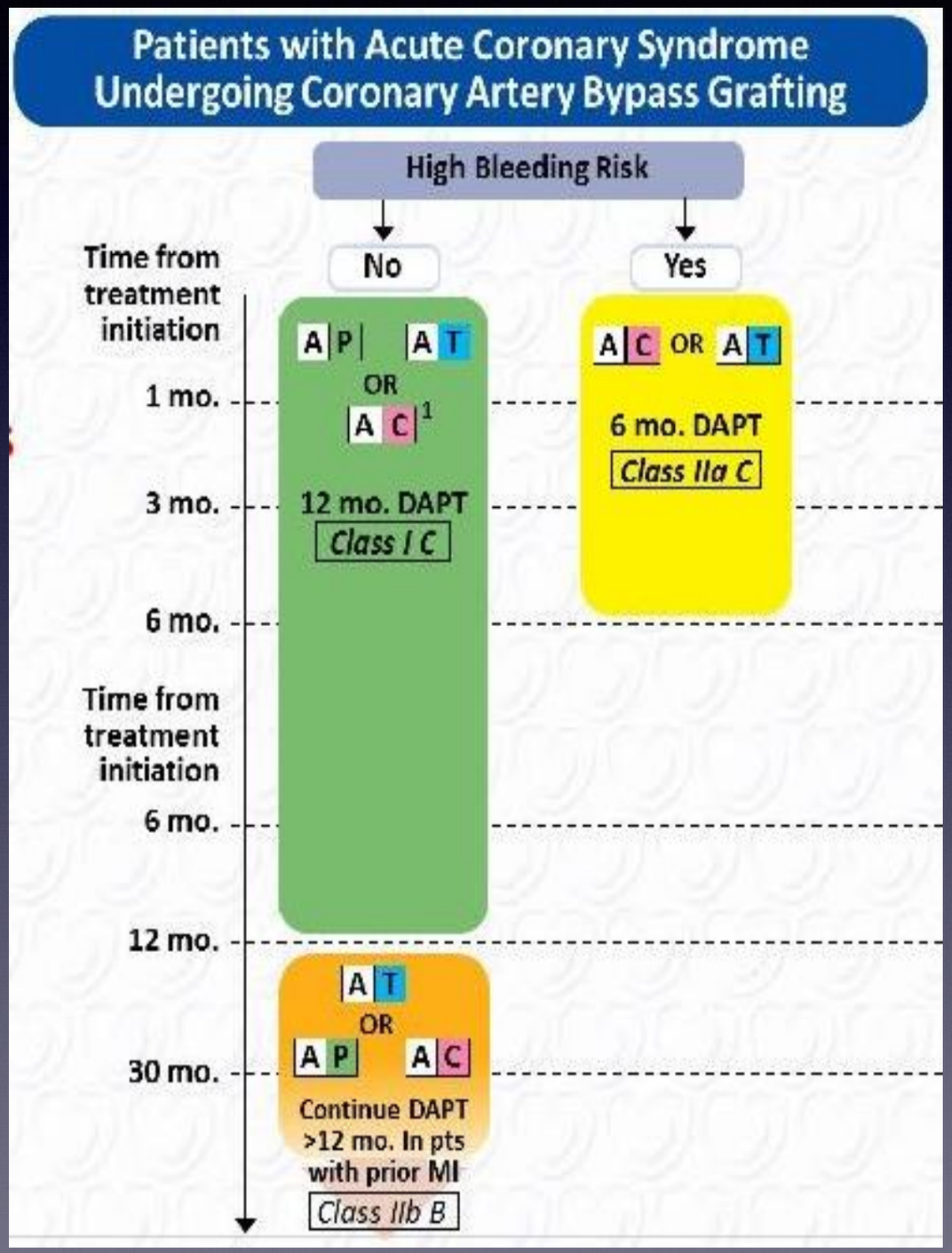


No. at Risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

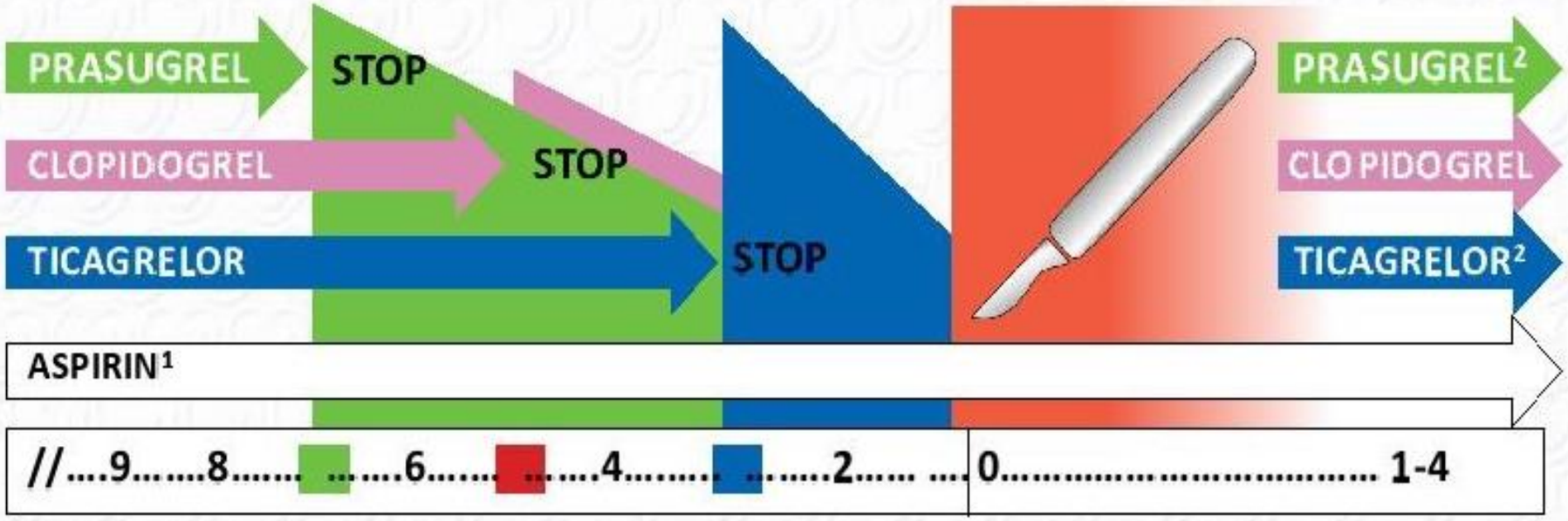
Safety endpoint



DAPT IN CABG



- Continue aspirin at a low daily regimen throughout the perioperative period
- Resume P2Y12 inhibitor therapy post-operatively as soon as is deemed safe
- In patients with ACS (NSTE-ACS or STEMI) continuation up to 12 months (IA)
- High risk of severe bleeding DAPT for 6 months should be considered. (IIA)
- High ischaemic risk DAPT for longer than 12 and up to 36 months may be considered (IIB)



= Expected average platelet function recovery

[1] Decision to stop aspirin throughout surgery should be made on a single case basis taking into account the surgical bleeding risk.

[2] In patients not requiring OAC.

Postponing surgery for at least 3 days after **discontinuation** of ticagrelor, at least 5 days after clopidogrel, and at least 7 days after prasugrel

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In non CABG surgery?

Recommendations	Class	Level
It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.	I	B
After coronary stent implantation, elective surgery requiring discontinuation of the $P2Y_{12}$ inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the peri-operative period.	IIa	B
Discontinuation of $P2Y_{12}$ inhibitors should be considered at least 3 days before surgery for ticagrelor, at least 5 days for clopidogrel and at least 7 days for prasugrel.	IIa	B
A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery.	IIa	C
In patients with recent MI or other high ischaemic risk features requiring DAPT, elective surgery may be postponed for up 6 to months.	IIb	C
If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.	IIb	C
It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non cardiac surgery.	III	B

