Conoscere e Curare il Cuore 2019

DOMENICA 3 MARZO

LA DE-ESCALATION THERAPY DOPO SCA. E' RAGIONEVOLE PASSARE PRECOCEMENTE DAL PRASUGREL (O TICAGRELOR) AL CLOPIDOGREL?

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Conflicts of interest

Payment as an individual for consulting fee or honorarium from:

- Astra Zeneca
- Bayer
- Boehringer-Ingelheim
- Chiesi
- Daiichi Sankyo
- Novartis
- Pfizer

La de-esclation therapy dopo SCA. Potrebbe essere ragionevole passare precocemente dal prasugrel (o ticagrelor) al clopidogrel

De-escalation (switching from prasugrel or ticagrelor to clopidogrel) as a strategy to reduce long-term bleeding events without a trade-off in ischemic protection

Angiolillo DJ, Rollini F, et al. Circulation. 2017

What is new in the 2018 Guidelines?

New recommendations

Double-kissing crush technique preferred over provisional T-stenting in true left main bifurcations

Cangrelor in PY_{12}-inhibitor naïve patients undergoing PCI

GP IIb/II Ia inhibitors for PCI in $P2Y_{12}$-inhibitor naïve patients with ACS undergoing PCI

Dabigatran 150-mg dose preferred over 110-mg dose when combined with single antiplatelet therapy after PCI

De-escalation of $P2Y_{12}$-inhibitor guided by platelet functon testing in ACS patients

Routine non-invasive imaging surveillance in high-risk patients 6 months after revascularization

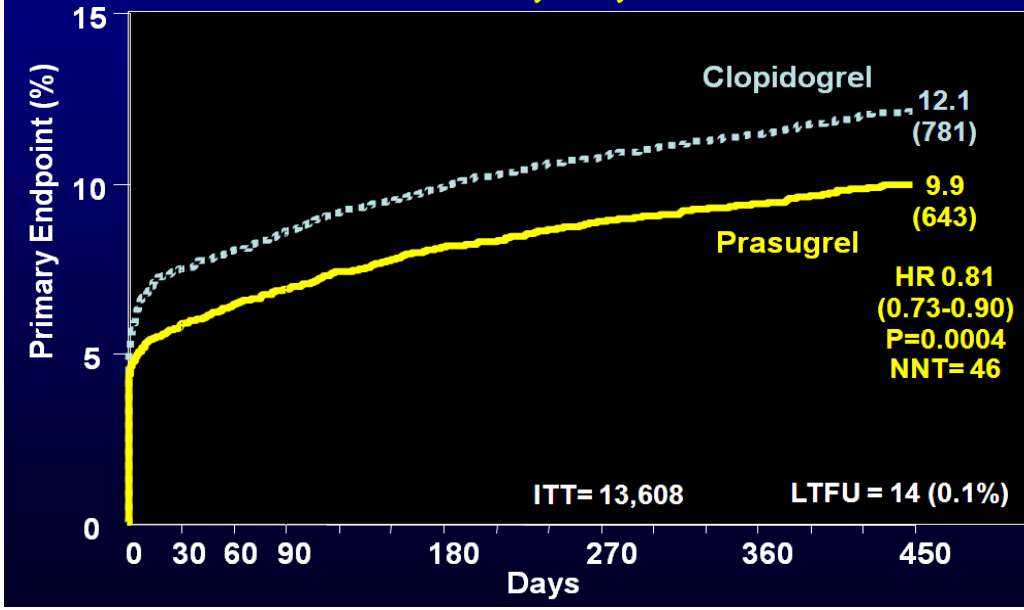
Routine revascularization of non-IRA lesions in myocardial infarction with cardiogenic shock

Current generation BRS for clinical use outside clinical studies

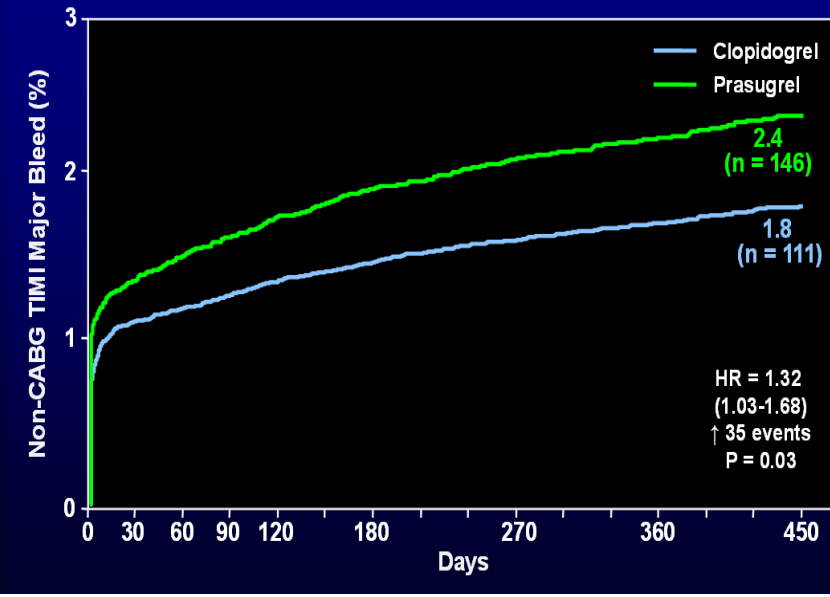
	Class IIb		Class III

Changes compared with the 2014 version of the Myocardial Revascularization Guidelines that were due to updates for consistency with other ESC Guidelines published since 2014 are not shown.

