Platelet Reactivity Testing to Guide P2Y12 Inhibitor De-Escalation After Acute Coronary Syndrome

The EPIC17-VERONICA Randomized Clinical Trial

***VER**ifynow to **O**ptimise platelet i**N**h**I**bition in **C**oronary **A**cute syndromes*

Iñigo Lozano, MD, PhD, on behalf of the EPIC17-VERONICA investigators

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Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Grant/Research Support	Abbott, BBraun, Biotronik, Terumo
Consultant Fees/Honoraria	Medtronic, Boston Scientific

All Relevant Financial Relationships have been mitigated.
Faculty disclosure information can be found on the app

Background

Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study

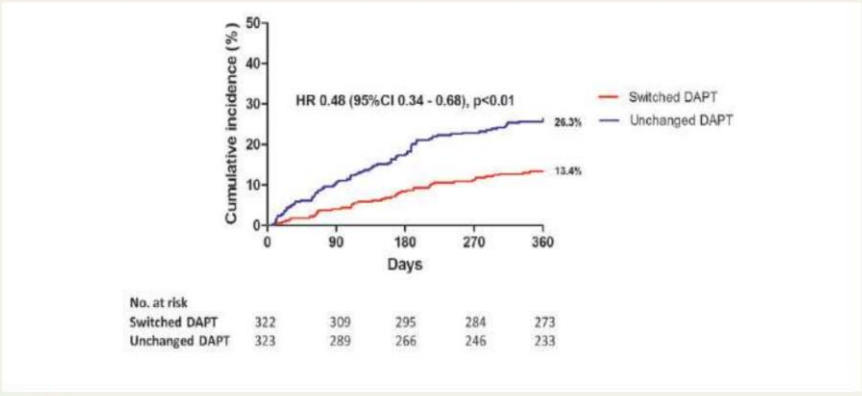
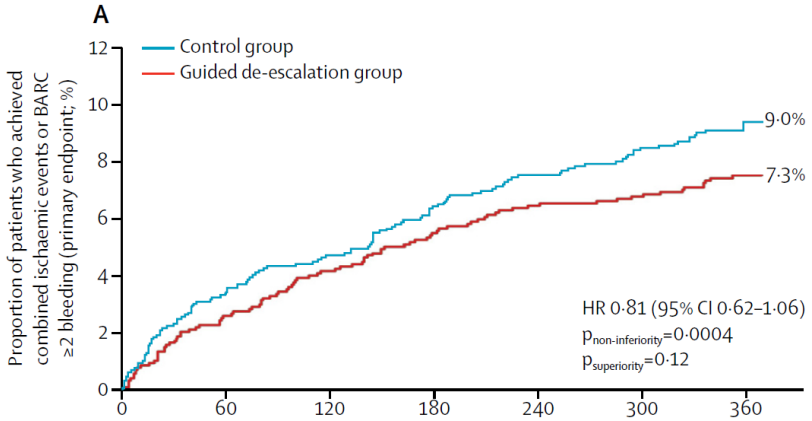


Figure 2 Incidence of the primary endpoint (net clinical benefit) at 1 year. HR, Hazard ratio.

Eur Heart J. 2017;38(41):3070-8

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



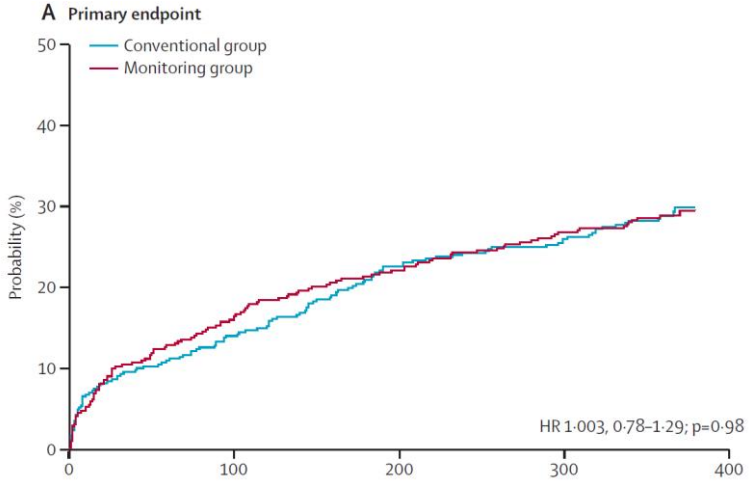
***Lancet* 2017; 390: 1747–57**

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Key question: *can PFT prospectively help to tailor the best approach?*

