FEDERAZIONE
CENTRI PER LA DIAGNOSI
DELLA TROMBOSI E LA
SORVEGLIANZA DELLE TERAPIE
ANTITROMBOTICHE (FCSA)

F.C.S.A.

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Terapia antiaggregante piastrinica: quale ruolo per il laboratorio?

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Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

Conflitti di interesse
MARCO CATTANEO

Research Support/P.I.	**Eli Lilly, Daiichi Sankyo, AstraZeneca, Evolva**
Employee	**No relevant conflicts of interest to declare**
Consultant	**No relevant conflicts of interest to declare**
Major Stockholder	**No relevant conflicts of interest to declare**
Speakers Bureau	**No relevant conflicts of interest to declare**
Honoraria	**Eli Lilly, Daiichi Sankyo, AstraZeneca, MSD, Evolva**
Scientific Advisory Board	**Eli Lilly, Daiichi Sankyo, AstraZeneca, Evolva, The Medicines Company, MSD, Novartis, Sanofi**
(Other)	**Il mio laboratorio è specializzato in test di funzione piastrinica**

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

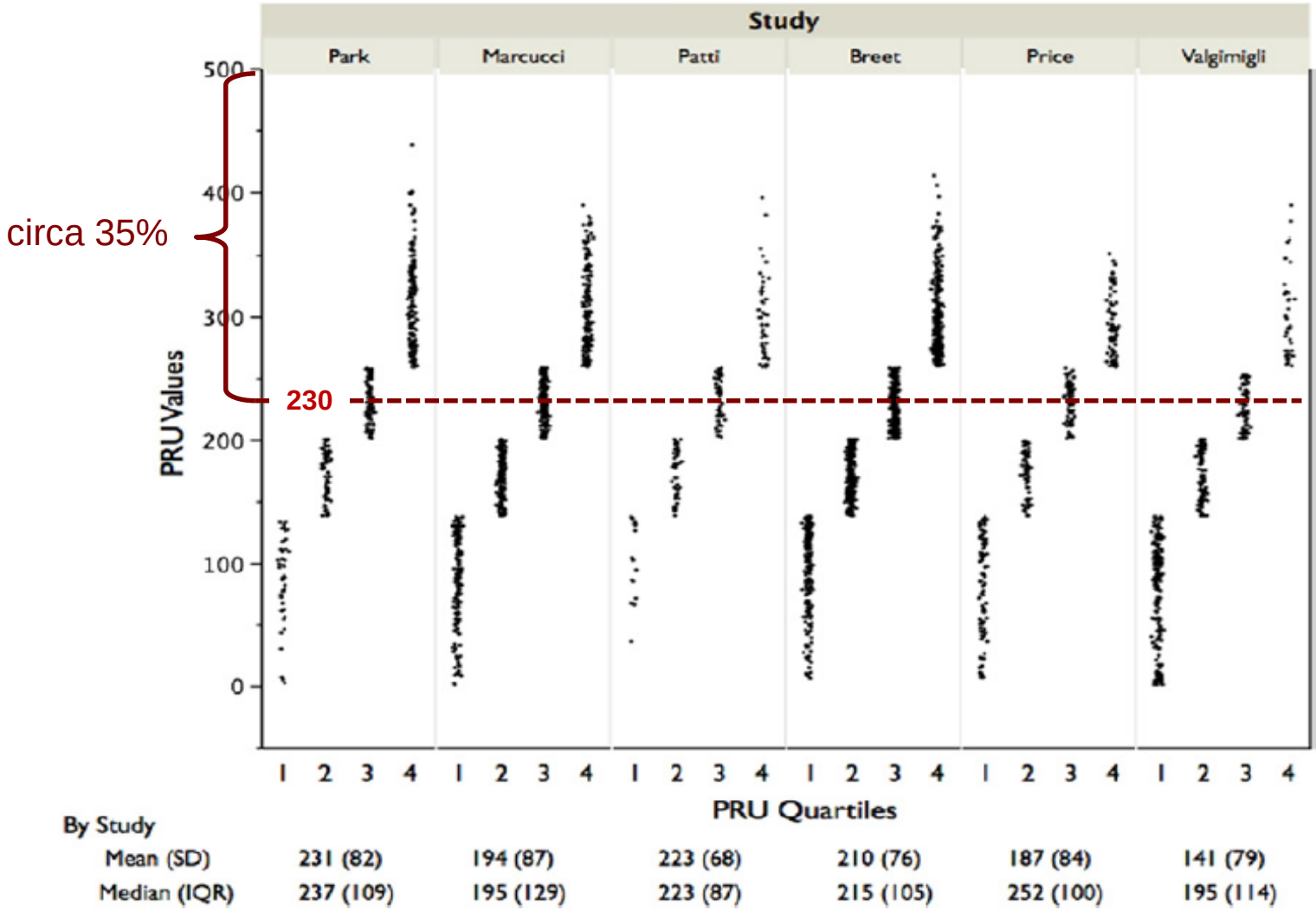
Measures to minimize bleeding while on dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.[43,44]	I	A
In patients treated with DAPT, a daily aspirin dose of 75 - 100 mg is recommended.[45–47,51,52]	I	A
A PPI in combination with DAPT[c] is recommended.[70,79,80,86,87]	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.[58–60]	III	A

DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PPI proton pump inhibitor.
[a]Class of recommendation.
[b]Level of evidence.
[c]While the evidence that a PPI does not increase the risk of cardiovascular events was generated with omeprazole, based on drug–drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, while pantoprazole and rabeprazole have the lowest.

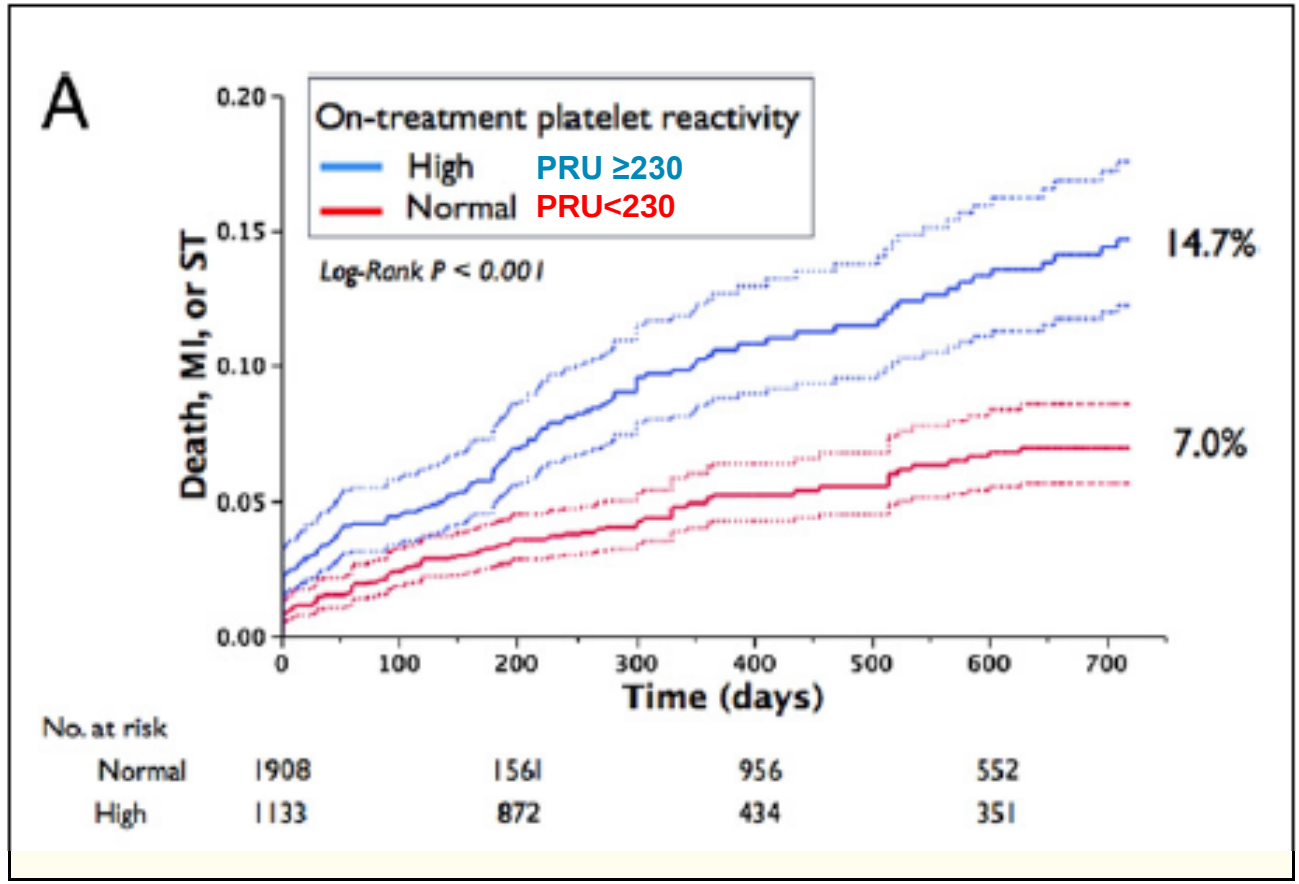
Valgimigli et al, EHJ 2017

Distribuzione di “Platelet Reactivity Units” (PRU), misurati con VerifyNow P2Y12 in pazienti trattati con Clopidogrel, in **6 studi osservazionali**



Brar et al, JACC 2011:58:1945–54

Incidenza di MACE in pazienti trattati con clopidogrel, in funzione della loro reattvità piastrinica: metanalisi di **6 studi osservazionali**



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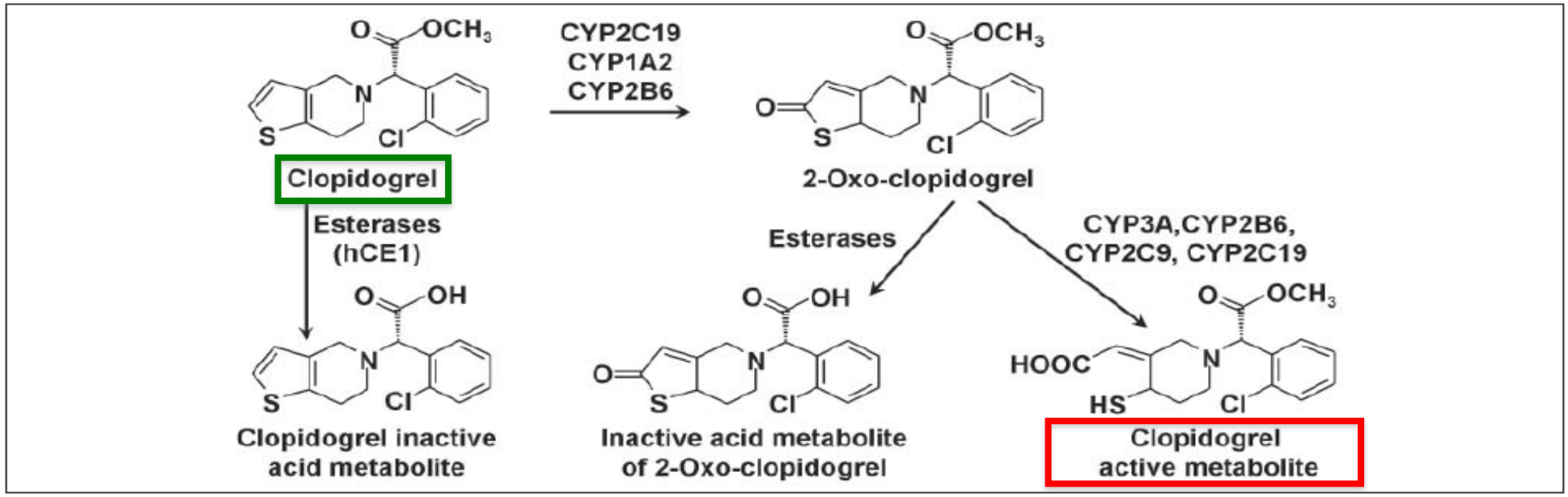
Principali variabili che condizionano la risposta farmacodinamica al clopidogrel

