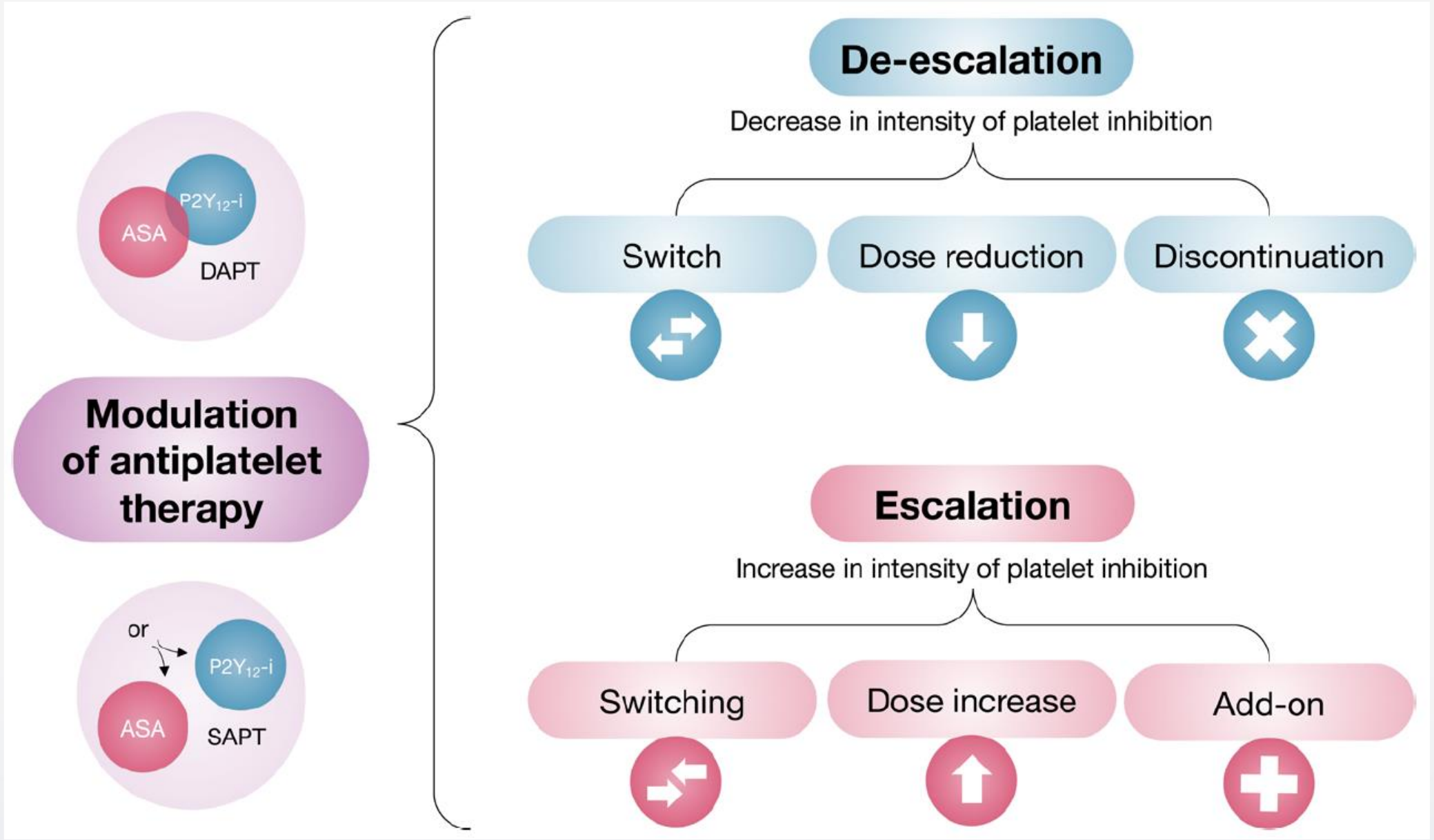
When to Escalate or De-Escalate in ACS/PCI

Tullio Palmerini, MD

University of bologna, Italy

Disclosure

- Lecure fees from Abbott, Medtronic, Edwards Lifescience

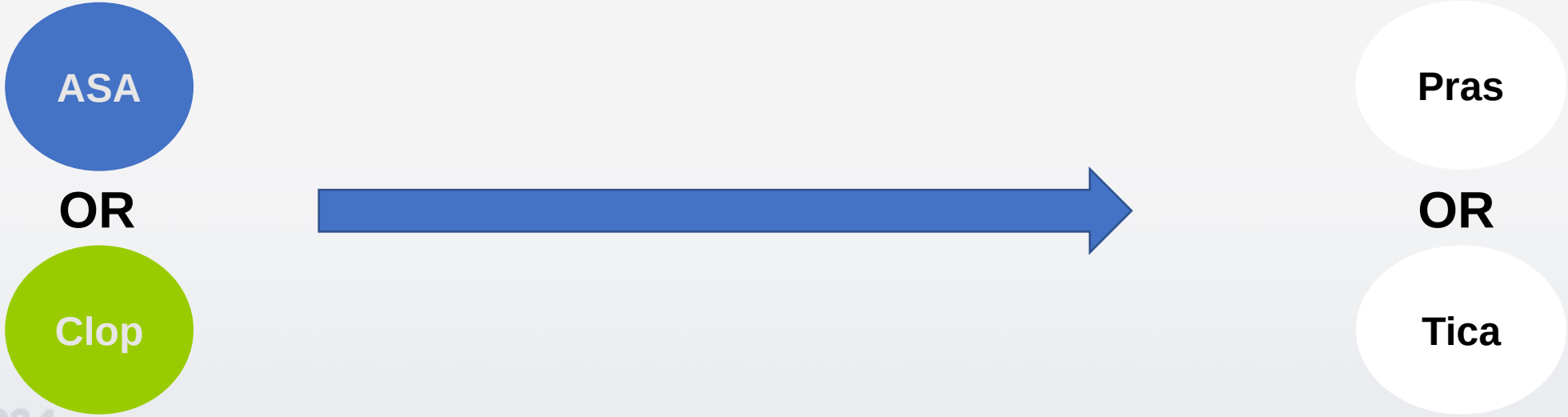


Capodanno et al; Circulation 2023

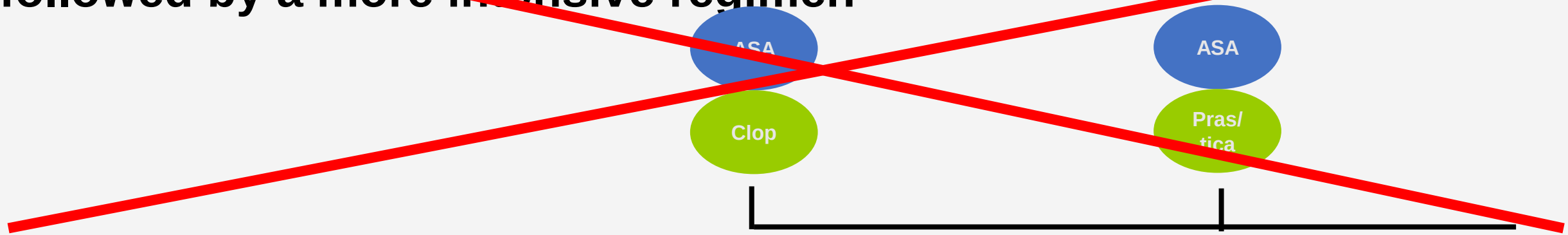
Escalation antiplatelet therapy

- **Why:** to reduce the risk of ischemic events with no tradeoff with bleeding
- **In which patient:** patient with stable coronary artery disease at HTR
- **How:** unguided or guided (platelet function or genetic test)

