S.I.Te.C.S.
SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE

IL SOGGETTO AD ALTO RISCHIO CARDIOVASCOLARE Parte 2 (ECM n 200-271737)

Moderatore: A.L. Catapano

14.00 – 14.30 **FH: dai registri alla pratica clinica** • *M. Casula*

14.30 – 15.00 **Soggetti con sindrome coronarica acuta: recenti evidenze dai trial clinici** • *S. De Servi*

15.00 – 15.30 **Il soggetto nefropatico** • *A. Baragetti*

15.30 – 16.00 **Il paziente con malattia vascolare periferica (PVD)** • *A. Zambon*

Stefano De Servi
UO Cardiologia
IRCCS Multinmedica, Sesto San Giovanni

ORIGINAL ARTICLE FREE PREVIEW

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

Roxana Mehran, M.D., Usman Baber, M.D., Samin K. Sharma, M.D., David J. Cohen, M.D., Dominick J. Angiolillo, M.D., Ph.D., Carlo Briguori, M.D., Ph.D., Jin Y. Cha, B.S., Timothy Collier, M.Sc., George Dangas, M.D., Ph.D., Dariusz Dudek, M.D., Ph.D., Vladimír Džavík, M.D., Javier Escaned, M.D., Ph.D., et al.

ORIGINAL ARTICLE FREE PREVIEW

A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

Daniel M.F. Claassens, M.D., Gerrit J.A. Vos, M.D., Thomas O. Bergmeijer, M.D., Renicus S. Hermanides, M.D., Ph.D., Arnoud W.J. van 't Hof, M.D., Ph.D., Pim van der Harst, M.D., Ph.D., Emanuele Barbato, M.D., Ph.D., Carmine Morisco, M.D., Ph.D., Richard M. Tjon Joe Gin, M.D., Folkert W. Asselbergs, M.D., Ph.D., Arend Mosterd, M.D., Ph.D., Jean-Paul R. Herrman, M.D., Ph.D., et al.

ORIGINAL ARTICLE FREE PREVIEW

Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

Stefanie Schüpke, M.D., Franz-Josef Neumann, M.D., Maurizio Menichelli, M.D., Katharina Mayer, M.D., Isabell Bernlochner, M.D., Jochen Wöhrle, M.D., Gert Richardt, M.D., Christoph Liebetrau, M.D., Bernhard Witzenbichler, M.D., David Antoniucci, M.D., Ibrahim Akin, M.D., Lorenz Bott-Flügel, M.D., et al., for the ISAR-REACT 5 Trial Investigators*

6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial

Joo-Yong Hahn*, Young Bin Song*, Ju-Hyeon Oh, Deok-Kyu Cho, Jin Bae Lee, Joon-Hyung Doh, Sang-Hyun Kim, Jin-Ok Jeong, Jang-Ho Bae, Byung-Ok Kim, Jang Hyun Cho, Il-Woo Suh, Doo-il Kim, Hoon-Ki Park, Jong-Seon Park, Woong Gil Choi, Wang Soo Lee, Jihoon Kim, Ki Hong Choi, Taek Kyu Park, Joo Myung Lee, Jeong Hoon Yang, Jin-Ho Choi, Seung-Hyuk Choi, Hyeon-Cheol Gwon, for the SMART-DATE investigators†

Original Investigation

June 25, 2019

Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention

The SMART-CHOICE Randomized Clinical Trial

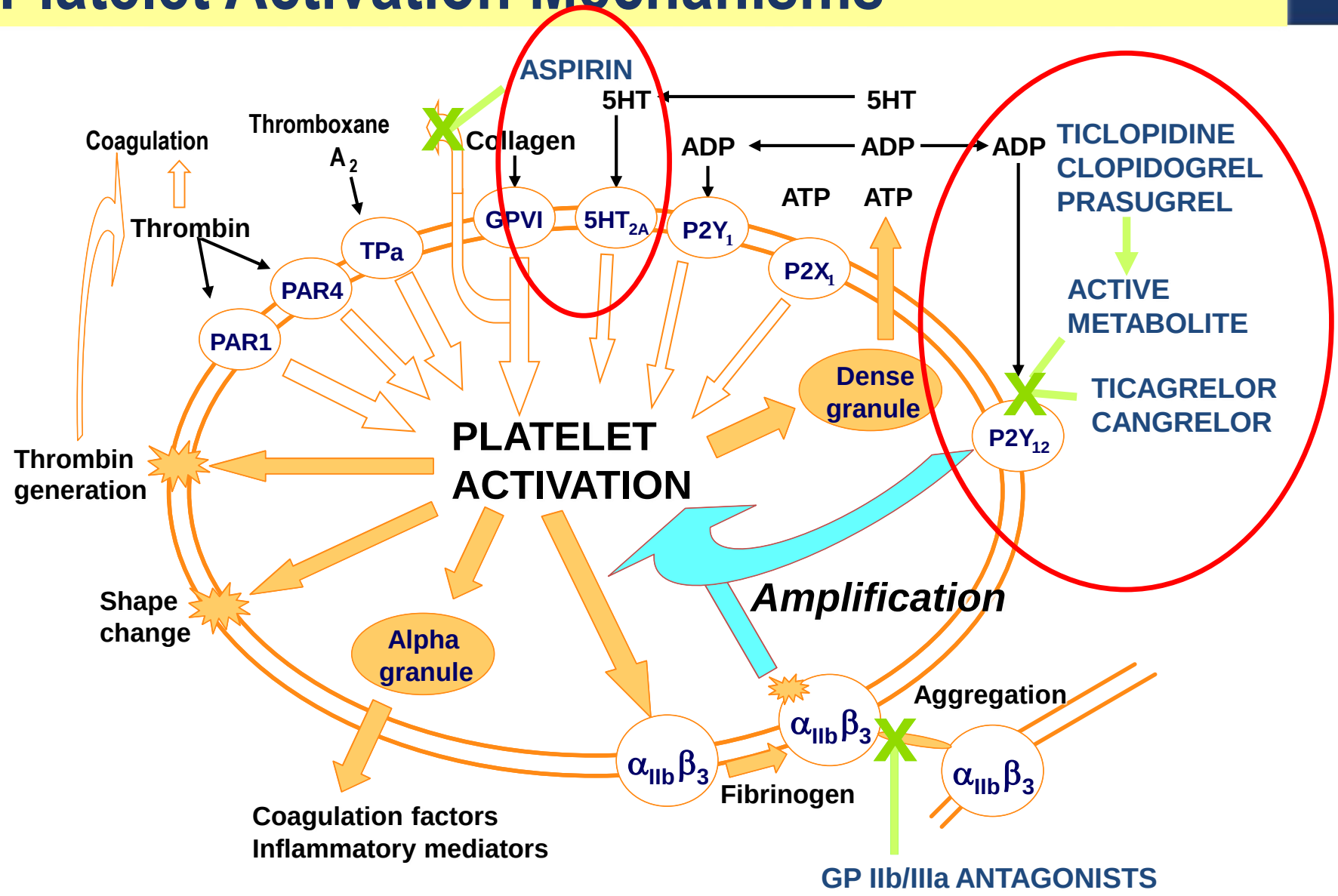
June 25, 2019

Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI

The STOPDAPT-2 Randomized Clinical Trial

Hirotoshi Watanabe, MD[1]; Takenori Domei, MD[2]; Takeshi Morimoto, MD[3]; et al

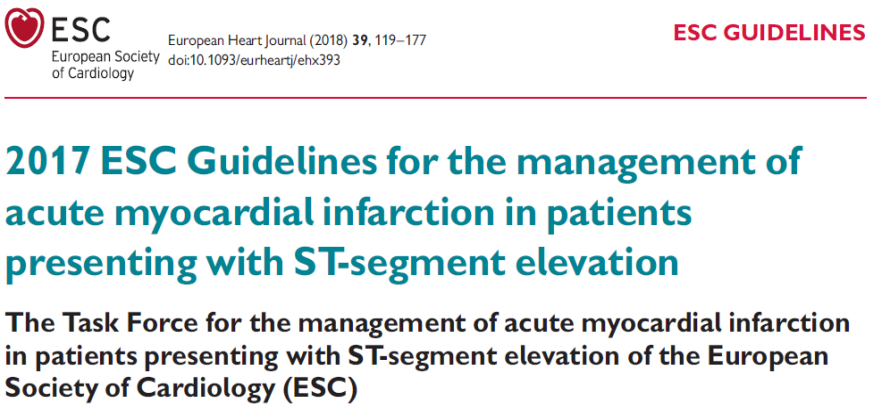
Platelet Activation Mechanisms



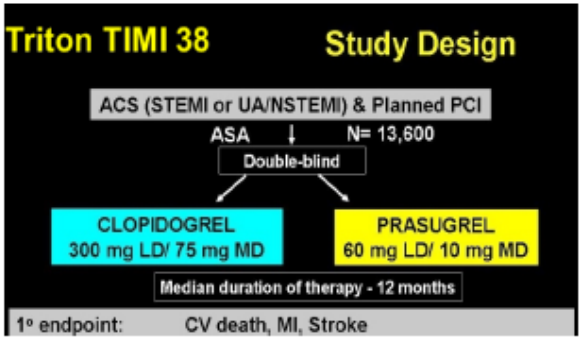
Cornerstones of DAPT in ACS

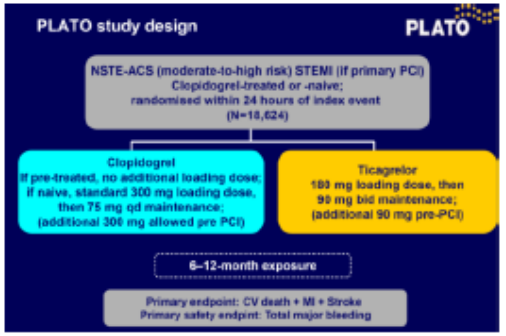
- 1) Prasugrel and ticagrelor are recommended instead of clopidogrel, the first $P2Y_{12}$ inhibitor used for DAPT (class I-A)

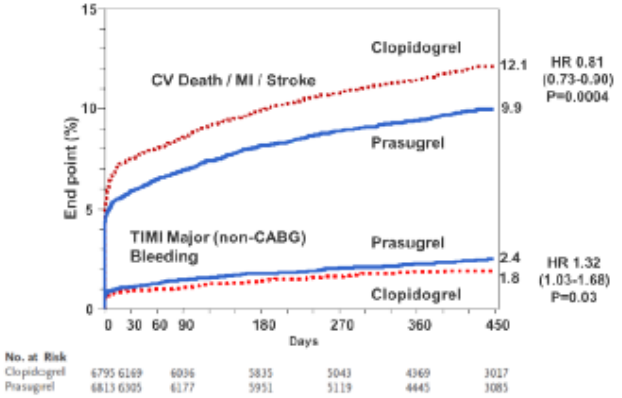
- 2) DAPT should be prolonged for 1 year unless there is an excessive bleeding risk (class I-A)