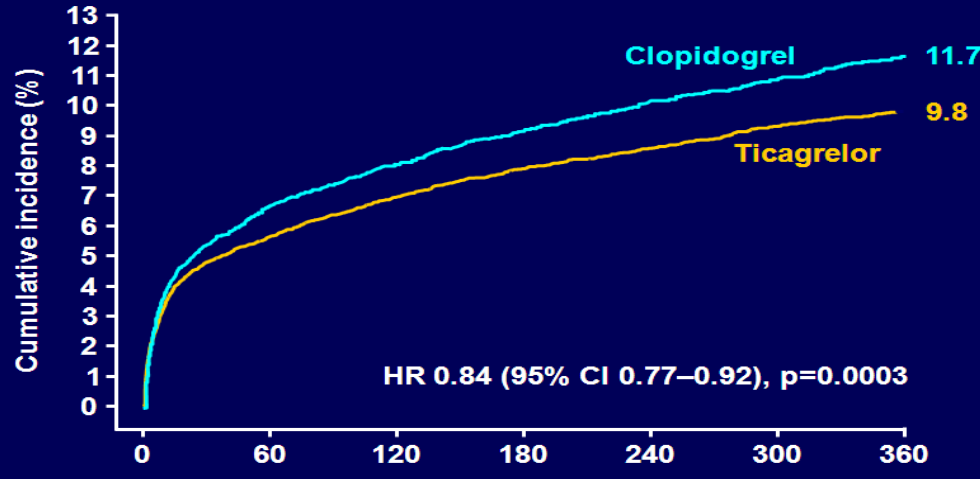
Primary Endpoint CV Death, MI, Stroke



Non-CABG TIMI Major Bleed
All ACS Population

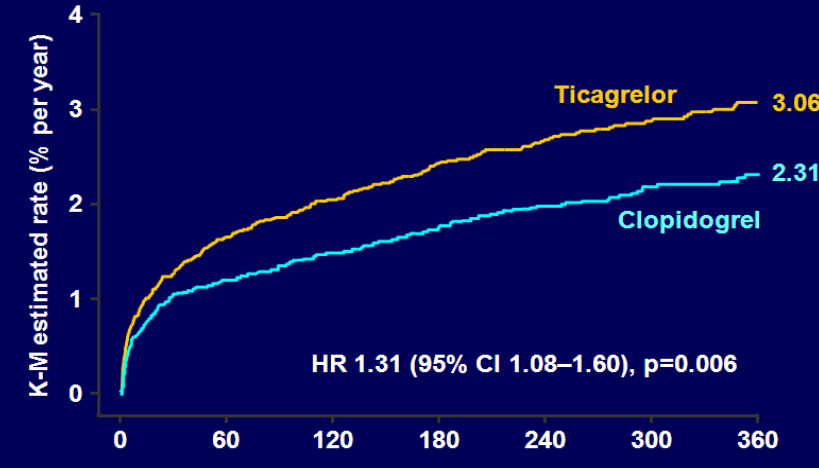


K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

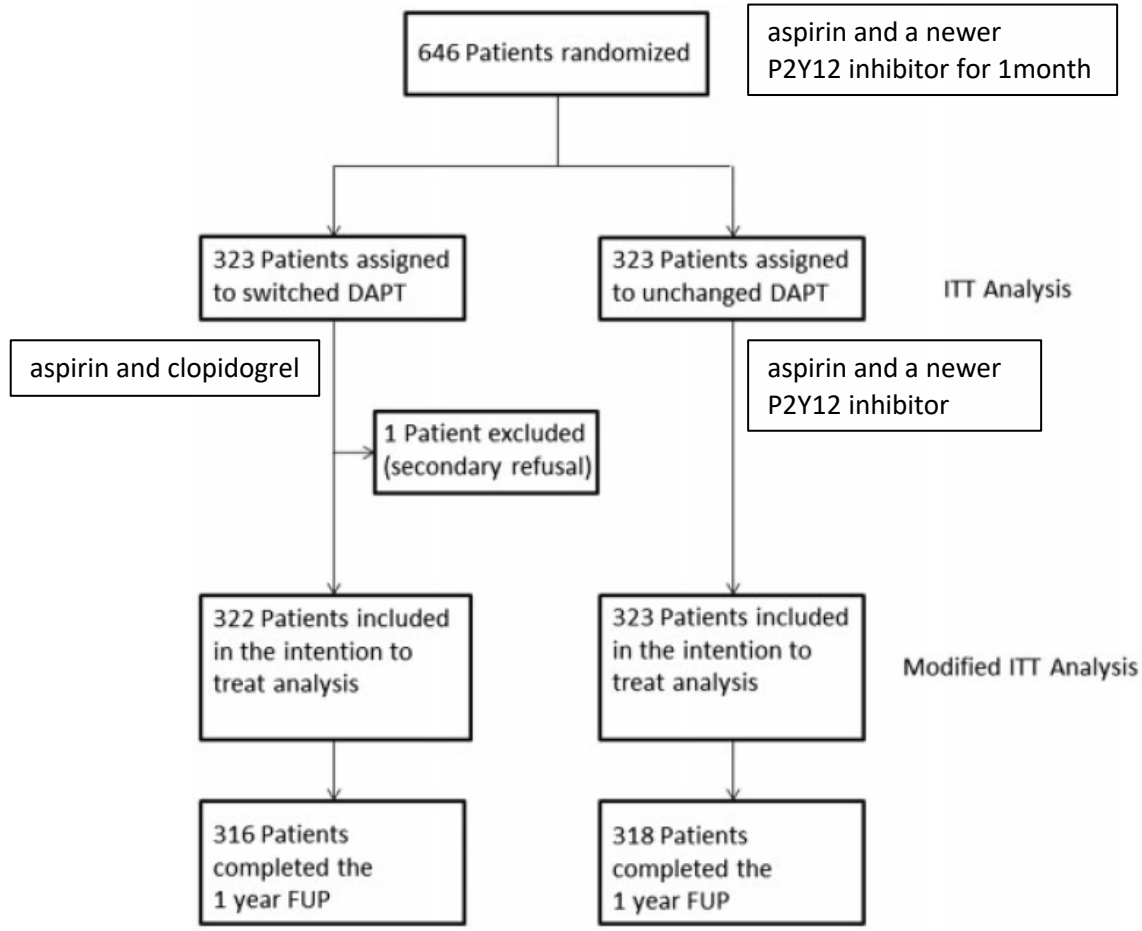


Time to non-procedure-related PLATO major bleeding

Completeness of follow-up 99.97% = five patients lost to follow-up



TOPIC Study

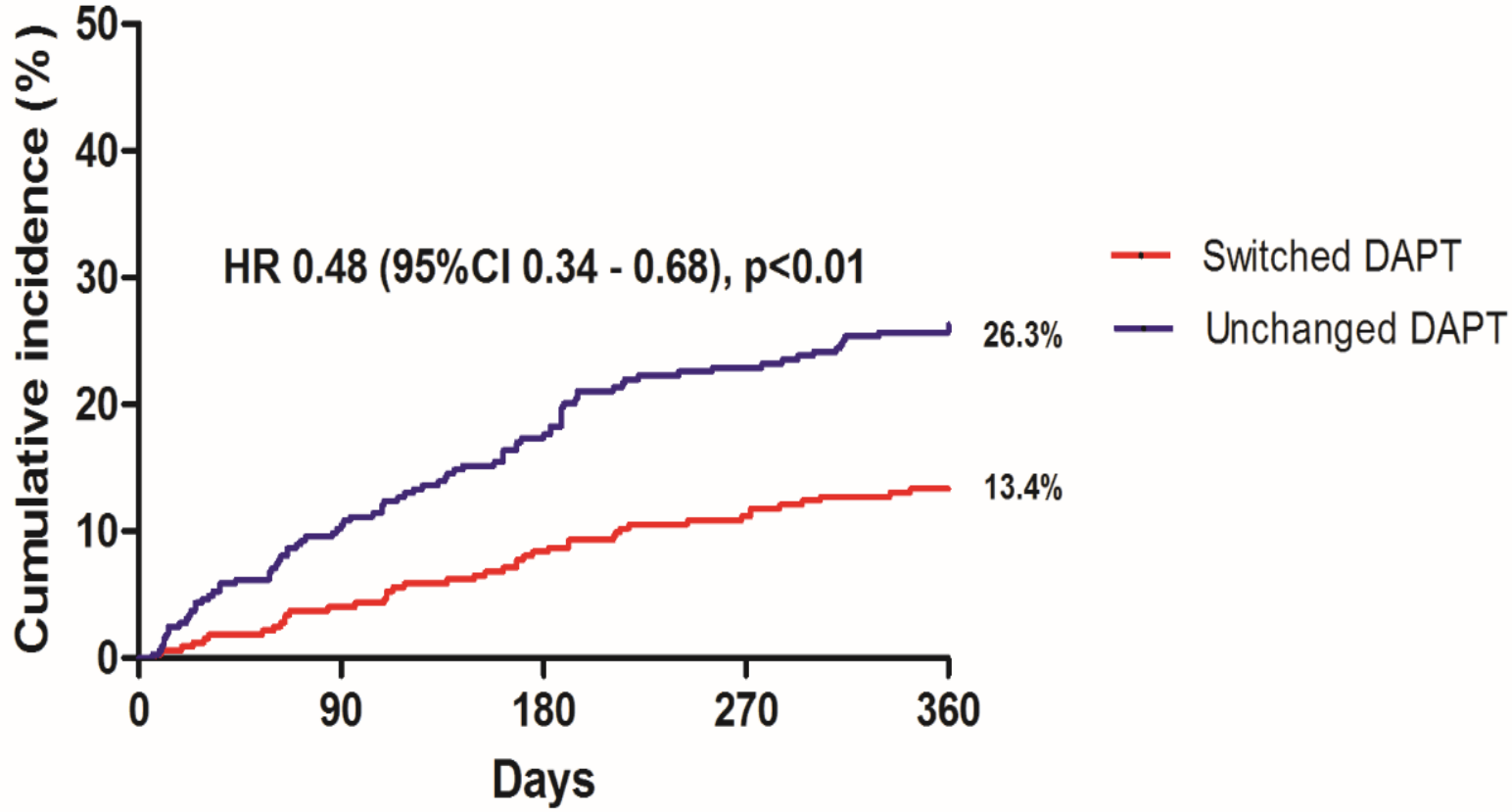


Cuisset T et al. Eur Heart J. 2017

TOPIC Study

Primary Endpoint

Death, Urgent revasc., Stroke, BARC ≥ 2

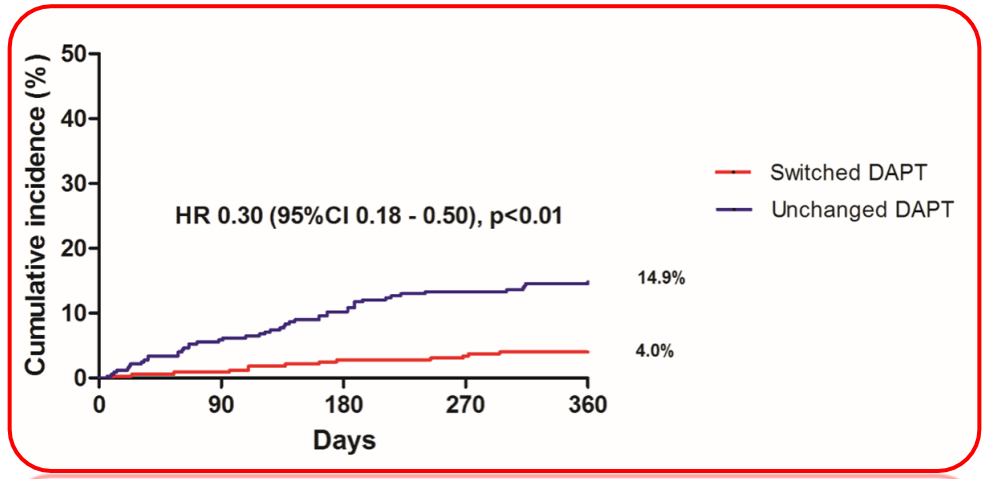


Better Prognosis with switched DAPT

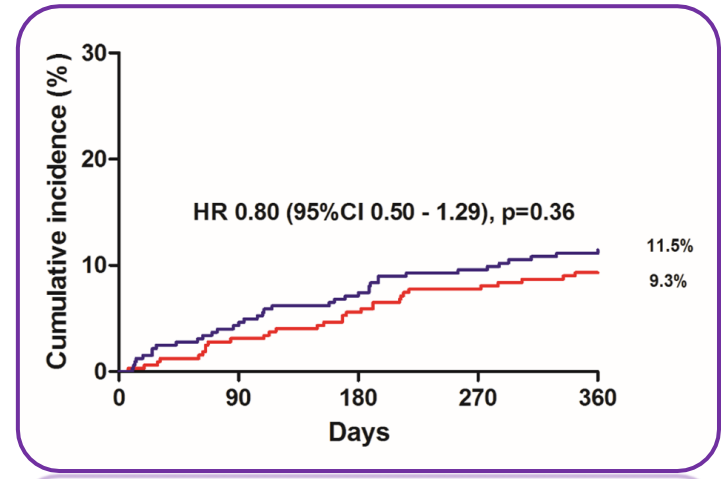
Cuisset T et al. Eur Heart J. 2017

TOPIC Study

BARC bleeding ≥ 2

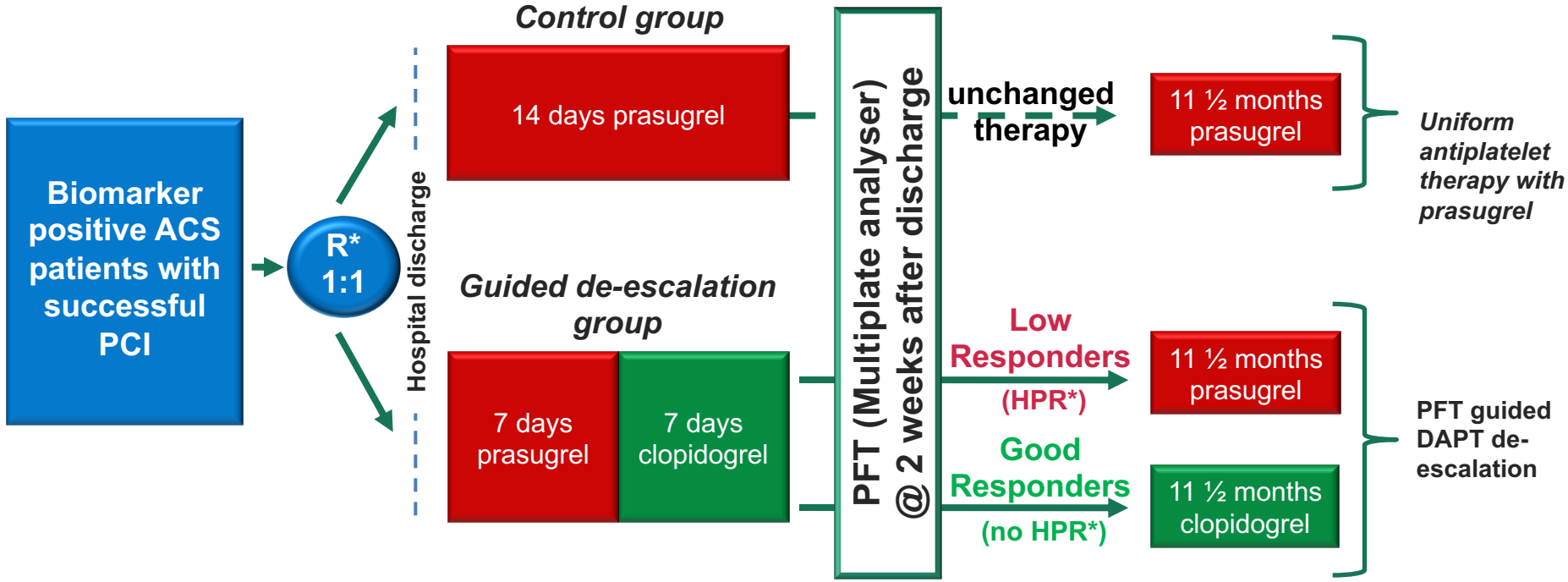


Any ischemic endpoint



Cuisset T et al. Eur Heart J. 2017

Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS)



Sibbing D, et al. Lancet. 2017

TROPICAL ACS

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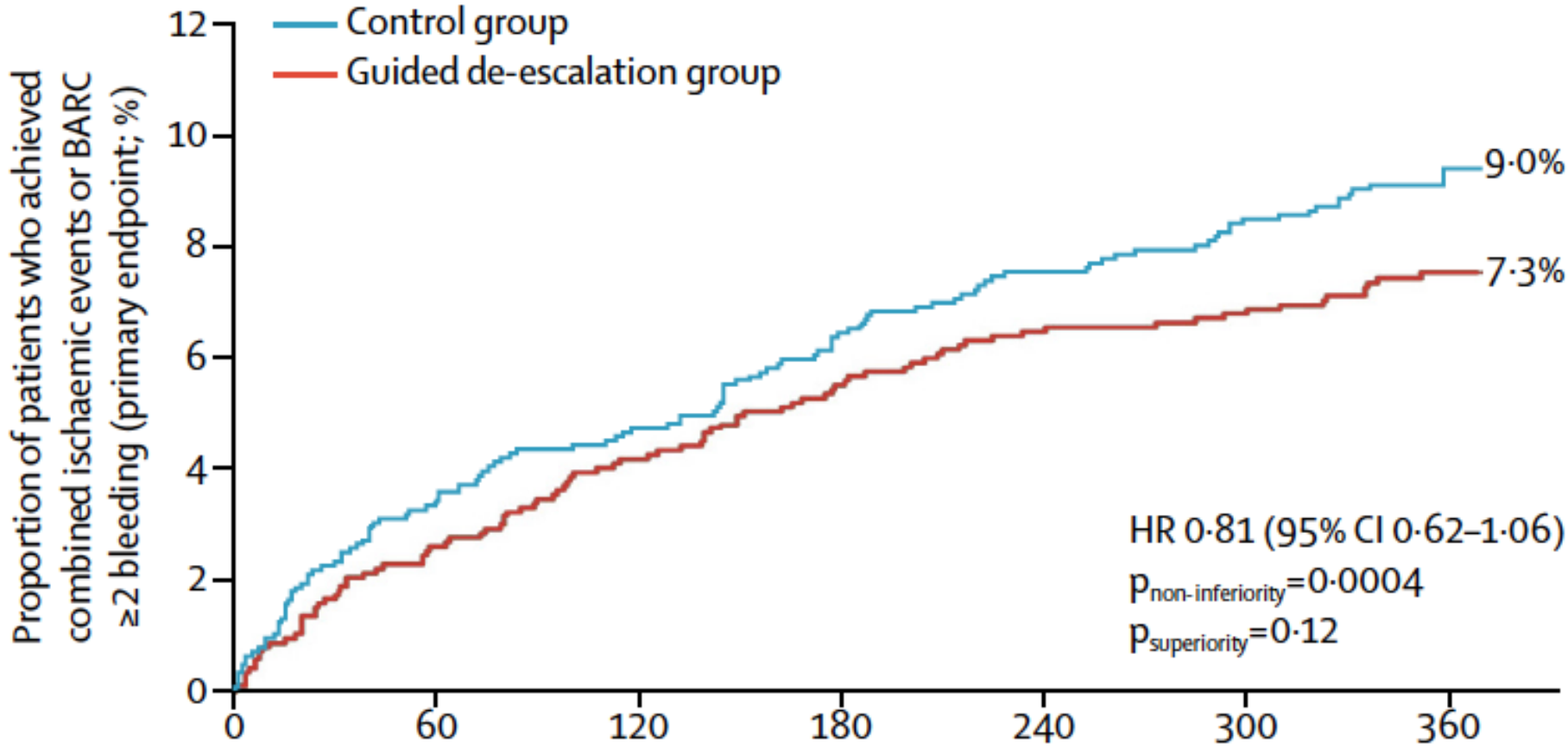

