TICAGRELOR VERSUS CLOPIDOGREL AFTER THROMBOLYTIC THERAPY IN PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION: A RANDOMIZED CLINICAL TRIAL

Otavio Berwanger, MD, PhD - On behalf of the TREAT Trial Steering Committee and Investigators

Funding Source: *Astra Zeneca (Investigador Initiated Trial)*

Treat TRIAL

Background

- Access to timely primary PCI is not available for a large proportion of patients with STEMI, particularly in low and middle income countries.
- Thus, in several settings, fibrinolytic therapy represents the primary reperfusion strategy.
- The safety of ticagrelor in STEMI patients in the first 24 hours after fibrinolysis remains uncertain.

Study Design

Male and Female Patients (Age ≥ 18 years and ≤ 75 years) with STEMI with onset in the previous 24h and treated with fibrinolytic therapy (N=3,799)

Ticagrelor
180 mg as early as possible after the index event and not >24 h post event
90 mg twice daily for 12 months

ITT

Clopidogrel
300 mg as early as possible after the index event and not >24 h post event
75 mg/day for 12 months

ITT

Follow up visits at hospital discharge or 7th day, 30 days, 6 and 12 months

Primary safety outcome: TIMI Major Bleeding
Secondary safety outcomes: Other bleeding events (PLATO trial, BARC, TIMI)
Exploratory efficacy outcomes: CV death, MI, or stroke

CV = cardiovascular ; MI = Myocardial infarction; TIA = transient ischemic attack
TIMI = Thrombolysis in Myocardial Infarction; BARC = Bleeding Academic Research Consortium

AHJ in press

TREAT Trial

- **Design:** Academically-led, phase III, non-inferiority, international, multicenter, randomized, and open-label study with blinded-outcome assessment
- **Prevention of Bias:** concealed allocation (central web-based randomization) + intention-to-treat analysis.
- **Trial Size:** 3,794 patients .This sample size provides greater than 90% statistical power, considering an event rate of 1.2%, noninferiority (absolute) margin of 1.0%, a one-sided alpha of 2.5%, and assuming a 1:1 allocation ratio.
- **Quality Control:** e-CRF, Risk-Based monitoring visits (On-Site, Remote and Centralized visits) + data management.

Key Exclusion Criteria

- Contraindication against the use of clopidogrel or ticagrelor
- Need for oral anticoagulation therapy
- Dialysis required
- Known clinically important thrombocytopenia
- Known clinically important anemia
- Pregnancy or lactation

Steering Committee

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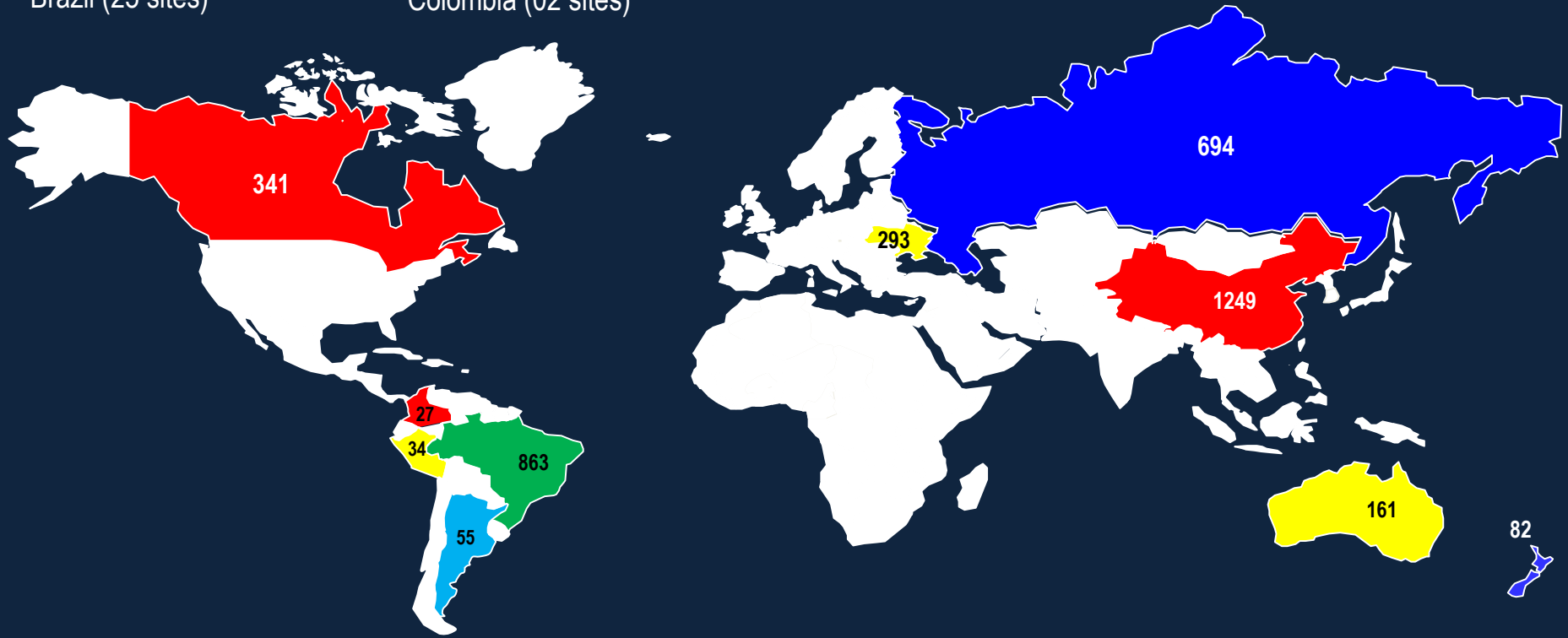
- Prof. Oleg Averkov (Russia)
- Prof. Carlos Tajer (Argentina)
- Prof. Shaun Goodman (Canada)

