



Joint Meeting of Coronary Revascularization 8th to 9th December 2017

A Novel Clinical Application Combining Genotyping and Platelet Function Testing In Patients With Acs - A Case Series

Shirley Tan Siang Ning

Research Pharmacist

Clinical Research Centre, Sarawak General Hospital



DAPT in Acute Coronary Syndromes

Medical therapy¹

- ♥ **Aspirin + P2Y12 Inhibitor** (ticagrelor or clopidogrel) for 12 months (1A)
- ♥ Ticagrelor is recommended over clopidogrel, unless bleeding risk outweighs potential ischaemic benefit. (1B)

Coronary Stent Implantation¹

- ♥ **Aspirin + P2Y12 Inhibitor** recommended for 12 months unless there are contraindications such as excessive risk of bleeding (1A)



INTRODUCTION

- ♥ Recurrent major adverse cardiovascular events (MACE) despite on DAPT.
- ♥ One of the reasons of clopidogrel suboptimal response is attributed to genetic polymorphisms of CYP2C19
- ♥ Routine genotyping and PFT to guide antiplatelet therapy is currently not recommended. (Class III).¹
- ♥ Evidence gap on on-therapy patients readmitted with MACE.



INTRODUCTION

- ♥ Prevalences of Aspirin and Clopidogrel high on-treatment platelet reactivity (HPR) (%)^{2,3}

	Caucasians	Asian	Malaysia
Aspirin HPR	<10	<10	~ 11.5
Clopidogrel HPR	~5-44	~Up to 50	~ 20-30



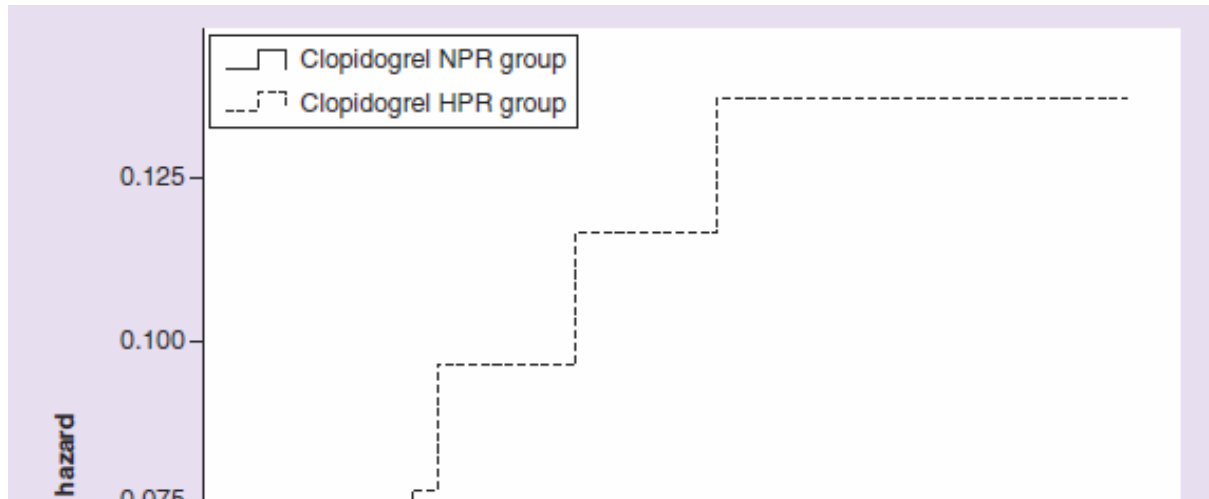
INTRODUCTION

♥ Prevalences of CYP2C19 genetic polymorphism(%)^{2,4,5,6}

	Caucasians	Asian	Malaysia
CYP2C19 *2	~15	~29-35	~40-50
CYP2C19 *3	<1	~2-9	~12.7
CYP2C19*17	~3-21	~5	~6

