Nom de Séance

Reste t-il une place aux tests antiplaquettaires et génétiques ?

P.BARRAGAN. Ollioules , France

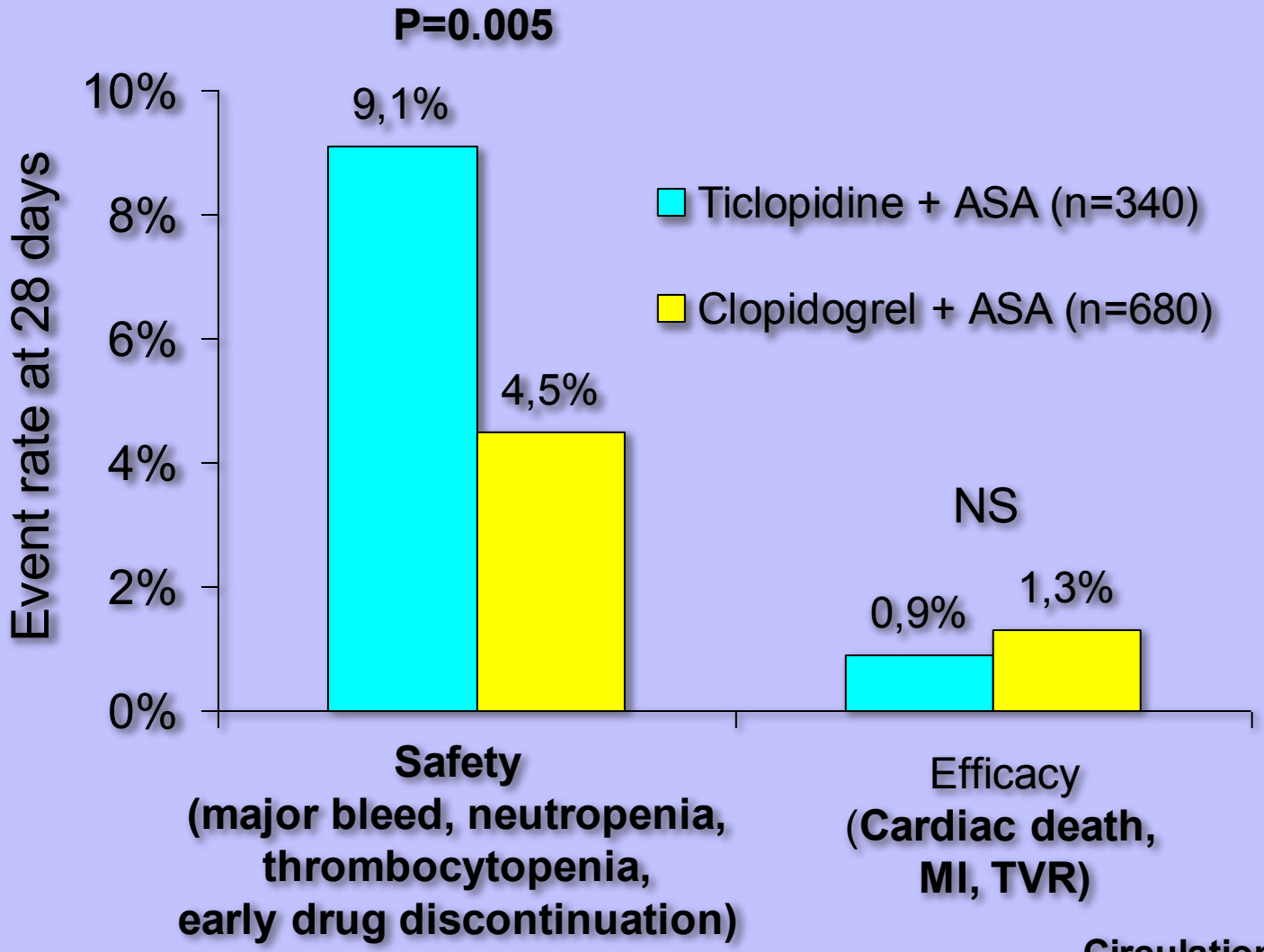
Déclaration de conflits d'intérêts

AUCUN

CoSAC
Le congrès des Sociétés Africaines de Cardiologie

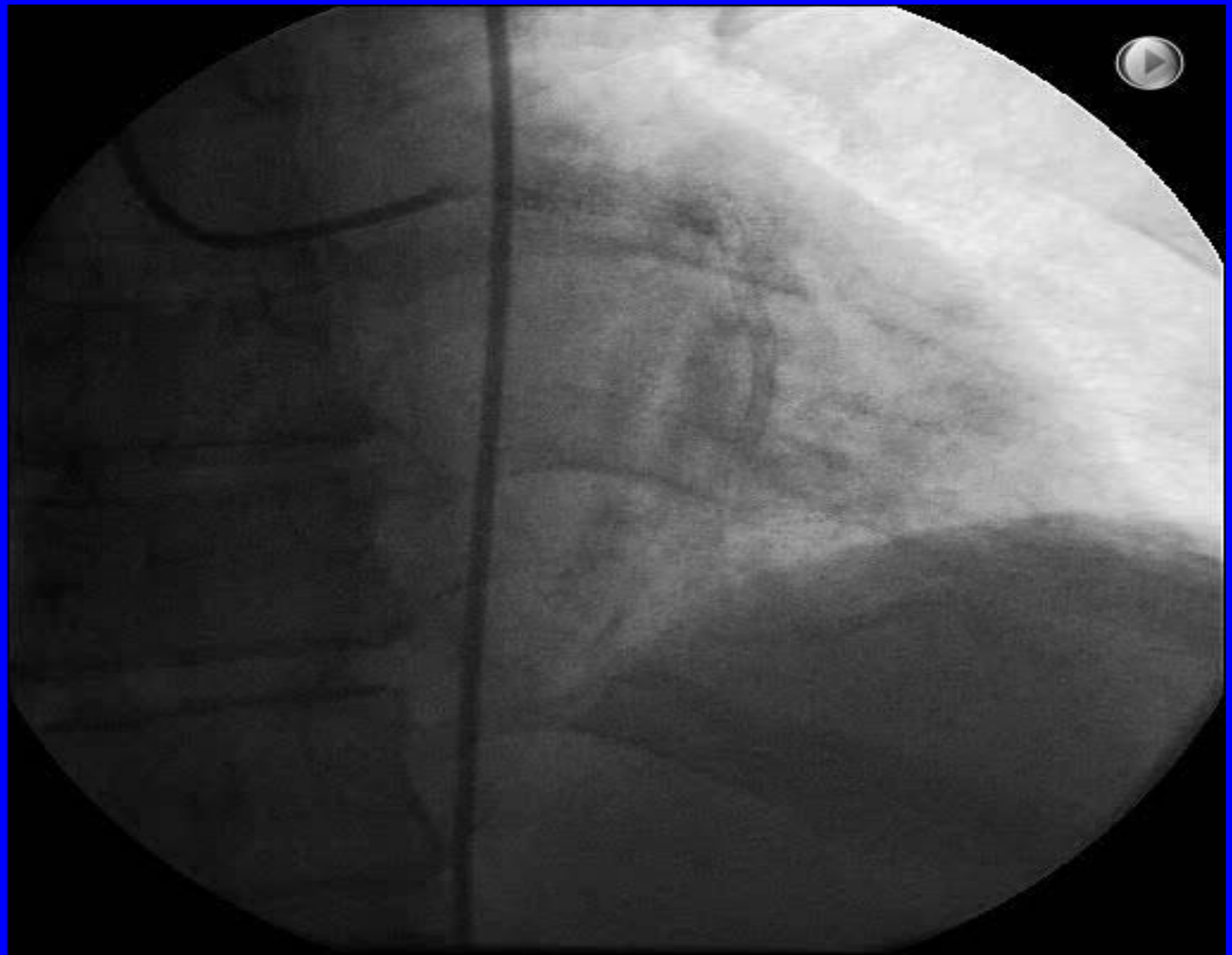
STCCCV
Société Tunisienne de Cardiologie & de Chirurgie Cardio-Vasculaire

