TICAGRELOR VERSUS CLOPIDOGREL IN PATIENTS WITH STEMI TREATED WITH FIBRINOLYTIC THERAPY: 12-MONTH RESULTS FROM THE TREAT Trial.

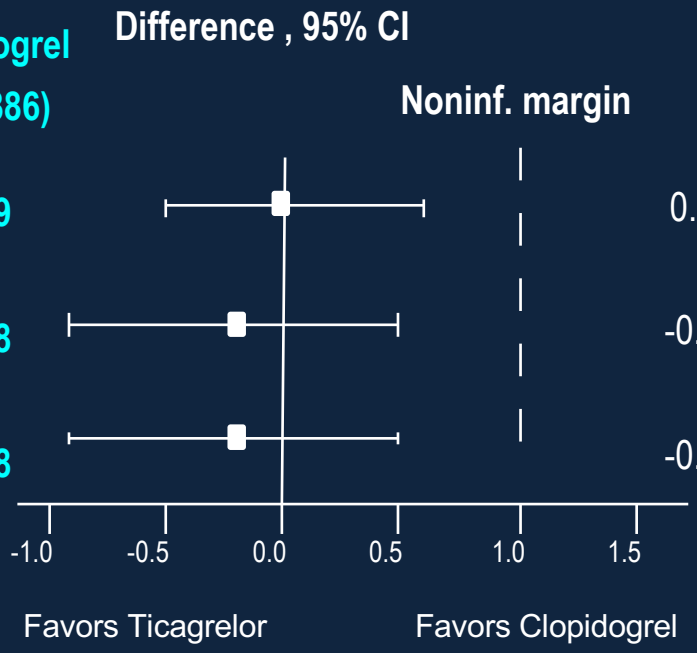
Otavio Berwanger, MD, PhD - On behalf of the TREAT Trial Steering Committee and Investigators

Funding Source: *Astra Zeneca (Investigator-Initiated Trial)*

TREAT Trial – 30 Day Results

Ticagrelor vs. Clopidogrel in Patients with STEMI Treated with Fibrinolytics

	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
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



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.

ACC LBCT 2018
Berwanger O et al. JAMA Cardiology 2018;3:391-399.

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)

Key exclusions: contra-indications to study drugs, use of OACs, dialysis, clinically important thrombocytopenia or anemia

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

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

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

Primary safety outcome: TIMI Major Bleeding
Secondary safety outcomes: All bleeding events (TIMI, PLATO trial, and BARC classification)
Secondary efficacy outcomes: CV death, MI, or stroke and
CV death, MI, stroke, severe recurrent ischemia, TIA, other arterial thrombotic events

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

Berwanger O et al. American Heart Journal 2018;202:89-96..