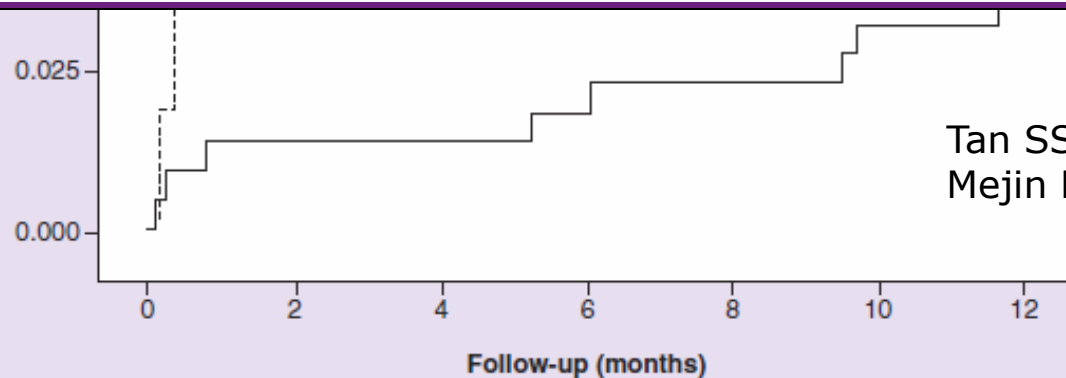


Genotype-PCI (2017)²



platelet reactivity (HPR), but unable to achieve statistical significance.

- Clopidogrel HPR was an independent predictor of MACE at 1-year post-PCI with drug eluting stents.
- Having clopidogrel HPR could potentially be a modifiable risk factor guided by platelet function tests.



Tan SSN, Fong AYY,
Mejin M et al.

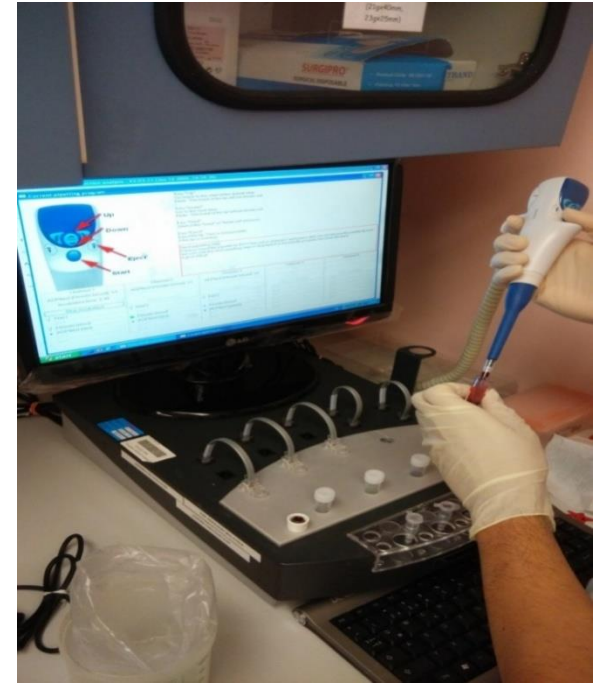


OBJECTIVE & METHODS

- ♥ To determine the **CYP2C19 genotype** and **platelet function testing** of on therapy patients (aspirin and clopidogrel) with recurrent MACE.
- ♥ All patients were prescribed with aspirin and clopidogrel after hospital admission with ACS, and subsequently **readmitted with another ACS event.**



