



Insights from ISAR REACT5 trial



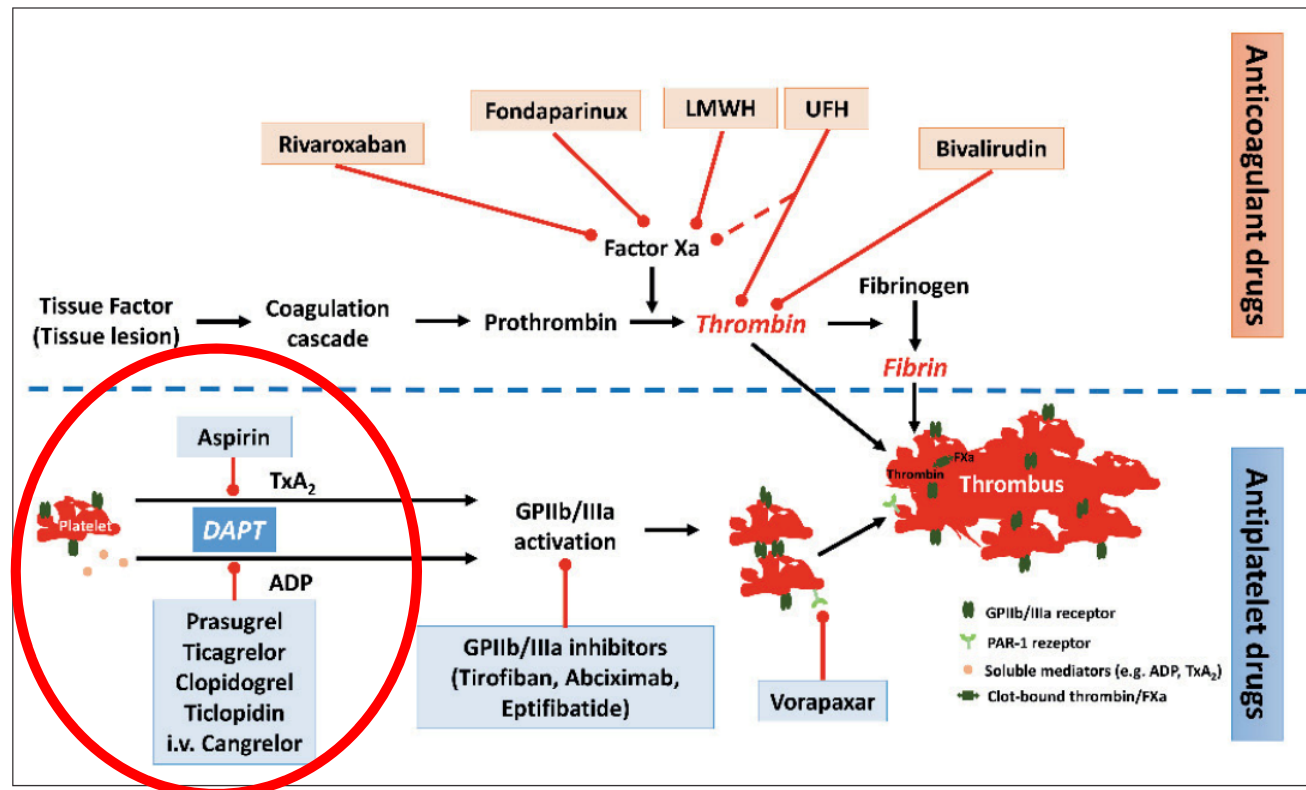
Mamas A. Mamas
Professor of Cardiology
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 @MMamas1973





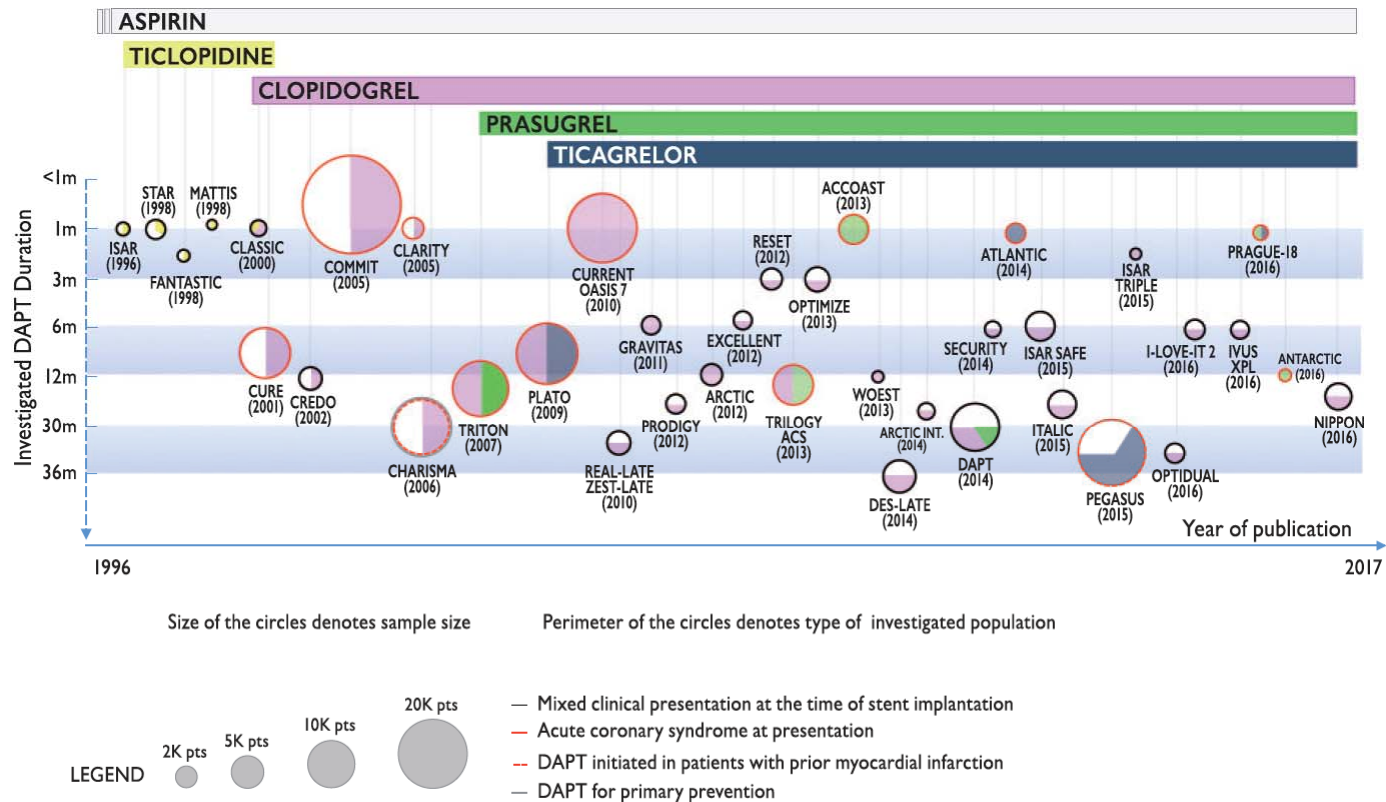
Antithrombotic drugs in the treatment of ACS



