Int J Cardiovasc Sci. 2024; 37:e20230070

ORIGINAL ARTICLE

Effect of Ticagrelor on Left Ventricular Function in Patients with Mildly Reduced Ejection Fraction after Acute Myocardial Infarction

Ilkin Guliyev,[1] Engin Algül,[2] Gökhan Gökalp,[3] Faruk Aydınyılmaz,[4] Nail Burak Özbeyaz,[3] Hamza Sunman[2]

Gumushane State Hospital, Cardiology,[1] Gumushane – Turkey
Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Cardiology,[2] Ankara – Turkey
Pursaklar State Hospital,[3] Ankara – Turkey
Erzurum Regional Education and Research Hospital,[4] Erzurum – Turkey

Abstract

Background: There are limited data about the effect of new $P2Y_{12}$ inhibitors on left ventricular ejection fraction (LVEF) after acute myocardial infarction (AMI).

Objectives: We aimed to investigate the effect of ticagrelor on left ventricular function, compared to clopidogrel in patients with heart failure with mildly reduced ejection fraction (HFmrEF) after AMI.

Methods: In this cross-sectional, single-center study, we included 251 patients with LVEF between 40% and 50% after AMI before discharge. The patients were divided into 2 groups according to the use of ticagrelor (166 patients) and clopidogrel (85 patients). At the end of the 12-month period, LVEF changes were assessed by echocardiography. $P < 0.05$ was considered statistically significant.

Results: The mean LVEF before discharge was 46.5% ± 3.6%, and no difference was observed between the ticagrelor and clopidogrel groups ($p = 0.20$). At the end of the first year, the mean LVEF of the patients increased to 49.8% ± 7.6% in both groups. The use of ticagrelor (β ± SE = 2.05 ± 0.93; $p = 0.029$), low creatinine level (β ± SE = −10.44 ± 2.35; $p < 0.001$), low troponin level (β ± SE = −0.38 ± 0.14; $p = 0.006$), and low heart rate (β ± SE = −0.98 ± 0.33; $p = 0.003$) were found to be independent predictors of the increase in LVEF (β ± SE 2.05 ± 0.93; 95% confidence interval: 0.21 to 3.90; $p = 0.029$).

Conclusion: In our study, ticagrelor improved left ventricular function in 12 months follow-up compared to clopidogrel in patients with HFmrEF after AMI.

Keywords: Acute Myocardial Infarction; Clopidogrel; Systolic Heart Failure; Ticagrelor.

Introduction

Ischemic heart disease is a leading cause of heart failure, which often develops as a complication of acute myocardial infarction (AMI).[1] The treatment of AMI has improved dramatically in recent decades with the advent of early reperfusion strategies, including percutaneous coronary intervention and evidence-based pharmacotherapies.[2-4]

Left ventricular ejection fraction (LVEF) is a significant parameter that determines early- and long-term prognosis after AMI.[5, 6] In addition to revascularization, morbidity and mortality advantages have been achieved with medical treatments such as beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, and statins. Current guidelines differentiate heart failure into 3 groups: reduced ejection fraction, mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction.[7] While recent studies in patients with AMI and heart failure with low LVEF are promising, the expected results of studies about heart failure with mildly reduced and preserved LVEF have yet to be achieved.[8, 9]

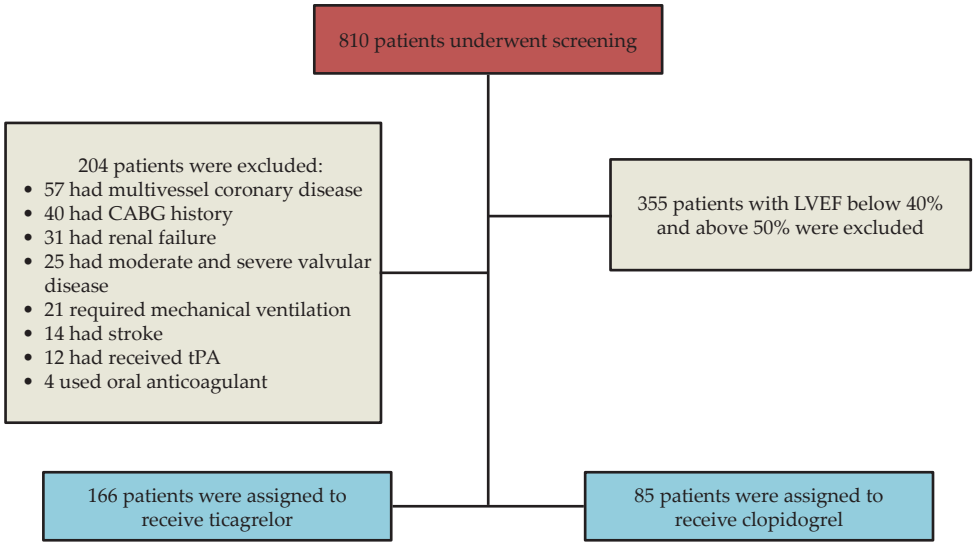
Mailing Address: Ilkin Guliyev
Medical Park Hospitals Group, Cardiology. Tokat Tokat, 60100 – Turkey
E-mail: quliyevilkin@gmail.com

DOI: https://doi.org/10.36660/ijcs.20230070

Manuscript received May 2, 2023; revised manuscript November 14, 2023; accepted December 13, 2023.

