TREATING UNSTABLE ANGINA

TITLE: Randomized comparison of subcutaneous heparin, intravenous heparin, and aspirin in unstable angina
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Clinical question. **For patients with unstable angina, how effective is subcutaneous heparin compared with intravenous heparin or aspirin?**

Background. Intravenous (IV) heparin is currently a mainstay of therapy for unstable angina, but subcutaneous heparin is cheaper, easier to give, and equally effective for conditions such as deep-venous thrombosis (DVT). This study compares the efficacy of intravenous heparin with that of aspirin and of subcutaneous (SQ) heparin for patients with unstable angina.

Population studied. This multicenter Italian trial enrolled 108 patients with unstable angina, defined as typical chest pain at rest or minimum effort with reversible ST changes or an episode of chest pain that lasted more than 20 minutes with doubling of creatinine kinase. Of 399 possible subjects enrolled, 56 were excluded because of age greater than 70 years, recent stroke or surgery, uncontrolled hypertension, or contraindications to aspirin or heparin. The remaining 343 patients had 24 hours of anti-anginal therapy with aspirin, nitrates, nifedipine, and metoprolol. Those with no angina and less than three ischemic episodes as determined by Holter monitor in the second 24-hour period were also excluded from the trial. Of the remaining 108 patients, 71 were smokers, 22 had diabetes mellitus, and 23 had hypertension. All had arteriography: 66 had greater than 50% occlusion of the left main artery and 39 had greater than 70% occlusion of the proximal anterior descending arteries. Thus, the patients enrolled in this trial seem to be similar to those family physicians admit to rule out unstable angina, ie, those for whom history or other circumstances do not warrant immediate catheterization. Some may be concerned that Italian patients and medical care may not be generalizable to the United States, but there is no reason to think that Italians would respond differently to these treatments than would any other ethnic group. The criteria for unstable angina and the medical management are appropriate, and the clinical and angiographic data also suggest a similar population.

Study design and validity. This is a well-designed study. After the initial day of therapy (the run-in period), patients were randomly assigned to one of three groups: (1) buffered aspirin, 325 mg/d; (2) IV heparin, with a loading dose of 5000 units, followed by 1000 units per hour and adjusted to maintain partial thromboplastin time (PTT) 1.5 to 2.0×baseline, and (3) SQ heparin, with a loading IV dose of 5000 units, followed by SQ doses every 8 hours, with dosage adjusted for age and sex (men weighing >65 kg=10,000 units, <65 kg=7500 units, and women >90 kg=10,000 units, 65–90 kg=7500 units, <65 kg=5000 units) and the durations between doses adjusted once a day to keep the PTT between 1.5 and 2.0. The timing and clinical role of angiography are not described. All patients were followed for a total of 4 weeks. A relative weakness of this study is that the power to detect a difference between the two heparin groups is only moderate because the frequency of angina and ischemia in both heparin regimens is so low.

Outcomes measured. The primary outcomes of the study were the amount of myocardial ischemia as determined by the number of anginal attacks (anginal attacks not defined by the authors), the total number of ischemic episodes (anginal attacks plus episodes of silent ischemia, defined as .1 mV ST change for at least 60 seconds), and the overall duration of ischemia in minutes per day. All Holter monitor recordings were reviewed blindly. While myocardial infarction, revascularization, bleeding events, serial hematocrits, and deaths were also documented, the sample size was too small to detect a clinically important difference. While the number of anginal attacks was monitored based on weekly patient reports for 1 month, physicians had the option of stopping SQ heparin after 3 days. Therefore, patients "doing well" on SQ heparin would have been more likely to be continued on this medication. This "selection bias" would have the effect of inflating the apparent efficacy of SQ heparin. As is common in studies of acute cardiac interventions, no long-term or functional outcomes are described.

Results. The three treatment groups had similar demographic, clinical, and angiographic characteristics. Compared with the run-in day, the IV and SQ heparin groups

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had similar and dramatic reductions of the number of anginal attacks (91% and 86%, respectively), episodes of silent ischemia (56% and 46%, respectively), and duration of ischemia (66% and 61%, respectively). Aspirin therapy did not significantly affect any of the major outcomes. The only bleeding complications recorded were minor, with 2 patients each in the aspirin and IV heparin groups reporting epistaxis or ecchymosis.

Recommendations for clinical practice. **This study provides strong evidence of the superiority of heparin for short-term relief of persistent chest pain and silent ischemia in patients with unstable angina. The evidence is relatively strong that subcutaneous heparin works as well as intravenous heparin, although we await a study that has the power to make a definitive comparison between the two regimens. Given the ease, low cost, and possibility of outpatient use, it would be reasonable to give subcutaneous heparin to patients who are stable but have persistent chest pain. A larger study addressing patient-oriented outcomes, such as reinfarction rates and long-term efficacy and survival, is needed.**

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VENOUS THROMBOEMBOLISM

TITLE: A Comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism
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Clinical question. **Following an initial episode of deep-venous thrombosis (DVT) or pulmonary embolism (PE), what is the comparative efficacy of 6 weeks vs 6 months of oral anticoagulant therapy in preventing recurrence of venous thromboembolism?**

Background. Although secondary prophylaxis with oral coagulation is routinely given for deep-venous thrombosis and pulmonary embolism, the optimal duration of therapy is open to debate. Several randomized trials have suggested that the duration of anticoagulation can be shortened from a few months to a few weeks without increasing the risk of recurrence. Some of these studies, however, have been criticized for either an inadequate sample size or a lack of objective criteria for the diagnosis of venous thromboembolism.

Population studied. Patients studied included individuals at least 15 years old who presented to one of 16 medical centers in Sweden with an acute pulmonary embolism or deep-vein thrombosis in the leg, iliac veins, or both. Initial diagnoses were confirmed by venography in cases of deep-vein thrombosis and with perfusion-ventilation scanning or angiography in cases of pulmonary embolism.

Of 1185 patients evaluated at the 12 hospitals that kept logs of encounters, 40% were excluded on the basis of the following prespecified criteria: absence of radiographically confirmed venous thromboembolus, pregnancy, allergy to study medications, an indication for continuous oral anticoagulation, total paresis, venous ulcer or arterial insufficiency of the affected leg, congenital deficiency of antithrombin III, protein S or protein C, unwillingness to give oral consent, and unavailability for follow-up. The proportion of patients excluded for any particular reason was not specified. It would have been useful to know whether patients were excluded largely on the basis of medical contraindications or refusal to participate since these reasons for exclusion would result in different samples of patients and have very different implications for the generalizability (also called external validity) of the study.

Study design and validity. This study was a randomized controlled trial. After at least 5 days of intravenous or subcutaneous heparin, 897 patients were randomly assigned to either 6 weeks (n=443) or 6 months (n=454) of oral anticoagulation. Patients received warfarin or dicoumarin with a targeted international normalized ratio (INR) of 2.0 to 2.5, and were followed for 2 years. Comparison of the two treatment groups revealed similarities across a number of characteristics including sex, family history, and site of and risk factors for thromboembolism. The treatment groups differed in that fewer patients in the 6-week group had previously received thrombolytic therapy. However, the total number of patients who had such therapy was small, and thus not likely to make a difference. A few patients in both treatment groups also received oral anticoagulation for either a longer or shorter period than intended. The mean duration of treatment, however, increased by less than 0.1 month per patient and probably would have an insignificant impact on the results.

Outcomes measured. The principal endpoints of the trial were major hemorrhage during oral anticoagulation, recurrent venous thromboembolism, and death during a 2-year study period.