Aspirin Versus Heparin to Prevent Myocardial Infarction During the Acute Phase of Unstable Angina

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Background. Antiplatelet therapy with aspirin and antithrombotic therapy with heparin both prevent the complications of unstable angina; however, no definitive data exist on the relative clinical efficacy of the two drugs.

Methods and Results. Aspirin (325 mg bid) or heparin (5000-U intravenous bolus followed by a perfusion titrated to the APTT) were compared in a double-blind randomized trial of 484 patients in two cohorts enrolled sequentially. The study was initiated at admission to hospital at a mean of 8.3±7.8 hours after the last episode of pain. End points were assessed 5.7±3.3 days later, when the decision for long-term management was made. Myocardial infarction occurred in 2 (0.8%) of the 240 patients randomized to heparin and in 9 (3.7%) of the 244 randomized to aspirin (P=.035), an odds ratio of 0.22 and a risk difference of 2.9% (95% confidence limits, 0.3% to 5.6%) with heparin. The only death resulted from a myocardial infarction in an aspirin patient. Survival curves with Cox logistic regression analysis showed that the improvement in survival without myocardial infarction with heparin (P=.035) was independent of other baseline characteristics.

Conclusions. This study documents that heparin prevents myocardial infarction better than aspirin during the acute phase of unstable angina. (Circulation. 1993;88[part 1]:2045-2048.)

Key Words • anticoagulants • antiplatelet drugs • atherosclerosis • angina

Therapeutic trials with aspirin,1-4 ticlopidine,5 and heparin3,4,6,7 have demonstrated that inhibition of platelet function and thrombin generation prevent the complications associated with unstable angina. These results are consistent with the well-documented role of platelet aggregation and thrombus formation in the etiology of this syndrome.

In a previous double-blind, randomized, placebo-controlled trial involving 479 patients with acute unstable angina,3 we demonstrated that aspirin, heparin, and the combination of both drugs significantly reduced the incidence of myocardial infarction compared with placebo. The infarction rate was 12% in placebo patients, 3.3% in aspirin patients, 0.8% in heparin patients, and 1.6% with the combination of aspirin and heparin. The difference between the aspirin and heparin groups did not attain statistical significance. The Data and Safety Monitoring Board recommended that the placebo arm and the combined aspirin and heparin arm of the trial be discontinued but that an additional 245 patients be randomized to either aspirin or heparin so that the two drugs could be directly compared in a trial with a more adequate sample size.

Therefore, the purpose of the present study was to compare aspirin and heparin for the prevention of myocardial infarction during the acute hospitalization phase of unstable angina.

Methods

Patient Selection

Patients consulting at the emergency room for unstable angina with chest pain present within the preceding 24 hours were considered for the study. The diagnosis of unstable angina was based on a history of an accelerating pattern of chest pain occurring at rest or with minimal exertion or chest pain of at least 20 minutes' duration. Electrocardiographic changes compatible with ischemia were required for the diagnosis, or in their absence, inclusion in the study required independent confirmation of the diagnosis by two cardiologists. The qualifying event was later confirmed to be an acute non-Q-wave myocardial infarction in 44 patients enrolled in the study, as documented by a doubling of the plasma creatine kinase (CK) values with elevated MB-CK obtained in the first few hours after admission. These patients were continued in the study.

Patients taking aspirin or other platelet-active drugs on a regular basis, patients with coronary angioplasty within 6 months or coronary bypass surgery within 12 months, patients with a contraindication to aspirin or heparin, and patients with unstable angina secondary to another cause were excluded. Chronic aspirin use accounted for 48% and 62% of all exclusions in the first and second parts of the trial, respectively. The study was approved by our hospital ethics committee, and signed

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informed consent was obtained from all patients before randomization.

**Study Design**

The design of the extension trial was identical to the first study except for randomization to only an aspirin and a heparin group, deleting the combined treatment arm and the placebo arm. Screening and selection of patients, entry criteria, drug dosages, study design, and the duration of follow-up were the same. Patients were randomized in a double-blind fashion to either aspirin plus placebo-heparin or to heparin plus placebo-aspirin. The study medications were started as soon as possible after admission in the emergency room, or if the patients were rapidly transferred, in the coronary care unit. Aspirin was administered at a dose of 650 mg followed by 325 mg bid. In the other group, an intravenous heparin bolus of 5000 U was followed by an infusion at a rate of 1000 U/hour. A partial thromboplastin time was obtained 6 hours after the bolus injection, 6 hours after any adjustment in the infusion rate, and daily when the values were within the therapeutic range. The results were communicated only to the pharmacist of the hospital, who adjusted the infusion rate according to a predefined algorithm to maintain the coagulation time at 1.5 to 2.5 times control values. All randomized patients received the study medication. Medications other than antiplatelet and anticoagulant drugs were prescribed during hospitalization at the discretion of the treating physician. Recurrence of chest pain on study medication was an indication for more intensive medical therapy and for urgent coronary arteriography with a view to angioplasty or bypass surgery.

