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Ticagrelor Versus Clopidogrel in Patients With STEMI Treated With Fibrinolysis

TREAT Trial

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ABSTRACT

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

OBJECTIVES The purpose of this study was to evaluate the efficacy of ticagrelor when compared with clopidogrel in STEMI patients treated with fibrinolytic therapy.

METHODS This international, multicenter, randomized, open-label with blinded endpoint adjudication trial 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 thrombotic events at 12 months.

RESULTS The combined outcome of cardiovascular mortality, myocardial infarction, or stroke occurred in 129 of 1,913 patients (6.7%) receiving ticagrelor and in 137 of 1,886 patients (7.3%) receiving clopidogrel (hazard ratio: 0.93; 95% confidence interval: 0.73 to 1.18; p = 0.53). The composite of cardiovascular mortality, myocardial infarction, stroke, severe recurrent ischemia, transient ischemic attack, or other arterial thrombotic events occurred in 153 of 1,913 patients (8.0%) treated with ticagrelor and in 171 of 1,886 patients (9.1%) receiving clopidogrel (hazard ratio: 0.88; 95% confidence interval: 0.71 to 1.09; p = 0.25). The rates of major, fatal, and intracranial bleeding were similar between the ticagrelor and clopidogrel groups.

CONCLUSION Among patients age <75 years with STEMI, administration of ticagrelor after fibrinolytic therapy did not significantly reduce the frequency of cardiovascular events when compared with clopidogrel. (Ticagrelor in Patients With ST Elevation Myocardial Infarction Treated With Pharmacological Thrombolysis [TREAT]; NCT02298088)
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ABBREVIATIONS AND ACRONYMS

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Large-scale randomized trials (1,2) have established that dual antiplatelet therapy with aspirin and clopidogrel reduces major cardiovascular events in fibrinolytic-treated ST-segment elevation myocardial infarction (STEMI) patients. Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor $P2Y_{12}$, provides faster, greater, and more consistent $P2Y_{12}$ inhibition than clopidogrel (3,4).

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In the PLATO (Platelet Inhibition and Patient Outcomes) trial, treatment with ticagrelor compared with clopidogrel provided a reduction in the rate of major cardiovascular events (5). Despite these benefits, the trial included only patients undergoing primary percutaneous coronary intervention (PCI), and patients who received fibrinolytic therapy in the preceding 24 h were excluded. Therefore, evidence on the longer-term effects of ticagrelor in patients with STEMI treated with fibrinolytic therapy is lacking. We have previously published the primary results from the TREAT (TicagRElor in pAtients with ST-elevation myocardial infarction treated with pharmacological Thrombolysis) trial (6), and demonstrated that ticagrelor utilization was safe, as the primary endpoint of major bleeding at 30 days was comparable between the ticagrelor and clopidogrel groups. A meta-analysis of TREAT and 4 other trials found similar results with regards to safety at 30 days (7,8). In the current paper, we report the secondary analysis of 12-month efficacy and safety data.

METHODS

STUDY DESIGN. The trial design and 30-day results have been published (6,9). Briefly, the TREAT trial was an academically-led, phase 3, international, multicenter, randomized, open-label study with blinded-outcome assessment that involved 10 countries (Argentina, Australia, Brazil, Canada, China, Colombia, New Zealand, Peru, Russia, and Ukraine). The steering committee, consisting exclusively of academic members, designed and oversaw the conduct of the trial. An independent data monitoring committee monitored the trial and had access to the unblinded data. Site management, data management, and analysis were performed by the Research Institute-Heart Hospital (HCor). The Steering Committee members vouch for the accuracy and completeness of the reported data. The study design