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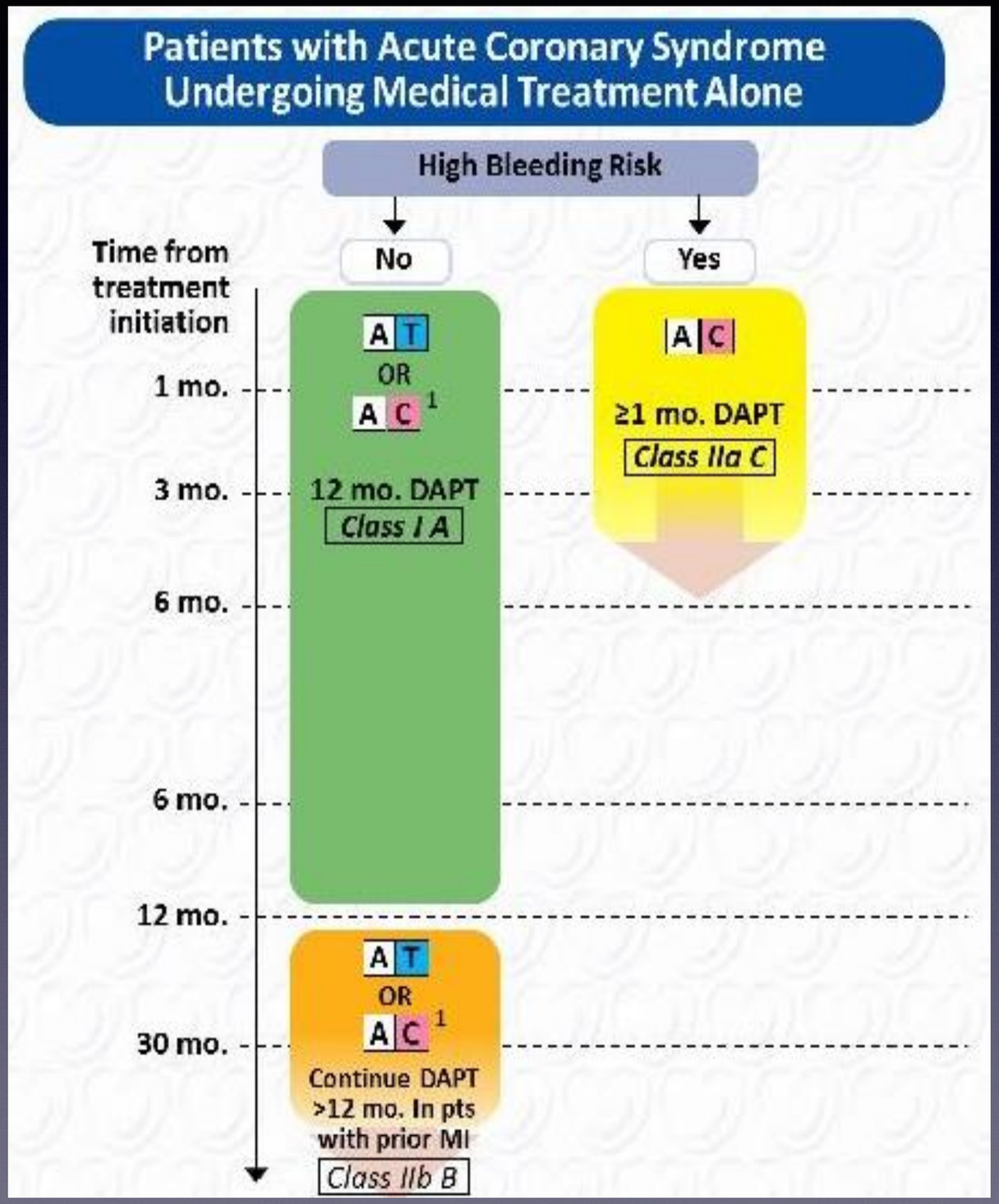
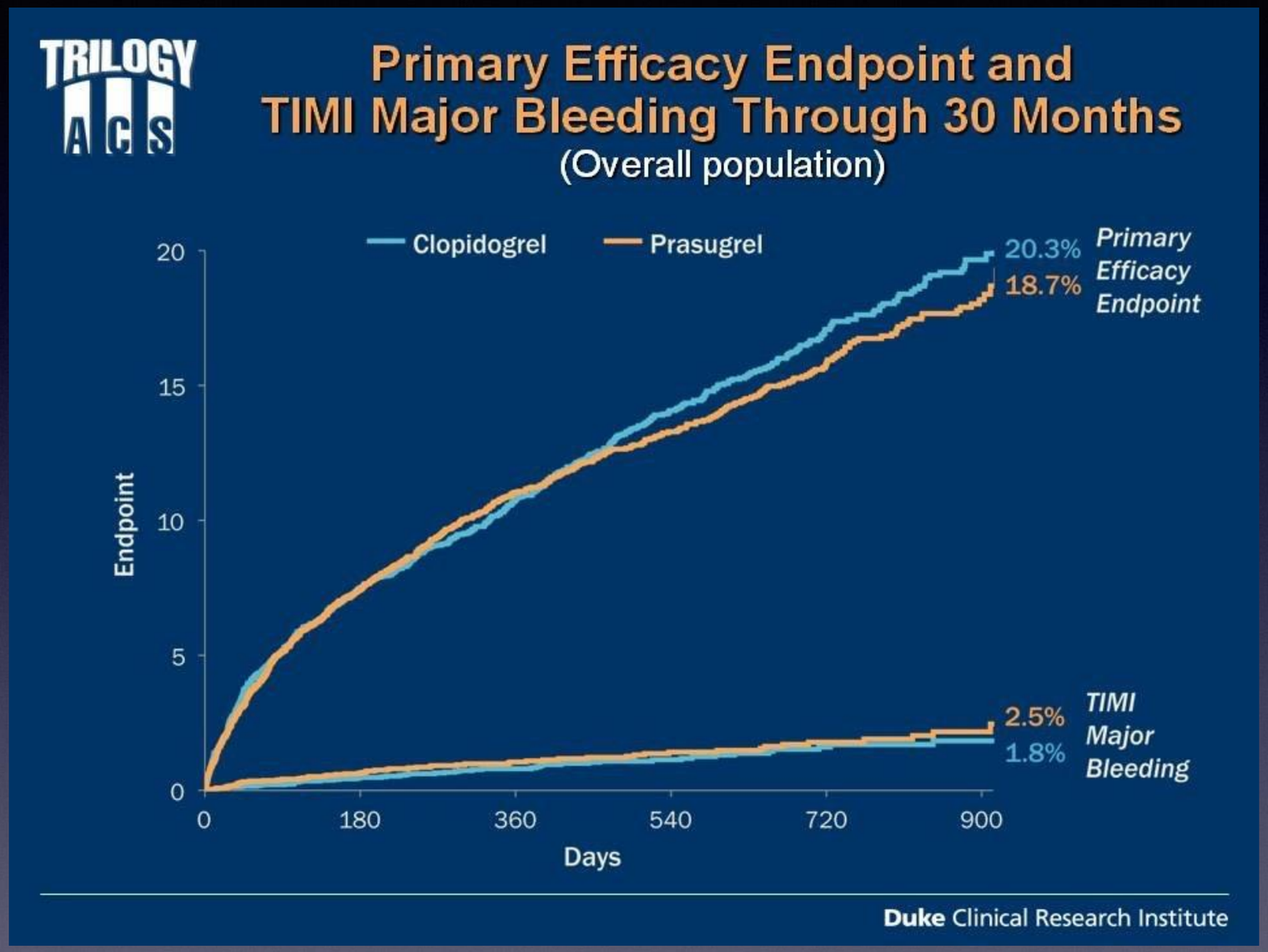
DAPT in Medical Treatment alone



- In patients with ACS DAPT with ticagrelor or clopidogrel for 12 months (IA)
- Ticagrelor is recommended over clopidogrel
- In High risk of bleeding, DAPT (Clopidogrel) for at least 1 month should be considered (IIa)
- In high ischaemic risk ticagrelor 60 mg b.i.d. on top of aspirin for longer than 12 months and up to 36 months may be considered (IIb)
- Prasugrel is not recommended in medically managed ACS patients

(TRILOGY STUDY)

TRILOGY STUDY



No superiority of prasugrel vs clopidogrel
Higher bleeding risk

Roe T et al. TRILOGY ACS Investigators TA. Prasugrel versus clopidogrel for acute coronary syndrome without revascularization. N Engl J Med . 2012;367:1297–1309.

Switching p2y12

CLOPIDOGREL ->TICAGRELOR

Only switch between $P2Y_{12}$ inhibitors that has been investigated in a trial powered for clinical endpoint

In PLATO, nearly 50% of patients randomly · allocated to receive ticagrelor had been pre-treated with clopidogrel.

The efficacy and safety of ticagrelor were not affected by previous clopidogrel exposure.

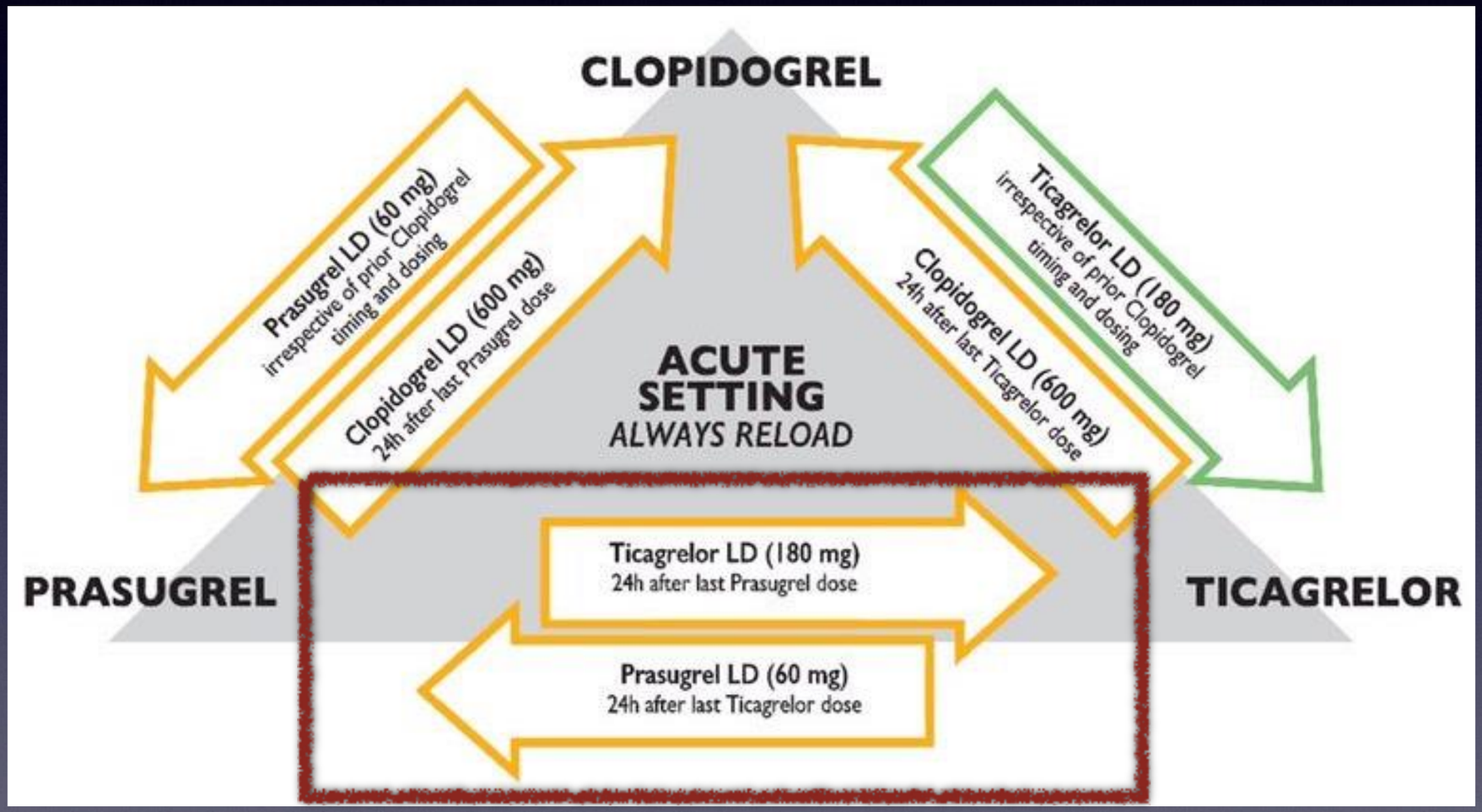
CLOPIDOGREL->PRASUGREL

In TRITON-TIMI 38 trial mandated that previous exposure of patients to a $P2Y_{12}$ receptor inhibitor should be an exclusion criterion for study entry.