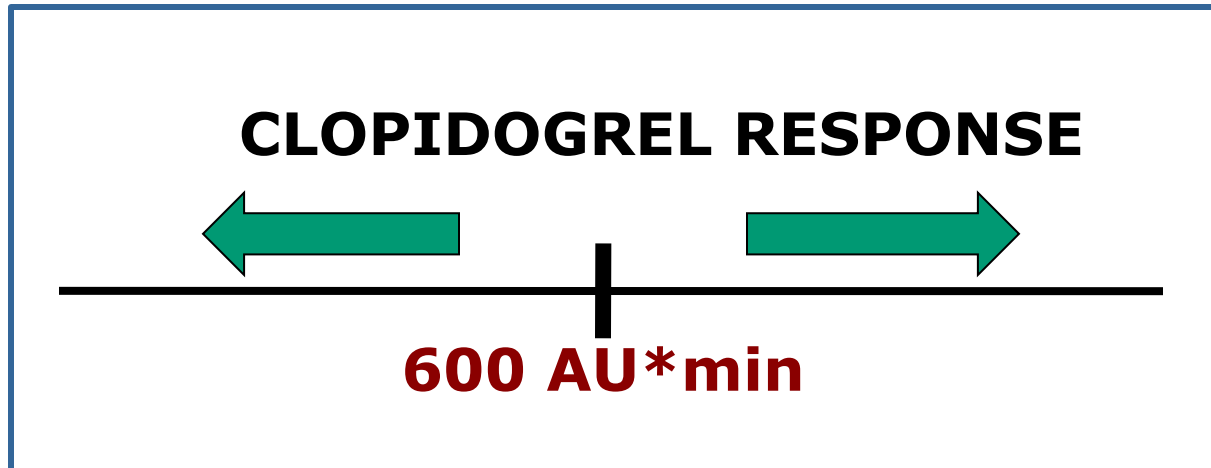
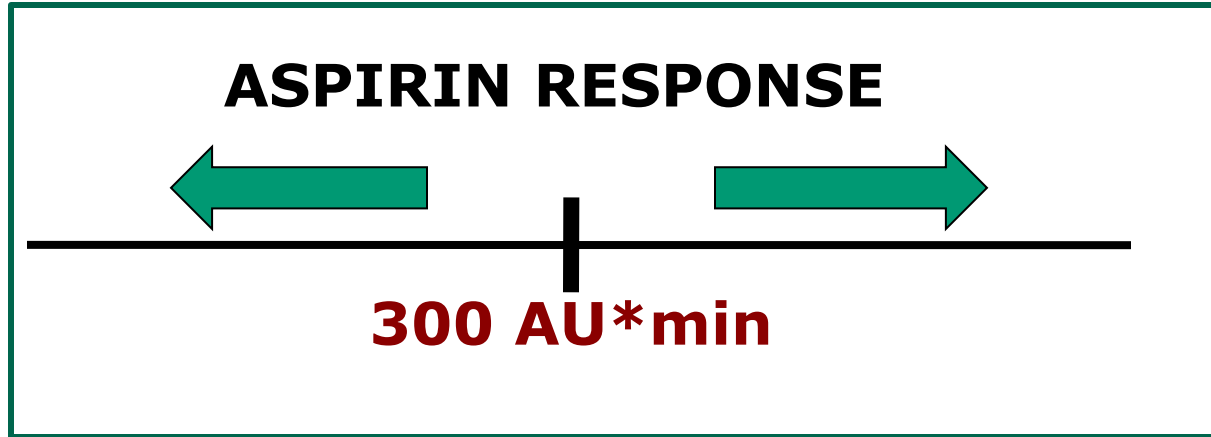
Multiple Platelet Function Analyzer – Multiplate®



