

Adding Heparin to Aspirin Reduces the Incidence of Myocardial Infarction and Death in Patients With Unstable Angina

A Meta-analysis

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Objective.—To estimate the risk of myocardial infarction (MI) and death in patients with unstable angina who are treated with aspirin plus heparin compared with patients treated with aspirin alone.

Data Sources.—Studies were retrieved using MEDLINE, bibliographies, and consultation with experts.

Study Selection.—Only published trials that enrolled patients with unstable angina, randomized participants to aspirin plus heparin vs aspirin alone, and reported incidence of myocardial infarction or death were included in the meta-analysis.

Data Extraction.—Patient outcomes including MI or death, recurrent ischemic pain, and major bleeding during randomized treatment; revascularization procedures after randomization; and MI or death during the 2 to 12 weeks following randomization were extracted by 2 authors, 1 of whom was blinded to the journal, institution, and author of each study.

Data Synthesis.—Six randomized trials were included. The overall summary relative risk (RR) of MI or death during randomized treatment was 0.67 (95% confidence interval [CI], 0.44-1.02) in patients with unstable angina treated with aspirin plus heparin compared with those treated with aspirin alone. The summary RRs for secondary endpoints in patients treated with aspirin plus heparin compared with those treated with aspirin alone were 0.68 (95% CI, 0.40-1.17) for recurrent ischemic pain; 0.82 (95% CI, 0.56-1.20) for MI or death 2 to 12 weeks following randomization; 1.03 (95% CI, 0.74-1.43) for revascularization; and 1.99 (95% CI, 0.52-7.65) for major bleeding. We found no statistically significant heterogeneity among individual study findings.

Conclusions.—Our findings are consistent with a 33% reduction in risk of MI or death in patients with unstable angina treated with aspirin plus heparin compared with those treated with aspirin alone. The bulk of evidence suggests that most patients with unstable angina should be treated with both heparin and aspirin.

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UNSTABLE ANGINA, ranging from progressive angina to angina at rest, results from intracoronary plaque disruption causing increased stenosis and, in some cases, intermittent thrombosis.¹ Prospective studies have found that 12%

of patients admitted to the hospital with unstable angina progress to myocardial infarction (MI) within 2 weeks of diagnosis.^{2,3} One-year mortality of patients with unstable angina ranges from 5% to 14% with approximately half of these deaths occurring within 4 weeks of diagnosis.⁴ In patients with unstable angina, aspirin reduces the risk of thrombosis by inhibiting platelet aggregation and decreases the risk of cardiac death or nonfatal MI by 30% to 51%.⁵⁻⁷

Heparin binds to antithrombin III and induces a conformational change that results in rapid inhibition of thrombin.⁸ This inhibition of thrombin prevents propagation of an established thrombus and al-

lows time for endogenous fibrinolysis to occur. In theory, adding heparin to aspirin should reduce intracoronary obstruction, improve coronary blood flow, reduce myocardial ischemia, and ultimately decrease cardiac morbidity and mortality in patients with unstable angina.⁹ Several randomized clinical trials have demonstrated a trend toward reduced risk of death or nonfatal myocardial infarction in patients with unstable angina treated with aspirin plus intravenous heparin compared with patients treated with aspirin alone.^{7,10-14} However, it has not been established definitively that the combination of aspirin plus heparin is superior to aspirin alone. We performed a meta-analysis of published randomized trials to determine whether treatment with intravenous heparin and aspirin is more effective than treatment with aspirin alone in preventing MI or death in patients with unstable angina.

METHODS

Literature Review

We performed a literature search using the MEDLINE database (January 1966 to September 1995) with the keywords "aspirin," "heparin," and "unstable angina." The search was not restricted to citations in the English-language literature. In addition, a manual search was done using reference lists from identified articles and consultation with experts.