CLASSICS - clopidogrel versus ticlopidine after coronary stenting

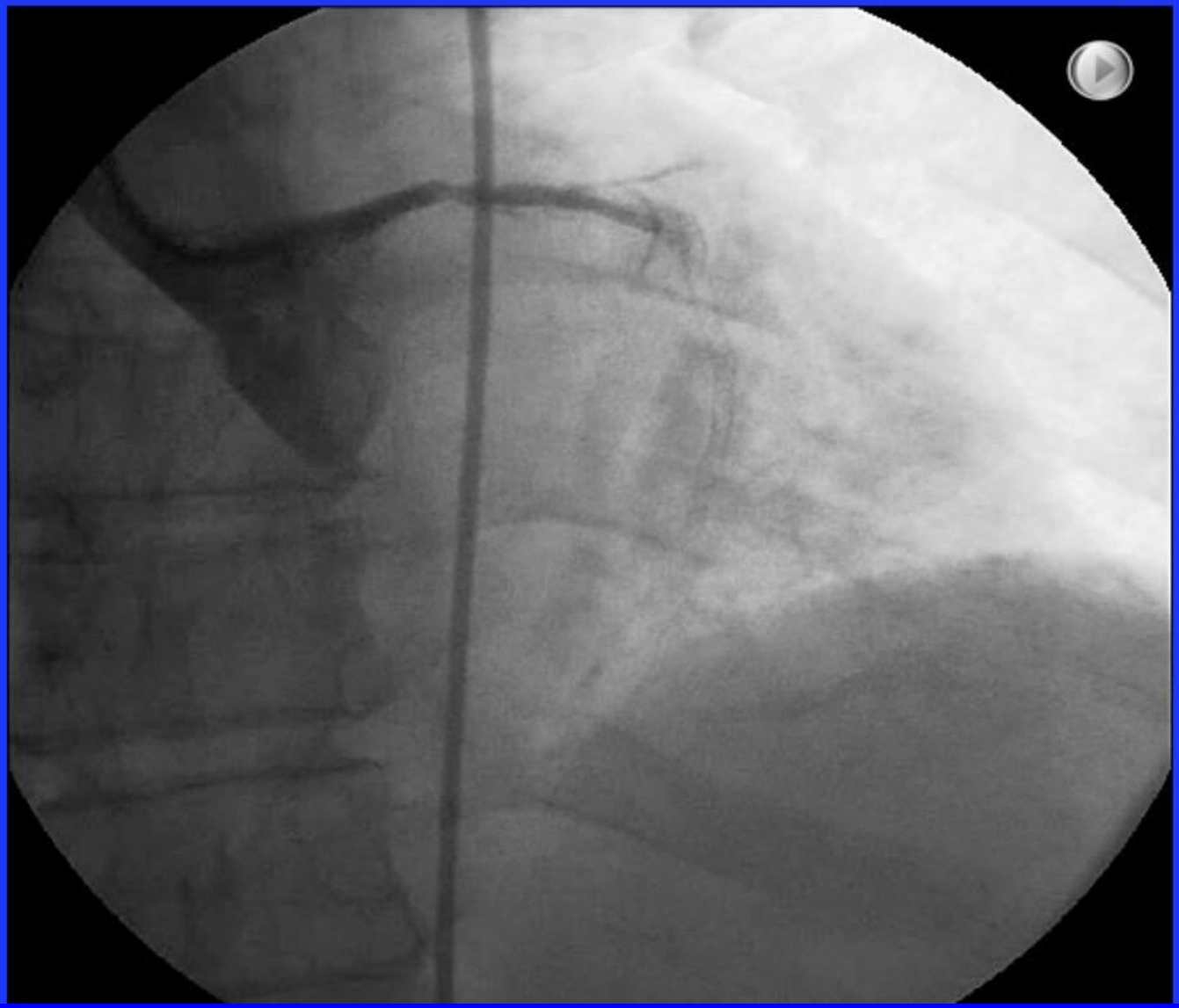


Circulation 2000;102:624

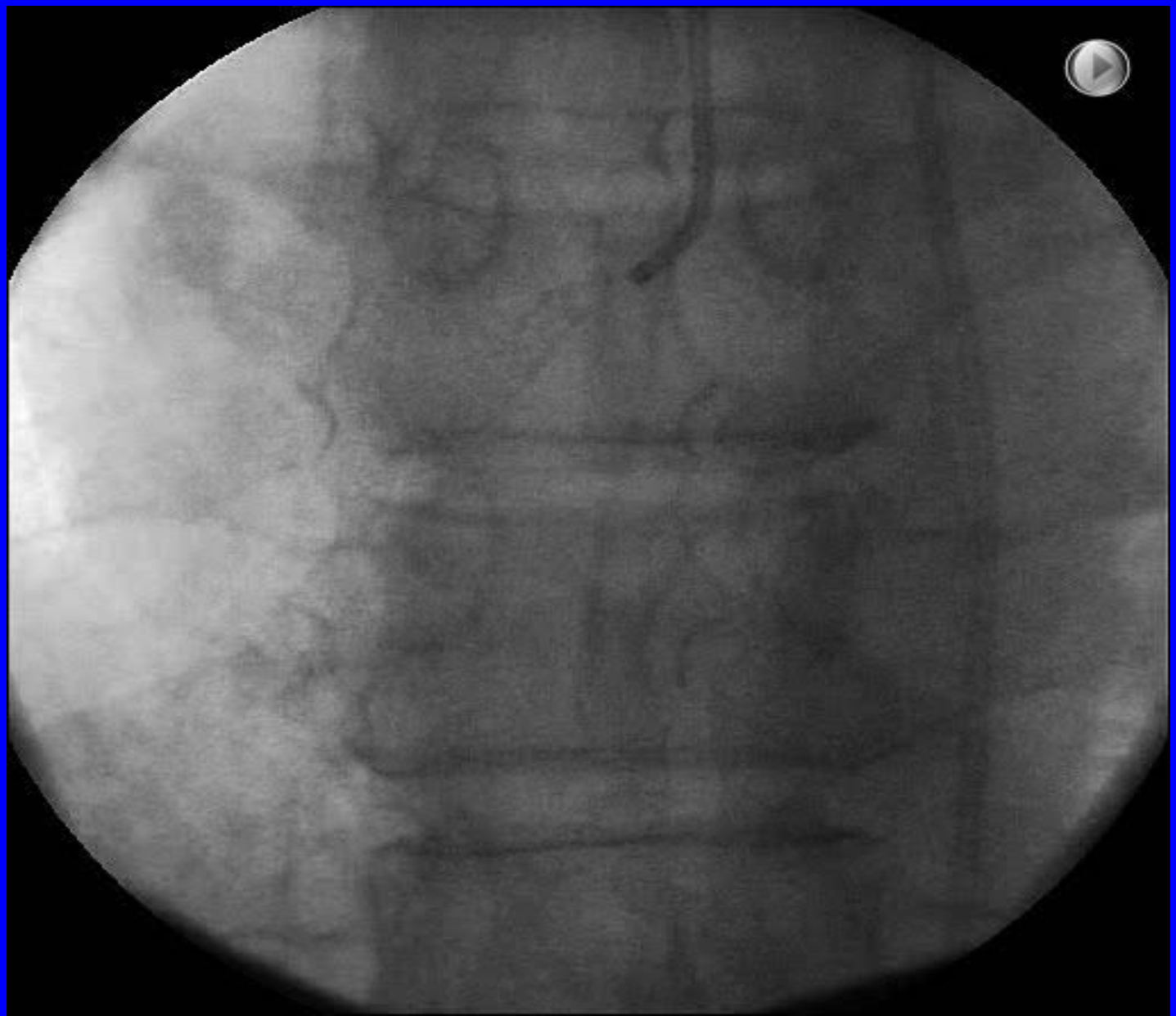
SAT at D+6 : plavix 75 +ASA75/day



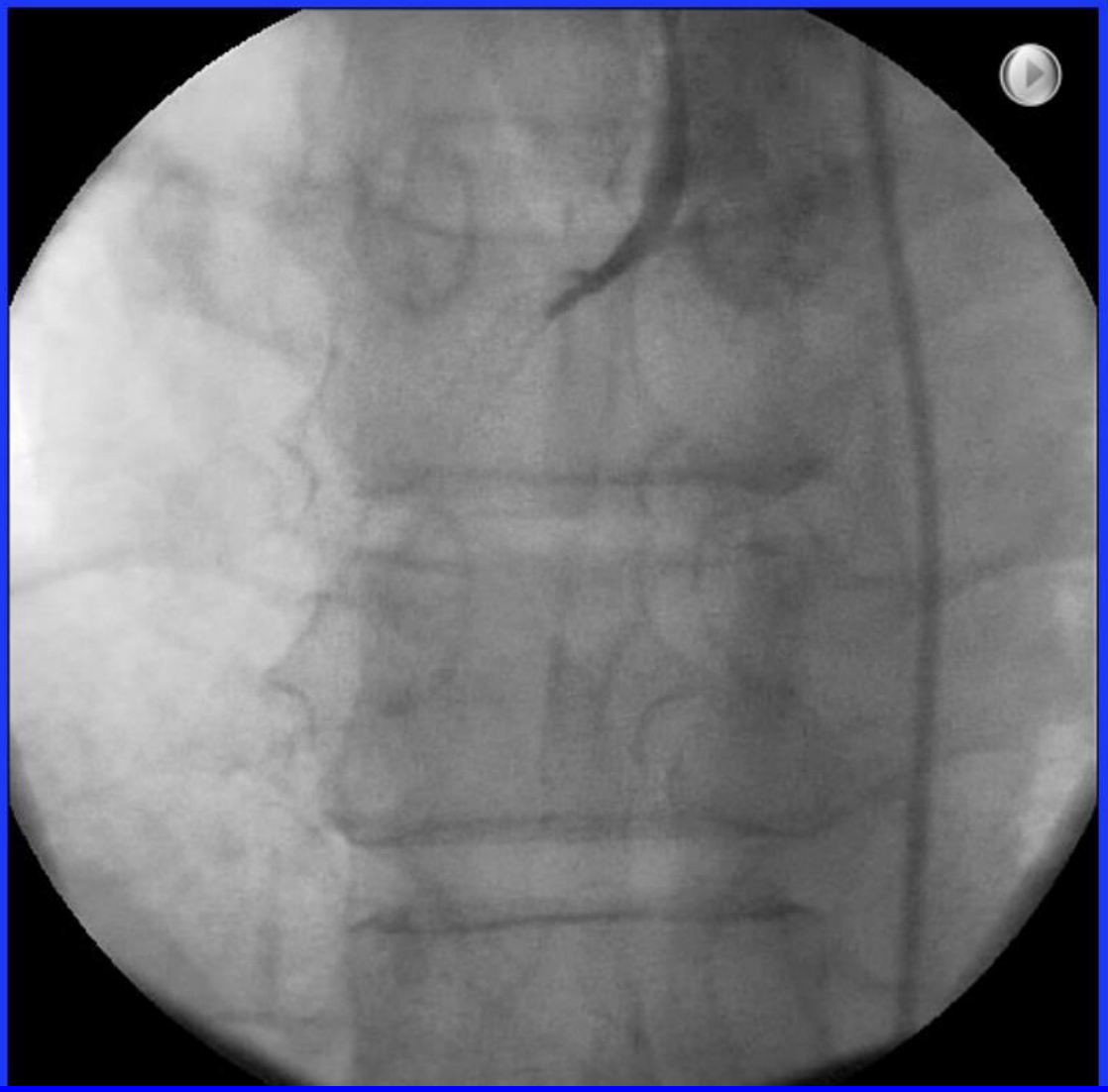
SAT at D+6 : plavix 75 +ASA75/day



SAT at D+6 : plavix 75 x 1+ASA 75

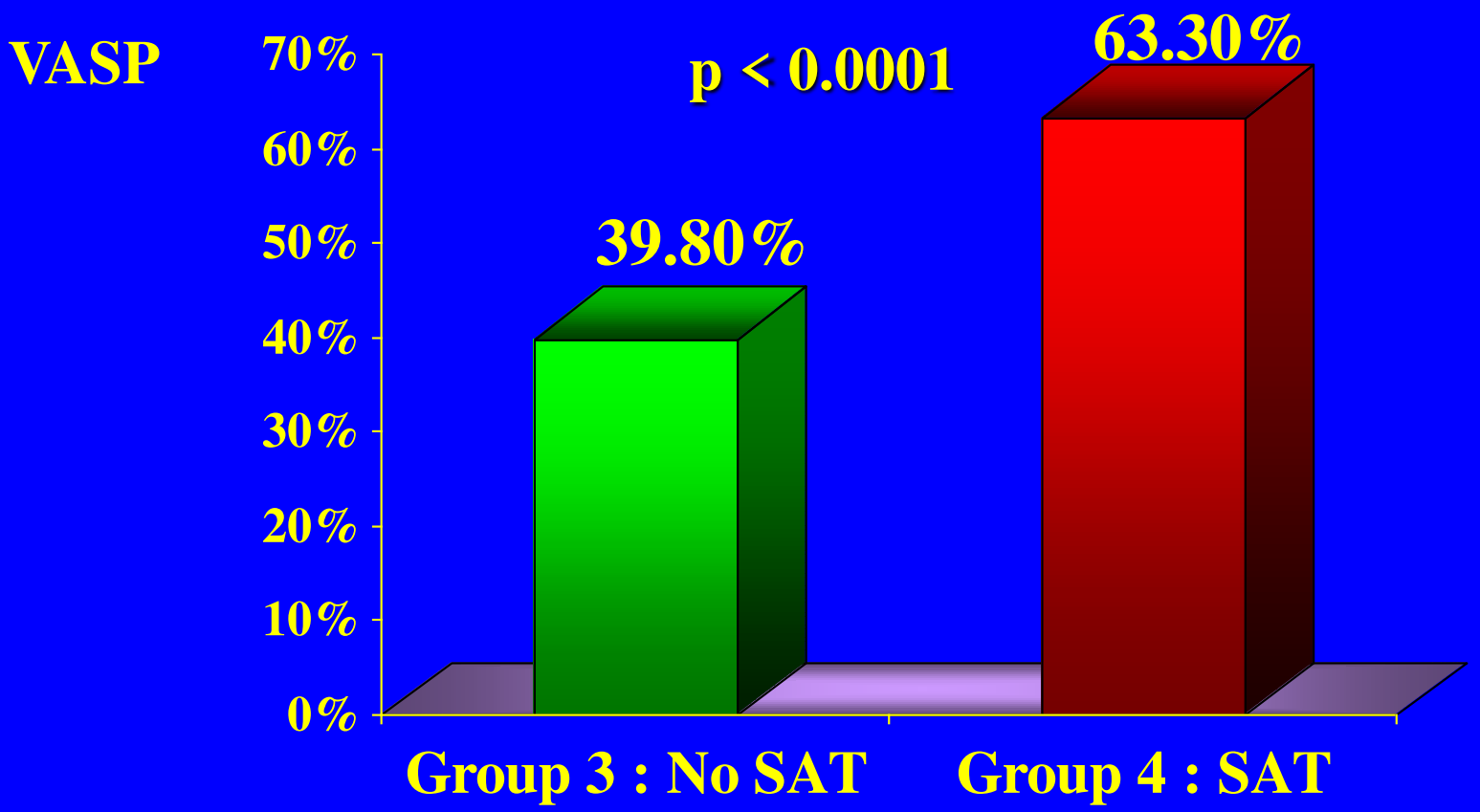


SAT at D+6 : plavix 75 x 1+ASA 75



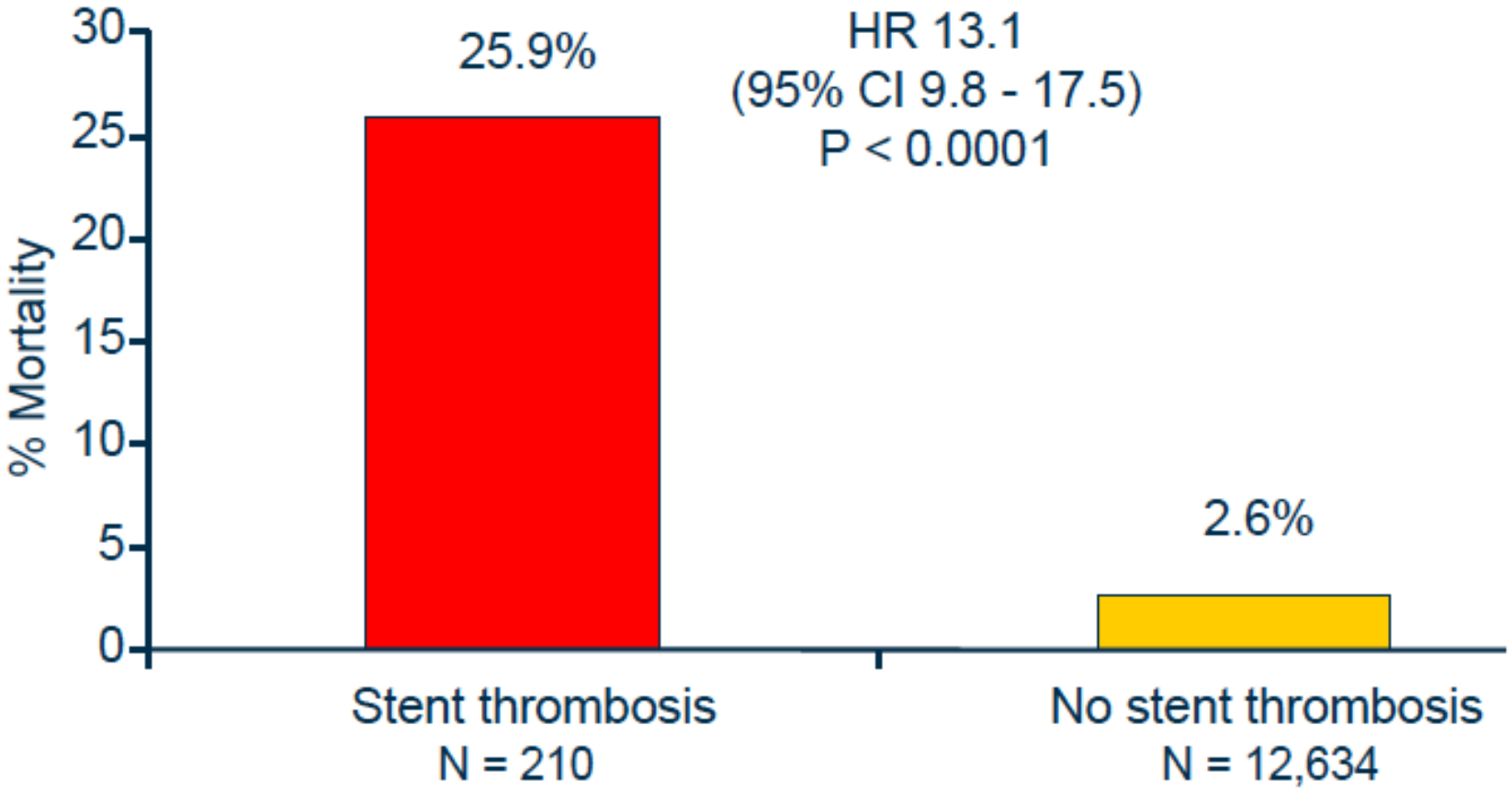
Resistance to Thienopyridines :