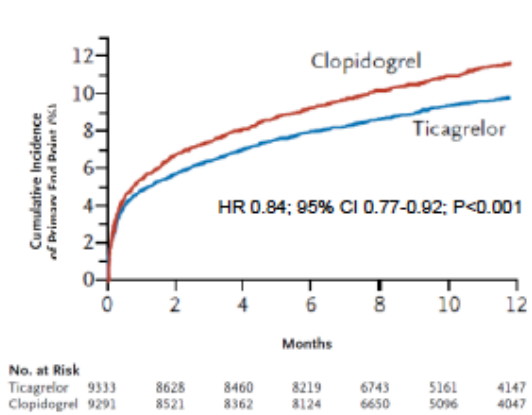


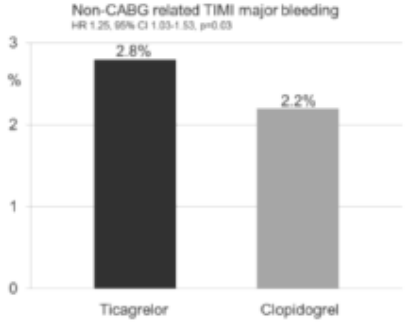
Background









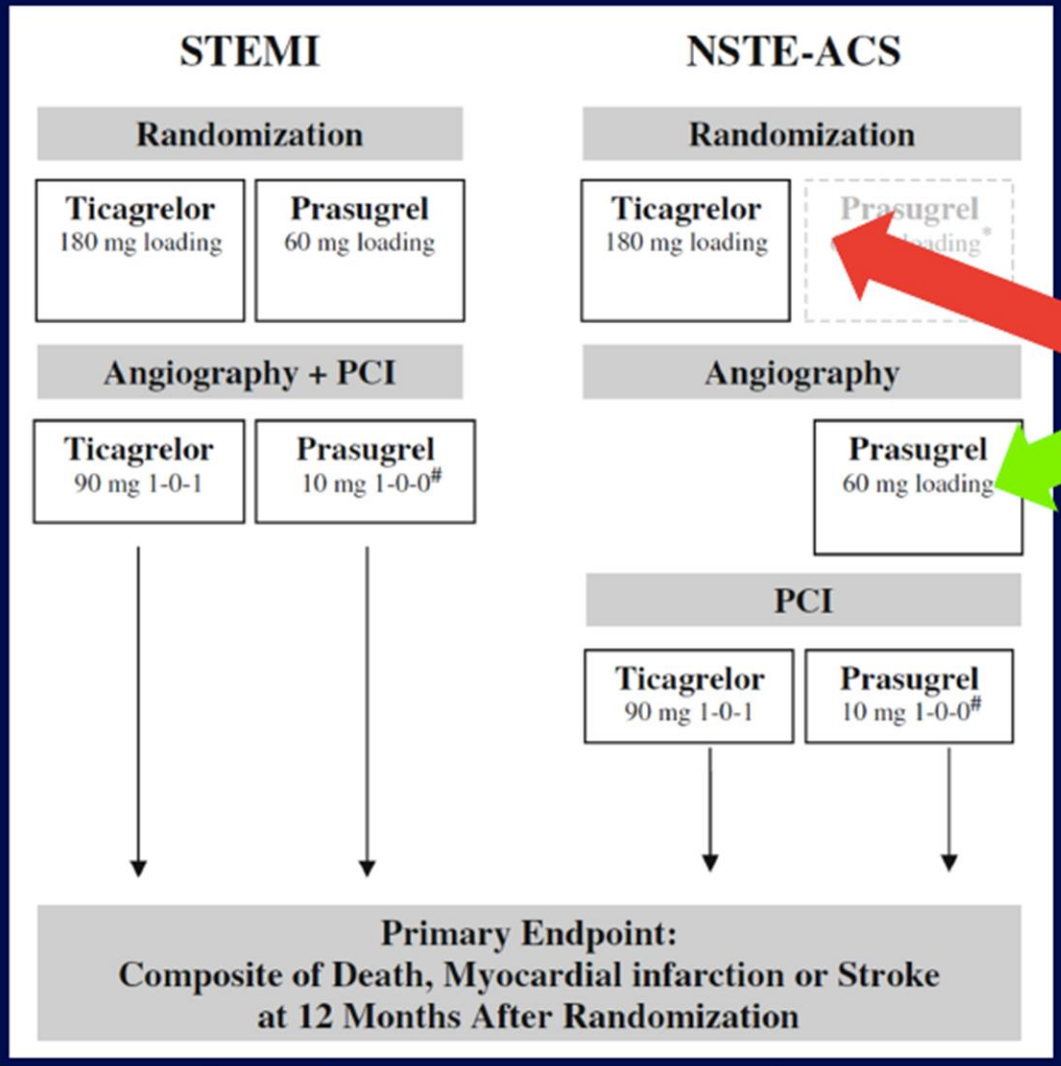


Wiviott et al, N Engl J Med 2007

Wallentin et al, N Engl J Med 2009

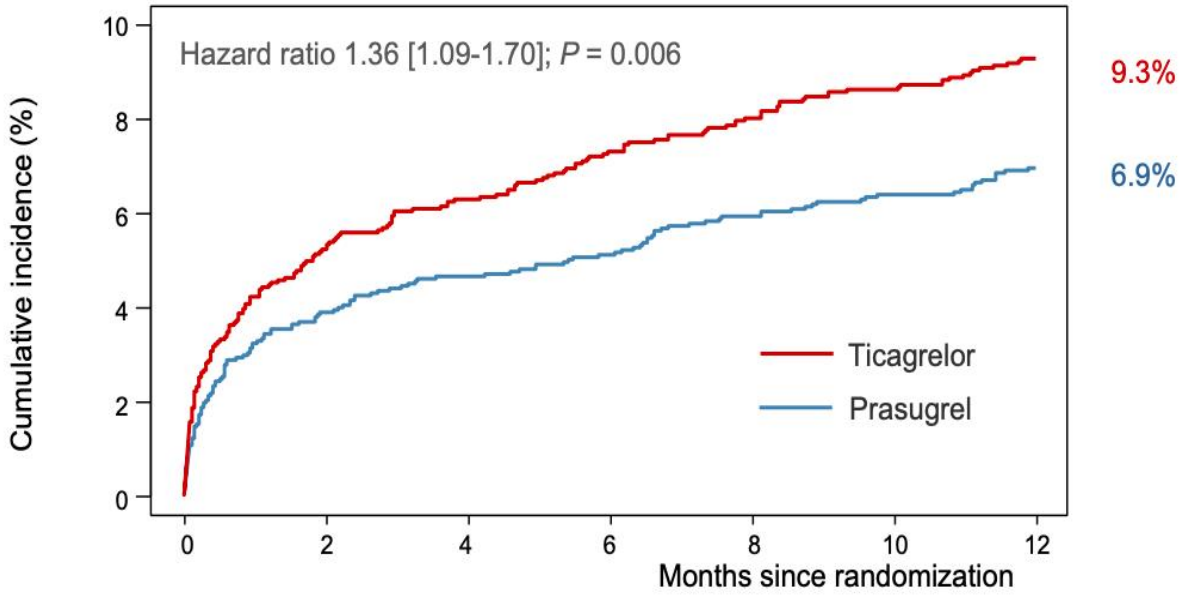
ISAR-REACT 5

2019



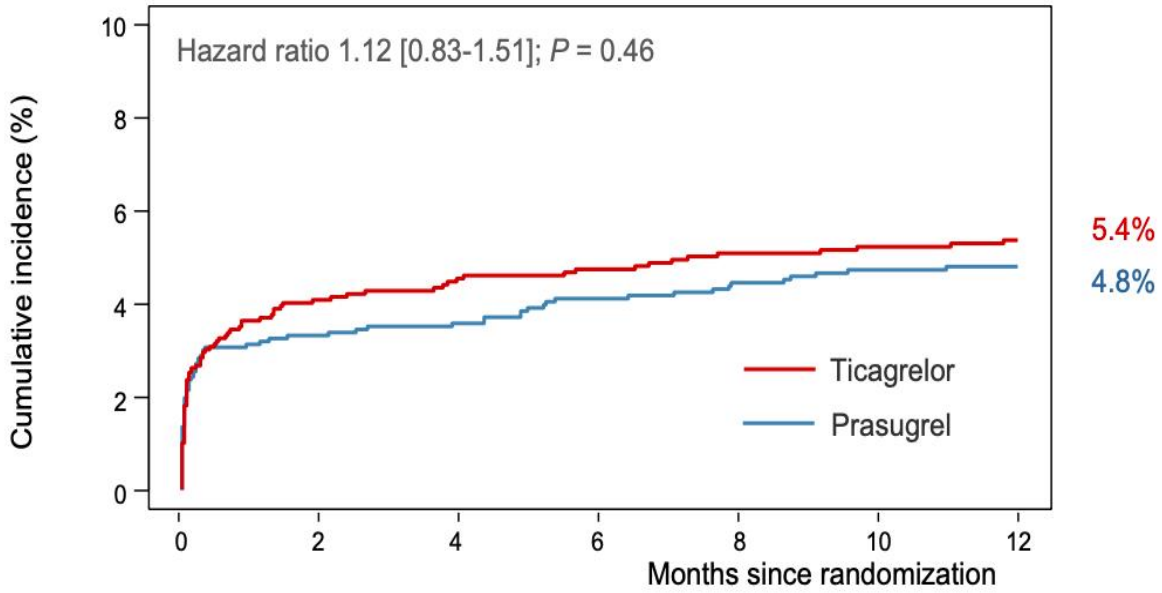
Timing

Primary End point
(Composite of Death, MI, or Stroke)



No. at Risk							
Ticagrelor	2012	1877	1857	1835	1815	1801	1772
Prasugrel	2006	1892	1877	1862	1839	1829	1803

BARC Type 3-5 Bleeding
(Safety End point)



No. at Risk

Ticagrelor	1989	1441	1399	1356	1319	1296	1266
Prasugrel	1773	1465	1427	1397	1357	1333	1307

How long should DAPT be administered in ACS patients ?

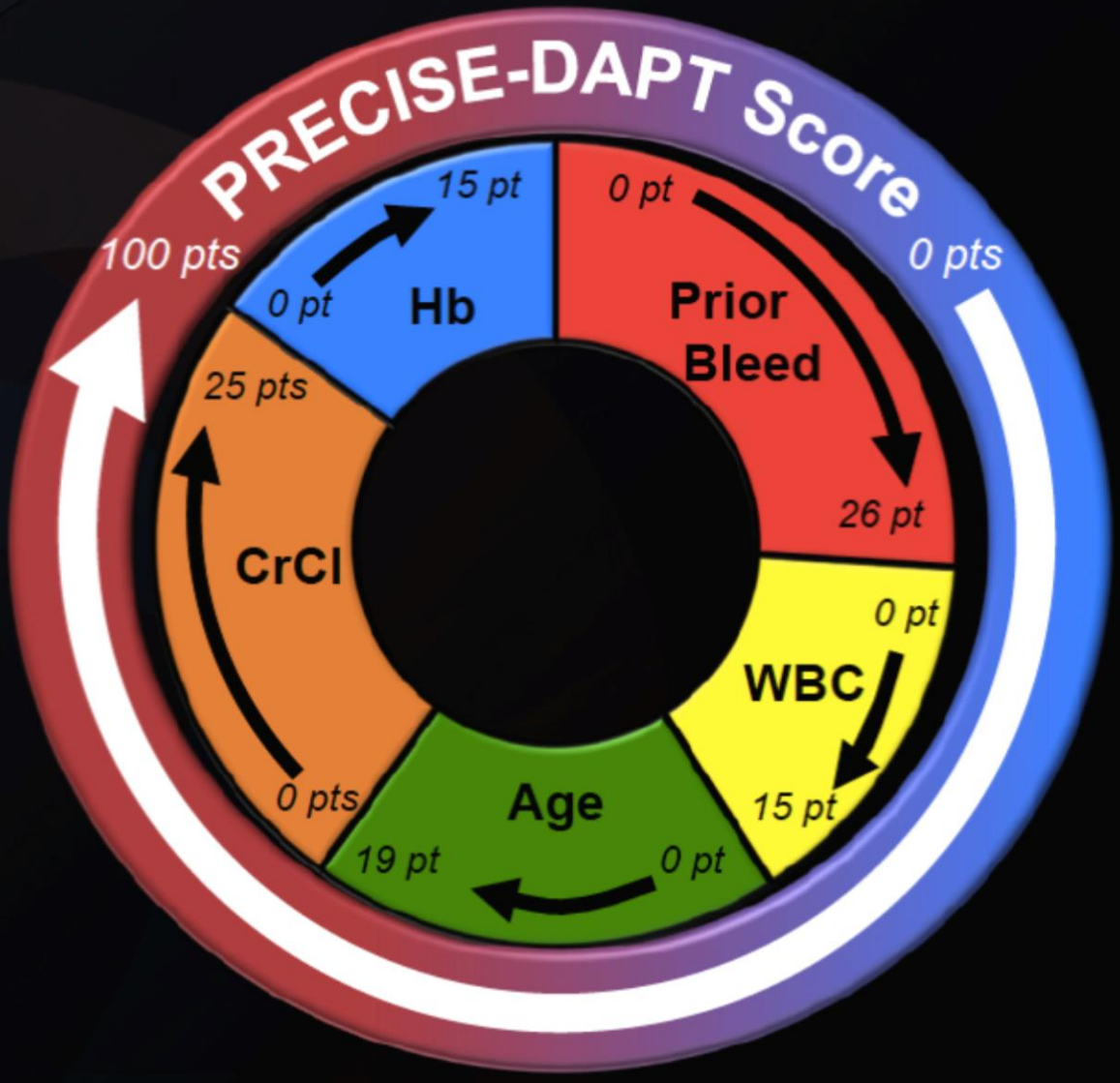
- DAPT should be shortened (6 months) in patients with excessive/high risk of bleeding (introduction of the PRECISE-DAPT score)

