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Effect of Ticagrelor on Left Ventricular Remodeling in Patients With ST-Segment Elevation Myocardial Infarction (HEALING-AMI)

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the effect of ticagrelor versus clopidogrel on left ventricular (LV) remodeling after reperfusion of ST-segment elevation myocardial infarction (STEMI) in humans.

BACKGROUND Animal studies have demonstrated that ticagrelor compared with clopidogrel better protects myocardium against reperfusion injury and improves remodeling after myocardial infarction.

METHODS In this investigator-initiated, randomized, open-label, assessor-blinded trial performed at 10 centers in Korea, patients were enrolled if they had naive STEMI successfully treated with primary percutaneous coronary intervention (PCI) and at least 6-month planned duration of dual-antiplatelet treatment. The coprimary endpoints were LV remodeling index (LVRI) (a relative change of LV end-diastolic volume) measured on 3-dimensional echocardiography and N-terminal pro–B-type natriuretic peptide level at 6 months.

RESULTS Among initially enrolled patients with STEMI (n = 336), 139 in each group completed the study. LVRI at 6 months was numerically lower with ticagrelor versus clopidogrel (0.6 ± 18.6% vs. 4.5 ± 16.5%; p = 0.095). Ticagrelor significantly reduced the 6-month level of N-terminal pro-B-type natriuretic peptide (173 ± 141 pg/ml vs. 289 ± 585 pg/ml; p = 0.028). These differences were prominent in patients with pre-PCI TIMI (Thrombolysis In Myocardial Infarction) flow grade 0. By multivariate analysis, ticagrelor versus clopidogrel reduced the risk for positive LV remodeling (LVRI >0%) (odds ratio: 0.56; 95% confidence interval: 0.33 to 0.95; p = 0.030). The LV end-diastolic volume index remained unchanged during ticagrelor treatment (from 54.7 ± 12.2 to 54.2 ± 12.2 ml/m^2; p = 0.629), but this value increased over time during clopidogrel treatment (from 54.6 ± 11.3 to 56.4 ± 13.9 ml/m^2; p = 0.056) (difference −2.3 ml/m^2; 95% confidence interval: −4.8 to 0.2 ml/m^2; p = 0.073). Ticagrelor reduced LV end-systolic volume index (from 27.0 ± 8.5 to 24.7 ± 8.4 ml/m^2; p < 0.001), whereas no reduction was seen with clopidogrel (from 26.2 ± 8.9 to 25.6 ± 11.0 ml/m^2; p = 0.366) (difference −1.8 ml/m^2; 95% confidence interval: −3.5 to −0.1 ml/m^2; p = 0.040).

CONCLUSIONS Ticagrelor was superior to clopidogrel for LV remodeling after reperfusion of STEMI with primary PCI. (High Platelet Inhibition With Ticagrelor to Improve Left Ventricular Remodeling in Patients With ST Segment Elevation Myocardial Infarction [HEALING-AMI]; NCT02224534) (J Am Coll Cardiol Intv 2020;13:2220–34)

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Impaired left ventricular (LV) systolic function after acute myocardial infarction (AMI) is the most important cause of congestive heart failure and a major determinant of long-term prognosis (1–3). Of note, the prevalence of HF is projected to increase from approximately 6 million to more than 8 million patients by 2030 in the United States (1). Advances in mechanical and pharmacological management have markedly reduced short-term mortality in patients with AMI (1–3). However, the reduction of short-term mortality with timely reperfusion therapy without optimal long-term therapeutic strategies has paradoxically increased the incidence of congestive heart failure, mainly because of adverse LV remodeling (4). Consequently, the quest to facilitate post-infarction LV repair is an area of ongoing investigation.

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Myocardial wound healing following AMI is a complex process, which might precipitate adverse LV remodeling, LV dysfunction, and debilitating congestive heart failure (4). During this process, the monocyte is the key cell line for myocardial injury, repair, and remodeling (5). Although inflammatory cells promote cardiac repair by mobilizing fibroblasts into the interstitial space and facilitating angiogenesis, persistent inflammatory milieu in the infarct myocardium incurs adverse LV remodeling or ventricular aneurysm. In addition, platelets also play a pivotal role in promoting systemic and cardiac inflammatory responses following myocardial infarction (MI) (6,7). Consequently, platelets that accumulate within infarcted myocardium contribute to regional inflammation, LV remodeling, and rupture. This suggests a cardioprotective potential of antiplatelet agents after AMI (8–11). In animal studies, ticagrelor reduced post-MI myocardial damage compared with clopidogrel, through lesser expression of inflammation markers, attenuation of infarct size and fibrosis, and favorable effects on LV remodeling (8–11).

In human myocardium, it is still uncertain if antiplatelet treatments have favorable influence on cardiac remodeling after AMI. The REMODELING (Role of Platelet Reactivity in LV Remodeling After ST-Segment Elevation Myocardial Infarction) study first suggested a close relationship between platelet reactivity and the risk for subsequent LV remodeling in patients with ST-segment elevation MI (STEMI) during clopidogrel treatment (7). A meta-analysis showed that compared with clopidogrel, potent oral $P2Y_{12}$ inhibitors might prevent ventricular arrhythmia, congestive heart failure admission, and cardiogenic shock (12). However, there has been no human study to prove the association between antiplatelet regimens and adverse post-MI LV remodeling. Therefore, we sought to investigate whether ticagrelor treatment might be superior to clopidogrel treatment in terms of LV remodeling in patients with STEMI.

ABBREVIATIONS AND ACRONYMS

3DE = 3-dimensional echocardiography

AMI = acute myocardial infarction

CI = confidence interval

LV = left ventricular

LVEDV = LV end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = LV end-systolic volume

MI = myocardial infarction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OR = odds ratio

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

METHODS

STUDY DESIGN AND PATIENTS. The HEALING-AMI (High Platelet Inhibition With Ticagrelor to Improve Left Ventricular Remodeling in Patients With ST-Segment Elevation Myocardial Infarction) study (NCT02224534) was a prospective, randomized, open-label, blinded-endpoint, multicenter trial conducted at 10 academic centers in South Korea. The study protocol was approved by the Institutional Review Board of each center. All participants provided written informed consent at the time of enrollment. An independent data and safety monitoring committee reviewed the safety profile. Study monitoring for patients was done by external service provider (C&R Research, Seoul, Korea). The study adhered to the

