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Original Article

Effect of enoxaparin on clinical events after percutaneous coronary intervention

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Abstract: Objective: To explore the influence of enoxaparin on clinical events after percutaneous coronary intervention (PCI). Methods: We recruited 400 patients that had undergone the percutaneous coronary intervention without complications in the Cardiology Department of Changhai Hospital consecutively from May 2011 to December 2012. The patients were randomly assigned to receive anticoagulation therapy (enoxaparin) or no anticoagulant. Patients were assessed for major adverse cardiac and cerebrovascular events (MACCEs) during hospitalization and at 1 and 12 months after PCI. Results: There were no significant differences in the frequency of MACCEs between the two groups during hospitalization, at 1 month or 12 months post-PCI. During hospitalization, MACCEs occurred in 1.5% of the anticoagulation group versus 1.6% of the non-anticoagulation group (P>0.9). The groups had comparable rates of major bleeding (3.6% vs 2.1%, P=0.37), but minor bleeding was increased in the anticoagulation group (29.1% vs. 18.7%, P=0.016). At 1 month post-PCI, MACCEs occurred in 1.5% of the anticoagulation group and 2.6% of the non-anticoagulation group, (P=0.5), and at 12 months post-PCI, the rates were 5.6% vs. 6.2%, respectively (P=0.8). Conclusions: The frequency of MACCEs after PCI in the non-anticoagulation group was not significantly increased compared with that of the anticoagulation group. However, the rate of minor bleeding during hospitalization is significantly lower in non-anticoagulation group than that in anticoagulation group. The results suggest that routine anticoagulation therapy after PCI is not necessary for patients without procedure complications.

Keywords: Percutaneous coronary intervention, enoxaparin, major adverse cardiac and cerebrovascular events (MACCEs), bleeding

Introduction

Heart disease is one of the most common causes of mortality and hospital admissions worldwide. Percutaneous coronary intervention, or angioplasty, is a non-surgical procedure used to open the narrowed arteries in patients with heart disease, and commonly includes stent placement to permanently keep the arteries open. To prevent stent thrombosis after percutaneous coronary intervention (PCI), traditional treatment mainly includes dual antiplatelet therapy and heparin therapy [1, 2]; with the combined application of anti-platelet drugs clopidogrel and aspirin, complications of stent thrombosis after PCI have been reduced [3, 4]. However, routine use of heparin is not recommended by the guideline any longer. Revised guidelines for patients with unstable angina and non-ST segment elevated myocardial infarction (NSTEMI) from ACCF/AHA in 2011 and 2012 recommend that patients without complications and with simple disease, anticoagulation therapy can be stopped after PCI (IB) [5, 6]. China's Guidelines for Percutaneous Coronary Artery Treatment in 2012 recommends that anticoagulation therapy can be stopped after PCI, except when special circumstances exist, e.g. high-risk factors for thrombosis [7]. However, use of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) after PCI is common in actual clinical practice. Therefore, we investigated the use of LMWH in ten large hospitals in Shanghai. In three hospitals, LMWH is used after PCI only in cases with complicated disease, such as stent overlap and stent malapposition. In the other seven hospitals, LMWH is used conventionally for 3-5 days