Data Monitoring Committee (DMC)

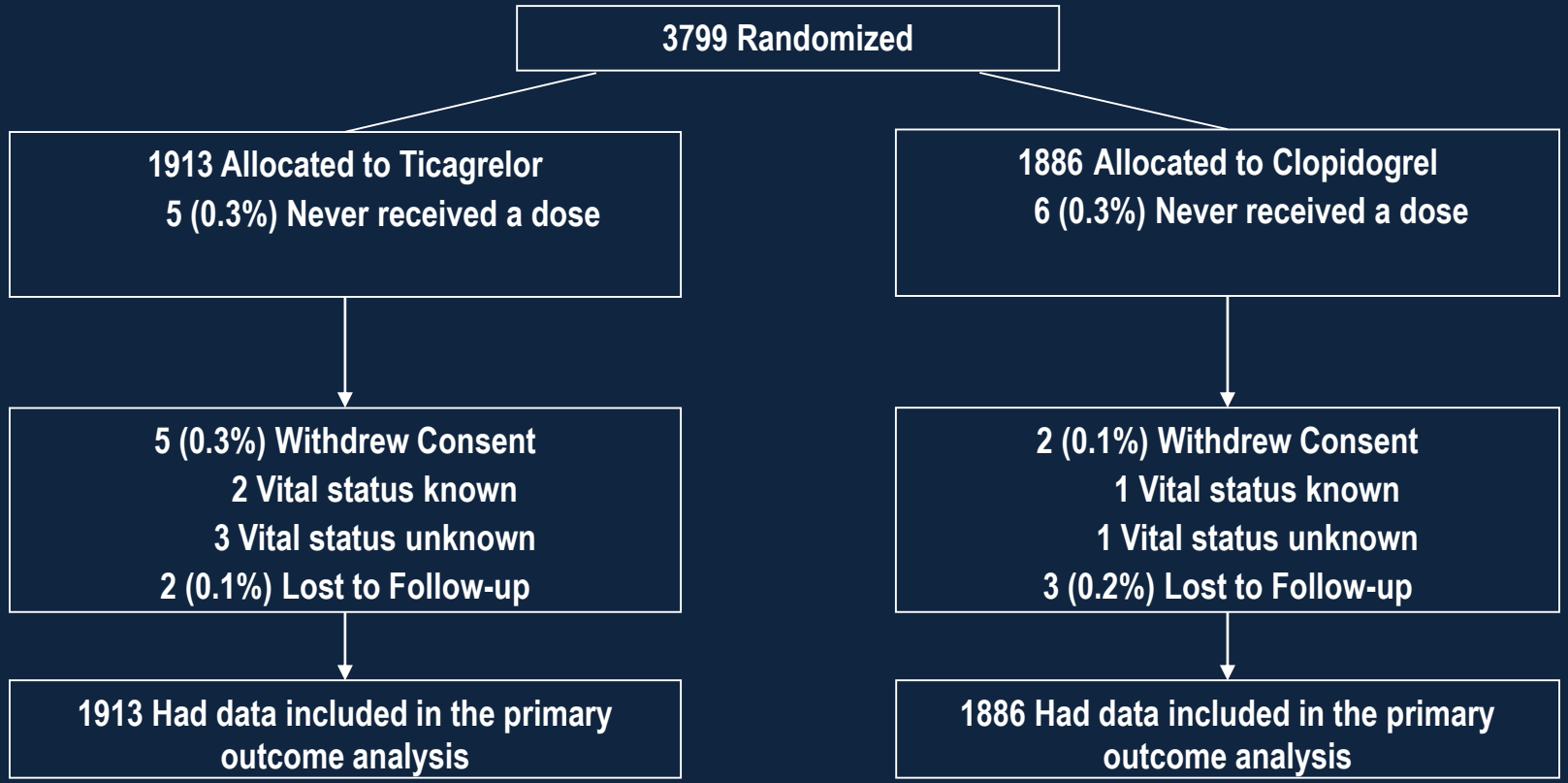
- John H. Alexander (Chair);
- Karen Pieper (Voting Member)
- Stefan James (Voting Member)
- Tiago Mendonça (DMC statistician)