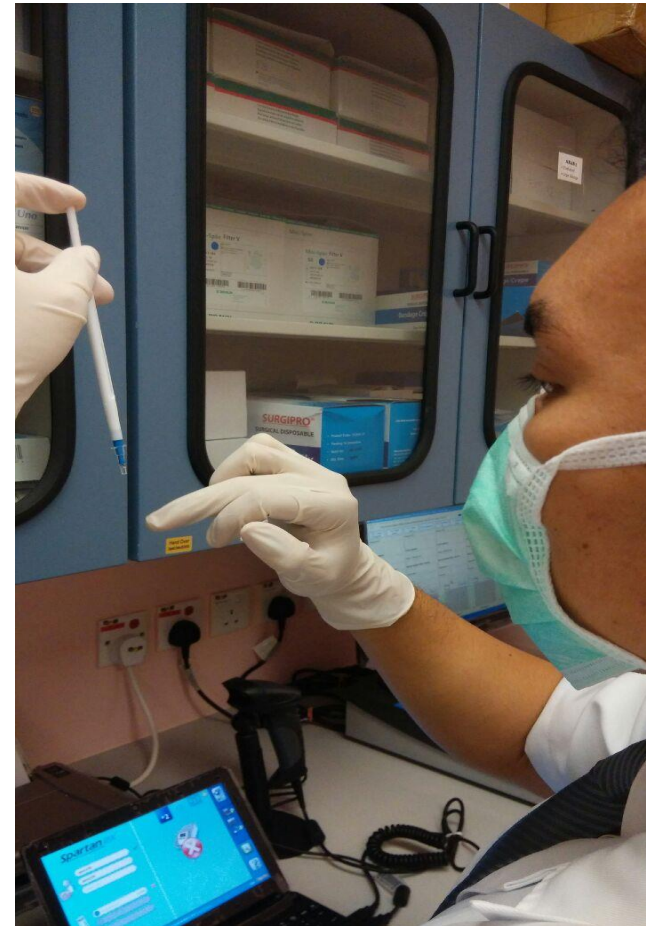
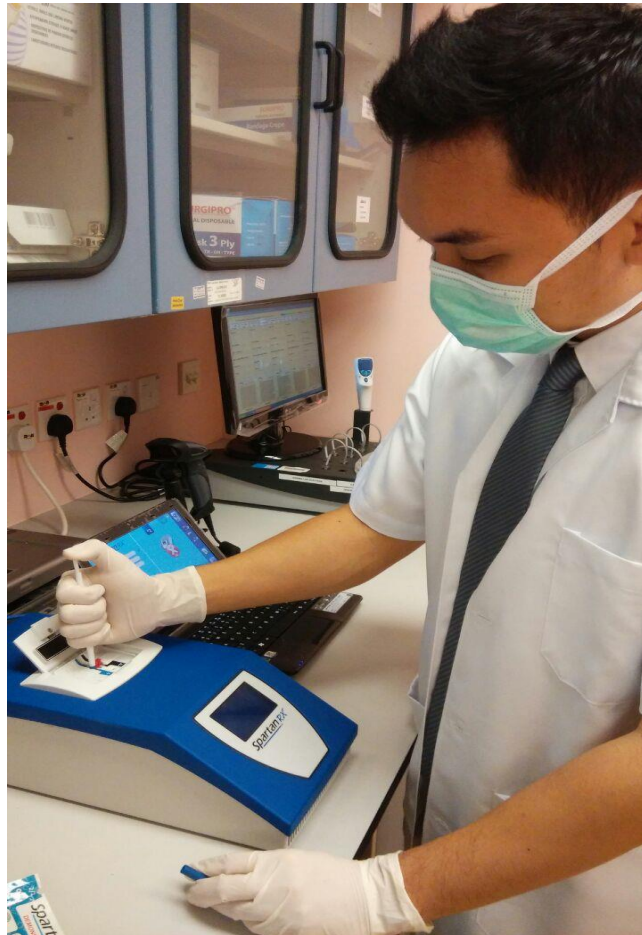
Antiplatelet Response^{2,7}

Responders

Suboptimal Responders



Spartan Rx (CYP2C19 *2/*3/*17 alleles)



DEMOGRAPHIC DATA (n=12)

	CYP2C19 *1/*1	Presence of CYP2C19 *2/ *3/*17
N	6	6
Revascularisation	5	4
Clopidogrel OPR [Median (IQR)] AU*min	394 (271)	717 (603)
Number of Clopi HPR	0	4 (66.7)
Switched to Ticagrelor	2	4



CASE STUDY (1)



Mr. DAL
44 yo

- Anterior STEMI with DVD.
- Staged PCI to LAD with DCS.
- Concomitant Disease: Erb's Palsy

35days
→

Readmitted with new anterior STEMI. PFT done.