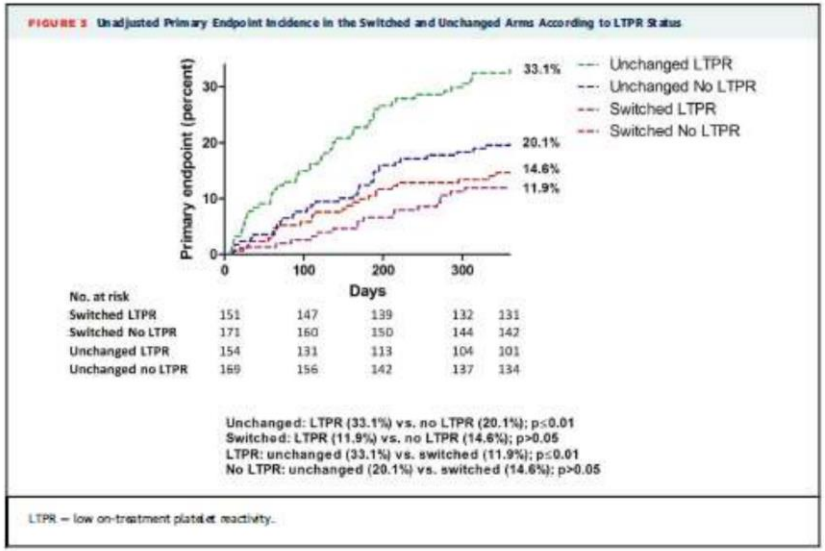
Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial



***Lancet* 2016; 388: 2015–22**

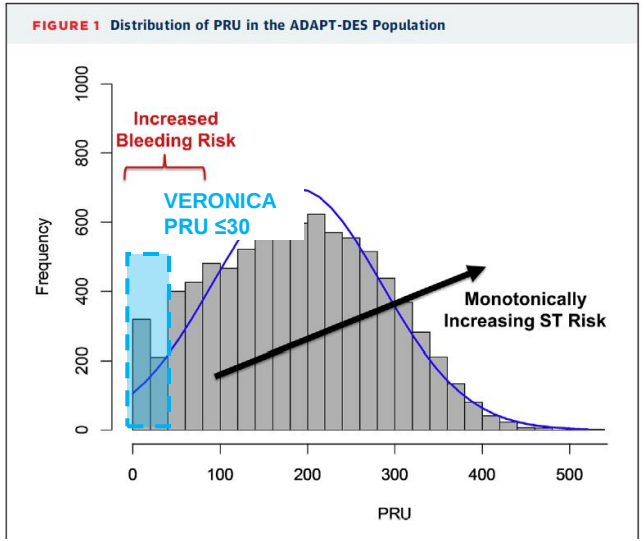
Benefit of Switching Dual Antiplatelet Therapy After Acute Coronary Syndrome According to On-Treatment Platelet Reactivity

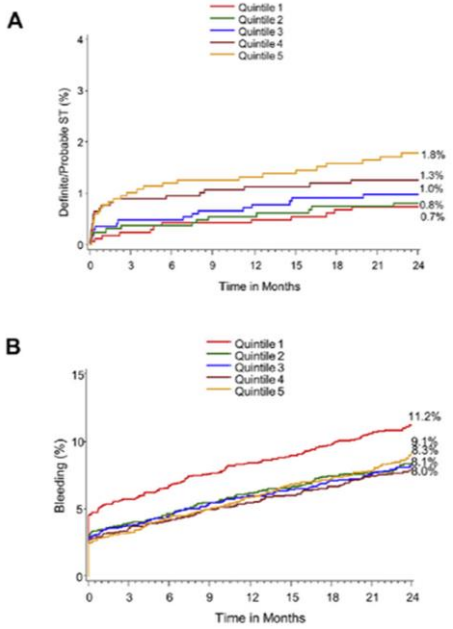
The TOPIC-VASP Pre-Specified Analysis of the TOPIC Randomized Study



JACC Cardiovasc Interv. 2017;10(24):2560-70

Background: the low-PRU evidence gap





High PRU: well characterised

Stent thrombosis risk rises steadily with platelet reactivity on clopidogrel

Low PRU: much less evidence

Linked to bleeding, but no randomised data on how to manage these patients

VERONICA randomised only patients with PRU ≤30 to continue potent P2Y12 inhibition or de-escalate to clopidogrel

