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Efficacy and Safety of Switching from Clopidogrel to Ticagrelor at the Time of Discharge in STEMI Patients Treated with a Pharmacoinvasive Approach

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ABSTRACT

Objective: The aim of the study was to search for the efficacy and safety of switching from clopidogrel to ticagrelor at the time of discharge in ST-segment elevation myocardial infarction (STEMI) patients treated with a pharmacoinvasive approach.

Materials and Methods: STEMI patients who were managed with pharmacoinvasive approach were involved in the study population. Patients were divided into two groups as clopidogrel and ticagrelor depending on the choice of P2Y12 inhibitor at the time of discharge. All-cause mortality, stent thrombosis, recurrent myocardial infarction, need for target lesion revascularization, and any major bleeding (BARC classification ≥2) were defined as composite clinical end points at the end of the 12th month follow-up.

Results: A total of 194 patients (male: 156 patients, 80.4%; mean age 60.2±11.5 years) were involved in the study population (130 clopidogrel and 64 ticagrelor patients). The median time interval for switching time to ticagrelor was 48 (48–72) h. In a subgroup analysis for patients with a stented segment ≥30 mm, discharge with clopidogrel was related to 6.9 times increase in composite end points compared to patients discharged with ticagrelor (odds ratio: 6.955, confidence interval 95%: 1.512–30.980, p=0.012).

Conclusion: Switching from clopidogrel to ticagrelor at the 48th h following fibrinolytic administration had similar safety end points in STEMI patients managed with pharmacoinvasive approach. In a subgroup of study patients with a total stent length of ≥30 mm, switching to ticagrelor was found to be superior to clopidogrel regarding composite clinical end points.

Keywords: Clopidogrel, dual antiplatelet therapy, pharmacoinvasive approach, ST-segment elevation myocardial infarction, ticagrelor

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INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is the recommended reperfusion approach for the ST-segment elevation myocardial infarction (STEMI) patients (1). Although access to pPCI facilities is wider currently in our country, some STEMI patients cannot be able to be transferred to these facilities within target time intervals for reperfusion. In current clinical practice, a pharmacoinvasive strategy is recommended for STEMI patients who do not have a pPCI access within target time intervals after emergency admission (2). Pharmacoinvasive strategy addresses fibrinolytic administration as the initial reperfusion choice and early transfer for subsequent PCI within the following 24 h. On the other hand, fibrinolysis may have a tendency to increase platelet reactivity and as a result paradoxical thrombotic milieu exists in STEMI patients managed with fibrinolytic agents (3, 4). Because of this high platelet reactivity (HPR), dual antiplatelet therapy (with 300 mg loading dose of clopidogrel) is recommended at the time of fibrinolysis; however, enough platelet inhibition may not be achieved for all patients (5).

Ticagrelor is a proven P2Y12 inhibitor with a faster, greater, and consistent platelet inhibition compared to clopidogrel (6), but its' clinical effects in the STEMI patients treated with pharmacoinvasive strategy are not clear. There is not enough evidence for the use of ticagrelor in the early post-fibrinolytic period; for example, in the PLATO study, patients treated with fibrinolytics within the first 24 h were excluded from the statistical analysis (7). Despite this exclusion from large-scale clinical trials, there are studies searching the role of ticagrelor in the early period following fibrinolytic administration (8). In the latest ESC Guidelines published in 2017, switching from clopidogrel to ticagrelor was recommended at the discretion of physician, but there was not any class or level of evidence for this recommendation (1).

The study aimed to search for the efficacy and safety of switching from clopidogrel to ticagrelor at the time of discharge in STEMI patients treated with a pharmacoinvasive approach.

MATERIALS and METHODS

Study Place and Design

Study population was retrospectively selected for statistical evaluation from the patients who were diagnosed as STEMI and was given fibrinolytic therapy for emergent reperfusion in rural area. We conducted study in our tertiary center hospital Baskent University Hospital Alanya Application and Research Center and enrolled STEMI patients treated initially with fibrinolytic therapy in rural hospitals and transferred to our hospital for diagnostic coronary angiography (CAG) and if needed percutaneous coronary intervention (PCI) from 2017 to 2019.

Ethical Approval

This study was approved by Baskent University Institutional Review Board (Project no: KA20/175) and supported by Baskent University Research Fund (Ethical Committee approval date: 12/05/2020).

