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ORIGINAL ARTICLE

Enoxaparin Versus Unfractionated Heparin in Acute Coronary Syndrome Without St-Segment Elevation: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Enoxaparin is a known alternative to the use of unfractionated heparin (UFH) in patients with acute coronary syndrome (ACS). However, the evidence about which of these medications would have the best benefit for these patients in 48 hours and 14 days is limited.

Objectives: Perform a meta-analysis of randomized controlled trials (RCTs) comparing the safety of enoxaparin versus UFH in ACS without ST-segment elevation (NSTE-ACS).

Methods: PubMed and Scopus databases were searched for RCTs that compared enoxaparin versus UFH in patients with NSTE-ACS. Risk ratios (RRs) for binary endpoints were computed with 95% confidence intervals (CIs). Heterogeneity was examined with I^2 statistics. Statistical significance was defined as P-value <0.05.

Results: Five RCTs with 17,644 patients were included, of whom 8,898 (50.4%) were treated with enoxaparin. There were no significant differences between groups in myocardial infarction (MI) at 48h (RR 0.87; 95% CI 0.75-1.01) and 14 days (RR 0.91; 95% CI 0.79-1.05), all-cause mortality at 48h (RR 1.02; 95% CI 0.62-1.69) and 14 days (RR 0.93; 95% CI 0.74-1.18), composite endpoint of death or MI at 48h (RR 0.87; 95% CI 0.75-1.00) and 14 days (RR 0.91; 95% CI 0.82-1.01), and urgent revascularization at 48h (RR 0.40; 95% CI 0.08-1.95).

Conclusion: These findings suggest that the use of enoxaparin in the treatment of NSTE-ACS presents similar results to UFH.

Keywords: Acute Coronary Syndrome; Enoxaparin; Heparin.

Introduction

Acute coronary syndrome (ACS) represents an important cause of hospitalizations worldwide. It is estimated that each year, seven million people around the world are diagnosed with such conditions.[1] Anticoagulants are effective therapeutic drugs for treating ACS without ST-segment elevation (NSTE-ACS). Nowadays, unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are vastly involved in optimized therapy discussions for NSTE-ACS.

During percutaneous coronary intervention (PCI) for both NSTE-ACS and ST-elevation myocardial infarction (STEMI), enoxaparin showed better safety outcomes as mortality and bleeding compared to UFH.[2] In addition, safety outcomes of enoxaparin versus UFH in NSTE-ACS with a 30-day follow-up period or during

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Central Illustration: Enoxaparin Versus Unfractionated Heparin in Acute Coronary Syndrome Without St-Segment Elevation: A Systematic Review and Meta-Analysis

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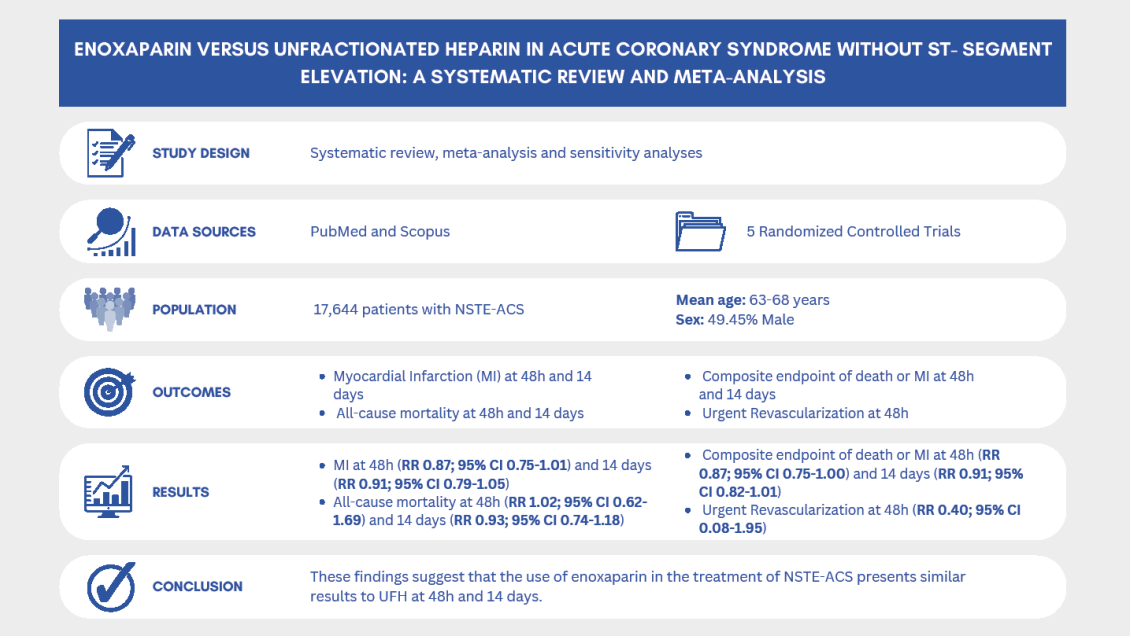

