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CLINICAL STUDY

Low-molecular weight heparin Enoxaparin in the treatment of acute coronary syndromes without ST segment elevation

Mitrovska S, Jovanova S

Department of Cardiology, Military Hospital, Skopje, Macedonia. **mitrovska2000@yahoo.com**

Abstract: *Objectives:* We compared the incidence of adverse cardiac outcomes of enoxaparin vs unfractionated heparin in the management of ACS-NSTE.
Background: Low-molecular-weight heparins are the potential new standard in the treatment of acute coronary syndromes without ST-segment elevation (ACS-NSTE). The benefit is addressed to significant diminution of the adverse clinical events – recurrent angina (RA), myocardial infarction (MI), heart failure (HF), cerebrovascular insult (ICV), coronary artery by-pass graft (CABG), percutaneous coronary intervention (PCI) and death.
Methods: Sixty patients with ACS-NSTE were randomised to receive Enoxaparin 1mg/kg body weight s.c twice daily (n=30) and unfractionated heparin (Heparin – "Biochemie" 25.000 IU/5 ml), according to Rashke nomogram (n=30). The end point were RA, MI, HF, ICV, CABG, PCI and death at day 180. The Kaplan-Meier estimation technique was used to compared the time to events for two treatments. A $p<0.05$ was considered to indicate significance.
Results: For 180 days, RA, MI, HF, ICV and death were lower in the Enoxaparin vs UFH group (36.6 % vs 73.3 %, p=0.001), (30 % vs 53.3 %, p=0.05), (13.3 % vs 23.3 %, p=0.31), (3.3 % vs 10 %, p=0.29), (3.3 % vs 10 %, p=0.31), respectively. CABG were similar 13.3 % (p=0.96). PCI were performing in 33.3 % in UFH vs 90 % in LMWH (p=0.0001).
Conclusion: The use of Enoxaparin in ACS-NSTE schows impressive decrease of incidence of ischemic events *(Fig. 7, Ref. 8).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: acute coronary syndrome without ST segment elevation, low-molecular-weight heparin, unfractionated heparin.

Numerous studies of patients with acute coronary syndrome performed in the past decade, indicate incremental benefit from intense pharmacological therapy. The focus is to integrate the use of new antithrombin inhibitors and new antiplatelet agents. Despite the broad spectrum of pharmacologic options, the dilemma concerning the optimal combination still exists (1). Low-molecular-weight heparins (LMWH), mainly Enoxaparin, are a potential new standard in the treatment of non-ST-segment elevation acute coronary syndromes (ACS-NSTE). The efficacy has been discussed in many trials and it is explained with pharmacokinetic and pharmacodynamic characteristics of the agent (2). Enoxaparin has a low molecular weight, high anti-Xa activity, low anti-IIa activity, bioavailability of 96 % and half-time elimination of 4–6 hrs.

Stable anticoagulant response, lower platelet activation, resistance to inactivation with platelet factor 4, and lower rate of thrombocytopenia provide no need of laboratory monitoring (3). These properties provide a significant diminution in frequency of adverse clinical outcomes, namely recurrent angina (RA), myocardial infarction (MI), heart failure (HF), the onset of cerebrovascular insult (ICV), performing of coronary artery by-pass graft (CABG), need of percutaneous coronary intervention (PCI) and death. These data support the conversion from unfractionated heparin to enoxaparin.

Department of Cardiology, Military Hospital, Skopje, Macedonia

Address for correspondence: S. Mitrovska, MD, MSMed, ul. Sole Stojcev, br. 1–2/8, 1000 Skopje, Macedonia.
Phone: +38923079509

Objectives

We compared the incidence of adverse cardiac outcomes of enoxaparin with that of unfractionated heparin in the management of ACS-NSTE.

