



## 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

# Disclosures



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- Support from the DZHK (German Center for Cardiovascular Research) for the ISAR-REACT 5 trial
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- DZHK (German Center for Cardiovascular Research)
- Deutsches Herzzentrum München

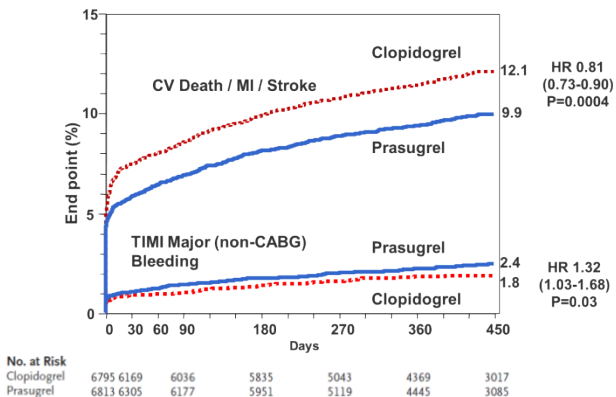
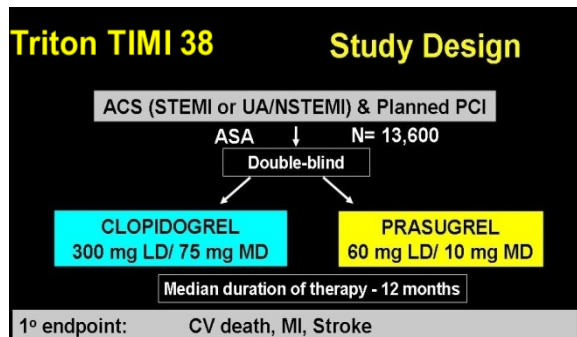
# Background



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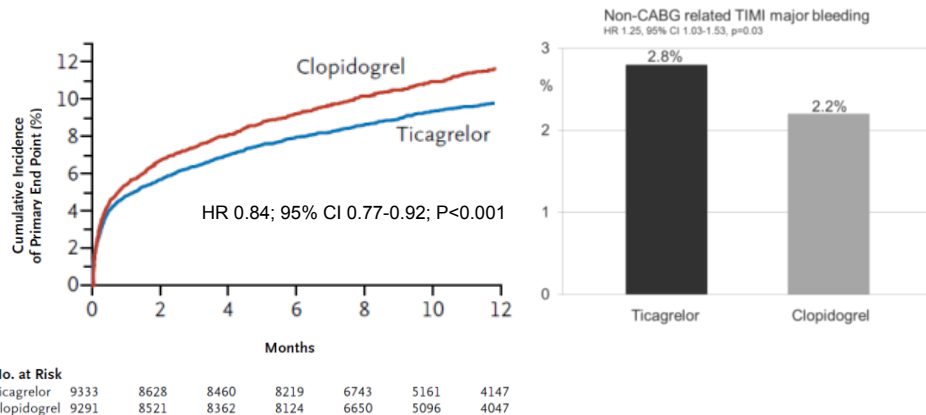
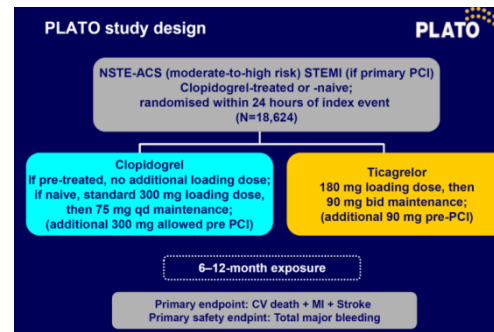


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# 2018 ESC/EACTS Guidelines on Myocardial Revascularization



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## NSTE-ACS:

### Recommendations

Class<sup>a</sup>

Level<sup>b</sup>

#### Pre-treatment and antiplatelet therapy

A P2Y<sub>12</sub> inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding.<sup>701,702,722,723</sup> Options are:

- Prasugrel in P2Y<sub>12</sub>-inhibitor naïve patients who proceed to PCI (60 mg loading dose, 10 mg daily dose).<sup>701</sup>
- Ticagrelor irrespective of the preceding P2Y<sub>12</sub> inhibitor regimen (180 mg loading dose, 90 mg b.i.d.).<sup>702</sup>
- Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated.<sup>722–724</sup>

I

A

I

B

I

B

I

B

## STEMI:

### Recommendations

Class<sup>a</sup>

Level<sup>b</sup>

#### Pre-treatment and antiplatelet therapy

A potent P2Y<sub>12</sub> 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.<sup>701,702,724,743</sup>

