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Efficacy of postprocedural anticoagulation after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

A post-hoc analysis of the randomized INNOVATION trial

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Abstract

There exists controversy on whether and for how long anticoagulation is necessary after primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI).

We aimed to study the impact of prolonged (>24 h) or brief (<24 h) postprocedural anticoagulation on infarct size assessed by cardiac magnetic resonance (CMR) after 30 days as well as on left ventricular ejection fraction (LVEF) and left ventricular (LV) remodeling evaluated by 2D-echocardiography after 9 months from the INNOVATION trial (*Clinical Trial Registration:* NCT02324348).

Of the 114 patients (mean age: 59.5 years) enrolled, 76 (66.7%) received prolonged anticoagulation therapy (median duration: 72.6 h) and 38 (33.3%) patients received brief anticoagulation therapy (median duration: 5 h) after primary PCI. There was no significant difference in infarct size (mean size: 15.6% after prolonged anticoagulation versus 19.8% after brief anticoagulation, $P = .100$) and the incidence of microvascular obstruction (50.7% versus 52.9%, $P = .830$) between the groups. Even after adjusting, prolonged anticoagulation therapy could not reduce larger infarct (defined as >75 percentile of infarct size; 19.7% versus 35.3%; adjusted odd ratio [OR]: 0.435; 95% confidence interval [CI]: 0.120–1.57; $P = .204$). Similar results were observed in subanalyses of major high-risk subgroups. Moreover, follow-up LVEF <35% (3.2% versus 7.4%; adjusted OR: 0.383; 95% CI: 0.051–2.884; $P = .352$) and LV remodeling (defined as >20% increase in LV end-diastolic volume; 37.1% versus 18.5%; adjusted OR: 2.249; 95% CI: 0.593–8.535; $P = .234$) were similar between groups.

These data suggest that prolonged postprocedural anticoagulation may not provide much benefit after successful primary PCI in patients with STEMI. However, further studies are needed.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, CI = confidence interval, CMR = cardiac magnetic resonance, INNOVATION = impact of immediate stent implantation versus deferred stent implantation on infarct size and microvascular perfusion in patients with ST-segment elevation myocardial infarction, IQR = interquartile ranges, LV = left ventricular, LVEF = left ventricular ejection fraction, MBG = myocardial blush grade, MVO = microvascular obstruction, OR = odd ratio, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction.

Keywords: infarct size, left ventricular ejection fraction, left ventricular remodeling, postprocedural anticoagulation, sT-segment elevation myocardial infarction

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1. Introduction

Procedural anticoagulation is recommended in all patients with ST-segment elevation myocardial infarction (STEMI) during primary percutaneous coronary intervention (PCI).[1,2] However, in the current era of primary PCI, the use of postprocedural anticoagulation has been empiric because studies investigating the impact of postprocedural anticoagulation after primary PCI on myocardial damage are very limited so far. In particular, there is no study answering these questions by using the current reference standard technique, which are cardiac magnetic resonance (CMR) and 2D-echocardiography. CMR not only enables exact infarct sizing but also detailed tissue characterization of the jeopardized and infarcted myocardium. These additional assessed parameters, primarily microvascular obstruction (MVO), but also myocardial infarct sizing provide strong prognostic information that is incremental to clinical, biomarker, electrocardiographic, and angiographic risk markers.[3,4] LVEF is the classical surrogate functional parameter, because it has been clearly associated with long-term morbidity and mortality after STEMI.[5] In addition, postinfarction LV remodeling has been usually reported to have an impaired prognosis, more often developing into clinical heart failure and resulting in increased mortality.[6] Using the database of "Impact of Immediate Stent Implantation Versus Deferred Stent Implantation on Infarct Size and Microvascular Perfusion in Patients With ST-Segment Elevation Myocardial Infarction (INNOVATION)" trial (*Clinical Trial Registration* – http://www.clinicaltrials.gov. Unique identifier: NCT02324348), therefore, we sought to evaluate whether prolonged postprocedural anticoagulation affected infarct size determined by CMR after 1 month and affected LVEF and LV remodeling assessed by 2D-echocardiography after 9 months of primary PCI.

2. Methods

2.1. Population

As previously described,[7] 114 patients with STEMI undergoing primary PCI at 2 sites were enrolled in the INNOVATION trial. Eligible patients were randomly assigned to the immediate stenting group and deferred stenting group in a 1:1 ratio after achievement of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow before stent implantation. The study was approved by the appropriate institutional review committees and all patients provided written informed consent. Figure 1 shows patient selection and study group classification for the present analysis.