Clinical Detection of Coronary Stent Thrombosis by Monitoring of Vasodilator Stimulated Phosphoprotein Phosphorylation



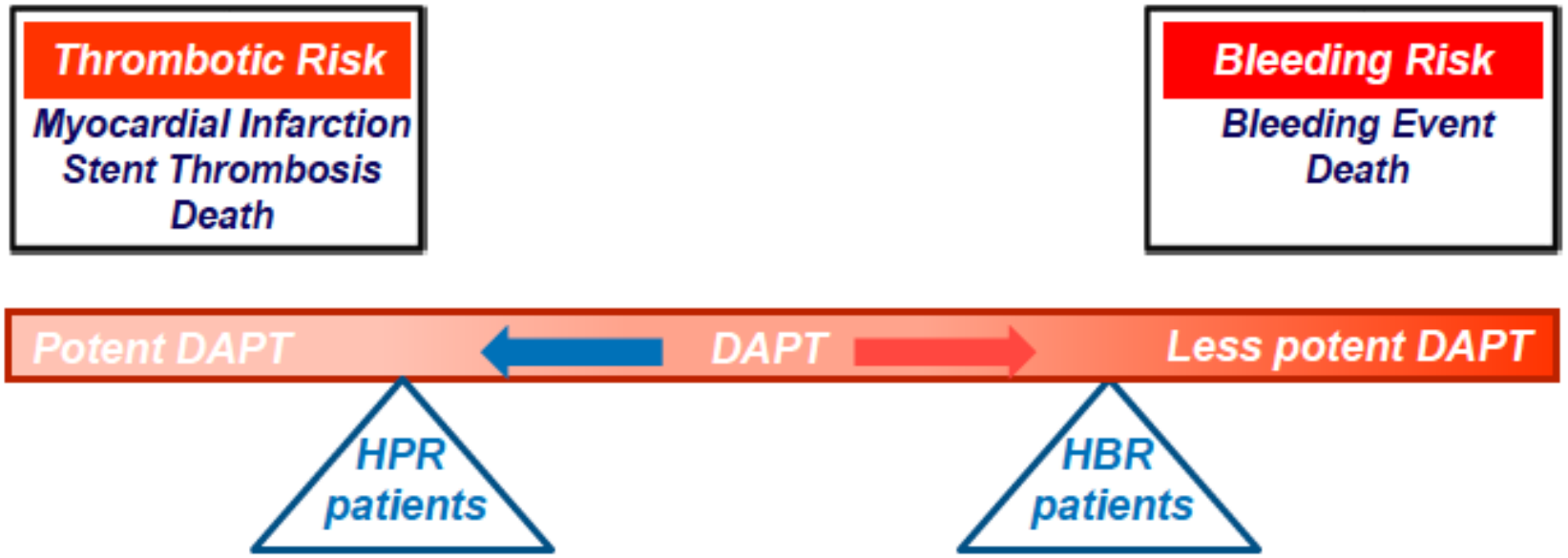
P.Barragan et al.AHA 2001

Mortalité après thrombose de stent

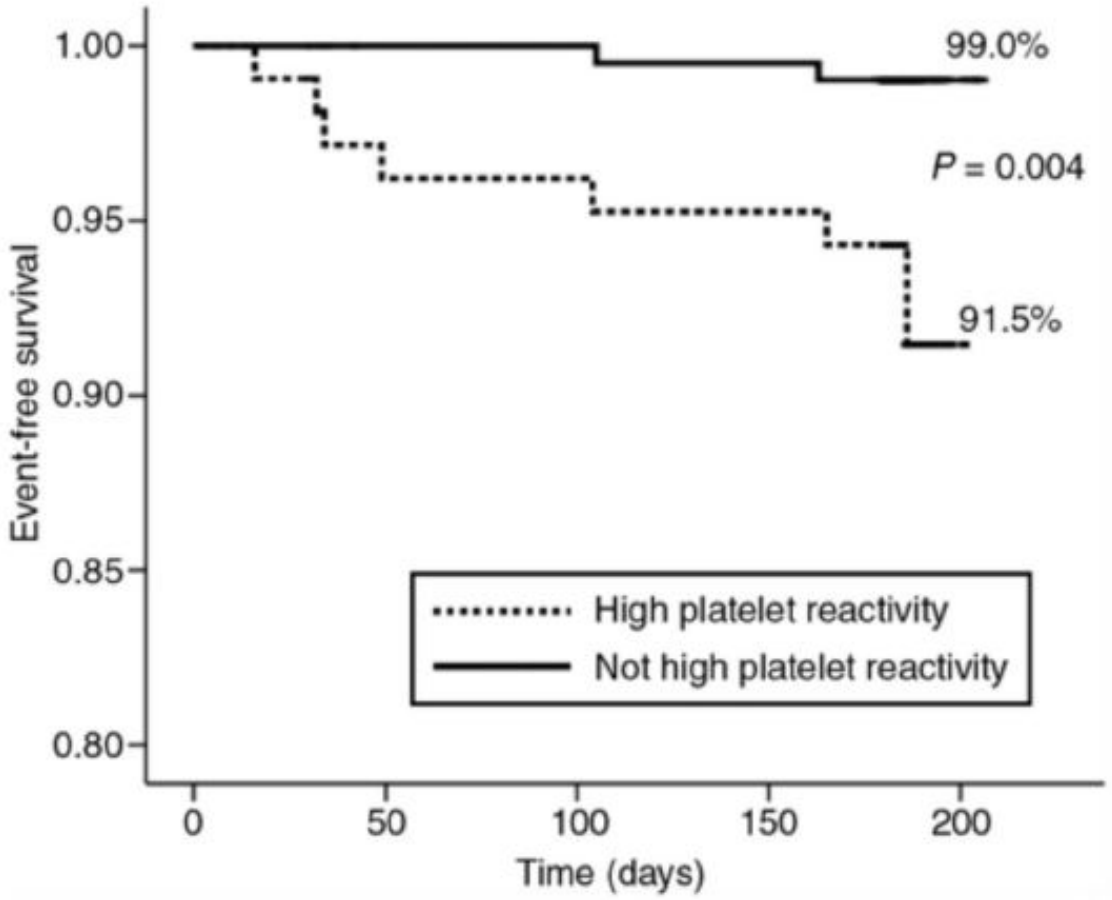


Wiviott et al.SCAI-ACCi2 2008

Le bon choix = bon équilibre risque de saignement vs réactivité plaquettaire rédiduelle