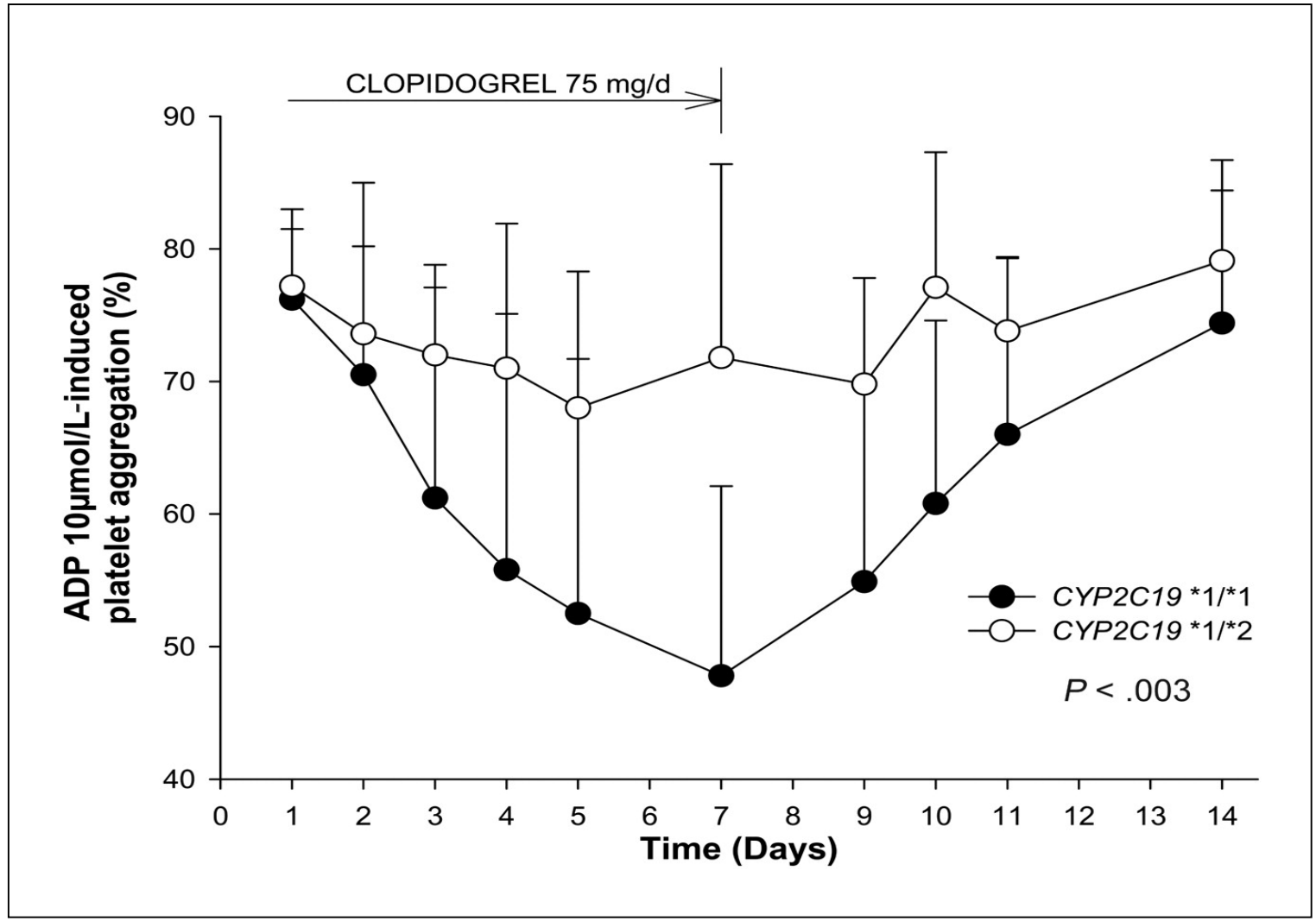
- Scarsa aderenza /sottodosaggio
- Mutazioni di isoforme del CYP
- Ridotto assorbimento (es., portatori della mutazione TT3435 di ABCB1, codificante per P-glicoproteina)
- InteractioInterazione con altri farmaci (PPI, statine, calcio antagonisti)
- Aumentato turnover piastrinico
- Età
- Elevato BMI
- Diabete mellito
- Variabilità di risposta a ADP
- **--- ---**

Struttura e vie metaboliche principali del clopidogrel



Cattaneo M, in “PLATELETS” 3rd ed, 2012 – Michelson AD, editor

Variazioni di aggregazione piastrinica indotta da ADP (10 μM) durante 7 giorni di terapia con clopidogrel 75 mg/d e nei 7 giorni dopo la sua sospensione: effetto del genotipo CYP2C19*2 (P < .003 Friedman test)



Hulot, J.-S. et al. Blood 2006;108:2244-2247

Influenza del polimorfismo C3435T di ABCB1 sui livelli plasmatici di clopidogrel e del suo metabolita attivo

	3435T/T	3435C/T e 3435C/C
Clopidogrel (ng/ml)	**13.3 +/- 5.2**	**49.7 +/- 41.6****
Clopidogrel metabolita attivo (ng/ml)	**2.5 +/-1 .2**	**6.6 +/- 3.6***

*** P <0.05 ** P <0.01**

Taubert D. Clin Pharmacol Ther. 2006 Nov;80(5):486-501

Monitoraggio di laboratorio della terapia con clopidogrel

Si è dimostrato sicuro, efficace e conveniente nell'ambito di

STUDI DI INTERVENTO?

RECLOSE 2-ACS

Incidenza di eventi trombotici (end point primario) nel corso di 2 anni, in pazienti con Sindrome Coronarica Acuta (SCA) in terapia con DAPT (aspirina + clopidogrel) sottoposti a PCI, in base alla loro reattività piastrinica

HRPR	LRPR	P
14.6%	8.7%	0.003

Parodi et al, JAMA 2011;306:1215-23

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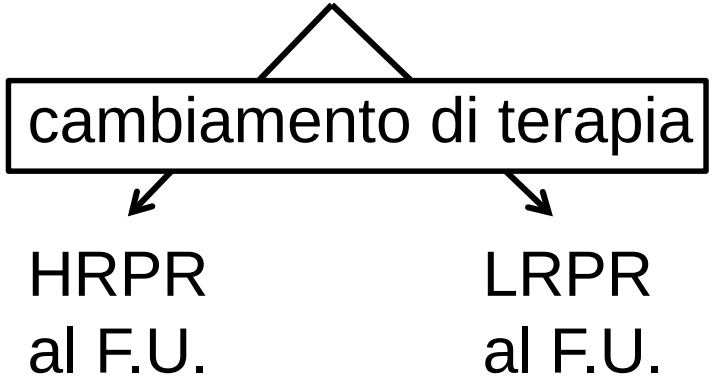

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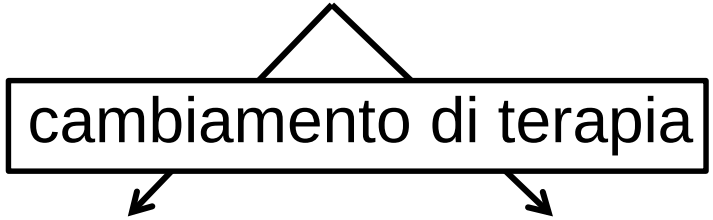
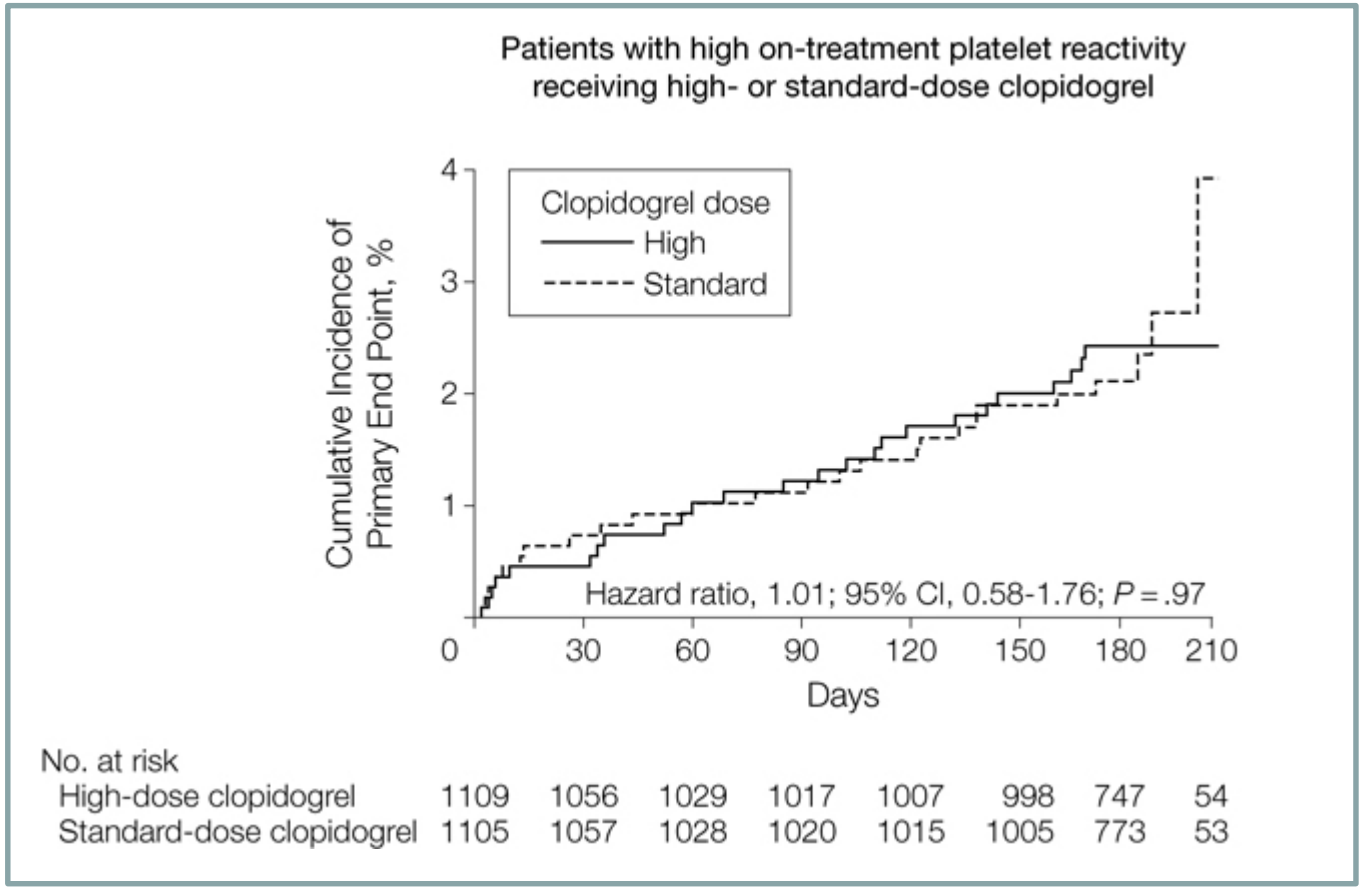


HRPR al F.U.	LRPR al F.U.	
14.9%	14.4%	0.91

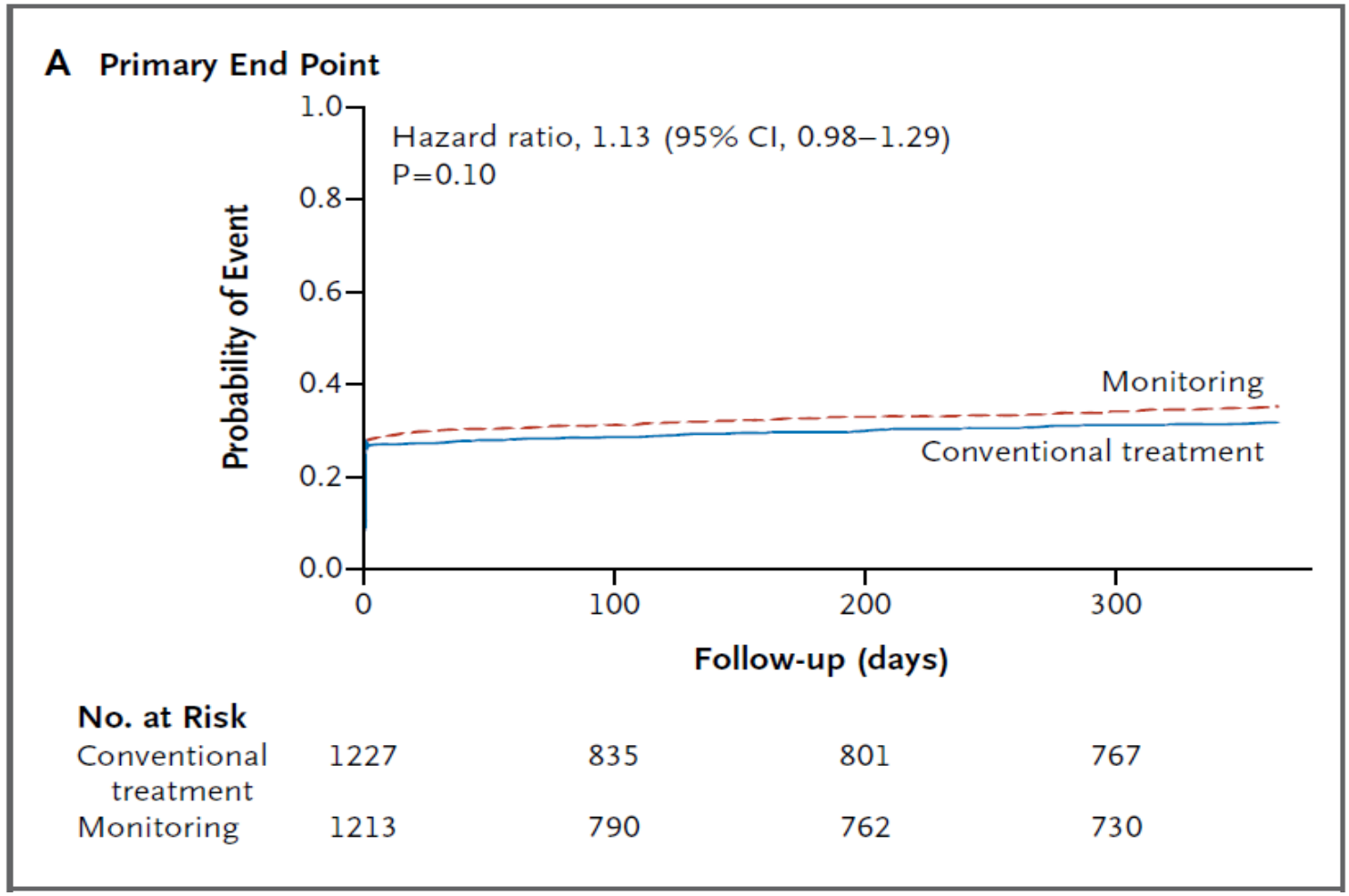
Parodi et al, JAMA 2011;306:1215-23

Incidenza cumulativa dell'end point primario di efficacia (Kaplan-Meier) GRAVITAS