2.2. Procedure

All patients received 300 mg of aspirin and a loading dose of the P2Y12 receptor inhibitor (600 mg of clopidogrel, 180 mg of ticagrelor, or 60 mg of prasugrel) before primary PCI. The selection of thienopyridine was left to the intensivist's discretion. Anticoagulation during primary PCI was performed with unfractionated heparin to achieve an activated clotting time of 250 s or longer throughout the procedure. The infusion of intracoronary abciximab (0.25 mg/kg) was highly recommended in most of the patients without a contraindication for glycoprotein IIb/IIIa receptor blockers after the guidewire was passed through the culprit lesion. All interventions were performed according to current PCI practice guideline. In the deferred stenting group, the second-stage stenting procedure was scheduled to be performed at 3–7 days after primary reperfusion procedure. If patients with concurrent STEMI and multivessel disease underwent primary PCI, intervention for noninfarct related artery was deferred in both the groups. Postprocedural anticoagulation for routine prophylaxis was defined as administration of specific anticoagulating agents (unfractionated heparin or low-molecular weight heparin) as per interventionist's discretion after primary PCI without separate indications. The duration of drug administration was left to the physician's preference; however, the reasons for performing prolonged postprocedural anticoagulation were not elucidated in this database. Dual antiplatelet therapy was maintained for >12

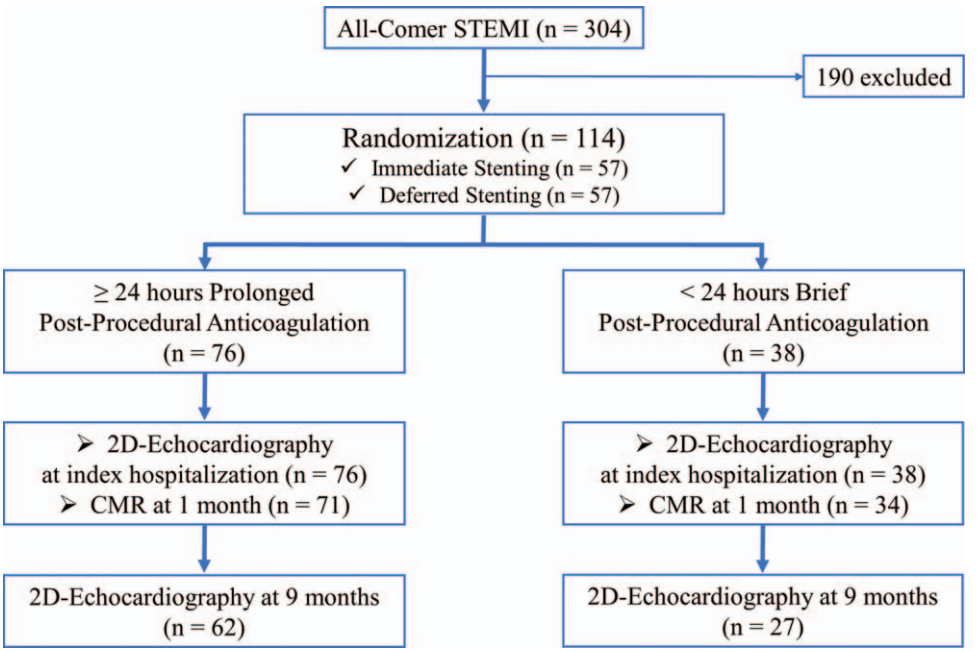

Figure 1. Study population. CMR = cardiac magnetic resonance, STEMI = ST-segment elevation myocardial infarction.

months; and β-blockers, angiotensin aldosterone system blockers, and statins were given to patients according to current medical guidelines. High-intensity statin was highly recommended before or after primary reperfusion procedure in all eligible patients.

2.3. Definitions

Markers of reperfusion were assessed by independent, blinded core electrocardiography (ST-segment resolution) and angiography (TIMI flow, corrected TIMI frame counts, myocardial blush grade (MBG), and TIMI myocardial perfusion grade) laboratories at the Sejong General Hospital, Bucheon, Korea, using standard definitions.[8] An independent Clinical Events Committee adjudicated all major adverse events. Clinical follow-up was performed in the outpatient clinics with laboratory analyses including follow-up 2D-echocardiography.

2.4. Contrast CMR imaging protocols and analysis

CMR imaging was performed using a 1.5-T whole-body scanner. Infarct tissue was defined as an area of hyperenhancement on late gadolinium enhancement images. MVO was defined as an area of hypo-enhancement within the hyper-enhanced infarct tissue. Quantitative core laboratory measurements of infarct and MVO sizes were obtained by a cardiac radiologist who was a specialist in CMR imaging at Sejong general hospital and was blinded to random assignment. Echocardiography was performed by independent experienced observers according to standard clinical practice guidelines using a commercially available equipment (Vivid 7, GE Medical Systems, Milwaukee, WI, USA; Acuson 512, Siemens Medical Solution, Mountain View, CA, USA; or Sonos 5500, Philips Medical System, Andover, MA, USA).

2.5. Study end points

The primary objective was to assess the relationship between the administration of postprocedural anticoagulation therapy and 30-day infarct size (percentage of total left ventricular mass) assessed by CMR after primary reperfusion procedure. Secondary outcomes were LVEF and occurrence of LV remodeling, which was defined as >20% increase in LV end-diastolic volume, assessed by 2D-echocardiography at the median period of 9 months follow-up. Bleeding events were also evaluated as safety end points.