Study drugs and in-study data collection were discontinued when definitive therapy was chosen for the patient, usually after coronary arteriography. Total duration of the study was 5.7±3.3 days, corresponding to the usual waiting period for coronary angiography in our institution at the time of the study. Coronary arteriography was performed in 92% of the patients, excluding 10 patients who refused the procedure, and it was not requested in 29 others because it would not have influenced management, usually because the coronary anatomy was already known. In the second part of the trial but not in the first part, 325 mg aspirin was routinely administered to all patients beginning 12 hours before discontinuation of the study drugs and continuing daily thereafter. This was done to prevent reactivation of the disease, as was observed in the first cohort after discontinuation of heparin when aspirin was not administered concomitantly.

**Study End Point**

The end point of this study was the occurrence of fatal and nonfatal myocardial infarction after randomization, during study drug administration. Myocardial infarction was diagnosed when the three usual diagnostic criteria were present: typical chest pain unrelieved by nitroglycerin and lasting at least 30 minutes, new ST-T changes or Q waves, and an increase in baseline CK levels to at least twice the upper limit of normal with abnormally high MB levels. Enzymes were measured every 4 hours for the first 24 hours and every 12 hours for the next 48 hours. This sampling schedule was reinitiated whenever chest pain recurred. The temporal relation between randomization and the occurrence of myocardial infarction was carefully assessed, and in no patient did a classification problem exist. End point events were classified prospectively before unblinding of the study and were analyzed by the intention-to-treat principle. Since all patients received therapy, this analysis was also a drug efficacy analysis.

**Statistical Analyses**

Data were collected on a Dataflex program (version 2.2) and transferred to a BMDP file for statistical analyses. Baseline features were compared with the t test and $\chi^2$ statistics. The event rate in the two groups was compared using a $\chi^2$ test. The risk difference and its 95% confidence limits were calculated as described by Fleiss. Survival curves were constructed using Cox logistic regression analysis to account for the differences in the baseline characteristics. The only interim look at the data was after the first part of the trial, only minimally affecting the power of the analysis. A P value less than .05 was considered significant.

**Results**

As shown in the Table, the clinical and angiographic features of the two study groups were similar. Slightly
Survival curves for the patients randomized to aspirin or to heparin. A Cox regression logistic analysis was used to correct the baseline differences between the two groups, even though none were significant. The difference between the two survival curves was statistically significant ($P = .035$). MI indicates myocardial infarction.

More patients in the aspirin group had a previous myocardial infarction, but the ejection fraction was the same in the two study groups. Mean age was 58 years, and 75% of the population were men. The time to enrollment in the study after the last episode of chest pain was similar in the two groups, and the total duration of the study was slightly longer in the heparin group. More patients were smokers in the aspirin group. Although ischemic ST-T changes on admission were recorded slightly more frequently in the aspirin patients, left main disease was marginally more frequent in the heparin group. None of the differences in the baseline characteristics achieved statistical significance.

Myocardial infarction during the study period occurred in 2 (0.8%) of the 240 patients in the heparin group and in 9 (3.7%) of the 244 patients in the aspirin group ($P = .035$). The odds ratio for myocardial infarction with heparin was 0.22 and the relative difference, 2.9% (95% confidence limits, 0.3 to 5.6%). The only death resulted from a myocardial infarction in an aspirin-treated patient. The results of the first and second parts of the trial were concordant: In the first part, one myocardial infarction occurred in 118 patients treated with heparin and 4 in 121 patients treated with aspirin; the corresponding figures in the second part were 1 of 122 patients treated with heparin and 5 of 123 treated with aspirin. The figure shows the survival curve for the two study groups. The Cox logistic regression analysis retained only the study drug as a predictive of fatal and nonfatal myocardial infarction ($P < .035$), with none of the differences in baseline characteristics influencing the results.

An extended factorial analysis of the 479 patients enrolled in the first trial (including 122 patients with combination therapy and 118 in the placebo group) and of the 245 additional patients yielded the following results: Four of the 362 patients with heparin experienced a fatal or nonfatal myocardial infarction compared with 23 of the 362 patients without heparin (odds ratio, 0.16; relative difference, 5.4%; 95% confidence limits, 2.5% to 8.0%; $P < .005$); 11 of the 366 who received aspirin had an event as compared with 16 of the 358 without aspirin (odds ratio, 0.66; relative difference, 1.5%; 95% confidence limits, −1.4 to 4.3%; NS).