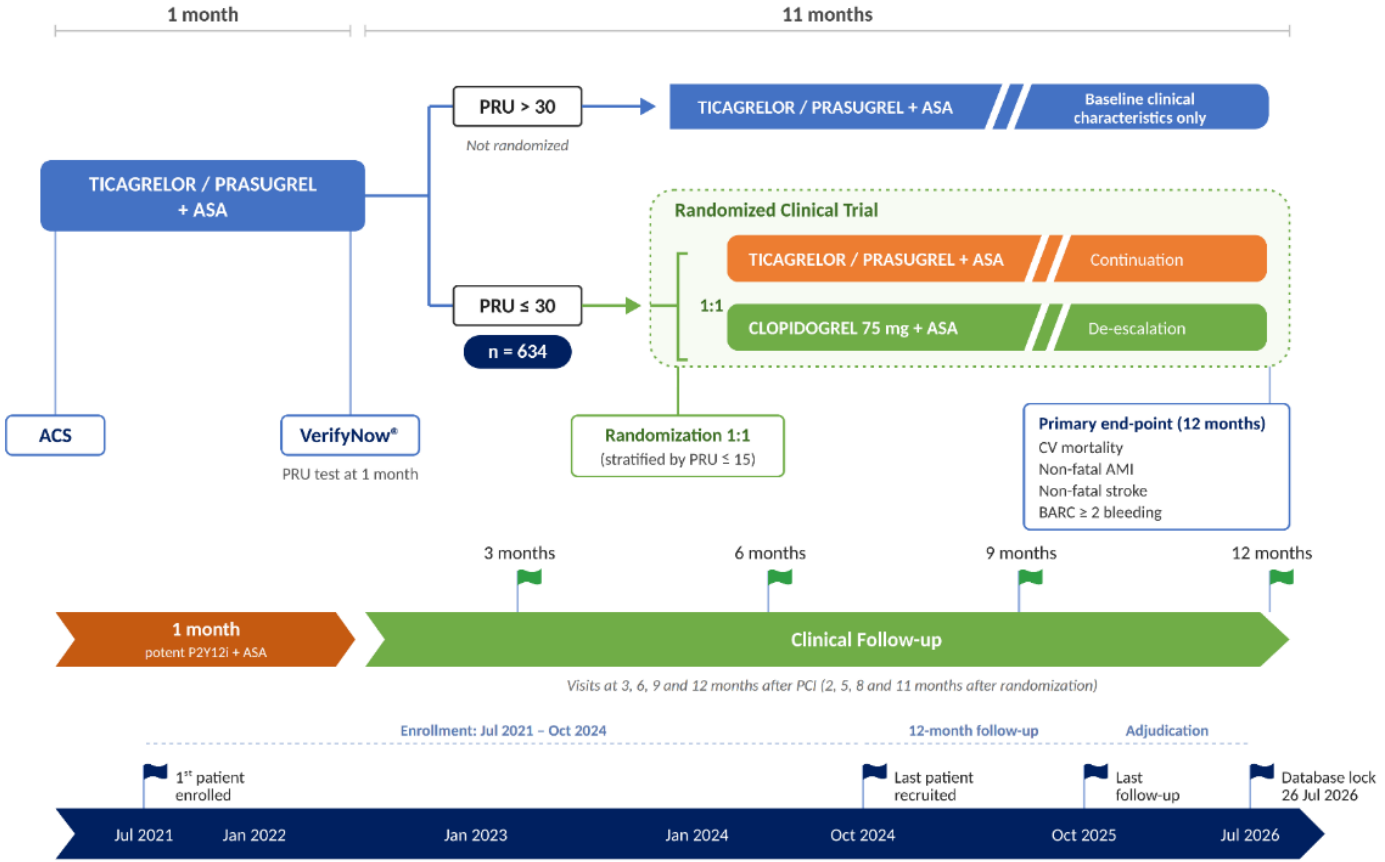
PRU = P2Y12 reaction units; ST = stent thrombosis. Source: ADAPT-DES (Kirtane AJ et al. J Am Coll Cardiol Intv 2015;8:1978–87), Figures 1–2.

