Guided de-escalation of antiplatelet treatment in ACS patients undergoing PCI

TROPICAL ACS

Results of the TROPICAL-ACS study: a randomised, investigator-initiated, open-label, multicentre-trial

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Munich Heart Alliance

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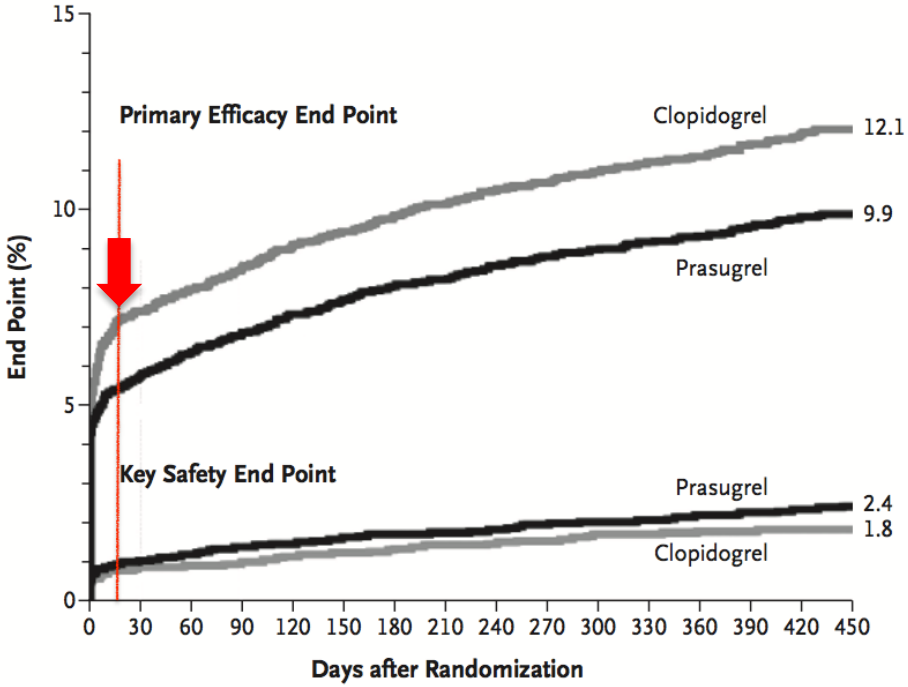
Background I – Platelet inhibition in ACS patients

- Current guidelines[1] recommend **uniform & potent platelet inhibition** with prasugrel or ticagrelor for 12 months after PCI for ACS
- However, **risk patterns** (early vs. late risk) for ischeamic and bleeding complications **differ over time**[2,3]

A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A	137, 148, 153
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B	153
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B	148, 164
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B	137

[1]Roffi et al., ESC ACS Guidelines, EHJ 2016, [2]Antman et al., JACC 2008; [3]Becker et al., EHJ 2011

Background II – Early anti-ischaemic benefit of potent inhibition



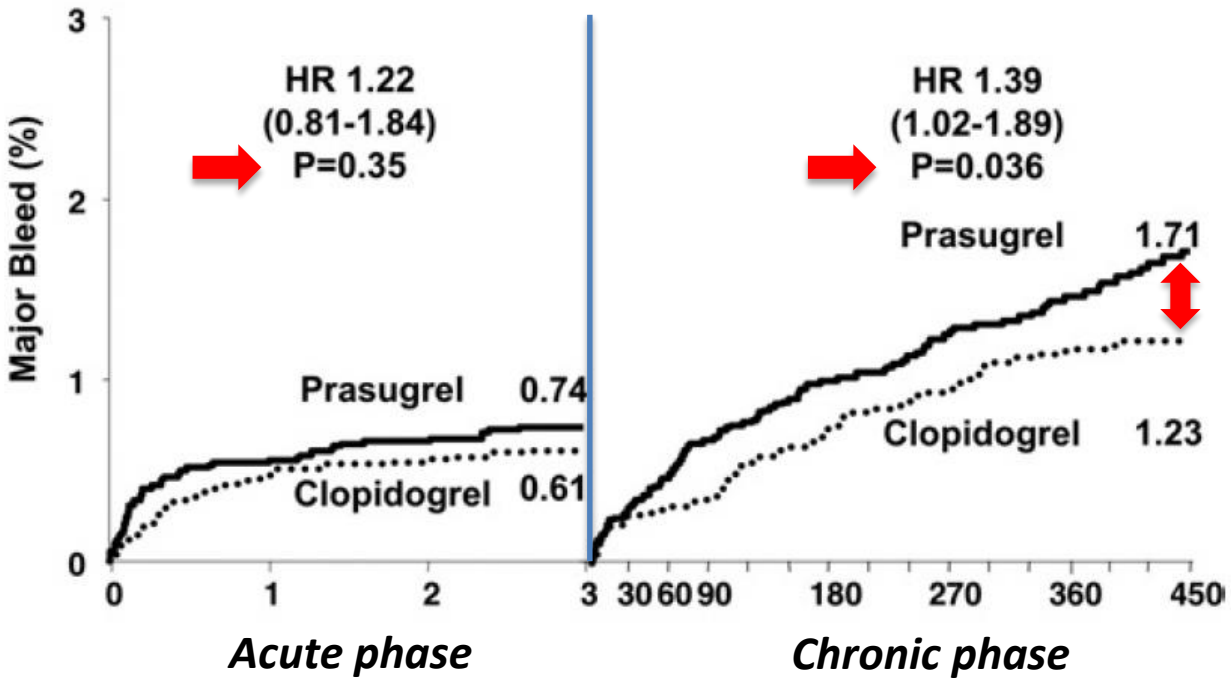
↓ 138 Events
Hazard ratio, 0.81;
95% CI, 0.73–0.90;
P<0.001

