







Original Article



Rationale and Design of the High Platelet Inhibition with Ticagrelor to Improve Left Ventricular Remodeling in Patients with ST-Segment Elevation Myocardial Infarction (HEALING-AMI) Trial

Yongwhi Park , MD, PhD¹, Si Wan Choi, MD, PhD², Ju Hyeon Oh , MD, PhD³, Eun-Seok Shin , MD, PhD⁴, Sang Yeub Lee, MD, PhD⁵, Jeongsu Kim , MD, PhD⁶, Weon Kim , MD, PhD⁷, Jeong-Won Suh, MD, PhD⁸, Dong Heon Yang, MD, PhD⁹, Young-Joon Hong, MD, PhD¹⁰, Mark Y Chan, MD, PhD¹¹, Jin Sin Koh, MD, PhD¹², Jin-Yong Hwang, MD, PhD¹², Jae-Hyeong Park , MD, PhD², Young-Hoon Jeong , MD, PhD¹, and HEALING-AMI Trial Investigators

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Correspondence to
Young-Hoon Jeong

Department of Internal Medicine, Gyeongsang National University Changwon Hospital, 11 Samjeongja-ro, Seongsan-gu, Changwon 51472, Korea.
E-mail: goodoctor@naver.com

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ORCID iDs

Yongwhi Park  <https://orcid.org/0000-0003-3626-9717>
Ju Hyeon Oh  <https://orcid.org/0000-0001-7007-9760>
Eun-Seok Shin  <https://orcid.org/0000-0002-9169-6968>
Jeongsu Kim  <https://orcid.org/0000-0001-6877-4289>
Weon Kim  <https://orcid.org/0000-0003-1264-9870>
Jae-Hyeong Park  <https://orcid.org/0000-0001-7035-286X>
Young-Hoon Jeong  <https://orcid.org/0000-0003-0403-3726>

¹Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, Korea

²Division of Cardiology, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Korea

³Department of Internal Medicine, Changwon Samsung Medical Center, Changwon, Korea

⁴Division of Cardiology, Department of Internal Medicine, Ulsan University Hospital, Ulsan, Korea

⁵Division of Cardiology, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Korea

⁶Division of Cardiology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Korea

⁷Division of Cardiology, Department of Internal Medicine, Kyung Hee University Hospital, Seoul, Korea

⁸Division of Cardiology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

⁹Division of Cardiology, Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea

¹⁰Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Korea

¹¹Department of Cardiology, Singapore National University Heart Centre, Singapore

¹²Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Korea

ABSTRACT

Background and Objectives: Impaired recovery from left ventricular (LV) dysfunction is a major prognostic factor after myocardial infarction (MI). Because P2Y₁₂ receptor blockade inhibits myocardial injury, ticagrelor with off-target properties may have myocardial protection over clopidogrel. In animal models, ticagrelor vs. clopidogrel protects myocardium against reperfusion injury and improves remodeling after MI. We aimed to investigate the effect of ticagrelor on sequential myocardial remodeling process after MI.

Methods: High platelet inhibition with ticagrelor to improve LV remodeling in patients with ST-segment elevation MI (HEALING-AMI) is an investigator-initiated, randomized, open-label, assessor-blinded, multi-center trial done at 10 sites in Korea. Patients will be enrolled if they have ST-segment elevation MI (STEMI) treated with primary percutaneous coronary intervention and a planned duration of dual antiplatelet treatment of at least 6 months. Screened patients will be randomly assigned (1:1) using an internet-based randomization with a computer-generated blocking with stratification across study sites to either ticagrelor or clopidogrel treatment. The co-primary primary endpoints are LV remodeling index with three-dimensional echocardiography and the level of N-terminal prohormone B-type

Trial Registration

ClinicalTrials.gov Identifier: NCT02224534

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Park Y, Jeong YH; Data curation: Park Y, Chan MY, Park JH; Formal analysis: Park Y; Funding acquisition: Jeong YH; Investigation: Park Y, Choi SW, Oh JH, Shin ES, Lee SY, Kim JS, Kim W, Suh JW, Yang DH, Hong YJ, Koh JS, Hwang JY, Jeong YH; Methodology: Park Y, Chan MY, Park JH, Jeong YH; Resources: Chan MY; Software: Park JH; Visualization: Chan MY; Writing - original draft: Park Y, Park JH, Jeong YH; Writing - review & editing: Park Y, Jeong YH.

natriuretic peptide (NT-proBNP) at 6 months representing post-MI remodeling processes. Changes of LV end-systolic/diastolic volume indices and LV ejection fraction between baseline and 6-month follow-up will be also evaluated. Analysis is per protocol.

Conclusions: HEALING-AMI is testing the effect of ticagrelor in reducing adverse LV remodeling following STEMI. Our trial would show the benefit of ticagrelor vs. clopidogrel related to the recovery of post-MI LV dysfunction beyond potent platelet inhibition.

Trial Registration: ClinicalTrials.gov Identifier: NCT02224534

Keywords: Myocardial infarction; Ventricular Remodeling; Platelet; Ticagrelor; Clopidogrel

INTRODUCTION

The impaired left ventricular (LV) function after acute myocardial infarction (AMI) is the most important cause of heart failure (HF) and a major determinant of long-term prognosis.^{1,3)} Timely early reperfusion therapy, either with pharmacological or mechanical regimens, markedly has reduced short-term mortality and the loss of myocardium in AMI patients.^{1,2)} However, the morbidity and mortality of post-MI HF remain high despite the advanced interventional devices and techniques.¹⁾ The reduction of short-term mortality with efficient acute care in company with insufficient long-term therapeutic options to treat MI survivors might contribute to persistently high prevalence of HF. The size of the infarct area, wound healing process, and chronic LV remodeling are the major determinants of HF after AMI, which are partly reduced by timely reperfusion therapy and conventional pharmacotherapy.^{4,5)} However, additional therapeutic strategies are still required to facilitate the wound healing and preclude the development of HF following large-sized MI.