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Summary of the main findings.

PCI had been assessed by previous meta-analysis.[2,3] However, safety outcomes have never been analyzed grouped at 48 hours and 14 days and the evidence remains limited.

In light of this lack of analyses, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing enoxaparin versus UFH in patients with NSTE-ACS.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024499921.

Search Strategy and Data Extraction

PubMed and Scopus were systematically searched from inception to January 9, 2024, with the following search terms: ("Acute coronary syndrome*" OR "ACS" OR "unstable angina" OR "Non-ST Elevated Myocardial Infarction" OR "NSTEMI" OR "Non-ST-Elevation Myocardial Infarction" OR "Non-ST Elevation Myocardial Infarction" OR "Non-ST-Elevation Myocardial Infarction") AND ("Enoxaparin" OR "enoxaparine" OR "clexane" OR "lovenox") AND ("Unfractionated Heparin" OR "UFH"). Aiming the inclusion of additional studies, references of the included articles and systematic reviews were evaluated. Two authors (M.L.S.B. and M.E.C.S.) independently extracted baseline characteristics and data outcomes following predefined search criteria. Disagreements were resolved by consensus between three authors (M.L.S.B., M.E.C.S., and F.A.C.).

Eligibility Criteria

Studies with the following criteria were included: (1) RCTs; (2) comparing enoxaparin with UFH; (3) enrolling patients with ACS; and (4) reporting at least one of the outcomes of interest. Studies with the following criteria were excluded: (1) non-RCTs; and (2) overlapping populations.

Endpoints

Outcomes of interest were: (1) Myocardial infarction (MI) at 48h and 14 days; (2) all-cause mortality at 48h and 14 days; (3) urgent revascularization at 48h; and (4) composite endpoint of death or MI at 48h and 14 days.

Risk of Bias and Quality Assessment

The Cochrane Collaboration tool for assessing the risk of bias in randomized trials (Rob-2) was used to assess individual RCTs. Each trial received a score of high, low, or some concerns risk of bias in five domains: randomization process; deviations from the intended interventions; missing outcomes; measurement of the outcome; and selection of reported results. Two independent authors conducted the risk of bias assessment (E.B. and T.N.) and disagreements were resolved in unanimity with the senior author (F.C).

The quality of evidence was assessed according to the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) guidelines. Very low, low, moderate, or high-quality evidence grades were designed for the outcomes based on the risk of bias, inconsistency of results, imprecision, publication bias, and magnitude of treatment effects.

Statistical Analysis

The treatment effects for binary endpoints were evaluated using relative risk (RR) with a 95% confidence interval (CI). Statistical significance was defined as P-value <0.05. Heterogeneity was assessed with the Cochran Q-test and I^2 statistics; P-values <0.10 and I^2 values >25% were considered to indicate significance for heterogeneity. DerSimonian and Laird random-effects models were used for all endpoints. Sensitivity analysis was performed with leave-one-out procedures to identify influential studies and their effect on the pooled estimates. Statistical analyses were performed using the R software, version 4.2.3 (R Core Team, 2021, Vienna, Austria).

Results

Study Selection and Characteristics

As illustrated in Figure 1, the search strategy yielded 2,528 results. After removing duplicates and ineligible studies by title or abstract, ten studies were fully reviewed for inclusion and exclusion criteria. Of these, five were included in this meta-analysis. A total of 17,644 patients were included, of whom 8,898 (50.4%) were treated with enoxaparin. The mean age ranged from 63 to 68 years. Baseline characteristics are detailed in Table 1.

