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Unfractionated heparin–clopidogrel combination in ST-elevation myocardial infarction not receiving reperfusion therapy

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ABSTRACT

Objective: We sought explore the relative benefits of unfractionated heparin (UFH) compared with enoxaparin, alone or in combination with clopidogrel, in ST-segment elevation myocardial infarction (STEMI) patients not undergoing reperfusion therapy.
Methods: This is a propensity score study from The International Survey on Acute Coronary Syndromes in Transition Countries (ISACS-TC/NCT01218776) on patients admitted between October 2010–June 2013. There were a total of 1175 STEMI patients who did not receive mechanical or pharmacological reperfusion. Of these, 1063 were eligible for the aim of the study, being treated with UFH (522/1175; 44.4%) or enoxaparin (541/1175; 46%). Clopidogrel in combination with UFH or enoxaparin was given to 751 (63.9%) patients. The primary endpoint was in-hospital mortality. Secondary endpoints were intracranial hemorrhages, and clinically relevant bleedings.
Results: After adjustment for any confounders, UFH was associated with a lower risk of in-hospital mortality in clopidogrel users (multivariate adjusted regression analysis: odds ratio [OR]: 0.62, 95% Confidence Interval [CI] 0.41–0.94) as compared with clopidogrel non-users (OR: 0.94, 95% CI 0.55–1.60). The observed effect was not associated with combined enoxaparin and clopidogrel therapy. Major bleeding events were comparable in the enoxaparin group and UFH group (0.4% and 1.5% respectively, $p = 0.06$). The risk of major hemorrhage was nearly similar with combined UFH-clopidogrel therapy (1.4%) as compared with UFH alone (1.9%), $p = 0.67$.
Conclusion: UFH – Clopidogrel combination was associated with a large mortality reduction in STEMI patients not undergoing reperfusion therapy and did not significantly increase the risk of major bleeding.

1. Introduction

Clinical decision about whether to offer new anticoagulant agents or unfractionated heparin (UFH) therapy to patients who fail to receive any reperfusion therapy is still matter of uncertainty

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[1,2]. Differences in drugs' efficacy make comparison of treatments particularly relevant for care of these patients, as they are at high risk for death [3,4].

Aspirin and clopidogrel are accepted as standard adjunctive reperfusion treatment in patients with ST-segment elevation myocardial infarction (STEMI). The addition of heparins has been shown to reduce the risk of ischemic events among these patients, but anticoagulant and antiplatelet combination has been associated with increased bleeding [5,6].

We reviewed current practice in antithrombotic therapy of patients with STEMI who did not undergo any form of coronary reperfusion using the database of the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC, ClinicalTrials.gov, number NCT01218776). The aim of our study was to investigate the relative benefits of UFH compared with enoxaparin in STEMI patients not undergoing reperfusion therapy.

2. Methods

2.1. Study population

Between October 2010 to June 2013, a total of 2804 STEMI patients, from 45 hospitals (Appendix) were included in the ISACS-TC registry. Of these patients, 1175 (41.9%), did not get any form of reperfusion therapy. Patients were eligible for the study if they met the following criteria: age ≥18 years, symptoms consistent with acute cardiac ischaemia, documented evidence of persistent ST-segment elevation or new left bundle branch block on serial electrocardiograms and elevated biomarkers of myocardial necrosis. To avoid survival bias-as patients who were selected for the study would have to survive enough to have effective anticoagulation - a landmark time was used. We defined the landmark time as 6 h, based on the fact that often the peak time to effective anticoagulation after enoxaparin is not seen until 3–5 h after drug administration. Patients who died before the landmark time were excluded (n = 28).

We also excluded from the analysis patients who failed to receive any anticoagulant medications (n = 27), those who received fondaparinux (n = 44), and those who received other low molecular weight heparin (n = 13), leaving a total study sample of 1063 patients having admission therapy with enoxaparin or UFH (Fig. 1).