No randomized data exist in the setting of studies powered for clinical endpoint

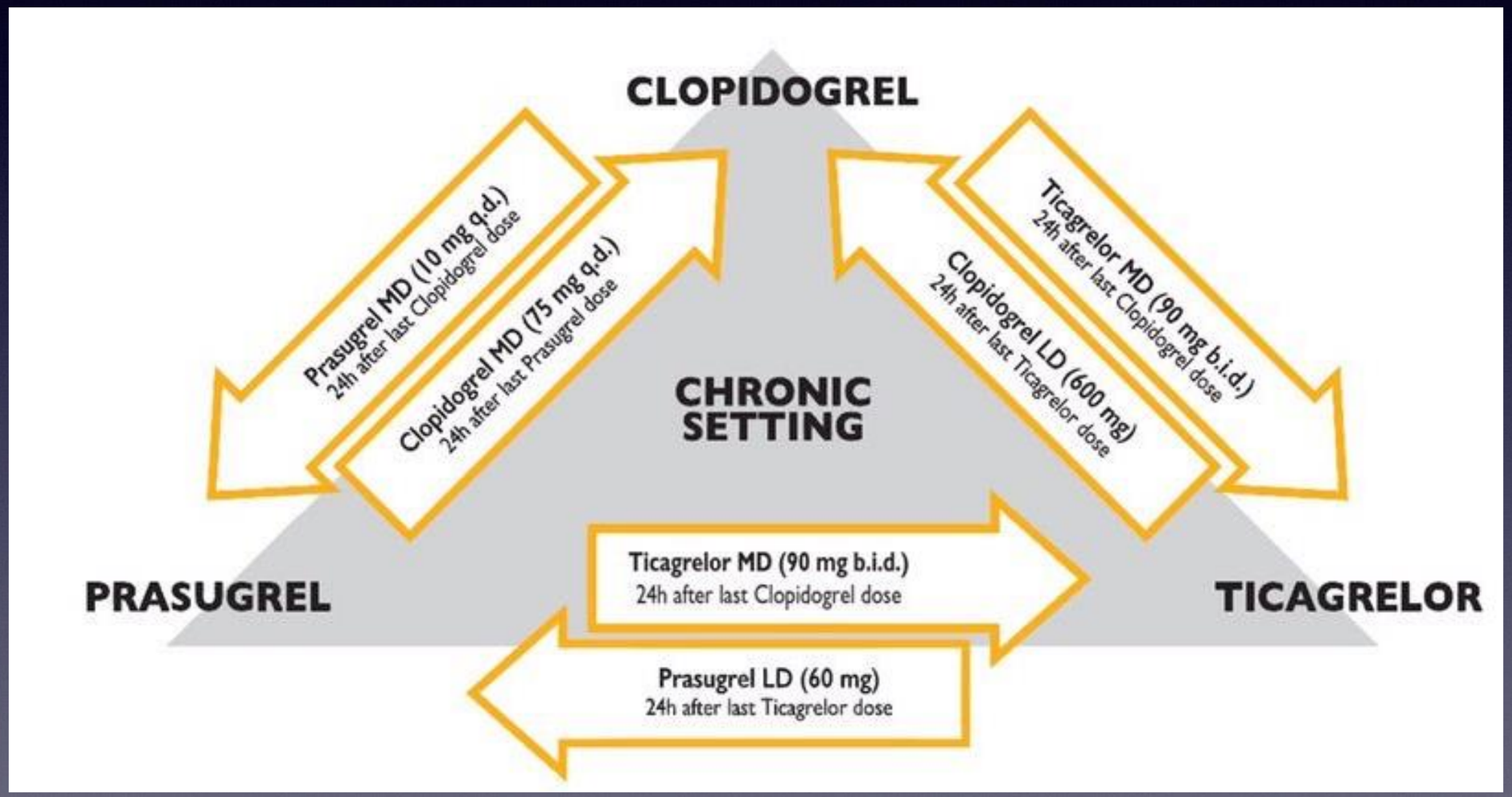
Recommendations	Class	Level
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contra-indications to ticagrelor exist.	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

Switching in acute setting



Switching from prasugrel to ticagrelor leads to transiently higher levels of platelet inhibition.

Switching in chronic setting



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DAPT & OAC

PAZIENTI CANDIDATI ALLA TERAPIA ANTICOAGULANTE :

-FA con CHA_2DS_2- VASc score ≥ 1 negli uomini, ≥ 2 nelle donne

-Protesi valvolari meccaniche

-Recente TVP o EP

-Trombosi arteriose

SE QUESTI PAZIENTI VANNO INCONTRO A PCI, SONO DA CONSIDERARSI

AD ALTO RISCHIO EMORRAGICO !

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CHA_2DS_2- VASc score

C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

HAS BLED

H	Hypertension: (uncontrolled, >160 mmHg systolic)	1
A	Abnormal renal function: Dialysis, transplant, Cr >2.26 mg/dL Abnormal liver function: Cirrhosis or Bilirubin >2x or AST/ALT >3x	1
S	Stroke: Prior history of stroke	1
B	Bleeding: Prior Major Bleeding or Predisposition to Bleeding	1
L	Labile INR: (Unstable/high INR), Time in Therapeutic Range < 60%	1
E	Elderly: Age > 65 years	1
D	Prior Alcohol or Drug Usage History (≥ 8 drinks/week) Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs)	1 1

MINIMIZZARE RISCHIO EMORRAGICO

- Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
- Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
- Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.
- Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.
- Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
- Use low-dose (≤100 mg daily) aspirin.
- Routine use of PPIs.

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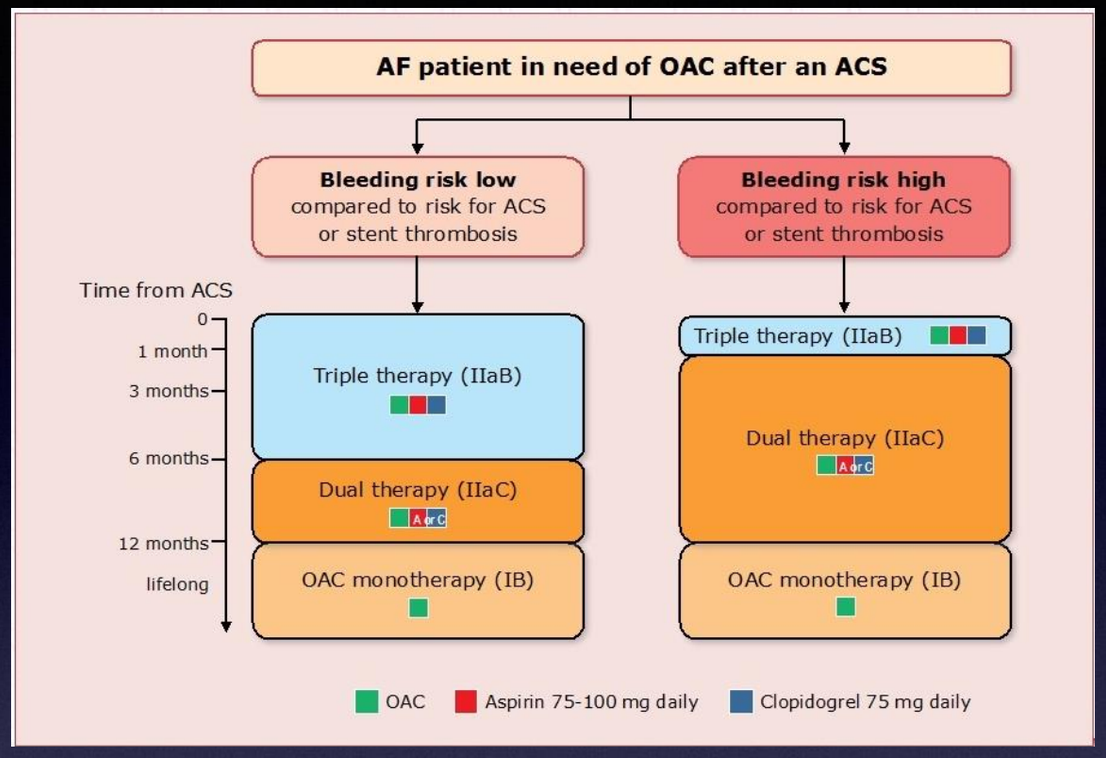
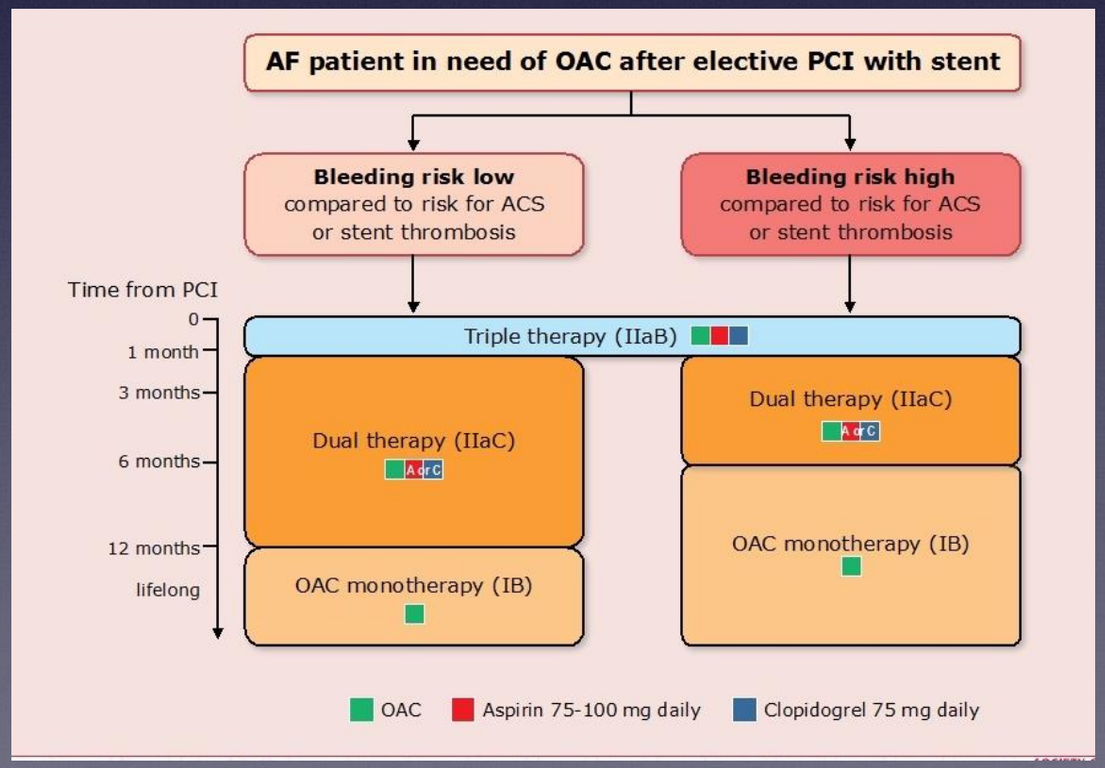
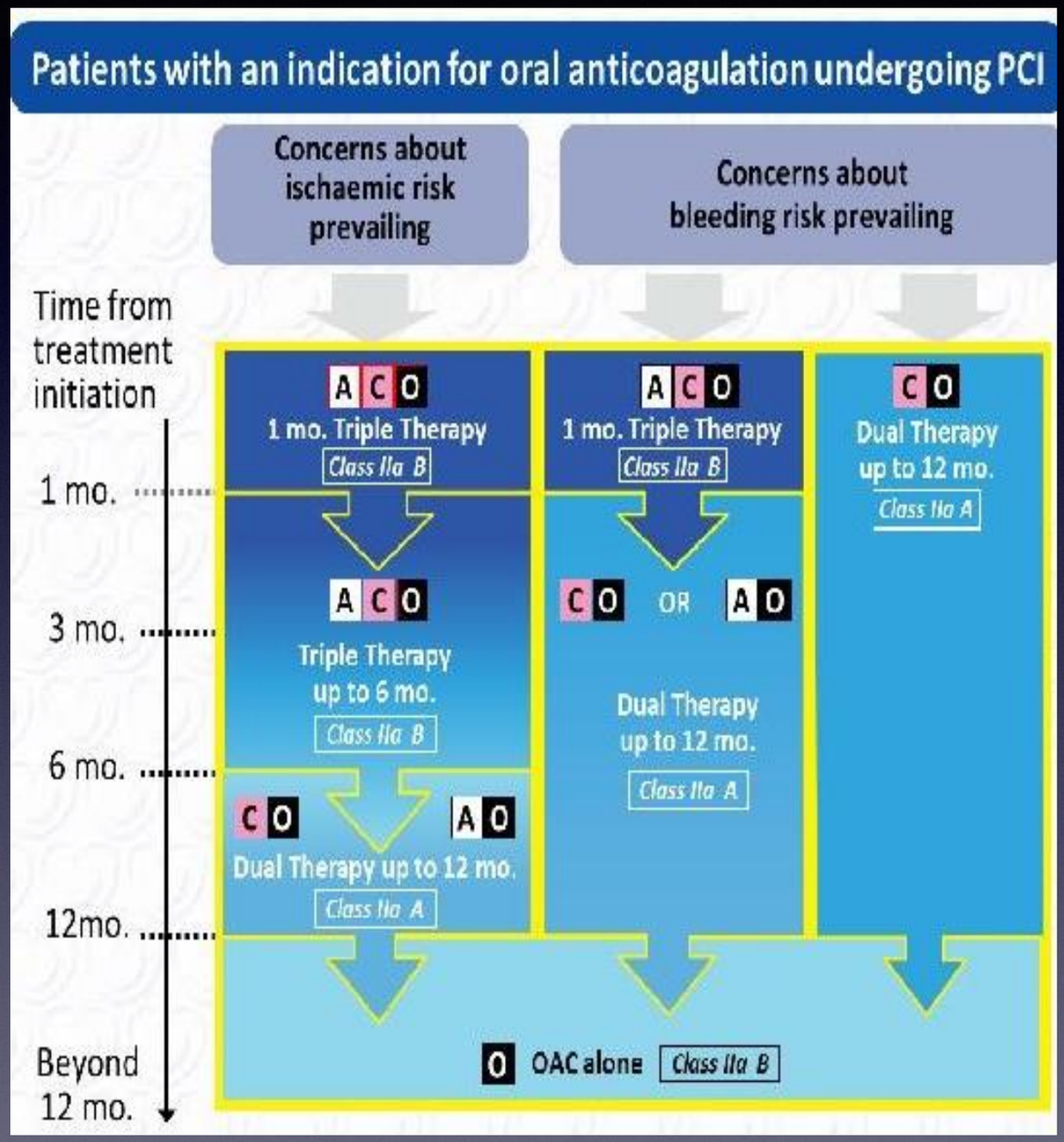
PAST & PRESENT…..WHAT'S NEW?







