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Technische Universität München

Deutsches Herzzentrum München
des Freistaates Bayern
Klinik a. d. Technischen Universität München

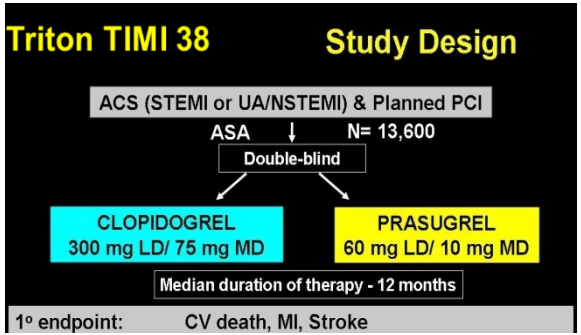
ISAR-REACT 5:

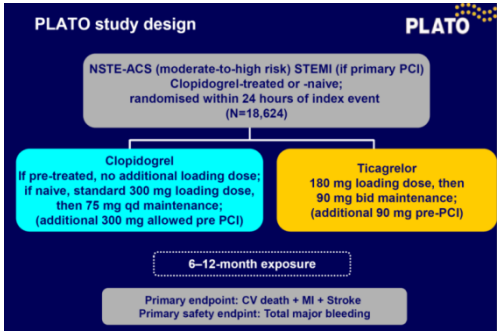
Ticagrelor vs. Prasugrel in Acute Coronary Syndromes

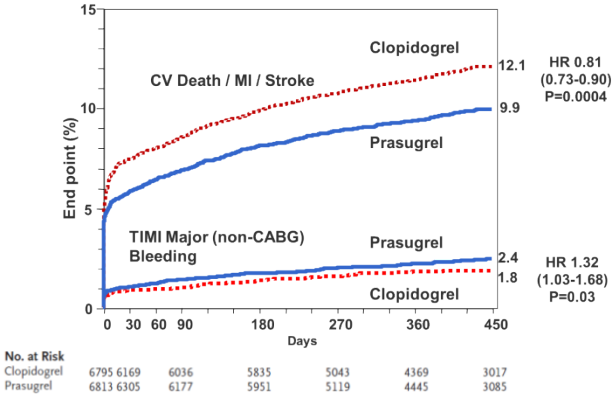
S. Schüpke, F.-J. Neumann, M. Menichelli, K. Mayer, I. Bernlochner, J. Wöhrle, G. Richardt, C. Liebetrau, B. Witzenbichler, D. Antoniucci, I. Akin, L. Bott-Flügel, M. Fischer, U. Landmesser, H. A. Katus, D. Sibbing, M. Seyfarth, M. Janisch, D. Boncompagni, R. Hilz, W. Rottbauer, R. Okrojek, H. Möllmann, 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, A. Kastrati,
for the ISAR-REACT 5 Investigators

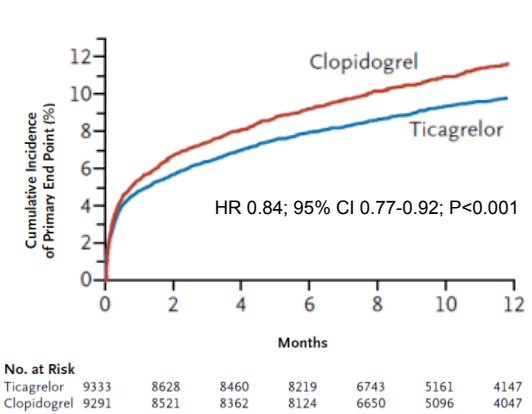
ESC Congress Paris 2019
Together with
World Congress of Cardiology

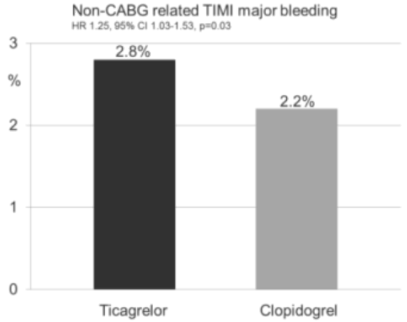
Background











Wiviott et al, N Engl J Med 2007

Wallentin et al, N Engl J Med 2009

2018 ESC/EACTS Guidelines on Myocardial Revascularization

NSTE-ACS:

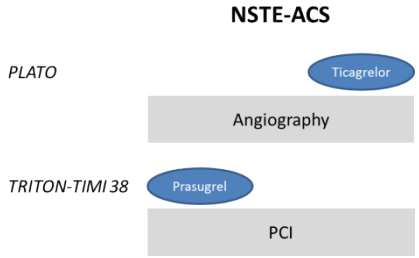
Recommendations	Class[a]	Level[b]
Pre-treatment and antiplatelet therapy		
A $P2Y_{12}$ inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding.[701,702,722,723] Options are:	I	A
• Prasugrel in $P2Y_{12}$-inhibitor naïve patients who proceed to PCI (60 mg loading dose, 10 mg daily dose).[701]	I	B
• Ticagrelor irrespective of the preceding $P2Y_{12}$ inhibitor regimen (180 mg loading dose, 90 mg b.i.d.).[702]	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated.[722–724]	I	B

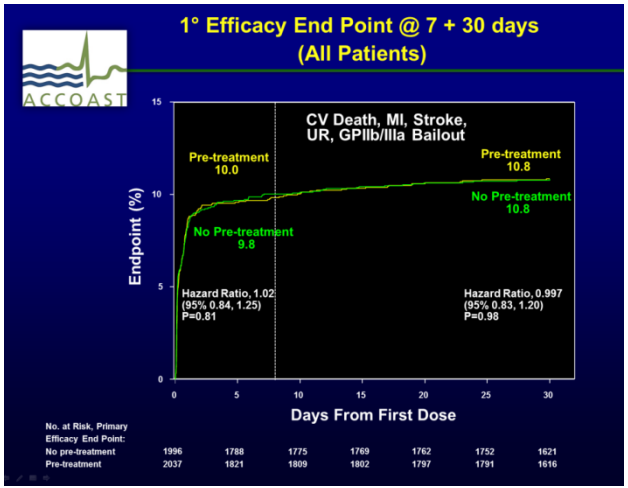
STEMI:

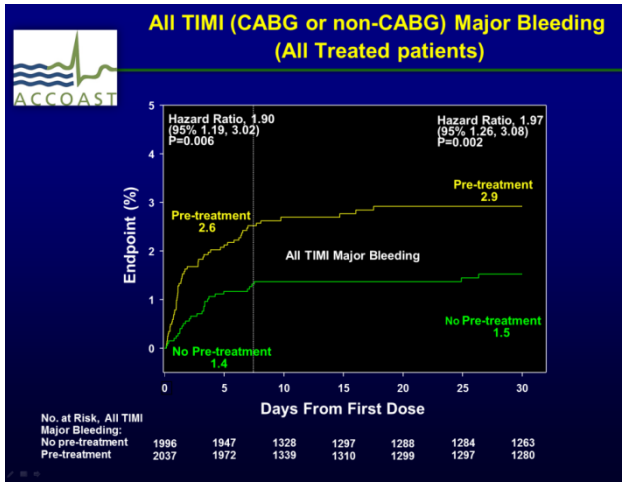
Recommendations	Class[a]	Level[b]
Pre-treatment and antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.[701,702,724,743]	I	A

ACCOAST

A Comparison of prasugrel at the time of PCI Or as pretreatment At the time of diagnosis in patients with NSTEMI







Montalescot et al, New Engl J Med 2013

2018 ESC/EACTS Guidelines on Myocardial Revascularization

NSTE-ACS:

Recommendations for antithrombotic treatment in patients with non-ST-elevation acute coronary syndromes undergoing percutaneous coronary intervention		
For pre-treatment in patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg b.i.d.), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
Administration of prasugrel in patients in whom coronary anatomy is not known is not recommended.[165]	III	B

Methods

Aim

- Head-to-head comparison of a Ticagrelor- versus a Prasugrel-based strategy in ACS patients with and without ST-segment elevation in terms of one-year clinical outcomes