Myocardial wound healing or repair following MI, a well-orchestrated complex process, has been considered to begin with an inflammatory phase characterized by replacement of the necrotic myocardium with granulated tissue, and is followed by a proliferative phase with the inhibition of inflammation and mobilization of collagen-based matrix, and by the final healing phase resulting in scar formation.^{4,5)} While on this process, adverse cardiac remodeling may precipitate impaired LV function and HF.^{4,5)} Although the wounding healing process after AMI is not fully elucidated, monocytes are key cell lines for myocardial injury, repair and remodeling including the entire process of scar formation and healing after the event.^{4,6-8)} In addition, it has been suggested that “platelets” play an important role in inhibiting further bleeding at the site of injury and subsequently initiating wound healing.⁹⁾ Furthermore, the crosstalk between platelets and inflammatory cells may involve in the wound healing process after AMI.¹⁰⁾ Activated platelets directly interact with monocytes and recruit macrophages,^{10,11)} which may suggest that uncontrolled activation of platelets boosts the adverse cardiac remodeling. Although the inflammatory cells promote cardiac repair by mobilizing the fibroblasts into the interstitial space and facilitating angiogenesis, persistent increase in inflammatory process (indicated by C-reactive protein [CRP]) is associated with ventricular aneurysm or adverse LV remodeling.^{8,12-14)} In post-MI LV remodeling, activated platelets may be important triggers for the first wave of inflammatory cells accumulating within the infarcted myocardium. Therefore, the phenotype of high platelet reactivity (HPR) in the presence of unpredictable and suboptimal antiplatelet agents might provoke excessive infiltration of inflammatory cells in the infarct myocardium.

There has been paucity of study in terms of the role of activated platelets during the wound healing process after MI. In a rat MI model, Liu and his colleagues¹⁵⁾ showed that platelets accumulation promote inflammatory response, LV remodeling and rupture.¹⁶⁾ These studies demonstrated that clopidogrel reduced platelet-leukocyte aggregates and the risk of LV rupture in the infarcted myocardium compared with no treatment or aspirin.¹⁵⁾¹⁶⁾ This suggested that antiplatelet agents might be a novel approach to improve cardiac remodeling in the early phase of cardiac healing. More interestingly, clopidogrel treatment did not reduce the extent of initial infarct size compared with untreated control despite the reduction of the risk of LV rupture during the acute phase and the risk of pathologic LV remodeling in the chronic phase of MI.¹⁵⁾¹⁶⁾ Another animal study utilizing a rat infarct model demonstrated that ticagrelor protected against reperfusion injury, and long-term (4-week) administration of ticagrelor improved heart function and attenuated the LV remodeling after myocardial injury.¹⁷⁾ However, there are little data to support this influence of HPR on inflammation and LV remodeling in human myocardium. Whilst, in our observational REMODELING (Role of platelet reactivity in left ventricular remodeling after ST-segment elevation myocardial infarction) study, we demonstrated an association between platelet reactivity and LV remodeling in patients with ST-segment elevation MI (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) (**Figure 1**).¹⁸⁾ Our study also supported the synergistic effect of platelet reactivity and inflammation (i.e., CRP) on LV remodeling in these patients. Indeed, ticagrelor was capable of reducing MI-induced myocardial damage (myocardial edema and infarct size) compared with clopidogrel in an animal study.¹⁹⁾ Moreover, another animal study showed that pre-treatment with ticagrelor reduced ischemia-reperfusion injury, which subsequently related to the improvement of heart function compared with clopidogrel.²⁰⁾ The latter observation may support the idea of potential benefit of potent P2Y₁₂ receptor inhibitor compared with clopidogrel in the prevention of LV remodeling after AMI. However, there has been no human study to prove this pleiotropic effect of ticagrelor.

Based on the results from animal and human experiments, we hypothesized that chronic treatment with ticagrelor vs. clopidogrel treatment might be associated with an improved LV remodeling process in large-sized MI patients. We describe herein the design of the high platelet inhibition with ticagrelor to improve left ventricular remodeling in patients with ST-segment elevation myocardial infarction (HEALING-AMI) study, an investigator-initiated, randomized, open-label, assessor-blinded, multi-center evaluation of ticagrelor vs. clopidogrel in STEMI patients undergoing primary PCI.

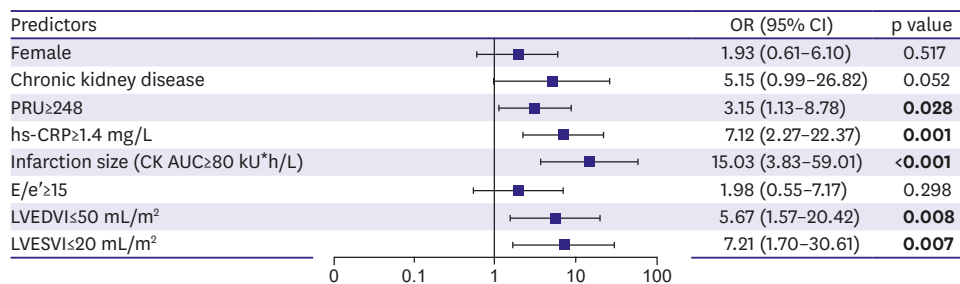


Figure 1. Predictors of adverse LV remodeling in the REMODELING trial.¹⁸⁾ AUC = area under the curve; CI = confidence interval; CK = creatine kinase; hs-CRP = high sensitivity C-reactive protein; LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; OR = odds ratio; PRU = P2Y₁₂ reaction units; REMODELING = role of platelet reactivity in left ventricular remodeling after ST-segment elevation myocardial infarction.