I

A

# ACCOAST

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



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## NSTE-ACS

PLATO

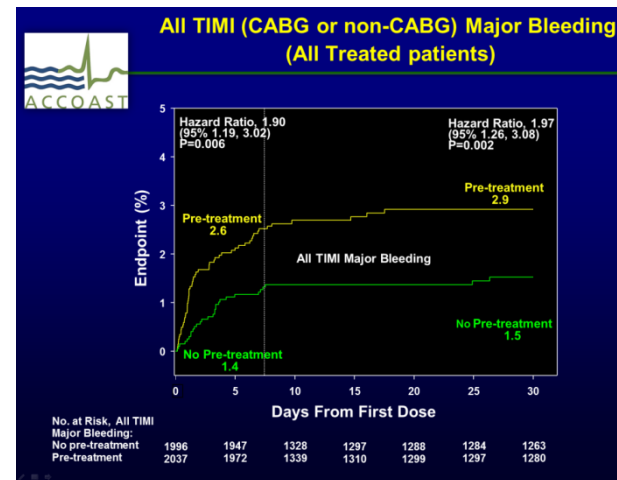
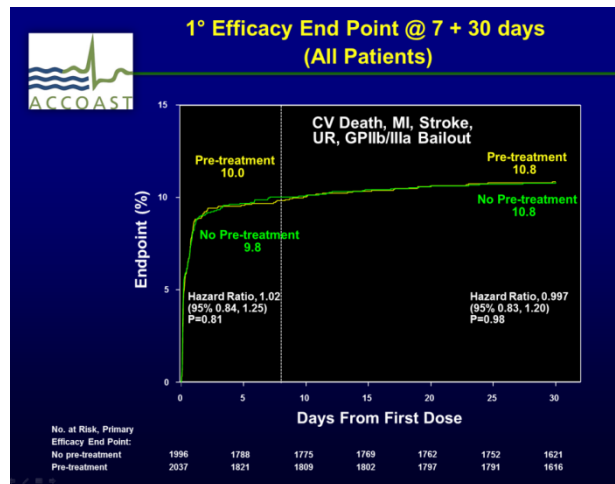
Ticagrelor

Angiography

TRITON-TIMI/38

Prasugrel

PCI



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# 2018 ESC/EACTS Guidelines on Myocardial Revascularization



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## 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. | <b>IIa</b> | <b>C</b> |
| Administration of prasugrel in patients in whom coronary anatomy is not known is not recommended. <sup>165</sup>                                                                                                                                                                                | <b>III</b> | <b>B</b> |



## 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



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- 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

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## 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  $\alpha$ -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



## 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



## 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



## 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

## 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  $\geq 75$  years of age or weight  $< 60$  kg

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## Unstable Angina, NSTEMI

### Randomization

**Ticagrelor**  
180 mg loading

*Prasugrel<sup>#</sup>*  
*60 mg loading*

### Angiography

**Prasugrel**  
60 mg loading

### PCI

**Ticagrelor**  
90 mg 1-0-1

**Prasugrel**  
10 mg 1-0-0\*



## Assumptions:

- Incidence of the primary end point: 10% with Ticagrelor, 12.9% with Prasugrel (22.5% RRR)
- $\alpha$ -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