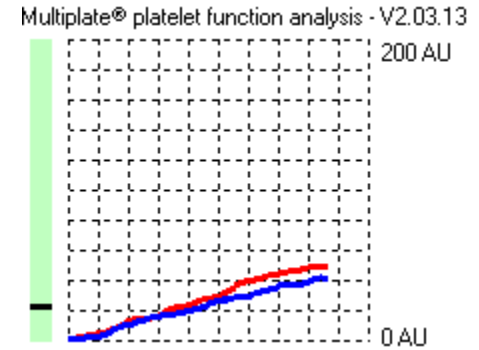
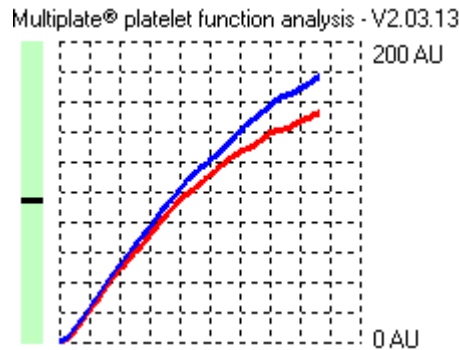
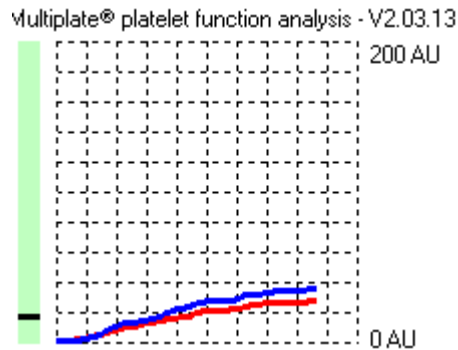
↓
**Ticagrelor
180mg stat,
then 90mg BD**

Repeat angiogram:
LAD mid stent thrombus in-situ.

Aspirin 75mg OD

Clopidogrel 75mg OD

Ticagrelor 180mg stat, 90 mg BD



CASE STUDY (1)

Spartan RX

CYP2C19 *2, *3, *17

*2	*1/*1
*3	*1/*3
*17	*1/*17

♥ CYP2C19
*3/*17

♥ Follow-up
at 1-month:
no event



CASE STUDY (2)



Ms. EAR
34 yo

- Inferior STEMI in June 2017.
- Minor disease RCA
- Non-smoker, young HTN; TIA in Dec 2014

ONE
day
→

Readmitted with
new inferior STEMI.

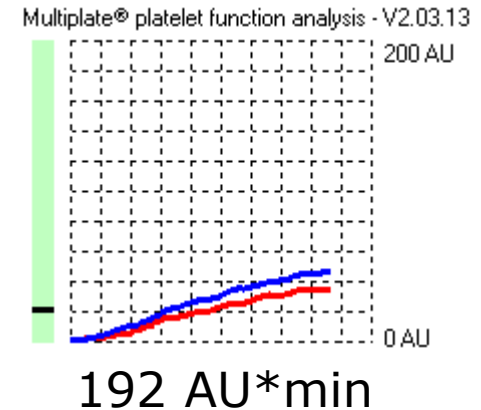
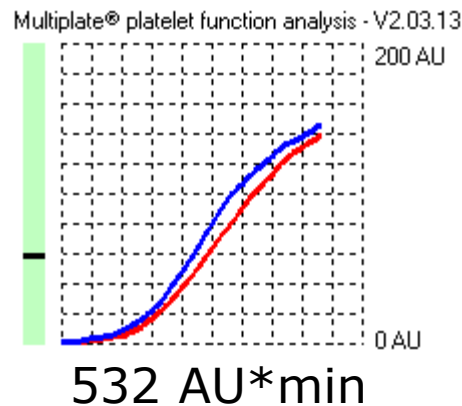
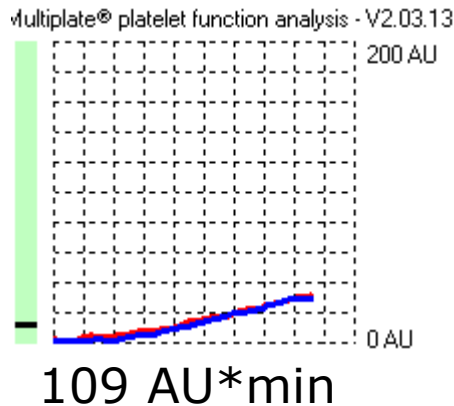
↓
Repeat angiogram:
SVD with acute
thrombosis at the mid to
distal RCA. PFT done.