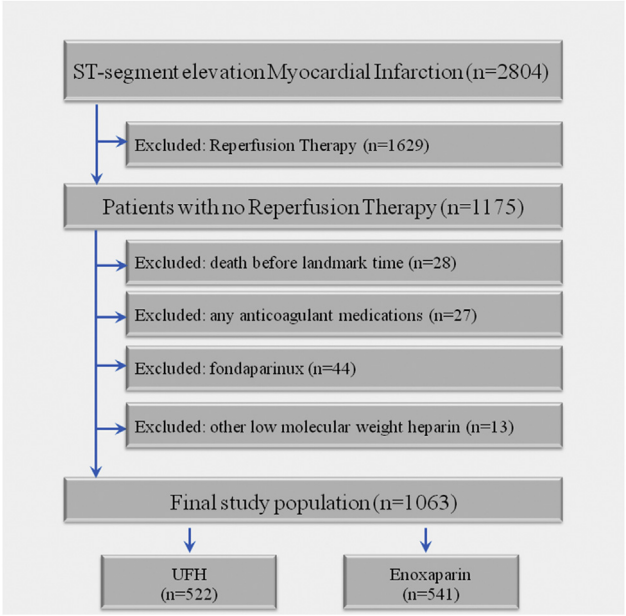

Fig. 1. Study flow chart.

Physicians participating to the registry were instructed to administer enoxaparin (for up to 8 days or hospital discharge), or UFH (for at least 48 h) at therapeutic doses on the basis of an approved institution-specific protocol. For patients younger than 75 years of age, enoxaparin was to be given as a fixed, 30 mg intravenous bolus followed by a subcutaneous injection of 1 mg/kg with injections administered every 12 h. For patients at least 75 years of age, the intravenous bolus was eliminated and the subcutaneous dose was reduced to 0.75 mg/kg every 12 h. Maximum doses of 100 mg in patients aged ≤75 years and 75 mg in patients aged >75 years were allowed for the first 2 subcutaneous injections. Patients with a serum creatinine greater than 175 μmol/L were administered doses renally adjusted to 1.0 mg/kg every 24 h. The UFH dosing strategy begun with an intravenous bolus of 60 U/kg of body weight (maximum 4000 U) followed by an infusion of 12 U/kg. The dose was adjusted to maintain the activated partial thromboplastin time in the commonly quoted therapeutic range of 1.5–2 times. The use of enoxaparin or UFH, as well as the use of combined aspirin/clopidogrel therapy and all other concomitant medications, was at discretion of the managing physician.

2.2. Data collection and outcomes

The enrolled hospitals were able to access information through the ISACS-TC database. They periodically uploaded their data to the central server of the ISACS-TC.

Data on patient demographics, cardiovascular risk factors, clinical history, electrocardiographic features, cardiac biomarkers results, acute therapy, and in-hospital death, were collected by the designated physician. Serial electrocardiograms (on admission, and at 90 and 180 min), and measurements of biomarkers of myocardial necrosis (on admission, and till 96 h after the qualifying event) were used by the treating physician to adjudicate the discharge diagnosis (STEMI) according to standardized definition [7]. The primary outcome endpoint was in-hospital mortality. The study ended at discharge or when subjects were lost because they died. Secondary endpoints were intracranial hemorrhages, and clinically relevant bleedings.

2.3. Statistical analysis

Data are presented as proportions, medians, or mean ± SD as appropriate. Chi-square test for discrete variables was used to compare UFH and enoxaparin with respect to baseline characteristics, antiplatelet treatment, and outcomes. Fisher's exact test was used in the analysis of categorical data where sample sizes were small. We used *t* test for continuous variables. Estimates of the odd ratios (OR) and associated 95% confidence intervals (CI) were obtained with the use of the logistic regression analysis. For removing the effects of selection bias in observational studies, the effect of UFH versus enoxaparin was estimated by multivariate adjusted regression. The result was further validated by propensity score regression [8].

The *multivariate adjusted regression model* was defined applying a backward selection procedure ($p < 0.20$) to a list of potential confounders. We, also introduced in the model clinically relevant variables, such as: age, sex, hypertension, smoking, previous myocardial infarction, previous angina pectoris, history of heart failure, previous coronary artery bypass graft (CABG), and previous percutaneous coronary intervention (PCI). Age was divided into three groups: younger than 60 years, 60–74 years and 75 years or older. Two-way interactions involving treatment methods and key