Roche Diagnostics; and has received personal fees from AstraZeneca, Bayer, Novo Nordisk, Roche Diagnostics, and Sanofi. Dr. Lopes has received institutional research grant and consulting fees from Bristol-Myers Squibb; institutional research grants from GlaxoSmithKline; and consulting fees from Bayer, Boehringer Ingelheim, Pfizer, Merck, and Portola. Dr. Fonseca has served as a consultant for AstraZeneca, Sanofi, Takeda, Abbott, Biolab, Amgen, EMS, Torrent, Novartis, Aché, and Bayer; has served on the Steering Committee of the JUPITER study; and initiated the BATTLE-AMI investigator trial. Dr. Goodman has received research grant support (e.g., Steering Committee or Data Monitoring Committee) and/or speaker/consulting honoraria (e.g., Advisory Boards) from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Daiichi-Sankyo, Eli Lilly, Fenix Group International, Ferring Pharmaceuticals, GlaxoSmithKline, Janssen/Johnson & Johnson, Luitpold Pharmaceuticals, Matrizyme, Merck, Novartis, Novo Nordisk A/C, Pfizer, Regeneron, Sanofi, Servier, and Tenax Therapeutics, as well as the Heart and Stroke Foundation of Ontario/University of Toronto, Canadian Heart Research Centre and MD Primer, Canadian VIGOUR Centre, Duke Clinical Research Institute, and PERFUSE study. Dr. Nicholls has received research support from AstraZeneca, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, and LipoScience; and has served as a consultant for and received honoraria from Akcea, AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, and Boehringer Ingelheim. Dr. Averkov has received lecturer and adviser fees from AstraZeneca. Dr. de Barros e Silva has received grants and personal fees from Pfizer. Dr. Granger has research contracts with Apple, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Janssen, Novartis, GlaxoSmithKline, Medtronic Foundation, Pfizer, the U.S. Food and Drug Administration, and the National Institutes of Health; and has served as a consultant for Abbvie, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Boston Scientific, Gilead, Pfizer, Daiichi-Sankyo, Novartis, Medtronic, Merck, Novo Nordisk, and Roche Diagnostics. Dr. White has served as Executive Committee member and National Coordinator for and received consulting fees for the ODYSSEY Trial (Sanofi) and ACCELERATE Study (Eli Lilly); has received research grant support from the National Institute of Health; has received Advisory Board fees, lecture fees, support towards travel and accommodation, and nonfinancial support from AstraZeneca; has served as a Steering Committee member and National Leader and received consulting fees for the STRENGTH Trial (Omthera Pharmaceuticals); has served on the Steering Committee and received consulting fees for the SPIRE Trial (Pfizer New Zealand); has served as National Lead Investigator and Steering Committee member and received consulting fees for the CAMELIA Trial (Elsai Inc.) and DalGenE Study (DalCor Pharma UK Inc.); has received Advisory Board fees from Sirtex and Actelion; has served on the Executive/Steering Committee, as National Country Lead, and received consulting fees for the AEGIS-II study (CSL Behring LLC); and has received Steering Committee member consulting fees from the HEART-FID study (Luitpold Pharmaceuticals). Dr. Nicolau has received research support from Amgen, Bayer, Bristol-Myers Squibb, Dalcor, Janssen, Sanofi, AstraZeneca, Boehringer Ingelheim, Novartis, Perfuse, and Pfizer; and has received consulting fees or honoraria from Sanofi, Amgen, and Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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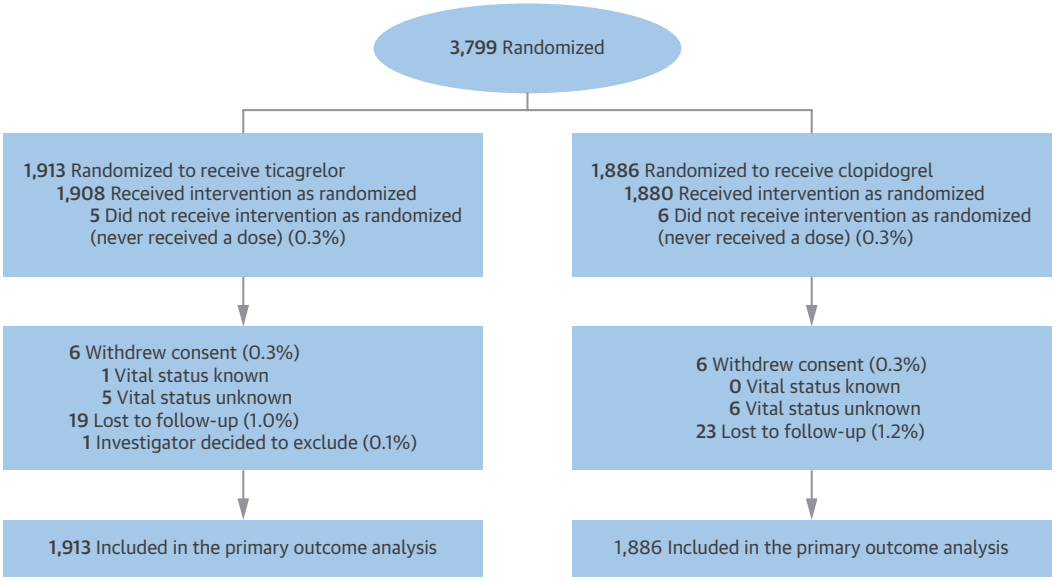
FIGURE 1 Flow of Patients in the TREAT Trial



For the majority of included patients, randomized treatment did not begin acutely, but hours after initiation of fibrinolytic therapy. In this sense, patients randomized to ticagrelor received the first dose of ticagrelor in a median time of 11.4 h after initiation of fibrinolytic therapy, and 90% were pre-treated with clopidogrel.

was approved by the appropriate national and institutional regulatory authorities and ethics committees, and all participants provided written informed consent.

PATIENTS. Patients were eligible for enrollment if they presented within 24 h of the onset of symptoms, had evidence of acute ST-segment elevation on their qualifying electrocardiogram (at least 2 mm in 2 contiguous peripheral or precordial leads in men and 1.5-mm elevation in V_1 to V_3 in women and 1 mm in limb leads), were <75 years of age, and received fibrinolytic therapy. Key exclusion criteria were any contraindication to the use of study drugs, use of oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer. The complete list of inclusion and exclusion criteria is provided in the Online Appendix.