Studies included in the meta-analysis met the following criteria: (1) a randomized clinical trial; (2) eligible participants were admitted to the hospital with the diagnosis of unstable angina or non-Q-wave myocardial infarction; (3) participants were assigned either to intravenous heparin and aspirin or to aspirin alone; and (4) the incidence of myocardial infarction (prolonged chest pain associated with Q waves or persistent ST changes on electrocardiogram and/or a 2-fold increase over baseline creatine

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kinase levels with elevated MB fractions) or death while on randomized treatment was reported. Clinical trials were included regardless of whether they included a heparin placebo in the aspirin only group or the patients had been taking aspirin prior to hospital admission.

Data Extraction

Two of us (A.O. and M.A.W.) independently reviewed each study that met the inclusion criteria. One of us abstracted data in an unblinded fashion; the other was blinded to journal, year of publication, authors, and institution. We evaluated each study with regard to patient selection, blinding, and adequacy of randomization, and recorded the dosage and duration of each treatment. Discrepant findings between reviewers were settled by discussion.

Heparin was given as a continuous infusion in 5 of 6 studies¹⁰⁻¹⁴ with the rate adjusted to achieve a goal partial thromboplastin time (PTT) of 1.5 to 2 times normal (Table 1). In the sixth study, heparin was administered as intermittent intravenous boluses and a goal PTT was not stated.⁷ The duration of heparin therapy was 2 to 7 days in all studies. Aspirin was given orally in the doses shown in Table 1 and continued indefinitely.

Incidence of MI or death during randomized treatment was abstracted as the primary outcome. In addition, data were abstracted on incidence of recurrent ischemic pain (anginal chest pain with ischemic ST-T changes on electrocardiogram) and major bleeding (bleeding requiring transfusion or fall in hemoglobin by at least 20 g/L) during randomized treatment. We also abstracted data on MI or death between discontinuation of randomized treatment and 12 weeks following randomization, and revascularization procedures (angioplasty or surgical bypass) during the 12 weeks following randomization.

Statistical Analysis

Rate ratios from each study were used as measures of effect in these analyses. The total numbers of patient outcomes in both the aspirin and aspirin plus heparin groups were recorded in 2×2 tables. To improve bias and precision properties, 0.5 was added to every cell in any table containing a zero.¹⁵ Relative risks (RRs) with 95% confidence intervals (CIs) were calculated individually for each study.¹⁶

The summary measure of effect in the meta-analysis for each endpoint is the odds ratio (OR).¹⁷ Since the sample cross-product has a highly skewed distribution, its natural log transformation is appropriate for purposes of estimation and hypothesis testing.¹⁵ The summary effect

Table 1.—Characteristics of 6 Randomized Trials of Aspirin Plus Heparin vs Aspirin Alone to Prevent Myocardial Infarction and Death in Patients Admitted to the Hospital With Unstable Angina

Source	Blinding	Aspirin Dose, mg	Goal Partial Thromboplastin Time	Duration of Heparin Therapy, d
Theroux et al, 1988 ¹⁰	Participants and investigators	325 twice daily	1.5-2 × normal	6
RISC Group, 1990 ⁷	None	75 daily	Not stated	5
Cohen et al, 1990 ¹¹	None	80/325 daily*	2 × normal	3-4
Cohen et al, 1994 ¹²	Participants	162.5 daily	2 × normal	3-4
Holdright et al, 1994 ¹³	Participants	150 daily	1.5-2 × normal	2
Gurfinkel et al, 1995 ¹⁴	Participants and investigators	200 daily	2 × normal	5-7

*Aspirin dose was 80 mg/d in the heparin plus aspirin group and 325 mg/d in the aspirin only group.

measure, or estimated overall RR, was calculated using the DerSimonian and Laird model which uses a random effects model to incorporate variance between study findings in a weighted average of rate ratios.^{18,19} Approximate 95% CIs were obtained on the natural log transformation scale and the limits reexpressed using the natural antilog transformation. A χ^2 statistic summing the squared deviation of each of the study natural log transformations of the OR from their weighted average was used to test whether a summary OR was appropriate for each endpoint. These calculations were substantiated using the log linear fits discussed next, and obtained using BMDP statistical software.²⁰

