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The Bleeding Safety of Ticagrelor in Patients with ST-Elevation Acute Coronary Syndrome Treated with Fibrinolytic Therapy

Aim	To compare hemorrhagic safety of ticagrelor and clopidogrel in patients with ST-segment elevation acute coronary syndrome (STEACS) after thrombolytic therapy (TLT).
Material and methods	This nonrandomized study included 183 patients followed up for 30 days. Hemorrhagic safety was compared in a group of patients with STEACS (n=71) after a thrombolytic treatment with alteplase and early ticagrelor treatment (180 mg followed by switching to 90 mg twice daily) and in a group of patients (n=112) with STEACS receiving TLT with alteplase and clopidogrel (loading dose, 600 mg followed by switching to 75 mg daily). Primary endpoint was hemorrhage associated with TLT; patients were followed up for 30 days.
Results	During the follow-up period, TLT-associated hemorrhages were observed in 11.3% of patients in the ticagrelor treatment group and in 10.7% of patients in the clopidogrel treatment group (p=0.9; odds ratio, 1.06 at 95% confidence interval, from 0.41 to 2.73). Intracranial hemorrhages and fatal hemorrhages were absent in both groups.
Conclusion	There were no significant differences in hemorrhagic safety between patients with STEACS after the TLT treatment with alteplase and early treatment with ticagrelor or clopidogrel.
Keywords	Acute coronary syndrome; ticagrelor; clopidogrel; thrombolytic therapy; hemorrhage; hemorrhagic safety
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Reperfusion strategy implemented through the pharmacoinvasive approach is essential for patients with acute ST-segment elevation acute coronary syndromes (STE-ACS) when a primary percutaneous coronary intervention (PCI) is impossible within the next 120 minutes after the first medical contact [1]. The STREAM study demonstrated the effectiveness of the pharmacoinvasive approach. The all-cause and cardiovascular mortality were comparable to those in the PCI group within the 12-month follow-up period [2].

Intravenous thrombolytic therapy (TLT) using streptokinase was first administered in acute myocardial infarction in 1958. Much later, in the 1980s, the efficacy of TLT in this pathology was demonstrated in the large randomized trial GISSI–I [3]. Second-generation (alteplase, prourokinase) and third-generation (tenecteplase, retaplase) thrombolytic agents appeared over time. They showed good results in vascular accidents (STE-ACS, ischemic cerebrovascular accident, pulmonary embolism) but increased the rate of bleeding [4].

The common use of PCI raised the issue of additional antiplatelet therapy in patients with the acute coronary syndrome (ACS) following TLT. Two large randomized trials (COMMIT, CLARITY) [5] showed a significant reduction in the rate of cardiovascular complication (CVCs) in the group of patients with STE-ACS following fibrinolysis who received clopidogrel and acetylsalicylic acid (ASA). The early administration of ticagrelor in patients with STE-ACS after thrombolysis was not investigated.

The large randomized trial PLATO [6] showed the absolute superiority of ticagrelor over clopidogrel in patients with ACS. However, fibrinolysis was one of the exclusion criteria in that study.

The recent randomized trial TREAT [7] also covered this issue. The objective of this study was to prove the hypothesis that clopidogrel is not superior over ticagrelor in patients with STE-ACS after TLT. It was concluded that, within the first 30 days, there were no significant differences between late administration of ticagrelor or clopidogrel in terms of thrombolysis-related bleeding [7, 8] and the rate of fatal and intracranial

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bleeding according to the TIMI [9] and BARC [10] criteria. It should be noted that in this study, patients were randomized to the ticagrelor or clopidogrel groups almost 12 hours after fibrinolysis.

Our objective was to assess the hemorrhagic safety of ticagrelor versus clopidogrel in patients with STE-ACS after TLT.

Materials and methods

A single-center, nonrandomized study was conducted between 2014 and 2019. The study included patients with STE-ACS who had undergone ineffective TLT using alteplase followed by PCI within 3 hours after completion of the first procedure. Moreover, antiplatelet therapy was initiated not later than 3 hours after the completion of fibrinolysis: ASA, ticagrelor, or clopidogrel.

The criteria for TLT futility were recurrent myocardial ischemia, unstable hemodynamics, and the absence of more than 50% decrease in ST-segment elevation in 60–90 minutes after the end of fibrinolysis.

The study included 183 patients. In the ticagrelor group (n = 71), ticagrelor was used as a $P2Y_{12}$ inhibitor at the loading dose of 180 mg no later than 3 hours after the end of thrombolysis followed by 90 mg twice a day. In the clopidogrel group (n = 112), clopidogrel was administered as $P2Y_{12}$ inhibitor at the loading dose of 600 mg not later than 3 hours after the end of thrombolysis followed by 75 mg/day every day.

The exclusion criteria were the age under 18 and over 75, noncompliance with drug therapy, contraindications for antiplatelets, survival-limiting diseases, cancer, chronic kidney failure, left ventricular ejection fraction less than 30%, previous PCI or coronary artery bypass grafting, previous continuous administration of $P2Y_{12}$ inhibitors or oral anticoagulants.

Follow-up was carried out during hospitalization and after discharge from hospital for 30 days after TLT.

Any significant bleeding, according to the TIMI (thrombolysis in myocardial infarction [9] and BARC (Bleeding Academic Research Consortium) [10] scores, were the endpoints of the study.