3,799 Patients from 10 Countries

Argentina (06 sites)
Australia (10 sites)
Brazil (25 sites)
Canada (17 sites)
China (47 sites)
Colombia (02 sites)
New Zealand (07 sites)
Peru (05 sites)
Russia (20 sites)
Ukraine (13 sites)



Flow Chart


3799 Randomized
1913 Allocated to Ticagrelor
5 (0.3%) Never received a dose
1886 Allocated to Clopidogrel
6 (0.3%) Never received a dose
5 (0.3%) Withdrew Consent
2 Vital status known
3 Vital status unknown
2 (0.1%) Lost to Follow-up
2 (0.1%) Withdrew Consent
1 Vital status known
1 Vital status unknown
3 (0.2%) Lost to Follow-up
1913 Had data included in the primary outcome analysis
1886 Had data included in the primary outcome analysis

Selected Baseline Characteristics

Characteristic	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
Median age, years	59.0	58.8
Male, %	77.4	76.8
CV risk factors, %		
Habitual smoker	46.1	46.6
Hypertension	56.0	56.8
Dyslipidemia	27.4	27.8
Diabetes Mellitus	17.4	16.1
History, %		
Myocardial Infarction	9.3	8.0
Percutaneous coronary intervention	5.9	5.3
Coronary-artery bypass grafting	0.8	0.7
Troponin-I positive, %	88.0	87.2

Treat TRIAL

Fibrinolytic Therapy

Medication	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
Start of randomised treatment		
Time from symptom to fibrinolytic administration, h, median	2.6	2.6
Time from fibrinolytic administration to randomization, h, median	11.4	11.5
Fibrinolytic Therapy , %		
Tenecteplase	39.6	39.8
Alteplase	19.7	19.2
Reteplase	16.8	16.6
Prourokinase	7.0	7.5
Urokinase	6.9	7.2
Streptokinase	5.7	5.6
Other	4.2	4.1

Co-Interventions, Procedures, and Adherence

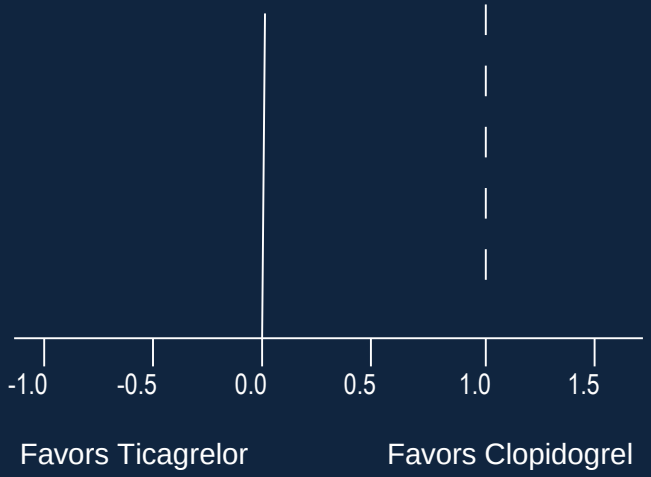
	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
Clopidogrel before randomization , %		
300 mg	87.0	86.0
Invasive procedure performed during index hospitalization , %		
PCI	56.7	55.6
Within 24 hours after randomization	42.4	42.0
Cardiac surgery	1.7	2.1
Adherence to study drug at 30 days Follow up, %		
Mean	89.9	90.7