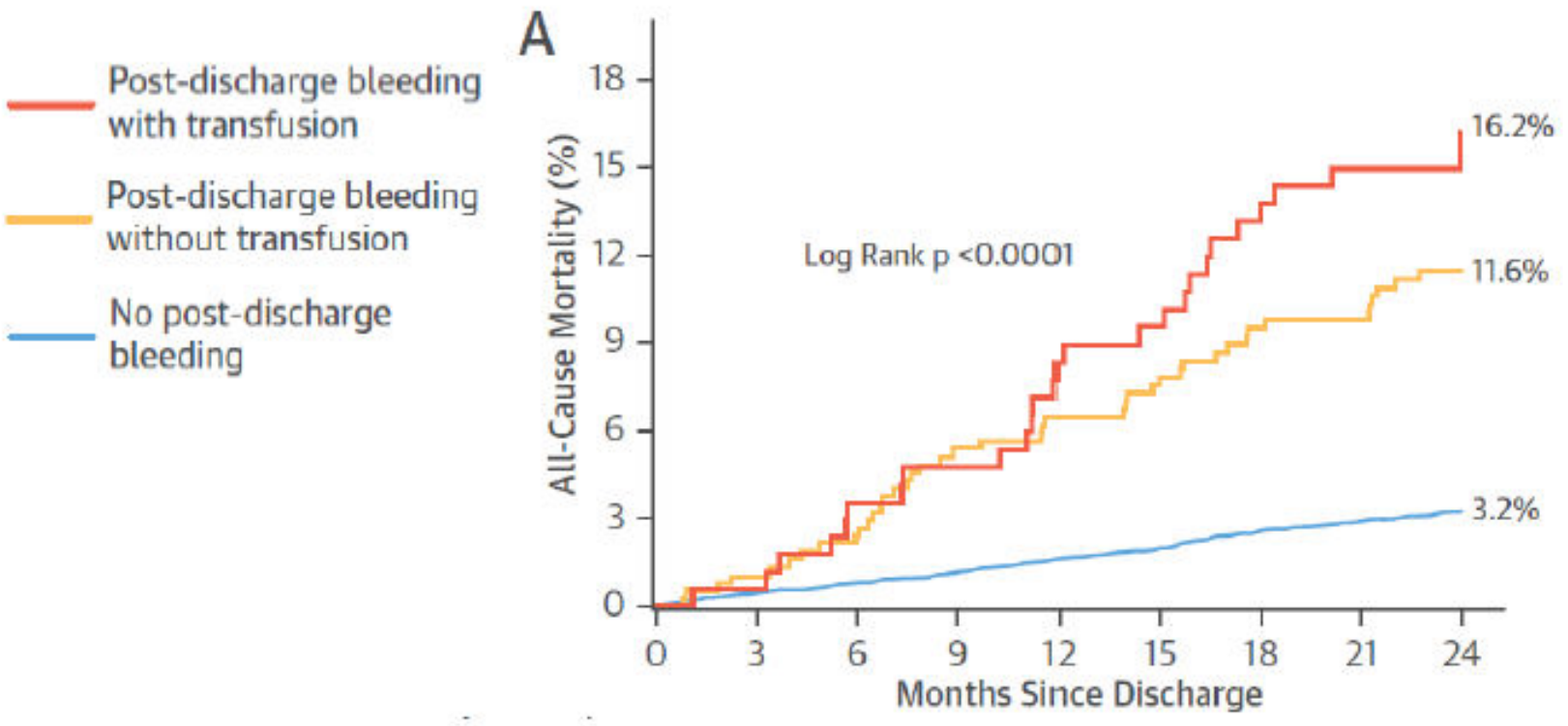


Plus d'évènements si haute réactivité plaquettaire



Price MJ et al;Eur Heart J 2008

Mortalité plus haute à 2 ans après saignement



Généreux et al.J Am Coll Cardiol 2015 ;66 : 1036-45

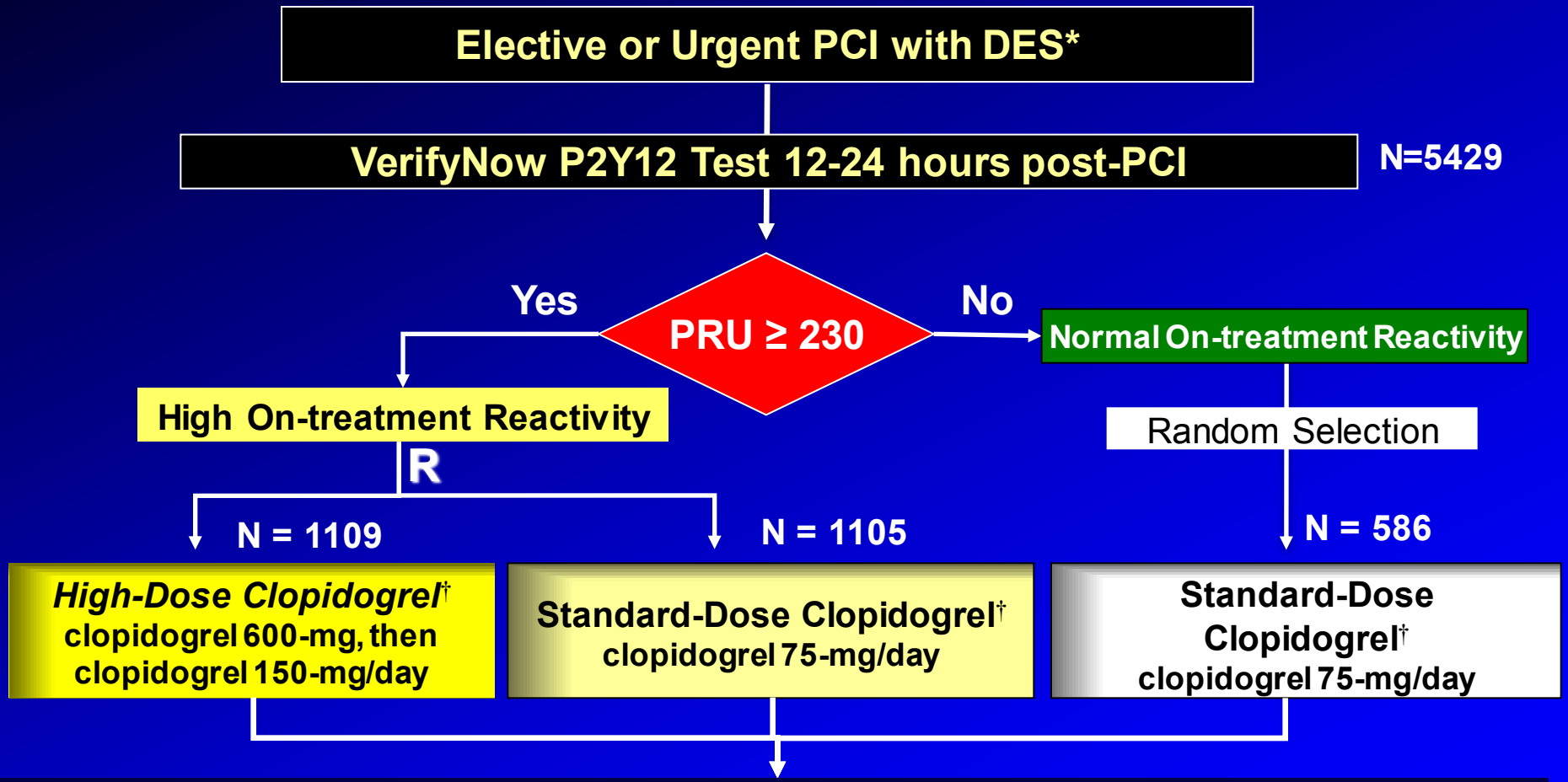
QUESTIONS :

1. Est-ce qu'une stratégie guidée peut nous aider à trouver ce juste équilibre?

2. Chez quels patients en particulier?

Price MJ et al , JAMA 2011

GRAVITAS Study Design



*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

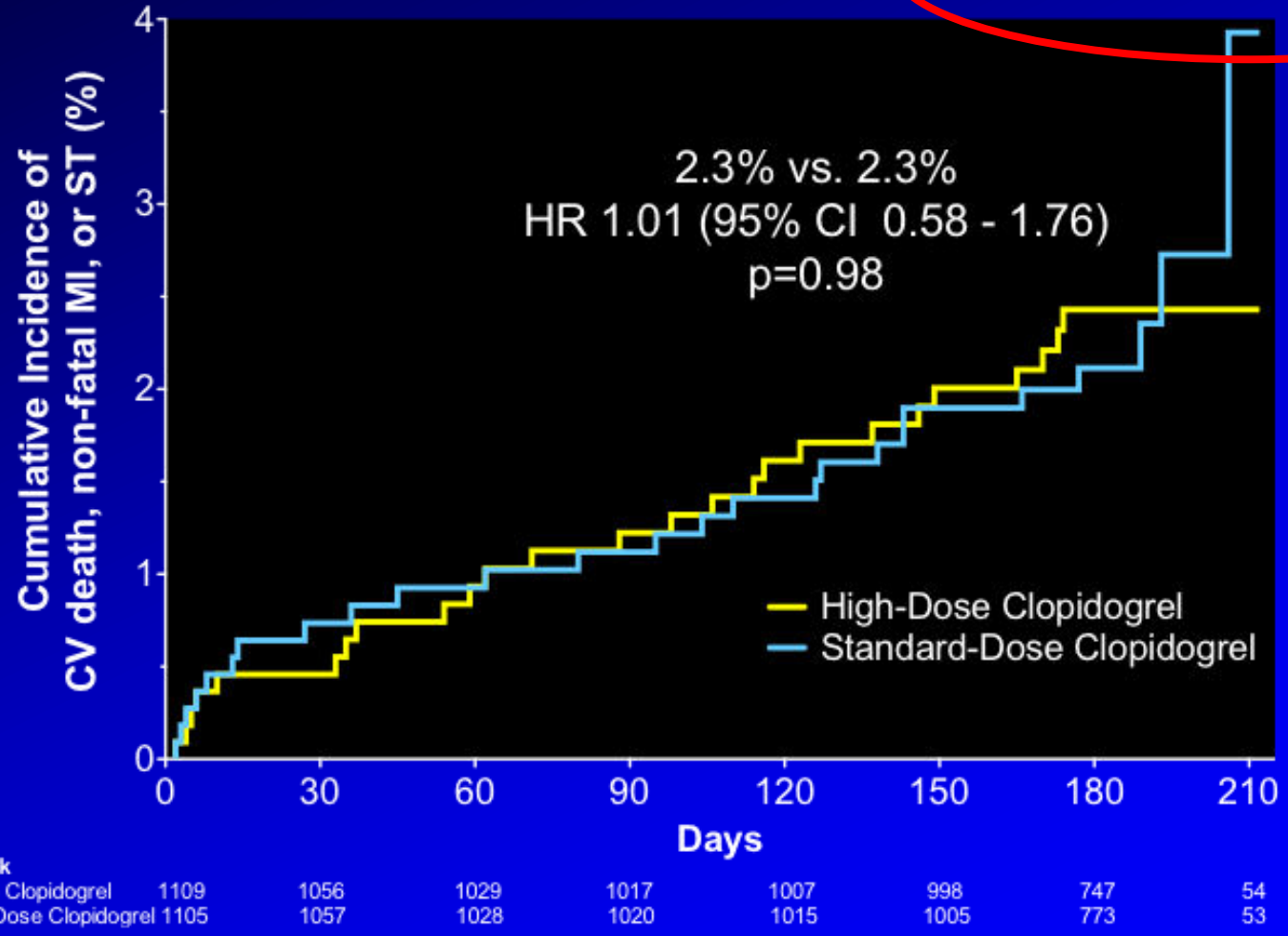
†placebo-controlled

All patients received aspirin (81-162mg daily)

GRAVITAS

Primary Endpoint @ 6 months: CV Death, MI, Stent Thrombosis

Only 10% of patients with +TnI

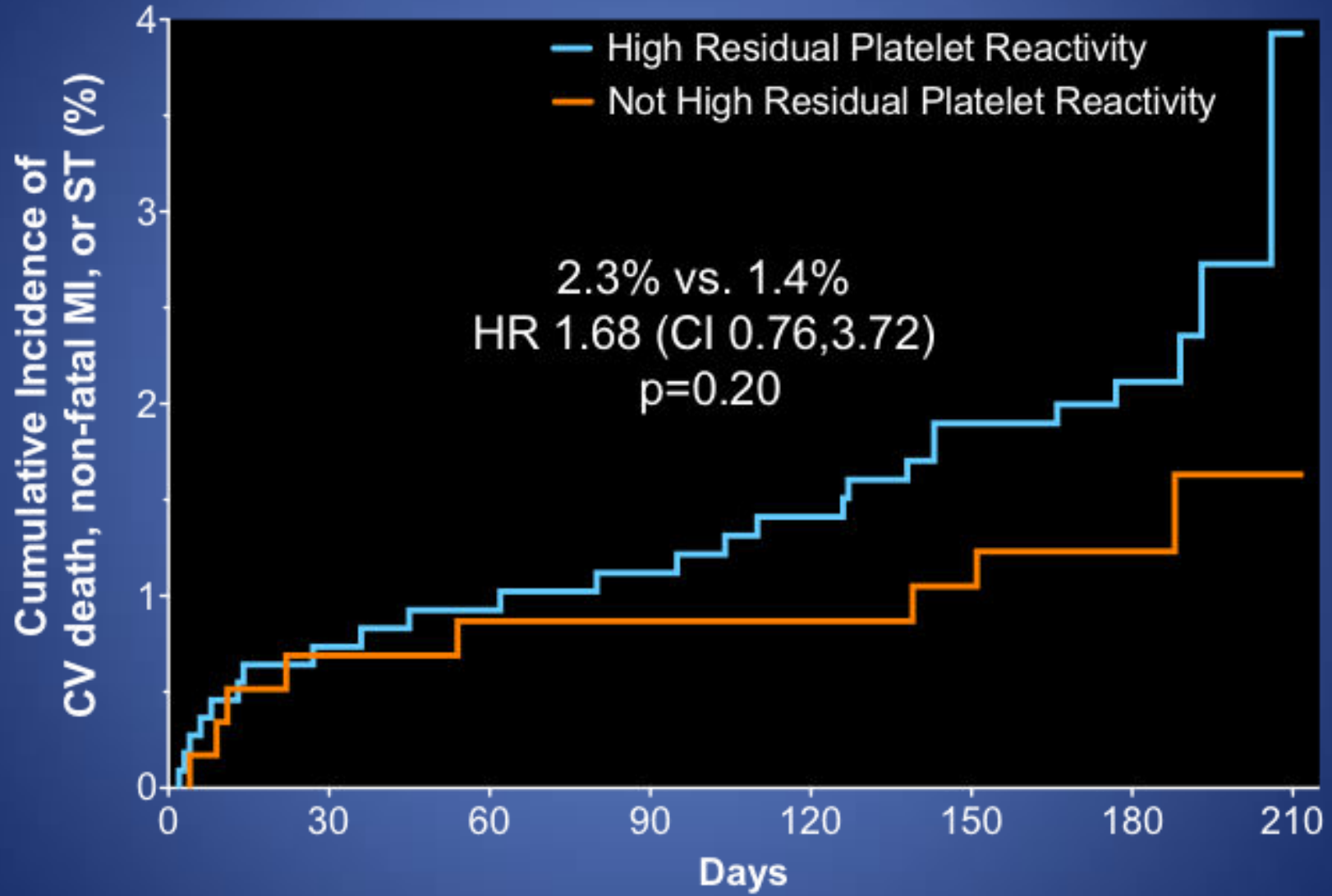


Observed event rates are listed; P value by log rank test.