Sibbing D, et al. Lancet. 2017

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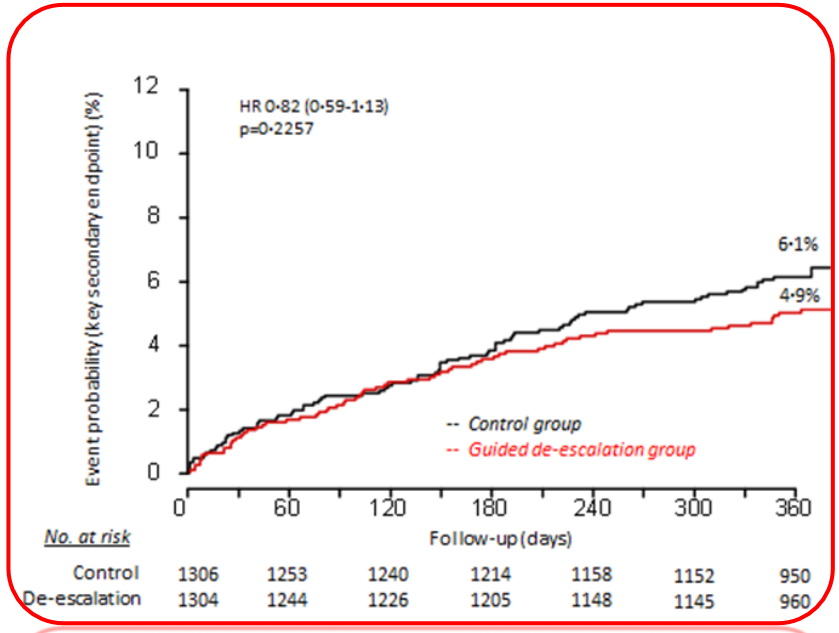
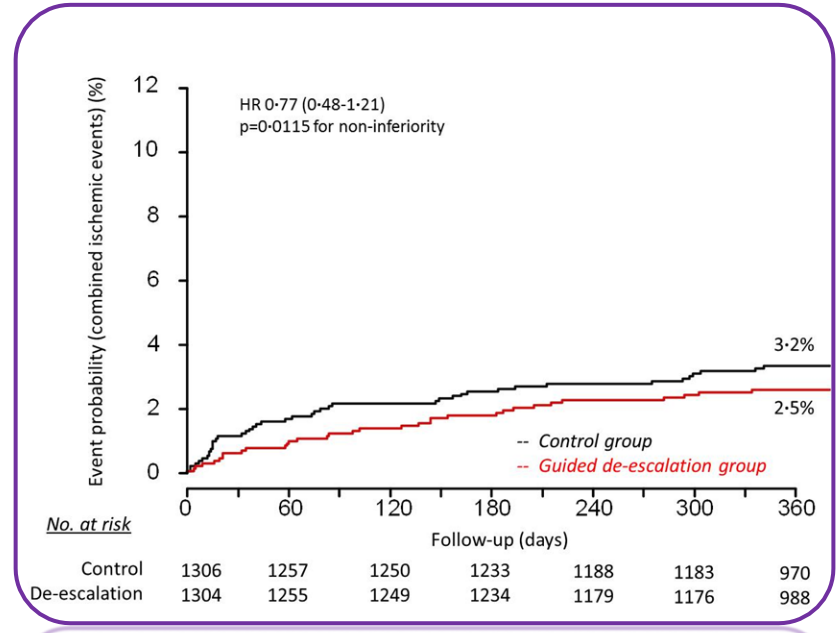
BARC bleeding ≥ 2



Any ischemic endpoint



Sibbing D, et al. Lancet. 2017

La de-esclation therapy dopo SCA. Non è ragionevole passare precocemente dal prasugrel (o ticagrelor) al clopidogrel

- Non abbiamo sufficiente evidenza
- HPR è un marker e non un target
- HPR è un maker “mobile”
- Disponibilità di cangrelor durante la PCI
- E’ una strategia futile

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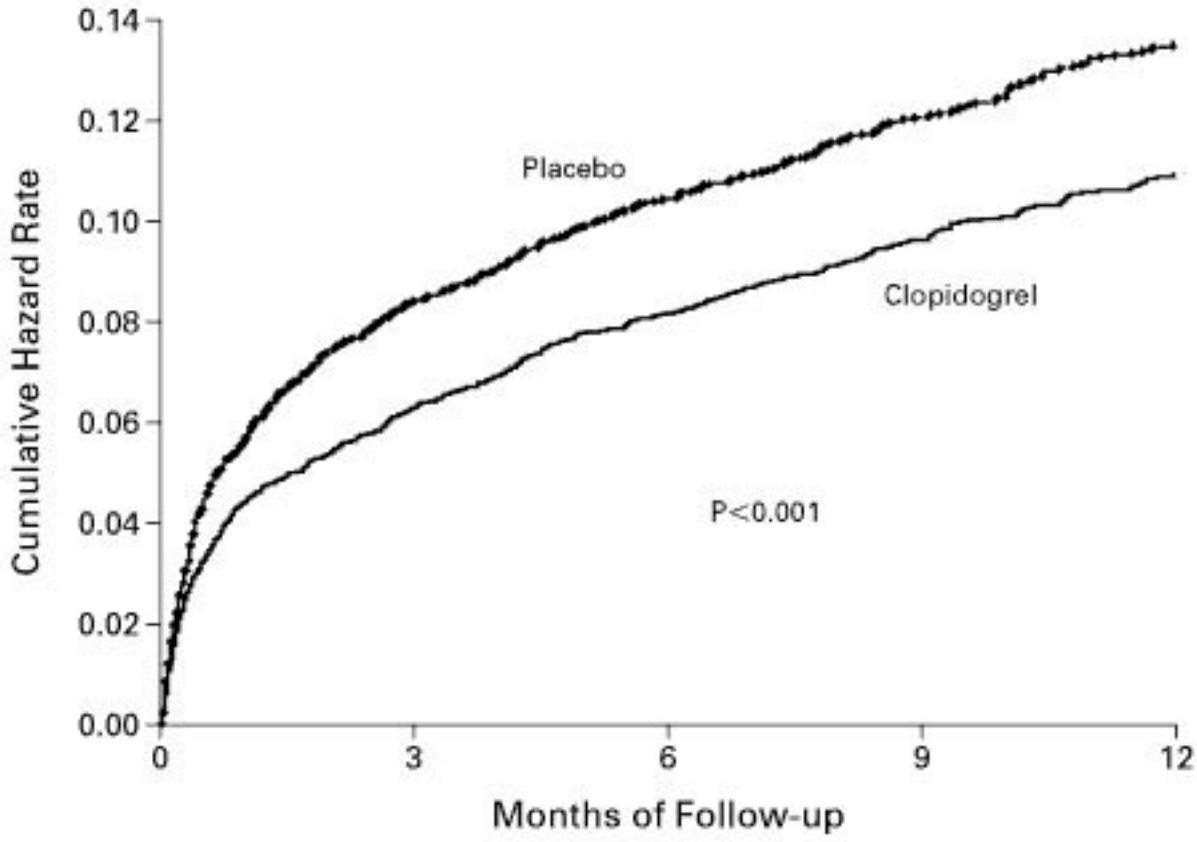
The CURE trial

The New England Journal of Medicine

EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*



No. at Risk					
Placebo	6303	5780	4664	3600	2388
Clopidogrel	6259	5866	4779	3644	2418

CURE N= 12,562 pts
DOUBLE BLIND

TOPIC N = 646 pts
OPEN-LABEL

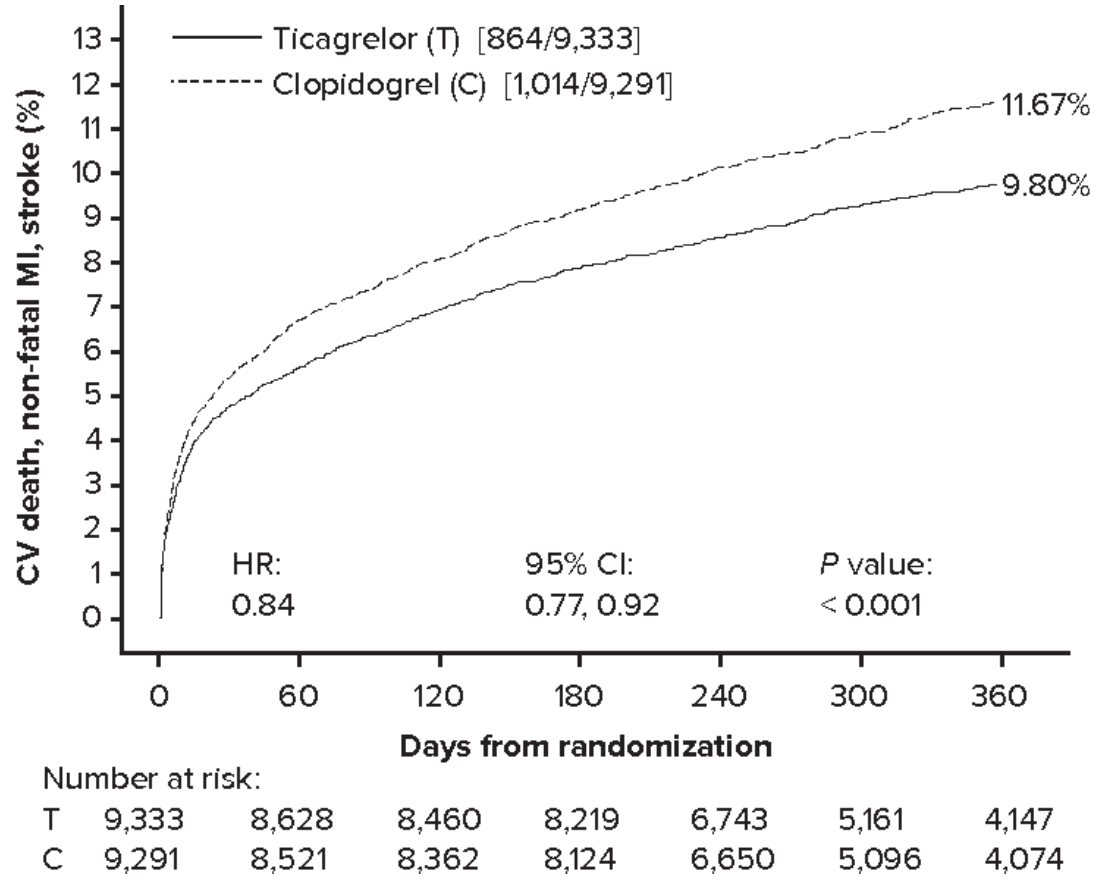
TROPICAL N = 2,610 pts
OPEN-LABEL

N Engl J Med 2001; 345:494-502

The PLATO trial

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Cumulative Kaplan–Meier estimates of the time to the first adjudicated occurrence of the primary efficacy end point



