

Overview of Randomized Trials of Intravenous Heparin in Patients With Acute Myocardial Infarction Treated With Thrombolytic Therapy

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Intravenous heparin is routinely given after thrombolytic therapy for patients with acute myocardial infarction in the United States and in some, but by no means all, other countries. Several trials have documented improved infarct-artery patency in patients treated with heparin; however, none was large enough individually to assess the effect of heparin on clinical outcomes. We performed a systematic overview of the 6 randomized controlled trials (1,735 patients) to summarize the available data concerning the risks and benefits of intravenous heparin versus no heparin after thrombolytic therapy. Mortality before hospital discharge was 5.1% for patients allocated to intravenous heparin compared with 5.6% for controls (relative risk reduction of 9%, odds ratio 0.91, 95% confidence interval 0.59 to 1.39). Similar rates of recurrent ischemia and reinfarction were observed among those allocated to heparin therapy or control. The rates of total stroke, intracranial hemorrhage, and

severe bleeding were similar in patients allocated to heparin; however, the risk of any severity of bleeding was significantly higher (22.7% vs 16.2%; odds ratio 1.55, 95% confidence interval 1.21 to 1.98). There was no significant difference in the observed effects of heparin between patients receiving tissue-type plasminogen activator and those receiving streptokinase or anisoylated plasminogen streptokinase activator complex, or between patients who did and did not receive aspirin. The findings of this overview demonstrate that insufficient clinical outcome data are available to support or to refute the routine use of intravenous heparin therapy after thrombolysis. It is not known if these findings are due to lack of statistical power, inappropriate levels of anticoagulation, or lack of benefit of intravenous heparin. Large randomized studies of heparin (and of newer antithrombotic regimens) are needed to establish the role of such therapy. (Am J Cardiol 1996;77:551-556)

Thrombolytic therapy has well-established benefits with regard to morbidity and mortality in patients with acute myocardial infarction.¹ Currently, adjunctive intravenous heparin is considered to be the standard of care after thrombolytic therapy in the United States,² and in some other countries—a practice that is not definitively supported by clinical outcome data from randomized trials. Although several trials have documented improved early infarct-artery patency in patients so treated,³⁻⁷ none has been large enough on its own to assess the effect of heparin therapy on clinical end points, such as death, recurrent ischemia, reinfarction, stroke, or bleeding. Trials of intravenous heparin, conducted before thrombolytic agents and aspirin were routinely given, seemed to suggest that heparin therapy produced proportional reductions in mortality of perhaps 5% to 20%, as well as reducing reinfarction, stroke, and pulmonary embolus.⁸

In the absence of a single trial of adequate size to evaluate the clinical efficacy of adding intravenous heparin to thrombolytic therapy for acute myocardial infarction, we performed a systematic overview of the available data on the risks and benefits from randomized trials of intravenous heparin therapy.

METHODS

Selection of trials: All published, randomized, controlled trials comparing intravenous heparin therapy with no heparin in patients with acute myocardial infarction treated with thrombolytic therapy were identified using the MEDLINE Information System. The terms "thrombolytic therapy," "heparin," and "myocardial infarction" were used for the search. The search was supplemented with additional references, bibliographic searches, and personal communication with researchers and clinicians interested in these areas.

Patient enrollment criteria were similar in the 6 trials identified, except that the Heparin-Aspirin Reperfusion Trial (HART),³ the trial of Bleich et al.,⁵ European Cooperative Study Group (ECSG),⁴ and the Optimization Study of Infarct Reperfusion Investigated by ST-Monitoring (OSIRIS)⁹ trials included patients who presented within 6 hours of symptom onset, whereas the Duke University Clinical Cardiology Study (DUCCS)⁶ investigators en-

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TABLE I Summary of Six Trials Identified for Analysis

