Research Article

Wang Hai-long, Pang Xiao-hua,Yang Jian-jun*

The efficacy and safety of enoxaparin: a meta-analysis

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Abstract: The efficacy and safety of enoxaparin (ENOX) in percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) remains unaddressed. The primary endpoint evaluated was myocardial infarction (MI) or death. The secondary endpoint was defined as major bleeding complications. Studies comparing the differences in the efficacy and safety of ENOX versus unfractionated heparin (UFH) in PCI for the treatment of STEMI were evaluated. We presented the odds ratios for individual studies and performed heterogeneity, quality assessment, and publication bias analysis. This meta-analysis examined four randomized controlled trials (RCTs), and 5585 patients were included (2334 ENOX patients and 3251 UFH patients). The follow-up period of the endpoints was 30 or 90 days. Compared with UFH, ENOX significantly reduced the incidence of MI (OR, 0.74; P<0.01) and death (OR, 0.74; P<0.03), while there was no significant difference between the two treatments on major bleeding (OR,0.81; P=0.33). The findings from this meta-analysis suggested that the efficacy and safety of ENOX in the treatment of STEMI patients undergoing PCI were significantly better than patients treated with UFH. According to this meta-analysis, ENOX is the preferred anticoagulant for STEMI patients receiving PCI compared to UFH.

Keywords: Enoxaparin; Percutaneous coronary intervention; ST-elevation myocardial infarction; Unfractionated heparin; Meta-analysis.

1 Introduction

Unfractionated heparin (UFH) is the standard anticoagulant regimen for ST-elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI). The use of UFH undergoing PCI is based on the recommended evidence level of C in the guidelines of the European Society of Cardiology and the American College of Cardiology [1,2]. However, this recommendation is not based on outcomes of randomized controlled trials (RCTs) but rather from the common clinical practice of administering anticoagulant therapy for STEMI patients undergoing PCI.

There are few available studies on the efficacy and safety of enoxaparin (ENOX) in STEMI patients undergoing primary PCI [3] and the clinical application of the treatment has been controversial. Recently, there has been analyses of RCTs comparing ENOX with UFH in STEMI populations undergoing PCI [4-7]. Thus, we conducted a systematic review and meta-analysis to explore the differences in the efficacy and safety of ENOX compared with UFH for PCI in STEMI patients.

2 Methods

2.1 Search strategy

The present meta-analysis was performed according to The Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA) guidelines [8]. Two investigators used the PubMed, EMBASE, and MEDLINE databases to independently search English language entries published prior to April 2018. Subject words or keywords were applied to select articles included the following terms: “STEMI or ST elevation myocardial infarction,” “PCI or percutaneous coronary intervention,” “Heparin,” “enoxaparin” Publication language was limited to English.

***Corresponding author: Yang Jian-jun,** Department of Cardiology, Chongqing Three Gorges Central Hospital, 165# Xincheng road, Wanzhou, Chongqing, China. Email:wangjinlong2007666@163.com
Wang Hai-long, Pang Xiao-hua, Department of Cardiology, Chongqing Three Gorges Central Hospital, Wanzhou, Chongqing, China

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2.2 Study selection

We screened out RCTs of STEMI patients who underwent PCI for ENOX versus UFH. This study included only RCTs of STEMI patients undergoing PCI. The measurement period for the follow-up data was 30 or 90 days. We excluded studies whose follow-up period was not 30 or 90 days, studies that were not RCTs, studies involving stable angina pectoris or non ST-segment elevation acute coronary syndrome (NSTE-ACS) patients, and studies in which patients did not undergo PCI. We had no restrictions on the qualification of the research results.

2.3 Data extraction and quality assessment

Three reviewers (HL Wang, JJ Yang, and XH Pang) independently extracted the following data: first author, research design, publication year, sample size, clinical baseline characteristics, interventions, follow-up period, and outcomes data. The primary endpoint was defined as death or MI, while the secondary endpoint was defined as major bleeding complications. All four studies reported death or MI, and only three have reported major bleeding [4,6,7].