METHODS

Study hypotheses and objectives

Activated platelets have diverse impacts on the whole aspect of AMI.⁹⁻¹¹⁾ During the plaque rupture, platelets are immediately activated and aggregated, and consequently initiate the thrombotic occlusion in coronary arteries. At the time of reperfusion, platelets expand the infarct size through formation of microemboli and release of vasoconstrictors.

After PCI, the phenotype of HPR is closely associated with the risk of ischemic event in MI survivors. In addition, our preliminary REMODELING study has suggested another potential role of activated platelets in post-MI LV healing process based on echocardiographic evaluation.¹⁸⁾ Another experimental analysis also supported the strong relationship between platelet reactivity and the level of N-terminal prohormone B-type natriuretic peptide (NT-proBNP) at one month among post-MI patients.²¹⁾ These findings may represent that activated platelets have the systemic effects in arterial vasculatures and the local effects within the infarcted myocardium among MI patients. Built on these data, we hypothesize that clinical benefit of ticagrelor may be related with its protective effects on thrombotic event occurrence and pathologic LV remodeling process in post-MI patients.

We designed the HEALING-AMI study to compare the influence of ticagrelor vs. clopidogrel on chronic LV remodeling process measured by three-dimensional (3D) echocardiography and NT-proBNP in STEMI patients undergoing primary PCI. The primary objective of the HEALING-AMI study is to demonstrate the adjunctive role of long-term ticagrelor therapy in enhancing the recovery of LV dysfunction. Moreover, this study will determine whether the high platelet inhibition by P2Y₁₂ inhibitor culminate the protection of infarcted myocardium.

Study design

This is a prospective, randomized, open-labeled, blinded endpoint, multi-center trial. The study population enrolled at 10 academic centers in Korea. The present study is an investigator-initiated study with a research grant from AstraZeneca Korea (Seoul, Korea). Other than financial sponsorship, the company has no roles in protocol development, study management, data collection, and data analysis. The design and execution of the trial, statistical analyses, and manuscript preparation is exclusively and independently performed by the investigators. This study protocol has been approved by the Institutional Review Board of each center (GNUH 2014-05-023). The study protocol was registered at www.ClinicalTrials.gov (NCT02224534).

Trial status

The HEALING-AMI began recruitment on October 20, 2014 and the recruitment has been completed on June 20, 2018. Considering the 6-month follow-up period, overall trial end date is scheduled on December 2018.

Study population and randomization

After arrival on emergency room, suspected STEMI patients planned to primary PCI are eligible for the initial randomization if they are at least 18 years of age and have clinical symptoms of AMI of >30 minutes and <12 hours.²⁾ Specific electrocardiographic (ECG) criteria for STEMI is considered suggestive of ongoing acute coronary artery occlusion in the following cases: at least two contiguous leads with ST-segment elevation ≥ 2 mm in men, or ≥ 1.5 mm in women in leads V2–V3 and/or ≥ 1 mm in the other leads (in the absence of LV

hypertrophy or new left bundle branch block [LBBB]).²⁾ If patients showed cardiogenic shock, refractory ventricular arrhythmias or atrial fibrillation at the time of randomization, these patients were excluded from the randomization. The detailed inclusion and exclusion criteria are summarized in **Table 1**.

If all eligible clinical criteria are met and written informed consent is achieved, patients are randomly assigned and administered with 180-mg ticagrelor or 600-mg clopidogrel loading (1:1 fashion) in the emergency room based on computer-generated sequential block randomization (**Figure 1**). Because the large-sized infarcted myocardium may be important to evaluate the benefit of antiplatelet agent on post-MI LV remodeling, we enrolled STEMI patients with the infarct-related artery located in the proximal or mid portion of major epicardial coronary artery with thrombolysis in myocardial infarction (TIMI) 0, 1, or 2 grade flow at the time of initial diagnostic coronary angiography. If the infarct-related artery is not suitable for PCI, patients are excluded from the final study arm (**Table 1**).

The final treatment arms include only cases of STEMI patients treated with uneventful primary PCI for the aforementioned lesion (**Figure 2**). According to the consideration of calculated sample size, approximately 320 patients consist of the cohort. The patient assigned to the TICA group have ticagrelor 90 mg twice daily, whereas those assigned to the CLPD group have clopidogrel 75 mg daily during the entire study period. To evaluate post-MI

Table 1. Inclusion and exclusion criteria

Inclusion criteria	
1.	Ages eligible for study: 18 years and older
2.	The first-time onset STEMI patients uneventfully treated with primary PCI
3.	Patients undergoing PCI within 12 hours after the onset of symptom
4.	The infarct-related artery must have TIMI 0, 1, or 2 grade flow at the time of initial diagnostic angiography (before wire passage)
5.	Primary PCI with plans to treat only 1 epicardial coronary artery (proximal or mid-portion)
Clinical exclusion criteria	
1.	Previous history of myocardial infarction
2.	Left bundle branch block on ECG at the time of screening
3.	Cardiogenic shock at the time of randomization
4.	Refractory ventricular arrhythmias or atrial fibrillation
5.	New York Heart Association class IV congestive heart failure
6.	Severe or malignant hypertension (systolic BP >180 mmHg and/or diastolic BP >120 mmHg)
7.	Fibrinolytic therapy
8.	History of hemorrhagic stroke
9.	Intracranial neoplasm, arteriovenous malformation, or aneurysm
10.	Ischemic stroke within 3 months prior to screening
11.	Platelet count <100,000/mm ³ or hemoglobin <10 g/dL
12.	A need for oral anticoagulation therapy that cannot be safely discontinued for the duration of the study
13.	Women who are known to be pregnant, have given birth within the past 90 days, or are breast-feeding
14.	Unable to cooperate with protocol requirements and follow-up procedures
15.	A history of P2Y ₁₂ receptor inhibitor pretreatment (at least prior 1 month)
16.	An increased risk for bradycardia
17.	Concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
Angiographic exclusion criteria	
1.	Distal territory lesion of infarct-related artery
2.	Coronary anatomy that may require coronary artery bypass graft surgery within 6 months
3.	Anticipated multi-vessel intervention during the index procedure (planned, staged procedures are permitted within 6 months)
4.	The presence of features that are highly unfavorable for PCI
5.	Myocardial infarction caused by thrombosis within or adjacent to a previously implanted stent
6.	An unprotected left main stenosis >50% or that will require intervention