**Ticagrelor 180mg
stat, then 90mg BD**
↓

Aspirin 75mg OD

Clopidogrel 75mg OD

Ticagrelor 180mg stat, 90 mg BD



CASE STUDY (2)

Spartan RX

CYP2C19 *2, *3, *17

*2	*1/*1
*3	*1/*1
*17	*1/*1

- ♥ CYP2C19 *1/*1
- ♥ Follow-up at 1-month: no event

- ♥ After further interview, patient is regularly taking morning after pills for years. She also had recent depot 3 monthly injection.
- ♥ Patient was then discharged well, and to arrange for contraceptive clinic appointment to review which non-estrogen based contraceptives suitable.



CASE STUDY (3)



Mdm
MBA
61 yo

- UA in Jan 2016.
- Angiogram in Mac 2017:
SVD with POBA to dLCX.

17
days
→

Readmitted with
NSTEMI. PFT done.

Ticagrelor 180mg
stat, then 90mg
BD. Discharge well.

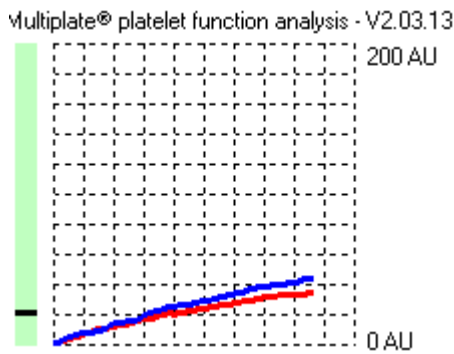
↓ 34
days

Repeat PFT at daycare.

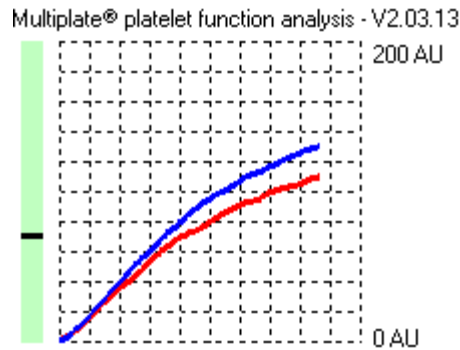
- 1) Ex-smoker
- 2) Strong family hx of IHD
- 3) Hypertension
- 4) DM on insulin

Aspirin 75mg OD

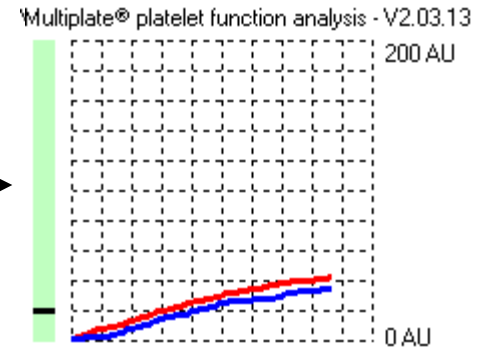
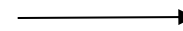
Clopidogrel 75mg OD Ticagrelor 180mg stat, 90 mg BD



198 AU*min



640 AU*min



895 AU*min



CASE STUDY (3)

Spartan RX

CYP2C19 *2, *3, *17

*2	*1/*2
*3	*1/*1
*17	*1/*1

♥ CYP2C19
*1/*2

♥ Follow-up
at 1-month:
no event



CASE STUDY (4)



Mr.
CSC
74 yo

- Underlying SVD. STEMI in July 2017.
- Ex-smoker.
- Angiogram 2017: SVD and PCI to LAD with DES.