Methods

The study was a prospective randomised open-labeled two-center study. A total of 60 patients with ACS-NSTE were randomised to receive LMWH-Enoxaparin (Clexane, Aventis Pharma) 1 mg/kg body weight s.c. twice daily (n=30) and weight-adjusted unfractionated heparin (UFH-Heparin "Biochemie" 25.000 IU/5 ml), according to Rashke nomogram (n=30). This nomogram provides an achievement of activated partial thromboplastin time (aPTT) within the target range of anticoagulation, 60–85 sec. (80 IU/kg iv bolus, followed by 18 IU/kg/h infusion for 24 hrs i.e.5000 IU iv bolus, 1000 IU/h for 70-kg body

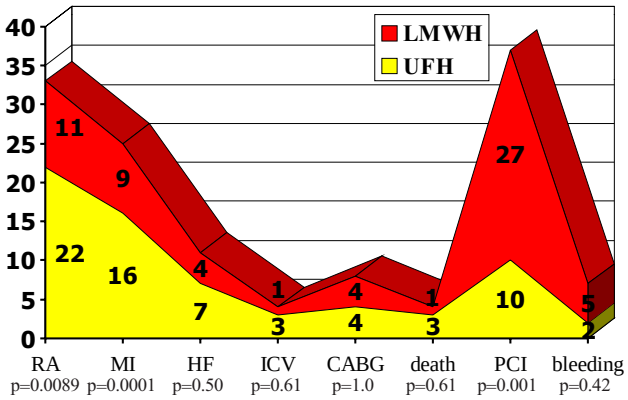

Fig. 1. Adverse cardiovascular events at 180 day.

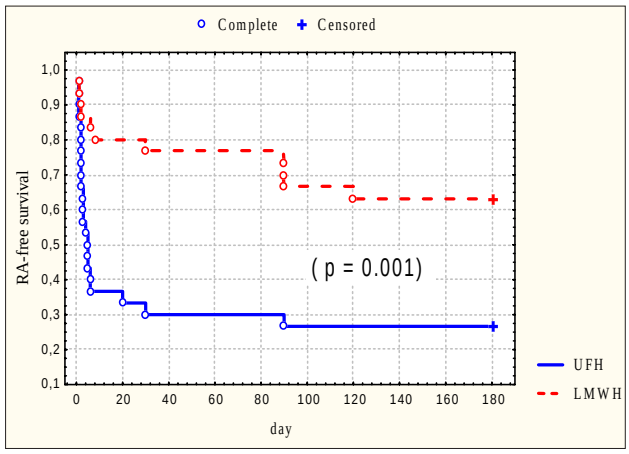

Fig. 2. Kaplan-Meier survival curves. Reccurrent angina-free survival at day 180.

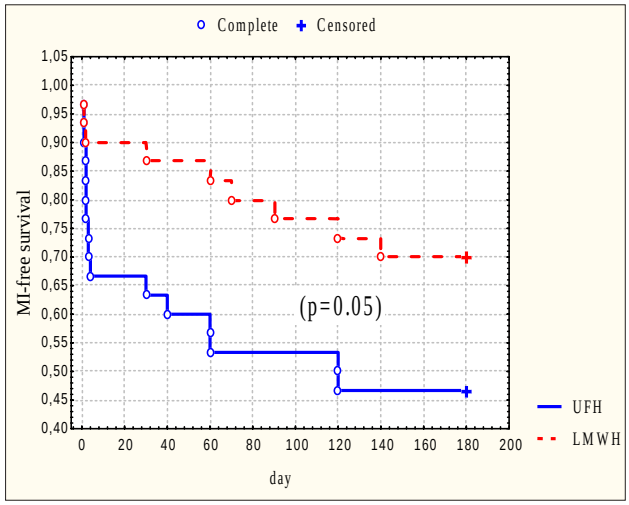

Fig. 3. Kaplan-Meier survival curves. Myocardial infarction-free survival at day 180.

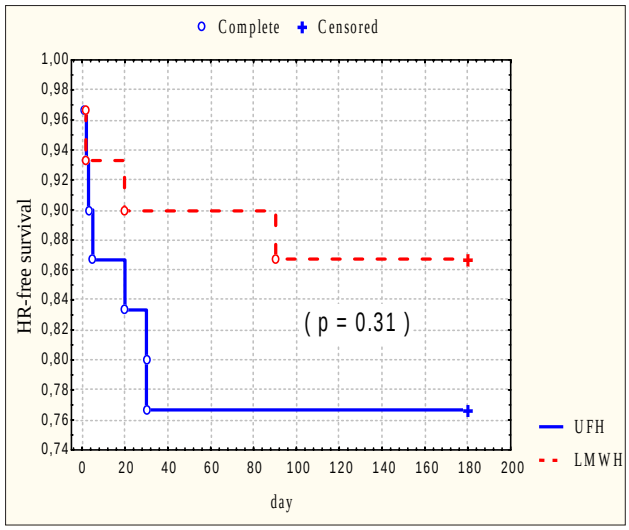

Fig. 4. Kaplan-Meier survival curves. Heart failure-free survival at 180 day.