RANDOMIZATION AND STUDY TREATMENT. Patients were randomly assigned, in a 1:1 ratio, to receive ticagrelor with a loading dose of 180 mg or clopidogrel (with a loading dose of 300 to 600 mg) as early as possible after the index event and not >24 h post-event. Randomization was performed in a concealed fashion with the use of an automated web-based system, in permuted blocks of 4, stratified according to site. Patients pre-treated with clopidogrel before randomization were still eligible; if randomized to ticagrelor, the trial loading dose was recommended, and if randomized to clopidogrel, they could receive an additional 300 mg of clopidogrel at the discretion of the investigator and in accordance to local guidelines if undergoing PCI. The randomized maintenance therapy for ticagrelor was 90 mg twice daily and for clopidogrel was 75 mg once daily.

All patients received aspirin 75 to 100 mg daily during all follow-up unless intolerant. For patients not previously receiving aspirin, a loading dose of 162 to 325 mg was recommended. Investigators were encouraged to follow appropriate guidelines (10,11) in the other aspects of managing STEMI; decisions about the use of other treatments for acute STEMI and subsequent revascularization procedures were left to the discretion of the treating physicians. Compliance was assessed by investigators and research coordinators by pill count and patient report.

OUTCOMES. The previously reported primary outcome was major bleeding, according to the Thrombolysis In Myocardial Infarction (TIMI) definition at 30 days (6). The efficacy outcomes for the current publication included the composite outcome of death from vascular causes, myocardial infarction, or stroke (similar to the PLATO primary outcome), and the same composite outcome with the addition of

TABLE 1 Characteristics of the Patients at Baseline

	Ticagrelor (n = 1,913)	Clopidogrel (n = 1,886)
Age, yrs	59.0 (51.6-65.2)	58.8 (51.6-65.5)
Female	433/1,913 (22.6)	437/1,886 (23.2)
Body weight, kg	76.5 (68.0-88.0)	77.0 (67.0-87.0)
Body weight <60 kg	148/1,911 (7.7)	150/1,885 (8.0)
BMI, kg/m^2	26.5 (24.0-29.8)	26.5 (24.0-29.4)
Race*		
White	1,100/1,913 (57.5)	1,077/1,886 (57.1)
Black	73/1,913 (3.8)	61/1,886 (3.2)
Asian	631/1,913 (33.0)	639/1,886 (33.9)
Other	109/1,913 (5.7)	109/1,886 (5.8)
Cardiovascular risk factor		
Never smoker	637/1,913 (33.3)	657/1,886 (34.8)
Previous smoker	380/1,913 (19.9)	336/1,886 (17.8)
Habitual smoker	896/1,913 (46.8)	893/1,886 (47.3)
Hypertension	1,082/1,913 (56.6)	1,076/1,886 (57.1)
Dyslipidemia	533/1,913 (27.9)	531/1,886 (28.2)
Diabetes mellitus	336/1,913 (17.6)	303/1,886 (16.1)
Other medical history		
MI	181/1,913 (9.5)	152/1,886 (8.1)
Stroke	88/1,913 (4.6)	89/1,886 (4.7)
PCI	112/1,913 (5.9)	99/1,886 (5.2)
CABG	15/1,913 (0.8)	13/1,886 (0.7)
Congestive heart failure	37/1,913 (1.9)	36/1,886 (1.9)
Peripheral arterial disease	17/1,913 (0.9)	16/1,886 (0.8)
Atrial fibrillation	21/1,913 (1.1)	24/1,886 (1.3)
Chronic obstructive pulmonary disease	51/1,913 (2.7)	45/1,886 (2.4)
Asthma	28/1,913 (1.5)	45/1,886 (2.4)
Gout	39/1,913 (2.0)	32/1,886 (1.7)
ECG findings at study entry		
ST-segment elevation (anterior alone)	640/1,905 (33.6)	665/1,878 (35.4)
ST-segment elevation (anterior and inferior)	63/1,905 (3.3)	60/1,878 (3.2)
ST-segment elevation (inferior alone)	588/1,905 (30.9)	565/1,878 (30.1)
ST-segment elevation (other)	293/1,905 (15.4)	303/1,878 (16.1)
Left bundle block	18/1,905 (0.9)	24/1,878 (1.3)
Positive troponin I test at study entry	1,544/1,752 (88.1)	1,511/1,728 (87.4)
Killip class (II, III, or IV)	160/1,913 (8.4)	170/1,886 (9.0)

Values are median (interquartile range) or n/N (%). *Race was self-reported. Body mass index (BMI) denotes the weight in kilograms divided by the square of the height in meters. ST-segment elevation denotes ST-segment elevation myocardial infarction.

CABG = coronary artery bypass graft; ECG = electrocardiographic; MI = myocardial infarction; PCI = percutaneous coronary intervention.

severe recurrent ischemia, transient ischemic attack, or other arterial thrombotic events at 12 months. Finally, we evaluated individual components of the composite efficacy outcomes and all-cause mortality at 12 months. Secondary safety outcomes at 12 months included: major, clinically relevant nonmajor bleeding or minor bleeding according to the TIMI definition, and major or minor bleeding according to the PLATO trial and the Bleeding Academic Research Consortium definitions.