Switch to a more potent drug



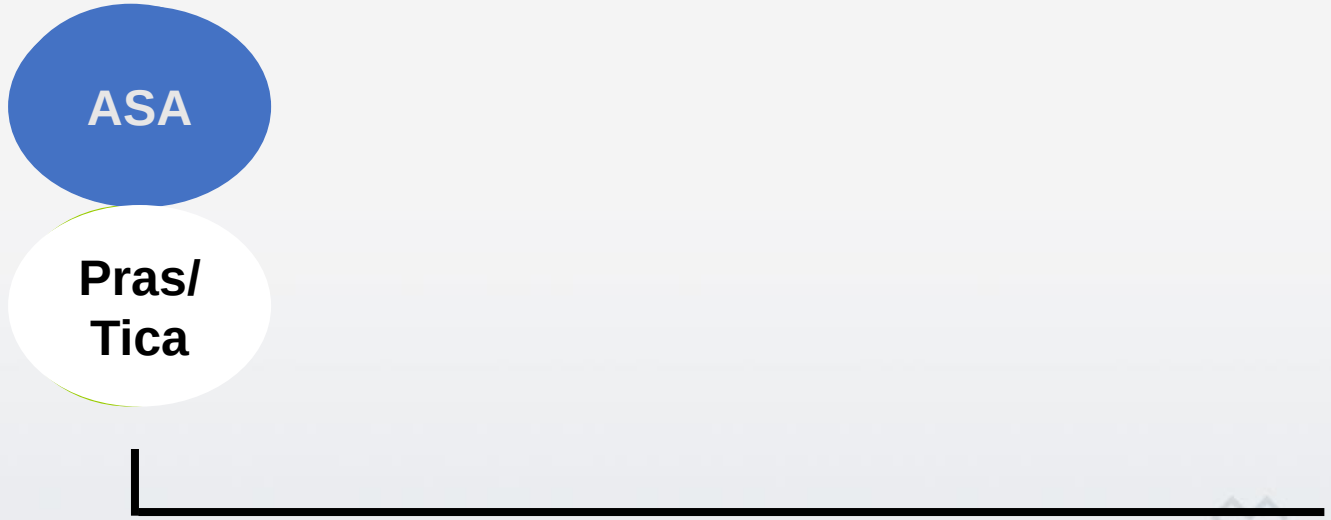
LITERAL DEFINITION: a period of DAPT with clopidogrel plus ASA followed by a more intensive regimen



BROADER DEFINITION: intensification of DAPT upfront compared to the default strategy

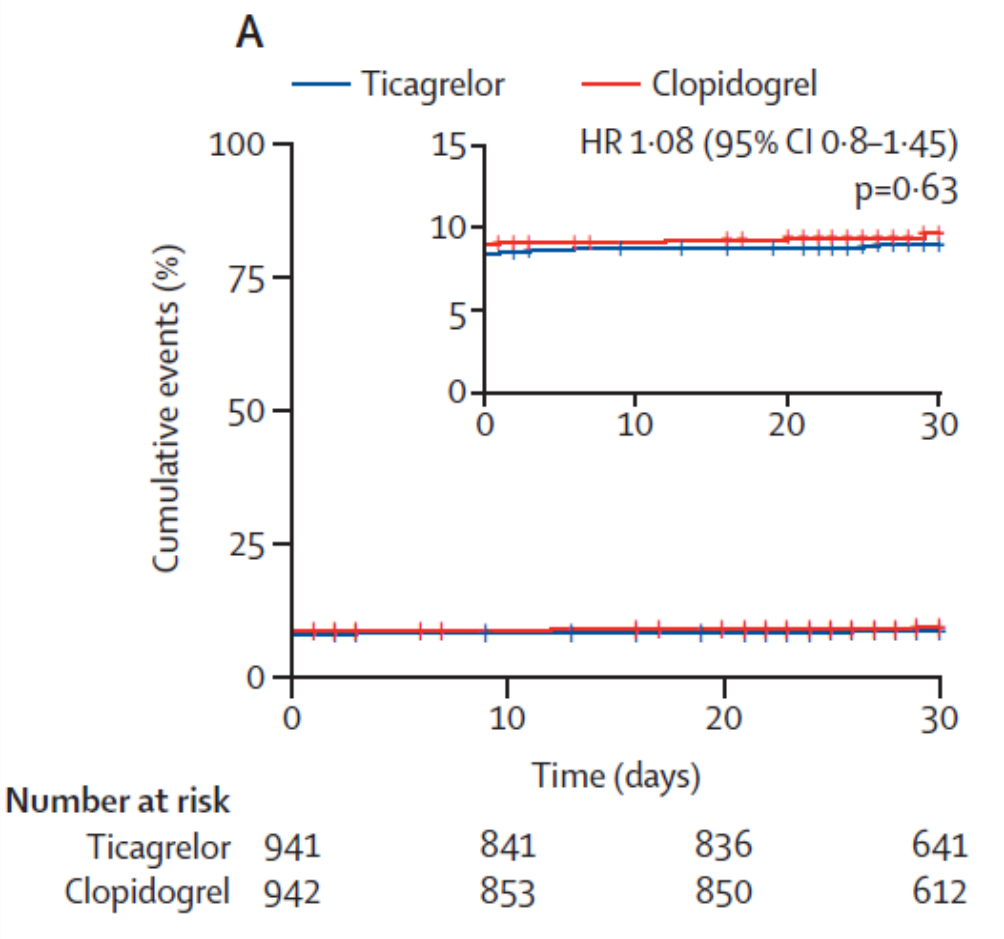
Clinical context

- Stable patient
- High thrombotic risk
- Low bleeding risk



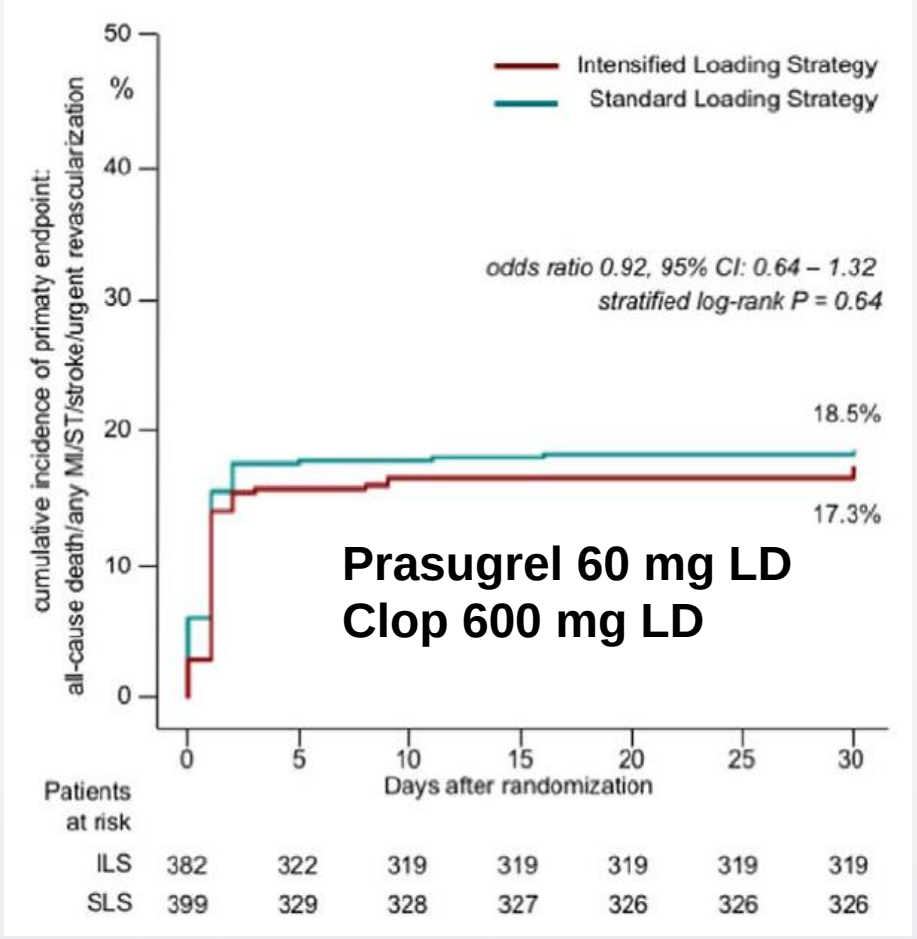
Unguided escalation antipaltelet therapy

ALPHEUS trial (1910 pts)