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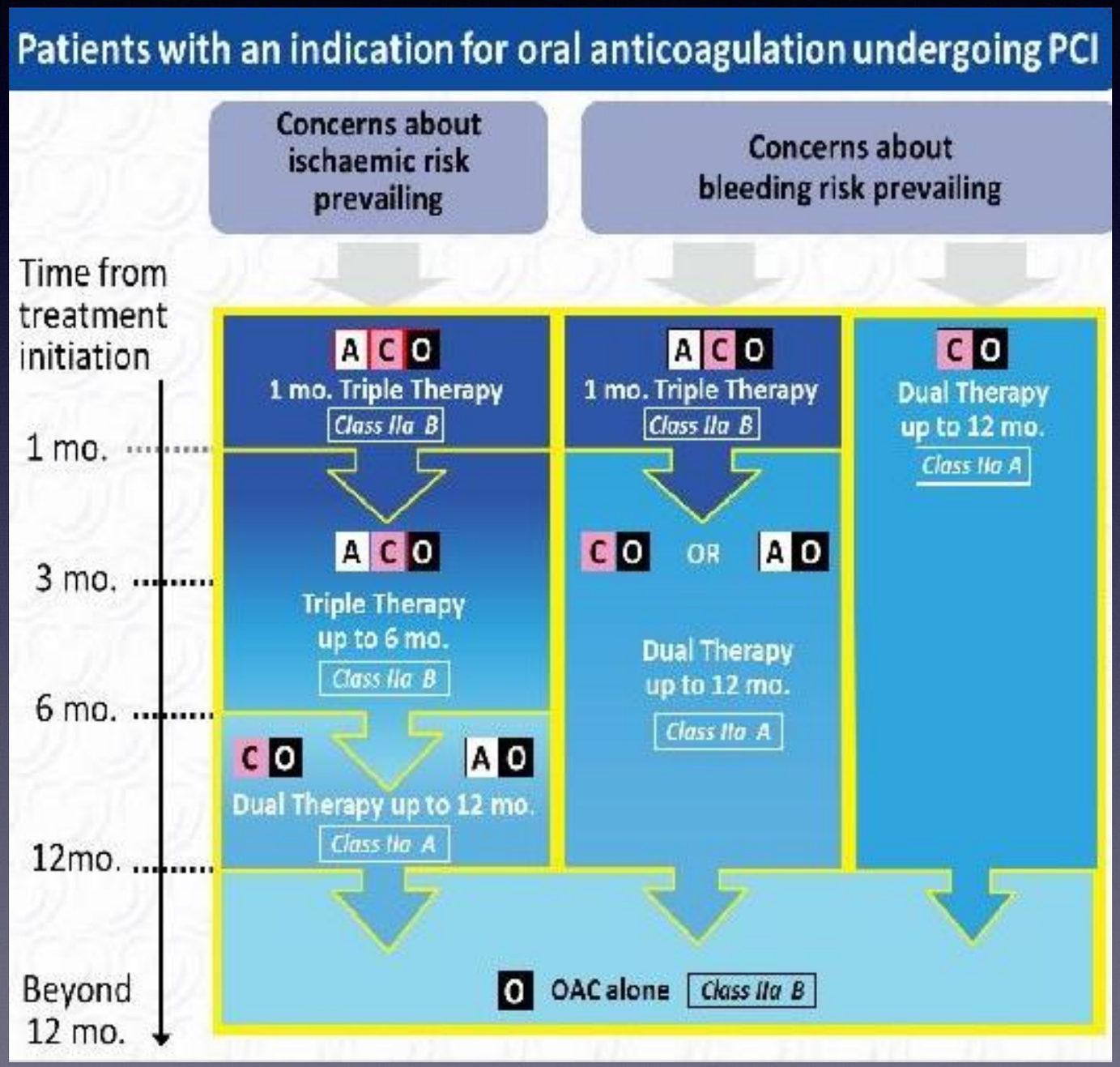
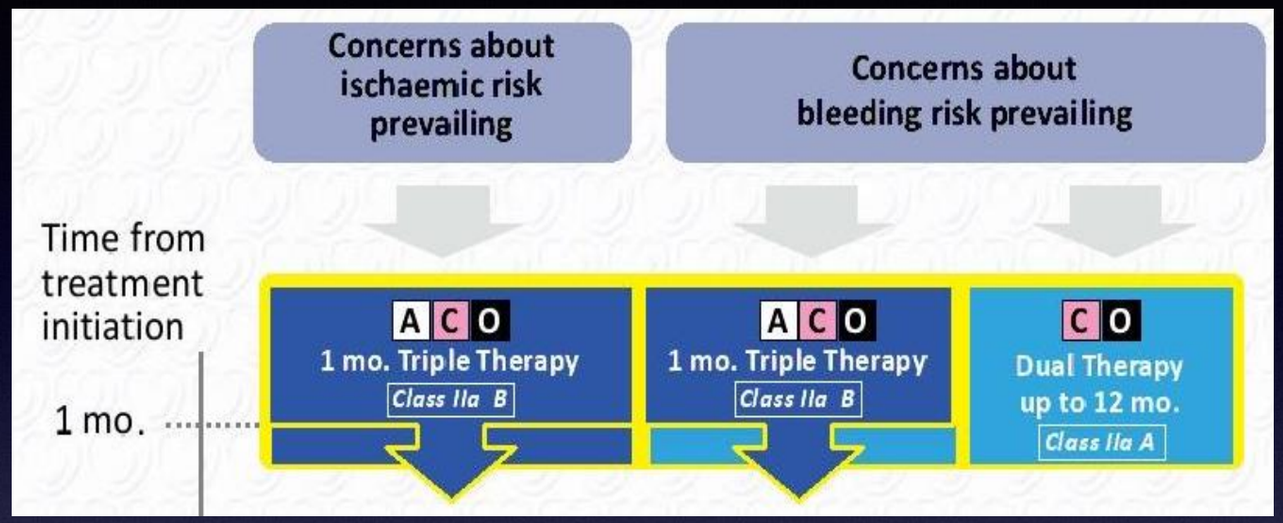
What's news?

- Focused on bleeding/ischaemic risk
- Triple therapy for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk
- Dual therapy with clopidogrel 75 mg/day and OAC should be considered in high bleeding risk (HAS-BLED ≥ 3)
- Use of NOAC + DAPT
- Rivaroxaban15 mg q.d. may be used
- Ticagrelor and prasugrel not recommended as part of triple therapy



TRIPLE THERAPY



High ischaemic risk is considered as an acute clinical presentation or anatomical/procedural features which might increase the ris

• Prior stent thrombosis on adequate antiplatelet therapy.
• Stenting of the last remaining patent coronary artery.
• Diffuse multivessel disease especially in diabetic patients.
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min).
• At least three stents implanted.
• At least three lesions treated.
• Bifurcation with two stents implanted.
• Total stent length >60 mm.
• Treatment of a chronic total occlusion.

DUAL THERAPY
Clopidogrel 75 mg+ OAC

• Short life expectancy.
• Ongoing malignancy.
• Poor expected adherence.
• Poor mental status.
• End stage renal failure.
• Advanced age.
• Prior major bleeding/prior haemorrhagic stroke.
• Chronic alcohol abuse.
• Anaemia.
• Clinically significant bleeding on dual antithrombotic therapy.

WOEST STUDY

WOEST

573 patients underwent 1:1 randomization
(therapy for 1 month after BMS or 1 year after DES)

Double therapy group:

OAC + 75mg Clopidogrel qd

Triple therapy group

OAC + 75mg Clopidogrel qd + 80mg Aspirin qd

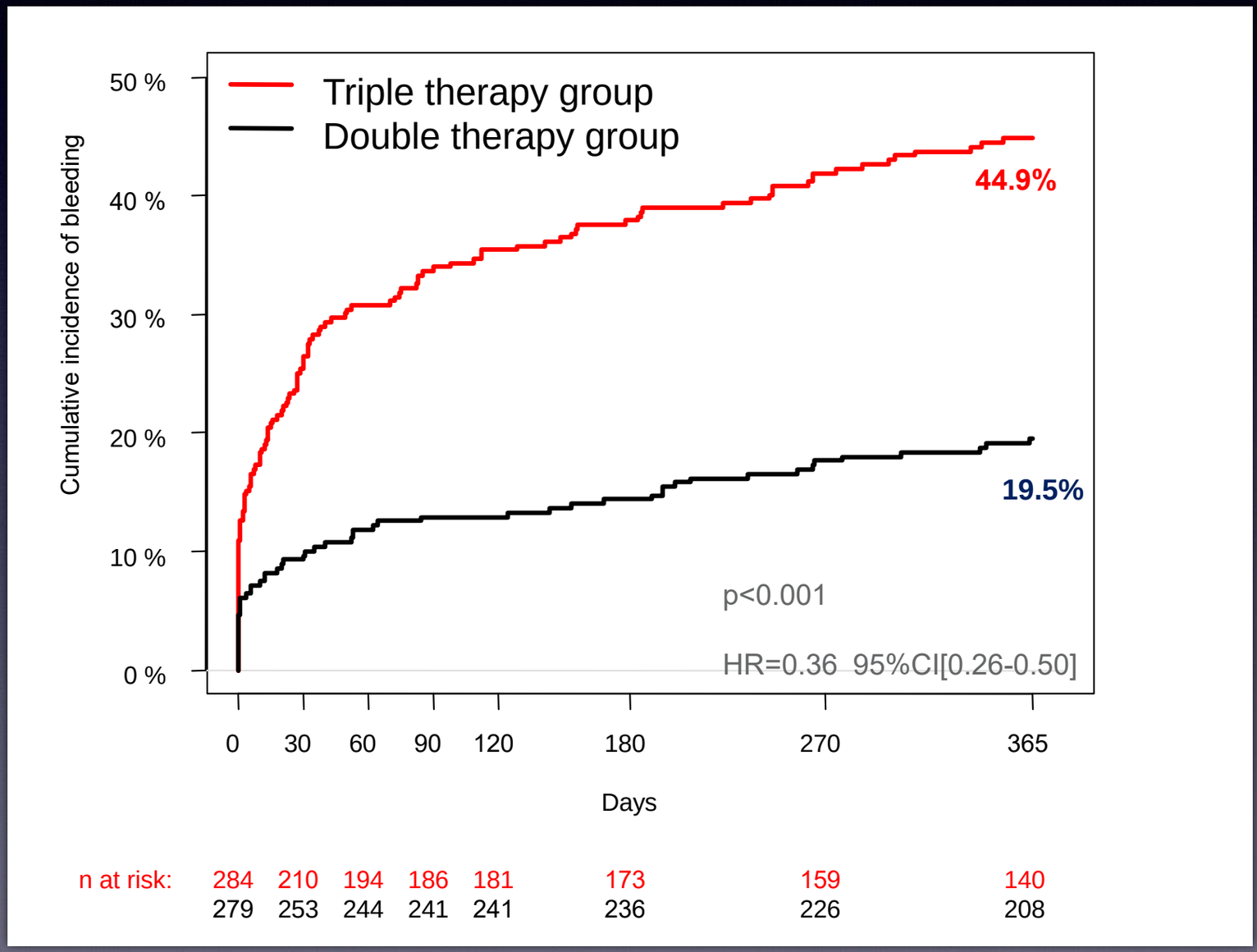
Primary Endpoint: **The occurence of all bleeding events (TIMI criteria)**

Secondary Endpoints:

- **Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation**

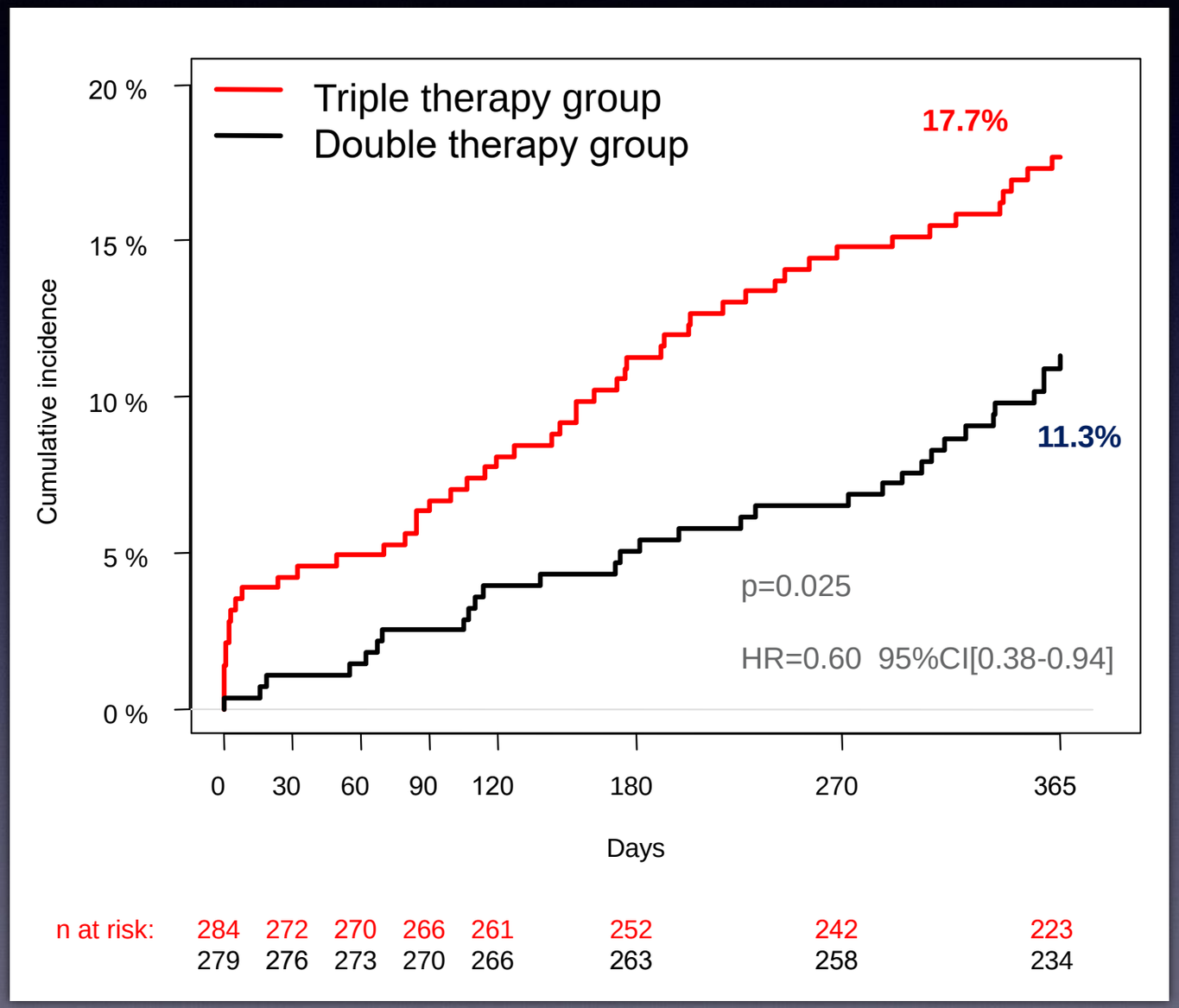
without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, c

Primary endpoints
TIMI bleeding events



without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, c

Secondary endpoint
Death, MI, Stroke, ST



without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, c

WOEST

1. First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting

2. In this study which was specifically designed to detect bleeding events, the bleeding rate was higher than expected

3. OAC plus clopidogrel causes **less bleeding than triple antithrombotic therapy**, but now shown in a randomized way

4. With double therapy there is **no excess of thrombotic/thromboembolic events** stroke, stent thrombosis, myocardial infarction or death

