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Safety of ticagrelor post fibrinolysis in STEMI patients

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Objective: *to assess the safety of ticagrelor in patients with ST-elevation myocardial infarction treated with fibrinolytic therapy.*

Materials and methods: *This unicenter, non randomized trial enrolled 200 patients (less than 75 years) diagnosed with ST-segment elevation myocardial infarction who received streptokinase from March to May 2018. One hundred Patients received ticagrelor (180-mg loading dose followed with 90 mg twice daily) while other 100 patients received clopidogrel (300-mg loading dose then 75 mg daily). Both P2Y12 inhibitors were administrated 2 hours after streptokinase, all population were naïve for any P2Y12 inhibitors pretreatment.The primary end point was thrombolysis in myocardial infarction (TIMI) major and minor bleedings through 60 days.*

Results: *At 60 days, TIMI major bleeding had occurred in 4 % of patients who received ticagrelor and in 3 % of patients who recieved clopidogrel (Odds ratio =1.3472, 95 % CI =0.293 % to 6.18 %; P =0.7014 for safety). No rates of fatal or intracranial bleeding occurred. Minor and minimal bleeding had occurred in 14 % of patients on ticagrelor and in 11 % of patients on clopidogrel (Odds ratio =1.3171; 95 % CI =0.566 % to 3.06 %; P =0.5221 for safety). After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ≥3), Bleeding rates not increased in ticagrelor group (Odd ratio=1.611; 95 % CI=0.52–4.9; NNT for harm=8.4; P=0.40). RRR of bleeding rates in the clopidogrel group was only 1.25 %.*

Conclusion: *In patients younger than 75 years with ST-segment elevation myocardial infarction, delayed administration of ticagrelor for 2 hours after fibrinolytic therapy was safe and non inferior to clopidogrel for TIMI major and minor bleeding up to 60 days even in patients with high risk of bleeding (HAS-BLED score ≥3).*

Key words: *Anti platelets, Myocardial infarction, Fibrinolysis, Bleeding.*

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1. Introduction

Fibrinolytic therapy is an important reperfusion strategy in settings where primary PCI cannot be offered in a timely manner especially in developing countries outside Europe and United States of America. The largest absolute benefit is seen among patients at highest risk, including the elderly, and when treatment is offered <2h after symptom onset [1]. Intravenous streptokinase was first used in myocardial infarction (MI) in 1958. Improved survival was demonstrated in this indication in the 1980s with the publication of the first large-scale randomized GISSI–I trial [2]. Other thrombolytic agents, such as tissue plasminogen activator (t-PA), were developed and tested in a large number of clinical trials. All demonstrated a benefit in critical settings such as MI and severe PE, but they also revealed an increased bleeding risk [3]. As regard adjunctive anti platelet therapy, Clopidogrel added to aspirin reduces the risk of cardiovascular events and overall mortality in patients treated with fibrinolysis and should be added to aspirin as an adjunct to lytic therapy. Two large, randomized clinical trials have established the safety of aspirin plus clopidogrel for reducing MACE in STEMI patients treated with fibrinolysis (CLARITY and COMMIT) [4]. Only few trials looked at the safety of ticagrelor in this setting while the large randomized PLATO trial, which established ticagrelor's supremacy over clopidogrel in ACS, excluded patients treated with fibrinolysis [5]. ESC guidelines of STEMI management on 2017 recommended the switch from clopidogrel to potent P2Y12 inhibitors (ticagrelor or prasugrel) after at least 48 hours as regard the safety. This switch is passed only on expert opinions (class IIb) [6].