In-Hospital Treatments

Medication	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
In-hospital treatment , %		
Aspirin	98.8	98.9
Unfractioned heparin	39.6	39.4
Low- molecular-weight heparin	69.1	68.8
Fondaparinux	4.1	4.1
Bivalirudin	0.7	1.4
Glycoprotein IIb/IIIa inhibitor	5.3	4.9
Beta-blocker	73.7	74.0
ACE inhibitor or ARB	69.8	68.1
Statin	93.0	93.4
Proton pump-inhibitor	54.9	56.6

Major Bleeding at 30 Days

	Ticagrelor (n=1913)	Clopidogrel (n=1886)	Difference , 95% CI	Noninf. margin	P noninf.
TIMI Major Bleeding (Primary Endpoint)					

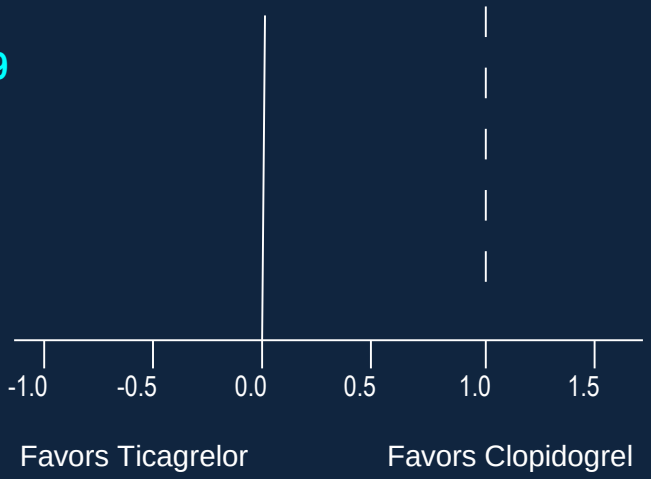


Data presented as no. (%)

* Absolute difference (in percentage) presented as bilateral 95% confidence interval.

† 1% absolute difference margin non inferiority test. Non-inferiority test was done considering an one sided test.

Major Bleeding at 30 Days

	Ticagrelor (n=1913)	Clopidogrel (n=1886)	Difference , 95% CI	Noninf. margin	P noninf.
TIMI Major Bleeding (Primary Endpoint)	0.73	0.69			

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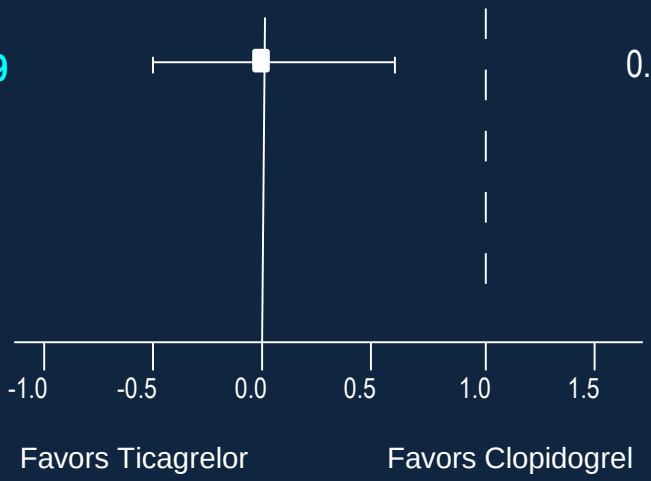
	Ticagrelor (n=1913)	Clopidogrel (n=1886)	Difference , 95% CI	P noninf.
TIMI Major Bleeding (Primary Endpoint)	0.73	0.69	0.04 [-0.49; 0.58]	<0.001