BP = blood pressure, ECG = electrocardiographic; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction.

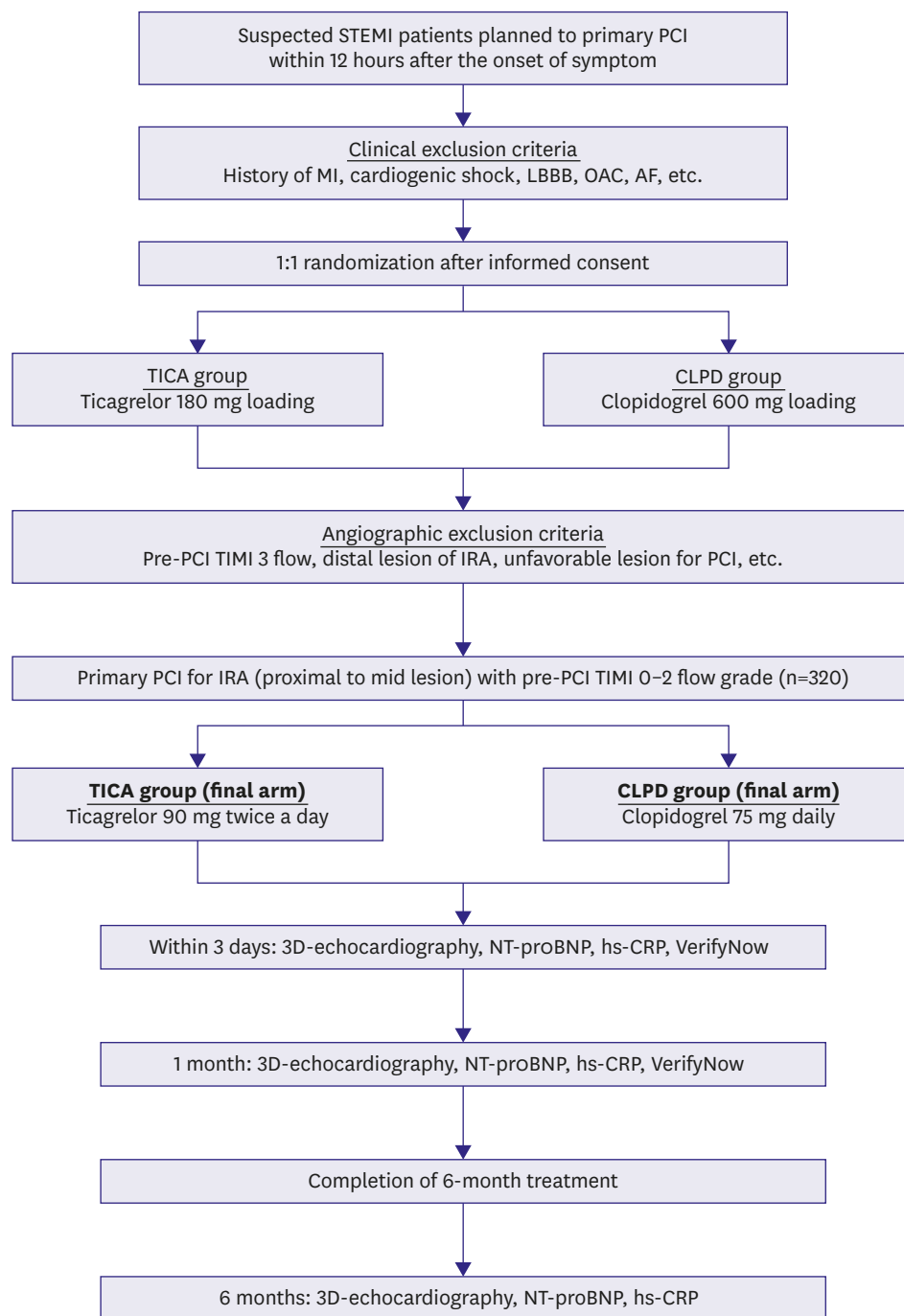


Figure 2. Flow diagram of the HEALING-AMI trial.

AF = atrial fibrillation; HEALING-AMI = high platelet inhibition with ticagrelor to improve left ventricular remodeling in patients with ST-segment elevation myocardial infarction; hs-CRP = high-sensitivity C-reactive protein; IRA = infarct related artery; LBBB = left bundle branch block; MI = myocardial infarction; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction; 3D = three-dimensional.