Treat TRIAL

HCor Research Institute

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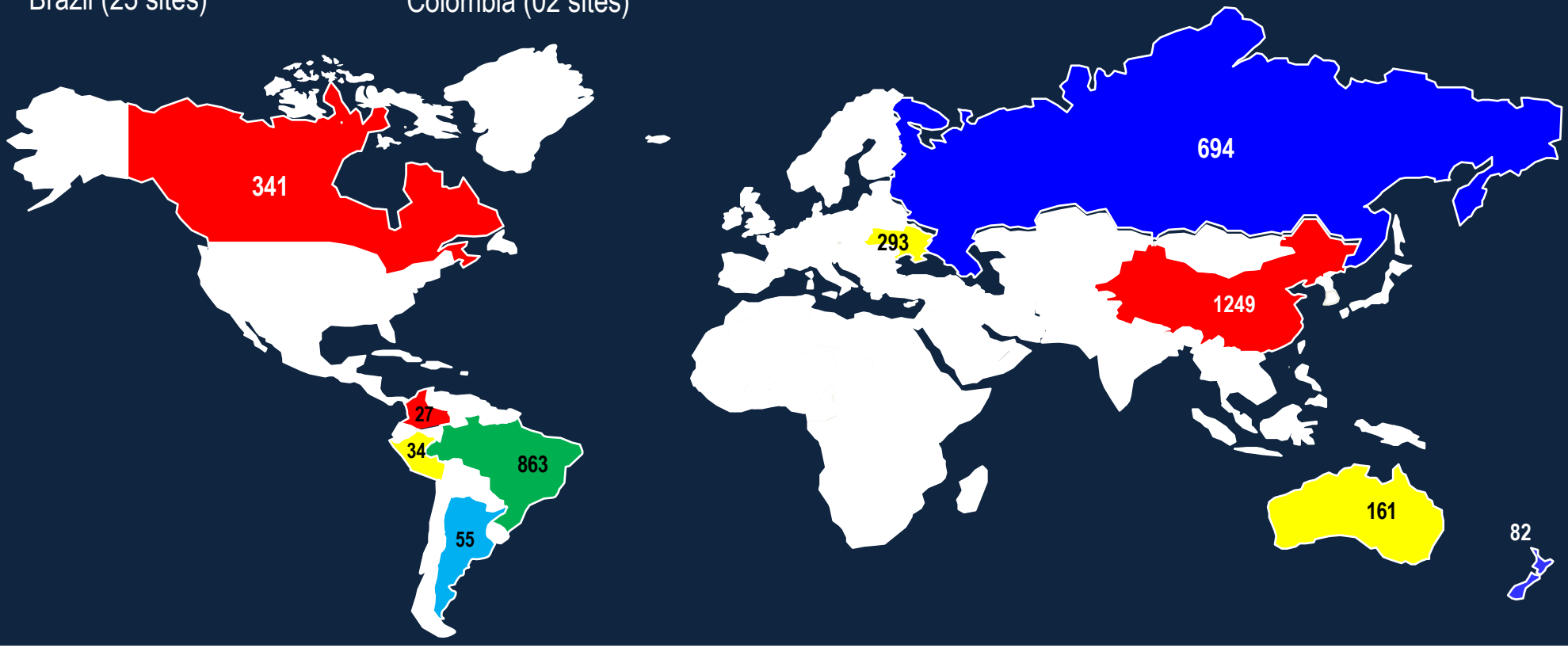
TREAT Trial