DAPT, dual antiplatelet therapy; LMWH, low molecular weight heparin; UFH, unfractionated heparin
Sibbing et al. Thromb Haemost 2017;117:1240–8



History of DAPT therapy in patients with coronary disease, a 20 year journey





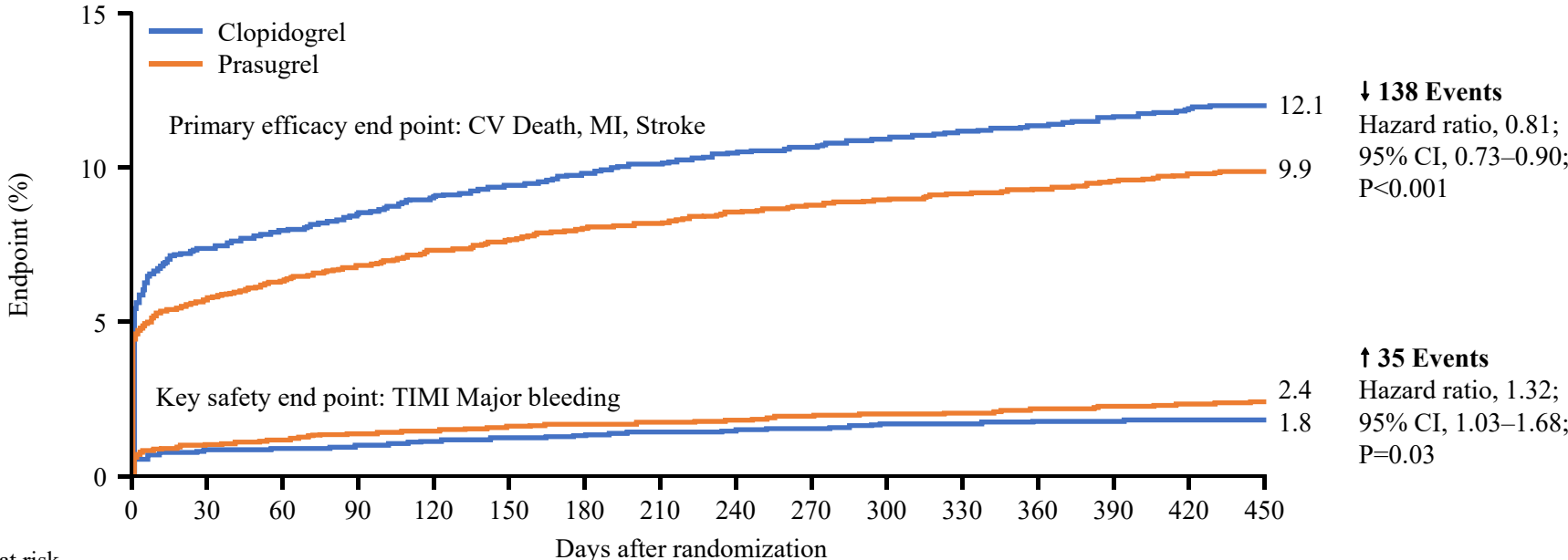
The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2007 VOL. 357 NO. 20



Prasugrel versus Clopidogrel in Patients
with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesenmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON-TIMI 38 Investigators*



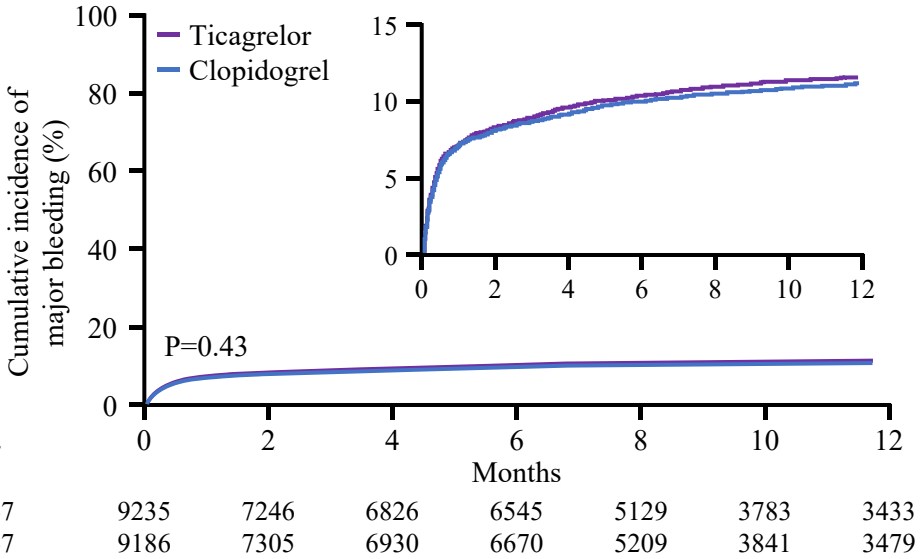
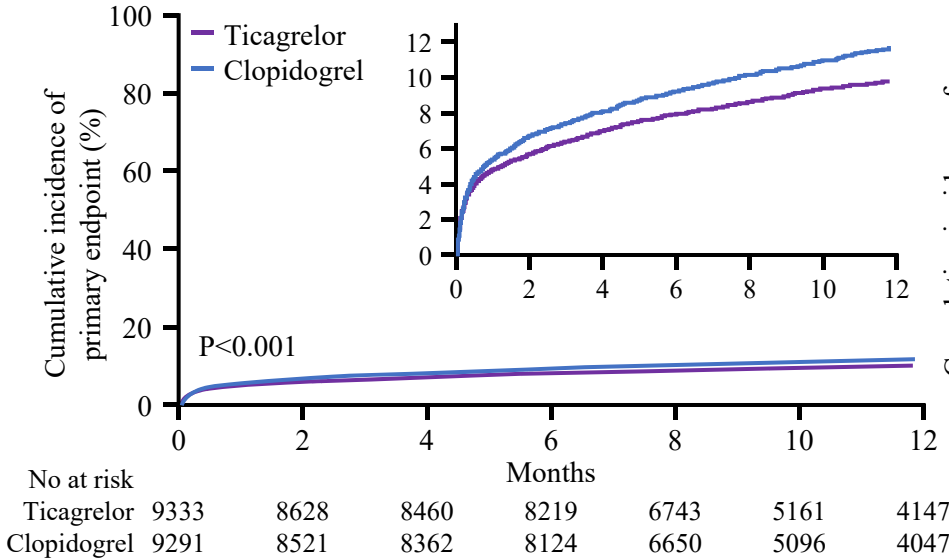
No. at risk	Days after randomization															
	0	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450
Clopidogrel	6795	6169	6036	5835	5643	5451	5259	5067	4875	4683	4491	4300	4108	3916	3724	3532
Prasugrel	6813	6305	6177	5985	5793	5601	5409	5217	5025	4833	4641	4449	4257	4065	3873	3681