Aims and design

***Key question:** can PFT prospectively select de-escalation candidates?*

- **Aim:** Evaluate the benefit of de-escalation to clopidogrel in ACS patients with low platelet reactivity (VerifyNow, Werfen).
- **Design:** Multicenter, randomized, open-label superiority trial, 16 sites in Spain.
- **Population:** ACS + bioresorbable-polymer SES, on ASA + prasugrel 10 mg /ticagrelor q.d 180 mg bid.
- **Primary end point:** NACE (CV death, nonfatal MI, nonfatal stroke, BARC ≥ 2).
- **Secondary end point:** Individual components plus total death, definite stent thrombosis and unplanned revascularization.
- **Eligibility:** VerifyNow P2Y12 assay, 30–40 days post-PCI, randomized 1:1 those with PRU≤ 30.
- **Intervention:** De-escalate to clopidogrel vs. continue potent P2Y12 inhibitor (control).

Roadmap

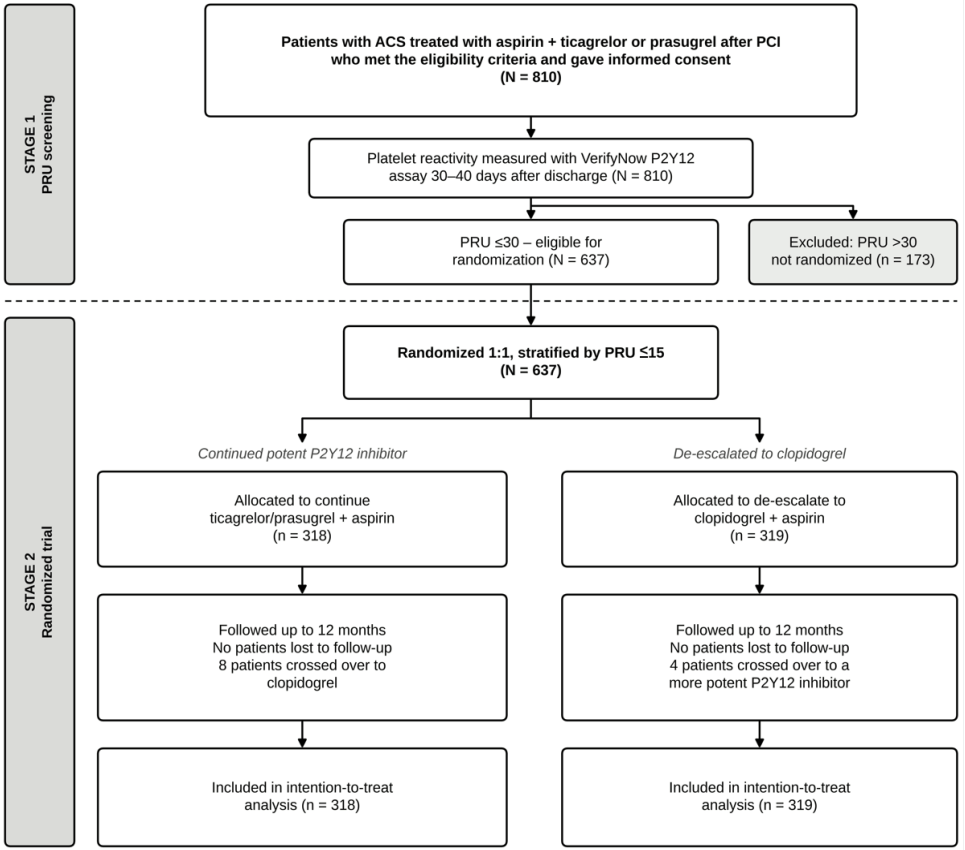

1 month
11 months
PRU > 30
Not randomized
TICAGRELOR / PRASUGREL + ASA
Baseline clinical characteristics only
TICAGRELOR / PRASUGREL + ASA
Randomized Clinical Trial
TICAGRELOR / PRASUGREL + ASA
Continuation
1:1
CLOPIDOGREL 75 mg + ASA
De-escalation
PRU ≤ 30
n = 634
ACS
VerifyNow®
PRU test at 1 month
Randomization 1:1
(stratified by PRU ≤ 15)
Primary end-point (12 months)
CV mortality
Non-fatal AMI
Non-fatal stroke
BARC ≥ 2 bleeding
3 months
6 months
9 months
12 months
1 month
potent P2Y12i + ASA
Clinical Follow-up
Visits at 3, 6, 9 and 12 months after PCI (2, 5, 8 and 11 months after randomization)
Enrollment: Jul 2021 – Oct 2024
12-month follow-up
Adjudication
1st patient enrolled
Last patient recruited
Last follow-up
Database lock 26 Jul 2026
Jul 2021
Jan 2022
Jan 2023
Jan 2024
Oct 2024
Oct 2025
Jul 2026

