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The Effectiveness and Safety of Concomitant Ticagrelor Use with Fibrinolytic In ST-Elevation Myocardial Infarction Patients

ST-Elevasyonlu Miyokard Enfarktüslü Hastalarda Fibrinolitik ile Birlikte Kullanılan Tikagrelorun Etkinliği ve Güvenliği

ABSTRACT

Objective:
The effectiveness and safety of administration of ticagrelor simultaneously with fibrinolytic in ST-elevation miyocard infarction (STEMI) remains unclear. Our study aims to compare and evaluate ticagrelor and clopidogrel in STEMI patients treated with fibrinolytic.

Material and Methods:
This retrospective and cross-sectional study was conducted in a non-PCI-capable hospital between November 2017 and January 2021. The study consisted of 180 STEMI patients over 18 years of age who were given fibrinolytic therapy and had no absolute contraindications for treatment. Ticagrelor was given to 94 patients and clopidogrel was given to 86 patients. Loading doses were given to patients concurrently with fibrinolysis, followed by maintenance doses. The primary outcome was six-month follow-up for all-cause mortality, major cardiovascular events, stroke, recurrent MI, target artery revascularization, and severe bleeding. The secondary outcome was to evaluate patients over 75 years of age, use of rivaroxaban, and major adverse events that will develop in patients with chronic kidney disease.

Results:
There was no substantial difference between the groups in terms of in-hospital death, GFR values (<60/≥60 ml/min./1.73 m²), Rivaroxaban use, fatal bleeding, BARC Bleeding Type 1-2, intracranial bleeding, mortality, stroke, target vessel revascularization, and recurrent MI (p>0.05). Mortality was observed in 5 of 86 patients using clopidogrel and in 4 of 94 patients using ticagrelor. (Log-rank test, p:0.63 HR=0.72 (95%CI, 0.19-2.67)). The BARC type 3-5 bleeding in patients using ticagrelor and clopidogrel were statistically similar. (Log-rank test, p:0.77 HR=1.23 (95%CI, 0.31 - 4.79)).

Conclusions:
In this study, we found that ticagrelor was equally effective and safe as clopidogrel when used with fibrinolytic treatment.

Key Words:
Dual antiplatelet therapy, Fibrinolysis, Ticagrelor, Pharmaco-invasive reperfusion, Clopidogrel

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ÖZ

Amaç:

ST-elevasyonlu miyokard enfarktüste tikagrelorun fibrinolitik ile aynı anda uygulanmasının etkinliği ve güvenliği belirsizliğini koruyor. Çalışmamız fibrinolitikler ile tedavi edilen (ST-elevasyonlu miyokard enfarktüsü) STEMI hastalarında tikagrelor ve klopidogrel karşılaştırmayı ve değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler:

Geriye dönük ve kesitsel olan bu çalışma, Kasım 2017 ile Ocak 2021 tarihleri arasında, PCI yeteneği olmayan hastanede gerçekleştirilmiştir. Çalışmaya fibrinolitik tedavi verilen ve tedavi için mutlak kontrendikasyonu olmayan 18 yaş üstü 180 STEMI'li hasta dahil edildi. Tikagrelor 94 hastaya, klopidogrel ise 86 hastaya verildi. Hastalara fibrinoliz ile eş zamanlı olarak yükleme dozları verildi, ardından idame dozları verildi. Birincil sonuç, tüm nedenlere bağlı mortalite, majör kardiyovasküler olaylar, inme, tekrarlayan miyokard enfarktüsü (MI), hedef damar revaskülarizasyonu ve majör kanama için altı aylık takipti. İkincil sonuç, 75 yaşın üzerindeki hastaları, rivaroksaban kullanımını ve kronik böbrek hastalığı olan hastalarda gelişecek majör advers olayları değerlendirmekti.

Bulgular:

Hastane içi ölüm, GFR değerleri (<60/≥60 ml/dk/1.73 m²), Rivaroxaban Kullanımı, Ölümcül Kanama, BARC Kanama Tip 1-2, kafa içi kanama, mortalite, inme, hedef damar revaskülarizasyonu ve tekrarlayan miyokard enfarktüsü (MI) açısından anlamlı fark bulunmadı (p>0.05). Klopidogrel kullanan 86 hastanın 5'inde ve tikagrelor kullanan 94 hastanın 4'ünde mortalite gözlenmiştir (Log-rank testi, p:0.63 HR=0.72 (%95GA, 0.19-2.67). Tikagrelor ve klopidogrel kullanan hastalarda BARC tip 3-5 kanaması istatistiksel olarak benzerdi (Log-rank testi, p:0.77 HR=1.23 (%95GA, 0.31 - 4.79)).

Sonuç:

Bu çalışmada, tikagrelorun fibrinolitik tedavi ile birlikte kullanımının etkinlik ve güvenlik açısından klopidogrel ile benzer olduğunu bulduk.

Anahtar Sözcükler:

İkili antiplatelet tedavi, Fibrinoliz, Ticagrelor, Farmako-invaziv reperfüzyon, Klopidogrel

INTRODUCTION

STEMI is an acute coronary syndrome requiring emergency reperfusion therapy. It is vital to restore coronary flow by reperfusion of the infarct-related artery as soon as possible to decrease mortality and morbidity (1-4). In STEMI patients, primary percutaneous coronary intervention (pPCI) is the recommended reperfusion method if administered on time (<120 minutes), but if pPCI is not possible and there are no contraindications, the preferred reperfusion therapy is fibrinolysis (1,5-8).