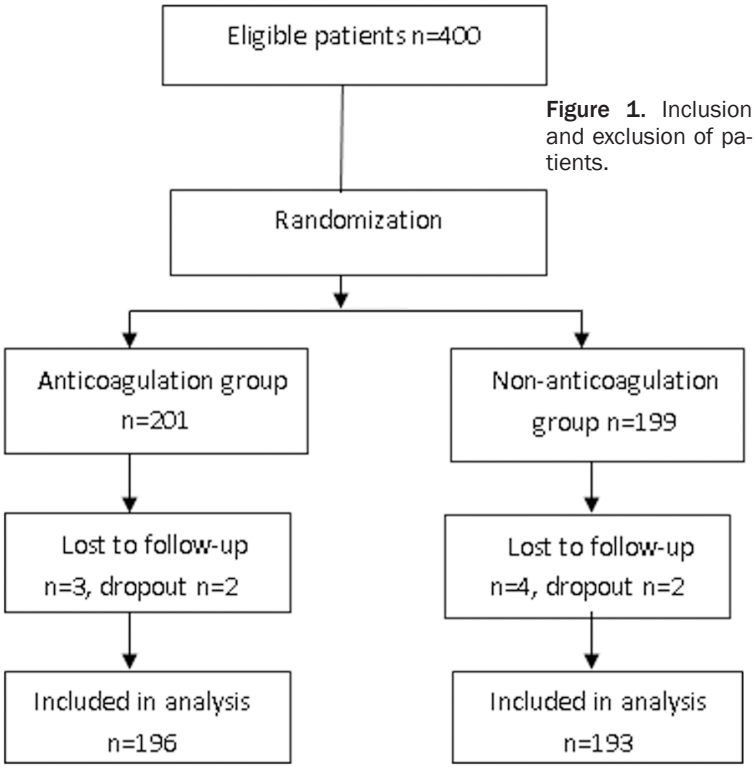

Figure 1. Inclusion and exclusion of patients.

after selective and emergency PCI. From these investigations, we found that the guidelines for anticoagulation therapy after PCI were not being followed. Excessive anticoagulation therapy is perhaps used, to some extent, due to the lack of studies regarding the effectiveness and safety of heparin anticoagulation after PCI in China. China's guidelines for anticoagulation after PCI were written similarly to guidelines abroad, based on clinical trials in other countries. Clinical studies about the use of heparin anticoagulation after PCI in patients in China are still lacking in order for the guidelines to be more accurate.

Materials and methods

Patients

400 patients were enrolled in a randomized, single-center, open and prospective trial (**Figure 1**). Patients enrolled had no complications after PCI from May, 2011 to December, 2012. Patients had four types of lesions; type A: 22 patients (5.6%), type B1: 97 patients (24.9%), type B2: 103 patients (26.5%), type C: 168 patients (43.2%). Patients were randomly assigned to two groups, enoxaparin (LMWH) or no anticoagulation. Inclusion criteria were: age 18 to 80 years, clinical diagnosis of stable angina pectoris, unstable angina, non ST segment elevated myocardial infarction or ST elevated myocardial infarction; willing to receive specified follow-up, treatment, laboratory examination and other research activities; and non-emergency operation. Exclusion criteria were: patients with serious liver or kidney damage (GFR<30 ml min/1.73 m^2), uncontrolled hypertension, hemoglobin <9 g/L, platelet count <100×10^9/L, serious cardiac insufficiency: left ventricle ejection fraction (LVEF) <30% or cardiogenic shock, patients who are taking anticoagulant drugs, e.g. warfarin, diameter of hematoma at the site of femoral artery puncture is bigger than 5 cm, history of hemorrhagic stroke in previous 3 months, allergy to aspirin, clopidogrel, heparin, enoxaparin or other LMWH, have history of thrombocytopenia induced by LMWH (platelet count reduced significantly in the past), inability to tolerate anti-platelet treatment, complications after PCI, such as coronary artery dissection, no-reflow, and use of platelet glycoprotein IIb/IIIa blockers.

Treatment protocol

All patients received aspirin 24 hours prior to PCI; 100-300 mg aspirin for patients who have previously been prescribed aspirin, and 300 mg aspirin for patients not routinely taking aspirin. All patients also received clopidogrel 6 hours prior to PCI; 300 mg clopidogrel for patients with a prior prescription, or 600 mg clopidogrel for patients who hadn't received clopidogrel previously. Patients who took LMWH 8-12 h prior to PCI received 0.3 mg/kg enoxaparin intravenously, but patients who received the standard subcutaneous dose of enoxaparin 8 h prior to PCI did not receive any more. During the operation, 2500 U unfractionated heparin is injected through the side wall of the sheath when the puncture succeeds and the artery