LV remodeling process, echocardiographic and NT-proBNP measurements will be scheduled during hospitalization, and 1 and 6 months after PCI.²²⁾ Biochemical profiles including VerifyNow P2Y₁₂ assay and high sensitivity C-reactive protein (hs-CRP) will be measured

	In-hospital			Follow-up	
	Pre-procedure	Procedure	Post-procedure	1 month	6 months
Informed consent	X				
Eligibility	X	X			
Demographics	X				
Medical history	X				
Physical exam	X				X
Vital status	X		X	X	X
NYHA class	X		X	X	X
12 lead ECG	X	X	X	X	
CK-MB, troponin I	X	X	X		
Baseline lab	X		X	X	X
hs-CRP	X		X	X	X
NT-proBNP			X	X	X
3D-echocardiography			X	X	X
VerifyNow P2Y ₁₂ assay		X	X	X	
Cardiac MRI (substudy)			X		X
Biomarkers (substudy)			X	X	
Compliance/drug accountability				X	X
Concomitant medications	X		X	X	X
MACE, AEs and SAEs (bleeding, dyspnea and so on)	X		X	X	X

Figure 3. Schedule of measurement.

AE = adverse event; CK-MB = creatine kinase-MB; CRP = high-sensitivity C-reactive protein; ECG = electrocardiography; hs-CRP = high-sensitivity C-reactive protein; MACE = major adverse cardiovascular event; MRI = magnetic resonance imaging; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; SAE = serious adverse event; 3D = three-dimensional.

according to the protocol (**Figure 3**). Patients will be also questioned about the adherence of medication and the occurrence of side effects by well-trained research coordinators.

Adjunctive pharmacological therapy and PCI procedure

The 300-mg aspirin loading is administered before the index PCI, whether or not taking it previously, and aspirin is further continued at 100 mg daily indefinitely. The choice of intra-procedural anticoagulant is at the discretion of the operator; unfractionated heparin, enoxaparin, and bivalirudin are all permitted. The unfractionated heparin, dosage per label instructions and local standard of care will be administered. Glycoprotein IIb/IIIa inhibitor can be used by the discretion of attending interventionists. During the study period, all patients receive guideline-recommended optimal medical treatment including beta blocker, angiotensin blocker and statin. Diuretics such as loop diuretic and aldosterone antagonist can be used at the discretion of the attending physician.

The goals of the PCI procedure are to achieve optimal angiographic efficacy of PCI with any stent while minimizing the risk of procedure-related complications. All interventions are performed using the standard technique. Primary PCI targeting a single epicardial coronary

artery is allowed. If multi-vessel intervention is mandatory, planned and staged procedures are permitted within the study period. Radial access is allowed and encouraged, as is use of arterial closure devices after femoral access. Other approved PCI techniques including thrombus aspiration may be utilized prior to stent implantation at the operator's discretion. Direct stenting and bifurcation stenting will be also allowed if needed. Intravascular ultrasound or any other imaging devices are also used according to the physician's discretion. At the end of procedure, TIMI frame count and myocardial blush grade are recommended to obtain (**Supplementary Data 1**).

Study endpoints

There are two primary endpoints in this study: 1) LV remodeling index measured by 3D-echocardiography (%) (a relative change in LV end-diastolic volume seen at 6-month follow-up compared with the baseline during admission); and 2) the level of NT-proBNP at 6-month follow-up. Co-primary endpoints are selected based on the previous reports.¹⁸⁾²¹⁾ Because LV function or volume is frequently preserved or slightly impaired following AMI, concomitant use of NT-proBNP may better predict the recovery of post-MI LV dysfunction and improve the risk stratification.²³⁾

Secondary endpoints include the following data measured by 3D-echocardiography:

1. Prevalence of pathologic LV remodeling (a relative >20% increase in end-diastolic volume seen at 6-month follow-up compared with the baseline during admission);
2. The changes of LV end-systolic/end-diastolic volume indices (mL/m²) and LV ejection fraction (%) between the baseline and 6-month follow-up.

Prespecified subgroup studies

Cardiac magnetic resonance imaging substudy

The primary endpoint of this substudy is the LV remodeling index between the acute phase and 6-month follow-up.

The secondary endpoints include the following:

1. LV ejection fraction (%), LV end-diastolic and end-systolic volume (mL) at 6 months, comparing acute phase magnetic resonance imaging (MRI);
2. Infarct size (grams and percentage of total LV mass) at 6 months and acute phase MRI;
3. Area-at-risk (AAR, grams and percentage of total LV mass) at 6 months and acute phase MRI.

Substudy of platelet-immune interaction

This substudy is designed to explore the basic mechanism how platelets do influence on the LV remodeling after AMI. The primary endpoint of this substudy is the count of monocyte-platelet aggregates. The secondary endpoints include the following:

1. The count of CD14⁺⁺CD16⁺CCR2⁺ monocyte-platelet aggregates;
2. The count of CD14⁺⁺CD16⁻CCR2⁺ monocyte-platelet aggregates;
3. The count of CD14⁺⁺CD16⁺CCR2⁺ monocyte subset;
4. The count of CD14⁺⁺CD16⁻CCR2⁺ monocyte subset;
5. The level of inflammatory biomarkers (nuclear factor κB, IL-1β, IL-6, IL-10, and monocyte chemoattractant protein-1).

Other prespecified studies

1. Inflammatory indicators: hs-CRP, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and fibrinogen;

2. Angiographic perfusion indicators: TIMI flow grades, myocardial blush grades and corrected TIMI frame count;
3. ECG indicators; degree of ST-segment resolution (%), prevalence of complete ST-segment resolution (>70%) (%);
4. Platelet function test: VerifyNow P2Y₁₂ assay (PRU, BASE);
5. Vascular function test: pulse wave velocity, EndoPAT, IIEF-5 questionnaire;
6. Safety endpoint: Platelet Inhibition and Patient Outcomes (PLATO) or Bleeding Academic Research Consortium (BARC) bleeding criteria.