2.6. Statistical analysis

Continuous variables were summarized as medians with interquartile ranges (IQR, 25th percentile – 75th percentile) or mean ± standard deviation and were compared by using the Student's *t*-test or the nonparametric Mann–Whitney *U* test. Binary variables were presented as numbers and percentages and were compared with the Pearson's Chi-Square test or the Fisher's Exact test. Correlation analysis was performed using Pearson's correlation coefficient. Because differences in baseline characteristics could significantly affect outcomes, sensitivity analyses were performed to adjust for confounders as much as possible. Adjusted multivariable logistic linear regression model was performed to assess the association between postprocedural anticoagulation and larger infarct (defined as >75 percentile of infarct size) assessed by CMR. Covariates included in multivariable model were selected if they were significantly different between the 2 groups or had predictive values, which are listed as follows: age, initial heart rate, initial glucose level, anterior STEMI, multivessel disease, symptom to reperfusion time, preprocedural TIMI flow grade, deferred stenting, prolonged postprocedural anticoagulation, and propensity score. The propensity score, which represents the probability of administration of prolonged anticoagulation therapy, was estimated irrespective of the outcomes by performing multiple logistic regression analysis. A fully nonparsimonious model was developed which included following variables: age, sex, body mass index, diabetes, hypertension, dyslipidemia, previous cerebrovascular accident, previous PCI, initial glucose and brain natriuretic peptide levels, anterior STEMI, multivessel disease, radial or femoral access, manual thrombus aspiration, deferred stenting, total length of stent implanted, complete revascularization, postprocedural TIMI flow, myocardial blush grade, and complete ST-segment resolution. The two-sided *P* values were considered; $P < .05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Baseline characteristics

From February 2013 to March 2015, a total of 304 patients were screened for enrollment in the INNOVATION trial. Of these patients, 114 patients were enrolled and randomly assigned to either the deferred stenting strategy ($n=57$) or the immediate stenting treatment ($n=57$). More than 80% of patients were males (83.3%), median age of 59.5 years (IQR, 49.8–69.3 years), and 30.7% of patients were suffering from diabetes mellitus. Median time between symptom onset and reperfusion was 198.5 min (IQR, 130.0–349.8 min), and frequency of preprocedural TIMI grade 0/1 flow was 92 (80.7%).

Among the 114 patients who underwent primary PCI, 76 (66.7%) patients received prolonged postprocedure anticoagulation therapy (>24 h), while 38 (33.3%) patients received brief anticoagulation (<24 h). As shown in Table 1, patients receiving prolonged postprocedural anticoagulation therapy appeared to be a lower-risk cohort; patients receiving prolonged postprocedural anticoagulation therapy were younger, tended to have a higher body mass index, tended to have lower incidence of previous cerebrovascular accident, and more likely to have lower levels of glucose at the time of index hospitalization. With regard to angiographic characteristics, multivessel disease was less frequent in the arm receiving prolonged postprocedural anticoagulation therapy. However, the frequency of anterior STEMI was similar between the two groups, and preprocedural TIMI flow grade or TIMI thrombus grade was also not different between the two groups. Regarding procedural characteristics (Table 2), manual thrombus aspiration was used more commonly in those receiving prolonged post-PCI anticoagulation therapy (84.2% versus 55.3%, $P=.001$). There was no between-group heterogenicity from the time of symptom onset to reperfusion (median time: 183.5 min versus 210.0 min, $P=.339$), and the frequency of deferred stenting was similar in both the anticoagulation groups (55.3% versus 39.5%, $P=.112$). After the procedure, the rate of post-TIMI grade 2 or 3, MBG grade 2 or 3, TIMI myocardial perfusion grade 2 or 3, and corrected TIMI frame count were also not significantly different. However, as compared to the patients treated with brief anticoagulation

Table 1

Baseline characteristics.