Design

- Investigator-initiated, randomized, multicenter, open-label

Study Centers

- Department of Cardiology and Angiology II, University Heart Center Freiburg · Bad Krozingen
- Ospedale Fabrizio Spaziani, Cardiology, Frosinone
- Deutsches Herzzentrum München, Munich
- Medizinische Klinik und Poliklinik Innere Medizin I, Klinikum rechts der Isar, Munich
- Ulm University Hospital, Cardiology, Ulm
- Heart Center Bad Segeberg
- Heart Center, Campus Kerckhoff of Justus-Liebig-University, Giessen
- Helios Amper-Klinikum Dachau, Cardiology & Pneumology, Dachau
- Careggi University Hospital Firenze, Florence
- University Clinic Mannheim, Cardiology, Mannheim
- Klinikum Landkreis Erding, Cardiology, Erding
- Department of Internal Medicine II, University Medical Center Regensburg
- Department of Cardiology, Charité - University Medicine Berlin
- University Clinic Heidelberg, Cardiology, Heidelberg
- Klinik der Universität München, Ludwig – Maximilians – University, Cardiology, Munich
- Helios University Hospital, University of Witten/Herdecke, Department of Cardiology, Wuppertal
- Schön Klinik Starnberger See, Berg
- Klinikum Neuperlach, Cardiology, Munich
- Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Cardiology, Mainz
- Universitätsmedizin Göttingen, Heart Center, Göttingen
- Klinikum Traunstein, Cardiology, Traunstein
- Klinikum Karlsruhe, Cardiology, Karlsruhe
- Klinikum Lippe, Cardiology, Lippe

Methods

Aim

- Head-to-head comparison of Ticagrelor versus Prasugrel in ACS patients with planned invasive strategy in terms of one-year clinical outcomes

Design

- investigator-initiated, randomized, open-label, multicenter

Hypothesis

- H_0: Hazard Ratio = 1
- 2-sided α-level of 0.05
- We assumed that Ticagrelor is superior to Prasugrel in ACS patients with planned invasive strategy in terms of one-year clinical outcomes

Organizational Structure

Steering Committee

- A. Kastrati, S. Schüpke, D.J. Angiolillo, D. Antoniucci, C. Hamm, K.-L. Laugwitz, F.-J. Neumann, G. Richardt, H. Schühlen, H. Schunkert

Data Safety Monitoring Board

- A. Schömig, F. Hofmann, K. Ulm

Event Adjudication Committee

- K. Tiroch, C. Jilek, D. Keta, A. Nusca, S. Paul, N. Sarafoff, C. Volmer

Data Coordinating Center

- ISAResearch Center, Munich, Germany

End points

Primary end point

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

Secondary end points

- Bleeding BARC type 3-5 (safety end point)
- Individual components of the primary end point
- Stent thrombosis (definite or probable)

Analysis population

- Intention-to-treat (primary end point and secondary efficacy end point): all patients as randomized
- Modified intention-to-treat (safety end point): all patients who received at least one dose of the randomly assigned study drug and were assessed for bleeding events up to 7 days after drug discontinuation

Eligibility Criteria

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

Study Schedule

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STEMI

Randomization

Ticagrelor	Prasugrel
180 mg loading	60 mg loading

Angiography + PCI

Ticagrelor	Prasugrel
90 mg 1-0-1	10 mg 1-0-0*

Unstable Angina, NSTEMI

Randomization

Ticagrelor	*Prasugrel#*
180 mg loading	*60 mg loading*

Angiography

Prasugrel
60 mg loading

PCI

Ticagrelor	Prasugrel
90 mg 1-0-1	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