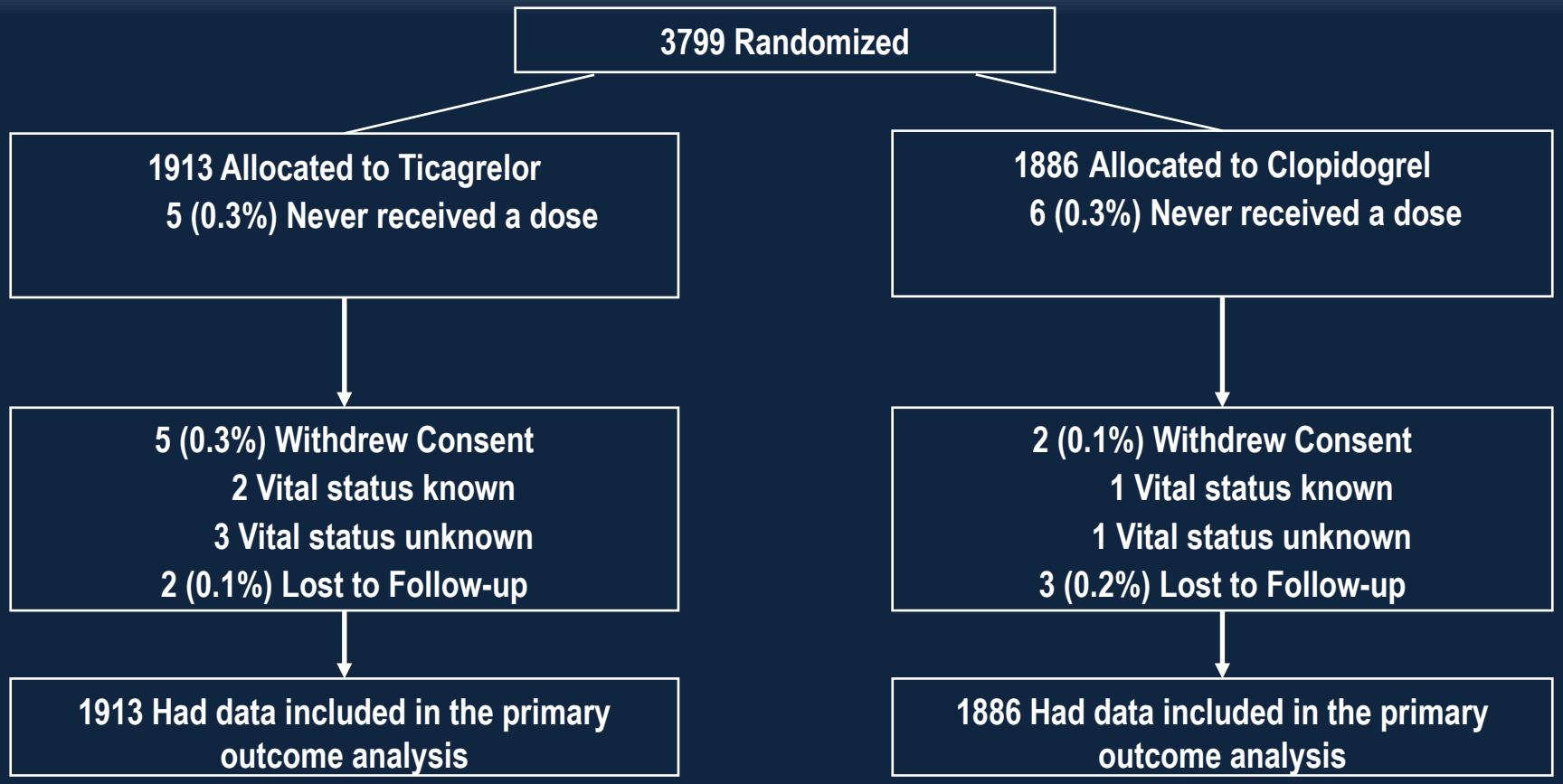
- **Design:** Academically-led, phase III, non-inferiority, international, multicenter, randomized, and open-label study with blinded-outcome adjudication
- **Prevention of Bias:** concealed allocation (central web-based randomization) + intention-to-treat analysis.
- **Trial Size:** 3,794 patients .This sample size provides greater than 90% statistical power, considering an event rate of 1.2% at 30 days, 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.

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 – 12 Months



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	46.8	47.3
Hypertension	56.6	57.1
Dyslipidemia	27.9	28.2
Diabetes Mellitus	17.6	16.1
History, %		
Myocardial Infarction	9.5	8.1
Percutaneous coronary intervention	5.9	5.2
Coronary-artery bypass grafting	0.8	0.7