TREAT is the most recent randomized trial aimed to assess the non inferiority of ticagrelor to clopidogrel in STEMI. TREAT trial enrolled 3,799 patients under the age of 75 who were randomized to 180 mg ticagrelor as early as possible after the index event (within 24 hours) then followed by 90 mg twice daily for 12 months or to 300 mg of clopidogrel as early as possible, followed by 75 mg/day for 12 months. Randomization of P2Y12 inhibitors applied with a delay of 11.5 hours post fibrinolysis. For the primary outcome of TIMI major bleeding, there was no difference between study arms, with major bleeds seen in approximately 0.7% of both groups. TIMI minimal bleeding occurred more often in ticagrelor-treated patients. The authors of TREAT trial concluded that a delayed administration of ticagrelor after fibrinolytic therapy was non inferior to clopidogrel for TIMI major bleeding at 30 days,» with no benefit on efficacy outcomes.» [7].

First generation fibrinolysis (Streptokinase) has a lower bleeding risk in comparison to new generations (t-PA or TNK). Peak activity of streptokinase is found in the blood about 20 minutes after dosing. Elimination kinetics of streptokinase follows a biphasic course. A small proportion of the dose is bound to anti-streptokinase antibodies and metabolized with a half-life of 18 minutes while most of it forms a streptokinase-plasminogen activator complex and is bio transformed with a half-life of about 80 minutes [8]. Regarding these pharmacokinetic data, the bleeding risk of streptokinase is declined after 2 hours of administration. We aimed in this trial to administer the potent P2Y12 inhibitor (Ticagrelor) just after 2 hours of streptokinase bolus intake (1.500.000 U).

2. Patients and methods

2.1. Study population

This single-center, prospective, non randomized trial performed from March 2018 to May 2018. Inclusion criteria were STEMI patients under 75 years who treated with streptokinase as a thrombolytic therapy. Exclusion criteria were previous ACS, PCI or CABG, previous pre treatment with P2Y12 inhibitors or OAC.

2.2. Study protocol

Designed as a safety and non inferiority trial to estimate both major and minor TIMI bleeding risks of ticagrelor to clopidogrel as an adjunctive therapy to fibrinolysis.

Sample size of 200 patients divided equally into two groups, after receiving fibrinolytic therapy (streptokinase standard dose 1.500.00 U) within 3 hours of diagnosed STEMI attack.

Group 1 (100 patients): received ticagrelor (180-mg loading dose 2 hours after streptokinase followed with dose 90 mg twice daily).

Group 2 (100 patients): received clopidogrel (300-mg loading 2 hours after streptokinase followed with dose 75 mg once daily).

2.3. Methods

For all patients full history, clinical examination, 12 leads electrocardiogram, trans thoracic echocardiography, laboratory investigations in form of cardiac troponins, serum creatinine, liver function test, complete CBC, HbA1C, coagulation profile including INR ratio were done to assess bleeding risks.

HAS-BLED risk score was used for bleeding risk assessment at baseline, a calculated HAS-BLED score is between 0 and 9 and based on eight parameters with a weighted value of 0–2. HAS-BLED stands for Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly >65 years, Drugs or alcohol [9]. Patients in both groups had been classified into low risk of bleeding if have score ⩽2 and classified into high risk of bleeding if have score ⩾3.

2.4. Study endpoints and definitions

The study end points were composite of major or minor TIMI clinically significant bleeding:

Major defined as any intracranial bleeding, any clinically overt signs of hemorrhage associated with a drop in hemoglobin of ⩾5 g/dL or a ⩾15 % absolute decrease in haematocrit, any fatal bleeding (bleeding that directly results in death within 7 days).

Minor defined as any clinically overt bleeding, resulting in hemoglobin drop of 3 to <5 g/dl or ⩾10 % decrease in haematocrit [10].

2.5. Statistical analysis

The association between variables and treatment groups was investigated by chi-square or Fisher exact tests. Parametric unpaired Z score test was applied to evaluate differences for continuous variables between both groups. The association between type of treatment and clinical endpoints was expressed as the odds ratio (OR), and the 95 % confidence interval (CI) also was reported. Relative risk reduction (RRR) analysis was applied to detect the valuable reduction of bleeding outcomes between two groups. A p value less than 0.05 were considered significant (2-sided). All analyses were carried out using Stata 12 software (StataCorp LP, College Station, Texas).