Statistics

- **Aim of the study:** Built on TOPIC-VASP (33.1 % vs 11.9 %)
- **More conservative approach:** 22 % vs. 14 %
- **Sample size:** 634 patients (317/arm) for 80% power* (real 75 %)
- **Intention-to-treat**; two-sided P < .05
- **Cumulative incidence:** Kaplan-Meier or Gray's test (when competing events)
- **Treatment effect:** Cox model, Fine-Gray model (competing events)
- **Stratified by PRU ≤15** (one model, separate baseline hazard functions)
- **Missing data**: Multiple imputation by chained equations
- **Sensitivity:** Cross-over, bleeding BARC ≥ 3

Patient Flow

- **810 patients** tested with VerifyNow
- **637 (78.6 %)** PRU ≤30 → randomized 1:1
- **318** continued potent P2Y12 inhibitor; **319** de-escalated to clopidogrel
- **Follow-up:** complete to 11 months; no patients lost
- **Crossover:** 12 patients, 8 to clopidogrel, 4 to prasugrel/ticagrelor



Baseline Characteristics

CHARACTERISTIC	Ticagrelor/Prasugrel (n = 318)	Clopidogrel (n = 319)
Age, mean (SD), y	60.5 (9.5)	61.3 (9.8)
Female sex, n (%)	55 (17.3)	63 (19.7)
Diabetes mellitus, n (%)	70 (22.0)	59 (18.5)
Prior myocardial infarction, n (%)	30 (9.4)	33 (10.3)
Type of ACS, n (%)		
Unstable angina	30 (9.5)	33 (10.3)
NSTEMI	132 (41.6)	139 (43.6)
STEMI	155 (48.9)	147 (46.1)
eGFR (CKD-EPI) <60 mL/min/1.73 m², n (%)	20 (6.4)	31 (9.7)
BMI, mean (SD), kg/m²	28.1 (4.2)	27.3 (4.0)
P2Y12 inhibitor at discharge, n (%)		
Prasugrel	76 (23.9)	80 (25.1)
Ticagrelor	241 (75.8)	239 (74.9)
No. of lesions treated, mean (SD)	1.36 (0.70)	1.46 (0.81)
ACE inhibitor/ARB, n (%)	230 (76.4)	196 (65.1)
No. of vessels treated, mean (SD)	1.24 (0.50)	1.29 (0.57)
Treated vessel, n (%)		
Left main	5 (1.6)	8 (2.5)
Left anterior descending	183 (57.7)	172 (53.9)
Circumflex	87 (27.5)	100 (31.3)
Right coronary artery	120 (37.9)	130 (40.8)
PRU, median (IQR)	4 (2–7)	4 (2–6)

Results: Primary and secondary

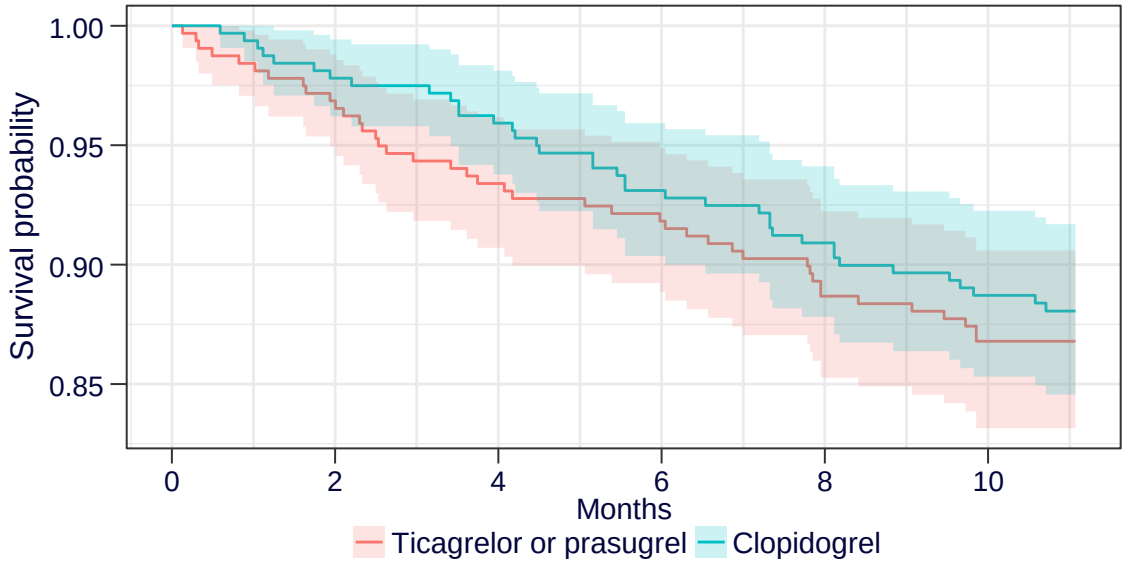
OUTCOME, n (%)	Ticagrelor/ Prasugrel (n = 318)	Clopidogrel (n = 319)	HR (95% CI); p-value[1]
Primary endpoint (NACE)	**42 (13.2)**	**38 (11.9)**	**0.88 (0.57 to 1.37); 0.737**
Cardiovascular death	0 (0.0)	3 (0.9)	—
Myocardial infarction	4 (1.3)	9 (2.8)	2.38 (0.73 to 7.78); 0.453[1]
Stroke	2 (0.6)	2 (0.6)	—
Bleeding, BARC ≥ 2	38 (11.9)	28 (8.8)	0.76 (0.46 to 1.24); 0.527[1]
Unplanned revascularization	6 (1.9)	13 (4.1)	2.88 (1.03 to 8.06); 0.173[1]