2.4 Statistical analysis

Risk of bias was assessed using the criteria of the Cochrane back-review group in each study [9]. Data analysis was completed under the Cochrane Collaboration and PRISMA Statement. I^2 statistical analysis was applied to assess statistical heterogeneity between studies. High, moderate, and low heterogeneity were respectively defined as I^2 values of 75%, 50%, and 25%. When I^2 values were less than 25%, the fixed-effects model was performed [10], and the fixed-effect model was accepted. Hypothesis testing results were defined as statistical difference at $P<0.05$ and significant statistical difference at $P<0.01$. Funnel plots, Begg's tests, and Egger's tests were employed to evaluate publication bias and small sample research effects. All statistical analyses were performed using Review Manager 5.1 (RevMan).

3 Results

3.1 Study selection

The initial screening obtained a total of 972 references from the PubMed, Medline, and EMBASE databases. After careful inspection, we removed 173 duplicate publications. Of the remaining 799 references, we have further excluded 457 by screening of the title and/or abstract since they were not relevant to our study. We carefully reviewed the remaining 25 full-text articles. Among them, we excluded 21 articles because they were non-RCTs, commentaries, editorials, or had no extractable clinical results. Finally, our meta-analysis included four RCTs [4-7] (Fig. 1).

3.2 Study characteristics and quality assessment

There were four RCTs included in this meta-analysis. A total of 5585 STEMI patients undergoing PCI were included in our meta-analysis, comprising 2334 ENOX patients and 3251 UFH patients. The average age of the population was similar between these studies. The baseline characteristics of the selected RCTs are listed in Table 1. The population characteristics of the selected RCTs are listed in Table 2. From the perspective of quality assessment, the four RCTs were considered to have low risks of bias. The funnel plot showed symmetry, which indicated low possible publication bias, and the Egger's test showed that publication bias was not statistically significant for the research studies [4-7].

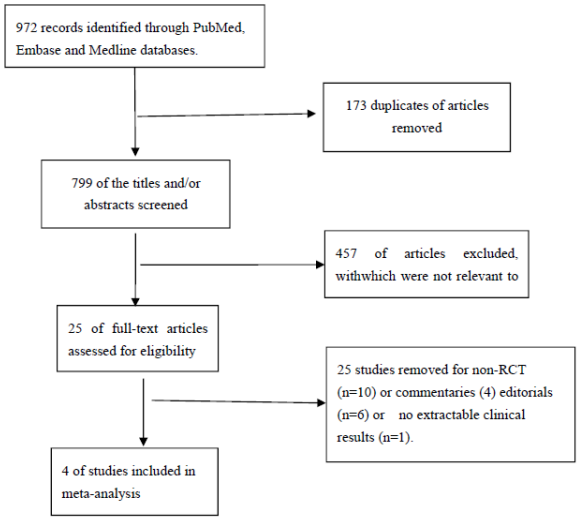

Figure 1: Search strategy conducted for all included trials. Abbreviations: MeSH, medical subject headings.

Table 1: Characteristics of randomized studies.