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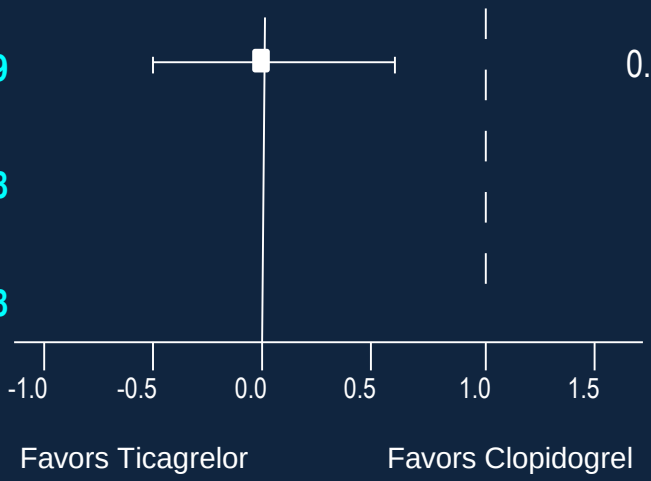
PLATO Major Bleeding	1.20	1.38		
BARC Type 3 - 5 Bleeding	1.20	1.38		



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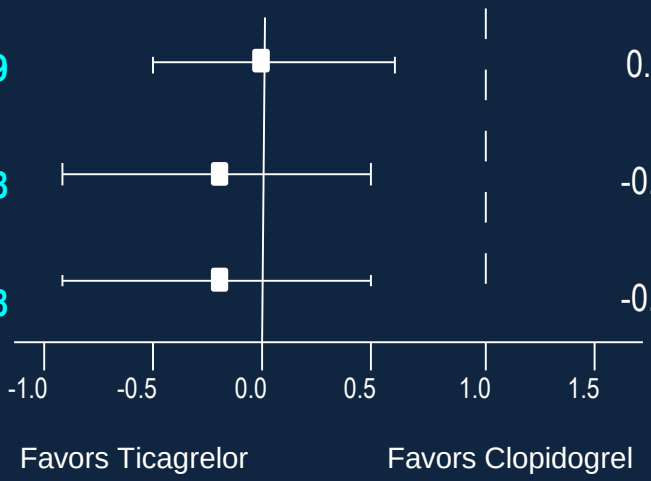
TIMI Major Bleeding (Primary Endpoint)	0.73	0.69	0.04 [-0.49; 0.58]	<0.001
PLATO Major Bleeding	1.20	1.38	-0.18 [-0.89; 0.54]	0.001
BARC Type 3 - 5 Bleeding	1.20	1.38	-0.18 [-0.89; 0.54]	0.001