The primary and secondary outcomes were adjudicated with the use of pre-specified criteria by an independent clinical events committee whose members were unaware of the group assignments. Detailed definitions of outcomes are provided in the Online Appendix.

STATISTICAL ANALYSIS. The sample size was calculated based on our primary outcome (TIMI major bleeding rates at 30 days) as previously reported (6,9). Given that the trial was not originally powered to assess efficacy outcomes, the analysis of major cardiovascular events was considered to be exploratory. Nevertheless, the efficacy analyses were prespecified in our statistical analysis plan.

Continuous variables are reported as mean ± SD or medians (interquartile range [IQR]) as appropriate. Categorical variables are summarized as frequencies. Continuous variables were compared between groups using Student's *t*-tests or Mann-Whitney *U* tests if the normality assumptions required for the first test were not satisfied. Comparisons between qualitative variables were performed with the Fisher exact test.

All patients who had been randomized to a treatment group were included in the intention-to-treat analyses. Outcomes were analyzed with the use of a Cox proportional hazards model. The point estimate and 2-sided 95% confidence interval (CI) for the hazard ratio (HR) were calculated for each outcome. Proportional hazard assumptions were checked by visual inspection and a weighted residuals test. Prespecified efficacy analyses were performed in subgroups according to sex, diabetes mellitus, time from start of index event to randomization (>12 or ≤12 h), Killip risk score, use of clopidogrel before randomization, treatment with fibrin- or nonfibrin-specific fibrinolytics, and PCI procedures. We also conducted sensitivity analyses in the "per-protocol" and in the "as-treated" populations, as well as analyses adjusted for sex, diabetes mellitus, clopidogrel prerandomization, time from chest pain onset until randomization, and PCI procedures (Online Appendix). All reported p values are 2-sided. All analyses were performed with the use of R (R Foundation for Statistical Computing, Vienna, Austria) (12).

RESULTS

STUDY PATIENTS AND STUDY DRUGS. We recruited 3,799 patients from 152 centers in 10 countries from November 2015 through November 2017. The follow-up period for the 12-month data ended in November 2018, when information on vital status was available for all patients except 55 (**Figure 1**). **Table 1** presents the baseline characteristics. The mean age was 58 ± 9.5 years, 77.1% were men, 47.1% were

current smokers, and 8.8% had a history of myocardial infarction. A total of 99.9% of the patients received a fibrinolytic agent, of whom 75.9% received a fibrin-specific agent. The 2 treatment groups were well balanced, as demonstrated by the baseline characteristics in **Table 1** and the nonstudy medications and procedures (Online Table 1). Both groups had a median of 2.6 h (IQR: 1.5 to 4.3 h) from chest pain to fibrinolytic therapy and were randomized a median of 11.4 h (IQR: 5.8 to 18.1 h) after fibrinolytic therapy. In both groups, 89.4% of patients received clopidogrel prior to randomization, usually at the 300-mg dose. A total of 98.8% of the patients received aspirin. The overall rate of adherence to the study drugs at 12 months was 90.4%, as assessed by the site investigators.

EFFICACY OUTCOMES. The efficacy outcomes at 12 months are shown in **Table 2**. The composite outcome of death from vascular causes, myocardial infarction, or stroke occurred in 129 of 1,913 patients (6.7%) receiving ticagrelor and in 137 of 1,886 patients (7.3%) receiving clopidogrel (HR: 0.93; 95% CI: 0.73 to 1.18; p = 0.53) (**Central Illustration**). The composite outcome of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, transient ischemic attack, or other arterial thrombotic events occurred in 153 of 1,913 patients (8.0%) treated with ticagrelor and in 171 of 1,886 patients (9.1%) receiving clopidogrel (HR: 0.88; 95% CI: 0.71 to 1.09; p = 0.25) (**Central Illustration**). For both composite outcomes, results were similar for the per-protocol and as-treated analyses (Online Table 2). The rates of individual outcomes of total and cardiovascular mortality and myocardial infarction were similar in the ticagrelor and clopidogrel groups. Stroke, severe recurrent ischemia, and other arterial thrombotic events were numerically lower in the ticagrelor than in the clopidogrel group, but the numbers of events were low, and the differences were not statistically significant.

BLEEDING OUTCOMES. **Table 3** presents the safety outcomes. TIMI major bleeding at 12 months occurred in 20 of 1,913 patients (1.0%) in the ticagrelor group and in 23 of 1,886 patients (1.2%) in the clopidogrel group (HR: 0.86; 95% CI: 0.47 to 1.56; p = 0.61). Major bleeding as assessed by the PLATO criteria occurred in 30 of 1,913 patients (1.6%) in the ticagrelor group and in 40 of 1,886 patients (2.1%) in the clopidogrel group (HR: 0.74; 95% CI: 0.46 to 1.18; p = 0.21) and Bleeding Academic Research Consortium types 3 to 5 bleeding occurred in 31 of 1,913 (1.6%) in the ticagrelor group and in 37 of 1,886 (2.0%) in the clopidogrel group (HR: 0.82; 95% CI: 0.51 to 1.33; p = 0.43). The rates of fatal (0.3% vs. 0.2%; p = 0.55) and intracranial bleeding (0.3% vs. 0.2%; p = 0.76) were similar between the ticagrelor and the clopidogrel groups, respectively. TIMI minimal bleeding (5.9% vs. 2.9%; p < 0.01), as well as TIMI bleeding requiring medical attention (3.8% vs. 2.1%; p < 0.01), were more common with ticagrelor than with clopidogrel.

