HHS Public Access

Author manuscript

J Thromb Thrombolysis. Author manuscript; available in PMC 2021 March 25.

Published in final edited form as:

J Thromb Thrombolysis. 2019 November ; 48(4): 661–667. doi:10.1007/s11239-019-01953-3.

Ticagrelor after pharmacological thrombolysis in patients with ST-segment elevation myocardial infarctions: insight from a trial sequential analysis

Mohammed Osman[1], **Babikir Kheiri**[2], **Amanda Jo Shigle**[1], **Maryam Saleem**[1], **Khansa Osman**[3], **Partho P. Sengupta**[1], **Jason A. Moreland**[1]

[1]Division of Cardiology, West Virginia University School of Medicine, 1 Medical Center Drive, Morgantown, WV 26506, USA

[2]Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

[3]Michigan State University, Flint, MI, USA

Abstract

Few randomized controlled trials (RCTs) have compared ticagrelor to clopidogrel after thrombolytic therapy in patients with ST-segment elevation myocardial infarction (STEMI). To assess the quality of the current evidence, a trial sequential analysis (TSA) of all the available RCTs was performed. A literature search through electronic databases for relevant RCTs was completed. Trial sequential boundaries were applied to the meta-analysis to guard against statistical error, calculate the information size (IS), and assess the quality of the currently available evidence. The safety outcome was bleeding at 30-days and the efficacy outcome was major adverse cardiovascular events at 30-days. There were 3 RCTs with a total of 3999 patients were included. For the safety and efficacy outcomes, there was no difference between the ticagrelor and clopidogrel groups (RR 0.94; 95% CI 0.56–1.60, p = 0.83) and (RR 0.87; 95% CI 0.49–1.52, p = 0.62), respectively. The corresponding TSA revealed an IS of 20,928 and 37,266 for safety and efficacy outcomes, respectively. The Z-curves for both outcomes failed to cross the conventional boundary of significance and TSA boundary, indicating no statistical difference between the ticagrelor and clopidogrel group and lack of firm evidence from the currently available RCTs to draw conclusion. Based on the current available RCTs, there is not enough evidence to support or refute better outcomes with ticagrelor in patients with STEMI treated with thrombolytics. Larger RCTs with enough power are needed before firm recommendations can be applied.

Keywords

Acute coronary syndrome; St-segment elevation myocardial infarction; Ticagrelor; Clopidogrel; Thrombolytics

✉Mohammed Osman, mohammed.osman@hsc.wvu.edu.

Conflict of interest All the authors declare that they have no conflict of interest.

Introduction

Primary percutaneous coronary intervention (PCI) is the frontline therapy for patients with ST-segment elevation myocardial infarction (STEMI) [1]. However, many hospitals are considered non-PCI capable facilities and therefore thrombolytics are the only available treatment option. Ticagrelor (a reversible P2Y12 inhibitor) has been shown to be superior to clopidogrel in patients with STEMI treated with PCI in the PLATO (Platelet Inhibition and Patient Outcomes) trial. However, patients treated with thrombolytics were excluded and guidelines continue to recommend the use of clopidogrel over ticagrelor in this patient population [2]. Few randomized controlled trials (RCTs) have compared ticagrelor to clopidogrel in patients with STEMI treated with thrombolytics [3–5].

Trial sequential analysis (TSA) is an advanced meta-analysis technique that is used to evaluate the accumulative evidence from previous trials in a sequential manner over time to determine if there is enough evidence to draw firm conclusions [6]. Hence, for this study we performed TSA of all the available RCTs comparing ticagrelor to clopidogrel in patients with STEMI who were treated with thrombolytic therapy.

Methods

A literature search for electronic database was conducted for RCTs comparing ticagrelor to clopidogrel in patients with STEMI who were treated with thrombolytic therapy. The safety outcome of interest was 30-day bleeding which was defined as per the Bleeding Academic Research Consortium criteria (BARC ≥ 2). The efficacy outcome of interest was 30-day major adverse cardiovascular events (MACE) as defined by each individual trial. The protocol of the review has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42018091336). The results of the meta-analysis have been previously published and, in this paper, the results of the TSA will be presented [7].