Fibrinolysis, which breaks down thrombosis causing coronary artery occlusion, may induce a prothrombotic state (9-11). Therefore, additional treatment is needed to prevent the recurrence of thrombosis. In two large-scale randomized controlled trials (RCT), dual antiplatelet therapy (aspirin and clopidogrel) was found to decrease major cardiovascular events in STEMI patients treated with fibrinolytic (10,11). Clinical experience with the use of ticagrelor in combination with fibrinolytic is limited. Therefore, there is no evidence of long-term effects of ticagrelor, which provides quicker and more effectively P2Y12 inhibition than clopidogrel in STEMI patients treated with fibrinolytic (11-14). Current guidelines advise dual antiplatelet medication (aspirin and clopidogrel) for STEMI patients treated with fibrinolytic (1,4,15).

Studies have shown that fibrinolytic-treated STEMI patients switching from clopidogrel to ticagrelor are linked with similar bleeding and ischemic results compared to patients continuing clopidogrel therapy (16-20). Information on co-administration of ticagrelor with fibrinolytic is insufficient.
In addition, there is little experience with patients over 75 years of age, those with chronic kidney disease (CKD), and patients at high risk of bleeding who take rivaroxaban.

Our study aims to compare and evaluate concomitant ticagrelor versus clopidogrel treatment in fibrinolytic-treated STEMI in terms of their effects on major adverse cardiac and cerebrovascular events (MACCE), death, myocardial infarction, target artery revascularization, stroke, and severe bleeding.

MATERIAL and METHODS

Study design and settings

The retrospective cross-sectional study was carried out between November 2017 and January 2021 in Cizre Dr.Selahattin CIZRELIOGLU State Hospital (SIRNAK/TURKEY), a level 2 hospital without PCI capability. Fibrinolytic and ticagrelor were administered to patients diagnosed with STEMI in our hospital. Afterward, the patients were referred to the PCI-capable centers. The data of the patients who reapplied to our hospital for follow-up examination after discharge from PCI-capable centers were collected. The epicrisis reports were accessed from the hospital's digital archive with the official permission of the hospital management. Work permit and data usage permission were approved by the management of Cizre Dr.Selahattin CIZRELIOGLU State Hospital
(No: 84410283/469/E-84410283-469-623 Date: 27 July 2021).

The study was approved, and the requirement for informed consent was waived by the Ethics Commission. (No: 2021-208-decision number:11/6 Date: 05th August 2021). The study was conducted in line with the Declaration of Helsinki. Work permit and data usage permission were approved by the management of Cizre Dr.Selahattin CIZRELIOGLU State Hospital.(No: 84410283/469/E-84410283-469-623 Date: 27 July 2021).

Selection of participants

All STEMI patients over 18 (including those over 75) who applied with clinical and electrocardiogram (ECG) indications for fibrinolytic therapy and had no absolute contraindications were enrolled in the study (21). Patients with major contraindications, coronary artery bypass grafting (CABG), or medical treatment decisions as a result of PCI, who did not undergo PCI due to bleeding and whose records could not be reached were excluded from the study.

Study Protocol

Patients who were found to have acute STEMI in the ECG at the time of admission to the emergency department within 12 hours after the commencement of symptoms and patients who were suitable for fibrinolytic treatment were included in the research. Intravenous doses of tenecteplase (half dose for patients over 75 years of age) calculated according to the administration protocol recommended in the guideline were administered to patients without absolute contraindications for fibrinolytic therapy (1). All patients received concomitant antiplatelet and anticoagulant therapy with fibrinolytic therapy. The patients were loaded with 300 mg of acetylsalicylic acid and then continued as 100 mg per day. Low molecular weight heparin was given as an anticoagulant according to the recommended dose in the guideline (1).

As the clopidogrel treatment protocol, patients were given 300 mg loading dose and 75 mg maintenance dose, and as the ticagrelor treatment protocol, patients were given 180 mg loading dose and 90 mg maintenance dose twice.

After discharge, the first given inhibitor was continued without change. Patients who switched from one inhibitor to another were excluded from the study. In addition, without delaying the referral to the emergency department, left ventricular ejection fraction (LVEF) and left atrial (LA) diameter were calculated by echocardiography. LVEF value was grouped according to the ESC Guidelines (1). Patients treated with fibrinolytic were referred to a certified PCI center for an early invasive coronary angiography procedure 2 to 24 hours later. Failed fibrinolytic ECG criterion was accepted as at least 50 percent unresolved ST elevation on the electrocardiogram (22). Chronic kidney disease (CKD) was defined as Cockcroft-Gault formula estimated Glomerular filtration rate (GFR) <60 mL/min. (ml/min./1.73 m^2) (23). The Global Registry of Acute Coronary Events (GRACE) risk score was calculated for pre-reperfusion risk assessment in the acute phase (24). The GRACE risk score was divided into groups as low (≤108), medium (109-140), and high (>140).

Pain to door time (minute), Door to needle time (minute), Pain-to-needle time (minute), Needle-to-balloon time (minute) were recorded. Collected data included demographic characteristics, existing disease histories, Killip classification, smoking history, and laboratory tests.

Clinical Follow-up

Bleedings were classified according to Bleeding Academic Research Consortium (BARC) definitions (25). BARC scale 3-5 bleeding was accepted as major bleeding. After concomitant P2Y12 inhibitor therapy with a fibrinolytic, patients were followed for six months with medical consultation or by phone call to record MACCE: mortality, myocardial infarction, target artery revascularization, stroke, and major bleeding.

Outcome Measures

Primary outcome: 6-month follow-up for all-cause mortality, major cardiovascular events, stroke, recurrent MI, target artery revascularization, and major bleeding.
Secondary outcome: Evaluation of patients at high risk for major adverse events, that is, those with CKD, over 75 years of age and using rivaroxaban.

Data Analysis (Evaluation of Data Collection Tools)

Parametric tests were employed instead of a normality test to comply with the Central Limit Theorem (26). Continuous variables were analyzed using mean±standard deviation, minimum and maximum values, while categorical data were analyzed using percentages and frequencies values. The student's t-test statistic was applied to compare the means of the two groups. The association among categorical data was evaluated using the Chi-Square, Fisher's Exact test, and Student's t-test statistic.