Wiviott et al. N Engl J Med 2007;357:2001–15



**Ticagrelor versus Clopidogrel in Patients with Acute
Coronary Syndromes**

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D.,
 Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc.,
 Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H.,
 Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D.,
 for the PLATO Investigators*



CI, confidence interval; HR; hazard ratio; MI, myocardial infarction
 Wallentin L et al. N Engl J Med. 2009;361:1045-57



Both Prasugrel and Ticagrelor are superior to Clopidogrel: Which should we use?



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ABSTRACT

BACKGROUND

Dual-antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications of acute coronary syndromes and percutaneous coronary intervention.

METHODS

To compare prasugrel, a new thienopyridine, with clopidogrel, we randomly assigned 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) for 6 to 15 months. The primary efficacy end point

From Brigham and Women's Hospital and Harvard Medical School, Boston (S.D.W., E.B., C.H.M., S.A.M., C.M.G., E.M.A.); Institut de Cardiologie and INSERM Unit 856, Pitié-Salpêtrière University Hospital, Paris (G.M.); Instytut Kardiologii, Warsaw, Poland (W.R.); Bikur Cholim Hospital, Jerusalem, Israel (S.G.); Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany (F.-J.N.); Azienda Ospedaliero-Universitaria di Parma, Parma, Italy (D.A.); Azienda Ospedaliera Civile di Legnano, Legnano, Italy (S.D.S.); and Eli Lilly Research Labo-

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y₁₂ that has a more rapid onset and more pronounced platelet inhibition than clopidogrel.

METHODS

In this multicenter, double-blind, randomized trial, we compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation.

From the Uppsala Clinical Research Center, Uppsala, Sweden (L.W., C.H., S.J.); Duke Clinical Research Institute, Durham, NC (R.C.B., K.W.M., R.A.H.); Grochowski Hospital, Warsaw, Poland (A.B.); Thrombolysis in Myocardial Infarction Study Group, Brigham and Women's Hospital, Boston (C.P.C., B.M.S.); AstraZeneca Research and Development, Mölndal, Sweden (H.E.); and Wilmington, DE (J.H.); Århus University Hospital, Århus, Denmark (S.H.); Universitätsklinikum Heidel-



ESC 2018 Guidelines on myocardial revascularisation



NSTE-ACS:

Recommendations	Class ^a	Level ^b
Pre-treatment and antiplatelet therapy		
A P2Y ₁₂ inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding. ^{701,702,722,723} Options are:	I	A
<ul style="list-style-type: none"> • <u>Prasugrel</u> in P2Y₁₂-inhibitor naïve patients who proceed to PCI (60 mg loading dose, 10 mg daily dose).⁷⁰¹ • <u>Ticagrelor</u> irrespective of the preceding P2Y₁₂ inhibitor regimen (180 mg loading dose, 90 mg b.i.d.).⁷⁰² • Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated.⁷²²⁻⁷²⁴ 	I	B
	I	B
	I	B

STEMI:

Recommendations	Class ^a	Level ^b
Pre-treatment and antiplatelet therapy		
A potent P2Y ₁₂ inhibitor (<u>prasugrel</u> or <u>ticagrelor</u>), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding. ^{701,702,724,743}	I	A



Coronary artery disease

ORIGINAL RESEARCH ARTICLE

Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention

Ivan Olier,^{1,2} Alex Sirker,³ David J R Hildick-Smith,⁴ Tim Kinnaird,^{1,5} Peter Ludman,⁶ Mark A de Belder,⁷ Andreas Baumbach,⁸ Jonathan Byrne,⁹ Muhammad Rashid,^{1,10} Nick Curzen,¹¹ Mamas A Mamas,^{1,10} on behalf of the British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research