weight). The anti-Xa activity has been used as a marker to assess anticoagulation with Enoxaparin and aPTT to assess anticoagulation with UFH. They were measured six hours after the initial bolus dose, and every further 6 hrs. The blood specimens were collected in siliconized Vacutainer tubes (Belliver Industrial Estate, Plymouth,UK) with 3.3 % acidum citricum. The analyses were performed with Humaclot analyzer, the aPTT (Dade/ /Bering), Pathrombin 52, and anti-Xa (Berichrom Heparin) in Central Biochemical Lab. at Military Hospital, Skopje, Macedonia. We evaluated the incidence of RA, MI, HF, ICV, CABG, death and TVR at day 180. In addition, we followed the incidence of hemorrhagic complications and the duration of the hospitalization period.

Statistical analysis

The statistical analyses were performed by using the commercial statistical package, Statistica for Windows, Version 6.0. The Kruskal–Wallis ANOVA analysis was used for nonparametric variables, Wilcoxon Matched Pairs Test for two dependent samples, and Pearson Product Moment Correlation for correlation between two heparin types and outcomes. The Kaplan-Meier estimation technique was used to compare the time to events for two treatments. A p value <0.05 was considered to indicate significance.

Results

For 180-day follow-up, the end points, namely RA, MI and HF, were lower in the Enoxaparin group than in the UFH group (36.6 % vs 73.3 %, p=0.001), (30 % vs 53.3 %, p=0.05), (13.3 % vs 23.3 %, p=0.31) respectively. The onset of ICV was 3.3 % in LMWH vs 10 % in UFH group (p=0.29). The frequency of CABG performances were similar in both groups, namely 13.3 % (p=0.96). Death was in 10 % in UFH group vs 3.3 % in LMWH group (p=0.31). PCI was performed in 33.3 % in UFH vs 90 % in LMWH (p=0.0001). The incidence of minor hemorrhagic complications was 16.7 % in LMWH vs 6.7 % in UFH (p=0.24) (Fig. 1). The period of hospitalization was shorter in Enoxaparin vs UFH (233 vs 403 days, D=0.6, p=0.0001).

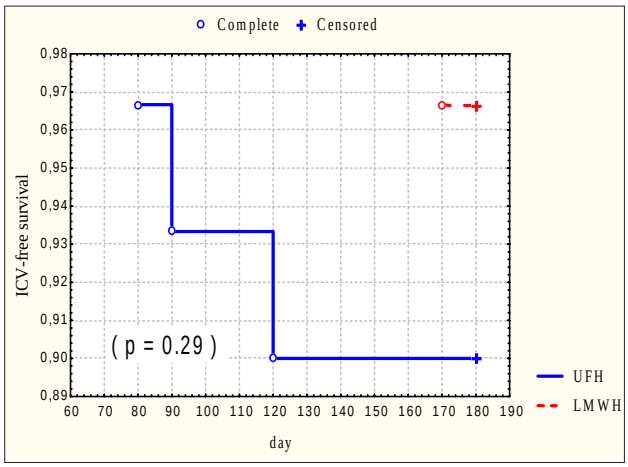

Fig. 5. Kaplan-Meier survival curves. ICV-free survival at 180 day.

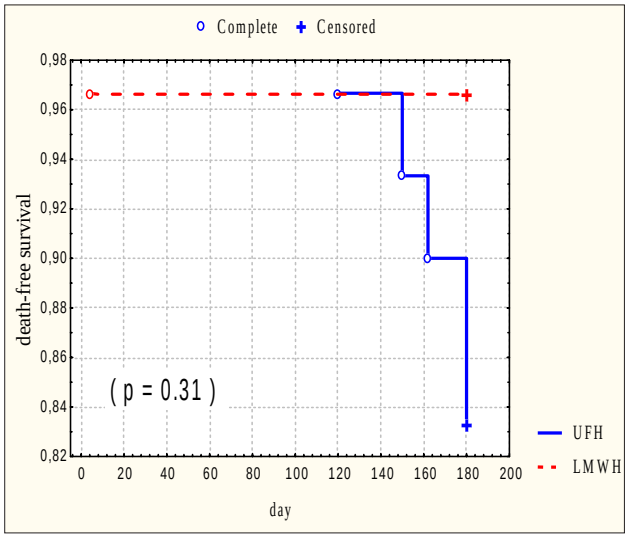

Fig.6. Kaplan-Meier survival curves. Death-free survival at day 180.