5. Less all-cause mortality with double therapy

without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, c

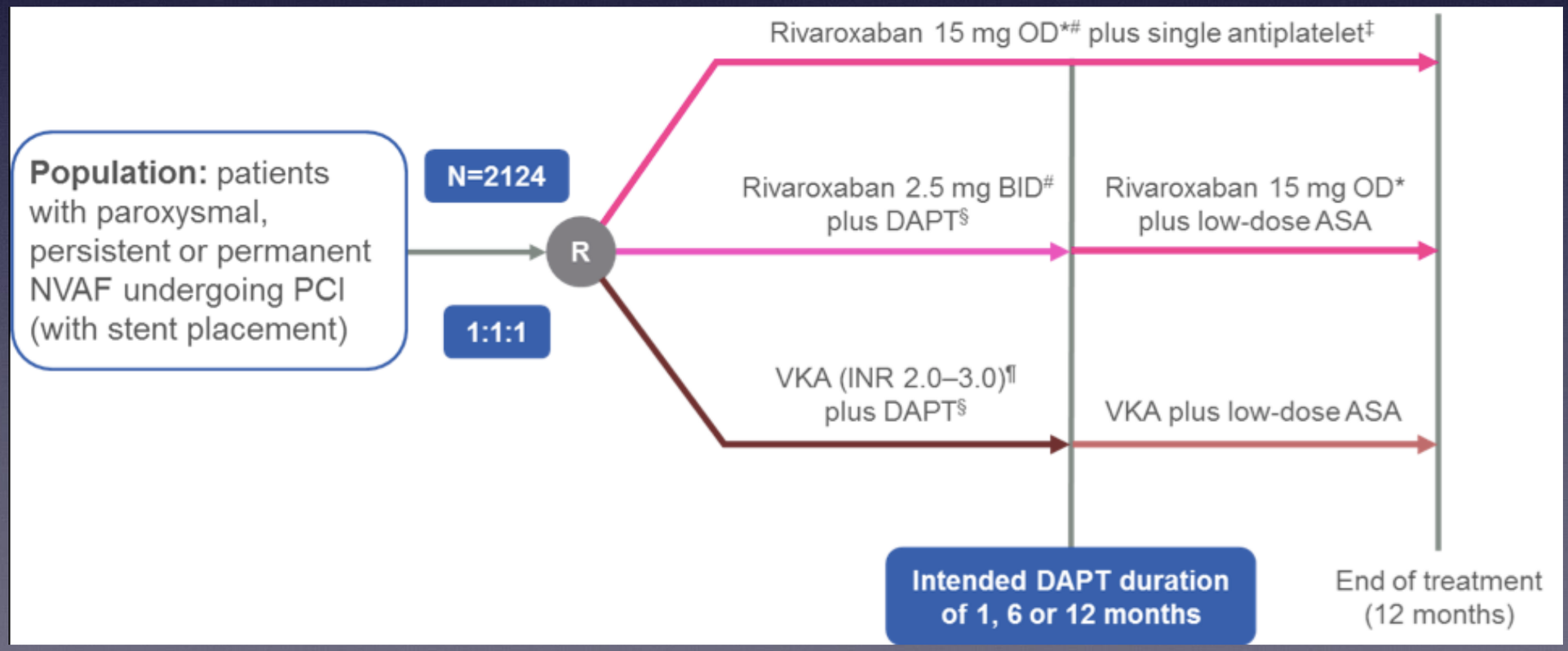
PIONEER-AF

Treatment arms

1. Group 1: rivaroxaban 15 mg/d plus clopidogrel 75 mg/d for 12 months **(WOEST trial-like strategy)**

2. Group 2: rivaroxaban 2.5 mg twice daily with DAPT for 1, 6, or 12 months

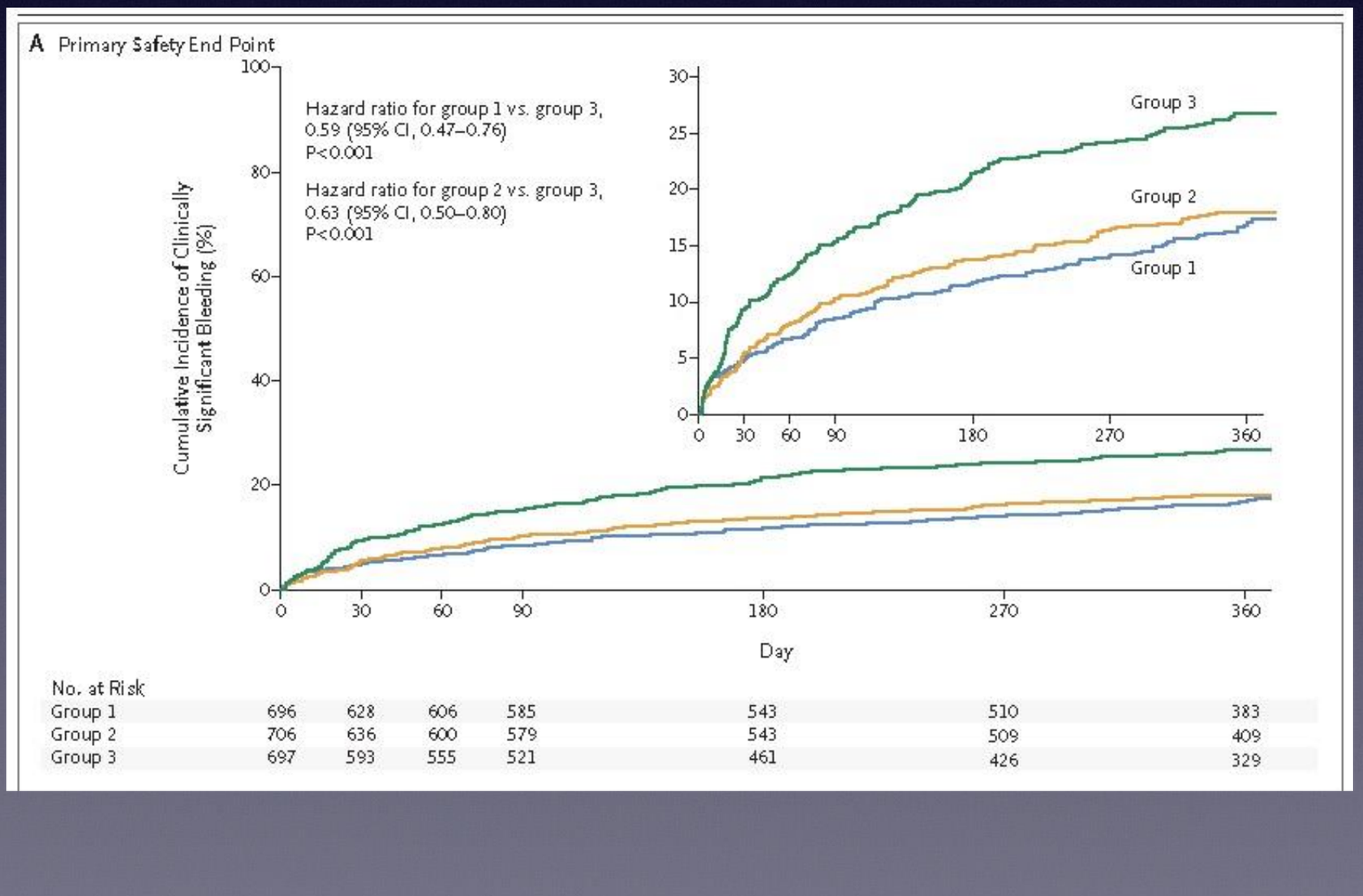
3. Group 3: vitamin K antagonist (VKA) once daily with DAPT for 1, 6, or 12 months (traditional triple therapy)



Gibson CM et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423–2434.