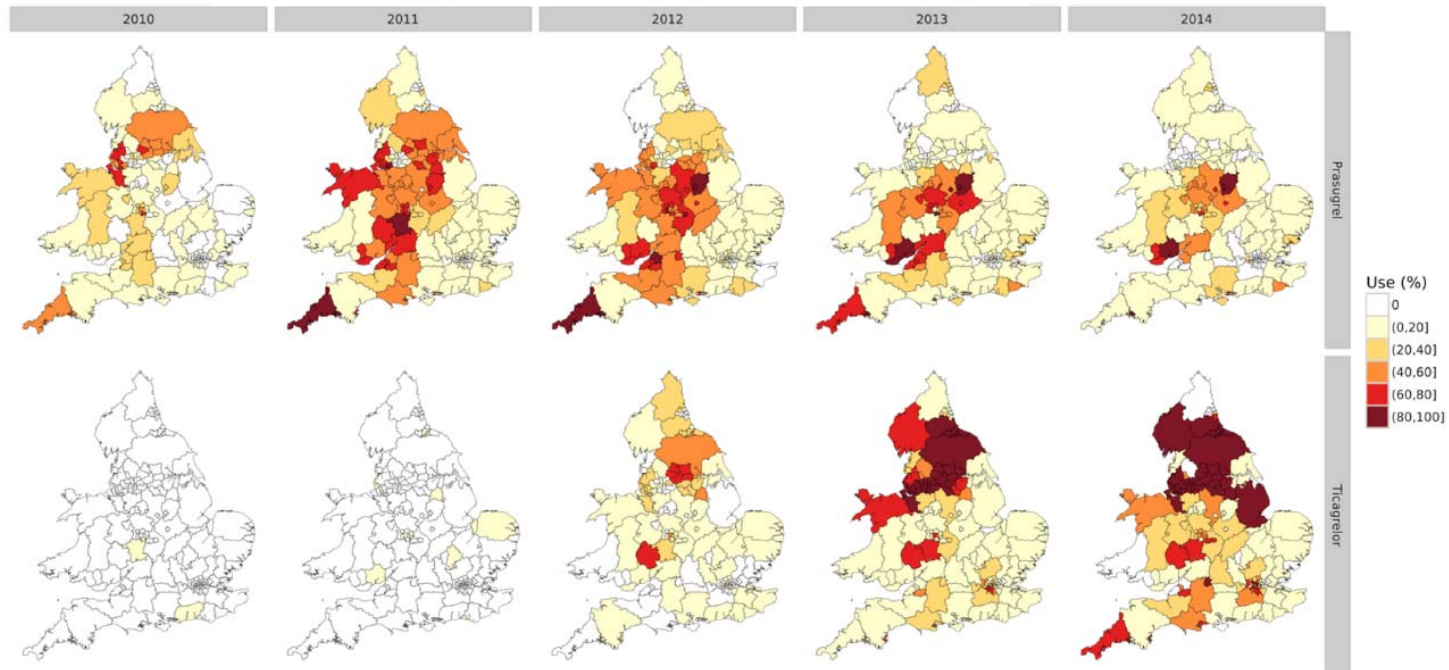


Figure 2 Changes in use of antiplatelet drugs in primary care trusts in England and local health boards in Wales.

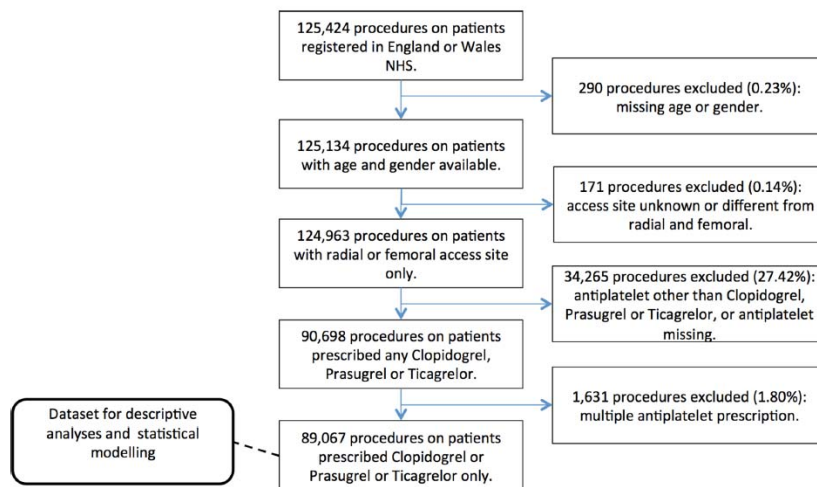
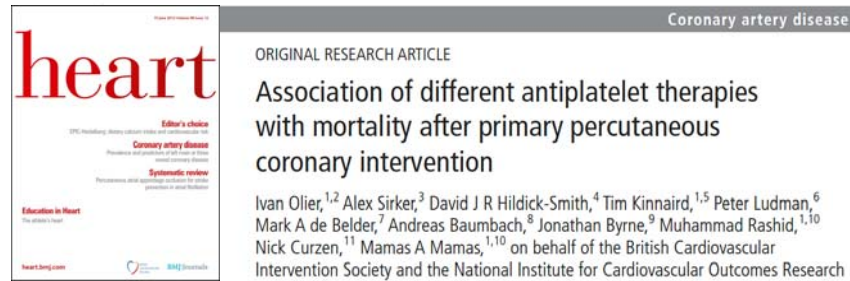
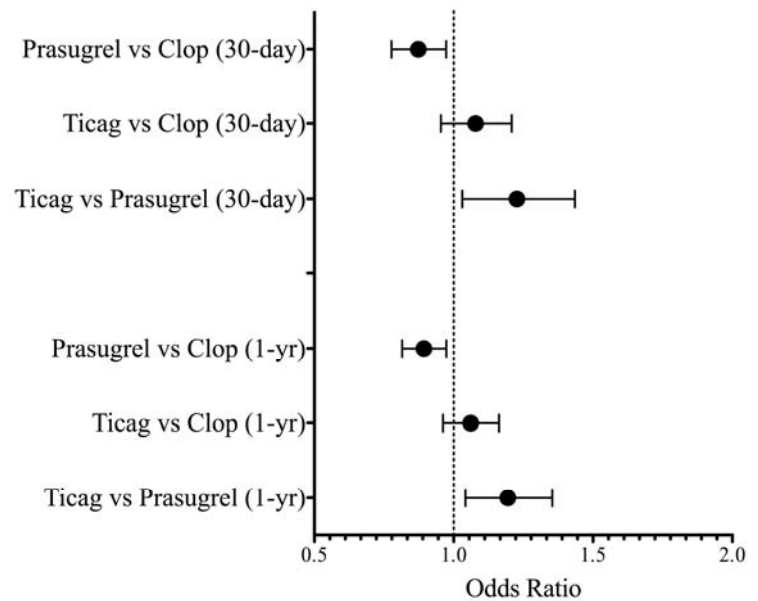


Figure 1 Flow chart for procedure inclusion/exclusion. NHS, National Health Service.





THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

S. Schüpke, F.-J. Neumann, M. Menichelli, K. Mayer, I. Bernlochner, J. Wöhrle, G. Richardt, C. Liebetrau, B. Witzenbichler, D. Antoniucci, I. Akin, L. Bott-Flügel, M. Fischer, U. Landmesser, H.A. Katus, D. Sibbing, M. Seyfarth, M. Janisch, D. Boncompagni, R. Hiltz, W. Rottbauer, R. Okrojek, H. Möllmann, W. Hochholzer, A. Migliorini, S. Cassese, P. Mollo, E. Xhepa, S. Kufner, A. Strehle, S. Leggewie, A. Allali, G. Ndrepepa, H. Schühlen, D.J. Angiolillo, C.W. Hamm, A. Hapfelmeier, R. Tölg, D. Trenk, H. Schunkert, K.-L. Laugwitz, and A. Kastrati, for the ISAR-REACT 5 Trial Investigators*



Trial

- Randomized controlled, multi-centre trial in patients in whom invasive management planned, randomized to receive Ticagrelor or Prasugrel

Primary Endpoint

- Composite of death, myocardial infarction or stroke at 12 months

Secondary Endpoints

- BARC 3-5 Bleeding (safety endpoint)
- Individual components of primary endpoint
- Stent thrombosis



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Major Inclusion Criteria

- Hospitalization for an acute coronary syndrome with planned invasive strategy

Major Exclusion Criteria

- Active bleeding
- Need for oral anticoagulation
- History of stroke or TIA
- Renal insufficiency requiring dialysis
- Moderate or severe hepatic dysfunction
- Concomitant therapy with strong CYP3A4 inhibitors, strong CYP3A inducers, CYP3A substrates with narrow therapeutic indices



Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

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STEMI

Randomization

Ticagrelor
180 mg loading

Prasugrel
60 mg loading

Angiography + PCI

Ticagrelor
90 mg 1-0-1

Prasugrel
10 mg 1-0-0*

Duration of ADP receptor therapy: 12 months
Concomitant ASA: 75-150 mg/d

In patients with known coronary anatomy

* Prasugrel 5 mg in patients ≥ 75 years of age or weight < 60 kg

Protocol

Unstable Angina, NSTEMI

Randomization

Ticagrelor
180 mg loading

Prasugrel#
60 mg loading

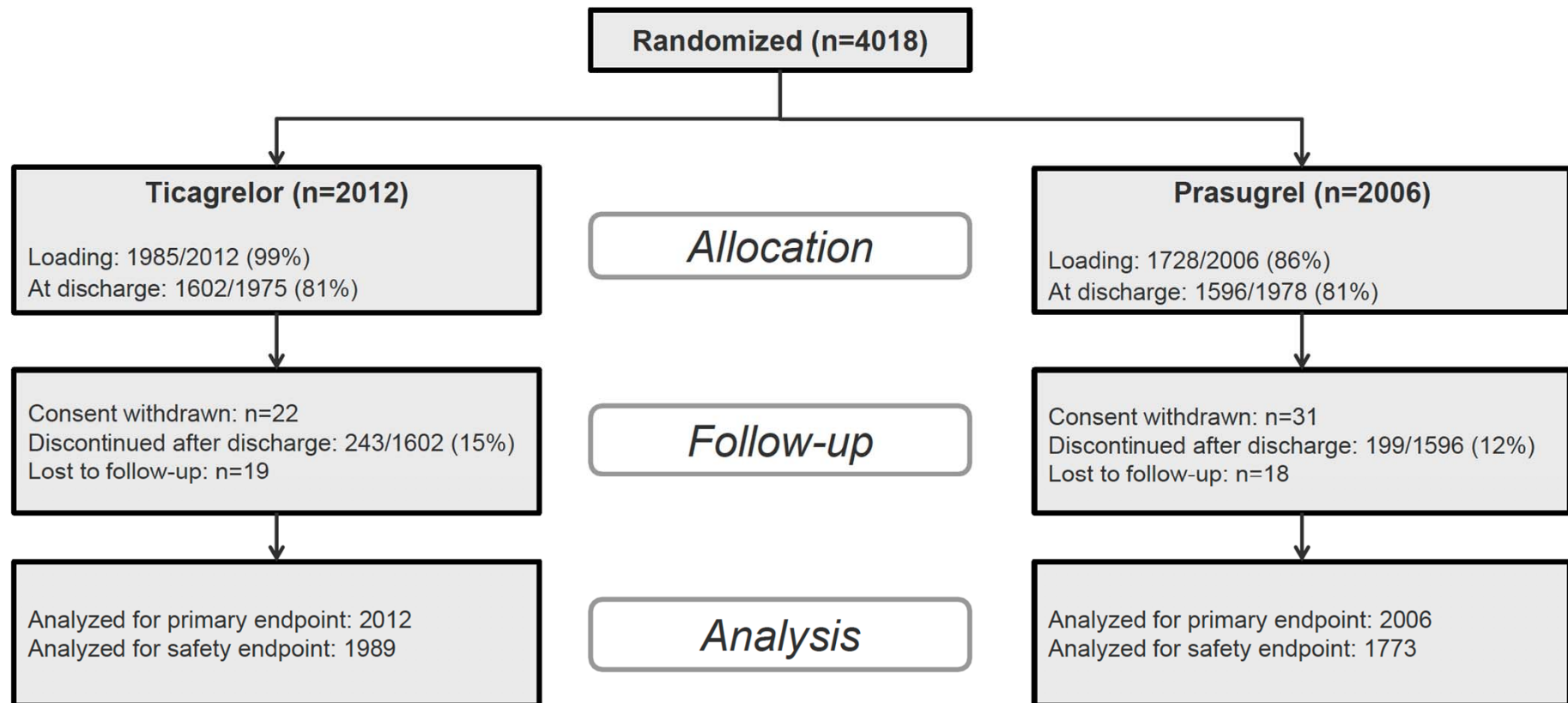
Angiography

Prasugrel
60 mg loading

PCI

Ticagrelor
90 mg 1-0-1

Prasugrel
10 mg 1-0-0*





Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ticagrelor Group (N=2012)	Prasugrel Group (N=2006)
Age — yr	64.5±12.0	64.6±12.1
Female sex — no. (%)	478 (23.8)	478 (23.8)
Cardiovascular risk factors — no./total no. (%)		
Diabetes	463/2011 (23.0)	429/2005 (21.4)
Use of insulin for diabetes	143/2011 (7.1)	137/2005 (6.8)
Current smoker	682/2002 (34.1)	667/1999 (33.4)
Arterial hypertension	1432/2008 (71.3)	1384/2003 (69.1)
Hypercholesterolemia	1178/2007 (58.7)	1163/2003 (58.1)
Medical history — no./total no. (%)		
Myocardial infarction	311/2010 (15.5)	320/2005 (16.0)
PCI	453/2011 (22.5)	463/2004 (23.1)
Aortocoronary bypass surgery	115/2011 (5.7)	130/2005 (6.5)
Cardiogenic shock — no. (%)	31 (1.5)	34 (1.7)
Blood pressure — mm Hg		
Systolic†	144±25	143±24
Diastolic‡	82±15	82±14
Heart rate — beats/min‡	77±16	76±16
BMI¶	27.8±4.6	27.8±4.4
Weight <60 kg — no./total no. (%)	108/2003 (5.4)	94/1988 (4.7)
Creatinine level — mg/dL‡	88.27	88.21
Diagnosis at admission — no. (%)		
Unstable angina	249 (12.4)	261 (13.0)
NSTEMI	930 (46.2)	925 (46.1)
STEMI	833 (41.4)	820 (40.9)
Treatment strategy — no./total no. (%)**		
PCI	1676/2009 (83.4)	1701/2005 (84.8)
CABG	47/2009 (2.3)	36/2005 (1.8)
Conservative therapy	285/2009 (14.2)	268/2005 (13.4)
Other ††	1/2009 (<0.1)	0

- 41% patients STEMI, 46% NSTEMI
- > 99.5% of patients received coronary angiography
- 84% of patients underwent PCI, 2% CABG and 14% medically managed



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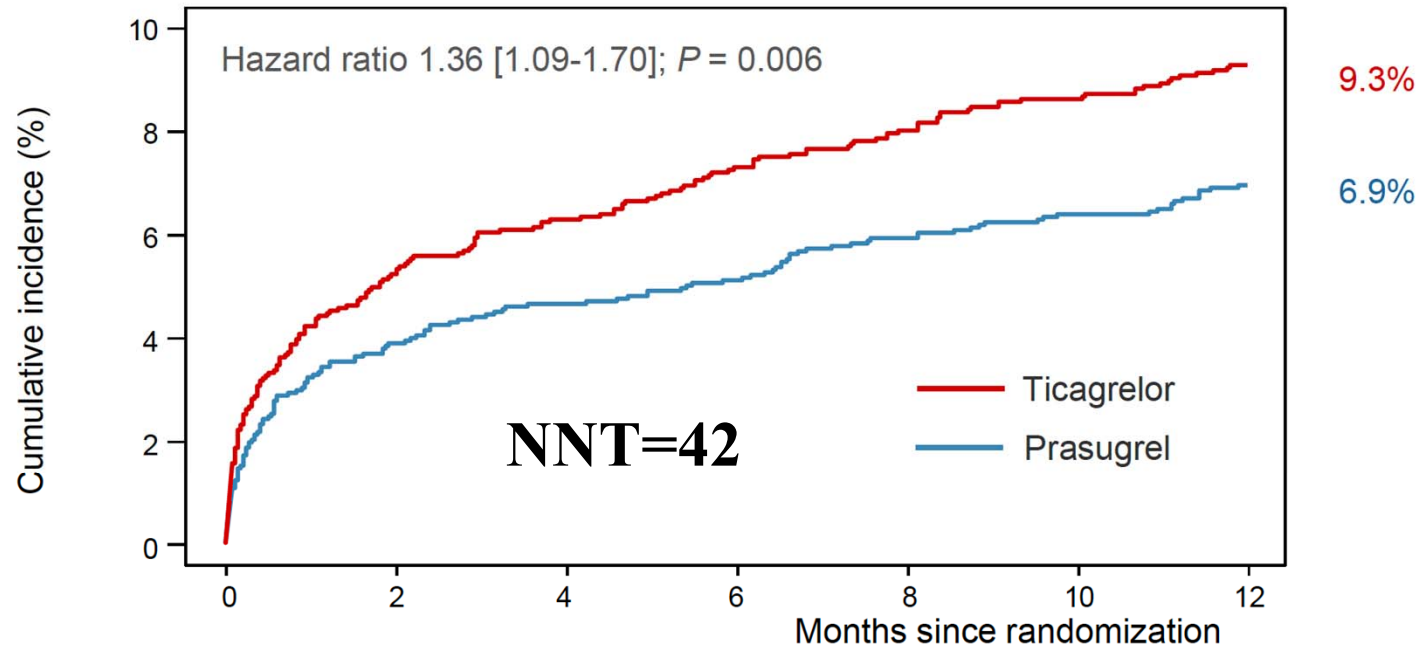
Table S3. Diagnosis and Drug Therapy at Discharge

Characteristics	Ticagrelor (N = 2012)	Prasugrel (N = 2006)
Final diagnosis of acute coronary syndrome		
– no. (%)*	1830/2006 (91.2)	1813/2004 (90.5)
– unstable angina	189/1830 (10.3)	173/1813 (9.5)
– Non-ST-segment elevation MI	834/1830 (45.6)	827/1813 (45.6)
– ST-segment elevation MI	807/1830 (44.1)	813/1813 (44.8)
Therapy at discharge – no. (%)†		
– Aspirin	1866/1975 (94.5)	1878/1978 (94.9)
– Ticagrelor	1602/1975 (81.1)	14/1978 (0.7)
– Prasugrel	21/1975 (1.1)	1596/1978 (80.7)
– Clopidogrel	90/1975 (4.6)	117/1978 (5.9)
– Oral anticoagulant drugs	82/1975 (4.2)	100/1978 (5.1)



Primary End point

(Composite of Death, MI, or Stroke)

