

Escalation of antithrombotic therapy: Why, in Whom and How

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Disclosure

- Lecure fees from Abbott, Medtronic, Edwards Lifescience

Escalation

Increase in intensity of platelet inhibition

Switching



Dose increase



Add-on



Escalation antiplatelet therapy

- **Why:** to reduce the risk of ischemic events with no tradeoff with bleeding

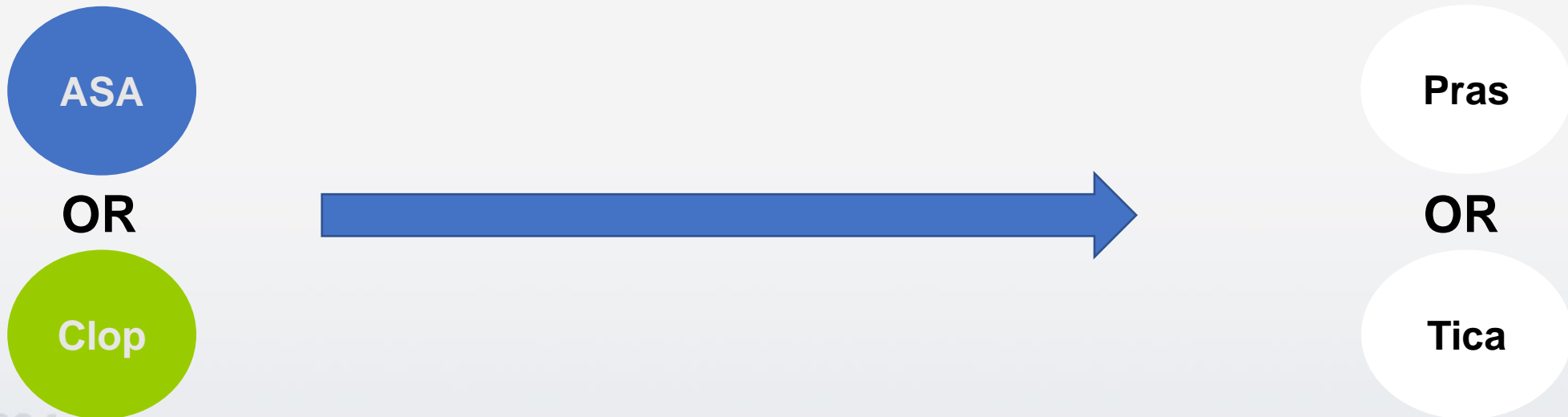
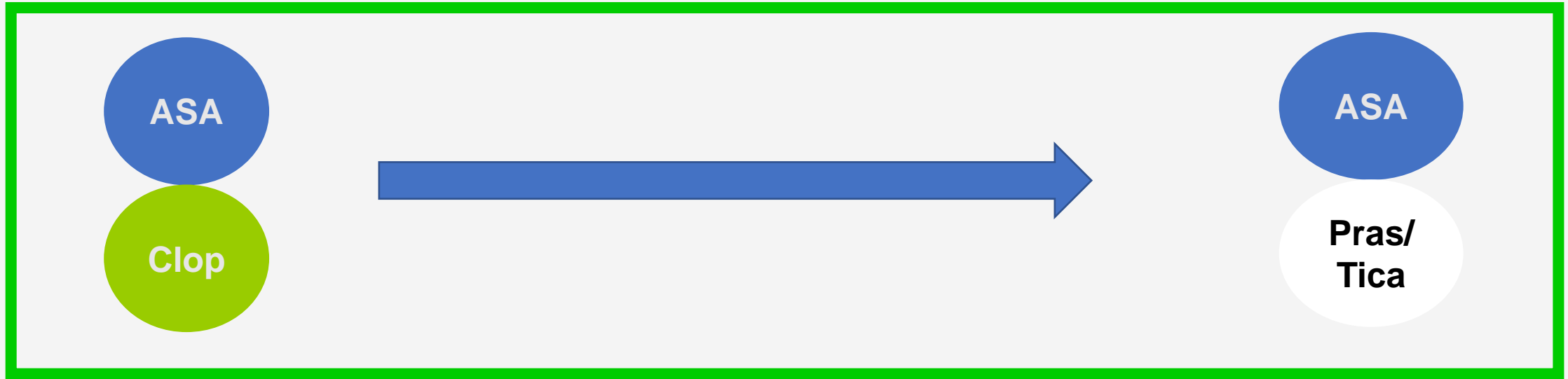
- **In which patient:** patients with stable CAD (specific subgroup of ACS?)