TABLE 2 Efficacy Events at 12 Months

Secondary Outcomes at 12 Months	Ticagrelor (n = 1,913)	Clopidogrel (n = 1,886)	HR, % (95% CI)*	p Value*
Death from vascular causes, MI, or stroke	129 (6.7)	137 (7.3)	0.93 (0.73–1.18)	0.53
Death from vascular causes, MI, stroke, severe recurrent ischemia, TIA, or other arterial thrombotic event	153 (8.0)	171 (9.1)	0.88 (0.71–1.09)	0.25
Death (from vascular causes)	72 (3.8)	78 (4.1)	0.91 (0.66–1.25)	0.56
MI	48 (2.5)	49 (2.6)	0.96 (0.65–1.43)	0.85
Fatal	15 (0.8)	14 (0.7)	1.05 (0.51–2.18)	0.89
Nonfatal	33 (1.7)	35 (1.9)	0.93 (0.58–1.49)	0.75
Total stroke	26 (1.4)	29 (1.5)	0.88 (0.52–1.50)	0.65
Hemorrhagic	8 (0.4)	9 (0.5)	0.88 (0.34–2.27)	0.79
Ischemic	16 (0.8)	20 (1.1)	0.79 (0.41–1.52)	0.48
Ischemic stroke with hemorrhagic transformation	1 (0.1)	0 (0.0)		
Uncertain	1 (0.1)	0 (0.0)		
TIA	0 (0.0)	2 (0.1)		
Severe recurrent ischemia	23 (1.2)	33 (1.7)	0.68 (0.40–1.17)	0.16
Other arterial thrombotic events	2 (0.1)	4 (0.2)	0.49 (0.09–2.69)	0.41
Death (from any cause)	80 (4.2)	86 (4.6)	0.92 (0.68–1.24)	0.57

Values are n (%) unless otherwise indicated. *p values and hazard ratios were calculated by Cox regression analysis.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction. TIA = transient ischemic attack.

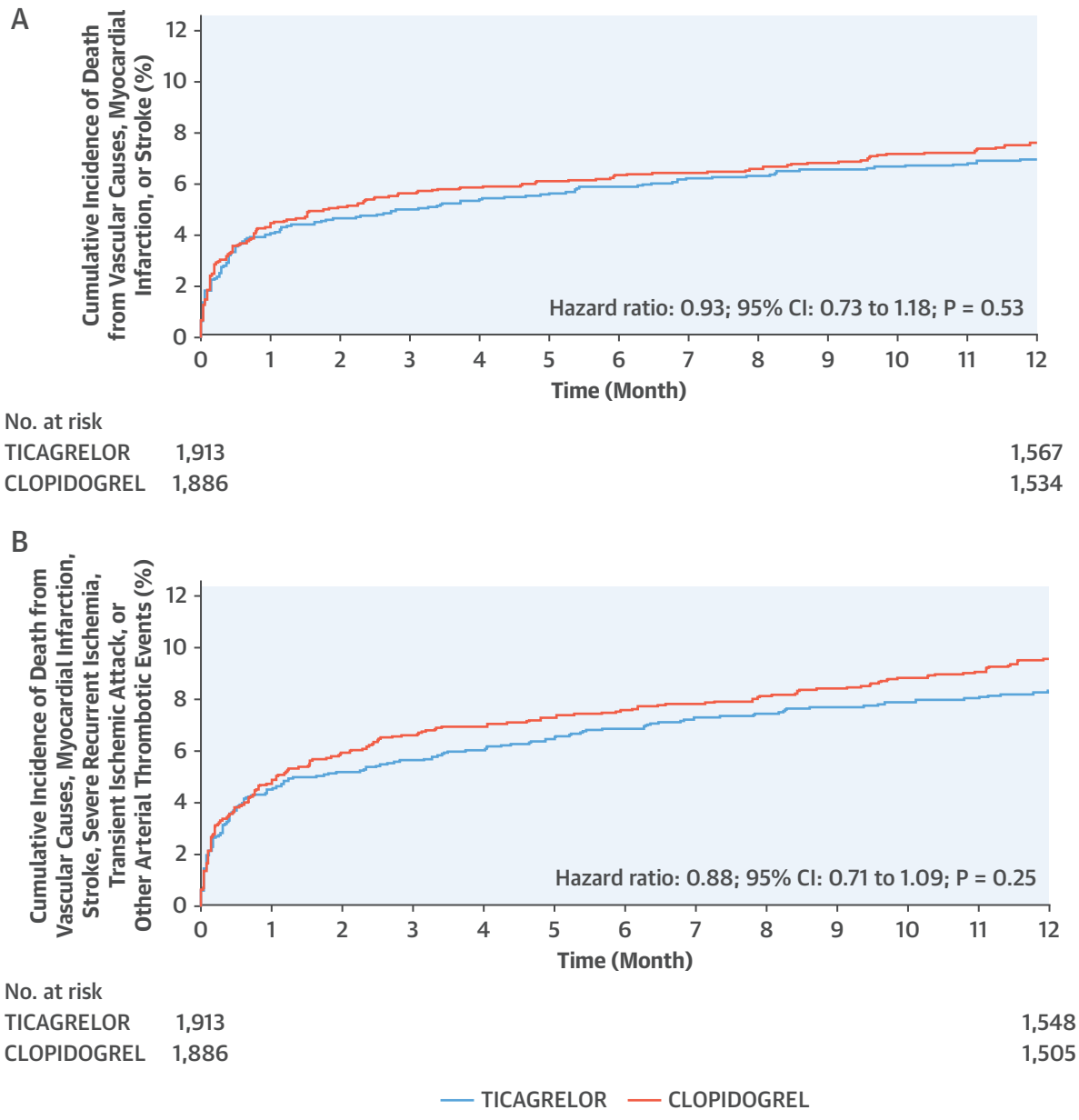
OTHER ADVERSE EVENTS. Discontinuation of the study drug due to serious adverse events was similar between the ticagrelor and clopidogrel groups (0.7% vs. 0.3%; p = 0.24) (Online Table 3). Dyspnea was more common in the ticagrelor group than in the clopidogrel group (in 23.9% vs. 13.7% of patients, respectively) (Online Table 4). Few patients discontinued the study drug because of dyspnea (1.9% of patients in the ticagrelor group and no patients in the clopidogrel group). The frequencies of other serious adverse events were similar between groups.