The primary endpoint in this meta-analysis was MI or death while on randomized treatment. Relationships among the 3 dichotomous factors—myocardial infarction or death, treatment regimen, and study—were explored further by fitting a hierarchical log-linear model to the cell counts.²¹ This approach models the natural log cell frequencies as linear combinations of main effects, and second-order and third-order interactions. A likelihood ratio χ^2 statistic was used to test the statistical significance of the third-order interaction parameter, effectively a test for heterogeneity in the ORs across studies. Likelihood ratio χ^2 s were examined to identify the most parsimonious “best” fit to the cell counts. For these data, the likelihood ratio χ^2 statistic provided a test of the statistical significance of the second-order interaction parameter, which measured the variation in MI and death rate across treatment regimen, controlling for study.

We examined potential for publication bias using the correlation between number of subjects and RR in each study. If small studies with negative results were less likely to be published, then the correlation between number of subjects and RR would be high. If publication bias does not exist, then no significant correlation between number of subjects and RR would be evident.

RESULTS

Study Selection

An initial search using MEDLINE, reference review, and expert consultation yielded 135 citations. Of these, 19 were randomized trials.^{7,9-14,22-33} Among these trials, we found 8 that enrolled participants with unstable angina, randomized participants to aspirin or heparin plus aspirin, and reported the risk of MI or death during randomized treatment.^{7,9-14,30} One of the 8 trials was excluded because we could not determine whether all patients were treated with aspirin.³⁰ Another was excluded because only a portion of the patients in the study received aspirin.⁹ Thus, 6 trials with a total of 1353 patients met all inclusion criteria for the meta-analysis.^{7,10-14} Characteristics of these trials are shown in Table 1.

All 6 trials excluded participants who had evolving Q-wave MI on admission; coronary artery bypass grafting within 12 months prior to admission; a contraindication to aspirin or anticoagulation; or had already been anticoagulated at admission. Unstable angina was diagnosed using the following criteria: (1) recent onset (less than 1 month) of prolonged or recurrent chest pain suggestive of myocardial ischemia^{7,11-14}; (2) pain of increasing severity, at rest or with minimal effort^{7,10-14}; and (3) last episode of pain occurring within 48 hours of admission.¹⁰⁻¹⁴ Patients thought to be having non-Q-wave MI on admission were included under the definition of unstable angina.

Summary Effect on MI and Death

The findings of each of the 6 trials demonstrated a trend toward improved outcome using aspirin plus heparin compared with aspirin alone, but none of the findings reached statistical significance (Table 2). The incidence of MI or death during heparin therapy was 7.9% (55/698) in participants treated with aspirin plus heparin, and 10.4% (68/655) in participants treated with aspirin alone. The summary RR of MI or death during randomized treatment was 0.67 (95% CI,

Table 2.—Incidence of Myocardial Infarction or Death and Relative Risk of Myocardial Infarction or Death During Treatment With Heparin From 6 Randomized Trials in Patients Admitted to the Hospital With Unstable Angina

Source	Myocardial Infarction or Death, No.* (%)		RR (95% CI)†
	Aspirin	Aspirin Plus Heparin	
Theroux et al, 1988 ¹⁰	4/121 (3)	2/122 (2)	0.50 (0.18-2.66)
RISC Group, 1990 ⁷	7/189 (4)	3/210 (1)	0.39 (0.18-1.47)
Cohen et al, 1990 ¹¹	1/32 (3)	0/37 (0)	0.29 (0.06-6.87)
Cohen et al, 1994 ¹²	9/109 (8)	4/105 (4)	0.46 (0.24-1.45)
Holdright et al, 1994 ¹³	40/131 (31)	42/154 (27)	0.89 (0.66-1.29)
Gurfinkel et al, 1995 ¹⁴	7/73 (10)	4/70 (6)	0.60 (0.29-1.95)
Summary	68/655 (10)	55/698 (8)	0.67 (0.44-1.02)‡

*Number of patients who had a myocardial infarction or died during randomized treatment/total number of participants assigned to the treatment group.