Trial sequential analysis (TSA)

In a single randomized clinical trial, sequential hypothesis testing is used to predict whether a trial could be terminated early because of sufficient evidence (interim analysis). Similarly, sequential monitoring boundaries are applied to a meta-analysis by calculating the information size (IS) (sample size contributed by the studies included in the meta-analysis), in order to obtain more reliable results and avoid false statistical inference. By this method, TSA boundaries are applied to the meta-analysis to guard against the risk of false-positive (type I error) and false negative (type II error) results.

By adding the trials one by one, a Z-curve representing accumulation of evidence from trials over time is constructed. If the Z-curve crosses the Alpha boundary of significance, sufficient statistical significance has been achieved favoring the intervention. On the contrary, if the Z-curve crosses the futility boundary, sufficient statistical evidence is available to conclude no effect of the examined intervention. To guard against statistical errors, another boundary, the TSA boundary, is applied and if the Z-curve crosses the TSA boundary, a sufficient level of evidence for the anticipated intervention effect has been

reached and no further studies are needed. However, if the Z-curve fails to cross the TSA boundary and the required IS has not been reached, evidence to reach a conclusion is insufficient and more studies are needed [6]. We performed our analysis to maintain an overall two-sided type-I error rate at 5% (Alpha boundary), 20% relative risk reduction for ticagrelor, and we calculated the required IS size with 80% power. We also performed multiple sensitivity analysis with assumption of 10%, 25% and 35% relative risk reduction in safety and efficacy outcomes with the use of ticagrelor. Analysis was conducted using the TSA software, Copenhagen Trial Unit, version 0.9.5.10 Beta.

Results

Only 3 RCTs with a total of 3999 patients were included in the meta-analysis. The search was updated, and no new trials have been published, baseline characteristic of the included trial are shown in Table 1 [3–5]. For the safety outcome (BARC ≥ 2), there was no difference between the ticagrelor and clopidogrel groups (1.3 vs. 1.4%, RR 0.94; 95% CI 0.56–1.60, p = 0.83). The corresponding TSA revealed an IS of 20,928. The Z-curve failed to cross the conventional boundary of significance indicating no statistical difference between the ticagrelor and clopidogrel group. Additionally, the Z-curve failed to cross the TSA boundary indicating lack of firm evidence from the currently available RCTs to draw a conclusion (Fig. 1).

Similarly, for the efficacy outcome (30-day MACE), there was no difference between the two groups (3.8 vs. 4.3%; RR 0.87; 95% CI 0.49–1.52, p = 0.62). The corresponding TSA showed an IS of 37,266, the Z-curve failed to cross the conventional boundary suggesting no difference between the two groups and the corresponding TSA boundary was not crossed by the Z-curve indicating lack of firm evidence to draw final conclusion (Fig. 2). Multiple sensitivity analysis with the assumption of 10%, 25% and 30% relative risk reduction in safety and efficacy outcomes for the use of ticagrelor were performed and yielded similar results.

Discussion

The findings from the current TSA of the RCTs comparing ticagrelor to clopidogrel in patients with STEMI treated with thrombolytics suggest that there is a paucity of data and based on the current available evidence, there is a risk of type II statistical error (i.e. concluding that there is no difference between the two medications in terms of safety and efficacy while a true difference exists in reality).

The largest RCT to address the question of safety and efficacy of ticagrelor in STEMI patients treated with thrombolytics is the TREAT trial [4]. The TREAT trial was a multicenter, open label, RCT that included a total of 3799 patients randomized to receive ticagrelor or clopidogrel after thrombolytic therapy. In the 30-day follow up there was no difference between ticagrelor and clopidogrel in terms of safety or efficacy outcomes. Additionally, the trial reported similar outcomes between ticagrelor and clopidogrel in the long term follow up at 12 months [4].

Although the TREAT trial suggested that ticagrelor is safe in patients with STEMI treated with thrombolytics compared to clopidogrel, there was no added benefit of ticagrelor in term of reducing ischemic events in contrast to what was reported by the PLATO trial. The PLATO trial which was the landmark study that revealed the superiority of ticagrelor over clopidogrel in patients with acute coronary syndrome [2, 4]. The difference in the outcomes between these two trials can be attributed to several key variations in their designs. First, the two trials studied different patient populations. The PLATO trial excluded patients who received thrombolytics, however these patients were the main population included in the TREAT trial. Second, the PLATO trial recruited a total of 18,624 patients compared to only 3799 patients in the TREAT trial. The large sample size within the PLATO trial allowed the study to achieve enough power to detect differences in ischemic outcomes. In comparison, the TREAT trial was not powered to detect these differences due to the smaller population. Based on our current TSA, a sample size of over 20,000 patients would be needed to detect a significant difference in bleeding outcomes between ticagrelor and clopidogrel and over 35,000 patients to determine a significance difference in MACE while avoiding any potential type-II statistical error.