and the [l]Singapore National University Heart Center, Singapore National University Hospital, Singapore, Singapore. *Drs. Y. Park and Koh contributed equally to this paper. This study is supported by research grants from AstraZeneca Korea and the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT, and Future Planning (NRF-2015R1A5A2008833). The HEALING-AMI study was an investigator-initiated study with a research grant from AstraZeneca Korea. However, the company had no role in protocol development, study management, data collection, or data analysis other than financial sponsorship. Dr. Jeong has received honoraria for lectures from AstraZeneca, Sanofi, Daiichi-Sankyo/Lilly, Haemonetics, Otsuka, Han-mi Pharmaceuticals, and Yuhan Pharmaceuticals; and has received research grants or support from AstraZeneca, Haemonetics, Han-mi Pharmaceuticals, and Yuhan Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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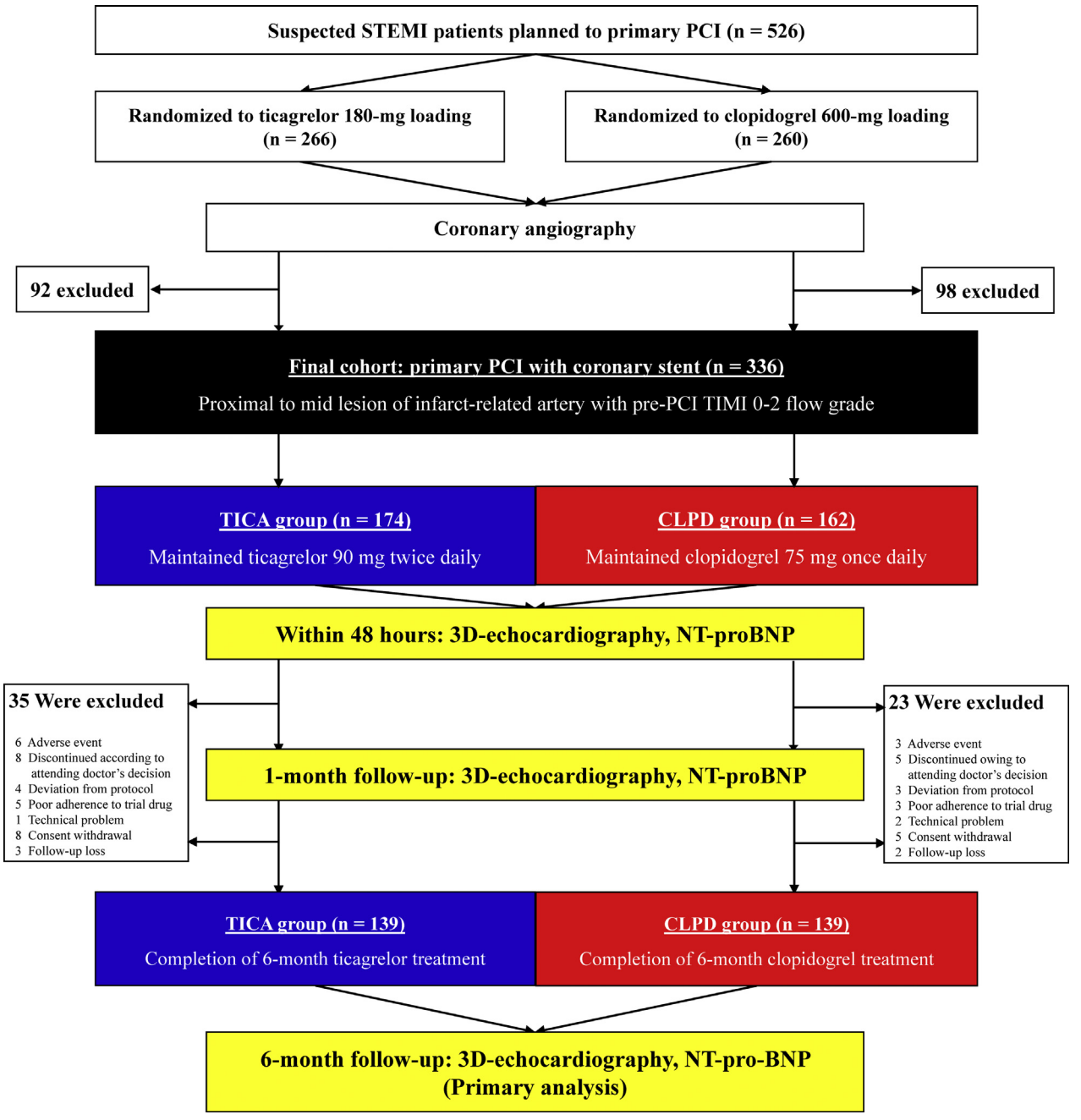
FIGURE 1 Study Design



3D = 3-dimensional; CLPD = clopidogrel; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TICA = ticagrelor; TIMI = Thrombolysis In Myocardial Infarction.

ethical principles of the Declaration of Helsinki, to specifications of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and to Good Clinical Practice.

Patients were eligible for the initial randomization if they had suspected naive STEMI (2). If patients showed cardiogenic shock or atrial fibrillation at the enrollment stage, they were excluded from the initial randomization. The Supplemental Appendix

(Supplemental Table S1) lists all inclusion and exclusion criteria; the study protocol and further details were published previously (13).

RANDOMIZATION. If all eligible clinical criteria were met and the written informed consent was obtained in the emergency department, patients were randomly assigned to 180 mg ticagrelor or 600 mg clopidogrel loading (1:1 fashion) in the emergency department before the index percutaneous coronary intervention (PCI), on the basis of computer-generated sequential block randomization (**Figure 1**). All patients also received 300 mg aspirin orally whether taking it previously or not.

PROCEDURES. All PCI procedures were performed according to the standard technique (2). We finally enrolled patients with naive STEMI undergoing uneventful primary PCI (final treatment arms) for the infarct-related artery located in the proximal or midportion of a major epicardial coronary artery with TIMI (Thrombolysis In Myocardial Infarction) flow grade 0, 1, or 2 at the time of coronary angiography (**Figure 1**). If PCI was performed for other lesions or the infarct-related artery was not suitable for PCI, patients were excluded from the final arm.

Following procedures, patients initially treated with ticagrelor loading received ticagrelor 90 mg twice daily, whereas those first assigned to clopidogrel loading maintained with clopidogrel 75 mg once daily during the entire study period. Aspirin was continued at 100 mg once daily indefinitely for both groups. All patients were treated with the guideline-recommended optimal pharmacological therapy.

During 6-month follow-up, data regarding clinical status and adverse events were collected at 1, 3, and 6 month(s). Adherence to pharmacological therapy (e.g., aspirin and $P2Y_{12}$ inhibitor) was also assessed by meticulous interview, tablet counting, and dedicated questionnaires.

LV REMODELING MEASUREMENTS. To assess the sequential post-MI LV remodeling process, 3-dimensional echocardiography (3DE) was performed and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured within 48 h post-PCI and at 1- and 6-month follow-up. Three-dimensional echocardiography is widely accepted and has shown higher levels of agreement with cardiac magnetic resonance over unenhanced 2-dimensional echocardiography for LV volumes and LV ejection fraction (LVEF) (14). Because neurohumoral activation, best represented by NT-proBNP level, is closely correlated with infarct size and LV dysfunction in patients with STEMI, this scale can provide powerful prognostic information regarding clinical outcome and recovery of LV dysfunction (15).

Real-time 3DE. Standard echocardiographic recordings and calculations were performed in a standardized manner using Vivid E9 echocardiographic machines (GE Vingmed Ultrasound, Horten, Norway) and stored in a digital format. LVEF, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) were measured according to previously published details (16) (Supplemental Figure S1).

LV remodeling index was calculated as the relative change in LVEDV seen at 6-month follow-up compared with baseline. Positive LV remodeling (LV remodeling index >0%) indicated an increase in LVEDV between baseline and 6-month follow-up. In addition, pathological LV remodeling (LV remodeling index >20%) was defined as an increase of more than 20% in LVEDV over 6 months (7). As the reference values of LV volumes are significantly influenced by body mass, indexed values of LVEDV or LVESV were used for analysis (16).

NT-proBNP. NT-proBNP was measured using an electrochemiluminescent immunoassay using an Elecsys 2010 instrument (Roche Diagnostics, Mannheim, Germany) at each study center. The NT-proBNP assay had intra-assay precision between 1.2% and 1.5% and interassay precision between 4.4% and 5.0%. During the trial in progress, we revised the protocol to include the level of NT-proBNP as another primary endpoint on the basis of our pivotal analysis (17); 263 patients (94.6% of the total cohort) had available data regarding this biomarker.

PLATELET FUNCTION TEST. To compare the level of platelet aggregation during the assigned treatment, the VerifyNow $P2Y_{12}$ assay (Accriva, San Diego, California) was performed at the time of PCI (immediately after arterial sheath insertion), before hospital discharge, and at 1-month follow-up. This assay is a whole-blood, point-of-care, turbidimetric optical detection assay designed to measure agonist-induced platelet aggregation (7,13). Blood samples were collected in 3.2% citrate Vacuette tubes (Greiner Bio-One Vacuette North America, Monroe, North Carolina). The measurement protocol followed the manufacturer's recommendation, and the details are described elsewhere (7,13). The cartridge contains fibrinogen-coated polystyrene beads, 20 μmol/l adenosine diphosphate, and 22 nmol/l prostaglandin E_1; the optical signal of this channel is reported as $P2Y_{12}$ reaction units. High platelet reactivity was defined as $P2Y_{12}$ reaction units >208, on the basis of the consensus document (18).