†RR indicates relative risk; and CI, confidence interval for myocardial infarction or death in the aspirin plus heparin compared with the aspirin group.

‡Summary RR estimate and 95% CI from meta-analysis.

0.44-1.02; $P = .06$) in patients treated with aspirin plus heparin compared with those treated with aspirin alone (Figure 1). The result of a test for heterogeneity was not statistically significant ($P = .78$).

Incidence of MI or death from discontinuation of randomized therapy to 12 weeks after randomization was reported in 4 studies (Table 3).^{7,10,12,13} Based on data from these 4 studies, the risk of late MI or death was 12.4% (73/591) in participants treated with aspirin plus heparin and 13.8% (76/550) in participants treated with aspirin alone. The summary RR for MI or death from discontinuation of randomized therapy to 12 weeks after randomization was 0.82 (95% CI, 0.56-1.20; for test of heterogeneity, $P = .76$) in patients treated with aspirin plus heparin compared with those treated with aspirin alone. Of note, 1 of these 4 studies continued anticoagulation therapy with warfarin in the heparin plus aspirin group after heparin was discontinued.¹² Removing the findings of this trial from the summary results did not significantly alter the summary RR estimate.

Summary Effects on Ischemic Pain, Revascularization Procedures, and Major Bleeding

Recurrence of ischemic pain was reported in 5 of the 6 studies (Table 3).¹⁰⁻¹⁴ The within study effect of heparin plus aspirin compared with aspirin alone for recurrent ischemic pain was heterogeneous across studies (for test of heterogeneity, $P = .02$). Heterogeneity was primarily due to 1 trial¹¹ that used 80 mg of aspirin daily in the group receiving heparin and 325 mg of aspirin daily in the group not receiving heparin (Table 1). With this study excluded from the analysis, the incidence of recurrent ischemic pain during randomized treatment was 17.3% (78/451) in participants treated with aspirin plus heparin, and 22.6% (98/434) in participants treated with aspirin alone, and the summary

RR for recurrent ischemic pain was 0.68 (95% CI, 0.4-1.17; for test of heterogeneity, $P = .08$) in patients treated with aspirin plus heparin compared with those treated with aspirin alone.

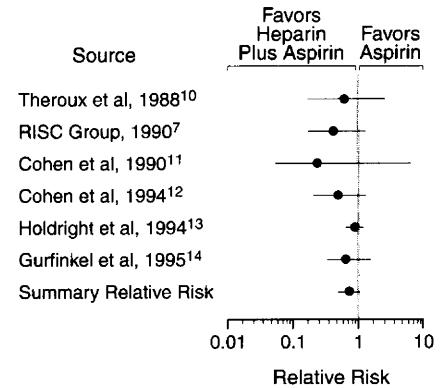
Five studies¹⁰⁻¹⁴ reported the number of patients in each treatment group who underwent coronary artery bypass grafting or percutaneous transluminal coronary angioplasty within 12 weeks after randomization (Table 3). Of participants treated with aspirin plus heparin, 23.8% (116/488) underwent revascularization, compared with 23.4% (109/466) of those treated with aspirin alone. The summary RR for revascularization procedures was 1.03 (95% CI, 0.84-1.43; for test of heterogeneity, $P = .41$) in patients treated with aspirin plus heparin compared with those treated with aspirin alone.

Overall, 0.4% (3/655) of patients treated with aspirin alone and 1.5% (10/698) of patients treated with aspirin plus heparin developed major bleeding during randomized treatment. Based on data from all 6 trials, the summary RR for major bleeding was 1.89 (95% CI, 0.66-5.38; for test of heterogeneity, $P = .68$) in patients treated with aspirin plus heparin compared with those treated with aspirin alone (Table 3).

COMMENT

Unstable angina is an important medical problem associated with a high incidence of MI and death. Many physicians routinely treat patients with unstable angina with both aspirin and heparin, but adding heparin to aspirin has not been demonstrated to reduce the incidence of MI and death compared with treatment with aspirin alone.