SUBGROUP ANALYSIS. The treatment comparisons of ticagrelor versus clopidogrel for the efficacy outcomes were consistent among all subgroups (**Figure 2**).

DISCUSSION

Primary PCI represents the preferred reperfusion method in patients with STEMI (11). Nevertheless, fibrinolytic therapy is still commonly used worldwide

CENTRAL ILLUSTRATION **Ticagrelor Versus Clopidogrel in Patients with STEMI Treated with Fibrinolysis**



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Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of the primary efficacy outcome. **(A)** Composite outcome of death from vascular causes, myocardial infarction, or stroke. **(B)** Composite outcome of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, transient ischemic attack, or other arterial thrombotic. STEMI = ST-segment elevation myocardial infarction.

(13). Recent guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel as adjuncts to fibrinolytic-treated patients with STEMI to improve clinical outcomes. On the other hand, by the time they were published, the same guidelines did not recommend the use of ticagrelor within 24 h of fibrinolytic therapy due to the lack of data confirming the safety of this approach (14,15).

The TREAT trial was planned to fill this gap in the published data, as it was primarily designed to assess

whether ticagrelor was noninferior to clopidogrel with respect to safety at 30 days (6). The main findings demonstrated similar 30-day major bleeding rates between ticagrelor and clopidogrel after fibrinolytic therapy. Thus, other secondary analyses regarding efficacy and safety outcomes should be considered as exploratory. However, the interpretation of any trial should depend on the totality of the results (i.e., the primary and secondary outcomes). In this sense, one of the key pre-specified analyses of the TREAT trial is, as reported by the current paper, efficacy and safety outcomes at 12 months.

According to our findings, in patients under 75 years of age with STEMI who received fibrinolytic therapy as their initial reperfusion strategy, administration of ticagrelor did not reduce the rates of major cardiovascular events compared with clopidogrel at 12 months. Results were consistent in the intention-to-treat, as-treated, and per-protocol analyses. The more intense platelet inhibition with ticagrelor is suggested by the observation of higher rates of minimal bleeding among patients receiving ticagrelor, although there was no significant increase in the rate of severe, major, or life-threatening bleeding.

The similar efficacy between ticagrelor and clopidogrel at 12 months in our trial is apparently in contrast to the PLATO trial, including the PLATO-STEMI subgroup analysis. Nevertheless, this comparison should be interpreted with caution. In contrast to TREAT, the PLATO trial was adequately powered to assess efficacy at 12 months. In the PLATO trial, 18,624 patients were included and 1,878 primary outcome events (cardiovascular mortality, myocardial infarction, and stroke) were observed. Similarly, the PLATO-STEMI subgroup analysis for the primary outcome was based on 715 events in 7,544 patients. In contrast, in TREAT, only 266 events were observed in 3,799 patients for the same PLATO primary endpoint. Thus, our statistical power was limited to detect potential clinical outcome differences between groups, and the wide CIs around our effect estimates for all efficacy outcomes do not rule-out effect sizes similar to those observed by the PLATO trial. Assuming the observed HR from PLATO of 0.84 to be true, then, the observed HR in TREAT with 266 events fall well within random variability around that HR. The probability of observing an HR of 0.93 or worse (by chance) with 266 events and a true HR of 0.84 is approximately 20%. In fact, a post-hoc analysis comparing ticagrelor with clopidogrel in 4,949 PLATO patients with STEMI that were treated with primary PCI within 12 h of admission described results similar to ours (HR: 0.91; 95% CI: 0.75 to 1.12) (16).