Price, M. J. et al. JAMA 2011;305:1097-1105

Proporzione di pazienti con end point primario
ARCTIC

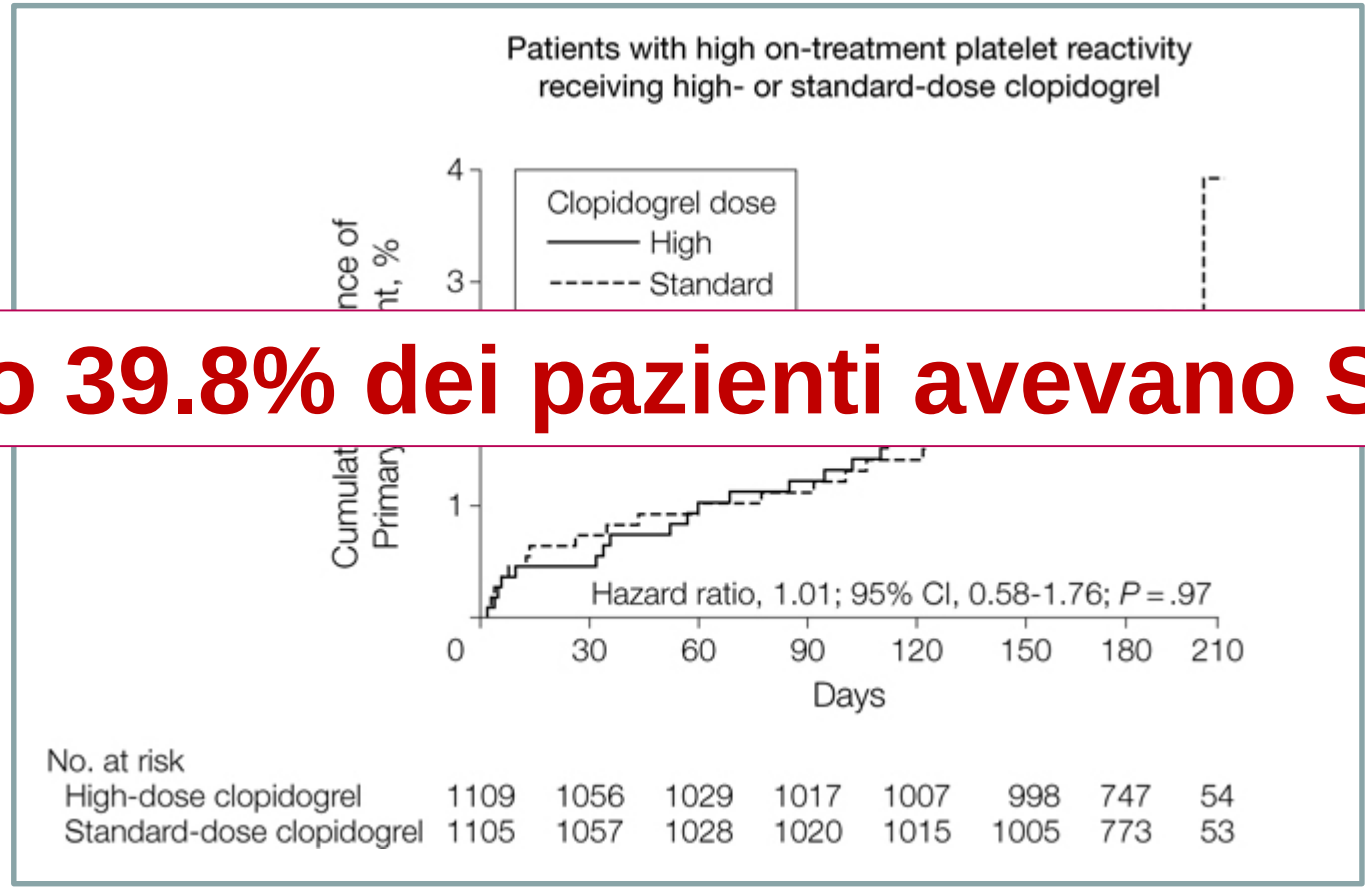


Collet et al, NEJM 2012

Critiche agli studi GRAVITAS e ARCTIC

1. La maggior parte dei pazienti arruolati avevano una patologia coronarica stabile: basso rischio di eventi CV
2. …
3. …
4. …
5. …
n. …

Incidenza cumulativa dell'end point primario di efficacia (Kaplan-Meier) GRAVITAS



Solo 39.8% dei pazienti avevano SCA

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Proporzione di pazienti con end point primario
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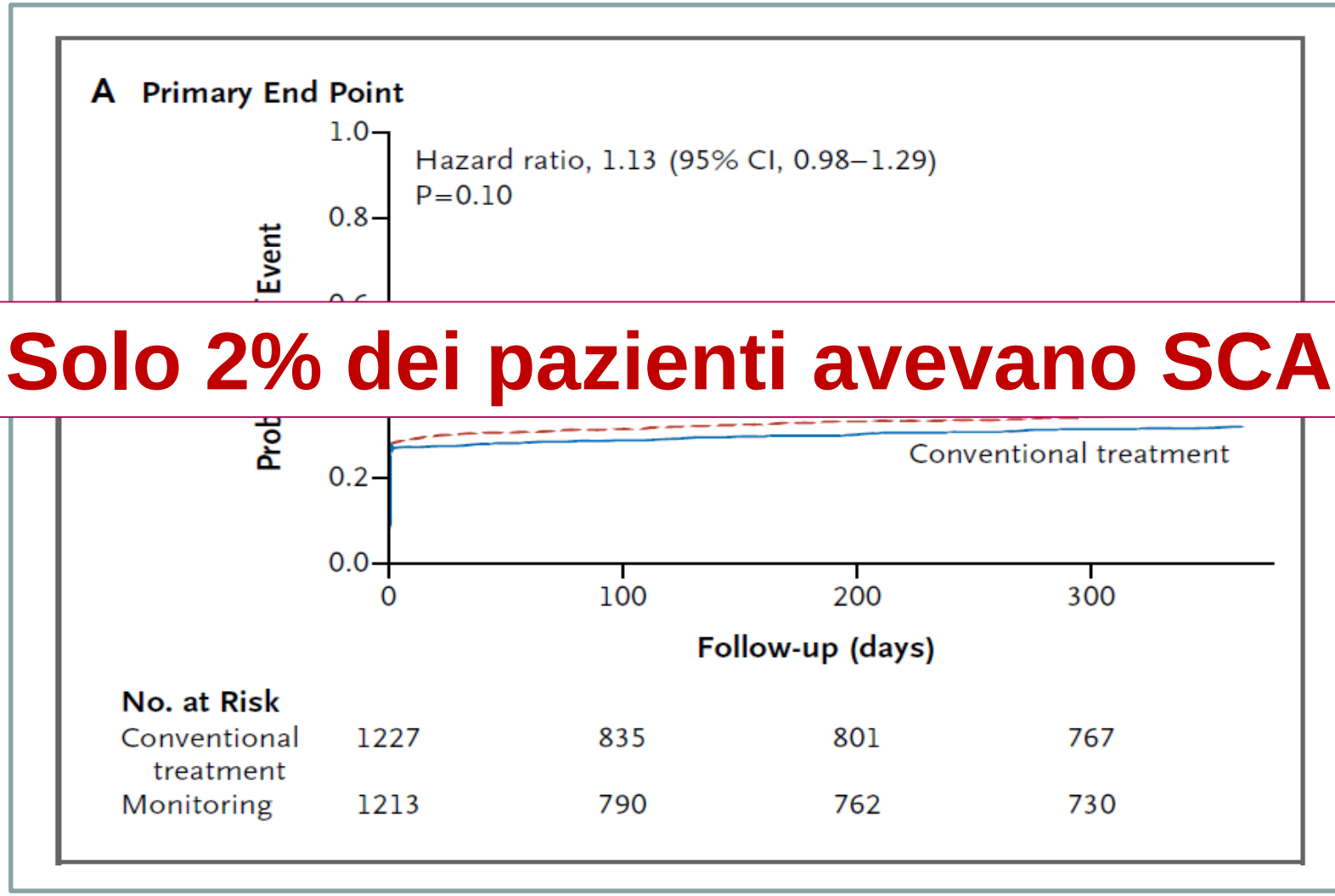

Solo 2% dei pazienti avevano SCA

Collet et al, NEJM 2012

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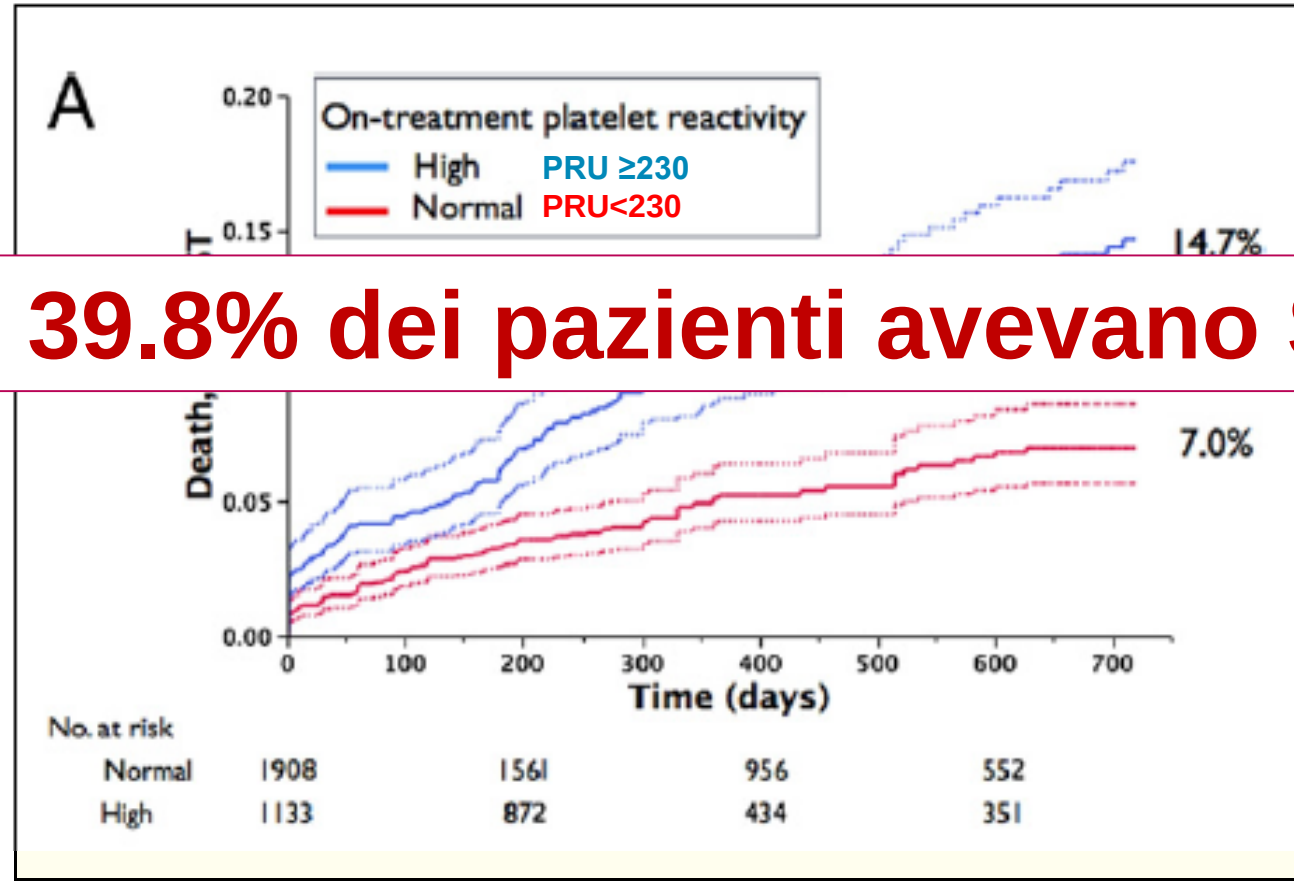

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HRPR	LRPR	P
14.6%	8.7%	0.003