Pooled analysis of all studies

At 48h, there were no significant differences between groups in MI (Figure 2), all-cause mortality (Figure 3), a composite endpoint of death or MI (Figure 4), and urgent revascularization (Figure 5).

At 14 days, there were no significant differences between groups in MI (Figure 2), all-cause mortality (Figure 3), and the composite endpoint of death or MI (Figure 4).

Sensitivity Analysis

We performed a leave-one-out sensitivity analysis for all outcomes. There was a significant reduction in the composite endpoint of death or MI omitting SYNERGY 2004 (RR 0.81; CI 0.68-0.98). The other outcomes showed stability in the leave-one-out

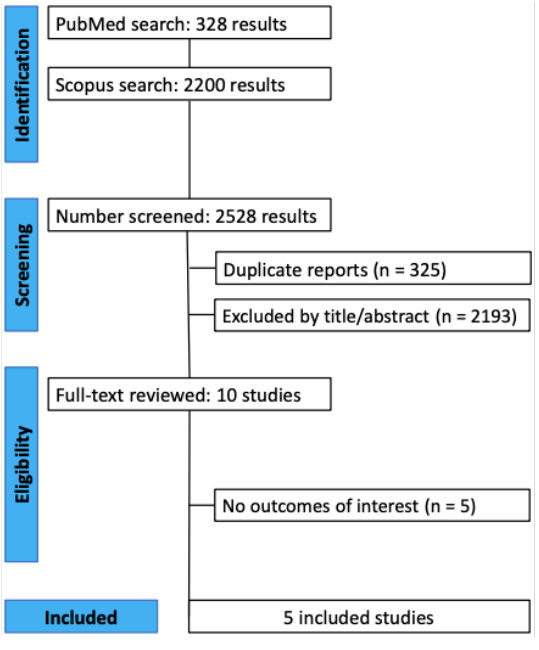

Figure 1 - PRISMA flow diagram of study screening and selection.

Table 1 - Baseline characteristics of included studies

Study	Ahmed 2011*	TIMI 11B 1999†	ESSENCE Trial 1998†	Acute II 2002†	SYNERGY 2004†
Study design	RCT	RCT	RCT	RCT	RCT
Follow-up (days)	30	43	30	30	30
Number of patients (UFH/Enoxa)	30/30	1957/1953	1564/1607	210/315	4985/4993
Male UFH/Enoxa, n (%)	NA	1256 (64.2)/ 1276 (65.3)	1033 (66.1)/ 1079 (67.1)	141 (67.1)/ 207 (65.7)	3301 (66.2)/ 3297 (66.0)
Age (years) UFH/Enoxa, median (IQR) or mean (SD)	NA	66 (57-72)/ 65 (56-73)	64 (65)/ 63 (64)****	63.7 (12.9)/ 64.6 (11.7)	68.0 (61.0-75.0)/ 68.0 (61.0-75.0)
Hypertension UFH/Enoxa, n (%)	NA	974 (49.8)/ 968 (49.6)	853 (54.5)/ 857 (53.3)	121 (57.6)/ 184 (58.4)	3378 (67.8)/ 3411 (68.3)
Hypercholesterolemia/Dyslipidemia UFH/ Enoxa, n (%)	NA	619 (31.6)/ 661 (33.8)	692 (44.2)/ 720 (44.8)	128 (61.0)/ 203 (64.4)	2947 (59.4)/ 2889 (58.3)
DM UFH/Enoxa, n (%)	NA	393 (20.1)/ 385 (19.7)	339 (21.7)/ 360 (22.4)	45 (21.4)/ 75 (23.8)	1502 (30.1)/ 1424 (28.5)
Current smoker UFH/Enoxa, n (%)	NA	527 (26.9)/ 521 (26.7)	369 (23.6)/ 399 (24.8)	63 (30.0)/ 89 (28.3)	1226 (24.6)/ 1178 (23.6)
Prior angina UFH/Enoxa, n (%)	NA	1125 (57.5)/ 1106 (56.6)	NA	133 (63.3)/ 187 (59.4)	2269 (45.5)/ 2287 (45.8)
Prior MI UFH/Enoxa, n (%)	NA	633 (32.3)/ 607 (31.1)	745 (47.6)/ 723 (45.0)	72 (34.3)/ 106 (33.7)	1374 (27.7)/ 1420 (28.5)
Prior CABG UFH/Enoxa, n (%)	NA	258 (13.2)/ 267 (13.7)	303 (19.4)/ 317 (19.7)	24 (11.4)/ 40 (12.7)	853 (17.1)/ 805 (16.1)
Prior PTCA/PCI UFH/Enoxa, n (%)	NA	232 (11.9)/ 223 (11.4)	332 (21.2)/ 346 (21.5)	0 (0.0)/ 2 (0.6)	964 (19.3)/ 1044 (20.9)