Table 1. Patient characteristics

	Anticoagulation group (n=196)	Non-anticoagulation group (n=193)	*P* value
Male, *n* (%)	137 (69.9)	133 (68.9)	0.83
Age, mean ± SD (year)	63.17±10.82	62.80±10.31	0.73
Weight, mean ± SD (kg)	68.60±11.12	68.89±10.20	0.79
BMI, mean ± SD (kg/m^2)	24.70±3.19	24.82±2.96	0.71
Smoking history *n* (%)	83 (42.3)	75 (38.9)	0.48
Diabetes history *n* (%)	57 (29.1)	49 (25.4)	0.41
Family history of CVD *n* (%)	7 (3.6)	13 (6.7)	0.16
Hypertension history *n* (%)	133 (67.9)	139 (72.0)	0.37
Systolic pressure, mean ± SD (mmHg)	133.03±17.37	132.54±18.70	0.79
Diastolic pressure, mean ± SD (mmHg)	78.53±10.65	76.50±10.31	0.057
Hyperlipidemia *n* (%)	74 (37.8)	62 (32.1)	0.24
Previous myocardial infarction *n* (%)	14 (7.1)	20 (10.4)	0.26
PCI history *n* (%)	27 (13.8)	29 (15.0)	0.73
CABG history *n* (%)	0 (0)	2 (1.0)	0.25$^{\Delta}$
Gastrointestinal bleeding history *n* (%)	9 (4.6)	10 (5.2)	0.79
Cerebral infarction history *n* (%)	22 (11.2)	23 (11.9)	0.83
Cerebral hemorrhage history *n* (%)	0 (0)	2 (1.0)	0.25$^{\Delta}$
Stable angina pectoris *n* (%)	26 (13.3)	20 (10.04)	0.38
Unstable angina *n* (%)	137 (69.9)	140 (72.5)	0.57
NSTEMI *n* (%)	20 (10.2)	19 (9.8)	0.91
STEMI *n* (%)	13 (6.6)	14 (7.3)	0.81
Cr, mean ± SD (mmol/L)	79.91±20.61	78.76±20.79	0.58
EGFR<60 (mL.1.73 m^2) *n* (%)	14 (7.1)	12 (6.2)	0.751

Notes: BMI: body mass index; CVD: cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; PPI: proton pump inhibitor; Cr: creatinine; EGFR: glomerular filtration rate; SD: standard deviation; $^{\Delta}$*P* value calculated by Fisher test.

sheath is put in. 5000-7000 U (or 70-100 U/kg) heparin is added intravenously before inserting the guide catheter for patients who are assigned to the enoxaparin treatment group, and 1000-2000 U is added each hour during the follow up time at the doctor's discretion, in order to maintain activated clotting time (ACT) in the range of 300-500 s. Postoperative medication: aspirin 100 mg/d and clopidogrel 75 mg/d are used conventionally after the operation, and enoxaparin is added in anticoagulation group. 40 mg enoxaparin is administered subcutaneously every 12 hours if patients' weight is less than 60 kg, if patient's weight is over 60 kg, 60 mg enoxaparin is given, once every 12 hours subcutaneously. Heparin is not used in the non-anticoagulation group. Angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, nitrates, calcium channel blockers and statins are used according to each patient's situation to control other risk factors.

PCI is performed by two doctors with extensive experience in cardiac intervention. Examination by coronary angiography is performed conventionally through the radial artery and femoral arteries. Quantitative coronary angiography (QCA) is used to test stenosis (degree of the lesion) and differentiate the target lesions according to the lesion classification of the American College of Cardiology/American Heart Association (ACC/AHA). If the diameter of the target lesion was ≥70%, and the reference diameter was 2.5~4.0 mm, a coronary stent was implanted in a standard protocol. The stent size was chosen according to the lesion. PCI was considered successful if: residual stenosis after implanting the stent was <20%, forward flow reached thrombolysis of myocardial infarc-

Table 2. Coronary angiography and PCI results

	Anticoagulation group (n=196)	Non-anticoagulation group (n=193)	*P* value
Viable radial artery *n* (%)	155 (79.1)	153 (79.3)	0.988
Left main coronary artery disease *n* (%)	2 (1.0)	2 (1.0)	>0.9$^{\Delta}$
Bifurcation lesion *n* (%)	32 (16.3)	41 (21.2)	0.21
Type A lesion *n* (%)	11 (5.6)	11 (5.7)	0.97
Type B1 lesion *n* (%)	41 (20.9)	56 (29.0)	0.065
Type B2 lesion *n* (%)	54 (27.6)	49 (25.4)	0.623
Type C lesion *n* (%)	91 (46.4)	77 (39.7)	0.18
Average length of stent, mean ± SD (mm)	23.67±6.74	22.53±6.02	0.079
Diameter of lesion, mean ± SD (mm)	2.84±1.26	2.930±1.50	0.67
Average diameter of stent, mean ± SD (mm)	3.11±0.48	3.10±0.43	0.678
Use of long stent *n* (%)	69 (35.2)	52 (26.9)	0.078
More than two stents *n* (%)	85 (43.4)	73 (37.8)	0.27
More than two lesions of vasculopathy *n* (%)	37 (18.7)	29 (15.0)	0.33

Note: $^{\Delta}$is *P* value calculated by Fisher's exact test. SD: standard deviation.