N Engl J Med 2009;361:1045-57

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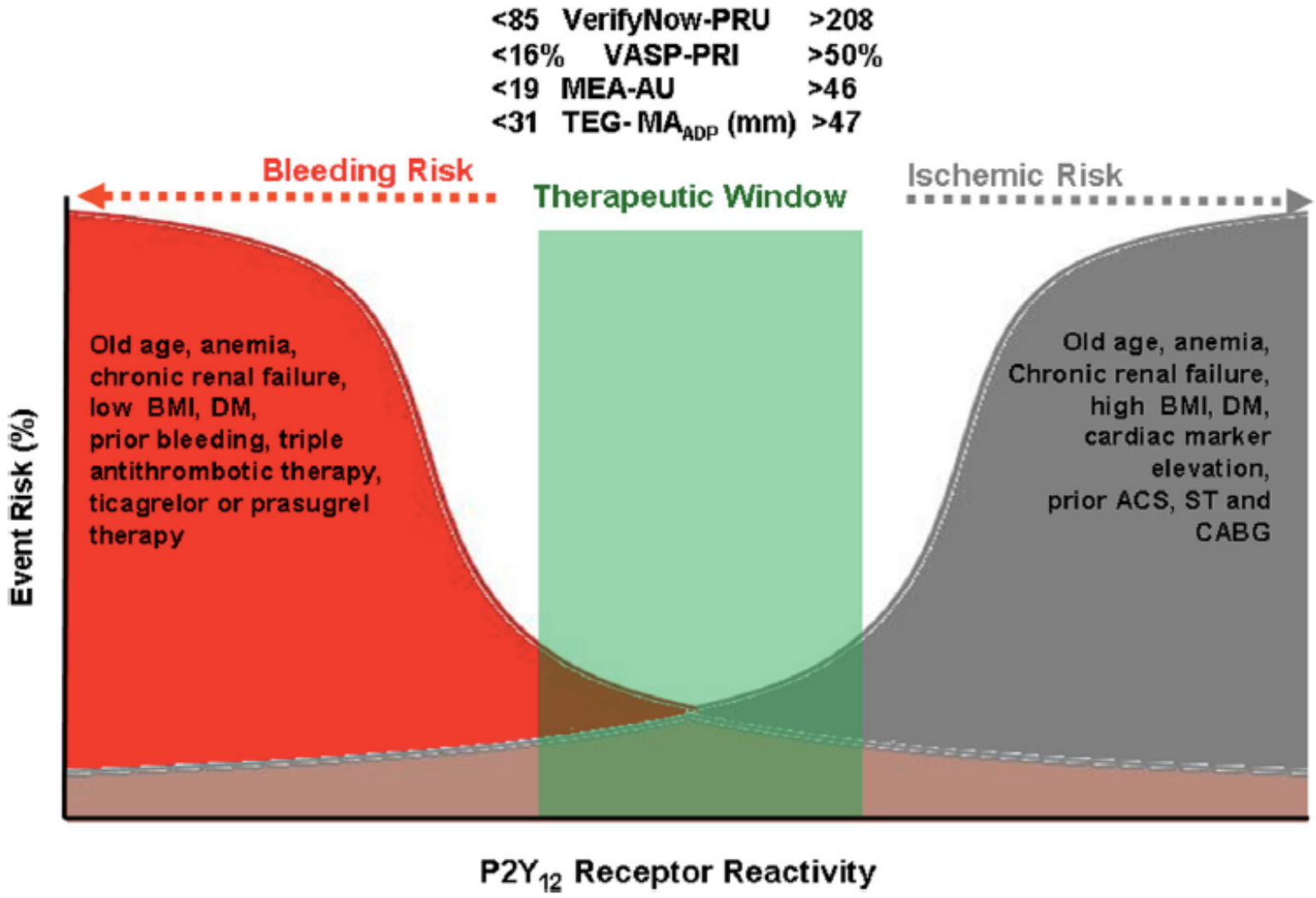
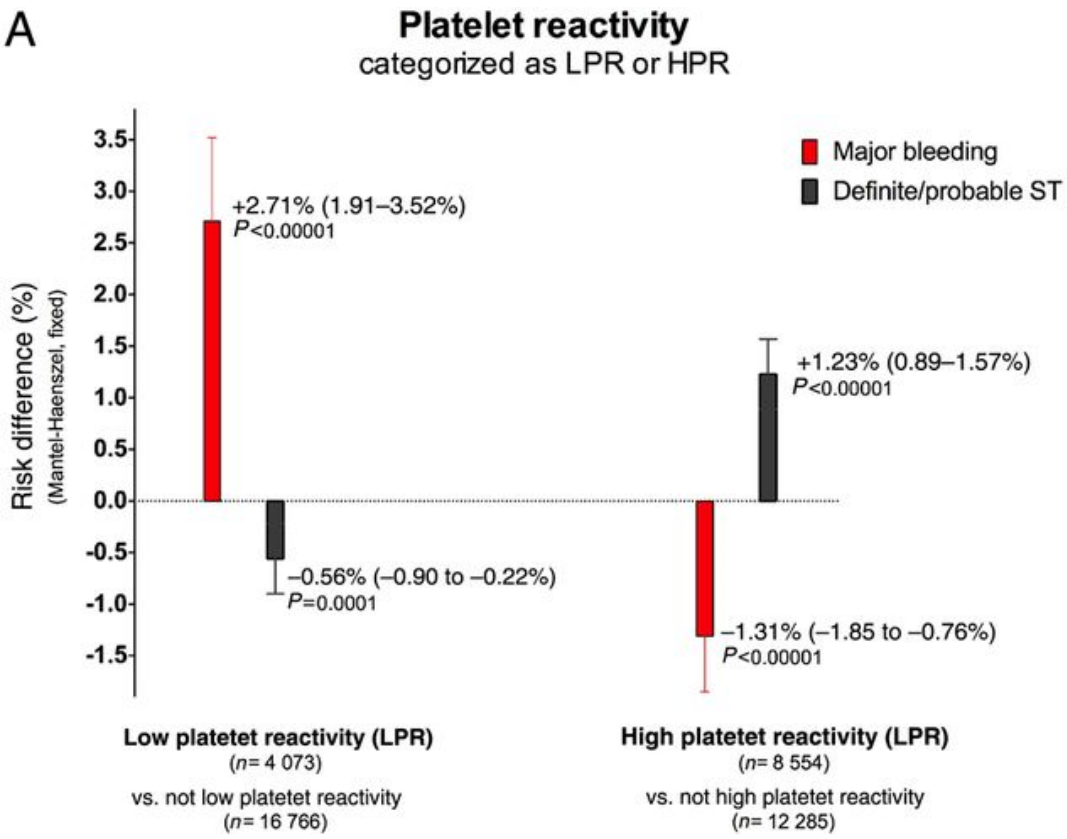
Evidence for $P2Y_{12}$ receptor reactivity associated with post-PCI ischemic and bleeding events

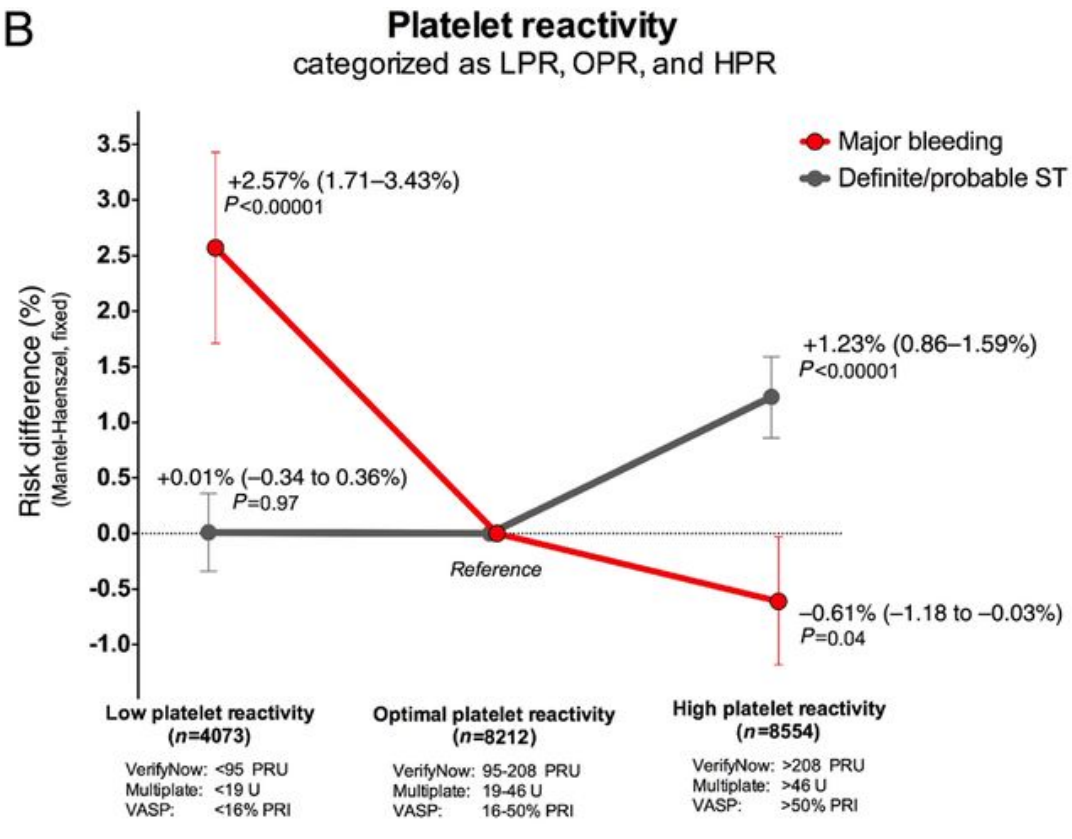


Tantry U et al, J Am Coll Cardiol 2013;62:2261–73

Absolute risk of stent thrombosis and bleeding according to platelet reactivity levels



Risk estimates when platelet reactivity is categorized into groups of low platelet reactivity or high platelet reactivity.

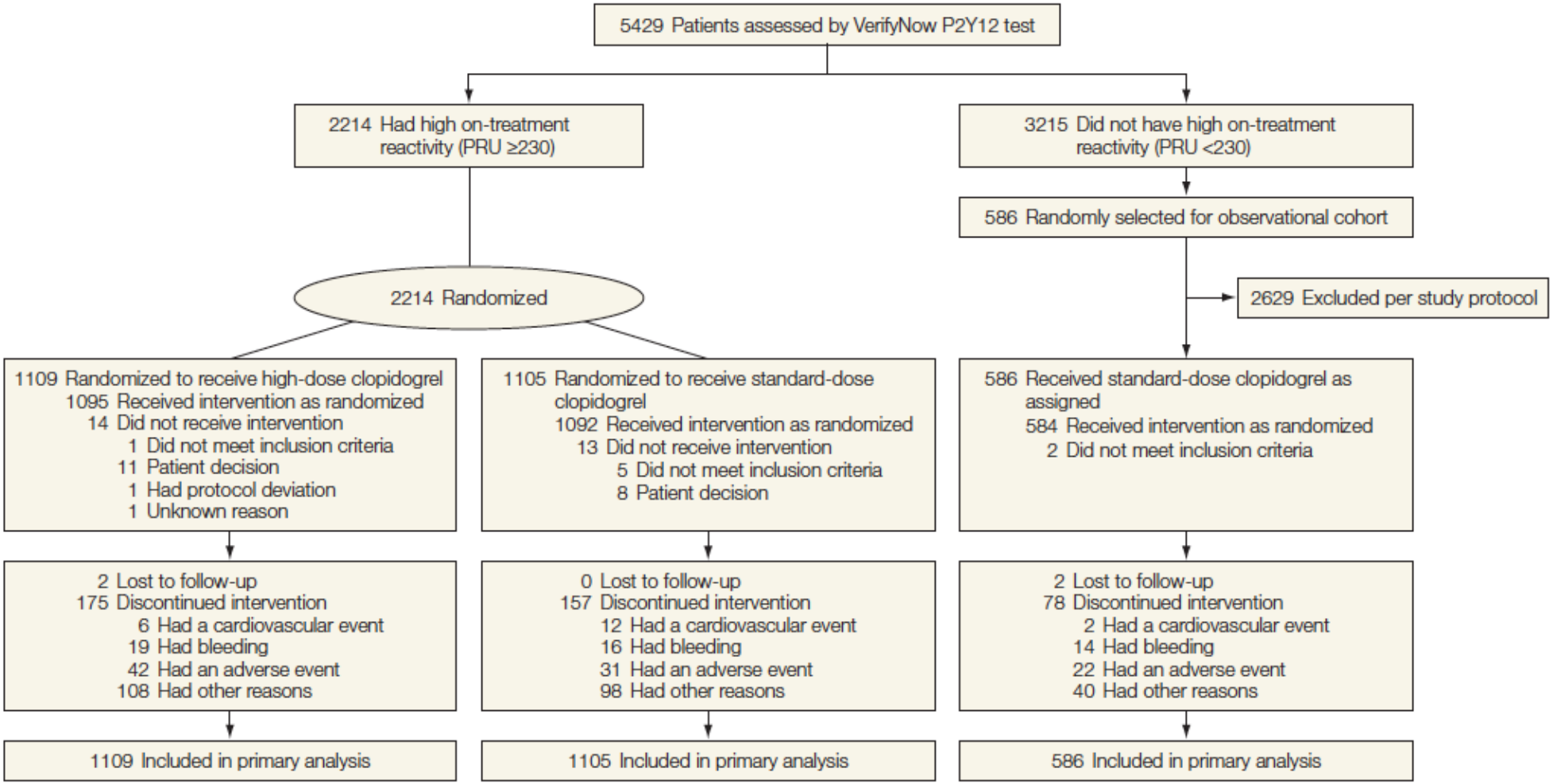


A comparison of platelet reactivity categorized as low, optimal, or high. ST, stent thrombosis.

Aradi D et al. Eur Heart J. 2015 Jul 14;36(27):1762-71.