Total survival was calculated using Kaplan-Meier curves. The difference in mortality and bleeding time compared to the P2Y12 inhibitor group was determined by the Log-Rank test, and the Hazard ratio coefficient was given with a 95% confidence interval. TIME (day) was used as the variable, including the follow-up time or the time to reach the relevant event (Death and Bleeding).

The risk coefficients (Relative Risk) of the variables thought to be associated with the P2Y12 inhibitor were given a 95% Confidence interval. The data was accepted with a suitable statistical threshold of $p<0.05$. The www.e-picos.com New York software and the MedCalc statistical package tool were used to analyze the data.

RESULTS

A total of 180 patients, 24 of whom were over 75 years old, who were diagnosed with STEMI and started fibrinolytic therapy in the emergency department between 2017 and 2021 were included in the study. In this process, 9 STEMI patients with cardiac arrest in the emergency department and four data loss or inaccessibility were excluded (Figure 1).

The average age of the total patients included in the trial was 61.2±11.4, the mean age of those treated with clopidogrel was 60.5±11.4, and those treated with ticagrelor were 61.8±11.5, showing no substantial difference (Table I).

There was no difference in the mean GRACE risk score, symptom-door-needle-angio times, echocardiographic findings, length of hospital stay, and laboratory and cardiac parameters according to the P2Y12 inhibitor applied (Table I).

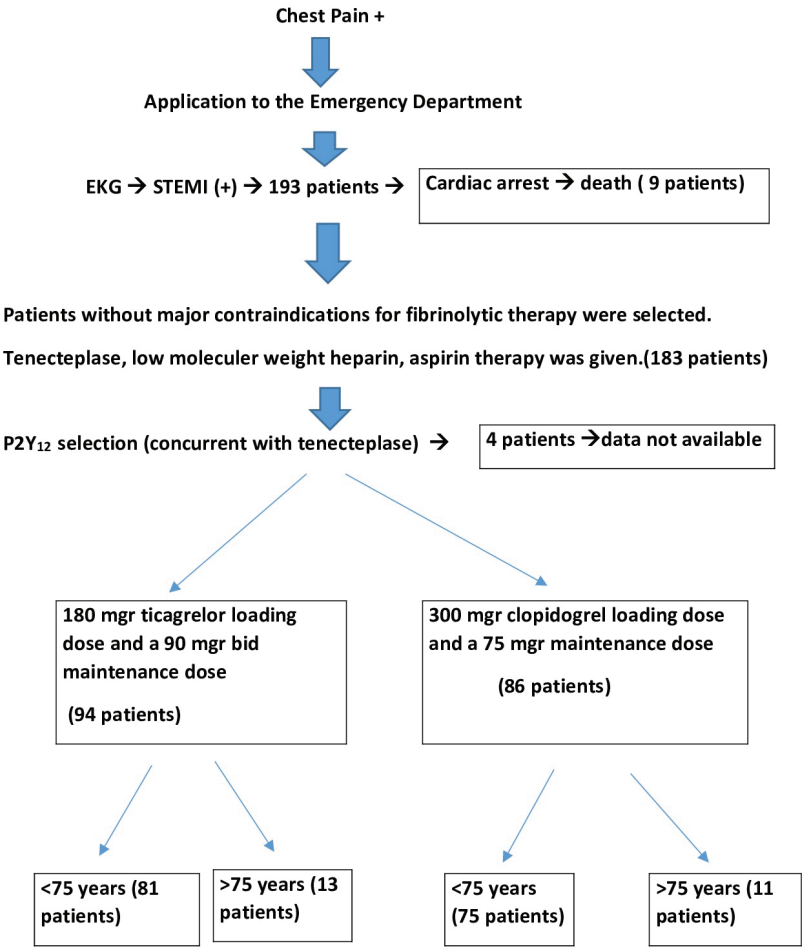

Figure 1: Patient Flow in the Study.

	Total n=180	Clopidogrel n=86	Ticagrelol n=94	
Properties	**x̄±SD**	**x̄±SD**	**x̄±SD**	**P value**
Age	61.2±11.4	60.5±11.4	61.8±11.5	0.44
Hospitalization Period	5.8±1.8	5.8±1.9	5.9±1.6	0.86
Glucose (mg/dL)	159.09±79.62	164.35±93.967	161.78±7.399	0.84
Creatinine (mg/dL)	0.95±0.29	0.941±0.317	0.974±0.295	0.46
Na (mmol/L)	139.17±3.26	138.77±3.03	139.62±3.373	0.08
K (mmol/L	4.138±0.53	4.155±0.53	4.134±0.535	0.79
Albumin (g/dL)	3.408±0.501	3.482±0.507	3.348±0.474	0.07
Total protein (g/dl)	7.669±1.075	7.794±1.086	7.538±1.05	0.11
HBG (g/dL)	14.266±1.528	14.196±1.384	14.243±1.667	0.84
HCT (%)	42.586±4.314	42.327±3.754	42.627±4.739	0.64
AST (U/L)	29.39±21.389	27.62±16.95	29.96±24.26	0.45
ALT (U/L)	21.18±16.32	19.3±10.14	22.31±19.95	0.2
Total cholesterol, mg/dL	177.44±55.771	178.15±40.127	175.55±66.477	0.94
Triglyceride,mg/dL	139.318±100.831	135.365±68.188	141.894±121.998	0.66
HDL cholesterol, mg/dL	42.78±9.865	42.954±9.253	42.621±10.442	0.82
LDL cholesterol, mg/dL	110.349±31.455	110.242±30.823	111.182±31.516	0.84
WBC (10^3/mm^3)	12.265±3.653	12.365±3.978	12.178±3.325	0.73
PLT (10^3/mm^3)	269.512±66.149	269.459±61.513	269.395±70.186	0.99
MPV (um^3)	9.757±0.813	9.739±0.754	9.804±0.903	0.61
CRP (mg/L)	1.78±2.235	1.636±1.454	1.945±1.706	0.35
INR	1.176±0.087	1.179±0.116	1.189±0.093	0.54
LVEF (%)	0.462±0.115	0.464±0.116	0.453±0.12	0.49
LA diameter (cm)	3.437±0.503	3.469±0.485	3.413±0.535	0.46
eGFR, mL/min/1.73 m2	91.103±21.38	93.108±22.71	88.428±20.906	0.15
cTnI (ng/mL)	1.89±1.68	2.09±1.941	1.71±1.36	0.14
GRACE Risk Score (Hospital Mortality)	130.11±24.002	130±21.848	131.16±25.556	0.74
Symptom to Door Time (min)	160.1±87.2	169.8±99.6	151.1±73.5	0.16
Door to Needle Time(min)	25.6±6.6	25.2±6.4	25.9±6.7	0.42
Symptom to Needle Time(min)	185.7±87.9	195.1±100.6	177.1±73.9	0.18
Needle angiography time(min)	364.5±127.5	371.5±137.6	358.1±117.9	0.48