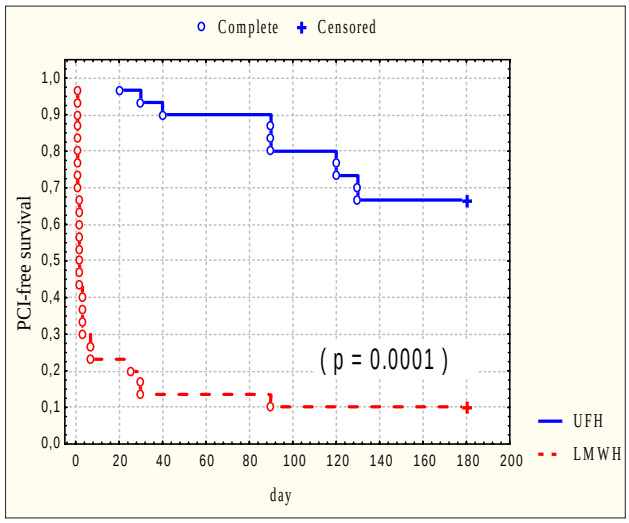

Fig.7. Kaplan-Meier survival curves. PCI-free survival at 180 day.

We noted a longer period free of adverse cardiac events in enoxaparin vs UFH group (Figs 2, 3, 4, 5, 6, 7).

Discussion

Understanding the pathophysiology of ACS leads to the development of novel therapeutic agents and treatment strategies, namely rapid reperfusion strategies. Pharmacological, mechanical and combined strategies promise improved clinical outcomes. Despite this advance, the controversy of, conservative vs invasive reperfusion still exists (4). In March 2002, the American College of Cardiology/American Heart Association published the management guidelines for unstable angina and non-ST-segment elevation myocardial infarction. The guidelines suggest risk stratification of patients and distinction of those who will benefit most from conservative (low and intermediate risk score) or invasive (high risk score) approach (5). In 2003, the CATH Clinical Consensus Panel Scientific Round Table, a group of interventional cardiologist-clinicians, academic scholars and clinical investigators produce evidence-based consensus focusing on pharmacological therapy for ACS with an emphasis on antithrombotic and antiplatelet therapy. The new ADP receptor antagonists, LMWH, GP IIb/IIIa inhibitors will enhance outcomes in ACS (6). When defining the pharmacologic reperfusion the most important role is played by the type of heparin.

Thus, there is a strong relationship between the type of heparin and adverse events. Key factors to the choice of the type of heparin are efficacy, safety, reduction in mortality, cost-effectiveness. Many trials have shown that LMWH have superiority over UFH in diminution of adverse cardiac

outcomes. ESSENCE (Efficacy and Safety Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) showed incidence of composit end-point in 19.8 % in enoxaparin group, vs 23.3 % in UFH group (7). In EVET (Enoxaparin Versus Tinzaparin in Non-ST-segment Elevation Acute Coronary Syndromes) study, the incidence of primary end-point in enoxaparin vs tinzaparin group was 12.3 % vs 21.1 % (8). FRAXIS, ACUTE II, FRISC, NICE-2, NICE-3 also show superiority of LMWH vs UFH in reducing the cardiac events.

The results given in our study are in correlation with these large clinical studies. We concluded the superiority of enoxaparin over UFH in the prevention of RA (36.6 % vs 73.3 %), MI (30 % vs 53.3 %), HF (13.3 % vs 23.3 %), ICV (3.3 % vs 10 %), and death (3.3 % vs 10 %). We noted shorter hospitalization period in enoxaparin group 233 vs 403 days (D=0.6, p=0.0001). The incidence of minor hemorrhagic complications were 16.7 % in LMWH vs 6.7 % in UFH. PCI were performing in 33.3 % in UFH vs 90 % in LMWH. We explain this inverse relationship with the influence of the subjective factor i.e. the type of cardiologist, namely interventional or clinician.

Namely, enoxaparin was used at the center were cath lab was.

Conclusion

The use of Enoxaparin in ACS-NSTE schows an impressive decrease in ischemic events, stable anticoagulation effect, no need of lab monitoring, shorter period of hospitalization.

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