«Solo» 100% dei pazienti avevano SCA

cambiamento di terapia

HRPR al F.U.	LRPR al F.U.	
14.9%	14.4%	0.91

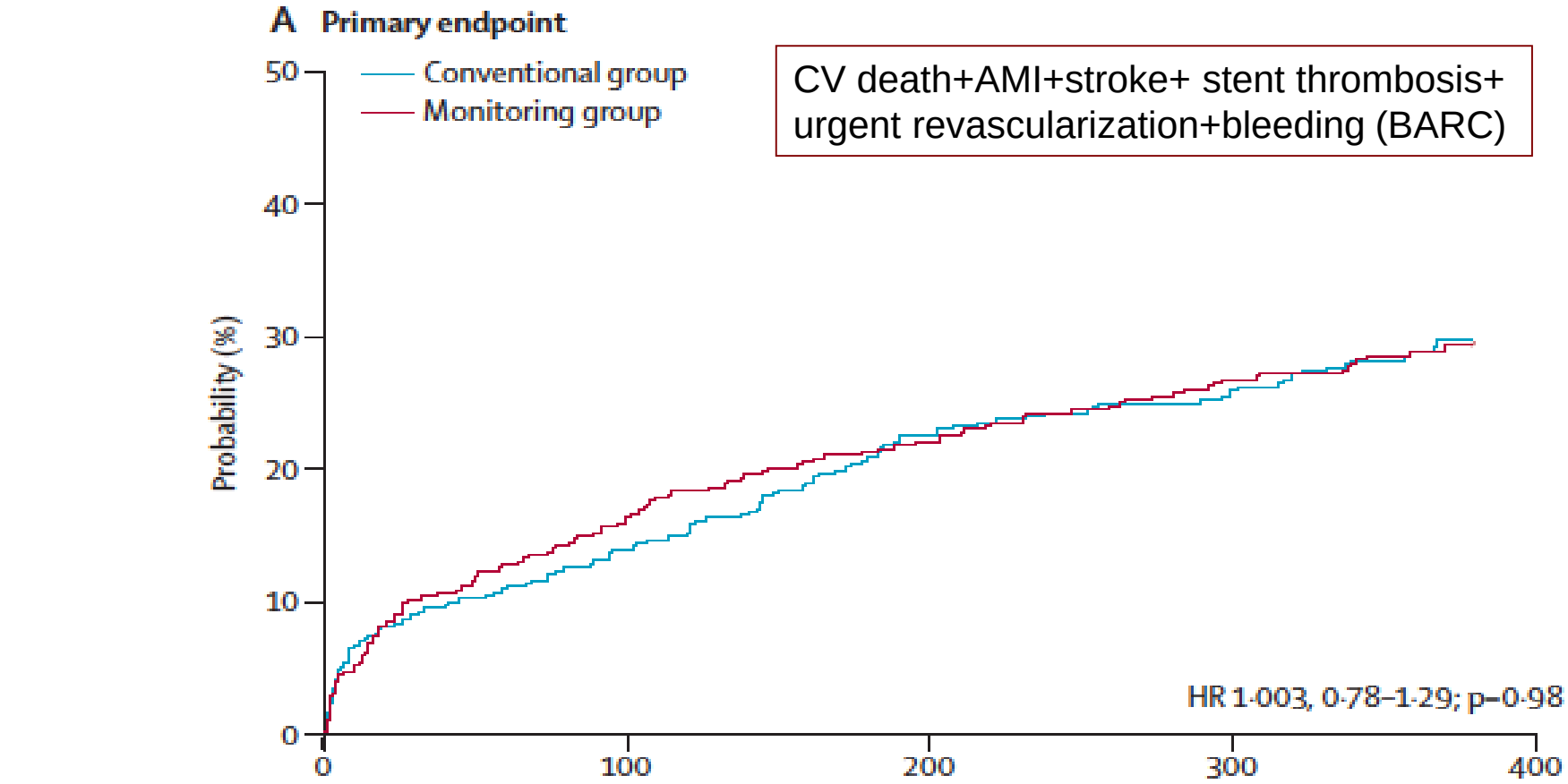
Parodi et al, JAMA 2011;306:1215-23

ANTARCTIC trial

- Pazienti ≥75 anni sottoposti a PCI+stent per **SCA**
- Trattamenti: prasugrel 5 mg+ ASA: A) nessun monitoraggio (n=435); B) con monitoraggio (n=442)
- End-point primario: mortalità CV + IMA + ictus + trombosi di stent + rivascolarizzazione urgente + emorragia (BARC)
- Follow-up: 12 mesi

Cayala et al, Lancet 2016

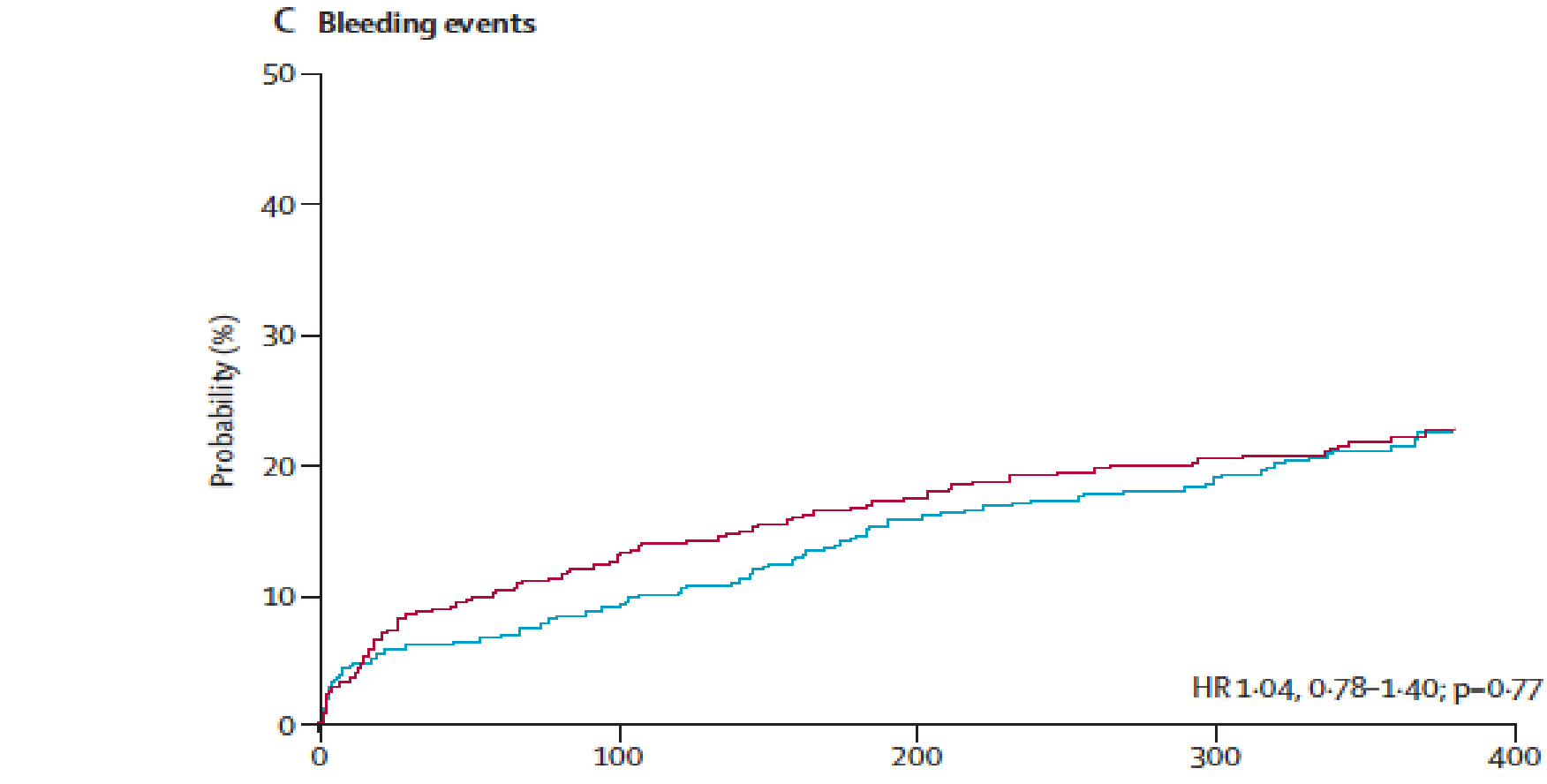
End-point primario
ANTARCTIC



CV death+AMI+stroke+ stent thrombosis+ urgent revascularization+bleeding (BARC)

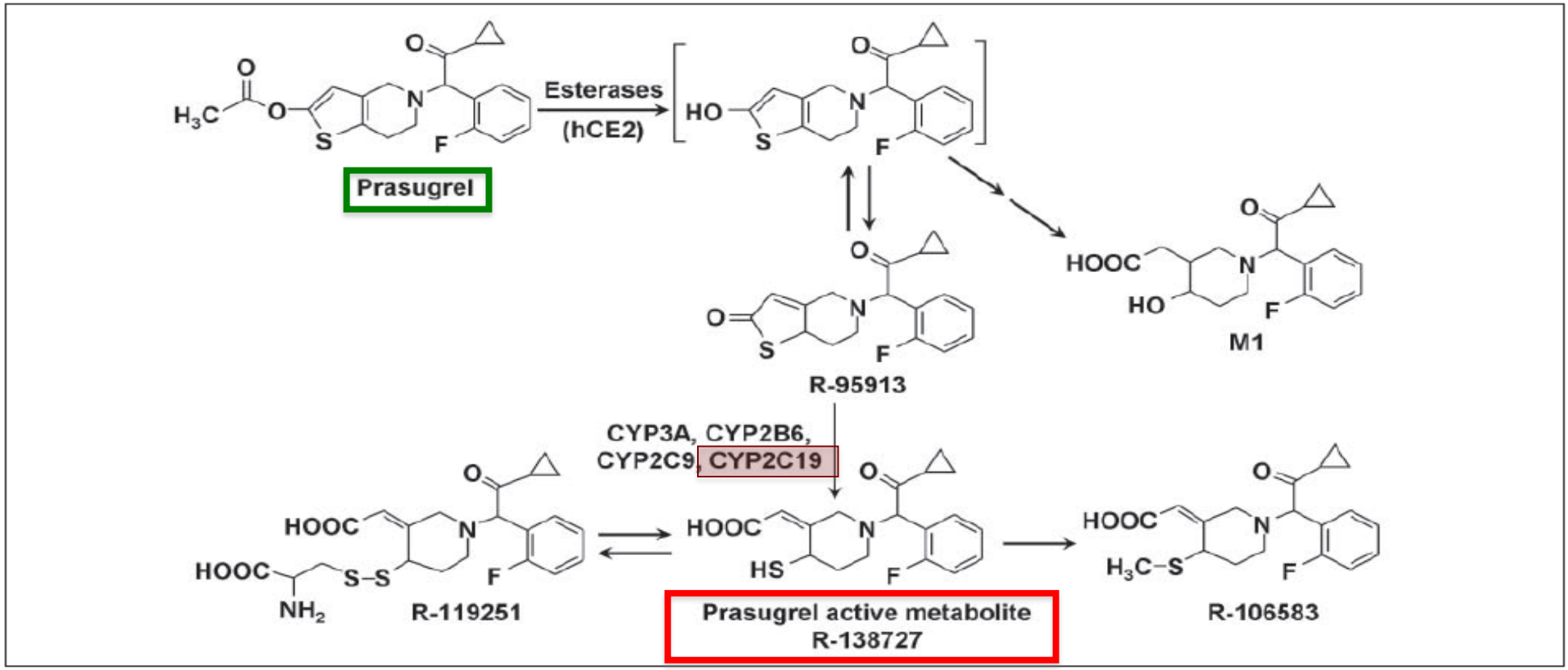
Cayala et al, Lancet 2016

Complicanze emorragiche (BARC)
ANTARCTIC



Cayala et al, Lancet 2016

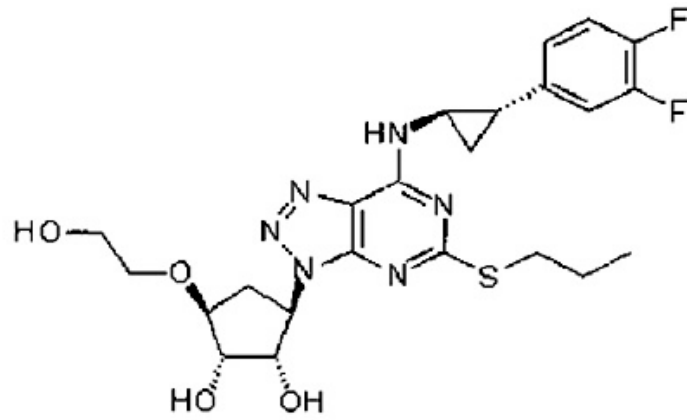
Struttura e vie metaboliche principali del prasugrel



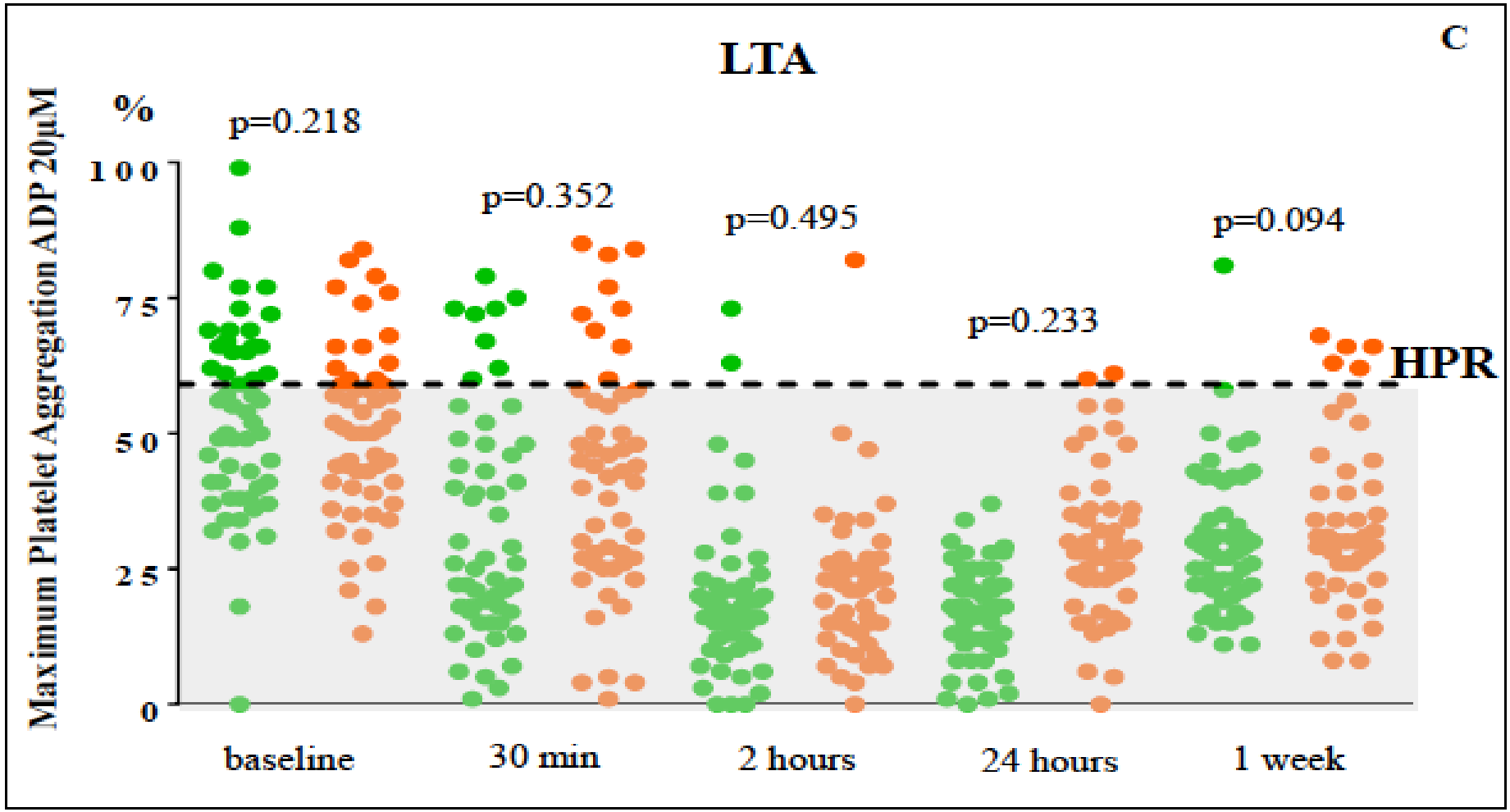
Cattaneo M, in “PLATELETS” 3rd ed, 2012 – Michelson AD, editor