Central Illustration: Effect of Ticagrelor on Left Ventricular Function in Patients with Mildly Reduced Ejection Fraction after Acute Myocardial Infarction

INTERNATIONAL JOURNAL OF Cardiovascular SCIENCES



Changes in follow-up of patients with HFmrEF

	Overall n = 251	Clopidogrel group n = 85		Ticagrelor group n = 166	
Baseline LVEF (%)	46.5±3.6	46.2±3.5	p=0.4	46.7±3.7	p=0.09
Final LVEF (%)	49.8±7.6	48.1±7.5		51.0±7.6	

Int J Cardiovasc Sci. 2024; 37:e20230070

CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; tPA tissue plasminogen activator.

New research and evaluation of the effects of treatment methods are especially necessary for HFmrEF.

It is well known that ticagrelor is one of the most important antiplatelet agents for AMI.[10] Although it is known that ticagrelor increased survival after AMI and was associated with an increase in LVEF, its effect on patients with HFmrEF is unknown. Ticagrelor has cardioprotective effects by increasing the level of adenosine in the blood, and it has been shown to reduce the infarct area and improve LVEF in animal models.[3,11,12] In addition, in the literature, patients with HFmrEF after AMI have been investigated for in-hospital and long-term prognosis, but there is no study investigating the effect of antiplatelet agents on LVEF in patients with HFmrEF.[13,14] For these reasons, we aimed to investigate the effect of ticagrelor on left ventricular function in patients with HFmrEF after AMI.

Methods

Study population

This retrospective, cross-sectional, single-center study included patients admitted to the Ankara Diskapi Yildirim Beyazit Training and Research Hospital for ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) between May 2016 and June 2018.

STEMI was diagnosed in patients with the presence of chest pain that was suggestive of myocardial ischemia for longer than 20 minutes, within 12 hours of symptom onset, and accompanied by a persistent new elevation of the ST segment on the electrocardiogram or new left bundle branch block.[4] NSTEMI was diagnosed in patients determined to have symptoms consistent with acute coronary syndrome and high troponin levels, but without electrocardiographic changes consistent with STEMI.[3]

According to the guidelines and clinical situation, loading dose of oral clopidogrel or ticagrelor with aspirin and weight-adjusted heparin were administered to each patient at the time of diagnosis.[3,4] Demographic and clinical characteristics, laboratory results, medical and therapeutic procedures, and past medical history were acquired from the hospital's electronic medical record management system. The medical treatment of the patients was planned according to the latest European Society of Cardiology Heart Failure guidelines,[7] and all patients were receiving an appropriate dose of beta-blockers, ACEI/ARB, and statin, in addition to dual antiplatelet therapy, unless they were contraindicated.

The medical ethics committees of the Diskapi Yildirim Beyazit Training and Research Hospital approved this study (November 12, 2018; number: 56/36).

Echocardiography

Study patients underwent echocardiography before hospital discharge and at the end of 12 months after revascularization. Both assessments were performed with Philips Healthcare iE33 xMATRIX Echocardiography (Philips Medical System, Andover, MA, United States) and S5-1 transducer in the left lateral decubitus position following the recommendations. All measurements were performed with single-lead, continuous electrocardiographic monitoring. In the parasternal long-axis section, baseline measurements such as left ventricular end-systolic and end-diastolic diameter, left atrial diameter, and wall thickness were taken. LVEF was measured using the modified Simpson method in images taken from the apical 2- and 4-chamber image window. Echocardiography was obtained by 2 echocardiography specialists.

Follow-up

The follow-up data were obtained from the national medical records database, and all hospital admissions during 12 months were investigated.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS), version 20 (IBM SPSS Inc., Chicago, IL, United States). The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. The normal distribution of numerical variables was shown as mean ± standard deviation, and abnormally distributed variables were shown as median (interquartile range). Categorical variables were expressed as numbers and percentages. Student's unpaired t test (between 2 independent groups) and Mann-Whitney U test (in non-normally distributed numerical variables) were used to determine the risk factors that differed between both groups. One-way ANOVA test (for normally distributed numerical variables) was used to detect risk factors that differed between the two groups. After conducting the one-way ANOVA, post hoc tests were employed to further explore group differences. Specifically, Tukey's test was utilized in cases where variances were homogeneous, while Tamhane's T2 test was applied in instances where variances were not equal. These post hoc tests were chosen to provide a comprehensive examination of pairwise group differences. The chi-square test was used to compare categorical data. To compare pre- and post-LVEF values in patients with mildly reduced LVEF, the t test was performed on dependent groups. The change between final LVEF (%) and baseline LVEF (%) was shown as delta LVEF (ΔEF). The relationship between ΔEF and numerical variables was analyzed by Spearman correlation analysis. Mixed model regression analysis was used to determine independent risk factors affecting ΔEF. During follow-up, in some patients, HFmrEF changed to low LVEF or preserved LVEF groups. Thus, the independent stepwise multivariate logistic regression model was used to investigate parameters associated with the transition of patients with HFmrEF to reduced LVEF or preserved LVEF groups. Possible risk factors found to be significant were included in the multivariate regression model. $P < 0.05$ was accepted as statistically significant. The interobserver agreement of echocardiography was assessed by measuring intraclass correlation coefficients.