[1] Holm-adjusted p-values in the secondary outcomes

No cases of definite stent thrombosis occurred in either group
One non-cardiac death (pancreatic cancer, control group)

Results: Primary Endpoint (NACE)

HR 0.88 (0.57 to 1.37); p =0.737

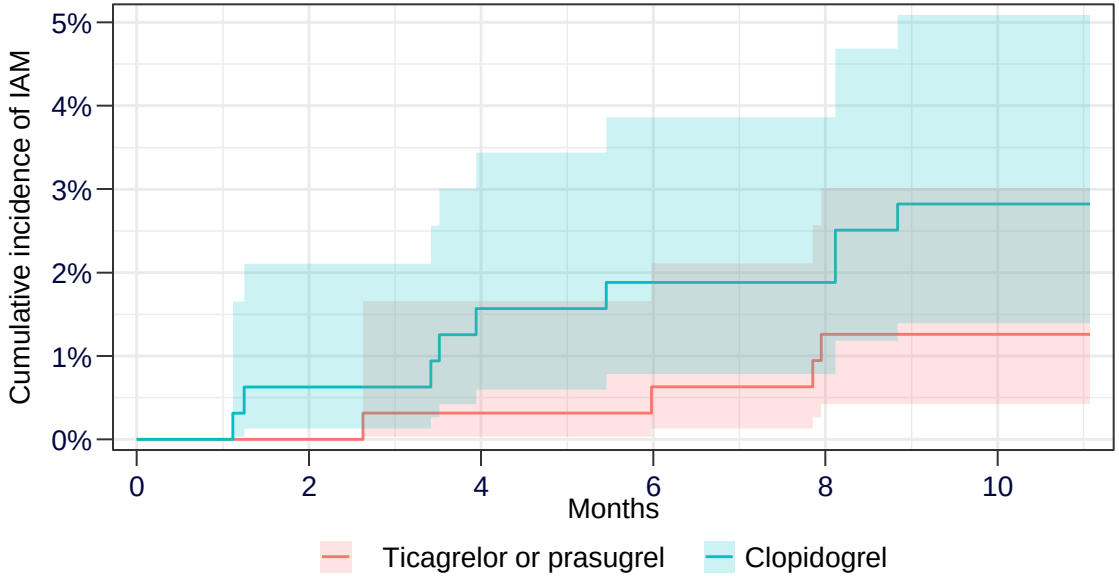


Ticagrelor or prasugrel												
At Risk	318	313	308	300	297	295	292	287	282	281	276	18
Events	0	5	10	18	21	23	26	31	36	37	42	42
Clopidogrel												
At Risk	319	317	312	311	306	302	297	295	290	286	283	26
Events	0	2	7	8	13	17	22	24	29	33	36	38