**The significance level of the results was not presented. †Statistical significance was defined as P-value <0.05. IQR: interquartile range; CABG: coronary artery bypass graft; DM: diabetes mellitus; MI: myocardial infarction; NA: not available; PTCA: percutaneous transluminal coronary angioplasty; SD: standard deviation; UFH: unfractionated heparin.*

procedures. The sensitivity analysis is detailed in Supplementary Material 1, Figures S1-S7.

Risk of Bias and Quality of Evidence

Figure 6 outlines the individual appraisal of each RCT included in this systematic review and meta-analysis. A low risk of bias was assigned to one study included. Two studies were classified as having some concerns about the risk of bias due to some concerns about the risk of bias in at least one domain assessed by RoB-2. Meanwhile, two studies were classified as having a high risk of bias due to a high risk of bias in at least one evaluated domain.

According to the GRADE assessment, moderate-quality evidence was assigned for the outcomes of MI at 14 days, composite endpoint of death or MI at 48h and 14 days. Low-quality evidence was assigned for the outcomes of all-cause mortality at 48h and 14 days and MI at 48h. Very low-quality evidence was assigned for the outcome of urgent revascularization at 48h. Quality assessment is detailed in Supplementary Material 2.

Discussion

In this systematic review and meta-analysis encompassing five RCTs and 17,644 patients, we undertook an assessment of safety outcomes at 48 hours and at 14 days of enoxaparin and UFH for NSTE-ACS treatment. The key finding of this pooled analysis was that there was no statistically significant difference

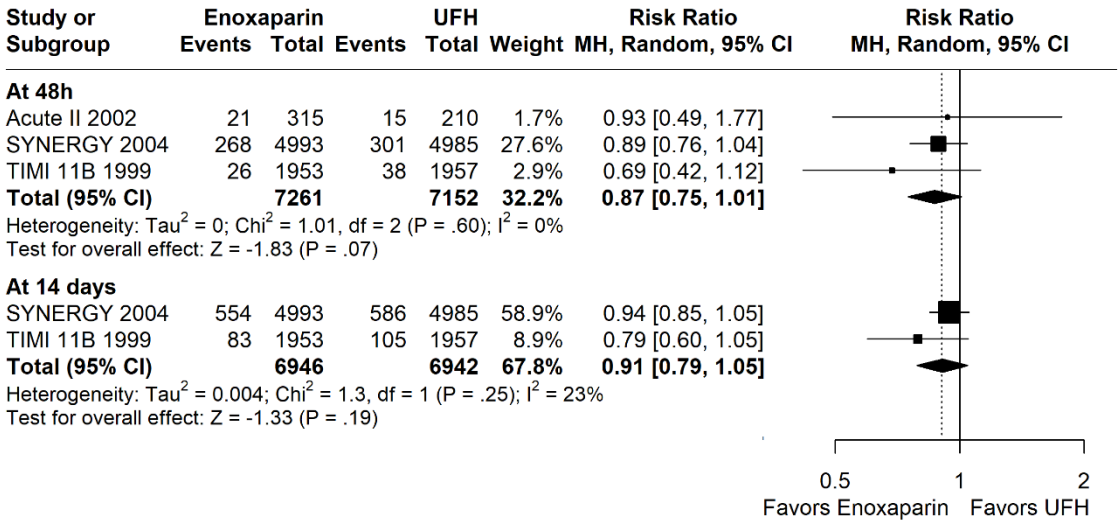

Figure 2 - Forest plots of pooled comparisons of MI at 48h and 14 days
UFH: unfractionated heparin; CI: confidence interval; TIMI: Thrombolysis in Myocardial Infarction; MH: Mantel-Haenszel Method.