Recommendations	Class[a]	Level[b]
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥25).[20,23,40]	I	A
In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.[13,18,143]	IIa	B

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 213–254
doi:10.1093/eurheartj/ehx419
ESC GUIDELINES

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

PRECISE DAPT score: weight of the single predictors

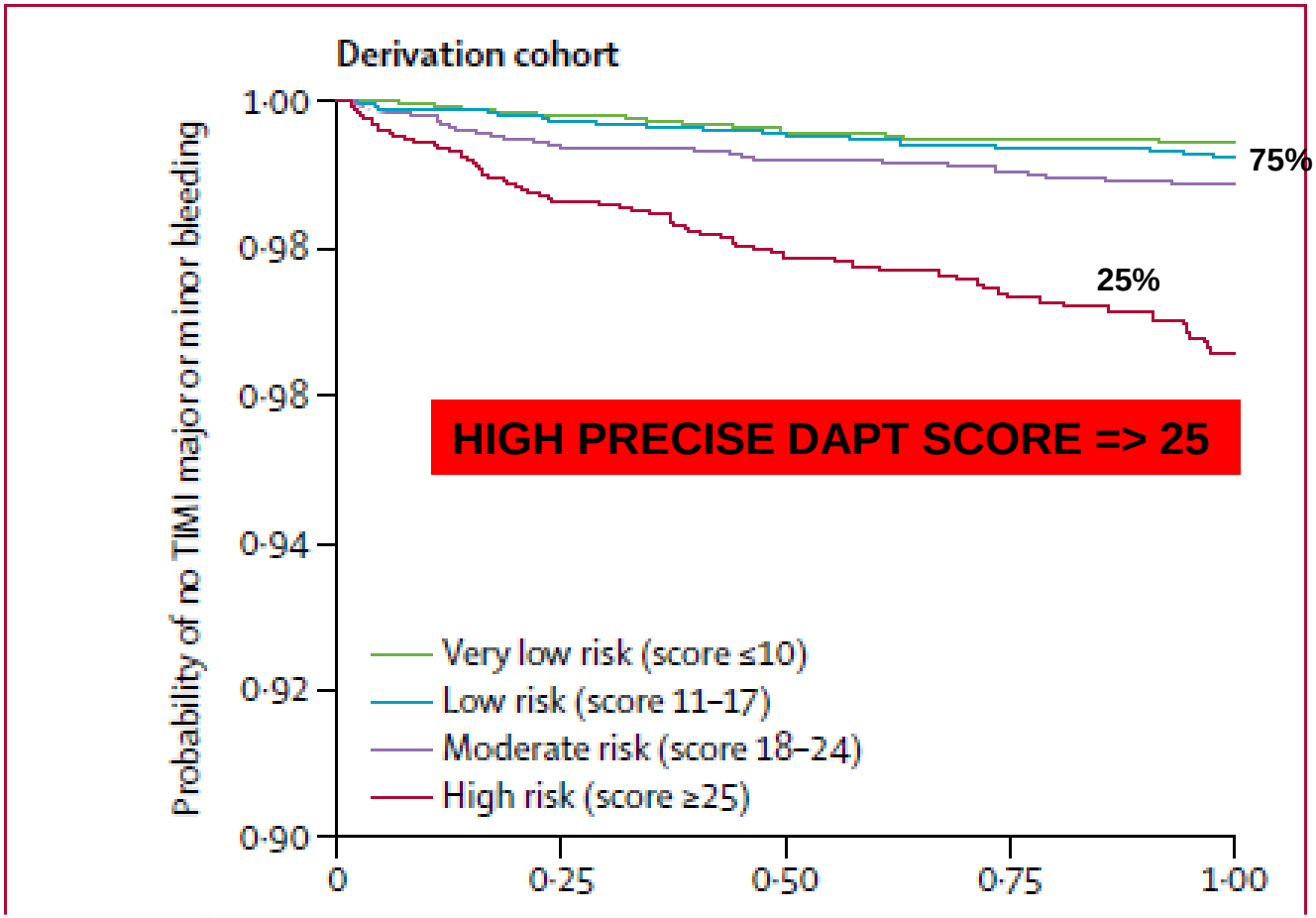


Lancet 2017 Mar 11;389(10073):1025-1034

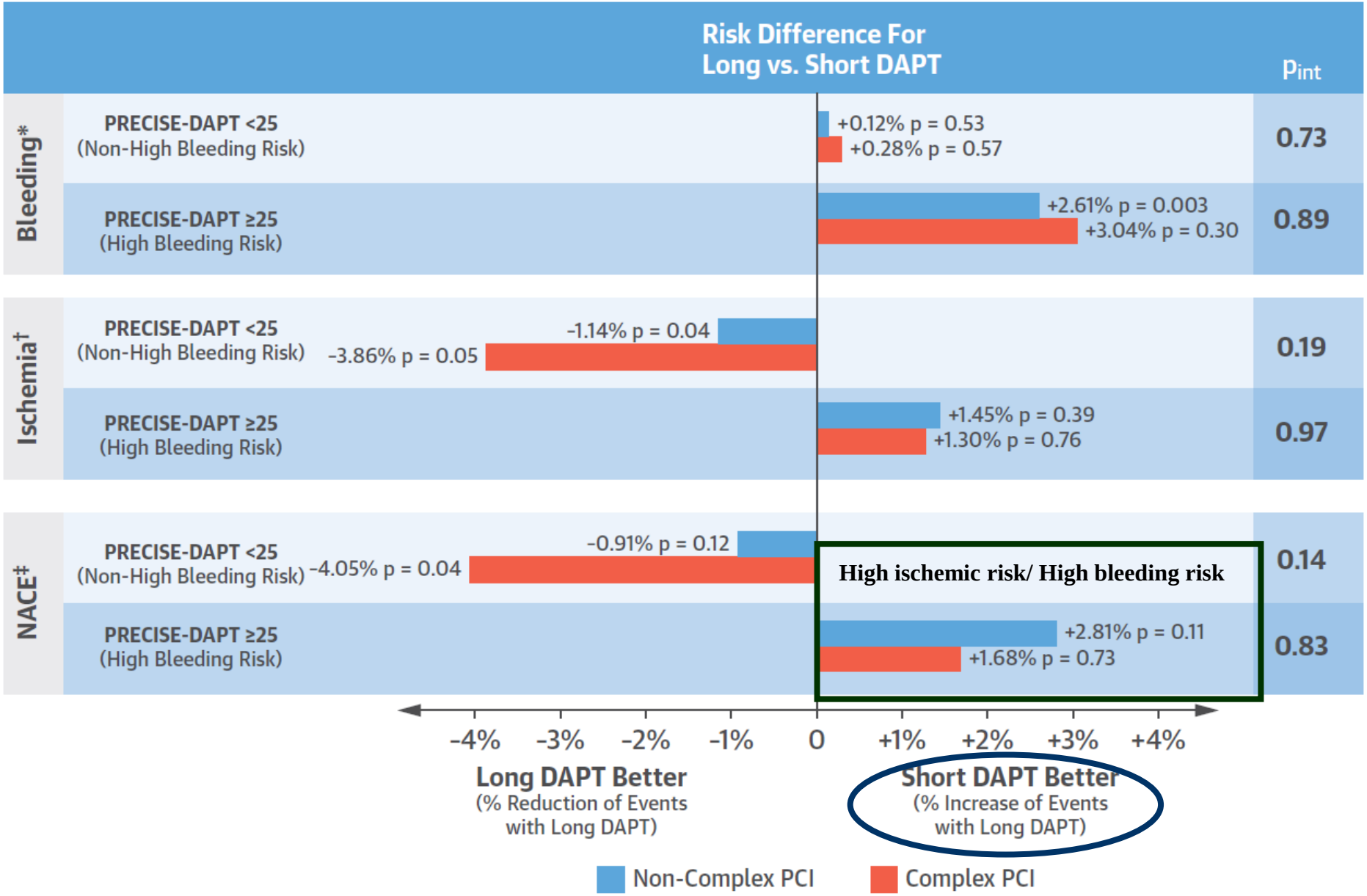
Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials

Francesco Costa*, David van Klaveren*, Stefan James, Dik Heg, Lorenz Räber, Fausto Feres, Thom
Antonio Colombo, Philippe Gabriel Steg, Thomas Zanchin, Tullio Palmerini, Lars Wallentin, Deepa
Ewout W Steyerberg, Marco Valgimigli, for the PRECISE-DAPT Study Investigators

Probability of TIMI major/minor bleeding



CENTRAL ILLUSTRATION PRECISE-DAPT Score and Complex Percutaneous Coronary Intervention



Costa, F. et al. J Am Coll Cardiol. 2019;73(7):741-54.

How to select the duration of DAPT ?