GRAVITAS

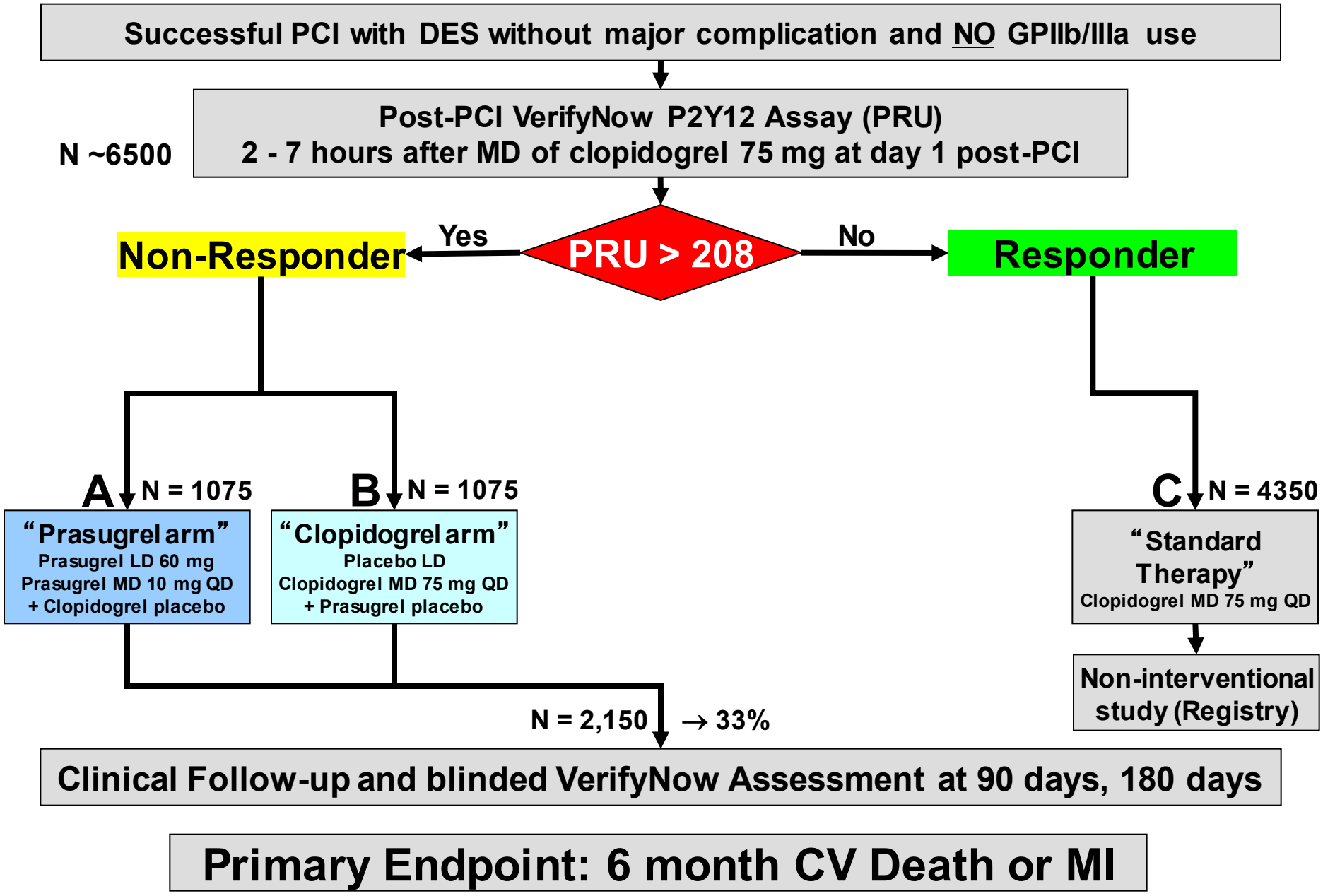
Price MJ et al, JAMA. 2011;305(11):1097-1105

Secondary Comparison@ 6 months: High vs. Not High Reactivity



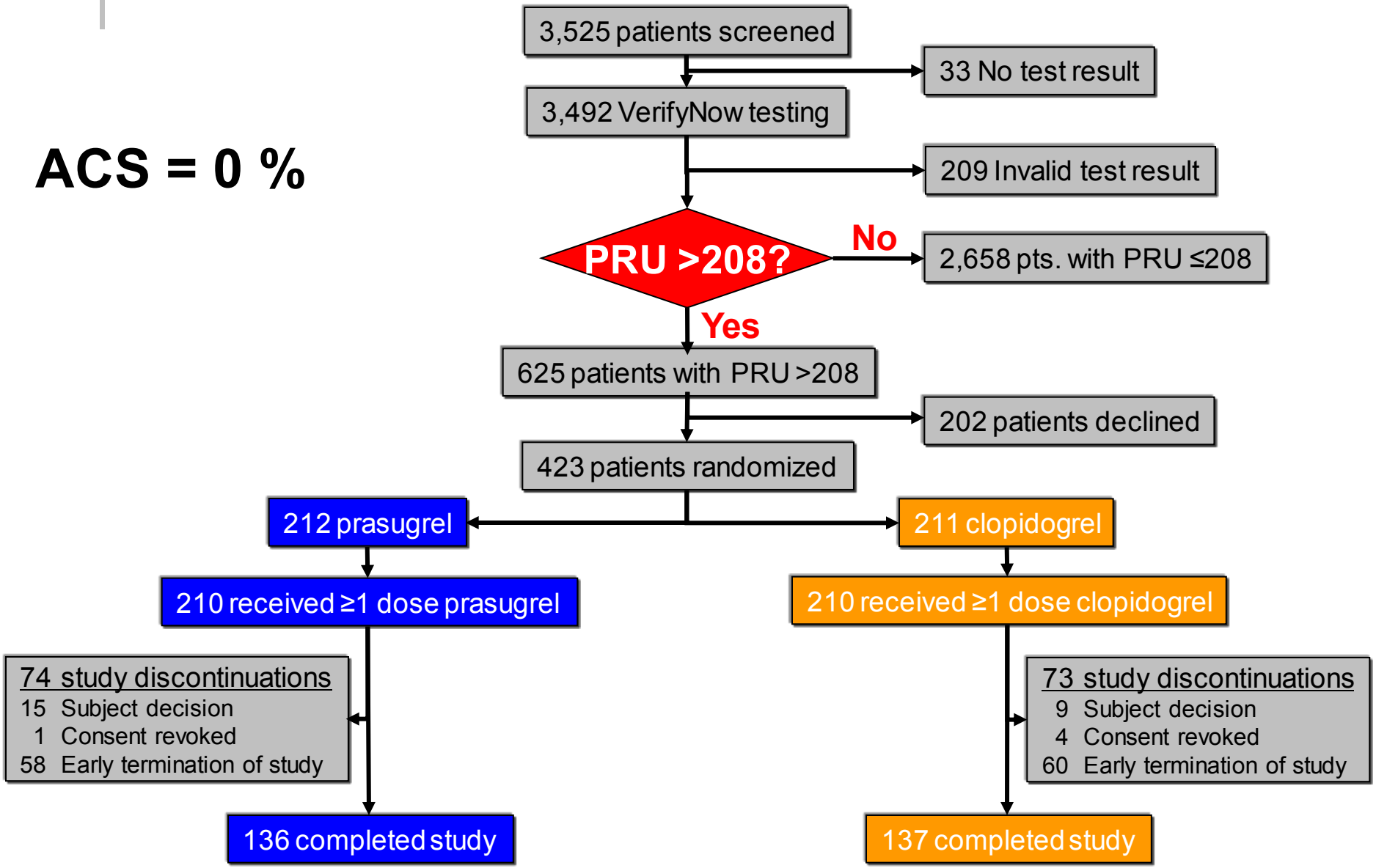
No. at Risk								
High Residual Reactiivty	1105	1057	1028	1020	1015	1005	773	53
Not High Residual Reactivity	586	565	552	551	549	546	415	19

Flow-chart **TRIGGER-PCI** Study



Disposition of patients in TRIGGER-PCI

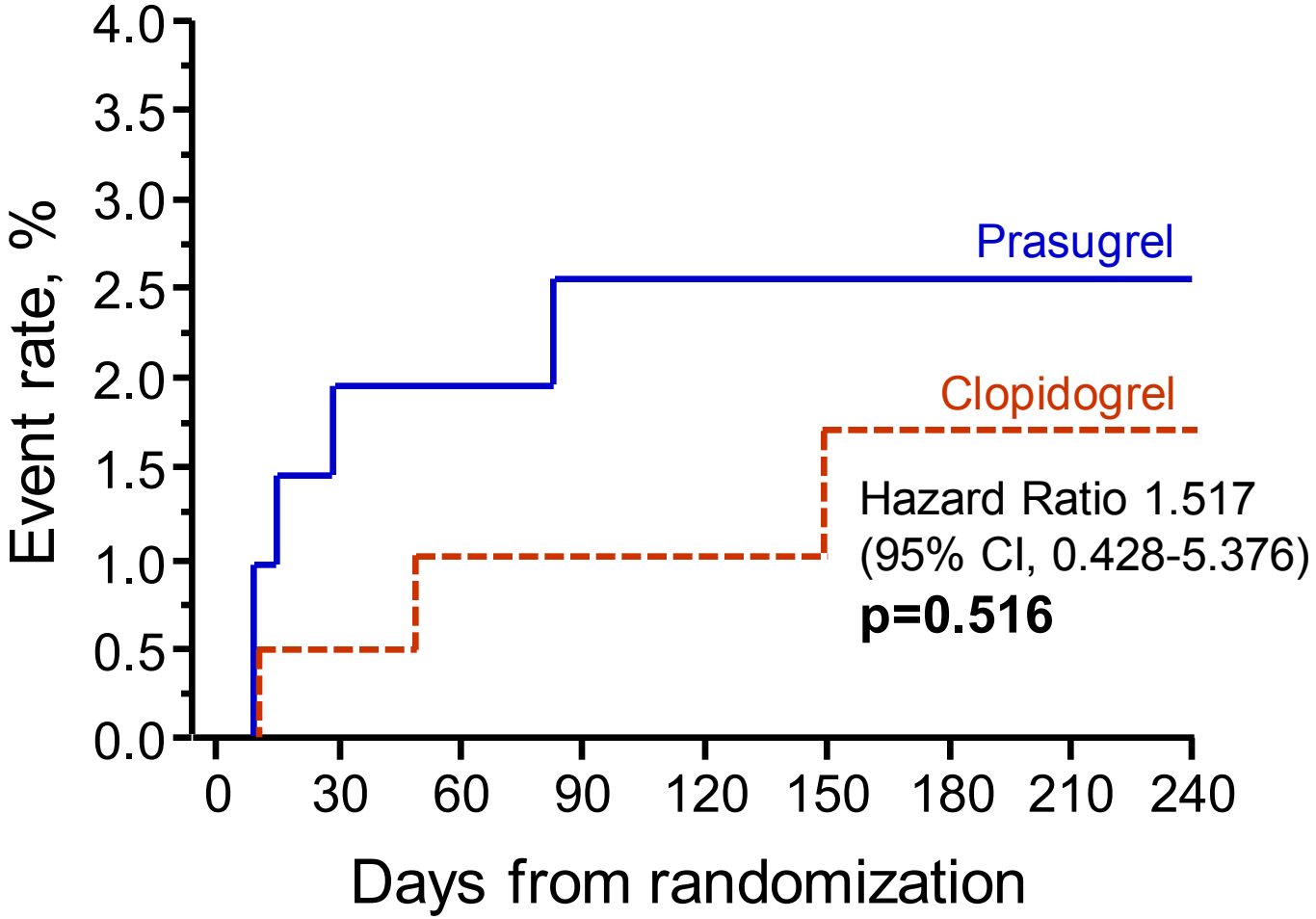
ACS = 0 %



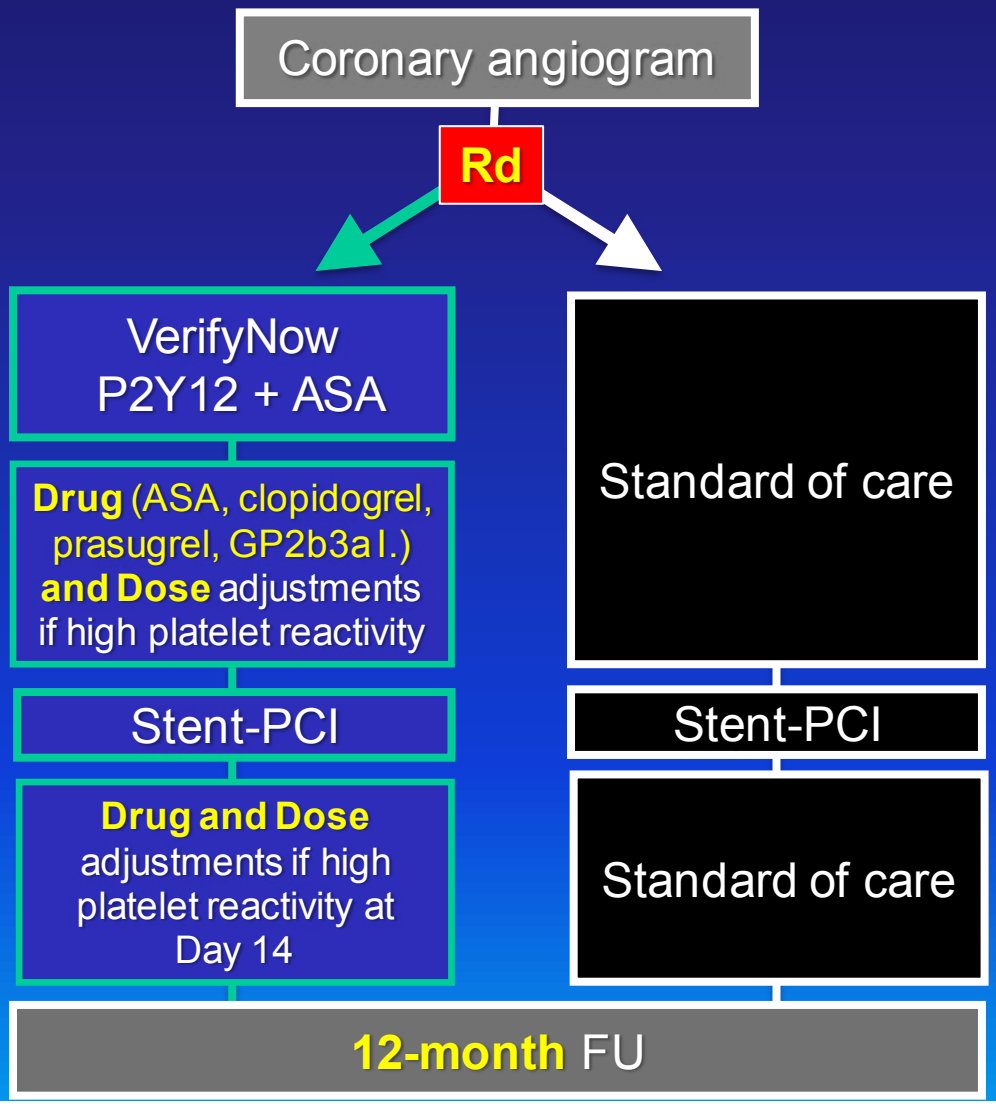
Summary of primary and secondary CEC-adjudicated efficacy endpoints