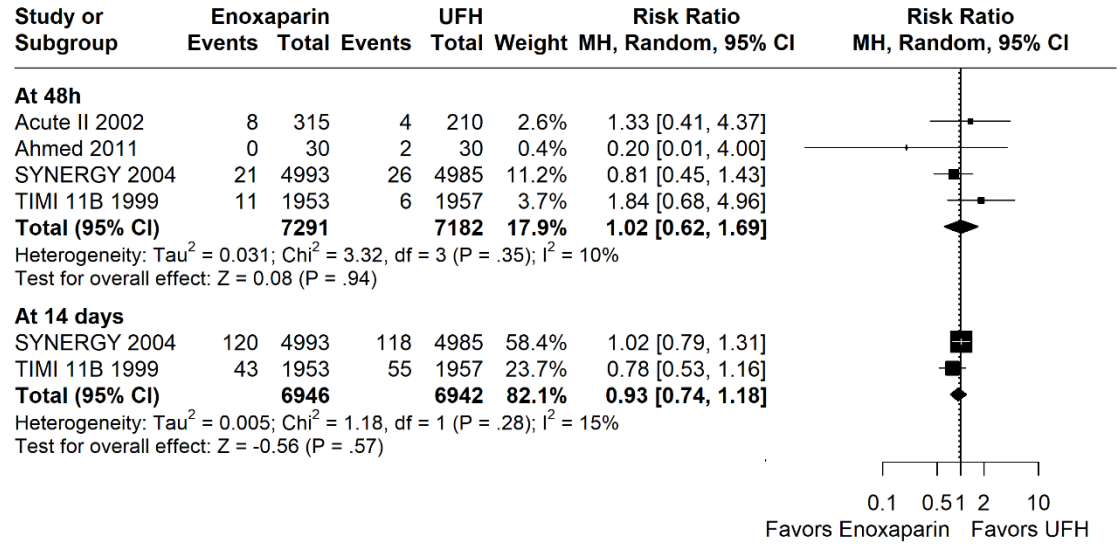

Figure 3 - Forest plots of pooled comparisons of all-cause mortality at 48h and 14 days.
UFH: unfractionated heparin; CI: confidence interval; TIMI: Thrombolysis in Myocardial Infarction; MH: Mantel-Haenszel Method.

between enoxaparin and UFH in MI, all-cause mortality, the composite endpoint for death or MI at 48h and 14 days, and urgent revascularization at 48h.

After the advent of heparin as an anticoagulant medication, UFH became the main drug for this purpose until newer substances emerged.[4] Enoxaparin is a form of LMWH and is derived from heparin itself, being widely used and researched since it was approved in 1993. As with other types of LMWHs, it acts as an anticoagulant medication, which is extremely important in the