Streamlined decision making model

Assess the bleeding risk first:

- if low, assess the ischemic risk
- if high, forget about prolonged DAPT

Background

- 30% of Caucasians show an inadequate response to clopidogrel resulting in more stent thrombosis

- CYP2C19 Wild type (*1/*1) = normal response
- *2 and *3 loss-of-function alleles = inadequate response

- In wild type patients, clopidogrel demonstrated similar efficacy compared to potent P2Y12 inhibitors[2,3]

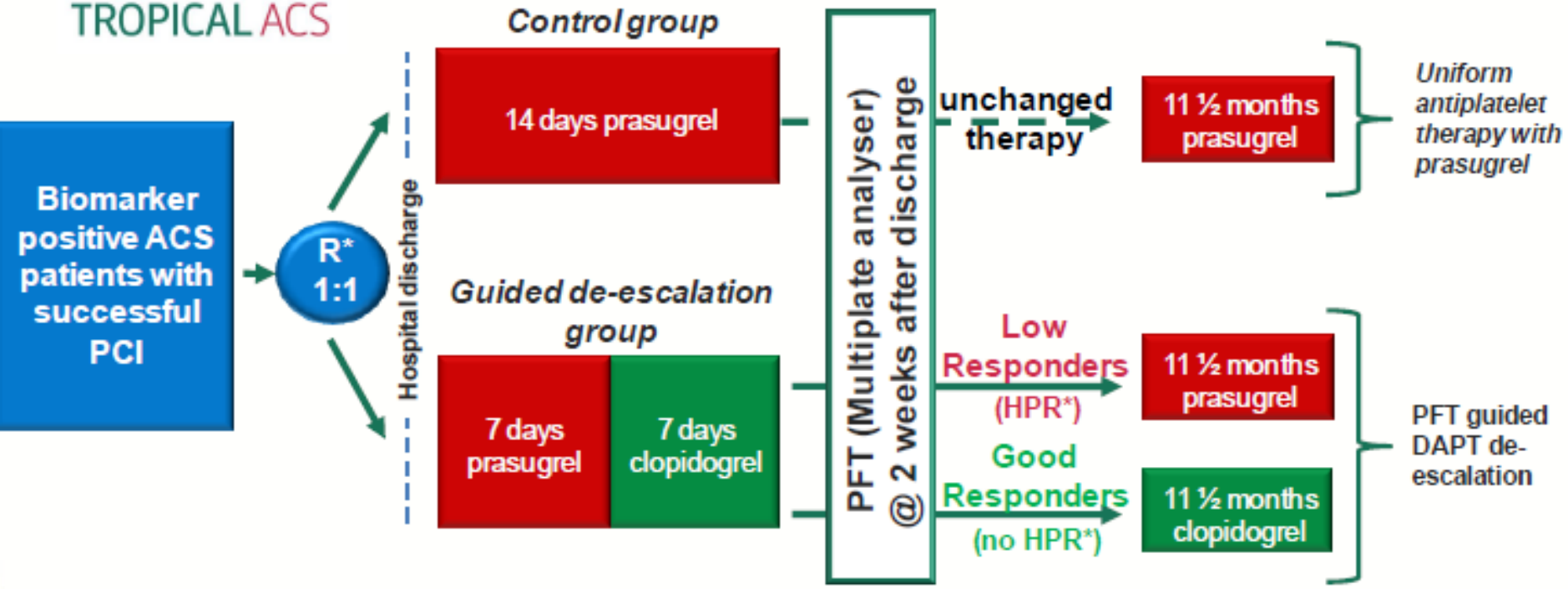
2: Mega et al. Lancet 2010, 3: Wallentin et al. Lancet 2010

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†

Trial Design

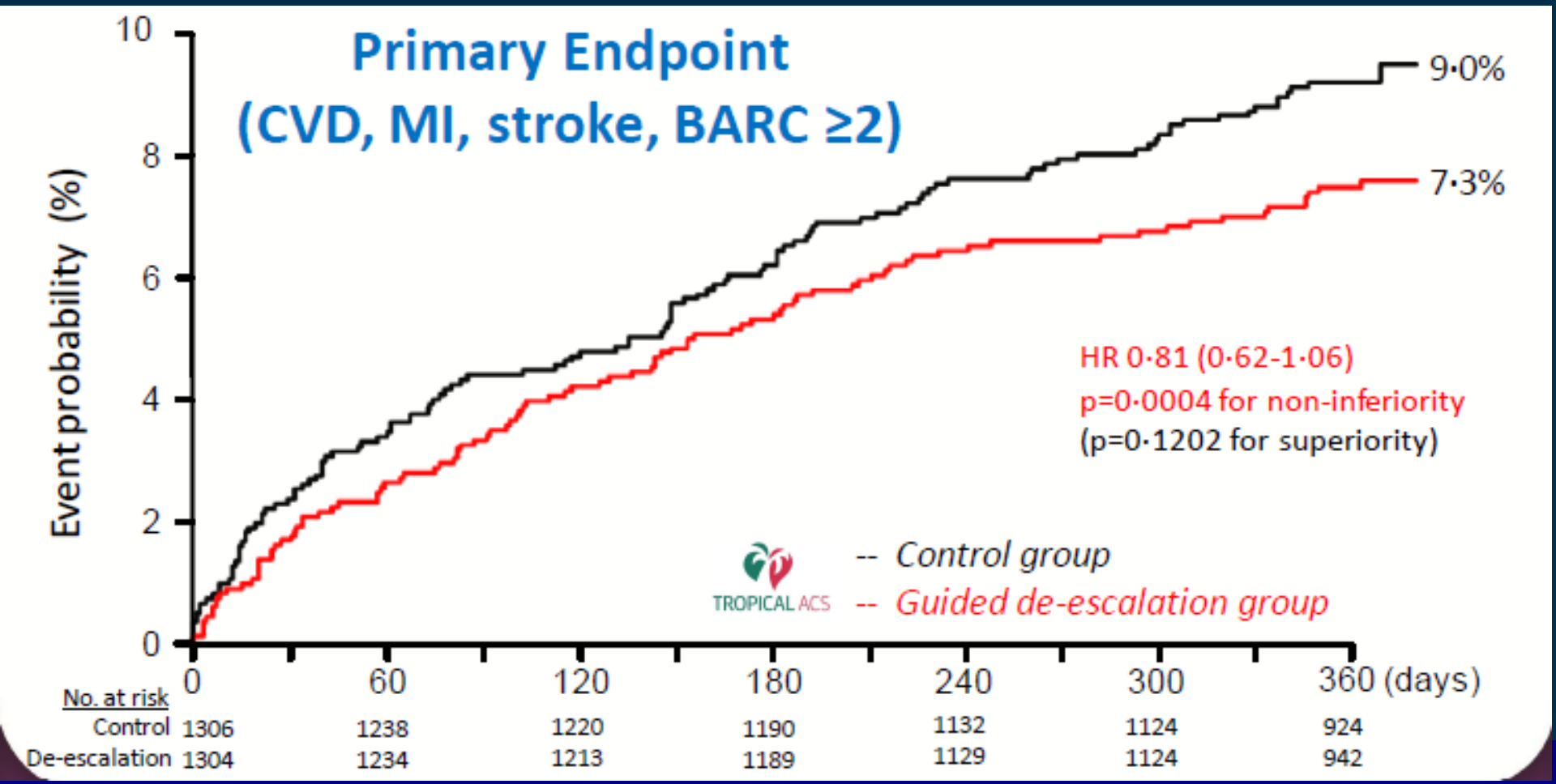
TROPICAL ACS



THE LANCET
Published Online August 27, 2017

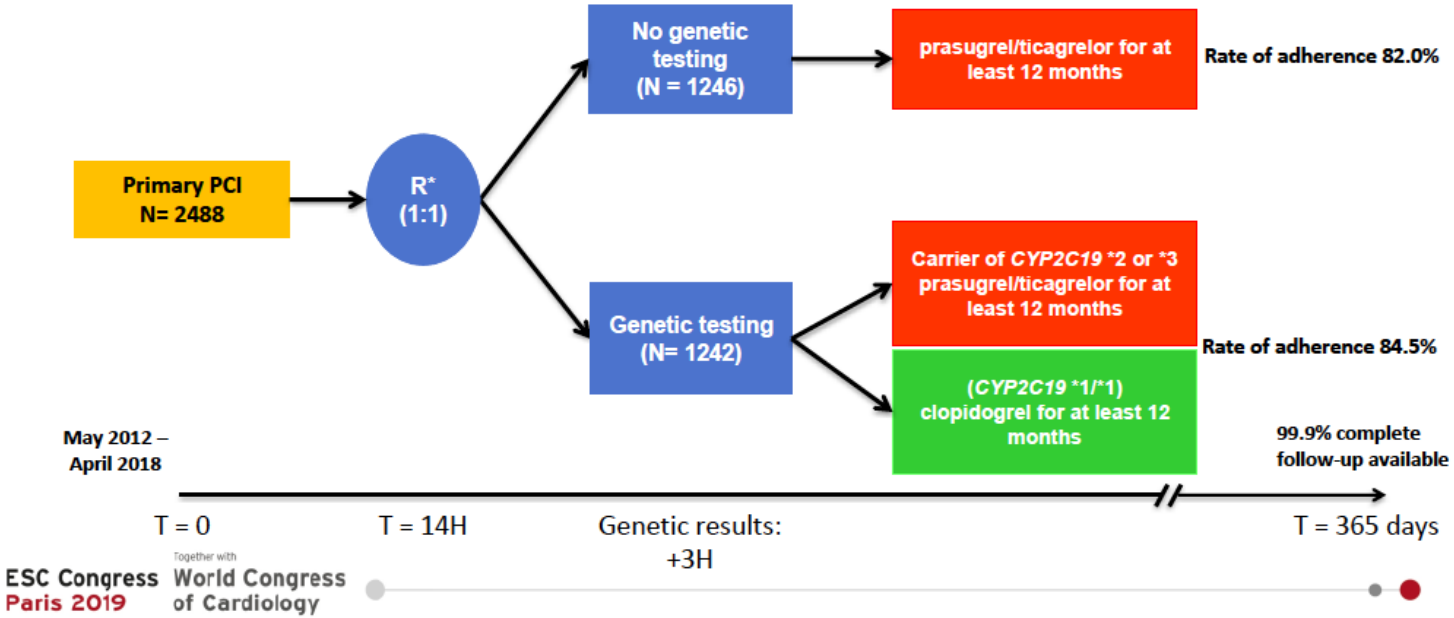
Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial

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†

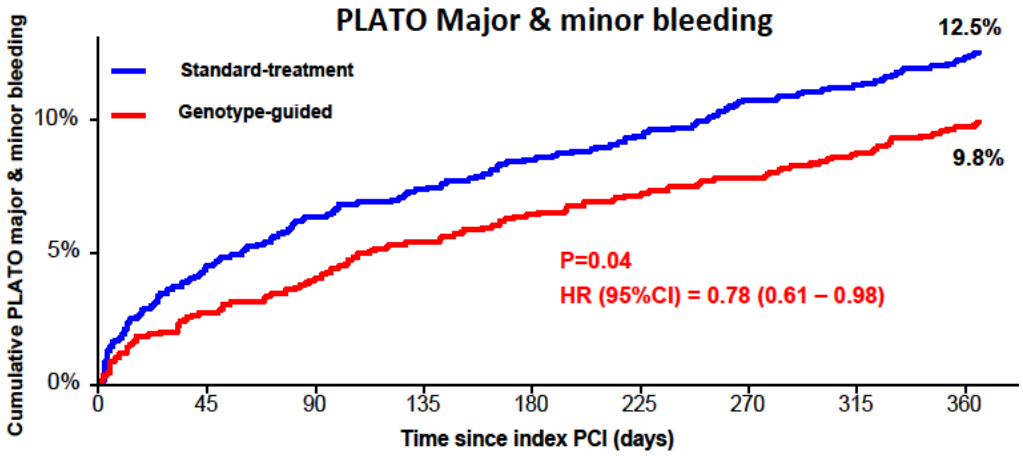


THE LANCET
Published Online
August 27, 2017

Trial patients and follow-up data

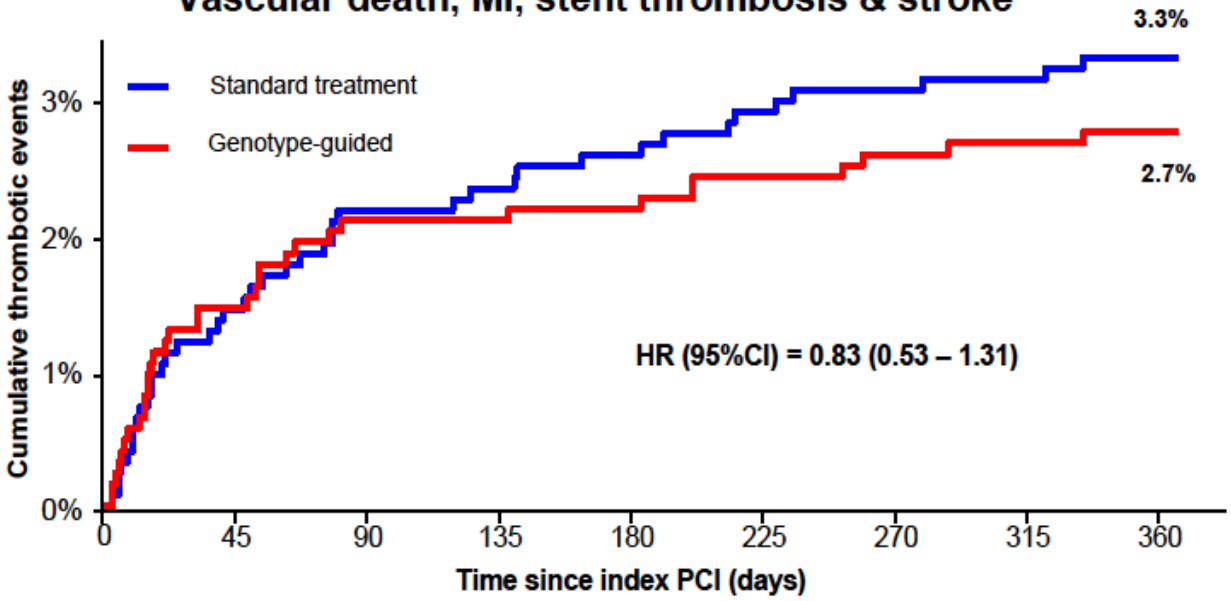


Co-primary outcome



Thrombotic outcome

Vascular death, MI, stent thrombosis & stroke

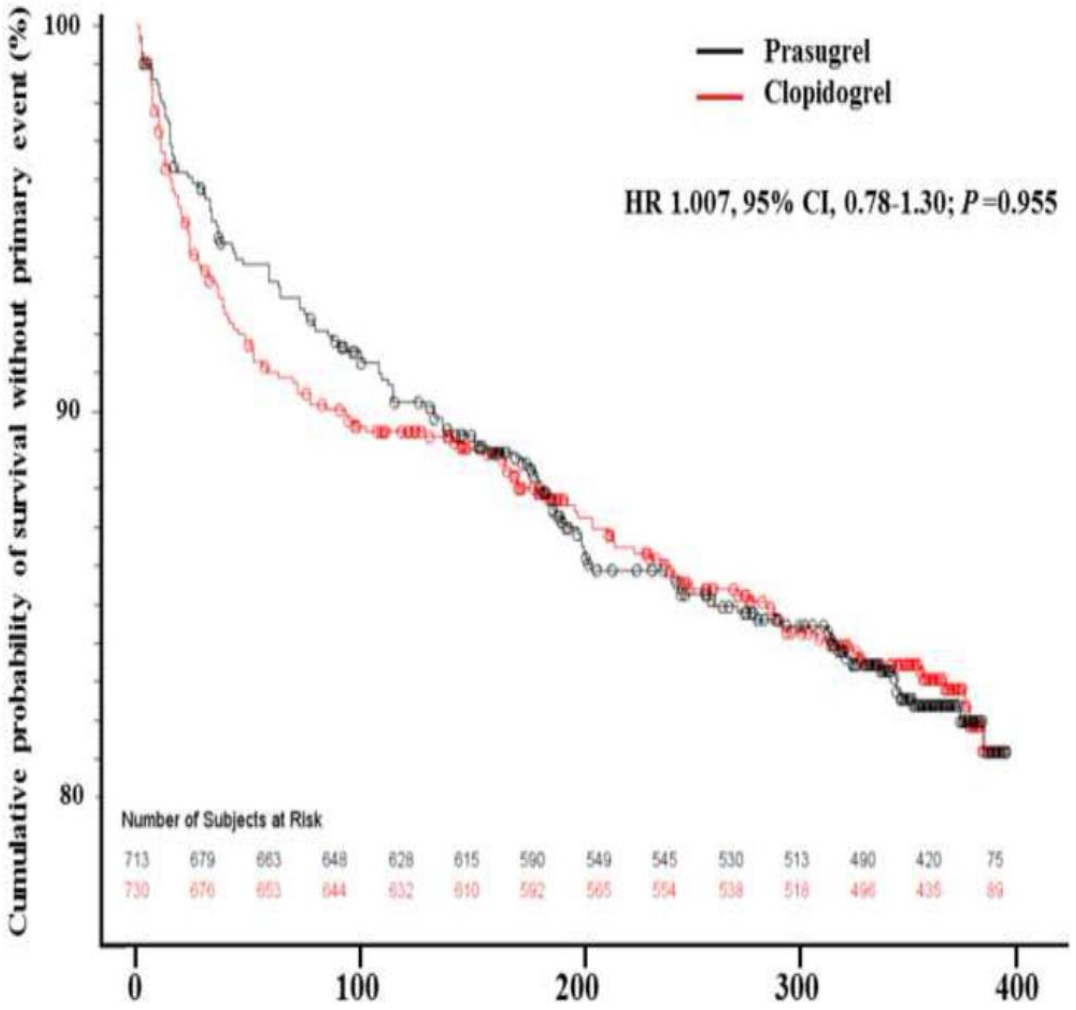


A comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization: the Elderly ACS-2 randomised trial

Circulation

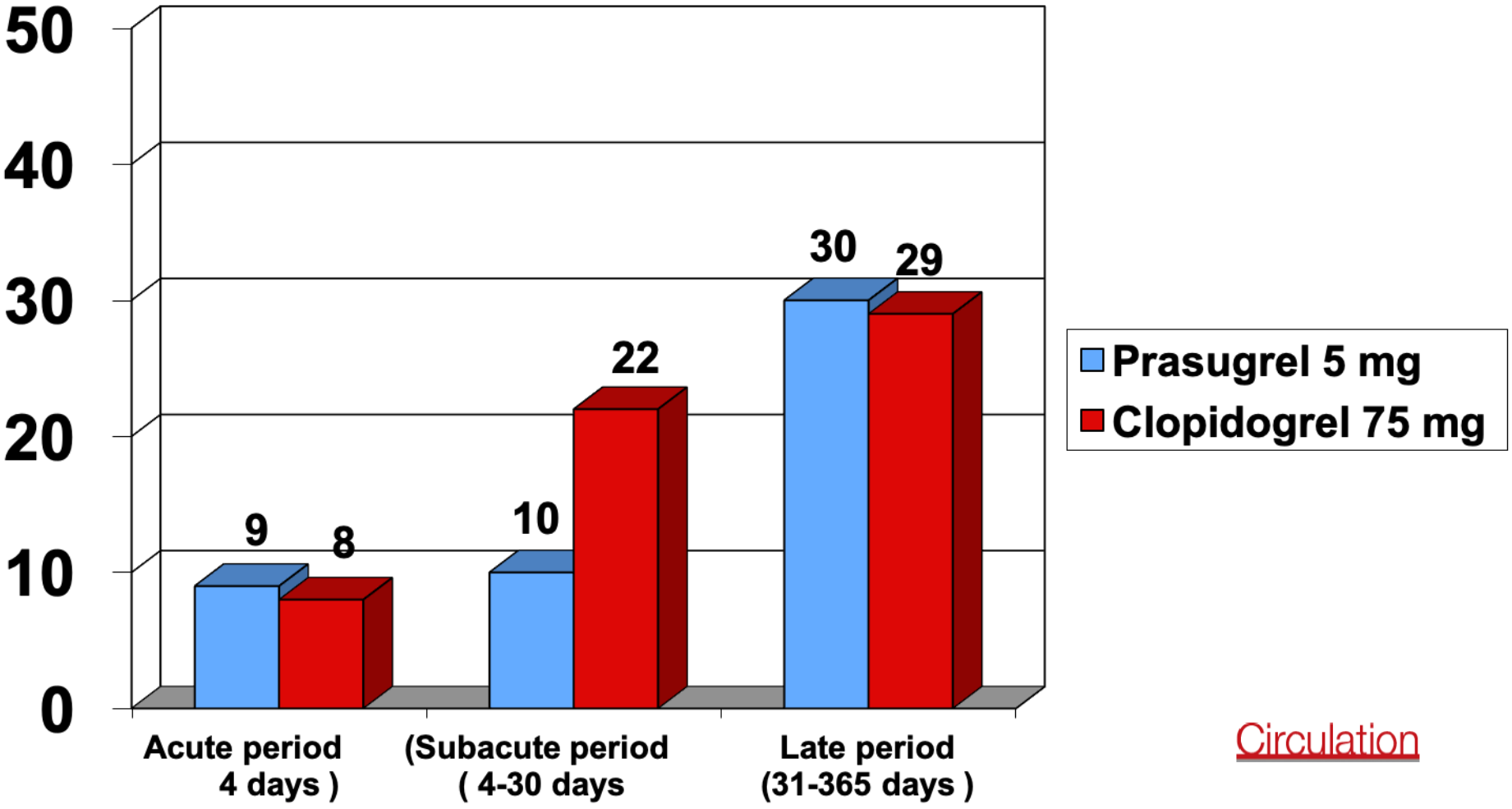
American Heart Association

10.1161/CIRCULATIONAHA.117.032180



A comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization: the Elderly ACS-2 randomised trial

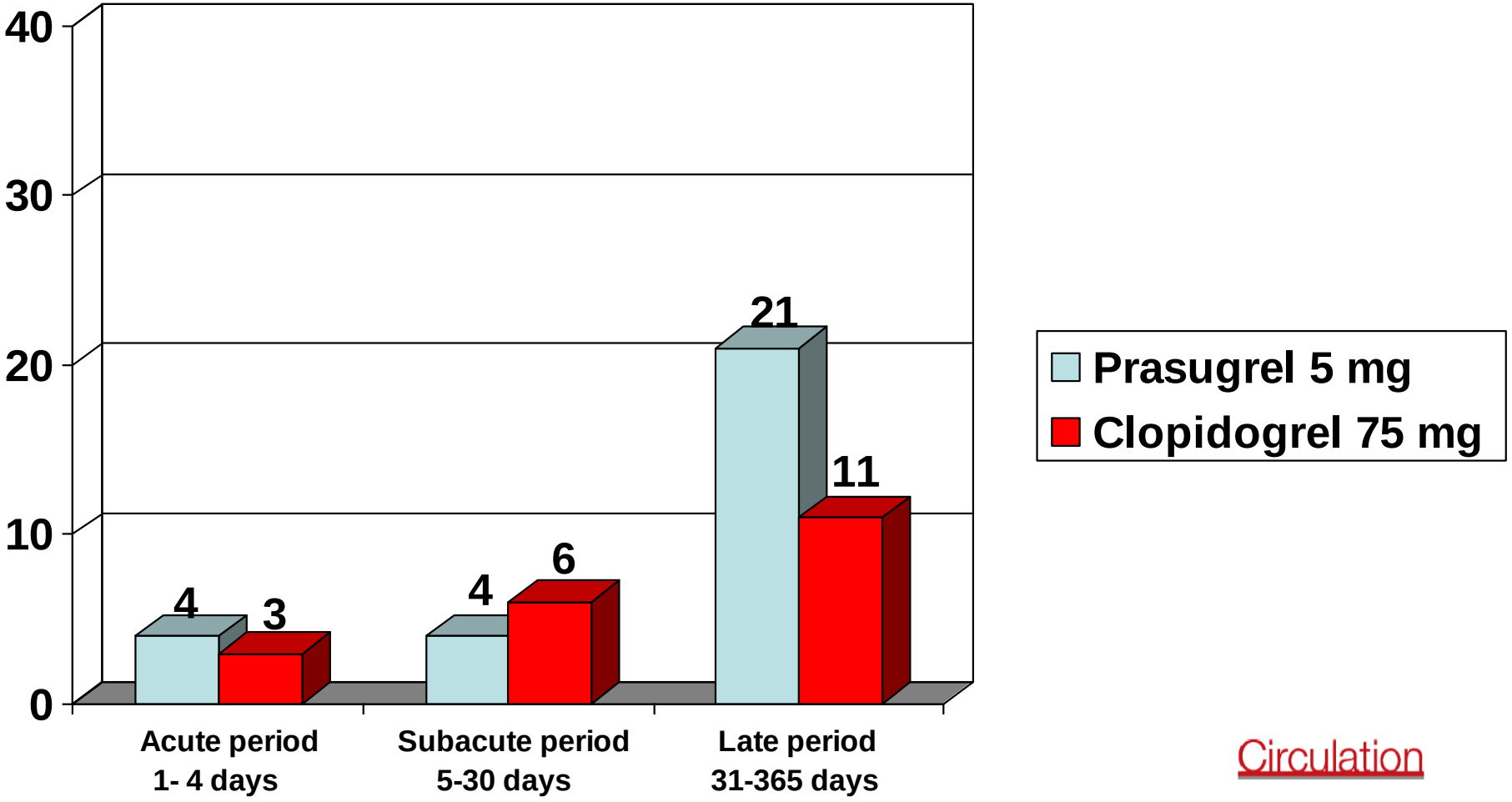
ISCHEMIC EVENTS OVER TIME : PRASUGREL 5 mg vs CLOPIDOGREL