Results

Initially, 810 patients with AMI were screened for successful ad-hoc revascularization of the culprit vessel and in-hospital staged complete revascularization. We included 251 patients with LVEF of 40% to 50% evaluated by echocardiography before discharge (48 to 72 hours after admission) in the analysis (Figure 1). The intraclass correlation coefficient between 2 echocardiographers was 0.91 (95% confidence interval 0.86 to 0.93) for LVEF.

All patients were treated with in-hospital staged complete revascularization. Baseline demographic, clinical, laboratory, and echocardiographic findings are

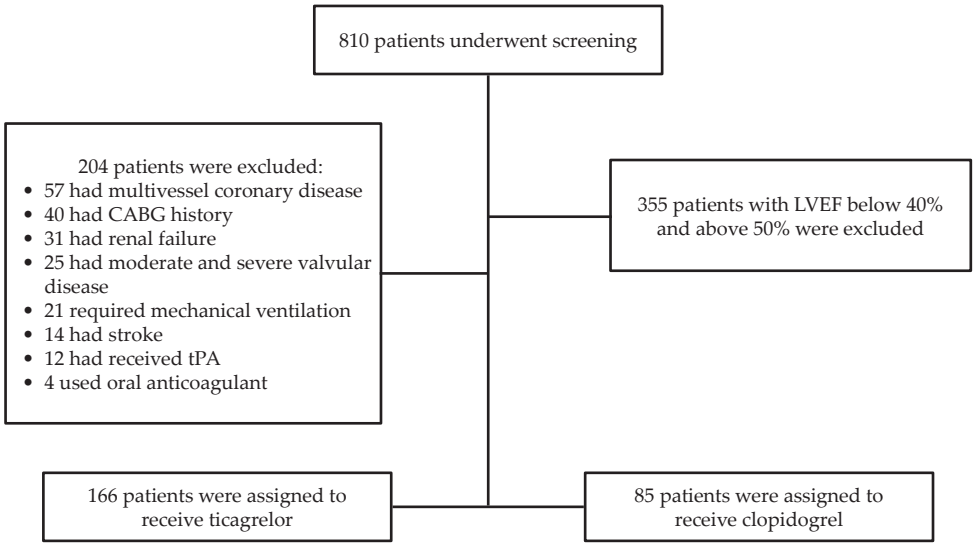


Figure 1 – Included and excluded patients.
CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; tPA tissue plasminogen activator.

shown in Table 1. The mean age of the patients was 61.5 ± 11.2 years. Type 2 diabetes, hypertension, body mass index, and use rates of ACEI/ARB and beta-blockers were similar between both groups.

Demographic characteristics, AMI type, and distribution ratio of antiplatelet therapy types did not differ significantly in patients whose LVEF decreased, remained unchanged, and increased at 12 months (Table 2). The mean LVEF before discharge was 46.5% ± 3.6% in both groups, and no difference was observed between the ticagrelor and clopidogrel groups. At the end of the first year, the mean LVEF of the patients increased to 49.8% ± 7.6% in both groups. During follow-up, LVEF fell below 40% in 14 (5.6%) patients, remained between 40% and 50% in 141 (56.2%), and increased to over 50% in 96 (38.2%). In the ticagrelor group, LVEF was decreased in 10 patients (6%) and increased in 69 (41.6%). In the clopidogrel group, LVEF was decreased in 4 patients (4.7%) and increased in 27 (31.8%) (Table 3; Figures 2 and 3).

The relationship between the change in LVEF after follow-up compared to the LVEF before discharge (ΔEF) and the demographic and clinical characteristics of the patients are shown in Table 4. The following factors were correlated with increased ΔEF: increased age, use of ticagrelor, low creatinine level, low troponin level, low heart rate, and decreased diameter of the left atrium. No other demographic and clinical findings were found to be correlated with ΔEF.

The following independent parameters affected the increase in ΔEF: ticagrelor use, low creatinine level, low troponin level, and low heart rate (Table 4). In the stepwise logistic regression model that included possible risk factors (creatinine, NT-proBNP) affecting the decreased LVEF during follow-up, creatinine and increased NT-proBNP were found to be independent risk factors affecting reduced LVEF (Table 5).

In the stepwise logistic regression model that included the possible risk factors (creatinine, 24-hour troponin, NT-proBNP, heart rate, and left atrium) that affected LVEF increase during follow-up, low creatinine level, NT-proBNP level, and low heart rate were found to be independent risk factors affecting increased LVEF (Table 5).

Discussion

In our study, we compared the effect of ticagrelor versus clopidogrel on LVEF in the 1-year follow-up of patients with HFmrEF after AMI. The results of this study show that patients receiving ticagrelor had more improvement in LVEF than those receiving clopidogrel. This is the first study in the literature evaluating the effect of antiaggregant therapy on LVEF in patients with HFmrEF after AMI.