TRITON TIMI-38

↑ 35 Events
Hazard ratio, 1.32;
95% CI, 1.03–1.68;
P=0.03

Wiviott et al., NEJM 2007

Background III – Late excess & growing bleeding risk over time



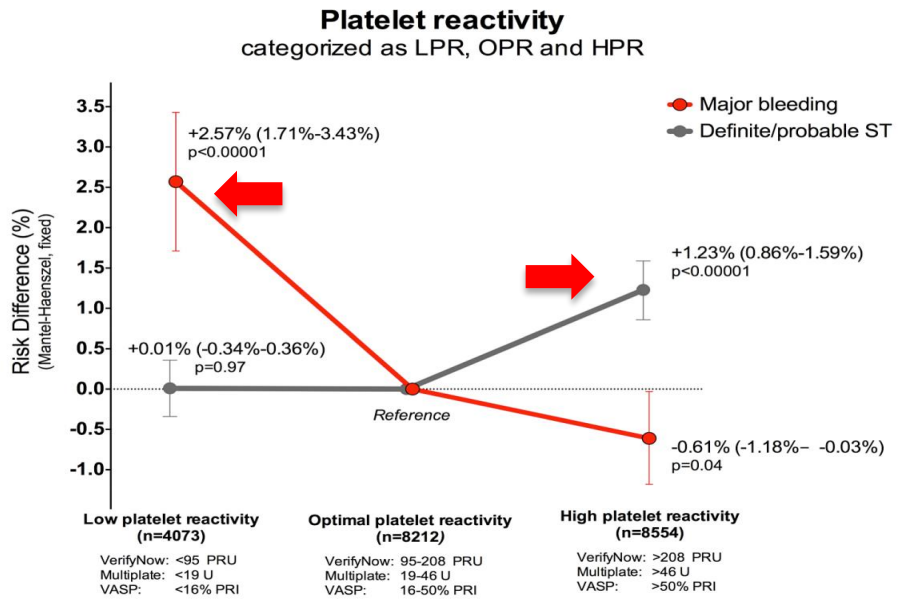
Antman et al., JACC 2008

Background IV – Concept of de-escalation

- Conceptually, a stage-adapted treatment with **de-escalation from potent drugs to the less potent clopidogrel** early after an ACS may be beneficial.
- To date, **solid evidence showing safety of de-escalation** is lacking.
- Despite of this, **DAPT de-escalation is commonly done** for clinical (e.g. bleeding, side-effects) and economic (generic clopidogrel) reasons (TRANSLATE-ACS[1]).
- A potential obstacle for de-escalation could be **clopidogrel´s large response variability**[2] - any de-escalation regimen should account for this issue

[1]Zettler et al., AHJ 2017, [2]Gurbel et al., Circulation 2003

Background V – Levels of platelet inhibition & outcomes



Collaborative meta analysis:

- 17 studies
- 20,839 patients

- **Platelet function testing (PFT)** could serve to make **de-escalation safer** by identifying low responders to clopidogrel.