Randomized studies	Year	Sample size		Inclusion criteria	Exclusion criteria	Endpoints	Mean follow-up Period
		ENOX	UFH				
ExTRACT-TIMI	2007	1103	1075	Patients were at least 18 years of age, had at least 20 min of ischemic symptoms while at rest within 6 h before randomization, had ST-segment elevation of at least 0.1 mV in 2 limb leads or of 0.2 mV in at least 2 contiguous precordial leads or left bundle branch block, and were scheduled to undergo fibrinolysis.	Patients who did not undergo PCI and were not blinded.	Death, MI, major bleeding.	30 days
FINESSE	2010	759	1693	Patients presenting within 6 h of symptom onset with ST-segment elevation or new left bundle branch block, the estimated time to diagnostic catheterization was 1 to 4 h from randomization, patients were not at low risk.	Patients who received any UFH within 24 h of randomization, had a history of allergy to enoxaparin, had an estimated creatinine clearance<30 ml/min adjusted for sex.	Death, MI.	90 days
ATOLL	2011	450	456	Patients with STEMI were older than 17 years (without an upper age limit) and had an indication for primary PCI within 12 h of symptom onset. Patients presenting between 12 h and 24 h of symptom onset with persistent ischemic symptoms or persistent or recurrent ST-elevation on ECG, and an indication for primary PCI, patients with shock or cardiac arrest (<10 min) in the setting of STEMI.	Patients who received anticoagulant of any type (unfractionated heparin, low molecular weight heparin, fondaparinux, warfarin) before randomization were excluded. Patients who received thrombolytic agents for the present episode, a short life expectancy, childbearing potential, and known contraindications to treatment with aspirin, thienopyridines, or heparins.	Death, MI, major bleeding	30 days
R Welsh et al.	2015	22	23	STEMI patients undergoing primary PCI.	NSTEMI patients, not received primary PCI.	Death, MI, major bleeding	30 days

3.3 Outcome of death

ENOX treatment showed the relative risk decrease of 27.0% in the rate of death compared to UFH. Of the data on death extracted from the four RCTs, there was almost no heterogeneity between the outcomes (P = 0.51, I^2 =0%). The ENOX group showed lower incidences of death than the UFH group in PCI for STEMI (OR, 0.74; 95% CI, 0.56–0.97; P< 0.05).

3.4 Outcome of myocardial infarction

ENOX treatment during the follow-up period showed a relative risk decrease of 21.3% in the rate of MI compared to that of UFH. ENOX results for STEMI patients undergoing PCI were associated with significantly lower incidences of MI than UFH results (OR: 0.74, 95% CI: 0.6.–0.90; P < 0.01; I^2 = 0%).

Table 2: Patient characteristics in each randomized trial.

Demographics	ExTRACT-TIMI		FINESSE		ATOLL		R Welsh et al.	
	ENOX (n=1103)	UFH (n=1075)	ENOX (n=759)	UFH (n=1693)	ENOX (n=450)	UFH (n=460)	UFH (n=22)	UFH (n=23)
Age, mean	NA	NA	63	63	59	60	54	53
Male sex (n)	NA	NA	204	438	353	359	19	18
Smoking history (n)	NA	NA	529	1081	199	218	NA	NA
Prior MI (n)	NA	NA	72	194	28	24	NA	NA
Hypertension (n)	NA	NA	298	875	205	207	9	11
Diabetes mellitus (n)	NA	NA	94	286	63	69	2	0
Killip class 1 (n)	NA	NA	665	1513	415	409	21	23

NA: not available

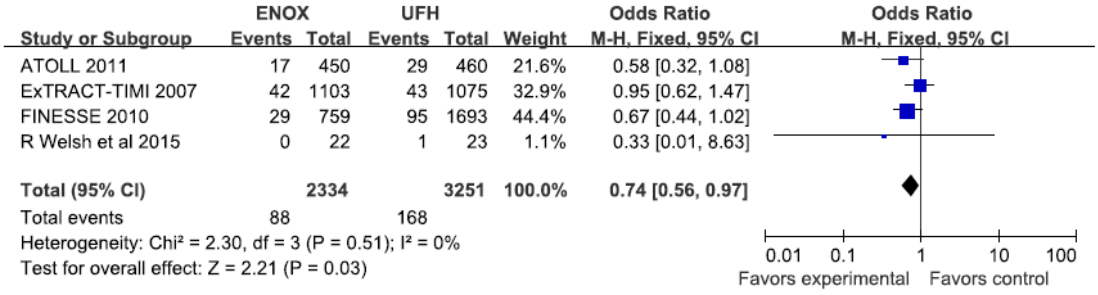

Figure 2: Fixed-effect meta-analysis for death. The figure presents the number of events, the number of patients in the treatment and control groups, the odds ratio (OR) and 95% confidence interval (CI) for each trial, the overall OR estimate with 95% CI and the P value for the association test, the P value for the heterogeneity test, and between-trial inconsistency (I2) measures.