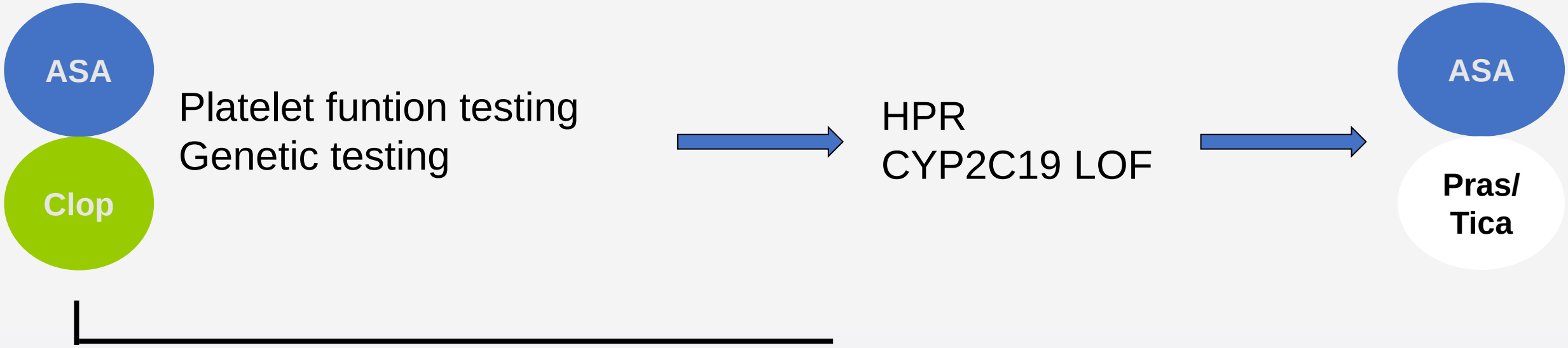
Silvain et al; Lancet 2020; 396:1737-44

SASSICAIA trial (781 pts)

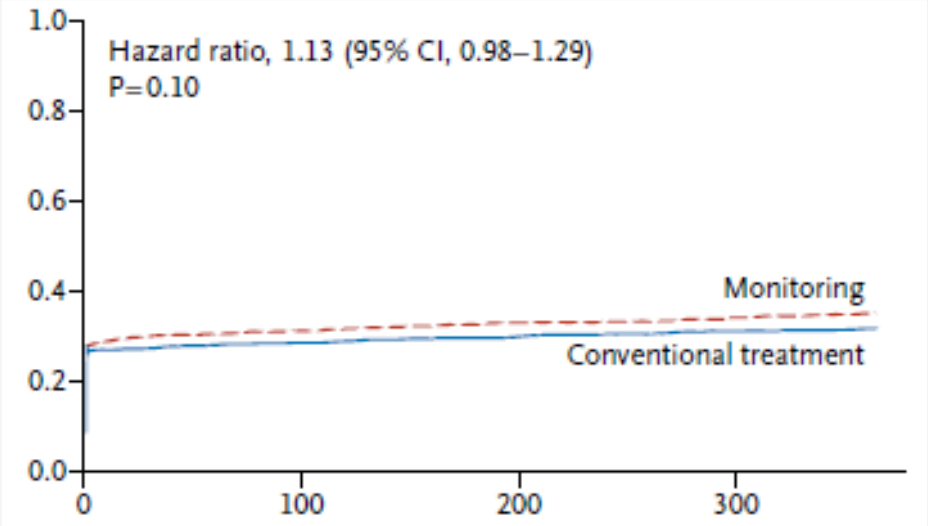


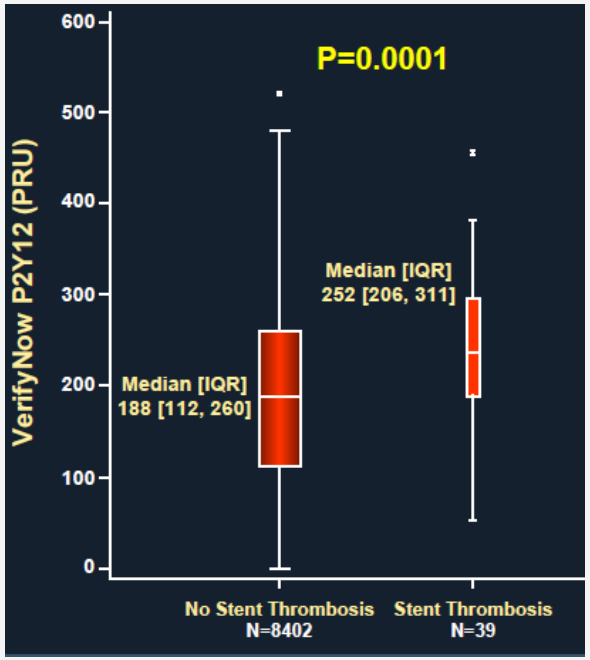
Mehilli et al; Circ Cv Int 2020 13e

Escalation «guided» antiplatelet therapy



ARCTIC, *NEJM 2012*

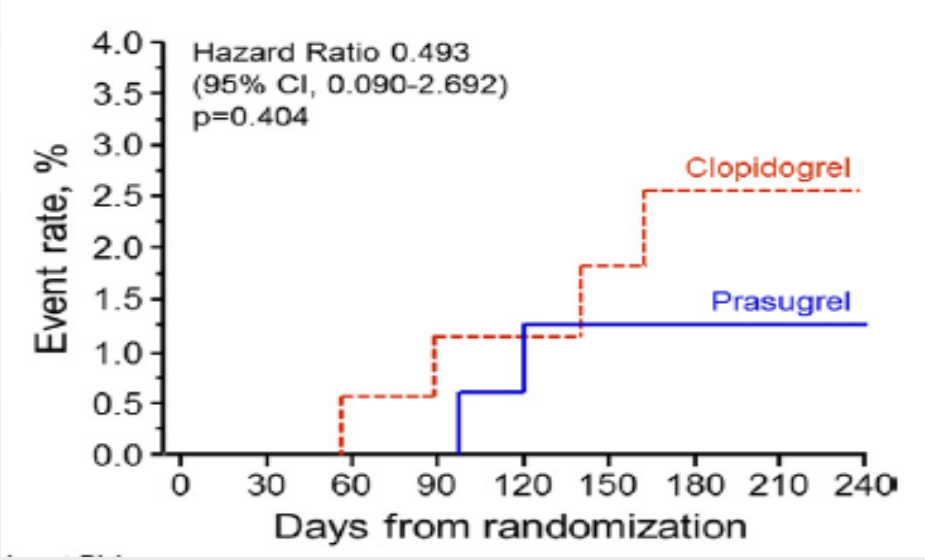




	Sensitivity	Specificity	PPV	NPV
Stent thrombosis, definite or probable	65·2%	57·5%	1·2%	99·5%
Stent thrombosis, definite	66·0%	57·4%	1·0%	99·6%
Myocardial infarction	52·1%	57·6%	3·8%	97·4%
Clinically relevant bleeding	38·2%	57·0%	5·5%	93·4%
Death, all-cause	54·5%	57·5%	2·4%	98·5%
Cardiovascular	53·6%	57·4%	1·4%	99·1%
Non-cardiovascular	55·9%	57·4%	0·9%	99·5%