	Overall (n=114)	Prolonged anticoagulation (n=76)	Brief anticoagulation (n=38)	P value
Age (year)	59.5±11.8	57.8±11.7	63.0±11.2	.026
Gender (male)	95 (83.3)	65 (85.5)	30 (78.9)	.374
Body mass index (kg/m^2)	24.5±3.2	24.9±3.5	23.8±2.4	.075
Vital sign				
Systolic blood pressure (mmHg)	129.2±22.5	127.9±19.1	131.7±28.4	.462
Diastolic blood pressure (mmHg)	79.0±16.6	78.6±15.5	19.9±18.8	.691
Heart rate (/min)	77.0±16.6	76.4±15.4	78.3±19.0	.574
Diabetes (%)	35 (30.7)	20 (26.3)	15 (39.5)	.151
Hypertension (%)	54 (47.4)	40 (52.6)	14 (36.8)	.111
Dyslipidemia (%)	40 (35.1)	30 (39.5)	10 (26.3)	.165
Current smoking (%)	60 (52.6)	42 (55.3)	18 (47.4)	.426
Previous cerebrovascular accident (%)	6 (5.3)	2 (2.6)	4 (10.5)	.094
Previous PCI (%)	2 (1.8)	1 (1.3)	1 (2.6)	>.99
Killip class ≥ II (%)	5 (4.4)	2 (2.6)	3 (7.9)	.311
WBC (10^3/μL)	11,790±3780	11,816±3762	11,737±3867	.917
Hemoglobin (g/dL)	15.0±3.3	15.1±3.8	14.7±1.9	.482
Glucose (mg/dL)	167.8±63.2	156.3±53.4	190.9±74.9	.015
Liver profile				
AST (U/L)	54.2±80.2	51.1±71.7	60.6±95.9	.554
ALT (U/L)	32.2±34.5	29.5±19.7	37.6±52.9	.367
Lipid profile				
Total cholesterol (mg/dL)	182.7±41.4	183.8±38.9	180.6±46.5	.707
LDL (mg/dL)	123.9±36.9	125.8±35.8	120.3±39.2	.461
HDL (mg/dL)	42.2±9.5	41.4±7.6	43.9±12.2	.243
TG (mg/dL)	128.4±112.4	137.8±117.4	110.3±101.1	.222
CRP (mg/dL)	22.1±32.8	23.1±34.5	19.8±28.9	.642
Brain natriuretic peptide (pg/mL)	119.5 (35.0–312.8)	101.0 (33.0–304.0)	152.0 (48.0–359.0)	.378
Culprit lesion (%)				.045
LAD	69 (60.5)	45 (59.2)	24 (63.2)	
LCx	5 (4.4)	1 (1.3)	4 (10.5)	
RCA	40 (35.1)	30 (39.5)	10 (26.3)	
Anterior STEMI	69 (60.5)	45 (59.2)	24 (63.2)	.684
Extent of CAD (%)				.013
1 VD	41 (36.0)	33 (43.4)	8 (21.1)	
2 VD	45 (39.5)	30 (39.5)	15 (39.5)	
3 VD	28 (24.6)	13 (17.1)	15 (39.5)	
Multi-vessel disease	73 (64.0)	43 (56.6)	30 (78.9)	.019
Lesion type B2C	104 (91.2)	70 (92.1)	34 (89.5)	.640
LM as culprit lesion (%)	3 (2.6)	2 (2.6)	1 (2.6)	>.99
Pre-TIMI				.764
0	73 (64.0)	48 (63.2)	25 (65.8)	
1	19 (16.7)	14 (18.4)	5 (13.2)	
2	22 (19.3)	14 (18.4)	8 (21.1)	
TIMI thrombus grade				.408
1	3 (2.6)	1 (1.3)	2 (5.3)	
2	1 (0.9)	0 (0.0)	1 (2.6)	
3	10 (8.8)	6 (7.9)	4 (10.5)	
4	15 (13.2)	10 (13.2)	5 (13.2)	
5	85 (74.6)	59 (77.6)	26 (68.4)	

CAD = coronary artery disease, CRP = C-reactive protein, HDL = high-density lipoprotein, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, ALT = alanine aminotransferase, AST = aspartate aminotransferase, LDL = low-density lipoprotein, LM = left main coronary artery, PCI = percutaneous coronary intervention, RCA = right coronary artery, STEMI = ST-segment elevation myocardial infarction, TG = triglyceride, TIMI = thrombolysis in myocardial infarction, VD = vessel disease, WBC = white blood count.

therapy, those treated with prolonged postprocedural anticoagulation therapy were significantly less likely to achieve complete revascularization (75.0% versus 92.1%, P=.042) and complete ST-segment resolution (34.2% versus 54.1%, P=.044) after 60 min of primary PCI.

The median time for postprocedural anticoagulation therapy was 72.6 (IQR, 50.0–91.2 h) h in the prolonged postprocedural anticoagulation group and 5.0 (IQR, 5.0–12.0 h) h in the brief anticoagulation group (Table 2). The use of intracoronary or intravenous abciximab was frequent in those receiving prolonged postprocedural anticoagulation therapy (80.3% versus 60.5%, P=.024). After primary PCI, the peak level of the creatine kinase-myocardial band was similar and the duration of hospitalization did not differ significantly between the two groups. Discharge prescription of guideline recommended optimal therapies were not influenced by the duration of post-PCI anticoagulation therapy, except for angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor

Table 2

Peri-procedural characteristics.