Trial	Lytic Rx	Heparin Dose	Aspirin Dose	End Points
ISIS-2 pilot study	SK vs placebo	1,000 U/hr × 48 hr starting 12 hr after SK; no adjustment	325 mg qod vs placebo	Death, reinfarction, and bleeding
HART	t-PA	5,000 U bolus, then 1,000 U/hr with t-PA for 7 d; adjusted to keep aPTT 1.5–2.0 × control	80 mg/d for non-heparin-treated patients	IRA patency
ECSG	t-PA	5,000 U bolus, then 1,000 U/hr in blinded fashion; constant infusion until cath. at 48–120 hr	All patients 250 mg IV bolus or 300 mg PO bolus, then 75–125 mg PO qod	IRA patency, infarct size by CPK and bleeding
Bleich et al ⁵	t-PA	5,000 U bolus, then 1,000 U/hr within 1 hour of t-PA; adjusted to keep aPTT 1.5–2.0 × control until cath. at 48–72 hr	None	IRA patency and bleeding
DUCCS	APSAC	15 U/kg/hr 4 hr after APSAC for 5 d; adjusted to keep aPTT between 50 and 90 seconds	All patients 325 mg/d PO	Combined death/MI or recurrent ischemia; IRA patency
OSIRIS	SK	10,000 U bolus, then 1,000 U/hr for 24 hr	All patients	EF, IRA patency, and reperfusion

APSAC = anisoylated plasminogen streptokinase activator complex; aPTT = activated partial thromboplastin time; CPK = creatine phosphokinase; cath. = cardiac catheterization; DUCCS = Duke University Clinical Cardiology Study 1; ESCG = European Cooperative Study Group; EF = ejection fraction; HART = Heparin-Aspirin Reperfusion Trial; IRA = infarct-related artery; ISIS-2 = International Study of Infarct Survival; IV = intravenous; MI = myocardial infarction; OSIRIS = Optimization Study of Infarct Reperfusion Investigated by ST-Monitoring; PO = by mouth; qod = every other day; SK = streptokinase; t-PA = tissue-type plasminogen activator.

rolled patients symptomatic up to 12 hours and the International Study of Infarct Survival-2 (ISIS-2) pilot study¹⁰ criteria allowed inclusion of patients presenting up to 24 hours after symptom onset. Details of the heparin dosing regimen were available for each trial. Aspirin was used routinely in all patients in 3 studies, in controls only in 1 study, allocated at random in 1 study, and not used at all in 1 study. The follow-up period for each trial was until hospital discharge. Information was obtained from the published reports and supplemented by correspondence with the investigators on death, reinfarction, stroke, recurrent ischemia, and bleeding. Reinfarction and bleeding were generally classified based on clinical criteria without rigid and uniform definition across the studies. Severe bleeding was typically defined as bleeding associated with hemodynamic compromise or requiring blood transfusion.

Statistical analysis: The associations between heparin and each of the clinical outcome measures of interest were estimated within each trial and expressed using odds ratios (OR) with corresponding 95% confidence intervals (CI). Homogeneity of the observed effect of treatment was assessed by visual inspection of the individual OR and by using Breslow's test of homogeneity. In the absence of clear evidence of heterogeneity, estimates of the OR and 95% CI across all trials were calculated using the Cochran-Mantel-Haenszel weighted averaging method. A subsidiary analysis compared the overall effect of heparin in trials that used tissue-type plasminogen activator (t-PA) for thrombolysis (HART, ESCG, Bleich) with that in trials that used streptokinase or anisoylated plasminogen

streptokinase activator complex (APSAC) (ISIS-2 pilot, DUCCS, OSIRIS). The purpose was to test the hypothesis that, because t-PA has less of a systemic fibrinolytic effect than APSAC or streptokinase, heparin may be more important with t-PA therapy. Another subsidiary analysis involved a comparison of the effects of heparin in patients who were to be given aspirin (ESCG, DUCCS, OSIRIS, and half of ISIS-2 pilot) with patients who were not to receive aspirin (HART, Bleich, and half of ISIS-2 pilot). The purpose of this analysis was to investigate whether the effects of intravenous heparin on clinical outcomes and on bleeding complications were different with and without aspirin.

RESULTS

Only 6 randomized, controlled trials comparing intravenous heparin with no heparin in patients with acute myocardial infarction treated with thrombolytic therapy were identified (Table I). A total of 1,735 patients were included in the analysis after excluding 8 patients from the ESCG group for whom clinical outcome data were missing. The data for clinical outcomes for each trial are listed in Table II. Figures 1 and 2 show the OR for major clinical outcomes for all patients and for patients based on type of thrombolytic therapy and whether aspirin was used.