The GRAVITAS Randomized Trial

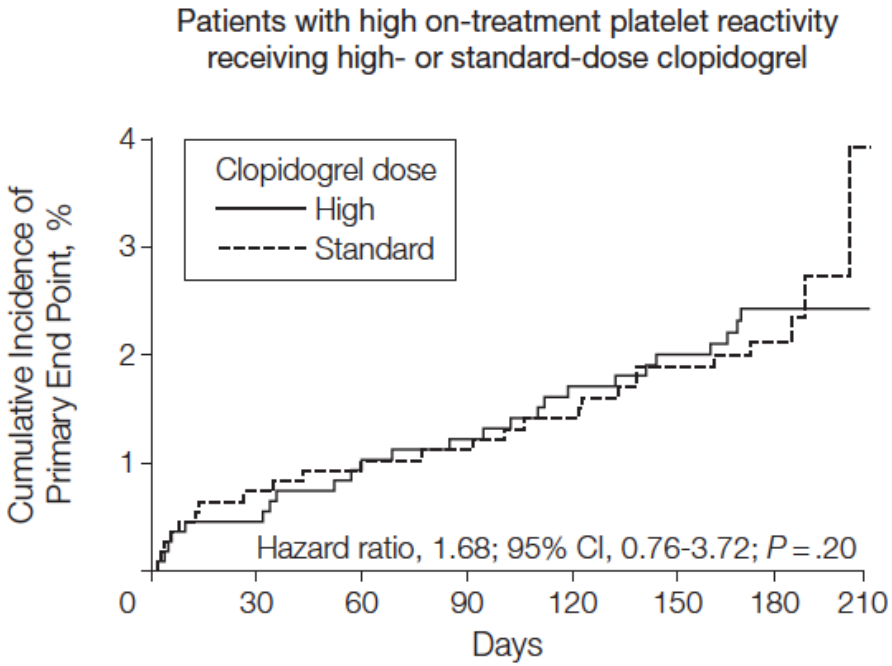
Trial design

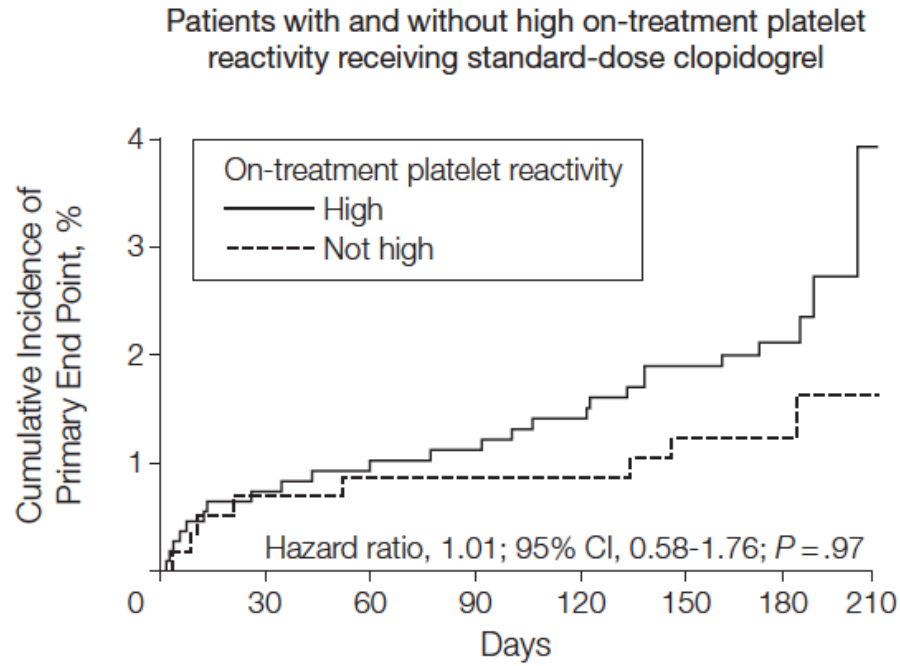


JAMA. 2011 Mar 16;305(11):1097-105.

The GRAVITAS Randomized Trial

Cumulative Kaplan-Meier estimates of the time
to the first adjudicated occurrence of the primary efficacy end point

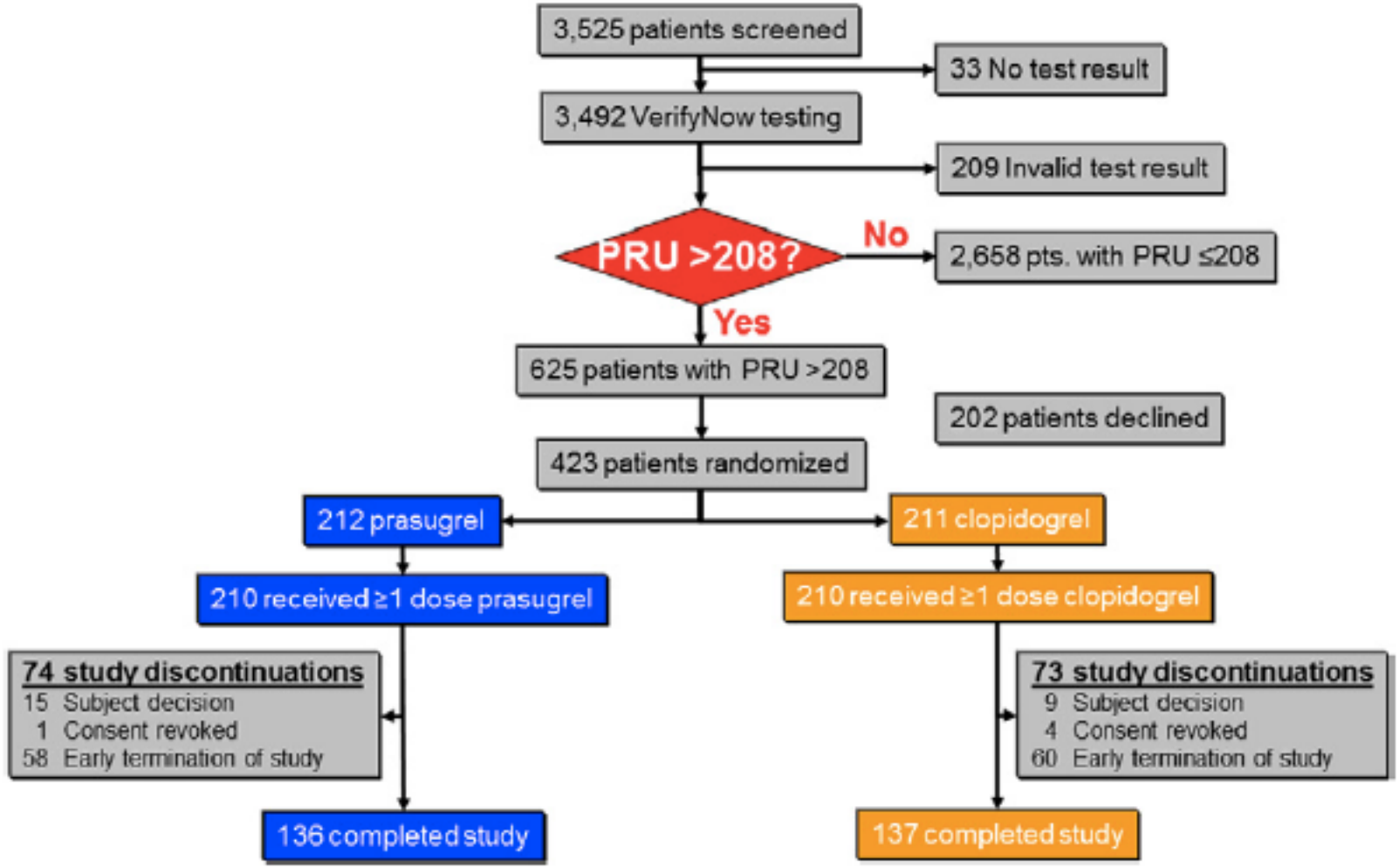




JAMA. 2011 Mar 16;305(11):1097-105.