All patients gave their permission for the processing of personal data and medical interventions. The study followed the principles of the Declaration of Helsinki.

Statistical processing of the findings was carried out using Statistica 13.3 (TIBCO Software Inc., 2017, USA). The results are described as the median and the interquartile range (25th and 75th percentile) with the asymmetric distribution. The distribution of quantitative variables was estimated using the Kolmogorov-Smirnov/Lilliefors test. The categorical data were compared using the Mann-Whitney U-test. The Yates corrected chi-square test was used to compare categorical variables [22].

The odds ratio (OR) of the adverse outcomes was calculated using fourfold tables. The 95% confidence interval (CI) was also determined for OR. The intergroup differences were statistically significant at $p<0.05$.

Results

There were no significant differences between the groups in terms of clinical and demographic data (Table 1).

The analysis of findings did not reveal any significant differences between the groups in the rate and risk of hemorrhagic complications (Table 2).

Table 1. Clinical and anamnestic characteristics of the groups

Parameter	Ticagrelor group (n=71)	Clopidogrel group (n=112)	p
Age, years	61 [52.8; 65.1]	63 [51.9; 66.3]	0.84
Female, % (abs.)	15.5 (11)	16.1 (18)	0.92
Hypertension, % (abs.)	100 (71)	100 (112)	1.0
Dyslipidemia, % (abs.)	95.8 (68)	93.8 (105)	0.8
Diabetes mellitus, % (abs.)	23.9 (17)	20.6 (23)	0.72
Generalized atherosclerosis, % (abs.)	45.1 (32)	50 (56)	0.62
Atrial fibrillation, % (abs.)	1.4 (1)	1.79 (2)	0.69
Smoking, % (abs.)	33.8 (24)	36.6 (41)	0.82
History of myocardial infarction, % (abs.)	36.6 (26)	34.8 (39)	0.93
Continuous use of nonsteroidal anti-inflammatory drugs, % (abs.)	39.4 (28)	36.6 (41)	0.82
Time from the end of thrombolytic therapy to the initiation of ticagrelor or clopidogrel, min	124 [60; 178]	118 [70; 172]	0.72

Table 2. Results

Parameter	Ticagrelor group (n=71)	Clopidogrel group (n=112)	p
TIMI bleeding classification, % (abs.)			
Minor	7 (5)	8 (9)	0.86
Moderate	2.8 (2)	0.9 (1)	0.69
Major	1.4 (1)	1.8 (2)	0.69
BARC bleeding classification, % (abs.)			
Type 1	5.6 (4)	6.3 (7)	0.88
Type 2	4.2 (3)	2.7 (3)	0.88
Types 3-5	1.4 (1)	1.8 (2)	0.69
Intracranial bleeding, % (abs.)	0	0	1.0
Fatal bleeding, % (abs.)	0	0	1.0
Total, % (abs.)	11.3 (8)	10.7 (12)	0.90

Discussion

Ticagrelor is the most commonly used direct $P2Y_{12}$ inhibitor. The PLATO study showed that ticagrelor has advantages over clopidogrel in patients with ACS. The replacement of clopidogrel with ticagrelor reduces cardiovascular risk without increasing the risk of bleeding [6]. However, the group of patients who had undergone TLT was excluded from the study. Thus, there is no evidence of safe early administration of ticagrelor in patients who received TLT.

The 2017 Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation Guidelines of the European Society of Cardiology [1] recommend the use of clopidogrel as a $P2Y_{12}$ inhibitor in patients after fibrinolysis, and replacement with ticagrelor or prasugrel is indicated only 48 hours after the administration of the thrombolytic. However, this recommendation is based only on expert opinion (class IIb).

The only large randomized study of hemorrhagic safety in patients with STE-ACS after thrombolysis and early administration of ticagrelor was the TREAT study, which showed the safety of early (within 24 hours) use of ticagrelor in this patient group [7, 11].

The main objective of our study was to assess hemorrhagic safety in such situations within 30 days after fibrinolysis. The effect of this strategy on severe («massive») CVCs was not performed.

No significant differences in the rate of severe bleeding between the groups of early administration of ticagrelor and clopidogrel after TLT (OR 0.79, 95% CI 0.07–8.83; p=0.69) were observed in our study. We also did not detect any significant changes between the groups in the rate of minor bleeding (OR 1.12, 95% CI 0.4–3.08; p=0.88), which contradicts the findings of the TREAT study that bleeding was more common in the ticagrelor group [7].

The main difference between our study and the TREAT study was that the median time between the end of TLT and the initiation of $P2Y_{12}$ inhibitor in the TREAT study was 11.4 hours [8], and in our study, these drugs were initiated no later than 3 hours after the end of thrombolysis.

Our study showed no differences in hemorrhagic safety between the groups of early administration of ticagrelor or clopidogrel (within 3 hours after the end of TLT) in patients with STE-ACS not older than 75 years – that is, this pharmacoinvasive approach is safe in the real-world clinical practice. However, further studies are needed to investigate the early administration of ticagrelor after TLT in patients with STE-ACS.

Conclusions

There are no significant differences in terms of hemorrhagic safety between the groups of patients with ST-segment elevation acute coronary syndrome after thrombolytic therapy with alteplase and early administration of ticagrelor or clopidogrel.

No conflict of interest is reported.

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