Escalation APT trial control arm: clopidogrel ACS treated with clopidogrel

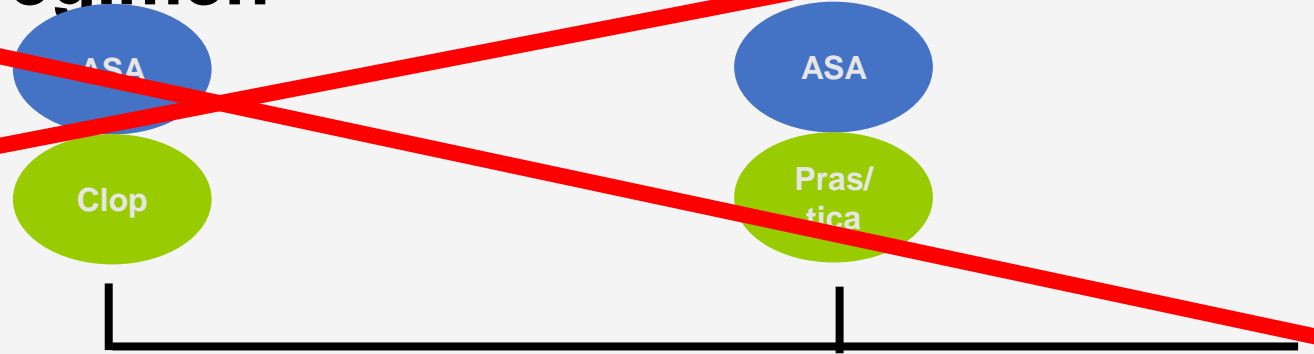
Escalation therapy versus suboptimal therapy in ACS

- **How:** guided or unguided

Switch to a more potent drug



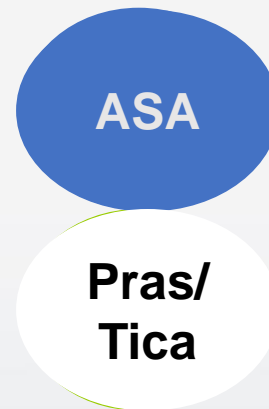
LITERAL DEFINITION: a period of DAPT with clopidogrel plus ASA followed by a more intensive regimen