Aradi, …, Sibbing, EHJ 2015

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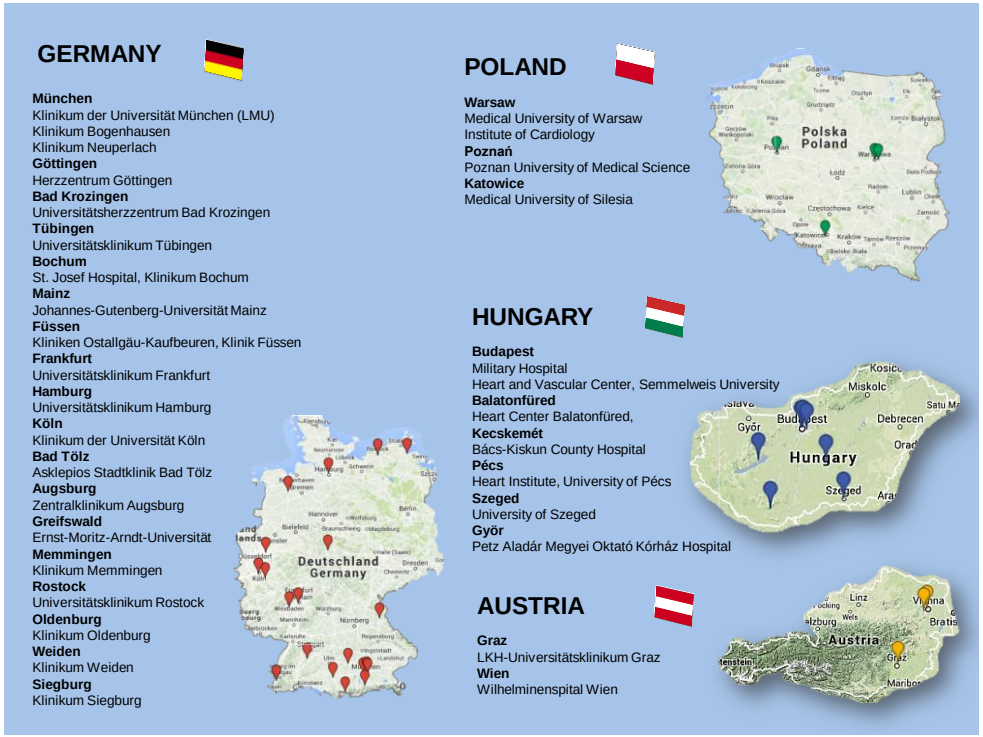
Trial Objective

In the **TROPICAL-ACS*** trial we aimed to investigate the **safety** and **efficacy** of **early de-escalation** of antiplatelet treatment from prasugrel to clopidogrel **guided** by platelet function testing (PFT).

** TROPICAL-ACS: **T**esting **R**esponsiveness T**o** **P**latelet **I**nhibition On **C**hronic **A**ntiplatel**e**t Treatment For **A**cute **C**oronary **S**yndromes*

Trial Conduct (33 study sites in Europe)



Academic Sponsor
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Study Monitoring and Data Management
Monitoring: Münchner Studienzentrum (MSZ)
Data Management: Technische Universität Dresden (KKS)

Data Safety and Monitoring Board (DSMB)
Albert Schömig, Helmut Schühlen, Martin Hadamitzky

Independent Event Adjudication Committee (EAC)
Dritan Poci, Jürgen Pache, Ute Wilbert Lampen

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Inclusion Criteria

- Biomarker positive ACS
- Successful PCI
- Planned DAPT for 12 months after PCI
- Written informed consent

Key Exclusion Criteria

- Age <18 years and >80 years
- Contraindications to study drugs
- Active bleeding
- History of TIA or stroke
- Concomitant treatment with anticoagulants (e.g. VKA, NOACS)
- Indication for major surgery

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Primary study endpoint

Composite endpoint consisting of

- Death from cardiovasular cause
- Myocardial infarction
- Stroke
- Bleeding events grade 2 or above (BARC criteria)

„Net-clinical benefit“:
assessed for non-inferiority
@ 1 year follow-up

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Secondary study endpoints

- **Bleeding events 2 or above according to BARC criteria**
  - = key secondary EP: assessed for superiority
- Death from any cause
- Stent thrombosis according to ARC criteria
- Ischemic components (combined & singular) of the primary endpoint
- Urgent revascularization