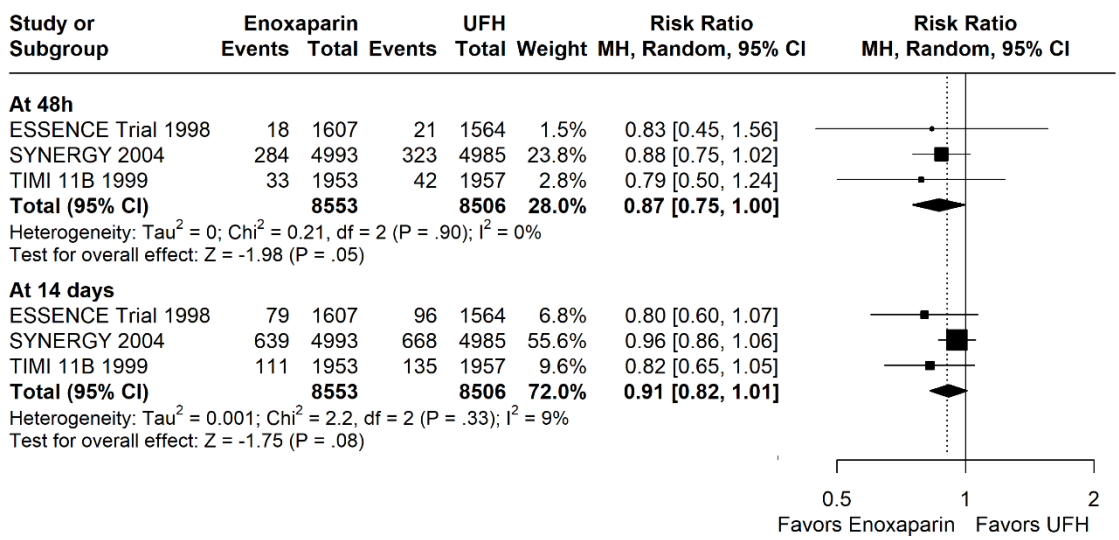

Figure 4 - Forest plots of pooled comparisons of the composite endpoint of death or MI at 48h and 14 days.
UFH: unfractionated heparin; CI: confidence interval; TIMI: Thrombolysis in Myocardial Infarction; MH: Mantel-Haenszel Method.

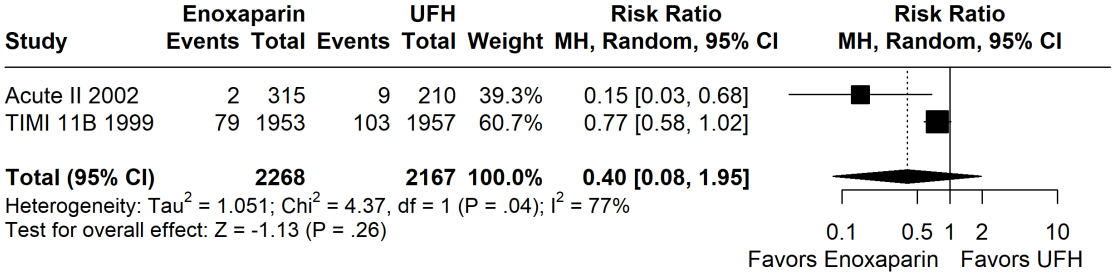

Figure 5 - Forest plots of pooled comparison of urgent revascularization at 48h.
UFH: unfractionated heparin; CI: confidence interval; TIMI: Thrombolysis in Myocardial Infarction; MH: Mantel-Haenszel Method.

treatment of MIs. Enoxaparin has often been regarded in the literature as a safe and effective alternative to UFH both in MIs with and without ST-segment elevations,[2,5-7] having also some important advantages to UFH in its pharmacokinetic and pharmacodynamics, such as a higher bioavailability, not requiring constant laboratory monitoring; a longer half-life (t½), allowing for greater convenience and cost reduction associated with a once a day administration;[8,9] and a greater specific factor Xa than factor IIa inhibition.[10]

In 2007, Murphy et al.[11] performed a meta-analysis of 12 RCTs, including 49,088 patients and comparing enoxaparin to UFH across the ACS spectrum, encompassing both STEMI and NSTE-ACS cases, of whom 21,945 patients were being treated specifically for NSTE-ACS. In contrast to the findings of our meta-analysis, this study found a consistent reduction of mortality and MIs over the NSTE-ACS trials when using enoxaparin, with even greater results in the STEMI patients. However, this result came coupled with a slight increase in major bleedings for the patients found in the NSTE-ACS RCTs but was not considered a statistically significant figure and may be explained in part by the greater use of revascularization procedures in the NSTE-ACS trials; the different drug