Mortality: The nonsignificantly lower odds of death in patients allocated to heparin (OR 0.91, 95% CI 0.59 to 1.39) corresponds to an absolute difference of 5 deaths/1,000 patients treated. The nonsignificant effect of heparin on mortality observed in patients receiving t-PA (OR 0.84, 95% CI 0.43 to

TABLE II Summary Data											
Trial	ISIS-2 Pilot (n = 413)	HART (n = 205)	ECSG (n = 644*)	Bleish (n = 95)	DUCCS (n = 250)	OSIRIS (n = 128)	Totals (%) (n = 1,735)	HPA Only (%) (n = 944)	SK/APASAC (%) (n = 791)	Hep. + ASA (%) (n = 1,239)	Hep. Only (%) (n = 504)
Heparin Control	210	106	324	46	128	64	878	476	402	622	256
Death	203	99	320	49	122	64	857	468	389	609	248
Heparin Control	15	2	9	6	12	1	45 (5.13)	17 (3.57)	28 (6.96)	30 (4.82)	15 (5.86)
Reinfarction	17	4	11	5	8	3	48 (5.60)	20 (4.27)	28 (7.20)	29 (4.76)	20 (8.06)
Heparin Control	4	4	10	No data	9	2	29 (3.49)	14 (3.36)	15 (3.73)	22 (3.54)	7 (3.33)
Recurrent Ischemia	11	1	10	No data	4	1	27 (3.34)	11 (2.62)	16 (4.11)	20 (3.28)	7 (3.52)
Heparin Control	No data	8	52	3	35	13	111 (16.62)	63 (13.24)	48 (25.00)	98 (18.99)	11 (7.24)
Stroke	No data	2	57	4	31	13	107 (16.36)	63 (13.46)	44 (23.66)	99 (19.57)	6 (4.05)
Heparin Control	1	0	4	2	2	3	12 (1.37)	6 (1.26)	6 (1.49)	9 (1.45)	3 (1.17)
Intracranial hemorrhage	1	1	1	0	1	2	6 (0.70)	2 (0.43)	4 (1.03)	4 (0.66)	1 (0.81)
Heparin Control	No data	0	2	0	2	0	4 (0.60)	2 (0.42)	2 (1.04)	4 (0.78)	0 (0.00)
Severe bleeding	No data	1	0	0	0	1	2 (0.31)	1 (0.21)	1 (0.54)	1 (0.20)	1 (0.68)
Heparin Control	1	4	No data	1	14	6	26 (4.69)	5 (3.29)	21 (5.22)	14 (4.70)	6 (2.34)
Any bleeding	1	5	No data	1	7	4	18 (3.35)	6 (4.05)	12 (3.08)	12 (4.15)	6 (2.42)
Heparin Control	31	14	73	27	41	13	199 (22.67)	114 (23.95)	85 (21.14)	141 (22.67)	58 (22.66)
	30	10	57	16	21	5	139 (16.22)	83 (17.74)	56 (14.40)	97 (15.93)	42 (16.93)

* Six hundred fifty-two patients were enrolled, but data not available for 8 patients.
Hep. + ASA = trials in which patients received heparin and aspirin in the treatment group; Hep. Only = trials in which patients received only heparin and no aspirin in the treatment group; Severe bleeding = bleeding associated with hemodynamic compromise or requiring blood transfusion; SK/APASAC = trials using streptokinase or onisoylated plasminogen streptokinase activator complex; HPA Only = trials using tissue-type plasminogen activator exclusively as thrombolytic agent; other abbreviations as in Table I.