Stone et al; Lancet 2013

TRIGGER PCI, *JACC 2012*



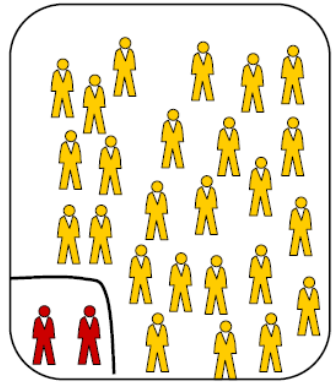
Positive predictive value

Disease

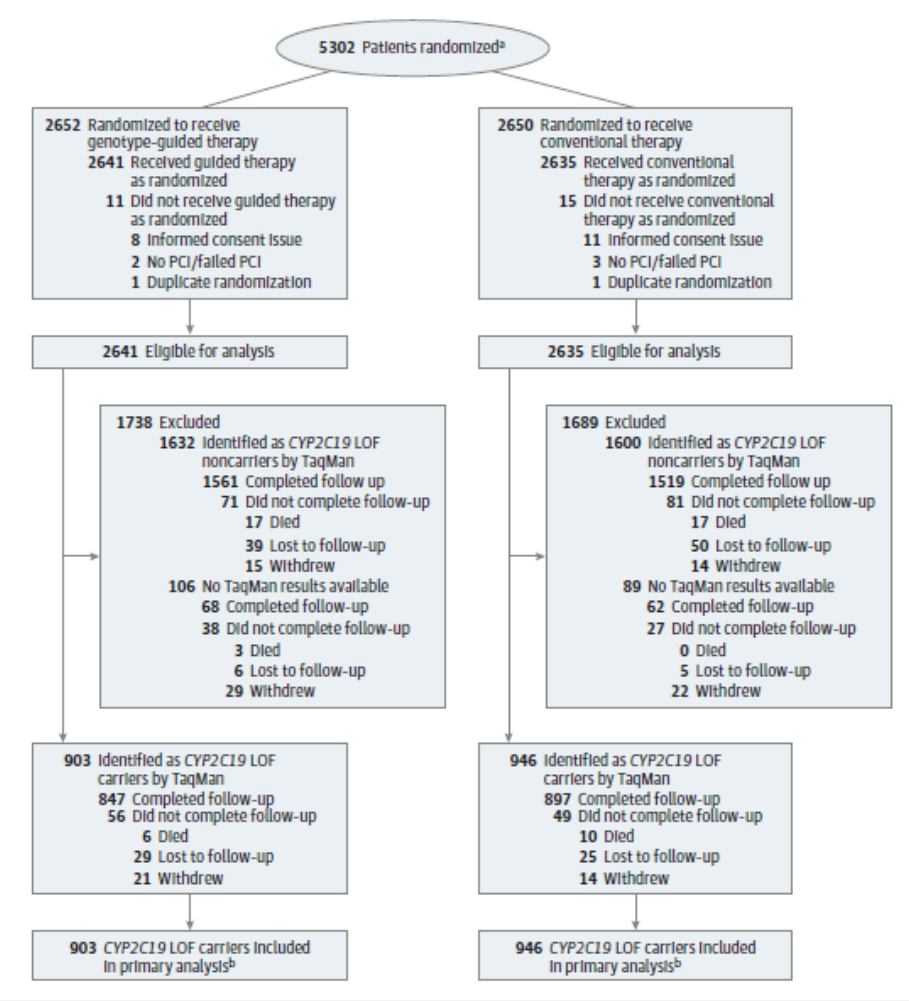
No Disease

Test positive

TEST	No dis.	Disease
POSITIVO (+)	a=25	b=2
NEGATIVO (-)	c=4	d=55



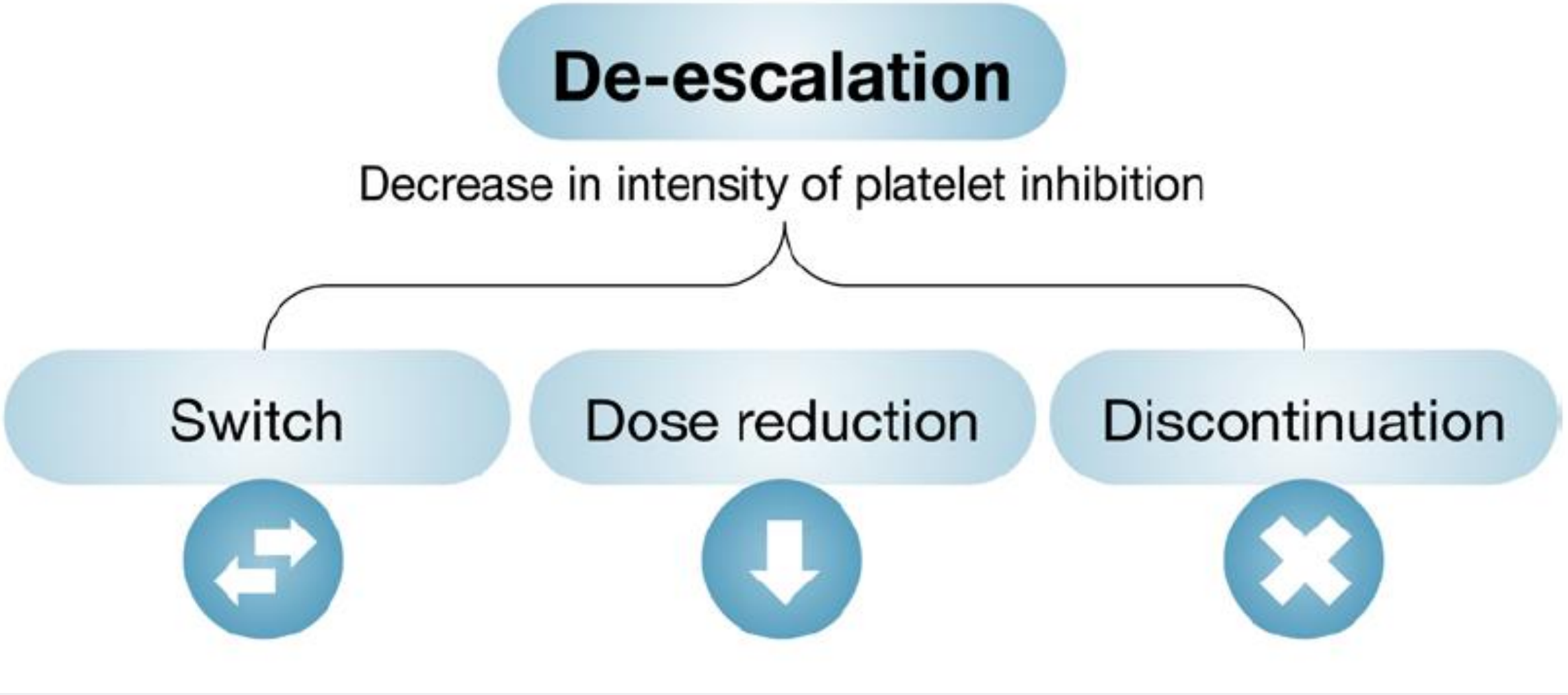
TAILOR PCI trial



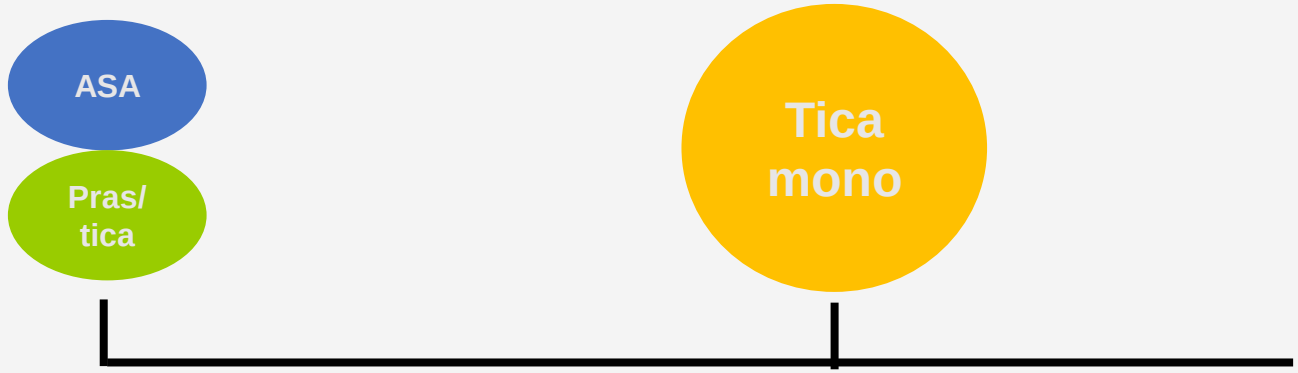
LOF treated with clop

CYP2C19 LOF	No. (%)	
	Genotype-guided therapy (N = 903)	Conventional therapy (N = 946)
Primary end point		
CV death, MI, stroke, severe recurrent ischemia, stent thrombosis	35 (4.0)	54 (5.9)
Secondary end points		
Severe recurrent ischemia	19 (2.2)	29 (3.2)
BARC bleeding		
2,3,5[c,d]	26 (3.0)	16 (1.8)
3,5[c,d]	17 (2.0)	14 (1.5)
TIMI major or minor bleeding (primary adverse events end point)	16 (1.9)	14 (1.6)
Myocardial infarction	11 (1.3)	14 (1.5)
Major bleeding	11 (1.3)	11 (1.2)
Death from any cause	6 (0.7)	10 (1.1)
CV death	4 (0.5)	8 (0.9)
Stent thrombosis	2 (0.2)	8 (0.9)
Minor bleeding	5 (0.6)	3 (0.3)
Stroke	2 (0.2)	4 (0.4)