Table I: Difference Evaluation with P2Y12 inhibitor Used in Patients with STEMI Diagnosis.

* Significant at the p<0.05 level (Student's t-test).

Values are reported as mean ± SD for continuous traits. Na: sodium, K: potassium, HBG: Hemoglobin, HTC: Hematocrit, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, WBC: White blood cells, PLT: Platelets, MPV: mean platelet volume, CRP: C reactive protein, INR: international normalized ratio, LVEF: left ventricular ejection fraction, LA: left atrium, eGFR: estimated glomerular filtration rate, cTnI, cardiac troponin-I, GRACE: Global Registry of Acute Coronary Events

Relationship of the used P2Y12 inhibitor with age: (Table II)

N:180	Clopidogrel n=86			Ticagrelol n=94		
Age	**≤75 n=75**	**>75 n=11**	**P value**	**≤75 n=81**	**>75 n=13**	**P value**
	n(%)	**n(%)**		**n(%)**	**n(%)**	
Mortality						
No	70(93.3)	11(100)	0.99	77(95.1)	13(100)	0.99
Yes	5(6.7)	-		4(4.9)	-	
Stroke						
No	74 (98.79)	10 (90.9)	0.24	81(100)	11(84.6)	**0.02**
Yes	1(1.3)	1(9.1)		-	2(15.4)	
Revascularization						
No	71(94.7)	11(100)	0.99	78(96.3)	12(92.3)	0.45
Yes	4(5.3)	-		3(3.7)	1(7.7)	
Recurrent MI						
No	71(94.7)	11(100)	0.99	78(96.3)	12(92.3)	0.45
Yes	4(5.3)	-		3(3.7)	1(7.7)	
BARC bleeding type						
Type 1-2	8(72.7)	4(80)	0.99	5(55.6)	7(87.5)	0.29
Type 3-5	3(27.3)	1(20)		4(44.4)	1(12.5)	
Fatal Bleeding						
No	73(97.3)	11(100)	0.99	78(96.3)	13(100)	0.99
Yes	2(2.7)	-		3(3.7)	-	
eGFR, mL/min/1.73 m2						
<60	5(6.7)	2(18.2)	0.22	6(7.4)	3(23.1)	0.11
≥60	70(93.3)	9(81.8)		75(92.6)	10(76.9)	

Table II: Age Relationship Evaluation by the P2Y12 inhibitor used.

** Significant at the p<0.05 level (Fisher's Exact Test).*
Values are reported as n (%) for dichotomous traits. MI: myocardial infarction, BARC: Bleeding Academic Research Consortium, eGFR: estimated glomerular filtration rate

In patients treated with Clopidogrel; age (≤75/>75) was not associated with mortality, stroke, target vessel revascularization, MI, BARC bleeding Type (3-5/1-2), fatal bleeding, and GFR (p>0.05). In patients treated with Ticagrelor; age (≤75/>75) was not associated with mortality, target vessel revascularization, MI, BARC bleeding Type (3-5/1-2), fatal bleeding, and GFR (p>0.05). However, stroke was associated with age (p<0.05). While stroke did not develop in those younger than 75 years of age, 15.4% of those older than 75 years had an ischemic stroke.

Relationship and Difference of the used P2Y12 inhibitor with Mortality. (Table III)

Table III: Relationship and Difference Evaluation with Mortality by the P2Y12 Inhibitor Used.