Schulz (Schüpke) et al, J Cardiovasc Transl Research 2014

Sample Size Calculation

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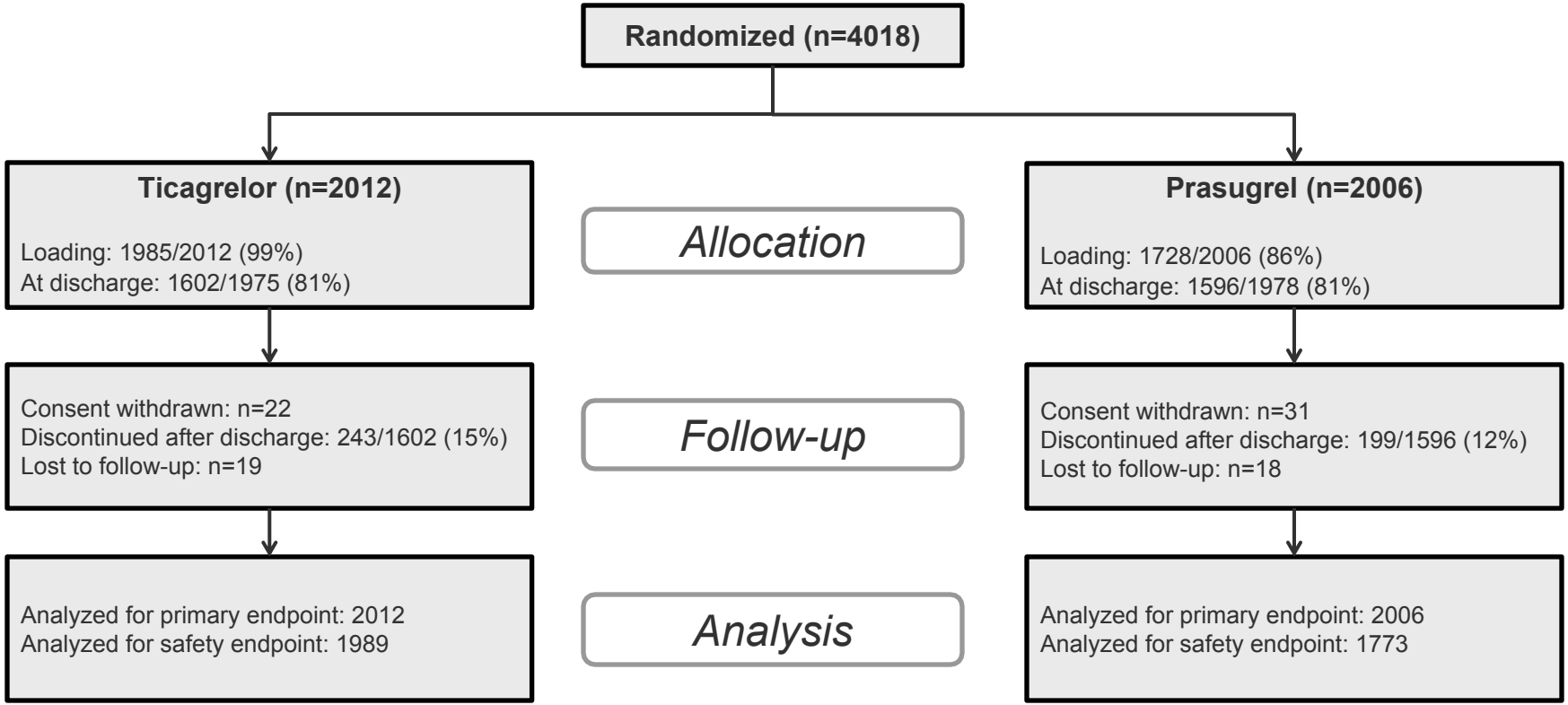
Assumptions:

- Incidence of the primary end point: 10% with Ticagrelor, 12.9% with Prasugrel (22.5% RRR)
- α-level 0.05 (two-sided); power 80%

Sample size:

- **1895** patients per group
- to accommodate for possible losses to follow-up the inclusion of **4000 patients** was planned

Study Flow


Randomized (n=4018)
Ticagrelor (n=2012)
Loading: 1985/2012 (99%)
At discharge: 1602/1975 (81%)
Prasugrel (n=2006)
Loading: 1728/2006 (86%)
At discharge: 1596/1978 (81%)
Allocation
Consent withdrawn: n=22
Discontinued after discharge: 243/1602 (15%)
Lost to follow-up: n=19
Consent withdrawn: n=31
Discontinued after discharge: 199/1596 (12%)
Lost to follow-up: n=18
Follow-up
Analyzed for primary endpoint: 2012
Analyzed for safety endpoint: 1989
Analyzed for primary endpoint: 2006
Analyzed for safety endpoint: 1773
Analysis

Baseline Characteristics (1/2)