Patients and Data Collection

STEMI patients who do not have any access for pPCI within 120 min following the first emergency admission are managed by fibrinolytic administration as a primary reperfusion strategy and are transferred to our hospital for further diagnostic and coronary intervention. According to European Society of Cardiology 2017 Guidelines for the management of acute myocardial infarction (MI) in patients presenting with STEMI, clopidogrel 300 mg, acetylsalicylic acid 300 mg, and intravenous enoxaparin 0.3 cc had also been used as adjunctive antiplatelet and anticoagulant drugs. Diagnostic CAG and if needed subsequent PCI are performed within 24 h following transfer. If successful reperfusion had not been achieved with fibrinolytic therapy, rescue PCI can also be performed in our 7/24 catheter laboratory. Decision of continuing with clopidogrel or switching to ticagrelor was taken by the interventional cardiologist. Depending on the decision of P2Y12 inhibitor choice, switching to ticagrelor was performed during hospitalization after 48 h passed from the fibrinolytic administration recommended as in current guidelines. Ticagrelor loading was performed as oral 180 mg after 24 h following the last clopidogrel dosage.

Flow of retrospective patient search is expressed in Figure 1. We excluded patients who were managed with other than PCI for the destination STEMI therapy such as coronary artery bypass grafting (CABG) or medical treatment. Patients were kept under clinical follow-up for the 1st year after index hospitalization. Clinical outcomes were defined for efficacy as all-cause mortality, stent thrombosis, recurrent MI, and need for target lesion revascularization and for safety as in-hospital minor or major bleeding complications. Major bleeding was defined as BARC ≥ Class 2 bleedings (9). Composite clinical end point was defined as presence of all-cause mortality, stent thrombosis, need for target lesion revascularization, recurrent MI, or any major bleeding.

Evaluation of Coronary Angiographies

Recordings of coronary angiographies were reevaluated retrospectively for any overlooked procedural problem. Average stent diameters, total length of stents, and number of stents used were recorded and compared between clopidogrel and ticagrelor groups. Coronary angiographic evaluation was performed by two invasive
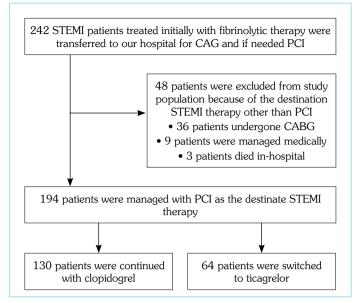

Figure 1. Consort diagram of the study population

cardiologists independently. Stent diameter and length were decided after repeated intracoronary nitroglycerin doses. The choice of drug-eluting stent or bare metal stent was depended on decision of the primary operator. Likewise, the preference of the vascular access route was depended on the primary operator. Successful PCI was defined as the achievement of a final TIMI 2-3 distal flow.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation or median (25th–75th percentile) and categorical variables were expressed as percentage (%). Normal distribution of continuous variables was tested with Kolmogorov–Smirnov normality test. If continuous variables distributed, normally differences between two groups were compared with the Student's t-test and did not distribute normally with the Mann–Whitney U-test. Categorical variables between two groups were compared with the Chi-square and the Fisher's exact tests. Factors affecting the clinical outcomes for efficacy and safety were searched with the univariate binary logistic regression analysis and the most related factors were tested with the multiple binary logistic regression analysis performed with backward stepwise method. $P<0.05$ was accepted as statistically significant. All data were evaluated on SPSS statistical package program (Version 22.0, Chicago IL, USA).

RESULTS

Basal Characteristics of Study Population

A total of 242 patients managed with fibrinolytic therapy at admission were searched from hospital database. Thirty-six patients undergone CABG, nine patients were followed by medical therapy, and three patients died during in-hospital follow-up. One hundred and ninety-four patients were enrolled in the final study population (male: 156 patients, 80.4%; mean age 60.2±11.5 years). Time of fibrinolytic administration following onset of symptoms was 60 (60–150) min and time of diagnostic CAG (and PCI if needed) after fibrinolytics was 5 (4–10) h. Success of fibrinolytic therapy was 66.5% and one-third of study population undergone