TICAGRELOR

- Antagonista diretto e reversibile del $P2Y_{12}$
- pIC_{50} = 7.9 per aggregazione piastrinica indotta da ADP 30 μM
- Selettivo per $P2Y_{12}$
- $T_{1/2}$ 7-8.5h
- Tmax 2 h

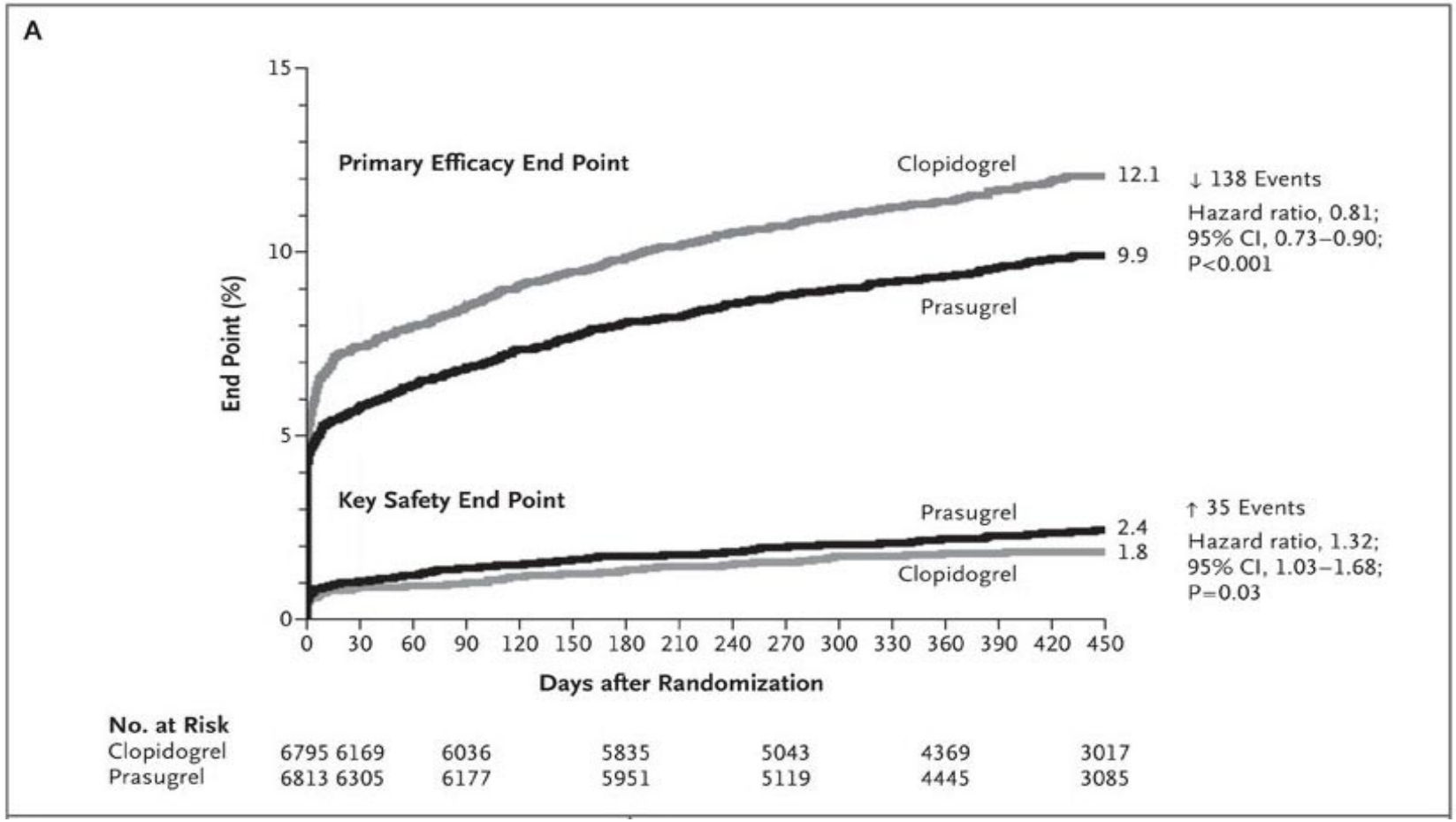


Variazioni di prevalenza di “HTPR” passando da terapia con clopidogrel a terapia con **prasugrel** o **ticagrelor**



Rollini et al, Eur Heart J 2016

Kaplan-Meier di incidenza di end point primario
TRITON-TIMI 38



Wiviott S et al. N Engl J Med 2007

Incidenze di end point primario e di emorragie non-CABG
PLATO

Events	Ticagrelor no/total (%)	Clopidogrel no/total (%)	Hazard Ratio (95% C.I.)	p
Primary end point (composite of vascular death, myocardial infarction or stroke)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77-0.92)	<.001
Non-CABG-related major bleedings, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03-1.53)	.03

Wallentin L et al. N Engl J Med 2009;361:1045-1057

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Measures to minimize bleeding while on dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
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Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.[58–60]	III	A

DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PPI proton pump inhibitor.
[a]Class of recommendation.
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Valgimigli et al, EHJ 2017

È possibile “resuscitare” il monitoraggio di laboratorio della terapia con clopidogrel?

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

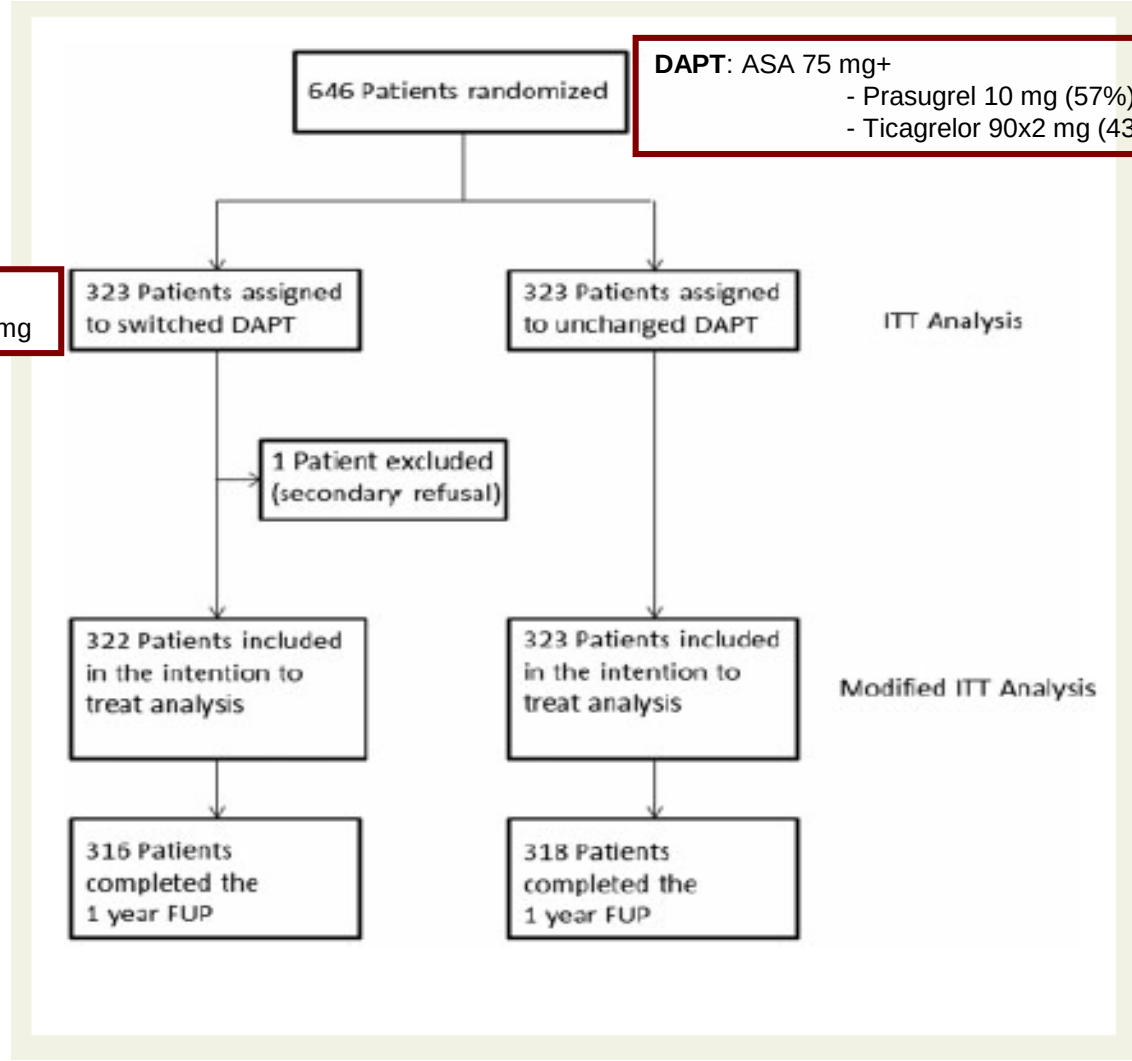
Dirk Sibbing, Dániel Aradi*, Claudius Jacobshagen, Lisa Gross, Dietmar Trenk, Tobias Geisler, Martin Orban, Martin Hadamitzky, Béla Merkely, Róbert Gábor Kiss, András Komócsi, Csaba A Dézsi, Lesca Holdt, Stephan B Felix, Radoslaw Parma, Mariusz Klopotowski, Robert H G Schwinger, Johannes Rieber, Kurt Huber, Franz-Josef Neumann, Lukasz Koltowski, Julinda Mehilli, Zenon Huczek, Steffen Massberg, on behalf of the TROPICAL-ACS Investigators†*

Lancet 2017; 390: 1747–57

Disegno dello studio
TOPIC

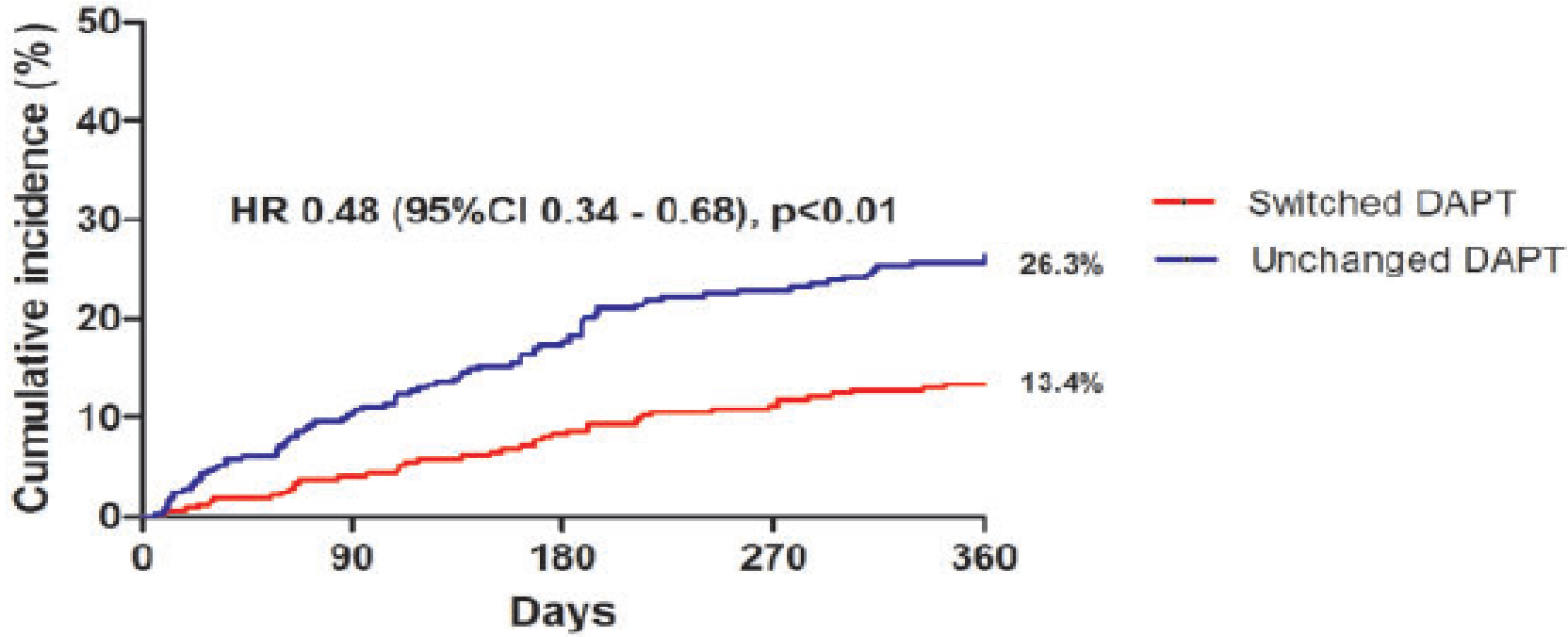
DAPT: ASA 75 mg+
- Prasugrel 10 mg (57%)
- Ticagrelor 90x2 mg (43%)