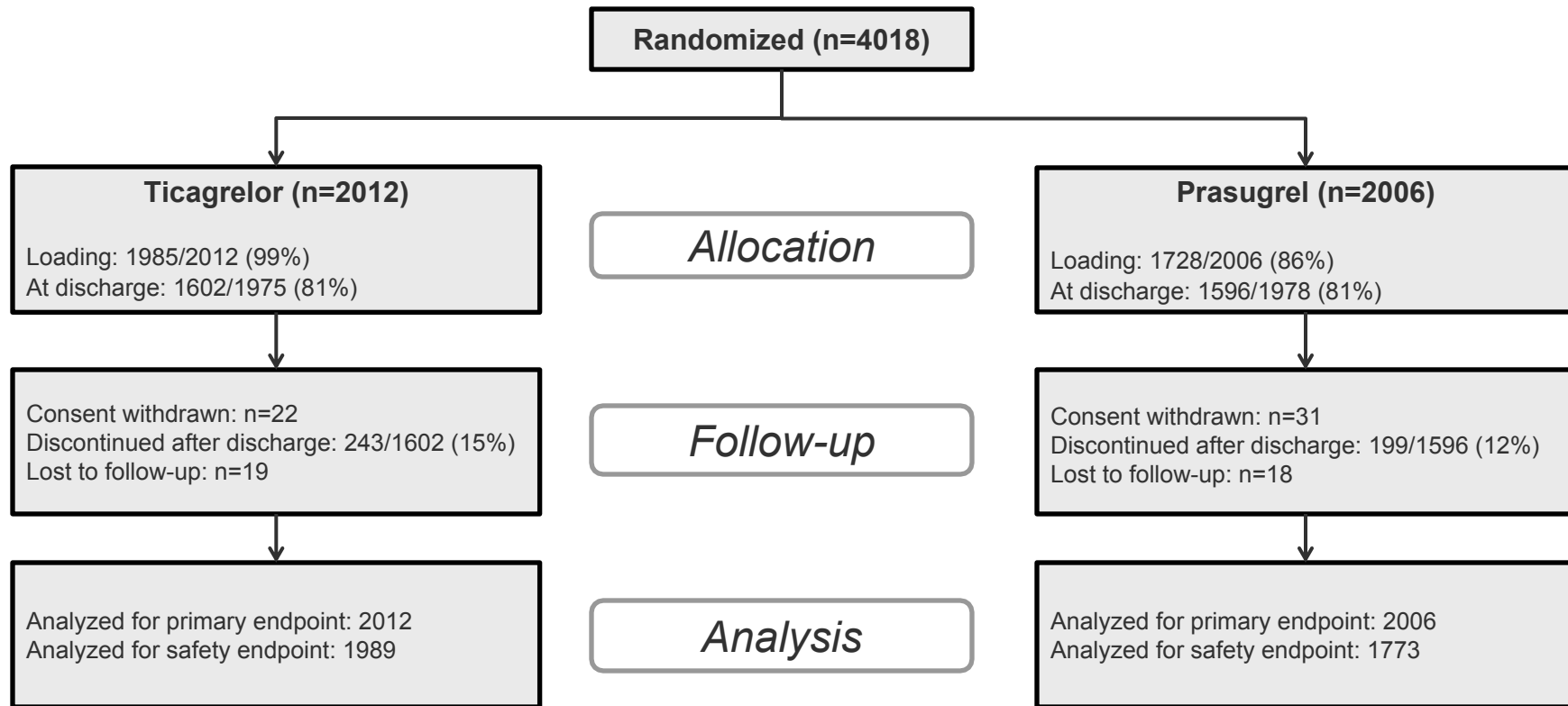
# Study Flow



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# Baseline Characteristics (1/2)



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|                                           | Ticagrelor  | Prasugrel   |
|-------------------------------------------|-------------|-------------|
| <b>Age – years</b>                        | 64.5 ± 12.0 | 64.6 ± 12.1 |
| <b>Women – %</b>                          | 23.8        | 23.8        |
| <b>Body mass index – kg/m<sup>2</sup></b> | 27.8 ± 4.6  | 27.8 ± 4.4  |
| <b>Diabetes – %</b>                       | 23.0        | 21.4        |
| – Insulin-treated – %                     | 7.1         | 6.8         |
| <b>Current smoker – %</b>                 | 34.1        | 33.4        |
| <b>Arterial hypertension – %</b>          | 71.3        | 69.1        |
| <b>Hypercholesterolemia – %</b>           | 58.7        | 58.1        |
| <b>Prior MI – %</b>                       | 15.5        | 16.0        |
| <b>Prior PCI – %</b>                      | 22.5        | 23.1        |
| <b>Prior CABG – %</b>                     | 5.7         | 6.5         |
| <b>Cardiogenic shock – %</b>              | 1.5         | 1.7         |

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# Baseline Characteristics (2/2)



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## Ticagrelor

## Prasugrel

### Blood pressure

- Systolic – mmHg
- Diastolic – mmHg

144 ± 25

143 ± 24

82 ± 15

82 ± 14

### Heart rate – beats/min

77 ± 16

76 ± 16

### Diagnosis at admission – %

- Unstable angina
- NSTEMI
- STEMI

12.4

13.0

46.2

46.1

41.4

40.9

### Coronary angiography – %

99.6

99.8

### Treatment strategy – %

- PCI
- CABG
- Conservative
- Other

83.5

84.8

2.3

1.8

14.2

13.4

<0.1

0

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# Angiographic Characteristics

(Patients with Angiography)



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## 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)