@ 1 year follow-up

Trial Design

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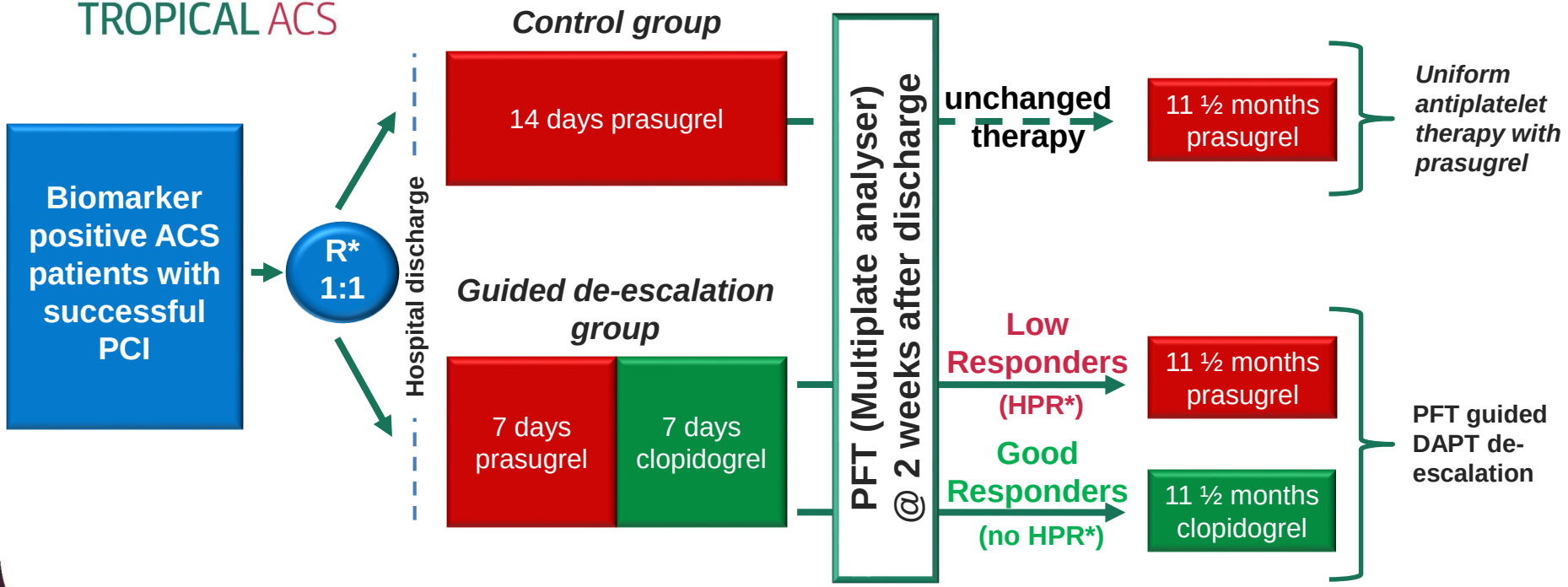

*HPR denotes high platelet reactivity

- For further details on TROPICAL-ACS trial design see: Sibbing et al., Thromb Haemost. 2017;117:188-195 -