From a pharmacology and pharmacodynamics perspective, there are several differences between clopidogrel and ticagrelor. The P2Y12 receptor is a primary receptor involved in the platelet aggregation through the adenosine diphosphate (ADP) activation of the glycoprotein IIb/IIIa receptor [8]. Clopidogrel is classified as a thienopyridine; it is a prodrug that requires metabolic activation to covalently and irreversibly bind to the P2Y12 receptor. On the other hand, ticagrelor directly inhibits the binding of ADP to the P2Y12 receptor and exhibits reversible inhibition. Ticagrelor provides an earlier onset of action, more potent platelet inhibition effects, and less variability when compared to clopidogrel [9]. Due to the more potent effect on platelet inhibition, there is potentially an increased risk of bleeding when ticagrelor is administered after thrombolytic therapy. Unlike other P2Y12 inhibitors, ticagrelor’s reversible mechanism of action has allowed for the recent development of a neutralizing monoclonal antibody. Currently, the reversal agent has only been studied in healthy patients and the results revealed an immediate and sustained neutralization of ticagrelor’s antiplatelet affects. Although more literature is needed to evaluate the novel reversal agent, this could be a potential benefit in regard to ticagrelor utilization in patients who receive thrombolysis and are at an increased risk of bleed [10].

Limitations

The current analysis has several limitations which need to be acknowledged. First, the original meta-analysis was a study level which lacked patient level data. Second, among the three included studies, the TREAT trial recruited the highest number of patients and consequently had the heaviest weight on the analysis. Third, the included trials had different inclusion criteria, dosing and follow up duration.

Conclusion

Based on the current literature, there is not enough evidence to support or refute better efficacy or safety outcomes with ticagrelor when compared to clopidogrel in patients with

STEMI treated with thrombolytics. Larger RCTs with enough power are needed before firm recommendations can be drawn.

References

1. O'Gara PT, Kushner FG, Ascheim DD et al. (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 127:e362–e425 [PubMed: 23247304]
2. Wallentin L, Becker RC, Budaj A et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361:1045–1057 [PubMed: 19717846]
3. Alexopoulos D, Perperis A, Koniari I et al. (2015) Ticagrelor versus high dose clopidogrel in ST-segment elevation myocardial infarction patients with high platelet reactivity post fibrinolysis. J Thromb Thrombolysis 40:261–267 [PubMed: 25680893]
4. Berwanger O, Lopes RD, Moia DDF et al. (2019) Ticagrelor versus clopidogrel in patients with STEMI treated with fibrinolysis: TREAT trial. J Am Coll Cardiol 73:2819–2828 [PubMed: 30898608]
5. Dehghani P, Lavoie A, Lavi S et al. (2017) Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. Am Heart J 192:105–112 [PubMed: 28938956]
6. Wetterslev J, Jakobsen JC, Gluud C (2017) Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 17:39 [PubMed: 28264661]
7. Kheiri B, Osman M, Abdalla A et al. (2018) Ticagrelor versus clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized clinical trials. J Thromb Thrombolysis 46:299–303 [PubMed: 29934940]
8. Damman P, Woudstra P, Kuijt WJ et al. (2012) P2Y12 platelet inhibition in clincal practice. J Thromb Thrombolysis 33(2):143–153 [PubMed: 22183178]
9. Wallentin L (2009) P2Y(12) inhibitors: differences in properties and mechanisms of action and pontentail consequences for clinical use. Eur Heart J 30(16):1964–1977 [PubMed: 19633016]
10. Bhatt DL, Pollack CV, Weitz JI et al. (2019) Antibody-based ticagrelor reversal agent in healthy volunteers. N Engl J Med 380:1825–1833 [PubMed: 30883047]

Highlights

- Few randomized controlled trials (RCTs) have compared ticagrelor to clopidogrel after thrombolytic therapy in patients with ST-segment elevation myocardial infarction (STEMI).
- To assess the quality of the current evidence, a trial sequential analysis of all the available RCTs was performed.
- Based on the current available trials, there is not enough high-quality evidence make firm conclusion on the outcomes with ticagrelor in patients with STEMI treated with thrombolytics.
- Larger RCTs with enough power are needed before firm recommendations can be applied.