Table 1 – Characteristics of the patients at baseline

Characteristic	Overall n = 251	Clopidogrel treatment group n = 85	Ticagrelor treatment group n = 166	P value
Age (years)	61.5±11.2	61±11.9	61.9±10.6	0.08
Female sex (n, %)	72 (28.7)	27 (31.8)	45 (27.1)	0.440
Medical history (n, %)				
Diabetes mellitus	80 (31.9)	31 (36.5)	49 (29.5)	0.263
Hypertension	121 (48.2)	45 (52.9)	76 (45.8)	0.283
Coronary artery disease	73 (29.1)	33 (38.7)	40 (24.1)	0.015
Smoker	129 (51.4)	34 (40)	95 (57.2)	0.01
Heart rate (beats/min)	76.8±14.2	77.8±14	76±14.3	0.419
Systolic blood pressure (mmHg)	133.2±27.8	129.1±27.9	135.5±27.7	0.098
Diastolic blood pressure (mmHg)	78.5±14.3	77±14.3	79.3±14.3	0.233
Body mass index† (kg/m^2)	27.8±4.6	27.8±4.2	27.8±4.8	0.925
Fasting plasma glucose (mg/dl)	125 (101-170)	118 (97-172)	128(103-168)	0.037
Hemoglobin (g/dl)	14.4±1.8	14.0±1.9	14.5±1.7	0.035
Leukocyte (10^3/uL)	10.9±3.5	10.4±3.1	11.3±3.7	0.002
Fasting total cholesterol (mg/dl)	188.3±41.4	192.9±38.2	186.2±42.8	0.449
Serum creatinine (mg/dl)	1.0±0.2	1.1±0.3	1.0±0.2	0.227
Median cardiac troponin level (ng/mL)	15.3 (4.2-43.5)	12.0 (1.4-35.0)	18.5 (5.1-61.7)	<0.001
Median N-terminal pro-B-type natriuretic peptide (pg/ml)	1171 (517-2649)	1812 (682-3807)	998 (469-2231)	0.750
Left ventricular variables				
LVEF (%)	46.54±3.6	46.18±3.5	46.7±3.7	0.257
End-diastolic diameter (cm)	5.4±0.3	5.5±0.3	5.5±0.3	0.01
Interventricular septum thickness (cm)	1.1±0.1	1.1±0.2	1.1±0.1	0.540
Posterior wall thickness (cm)	1.0±0.1	1.0±0.1	1.0±0.1	0.464
Left atrium diameter (cm)	3.6±0.3	3.7±0.3	3.6±0.3	<0.004
Clinical features of acute coronary syndrome (n, %)				
NSTEMI	83(33.1)	50(58.8)	33(19.9)	<0.001
STEMI	168(66.9)	35(41.2)	133(80.1)	

**Pilus-minus values are means ± standard deviation. †The body mass index is the weight in kilograms divided by the square of the height in meters. LVEF: Left ventricular ejection fraction. STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infaction*

Margolis et al.[14] compared in-hospital events and short- and long-term mortality rates of AMI patients with HFmrEF to other groups. The mean follow-up mortality rate of 3.5 years was higher in the HFmrEF group compared to the preserved LVEF group (9.8% versus 7.2%, $p < 0.01$), but lower than in the low LVEF group (29.8% versus 9.8%, $p < 0.001$). However, their study did not compare antiaggregant types or evaluate

Table 2 – LVEF change according to demographic and clinical characteristics

Variables	LVEF at 12 months of follow-up			p
	Worsened n = 14	Unchanged n = 141	Improved n = 96	
Age (years), mean±SD	66.2±13.7	62.8±11.2	61.6±11	0.328
Female sex (n, %)	7 (50.0)	39 (27.7)	26 (27.1)	0.220
Diabetes mellitus (n, %)	3 (21.4)	47 (33.3)	30 (31.3)	0.710
Hypertension (n, %)	8 (57.1)	64 (45.4)	49 (51.0)	0.533
Coronary artery disease (n, %)	5 (35.7)	47 (33.3)	21 (21.9)	0.125
Smoker (n, %)	7 (50.0)	71 (50.4)	51 (53.1)	0.911
Heart rate (bpm), mean ± SD	81±11.7	78.7±13.7	73.5±14.7	0.012*
Body mass index (kg/m²), mean ± SD	26.9±4.9	28±4.6	27.7±4.7	0.620
Serum creatinine (mg/dl), mean ± SD	1.3±0.4	1.1±0.3	0.9±0.2	0.004*
Antiplatelet (n, %)				
Clopidogrel	4 (28.6)	54 (38.3)	27 (28.1)	0.245
Ticagrelor	10 (71.4)	87 (61.7)	69 (71.9)	
AMI (n, %)				
NSTEMI	4 (28.6)	44 (31.2)	35 (36.5)	0.660
STEMI	10 (71.4)	97 (68.8)	61 (63.5)	

AMI: acute nyocardial infarciton; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; SD: standard deviation; STEMI: ST-elevation myocardial infarction.