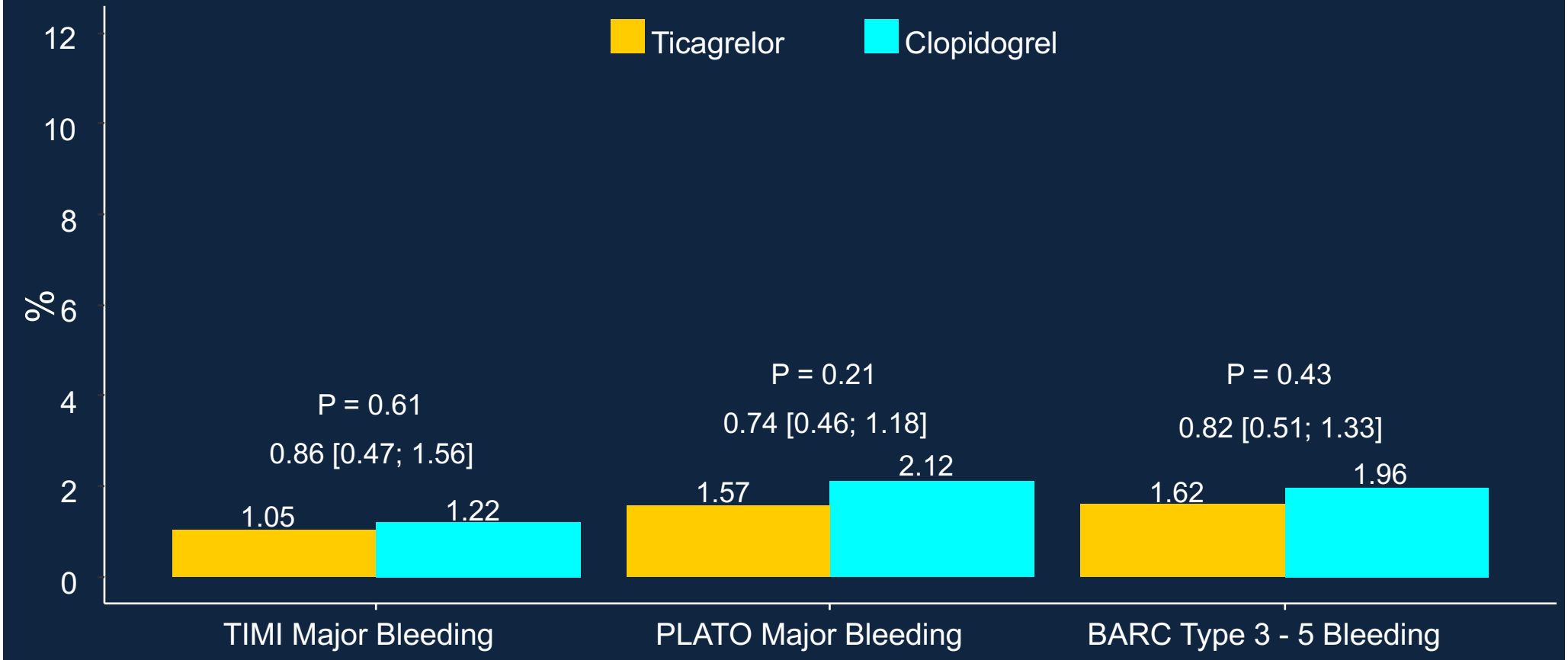
Co-Interventions,Fibrinolytic Therapy

Medication	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
Start of randomized treatment		
Time from fibrinolytic administration to randomization, h, median	11.4	11.5
Fibrinolytic Therapy , %		
Fibrin-Specific	76.2	75.6
Non Fibrin-Specific	23.8	24.4
Clopidogrel before randomization , %	87.0	85.9
Invasive procedure performed during study, %		
PCI	60.4	58.7
Within 24 hours after randomization	42.3	42.0
Cardiac Surgery, %	3.2	3.1
Adherence to study drug at 12 months Follow up, %	89.1	92.5