Switched DAPT:
ASA 75 mg+ Clopidogrel 75 mg



Modified from Cuisset et al, Eur Heart J 2017

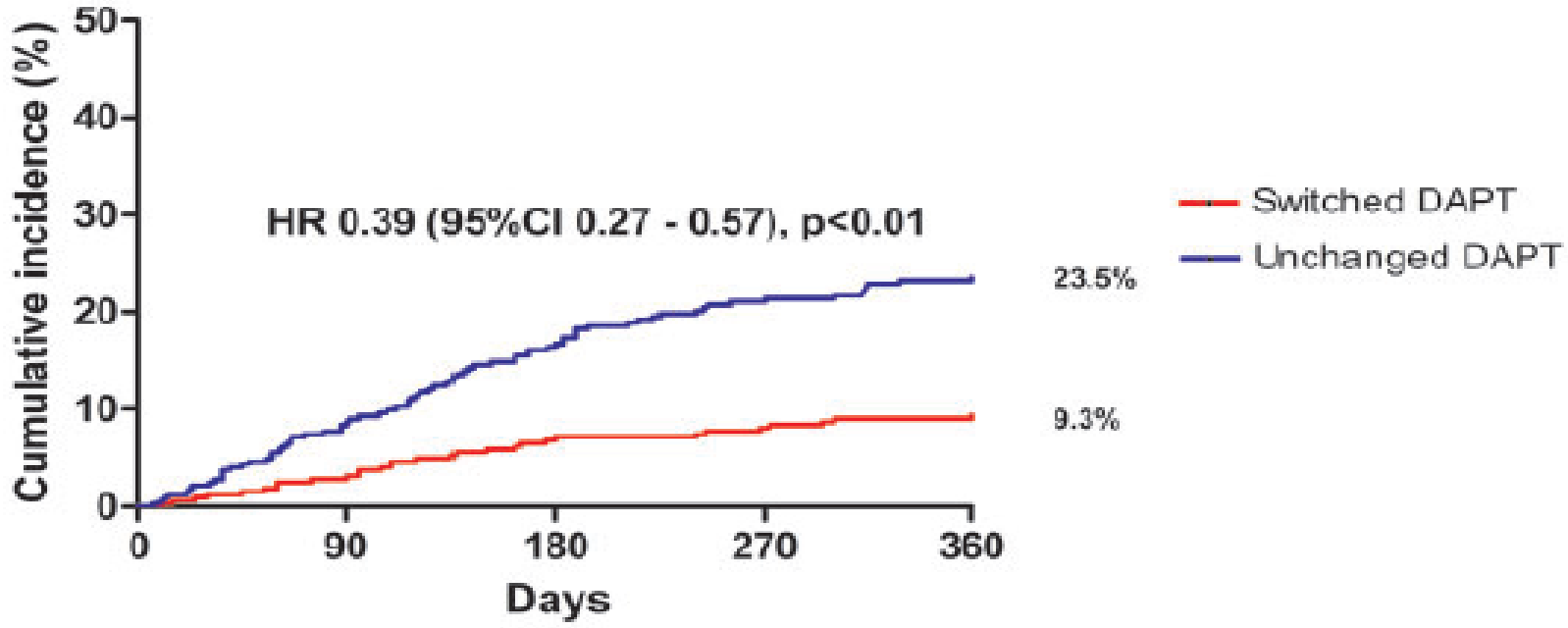
Incidenza dell'end point primario (beneficio clinico netto) – TOPIC



No. at risk					
Switched DAPT	322	309	295	284	273
Unchanged DAPT	323	289	266	246	233

Cuisset et al, Eur Heart J 2017

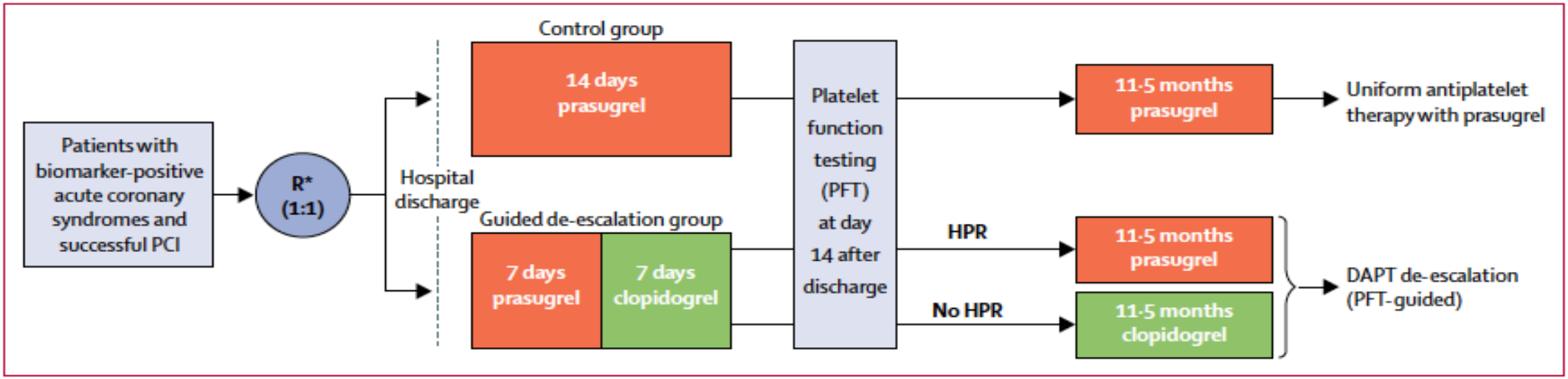
Incidenza di emorragie BARC≥2 a 1 anno
TOPIC



No. at risk					
Switched DAPT	322	312	299	294	286
Unchanged DAPT	323	295	269	251	242