We found 6 randomized trials of treatment with aspirin plus intravenous heparin compared with treatment with aspirin alone in patients with unstable angina. Each of these trials reported a trend toward decreased risk of MI or death in patients with unstable angina treated with both heparin and aspirin,



Relative risk of myocardial infarction or death during hospitalization.

but none of the trials was large enough to demonstrate a statistically significant benefit. Combining data from these 6 trials using formal meta-analytic techniques resulted in a summary RR estimate of 0.67 (95% CI, 0.44-1.02), suggesting a 33% reduction in MI or death during heparin therapy in patients treated with heparin plus aspirin compared with patients treated with aspirin alone. This result closely approached statistical significance.

In 1 trial,¹³ 31% (40/131) of participants in the aspirin group and 27% (42/154) of participants in the aspirin plus heparin group developed MI or died during randomized treatment. This incidence of MI or death was markedly higher than the average incidence of 5.3% (28/254) in the aspirin groups and 2.4% (13/544) in the aspirin plus heparin groups reported in the 5 other trials. The explanation for this increased risk of death or MI is unclear. It is possible that participants in this trial were sicker at baseline, or that the investigators used a more sensitive definition of MI. When we performed a post hoc meta-analysis excluding this trial, the summary RR was 0.45 (95% CI, 0.23-0.89), suggesting a 55% reduction in MI or death in patients treated with aspirin plus heparin compared with patients treated with aspirin alone. This result was statistically significant, but because it was a post hoc analysis, the findings should be viewed with caution.

Depending on whether the 1 trial with a markedly high incidence of MI or death is excluded, the average risk of MI or death in the combined studies is either 5.3% or 10.4% for patients treated with aspirin alone. If we assume that adding heparin to aspirin reduces the risk of MI or death by 33% to 55% (depending on whether the 1 trial was excluded), the absolute risk reduction of MI or death during treatment is 2.9% to 3.4% for patients with unstable angina treated

Table 3.—Relative Risk of Recurrent Ischemic Pain and Major Bleeding During Treatment With Heparin, Relative Risk of Revascularization Procedures Following Randomization, and Relative Risk of Myocardial Infarction or Death During the 2-12 Weeks Following Randomization in Patients With Unstable Angina*

Source	RR (95% CI) of Recurrent Ischemic Pain	RR (95% CI) of Major Bleeding	RR (95% CI) of CABG or PTCA	RR (95% CI) of MI or Death at 2-12 wk
Theroux et al, 1988 ¹⁰	0.64 (0.41-1.24)	1.98 (0.50-10.63)	0.97 (0.75-1.28)	0.50 (0.25-1.60)
RISC Group, 1990 ⁷	NA	NB	NA	0.77 (0.46-1.63)
Cohen et al, 1990 ¹¹	1.98 (1.01-4.19)†	NB	0.59 (0.93-2.67)	NA
Cohen et al, 1994 ¹²	0.36 (0.23-0.82)	7.06 (0.46-135.15)	0.78 (0.47-1.57)	0.75 (0.41-1.80)
Holdright et al, 1994 ¹³	0.74 (0.52-1.17)	0.85 (0.12-13.47)	1.08 (0.65-2.03)	0.97 (0.72-1.36)
Gurfinkel et al, 1995 ¹⁴	1.20 (0.82-1.78)	5.21 (0.34-106.67)	0.81 (0.42-2.06)	NA
Summary	0.68 (0.40-1.17)	1.89 (0.66-5.38)	1.03 (0.84-1.43)	0.82 (0.56-1.20)

*RR indicates relative risk; 95% CI, confidence interval for patients treated with aspirin plus heparin compared with those treated with aspirin alone; MI, myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; NA, not available; and NB, no major bleeding in the aspirin group or the aspirin plus heparin group.