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

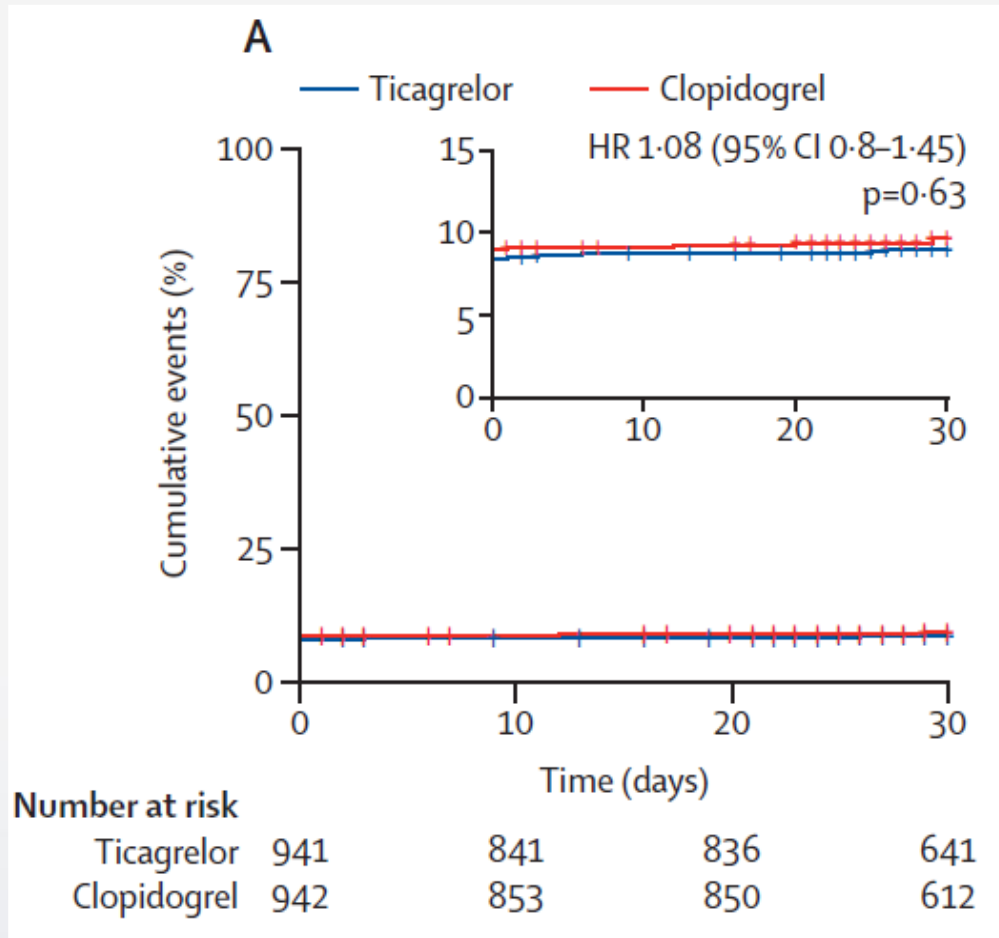
Clinical context

- Stable patient
- High thrombotic risk
- Low bleeding risk