Data collection and statistical considerations

Data collection and monitoring

The principal investigator, the study coordinator, and the Clinical Trials Center at Gyeongsang National University Hospital (executive committee) are jointly responsible for all aspects of the study protocol and amendments. Site data collection will be performed by a dedicated affiliated research coordinator. Relevant data will be collected and entered into a computerized database by specialized personnel at the clinical data-management center. Data coordination and site management services will be performed by outside contract research organization (C&R Research, Seoul, Korea). At appropriate intervals, designated trial monitors will review all investigational data for accuracy and completeness, ensuring protocol compliance. All data will be verified with the use of hospital records or telephone interviews, and all adverse clinical events will be adjudicated by an events committee whose members are unaware of patients' treatment assignments.

Sample size calculations

Based on echocardiographic data from the REMODELING trial,¹⁸⁾ the prevalence of LV remodeling at 1 month was 24.0% on clopidogrel and significantly associated with the level of platelet reactivity measured by VerifyNow P2Y₁₂ assay (**Figure 4**). The prevalence of LV remodeling in the 1st quartile (cutoff of 177 PRU) was 10.7%, which might indicate the chance of LV remodeling occurrence during low platelet reactivity by ticagrelor.²⁴⁾ The mean level of LV remodeling index was -5.2% in the total cohort, whereas this value was -9.9% in the patients with the 1st quartile. We assume the total data of REMODELING as the CLPD group, while the 1st quartile data as the TICA group. Exploratory data analysis showed that

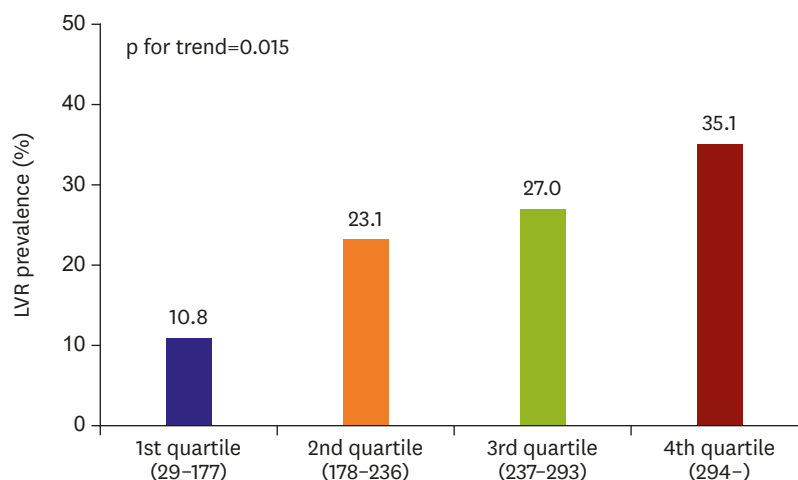


Figure 4. Incidence of adverse LV remodeling according to distribution of platelet reactivity (PRU measured by VerifyNow test).¹⁸⁾
LV = left ventricular; LVR = left ventricular remodeling; PRU = P2Y₁₂ reaction units.

Table 2. Quartiles for each group from the original data

Group_1	p_0	p_5	p_10	p_15	p_20	p_80	p_85	p_90	p_95	p_100
1	-109.9	-50	-37.7	-30.5	-22.9	12.1	14.3	21.55	28.9	59.4
2	-109.9	-52.1	-40.8	-36.7	-26.9	10.8	12.4	20	29.9	33.6

Table 3. Sample sizes calculated for several scenarios using the truncated data

Type I and II errors	Number for each group	Total number	Adjusted number considering 15% drop-outs
$\alpha=0.05, 1-\beta=0.8$	139	278	320
$\alpha=0.05, 1-\beta=0.9$	193	386	444
$\alpha=0.10, 1-\beta=0.8$	102	204	235
$\alpha=0.10, 1-\beta=0.9$	148	296	341

the standard deviations tend to be too large, which hinders us to get appropriate sample sizes as planned. Thus, we truncated the lower and upper 15% of the original data to adjust the means and the standard deviations hoping to get reasonable sample sizes (**Tables 2 and 3**).

In order to have 80% of statistical power at 5% of significance level, we need to recruit about 160 subjects for the CLPD and TICA groups, considering the 15% drop-outs. Therefore, the total number of patients is estimated at 320 STEMI patients (up to 160 in each group) to achieve 5% of 2-sided alpha error and 80% of study power in the superiority model considering 15% drop out rate. Sample size was calculated with the use of PASS software.

Based on NT-proBNP data from the RECOVERY trial,²¹⁾ NT-proBNP levels at 1 month were $680 \pm 1,102$ and $1,852 \pm 5,114$ pg/mL during ticagrelor and clopidogrel, respectively. Assuming the 6-month difference of NT-proBNP by 400 pg/mL between the treatment arms, at least 105 patients in each group were needed with a power of 95%, a two-sided 2-sided alpha error=0.05, and a standard deviation of 800 pg/mL. Considering a 15% drop-out rate, we will enroll at least 121 patients in each group.

Statistical analysis

Because the HEALING-AMI trial is focusing on the long-term process of post-MI LV remodeling (between the baseline and 6-month follow-up), the main analysis will be based on the per-protocol protocol. This per-protocol analysis will be performed only in patients completing the whole study protocols and measurements with no major violations. All enrolled subjects who have received same or more than 1 study drug and have provided safety information, are counted in the safety analysis.

The per-protocol analysis on the primary endpoint will be presented with the Student unpaired t-test. The results of secondary endpoints and subgroup studies will be compared based on the χ^2 test (or Fisher's exact test) or Student unpaired t-test, as appropriate. The correlations between LV remodeling and laboratory parameters will be assessed based on Pearson or Spearman analysis.