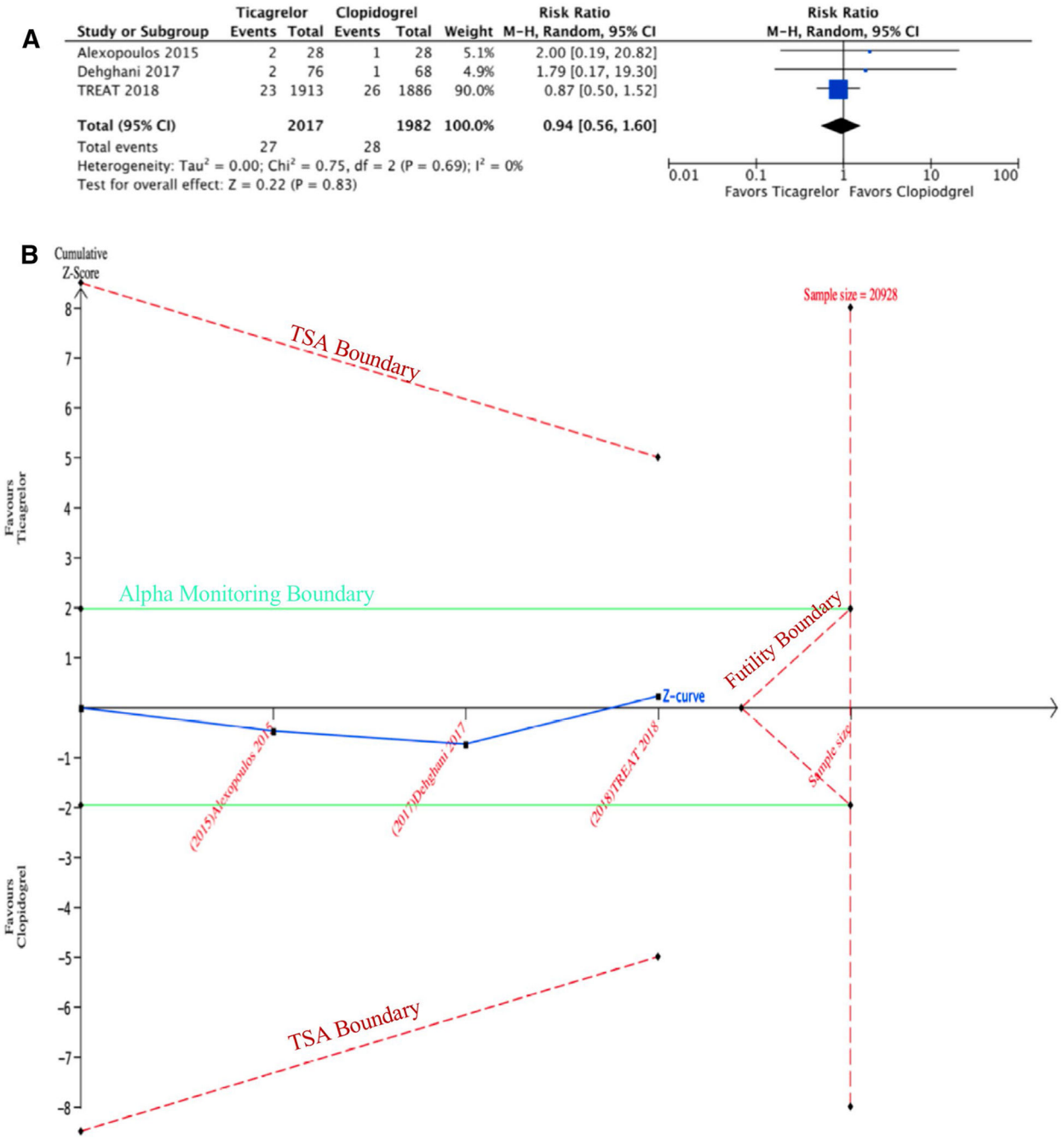

Fig. 1.