TABLE 1 Baseline Clinical and Angiographic Characteristics

	Ticagrelor Group (n = 139)	Clopidogrel Group (n = 139)	p Value
Age, yrs	58.7 ± 10.9	58.1 ± 10.9	0.622
Male	120 (86.3)	121 (87.1)	0.860
BMI, kg/m^2	24.8 ± 3.1	24.8 ± 2.9	0.964
Symptom-to-balloon time, min	235.5 ± 215.5	219.9 ± 209.1	0.540
Door-to-balloon time, min	50.3 ± 19.8	49.0 ± 17.9	0.576
Killip class			0.620
1	111 (79.9)	114 (82.0)	
2	17 (12.2)	18 (12.9)	
3	11 (7.9)	7 (5.0)	
Comorbidities			
Hypertension	50 (36.0)	52 (37.4)	0.901
Diabetes mellitus	25 (18.0)	35 (25.2)	0.189
Dyslipidemia	72 (51.8)	74 (53.2)	0.904
Current smoking	72 (51.8)	77 (55.4)	0.631
Chronic kidney disease	13 (9.4)	11 (7.9)	0.699
Previous revascularization	6 (4.3)	6 (4.3)	1.000
Previous stroke	3 (2.2)	2 (1.4)	1.000
Discharge medications			
Aspirin	139 (100)	139 (100)	1.000
Beta-blocker	123 (88.5)	118 (84.9)	0.377
ACE inhibitor or ARB	111 (79.9)	106 (76.3)	0.469
Statin	136 (97.8)	138 (99.3)	0.622
Rosuvastatin 20 mg	93 (66.9)	100 (71.9)	
Atorvastatin 40 mg	43 (30.9)	38 (27.3)	
Calcium-channel blocker	3 (2.2)	7 (5.0)	0.335
Proton pump inhibitor	67 (48.2)	71 (51.1)	0.719
Furosemide	12 (8.6)	13 (9.4)	1.000
Aldosterone antagonist	7 (5.0)	5 (3.6)	0.769
Laboratory data at discharge			
WBC count, ×10^3/mm^3	8.7 ± 2.4	8.8 ± 2.4	0.725
Hb, g/dl	13.4 ± 1.6	13.6 ± 1.6	0.311
Platelet count, ×10^3/mm^3	220.8 ± 56.7	245.0 ± 60.0	0.547
GFR, ml/min/1.73 m^2	87.4 ± 23.0	91.6 ± 23.7	0.134
hsCRP, mg/l	2.2 ± 3.4	1.7 ± 3.1	0.269
HbA_{1c}, %	6.1 ± 1.2	6.4 ± 1.5	0.101
LDL-C, mg/dl	132.2 ± 41.8	130·1 ± 42.3	0.745
Peak CK-MB, ng/ml	213.1 ± 109.5	211.4 ± 134.4	0.887
VerifyNow $P2Y_{12}$ assay, PRU			
At the time of PCI	239 ± 60	240 ± 53	0.828
At discharge	40 ± 49	174 ± 70	<0.001
At 30 days	34 ± 52	159 ± 69	<0.001
Prevalence of HPR (PRU >208)			
At the time of PCI	105 (75.5)	105 (75.5)	1.000
Before discharge	2 (1.4)	40 (28.8)	<0.001
At 1 month	3 (2.2)	27 (19.4)	<0.001
Radial access	75 (54.0)	78 (56.1)	0.552
Anticoagulant during the procedure			0·163
Unfractionated heparin	110 (79.1)	100 (71.9)	
Low-molecular weight heparin	29 (20.9)	39 (28.1)	
Bailout use of glycoprotein IIb/IIIa inhibitor	25 (18.0)	20 (14.4)	0.416
Aspiration thrombectomy	58 (41.7)	61 (43.9)	0.716
Use of intravascular ultrasound	79 (56.8)	82 (59.0)	0.808
Infarct-related artery			0.824
Left anterior descending coronary artery	81 (58.3)	84 (60.4)	
Left circumflex coronary artery	15 (10.8)	12 (8.6)	
Right coronary artery	43 (30.9)	43 (30.9)	
Intervention method			0.058
Drug-eluting stent	136 (97.8)	130 (93.5)	
Bare-metal stent	1 (0.7)	1 (0.7)	
Bioresorbable scaffold	2 (1.4)	8 (5.8)	

Continued on the next page

TABLE 1 Continued

	Ticagrelor Group (n = 139)	Clopidogrel Group (n = 139)	p Value
Number of stents	1.2 ± 0.4	1.2 ± 0.4	0.319
Total stent length, mm	33.2 ± 14.2	29.1 ± 13.2	0.014
Minimum stent diameter, mm	3.3 ± 0.5	3.2 ± 0.5	0.010
Pre-PCI TIMI flow grade			0.156
0	101 (72.7)	105 (75.5)	
1	8 (5.8)	14 (10.1)	
2	30 (21.6)	20 (14.4)	
Post-PCI TIMI flow grade			0.494
2	22 (15.8)	18 (12.9)	
3	117 (84.2)	121 (87.1)	
TIMI blush grade			0.791
0	3 (2.2)	4 (2.9)	
1	8 (5.8)	2 (1.4)	
2	62 (44.6)	68 (48.9)	
3	66 (47.5)	65 (46.8)	
Corrected TIMI frame count	35.4 ± 20.6	35.0 ± 19.6	0.892

Values are mean ± SD or n (%).

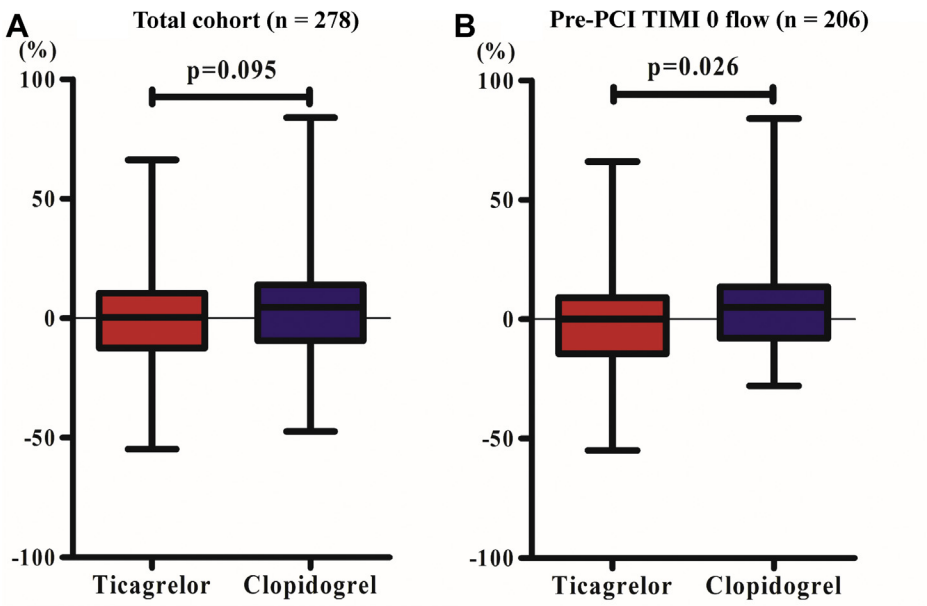
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CK-MB = creatine kinase MB; GFR = glomerular filtration rate calculated by MDRD (Modification of Diet in Renal Disease) equation; Hb = hemoglobin; HbA_{1c} = glycated hemoglobin; HPR = high platelet reactivity; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention; PRU = $P2Y_{12}$ reaction units; TIMI = Thrombosis In Myocardial Infarction; WBC = white blood cell.