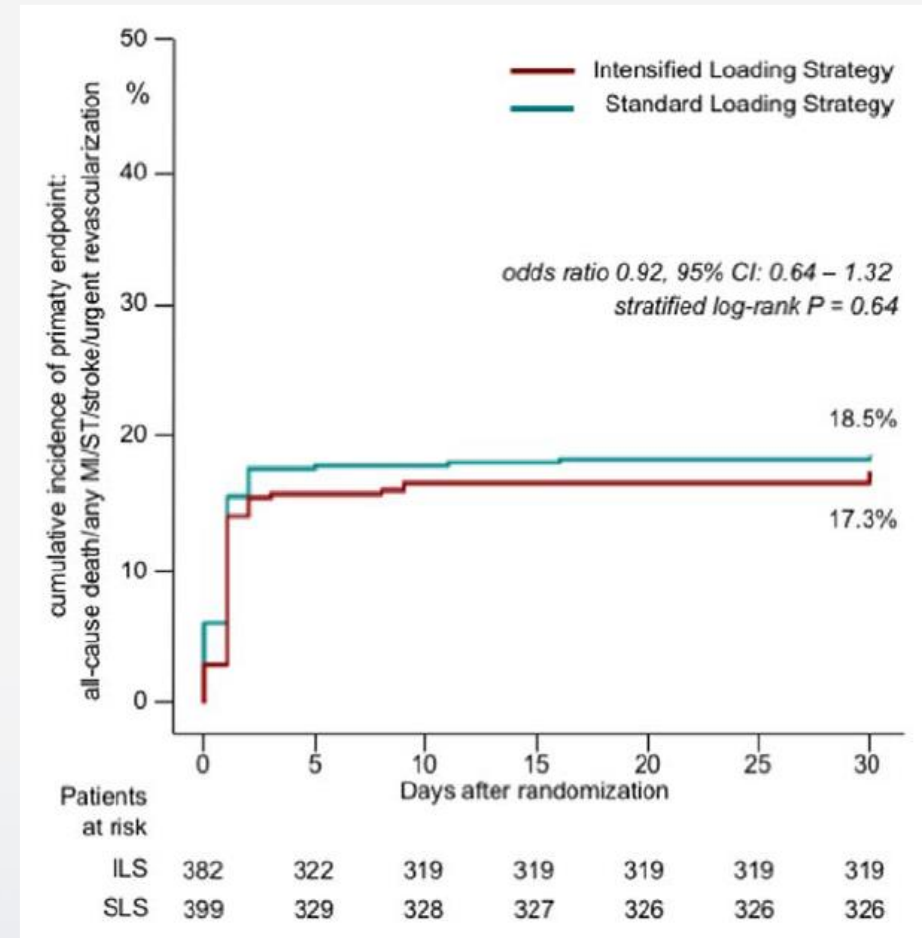


Prasugrel or ticagrelor in stable patients

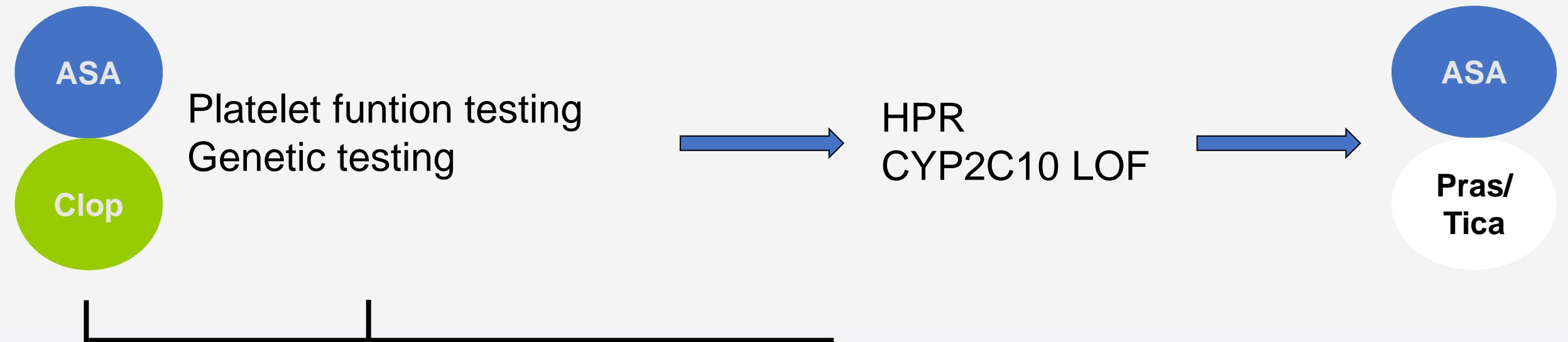
ALPHEUS trial (1910 pts)