The TRIGGER-PCI Study

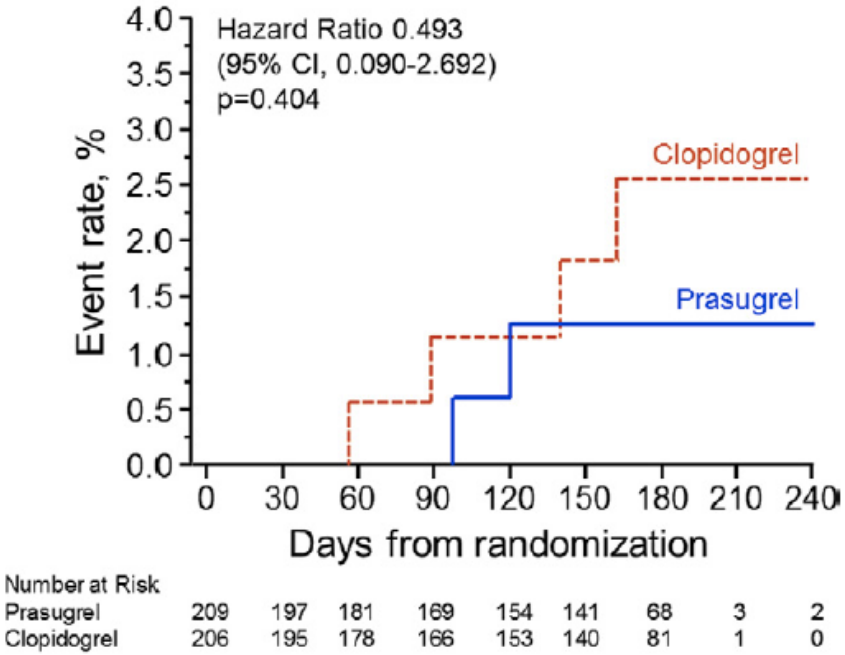
Trial design

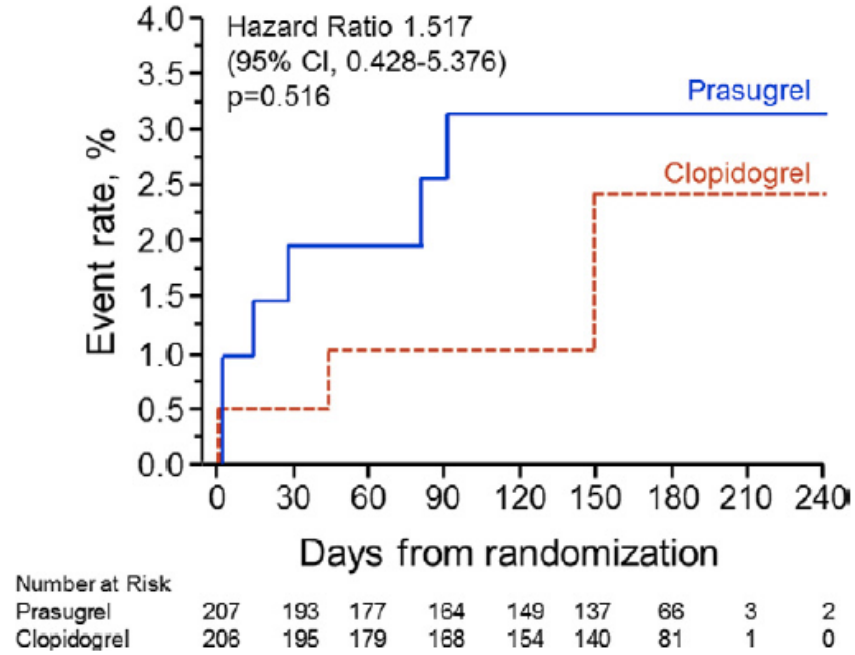


J Am Coll Cardiol 2012;59:2159–64

The TRIGGER-PCI Study

Cumulative Composite Incidence of Efficacy and Bleeding Events

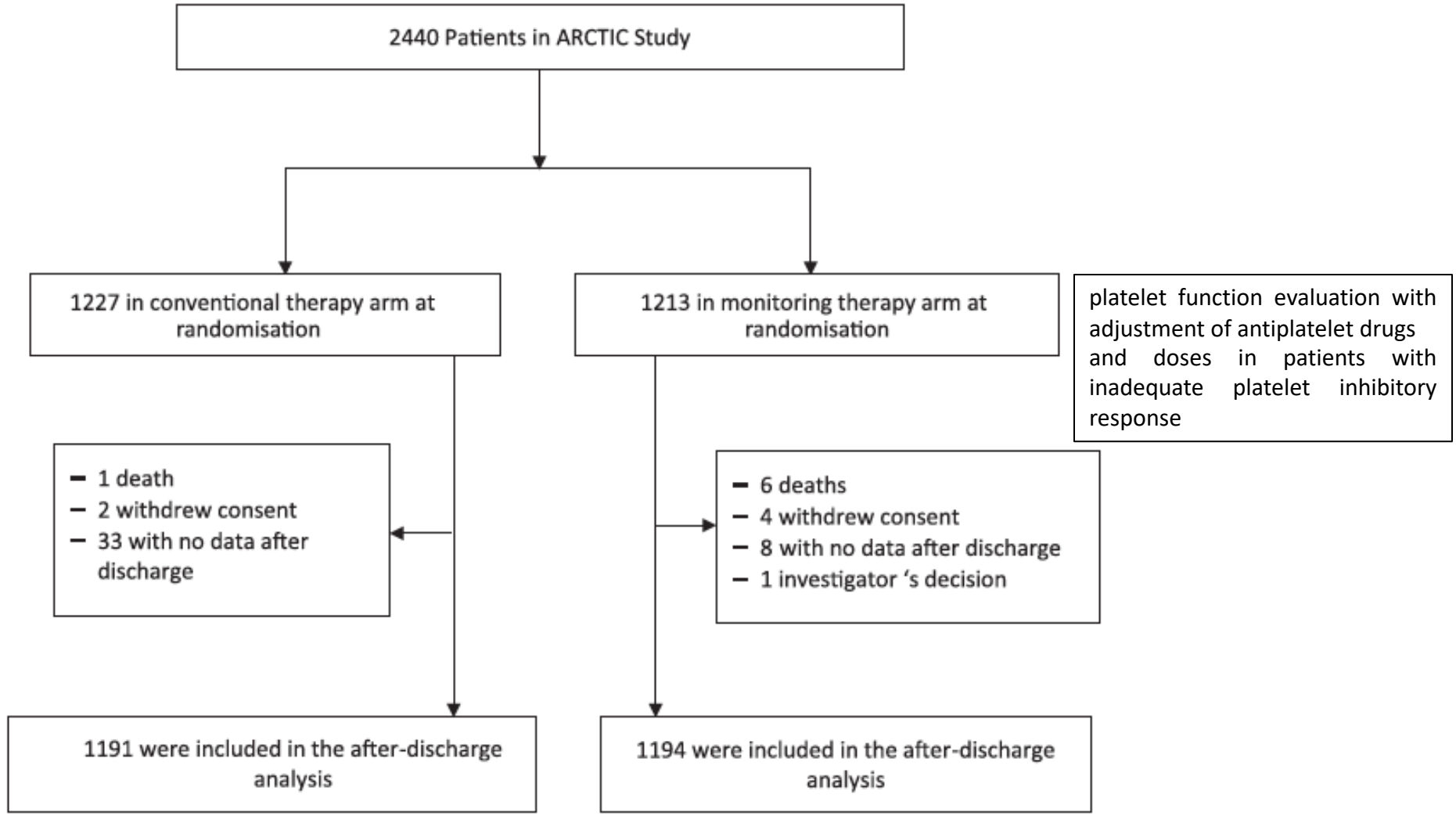




J Am Coll Cardiol 2012;59:2159–64

The ARCTIC Study

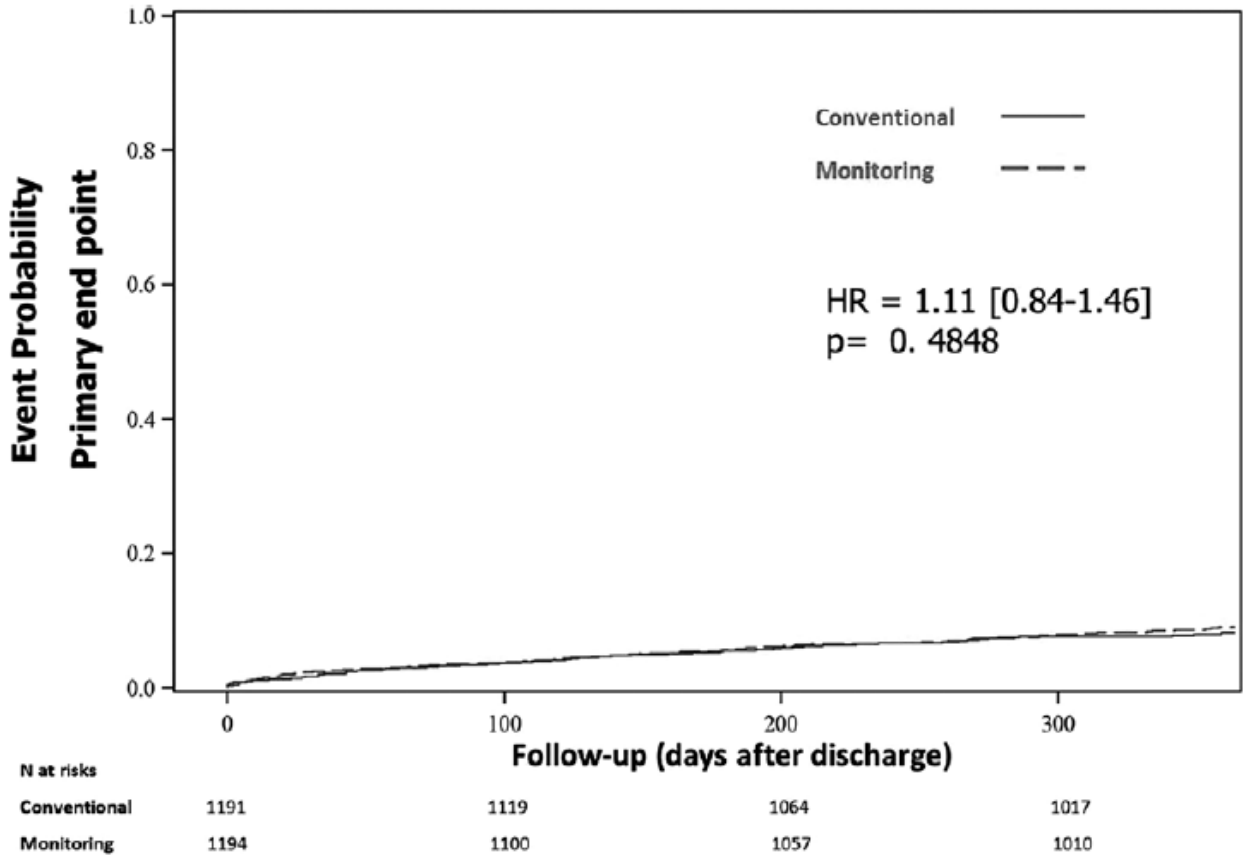
Trial design



Circulation. 2014;129:2136-2143

The ARCTIC Study

Primary outcome events (any death, myocardial infarction, stent thrombosis, stroke or transient ischemic attack, and urgent revascularization)



"On-treatment platelet hyperreactivity cannot be considered as a risk factor requiring intervention for secondary prevention after percutaneous coronary revascularization".

Circulation. 2014;129:2136-2143

La de-esclation therapy dopo SCA. Non è ragionevole passare precocemente dal prasugrel (o ticagrelor) al clopidogrel

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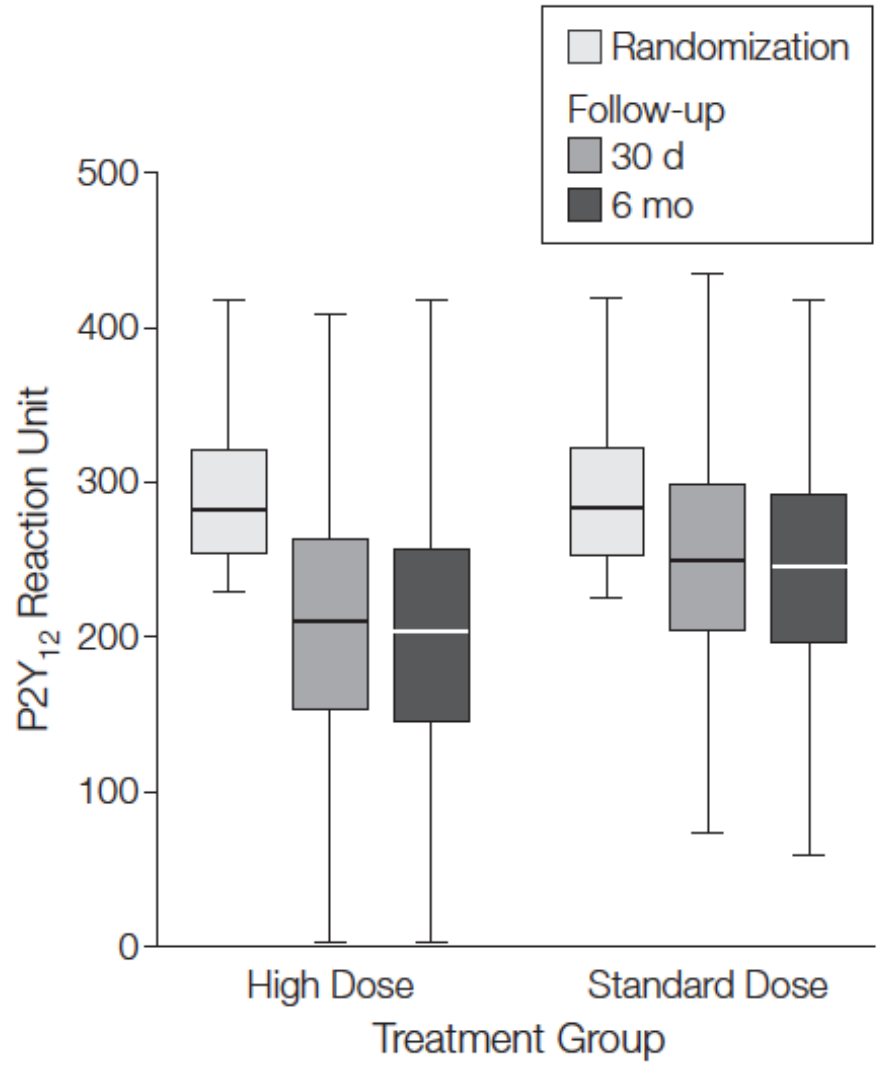
The GRAVITAS Randomized Trial

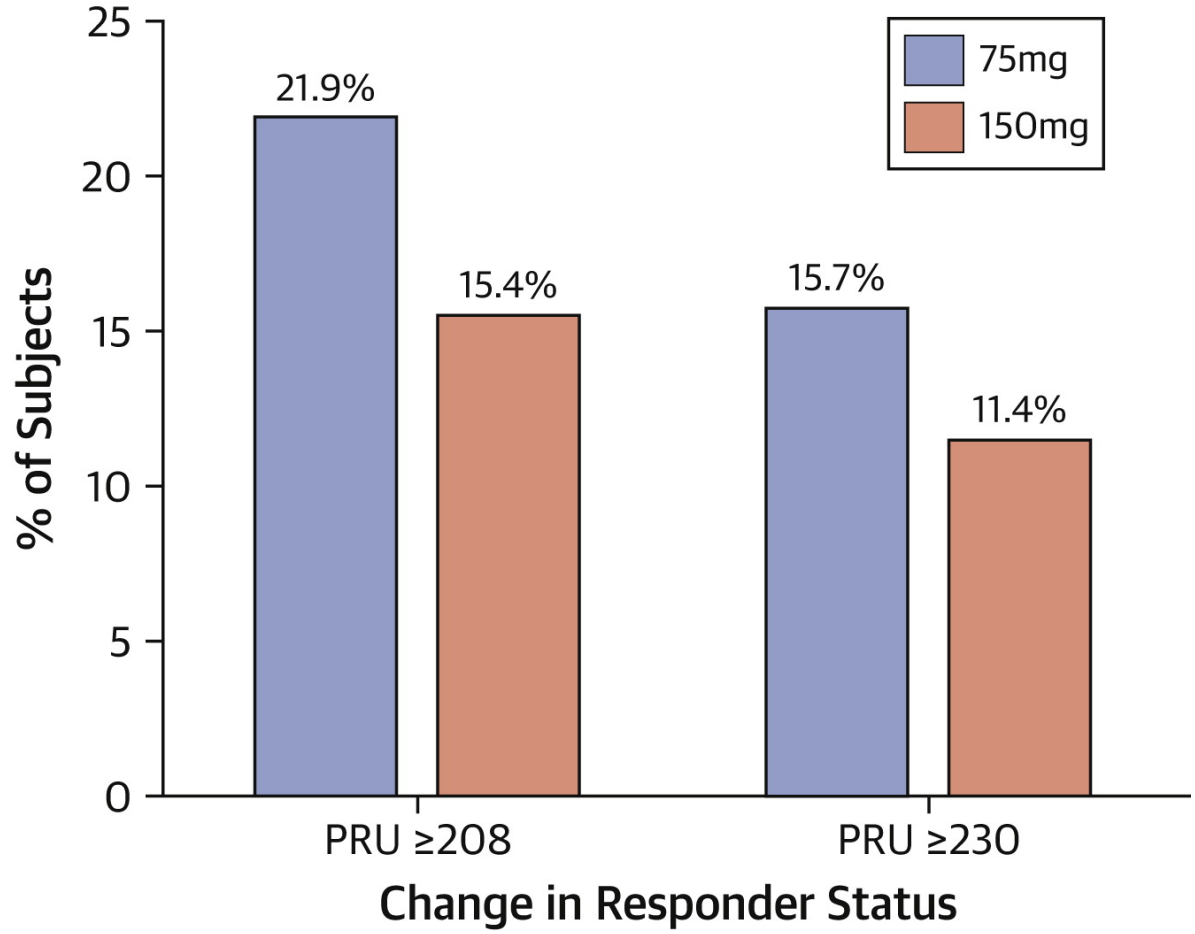
Pharmacodynamic effect of high and standard-dose clopidogrel in randomized patients with high on-treatment platelet reactivity



JAMA. 2011 Mar 16;305(11):1097-105.