Table 1. Demographic and clinical data of study population

	Clopidogrel group (130 patients)	Ticagrelor group (64 patients)	p
Time to fibrinolytic administration (min)	60 (60–120)	60 (30–180)	0.139
Time to diagnostic CAG (h)	6 (4–12)	5 (4–10)	0.117
Rescue PCI %, (n)	29.2% (38)	40.6% (26)	0.133
Mean age (years)	61.2 (11.9)	58.1 (10.3)	0.075
Male gender %, (n)	79.2% (103)	82.8% (53)	0.555
Anterior myocardial infarction %, (n)	50.0% (65)	43.7% (28)	0.413
Heart rate (beats/min)	78.1 (13.7)	76.6 (11.3)	0.437
Systolic blood pressure (mmHg)	127.5 (23.1)	127.1 (20.9)	0.912
Diastolic blood pressure (mmHg)	77.5 (12.5)	77.8 (12.1)	0.885
LV ejection fraction at admission %, (n)	46.6 (9.1)	46.0 (7.3)	0.601
Diabetes mellitus %, (n)	21.5% (28)	12.5% (8)	0.128
Hypertension %, (n)	44.6% (58)	34.3% (22)	0.173
Hyperlipidemia %, (n)	12.3% (16)	12.5% (8)	0.969
Smoking %, (n)	59.2% (77)	64.0% (41)	0.517
Family history for premature CAD %, (n)	28.4% (37)	18.7% (12)	0.143
Myocardial infarction history %, (n)	12.3% (16)	9.3% (6)	0.545
CABG history %, (n)	2.3% (3)	0.0% (0)	0.221
PCI history %, (n)	15.3% (20)	10.9% (7)	0.400
Cerebrovascular event history %, (n)	0.7% (1)	1.5% (1)	0.552

CAG: Coronary angiography; PCI: Percutaneous coronary intervention; LV: Left ventricle; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting

Table 2. Angiographical data of study population

	Clopidogrel group (130 patients)	Ticagrelor group (64 patients)	p
Absence of distal coronary flow %, (n)	16.1% (21)	39.0% (25)	<0.001
Bifurcation intervention %, (n)	7.6% (10)	18.7% (12)	0.022
Mean stent length (mm)	30.0 (14.6)	36.3 (15.9)	0.007
Mean stent diameter (mm)	2.99 (0.47)	2.95 (0.35)	0.557
Mean implanted stent number	1.35 (0.63)	1.56 (0.77)	0.039
Bare metal stent implantation %, (n)	8.4% (11)	10.9% (7)	0.367
Radial artery access %, (n)	10.7% (14)	12.5% (8)	0.311

a rescue PCI procedure. Three patients died during in-hospital follow-up (overall mortality rate was 1.2%) (of 242 patients, all searched population). Anterior wall MI involvement was detected in 47.9% (93 patients) of study population. Total length of stent implantation was 32.3±17.5 mm and mean stent diameter was 2.98±0.43 mm. Number of overlapping stents implanted was 1.42±0.68 per culprit vessel. One hundred and thirty patients (67.0%) discharged with clopidogrel and 64 patients (33.0%) discharged with ticagrelor. Median time interval for switching from clopidogrel to ticagrelor in ticagrelor group was 2 (2–3) days. Intolerance to clopidogrel or ticagrelor was not statistically significant between two groups (3.8% vs. 4.6%) (p=0.720). One patient in ticagrelor group stopped drug in 5th month of follow-up because of dyspnoea. Demographic and clinical data of study population are expressed in Table 1 and angiographic findings are expressed in Table 2. Evaluation of angiographic data revealed that in tica-

grelor group, absence of distal coronary flow at the time of PCI (16.1% vs. 39.0%) (p<0.001) and bifurcation intervention (7.6% vs. 18.7%) (p=0.022) was more common than clopidogrel group. Besides this finding, total stent length (30.0±14.6 vs. 36.3±15.9 mm) (p=0.007) and number of implanted stents (1.35±0.63 vs. 1.56±0.77) (p=0.039) were higher in ticagrelor group.