Results: Myocardial infarction

HR 2.38 (0.73 to 7.78); p[1] = 0.453

[1] Holm-adjusted p-value

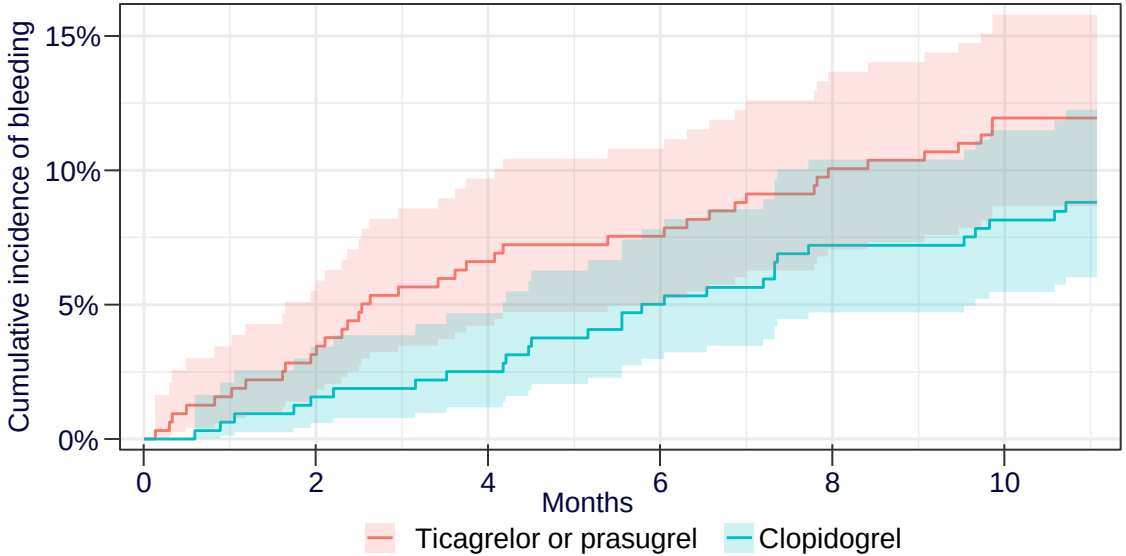


Ticagrelor or prasugrel						
At Risk	318	318	317	315	313	312
Events	0	0	1	2	4	4
Clopidogrel						
At Risk	319	317	314	313	313	309
Events	0	2	5	6	6	9

Results: Bleeding BARC ≥ 2

HR= 0.76 (0.46 to 1.24); p[1] = 0.527

[1] Holm-adjusted p-value

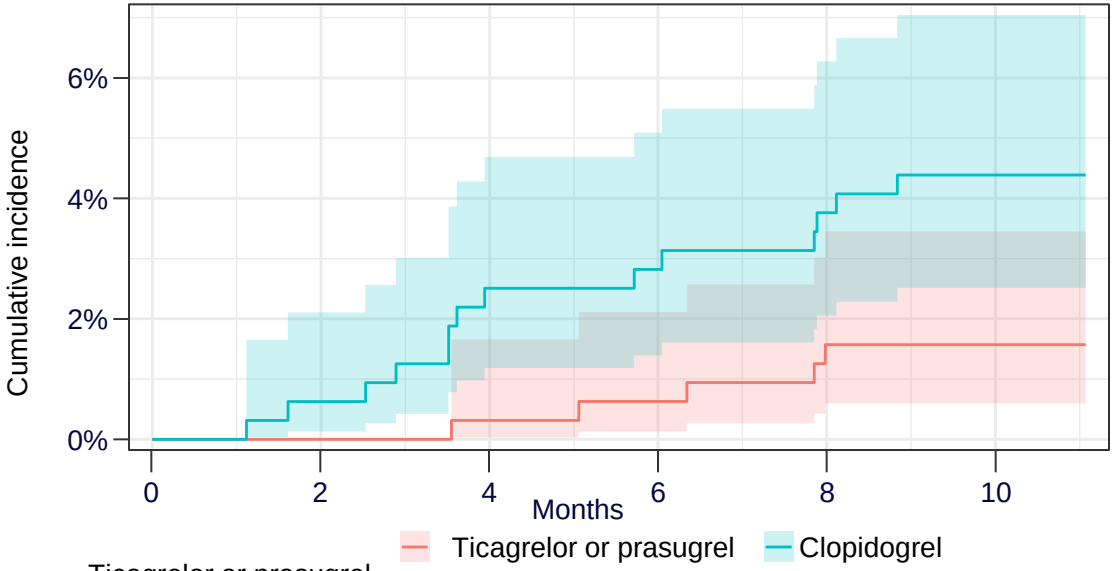


Ticagrelor or prasugrel						
At Risk	318	308	297	294	286	280
Events	0	10	21	24	32	38
Clopidogrel						
At Risk	319	313	310	301	294	291
Events	0	5	8	16	23	26

