Post-Procedural Anticoagulation After Primary Percutaneous Coronary Intervention for Anterior Acute Myocardial Infarction With Severe Left Ventricular Dysfunction

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Background: Patients with anterior acute myocardial infarction (AMI) and left ventricular (LV) dysfunction have an increased risk of LV thrombus (LVT). In the thrombolytic era, short-term anticoagulation using low-molecular-weight heparin during hospitalization proved to significantly reduce LVT formation, but, the effect of this prophylactic approach remains unclear in the current era. Therefore, we conducted a study to evaluate the effects of post-procedural anticoagulation (PPAC) using enoxaparin in addition to dual antiplatelet therapy (DAPT) after primary percutaneous coronary intervention (PCI) in such patients.

Methods and Results: A total of 426 anterior AMI patients with LV ejection fraction $\leq 40\%$ were retrospectively enrolled and classified into 2 groups based on whether they received PPAC (enoxaparin SC for at least 7 days). All patients received primary PCI and DAPT. The primary endpoint was definite LVT at 30 days diagnosed by echocardiography. The secondary endpoints were 30-day mortality, embolic events, and major bleeding events. PPAC was independently associated with a lower incidence of LVT (odds ratio 0.139, 95% confidence interval 0.032–0.606, $P=0.009$). The 30-day mortality, embolic events, and major bleeding events were not statistically different between groups.

Conclusions: Short-term PPAC using enoxaparin after primary PCI may be an effective and safe way to prevent LVT in patients with anterior AMI and LV dysfunction.

Key Words: Acute myocardial infarction; Anticoagulation; Left ventricular thrombus; Percutaneous coronary intervention

Patients with anterior acute myocardial infarction (AMI) and left ventricular (LV) dysfunction have an increased risk of LV thrombus (LVT) formation, which can lead to systemic embolism and even death.¹ Although the prevalence of LVT has been reduced with the advent of primary percutaneous coronary intervention (PCI) and routine use of dual antiplatelet therapy (DAPT), a recent meta-analysis showed that 9.1% of anterior AMI patients were developing LVT in the current era.² Warfarin, as a prophylactic strategy in addition to DAPT after primary PCI, is therefore utilized and was once recommended by guidelines for patients with increased risk of LVT formation.^{3,4} However, results from recent studies and meta-analysis do not support the additional use of warfarin in such patients because it brings no mortality benefit while increasing the frequency of major bleeding.^{5–7} Thus, identifying other safe and effective strategies to prevent LVT formation in high-risk patients remains worthwhile. In the pre-PCI era, short-term anticoagulation using

low-molecular-weight heparin (LMWH) during hospitalization was proved to significantly reduce LVT formation in anterior AMI.^{8–10} Furthermore, LMWH seems to have less hemorrhagic risk than that observed with warfarin, and thus may represent a more promising tool for prophylaxis against LVT formation. However, it is unclear whether this prophylactic benefit still exists when patients are managed with primary PCI according to contemporary practice. Despite routine administration of LMWH after primary PCI, known as post-procedure anticoagulation (PPAC), is not recommended in the latest ST-segment elevation myocardial infarction (STEMI) guideline,¹¹ so the role of PPAC as prophylaxis against LVT formation in high-risk patients has not been well established. Therefore, the aim of the current study was to evaluate whether in-hospital PPAC using enoxaparin after primary PCI contributed to a lower incidence of LVT in patients with anterior AMI and LV dysfunction, and to assess its association with 30-day outcomes.

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Figure 1. Transthoracic echocardiography revealed the absence of left ventricular thrombus on admission (**A**), and its presence at 30 days follow-up (**B**, white arrow).