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	Ticagrelor	Prasugrel
Age – years	64.5 ± 12.0	64.6 ± 12.1
Women – %	23.8	23.8
Body mass index – kg/m²	27.8 ± 4.6	27.8 ± 4.4
Diabetes – %	23.0	21.4
– Insulin-treated – %	7.1	6.8
Current smoker – %	34.1	33.4
Arterial hypertension – %	71.3	69.1
Hypercholesterolemia – %	58.7	58.1
Prior MI – %	15.5	16.0
Prior PCI – %	22.5	23.1
Prior CABG – %	5.7	6.5
Cardiogenic shock – %	1.5	1.7

Baseline Characteristics (2/2)

	Ticagrelor	Prasugrel
Blood pressure		
– Systolic – mmHg	144 ± 25	143 ± 24
– Diastolic – mmHg	82 ± 15	82 ± 14
Heart rate – beats/min	77 ± 16	76 ± 16
Diagnosis at admission – %		
– Unstable angina	12.4	13.0
– NSTEMI	46.2	46.1
– STEMI	41.4	40.9
Coronary angiography – %	99.6	99.8
Treatment strategy – %		
– PCI	83.5	84.8
– CABG	2.3	1.8
– Conservative	14.2	13.4
– Other	<0.1	0

Angiographic Characteristics
(Patients with Angiography)

	Ticagrelor	Prasugrel
Access site – %		
– Femoral	62.2	63.0
– Radial	37.3	36.5
– Other	0.5	0.5
No. of diseased coronary vessels – %		
– No obstructive CAD	8.5	8.2
– One vessel	30.0	29.1
– Two vessels	26.0	27.7
– Three vessels	35.5	35.0
Left ventricular ejection fraction – %	51.6 ± 11.3	52.0 ± 11.2

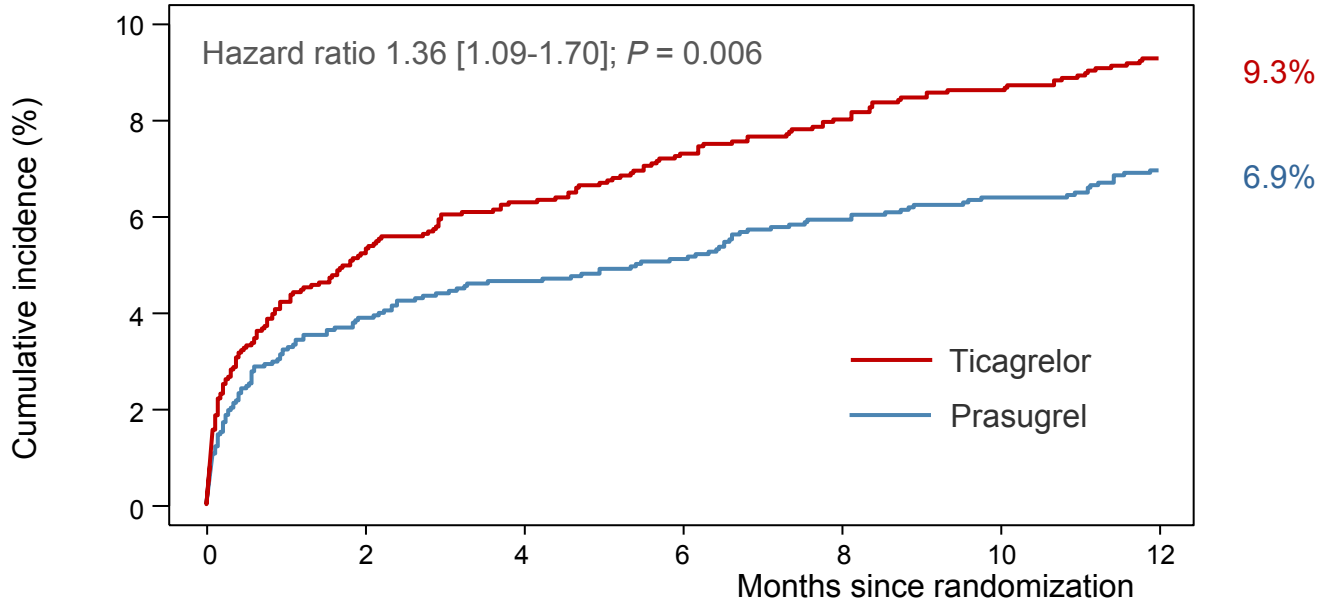
Procedural Characteristics
(Patients with PCI)