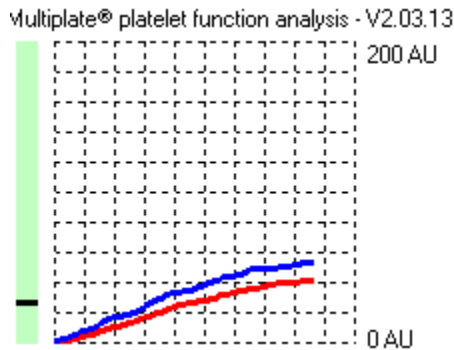
7 days
→

Readmitted with unstable angina. PFT done.



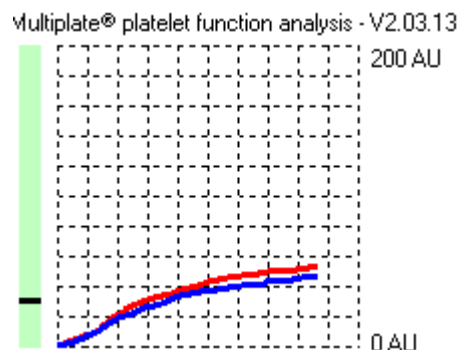
Repeat angiogram:
Patent stent.

Aspirin 75mg OD



240 AU*min

Clopidogrel 75mg OD



283 AU*min



CYP2C19

*1/*1



Follow-up at
1-month: no
event



DISCUSSIONS (1)

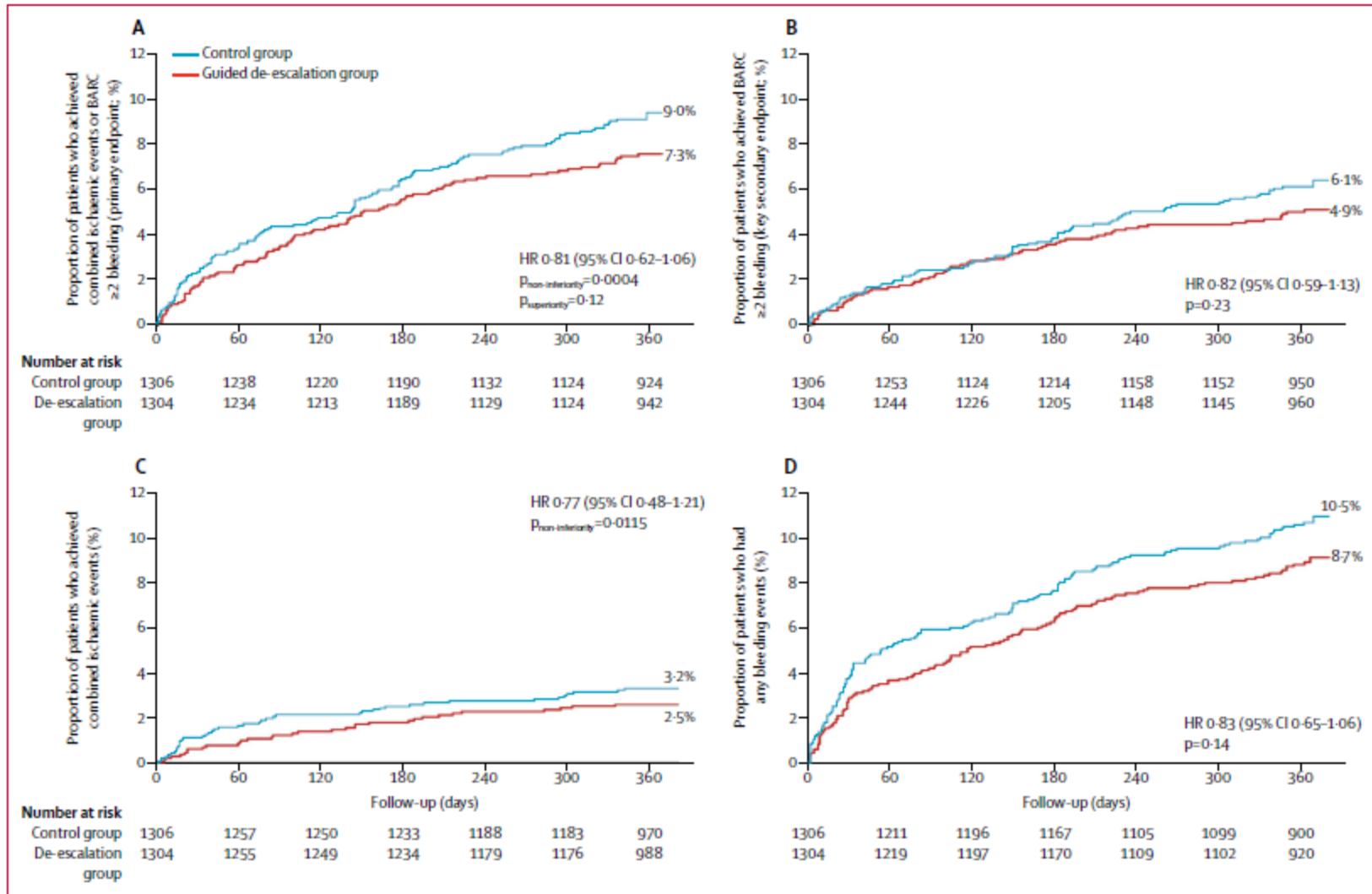
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