Methods

Study Population

Patients who presented with anterior AMI and LV ejection fraction (LVEF) $\leq 40\%$ at admission and who underwent primary PCI at the Second Xiangya Hospital between January 2011 and December 2016 were retrospectively enrolled in this study. The diagnosis of anterior AMI was based on chest pain lasting >30 min, persistent ST-segment elevation (≥ 0.2 mV), or Q waves in the precordial leads (V1–V6) on 12-lead ECG and later confirmed by increased cardiac markers (e.g., cardiac troponin I (cTnI) >99 th percentile upper reference limit). LVEF was obtained from the first transthoracic echocardiography performed within 48 h of admission. Patients were excluded from the analysis if they (1) presented with LVT or other indications for anticoagulation, including atrial fibrillation, mechanical valves, deep venous thrombosis, etc; (2) had contraindications to anticoagulation; (3) underwent a rescue or planned PCI immediately after thrombolysis; and (4) had records with missing or incomplete data. Patients were classified into 2 groups based on whether they routinely received PPAC therapy. The decision concerning routine PPAC therapy or not was at the physician's discretion. Our departmental policy for routine PPAC was to use enoxaparin (1 mg/kg, maximum 100 mg, SC every 12 h) after primary PCI for 7 days. Enoxaparin was injected in the abdominal region. Baseline demographic, procedural, and echocardiographic data were obtained from the medical records by trained staff. All patients completed 30 days of post-hospitalization follow-up. The study was conducted in accordance with the Declaration of Helsinki.

Standard Therapy

All patients received 300 mg of aspirin and a loading dose of a P2Y₁₂ receptor inhibitor (300 mg of clopidogrel or 180 mg of ticagrelor) before primary PCI. An intravenous bolus of weight-adjusted unfractionated heparin was administered to achieve an activated clotting time of 200–250 s during the procedure. Additional heparin was given at a dose guided by the activated clotting time. The use of

glycoprotein IIb/IIIa inhibitor (tirofiban, intracoronary or intravenous bolus at 25 μ g/kg and 0.15 μ g/kg/min maintenance infusion for 12–24 h) was left to the operator's discretion. Thrombus aspiration was recommended if there was a relevant thrombus. Direct stenting (without balloon predilatation) implantation was performed whenever possible. Post-PCI medication consisted of DAPT with life-long aspirin 100 mg/day, and clopidogrel 75 mg/day for at least 12 months. Beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and statins were also given according to current guidelines.

Echocardiographic Assessment of LVT

The presence of LVT was assessed using transthoracic echocardiography, which was undertaken within 48 h of admission (baseline data) and repeated at 30-day follow-up. LVT was defined as an echo-dense mass adjacent to an abnormally contracting myocardial segment. To qualify as LVT, the mass had to be distinguishable from the underlying myocardium, have a clear thrombus blood interface, and be visible in >2 views. Echocardiographic findings were interpreted independently by 2 expert cardiologists. Examples of the absence or presence of LVT are illustrated in **Figure 1**.

Study Endpoint

The primary endpoint was definite LVT at 30 days diagnosed by echocardiography. Detection of thrombus at baseline was an exclusion criterion for protocol participation. The secondary endpoints were 30-day mortality, embolic events, and major bleeding events. The embolic events were defined as ischemic stroke diagnosed by neurological examination (NIHSS) and MRI scanning, and peripheral embolism verified by angiography. Major bleeding was defined as intracranial hemorrhage, ≥ 5 g/dL decrease in hemoglobin concentration or $\geq 15\%$ absolute decrease in hematocrit according to Thrombolysis in Myocardial Infarction (TIMI) criteria.¹² The decision on endpoint events was adjudicated through the use of original source documentation by an independent committee unaware of the treatment allocation.