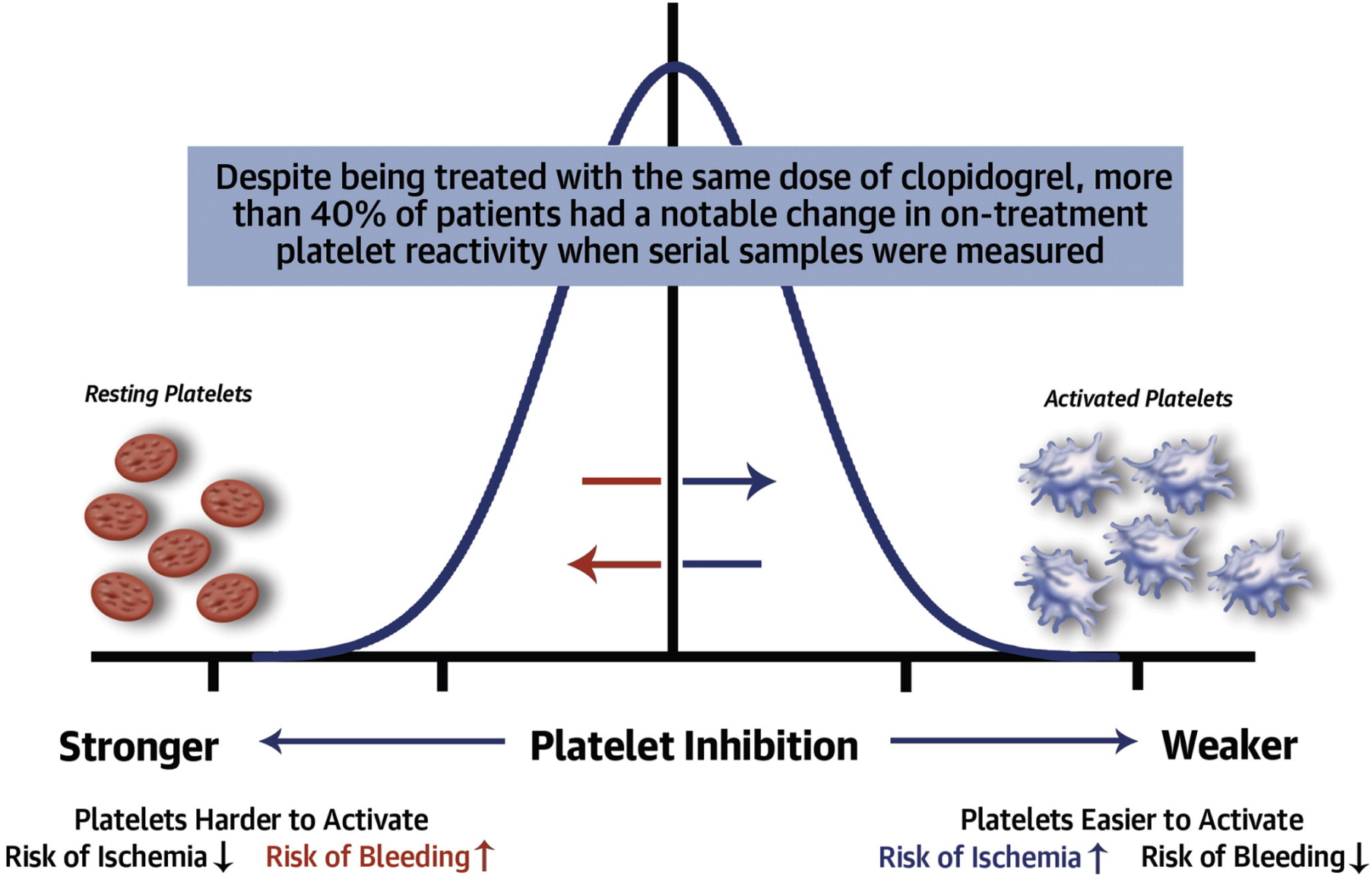
The ELEVATE-TIMI 56 Randomized Trial

Proportion of individuals with a change in responder status between periods



Hochholzer W et al, J Am Coll Cardiol. 2014 Jul 29;64(4):361-8

The ELEVATE-TIMI 56 Randomized Trial



Hochholzer W et al, J Am Coll Cardiol. 2014 Jul 29;64(4):361-8

EDITORIAL COMMENT

The Chronovariability of Platelet Reactivity

A Hurdle in the Road to Personalized Antiplatelet Therapy?*

Ori Ben-Yehuda, MD

"Residual platelet reactivity can be considered as a "holistic" test, which may reflect compliance, dose, drug absorption, genetics, and underlying inflammation".

"The findings … provide an important caution in categorizing individual patients in terms of their platelet reactivity".

J Am Coll Cardiol. 2014 Jul 29;64(4):361-8.

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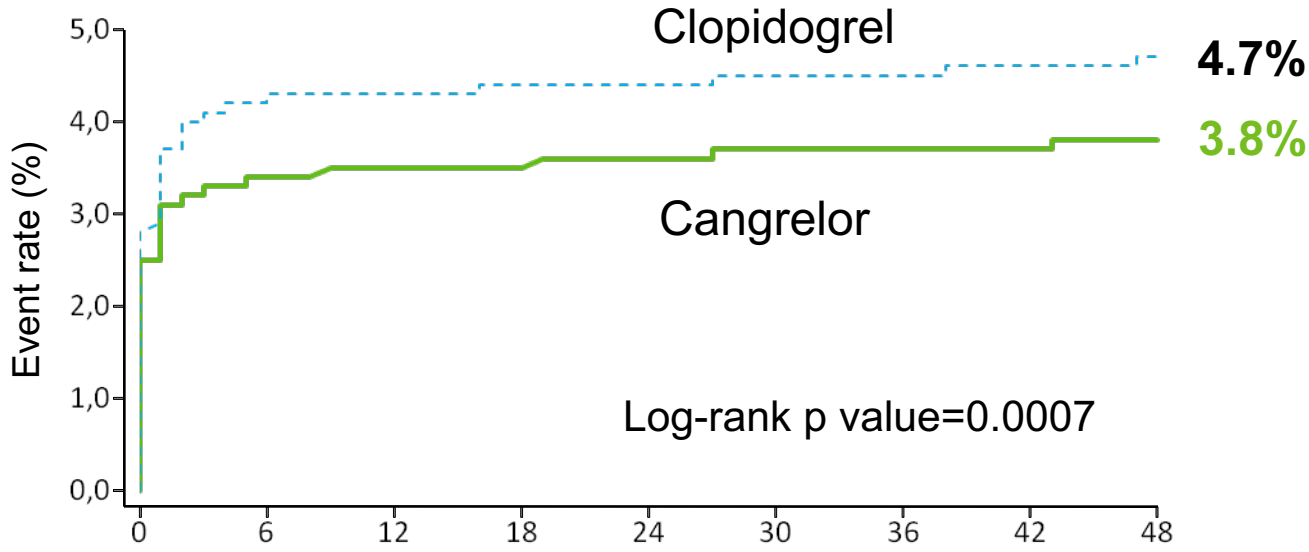
Champion trials pooled analysis

Death/ MI/ IDR/ Stent Thrombosis within 48 h



No. patients at risk									
Cangrelor:	12,475	12,053	12,040	12,033	12,021	12,006	12,002	11,994	11,985
Clopidogrel:	12,435	11,903	11,897	11,891	11,882	11,874	11,866	11,853	11,843

Steg PG, et al. Lancet 2013

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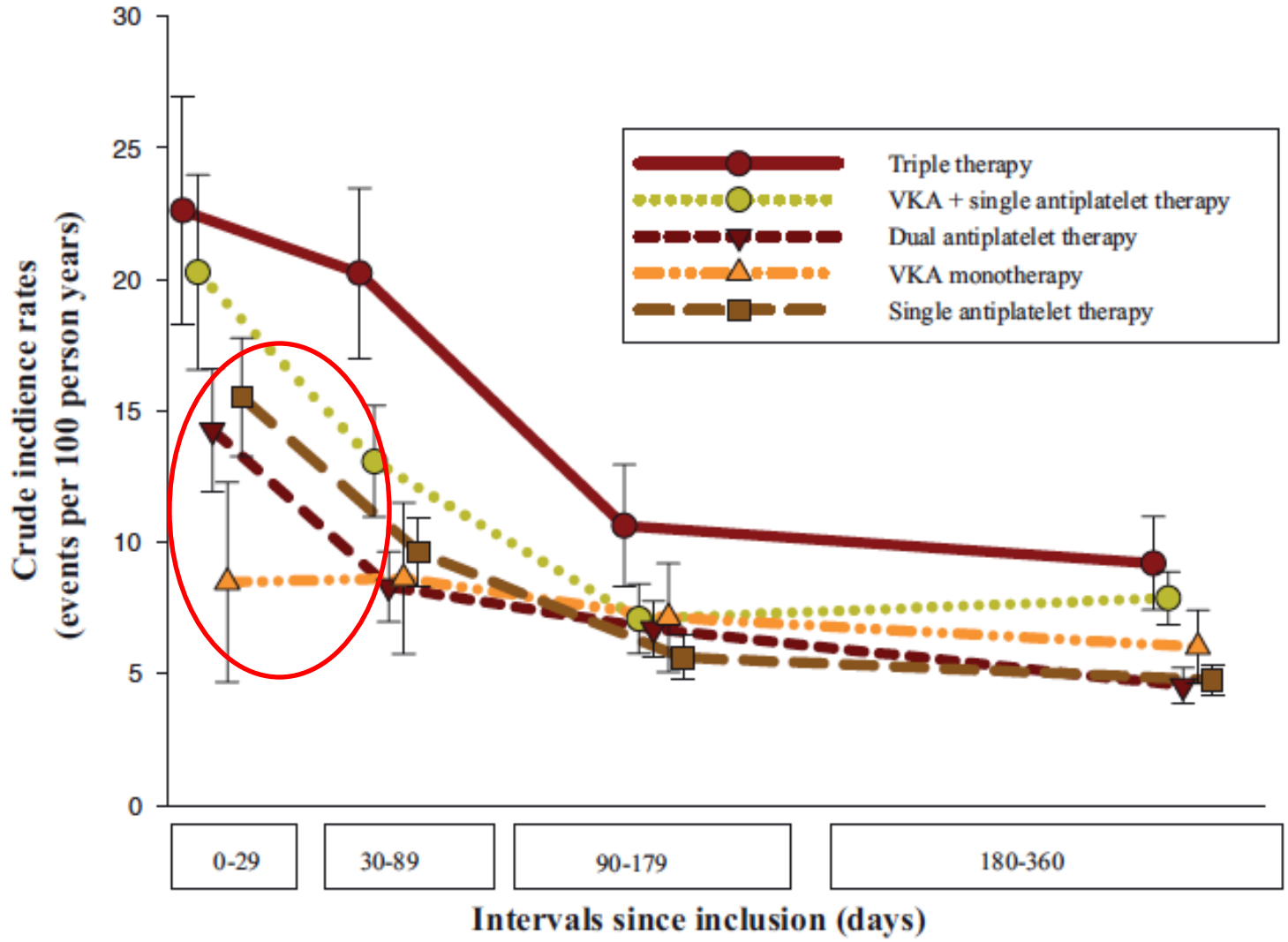
Crude incidence rates of fatal and nonfatal bleeding according to antithrombotic regimen



Lamberts M et al. Circulation 2012;126-1185-1190

TOPIC Study

Primary Endpoint

Death, Urgent revasc., Stroke, BARC ≥ 2

Table 3 Endpoints at 1 year

	Switched DAPT	Unchanged DAPT	HR (95%IC)	*P*-value
Net clinical benefit	43 (13.4%)	85 (26.3%)	0.48 (0.34–0.68)	<0.01
Any ischaemic event	30 (9.3%)	37 (11.5%)	0.48 (0.34–0.68)	0.36
Cardiovascular death	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
Unplanned revascularization	28 (8.7%)	30 (9.3%)	0.93 (0.56–1.55)	0.78
Stroke	1 (0.3%)	3 (0.9%)	0.37 (0.05–2.60)	0.32
All bleedings	30 (9.3%)	76 (23.5%)	0.39 (0.27–0.57)	<0.01
Bleeding BARC ≥ 2	13 (4.0%)	48 (14.9%)	0.30 (0.18–0.50)	<0.01
TIMI major	1 (0.3%)	4 (1.2%)	0.30 (0.05–1.73)	0.18
TIMI minor	9 (2.8%)	26 (8.0%)	0.37 (0.19–0.71)	<0.01
TIMI minimal	20 (6.2%)	46 (14.2%)	0.44 (0.27–0.71)	<0.01