	Ticagrelor	Prasugrel
Target vessel – %		
– Left main	2.2	2.2
– LAD	44.5	42.2
– LCx	20.6	20.3
– RCA	31.0	33.5
Drug-eluting stent – %	89.3	90.7
Periprocedural antithrombotic medication – %		
– Acetylsalicylic acid	89.7	90.1
– Unfractionated heparin	94.3	93.8
– Low molecular weight heparin	4.4	3.8
– Bivalirudin	7.5	8.3
– GPIIb/IIIa inhibitor	13.1	11.6

Discharge

	Ticagrelor	Prasugrel
Final diagnosis of ACS – %	91.2	90.5
– Unstable angina	10.3	9.5
– NSTEMI	45.6	45.6
– STEMI	44.1	44.8
Therapy at discharge – %		
– Acetylsalicylic acid	94.5	94.9
– Ticagrelor	81.1	0.7
– Prasugrel	1.1	80.7
– Clopidogrel	4.6	5.9
– Oral anticoagulant drugs	4.2	5.1
– Betablocker	83.1	83.2
– ACE inhibitor/ARB	84.0	85.4
– Statin	91.6	92.6

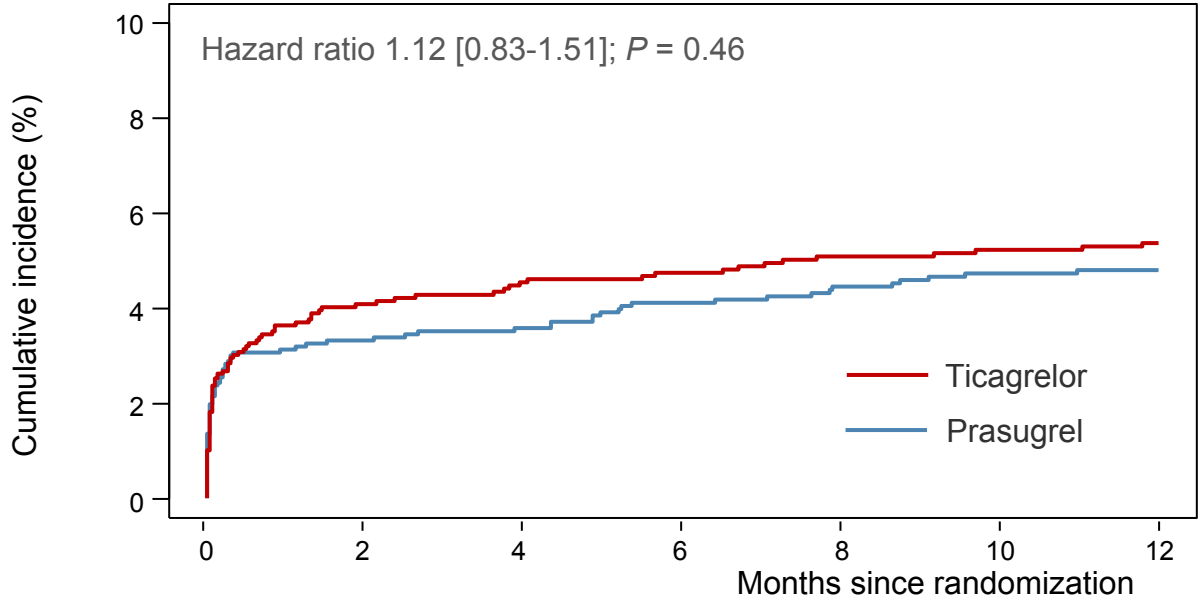
Primary End point
(Composite of Death, MI, or Stroke)