N:180	**Clopidogrel n=86**			**Ticagrelol n=94**		
Mortality	**Survival n=81**	**Non-Survival n=5**	**p**	**Survival n=90**	**Non-Survival n=4**	**p**
	n(%)	**n(%)**		**n(%)**	**n(%)**	
Gender						
Male	55(67.9)	3(60)	0.66	67(74.4)	3(75)	0.99
Female	26(32.1)	2(40)		23(25.6)	1(25)	
HT						
No	52(64.2)	3(60)	0.99	62(68.9)	1(25)	0.1
Yes	29(35.8)	2(40)		28(31.1)	3(75)	
Hyperlipidemia						
No	66(81.5)	3(60)	0.25	69(76.7)	3(75)	0.99
Yes	15(18.5)	2(40)		21(23.3)	1(25)	
DM						
No	57(70.4)	2(40)	0.18	66(73.3)	3(75)	0.99
Yes	24(29.6)	3(60)		24(26.7)	1(25)	
CHF						
No	73(90.1)	5(100)	0.99	85(94.4)	4(100)	0.99
Yes	8(9.9)	-		5(5.6)	-	
CHD						
No	70(86.4)	4(80)	0.54	83(92.2)	5(100)	0.3
Yes	11(13.6)	1(20)		7(7.8)	3(75)	
AF						
No	73(90.1)	3(60)	0.1	76(84.4)	4(100)	0.99
Yes	8(9.9)	2(40)		14(15.6)	-	
CVD						
No	81(100)	5(100)	-	87(96.7)	4(100)	0.99
Yes	-	-		3(3.3)	-	
Smoking						
No	22(27.2)	2(40)	0.62	22(24.4)	1(25)	0.99
Yes	59(72.8)	3(60)		68(75.6)	3(75)	
Killip Classification						
1	63(77.8)	2(40)	0.09	67(74.4)	1(25)	0.06
2-4	18(22.2)	3(60)		23(25.6)	3(75)	
MI Type						
Anterior	31(38.3)	2(40)	0.7	37(41.1)	3(75)	0.44
Lateral	20(24.7)	1(20)		23(25.6)	-	
Inferior	17(21)	2(40)		15(16.7)	1(25)	
Posterior	13(16)	-		15(16.7)	-	
Failed Thrombolytic (ECG criterion)						
No	60(74.1)	2(40)	0.13	69(76.7)	1(25)	**0.05**
Yes	21(25.9)	3(60)		21(23.3)	3(75)	
Rivaroxaban Usage						
No	73(90.1)	3(60)	0.1	76(84.4)	4(100)	0.99
Yes	8(9.9)	2(40)		14(15.6)	-	
eGFR, mL/min/1.73 m2						
<60	5(6.2)	2(40)	**0.051**	9(10)	-	0.99
≥60	76(93.8)	3(60)		81(90)	4(100)	
GRACE score						
Low	19(23.5)	-	0.32	14(15.6)	-	0.57
Mod.	36(44.4)	2(40)		46(51.1)	3(75)	
High	26(32.1)	3(60)		30(33.3)	1(25)	
LVEF Classification						
<40	21(25.9)	2(40)	0.34	28(31.1)	2(50)	0.63
40-49	17(21)	2(40)		18(20)	1(25)	
≥50	43(53.1)	1(20)		44(48.9)	1(25)	
BARC bleeding type						
Type 1-2	10(83.3)	2(50)	0.24	12(83.7)	-	**0.01**
Type 3-5	2(16.7)	2(50)		2(14.3)	3(100)	
	x̄±SD	**x̄±SD**	**p**	**x̄±SD**	**x̄±SD**	**p**
INR	1.16±0.08	1.42±0.28	0.11	1.18±0.09	1.25±0.13	0.18
Troponin I	2.07±1.98	2.26±1.26	0.84	1.72±1.42	1.43±0.35	0.22
LVEF %	0.46±0.11	0.38±0.14	0.1	0.45±0.11	0.39±0.21	0.3
GRACE Risk Score (Hospital Mortality)	129.06±21.76	145.2±19.11	0.11	131.1±25.9	133.5±16.7	0.85

** Significant at the p<0.05 level (Chi-Square-Fisher's Exact test/Student's t-test).*

Values are reported as mean ± SD for continuous traits and n(%) for dichotomous traits. HT: hypertension, DM: diabetes mellitus, CHD: coronary heart disease, CHF: congestive heart failure, AF: atrial fibrillation, CVD: cerebrovascular disease, MI: myocardial infarction, ECG: electrocardiogram, eGFR: estimated glomerular filtration rate, GRACE: Global Registry of Acute Coronary Events, LVEF: left ventricular ejection fraction, BARC: Bleeding Academic Research Consortium, INR: international normalized ratio

In patients treated with Clopidogrel; Mortality was not associated with gender, disease, and smoking history, Cardiac Parameter result, BARC blood type (3-5/1-2), LVEF value and Classification, target vessel revascularization, recurrent MI, Failed fibrinolytic ECG criteria, Rivaroxaban use, and GRACE risk score (p>0.05). However, GFR status was linked to mortality (p=0.05). In those with mortality, 40% had a GFR <60 mL/min/1.73 m², and without mortality, 6.2% had GFR <60 mL/min/1.73 m².

In patients treated with Ticagrelor; Mortality was not associated with gender, disease, and smoking history, LVEF value and Classification, target vessel revascularization, recurrent MI, Criteria for failed fibrinolytic ECG, Rivaroxaban use, GFR, and GRACE risk score (p>0.05). However, failed fibrinolytic ECG criteria were associated with mortality (p<0.05). Failed fibrinolytic ECG criteria were observed in 75% of those with mortality and 23.5% without mortality. BARC bleeding type (3-5 / 1-2) was also associated with mortality (p<0.05). BARC type 3-5 bleeding was detected in 3 patients (100%) with mortality and two patients (14.3%) without mortality.

There was no difference in the risks of in-hospital death, Killip classification 2-4, Failed fibrinolytic ECG criterion, GFR, Rivaroxaban USE, Fatal Bleeding, BARC Bleeding Type (3-5/1-2), Intracranial Bleeding, Mortality, ischemic stroke, target vessel revascularization, and presence of recurrent MI in patients treated with Ticagrelor against treated with Clopidogrel (p>0.05) (Figure 2).