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 Klopotoski, 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†*

Findings Between Dec 2, 2013, and May 20, 2016, 2610 patients were assigned to study groups; 1304 to the guided de-escalation group and 1306 to the control group. The primary endpoint occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group ($p_{\text{non-inferiority}}=0.0004$; hazard ratio [HR] 0.81 [95% CI 0.62–1.06], $p_{\text{superiority}}=0.12$). Despite early de-escalation, there was no increase in the combined risk of cardiovascular death, myocardial infarction, or stroke in the de-escalation group (32 patients [3%]) versus in the control group (42 patients [3%]; $p_{\text{non-inferiority}}=0.0115$). There were 64 BARC 2 or higher bleeding events (5%) in the de-escalation group versus 79 events (6%) in the control group (HR 0.82 [95% CI 0.59–1.13]; $p=0.23$).



TROPICAL-ACS (2017)⁸



DISCUSSIONS (2)

- ♥ The off-patent clopidogrel remains the P2Y12 Inhibitor of choice.
- ♥ Role of PFT and/or genotype guided therapy in **escalating treatment in high risk patients & on-therapy patients** who were readmitted with recurrent ischemic events could be explored.





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- ♥ 3. Gurbel PA, Jeong Y-H, Tantry US. Personalized antiplatelet therapy: state of the art. *JRSM Cardiovascular Disease*. 2012 September 1, 2012;1(6).
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- ♥ 5. Serebruany VL, Steinhubl SR, Berger PB, et al. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol* 2005;45:246–251.
- ♥ 6. Mejin M, Tiong WN, Lai LY, Tiong LL, Bujang AM, Hwang SS, et al. CYP2C19 genotypes and their impact on clopidogrel responsiveness in percutaneous coronary intervention. *Int J Clin Pharm*. 2013 Aug;35(4):621-8.
- ♥ 7. Weisser H, Von Pape K, Dzijan-Horn M, Calatzis A. Control of aspirin effect in chronic cardiovascular patients using two whole blood platelet function assays: PFA-100 and multiple electrode aggregometry. *Clin Chem Lab Med* 2006;44:A81–A198.
- ♥ 8. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *The Lancet*. 2017 2017/10/14;390(10104):1747-57.





THANK YOU.