Pereira et al; JAMA 2020;324761-71

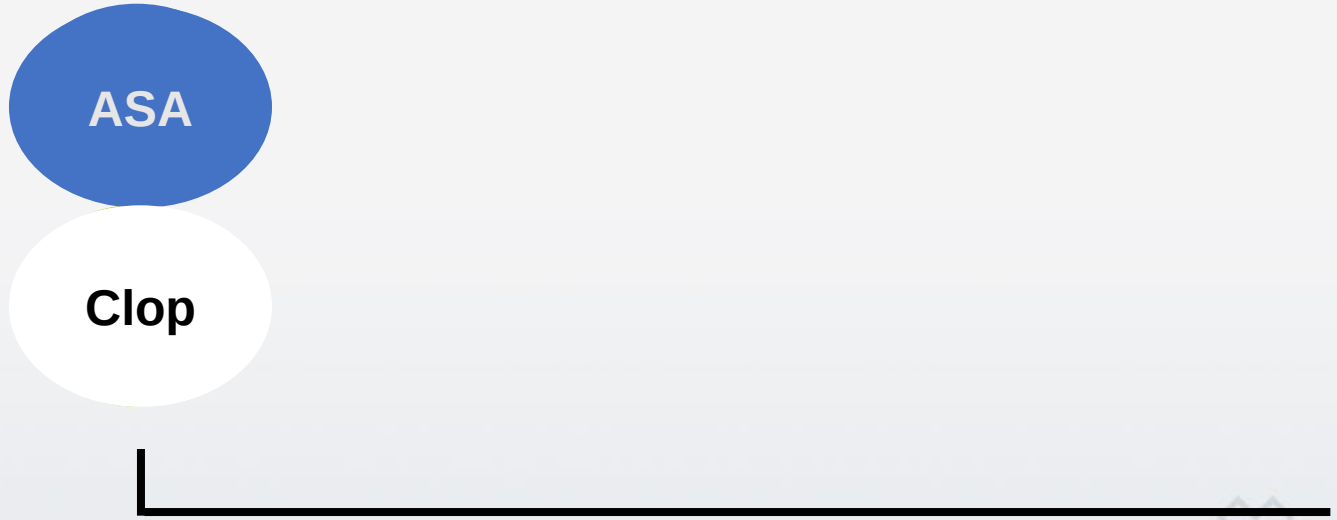

De-escalation
Decrease in intensity of platelet inhibition
Switch
Dose reduction
Discontinuation

LITERAL DEFINITION: a period of DAPT with Pras/Tica followed by a less intensive regimen



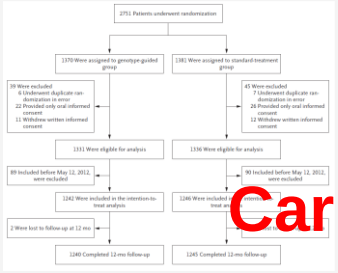
BROADER DEFINITION: depotentiation of DAPT upfront compared to the default strategy

- Genetic studies using clop upfront
- Platelet function studies

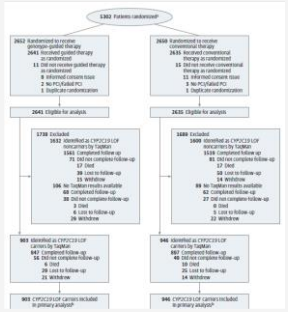


Are genetic guided strategies truly de-escalation strategies?

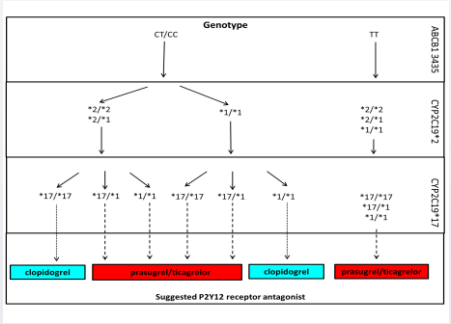
- **POPULAR GENETIC**



- **TAILOR PCI**



- **PHARMACLO**

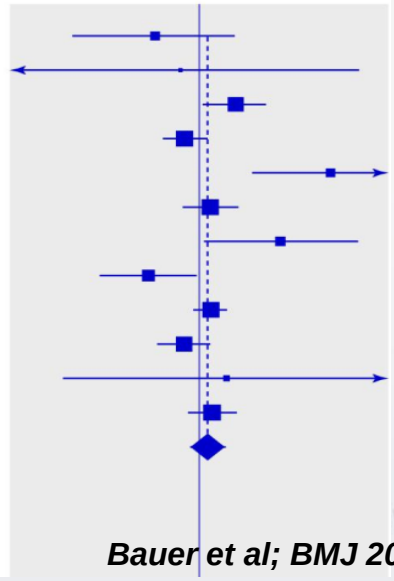


EXPERIMENTAL ARM

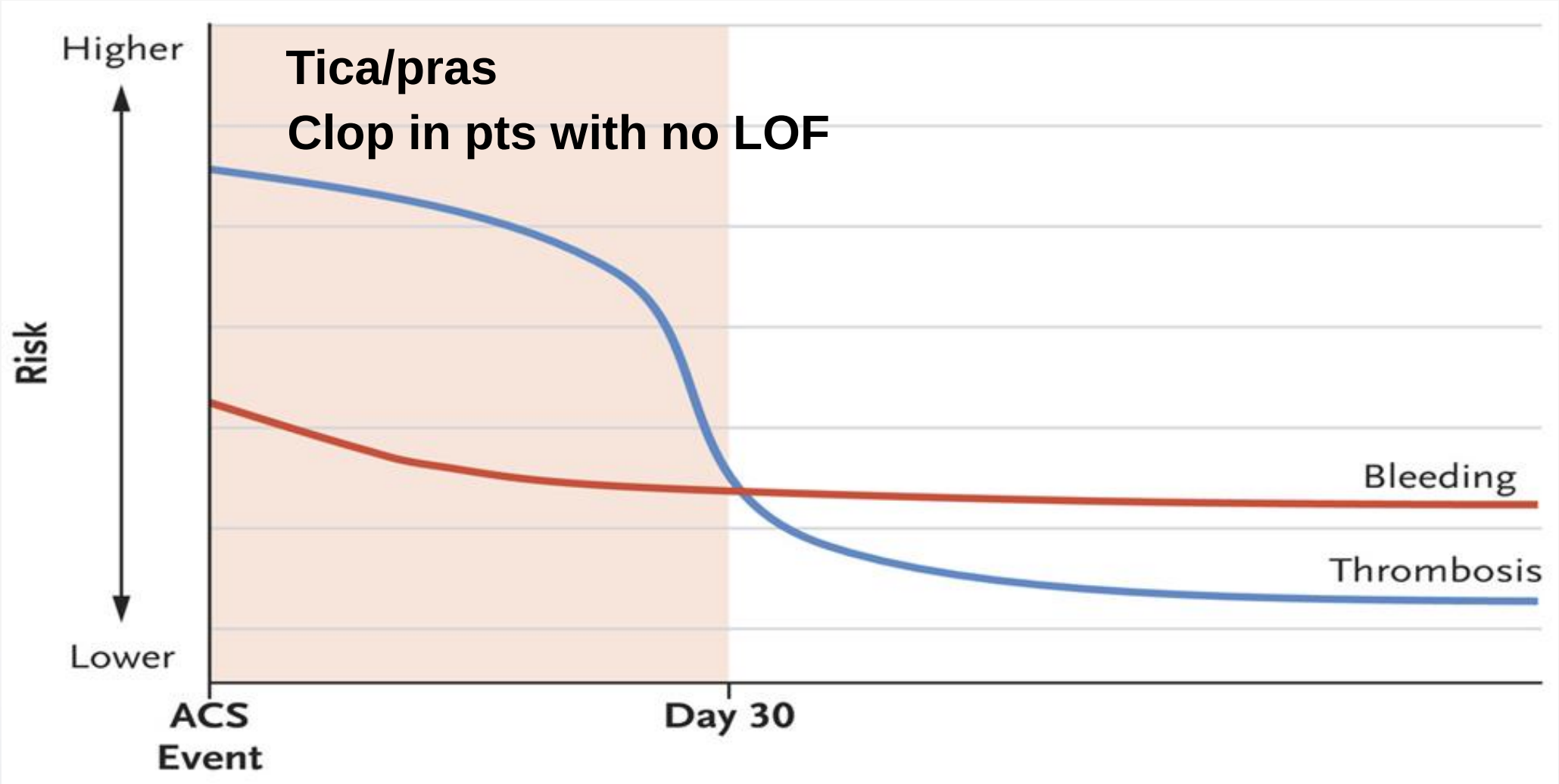
Carriers of LOF — **Potent DAPT**

Non-carriers — **Clopidogrel**

Study	No with events/No in group: Carriers	Non-carriers
Major adverse cardiovascular events (MACE)		
Trenk 2006[63]	5/245	19/552
Malek 2008[64]	1/21	5/84
Mega 2009[34]	46/395	83/1064
Simon 2009[65]	76/635	218/1573
Collet 2009[66]	12/73	7/186
Sibbing 2009[67]	52/680	121/1805
Giusti 2009[68]	10/247	8/525
Tiroch 2010[70]	14/248	68/680
Wallentin 2010[18]	149/1388	332/3516
Pare 2010[19]	52/650	178/1880
Sawada 2010[72]	2/42	2/58
Bouman 2010b[20]	81/678	135/1304
Total	500/5302	1176/13 227
Test for heterogeneity: Q=30.1, τ^2=0.075, df=11, P=0.002, I^2=63.4% (95% CI, 31.9 to 80.3%)		
Test for overall effect: z=0.92, P=0.36		