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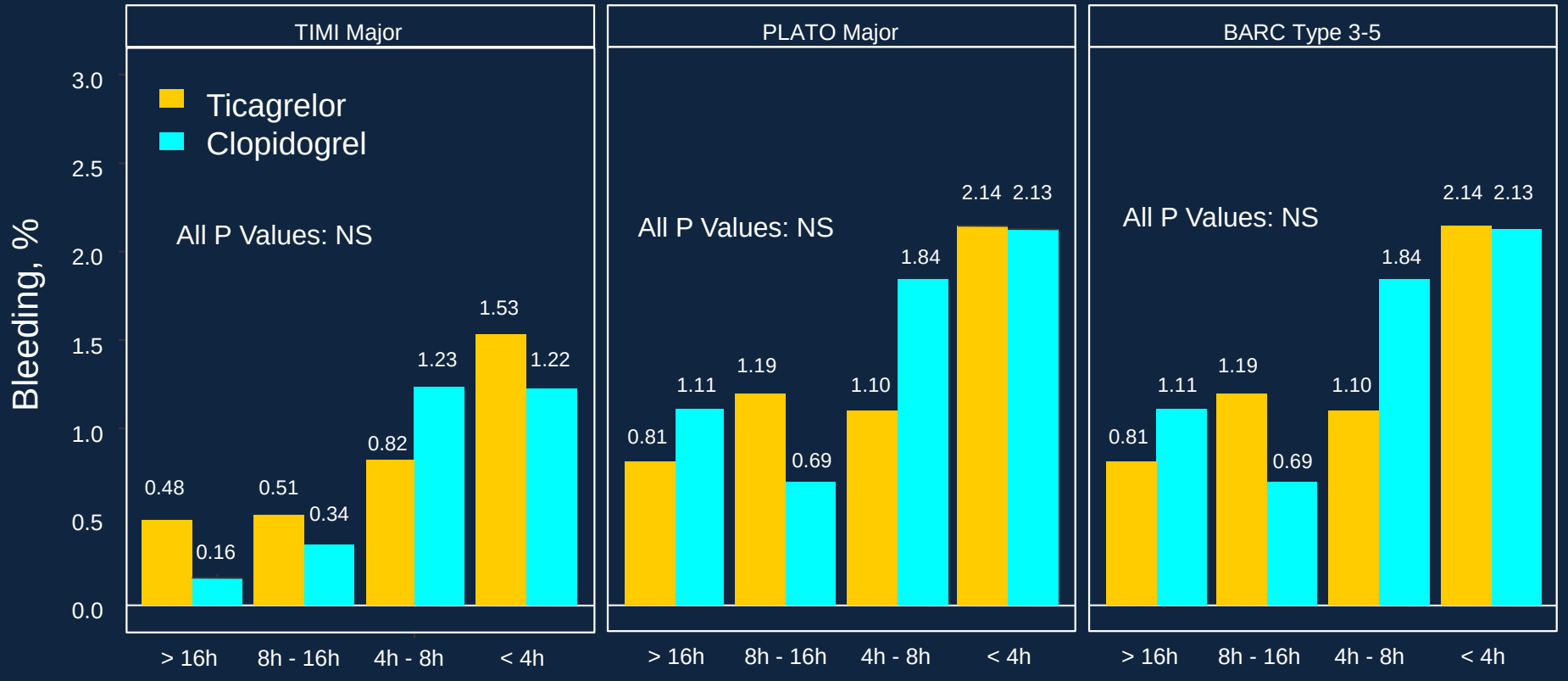
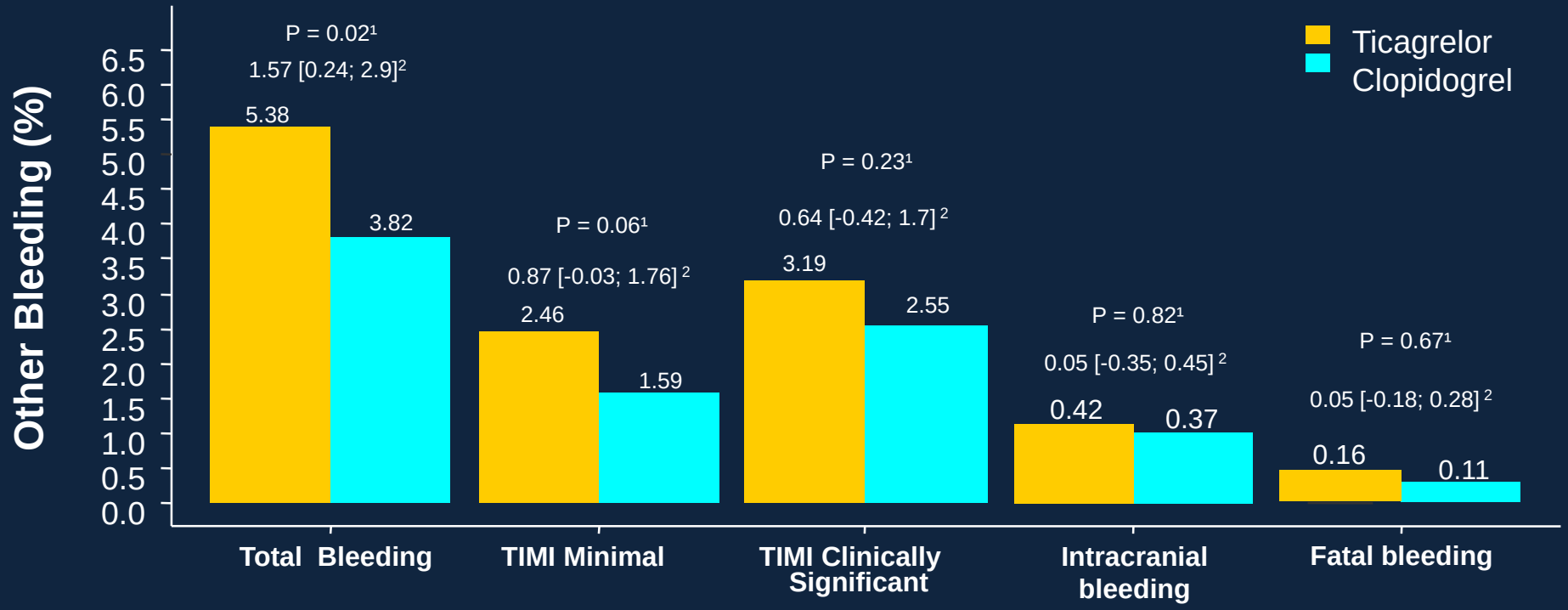
Safety by Time from Lysis