Circulation

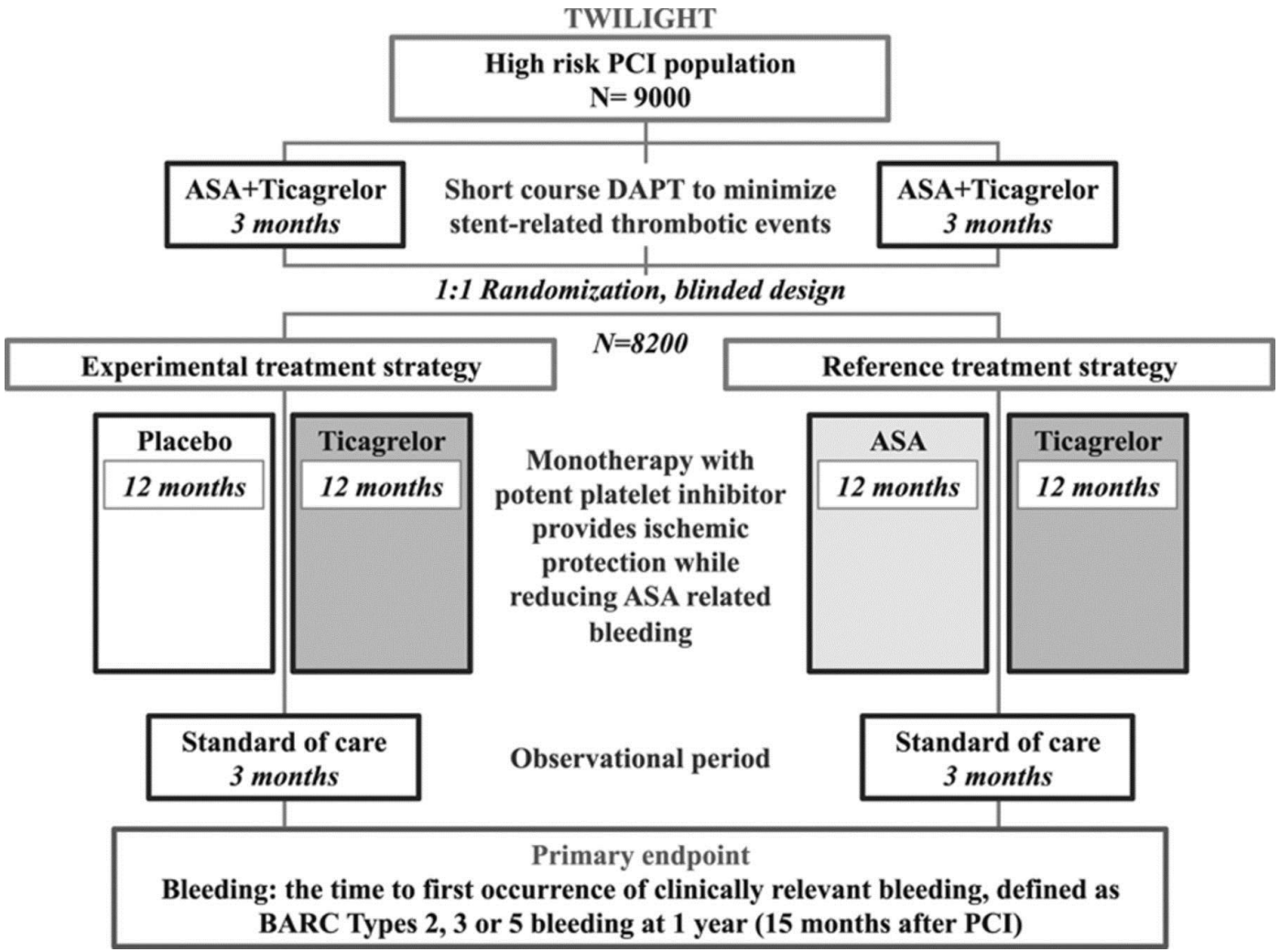
A comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization: the Elderly ACS-2 randomised trial

BLEEDING EVENTS OVER TIME : PRASUGREL 5 mg vs CLOPIDOGREL



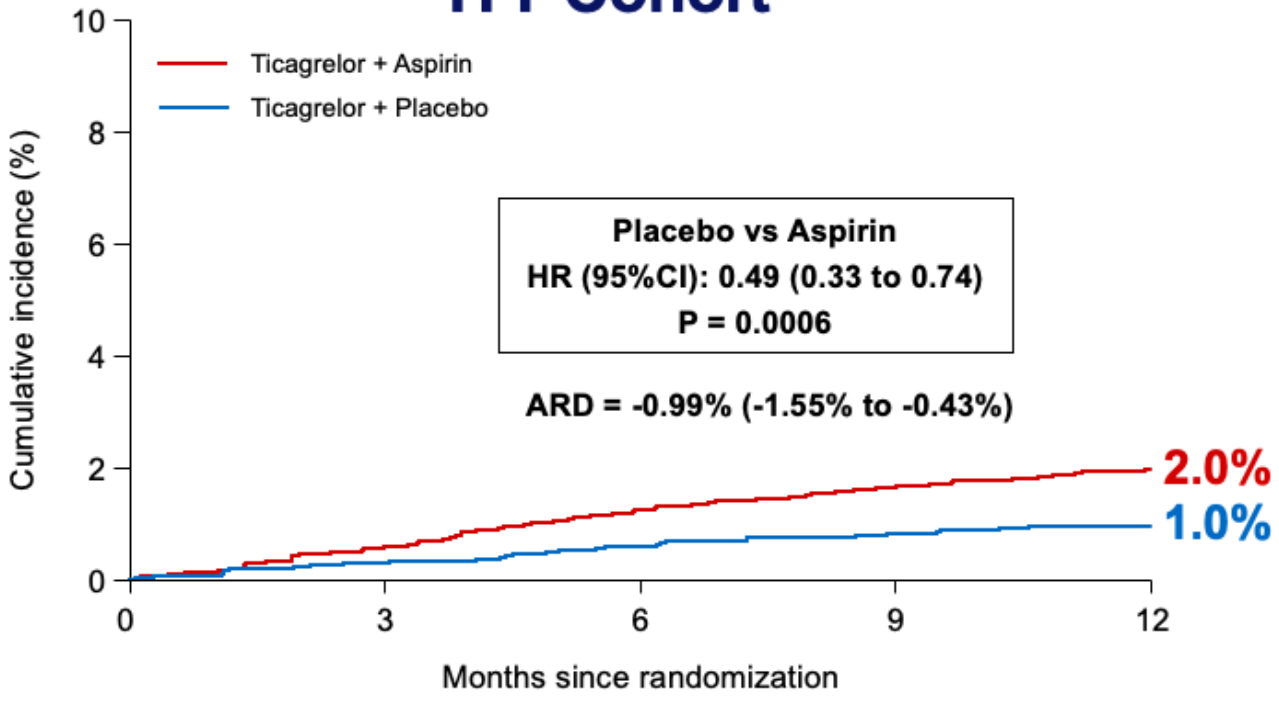
Circulation

Design of the TWILIGHT trial.



BARC 3 or 5 Bleeding

ITT Cohort



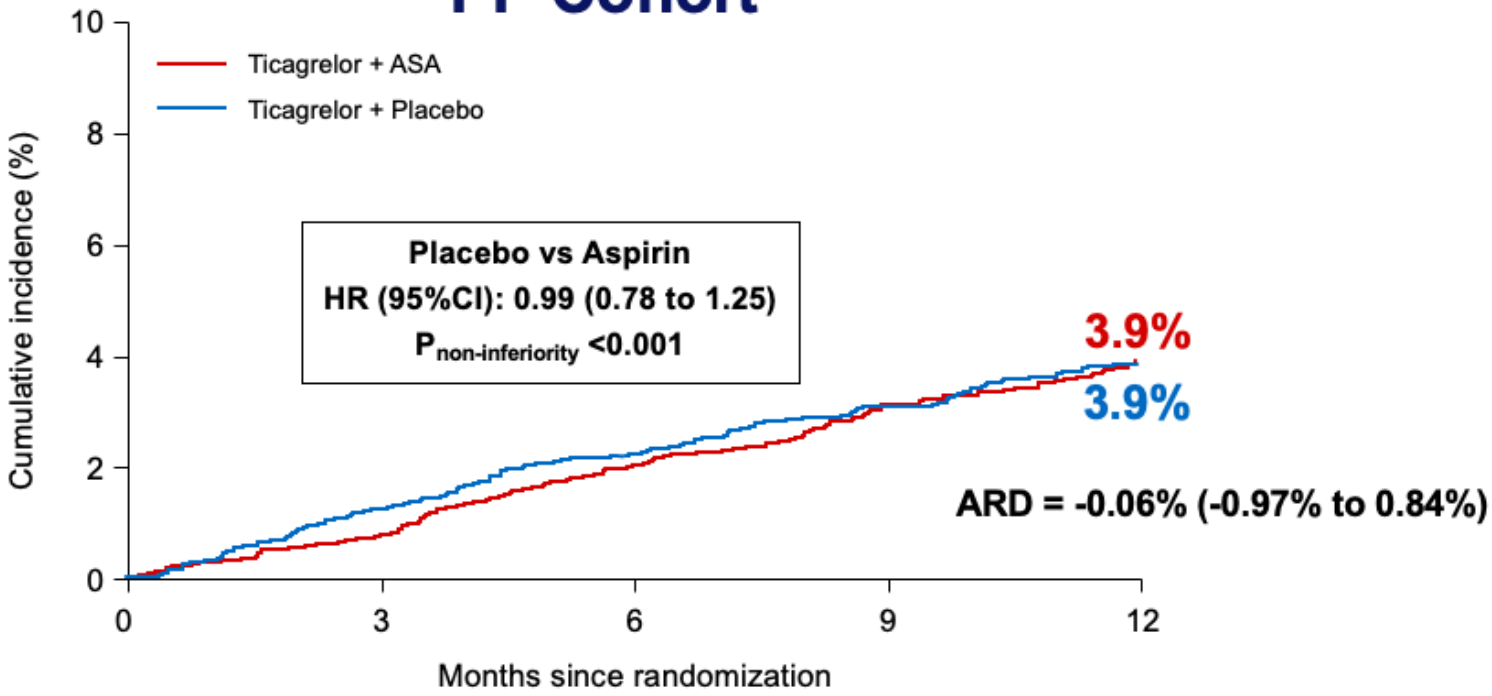
No. at risk					
Ticagrelor + Aspirin	3564	3516	3470	3426	3390
Ticagrelor + Placebo	3555	3504	3475	3440	3423