OUTCOMES. There were 2 primary endpoints: 1) LV remodeling index measured on real-time 3DE (relative change in LVEDV seen at 6-month follow-up compared with baseline during admission), representing structural changes after STEMI; and 2) the level of NT-proBNP at 6-month follow-up, representing neurohumoral activation after STEMI. Secondary endpoints included the following data measured by real-time 3DE: 1) the prevalence of adverse LV remodeling; and 2) changes in indexed LVESV and LVEDV and LVEF between baseline and 6-month follow-up. The safety endpoint was site-reported bleeding events according to the PLATO (Platelet Inhibition and Patient Outcomes) or the Bleeding Academic Research Consortium criteria (Supplemental Table S2) (19,20).

STATISTICAL ANALYSIS. The sample size was calculated using PASS software (NCSS Statistical Software, East Kaysville, Utah) for a superiority comparison of ticagrelor versus clopidogrel treatment in terms of primary endpoints. On the basis of the REMODELING trial, we assumed that the mean level of LV remodeling index would be −5.2% in the clopidogrel group and −9.9% in the ticagrelor group (7,13). After truncating the lower and upper 15% of the echocardiographic data to adjust the means and the SDs, the total number of patients was estimated at 320 patients with STEMI (~160 in each group) to achieve a 2-sided alpha error rate of 5% and 80% study power in the superiority model, considering a 15% dropout rate. On the basis of NT-proBNP data from our previous analysis (17), NT-proBNP levels at 1 month were 680 ± 1,102 and 1,852 ± 5,114 pg/ml during ticagrelor and clopidogrel treatment, respectively. Assuming a 6-month difference in NT-proBNP of 400 pg/ml between the groups, at least 105 patients in each group were needed, with power of 95%, a 2-sided alpha error rate of 0.05, and an SD of 800 pg/ml (17). Considering a 15% dropout rate, we needed to enroll at least 121 patients in each group.

The primary analysis was done according to the per protocol principle. The 6-month echocardiographic and NT-proBNP measurements were performed only in patients completing the whole study protocol (i.e., 6-month treatment with ticagrelor or clopidogrel) with no major violations. The Kolmogorov-Smirnov test was performed to analyze normality of distribution of continuous variables. Continuous variables are presented as mean ± SD or as median (interquartile range) as appropriate, while categorical variables are reported as frequencies and percentages. Student's unpaired *t*-test for parametric continuous variables and the Mann-Whitney *U* test for nonparametric continuous variables were used. Comparisons between categorical variables were performed using the Pearson chi-square test or Fisher exact test, as

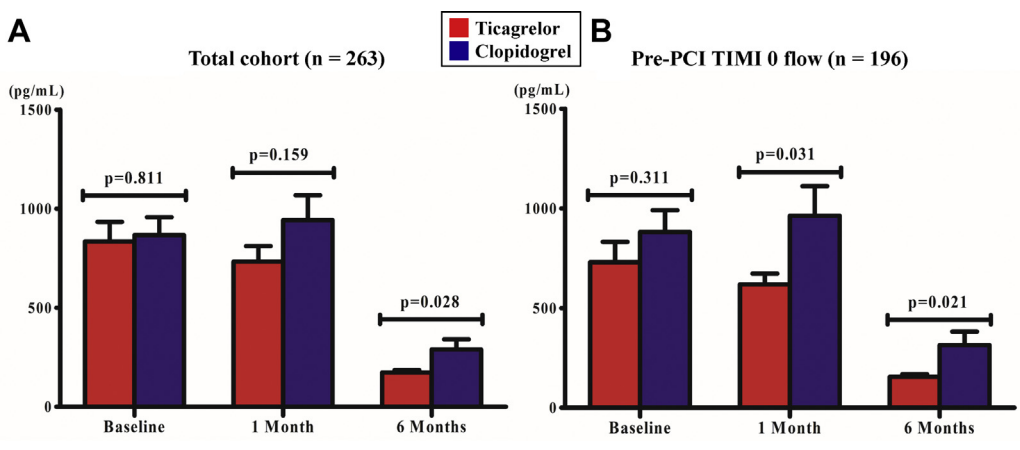
FIGURE 2 Left Ventricular Remodeling Index



(A) Total cohort and **(B)** patients with pre-PCI TIMI flow grade 0. The **central box** represents the values between the lower and upper quartiles, and the **middle line** is the median. The **vertical line** extends from the minimum to the maximum value. Abbreviations as in Figure 1.

appropriate. To evaluate determinants of adverse LV remodeling between baseline and 6-month follow-up, all demographic characteristics, laboratory measurements, and procedural factors were evaluated using univariate analysis. Variables with p values <0.10 in the univariate analysis were then entered into the multivariate analysis, providing odds ratios (OR) and 95% confidence intervals (CIs). Pairwise comparisons of the area under curve were performed according to DeLong analysis to compare the predictive performance of NT-proBNP levels at different time points using receiver-operating characteristic curve analyses. A p value <0.05 was considered to indicate statistical significance, and statistical analyses were

FIGURE 3 N-Terminal Pro-B-Type Natriuretic Peptide Level



(A) Total cohort and **(B)** patients with pre-PCI TIMI flow grade 0. Data are expressed as mean **(red and blue bars)** ± SEM **(horizontal bars)**. Abbreviations as in Figure 2.

TABLE 2 Prevalence of Adverse LV Remodeling and High Level of NT-proBNP

	Ticagrelor Group	Clopidogrel Group	Odds Ratio (95% CI)	p Value
Adverse LV remodeling between baseline and 6-month follow-up (n = 278)	(n = 139)	(n = 139)		
Pathologic LV remodeling (LV remodeling index >20%)	20 (14.4)	24 (17.3)	0.81 (0.42-1.54)	0.511
Positive LV remodeling (LV remodeling index >0%)	51 (36.7)	70 (57.9)	0.57 (0.35-0.92)	0.022
High level of NT-proBNP (≥800 pg/ml) (21) (n = 263)	(n = 131)	(n = 132)		
Baseline	46 (35.1)	48 (36.4)	0.95 (0.57-1.57)	0.833
1-month follow-up	43 (32.8)	43 (32.6)	1.01 (0.60-1.69)	0.966
6-month follow-up	0 (0)	9 (6.8)	0.48 (0.43-0.55)	0.003

Values are n (%).
CI = confidence interval; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

performed with SPSS software version 25.0 (SPSS, Chicago, Illinois).

RESULTS

From November 2014 through December 2017, 526 patients with suspected STEMI were screened for initial randomization. After coronary angiography, 92 patients in the ticagrelor group and 98 patients in the clopidogrel group were excluded depending on the angiographic exclusion criteria. Thus, 336 patients who underwent primary PCI constituted the final cohort (Figure 1). During the follow-up, 35 (20.1%) in the ticagrelor group and 23 (14.2%) in the clopidogrel group did not complete 6-month treatment, including 4 patients with major clinical events (non-cardiovascular death [n = 1] and ischemic stroke [n = 1] in the ticagrelor group, acute stent thrombosis [n = 1] and nonfatal intracranial hemorrhage [n = 1] in the clopidogrel group). Because real-time 3DE or NT-proBNP measurements at 6-month follow-up were available in 278 patients (278 for real-time 3DE and 263 for NT-proBNP), these subjects were included in the primary analysis.