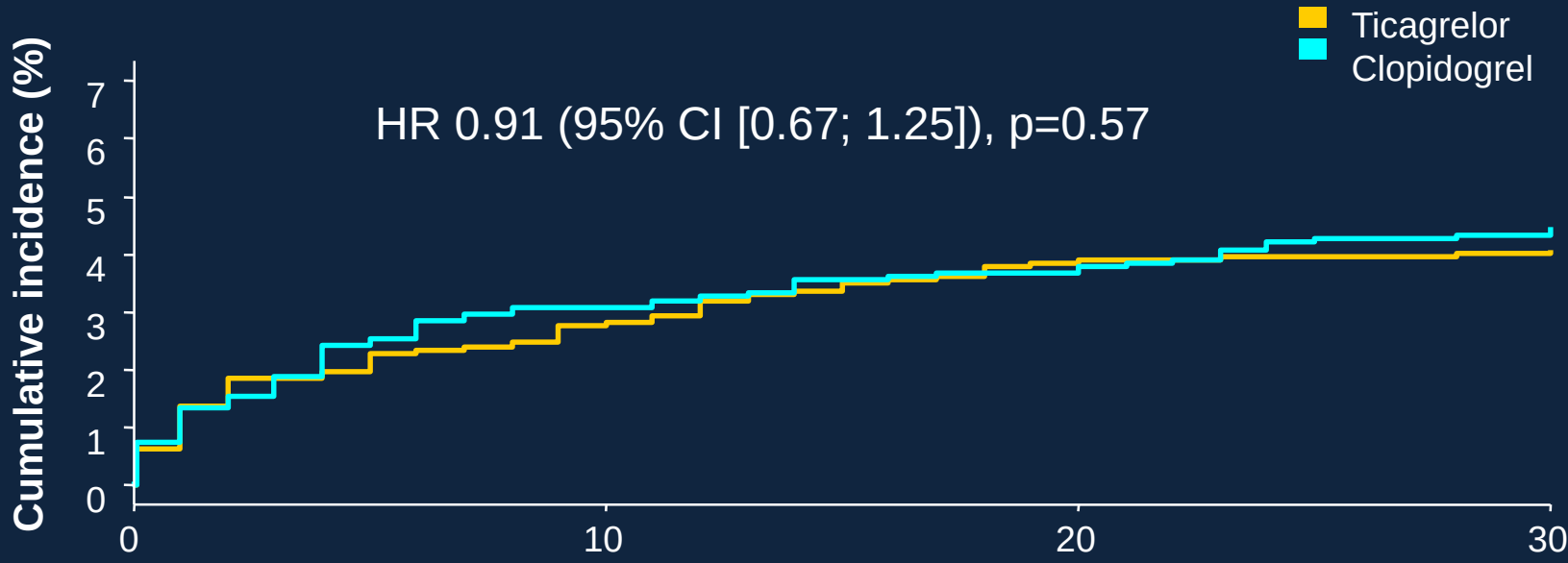
Time from fibrinolytic administration to randomization, hours

Other Bleeding Outcomes



Major bleeding refer to adjudicated events analysed.
*Proportion of patients (%)
1 two-sided proportions
2 Absolute difference (%), 95% CI = confidence interval

CV Death, MI, or Stroke



No. at risk				
Ticagrelor	1913	1855	1834	1658
Clopidogrel	1885	1824	1812	1613

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Exploratory Efficacy Outcomes