Mount Sinai

twilight

Key Secondary Endpoint: Death, MI or Stroke

PP Cohort



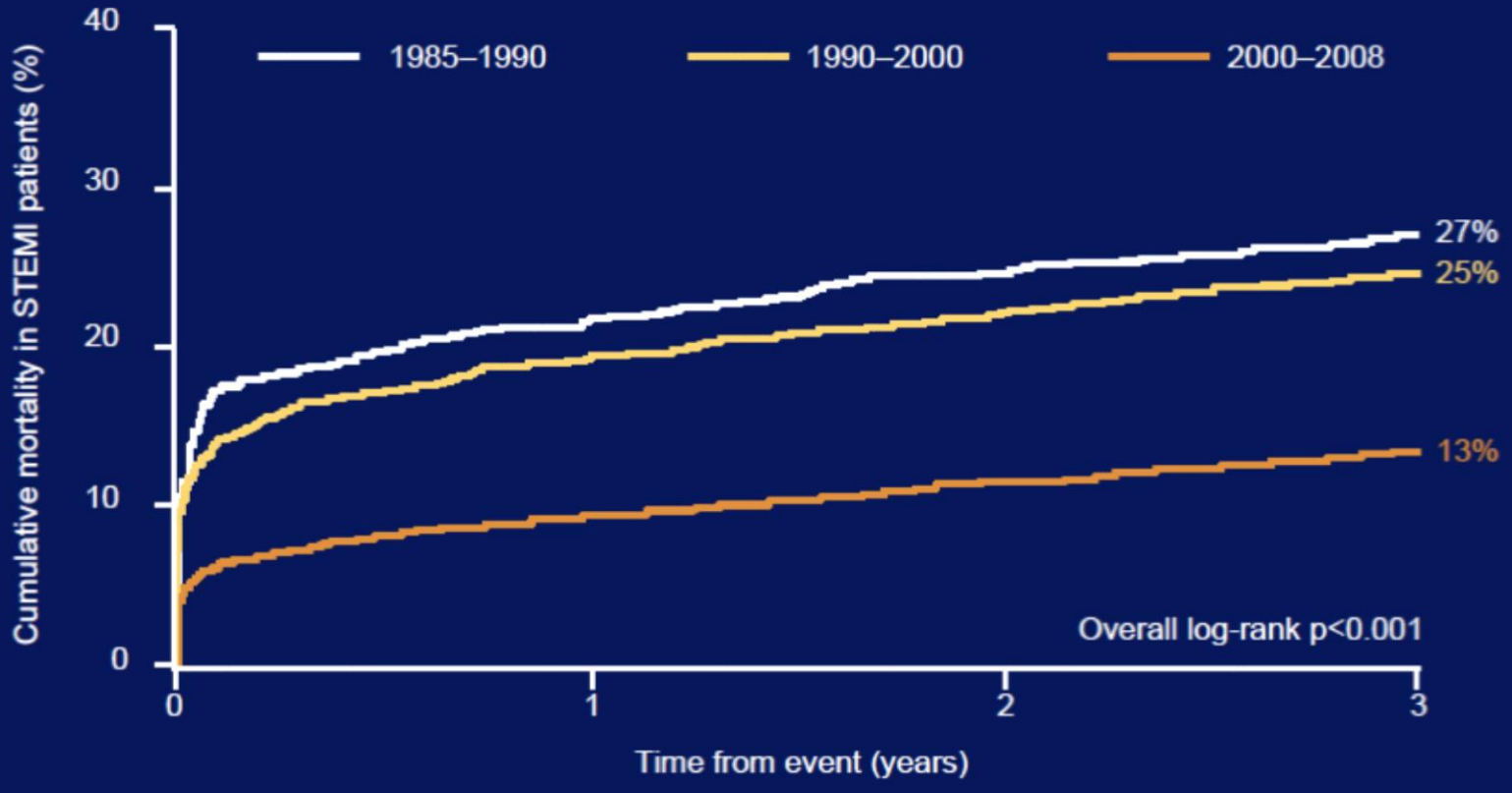
No. at risk					
Ticagrelor + Aspirin	3515	3466	3415	3361	3320
Ticagrelor + Placebo	3524	3457	3412	3365	3330

Mount Sinai

twilight

Despite improvements in survival rates, ~1 in 8 patients will die within 3 years of a STEMI

Prospective study of 3-year outcomes in a consecutive series of STEMI patients (n=6820)[Nauta 2011]



STEMI, ST-segment elevation myocardial infarction.
Adapted from: Nauta ST *et al*. PLoS One 2011;6:e26917.

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

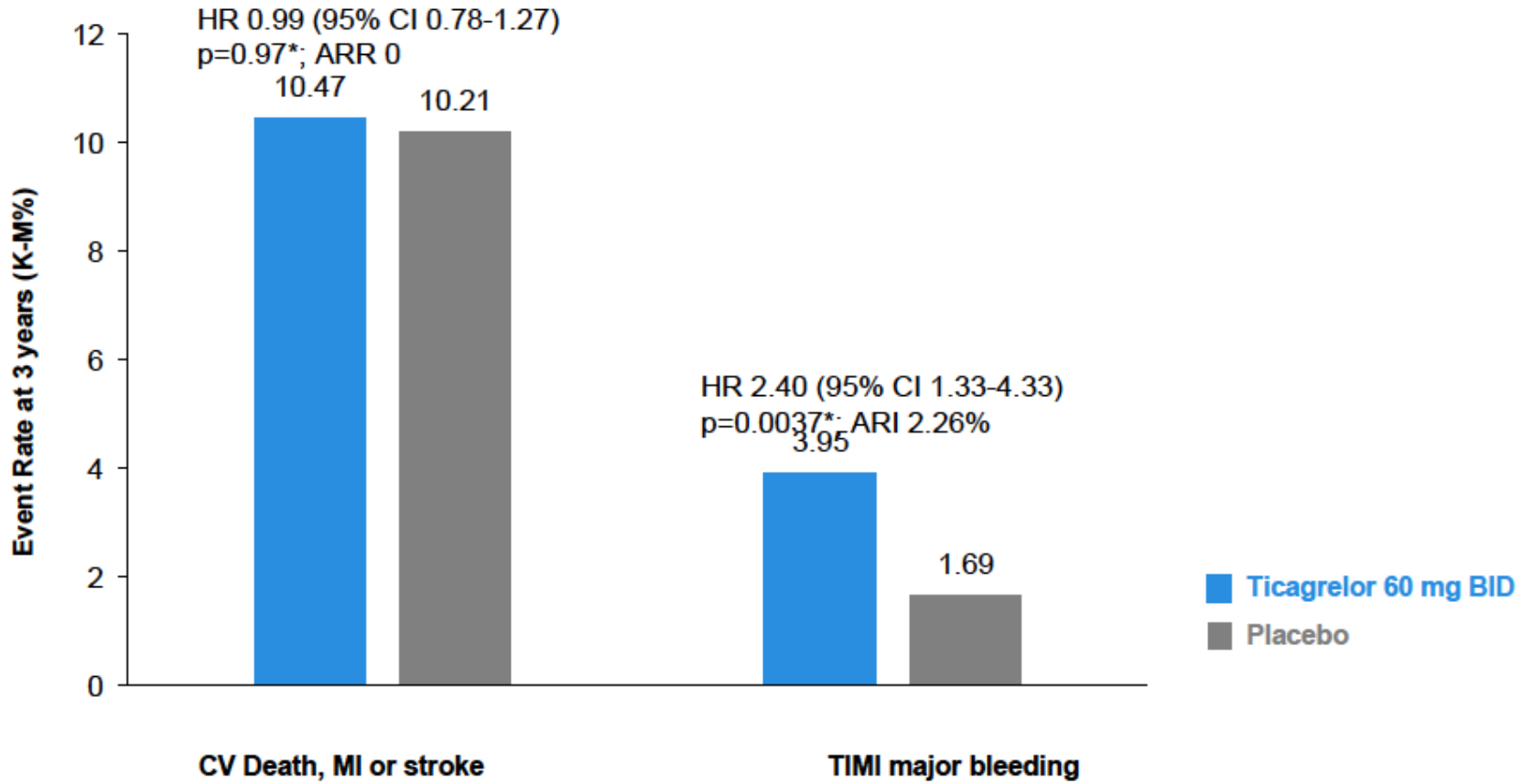
The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events[c] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIa	A
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events[e] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIb	A

[c]Diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15–59 mL/min/1.73 m^2.
[d]Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.
[e]At least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15–59 mL/min/1.73 m^2.
[f]See summary of product characteristics for reduced doses or contraindications for each NOAC in patients with CKD, body weight <60 kg, age >75–80 years, and/or drug interactions.

PEGASUS-TIMI 54 Patient Selection: Primary Endpoint (CV Death, MI or Stroke) and TIMI Major Bleeding in High Bleeding Risk Group

In the high bleeding risk population, there was no benefit of ticagrelor in reducing the rate of the primary endpoint, but there was a higher rate of TIMI major bleeding

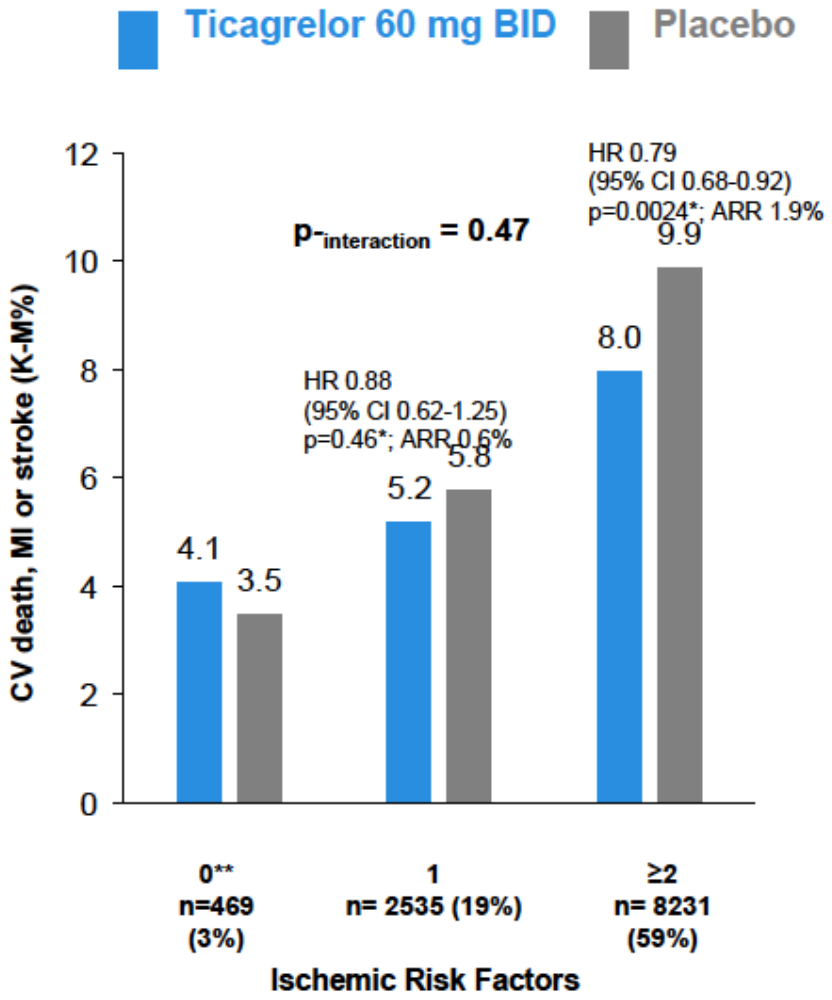


*Exploratory post-hoc sub-analysis. Findings should be considered hypothesis generating.