Table 3. Postoperative medications

	Anticoagulation group (n=196)	Non-anticoagulation group (n=193)	*P* value
PPI *n* (%)	72 (36.7)	59 (30.6)	0.20
ACEI *n* (%)	62 (31.6)	56 (29.0)	0.58
ARB *n* (%)	54 (27.6)	56 (29.0)	0.745
BB *n* (%)	133 (67.9)	115 (59.5)	0.09
Nitrates *n* (%)	131 (66.8)	119 (61.7)	0.289
CCB *n* (%)	57 (29.1)	57 (29.5)	0.92

Notes: PPI: proton-pump inhibitor; ACEI: angiotensin converse enzyme inhibitor; ARB: angiotensin receptor II blocker; BB: β blockers; CCB: calcium channel blocker.

tion (TIMI) grade 3 (normal), and no serious complications occurred.

Endpoints

Combined endpoints of major adverse cardiac and cerebral events (MACCEs) in 1 year, including cardiac death, nonfatal myocardial reinfarction, target vessel revascularization (TVR) and stroke. Patients were considered to have TVR if revascularization of the target vessel occurred due to any reason, including PCI or coronary artery bypass graft (CABG). PCI-related myocardial infarction [9] was considered to have occurred if patients with a normal baseline level of cardiac troponin (cTn) had an increase to five times of the upper limit of the reference value; or for patients who had increased baseline levels, cTn increased over 20%, and remained stable or decreased gradually. One of the following events was required to occur at the same time as the cTn increase: symptoms that indicated myocardial ischemia; new ischemic changes in the electrocardiogram (ECG); angiography results consistent with PCI complications; or new damage in viable myocardium or radiologic evidence of abnormal movements in the local ventricular wall. Acute myocardial infarction was considered to have occurred if serum cardiac markers increased or decreased over the upper limit of normal (99th percentile of the reference range), and at least one of the following symptoms occurred: symptoms of ischemia; significant elevation of ST segment/T wave change, or new appearance of a left bundle branch blockage; pathological Q wave appeared in ECG; new damage in viable myocardium or radiologic evidence of abnormal movements of the local ventricular wall; coronary thrombosis is found through angiography or autopsy. Bleeding events were classified according to TIMI bleeding grading score into major bleeding and minor bleeding. Standard TIMI hemorrhage classification of a major bleed: intracranial hemorrhage or clinical visible hemorrhage (including imaging) with a decrease in hemoglobin concentration ≥5 g/dl. Minor bleed includes clinical visible bleeding with a decrease in hemoglobin concentration of <5 g/dl.