Bauer et al; BMJ 2011

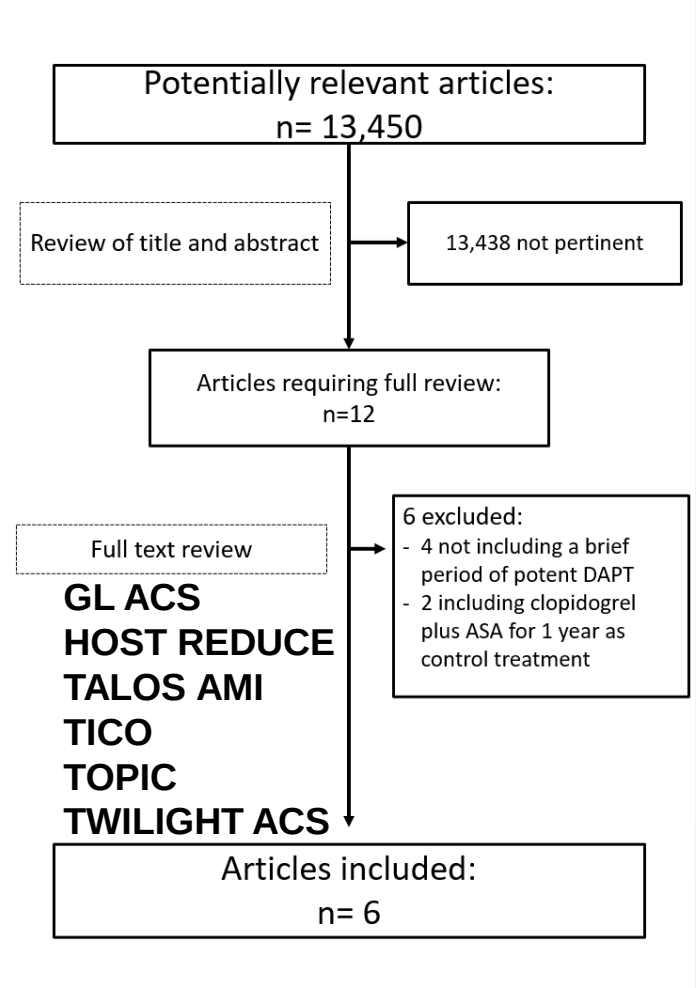


Rodriguez et al; NEJM 2021

Rationale for a meta-analysis on de-escalation AT

- **De-escalation antiplatelet therapy defined as a brief period of potent DAPT followed by a depotentiated antiplatelet regimen**
- **Consider only ACS patients treated with ASA + Prasugrel/Ticagrelor for 1 year as control arm**
- **Consider de-escalation as switching to depotentiated DAPT or ticagrelor monotherapy**

Reduced Mortality With Antiplatelet Therapy De-escalation After PCI in Acute Coronary Syndromes: A Meta-analysis



DE-ESCALATION STRATEGIES

Clop +ASA

Reduced dose pras + ASA

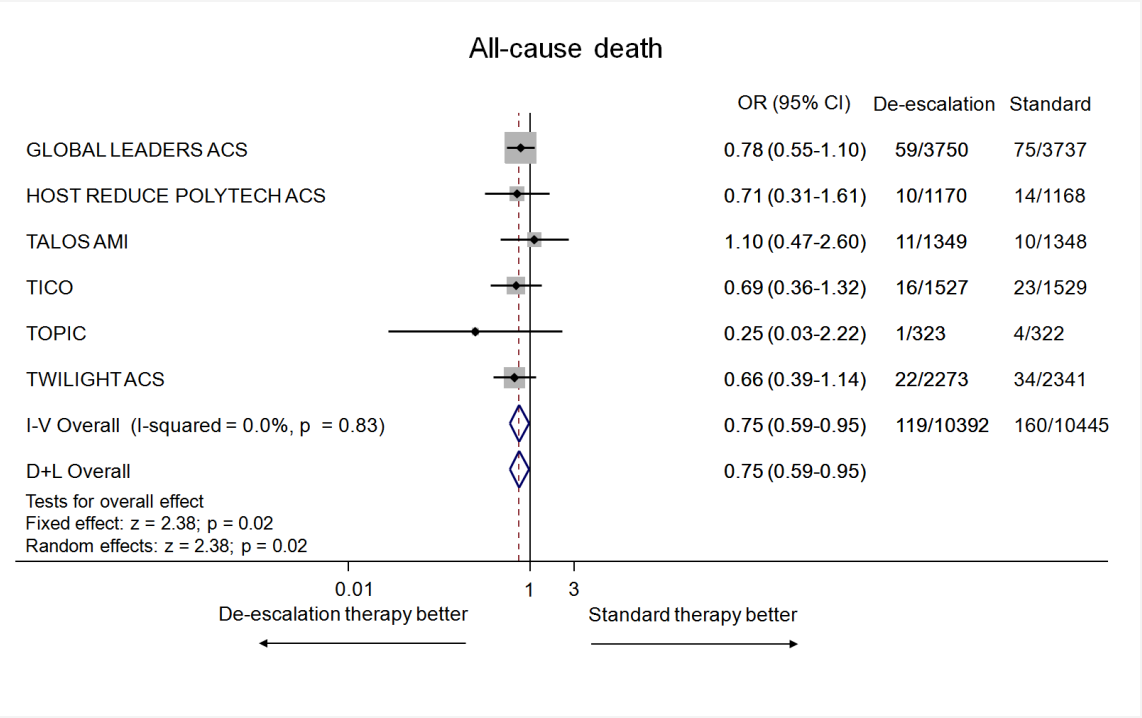
Tica monotherapy

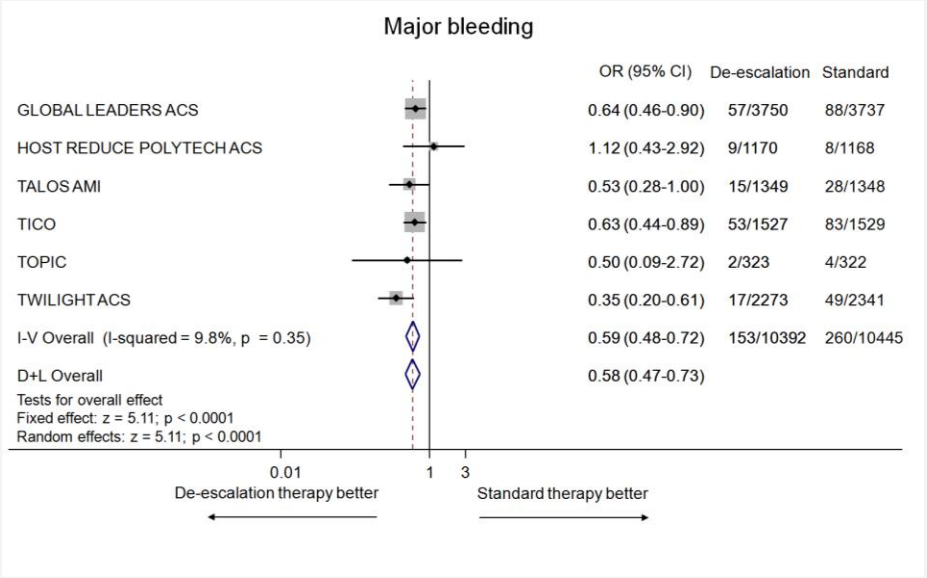
Pairwise aggregate meta-analysis of de-escalation antiplatelet therapy (n= 10,392) versus potent DAPT (n= 10,445) in patients with ACS undrgoing PCI