	Prasugrel N=212	Clopidogrel N=211	p HR (95% CI)
Days on study treatment(median)	174	174	-
Primary composite efficacy EP:			
CV death or MI	0	1 (0.5%)	-
Key secondary efficacy EPs:			
MI	0	1 (0.5%)	-
Rehospitalization for cardiac ischemic event	2 (0.9%)	4 (1.9%)	0.992 0.99 (0.14-7.03)
Urgent TVR	2 (0.9%)	1 (0.5%)	-
Definite ST	0	0	-
Stroke	0	1 (0.5%)	-
CV death	0	0	-
All cause death	0	1 (0.5%)	-

Non-CABG TIMI major, minor or minimal bleeding



ARCTIC trial design



Primary endpoint at 12 months:

- Death, MI, stroke, stent thrombosis, urgent revascularization

Statistical considerations:

- Assuming an annual risk of 9% and a 33% relative risk reduction (α risk at 5% and error β of 20%, bilateral test), 2,466 patients were necessary to demonstrate the superiority of the strategy of monitoring and adjustment

73% elective, 27% stabilized NSTE-ACS ,no STEMI

Collet JP, et al. Am Heart J 2011;161:5-1

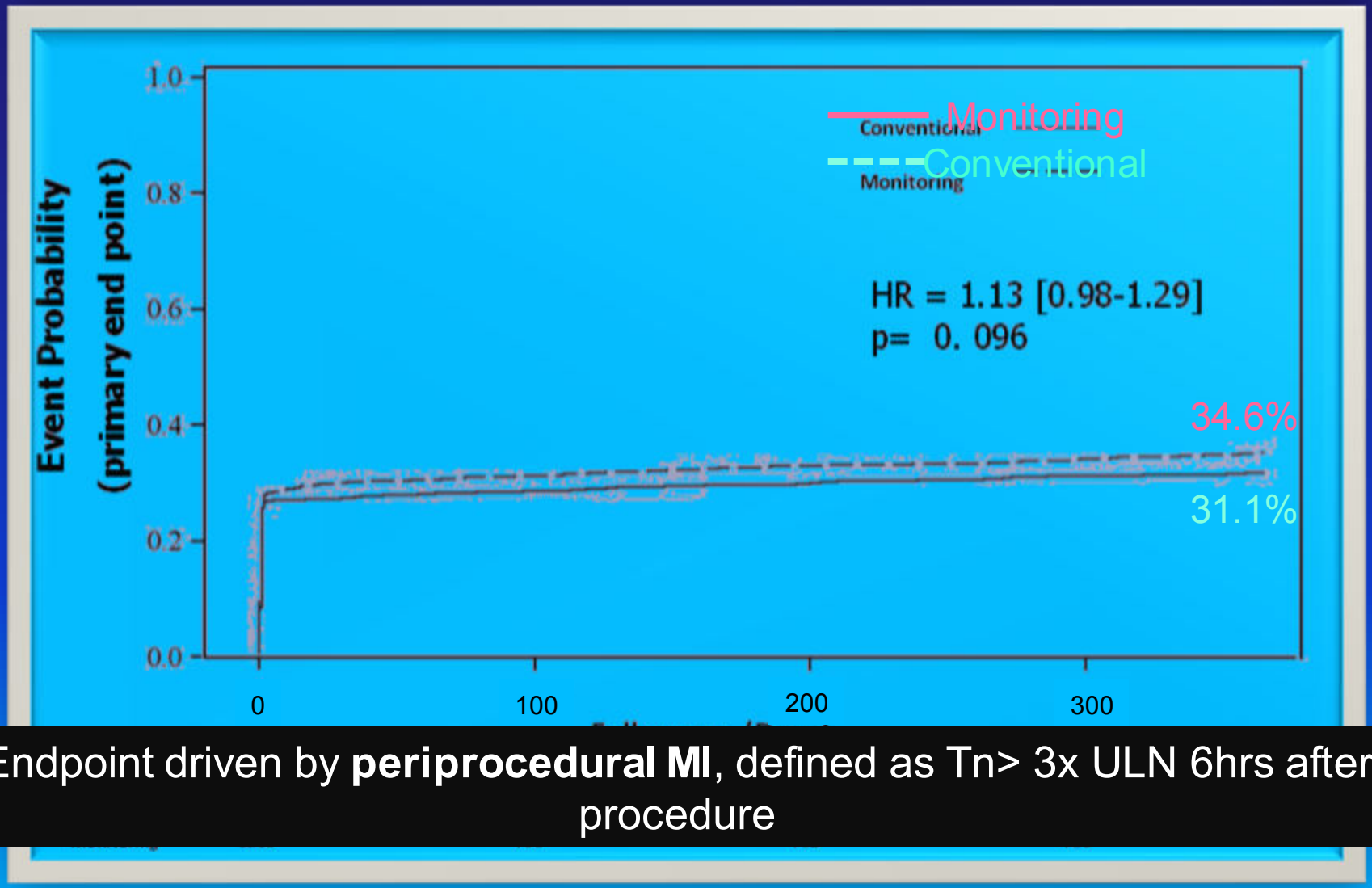
In-Lab monitoring and adjustment

	Conventional (n=1227)	Monitoring (n=1213)
Aspirin poor responders - %	NA	**7.6**
→On-table aspirin loading in poor responders - %	NA	→ 85
Thienopyridine poor responders - %	NA	**35**
→ On-table clopi. loading in poor responders - %	NA	→ 80
→ On-table prasu. loading in poor responders - %	NA	→ 3.3
→ On-table GP IIbIIIa↓ loading in poor responders - %	NA	→ 80

Predominant intervention after procedure: double-dose clopidogrel!

Primary Endpoint to 1 year

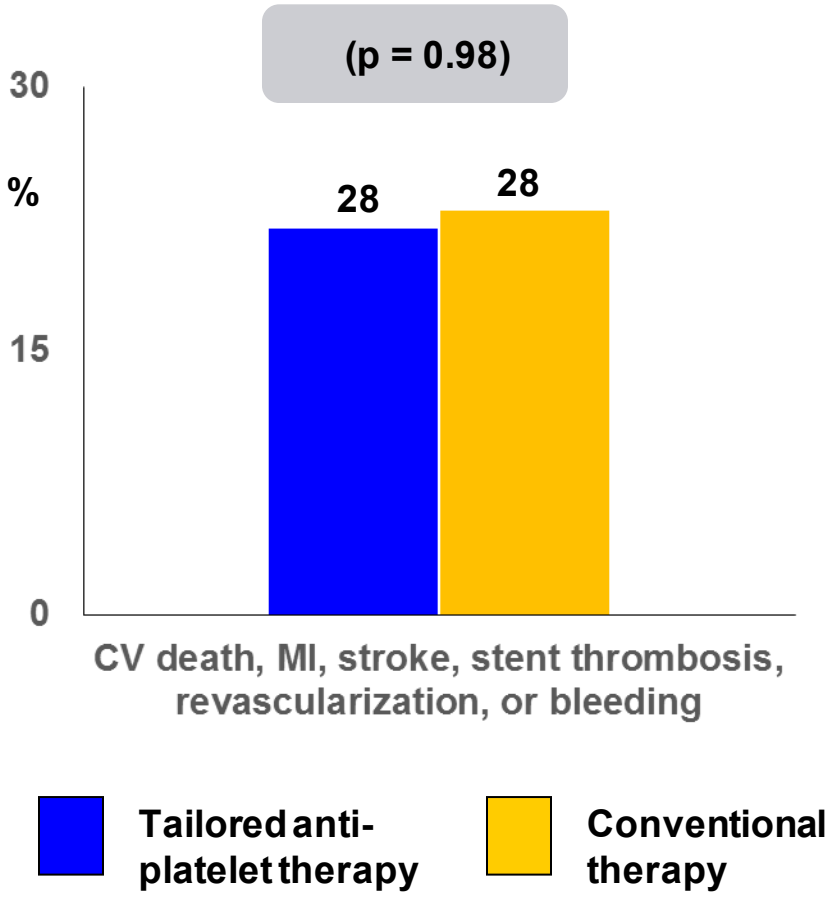
Death, MI, stroke, stent thrombosis, urgent revascularization



Endpoint driven by **periprocedural MI**, defined as Tn> 3x ULN 6hrs after procedure

ANTARCTIC

Trial design: Patients with acute coronary syndrome undergoing stenting were randomized to tailored antiplatelet therapy (n = 435) versus conventional therapy (n = 442). All patients were started on prasugrel 5 mg daily.



Results

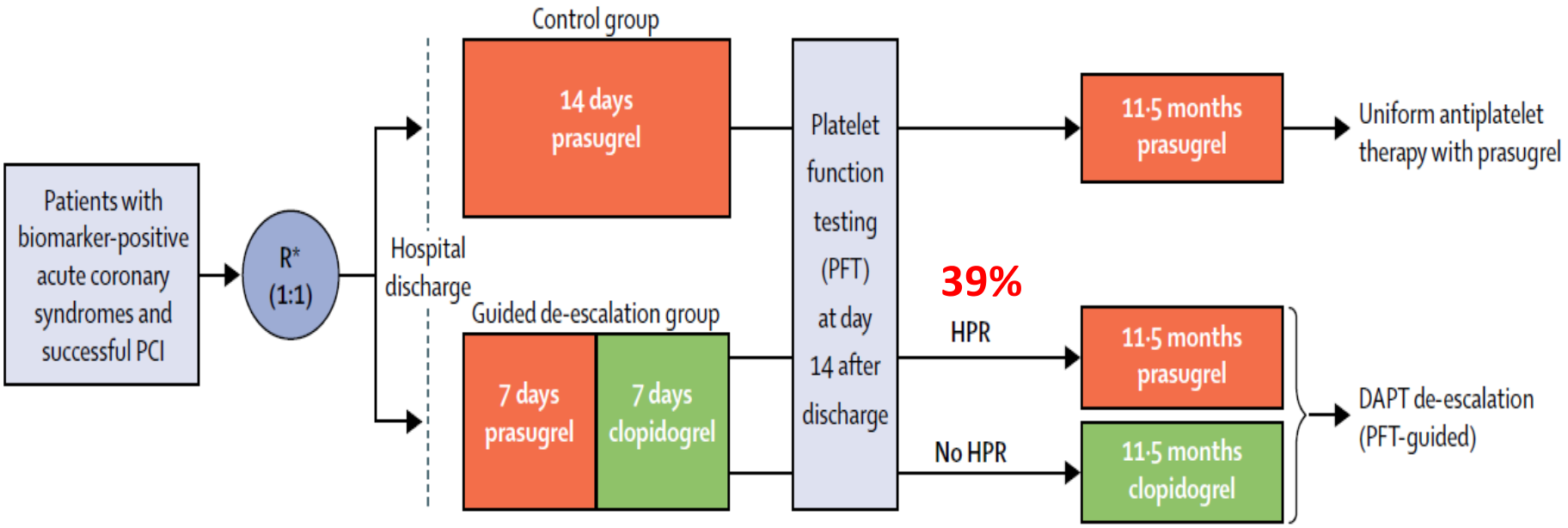
- CV death, MI, stroke, stent thrombosis, urgent revascularization, or bleeding at 1 year: 27.6% of the tailored therapy group versus 27.8% of the conventional therapy group (p = 0.98)
- CV death, MI, stent thrombosis, or urgent revascularization: 9.9% versus 9.3% (p = 0.80)

Conclusions

- Among elderly patients with acute coronary syndrome undergoing stenting, tailored antiplatelet therapy did not improve outcomes compared with conventional antiplatelet therapy
- Tailored antiplatelet therapy resulted in a large proportion of patients that were down-titrated to clopidogrel therapy