	Overall ($n=114$)	Prolonged anticoagulation ($n=76$)	Brief anticoagulation ($n=38$)	*P* value
Duration of anticoagulation (h)	50.2 (10.3–80.9)	72.6 (50.0–91.2)	5.0 (5.0–12.0)	<.001
Abciximab use	84 (73.7)	61 (80.3)	23 (60.5)	.024
Trans-femoral access	74 (64.9)	53 (69.7)	21 (55.3)	.127
Symptom to TIMI 3 flow time	198.5 (130.0–349.8)	183.5 (123.5–333.5)	210.0 (139.5–397.8)	.339
Manual thrombus aspiration	85 (74.6)	64 (84.2)	21 (55.3)	.001
Deferred stenting	57 (50.0)	42 (55.3)	15 (39.5)	.112
Complete revascularization	92 (80.7)	57 (75.0)	35 (92.1)	.042
Slow or no-reflow	33 (28.9)	22 (28.9)	11 (28.9)	>.99
Total length of stent implanted (mm)	26.2±13.0	25.3±12.7	27.9±13.7	.326
Final TIMI				.257
2	3 (2.6)	1 (1.3)	2 (5.3)	
3	111 (97.4)	75 (98.7)	36 (94.7)	
MBG				.121
0	5 (4.4)	1 (1.3)	4 (10.5)	
1	6 (5.3)	4 (5.3)	2 (5.3)	
2	14 (12.3)	11 (14.5)	3 (7.9)	
3	89 (78.1)	60 (78.9)	29 (76.3)	
MBG 2 or 3	103 (90.4)	71 (93.4)	32 (84.2)	.116
TMPG 2 or 3	99 (86.8)	68 (89.5)	31 (81.6)	.240
Final cTFC	34.9±13.7	35.2±13.3	34.4±14.5	.755
Peak CK-MB	230.1±158.3	221.1±146.3	248.0±180.1	.395
Complete STR	46 (40.7)	26 (34.2)	20 (54.1)	.044
Hospital stay (h)	114.6 (89.0–147.6)	117.8 (91.5–145.5)	99.1 (81.9–165.6)	.482
Discharge medications				
Aspirin	112 (98.2)	76 (100.0)	36 (94.7)	.327
Thienopyridine	113 (99.1)	76 (100)	37 (97.4)	.333
ACEI or ARB	79 (69.9)	59 (77.6)	20 (54.1)	.016
Beta blocker	96 (85.0)	68 (89.5)	28 (75.7)	.090
Statin	110 (97.3)	74 (97.4)	36 (94.7)	>.99

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CK-MB = creatine kinase-myocardial band, cTFC = corrected TIMI frame counts, MBG = myocardial brush grade, STR = ST-segment resolution, TIMI = thrombolysis in myocardial infarction, TMPG = TIMI myocardial perfusion grade.

blockers (ARB), and beta-blockers. Patients in the group of prolonged postprocedural anticoagulation were more likely to be received ACEI or ARB and tended to be prescribed beta-blockers on discharge (Table 2).

3.2. Safety end points

As presented in Table 3, the decision to use prolonged postprocedural anticoagulation had no effect on the rate of in-hospital major bleeding. There were no patients who had TIMI major bleeding in the prolonged postprocedural anticoagulation group, while only 1 patient had TIMI major bleeding in the brief postprocedural anticoagulation group. There were also no significant differences in the rates of in-hospital adverse clinical outcomes in patients who received prolonged postprocedural anticoagulation therapy for routine prophylaxis as compared to those who received brief anticoagulation therapy (Table 3).

3.3. Efficacy end points

The median duration between primary reperfusion and CMR in the overall population was 30.5 (IQR: 28.0–34.0 days) days (Table 4). The infarct size and the incidence of MVO were not significantly different between the two groups (15.6%±9.7% versus 19.8%±13.2%; $P=.110$ for infarct size; and 50.7% versus 52.9%; $P=.830$ for MVO incidence). The volume (mass) of MVO (0.40±0.58 g versus 0.49±0.70 g; $P=.505$) and the ratio of MVO to infarct size (1.85±2.43 versus 1.99±2.86; $P=.784$) were also not significantly different between the two groups. As continuous variables, duration of postprocedural

Table 3

In-hospital outcomes.

	Overall ($n=114$)	Prolonged anticoagulation ($n=76$)	Brief anticoagulation ($n=38$)	*P* value
TIMI major bleeding ($n=111$)	1 (0.9)	0 (0.0)	1 (2.7)	.327
All-cause death ($n=111$)	0 (0.0)	0 (0.0)	0 (0.0)	–
Myocardial re-infarction ($n=111$)	1 (0.9)	1 (1.3)	0 (0.0)	>.99
Any repeat revascularization ($n=111$)	2 (1.8)	1 (1.3)	1 (2.8)	.545
Acute or sub-acute stent thrombosis ($n=111$)	1 (0.9)	1 (1.3)	0 (0.0)	>.99
New heart failure ($n=111$)	1 (0.9)	0 (0.0)	1 (2.8)	.324

TIMI = thrombolysis in myocardial infarction.

Table 4

Cardiac magnetic resonance.