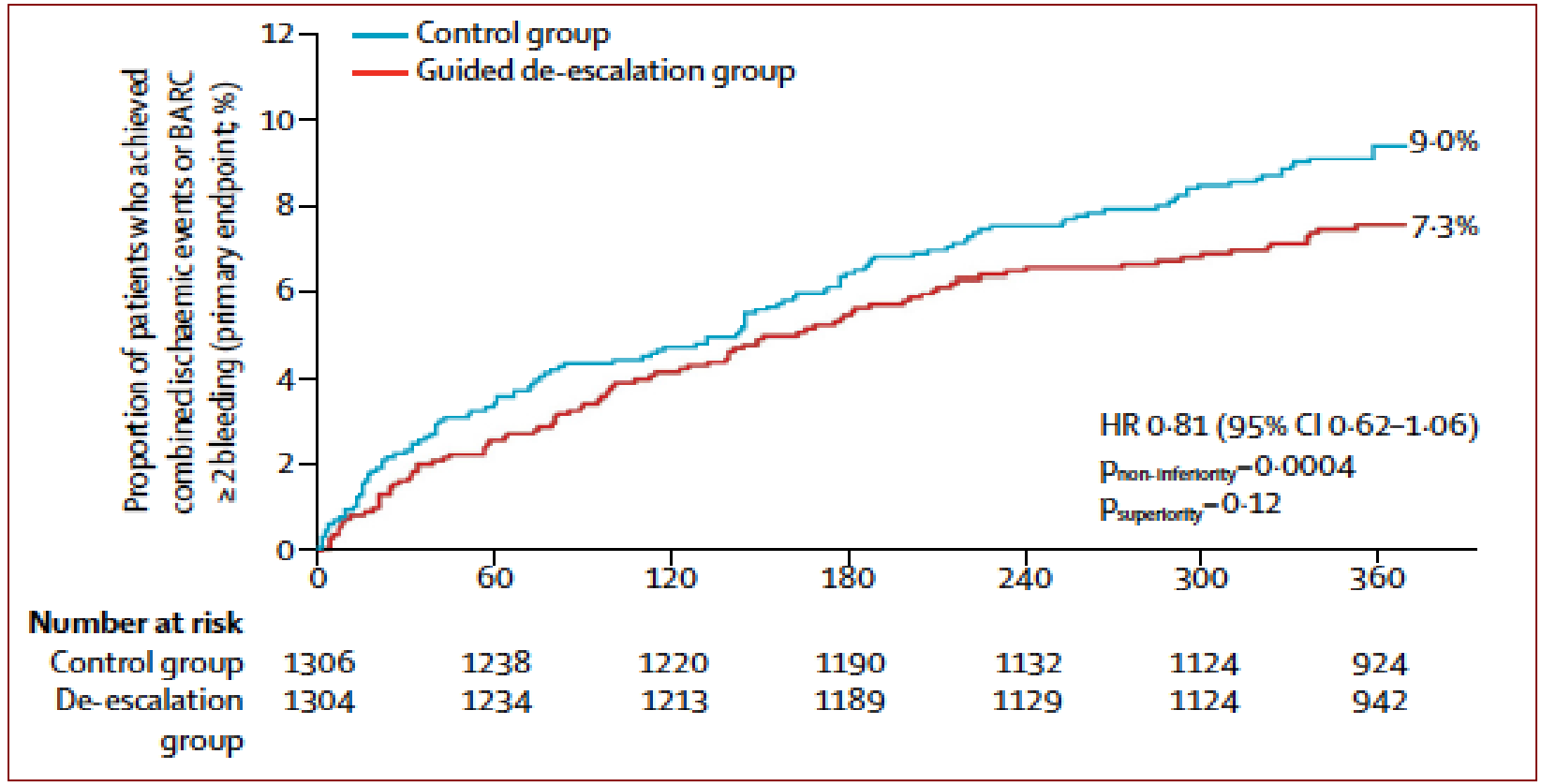
Cuisset et al, Eur Heart J 2017

Disegno dello studio
TROPICAL ACS



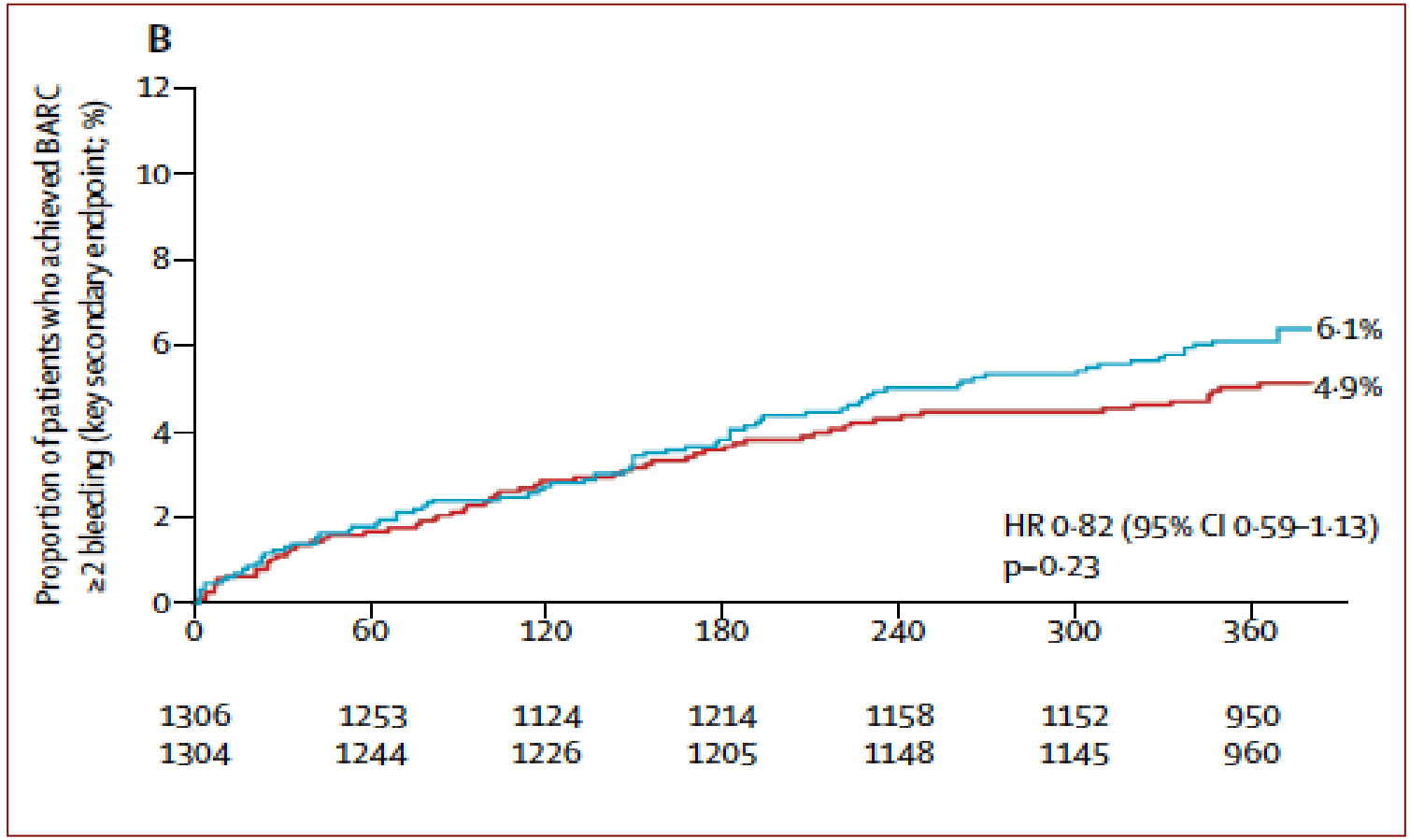
Sibbing et al, Lancet 2018©

Incidenza di end point primario (beneficio clinico netto) - TROPICAL ACS



Sibbing et al, Lancet 2018©

Incidenza di emorragie BARC≥2 a 1 anno
TROPICAL ACS



Sibbing et al, Lancet 2018

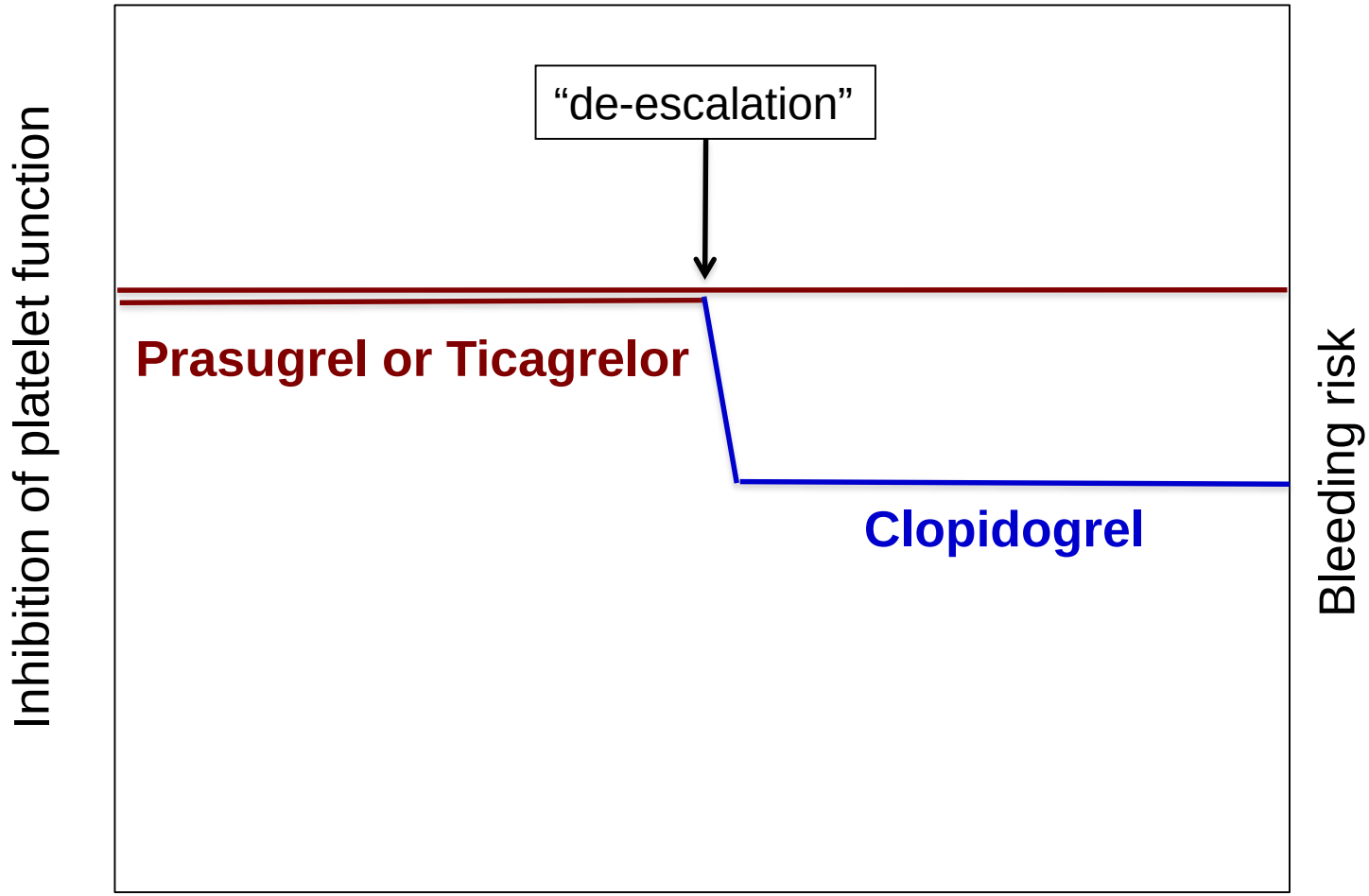
Conclusioni – TROPICAL-ACS

"In conclusion, a guided de-escalation of antiplatelet treatment was non-inferior to standard treatment with prasugrel in terms of net clinical benefit.

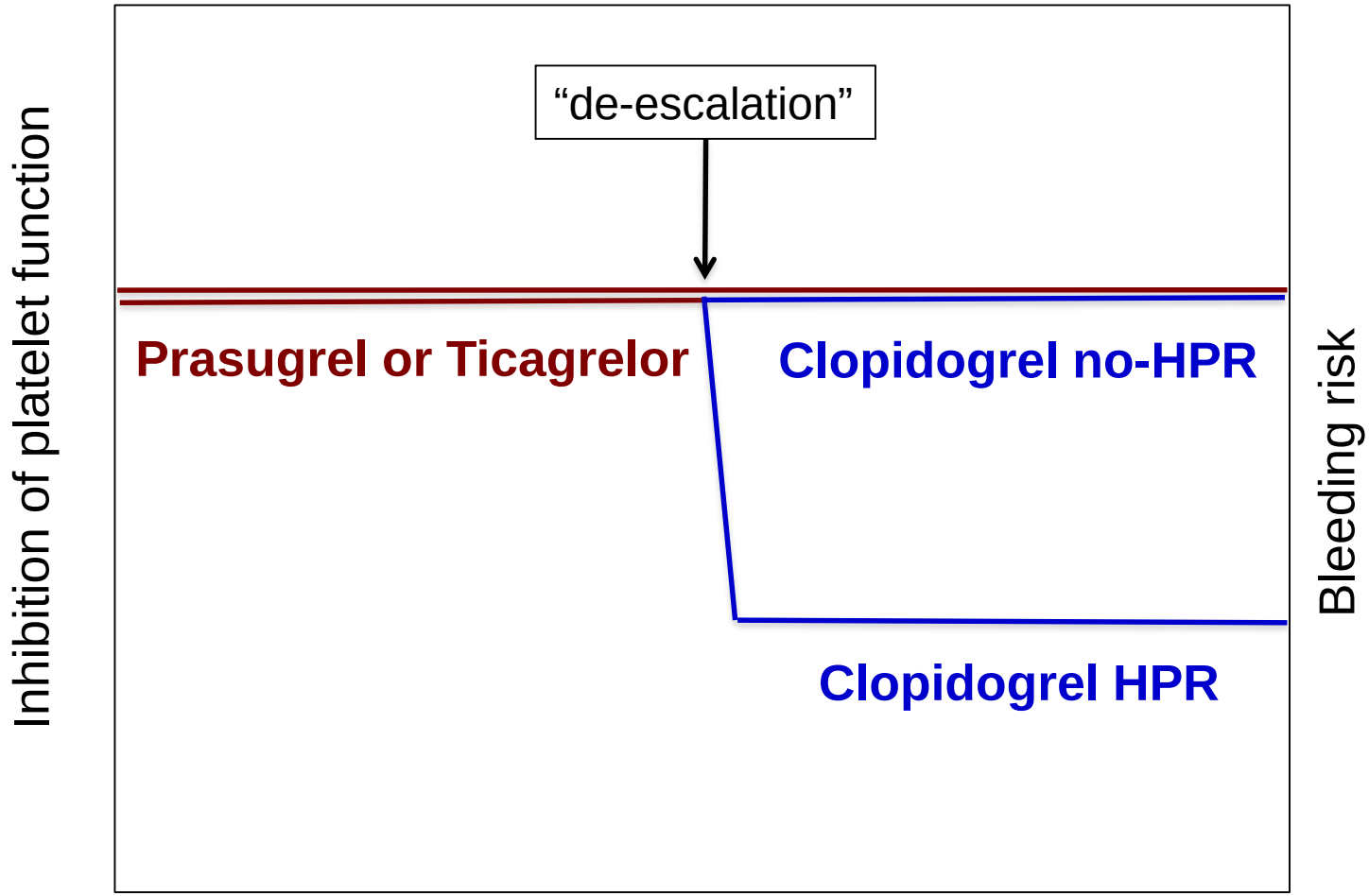
... Together, our trial provides important evidence for patients with acute coronary syndrome after successful PCI in whom early de-escalation is considered as an alternative strategy."

Sibbing et al, Lancet 2018

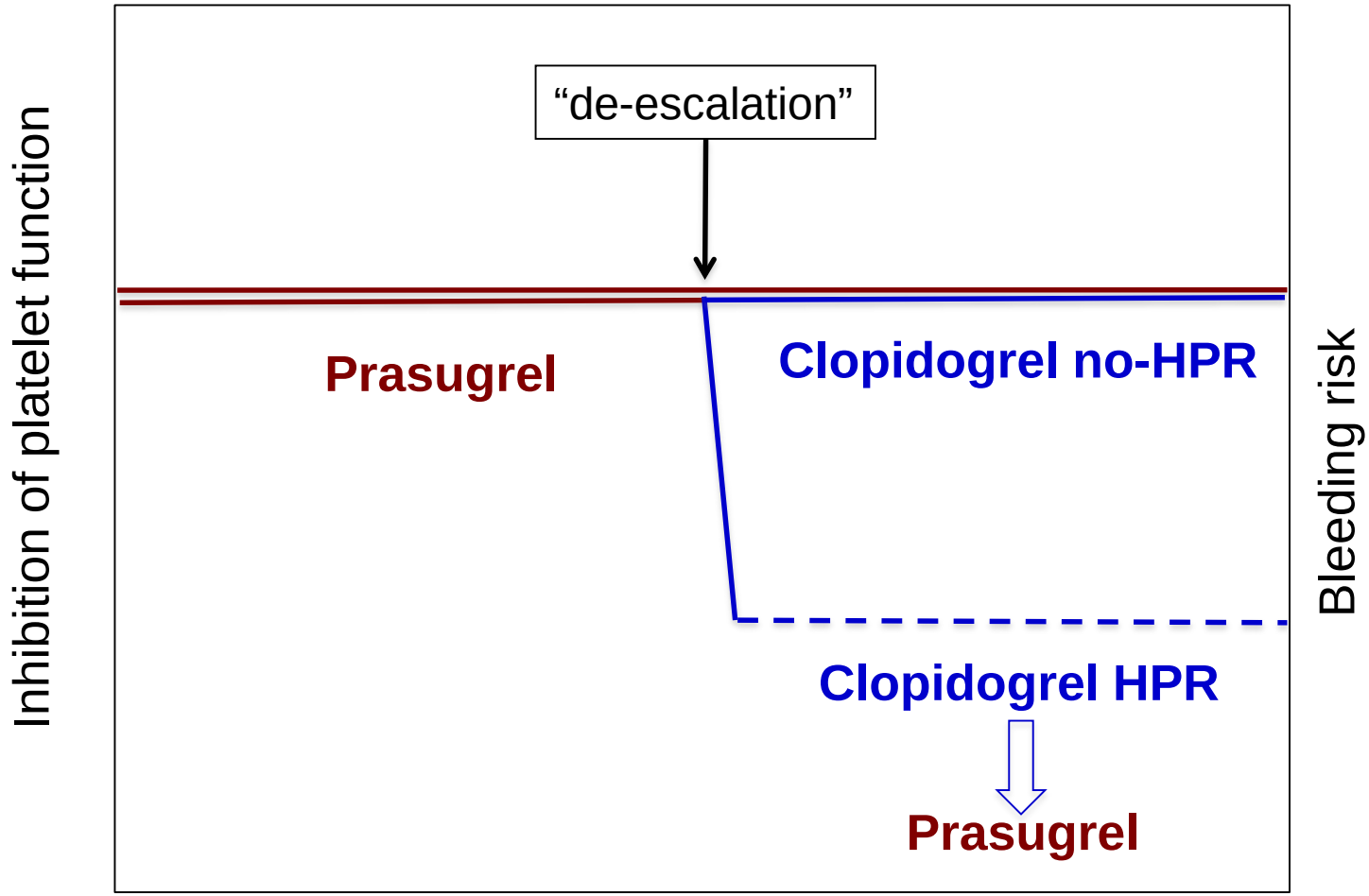
TOPIC


Inhibition of platelet function
“de-escalation”
Prasugrel or Ticagrelor
Clopidogrel
Bleeding risk