Baseline clinical and angiographic characteristics were well balanced between the groups, except for total stent length and stent diameter (Table 1). Most patients were treated with drug-eluting stents. During the entire follow-up period, questionnaire-reported bleeding episodes were common in both groups, and frequency of minor bleeding was higher in the ticagrelor versus clopidogrel group (Bleeding Academic Research Consortium type 1, 54.0% vs. 29.5%; OR: 2.80; 95% CI: 1.71 to 4.59; p < 0.001) (Supplemental Table S3).

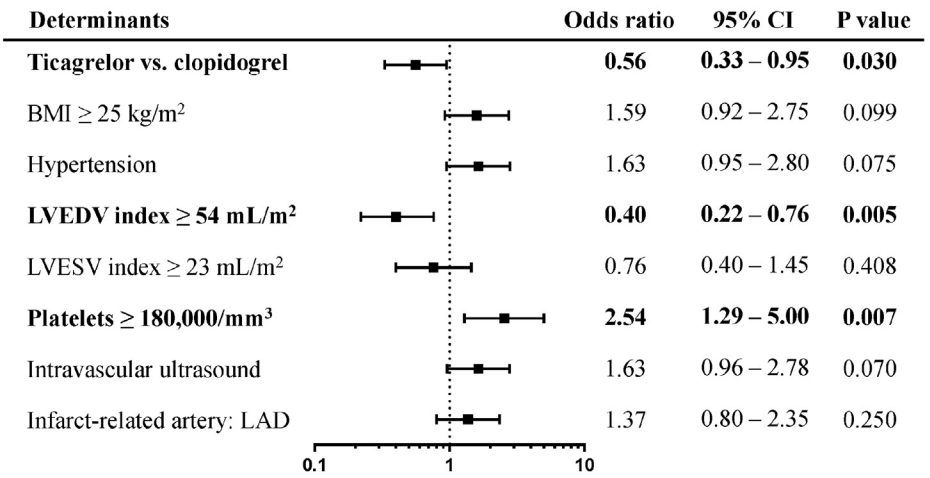
PRIMARY ENDPOINTS. The LV remodeling index (a relative change in LVEDV at 6-month follow-up compared with baseline) was numerically lower in the ticagrelor group (0.6 ± 18.6%) compared with the clopidogrel group (4.5 ± 19.8%), but this difference did not reach statistical significance (p = 0.095) (Figure 2A).

The baseline levels of NT-proBNP were similar between the ticagrelor (n = 131) and clopidogrel (n = 132) groups (835.6 ± 1,115.2 pg/ml vs. 867.3 ± 1,034.9 pg/ml; p = 0.811). At 6-month follow-up, ticagrelor users showed significantly lower levels of NT-proBNP compared with clopidogrel users (173.3 ± 141.5 pg/ml vs. 289.5 ± 585.4 pg/ml; p = 0.028) (Figure 3A). For both groups, NT-proBNP levels at 6-month follow-up dropped significantly compared with those at baseline and 1-month follow-up (p < 0.001 for all).

Importantly, among patients with pre-PCI TIMI flow grade 0, those in the ticagrelor group showed significantly lower values of LV remodeling index (−0.4 ± 18.9% vs. 5.7 ± 19.7%; p = 0.026) (Figure 2B). Ticagrelor compared with clopidogrel also significantly reduced levels of NT-proBNP at 30 days (619.0 ± 536.6 pg/ml vs. 963.0 ± 1,475.2 pg/ml; p = 0.031) and 6 months (155.3 ± 129.6 pg/ml vs. 314.4 ± 664.4 pg/ml; p = 0.021), respectively (Figure 3B). In addition, among patients with proximal portion of infarct-related artery, the benefit of ticagrelor treatment on LV remodeling index was prominent (−0.9 ± 18.5% vs. 5.7 ± 18.2%; p = 0.030).

PREVALENCE OF ADVERSE LV REMODELING AND HIGH LEVEL OF NT-proBNP. At 6 months, the prevalence of pathological LV remodeling did not differ between the groups (14.4% vs. 17.3% in the ticagrelor vs. clopidogrel group; p = 0.511) (Table 2). However, the risk for positive LV remodeling was lower in patients treated with ticagrelor compared with clopidogrel (36.7% vs. 57.9%; OR: 0.57; 95% CI: 0.35 to 0.92; p = 0.022). In the multivariate analysis, ticagrelor versus clopidogrel treatment reduced this risk by 44% (OR: 0.56; 95% CI: 0.33 to 0.95; p = 0.030) (Supplemental Table S4, Figure 4). When using the pre-defined cutoff of high NT-proBNP (≥800 pg/ml)

FIGURE 4 Determinants of Positive LV Remodeling (LV Remodeling Index >0%)



BMI = body mass index; CI = confidence interval; LAD = left anterior descending coronary artery; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

(21), this risk factor at 6-month follow-up was observed only in clopidogrel users (0% vs. 6.8%; OR: 0.48; 95% CI: 0.43 to 0.55; p = 0.003) (**Table 2**).

CHANGES IN LV VOLUME INDEXES AND LVEF. The LVEDV index in the ticagrelor group remained unchanged throughout the study period (p = 0.629), whereas this value in the clopidogrel group increased over time with a substantial upward trend (p = 0.056) (**Table 3, Figure 5A**). The 6-month change in LVEDV index in the ticagrelor group (−0.5 ± 10.5 ml/m^2) was numerically lower than that in the clopidogrel group (1.8 ± 10.9 ml/m^2) (Δ mean −2.3 ml/m^2; 95% CI: −4.8 to 0.2 ml/m^2; p = 0.073) (Supplemental Figure S2A).

Contrary to the LVEDV index, the LVESV index increased for 1 month and then significantly decreased for the next 5 months in both groups (**Figure 5B**). During the first month, ticagrelor users showed a smaller change in LVESV index compared with clopidogrel users (3.4 ± 7.5 ml/m^2 vs. 5.3 ± 70 ml/m^2; p = 0.032). From baseline to 6-month follow-up, the LVESV index was significantly reduced only in the ticagrelor group (−2.3 ± 7.3 ml/m^2; p < 0.001) but not in the clopidogrel group (−0.5 ± 7.2 ml/m^2; p = 0.366). This culminated in significant differences in the sequential changes of LVESV indexes between the groups (Δ mean −1.8 ml/m^2; 95% CI: −3.5 to −0.1 ml/m^2; p = 0.040) (Supplemental Figure S2B).

During the whole study period, LV systolic function improved over time in both groups (**Figure 5C**). Although the changes in LVEF in the clopidogrel group mainly occurred within 1 month, the LVEF in the ticagrelor group persistently increased throughout the study period (Supplemental Figure S2C).

RELATIONSHIP BETWEEN PLATELET REACTIVITY AND POSITIVE LV REMODELING. Platelet reactivity at the time of PCI was similar between the groups (**Table 1**). However, levels of platelet reactivity in the ticagrelor group were significantly decreased over time compared with those in the clopidogrel group (40 ± 49 $P2Y_{12}$ reaction units vs. 174 ± 70 $P2Y_{12}$ reaction units [p < 0.001] before discharge and 34 ± 52 $P2Y_{12}$ reaction units vs. 159 ± 69 $P2Y_{12}$ reaction units [p < 0.001] at 1 month). Prevalence of high platelet reactivity at the time of PCI was identical between the groups (75.5% vs. 75.5%; p = 1.000). Ticagrelor significantly reduced the risk for high platelet reactivity compared with clopidogrel at discharge (1.4% vs. 28.8%; p < 0.001) and 30 days (2.2% vs. 19.4%; p < 0.001), respectively. However, there were no significant differences in platelet reactivity and high platelet reactivity rate in patients with versus without positive LV remodeling (LV remodeling index >0%) (Supplemental Table S4).