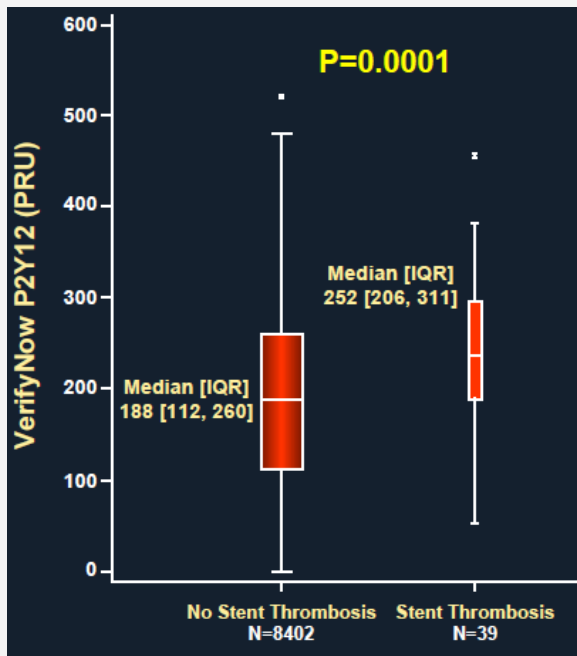
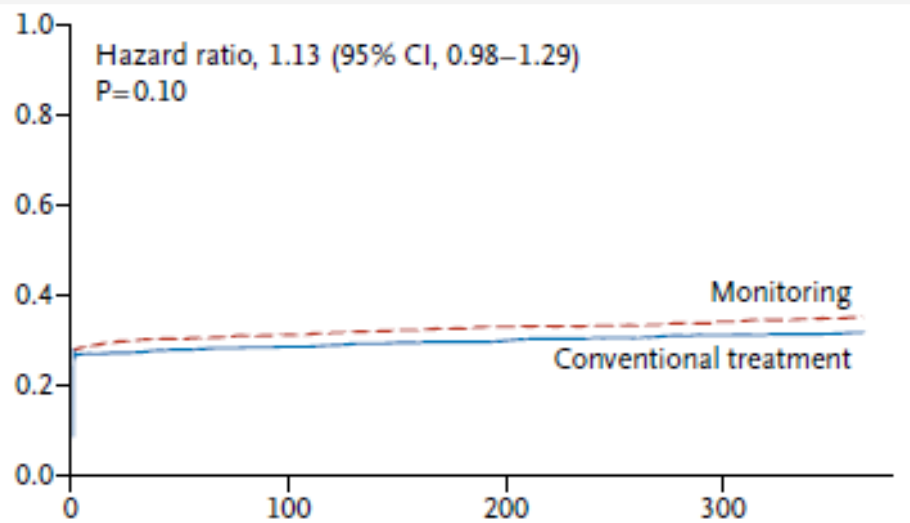
SASSICAIA trial (781 pts)