	Overall ($n=105$)	Prolonged anticoagulation ($n=71$)	Brief anticoagulation ($n=34$)	*P* value
Reperfusion to CMR time (Day)	30.5 (28.0–34.0)	31.0 (29.0–34.0)	28.5 (19.8–36.8)	.748
Myocardial mass (g)	90.6±20.8	89.5±21.9	93.0±18.3	.438
Infarct size (%)	16.9±11.0	15.6±9.7	19.8±13.1	.100
Infarct mass (g)	15.8±11.7	14.7±11.3	18.3±12.3	.138
Presence of MVO (%)	54 (51.4)	36 (50.7)	18 (52.9)	.830
MVO mass (g)	0.430±0.621	0.401±0.581	0.488±0.703	.505
MVO to infarct ratio	1.894±2.565	1.846±2.434	1.994±2.857	.784

CMR = cardiac magnetic resonance, MVO = microvascular obstruction.

anticoagulation was not linearly correlated to infarct size (Pearson coefficient, $r=-0.151$; $P=.125$). In multivariate logistic regression analysis, both larger infarct (adjusted odd ratio [OR]: 0.435; 95% confidence interval [CI]: 0.120–1.573; $P=.204$) and occurrence of MVO (adjusted OR: 0.896, 95% CI: 0.328–2.451, $P=.831$) did not show any difference between the two groups. Similar results were observed for larger infarct in the subanalyses of major high-risk subgroups (Fig. 2).

The first 2D-echocardiography study was performed during the initial hospitalization, and the second 2D-echocardiography study was completed after median 263 days (IQR, 186–298 days). Between the groups, there was no statistically significant difference in LVEF at baseline or at 9 months 2D-echocardiography, nor difference in ΔLVEF between the two 2D-echocardiographic studies (Table 5). After adjustment of the variables, prolonged postprocedural anticoagulation was not reported as an independent predictor of the LVEF <35% on follow-up 2D-echocardiography (3.2% versus 7.4%; adjusted OR: 0.383; 95% CI: 0.051–2.884; $P=.352$). Besides, LV remodeling, which was defined as >20% increase in LV end-diastolic volume in the 9-month follow-up 2D-echocardiography, occurred in 28/89 (31.5%) patients; and prolonged postprocedural anticoagulation therapy did not produce any beneficial effect on LV remodeling independently as analyzed by multivariate linear regression (37.1% versus 18.5%; adjusted OR: 2.249; 95% CI: 0.593–8.535; $P=.234$).

4. Discussion

In this post-hoc analysis of randomized study, it was investigated whether prolonged administration of postprocedural anticoagulation could reduce the size of myocardial infarction in STEMI patients undergoing primary PCI. The major finding of this study was that prolonged anticoagulation therapy did not reduce myocardial infarct size as evaluated by CMR as compared to the brief anticoagulation therapy. Exploratory subgroup analyses showed consistent neutral effects of prolonged anticoagulation in various subgroups. There were also no differences