a Forest plot for the meta-analysis comparing 30-day bleeding between ticagrelor and clopidogrel. **b**Trial sequential analysis for 30-day bleeding. The diversity-adjusted information size (sample size) is 20,928 (vertical red line). The cumulative Z-curve (blue line with small black squares representing each trial) failed to cross the traditional (horizontal green line) and the trial sequential monitoring boundary (concave red line), indicating lack of firm evidence supporting or refuting better 30-day bleeding in the ticagrelor group

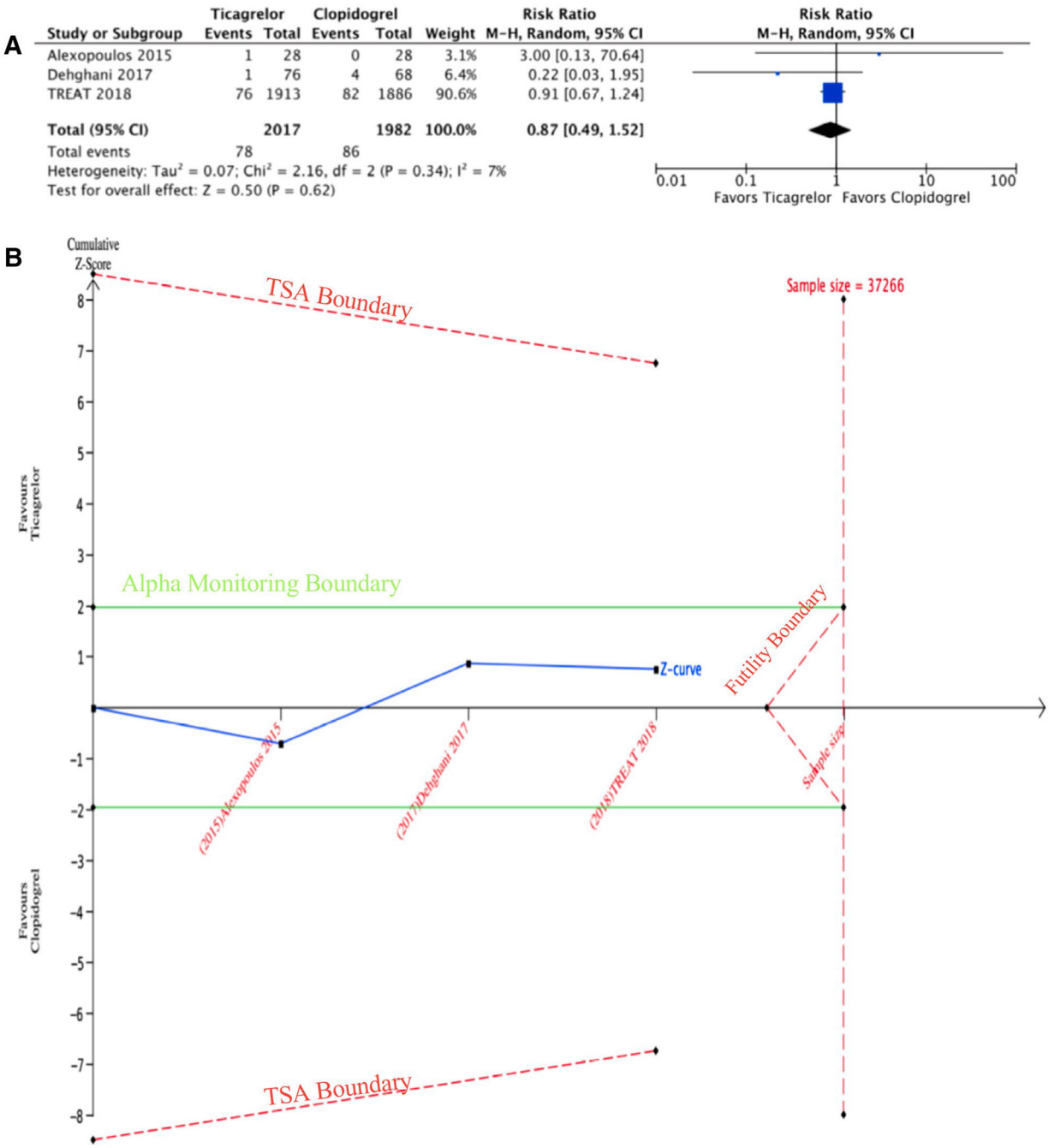

Fig. 2.