	Relative Risk (95% CI)	p-value
Death in Hospital	0,732(0,203-2,637)	p>0,05
Killip classification (2-4)	1,133(0,69-1,858)	p>0,05
Unsuccessful fibrinolytic (ekg criterion)	0,915(0,564-1,485)	p>0,05
GFR (<60/≥60) mL/dk	1,176(0,458-3,002)	p>0,05
Rivaroxaban use	1,281(0,601-2,731)	p>0,05
Fatal bleeding	1,372(0,235-8,018)	p>0,05
BARC bleeding	0,972(0,525-1,801)	p>0,05
BARC bleeding type (3-5/1-2)	1,029(0,555-1,906)	p>0,05
Intracranial bleeding	1,176(0,382-3,619)	p>0,05
Mortality	1,32(0,366-4,76)	p>0,05
Stroke	0,915(0,132-6,354)	p>0,05
Revascularization	0,915(0,236-5,546)	p>0,05
recurrent myocardial infarction	0,915(0,236-3,546)	p>0,05

** P<0.05 was accepted as significant. (Relative Risk)*

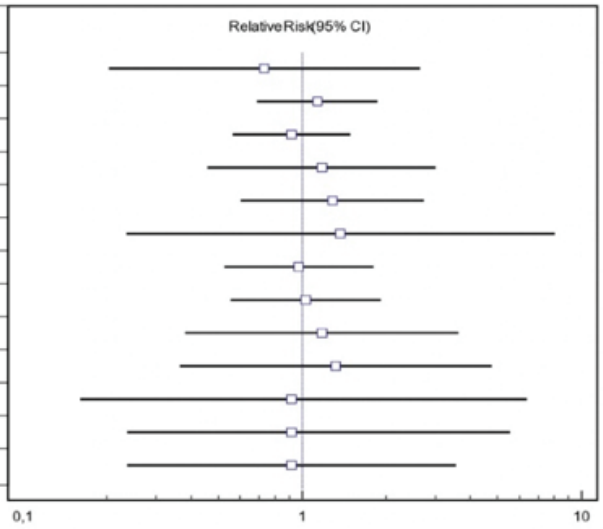

Figure 2: Relationship of clinical findings with P2Y12 inhibitor Use and relative risk coefficients (Ticagrelor/Clopidogrel).

As seen in Figure 3;
In this study, bleeding was detected in 16 of 86 patients using clopidogrel and in 17 of 94 patients using ticagrelor. In this case, the chi-square statistic was 0.007, and the p-value was 0.93, greater than 0.05 (Log-rank test, p:0.93 HR=0.97 (95%CI, 0.48 - 1.94)). Accordingly, the statistical result indicates that the survival curves did not differ significantly, or the factor (P2Y12 inhibitor) variable did not significantly affect the duration of bleeding (p>0.05).

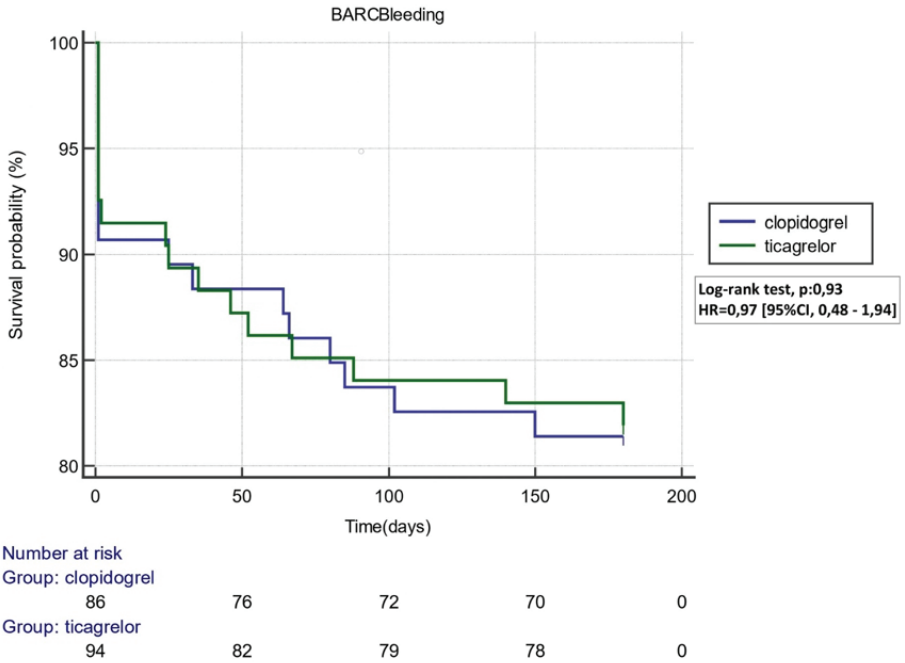

Figure 3: Graph of survival (survival) probabilities (%) vs. Time (Bleeding).

As seen in Figure 4;
In this study, BARC Type 3-5 bleeding was detected in 4 patients using clopidogrel and five patients using ticagrelor. In this case, the chi-square statistic was 0.086, and the p-value was 0.77, greater than 0.05 (Log-rank test, p:0.77 HR=1.23 (95%CI, 0.31 - 4.79)). Accordingly, the statistical result indicates that the survival curves did not differ significantly, or the factor (P2Y12 inhibitor) variable did not have a significant effect on the BARC type 3-5 bleeding duration (p>0.05).

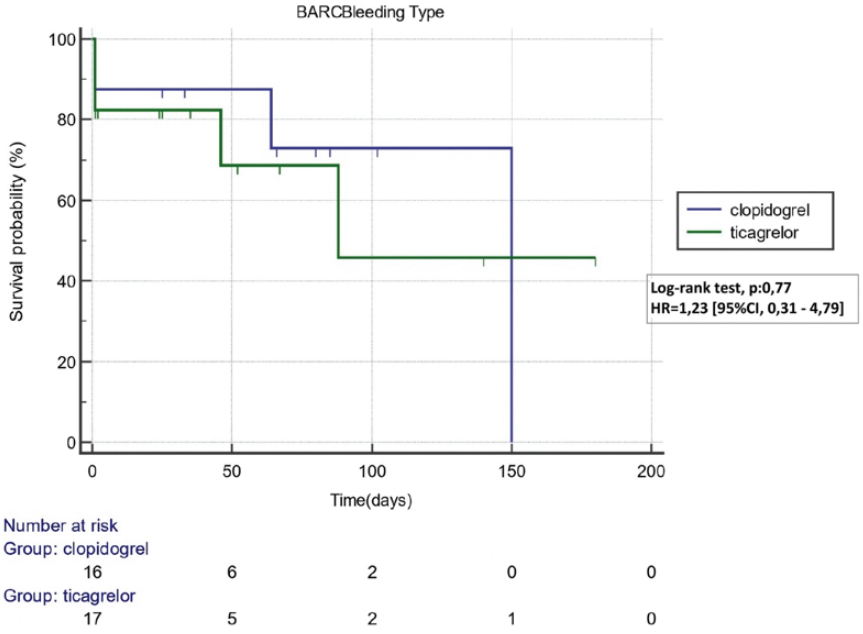

Figure 4: Graph of survival (survival) probabilities (%) vs. Time (BARC type 3-5/1-2).