ARI = absolute risk increase; ARR = absolute risk reduction; CV = cardiovascular; HR = hazard ratio; K-M = Kaplan Meier; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

Bonaca MP et al. Poster presented at: AHA Scientific Sessions 2018; November 10, 2018; Chicago, IL

PEGASUS-TIMI 54 Patient Selection: Primary Endpoint (CV Death, MI or Stroke) and TIMI Major Bleeding in Low Bleeding Risk Population by Number of Ischemic Risk Factors



**HR and p value not reported.

ARI = absolute risk increase; ARR = absolute risk reduction; CV = cardiovascular; HR = hazard ratio; K-M = Kaplan Meier; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

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ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

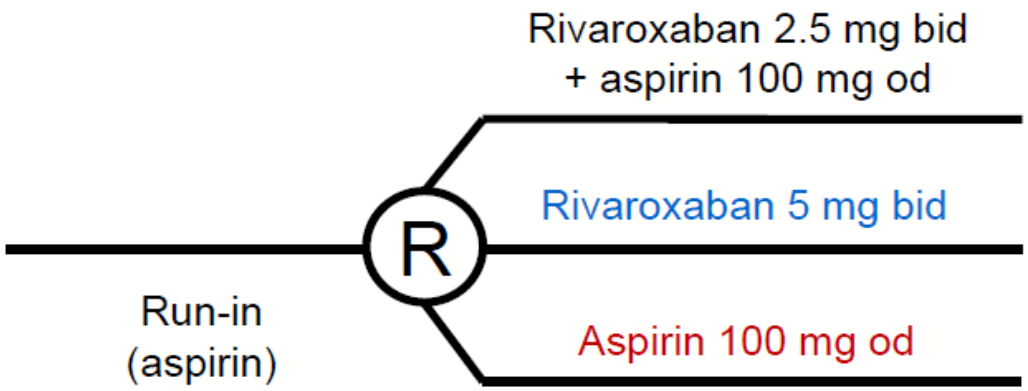
Table 9 Treatment options for dual antithrombotic therapy in combination with aspirin 75 – 100 mg daily in patients who have a high[a] or moderate[b] risk of ischaemic events, and do not have a high bleeding risk[c]

Drug option	Dose	Indication	Additional cautions	References
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year		289,290
Prasugrel	10 mg o.d or 5 mg o.d.; if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years	289,290,313
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min	297
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year		291–293,307,314

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

COMPASS design

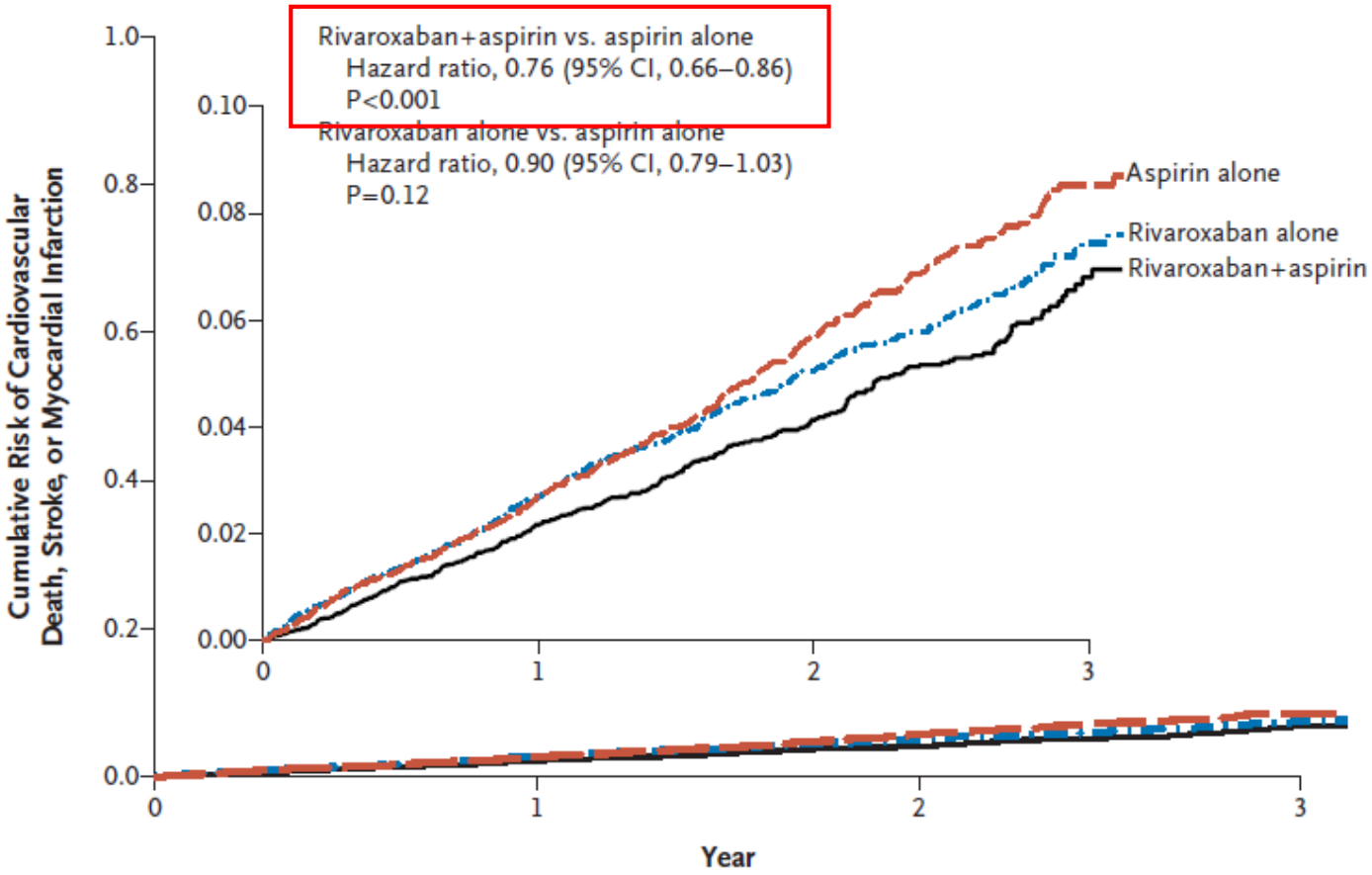
Stable CAD or PAD
2,200 with a primary outcome event



Expected follow up
3-4 years

ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease



Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

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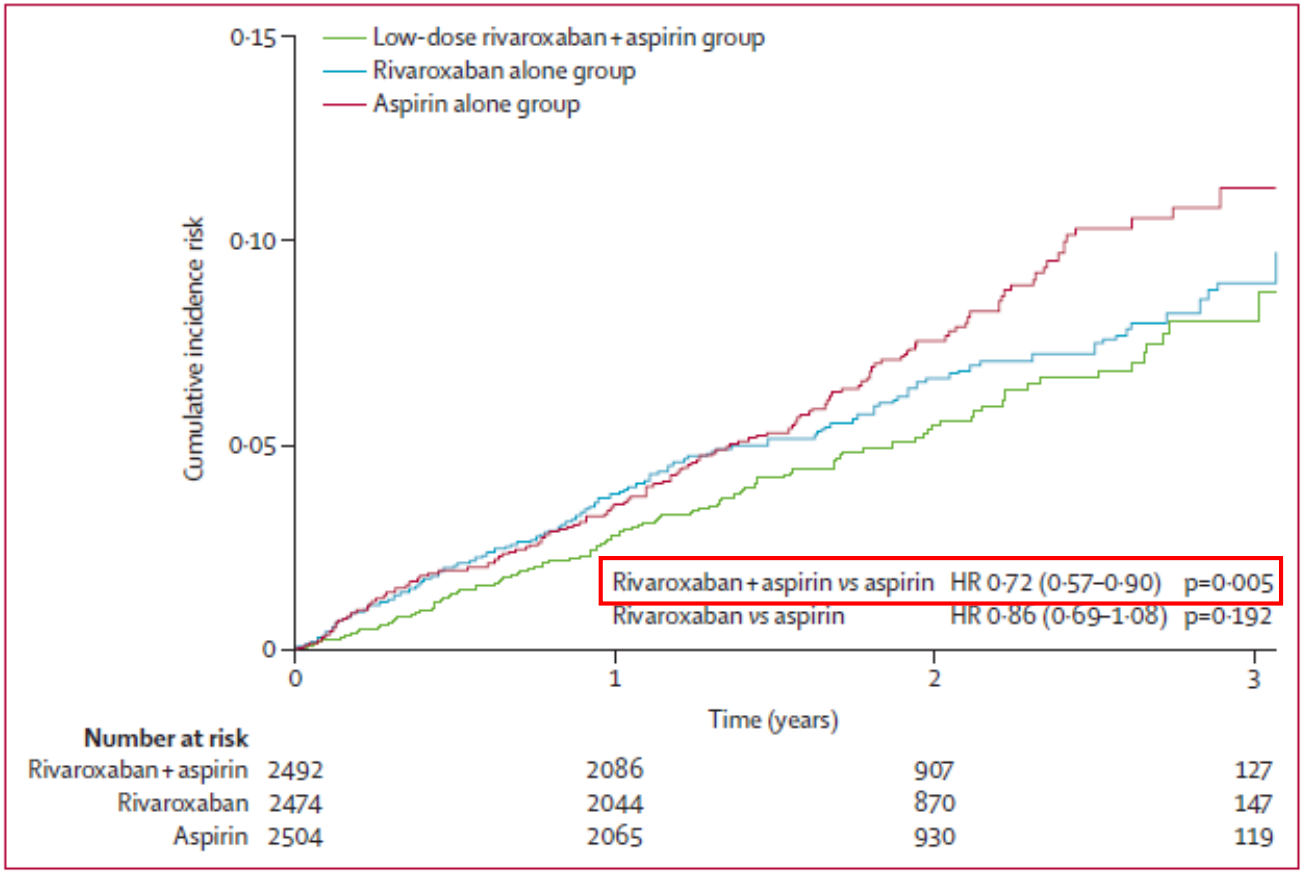

Final thoughts

In ACS patients the duration of DAPT should be tailored to individual ischemic and bleeding risk .

Patients with high bleeding risk need to reduce the duration of DAPT (3-6 months) .

Switching from potent to less potent $P2Y_{12}$ inhibitors is a good option in patients with both high ischemic and bleeding risk .

Final thoughts

When DAPT is discontinued , it is unknown whether aspirin or a $P2Y_{12}$ inhibitor should be continued . Further studies are needed in ACS patients .

Patients with a high ischemic risk and without a high bleeding risk need to receive a dual antithrombotic treatment beyond 1 year or for lifetime .