Bleeding complications were recorded in 4 aspirin-treated and 15 heparin-treated patients ($P = .008$). Serious bleeding, prospectively defined as a fall in hemoglobin by $\geq 2$ g or the need for transfusion, occurred in 2 aspirin and 4 heparin patients, with no intracranial hemorrhage or death.

**Discussion**

This study is the first to demonstrate a superiority of heparin over aspirin in the prevention of myocardial infarction in the acute phase of unstable angina. The degree of risk reduction with heparin compared with aspirin exceeded 75%. Heparin but not aspirin has also been shown to reduce the prevalence of refractory angina in this condition. Preventing myocardial infarction with its associated risk of cardiac death and controlling angina are the principal aims of therapy in patients hospitalized with unstable angina.

**Previous Studies**

In the study of Telford and Wilson, the incidence of myocardial infarction was 3% in heparin-treated patients and 17% in nonanticoagulated patients. Similarly, in our previous trial, heparin reduced the infarction rate from 12% to 0.8%. In contrast, the reduction in the myocardial infarction rate with heparin in the RISC study was much smaller and did not attain statistical significance. However, this study probably addresses a different population, because nearly half of the patients had a non-Q-wave infarction and because patients were enrolled up to 72 hours after the last episode of chest pain, often with a treadmill exercise test used for diagnosis. The daily dosage of heparin given after the first day was only 15 000 IU, with no adjustment to the APTT. Because the dose-response relation of heparin is nonlinear and because this dose is small, it is unlikely to maintain the APTT in the therapeutic range in most patients. The trial of Neri Serneri et al supports this conclusion: Continuous intravenous heparin adjusted to maintain the APTT within the therapeutic range was effective in preventing myocardial ischemia in unstable angina but fixed bolus injections of heparin were not.

**Clinical Implications**

The results of this study have important implications: They indirectly confirm the critical role of thrombus formation in unstable angina, define an optimal therapy, and establish standards for future comparisons with new forms of treatment. The similarity of the results observed in the initial cohort and in the extension study strengthens the validity of our conclusions. This study was limited to the acute phase of unstable angina and therefore the findings apply only to this time period.

Patients already on aspirin therapy were excluded from the study to avoid underestimation of the benefits of aspirin based on the theoretical consideration that occurrence of unstable angina while on aspirin therapy could indicate a relative failure of aspirin or a more active disease. Recent publications indicate, however, that this may not be the case: It appears that patients developing unstable angina while on aspirin are not at higher risk although one preliminary report contradicts this conclusion.

The clinical significance of the low absolute risk of myocardial infarction observed with heparin is some-
what reduced considering the low event rate also observed with aspirin therapy. Based on the results of this study, treatment of 100 patients with heparin will protect 2.9 patients from developing a myocardial infarction during the acute phase compared with treatment with aspirin alone. The mortality rate with these treatments is very low. Risk can be stratified in unstable angina, and treatment with heparin may be more important for the higher-risk patients with recurrent chest pain, electrocardiographic changes, or impaired left ventricular function. Aspirin, however, in any case, should be initiated before discontinuing heparin to avoid early reactivation of the disease and also to profit from the well-described long-term benefit of the drug. Doses lower than those used in this study are adequate for this purpose.

It would be useful to duplicate the results of this study in a larger scale trial; this is unlikely to be done, however, because the current trends in clinical research are toward investigation of the new direct thrombin inhibitors and of the specific inhibitors of the platelet membrane integrin receptors glycoprotein IIb/IIIa.

**Pathophysiological Considerations**

The initiating event in unstable angina is plaque fracture that triggers platelet activation and aggregation. Thrombin is generated, and fibrin is incorporated in the clot, progressively obstructing the residual coronary lumen, as documented by autopsy studies. At the stage of fibrin clot formation, the major mechanism implicated in unstable angina could be the thrombogenicity of clot-bound thrombin, which may account for the complications of recurrent ischemia and myocardial infarction and could also possibly explain reactivation after discontinuation of heparin.

Aspirin inhibits platelet aggregation by blocking thromboxane-A₂ synthesis but has little effect on thrombin-induced platelet aggregation. Heparin, on the other hand, inhibits thrombin-induced aggregation. Thus, aspirin can be expected to have a major effect on the process of platelet activation and aggregation that initiates unstable angina and its recurrences. Anti thrombotic agents would be expected to be more useful to control the active phase of the disease, where thrombin is the major aggregatory stimulus.

Newer drugs may be useful in the treatment of unstable angina. However, based on the results of this trial, heparin is currently recommended for the acute phase of unstable angina and aspirin for long-term therapy, with some overlap between the two treatments.

**References**

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