As seen in Figure 5;
In this study, mortality was observed in 5 of 86 patients using clopidogrel and in 4 of 94 patients using ticagrelor (Log-rank test, p:0.63 HR=0.72 (95%CI, 0.19-2.67)). Accordingly, the statistical result indicates that the survival curves did not differ significantly, or the factor (P2Y12 inhibitor) variable did not have a substantial effect on the time to exitus (p>0.05).

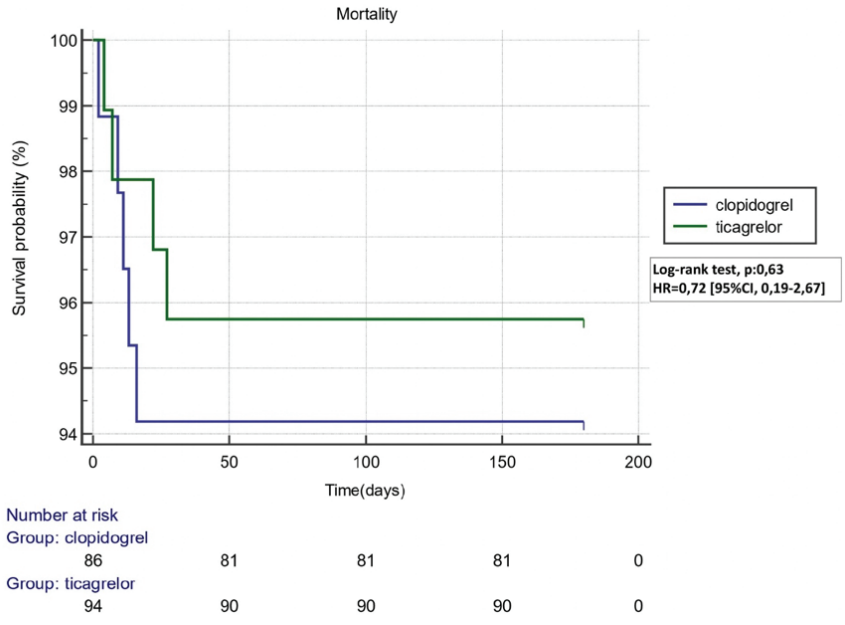

Figure 5: Graph of survival (survival) probabilities (%) vs. Time (Mortality).

DISCUSSION

In this study, we found the use of ticagrelor with fibrinolytic treatment was similar to clopidogrel in terms of MACCE, mortality, myocardial infarction, target artery revascularization, stroke, and severe bleeding (p>0.05).

Despite the decrease in the use of fibrinolytic in STEMI patients worldwide, fibrinolytic therapy continues to maintain its importance because there are still hospitals far from a PCI-capable center. As a result, updated information about STEMI patients treated with fibrinolytic is always needed. Although ticagrelor therapy provides many benefits compared to clopidogrel in reducing major cardiovascular events (MACE) in patients undergoing pPCI, data on its use with fibrinolytic are limited (27-29).

Therefore, new guidelines urge dual antiplatelet treatment with aspirin and clopidogrel in combination to fibrinolytic therapy in patients with STEMI (1,5,14,15). Use of ticagrelor was not recommended within 24 hours of fibrinolytic therapy due to the paucity of clinical studies supporting the safety of using ticagrelor with fibrinolytic in guidelines (1,5,14,15). Clinical studies of ticagrelor in STEMI patients receiving fibrinolytic have been done to fill this knowledge gap (16-20). Patients over 75 years of age were excluded from these studies, and some patients were switched to ticagrelor after using clopidogrel as first-line therapy. Ticagrelor was not advised for patients over 75 years of age treated with fibrinolytic.Our study is the first clinical trial to compare ticagrelor with clopidogrel simultaneously received with fibrinolytic in STEMI patients, including patients over 18 years of age (including 75 years of age), patients with CKD, and patients receiving rivaroxaban. The parameters in Table I in STEMI patients did not differ or correlate according to the P2Y12 inhibitor used, indicating no confounding effects between the patient groups (p>0.05). There was no difference or correlation between both the groups in terms of above 75 years of age, demographic and clinical characteristics, laboratory findings, left ventricular ejection fraction, MI type, GRACE risk score, symptom to needle time, failed thrombolytic ECG criteria, recurrent MI, BARC bleeding, and mortality (p>0.05). In STEMI patients younger than 75 years of age, similar TIMI major bleeding was detected within 30 days of a late switch from clopidogrel to ticagrelor after fibrinolytic therapy compared to patients who continued on clopidogrel (16).