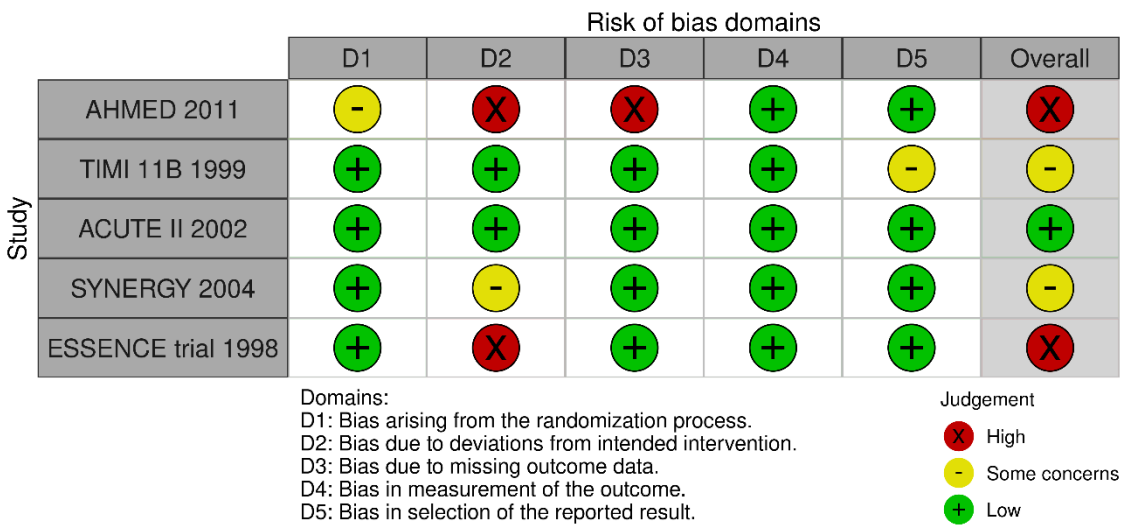

Figure 6 - Critical appraisal of RCTs according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.
TIMI: Thrombolysis in Myocardial Infarction.

uses protocols and differences in concomitant therapies such as thienopyridines. Additionally, the 2004 study conducted by Petersen et al.[12] presented evidence of the superiority of enoxaparin over UFH in NSTE-ACS patients, stating that no significant differences in major bleedings or in-hospital blood transfusions were detected while having a robust reduction in the composite endpoint for death/MI.

In contrast, the 2006 STEEPLE Trial published by Montalescot et al. [13] compared the use of enoxaparin to UFH in elective PCI in a total of 3,528 patients, finding bleeding rates similar to or lower than those treated with UFH, but also found a four-fold increase in the rate of achievement of target anticoagulation levels, highlighting once more the superior bioavailability of enoxaparin. In this sense, the study found little statistical evidence proving the superiority of enoxaparin despite patients treated with LMWH having more predictable levels of anticoagulation. A systematic review and meta-analysis published in 2018 by He et al.[3] encompassing four RCTs and 8,861 patients undergoing PCI for NSTE-ACS found no significant differences in the analysis of the composite endpoint for death/MI, reinforcing our findings. Another meta-analysis, including 12 trials and 17,157 patients and published in 2000 by Eikelboom et al.,[14] compared the two drugs and placebo in treating patients with NSTE-ACS. When comparing short-term use of enoxaparin to a placebo, they found a 66% reduction in death or MI and a 72% decrease in revascularization. Assessing the efficacy of short-term enoxaparin to UFH, a short and non-significant reduction of 12% in the risk of death or MI compared to heparin was found. However, when comparing the long-term use of enoxaparin (beyond 7 days and up to 90 days) to a placebo, they found no significant reduction in the risks of death, MI or need for revascularization. This study has some limitations. First, the GRADE assessment showed reasonably low evidence of the results obtained in our pooled data analysis. Second, two studies had some concerns about the risk of bias, and two studies had a high risk of bias. Third, some outcomes showed moderate to high heterogeneity and some studies had high weight in the pooled analysis. Due to these last two limitations, we performed a sensitivity analysis to assess the presence of dominant studies.

Conclusion

Our systematic review and meta-analysis brought a comprehensive overview of the currently available literature on the topic of the choice between the use

of enoxaparin or UFH in the treatment of NSTE-ACS at 48 hours and 14 days, weighing in on this ongoing debate. Our pooled data analysis reiterates that there is no significant statistical evidence of greater efficiency of enoxaparin over UFH in preventing mortality, MI, or urgent revascularization.

Author Contributions

Conception and design of the research: Bertoli ED; acquisition of data: Barros MLS, Lima PLG, Nienkötter TF, Floriano IT; analysis and interpretation of the data: Barros MLS, Lima PLG; statistical analysis: Pasqualotto E, Souza MEC; writing of the manuscript: Bertoli ED, Camerotte R; critical revision of the manuscript for intellectual content: Bertoli ED, Pasqualotto E, Kelly FA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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