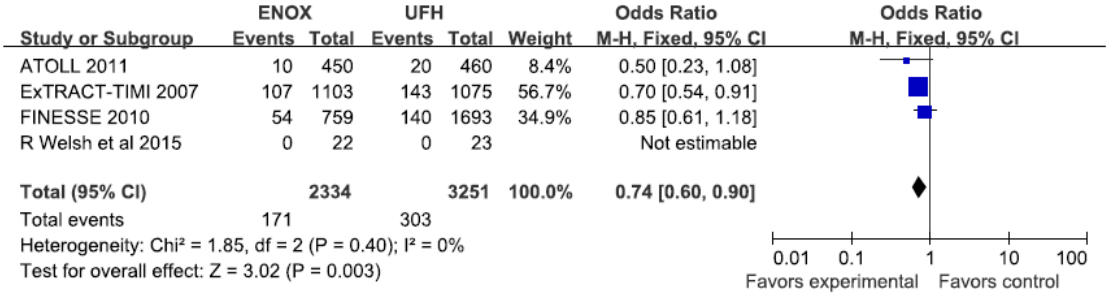

Figure 3: Fixed-effect meta-analysis for myocardial infarction.

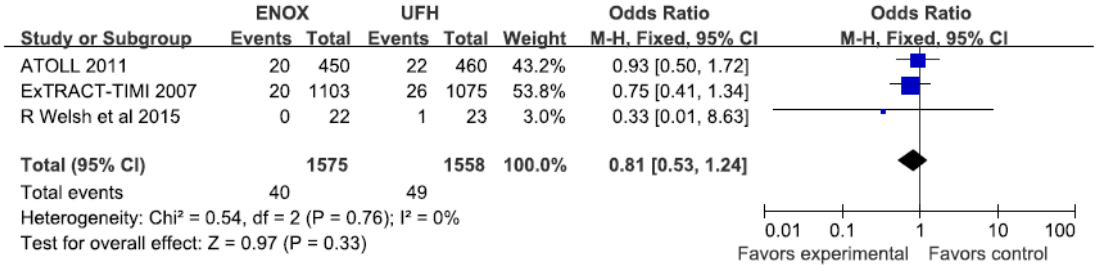

Figure 4: Fixed-effect meta-analysis for major bleeding.

3.5 Outcome of major bleeding

ENOX during the follow-up period showed a relative risk decrease of 19.2% in the rate of major bleeding compared to UFH. However, there was no statistical significance in major bleeding between ENOX and UFH groups (OR:0.81, 95%CI:0.53-1.24; P=0.33; I^2= 0%).

4 Discussion

Our meta-analysis found that the use of ENOX in STEMI patients who underwent PCI was related to a decrease in the rates of death and MI compared with UFH, and it did not increase the incidence of major bleeding complications compared with UFH. ENOX is a low-molecular-weight heparin; therefore, it is expected to have better efficacy than UFH based on its pharmacological properties [11]. First, ENOX exhibits more activity than UFH against activated factor X, which can reduce thrombin production. Second, ENOX does not bind to plasma proteins, so it has a more predictable anticoagulant response than UFH. In addition, the pleiotropic effects of ENOX can also indirectly enhance antithrombotic properties and anticoagulant effects [12-14]. Based on the above theoretical basis, ENOX may be more suitable than UFH in STEMI patients undergoing PCI.