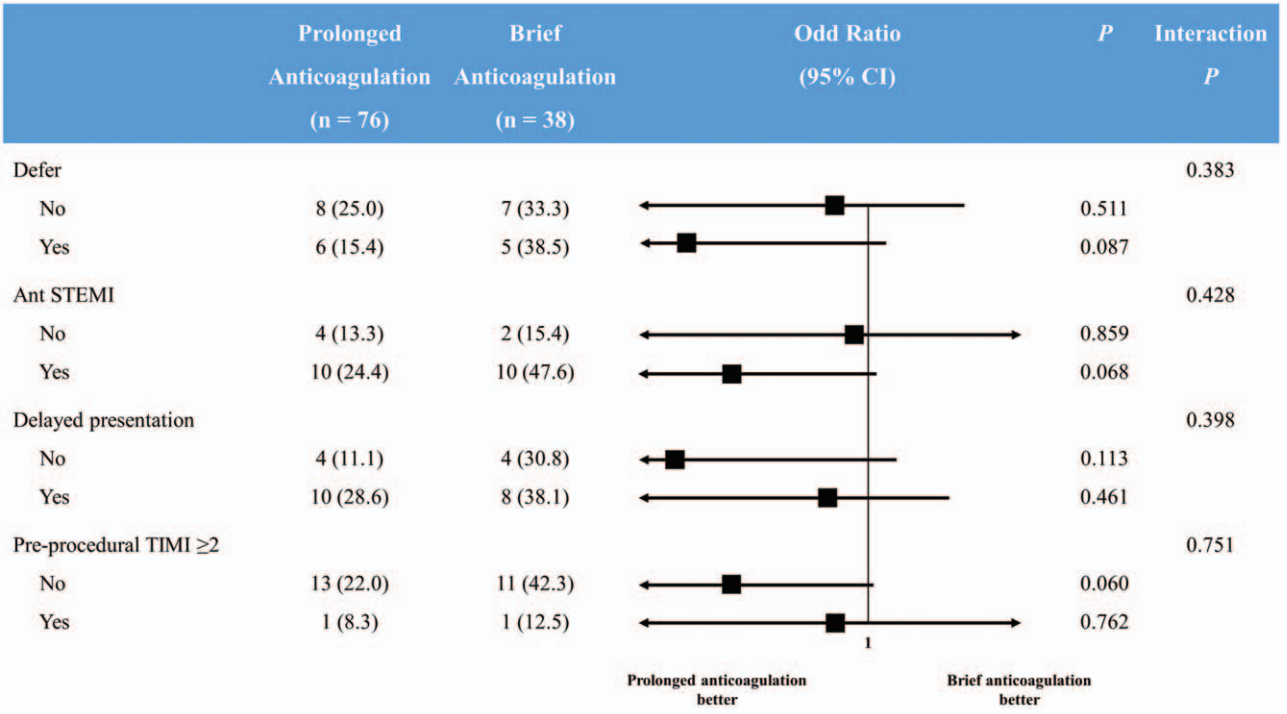

Figure 2. Subgroup analysis of larger infarct. Ant = anterior, OR = odd ratio, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction. Delayed presentation = defined as time from the symptom onset to reperfusion, which is > 180(min).

Table 5

2D-echocardiography.

Baseline				
	Overall (n=114)	**Prolonged anticoagulation (n=76)**	**Brief anticoagulation (n=38)**	***P* value**
LVEF (%)	48.8±10.1	49.1±10.0	48.2±10.5	.700
LVEF <35 (%)	9 (10.1)	7 (11.3)	2 (7.4)	.717
LVEDV (mL)	85.3±29.5	84.0±24.9	88.3±38.5	.530
E/*E*′	12.0±4.8	12.0±5.1	11.8±4.2	.894
LAVI (mL/BSA)	29.3±10.0	29.3±9.2	29.2±11.9	.672
LAVI >34 (mL/BSA)	25 (28.1)	17 (27.4)	8 (29.6)	.831
Follow-up				
	Overall (n=89)	**Prolonged anticoagulation (n=62)**	**Brief anticoagulation (n=27)**	***P* value**
LVEF (%)	52.5±9.1	52.8±8.6	51.9±10.4	.675
LVEF <35 (%)	4 (4.5)	2 (3.2)	2 (7.4)	.582
Δ LVEF (%)	3.7±7.6	3.7±8.0	3.7±6.8	.993
LVEDV (mL)	89.2±30.4	88.5±27.0	91.0±37.7	.719
Δ LVEDV (mL)	2.3 (-13.3 to 25.7)	2.3 (-13.4 to 26.2)	2.3 (-13.1 to 14.0)	.430
LV remodeling	28 (31.5)	23 (37.1)	5 (18.5)	.083
E/*E*′	10.1±3.2	9.8±3.1	11.0±3.4	.091
LAVI (mL/BSA)	31.0±9.4	29.3±9.2	29.2±11.9	.672
LAVI >34 (mL/BSA)	26 (29.2)	19 (30.6)	7 (25.9)	.653

BSA = body surface area, LAVI = left atrial volume index, LV = left ventricular, LVEDV = left ventricular end diastolic volume, LVEF = left ventricular ejection fraction.

either in LVEF or in the incidence of LV remodeling between the two groups.

Patients with STEMI are at high-risk for both recurrent ischemic events and hemorrhagic complications. Adverse ischemic events may result from persistent activation of the coagulation cascade and tissue factor upregulation in the pathogenesis of STEMI, inadequate antithrombin or platelet inhibition, and/or early therapy discontinuation because of bleeding.[9–11] Moreover, during the mechanical reperfusion process, thrombus material and other plaque debris may be distally embolized, contributing to MVO, and microembolization may underlie infarct expansion in the border zone.[9,12] Therefore, prolonged postprocedural anticoagulation therapy may theoretically reduce ischemic injury and recurrent ischemia after primary PCI. However, few studies have examined the practice of using post-PCI anticoagulation routinely without specific indications in the contemporary era of the drug-eluting stent and adjunct pharmacotherapy. Recently, some postrandomization subgroup analyses have reported that postprocedural anticoagulation is associated with an increased risk of bleeding without any evident benefit of reducing ischemic events.[13,14] Therefore, routine postprocedural anticoagulant therapy is not indicated after primary PCI, except when there is a separate indication for either full-dose anticoagulation (for instance, due to atrial fibrillation, mechanical valves, or left ventricular thrombus) or prophylactic doses for prevention of venous thromboembolism in patients requiring prolonged bed rest.[2] However, this recommendation belongs to Class IIa (moderate), and the level of evidence is C (consensus of opinion of the experts). Besides, the American College of Cardiology/American Heart Association guidelines currently do not provide a specific recommendation for postprocedural anticoagulation,[1] suggesting further study is required to determine the relative safety and efficacy of various antithrombotic regimens used for postprocedural anticoagulation. In this context, the authors assessed the impact of prolonged postprocedural anticoagulation therapy on infarct size by using CMR. In the study, we demonstrated that prolonged anticoagulation after primary PCI did not reduce size of myocardial infarction.