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Sample size calculation

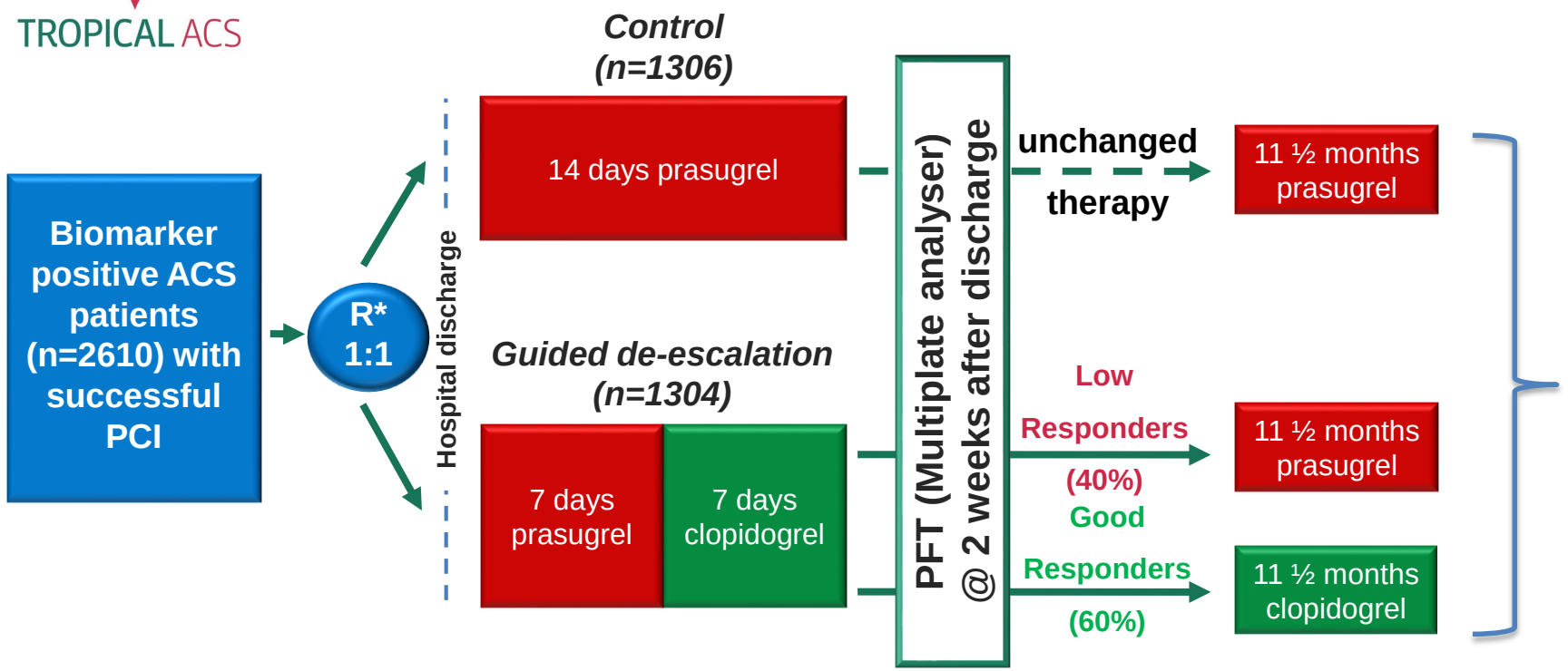
Primary hypothesis:

Non-inferiority of PFT-guided de-escalation vs. standard 1-year prasugrel treatment

Statistical assumptions:

- Incidence for the primary endpoint @ 1 year follow-up: 10.5%
- Non-inferiority margin of 30%
- Power: 80%, alpha-level: 5%
- Sample size: 1197 patients per group
- 1300 planned to compensate for losses to follow-up

Study patients & follow-up data



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Baseline Characteristics

	Control group (n = 1306)	Guided de-escalation group (n = 1304)
Age, years	59 (SD 10)	59 (SD 10)
Female sex	283 (22%)	275 (21%)
Previous PCI	186 (14%)	173 (13%)
Previous CABG	46 (4%)	39 (3%)
Previous MI	153 (12%)	140 (11%)
Diabetes mellitus	287 (22%)	240 (18%)
Current smoker	591 (45%)	591 (45%)
Arterial hypertension	806 (62%)	793 (61%)
Hyperlipidaemia	529 (41%)	546 (42%)