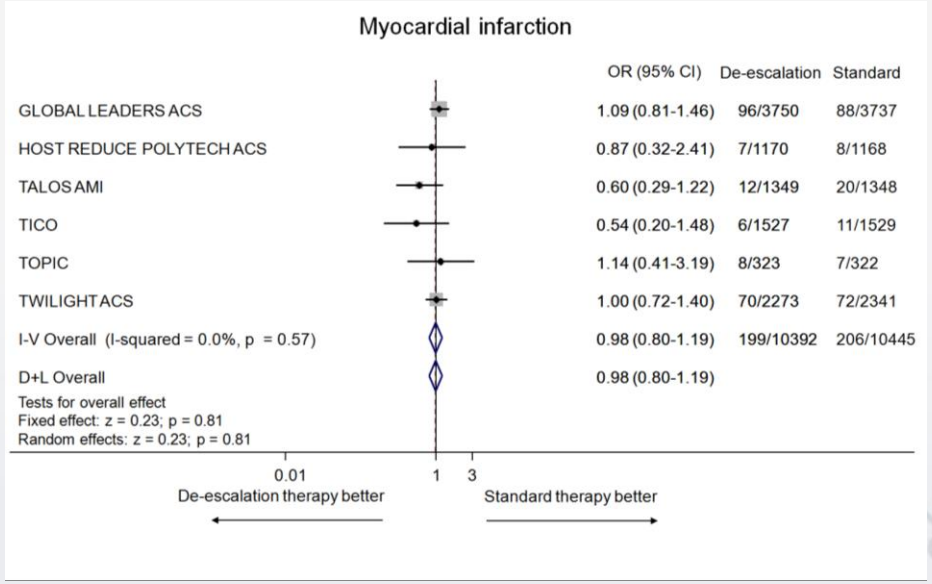
Network meta-analysis comparing de-escalation strategies each other

Primary endpoint: all-cause mortality

Palmerini et al; Circ Cv Int 2022

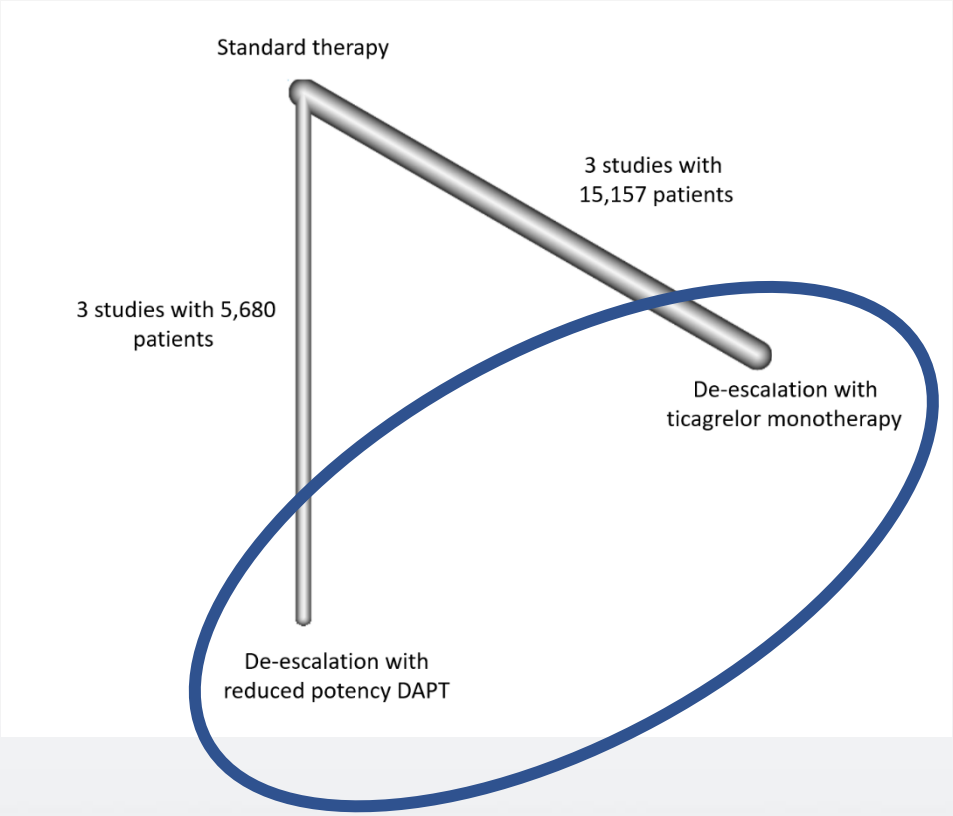






Palmerini et al; Circ Cv Int 2022

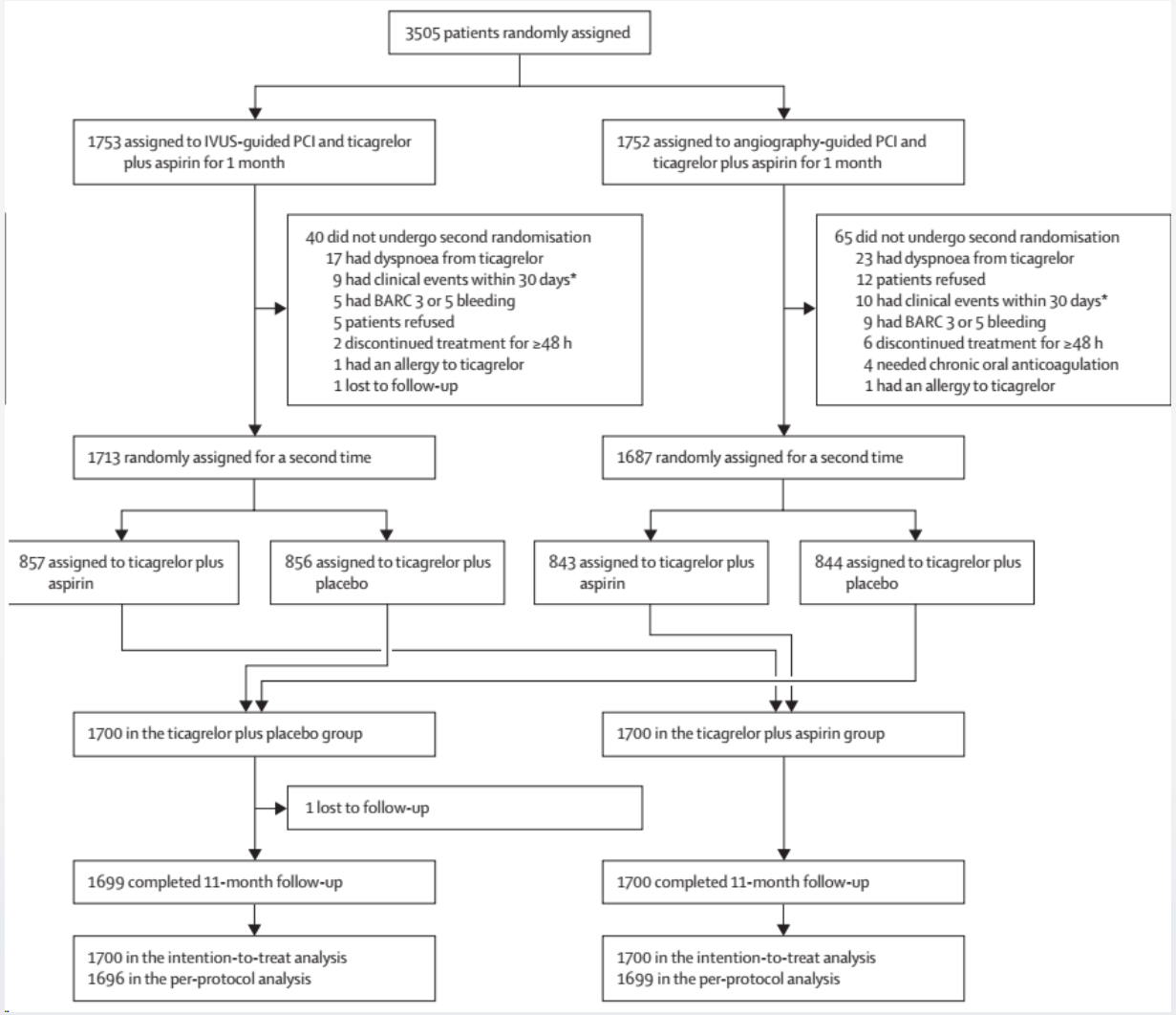
Network meta-analysis



	Odds ratio (95% CI)
All-cause death	
De-escalation with ticagrelor monotherapy vs standard therapy	0.74 (0.56-0.96)
De-escalation with reduced potency DAPT vs standard therapy	0.80 (0.45-1.42)
Ticagrelor monotherapy vs reduced potency DAPT	0.92 (0.49-1.72)
Major bleeding	
De-escalation with ticagrelor monotherapy vs standard therapy	0.55 (0.42-0.72)
De-escalation with reduced potency DAPT vs standard therapy	0.76 (0.43-1.35)
Ticagrelor monotherapy vs reduced potency DAPT	0.72 (0.38-1.36)
MACE	
De-escalation with ticagrelor monotherapy vs standard therapy	0.93 (0.72-1.21)
De-escalation with reduced potency DAPT vs standard therapy	0.73 (0.41-1.29)
Ticagrelor monotherapy vs reduced potency DAPT	1.27 (0.68-2.39)