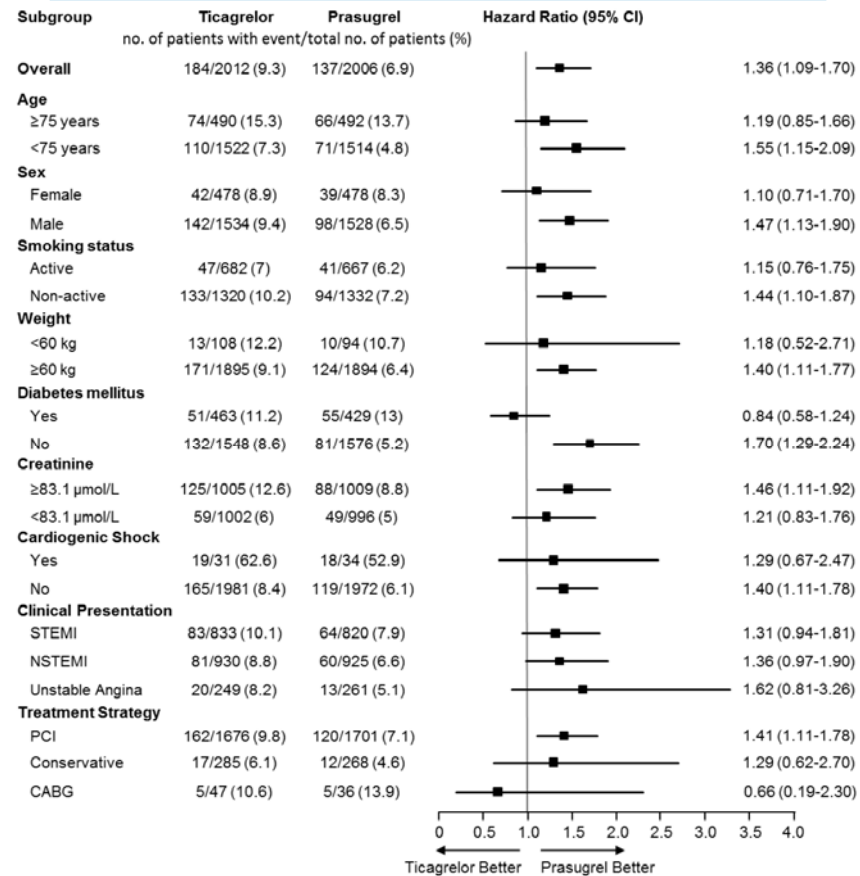


No. at Risk

Ticagrelor	2012	1877	1857	1835	1815	1801	1772
Prasugrel	2006	1892	1877	1862	1839	1829	1803



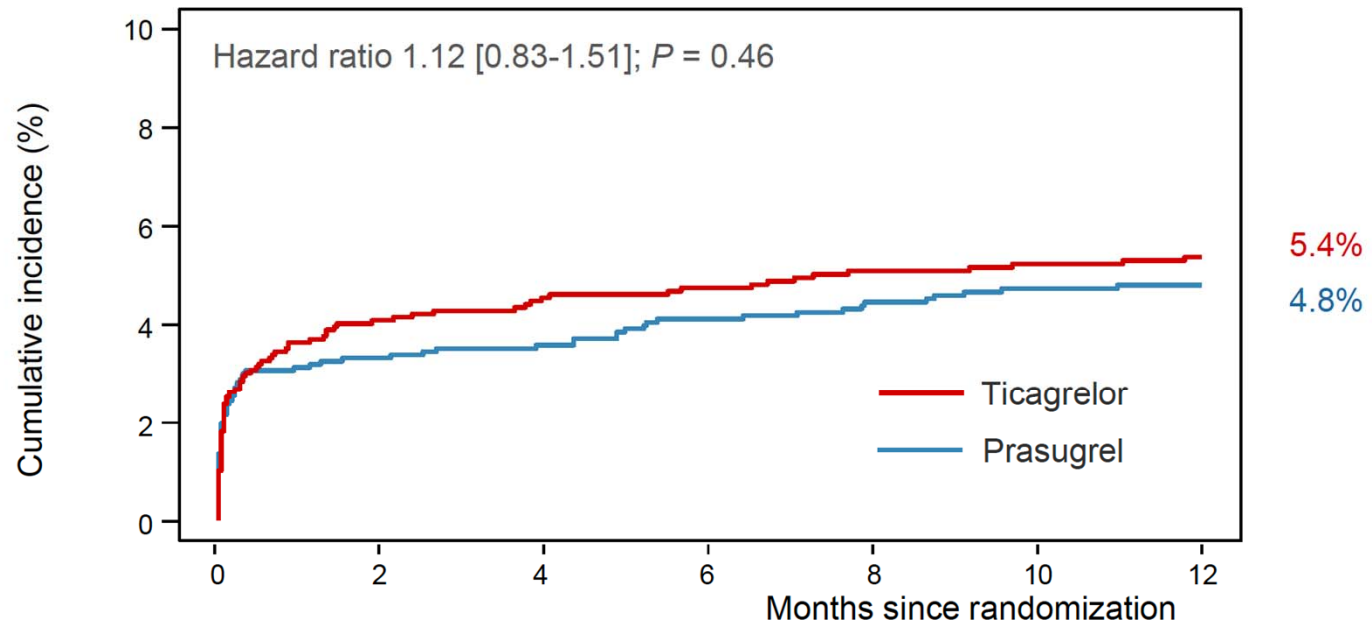
Primary End point (Composite of Death, MI, or Stroke)





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



Table 2. Clinical End Points.*

End Point	Ticagrelor Group (N=2012)	Prasugrel Group (N=2006)	Hazard Ratio (95% CI)	P Value
Primary end point: death, myocardial infarction, or stroke — no. (%)	184 (9.3)	137 (6.9)	1.36 (1.09–1.70)	0.006
Death — no. (%)				
From any cause	90 (4.5)	73 (3.7)	1.23 (0.91–1.68)	
From cardiovascular cause	63 (3.2)	59 (3.0)		
From noncardiovascular cause	27 (1.4)	14 (0.7)		
Myocardial infarction — no. (%)†	96 (4.8)	60 (3.0)	1.63 (1.18–2.25)	
Type 1 — no.	52	35		
Type 2 — no.	4	3		
Type 4a — no.	19	11		
Type 4b — no.	20	11		
Type 5 — no.	1	0		
STEMI — no.	31	14		
Stroke				
Any — no. (%)	22 (1.1)	19 (1.0)	1.17 (0.63–2.15)	
Ischemic — no.	16	17		
Hemorrhagic — no.	6	2		
Definite or probable stent thrombosis — no. (%)	26 (1.3)	20 (1.0)	1.30 (0.72–2.33)	
Definite stent thrombosis — no. (%)	22 (1.1)	12 (0.6)		
Secondary safety end point: BARC type 3, 4, or 5 bleeding — no./total no. (%)‡	95/1989 (5.4)	80/1773 (4.8)	1.12 (0.83–1.51)	0.46
BARC 3a	47	41		
BARC 3b	32	31		
BARC 3c	4	2		
BARC 4	8	2		
BARC 5a	1	0		
BARC 5b	3	4		





