# An excess dose of enoxaparin increased risk for death in the non–ST-segment elevation acute coronary syndrome

LaPointe NM, Chen AY, Alexander KP, et al. **Enoxaparin dosing and associated risk of in-hospital bleeding and death in patients with non ST-segment elevation acute coronary syndromes.** Arch Intern Med. 2007;167:1539-44.

**Clinical impact ratings:** Hospitalists ★★★★★☆☆ Cardiology ★★★★★★☆ Hematol/Thrombo ★★★★★★☆

## QUESTION

In patients with the non–ST-segment elevation acute coronary syndrome (ACS), what is the relation between enoxaparin dose and risk for in-hospital major bleeding and death?

## METHODS

**Design:** Cohort from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology and American Heart Association guidelines (CRUSADE) national quality improvement initiative.

**Setting:** 332 hospitals in the United States.

**Patients:** 10 687 patients (59% men, 82% white) who had symptoms of cardiac ischemia for > 10 minutes and positive cardiac markers (troponin or creatine kinase-MB fraction), ST-segment depression > 0.5 mm, or transient ST-segment elevation (0.6 to 1.0 mm for > 10 min). Patients who transferred to another hospital or had coronary artery bypass graft surgery during hospitalization were excluded from the analysis.

**Risk factors:** Excess (> 10 mg higher than recommended dose) and lower-than-recommended doses (> 10 mg lower than recommended dose) of enoxaparin. The recommended daily dose was 2 mg/kg (if creatine clearance ≥ 30 mL/min) or 1 mg/kg (if creatine clearance < 30 mL/min). Results were adjusted for baseline characteristics, including age; sex; race; body mass index; family history of coronary artery disease; renal impairment; history of diabetes, hypertension, and hypercholesterolemia; and previous myocardial infarction, stroke, coronary artery bypass graft surgery, percutaneous coronary intervention, and heart failure.

**Outcomes:** In-hospital major bleeding and death.

## MAIN RESULTS

2002 (19%) patients (median age 78 y) received excess doses, 3116 (29%) patients (median age 66 y) received lower-than-recommended doses, and 5569 (52%) patients (median age 66 y) received recommended doses of enoxaparin. An excess dose of enoxaparin led to a higher incidence of death than did the recommended dose (5.6% vs 2.4%) (Table). A lower-than-recommended dose did not increase risk for death (Table). Results for major bleeding are not reported because outcome assessors were not blinded to patients' enoxaparin dosage.

## CONCLUSION

An excess dose of enoxaparin increased risk for death in patients with the non–ST-segment elevation acute coronary syndrome.

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**Association between enoxaparin dose and death in patients with the non–ST-segment elevation acute coronary syndrome***

| Outcome | Adjusted odds ratio (95% CI) | |
|---|---|---|
| | Excess dose | Lower-than-recommended dose |
| Death | 1.35 (1.03 to 1.77) | 1.25 (0.93 to 1.68)† |

*CI defined in Glossary. Odds ratio adjusted for baseline characteristics, including age; sex; race; body mass index; family history of coronary artery disease; renal impairment; history of hypertension, diabetes, and hypercholesterolemia; previous myocardial infarction, stroke, coronary artery bypass graft surgery, percutaneous coronary intervention, and heart failure.
†Not significant.

## COMMENTARY

It is refreshing to see appropriate dosing of therapy evaluated in the study by LaPointe and colleagues because this topic is mostly overlooked in large randomized trials. Appropriate dosing is important for low-molecular-weight heparins (LMWHs), such as enoxaparin, because of renal excretion. Most large randomized trials have shown improved outcomes with weight-adjusted LMWH compared with conventional unfractionated heparin, at the expense of clinically significant bleeding (1). Failure to adjust dosing with advanced or early renal dysfunction is a serious issue in enoxaparin dosing, as shown in the study by LaPointe and colleagues and in other studies. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes trial showed increased risk for bleeding starting at a glomerular filtration rate ≤ 58 mL/min (2). Manufacturers of enoxaparin advise reducing the dosage by one half in patients with creatinine clearance < 30 mL/min, but no directions exist for dose adjustment in patients with creatinine clearances of 30 to 60 mL/min.

The role of obesity has been assessed in clinical trials in terms of safety of LMWH, and no differences were found for clinical endpoints, including bleeding (3). Advanced age is a risk factor for any form of anticoagulation, and use should be carefully monitored. The duration of therapy is especially important in these clinically vulnerable populations and should be limited to the minimum possible duration. Newer drugs, such as fondaparinux, or direct thrombin inhibitors, such as bivalirudin, may be alternatives for high-risk patients (2, 4). Current trial evidence supports equal clinical efficacy of bivalirudin in ACS compared with other antithrombotic agents, including platelet glycoprotein IIb/IIIa inhibitors and heparin. Recent evidence favors using bivalirudin in patients with renal dysfunction undergoing percutaneous coronary interventions including ACS (5), although it has to be dose-adjusted based on renal function.

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***References***

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