In-Hospital Treatments

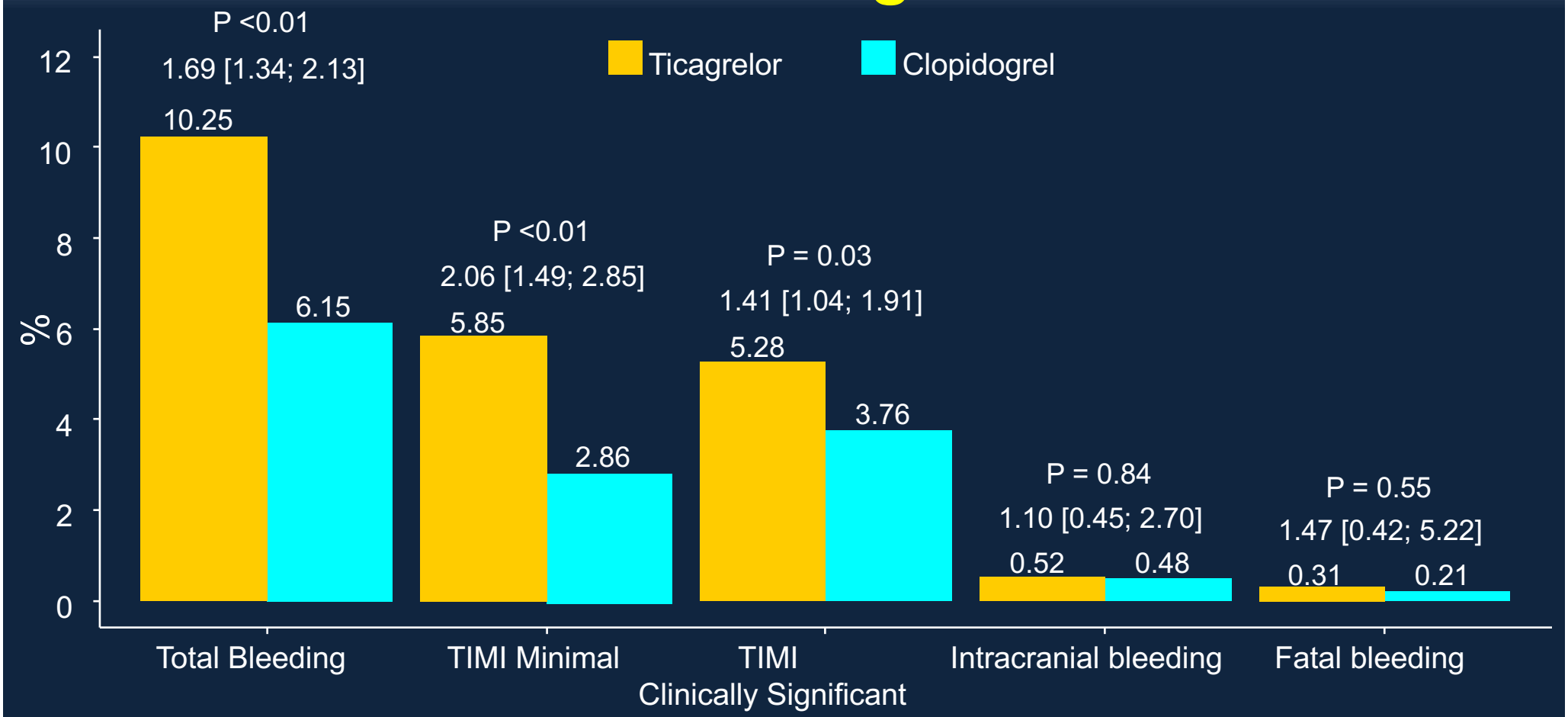
Medication	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
In-hospital treatment , %		
Aspirin	98.8	98.9
Unfractioned heparin	40.8	40.3
Low- molecular-weight heparin	70.0	69.6
Fondaparinux	4.1	4.1
Bivalirudin	0.7	1.4
Glycoprotein IIb/IIIa inhibitor	5.3	4.9
Beta-blocker	75.5	75.9
ACE inhibitor or ARB	60.5	60.3
Statin	93.1	93.5
Proton pump-inhibitor	55.9	57.3