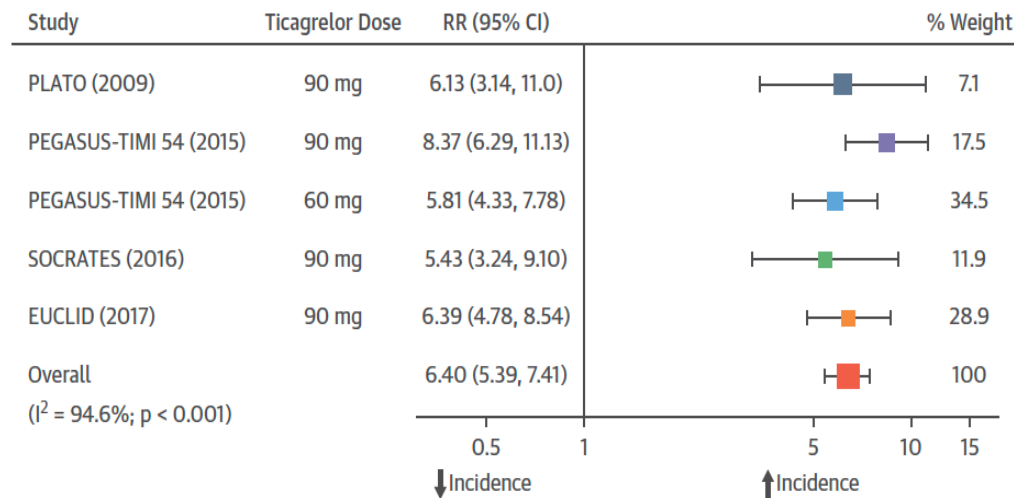
Premature Ticagrelor Discontinuation in Secondary Prevention of Atherosclerotic CVD

JACC Review Topic of the Week

Sameer Arora, MD,^{a,*} Kamal Shemisa, MD,^{b,*,†} Muthiah Vaduganathan, MD, MPH,^c Arman Qamar, MD,^c
Ankur Gupta, MD, PhD,^b Sushil K. Garg, MD,^d Dharam J. Kumbhani, MD, SM,^b Helen Mayo, MLS,^e
Houman Khalili, MD,^f Ambarish Pandey, MD, MScS,^b Sandeep R. Das, MD, MPH, MBA^f



FIGURE 2 Dyspnea-Related Discontinuation Risk for Ticagrelor Versus Comparator



ISAR REACT 5: Greater discontinuation of Ticagrelor (15%) vs Prasugrel (12%)
 $P < 0.05$, median time to discontinuation 84 days (Ticagrelor) vs 102 days (Prasugrel)



Ticagrelor or Prasugrel in Acute Coronary Syndromes — The Winner Takes It All?

Hani Jneid, M.D.

Suggested algorithm from NEJM editorial

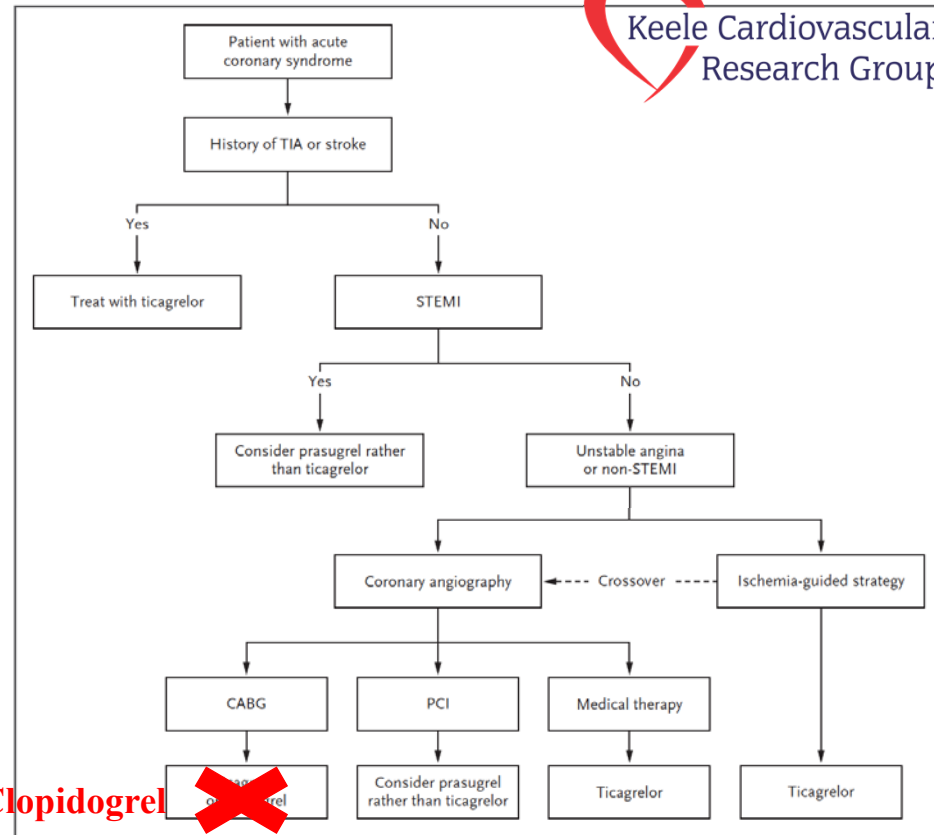


Figure 1. Proposed Algorithm for the Choice of an Oral P2Y₁₂ Receptor Inhibitor for Patients with an Acute Coronary Syndrome.

An ischemia-guided strategy involves an initial medical strategy with angiography reserved for patients who have evidence of recurrent ischemic symptoms or failed medical therapy, clinical indicators of high prognostic risk, or objective evidence of clinically significant ischemia. CABG denotes coronary-artery bypass grafting, PCI percutaneous coronary intervention, STEMI ST-segment elevation myocardial infarction, and TIA transient ischemic attack.



Summary

- RCTs show superiority of Prasugrel and Ticagrelor to Clopidogrel
- ISAR-REACT 5 RCT in ACS demonstrates superior outcomes of Prasugrel in ACS patients with a planned invasive management
- Superiority mainly driven by decreased risk of type 1 AMI and stent thrombosis
- Landmark trial providing insight into optimal anti-platelet therapy in patients treated with planned invasive strategy
- Advances personalization of antiplatelet therapy in ACS