Results: Unplanned revascularization

HR= 2.88 (1.03 to 8.06); p[1] = 0.173

[1] Holm-adjusted p-value



Ticagrelor or prasugrel						
At Risk	318	318	317	315	312	311
Events	0	0	1	2	5	5
Clopidogrel						
At Risk	319	317	311	310	307	304
Events	0	2	8	9	12	14

Results: MI and Revascularization

Myocardial infarction	Ticagrelor/ Prasugrel (n = 318)	Clopidogrel (n = 319)
Patients, n (%)	4 (1.3)	9 (2.8)
HR 2.38 (95%CI 0.73 to 7.78); adjusted p[1]: 0.453		
Type (Fourth Universal Definition)		
Type 1	3	5
Type 4c	1	4

Unplanned revascularization	Ticagrelor/ Prasugrel (n = 318)	Clopidogrel (n = 319)
Patients, n (%)	6 (1.9)	13 (4.1)
HR 2.88 (95%CI 1.03 to 8.06); adjusted p[1]: 0.173		
Procedures, both groups (n = 19)		
PCI / CABG	17 / 2	
Different lesion	13	
Restenosis	6 (5 with NSTEMI)	

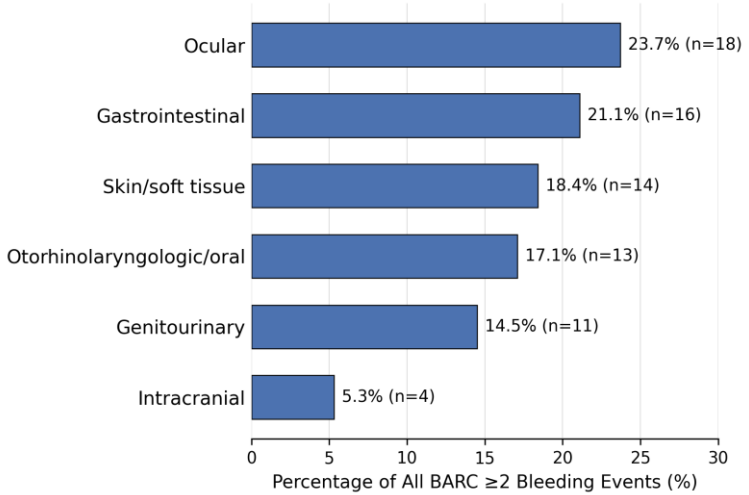
Intention-to-treat analysis. No definite stent thrombosis in either group.
[1] Holm-adjusted p-values

Results: Bleeding Outcomes

Bleeding, No. (%)	Ticagrelor/ Prasugrel (n = 318)	Clopidogrel (n = 319)
Patients, BARC ≥ 2	**38 (11.9)**	**28 (8.8)**
HR 0.76 (95% CI 0.46 to 1.24); adjusted p[1]: 0.527		
Type of bleeding (events)[a]		
BARC 2	35 (83.3)	27 (79.4)
BARC 3a	2 (4.8)	2 (5.9)
BARC 3b	3 (7.1)	2 (5.9)
BARC 3c	2 (4.8)	3 (8.8)
Total bleeding events	**42**	**34**

[a] Percentages of all BARC ≥2 events per group; some patients had >1 event.
Distribution of bleeding severity, P = .90 (χ^2).
ITT
[1] Holm-adjusted p-values

Anatomical site, all BARC ≥2 events (n = 76)



Limitations

- **Limitation of power:** Design and lower rate of events than anticipated.
- **Low risk population.**
- **Election of cut-off point of PRU ≤ 30:** Set by the research team.
- **Extrapolation of data from TOPIC-VASP,** with different method than VerifyNow.

Conclusions

- **First trial** to select candidates by confirmed very low platelet reactivity (PRU ≤30).
- **Neutral result:** No evidence that guided de-escalation reduces NACE.
- **Bleeding prediction:** Bleeding risk is multifactorial and cannot be predicted by platelet reactivity testing alone.
- **Take-home:** cannot recommend **routine** PFT-guided de-escalation over standard therapy in patients with low platelet reactivity.