Major Bleeding Events - 12 months



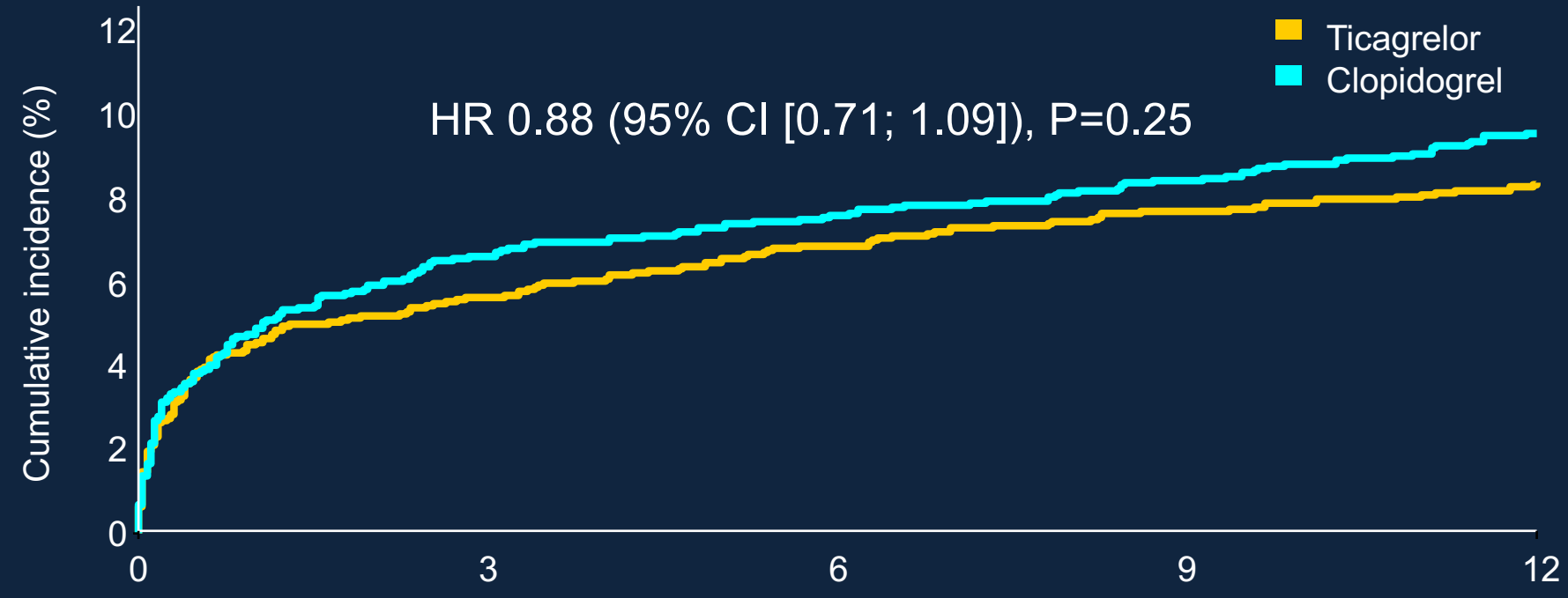
P values and hazard ratios [95% CI] were calculated by Cox regression analysis.

Other Bleeding Events



P values and hazard ratios [95% CI] were calculated by Cox regression analysis.