Composite End point Development at the End of the 12th Months

We did not detect any statistical difference between two groups for efficacy, safety, and composite clinical end points at the end of the 12th months (Table 3). Ten patients (5.1%) undergone a target lesion revascularization and 4 patients (2.0%) had a stent thrombosis within the 12 months follow-up period. Eight patients (4.1%) experienced a major bleeding complication (defined as BARC 2, 3, or 5) and we did not detect any intracranial bleed-

Table 3. Clinical end points for efficacy and safety between two groups at the end of 12 months

	Clopidogrel group (130 patients)	Ticagrelor group (64 patients)	p
Target lesion revascularization %, (n)	4.6% (6)	6.2% (4)	0.732
Stent thrombosis %, (n)	1.5% (2)	3.1% (2)	0.600
Non-fatal myocardial infarction %, (n)	6.9% (9)	7.8% (5)	0.822
Minor bleeding %, (n)	13.8% (18)	17.1% (11)	0.539
Major bleeding %, (n)	3.0% (4)	6.2% (4)	0.443
Death %, (n)	6.1% (8)	3.1% (2)	0.502
Composite end point %, (n)	14.6% (19)	15.6% (10)	0.853

ing. Ten patients (5.1%) died (all-cause mortality) in the follow-up period. In binary logistic regression analysis, total stent length (≥30 mm) and number of overlapping stents (≥2 stents) were found to be related to composite end point development (for total stent length odds ratio [OR]: 4.615 [confidence interval (CI) 95%: 1.367–15.370], p=0.014; for the presence of overlapping stents OR: 1.050 [CI 95%: 1.002–1.098], p=0.046) (Table 4). Presence of a total stented segment ≥30 mm was related to 4.6 times increase in composite end point development. Patients with a total stent length ≥30 mm (88 patients) were searched separately and composite end point development was detected in 22 patients (25.0%). Only discharge with clopidogrel was found to be related to adverse endpoints (OR: 6.955, CI 95%: 1.512–30.980, p=0.012) (Table 5). In this subgroup, discharge with clopidogrel was related to 6.9 times increase in composite end points compared to patients discharged with ticagrelor.

DISCUSSION

Complexity of coronary artery disease is an essential factor in the development of major adverse cardiac events in acute coronary syndrome patients (10, 11). Total stent length and number of stents implanted consecutively in culprit vessels are related to increased incidence of stent thrombosis and death. Existence of longer stents means longer metallic surface to be endothelized and increased number of stents implanted result in more overlapping areas. In a large-scale retrospective analysis, a total stent length over 31.5 mm was found to be related to increased stent thrombosis in 3 years of follow-up (10). In an ex vivo in porcine evaluation, overlapping stent areas were thought to be related to low coronary wall shear stress and unfavorable flow conditions (11). These overlapping areas are hard to be endothelized and defined as possible culprit factors for the development of stent thrombosis and stent restenosis (12). In this analysis for general study population, total stent length (≥30 mm) and number of overlapping stents (≥2 stents) were tested for the development of composite end points (p values were 0.014 and 0.046, respectively). Besides this, patients in ticagrelor group had higher total stent length and number of overlapping stents (p=0.007 and 0.039, respectively), and this difference means patients in ticagrelor group had a more complex and diffuse coronary artery disease. Anatomical complexity might be a main concern for interventional cardiologist for switching from clopidogrel to ticagrelor at the time of discharge in this study population. Despite this anatomical complexity, there was no statistical difference detected between clopidogrel and ticagrelor groups for composite clinical end-points. In a subgroup analysis involving the

Table 4. Multiple binary logistic regression analysis for the whole study population

Parameter	OR	95% CI	p
Bifurcation intervention	1.020	0.288–1.752	0.378
Total stent length ≥30 mm	4.615	1.367–15.370	0.014
Overlapping stents	1.050	1.002–1.098	0.046
Discharge with clopidogrel	1.008	0.408–1.608	0.519

Most related angiographical parameters were selected due to univariate binary logistic regression analysis. CI: Confidence interval; OR: Odds ratio

Table 5. Multiple binary logistic regression analysis for patients with a total stent length of ≥30 mm after selection of the most related angiographical factors due to univariate binary logistic regression analysis

Parameter	OR	95% CI	p
Bifurcation intervention	1.002	0.612–1.392	0.647
Overlapping stents	1.010	0.704–1.316	0.310
Discharge with clopidogrel	6.955	1.512–30.980	0.012

CI: Confidence interval; OR: Odds ratio

patients with a total stent length ≥30 mm, discharge with clopidogrel was found to be related to 6.9 times higher composite end point development (p=0.012). Regarding these results, switching from clopidogrel to ticagrelor at the time of discharge should be discussed, especially in STEMI patients with more complex and diffuse CAD reperfused with initial fibrinolytic therapy.