According to the TREAT study, the 12-month major cardiovascular event rates of ticagrelor and clopidogrel were similar in fibrinolytic-treated STEMI patients younger than 75 years of age (17). Welsh RC et al., found that switching from clopidogrel to ticagrelor after fibrinolysis was associated with reduced recurrent ischemic events at one year. Additionally, in this study, there were no substantial differences between major bleeding and intracerebral hemorrhage (18). In the MIRTOS study, there was no substantial difference between the ticagrelor and clopidogrel treated randomized groups of STEMI patients receiving fibrinolytic therapy in terms of MACE and major bleeding events (19). Coner A. et al., determined that switching from clopidogrel to ticagrelor at 48 hours following fibrinolytic administration was similarly safe (MACE and major bleeding) in patients (20). In our study, there was no difference in patients aged 18-75 year groups including the risks of; in-hospital death, fatal bleeding, barc bleeding type (3-5/1-2), intracranial bleeding, mortality, stroke, target vessel revascularization, and recurrent mi in those treated with ticagrelor compared with clopidogrel (p>0.05). There was no statistically significant difference between the ticagrelor and clopidogrel groups of major bleeding and mortality (major bleeding: Log-rank test, p:0.77 HR=1.23 (95% CI, 0.31 - 4.79) (mortality: Log-rank test, p:0.63 HR=0.72 (95%) CI, 0.19-2.67). We found that the concomitant administration of ticagrelor in STEMI patients who preferred pharmacoinvasive reperfusion therapy was safe for six months.

In a clinical study evaluating the factors affecting the in-hospital mortality of patients given fibrinolytic for STEMI, it was found that patients who developed mortality had high rates of CKD, diabetes mellitus (DM), GRACE score, Killip class 3-4, and had low LVEF found (30). Although the group of CKD patients using clopidogrel was associated with mortality in our study, it was not linked to patients using ticagrelor (p:0.051 p:0.99). There was no correlation between LVEF value, GRACE risk score, age, and history of diseases with mortality. Although the use of ticagrelor was not linked to major bleeding in patient groups with a high GRACE risk score, the use of clopidogrel was associated with increased major bleeding. Therefore, we determined that ticagrelor administration in addition to fibrinolytic therapy is safer than clopidogrel in patients with high GRACE risk scores. Considering its relationship with mortality, although major bleeding in patients using clopidogrel was not associated with mortality, major bleeding in the group of patients using ticagrelor had higher mortality.

In a trial comparing the effectiveness and safety of ticagrelor against clopidogrel in STEMI patients aged 75 and up, ticagrelor was linked to a lower risk of major cardiac and cerebrovascular events (MACCE) (31). However, it did not differ in terms of 1-year mortality and bleeding events. While there was no association with stroke in patients over 75 years of age using clopidogrel, it was linked to stroke in patients using ticagrelor (p>0.05 p<0.05, respectively). There is a paucity of evidence on the use of P2Y12 inhibitors in addition to fibrinolytic treatment in STEMI patients with chronic kidney disease (16,17). Studies have excluded patients with CKD (16,17). Since the administration of fibrinolytic in CKD patients is not a major contraindication, we included CKD patients in our study. Information in the literature regarding the use of fibrinolytic in CKD patients is generally based on experience with patients given alteplase (TPA) due to ischemic blood flow. There are currently no clinical studies comparing the use of ticagrelor and clopidogrel in CKD patients undergoing fibrinolytic treatment for STEMI (32,33). Although there are studies in the literature that reported increased major bleeding and mortality in CKD patients treated with fibrinolytic agents for ischemic stroke, there are also studies that concluded that CKD did not affect adverse outcomes such as major bleeding and death. In our study, although GFR <60 mL/min/1.73 m², was not associated with major bleeding and mortality in patients using ticagrelor, an increase was found in major bleeding and mortality in those using clopidogrel. We found that ticagrelor is a safer

alternative than clopidogrel in CKD patients medicated with fibrinolytic. In STEMI patients, Mega JL et al. discovered that using aspirin, clopidogrel, or rivaroxaban decreased the risk of mortality, heart attack, or stroke owing to cardiovascular events, and there was no substantial elevated risk of lethal bleeding when compared to placebo (34). No patients were using fibrinolytic in this clinical study, nor were there any use of ticagrelor. Our study compared ticagrelor and clopidogrel in patients using rivaroxaban revealed no relationship with major bleeding and mortality. Co-administration of a potent antiplatelet agent such as ticagrelor along with fibrinolysis may result in an increased risk of bleeding. While the MACCE and major bleeding results of studies to date have been encouraging, evidence for concomitant use of ticagrelor and fibrinolytic is still lacking. The studies have done so far may encourage more comprehensive studies. Limitations: Four patients were ruled out of the research due to the difficulty of following up on patients whose places of residence changed. Due to the 6-month follow-up of our patients, we could not comment on the 12-month effects. The most rigorous way to evaluate the benefits of treatment is through randomized controlled clinical trials. Due to the small number of patients, our results cannot be generalized but may be informative for future large-scale randomized clinical trials.

CONCLUSION

In STEMI patients, regardless of being over or under 75, ticagrelor therapy given concurrently with fibrinolytic therapy is comparable to clopidogrel including all mortality, major cardiovascular events, stroke, recurrent MI, target artery revascularization, and major bleeding. In conclusion, compared to clopidogrel, ticagrelor shows a similar safety profile over six months in STEMI patients treated with fibrinolytic.

Ethics Committee Approval:
The study was approved, and the requirement for informed consent was waived by the Ethics Commission. (No: 2021-208- decision number:11/6 Date: 05th August 2021). The study was conducted in line with the Declaration of Helsinki.
Work permit and data usage permission were approved by the management of Cizre Dr.Selahattin CIZRELIOGLU State Hospital (No: 84410283/469/E-84410283-469-623 Date: 27 July 2021)

Informed Consent:
Informed consent was not obtained as it was a retrospective clinical study.

Author Contributions:
Concept – M.D.,S.G.; Design - M.D.,S.G.; Supervision - M.D.,S.G.; Resources - M.D.,S.G.; Materials- C M.D.,S.G.; Data Collection and/or Processing - M.D.,S.G.; Analysis and/ or Interpretation - M.D.,S.G.; Literature Search - M.D.,S.G.; Writing Manuscript - M.D.,S.G.;; Critical Review - M.D.,S.G.
Conflict of Interest: The authors have no conflict of interest to declare.

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