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

Clinical End Points

	Ticagrelor (n=2012)	Prasugrel (n=2006)	HR [95% CI]
Death	90 (4.5)	73 (3.7)	**1.23 [0.91-1.68]**
– Cardiovascular	63 (3.2)	59 (3.0)	
– Non-cardiovascular	27 (1.4)	14 (0.7)	
Myocardial infarction	96 (4.8)	60 (3.0)	**1.63 [1.18-2.25]**
– STEMI	31	14	
Stroke	22 (1.1)	19 (1.0)	**1.17 [0.63-2.15]**
– Ischemic	16	17	
– Hemorrhagic	6	2	
Definite or probable stent thrombosis	26 (1.3)	20 (1.0)	**1.30 [0.72-2.33]**
Definite stent thrombosis	22 (1.1)	12 (0.6)	

Subgroup Analysis

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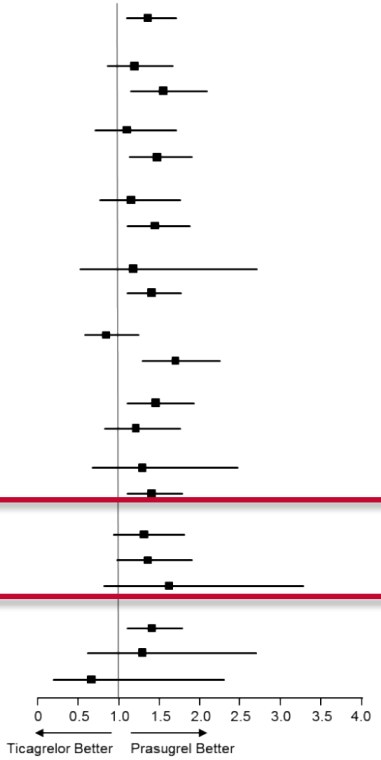
Subgroup	Ticagrelor	Prasugrel	Hazard Ratio (95% CI)
	no. of patients with event/total no. of patients (%)		
Overall	184/2012 (9.3)	137/2006 (6.9)	1.36 (1.09-1.70)
Age			
≥75 years	74/490 (15.3)	66/492 (13.7)	1.19 (0.85-1.66)
<75 years	110/1522 (7.3)	71/1514 (4.8)	1.55 (1.15-2.09)
Sex			
Female	42/478 (8.9)	39/478 (8.3)	1.10 (0.71-1.70)
Male	142/1534 (9.4)	98/1528 (6.5)	1.47 (1.13-1.90)
Smoking status			
Active	47/682 (7)	41/667 (6.2)	1.15 (0.76-1.75)
Non-active	133/1320 (10.2)	94/1332 (7.2)	1.44 (1.10-1.87)
Weight			
<60 kg	13/108 (12.2)	10/94 (10.7)	1.18 (0.52-2.71)
≥60 kg	171/1895 (9.1)	124/1894 (6.4)	1.40 (1.11-1.77)
Diabetes mellitus			
Yes	51/463 (11.2)	55/429 (13)	0.84 (0.58-1.24)
No	132/1548 (8.6)	81/1576 (5.2)	1.70 (1.29-2.24)
Creatinine			
≥83.1 µmol/L	125/1005 (12.6)	88/1009 (8.8)	1.46 (1.11-1.92)
<83.1 µmol/L	59/1002 (6)	49/996 (5)	1.21 (0.83-1.76)
Cardiogenic Shock			
Yes	19/31 (62.6)	18/34 (52.9)	1.29 (0.67-2.47)
No	165/1981 (8.4)	119/1972 (6.1)	1.40 (1.11-1.78)
Clinical Presentation			
STEMI	83/833 (10.1)	64/820 (7.9)	1.31 (0.94-1.81)
NSTEMI	81/930 (8.8)	60/925 (6.6)	1.36 (0.97-1.90)
Unstable Angina	20/249 (8.2)	13/261 (5.1)	1.62 (0.81-3.26)
Treatment Strategy			
PCI	162/1676 (9.8)	120/1701 (7.1)	1.41 (1.11-1.78)
conservative	17/285 (6.1)	12/268 (4.6)	1.29 (0.62-2.70)
CABG	5/47 (10.6)	5/36 (13.9)	0.66 (0.19-2.30)



Summary And Conclusion

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In ACS patients with or without ST-segment elevation, treatment with Prasugrel as compared with Ticagrelor significantly reduced the composite rate of death, myocardial infarction, or stroke without an increase in major bleeding.