RELATIONSHIP BETWEEN REAL-TIME 3D ECHOCARDIOGRAPHIC MEASUREMENTS AND NT-proBNP CONCENTRATIONS. In terms of endpoint measurements at 6 months, NT-proBNP concentrations showed moderate correlations with the

TABLE 3 Changes in LV Ejection Fraction and Volume Indexes

	Ticagrelor Group	Clopidogrel Group	Difference: Mean (95% CI)	p Value
LV end-diastolic volume index (ml/m^2)	(n = 139)	(n = 139)		
Baseline	54.7 ± 12.2	54.6 ± 11.3	−0.2 (−2.6 to 2.9)	0.913
1-month follow-up	54.2 ± 12.2	55.8 ± 12.6	−1.6 (−4.6 to 1.3)	0.275
6-month follow-up	54.2 ± 12.2	56.4 ± 13.9	−2.2 (−5.2 to 0.9)	0.171
LV end-systolic volume index (ml/m^2)	(n = 139)	(n = 139)		
Baseline	27.0 ± 8.5	26.2 ± 8.9	0.8 (−1.2 to 2.9)	0.428
1-month follow-up	30.5 ± 7.7	31.5 ± 8.2	−1.0 (−2.9 to 0.9)	0.303
6-month follow-up	24.7 ± 8.4	25.6 ± 11.0	−1.2 (−3.3 to 1.3)	0.412
LV ejection fraction (%)	(n = 139)	(n = 139)		
Baseline	51.5 ± 7.8	52.7 ± 8.6	−1.2 (−3.2 to 0.7)	0.214
1-month follow-up	53.8 ± 7.3	55.2 ± 7.4	−1.3 (−3.1 to 0.4)	0.127
6-month follow-up	55.2 ± 7.0	55.5 ± 7.8	−0.3 (−2.0 to 1.5)	0.769

Values are mean ± SD.
Abbreviations as in Table 2.

echocardiographic measurements (LVEDV index: r = 0.402; p < 0.001; LDESV index: r = 0.483; p < 0.001; LVEF: r = 0.354; p < 0.001). The 6-month levels of NT-proBNP were significantly correlated with the absolute changes (baseline and 6-month follow-up) in LVEDV index (r = 0.354; p < 0.001) and LDESV index (r = 0.383; p < 0.001).

According to the measurement time point, we evaluated the predictive power of NT-proBNP concentration for the occurrence of adverse LV remodeling (Supplemental Figure S3). Of those, the level of NT-proBNP (≥270 pg/ml) at 6 months showed the highest predictive value for adverse LV remodeling.

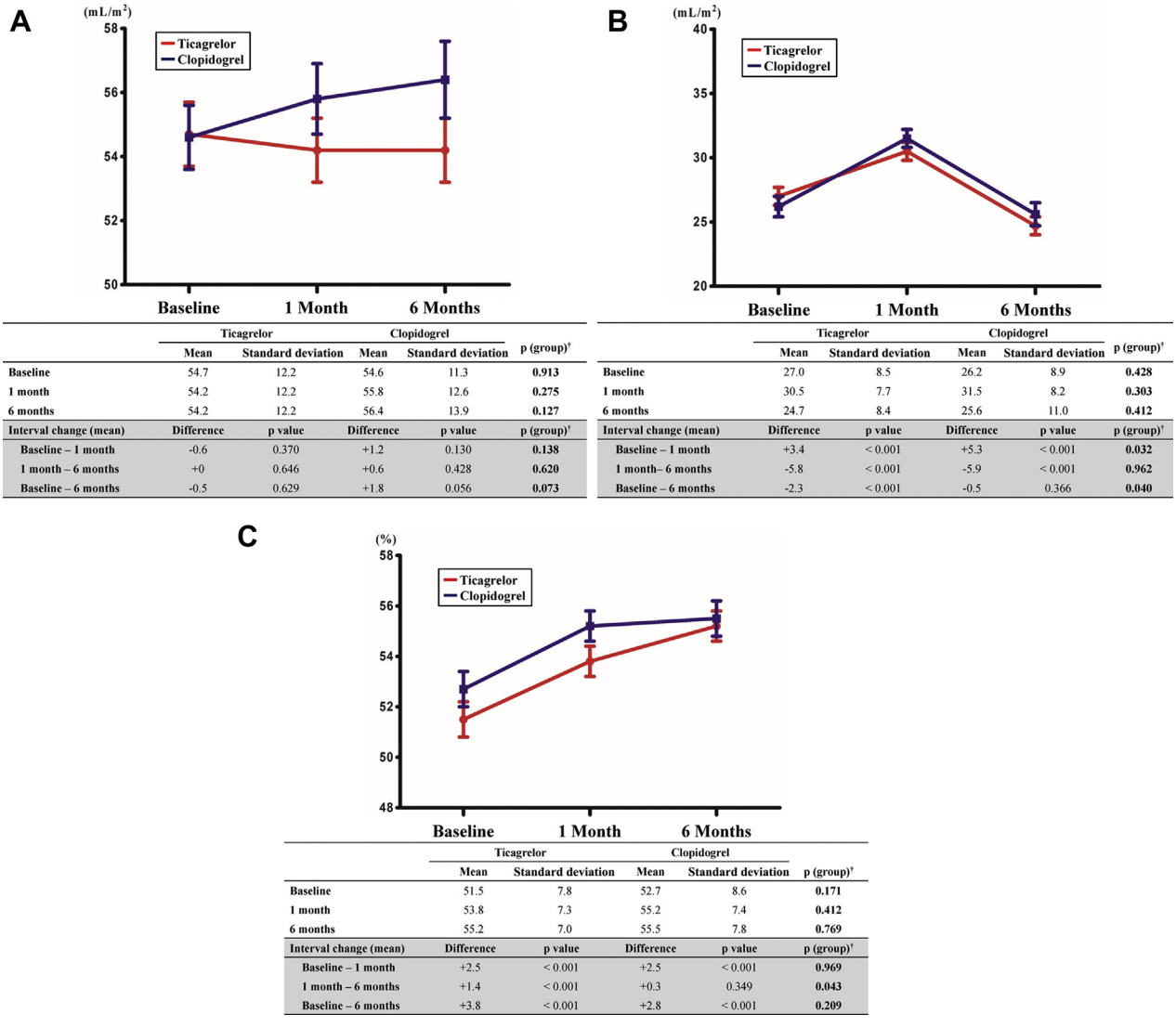
DISCUSSION

HEALING-AMI is the first human trial to evaluate the relationship between type of $P2Y_{12}$ inhibitor and LV remodeling process in patients with STEMI (**Central Illustration**) (22,23). The key findings are as follows: 1) ticagrelor versus clopidogrel was associated with favorable post-MI LV remodeling, demonstrated by 3DE (a structural indicator) and NT-proBNP (a neurohumoral marker); 2) compared with clopidogrel treatment, ticagrelor treatment reduced the risk for LV enlargement by 44%; 3) during ticagrelor versus clopidogrel treatment, differences in interval changes in indexed LVESV and LVEDV and NT-proBNP were prominent between baseline and 1 month, whereas this difference in LVEF change was manifested between 1 and 6 months (suggesting a potential cardioprotective effect of ticagrelor on the long-term repair process); and 4) the level of NT-proBNP at 6 months was significantly associated with structural LV remodeling over 6 months.