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## 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 |

|                                   | Ticagrelor | Prasugrel |
|-----------------------------------|------------|-----------|
| <b>Final diagnosis of ACS – %</b> | 91.2       | 90.5      |
| – Unstable angina                 | 10.3       | 9.5       |
| – NSTEMI                          | 45.6       | 45.6      |
| – STEMI                           | 44.1       | 44.8      |
| <b>Therapy at discharge – %</b>   |            |           |
| – 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

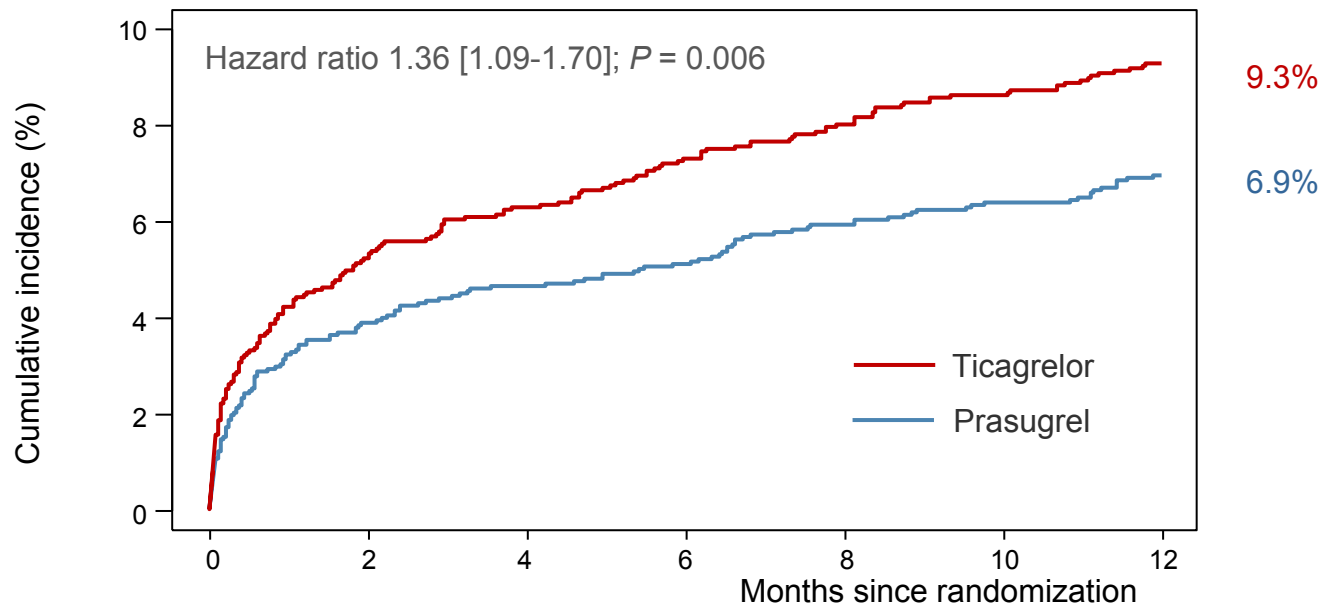
(Composite of Death, MI, or Stroke)



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## No. at Risk

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

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# BARC Type 3-5 Bleeding

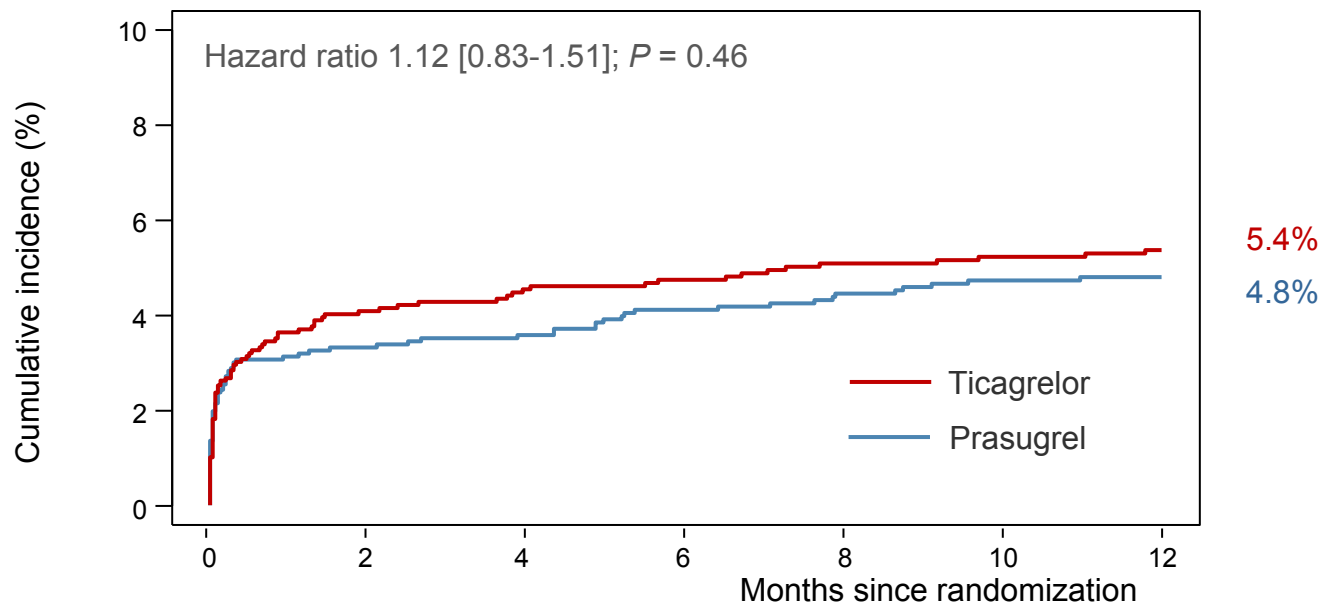
(Safety End point)