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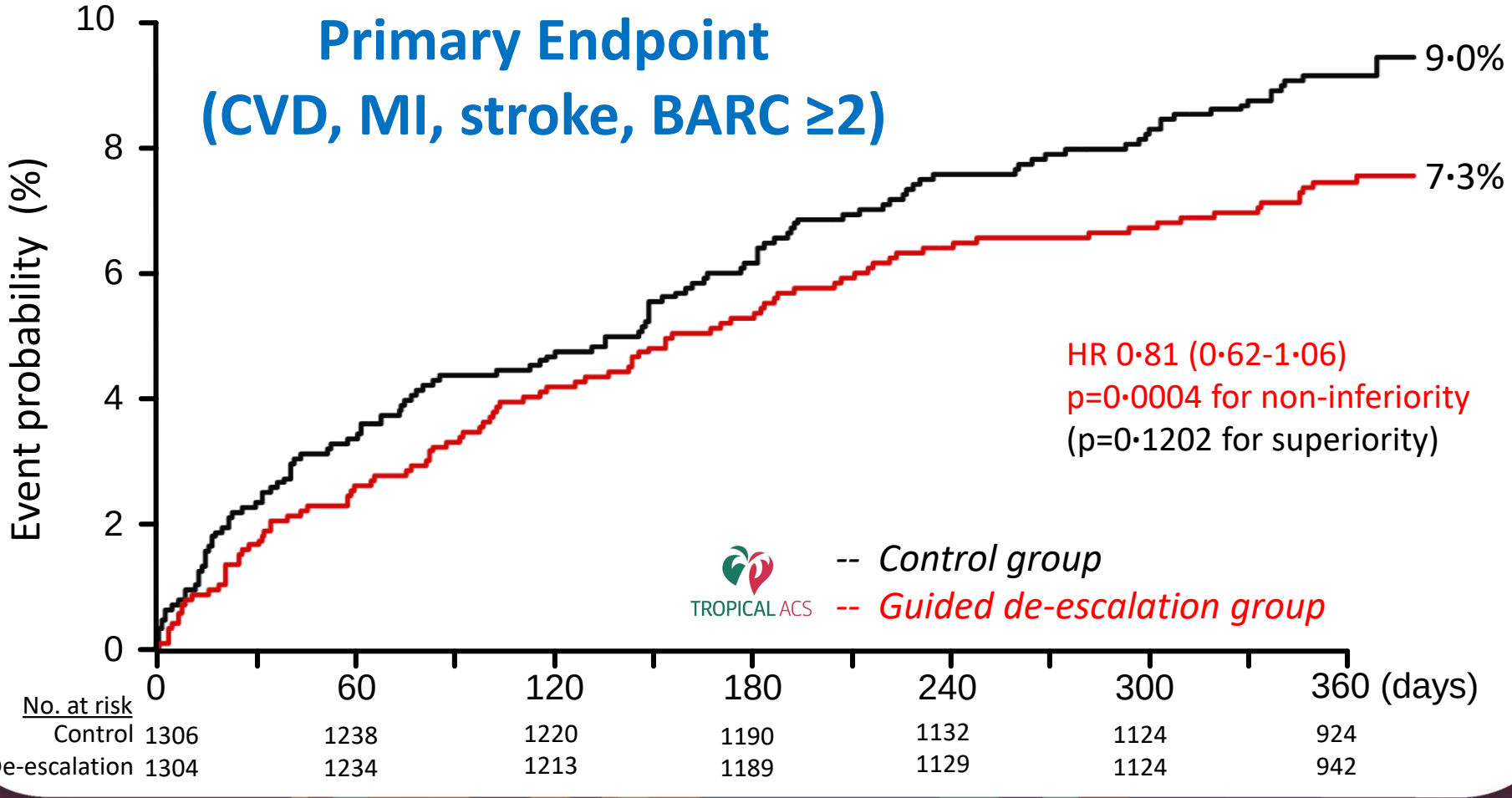
Procedural Characteristics

	Control group (n = 1306)	Guided de-escalation group (n = 1304)
STEMI	722 (55%)	731 (56%)
NSTEMI	584 (45%)	573 (44%)
Access site:		
Brachial	3 (<1%)	--
Femoral	541 (41%)	523 (40%)
Radial	762 (58%)	781 (60%)
Diseased vessels:		
1	682 (52%)	659 (51%)
2	345 (26%)	359 (28%)
3	279 (21%)	286 (22%)
Anticoagulant for PCI:		
Bivalirudin	55 (4%)	54 (4%)
LMWH	70 (5%)	72 (6%)
UFH	1181 (90%)	1178 (90%)
Stent type:		
DES	1002 (77%)	1003 (77%)
BMS	208 (16%)	224 (17%)
BVS	83 (6%)	68 (5%)
None (POBA)	13 (1%)	9 (1%)

Primary Endpoint (CVD, MI, stroke, BARC ≥2)