Clinical trials have demonstrated that an antiplatelet strategy with aspirin and a $P2Y_{12}$ inhibitor is the mainstay pharmacological regimen to prevent acute and chronic thrombotic complications of infarct-related arteries (2). In PLATO, including patients with acute coronary syndrome, ticagrelor achieved reductions not only in MI but also all-cause death and cardiovascular death in comparison with clopidogrel (19). However, another potent thienopyridine, prasugrel, compared with clopidogrel did not reduce the risk for cardiovascular death in patients with acute coronary syndrome (24). This disparity among $P2Y_{12}$ inhibitors has provided a strong impetus to investigate potential mechanisms beyond platelet $P2Y_{12}$ inhibition: extraplatelet pleiotropic effects (23). The most plausible mechanism explaining the pleiotropic effects of ticagrelor could be increased systemic and tissue adenosine levels by inhibiting erythrocyte reuptake through inhibition of the equilibrative nucleoside transporter-1. In animal studies, ticagrelor has been shown to decrease the expression of inflammation markers, infarct size, and fibrosis and to improve tissue remodeling (8–11). As a mechanism, adenosine-mediated effects of ticagrelor on vascular and other cells have been suggested (25). In addition, ticagrelor has significant 24-h systemic exposure of a direct active compound, compared with the short plasma exposure of active thienopyridine metabolites (~6 h) (23), which may induce a preferable effect on the LV remodeling process.

Animal studies have shown the beneficial effects of ticagrelor on LV remodeling and its related mechanisms. These observations supported its chronic effect through non-$P2Y_{12}$-mediated (adenosine-dependent) pathways (23). In a rat coronary ligation model, pre-treatment with ticagrelor, but not

FIGURE 5 Time-Dependent Changes in LV Volume Indexes



	Ticagrelor		Clopidogrel		
	Mean	Standard deviation	Mean	Standard deviation	p (group)†
Baseline	54.7	12.2	54.6	11.3	**0.913**
1 month	54.2	12.2	55.8	12.6	**0.275**
6 months	54.2	12.2	56.4	13.9	**0.127**
Interval change (mean)	Difference	p value	Difference	p value	p (group)†
Baseline – 1 month	-0.6	0.370	+1.2	0.130	**0.138**
1 month – 6 months	+0	0.646	+0.6	0.428	**0.620**
Baseline – 6 months	-0.5	0.629	+1.8	0.056	**0.073**

	Ticagrelor		Clopidogrel		
	Mean	Standard deviation	Mean	Standard deviation	p (group)†
Baseline	27.0	8.5	26.2	8.9	**0.428**
1 month	30.5	7.7	31.5	8.2	**0.303**
6 months	24.7	8.4	25.6	11.0	**0.412**
Interval change (mean)	Difference	p value	Difference	p value	p (group)†
Baseline – 1 month	+3.4	< 0.001	+5.3	< 0.001	**0.032**
1 month– 6 months	-5.8	< 0.001	-5.9	< 0.001	**0.962**
Baseline – 6 months	-2.3	< 0.001	-0.5	0.366	**0.040**

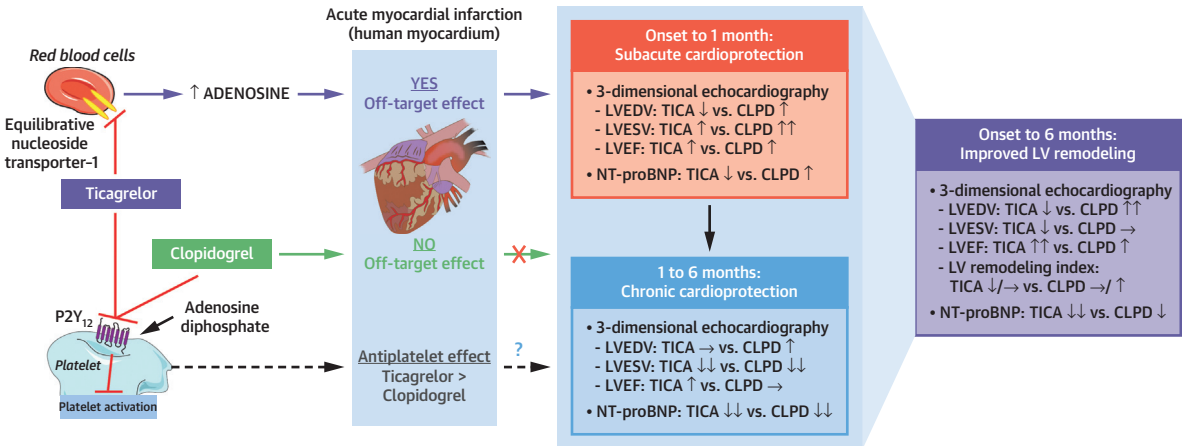
	Ticagrelor		Clopidogrel		
	Mean	Standard deviation	Mean	Standard deviation	p (group)†
Baseline	51.5	7.8	52.7	8.6	**0.171**
1 month	53.8	7.3	55.2	7.4	**0.412**
6 months	55.2	7.0	55.5	7.8	**0.769**
Interval change (mean)	Difference	p value	Difference	p value	p (group)†
Baseline – 1 month	+2.5	< 0.001	+2.5	< 0.001	**0.969**
1 month – 6 months	+1.4	< 0.001	+0.3	0.349	**0.043**
Baseline – 6 months	+3.8	< 0.001	+2.8	< 0.001	**0.209**

(A) LVEDV index, **(B)** LVESV index, and **(C)** LV ejection fraction (LVEF). Data are expressed as mean **(red and blue round points)** ± SEM **(error bars)**. †Comparison between the ticagrelor and clopidogrel groups. Abbreviation as in Figure 4.

clopidogrel, reduced infarct size. The latter was accompanied by an increase in myocardial adenosine levels, up-regulation of myocardial cycloxygenase-2 activity, and phosphorylation of Akt and endothelial nitric oxide synthase, effects that were reversed by adenosine receptor antagonism (8). Consecutively, 4-week ticagrelor administration was associated with reduced inflammation and fibrosis and improved LV remodeling (9). In another swine model using temporary (1 h) balloon occlusion, cardiac injuries (necrosis and edema measured on cardiac magnetic resonance) were decreased to a greater extent with ticagrelor than clopidogrel (10). Importantly, its beneficial effect on infarct size was blocked by A1/A2 receptor antagonist. After 6-week treatment, scar size decreased in ticagrelor-treated pigs versus controls, but not in clopidogrel-treated pigs (11). Ticagrelor treatment showed higher LVEF compared with clopidogrel treatment.

Contrary to the results of previous animal studies, the HEALING-AMI study showed the limited benefit of ticagrelor on adverse LV remodeling in human myocardium compared with clopidogrel. This finding would be related to the preserved LV systolic function

CENTRAL ILLUSTRATION **Proposed Mechanism of Ticagrelor in Improving Left Ventricular Remodeling**



Park, Y. et al. J Am Coll Cardiol Intv. 2020;13(19):2220–34.

Compared with clopidogrel, ticagrelor increases circulatory and tissue adenosine levels through the inhibition of equilibrative nucleoside transporter–1. Adenosine regulates multiple cellular and vascular functions attenuating acute and chronic inflammatory processes through multiple mechanisms. Potent inhibition of $P2Y_{12}$ receptor with ticagrelor compared with clopidogrel may mitigate acute inflammation after myocardial injury, which is mediated by the platelet microparticles and exosomes, inhibition of platelet-neutrophil complexes, and inflammatory M1 macrophage accumulation in infarcted myocardium. However, the results of the HEALING-AMI (Ticagrelor Versus Clopidogrel in Left Ventricular Remodeling After ST-Segment Elevation Myocardial Infarction) trial did not suggest a close association between the left ventricular remodeling process and the rate of high platelet reactivity. CLPD = clopidogrel; LVEDV = LV end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = LV end-systolic volume; TICA = ticagrelor.

and/or relatively small infarct size in human myocardium following the clinical situation of STEMI. In the present study, the prevalence of heart failure with reduced ejection fraction during hospitalization was low in both groups (7.2% and 9.4% of the ticagrelor and clopidogrel groups, respectively; p = 0.514). Moreover, after the 6-month treatment, the prevalence of heart failure with reduced ejection fraction was 2.2% in the ticagrelor group and 3.6% in the clopidogrel group (p = 0.473). This finding may mitigate the changes in echocardiographic parameters representing LV remodeling. If we selected patients with relatively large infarcts (e.g., pre-PCI TIMI flow grade 0) from our cohort, ticagrelor versus clopidogrel administration showed a prominent benefit for the LV remodeling process and NT-proBNP level (**Figures 2B and 3B**).