Outcomes at 30 days	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)	Hazard Ratio (95% CI)	P Value
Death from vascular causes, MI, or stroke	4.0	4.3	0.91 (0.67 to 1.25)	0.57
Death or MI	3.2	3.6	0.90 (0.63 to 1.27)	0.54
MI or stroke	2.0	2.3	0.85 (0.55 to 1.31)	0.47
Death (from vascular causes)	2.5	2.6	0.95 (0.63 to 1.41)	0.79
Total MI	1.0	1.3	0.79 (0.44 to 1.42)	0.43
Total stroke	0.9	1.1	0.89 (0.47 to 1.68)	0.71
Other arterial thrombotic events	0.1	0.2	0.33 (0.03 to 3.16)	0.34
Death (from any cause)	2.6	2.6	0.99 (0.66 to 1.47)	0.95

Conclusions and Implications

- In patients aged ≤ 75 years with ST-segment elevation myocardial infarction, administration of ticagrelor after fibrinolytic therapy was noninferior to clopidogrel for TIMI major bleeding at 30 days.
- Total bleeding was increased with ticagrelor and there was no benefit on exploratory efficacy outcomes.
- Ticagrelor is a reasonable option for patients ≤ 75 years who have received fibrinolytic therapy (and clopidogrel) within the past 24 hours, with comparable safety compared to clopidogrel.

Research

JAMA Cardiology | Original Investigation

Ticagrelor vs Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction
A Randomized Clinical Trial

The Writing Committee for the TREAT Study Group

IMPORTANCE The bleeding safety of ticagrelor in patients with ST-elevation myocardial infarction treated with fibrinolytic therapy remains uncertain.

OBJECTIVE To evaluate the short-term safety of ticagrelor when compared with clopidogrel in patients with ST-elevation myocardial infarction treated with fibrinolytic therapy.

DESIGN, SETTING AND PARTICIPANTS We conducted a multicenter, randomized, open-label with blinded end point adjudication trial that enrolled 3799 patients (younger than 75 years) with ST-segment elevation myocardial infarction receiving fibrinolytic therapy in 152 sites from 10 countries from November 2015 through November 2017. The prespecified upper boundary for noninferiority for bleeding was an absolute margin of 1.0%.

INTERVENTIONS Patients were randomized to ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300-mg to 600-mg loading dose, 75 mg daily thereafter). Patients were randomized with a median of 11.4 hours after fibrinolysis, and 90% were pretreated with clopidogrel.

MAIN OUTCOMES AND MEASURES The primary outcome was thrombolysis in myocardial infarction (TIMI) major bleeding through 30 days.

RESULTS The mean (SD) age was 58.0 (9.5) years, 2928 of 3799 patients (77.1%) were men, and 2177 of 3799 patients (57.3%) were white. At 30 days, TIMI major bleeding had occurred in 14 of 1913 patients (0.73%) receiving ticagrelor and in 13 of 1886 patients (0.69%) receiving clopidogrel (absolute difference, 0.04%; 95% CI, −0.49% to 0.58%; $P < .001$ for noninferiority). Major bleeding defined by the Platelet Inhibition and Patient Outcomes criteria and by the Bleeding Academic Research Consortium types 3 to 5 bleeding occurred in 23 patients (1.20%) in the ticagrelor group and in 26 patients (1.38%) in the clopidogrel group (absolute difference, −0.18%; 95% CI, −0.89% to 0.54; $P = .001$ for noninferiority). The rates of fatal (0.16% vs 0.11%; $P = .67$) and intracranial bleeding (0.42% vs 0.37%; $P = .82$) were similar between the ticagrelor and clopidogrel groups, respectively. Minor and minimal bleeding were more common with ticagrelor than with clopidogrel. The composite of death from vascular causes, myocardial infarction, or stroke occurred in 76 patients (4.0%) treated with ticagrelor and in 82 patients (4.3%) receiving clopidogrel (hazard ratio, 0.91; 95% CI, 0.67-1.25; $P = .57$).

CONCLUSIONS AND RELEVANCE In patients younger than 75 years with ST-segment elevation myocardial infarction, delayed administration of ticagrelor after fibrinolytic therapy was noninferior to clopidogrel for TIMI major bleeding at 30 days.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02298088.

Editor's Note page 1
Supplemental content

Group Information: The authors/writing committee and members of the TREAT Study Group are listed at the end of this article.

Corresponding Author: Otavio Berwanger, MD, PhD, Research Institute, Heart Hospital, Abilio Soares St 250, 12th Floor, 04005-000, São Paulo, SP, Brazil (otavioberwanger@gmail.com).

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Ticagrelor vs Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction: A Randomized Clinical Trial

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