3. Results

3.1. Study population

Demographic, clinical and bleeding risk stratification variables are presented in (Table 1). There were no significant differences between the two groups regarding age, gender, diabetes mellitus (DM), hypertension; previous bleeding or HAS-BLED score were equivalent in both groups.

3.2. TIMI major or minor bleeding rates

The endpoint of composite major and minor TIMI bleeding occurred in 18 % of the ticagrelor group (Group 1) and 14 % in the Group 2, with (odd ratio of 1.348; 95 % CI of harm = –6.29–14.25; NNT of harm = 25;P= 0.441 for safety). Isolated Major or minor bleeding occurred more in ticagrelor-treated patients with non significant differences (P=0.7 & 0.5 respectively). (Table 2 & Figure 1).

Table 1. **Demographic, clinical and bleeding risk stratification variables**

Variable	Group I 100 p	Group II 100 p	P value
Clinical variables			
Age	65±2	64±4	0.065
Female Gender	40 %	43 %	0.66
D.M	62 %	59 %	0.6651
HTN	49 %	55 %	0.396
Previous bleeding	11	9	0.638
HAS-BLED risk score			
Abnormal renal function	4	6	0.51
Abnormal liver function	5	6	0.75
Previous stroke	3	2	0.65
Labile INR	3	1	0.31
Elderly > 65 years	40	38	0.772
NSAID intake	50	40	0.156
Alcohol intake	-	1	-
Low risk of bleeding HAS-BLED <2	89	87	0.664
High risk of bleeding HAS-BLED >3	11	13	0.66
Adjunctive anticoagulants			
Un fractionated heparin	21	30	0.145
Low molecular weight heparin	79	70	0.143

Table 2. **Bleeding outcomes in study population**

Variable	Group I	Group II	Odd ratio	95% CI	RRR	NNT for harm	P value
Major TIMI bleeding	4%	3%	1.3472	0.29–6.18	1.333	100	0.7014
Minor TIMI bleeding	14%	11%	1.3171	0.56–3.06	1.272	33.3	0.5221
Total TIMI bleeding	18%	14%	1.3484	–6.29–14.25	1.285	25	0.441

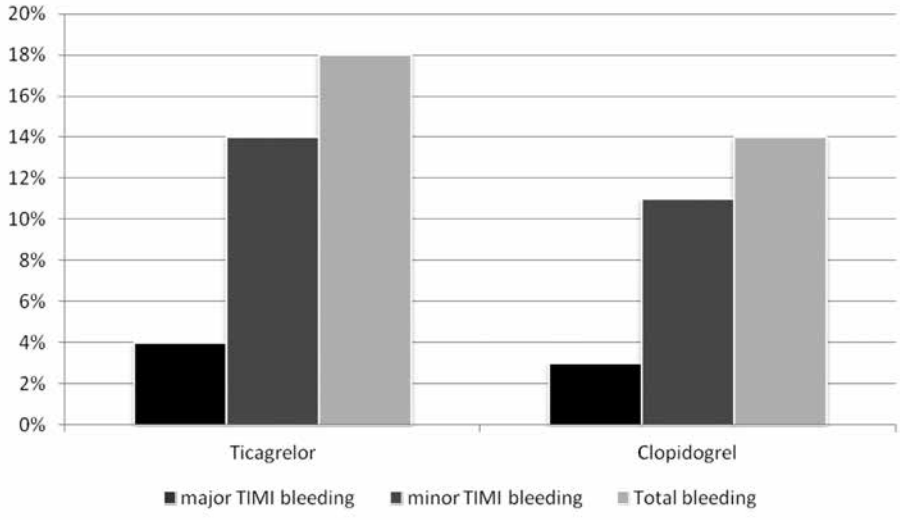

Figure 1. Bleeding outcomes in study population

3.3. Bleeding rates in high risk patients with HAS-BLED score ≥3

After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ≥3), Total TIMI bleeding rates remained similar in both groups (Odd ratio=1.611; 95% CI=0.52–4.9; NNT for harm=8.4; P=0.40). The relative risk reduction (RRR) of bleeding rates in the clopidogrel group was only 1.25%. (Table 3)