In the modern era of early reperfusion therapy, antiplatelet strategies to improve clinical outcomes by reducing infarct size have been disappointing (26). Conceptually, ticagrelor may bolster more complete and faster reperfusion, which consequently might decrease infarct size compared with clopidogrel. However, recent clinical trials using early administration of ticagrelor have largely shown the limited effects on reducing infarct size in patients with STEMI (27,28). The HEALING-AMI study also showed similar levels of cardiac injury biomarkers (i.e., peak creatine kinase MB and high-sensitivity troponin I) post-PCI between the groups (**Table 1**). In addition, a recent trial showed no differences in infarct size and microvascular obstruction at 1 month (measured by cardiac magnetic resonance) between ticagrelor and prasugrel treatments in patients with STEMI (28). A recent clinical study in patients with STEMI showed more potent $P2Y_{12}$ inhibition with intravenous cangrelor vs oral ticagrelor at the time of the first coronary balloon inflation. At 13 weeks post-PCI, there were no differences in cardiac magnetic resonance-depicted infarct size and LVEF between the 2 groups (29). Taken together, the antiplatelet effect of a $P2Y_{12}$ receptor inhibitor may restrictively explain the level of infarct size and the consequence of LV remodeling following AMI.

In patients with acute coronary syndrome, biomarker measurements have been potentially useful and more sensitive than echocardiographic measurement to predict clinical outcomes and LV remodeling (15,21). NT-proBNP concentrations are closely correlated with recovery of LV dysfunction and adverse outcome in patients with AMI, regardless of LVEF. In addition, serial measurements of NT-proBNP level have been used to compare the efficacy and safety of pharmacological intervention in patients with symptomatic heart failure (30), which

may suggest the suitability of NT-proBNP as a primary endpoint in the HEALING-AMI trial. The ICON (International Collaborative for NT-proBNP) study established cut points of NT-proBNP for identifying heart failure (15,30); a cut point of 300 pg/ml had 98% negative predictive value for ruling out risk for heart failure. The present trial suggests an intriguing relationship between LV enlargement and NT-proBNP concentration at 6 months. Patients with NT-proBNP less than about 300 pg/ml at 6 months showed decreased risk for LV enlargement (OR: 0.33; 95% CI: 0.18 to 0.58; $p < 0.001$) compared with other subjects.

Besides the benefit of ticagrelor observed with respect to NT-proBNP level, it comes into question if the changes in LV remodeling achieved by ticagrelor would translate into supplementary clinical benefit with longer follow-up periods. Changes in NT-proBNP were more prominent in the ticagrelor group than in the clopidogrel group, which suggests that ticagrelor may prevent the subsequent development of heart failure and the occurrence of worse clinical events. Indeed, the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated that a greater reduction in NT-proBNP by the treatment arms, without serial evaluation of LV volume indexes, was associated with a lower rate of cardiovascular death or heart failure hospitalization (30). Importantly, no patients in the ticagrelor group showed high levels of NT-proBNP (≥800 pg/ml) at 6 months (21). Therefore, the lower level of NT-proBNP at 6 months in ticagrelor users might translate into a favorable clinical prognosis compared with clopidogrel users. The current American and European guidelines use NT-proBNP in addition to echocardiography for diagnosing HF, recognizing its clinical usefulness to predict long-term clinical outcomes (31,32).

Contrary to our expectations, the pleiotropic effects of ticagrelor beyond $P2Y_{12}$ receptor antagonism could not be extrapolated to favorable clinical outcomes compared with another potent $P2Y_{12}$ inhibitor, prasugrel. In the ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) study, ticagrelor was associated with a higher incidence of the composite of death, MI, or stroke without increasing major bleeding compared with prasugrel in patients with acute coronary syndrome (33). There have been no explicit mechanisms to explain the clinical benefit of prasugrel over ticagrelor observed in this ISAR-REACT 5 study. Nevertheless, issues of drug adherence related to the typical side effects or twice-a-day regimen of ticagrelor might be a plausible mechanism, as described by the ISAR-REACT 5 investigators (33). In addition, a long-term follow-up duration (more than 1 year) would be required to evaluate whether the benefit of ticagrelor on LV recovery would have a good influence on clinical outcomes.

STUDY LIMITATIONS. First, the present study was an unblinded trial without placebo control. Second, this study was performed by per protocol analysis because primary endpoints used echocardiographic and NT-proBNP values after completeness of 6-month study-drug treatment. Third, the dropout rate during 6 months appeared high (20.1% in the ticagrelor group). The adherence rate during ticagrelor seemed low in Asian patients (e.g., increased adverse events such as bleeding and dyspnea). Korean data from the National Health Insurance Service showed premature discontinuation of ticagrelor of 35.5% between 3 and 6 months (34). Finally, we used 3DE to evaluate a primary endpoint, instead of cardiac magnetic resonance (14). The present study was performed at 10 academic hospitals, and structural measurements had been done 3 times serially in the same patients. Although real-time 3DE is widely used in patients with acute coronary syndrome, it requires proper image quality and offers limited spatial resolution. Analyses by independent investigators of the core laboratory and additional information from NT-proBNP may make up the shortage of 3DE.

CONCLUSIONS

HEALING-AMI is the first human study to demonstrate the influence of $P2Y_{12}$ inhibition on the LV remodeling process over time in patients with STEMI. Ticagrelor was superior to clopidogrel in terms of LV remodeling in patients with AMI, reducing NT-proBNP levels and improving 3-dimensional echocardiographic parameters, which was maintained even 1 month following STEMI. Clinical benefits of ticagrelor over clopidogrel in patients with STEMI might be related to a better recovery from post-MI LV dysfunction, as well as its potent platelet inhibition.

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PERSPECTIVES

WHAT IS KNOWN? Timely reperfusion therapy and secondary prevention with guideline-recommended medications have shown limited value to reduce the development of adverse LV remodeling. Recent animal studies have demonstrated the cardioprotective potential of antiplatelet agents to protect pathological LV remodeling after induced MI. In a recent meta-analysis, potent oral $P2Y_{12}$ inhibitors showed an effect on preventing ventricular arrhythmia, admission for heart failure, and cardiogenic shock compared with clopidogrel. Our previous REMODELING study suggested a possible relationship between platelet inhibition during clopidogrel and the cardiac repair process in patients with STEMI.

WHAT IS NEW? To the best of our knowledge, HEALING-AMI is the first human trial to evaluate the relationship between type of antiplatelet agent ($P2Y_{12}$ inhibitor) and LV remodeling in patients with STEMI. Ticagrelor versus clopidogrel was associated with favorable post-MI LV remodeling, demonstrated by 3DE (a structural indicator) and NT-proBNP (a biomarker); this favorable effect was prominent during 1 month and persisted up to 6 months.

WHAT IS NEXT? In patients with acute coronary syndrome, ticagrelor, not prasugrel, significantly reduced the risk for cardiovascular mortality in PLATO compared with clopidogrel. This disparity among $P2Y_{12}$ inhibitors has provided a strong impetus to search for potential mechanisms beyond platelet $P2Y_{12}$ inhibition: extraplatelet pleiotropic effects. Our trial now supports that the cardioprotective effect of ticagrelor might be related to the long-term LV repair process, as well as protection from ischemic events.

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APPENDIX For a list of study investigators, supplemental tables, figures, and references, please see the online version of this paper.