Escalation «guided» antiplatelet therapy



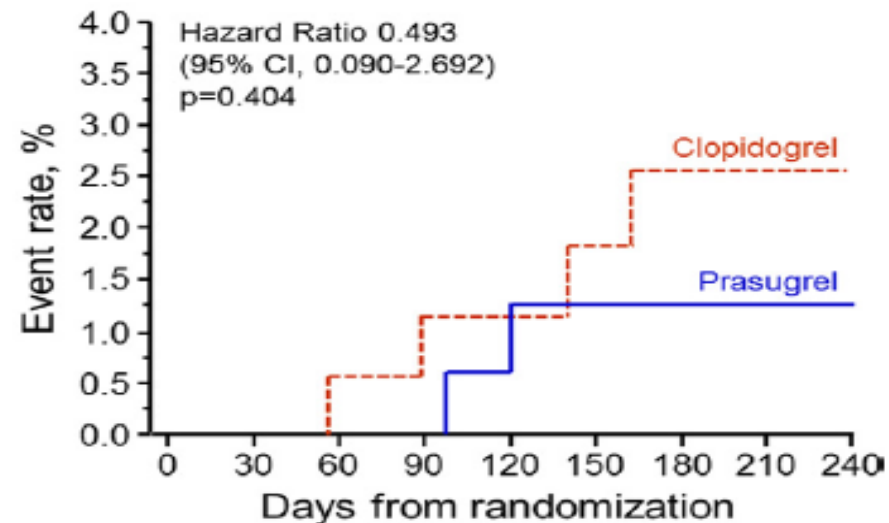
ARCTIC, NEJM 2012



	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%

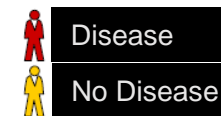
Stone et al; Lancet 2013

TRIGGER PCI, JACC 2012

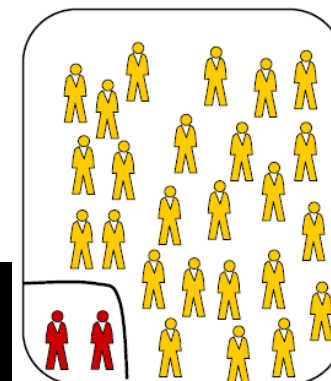


Positive predictive value

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

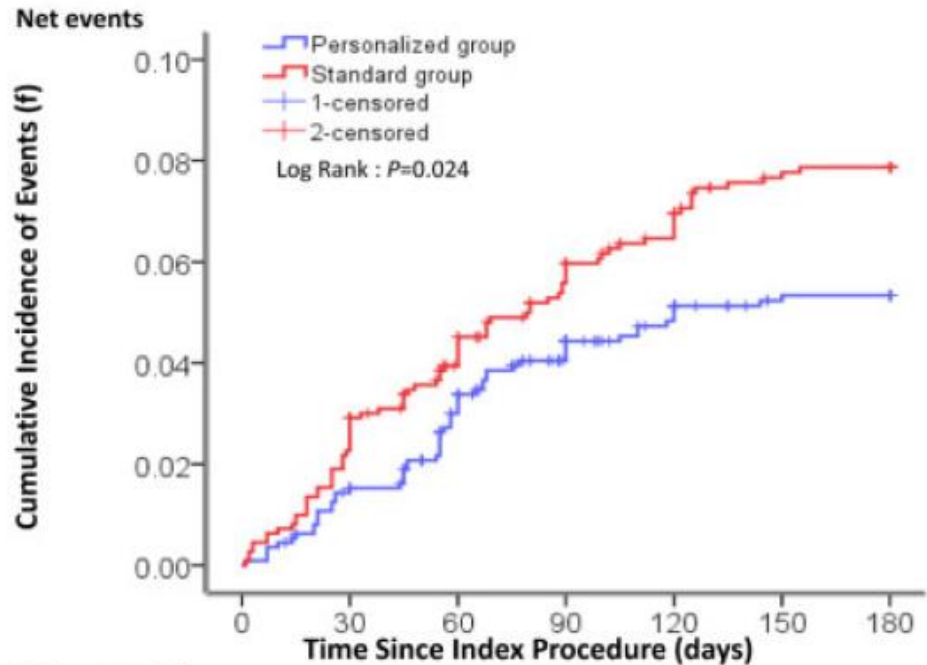


Test positive



PATH PCI trial

PL 12 (MAR > 55% TICA)



Patients at risk:

Days	0	30	60	90	120	150	180
Personalized	1123	1106	1086	1076	1068	1066	1066
Standard	1114	1082	1065	1050	1040	1032	1031

- Ethnic issue
- Single center
- Platelet Function Assay never validated in western population
- Mainly driven by urgent revascularization (unblinded study)



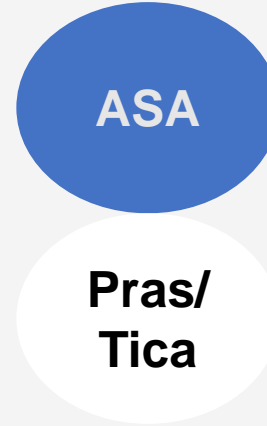
Genetic testing: escalation or de-escalation?