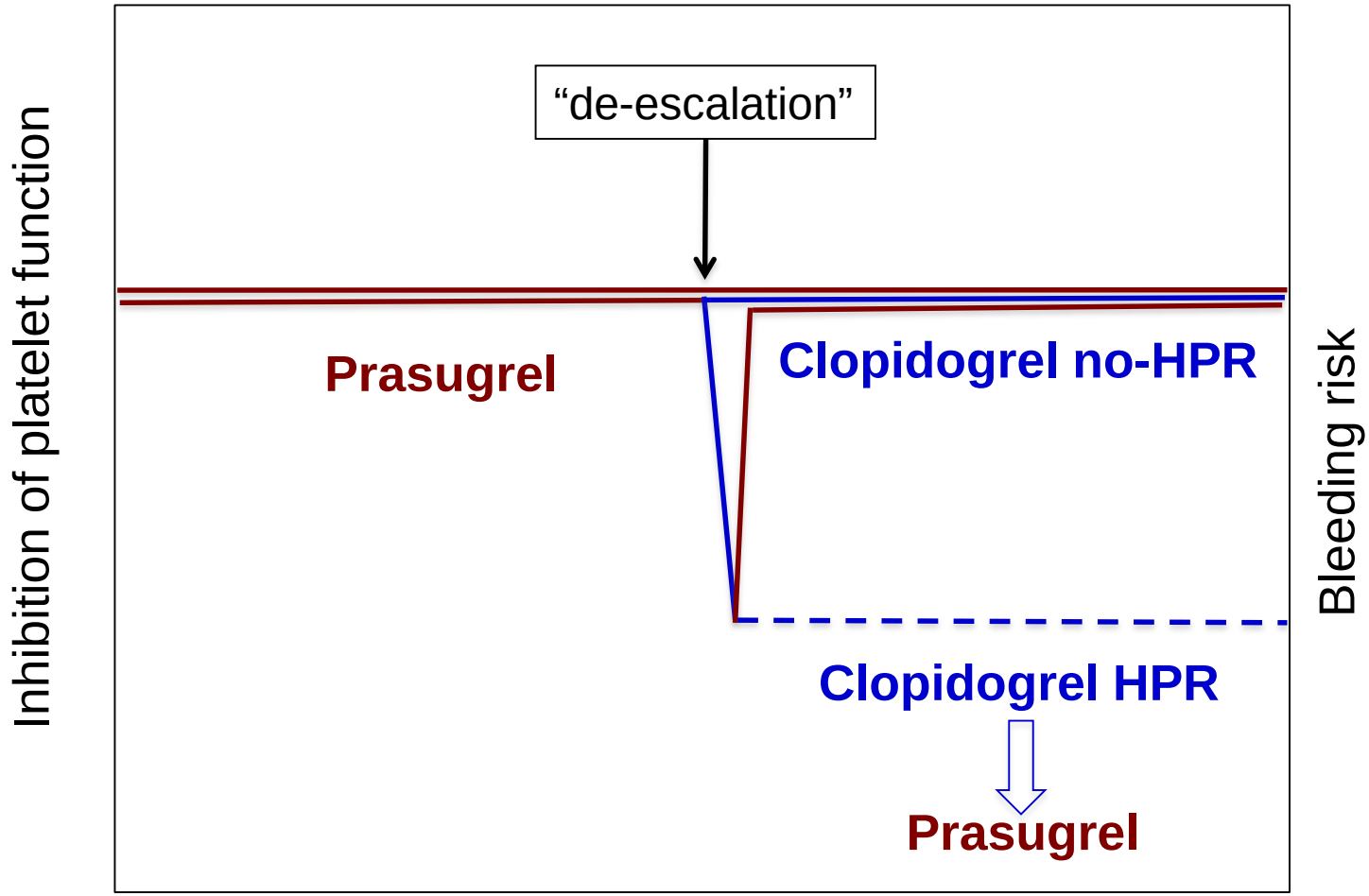
TOPIC


“de-escalation”
Prasugrel or Ticagrelor
Clopidogrel no-HPR
Clopidogrel HPR
Inhibition of platelet function
Bleeding risk

TROPICAL-ACS



TROPICAL-ACS



Conclusioni
TOPIC + TROPICAL ACS

- La riduzione dell'intensità di terapia antiaggregante in pazienti che possono beneficiarne (basso rischio CV e/o elevato rischio emorragico) dovrebbe essere impostata senza monitoraggio di laboratorio, come nello studio TOPIC
- DAPT con prasugrel o ticagrelor dovrebbe essere mantenuta senza monitoraggio di laboratorio nei pazienti che possono beneficiarne (elevato rischio CV e/o basso rischio emorragico)

Principali variabili che condizionano la risposta farmacodinamica al clopidogrel

- Scarsa aderenza /sottodosaggio
- Mutazioni di isoforme del CYP
- Ridotto assorbimento (es., portatori della mutazione TT3435 di ABCB1, codificante per P-glicoproteina)
- InteractioInterazione con altri farmaci (PPI, statine, calcio antagonisti)
- Aumentato turnover piastrinico
- Età
- Elevato BMI
- Diabete mellito
- Variabilità di risposta a ADP
- **--- ---**

Table 2 Multivariable Linear Regression Model for RPA After Stimulation With 5 μmol/l ADP

	Partial η^2	p Value
*CYP2C19** polymorphism	0.052	<0.001
Age (yrs)	0.010	0.006
Arterial hypertension	0.001	0.386
Diabetes mellitus	0.012	0.003
Body mass index (kg/m^2)	0.010	0.008
Platelets (× 10^9/l)	0.010	0.006
ACE inhibitors	0.001	0.403
Nitrates	<0.001	0.890
Verapamil/diltiazem	0.010	0.006
Previous balloon angioplasty	0.007	0.026
Previous CABG	0.001	0.435
Impaired LV function†	<0.001	0.945
CCS angina class III or IV	0.004	0.081

*Cytochrome P450 2C19 681G>A; †impaired LV function (ejection fraction <55%).
ADP = adenosine diphosphate; RPA = residual platelet aggregation; other abbreviations as in Table 1.

Hochholzer et al, JACC 2010

Table 2 Multivariable Linear Regression Model for RPA After Stimulation With 5 μmol/l ADP

	Partial η^2	p Value
*CYP2C19** polymorphism	0.052	<0.001
Age (yrs)	0.010	0.006
Arterial hypertension	0.001	0.386
Di		.003
Bo		.008
Pl		.006
AC		.403
Nit		.890
Verapamil/diltiazem	0.010	0.006
Previous balloon angioplasty	0.007	0.026
Previous CABG	0.001	0.435
Impaired LV function†	<0.001	0.945
CCS angina class III or IV	0.004	0.081

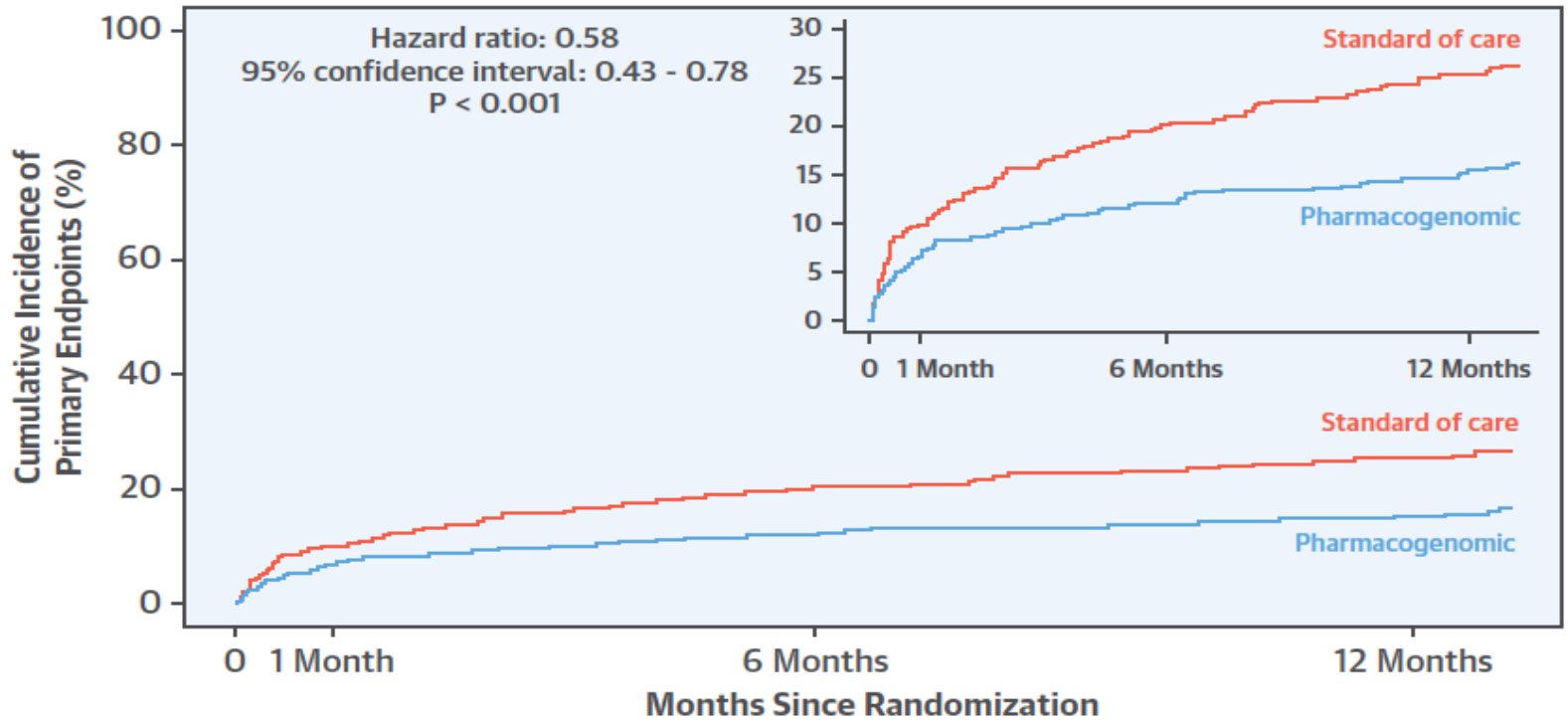
La presenza di CYP2C19*2 in combinazione con le variabili cliniche rilevanti rende conto del 11,5% della variabilità di risposta al clopidogrel

*Cytochrome P450 2C19 681G>A; †impaired LV function (ejection fraction <55%).
ADP = adenosine diphosphate; RPA = residual platelet aggregation; other abbreviations as in Table 1.

Hochholzer et al, JACC 2010

Approccio farmacogenomico alla scelta delle terapia antiaggregante: incidenza di end point primario a 12 mesi

CENTRAL ILLUSTRATION **Pharmacogenomic Approach to the Selection of Antiplatelet Therapy: Primary Composite Endpoint After 12 Months**



No. at risk				
Pharmacogenomic arm	448	416	390	295
Standard-of-care arm	440	397	349	280

Notarangelo, F.M. et al. J Am Coll Cardiol. 2018;71(17):1869-77.

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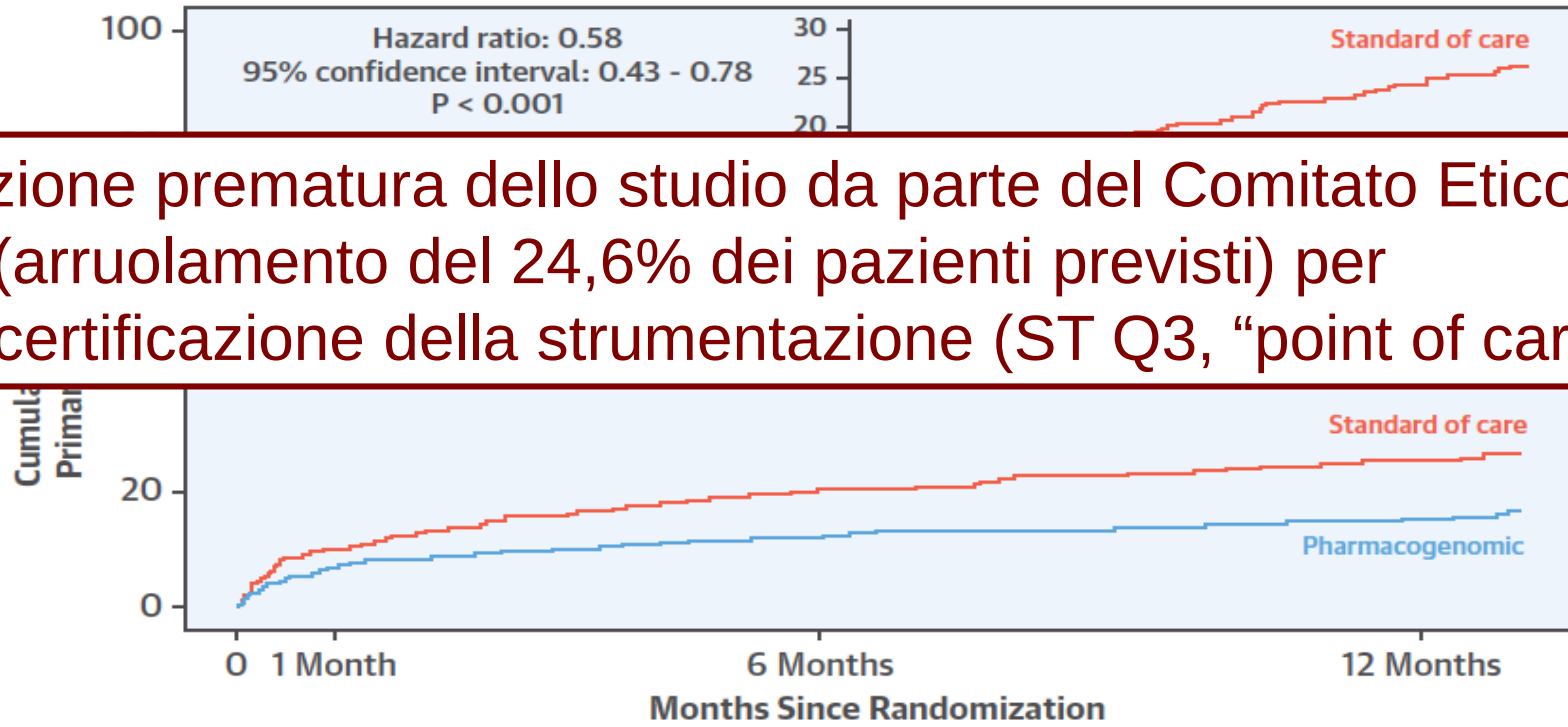

Interruzione prematura dello studio da parte del Comitato Etico (arruolamento del 24,6% dei pazienti previsti) per mancata certificazione della strumentazione (ST Q3, “point of care”)

No. at risk				
Pharmacogenomic arm	448	416	390	295
Standard-of-care arm	440	397	349	280

Notarangelo, F.M. et al. J Am Coll Cardiol. 2018;71(17):1869-77.


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