Table 3 – Changes in follow-up of patients with HFmrEF

	Overall n = 251	Clopidogrel group n = 85		Ticagrelor group n = 166	
Baseline LVEF (%)	46.5±3.6	46.2±3.5	p = 0.4	46.7±3.7	p = 0.09
Final LVEF (%)	49.8±7.6	48.1±7.5		51.0±7.6	
LVEF variable					
Worsened	14(5.6%)	4(4.7%)		10(6.0%)	
Unchanged	141(56.2%)	54(63.5%)		87(52.4%)	
Improved	96(38.2%)	27(31.8%)		69(41.6%)	

**Changes in LVEF were categorized as follows: worsened: < 40%; unchanged: 40% to 50%; and improved ≥ 50%. LVEF: left ventricular ejection fraction*

left ventricular function in the follow-up. They showed that patients with HFmrEF after STEMI differed from other groups in terms of mortality and that patients in this group could be evaluated separately.

The most important study demonstrating the clinical utility of ticagrelor is the PLATO trial.[10] At the end of the study, the composite outcome of cardiovascular death, myocardial infarction, and stroke significantly

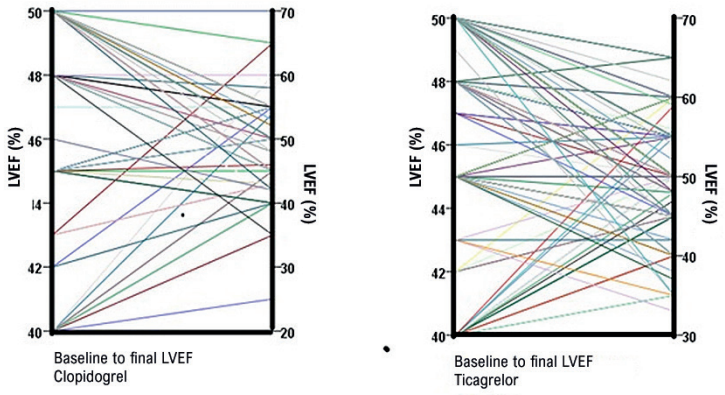


Figure 2 – Change from baseline LVEF (%) to final LVEF (%).
LVEF: left ventricular ejection fraction; EF: ejection fraction.

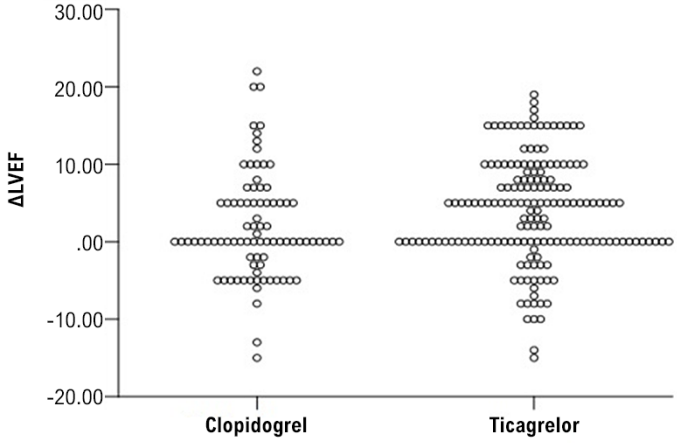


Figure 3 – Distribution of LVEF (%) change according to treatment groups.
ΔLVEF: final LVEF (%) – baseline LVEF (%); LVEF: left ventricular ejection fraction.

decreased (10.2% vs. 12.3%, p < 0.001) in the ticagrelor group compared to clopidogrel group at 30 days, and the absolute risk reduction achieved in the early period continued during the 1-year treatment. In the PLATO study, the reason why ticagrelor reduces all-cause mortality is not fully elucidated.

Previous studies[15,16] have shown that ticagrelor may have some pleiotropic effects, unlike clopidogrel. This effect is due to an increase in adenosine levels in patients using ticagrelor, and it has been shown that adenosine levels are higher than in patients receiving clopidogrel. Ticagrelor has an additional mechanism of action that increases local endogenous adenosine levels by inhibiting the balancing nucleoside transporter-1 (ENT-1: sodium-independent equilibrative nucleoside transporter 1). Ticagrelor does not have a significant direct effect on adenosine receptors (A1, A2A, A2B, A3).[17,18] Adenosine has several positive effects, such as vasodilatation, improved endothelial function, cardioprotection, platelet inhibition, ischemic preconditioning, and immune modulation, which may contribute to the clinical profile of ticagrelor.[19]

In the Acute Myocardial Infarction Study of Adenosine (AMISTAD) I and AMISTAD II studies, patients with STEMI had additional adenosine infusion after reperfusion, and the infarct area of the myocardium decreased.[20,21] However, in two other large studies, the benefit of intracoronary