The current meta-analysis evaluated the efficacy and safety of ENOX and UFH in STEMI patients undergoing PCI [15]. In both ENOX-treated and UFH-treated groups, we found that the risk of MI was significantly higher than the risk of death, and the mortality of the ENOX-treated group was statistically significantly lower than the UFH-treated group ($0.05>P>0.01$). Furthermore, the rates of MI for the ENOX-treated group were statistically significantly lower than those of the UFH-treated group ($P<0.01$). This meta-analysis showed that ENOX treatment in STEMI patients undergoing PCI further benefited, given their reduced rate of reinfarction. Major bleeding complications were low in both groups, and there were no statistically significant differences between the two treatments. Our meta-analysis showed that the higher the risk of STEMI in patients undergoing PCI, the greater the benefits of ENOX treatment compared with UFH treatment.

ENOX had been extensively studied and validated for its beneficial effects in STEMI patients [16]. The primary endpoint of death was 3.8% of patients in the ENOX-treated group compared with 5.2% of patients in the UFH-treated group, while the primary endpoint of MI was 7.3% of patients in the ENOX-treated group compared with 9.3% of patients in the UFH-treated group. There were no significant increases in the incidence of major bleeding in the ENOX group compared with the UFH group: the prevalence of major bleeding in the ENOX and UFH groups was 2.5% and 3.1% of patients, respectively. STEMI patients undergoing PCI, ENOX showed a statistically significant difference in reduction of death compared with UFH, and a statistically significant difference in reduction of MI compared with UFH.

This meta-analysis included only three RCTs for the incidence of major bleeding complications. Although the mean ratio of major bleeding for ENOX was decreased compared with UFH, there were smaller sample sizes and lower incidences. Therefore, the difference between the two groups was not statistically significant. However, for a single study, the major bleeding risk was still reduced in the ENOX group [16]. Some previous meta-analyses did show that enoxaparin appears to be superior to unfractionated heparin for reducing mortality and bleeding results in patients with ACS or ST-segment elevation myocardial infarction. But there was still a lack of meta analyses of randomized controlled trials of patients with STEMI undergoing primary PCI [17,18,19]. Our meta-analysis showed that STEMI patients undergoing PCI benefited significantly from the incidence of death and MI between ENOX and UFH and did not benefit in the rate of major bleeding.

4.1 Limitations

There are some limitations that should be considered when interpreting the results of this meta-analysis. Firstly, only four RCTs were included in this analysis, which minimizes the generalizability of the results. We only obtained statistical data from the study, which could have led to inherent bias, design bias, treatment bias, and publication bias. Second, instead of using statistical data at the individual patient level, we applied the rate of events published in the conclusion of each study. Therefore, selection bias cannot be eliminated in the studies, and some clinical discoveries were under the control of between-research heterogeneity. Finally, we did not compare specific methods for intravenous or subcutaneous administration of ENOX. Nonetheless, our data satisfies the crucial demand for a comprehensive comparison between the two guided methods, which might improve informed decision-making for patients and physicians to select the ideal treatment for STEMI patients undergoing PCI.

5 Conclusion

We found that the rate of death and MI in ENOX treatment was significantly lower than that associated with UFH treatment in STEMI patients undergoing PCI. Moreover, in patients with STEMI undergoing PCI, the reduction of MI during ENOX treatment was more significant than the reduction in death. To the best of our knowledge, this is the first meta-analysis to include RCTs evaluating the efficacy and safety of ENOX versus UFH in STEMI patients receiving PCI [15]. The findings from this study will help guide the planning of clinical treatment options, thereby improving patient quality of life and reducing medical costs. The limited data from these randomized studies showed no significant difference in the incidence of major bleeding.

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Author contributions

Data curation: Hailong Wang, Jianjun Yang, Xiaohua Pang.

Formal analysis: Hailong Wang, Jianjun Yang, Xiaohua Pang.

Methodology: Hailong Wang, Jianjun Yang, Xiaohua Pang.

Project administration: Jianjun Yang.

Validation: Jianjun Yang.

Writing of original draft: Hailong Wang.

Writing, review and editing: Hailong Wang.

Conflict of interest statement: Authors state no conflict of interest

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