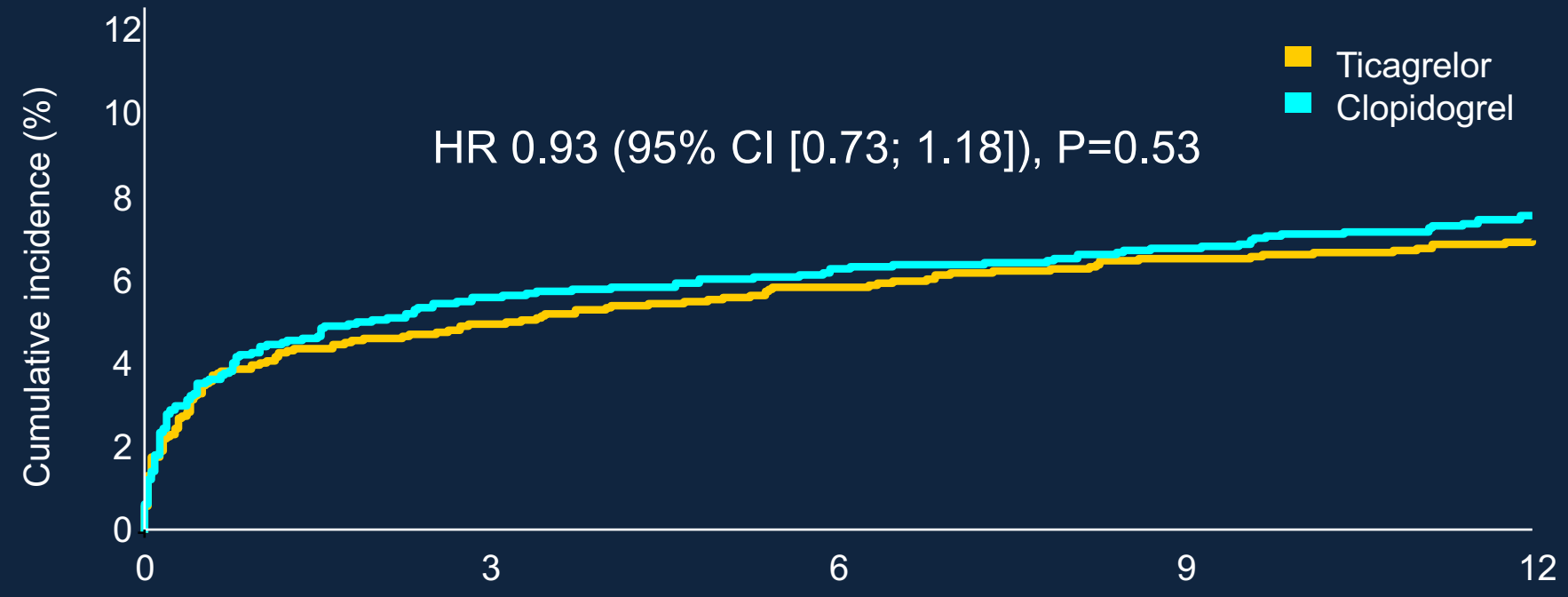
CV Death, MI, Stroke, Severe Recurrent Ischemia, TIA, or other Arterial Thrombotic Events – 12 months



No. at risk					
TICAGRELOR	1913	1796	1770	1744	1548
CLOPIDOGREL	1886	1754	1729	1706	1505

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

CV Death, MI, or Stroke – 12 months



No. at risk					
TICAGRELOR	1913	1808	1788	1764	1567
CLOPIDOGREL	1886	1772	1752	1734	1534

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

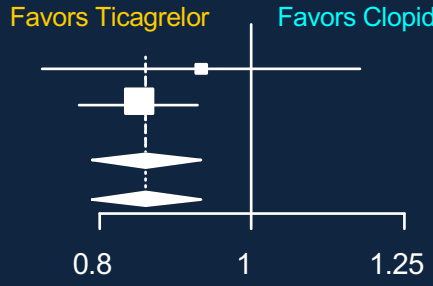
POOLED ANALYSIS

TREAT and PLATO

A) The composite outcome of death from vascular causes, myocardial infarction, or stroke

Study	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio [95% CI]	Weight (fixed)	Weight (random)
TREAT	129	1913	137	1886	0.93 [0.74; 1.17]	12.0%	12.1%
PLATO	864	9333	1014	9291	0.85 [0.78; 0.92]	88.0%	87.9%
Fixed effect model		**11246**		**11177**	**0.86 [0.79; 0.93]**	**100.0%**	--
Random effects model					**0.86 [0.79; 0.93]**	--	**100.0%**

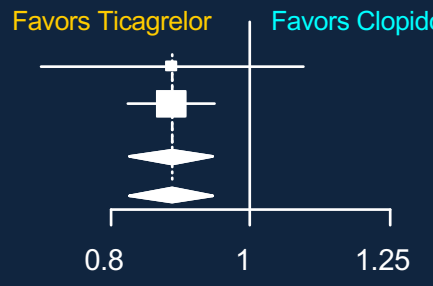
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$



B) The composite outcome of CV Death, MI, stroke, severe recurrent ischemia,TIA, or other arterial thrombotic events