Control arm



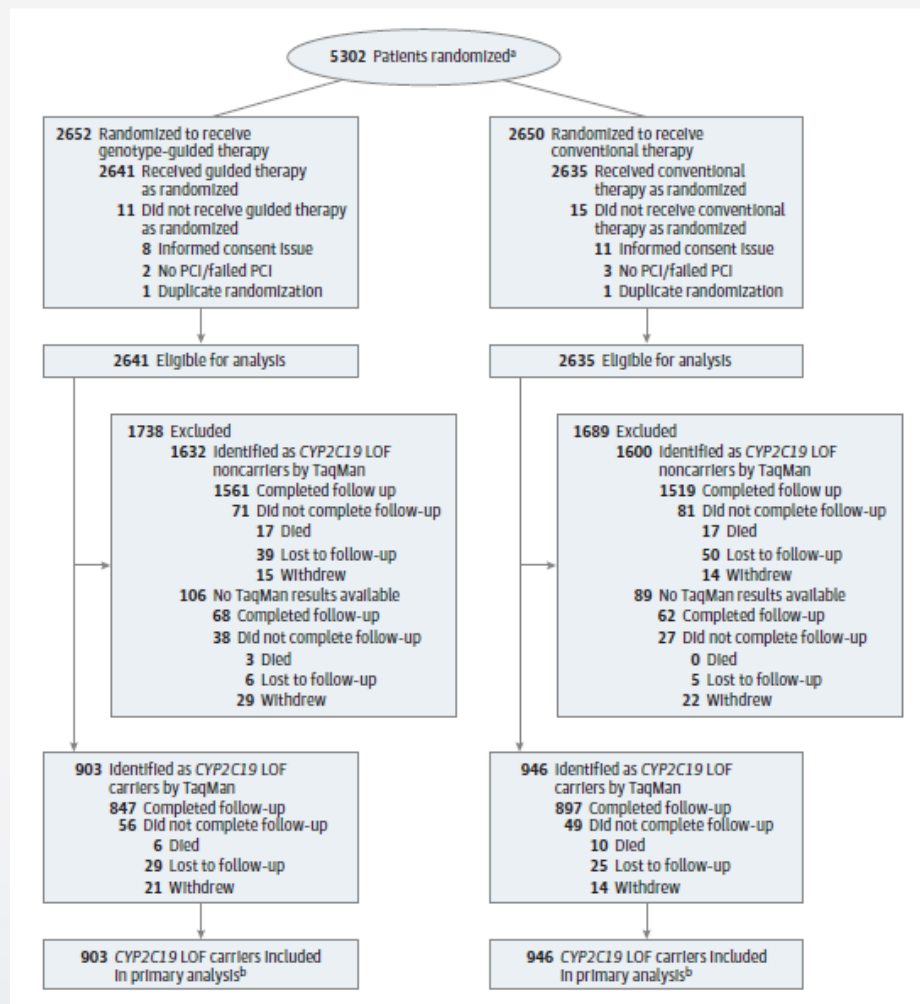
CYP2C19 LOF

Experimental arm



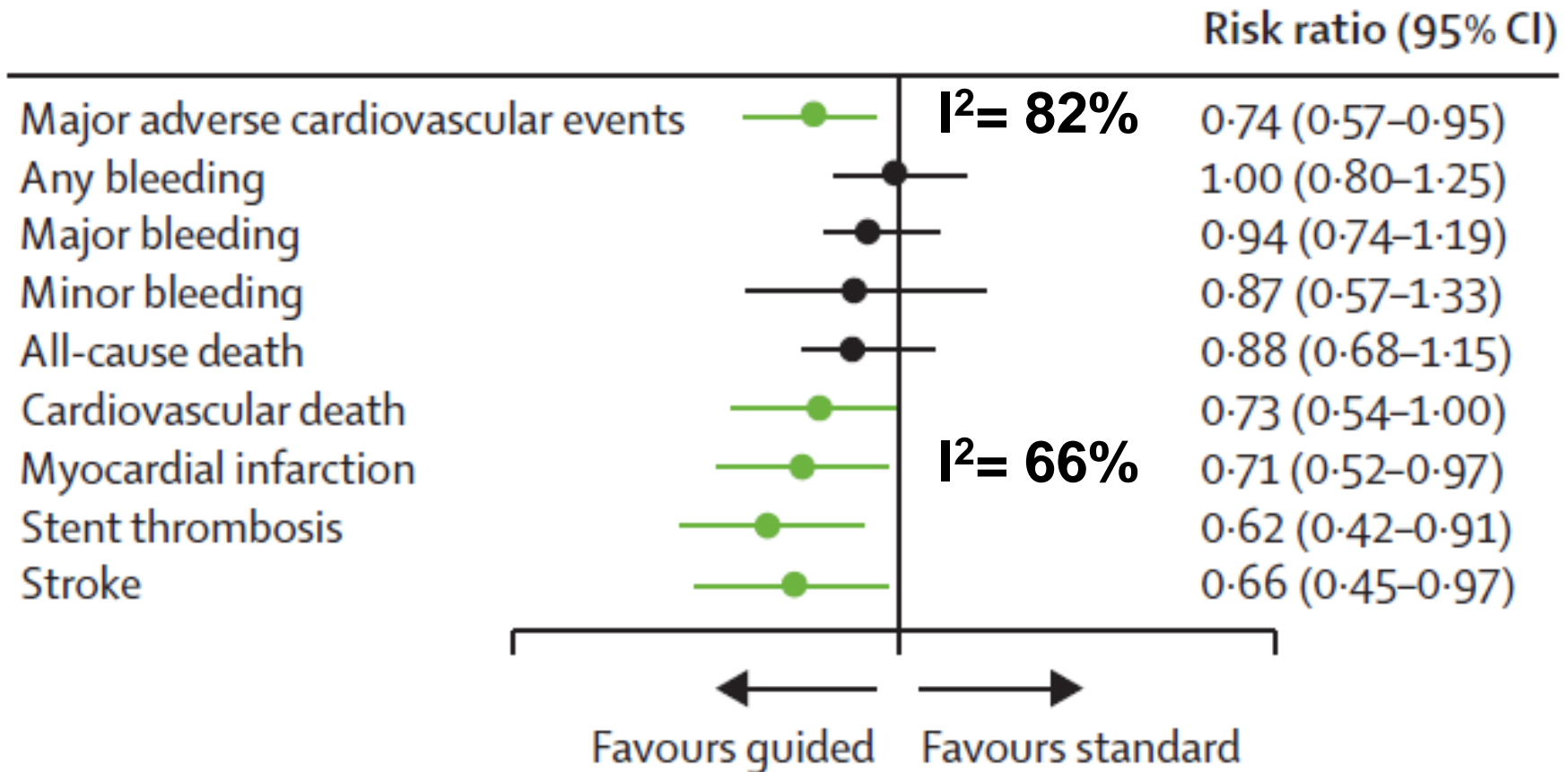
Trial	ACS	Control
PHARMACLO	97%	Clon
ADAPT	50%	Clon
TAILOR PCI	82%	Clon