Table 1. Baseline Characteristics of Study Patients

	PPAC (n=168)	No PPAC (n=258)	P value
Age (years)	61 (51–71)	62 (52–72)	0.212
Male	134 (79.8)	213 (82.5)	0.468
Diabetes mellitus	48 (28.6)	42 (16.3)	0.002
Hypertension	105 (62.5)	144 (55.8)	0.171
Hyperlipidemia	88 (33.3)	86 (52.4)	<0.001
Current smoker	100 (59.5)	152 (58.9)	0.901
Prior heart failure	18 (10.7)	24 (9.3)	0.633
Prior MI	17 (10.1)	27 (10.5)	0.909
Prior stroke	4 (2.4)	18 (7)	0.036
Prior PCI	24 (14.3)	33 (12.8)	0.745
Prior CABG	6 (3.6)	6 (2.3)	0.448
Heart rate (beats/min)	84 (74–96)	82 (73–97)	0.63
SBP (mmHg)	119 (104–132)	117 (101–134)	0.562
DBP (mmHg)	74 (65–82)	73 (65–82)	0.725
Killip class			0.061
I	13 (7.7)	24 (9.3)	
II	28 (16.7)	48 (18.6)	
III	98 (58.3)	118 (45.7)	
IV	29 (17.3)	68 (26.4)	
LVEF at admission (%)	25 (20–32)	25 (19–28)	0.278
LVEF at 30 days (%)	22 (20–36)	21 (14–31)	0.541
Peak troponin I (ng/mL)	71 (39–105)	63 (41–112)	0.31
Peak CK (U/L)	3,243 (1,588–3,930)	2,932 (1,026–3,012)	0.247
Peak CKMB (U/L)	311 (89–459)	298 (67–412)	0.643
NT-proBNP (pg/mL)	1,861 (797–4,767)	1,846 (542–3,719)	0.202
eGFR (mL/min/1.73m ²)	90.5 (77–113.5)	99 (80.8–112.2)	0.181
Paroxysmal AF	7 (4.2)	12 (4.6)	0.813

Data are expressed as mean±SD, as n (%), or as median (interquartile range). AF, atrial fibrillation; CABG, coronary artery bypass grafting; CK, creatine kinase; CKMB, creatine kinase myocardial bound; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; PPAC, post-procedural anticoagulation; SBP, systolic blood pressure.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data are reported as mean±SD or median with 25th and 75th percentiles (interquartile range, IQR), if not normally distributed, and were compared using Student's t-test. Categorical data are expressed as percentages and compared by the chi-square test or Fisher's exact test. To account for differences in baseline characteristics, multivariate logistic regression analysis was performed. All variables with P values <0.10 compared between the 2 groups were considered as baseline imbalances and included in the multiple regression model. The enter method and forward-stepwise method were used. All statistical tests were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). P<0.05 was regarded as statistically significant.

Results

A total of 426 patients were enrolled and of them, 168 (39.4%) routinely received PPAC, while 258 (60.6%) did not. The anticoagulant agent used for PPAC in this study was enoxaparin. Baseline clinical characteristics and laboratory variables according to PPAC use are listed in **Table 1**, and procedural data and concomitant medica-

tions are summarized in **Table 2**. Overall, the PPAC group tended to have more diabetes and multivessel disease but less hyperlipidemia and prior stroke. The patients in the PPAC group were also more likely to be receiving statins and ACEI/angiotensin-receptor blockers (ARB). No significant difference was observed between groups with regard to other baseline clinical characteristics. The baseline laboratory findings and key procedural characteristics were also similar between PPAC groups. Paroxysmal atrial fibrillation occurred in 19 patients: 7 of 168 (4.2%) in the PPAC group and 12 of 258 (4.6%) in the no-PPAC group.

Unadjusted 30-Day Outcomes

During hospitalization and the 30 days after discharge, patients receiving PPAC had a significantly lower incidence of LVT (2.4% vs. 8.1%, P=0.013). There was a trend towards a lower incidence of unadjusted mortality and embolic events in the PPAC group compared with the no-PPAC group, but it was statistically non-significant (2.4% vs. 4.8%, P=0.228; 1.8% vs. 3.5%, P=0.379). In detail, embolic events occurred in 11 patients: 3 of 168 in the PPAC group (2 ischemic strokes, 1 peripheral embolism), and 9 of 258 in the no-PPAC group (7 ischemic strokes, 2 peripheral embolism). Major bleeding events occurred in 11 patients: 5 (3%) of 168 in the PPAC group (1 intracra-