Cayla G, et al. Lancet 2016;Aug 29:[Epub]

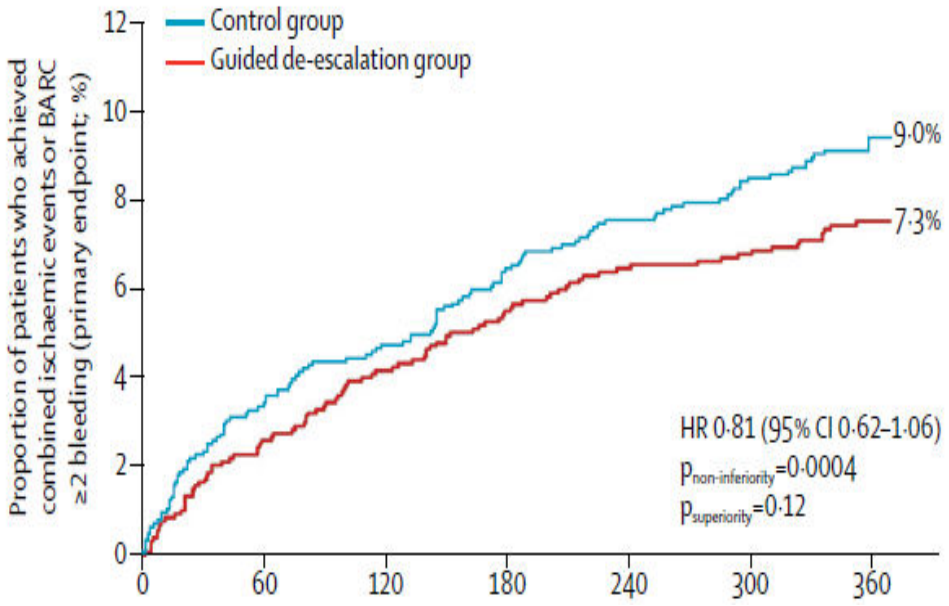
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial



TROPICAL-ACS study,
n=2610
HPR if Multiplate > 46 IU

Sibbing et al, LANCET 2017

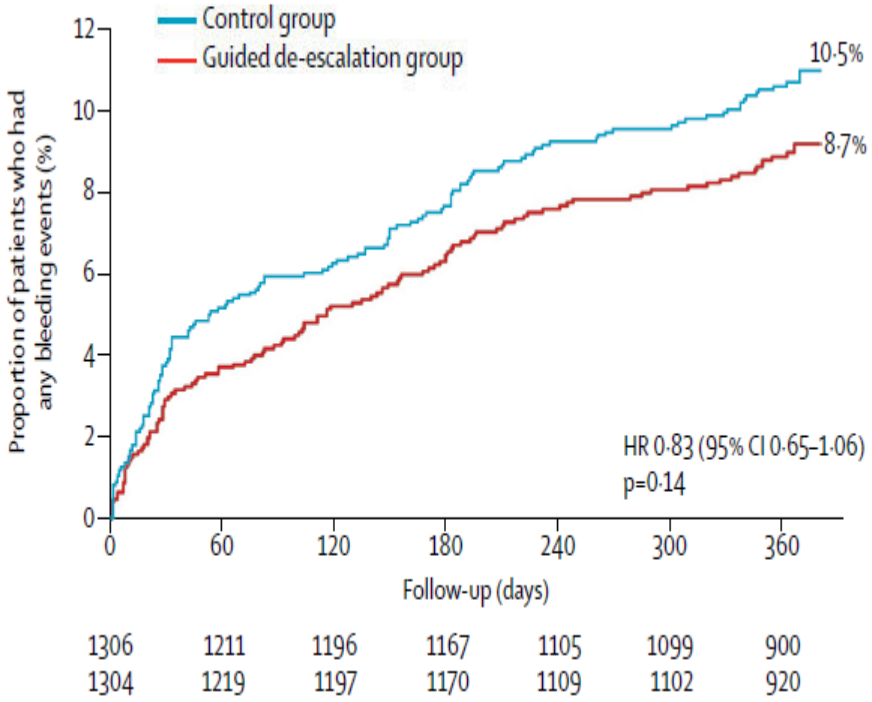
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial



Non inferiority of guided de-escalation strategy on PEP

Sibbing et al, LANCET 2017

Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

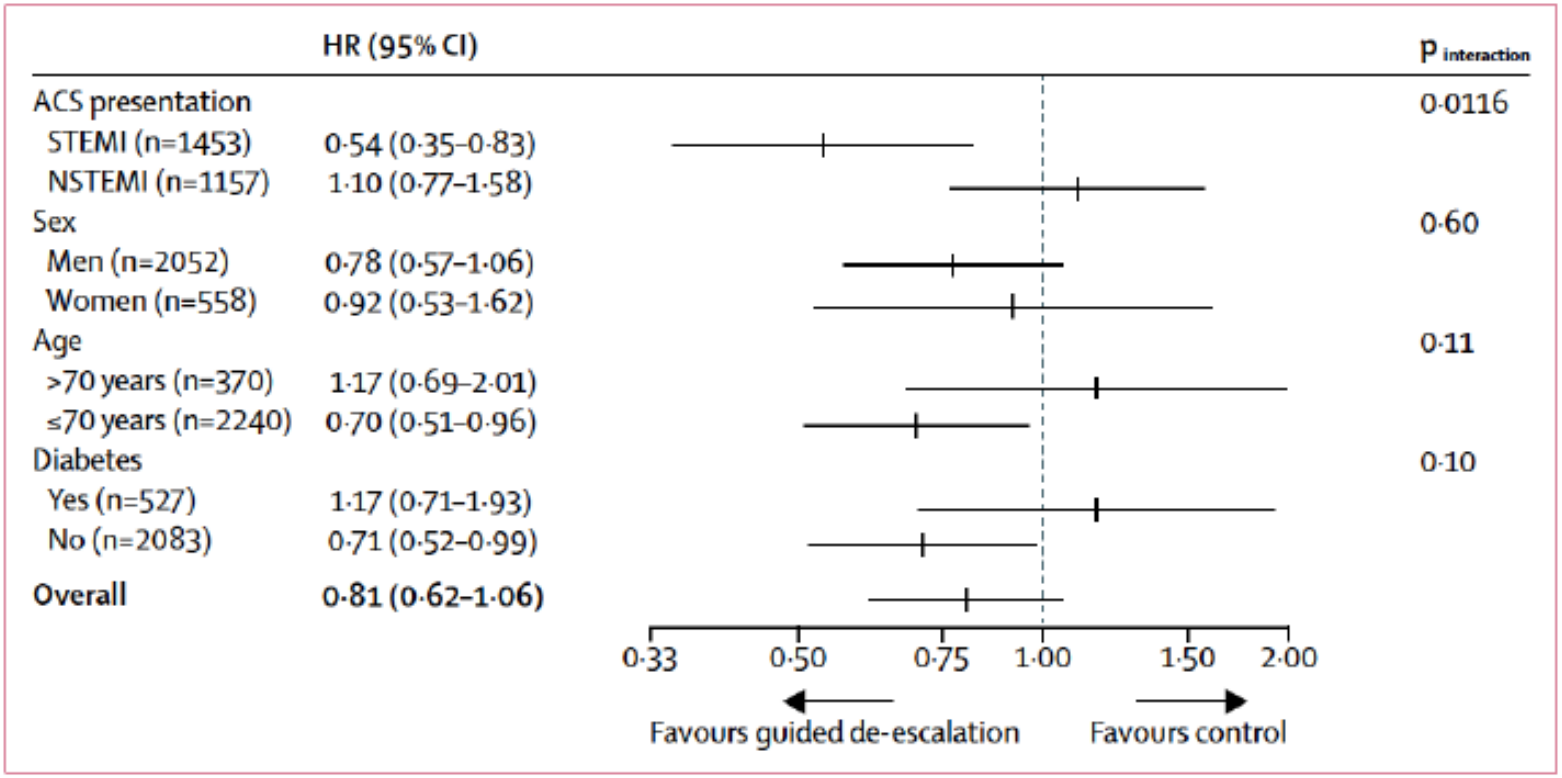


- 17%

Trend for less bleeding with guided de-escalation strategy

Sibbing et al, LANCET 2017

Tropical ACS – subgroups analysis

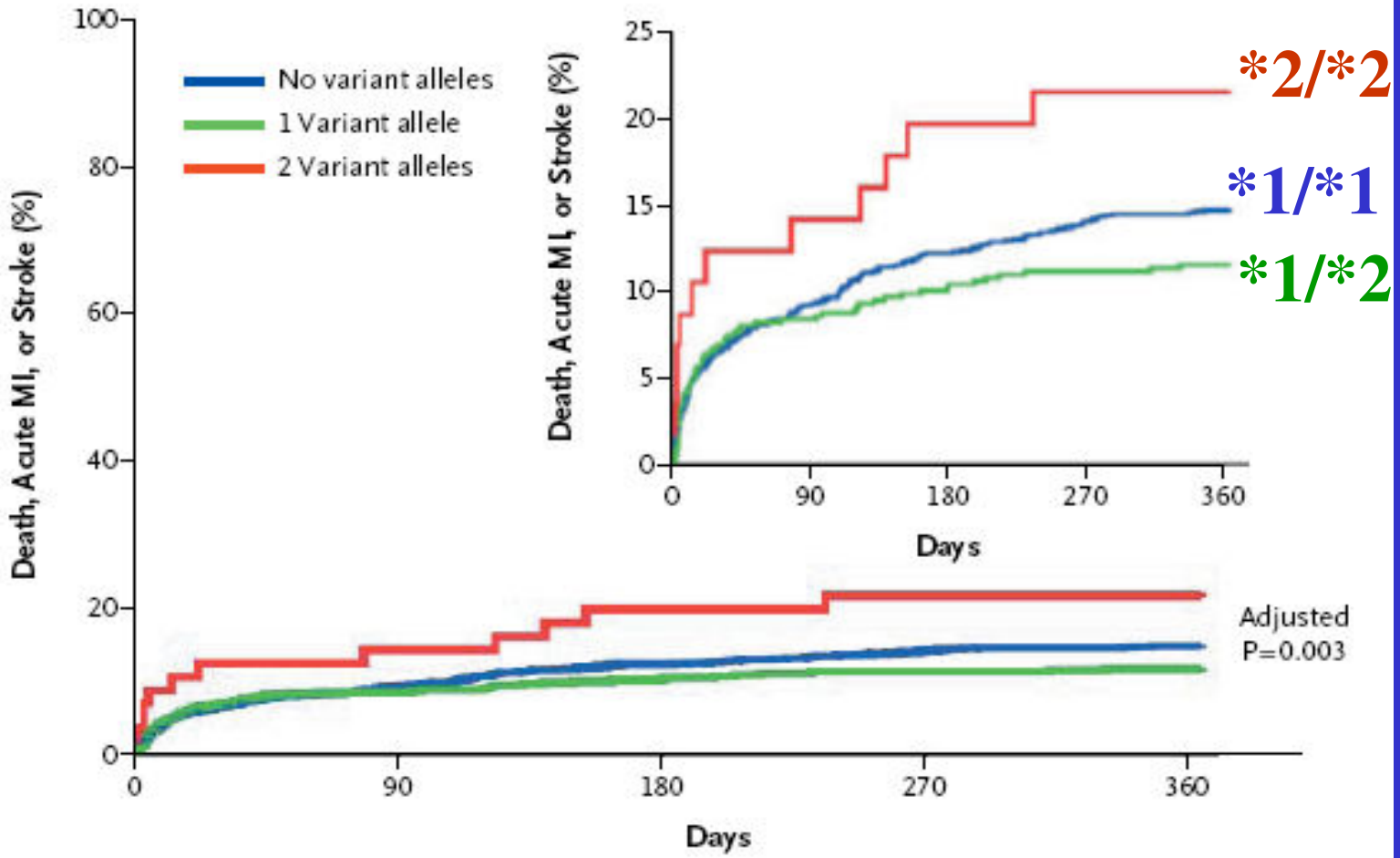


Tests génétiques au “chevet” du patient

SpartanRX

the Verigene System

Estimated Rates of All Death + Nonfatal MI + Stroke, According to *CYP2C19* Variant-Allele Polymorphisms