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## No. at Risk

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

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# Clinical End Points



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

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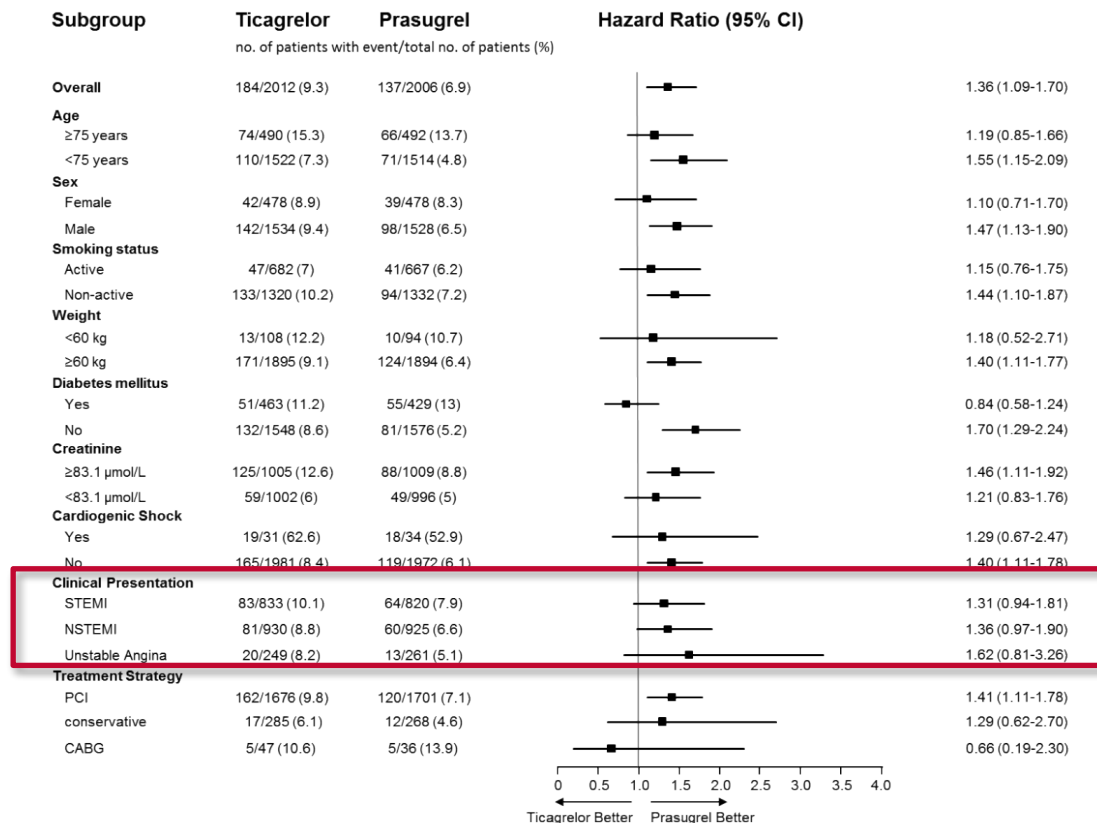
# Subgroup Analysis



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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.**



**Thank you to all Investigators,  
Study Teams, Committee Members,  
the DZHK, and Patients**



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ORIGINAL ARTICLE

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A. Kastrati, for the ISAR-REACT 5 Trial Investigators\*

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