TABLE 3 Bleeding Events at 12 Months

Safety Outcomes at 12 Months	Ticagrelor (n = 1,913)	Clopidogrel (n = 1,886)	HR, % (95% CI)*	p Value*
TIMI classification				
Minimal	112 (5.9)	54 (2.9)	2.06 (1.49–2.85)	<0.01
Clinically significant bleeding	101 (5.3)	71 (3.8)	1.41 (1.04–1.91)	0.03
Requiring medical attention	73 (3.8)	39 (2.1)	1.86 (1.26–2.74)	<0.01
Minor	12 (0.6)	12 (0.6)	0.98 (0.44–2.19)	0.97
TIMI major bleeding	20 (1.0)	23 (1.2)	0.86 (0.47–1.56)	0.61
TIMI major and minor	30 (1.6)	35 (1.9)	0.84 (0.52–1.37)	0.49
PLATO classification				
Minimal	142 (7.4)	62 (3.3)	2.29 (1.70–3.09)	<0.01
Minor	41 (2.1)	27 (1.4)	1.50 (0.92–2.44)	0.10
PLATO major bleeding	30 (1.6)	40 (2.1)	0.74 (0.46–1.18)	0.21
Other major	11 (0.6)	13 (0.7)	0.83 (0.37–1.86)	0.65
Major bleed, life threatening	21 (1.1)	26 (1.4)	0.77 (0.43–1.35)	0.36
PLATO major and minor	70 (3.7)	63 (3.3)	1.10 (0.78–1.54)	0.60
BARC classification				
BARC type 1	112 (5.9)	54 (2.9)	2.06 (1.49–2.85)	<0.01
BARC type 2	73 (3.8)	38 (2.0)	1.91 (1.29–2.82)	<0.01
BARC types 3–5	31 (1.6)	37 (2.0)	0.82 (0.51–1.33)	0.43
BARC type 3a	10 (0.5)	13 (0.7)	0.76 (0.33–1.73)	0.51
BARC type 3b	10 (0.5)	13 (0.7)	0.76 (0.33–1.73)	0.51
BARC type 3c	6 (0.35)	5 (0.3)	1.18 (0.36–3.88)	0.78
BARC type 4	0 (0.0)	1 (0.1)		
BARC type 5	8 (0.4)	5 (0.3)	1.58 (0.52–4.82)	0.42
Any bleeding	196 (10.2)	116 (6.2)	1.69 (1.34–2.13)	<0.01
Intracranial hemorrhage	10 (0.5)	9 (0.5)	1.10 (0.44–2.69)	0.84
Fatal bleeding	6 (0.3)	4 (0.2)	1.47 (0.42–5.21)	0.55
Intracranial fatal bleeding	5 (0.3)	4 (0.2)	1.23 (0.33–4.56)	0.76

Values are n (%) unless otherwise indicated. *p values and hazard ratios were calculated by Cox regression analysis.

BARC = Bleeding Academic Research Consortium; PLATO = Platelet Inhibition and Patient Outcomes; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 2.

Our findings regarding the combined outcome of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, transient ischemic attack, or other arterial thrombotic events yielded the same effect size (HR: 0.88) observed in the PLATO trial (HR: 0.88 in the main analysis and HR: 0.87 in the PLATO-STEMI subgroup analysis) for the same outcome.

Besides the low statistical power, we also explored whether other factors such as study population and trial design could also help to explain our findings. In addition to the paradoxical pro-thrombotic status post-fibrinolytic therapy, platelet reactivity is heightened after thrombolytic therapy during STEMI management and, therefore, the use of early potent $P2Y_{12}$ inhibitors such as ticagrelor would be theoretically beneficial for this patient population (17,18). In fact, pharmacodynamics studies in fibrinolytic-treated STEMI patients have demonstrated a greater reduction of platelet reactivity with ticagrelor than