Follow-up and end point assessments

The primary end point was a composite of cardiovascular death, unplanned hospitalization leading to urgent coronary revascularization, stroke, and bleeding episodes as defined by the BARC classification ≥ 2 at 1 year after ACS.[7] This combination of both ischaemic and bleeding

Cuisset T et al. Eur Heart J. 2017

TOPIC Study

Procedural characteristics

	All patients (n = 646)	Switched DAPT (n = 323)	Unchanged DAPT (n = 323)	P-value
Access site, n (%):				0.11
Femoral	28 (4%)	17 (5%)	11 (3%)	
Radial	618 (96%)	306 (95%)	312 (97%)	
Culprit lesion, n (%):				0.15
LMS	24 (4%)	7 (2%)	17 (5%)	
LAD	299 (46%)	155 (48%)	144 (45%)	
LCx	118 (18%)	65 (20%)	53 (16%)	
RCA	202 (31%)	95 (29%)	107 (33%)	
Venous graft	3 (1%)	1 (0%)	2 (1%)	
Number of vessel treated, n (%):				0.19
1	548 (85%)	266 (82%)	282 (87%)	
2	84 (13%)	48 (15%)	36 (11%)	
3	14 (2%)	9 (3%)	5 (2%)	
Stent type, n (%)				0.10
DES	585 (91%)	297 (92%)	288 (89%)	
BVS	21 (3%)	13 (4%)	8 (3%)	
BMS	24 (4%)	8 (3%)	16 (5%)	
None	16 (3%)	5 (2%)	11 (3%)	
Number of stent (m ± SD)	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7	0.39
Stent diameter, mm (m ± SD)	2.8 ± 0.6	2.8 ± 0.6	2.8 ± 0.5	0.43
Stent length, mm (m ± SD)	26.4 ± 16.4	26.9 ± 16.9	26.4 ± 15.8	0.64

Cuisset T et al. Eur Heart J. 2017

TROPICAL ACS

Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS)

No difference in bleeding events

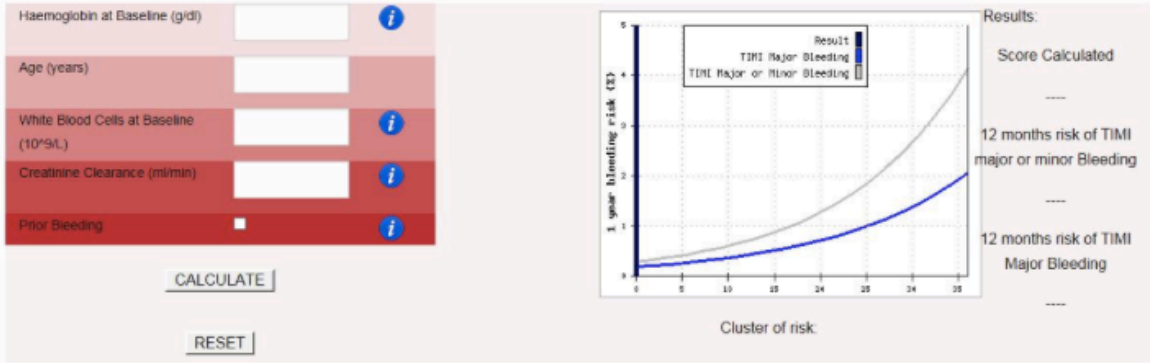
	Control group (n=1306)	Guided de-escalation group (n=1304)	Hazard ratio (95% CI)	p value
Bleeding events				
Key secondary endpoint (BARC bleeding ≥2)	79 (6%)	64 (5%)	0·82 (0·59–1·13)	0·23
BARC type 1 or 2	119 (9%)	98 (8%)	0·82 (0·63–1·07)	0·15
BARC type 3 or 5	20 (2%)	17 (1%)	0·85 (0·45–1·63)	0·63
Any BARC bleeding	137 (11%)	114 (9%)	0·83 (0·65–1·06)	0·14
Bleeding events				
BARC type 1	64 (5%)	52 (4%)	0·81 (0·56–1·17)	0·26
BARC type 2	61 (5%)	47 (4%)	0·77 (0·53–1·13)	0·19
BARC type 3	19 (2%)	17 (1%)	0·90 (0·47–1·73)	0·75
BARC type 4	1 (<1%)	2 (<1%)	2·02 (0·18–22·20)	0·57
BARC type 5	1 (<1%)	0	..	0·89

Data are n (%). p values presented are for superiority comparisons unless otherwise stated. BARC=Bleeding Academic Research Consortium. $p_{non\text{-}inf}$=p value for non-inferiority. p_{sup}=p value for superiority.

Table 3: **Clinical outcomes at 12 months' follow-up**

Sibbing D, et al. Lancet. 2017

PRECISE-DAPT SCORE



- **To Predict the risk of bleeding in individual patients with coronary artery disease, treated coronary stenting and subsequent dual antiplatelet therapy**
- **Dataset including 14,963 patients from 8 randomized clinical trials, enrolled in more than 130 clinical sites and 12 countries worldwide.**

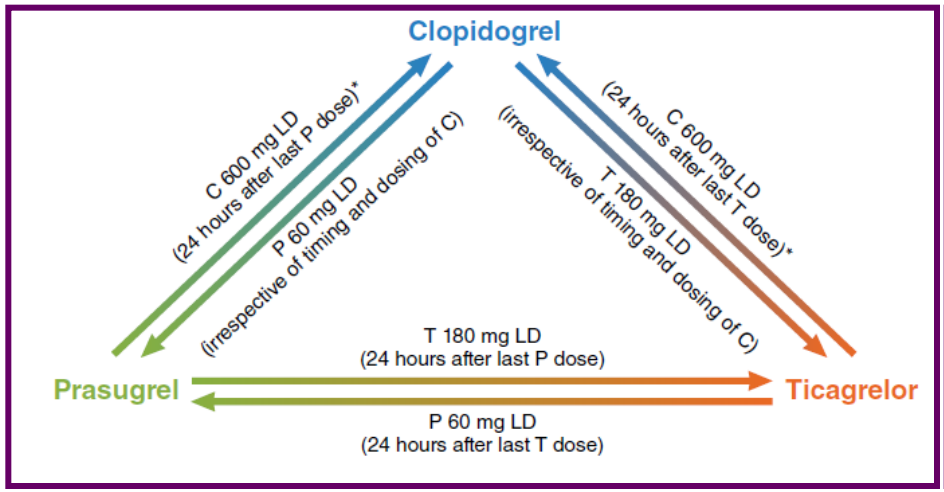
The PRECISE-DAPT Risk Score has been externally validated in two independent datasets. Data analysis, derivation and validation of the PRECISE-DAPT score were performed at the Erasmus Medical Center public health department.

La de-esclation therapy dopo SCA:

Da fare (bene) solo in bail-out.

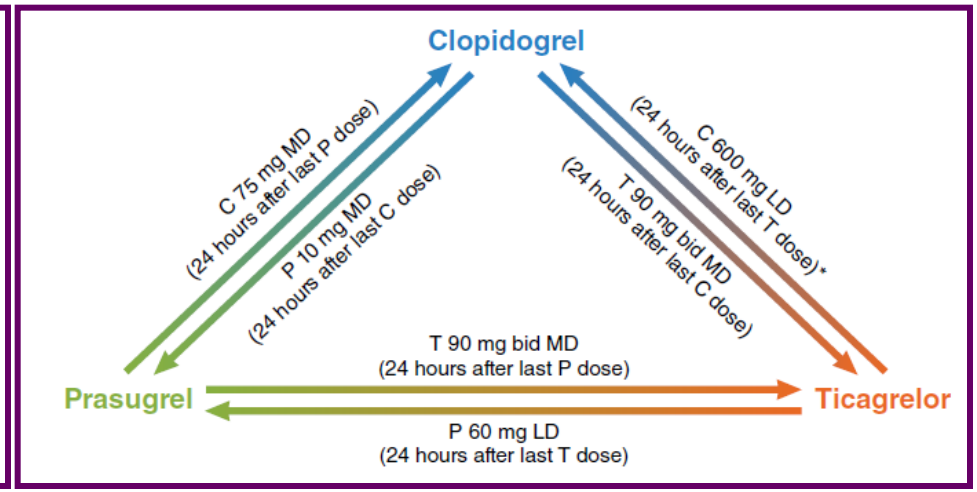
Expert Consensus Recommendations on Switching

SWITCHING BETWEEN ORAL $P2Y_{12}$ INHIBITORS



In the acute/early phase (≤30 days from the index event), switching should occur with the administration of a loading dose (LD) in most cases, with the exception of patients who are de-escalating therapy because of bleeding or bleeding concerns, in whom a maintenance dose (MD) of clopidogrel (C) should be considered. Timing of switching should be 24 hours after the last dose of a given drug, with the exception of when escalating to prasugrel (P) or ticagrelor (T), when the LD can be given regardless of the timing and dosing of the previous clopidogrel regimen.

*Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns.



In the late/very late phase (>30 days from the index event), switching should occur with the administration of an MD 24 hours after the last dose of a given drug, with the exception of patients changing from ticagrelor to prasugrel therapy, for whom an LD should be considered.

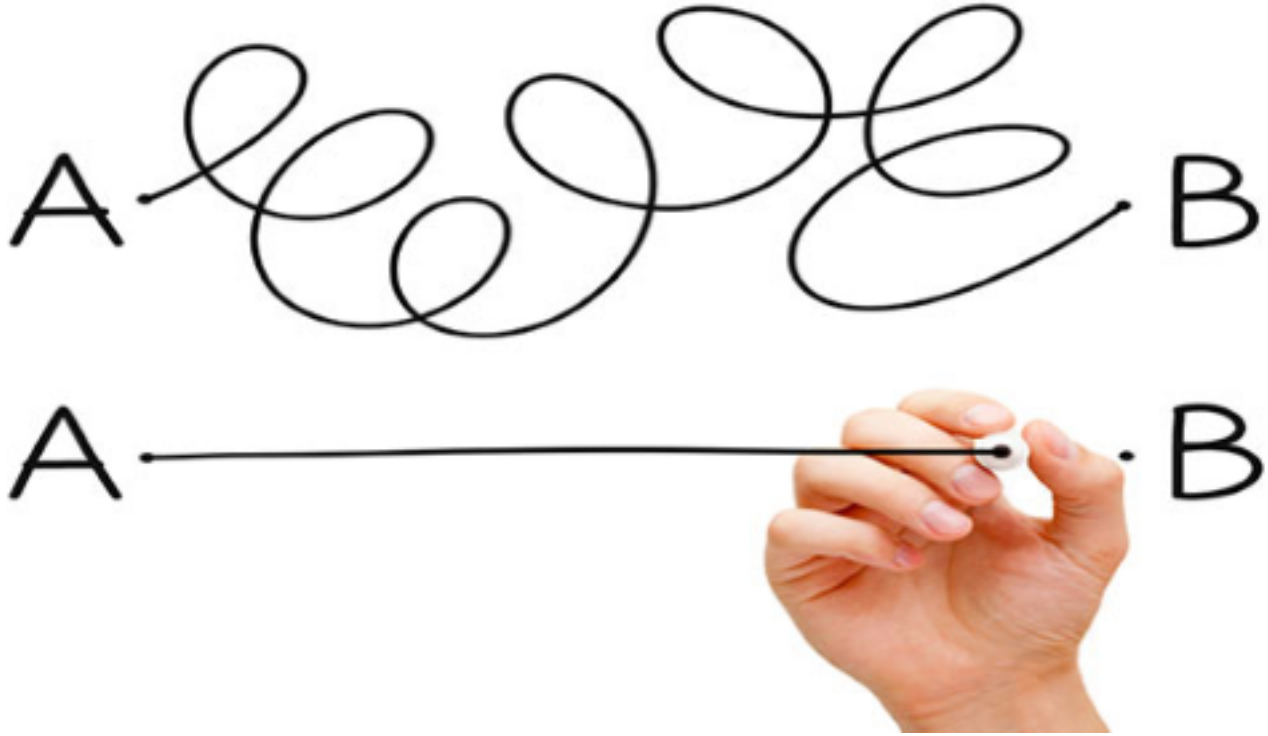
De-escalation from ticagrelor to clopidogrel should occur with administration of an LD 24 hours after the last dose of ticagrelor (but in patients in whom de-escalation occurs because of bleeding or bleeding concerns, an MD of clopidogrel should be considered).

*Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns.

Angiolillo DJ et al. Circulation. 2017;136:1955–1975.

La de-esclation therapy dopo SCA
Conclusioni

- Non è ragionevole passare precocemente e routinariamente dal prasugrel (o ticagrelor) al clopidogrel.
- Non è necessaria se si effettua una stratificazione accurata del rischio emorragico in fase acuta.
- E’ una strategia necessaria in bail-out in caso di sanguinamento.
- E’ importante eseguirla correttamente.


A
B
A
B


Keep it simple!