Table 4 –Findings related to ΔEF

Characteristic	R	P value
Age	0.278	0.048
Body mass index	0.034	0.590
Female sex	−0.094	0.139
Smoker	0.055	0.383
Diabetes mellitus	0.009	0.888
Hypertension	0.071	0.263
Coronary artery disease	0.121	0.056
Ticagrelor	0.315	0.009
Hemoglobin	0.038	0.552
Fasting total cholesterol	0.197	0.146
Serum creatinine	−0.349	0.001
Troponin	−0.311	0.003
N-terminal pro-B-type natriuretic peptide	−0.302	0.037
STEMI	−0.006	0.926
End-diastolic diameter	0.046	0.514
Heart rate	−0.321	0.001
Systolic blood pressure	−0.070	0.271
Diastolic blood pressure	−0.104	0.102
Interventricular septum thickness	−0.042	0.514
Posterior wall thickness	−0.088	0.170
Left atrium diameter	−0.297	0.015

ΔEF: final LVEF (%) – baseline LVEF (%); LVEF: left ventricular ejection fraction; STEMI: ST-elevation myocardial infarction.

Table 5 – Independent predictors of LVEF increases and decreases

Characteristic	β±SE	95% CI	p
ΔEF (%)			
Ticagrelor	2.05±0.93	0.21 to 3.90	0.029
Serum creatinine	−10.44±2.35	−15.09 to 5.80	<0.001
Troponin	−0.38±0.14	−0.66 to 0.11	0.006
Heart rate	−0.98±0.33	−1.62 to 0.33	0.003
	R^2=0.283; p=0.017		
	OR	**95% CI**	**p**
Worsened LVEF			
Serum creatinine	1.30	1.06 to 1.58	0.017
N-terminal pro-B-type natriuretic peptide	1.09	1.02 to 1.18	0.045
	Nagelkerke R^2=0.225; p=0.001		
Improved LVEF			
Serum creatinine	0.09	0.02 to 0.53	0.007
N-terminal pro-B-type natriuretic peptide	0.87	0.77 to 0.98	0.020
Heart rate	0.97	0.95 to 0.99	0.006
	Nagelkerke R^2=0.331; p<0.001		

ΔEF: final LVEF (%) – baseline LVEF (%); CI: confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio; SE: standard error.

adenosine given before reperfusion in patients with STEMI was not found.[22,23] The negative result of these studies was attributed to the immediate destruction of adenosine in the circulation due to the short half-life. Cardioprotective effects are thought to occur due to chronic adenosine elevation in patients using ticagrelor.[24]

In addition to causing a chronic increase in the level of adenosine, ticagrelor also has immunomodulatory regulation properties such as pleiotropic action. In a study conducted on healthy volunteers, ticagrelor has been shown to significantly reduce plasma granulocyte colony-stimulating factor, interleukin-8, and Tumor Necrosis Factor (TNF-α) levels and to increase anti-inflammatory interleukin-10 levels, compared to placebo and clopidogrel.[25]

The adenosine-mediated pleiotropic effect of ticagrelor has also been demonstrated in animal studies. Nanhwan et al.[26] performed 30-minute ligation on ’coronary arteries in rats. They randomized the rats to ticagrelor and clopidogrel groups, and gave different doses of ticagrelor and clopidogrel to examine the area of myocardial infarction. The myocardial infarct area of ticagrelor-treated subjects was less than that of clopidogrel-treated subjects. This effect of ticagrelor has been reported to be associated with the upregulation of nitric oxide release and cyclooxygenase-2 activation from endothelium via adenosine. In the same study, rats receiving ticagrelor had significantly improved LVEF and decreased myocardial infarct area compared to clopidogrel after a 4-week

follow-up. This demonstrated that ticagrelor improves LVEF even in non-thrombotic coronary conditions.

In another study on pigs, subjects were randomized to groups of ticagrelor, clopidogrel, placebo, and ticagrelor with adenosine A1/A2 receptor antagonists (8-[p-sulfophenyl] theophylline for purifying the effects of adenosine) after AMI.[11] Subjects were examined by cardiac magnetic resonance imaging, and it was found that the use of ticagrelor significantly reduced myocardial infarction area and myocardial edema compared to clopidogrel. However, cardioprotective effects were not observed in the group that used ticagrelor and adenosine antagonists together.

Ticagrelor has been shown to induce the release of adenosine triphosphate (ATP) from human erythrocytes, leading to an increase in extracellular adenosine concentrations. Both adenosine and ATP play pivotal roles in promoting vasodilation.[27] Adenosine primarily achieves this by directly relaxing vascular smooth muscle cells, while ATP functions by stimulating the endothelium to release vasodilatory mediators, including nitric oxide, endothelial hyperpolarizing factor, and prostacyclin. This mechanism not only contributes to promoting myocardial perfusion, but also holds particular importance in the context of vessel damage or hypoxia.[28]

Ndrepepa et al. reported that patients who successfully restored normal blood flow following the no-reflow phenomenon (NRP) experienced an improvement in their LVEF compared to pre-NRP levels.[29] Additionally, they found that NRP occurrence could serve as an independent predictor of mortality. The ONSET/OFFSET study demonstrated that platelet inhibition was more rapid and greater with ticagrelor than clopidogrel.[30] It is believed that, by reducing platelet adhesion to debris, it may decrease the occurrence of microembolization and improve reperfusion. Several studies have reported that the preoperative administration of a loading dose of ticagrelor can decrease the occurrence of the NRP in the context of primary percutaneous coronary intervention and effectively enhance coronary blood reperfusion.[31]

In our study, we found improvement in left ventricular systolic function in patients with HFmrEF receiving ticagrelor after AMI. This study serves as a starting point, and it is imperative to conduct further comprehensive research to elucidate the intricacies of the topic.