Predefined major protocol violations/deviations are missing data for the primary endpoint, violation of inclusion criteria, and additional protocol violations that will be possibly defined during the blind data review. Missing patients will be censored at the last follow-up visit. Alive or dead status will be specifically searched for all missing patients. Baseline characteristics will be tabulated and comparability/differences between the treatment groups will be examined by means of descriptive statistics.

DISCUSSION

For the measurements of LV volumes, remodeling and ejection fraction, cardiac MRI is acknowledged as the gold standard method.²⁵⁾ However, cardiac MRI is just utilized as an alternative modality just in case of non-diagnostic echocardiographic measurement.²⁵⁾ Indeed, cardiac MRI has limitations such as high cost, low availability, and less reliability in case of tachycardia frequently found in patients with STEMI. Given that the high agreement with cardiac MRI for the measurement of LV volume, 3D echocardiography may be a pragmatic method for the evaluation of LV remodeling.²⁶⁾ In addition, the HEALING-AMI trial included the level of NT-proBNP at 6 months as a co-primary endpoint to evaluate the LV dysfunction in patients with normal LV systolic function even after STEMI. The level of NT-proBNP at long-term is a sensitive marker associated with LV dysfunction and prognosis after MI.²⁾³⁾

Neurohormonal activation is a key mechanism of the LV remodeling and the progression of HF after AMI.⁴⁾ In patients with HF after AMI, NT-proBNP reflecting the neurohormonal activation after myocardial injury has a strong prognostic value, which is well correlated with infarct size, LV dysfunction and adverse outcome in patients with AMI.²³⁾ The measurement of NT-proBNP is useful for establishing a diagnosis, prognosis and disease severity in HF after AMI, irrespective of echocardiographic parameters.³⁾ Indeed, the majority of patients who survive a first-ever AMI have preserved or only slightly impaired LV systolic function.¹⁾²⁷⁾²⁸⁾ However, patients with preserved ejection fraction after AMI are also at high risk of HF and cardiac death.²⁹⁾ Importantly, the mortality rate related to HF with preserved ejection fraction (HFpEF) was not less than that caused by HF with reduced ejection fraction (HFrEF).²⁹⁾ Moreover, the prevalence of HFpEF has been less reduced over time than that of HFrEF despite the improvement of MI care.¹⁾²⁷⁾²⁸⁾ Our preliminary observation showed that HPR was associated with the high level of NT-proBNP.²¹⁾ Of importance, ticagrelor significantly reduced the risk of high 30-day NT-proBNP compared with clopidogrel (relative risk reduction=55%; 95% confidence interval=0.202–0.983; $p=0.045$). This suggested that strong platelet inhibition with ticagrelor might preclude the development of HFpEF after AMI. In addition, the assessment of NT-proBNP together with echocardiographic assessment may better predict the LV remodeling after AMI.

LV remodeling is the most frequent sequelae after STEMI and is furthermore a powerful predictor of subsequent HF and mortality. This prompts the therapeutic modalities to prevent pathologic LV remodeling after MI. The HEALING-AMI will provide the effect of ticagrelor going beyond potent platelet inhibition and shed light on the new therapeutic approach on LV remodeling after MI. In addition, the extensive substudies including platelet-immune interaction, cardiac MRI, angiography and vascular function will also enhance our understanding of the pathophysiologic mechanism of LV remodeling.

Our study has several limitations. First, current STEMI guidelines²⁾³⁰⁾ already recommend a potent P2Y₁₂ inhibitor (ticagrelor or prasugrel) in preference to clopidogrel in patients with STEMI undergoing primary PCI. The main purpose of the HEALING-AMI trial was to reveal the beneficial effect of ticagrelor on LV remodeling compared with traditional antiplatelet regimen. The positive result from HEALING-AMI would add more evidences regarding the favorable effect of ticagrelor on wound healing process, as well as its protective effect on atherothrombotic events. There have been crucial concerns regarding clinical benefit of standard-dose potent P2Y₁₂ inhibitor in East Asian patients with acute coronary syndrome.³¹⁾³²⁾ HEALING-AMI may touch another issue regarding clinical benefit of ticagrelor

in East Asian patients with enhanced thrombogenic profile (e.g., STEMI patients treated with primary PCI). Second, considerable portion of the initial randomized cohort was dropped out following coronary angiography, which may be related with prolonged enrollment period and the heterogeneity of the final cohorts. Finally, the size of the infarct area was not evaluated using the reliable method from the total cohort. Because differences in the initial infarct size between the groups may not be adjusted, its wide variance may affect accurate comparison in LV remodeling process.