Study	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio [95% CI]	Weight (fixed)	Weight (random)
TREAT	153	1913	171	1886	0.88 [0.72; 1.09]	10.6%	9.9%
PLATO	1290	9333	1456	9291	0.88 [0.82; 0.95]	89.4%	90.1%
Fixed effect model		**11246**		**11177**	**0.88 [0.83; 0.94]**	**100.0%**	--
Random effects model					**0.88 [0.83; 0.94]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$



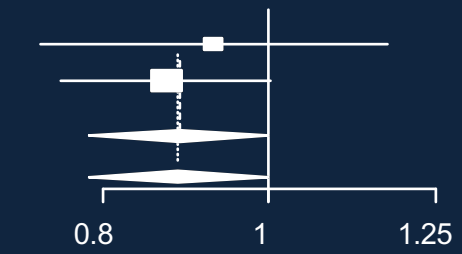
POOLED ANALYSIS

TREAT and PLATO-STEMI Subgroup

A) The composite outcome of death from vascular causes, myocardial infarction, or stroke

Study	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio [95% CI]	Weight (fixed)	Weight (random)
TREAT	129	1913	137	1886	0.93 [0.74; 1.17]	26.5%	26.7%
PLATO-STEMI	331	3752	384	3792	0.87 [0.76; 1.00]	73.5%	73.3%
Fixed effect model		**5665**		**5678**	**0.89 [0.79; 1.00]**	**100.0%**	**--**
Random effects model					**0.89 [0.79; 1.00]**	**--**	**100.0%**

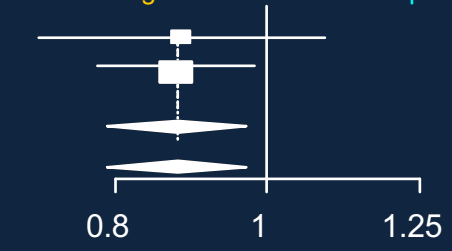
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.65$



B) The composite outcome of CV Death, MI, stroke, severe recurrent ischemia,TIA, or other arterial thrombotic events

Study	Ticagrelor Events	Ticagrelor Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio [95% CI]	Weight (fixed)	Weight (random)
TREAT	153	1913	171	1886	0.88 [0.72; 1.09]	24.3%	23.5%
PLATO-STEMI	466	3752	538	3792	0.88 [0.78; 0.98]	75.7%	76.5%
Fixed effect model		**5665**		**5678**	**0.88 [0.79; 0.97]**	**100.0%**	**--**
Random effects model					**0.88 [0.79; 0.97]**	**--**	**100.0%**

Heterogeneity: $I = 0\%$, $\tau = 0$, $p = 0.95$



Conclusions and Implications

- In patients aged under 75 years with ST-segment elevation myocardial infarction, administration of ticagrelor after fibrinolytic therapy may not reduce the frequency of major cardiovascular events at 12 months when compared with clopidogrel.
- Results suggest the safety of ticagrelor with regards to major bleeding, in comparison to clopidogrel, up to 12 months in fibrinolytic-treated STEMI patients.
- Finally, when TREAT and PLATO are combined in a pooled analysis, results suggest a reduction of major cardiovascular events, with no statistical heterogeneity evident between trials.

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Ticagrelor versus Clopidogrel in Patients with STEMI Treated with Fibrinolytic Therapy: TREAT Trial

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ABSTRACT

BACKGROUND The efficacy of ticagrelor in the long-term post ST-elevation myocardial infarction (STEMI) treated with fibrinolytic therapy remains uncertain.

OBJECTIVES To evaluate the efficacy of ticagrelor when compared with clopidogrel in STEMI patients treated with fibrinolytic therapy.

METHODS We conducted an international, multicenter, randomized, open-label with blinded endpoint adjudication trial that enrolled 3,799 patients (age < 75 years) with STEMI receiving fibrinolytic therapy. Patients were randomized to ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter The key outcomes were cardiovascular mortality, myocardial infarction, or stroke, and the same composite outcome with the addition of severe recurrent ischemia, transient ischemic attack, or other arterial

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