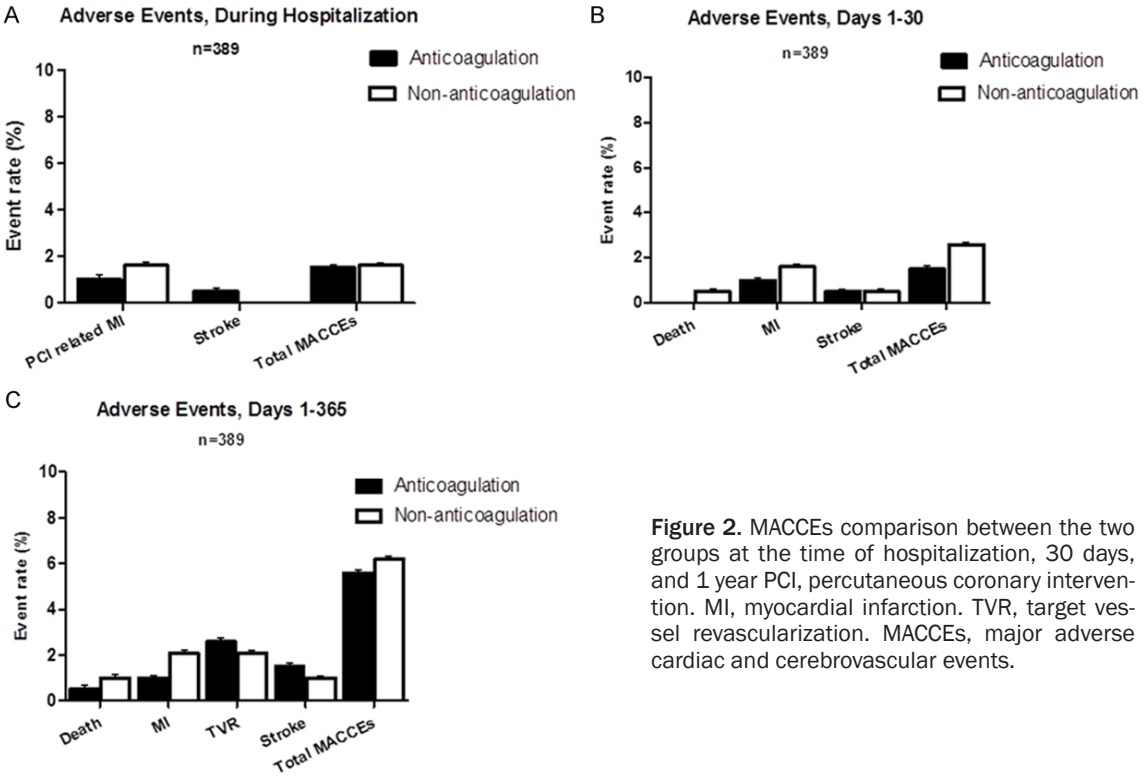

Figure 2. MACCEs comparison between the two groups at the time of hospitalization, 30 days, and 1 year PCI, percutaneous coronary intervention. MI, myocardial infarction. TVR, target vessel revascularization. MACCEs, major adverse cardiac and cerebrovascular events.

All data was entered into the case report form prospectively. The modes of follow-up included outpatient review, rehospitalization and (or) telephone follow-up. Endpoint events were judged and recorded by professionals during hospitalization and at 1 and 12 months after the PCI operation.

SAS18.0 was used for statistical analysis. Categorical variables were described as frequencies, and the chi-squared test is used for comparison between the treatment groups. Mean ± standard deviation is used to describe measurement data. For data with a normal distribution and homogeneity of variance, the student's t test is used for comparing treatment groups, otherwise, a nonparametric test is used. A logistic regression model was used for testing the association of minor bleeding with variables of: gender, age >70, hypertension, diabetes, hyperlipidemia, multivessel disease, bifurcation disease and heparin use after operation. $P<0.05$ was considered statistically significant.

Results

There were no differences between the treatment groups in any of the clinical characteristics (**Table 1**) or coronary angiography or PCI results (**Table 2**). Medication use postoperatively in all patients included aspirin, clopidogrel and statins. Proton pump inhibitors, ACE inhibitors, angiotensin receptor II blockers, beta-blockers, nitrates, and calcium channel blockers were used when necessary; frequency of use of these medications did not differ between treatment groups (**Table 3**). Assessment of patients during their hospitalization, 1, and 12 months after PCI was completed in 389 of 400 patients enrolled. MACCEs occurred in 6 patients during hospitalization (5 patients experienced PCI-related myocardial infarction and one had a stroke, **Figure 2A**). These patients were divided equally between the treatment groups (3 in each group: 1.5% of the anticoagulation group and 1.6% of the non-anticoagulation group, $P>0.9$, **Table 4**). The incidence of major bleeding was 3.6% in the anticoagulation group and 2.1% in the non-anticoagulation group, $P=0.37$). The incidence of minor bleeding was higher in the anticoagulation group (28.6%) than in non-anticoagulation group (19.7%, $P=0.016$). A logistic regression analysis showed only heparin use was significantly related to the development of minor bleeding during hospitalization, although