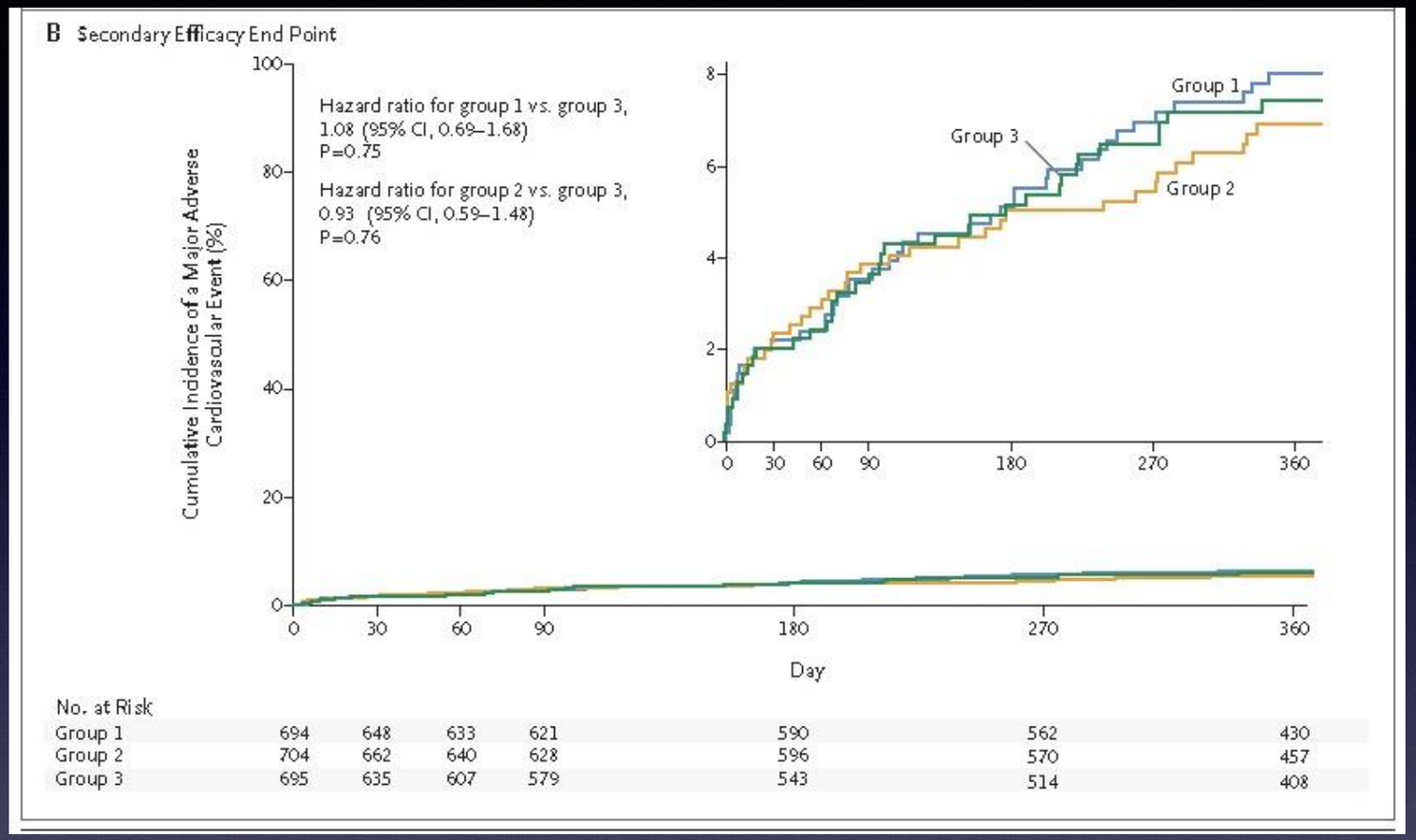
PIONEER-AF

Lower rate of clinically significant bleeding in Groups 1 and 2 vs Group 3



Group 1
best safety

No significant difference in MACE

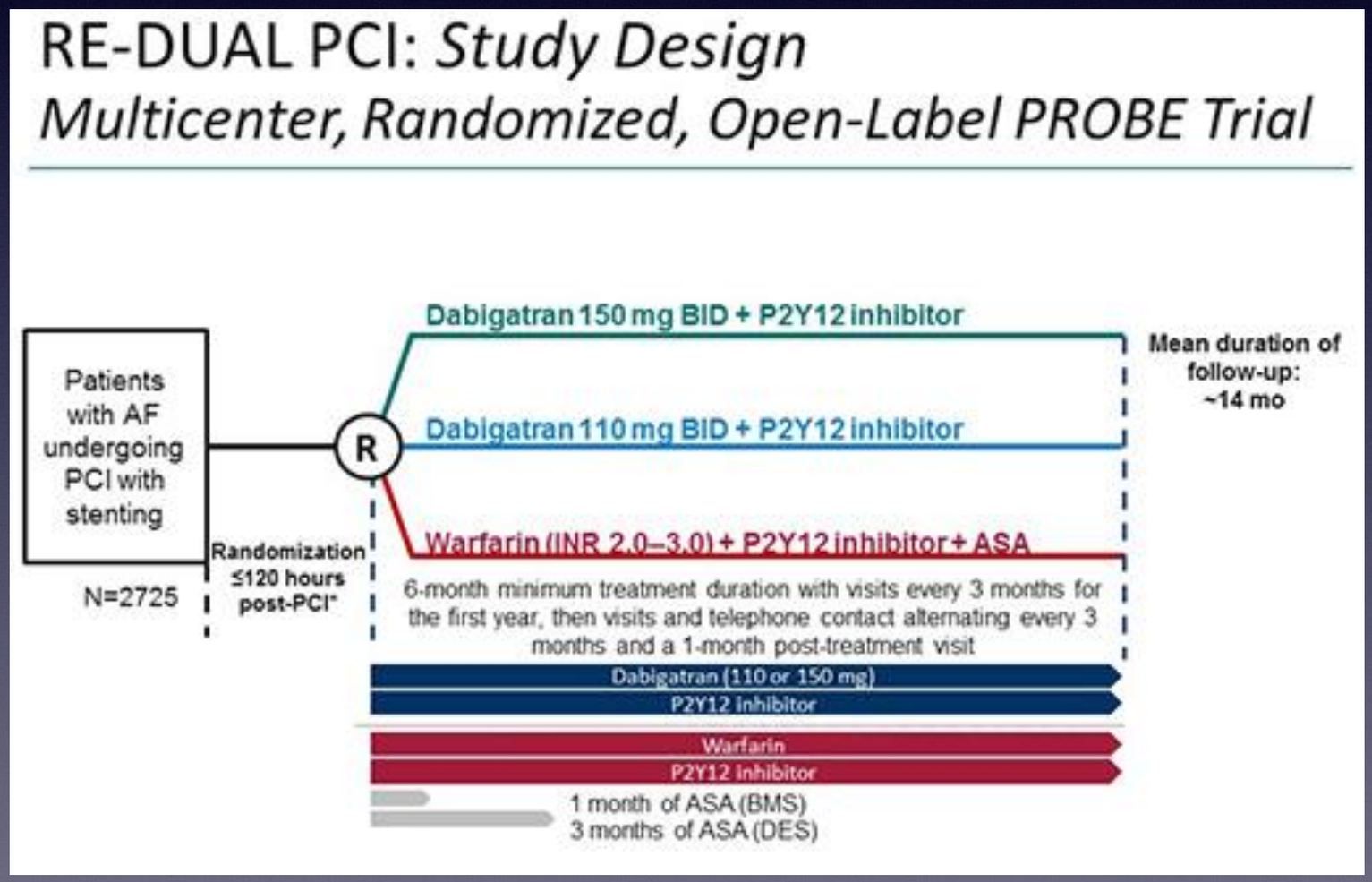


Group 1
best efficacy

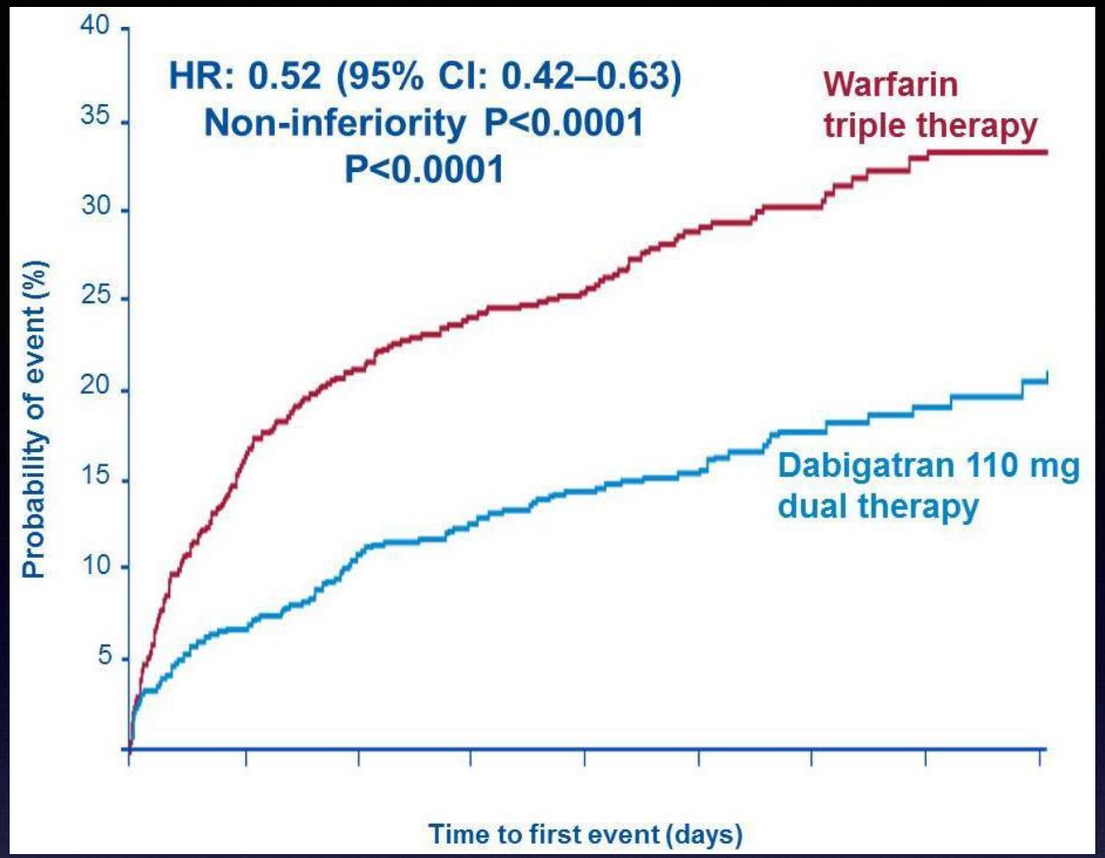
When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg q.d. may be used….IIb B

Redual PCI

- Treatment arms
  Dual therapy with dabigatran (110 or 150 mg twice daily) and a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor)
  Triple therapy with warfarin, a $P2Y_{12}$ inhibtor (clopidogrel or ticagrelor), and low-dose aspirin (for 1 or 3 months,



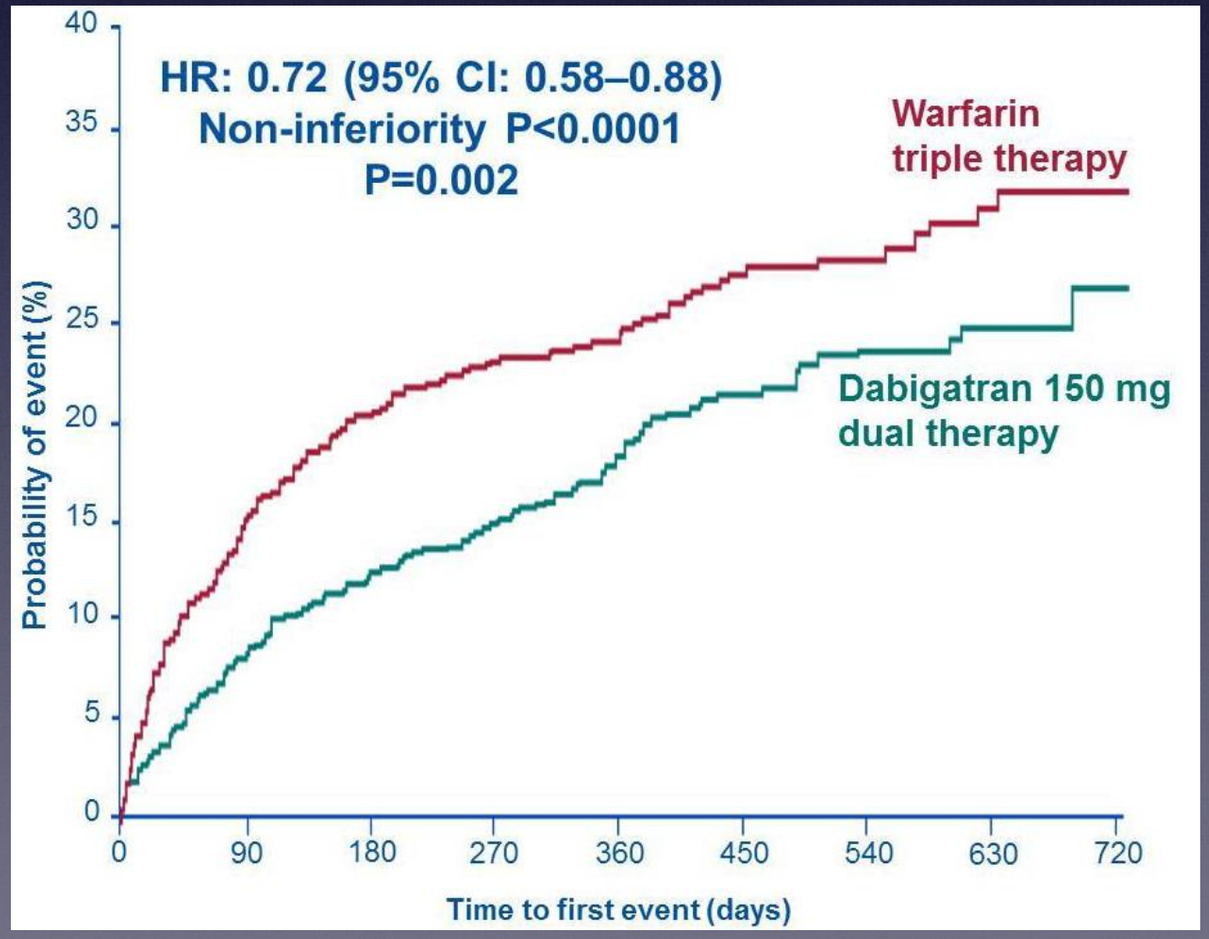
P. et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Eng J Med 2017; 377:



PRIMARY ENDOPOINT BLEEDINGS

48% lower risk in dabigatran 110 mg

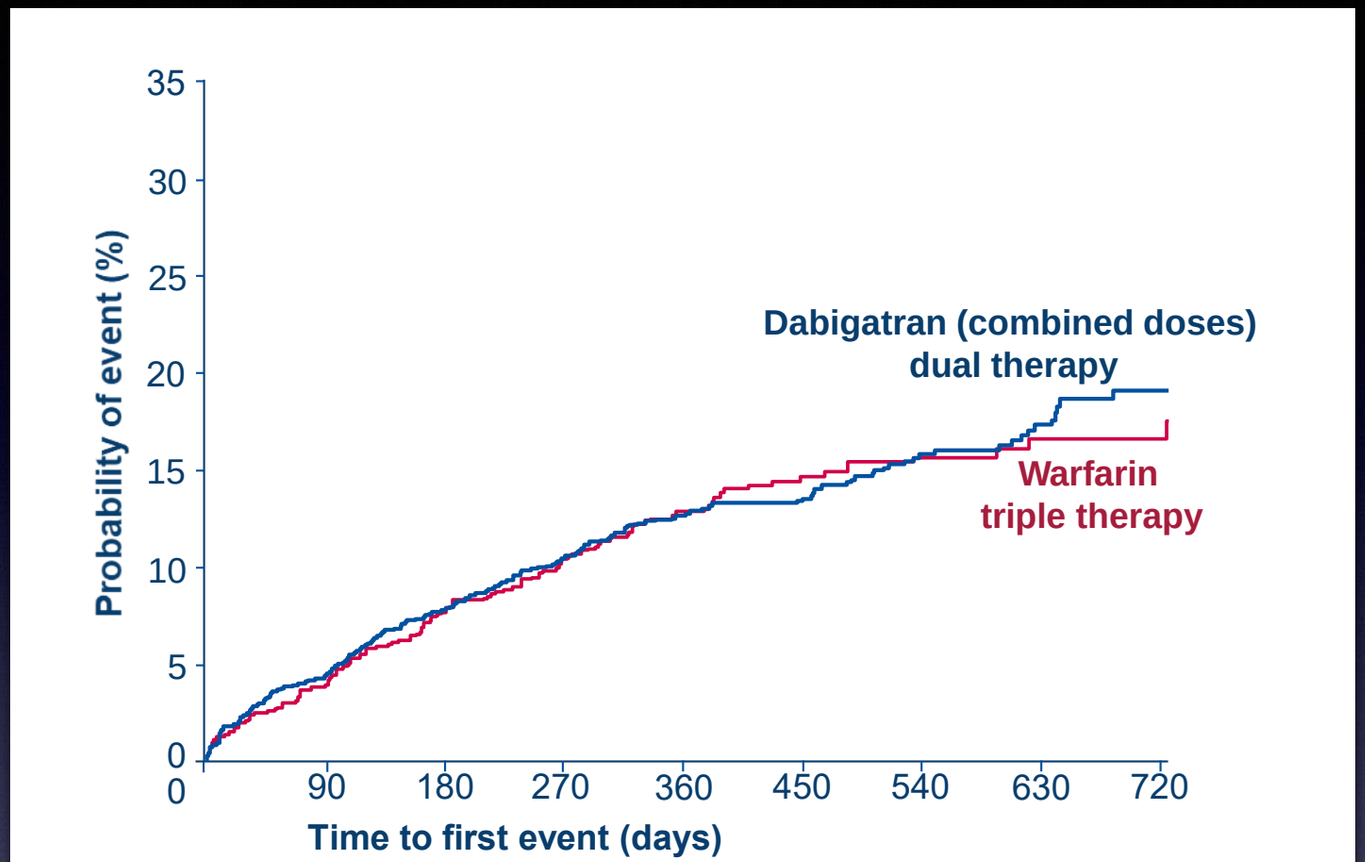
28% lower risk in dabigatran 150mg



SECONDARY EFFICACY ENDPOINTS

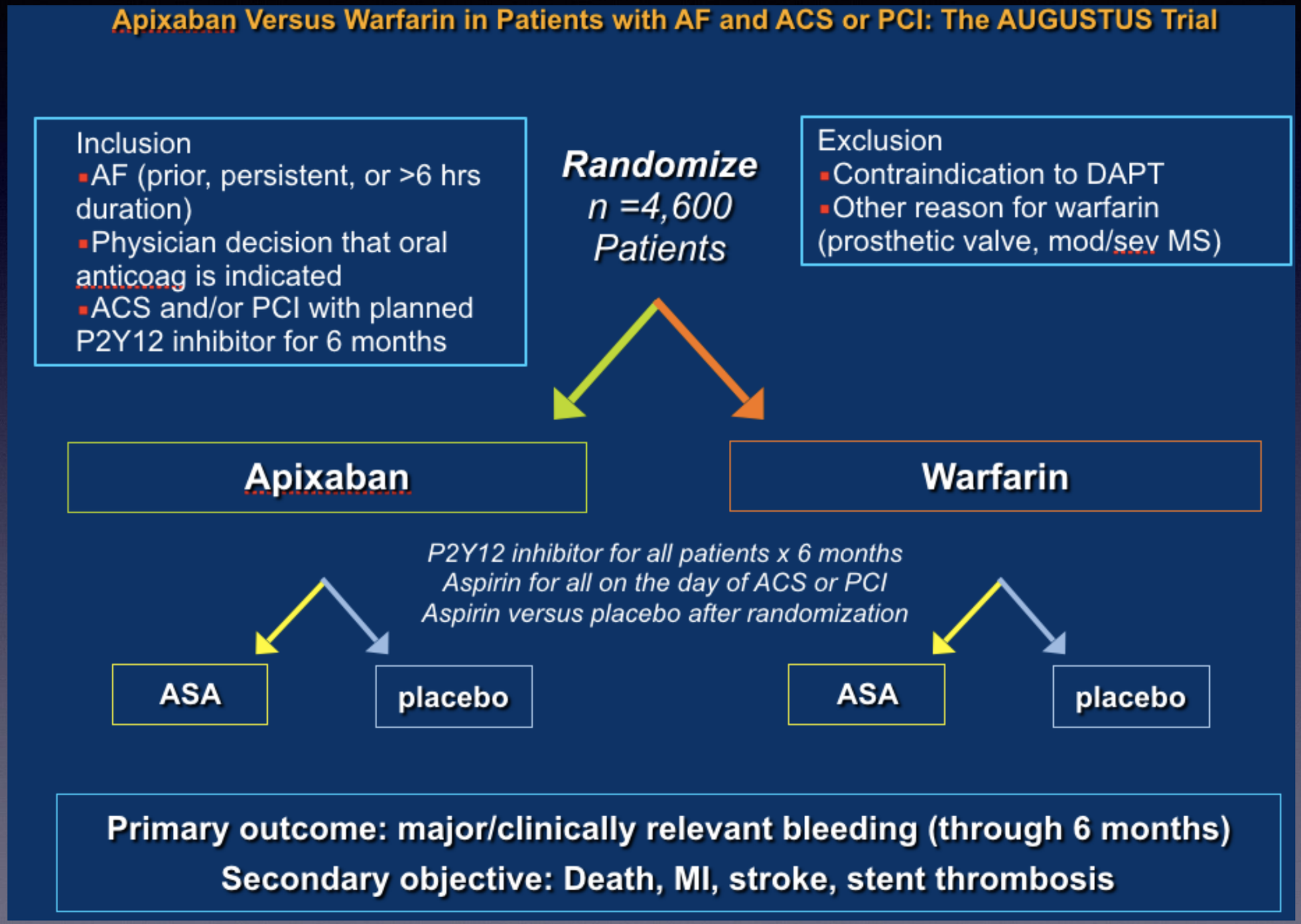
13,7 %in Dabigatran

13,4% in VKA

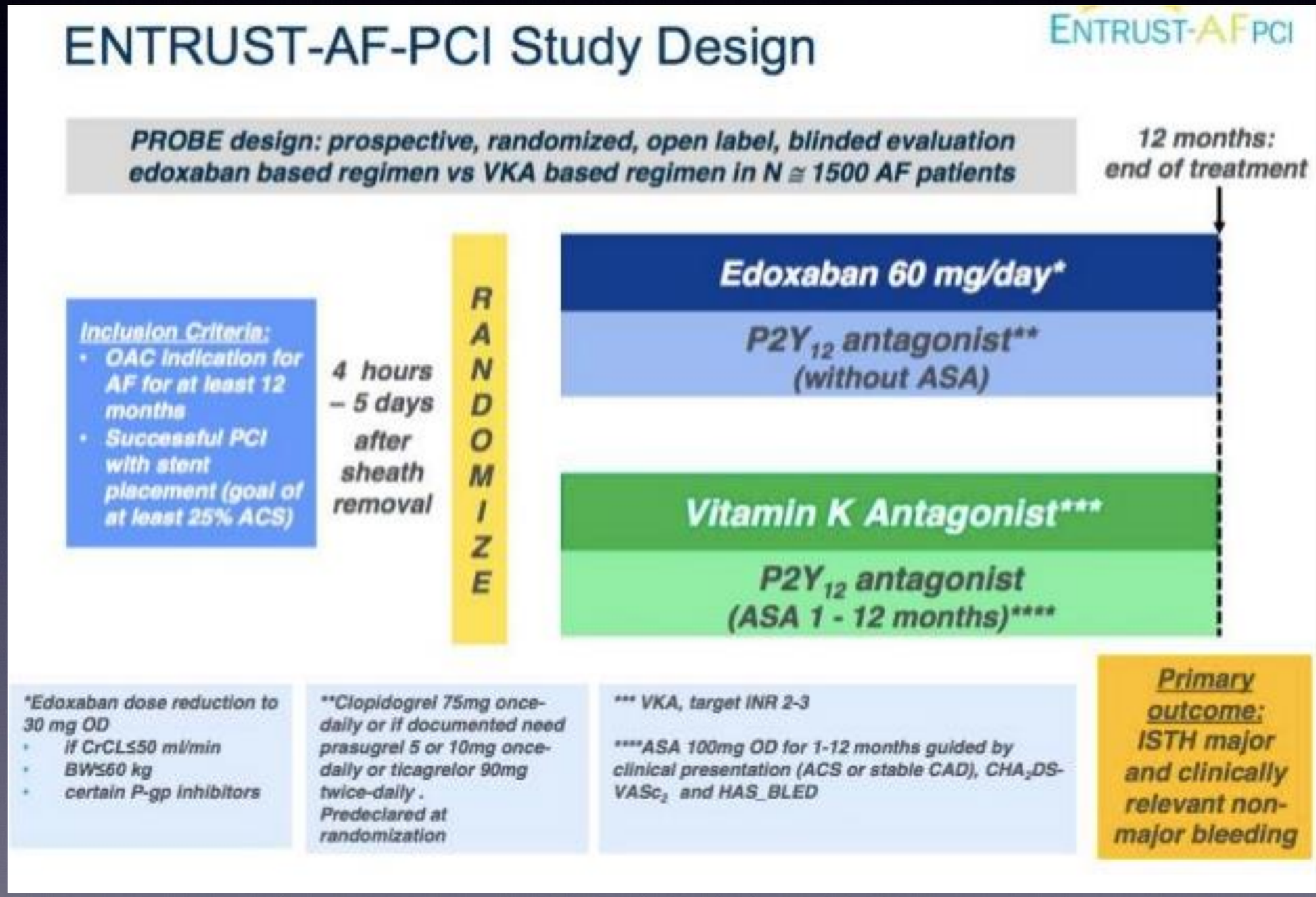


NON INFERIORITY

Augustus trial



ENTRUST AF-PCI



BLEEDING COMPLICATIONS

SANGUINAMENTI NON RILEVANTI

emorragia che non necessita di alcun trattamento medico o valutazioni ulteriore

es. ematomi cutanei o ecchimosi, epistassi autorisolventesi, emorragie congiuntivali minime.

Se paziente in DAPT: Continuare

Se paziente in OAC: Continuare

→ Attuare misure preventive

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BLEEDING COMPLICATIONS

SANGUINAMENTI LIEVI

emorragia che necessita di trattamento medico ma non richiede ospedalizzazione

es. emorragie urinarie, emorragie gastrointestinali senza perdite significative, epistassi non autorisolventesi, emorragie congiuntivali moderate, emottisi moderata

Se paziente in DAPT: Considerare **RIDUZIONE TIMING O DOWNGRADE** P2Y12 soprattutto se emorragie ricorrenti

Se paziente in DAPT +OAC: **downgrade** a OAC+Clopidogrel

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BLEEDING COMPLICATIONS

SANGUINAMENTI MODERATI

emorragia con perdita significativa ematica (Hb >3 g/dL), che richiede ospedalizzazione in paziente emodinamicamente stabile

es.emorragie a carico dell'apparato genitourinario, respiratorio, gastrointestinale con significativa perdita ematica o richiesta di trasfusione

Se paziente in DAPT: in acuto ->**STOP ASA.** Reintrodurre DAPT ad emostasi avvenuta, considerando **RIDUZIONE TIMING DAPT o DOWNGRADE** a Clopidogrel

Se paziente in OAC: STOP OAC fino ad emostasi avvenuta, salvo alto rischio trombotico.

in OAC+ SAPT: STOP SAPT

in OAC+ DAPT: STOP ASA (OAC+CLOPIDOGREL)

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BLEEDING COMPLICATIONS

SANGUINAMENTI GRAVI

emorragia con severa perdita ematica (Hb >5 g/dL), che richiede ospedalizzazione in paziente emodinamicamente stabile

es.emorragie a carico dell'apparato genitourinario, respiratorio, gastrointestinale con severa perdita ematica o richiesta di trasfusione

Se paziente in DAPT: in acuto ->**STOP ASA.** In caso di emorragia continua -> **STOP DAPT.**
Considerare successiva introduzione di SAPT (Clopidogrel) o DAPT con Clopidogrel se strettamente necessario

Se paziente in OAC: STOP OAC fino ad emostasi avvenuta, salvo alto rischio trombotico.

in OAC+ SAPT: STOP SAPT

in OAC+ DAPT: STOP ASA (OAC+CLOPIDOGREL)

TRASFUSIONE DI EMAZIE se Hb<7-8g/dL

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BLEEDING COMPLICATIONS

SANGUINAMENTI PERICOLOSI PER LA VITA

emorragia che necessita di trattamento tempestivo perché mettono a rischio la vita del paziente

es. emorragie urinarie, emorragie gastrointestinali con perdita massiva, emorragie intracraniche, spianli, intraoculari o qualsiasi perdita ematica che metta a rischio la vita del paziente

Se paziente in DAPT: STOP

Se paziente in OAC/OAC+SAPT/OAC+DAPT: STOP+ ANTIDOTO DOAC

TRASFUSIONE DI EMAZIE indipendentemente da Hb e PLT

SDENG!

SBAM!

rischio emorragico

rischio ischemico

GRAZIE!