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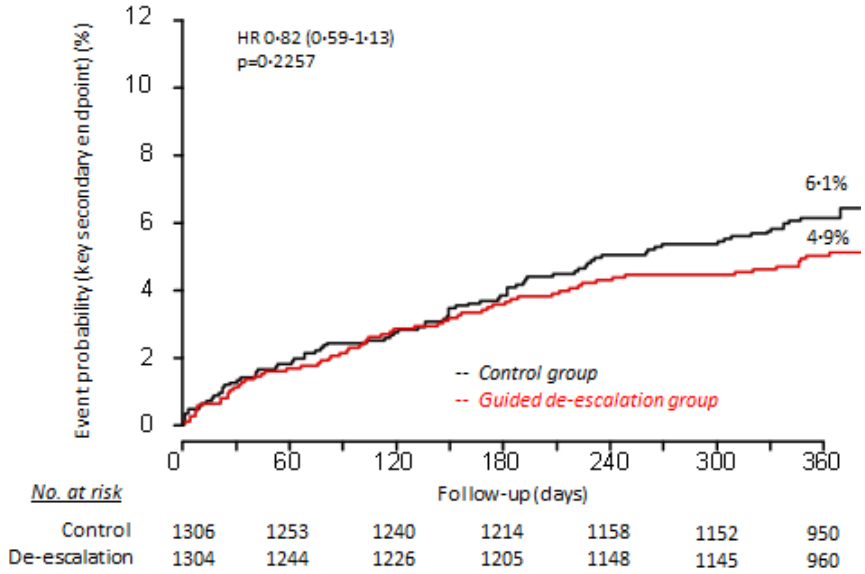
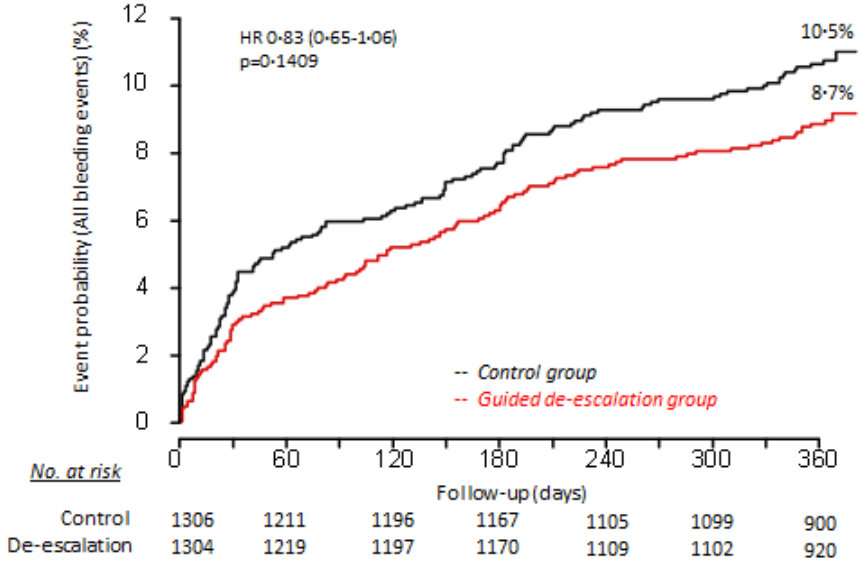
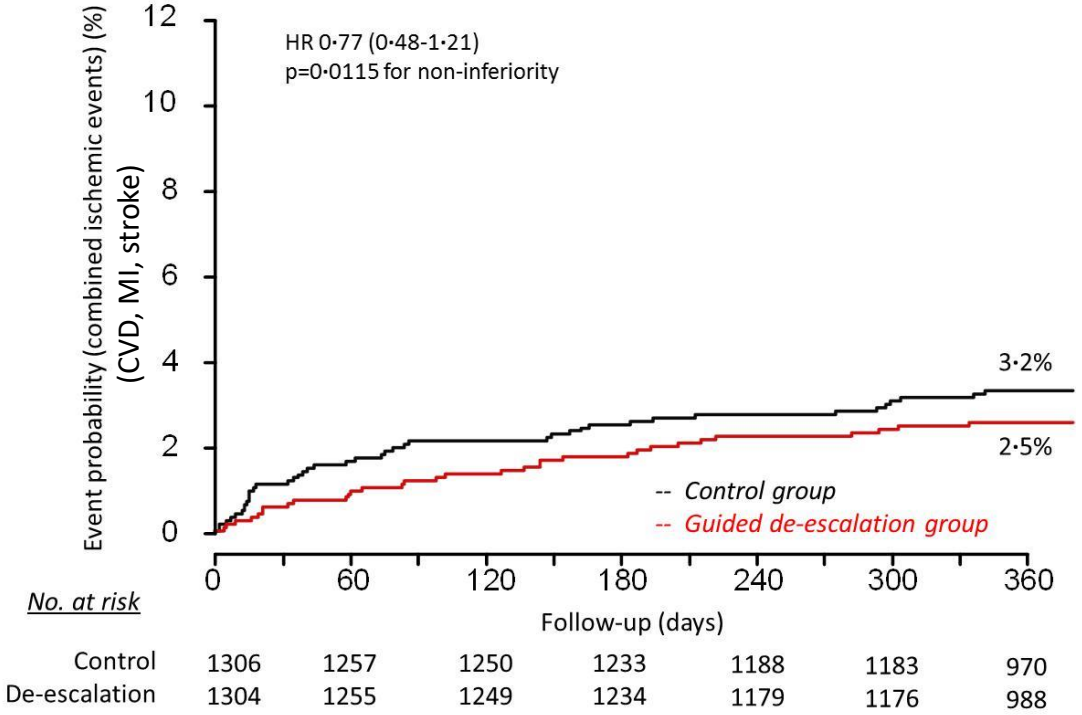
Key Secondary endpoint
Bleeding BARC ≥2