Table 4. Major clinical events

	Anticoagulation group (n=196)	Non-anticoagulation group (n=193)	*P* value
During Hospitalization			
Total (Death, MI, stroke or TVR) *n* (%)	3 (1.5)	3 (1.6)	>0.9[Δ]
PCI related MI *n* (%)	2 (1.0)	3 (1.6)	0.68[Δ]
Stroke (number, %)	1 (0.5)	0 (0)	>0.9[Δ]
TIMI bleeding			
Massive hemorrhage *n* (%)	7 (3.6)	4 (2.1)	0.37
Small hemorrhage *n* (%)	56 (28.6%)	38 (19.7%)	0.016
1-month follow-up			
Total (Death, MI, stroke or TVR) *n* (%)	3 (1.5)	5 (2.6)	0.50[Δ]
Death *n* (%)	0 (0)	1 (0.5)	0.50[Δ]
Myocardial infarction *n* (%)	2 (1.0)	3 (1.6)	0.68[Δ]
Stroke *n* (%)	1 (0.5)	1 (0.5)	>0.9[Δ]
12-month follow-up			
Total (Death, MI, stroke or TVR) *n* (%)	11 (5.6)	12 (6.2)	0.800
Death *n* (%)	1 (0.5)	2 (1.0)	0.621[Δ]
MI *n* (%)	2 (1.0)	4 (2.1)	0.446[Δ]
TVR *n* (%)	5 (2.6)	4 (2.1)	>0.9[Δ]
Stroke *n* (%)	3 (1.5)	2 (1.0)	>0.9[Δ]
Small hemorrhage *n* (%)	74 (37.8)	53 (27.5)	0.030

MI: Myocardial infarction. TVR: target vessel revascularization. [Δ]is *P* value calculated by Fisher's exact test.

Table 5. Binary logistic analysis of minor bleeding and related variables during hospitalization

Patient	OR value	95% C.I	P
Heparin use	1.664	1.014-2.731	0.044
Multivessel disease	1.748	0.960-3.183	0.068
Female	1.666	0.997-2.782	0.051
>70 years old	1.527	0.859-2.712	0.149
Hypertension	0.721	0.425-1.224	0.225
Diabetes	0.986	0.560-1.738	0.962
Hyperlipidemia	0.676	0.392-1.166	0.159
Bifurcation disease	1.289	0.703-2.363	0.412

Table 6. Binary logistic analysis of minor bleeding and related variables after one-year follow-up

Patient	OR value	95% C.I	P
Diabetes	2.875	1.135-7.285	0.026
Multivessel disease	3.041	1.153-8.016	0.025
Heparin use	0.897	0.363-2.251	0.897
>70 years old	2.094	0.785-5.586	0.140
Female	0.911	0.348-2.387	0.850
Hypertension	2.578	0.711-9.347	0.150
Hyperlipidemia	0.602	0.214-1.690	0.335
Bifurcation disease	1.388	0.462-4.165	0.559

involvement of multiple vessels and female gender were marginally significant (**Table 5**). At one month after PCI, 8 patients experienced MACCEs, 3 patients in the anticoagulation group and 5 patients in the non-anticoagulation group (1.5% and 2.6%, respectively, P=0.5, **Figure 2B**). At one year post-PCI, MACCEs happened to 23 patients, 11 patients in the anticoagulation group (5.6%), 12 patients in non-anticoagulation group (6.2%, P=0.8, **Figure 2C**). Minor bleeding occurred in 37.8% of patients in the anticoagulant group and 27.5% in the non-anticoagulant group after one year (**Table 4**). In a logistic regression analysis, diabetes and involvement of multiple vessels was significantly related to the development of minor bleeding after one-year follow-up (**Table 6**). Survival analysis shows no significant difference in cardiovascular events between the two groups (**Figure 3**).

Discussion

The use of a drug eluting stent (DES) is common with percutaneous coronary intervention; it solves the worst complication after target artery treatment, restenosis, which is reduced

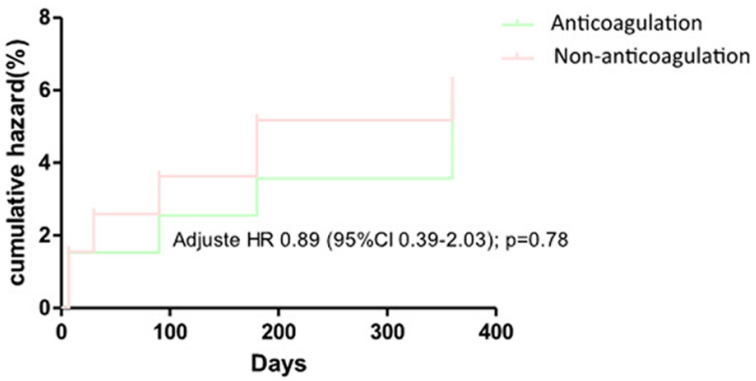

Figure 3. Cumulative incidence of MACCEs.