TAILOR PCI trial



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)

Guided escalation strategy



ESC guidelines for CCS

Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm

Aspirin 75–100 mg daily is recommended following stenting.²⁸⁴

I

A

Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1–3 months) is indicated due to risk or the occurrence of life-threatening bleeding.²⁸⁴

I

A

Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding.²⁸⁴

IIa

A

Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.²⁸⁴

IIb

C

Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of aspirin intolerance.

IIb

C

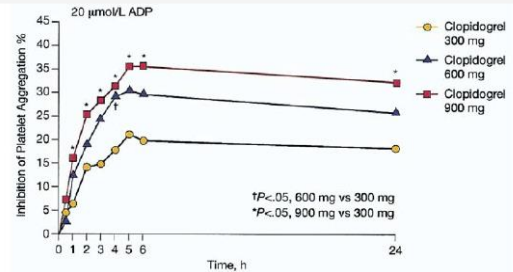
Escalation by dose increase

Clop 300 mg LD



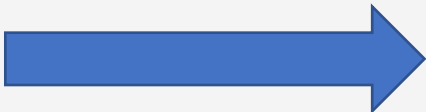
Clop 600/900 mg LD

ALBION trial



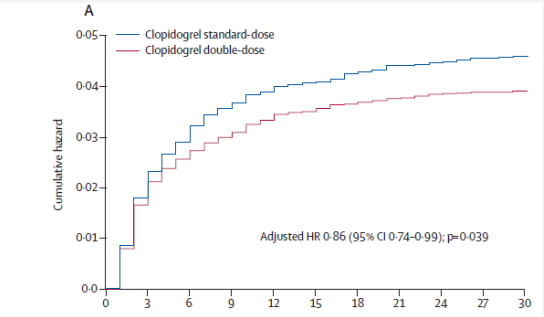
Montalescot et al; JACC 2006

Clop 75 mg MD



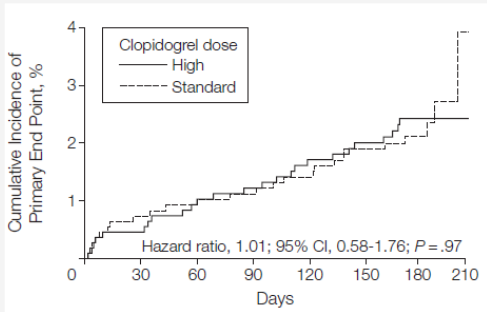
Clop 150 mg MD

CURRENT OASIS 7



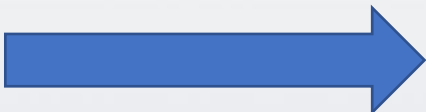
Mehta et al; Lancet 2010

GRAVITAS



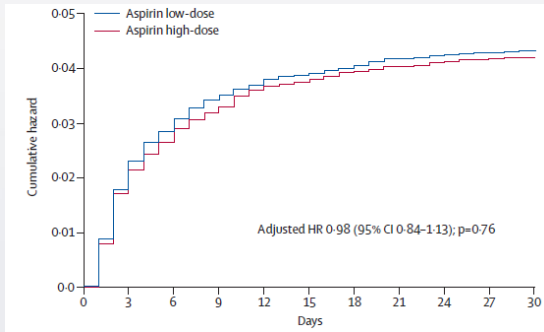
Price et al; JAMA 2011

ASA 75-100 mg MD



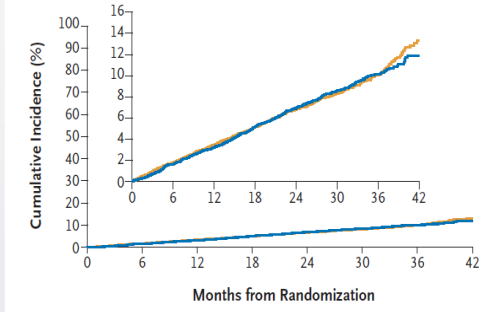
ASA 300-325 mg MD

CURRENT OASIS 7



Mehta et al; Lancet 2010

ADAPTABLE



Jones et al; nejm 2021

Add on SAPT

ASA

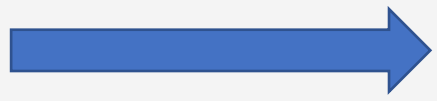
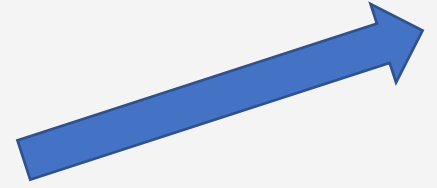
Clop

ASA

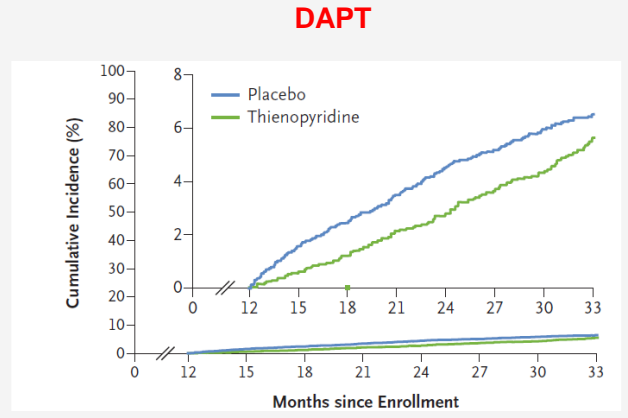
Tica

ASA

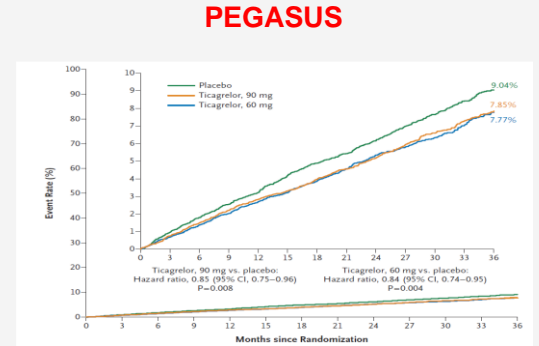
Riva



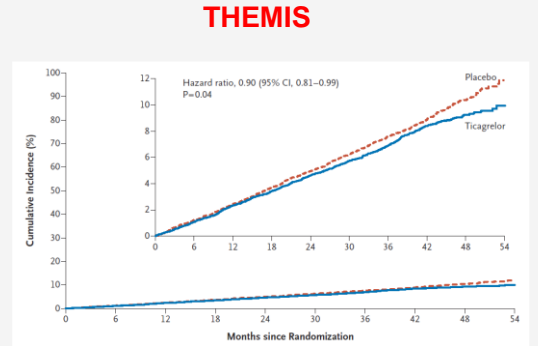
ASA 75-100 mg MD



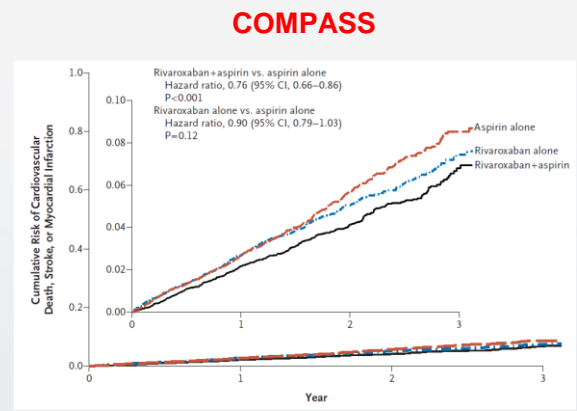
Mauri et al; nejm 2014



Bonaca et al; nejm 2015



Steg et al; nejm 2019



Eikelboom et al; nejm 2017

Conclusion

- **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**