	PPAC (n=168)	No PPAC (n=258)	P value
In-hospital medication			
Aspirin	162 (96.4)	247 (95.7)	0.721
P2Y12 receptor inhibitor	158 (94)	230 (89.1)	0.083
GIIb/IIIa receptor inhibitor	182 (70.5)	114 (67.9)	0.556
β-blockers	144 (85.7)	205 (79.5)	0.101
Statins	164 (97.6)	236 (91.5)	0.01
ACEI/ARB	144 (85.7)	166 (64.3)	<0.001
Symptom onset to balloon	221 (142–310)	233 (137–319)	0.426
Door-to-balloon	99 (72–144)	101 (75–132)	0.232
Multivessel disease	80 (47.6)	94 (36.4)	0.022
Arterial access site			
Radial	148 (88.1)	212 (82.2)	0.099
Femoral	38 (22.6)	71 (27.5)	0.257
Stent implanted	106 (63.1)	151 (58.5)	0.346
Thrombus aspiration	50 (29.8)	67 (26)	0.391
Pre-PCI TIMI flow			
0–1	120 (71.4)	199 (77.1)	0.185
2–3	48 (28.6)	59 (22.9)	
Post-PCI TIMI flow			
0–1	20 (11.9)	28 (10.9)	0.737
2–3	148 (88.1)	230 (89.1)	

Data are presented as n (%) or median (interquartile range). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; PCI, percutaneous coronary intervention; PPAC, post-procedural anticoagulation; TIMI, Thrombolysis in Myocardial Infarction.

nial hemorrhage, 2 gastrointestinal bleeding, 1 retroperitoneal bleeding and 1 arterial puncture site bleeding), and 6 (2.3%) of 258 in the no-PPAC group (2 intracranial hemorrhage, 3 gastrointestinal bleeding, 1 urogenital bleeding). The rate of major bleeding events was similar between groups ($P=0.759$). The detailed results of the unadjusted 30-day outcomes are presented in **Table 3**.

Adjusted 30-Day Outcomes

As shown in **Figure 2**, the significant decrease in LVT formation observed with PPAC persisted even after adjustment for baseline imbalances, which included history of diabetes mellitus, history of hyperlipidemia, prior stroke, Killip class, P2Y12 receptor inhibitor use, statins use, ACEI/ARB use, multivessel disease and radial artery access site (odds ratio (OR) 0.139, 95% confidence interval (CI) 0.032–0.606, $P=0.009$). No independent associations were observed between PPAC and mortality, embolic events, and major bleeding events. We also performed forward-stepwise logistic regression to simplify the regression model. Results also demonstrated the robustness of the association between PPAC and LVT formation (OR 0.150, 95% CI 0.040–0.565, $P=0.005$).

Discussion

The major finding in the present study was that PPAC using enoxaparin after primary PCI was independently associated with a decreased incidence of LVT in patients with anterior AMI and LV dysfunction.

The effect of short-term use of LMWHs for the treatment and prevention of LVT after AMI was well demonstrated in the pre-PCI era.^{8–10} Meurin et al conducted a

	PPAC (n=168)	No PPAC (n=258)	P value
Primary outcome			
LVT formation	4 (2.4)	21 (8.1)	0.013
Secondary outcomes			
Mortality	4 (2.4)	12 (4.8)	0.228
Embolic events	3 (1.8)	9 (3.5)	0.379
Ischemic stroke	2 (1.2)	7 (2.7)	
Peripheral embolism	1 (0.6)	2 (0.8)	
Major bleeding events	5 (3)	6 (2.3)	0.759
Intracranial	1 (0.6)	2 (0.8)	
Gastrointestinal	2 (1.2)	3 (1.2)	
Retroperitoneal	1 (0.6)	0 (0)	
Urogenital	0 (0)	1 (0.4)	
Arterial puncture site	1 (0.6)	0 (0)	

Data are presented as n (%). LVT, left ventricular thrombus; PPAC, post-procedural anticoagulation.

study of enoxaparin for short-term treatment of LVT and showed it is well tolerated and efficient in reducing the size and prevalence of thrombi.¹³ Another study by Kontny et al⁸ explored the prophylactic role of LMWH in patients with an AMI treated with thrombolysis. They showed that the addition of dalteparin during hospitalization led to a marked reduction in the formation of LVT compared with placebo (13.8 vs. 21.9%, $P=0.02$). Nevertheless, limited data are available regarding the effect of this prophylactic approach in AMI patients receiving primary PCI and DAPT. One observational study showed that 5 days of