All bleeding events (BARC 1 to 5)

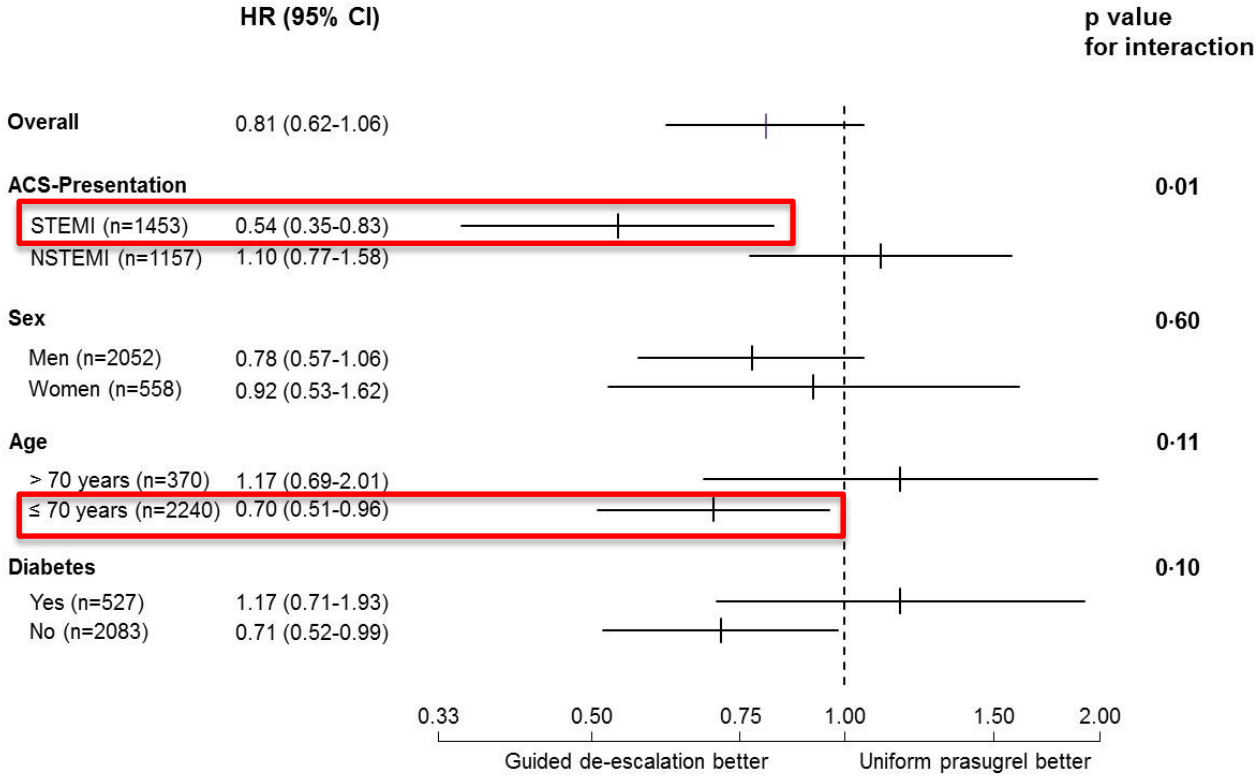


Ischemic events at 12 months follow-up



- All-cause mortality:
  12 events (1%) in control vs. 11 (1%) in guided de-escalation group, p=0.85
- Definite ST:
  3 events (0.2%) in control vs. 2 (0.2%) in guided de-escalation group, p=0.66

Subgroup Analyses (primary endpoint)



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Conclusions

- A **stage-adapted and individualized antiplatelet treatment** with initial potent platelet inhibition (prasugrel), followed by guided DAPT de-escalation to clopidogrel **proved to be feasible and safe when compared to conventional 12-month prasugrel therapy** in ACS patients undergoing PCI.
- **PFT-guided DAPT de-escalation** should be considered as an **alternative DAPT strategy** in ACS patients undergoing PCI.

TROPICAL-ACS: Online today @ THE LANCET

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

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Summary

Background Current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after an acute coronary syndrome managed with percutaneous coronary intervention (PCI). However, the greatest anti-ischaemic benefit of potent antiplatelet drugs over the less potent clopidogrel occurs early, while most excess bleeding events arise during chronic treatment. Hence, a stage-adapted treatment with potent platelet inhibition in the acute phase and de-escalation to clopidogrel in the maintenance phase could be an alternative approach. We aimed to investigate the safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing (PFT).

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Thanks for your attention!