Study limitations

Although this is the first study to investigate the effect of ticagrelor on LVEF in patients with HFmrEF, it has some limitations. Firstly, this is not a randomized study, and the measurement of LVEF with more reliable methods, such as global longitudinal strain and magnetic resonance imaging, could contribute to future studies. Secondly, STEMI ratio was higher in ticagrelor group. Thirdly, STEMI and NSTEMI were evaluated together and should be considered separately in future studies. Contrary to similar studies, having LVEF values after the follow-up period was a strength of our research, but the number of patients was relatively low. Given the limitations of our current study, it is evident that further comprehensive research is essential to provide a more robust understanding of this subject.

Conclusions

In our study, we found that ticagrelor significantly improved left ventricular systolic function in patients with mildly reduced LVEF after AMI compared to clopidogrel.

Author Contributions

Conception and design of the research: Guliyev I, Algül E; acquisition of data: Guliyev I, Gökalp G; analysis and interpretation of the data: Guliyev I, Algül E, Gökalp G; statistical analysis: Aydınyılmaz F, Özbeyaz NB; writing of the manuscript: Guliyev I; critical revision of the manuscript for intellectual content: Gökalp G, Aydınyılmaz F, Sunman H.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Diskapi Yildirim Beyazit Training and Research Hospital under the protocol number 56/36. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Roger VL. Epidemiology of Heart Failure. Circ Res. 2013;113(6):646-59. doi: 10.1161/CIRCRESAHA.113.300268.

2. Raposeiras-Roubín S, Abu-Assi E, López-López A, Bouzas-Cruz N, Castiñeira-Busto M, Cambeiro-González C, et al. Risk Stratification for the Development of Heart Failure after Acute Coronary Syndrome at the Time of Hospital Discharge: Predictive Ability of GRACE Risk Score. J Cardiol. 2015;66(3):224-31. doi: 10.1016/j.jjcc.2014.12.015.

3. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation. Eur Heart J. 2021;42(14):1289-367. doi: 10.1093/eurheartj/ehaa575.

4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77. doi: 10.1093/eurheartj/ehx393.

5. Multicenter Postinfarction Research Group. Risk Stratification and Survival after Myocardial Infarction. N Engl J Med. 1983;309(6):331-6. doi: 10.1056/NEJM198308113090602.

6. Halkin A, Singh M, Nikolsky E, Grines CL, Tcheng JE, Garcia E, et al. Prediction of Mortality after Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: The CADILLAC Risk Score. J Am Coll Cardiol. 2005;45(9):1397-405. doi: 10.1016/j.jacc.2005.01.041.

7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.

8. Harper AR, Patel HC, Lyon AR. Heart Failure with Preserved Ejection Fraction. Clin Med. 2018;18(Suppl 2):s24-s29. doi: 10.7861/clinmedicine.18-2-s24.

9. Reed BN, Sueta CA. A Practical Guide for the Treatment of Symptomatic Heart Failure with Reduced Ejection Fraction (HFrEF). Curr Cardiol Rev. 2015;11(1):23-32. doi: 10.2174/15748847086661311 17125508.

10. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2009;361(11):1045-57. doi: 10.1056/NEJMoa0904327.

11. Vilahur G, Gutiérrez M, Casani L, Varela L, Capdevila A, Pons-Lladó G, et al. Protective Effects of Ticagrelor on Myocardial Injury after Infarction. Circulation. 2016;134(22):1708-19. doi: 10.1161/CIRCULATIONAHA.116.024014.

12. Cattaneo M, Schulz R, Nylander S. Adenosine-Mediated Effects of Ticagrelor: Evidence and Potential Clinical Relevance. J Am Coll Cardiol. 2014;63(23):2503-9. doi: 10.1016/j.jacc.2014.03.031.

13. Karabağ Y, Çınar T, Çağdaş M, Rencüzoğulları İ, Tanık VO. In-Hospital and Long-Term Prognoses of Patients with a Mid-Range Ejection Fraction after an ST-Segment Myocardial Infarction. Acta Cardiol. 2019;74(4):351-8. doi: 10.1080/00015385.2018.1501140.

14. Margolis G, Khoury S, Ben-Shoshan J, Letourneau-Shesaf S, Flint N, Keren G, et al. Prognostic Implications of Mid-Range Left Ventricular Ejection Fraction on Patients Presenting with ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2017;120(2):186-90. doi: 10.1016/j.amjcard.2017.04.005.

15. Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromonot J, et al. Ticagrelor Increases Adenosine Plasma Concentration in Patients with an Acute Coronary Syndrome. J Am Coll Cardiol. 2014;63(9):872-7. doi: 10.1016/j.jacc.2013.09.067.