PPAC plus DAPT after primary PCI in patients with anterior AMI was associated with low LVT occurrence (4.7%).¹⁴ But that study did not have a control group, and thus it was not possible to draw a conclusion on whether short-term PPAC was effective in the prevention of LVT. Another randomized trial chose warfarin as the control group and reported that enoxaparin for 30 days was associated with a numerically higher (not statistically significant) risk of LV thrombus compared with a 3-month course of warfarin.¹⁵ However, the role of warfarin in preventing LVT remains controversial, which made it difficult to determine the precise contribution of PPAC to the prevention of LVT formation. In the present study, we compared patients who received PPAC (enoxaparin for 7 days after primary PCI) with those not receiving PPAC and found that the PPAC group had a significantly lower incidence of LVT. Even after adjusting for differences in baseline variables and other medical treatment, a role of PPAC in preventing LVT still existed. Notably, the prevalence of LVT formation in our study was relatively low compared with that reported in the previous study.^{2,14,15} The underlying reason is unclear, but we suspect it may be that most patients in our study received timely primary PCI, DAPT and optimal heart failure treatment. More importantly, the incidence of major bleeding was not increased in the PPAC group. All included patients received DAPT therapy for a minimum of 1 month, and most of them (98%) were recommended to continue this for 12 months. In the PPAC group, patients received enoxaparin. Although the addition of anticoagulant to DAPT, known as triple antithrombotic therapy, has been associated with increases in bleeding events,¹⁶⁻¹⁸ most studies on this topic have had long-term (>6 months) use of warfarin. One study investigating the short-term (1 month) use of triple antithrombotic therapy found no increase in bleeding complications,¹⁸ which is consistent with our results. From this perspective, short-term PPAC using enoxaparin might be a preferable prophylactic strategy to prevent LVT formation without increasing the risk of bleeding. However, these results need to be interpreted with caution. There are several types of LMWH with different chemical properties, which may lead to different

outcomes. It is unknown whether the effect of preventing LVT exists with other LMWHs. Meanwhile, the optimal duration of PPAC in patients such as those we studied is still unclear.

Our previous analysis had already shown that the presence of LVT after AMI indicates a 4-fold increased embolic risk and 2-fold higher long-term mortality rate.¹⁹ A reduction in LVT formation is supposed to benefit patients by decreasing mortality and embolic events. However, such benefits were not shown in the present study. Even though mortality and embolic events were numerically lower in the PPAC group, it was not statistically different. Considering the short follow-up duration (1 month), we could not draw a definitive conclusion. Thus, a large prospective study with a longer follow-up period is required to further explore the influence of PPAC.

Our results extend the application of PPAC to patients with anterior AMI and LV dysfunction after primary PCI. During the thrombolytic era, routine anticoagulation after fibrinolysis was suggested,²⁰ but routine PPAC after primary PCI has been shown to have an unfavorable benefit-risk profile,²¹ and is not indicated in current STEMI guidelines.¹¹ However, its use for specific indications, such as atrial fibrillation, LVT, mechanical heart valves, and deep venous thrombosis, is still indicated and has been examined by several previous studies.^{11,22,23} Our results suggested that PPAC after primary PCI in patients with anterior AMI and LV dysfunction may be necessary.

Study Limitations

Several should be emphasized. First, as a non-randomized retrospective observational analysis, this study cannot prove causality. Although multiple adjustments were performed to account for differences between groups, unmeasured confounders might be present. Second, the short-term follow-up limits the interpretation of the results. Third, the presence of LVT was detected by transthoracic echocardiography, which has limited sensitivity. Contrast-enhanced MRI is a better diagnostic modality with a higher sensitivity, but cost and availability limit its use in daily practice.²⁴

Conclusions

Short-term PPAC using enoxaparin after primary PCI may be an effective and safe way to prevent LVT formation in patients with anterior AMI and LV dysfunction. Large prospective randomized trials are required to verify this finding.

Disclosures

The authors declare no conflict of interest.

IRB Information

The present study has been granted an exemption from requiring ethics approval. Name of the Ethics Committee: Department of Medical Administration Research Ethics Committee. Reference number: none.

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