Complications related to mild bleeding were commonly reported with ticagrelor more than with clopidogrel in STEMI patients in their clinical follow-up. On the other hand, Song et al. (13) reported that major bleeding complications defined as BARC 2, 3, or 5 were similar between ticagrelor and clopidogrel patients. In our analysis, we did not find any differences neither minor nor major bleeding complications defined by BARC classification (p=0.539 and 0.443, respectively). It should be noticed that this study had a retrospective design and it was hard to question minor bleeding symptoms retrospectively, also type I error could not be ignored in evaluation of results.

Elderly patients were generally excluded from statistical analysis in large-scale clinical trials because of safety concerns (14–16).

In this study, patients in clopidogrel group had a mean age of 3 years higher than patients in ticagrelor group (61.2 vs. 58.1 years, p=0.075). Besides this age difference between study groups, regarding elderly patients over 75 years of age (14.4% of all study population), more than 80% of them were discharged with clopidogrel. Advanced age is a well-recognized risk factor for major bleeding complications (17) and also in our population majority of patients over 75 years of age continued their DAPT as aspirin plus clopidogrel. We could not be able to perform a statistical analysis for safety endpoint in patients over 75 years of age because size of ticagrelor group was very small for these elderly patients and because of the possibility of type I statistical error may affect data interpretation. Hence, in patients over 75 years of age, there has not been yet enough evidence for switching from clopidogrel to ticagrelor regarding safety concerns in STEMI patients treated with fibrinolytics as an initial reperfusion strategy.

In the previous studies, HPR was defined as post-fibrinolytic platelet reactivity to be higher than 208 P2Y12-Reaction Units and HPR frequently exists in post-fibrinolytic period in STEMI patients treated with fibrinolytics but there has not been offered an exact solution yet to prevent this in literature (18). In a small-scale study, PCI was performed with a median delay time of 2.5 days in STEMI patients treated with fibrinolytics as an initial reperfusion strategy and HPR was detected in 71.4% of study population at the time of PCI (18). In our study, we detected a median time interval of 2 days between fibrinolytic administration and ticagrelor switch. Theoretically, depending on the previous studies, HPR was still existing at the time switch in our population because in a substudy of PLATO trial, HPR was detected more common at the 28th day with clopidogrel compared to with ticagrelor (19). Yang et al. (20) demonstrated that a greater proportion of low HPR can be reached with switching to ticagrelor at the time of PCI within the 24 h following fibrinolytic administration and this suppression of HPR may extend up to 12 months of period. On the other hand, there are also studies which conflict with longer HPR existence (21, 22). Alexopoulos et al. (22) compared ticagrelor and even high loading dose of clopidogrel in STEMI patients with post-fibrinolysis HPR and reported a lower HPR in ticagrelor group at the 2nd and 24th h following PCI. In this paper, Alexopoulos et al. (22) also postulated that platelet reactivity equalized at the time of discharge between ticagrelor and clopidogrel groups. Exact time of decrement for HPR in post-fibrinolytic period is not clear and probably we need further studies to identify the proper time of switching from clopidogrel to ticagrelor in STEMI patients reperfused with fibrinolytics initially.

This study has some limitations; first of all, this was a single-center study with a retrospective design. Drug switching was depended at the discretion of interventional cardiologist at the time of discharge. In patients discharged with ticagrelor, more complex coronary lesions were detected at the time of PCI (absence of distal coronary flow, bifurcation intervention, etc.). If the study design had a prospective, randomized design, then results might be different between study groups. Effect of type of fibrinolytic agent was not searched in this study, inhibition of platelet functions can show difference with different fibrinolytic agents. Because of retrospective design of study, there might be possible inconvenience in questioning of side effects, especially related to minor bleeding.

CONCLUSION

Switching from clopidogrel to ticagrelor at the time of discharge following fibrinolytic administration in STEMI patients can be performed safely and ticagrelor was found to be superior to clopidogrel, especially in patients with more diffuse coronary artery lesions and longer stent implantations. In STEMI patients with diffuse CAD which were managed with pharmacoinvasive approach, switching from clopidogrel to ticagrelor should be discussed strongly at the time of discharge. Despite the limitations of the study related to the retrospective design mainly, we need prospective, randomized studies to evaluate the place of ticagrelor for STEMI patients managed with pharmacoinvasive approach.

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