4. Discussion

Ticagrelor is a novel reversible platelet inhibitor that is notable for its superior clinical efficacy and safety [11]. The efficacy and safety of ticagrelor in STEMI patients who treated with fibrinolysis remained unclear. In this study, we aimed to assess the short term safety of ticagrelor in this situation. ESC guidelines of STEMI management on 2017 recommended the switch from clopidogrel to ticagrelor after 48 hours as a safety time passed on expert opinions (class IIb) [6].

In this research, the incidence of major TIMI bleeding of ticagrelor compared to clopidogrel was nearly identical (odds ratio =1.3472, 95% CI =0.293% to 6.18%; P =0.7014 for safety). These results were in accordance with the conclusions drawn in TREAT study; 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 non inferiority). In this research, no increase of incidence of minor TIMI bleeding of ticagrelor compared to clopidogrel (odds ratio =1.3171; 95% CI =0.566% to 3.06%; P =0.5221 for safety). In TREAT, Minor and minimal bleeding were more common with ticagrelor than with clopidogrel (Table 2).

After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ≥3), Total TIMI bleeding rates remained similar in both groups (Odd ratio=1.611; 95% CI=0.52–4.9; NNT for harm=8.4; P=0.40). The relative risk reduction (RRR) of bleeding rates in the clopidogrel group was only 1.25% (Table 3).

Table 3. **Bleeding rates in high risk patients with HAS-BLED score ≥3**

Variable	High bleeding risk patients in Group I (11 patient)	High bleeding risk patients in Group II (13 patient)	Odd ratio	95% CI	RRR	NNT for harm	P value
Major TIMI bleeding	4/11	2/13	3.14	0.44–21.95	2	7.5	0.248
Minor TIMI bleeding	11/11	9/13	1.44	0.43–4.75	1.22	11	0.545
Total TIMI bleeding	15/11	11/13	1.611	0.52–4.92	1.25	8.4	0.40

These results confirm that ticagrelor as a potent antiplatelet is same as clopidogrel as regards the safety. In TREAT trial, the main concern was for the bit longer delay with a median of 11.4 hours between fibrinolysis and antiplatelet administration [7].

In contrast to TREAT, in this research the safety time between ticagrelor and streptokinase was reduced for only 2 hours apart. In clinical practice early adjunctive DAPT therapy in patients with STEMI is associated with a significant reduction of in-hospital MACCE regardless of the initial reperfusion strategy [12]. Further trials with a bit shorter delays, are still recommended.

The superiority of this research as regard TREAT trial could be detected in the following: The safety of ticagrelor was documented a 30 days more than TREAT. Safety outcome observed with only 2 hours apart between ticagrelor and fibrinolysis while in TREAT, 11.4 hours was needed to achieve the safety outcomes. The inferiority of this research as regard TREAT trial, that efficacy outcome was not considered as an endpoint. Meanwhile, TREAT showed no difference as regard efficacy. The small sample size is a major limitation in this research and could affect the outcome results.

Moreover, many key questions remain unanswered, what would happen in patients who received fibrinolysis and ticagrelor at the same time. Another concern is for elderly patients > 75 years, who were excluded from this research and from TREAT, and who would be particularly susceptible to bleeding even if they were started on ticagrelor 2 hours after fibrinolytics.

Conclusion

Among patients <75 years of age who were treated with first generation fibrinolysis (streptokinase) for STEMI, ticagrelor after only 2 hours from streptokinase administration was safe and non inferior to clopidogrel. There was no excess of major bleeding, fatal bleeding, or intracranial bleeding with ticagrelor vs. clopidogrel. Ticagrelor could be the first treatment option in patients who are considered hypo responders to clopidogrel or had allergy. Unless future trials show otherwise, ticagrelor is safe 2 hours after fibrinolysis for STEMI patients.

Conflicts of interest: None declared.

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