FIGURE 2 Subgroup Analysis

Subgroup	Ticagrelor	Clopidogrel	Hazard Ratio (95% CI)	P Value for Interaction
	No./Total No. (%)		Favors Ticagrelor / Favors Clopidogrel	
Sex				
Male	83/1480 (5.6%)	94/1449 (6.5%)	0.86 [0.64; 1.16]	0.38
Female	46/433 (10.6%)	43/437 (9.8%)	1.08 [0.71; 1.64]	
Diabetes Mellitus				
No	96/1577 (6.1%)	99/1583 (6.3%)	0.97 [0.74; 1.29]	0.39
Yes	33/336 (9.8%)	38/303 (12.5%)	0.77 [0.48; 1.22]	
Chest pain until randomization				
More than 12 hours	79/1200 (6.6%)	80/1192 (6.7%)	0.98 [0.72; 1.34]	0.61
12 hours or less	50/709 (7.1%)	56/689 (8.1%)	0.86 [0.59; 1.26]	
Killip class				
I	107/1753 (6.1%)	116/1716 (6.8%)	0.90 [0.69; 1.17]	0.48
II, III or IV	22/160 (13.8%)	21/170 (12.4%)	1.14 [0.63; 2.07]	
Clopidogrel pre-randomization				
No loading dose	17/196 (8.7%)	24/205 (11.7%)	0.73 [0.39; 1.35]	0.10
300 mg	108/1651 (6.5%)	98/1611 (6.1%)	1.08 [0.82; 1.42]	
More than 300 mg	4/51 (7.8%)	12/60 (20%)	0.37 [0.12; 1.14]	
Fibrinolytic therapy				
Non-specific	28/454 (6.2%)	28/459 (6.1%)	1.01 [0.60; 1.71]	0.71
Specific	100/1457 (6.9%)	108/1425 (7.6%)	0.90 [0.69; 1.19]	
PCI				
No or >24 h from randomization	88/1103 (8%)	96/1094 (8.8%)	0.91 [0.68; 1.21]	0.77
Within 24 h from randomization	41/810 (5.1%)	41/792 (5.2%)	0.98 [0.63; 1.51]	
PCI				
No or >30 d from randomization	72/824 (8.7%)	76/827 (9.2%)	0.95 [0.69; 1.31]	0.87
Within 30 d from randomization	57/1089 (5.2%)	61/1059 (5.8%)	0.91 [0.63; 1.30]	

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

with clopidogrel in both short- and long-term follow-up (19,20). The median time of thrombolytic administration to randomization was about 11 h, and the majority of patients in our trial received clopidogrel pre-randomization. The point estimate observed in a subgroup analysis of patients who did not receive a loading dose of clopidogrel before randomization was 0.73 (as opposed to 1.08 in patients who received 300 mg of clopidogrel). On the other hand, our subgroup analysis did not suggest statistically significant treatment interactions. Thus, this finding may be due to the play of chance. Whether a large trial including only patients who receive ticagrelor and clopidogrel before or at the same time of fibrinolytic therapy would yield different results from TREAT cannot be inferred from our data.

STUDY LIMITATIONS. The TREAT trial had limitations that merit consideration. Our trial does not address management of patients ≥75 years of age, who were excluded. Our trial was an investigator-initiated trial with limited funding, which did not allow a blinded double-dummy design. We attempted to minimize the risk of bias associated with the open-label nature of the study by performing blinded outcome adjudication. It should also be noted that the timing of drug administration in patients treated with lytics therapy could have impacted bleeding outcomes. Finally, as discussed, the major limitation of secondary analyses in our trial relates to the lack of adequate statistical power to assess efficacy and safety outcomes as 12 months.

Finally, despite the limitations, to the best of our knowledge, TREAT constitutes the largest randomized trial available evaluating ticagrelor in STEMI patients managed with fibrinolytics. In addition, it also represents the largest trial assessing dual antiplatelet therapy at 12 months post-fibrinolytic therapy, since the follow-up period in previous studies was restricted to 30 days (1,2). Therefore, our findings may provide additional data to inform physician's decisions, suggesting that ticagrelor may represent a

potentially safe alternative antiplatelet agent that can be used after fibrinolytic therapy. On the other hand, our 12-month results should be viewed as hypothesis-generating, and further studies of antithrombotic therapies in fibrinolytic-treated STEMI patients are needed. These include randomized trials and real-world evidence studies testing the use of ticagrelor at the same time of fibrinolytic therapy, especially in elderly patients, as well as studies testing strategies that could result in lower risk of bleeding (while preserving efficacy). Some of these strategies comprise the use of lower doses of ticagrelor combined with aspirin, as well as monotherapy with ticagrelor or other potent $P2Y_{12}$ inhibitors, versus standard dual antiplatelet therapy. Additionally, studies testing the efficacy and safety of the combination of low-dose direct oral anticoagulants with aspirin or with potent $P2Y_{12}$ inhibitors in selected patients are also warranted.

CONCLUSIONS

Among patients age <75 years with STEMI, administration of ticagrelor after fibrinolytic therapy may not significantly reduce the frequency of major cardiovascular events at 12 months when compared with clopidogrel. Finally, our results suggest the safety of ticagrelor, in comparison to clopidogrel, up to 12 months post-fibrinolytic-treated STEMI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients age <75 years with STEMI treated with fibrinolysis, ticagrelor did not reduce the frequency of major cardiovascular events at 12 months compared with clopidogrel.

TRANSLATIONAL OUTLOOK: Further studies are needed to define the optimum antithrombotic regimen following fibrinolytic therapy for patients with STEMI.

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KEY WORDS blinded adjudication, dual antiplatelet therapy, fibrinolysis, myocardial infarction, STEMI, ticagrelor

APPENDIX For an expanded Methods section, a list of committees and investigators, and supplemental tables, please see the online version of this paper.