to lower than 10% after PCI [10]. However, stent thrombosis (ST) then becomes a possible complication. Although the incidence of DES ST is low, its results are disastrous. To prevent ST, traditional treatments are general anticoagulation and anti-platelet therapy. With the combined application of anti-platelet drugs clopidogrel and aspirin, incidence of ST after PCI is further reduced. However, routine use of heparin is no longer recommended by the guidelines. Revised guidelines about unstable angina and non-ST segment elevated myocardial infarction (NSTEMI) from ACCF/AHA in 2011 and 2012 direct that patients without complications and with simple disease, do not need anticoagulation therapy after PCI (IB). China's Guidelines for Percutaneous Coronary Artery Treatment in 2012 recommends that anticoagulation therapy be stopped after PCI except when special circumstances exist, e.g. high-risk factors for thrombosis. However, in clinical practice in China, guidelines for anticoagulation therapy after PCI were not being followed completely, and excessive anticoagulation exists to some extent. This is a drain on time and financial resources, unnecessarily increasing the cost of healthcare in China. We were able to enroll 400 patients in 20 months in one hospital in Shanghai, so the impact of reducing minor bleeds, medication and testing costs by following the guidelines would be substantial across all of China.

Our study of 400 patients shows that the incidence of MACCEs during hospitalization, at one month and 12 months after PCI was similar in the anticoagulation group and non-coagulation group. There was no difference in the cumulative incidence of MACCEs (P=0.475). The only difference found was that the incidence of minor bleeding in the anticoagulation group is significantly higher than in the non-anticoagulation group during hospitalization (29.1% vs 18.7%, P=0.016), and this was related to heparin use.

There are many studies abroad studying the effectiveness and safety of heparin anticoagulation after PCI; Karrillon et al found that heparin anticoagulation does not reduce the incidence of stent restenosis after intracoronary stent implantation, but the use of LMWH increases bleeding complications [11]. Harjai et al divided 555 patients with acute myocardial infarction into 2 groups: heparin anticoagulation or no anticoagulation after intracoronary stent implantation in the CADILLAC study, and find that heparin anticoagulation does not reduce MACCEs in both the early and later stages [12]. Moreover, complications like bleeding are increased, and therefore, hospitalization expenses are higher. ATLAS is a large-scale study of the efficacy and safety of heparin anticoagulation after PCI. In this study, 2000 patients with high risk factors of stent thrombosis after PCI were randomly assigned to receive heparin anticoagulation or no anticoagulation. After 1-year follow-up of 1102 patients, death, myocardial infarction and acute TVR occurred in 1.8% of the patients receiving aspirin and 2.7% of the group receiving no anticoagulation (no statistical difference). The incidence of myocardial infarction was lower in the patients receiving aspirin (0.4% vs 1.6%). However, although there's a statistical difference in comparison, as the incidence is very low, there is little clinical significance. The incidence of minor bleeding was higher (25%) in the anticoagulation group than that in non-anticoagulation group (5.1%). This study suggests that even though the patients are at high risk for stent thrombosis, anti-platelet drugs are enough to prevent stent thrombosis for most patients after PCI.

Compared with UFH, LMWH has many desirable characteristics, e.g. high bioavailability, weaker promotion of platelet aggregation, detection of ACT is not necessary, and thrombocytopenia induction is weak [13, 14]. LMWH

has replaced UFH gradually during the perioperative period, and many clinical doctors now use LMWH conventionally after PCI to reduce the incidence of ischemia events, however, dose-dependent complications of bleeding can occur with UFH as well as LMWH [15-17]. When bleeding complications occur, patients may be forced to stop use of anti-platelet drugs [18, 19], and risks of an adverse event, e.g. death, myocardial infarction, stroke and stent thrombosis [20-25] increase, so prevention of bleeding events is as important as prevention of ischemia events after PCI.

There are many diverse types of lesions in the patients enrolled in this study. We have confirmed that discontinuation of Enoxaparin anticoagulation after PCI does not increase the incidence of cardiovascular events, even for patients with complicated lesions. It also reduces bleeding complications, which provides some value to anticoagulation treatment after PCI for complicated lesions and multi-vessel lesions. Therefore, our study suggests that use of an anticoagulant is safe and effective even for complicated lesions.

We conclude that, compared with the anticoagulation group, cardiovascular events occur with similar frequency in the non-anticoagulation group after PCI, and incidence of complications of minor bleeding is lower in the non-anticoagulation group than that in anticoagulation group during hospitalization. This study shows that anticoagulation treatment is not needed for patients without special complications after PCI.

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Disclosure of conflict of interest

None.

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