†Results from this trial were excluded from the meta-analysis of recurrent ischemic pain because of heterogeneity (see text).

with heparin plus aspirin compared with those treated with aspirin alone. Therefore, 29 to 34 patients would need to be treated with heparin for every 1 MI or death prevented. Despite the risks of intravenous heparin therapy including bleeding, thrombocytopenia, skin necrosis, hypersensitivity reactions, and catheter-related infections,³⁴ we believe that this low number needed to treat justifies treating patients with unstable angina with 2 to 7 days of heparin added to aspirin. However, it should be noted that the majority of primary outcome events in the 4 studies that reported MI and death separately were nonfatal MI. The number of deaths in these studies was too low to calculate a meaningful difference between therapies for death alone. The enhanced risk of bleeding on heparin might not be worth the benefit of reduced nonfatal MI for some patients.

Any benefit of adding heparin to aspirin most likely occurs because heparin prevents propagation of established thrombus and allows time for endogenous fibrinolysis to occur. In theory, prevention of further thrombus formation should act synergistically with the antiplatelet effects of aspirin to reduce intracoronary obstruction and reduce myocardial ischemia in patients with unstable angina.

Heparin alone has been demonstrated to reduce the incidence of recurrent ischemic pain in patients with unstable angina.^{32,35} There was heterogeneity in the findings of the 6 clinical trials regarding the benefit of adding heparin to aspirin for the prevention of recurrent ischemic pain. Much of this heterogeneity was due to the findings of 1 trial¹¹ that used 80 mg of aspirin per day in the aspirin plus heparin group, but 325 mg per day in the aspirin only group. While each dose should have provided adequate antiplatelet therapy, it is possible the higher dose also provided analgesia, reducing the observed benefit of heparin on recurrent pain. With this study re-

moved from the meta-analysis, the summary RR was 0.68 (95% CI, 0.40-1.17), suggesting a 32% risk reduction which is similar to the risk reduction found for MI or death. This finding is consistent with the results of 2 other studies that reported increased infarction rate and reactivation of unstable angina following discontinuation of heparin.^{36,37}

Because the anticoagulant effects of heparin are brief, any benefit of therapy is unlikely to last beyond the duration of treatment. Consistent with this theory, we found no reduction in risk of MI or death between 2 and 12 weeks following randomization in patients with unstable angina who received heparin and aspirin compared with those who received aspirin alone. This result underscores that heparin is a short-acting, temporizing therapy, and not an intervention that alters underlying atherosclerotic disease.

A high percentage of patients who are admitted to the hospital with unstable angina go on to have coronary angiography. The decision to revascularize is based on coronary anatomy and the degree of underlying atherosclerotic disease. Because heparin does not change underlying atherosclerotic disease, we did not expect heparin to reduce the incidence of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty following treatment for unstable angina. The results of our meta-analysis support this theory.

We found a RR of 1.89 (95% CI, 0.66-5.38) for major bleeding in patients with unstable angina treated with aspirin plus heparin compared with those treated with aspirin alone. This result is not statistically significant but is consistent with the results of other studies of the adverse effects associated with heparin therapy. If adding heparin to aspirin reduces the risk of MI or death by one third, we believe that the 1.5% incidence of major bleeding reported in patients treated with aspirin plus heparin com-

pared with the 0.4% incidence of major bleeding reported in patients treated with aspirin alone does not justify withholding heparin from patients with unstable angina.

Several limitations of this meta-analysis deserve comment. The summary RR may be overestimated if publication bias makes it more likely that studies showing benefit are published while those showing no benefit are not. If publication bias exists, small studies with negative findings are unlikely to be published, while small studies with positive findings are likely to be published. This could result in a correlation between study size and RR estimate. We found no such correlation among the 6 randomized trials in our meta-analysis ($r=0.25$; $P=.64$).

The validity of results from a meta-analysis depends on the quality of the trials included.³⁸ Formal weighting of the quality of individual studies in this meta-analysis was not done because all 6 were well-performed randomized controlled trials. A strength of these trials is that the primary outcomes (MI and death) were objective, and MI was diagnosed using standard criteria. In addition, follow-up among all 6 studies was excellent. Only 1 study¹¹ reported incomplete follow-up: 2 patients were lost to follow-up at 12 weeks.