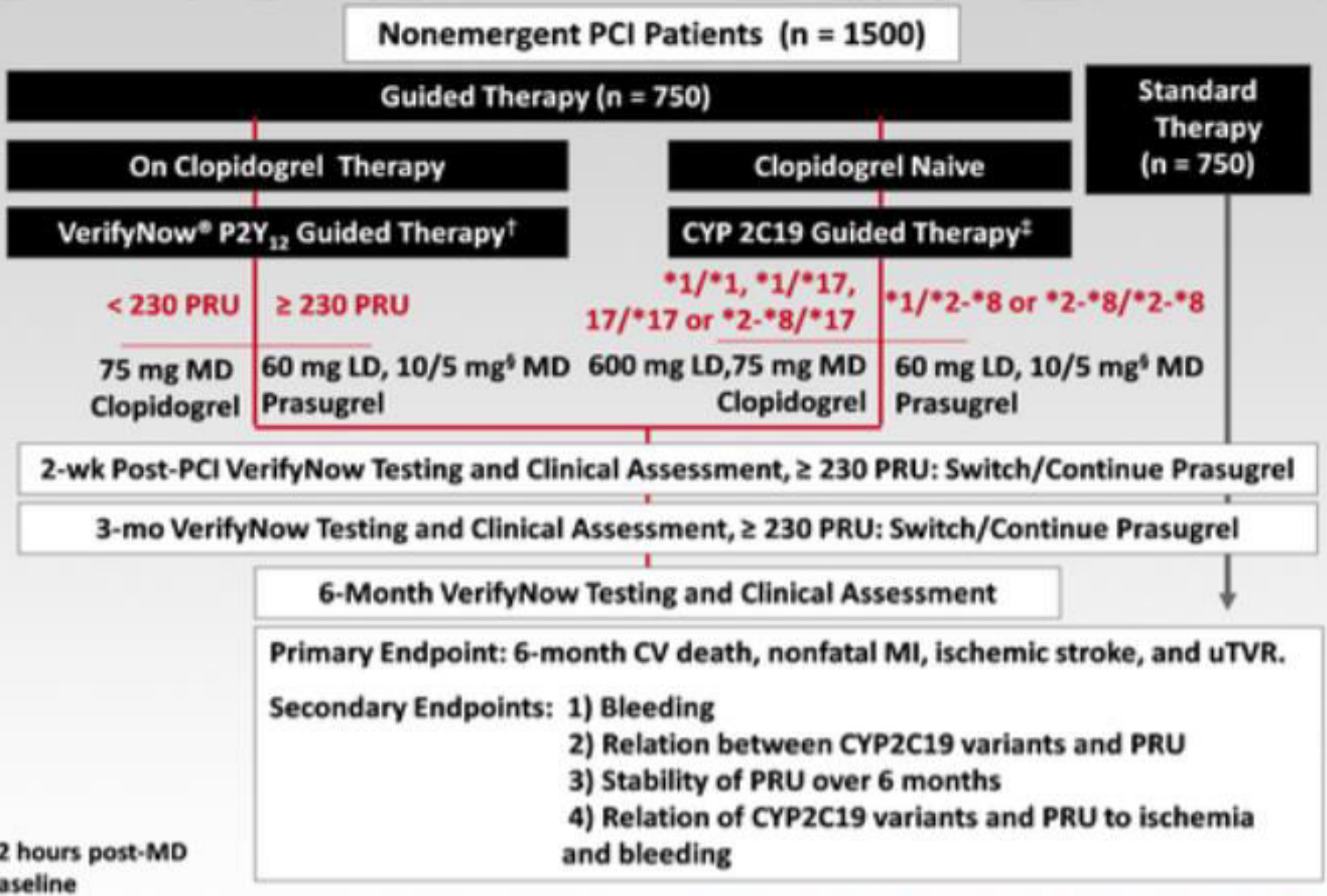
No. at Risk					
No variant alleles	1572	1334	1288	1211	1208
1 Variant allele	576	502	491	468	446
2 Variant alleles	58	47	44	42	40

Simon T. et al. N Engl J Med 2008;10.1056

Les Essais en cours

GeCCO	ACS 14 600	Cohorte observ.	Arrêt prématuré
PAPI-2	PCI 7 200	Randomisé	Arrêt prématuré
TARGET-PCI	PCI 1 500	Randomisé	Arrêt prématuré
POPGenetics	PCI 2 700	Randomisé	Recrutement
TAILOR-PCI	PCI 5 200	Randomisé	Recrutement
ADAPT	PCI 700	Randomisé	Terminé

Thrombocyte Activity Reassessment and GEnoTyping for PCI (TARGET-PCI)

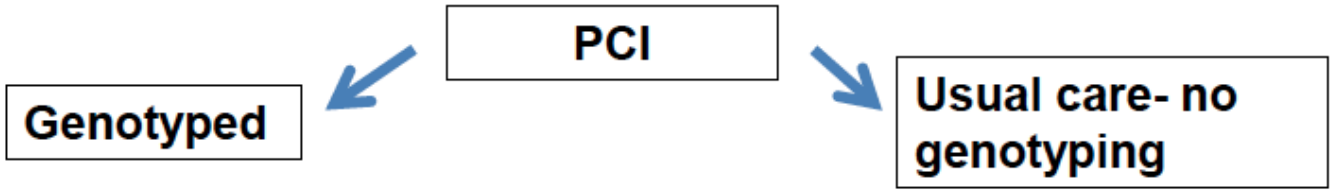


† ≥2 hours post-MD
‡ Baseline
§Participants <60 kg or >75 years get 5 mg

Available at: http://clinicaltrials.gov/ct2/show/NCT01177592

Assessment of prospective *CYP2C19* genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention (ADAPT)

The ADAPT study: *A Pragmatic Randomized Clinical Trial*



Primary endpoint
Proportion of participants receiving prasugrel/ticagrelor

Secondary endpoints

1. Agreement with the genotype guided antiplatelet recommendations
2. Clinical Outcomes: Major Adverse Cardiac Events and Major Bleeding

Assessment of prospective *CYP2C19* genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention (ADAPT)

Primary Outcome: Antiplatelet Drugs Prescribed

	Genotyped N=249	Usual Care N=255	P-value
Clopidogrel	174 (70%)	201 (79%)	0.03
Prasugrel or Ticagrelor	**75 (30%)**	**54 (21%)**	

Fisher's exact test

Assessment of prospective *CYP2C19* genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention (ADAPT)

Prasugrel/ ticagrelor use greater in the LOF carriers

	Genotyped		Usual Care
	No-LOF N=174	LOF carriers n=68	N=255
Clopidogrel	136 (78%)	32 (47%)	201 (79%)
Prasugrel or Ticagrelor	38 (22%)	36 (53%)	54 (21%)

P<0.001 P<0.001

Assessment of prospective *CYP2C19* genotype guided Dosing of AntiPlatelet Therapy in Percutaneous Coronary Intervention (ADAPT)

Clinical outcomes

	Genotyped (n=249)	Usual Care (n=255)	P-value
Follow-up time (months)	17.2 (7.5)	16.1 (8.2)	0.14
MACE	34 (13.7)	26 (10.2)	0.27
BARC 3 or 5 bleed	6 (2.4)	8 (3.1)	1.0

MACE= myocardial infarction, stroke, death from cardiovascular cause, stent thrombosis, urgent revascularization
BARC= Bleeding Academic Research Consortium

CONCLUSIONS: Intérêt de l'utilisation routinière des tests de fonction plaquettaires et génétiques ?

1.Patients stables : aucun car faible taux d'évènements

2.SCA : aucun si utilisation large des nouveaux P2Y12

3.Tests génétiques :aucune preuve clinique

(la fonction CYP2C19 contribuant seulement dans 5 à 10 % à la réponse du clopidogrel)

4.Utiles: si une « désescalade » est envisagée

30 000 tests fonctionnels/an seraient réalisés en France

CoSAC
Le congrès des Sociétés Africaines de Cardiologie

STCCCV
Société Tunisienne de Cardiologie & de Chirurgie Cardio-Vasculaire

Merci pour votre attention

CoSAC
Le congrès des Sociétés Africaines de Cardiologie

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Current Status of RCTs of Platelet Function Testing in PCI

Trial	Primary Endpoint	% biomarker positive	Intervention	Outcome
GRAVITAS	D/MI/ST (after procedure)	**10%**	Clopidogrel 150mg	No benefit
TRIGGER PCI	D/MI (after procedure)	**0%**	Prasugrel 10mg	No benefit
ARCTIC	D/MI/CVA/uTVR/ ST (including periproceudral MI)	**27% "stabilized" NSTEACS** ***(% biomarker positive not reported)***	*Recommended, but not required, personalized Rx* Actual: • mostly GPI during procedure • mostly Clop 150mg post	No Benefit – Endpoint driven by elevation in TnI 6hrs post-PCI (approx 32% of patients)

- Role of PFT in ACS not addressed

Why Not Prasugrel or Ticagrelor for All ACS Patients?

- Expensive
- Increased risk of bleeding
- Patients with low on-treatment reactivity (e.g., PRU<208), are at substantially lower risk of ischemic events compared with patients with higher reactivity
  - Absolute risk reduction will be lower (NNT higher) for patients with good response to clopidogrel
- Can PFT help us *select the most appropriate patient for clopidogrel or a newer oral P2Y12 inhibitor?*

Summary

- On-treatment reactivity (OTR) is a strong risk factor for post-PCI events
- Elective PCI patients in general have low event rates irrespective of OTR
  - More intensive inhibition with prasugrel or ticagrelor may increase bleeding more than reduce thrombotic events
- RCTs have not addressed "tailored" therapy in ACS
  - Can PFT identify patients who would benefit the least (or most) from ticagrelor or prasugrel – ie, help select the most appropriate oral $P2Y_{12}$ antagonist?
  - Guidelines recommend against "routine" PFT

Impact of High On-Aspirin Platelet Reactivity on Outcomes Following Successful DES Implant

ADAPT-DES: 8,526 all-comers patients who received dual antiplatelet therapy with aspirin and clopidogrel.

- Based on VerifyNow assay, high on-aspirin platelet reactivity (HAPR) found in 5.6% of patients
- HAPR was not associated with 2-year risks of MACE, stent thrombosis, MI, all-cause death, or bleeding
- Even in patients with clopidogrel resistance, which was itself tied to worse outcomes, HAPR was not related to adverse outcomes

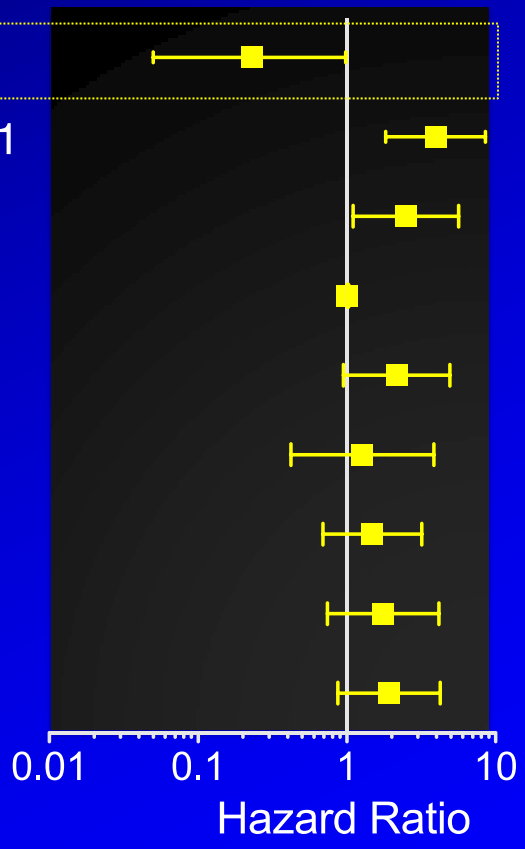
Conclusion: HAPR is not commonly seen in patients who undergo successful PCI with a drug-eluting stent, and when it is found it does not seem to have a big impact on clinical outcomes.

Chung CJ, et al. *Am Heart J.* 2018;Epub ahead of print.

GRAVITAS: Lower Reactivity Over Course of Trial Associated with Reduced With CV Death, MI, ST at 60 days

N=2796

	HR [95% CI]	P
PRU <208	0.23 [0.05, 0.98]	0.047
ACS	3.95 [1.83, 8.53]	<0.001
Diabetes	2.49 [1.10, 5.64]	0.028
Stent Length (per mm)	1.01 [1.01, 1.02]	0.003
Prior MI	2.16 [0.94, 4.93]	0.068
Beta Blocker	1.27 [0.42, 3.85]	0.668
CrCl <60	1.48 [0.69, 3.18]	0.668
Prior PCI	1.76 [0.74, 4.16]	0.201
Prior CABG	1.92 [0.87, 4.23]	0.108



*On-treatment reactivity treated as a time-varying covariate

CrCl = creatinine clearance, ACS = acute coronary syndrome, MI = myocardial infarction

GRAVITAS

Price MJ et al, *Circulation* 2011;124:1132-1137

Genotyping in daily practice?

Occurrence of CYP 2C19*2

Whites : 30 %

Blacks : 40 %

East Asians : 55 %

Patients at risk:

700 000 pts on 2 000 000 PCI/years