a Forest plot for the meta-analysis comparing 30-day major adverse cardiovascular events between ticagrelor and clopidogrel. **b**Trial sequential analysis for 30-day major adverse cardiovascular events. The diversity-adjusted information size (sample size) is 37,266 (vertical red line). The cumulative Z-curve (blue line with small black squares representing each trial) failed to cross the traditional (horizontal green line) and the trial sequential

monitoring boundary (concave red line), indicating lack of firm evidence supporting or refuting better 30-day major adverse cardiovascular events in the ticagrelor group

Table 1

Baseline characteristics of the studies included in the trial sequential analysis

Study	Patient population	Exclusion criteria	Dosing	Follow up	Definition of MACE
Alexopoulos [3]	Patients were eligible for enrollment if they had STEMI and underwent thrombolysis in the previous 3–48 h in a non-PCI-capable hospital	Excluded patients with a history of stroke/transient ischemic attack, bleeding diathesis, chronic oral anticoagulation treatment, contraindications to antiplatelet therapy, PCI or coronary artery bypass grafting < 3 months, hemodynamic instability, platelet count < 100,000/lL, hematocrit < 30%, creatinine clearance < 30 mL/min, severe hepatic dysfunction, use of strong CYP3A inhibitors or inducers, increased risk of bradycardia, severe chronic obstructive pulmonary disease, or periprocedural IIb/IIIa inhibitors administration	Ticagrelor 180 mg, followed by 90 mg bid until discharge or clopidogrel 600 mg followed by 150 mg daily	Index hospitalization	Death, myocardial infarction, stroke, ischemia driven revascularization procedure and bleeding according to BARC
Dehghani [5]	Patients were eligible for enrollment if they presented within 12 h after the onset of symptoms, had evidence of acute STEMI on their qualifying ECG (≥ 1 mV in ≥ 2 continuous leads) and due to anticipated delay to primary PCI, received TNK as the primary mode of reperfusion	Any contraindication for the use of clopidogrel or ticagrelor, a need for oral anticoagulation therapy, atrial fibrillation, an increased risk of bradycardia, PCI or coronary artery bypass surgery (CABG) during the previous 3 months, active bleeding or high risk of bleeding based on clinical assessment, known clinically important thrombocytopenia or anemia, concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer, and women of child-bearing age. Due to interference with the VerifyNow assay, all patients who received GP IIb/IIIa receptor antagonist before, during, or after PCI were also excluded from this study	Ticagrelor 180 mg followed by 90 mg BID or clopidogrel 300 mg LD followed by 75 mg daily	30 days	Death, re-infarction, revascularization, and stroke
TREAT [4]	Patients were eligible for enrollment if they presented within 24 h after the onset of symptoms, had evidence of acute ST-elevation on their qualifying electrocardiogram (at least 2 should be 1 mm in 2 contiguous peripheral or precordial leads in men and 1.5-mm elevation in V1–V3 in women and 1-mm in limb leads), were younger than 75 years, and received fibrinolytic therapy	Any contraindication against the use of clopidogrel or ticagrelor; need for oral anticoagulation therapy or aspirin doses per day more than 100 mg/day; concomitant oral or intravenous therapy with strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice N1 L/day), CYP3A substrates with narrow therapeutic indices (cyclosporine, quinidine), or strong CYP3A inducers (rifampin/rifampicin, phenytoin, carbamazepine); increased risk of bradycardia events; dialysis required; known clinically important thrombocytopenia; known clinically important anemia; any other condition that may put the patient at risk or influence study results in the investigator's opinion (e.g., cardiogenic shock, severe hemodynamic instability, active cancer); participant in another investigational drug or device study within 30-days; pregnancy or lactation; any condition that increases the risk for noncompliance or being lost to follow-up; involvement in the planning or conduct of the study; previous enrollment or randomization in this study; contraindications to fibrinolytic therapy	Ticagrelor 180-mg LD, 90 mg twice daily thereafter or clopidogrel 300-mg to 600-mg LD, 75 mg daily thereafter	30 days	Bleeding, death, recurrent ischemia, transient ischemic attack, or other arterial thrombotic events and all-cause mortality at 30 days

STEMI ST-elevation myocardial infarction, *BARC* Bleeding Academic Research Consortium (BARC) criteria, *ECG* electrocardiogram, *TNK* tenecteplase, *TREAT* ticagrelor versus clopidogrel in patients with STEMI treated with fibrinolysis trial

J Thromb Thrombolysis. Author manuscript; available in PMC 2021 March 25.