No significant difference of outcomes between the 2 groups of our study may be explained by the difference in the changes in clinical practice. Previous studies, in which excellent outcomes of primary percutaneous transluminal coronary balloon angioplasty alone were obtained with unfractionated heparin, incorporated a 60-hour to 1-week postangioplasty course of intravenous heparin.[15–17] However, the stent implantation during primary PCI is now being widely accepted as an important measure to effectively prevent ischemic events.[18] Therefore, the protective effect of postprocedural anticoagulation after coronary balloon angioplasty alone might become less significant. In addition, the introduction of the safer drug-eluting stent has further reduced the risk of peri-procedural ischemic complications.[19] Also, an assessment of the role of postprocedural anticoagulation in patients with acute myocardial infarction requires consideration of antiplatelet therapy. Antiplatelet agents are the core of medical management in patients with acute myocardial infarction; dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) is essential to mitigate the risk of ischemic events such as stent thrombosis after PCI.[1,2] When platelet function is profoundly inhibited by more aggressive antiplatelet therapy, the association of postprocedural anticoagulation might be attenuated.

Contrary to expectations, patients receiving prolonged postprocedural anticoagulation therapy in our study did not experience increased bleeding, likely because postprocedural anticoagulation was only administered for a median period of 3 days in the prolonged postprocedural anticoagulation group, which is a substantially shorter duration than that in previous studies in which bleeding was increased with this practice.[14,15,17] The manual thrombus aspiration and abciximab were used more commonly in patients receiving prolonged post-PCI anticoagulation therapy. Also, those receiving prolonged postprocedural anticoagulation therapy were significantly less likely to achieve complete revascularization and complete

ST-segment resolution after 60 min of primary PCI. It is assumed that prolonged post-PCI anticoagulation use might have been favored for those with suboptimal angiographic results.

4.1. Limitations

CMR is uniquely suited to provide important mechanistic and pathophysiological information on infarct size, MVO, and intramyocardial hemorrhage.[3,4] To the authors' knowledge, this is the first post-hoc analysis of randomized study to evaluate the impact of postprocedural anticoagulation on infarct size, LVEF, and LV remodeling in patients with STEMI undergoing primary PCI by using CMR and 2D-echocardiography. However, several limitations of the study should be emphasized. First, as a nonrandomized post-hoc analysis, this study cannot prove causality. Although multiple adjustments for confounding factors, including propensity score, were performed to account for differences between the groups, unmeasured confounders may not have been fully controlled for. Therefore, the present study should be considered hypothesis-generating; only a randomized trial can determine whether any benefits may be added from postprocedural anticoagulation for routine prophylaxis in patients undergoing primary PCI. Another limitation of the study is the number of patients enrolled and the number of events that occurred. Owing to the small number of patients enrolled, the present study cannot demonstrate sufficiently the differences in efficacy or safety between two anticoagulation regimens, and the limited number of adverse clinical outcomes in the present study precludes performing a comprehensive multivariable analysis to determine the predictors of such clinical outcomes. Third, a low-risk subgroup was focused, therefore, the present study cannot demonstrate sufficiently whether specific subsets of patients may most likely benefit from postprocedural anticoagulation to prevent thromboembolic complications, such as those with STEMI due to stent thrombosis, cardiogenic shock, and severe LV dysfunction. Fourth, the breakup of postprocedural anticoagulation use between patients with specific indications and those who received such therapy routinely after primary PCI was not elucidated in the present INNOVATION trial database. However, patients with (1) rescue PCI after fibrinolysis, (2) STEMI because of stent thrombosis, and (3) major coronary dissection (type D–F) after procedures achieving TIMI grade 3 flow were excluded; the number of patients with atrial fibrillation/atrial flutter was just 6/114 (5.3%); and there were no patients with mechanical valves requiring anticoagulation maintenance in the INNOVATION trial. Finally, costs were not determined, and as such we cannot state with certainty whether the use of postprocedural anticoagulation therapy increases the expenditure indeed, although this is likely with a median of 18.7-h-longer hospitalizations.

4.2. Future directions

Our results provide further evidence that although prolonged post-PCI anticoagulation was relatively safe, the use of such therapy contributed to delayed discharge and likely increased costs, without apparent benefit. In terms of clinical translation, our results highlight that the routine use of anticoagulation therapy after successful primary PCI should be avoided, and this antithrombotic regimen should be removed from standard clinical practice protocols to avoid automatic implementation. However, further studies are needed to determine the subgroups of patients with STEMI, in whom routine postprocedural anticoagulation therapy may be required after primary PCI.

5. Conclusion

In conclusion, data did not reveal any significant differences in patients' CMR, 2D-echocardiography, and clinical outcomes related to the prolonged or brief period of anticoagulation after the primary PCI for STEMI. Based on the results, there may not be additional benefit with a prolonged postprocedural anticoagulation; further studies are warranted to determine the role of post-PCI anticoagulation in this context.

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