Bias may result from inadequate blinding in randomized controlled trials. Table 1 shows that only 2 trials were double-blinded,^{10,14} 2 blinded only the participants,^{12,13} and 2 were unblinded.^{7,11} The trial by Cohen et al¹² was stopped early due to high withdrawal rates, particularly in the aspirin plus heparin arm. Biased findings from this trial are unlikely, however, because most of the difference in withdrawal between the 2 groups was due to medication intolerance or patient request and not to an increased rate of events in the aspirin plus heparin group. The trial by Gurfinkel et al¹⁴ was stopped prematurely because of much greater efficacy of a third arm, low-molecular-weight heparin plus aspirin. While terminating the trial early might have reduced the power of the study (and our meta-analysis) to detect a difference between unfractionated heparin and aspirin compared with aspirin alone, it should not have biased the outcomes.

The Agency for Health Care Policy and Research Clinical Practice Guideline³⁹ has recommended that, unless contraindicated, patients with unstable angina be treated with heparin for 2 to 5 days. This recommendation was based on a panel consensus in the absence of directly applicable clinical studies (strength of evidence=C). This meta-analysis provides statistical evidence to support the recommendation stated in this guideline.

Our conclusion is further supported by

2 randomized controlled trials comparing low-molecular-weight heparin plus aspirin with aspirin alone in patients with unstable angina.^{14,40} The first study randomized patients to 3 arms (low-molecular-weight heparin plus aspirin, unfractionated heparin plus aspirin, or aspirin alone) and found a RR of 0.07 (95% CI, 0.0-1.28) for MI and death in 68 patients treated with low-molecular-weight heparin compared with 73 patients treated with aspirin alone.¹⁴ This trial also compared low-molecular-weight heparin to unfractionated heparin and found a RR of 0.11 (95% CI, 0.01-2.17) for MI and death in patients treated with low-molecular-weight heparin plus aspirin compared with unfractionated heparin plus aspirin. The second study randomized patients to 2 arms (low-molecular-weight heparin plus aspirin or aspirin alone) and found a RR of 0.37 (95% CI, 0.20-0.68) for MI and death in 741 patients treated with low-molecular-weight heparin plus aspirin compared with 757 patients treated with aspirin alone.⁴⁰ In this large trial, major bleeding occurred in 0.5% of the aspirin group and 0.8% of the low-molecular-weight heparin group (RR, 1.53, 95% CI, 0.43-5.44).

If therapeutically equivalent, low-molecular-weight heparin might be preferred over unfractionated heparin for several reasons. Unlike unfractionated heparin, which has a bioavailability of only 30%, all low-molecular-weight heparins have a bioavailability that approaches 100%.⁴¹ Low-molecular-weight heparin is administered subcutaneously rather than intravenously, its half-life is longer than that of unfractionated heparin, and therapeutic monitoring is not needed.

While low-molecular-weight heparin and unfractionated heparin are different preparations, they have similar mechanisms of action.⁴¹ Including the 2 studies of low-molecular-weight heparin in our meta-analysis would have yielded a summary RR of MI or death during randomized treatment of 0.56 (95% CI, 0.40-0.80; for test of heterogeneity, $P=.52$) in patients with unstable angina treated with aspirin plus heparin compared with those treated with aspirin alone. We believe the possibility that low-molecular-weight heparin is superior to unfractionated heparin in patients with unstable angina should be explored in a randomized controlled trial.

CONCLUSION

This meta-analysis of 6 randomized controlled trials demonstrated a strong trend toward reduction in risk of MI or death during randomized therapy in patients with unstable angina treated with aspirin plus heparin compared with those treated with aspirin alone. Current evi-

dence suggests that unless heparin is contraindicated, most patients with unstable angina should be treated with both aspirin and heparin.

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