Palmerini et al; Circ Cv Int 2022

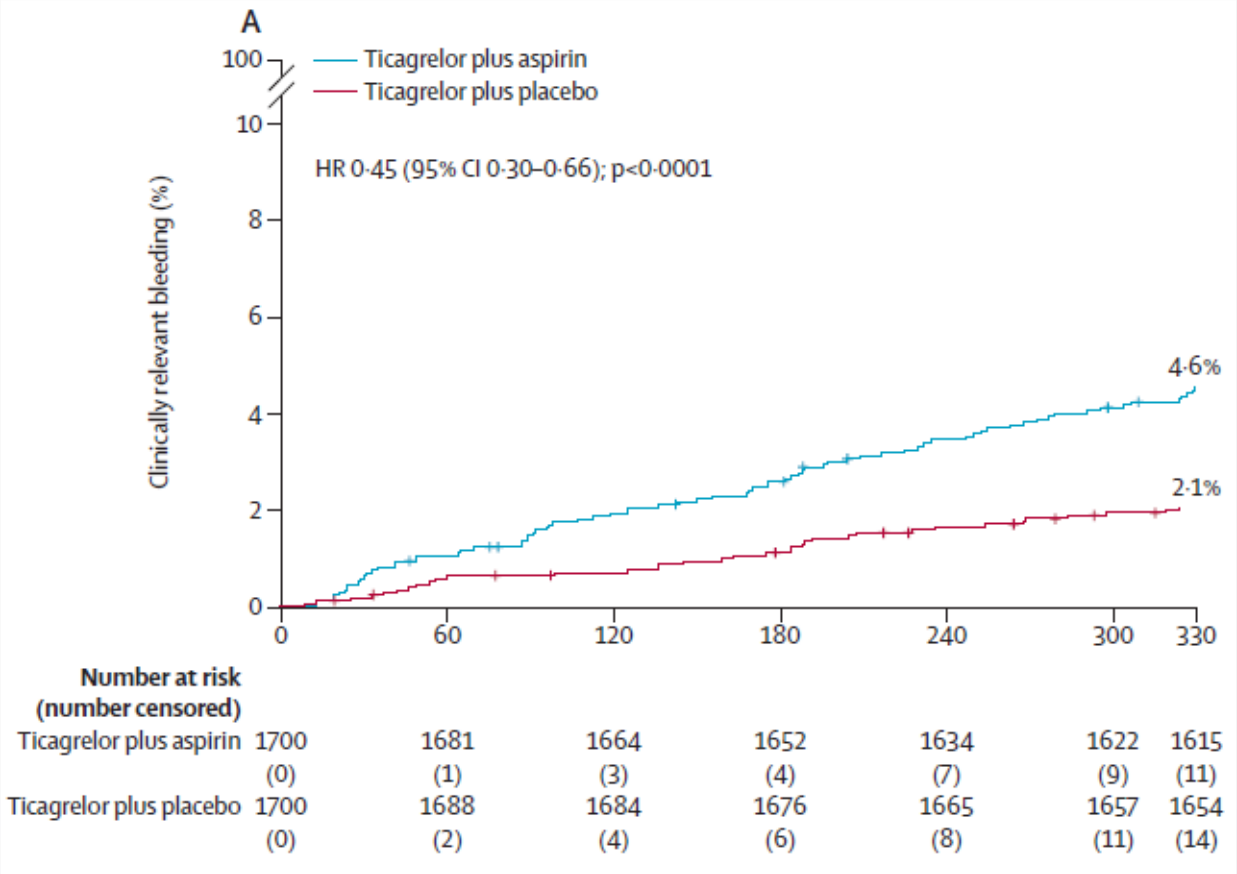
Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomised, placebo-controlled, double-blind clinical trial

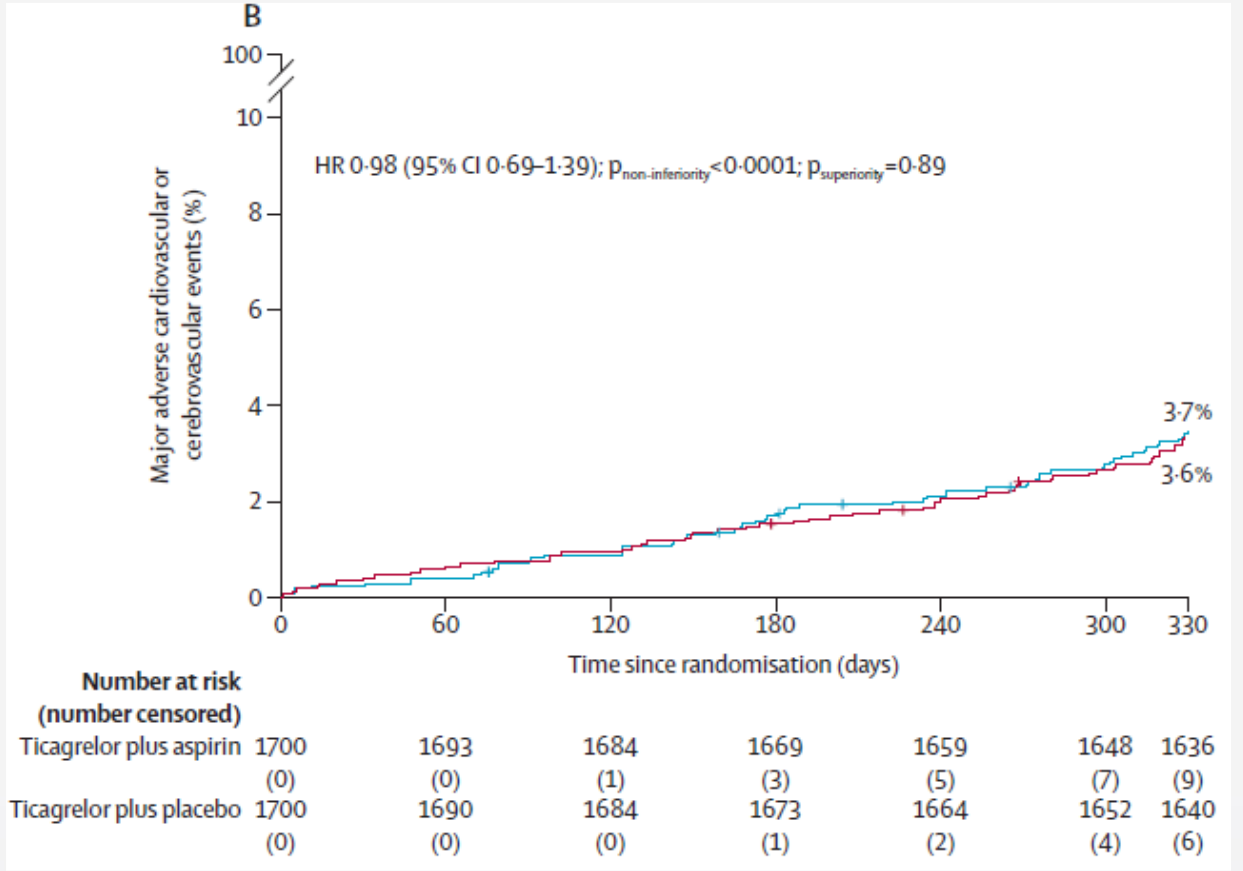


Double blind, placebo-controlled RCT with 3,400 patients with ACS

Primary superiority EP: BARC 2,3,or 5 bleeding
Primary non-inferiority EP: MACE

Ge et al; Lancet 2024





Ge et al; Lancet 2024

Conclusion

- **In patients with ACS undergoing PCI, de-escalation antiplatelet therapy, defined as a breief period of potent DAPT followed by depotentiated DAPT or ticagrelor monotherapy, is associated with reduced rates of major bleeding (and probably mortality) with no tradeoff with ischemic events compared with standard potent DAPT.**

- **Despite the need of a tailored approach for balancing ischemic and bleeding risk and the strong rationale for escalation antiplatelet therapy in specific clinical contexts, more data are needed for a broader implementation of this strategy.**