SUPPLEMENTARY MATERIAL

Supplementary Data 1

Methods of measurements

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REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67-492.
[PUBMED](#) | [CROSSREF](#)
2. Ibanez B, James S, Agewall S, 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;39:119-77.
[PUBMED](#) | [CROSSREF](#)
3. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Failure Society of America. *Circulation* 2017;136:e137-61.
[PUBMED](#) | [CROSSREF](#)
4. Burchfield JS, Xie M, Hill JA. Pathological ventricular remodeling: mechanisms: part 1 of 2. *Circulation* 2013;128:388-400.
[PUBMED](#) | [CROSSREF](#)
5. Liehn EA, Postea O, Curaj A, Marx N. Repair after myocardial infarction, between fantasy and reality: the role of chemokines. *J Am Coll Cardiol* 2011;58:2357-62.
[PUBMED](#) | [CROSSREF](#)
6. Anzai T. Post-infarction inflammation and left ventricular remodeling: a double-edged sword. *Circ J* 2013;77:580-7.
[PUBMED](#) | [CROSSREF](#)
7. Ziegler-Heitbrock L. The CD14⁺ CD16⁺ blood monocytes: their role in infection and inflammation. *J Leukoc Biol* 2007;81:584-92.
[PUBMED](#) | [CROSSREF](#)
8. Tapp LD, Shantsila E, Wrigley BJ, Pamukcu B, Lip GY. The CD14⁺CD16⁺ monocyte subset and monocyte-platelet interactions in patients with ST-elevation myocardial infarction. *J Thromb Haemost* 2012;10:1231-41.
[PUBMED](#) | [CROSSREF](#)
9. Nurden AT. Platelets, inflammation and tissue regeneration. *Thromb Haemost* 2011;105 Suppl 1:S13-33.
[PUBMED](#) | [CROSSREF](#)
10. Rondina MT, Weyrich AS, Zimmerman GA. Platelets as cellular effectors of inflammation in vascular diseases. *Circ Res* 2013;112:1506-19.
[PUBMED](#) | [CROSSREF](#)
11. Semple JW, Italiano JE Jr, Freedman J. Platelets and the immune continuum. *Nat Rev Immunol* 2011;11:264-74.
[PUBMED](#) | [CROSSREF](#)

12. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. *Lancet* 2006;367:356-67.
[PUBMED](#) | [CROSSREF](#)
13. Italiano JE Jr, Richardson JL, Patel-Hett S, et al. Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet α granules and differentially released. *Blood* 2008;111:1227-33.
[PUBMED](#) | [CROSSREF](#)
14. Swiatkiewicz I, Kozinski M, Magielski P, et al. Value of C-reactive protein in predicting left ventricular remodelling in patients with a first ST-segment elevation myocardial infarction. *Mediators Inflamm* 2012;2012:250867.
[PUBMED](#) | [CROSSREF](#)
15. Liu Y, Gao XM, Fang L, et al. Novel role of platelets in mediating inflammatory responses and ventricular rupture or remodeling following myocardial infarction. *Arterioscler Thromb Vasc Biol* 2011;31:834-41.
[PUBMED](#) | [CROSSREF](#)
16. Du XJ, Shan L, Gao XM, et al. Role of intramural platelet thrombus in the pathogenesis of wall rupture and intra-ventricular thrombosis following acute myocardial infarction. *Thromb Haemost* 2011;105:356-64.
[PUBMED](#) | [CROSSREF](#)
17. Ye Y, Birnbaum GD, Perez-Polo JR, Nanhwan MK, Nylander S, Birnbaum Y. Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction. *Arterioscler Thromb Vasc Biol* 2015;35:1805-14.
[PUBMED](#) | [CROSSREF](#)
18. Park Y, Tantry US, Koh JS, et al. Novel role of platelet reactivity in adverse left ventricular remodelling after ST-segment elevation myocardial infarction: the REMODELING trial. *Thromb Haemost* 2017;117:911-22.
[PUBMED](#) | [CROSSREF](#)
19. 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;34:2078-85.
[PUBMED](#) | [CROSSREF](#)
20. Vilahur G, Gutiérrez M, Casani L, et al. Protective effects of ticagrelor on myocardial injury after infarction. *Circulation* 2016;134:1708-19.
[PUBMED](#) | [CROSSREF](#)
21. Kang MG, Ahn JH, Jang JY, et al. Ticagrelor versus clopidogrel is associated with better recovery of LV function after AMI. *J Am Coll Cardiol* 2017;69:125.
[CROSSREF](#)
22. Sjöblom J, Muhrbeck J, Witt N, Alam M, Frykman-Kull V. Evolution of left ventricular ejection fraction after acute myocardial infarction: implications for implantable cardioverter-defibrillator eligibility. *Circulation* 2014;130:743-8.
[PUBMED](#) | [CROSSREF](#)
23. Thygesen K, Mair J, Mueller C, et al. Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. *Eur Heart J* 2012;33:2001-6.
[PUBMED](#) | [CROSSREF](#)
24. Storey RF, Angiolillo DJ, Patil SB, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy. *J Am Coll Cardiol* 2010;56:1456-62.
[PUBMED](#) | [CROSSREF](#)
25. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200.
[PUBMED](#) | [CROSSREF](#)
26. Jenkins C, Moir S, Chan J, Rakhit D, Haluska B, Marwick TH. Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging. *Eur Heart J* 2009;30:98-106.
[PUBMED](#) | [CROSSREF](#)
27. Gerczuk PZ, Kloner RA. An update on cardioprotection: a review of the latest adjunctive therapies to limit myocardial infarction size in clinical trials. *J Am Coll Cardiol* 2012;59:969-78.
[PUBMED](#) | [CROSSREF](#)
28. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015;175:996-1004.
[PUBMED](#) | [CROSSREF](#)

29. Gerber Y, Weston SA, Enriquez-Sarano M, et al. Mortality associated with heart failure after myocardial infarction: a contemporary community perspective. *Circ Heart Fail* 2016;9:e002460.
[PUBMED](#) | [CROSSREF](#)
30. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation* 2016;134:e123-55.
[PUBMED](#) | [CROSSREF](#)
31. Bae JS, Ahn JH, Tantry US, Gurbel PA, Jeong YH. Should antithrombotic treatment strategies in East Asians differ from Caucasians? *Curr Vasc Pharmacol* 2018;16:459-76.
[PUBMED](#) | [CROSSREF](#)
32. Kang J, Kim HS. The evolving concept of dual antiplatelet therapy after percutaneous coronary intervention: focus on unique feature of East Asian and "Asian paradox". *Korean Circ J* 2018;48:537-51.
[PUBMED](#) | [CROSSREF](#)