16. Jeong HS, Kim JH, Hong SJ. Pleiotropic Effects of Ticagrelor Beyond its Potent Antiplatelet Effects Contributing to Additional Clinical Benefits. JACC Cardiovasc Interv. 2018;11(17):1785. doi: 10.1016/j.jcin.2018.06.016.

17. Eltzschig HK, Faigle M, Knapp S, Karhausen J, Ibla J, Rosenberger P, et al. Endothelial Catabolism of Extracellular Adenosine During Hypoxia: The Role of Surface Adenosine Deaminase and CD26. Blood. 2006;108(5):1602-10. doi: 10.1182/blood-2006-02-001016.

18. Hack B, Witting PK, Rayner BS, Stocker R, Headrick JP. Oxidant Stress and Damage in Post-Ischemic Mouse Hearts: Effects of Adenosine. Mol Cell Biochem. 2006;287(1-2):165-75. doi: 10.1007/s11010-005-9093-3.

19. Cattaneo M, Schulz R, Nylander S. Adenosine-Mediated Effects of Ticagrelor: Evidence and Potential Clinical Relevance. J Am Coll Cardiol. 2014;63(23):2503-9. doi: 10.1016/j.jacc.2014.03.031.

20. Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, et al. Adenosine as an Adjunct to Thrombolytic Therapy for Acute Myocardial Infarction: Results of a Multicenter, Randomized, Placebo-Controlled Trial: The Acute Myocardial Infarction STudy of ADenosine (AMISTAD) Trial. J Am Coll Cardiol. 1999;34(6):1711-20. doi: 10.1016/s0735-1097(99)00418-0.

21. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW; AMISTAD-II Investigators. A Randomized, Double-Blinded, Placebo-Controlled Multicenter Trial of Adenosine as an Adjunct to Reperfusion in the Treatment of Acute Myocardial Infarction (AMISTAD-II). J Am Coll Cardiol. 2005;45(11):1775-80. doi: 10.1016/j.jacc.2005.02.061.

22. Desmet W, Bogaert J, Dubois C, Sinnaeve P, Adriaenssens T, Pappas C, et al. High-Dose Intracoronary Adenosine for Myocardial Salvage in Patients with Acute ST-Segment Elevation Myocardial Infarction. Eur Heart J. 2011;32(7):867-77. doi: 10.1093/eurheartj/ehq492.

23. Fokkema ML, Vlaar PJ, Vogelzang M, Gu YL, Kampinga MA, de Smet BJ, et al. Effect of High-Dose Intracoronary Adenosine Administration During Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction: A Randomized Controlled Trial. Circ Cardiovasc Interv. 2009;2(4):323-9. doi: 10.1161/CIRCINTERVENTIONS.109.858977.109.858977.

24. Kloner RA. Current State of Clinical Translation of Cardioprotective Agents for Acute Myocardial Infarction. Circ Res. 2013;113(4):451-63. doi: 10.1161/CIRCRESAHA.112.300627.

25. Thomas MR, Outteridge SN, Ajjan RA, Phoenix F, Sangha GK, Faulkner RE, et al. Platelet P2Y12 Inhibitors Reduce Systemic Inflammation and Its Prothrombotic Effects in an Experimental Human Model. Arterioscler Thromb Vasc Biol. 2015;35(12):2562-70. doi: 10.1161/ATVBAHA.115.306528.

26. Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, Birnbaum Y. Chronic Treatment with Ticagrelor Limits Myocardial Infarct Size: An Adenosine and Cyclooxygenase-2-Dependent Effect. Arterioscler Thromb Vasc Biol. 2014;34(9):2078-85. doi: 10.1161/ATVBAHA.114.304002.

27. Ohman J, Kudira R, Albinsson S, Olde B, Erlinge D. Ticagrelor Induces Adenosine Triphosphate Release from Human Red Blood Cells. Biochem Biophys Res Commun. 2012;418(4):754-8. doi: 10.1016/j.bbrc.2012.01.093.

28. van Giezen JJ, Sidaway J, Glaves P, Kirk I, Björkman JA. Ticagrelor Inhibits Adenosine Uptake in Vitro and Enhances Adenosine-Mediated Hyperemia Responses in a Canine Model. J Cardiovasc Pharmacol Ther. 2012;17(2):164-72. doi: 10.1177/1074248411410883.

29. Ndrepepa G, Tiroch K, Keta D, Fusaro M, Seyfarth M, Pache J, et al. Predictive Factors and Impact of no Reflow after Primary Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction. Circ Cardiovasc Interv. 2010;3(1):27-33. doi: 10.1161/CIRCINTERVENTIONS.109.896225.

30. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Patients with Stable Coronary Artery Disease: The ONSET/OFFSET Study. Circulation. 2009;120(25):2577-85. doi: 10.1161/CIRCULATIONAHA.109.912550.

31. Dai W, Ye Z, Li L, Su Q. Effect of Preoperative Loading Dose Ticagrelor and Clopidogrel on no-Reflow Phenomenon During Intervention in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. Drug Des Devel Ther. 2018;12:2039-49. doi: 10.2147/DDDT.S165431.