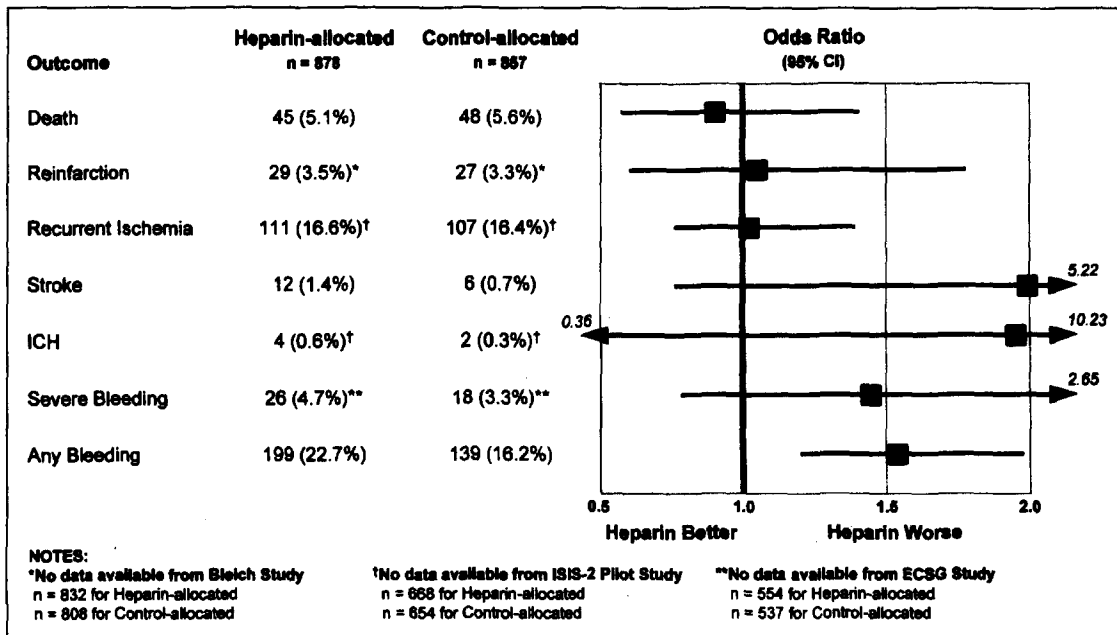


FIGURE 1. Odds ratios and 95% confidence intervals (CI) for intravenous heparin compared with no heparin for major clinical outcome events for all trials. ECSG = European Cooperative Study Group; ICH = intracranial hemorrhage; ISIS-2 = International Study of Infarct Survival-2; Severe Bleeding = bleeding associated with hemodynamic compromise or requiring blood transfusion.

1.64) was similar to that in patients receiving streptokinase or APSAC (OR 0.96, 95% CI 0.55 to 1.66). The observed effects of heparin on mortality were also not different in patients treated with and without aspirin (OR 1.01, 95% CI 0.59 to 1.71, and OR 0.72, 95% CI 0.36 to 1.45, respectively).

Strokes and bleeding: The rates of total stroke, intracranial hemorrhage, and severe bleeding tended to be higher in the heparin-treated patients, and the risk of bleeding of any severity was significantly higher (22.7% vs 16.2%; OR 1.55, 95% CI 1.21 to 1.98). The observed effects on these outcomes were similar in patients treated with t-PA or with streptokinase/APSAC, and were also similar in patients treated with or without aspirin.

Reinfarction and recurrent ischemia: Similar rates of recurrent ischemia and reinfarction were observed in patients allocated to heparin and in those allocated to control (OR 1.02, 95% CI 0.75 to 1.37, and OR 1.04, 95% CI 0.61 to 1.78, respectively). No difference was seen between t-PA and streptokinase/APSAC or between aspirin and no aspirin.

DISCUSSION

Heparin has been recommended as an adjunct to thrombolytic therapy because while the ruptured plaque is stabilizing, the substrate for thrombosis persists and thrombin activity increases, whereas the thrombolytic state is only transient.¹¹

This overview finds a nonsignificant 9% relative reduction in the odds of death with intravenous heparin compared with no heparin, but the CIs are wide so that the data are insufficient either to support or to refute the value of intravenous heparin for reducing mortality. There is also no evidence of reductions in reinfarction and recurrent ischemia. On the other hand, there is a nonsignificant trend toward an in-

creased risk of intracranial bleeding and stroke in patients allocated to heparin, and a clear excess of bleeding of any severity.

The use of aspirin in a large proportion of patients in this overview may have offset the potential benefits of heparin, which have been described in trials of heparin in acute myocardial infarction before routine use of thrombolytic and antiplatelet therapy.¹² The observed effects of intravenous heparin in the presence or absence of aspirin are, however, similar in the present overview, as are the effects observed in the presence of t-PA or streptokinase/APSAC.

Whether the absence of a significant survival benefit in this overview is due to lack of an effect of adding standard intravenous heparin regimens to current therapy for acute myocardial infarction or is due to lack of appropriate statistical power cannot be resolved by available data. To have adequate statistical power to detect a 10% relative risk reduction in mortality would require the randomization of 40,000 to 50,000 patients in a 2-arm trial. Large-scale randomized evidence about heparin versus no heparin in patients with acute myocardial infarction treated with thrombolytic therapy is limited to the ISIS-3,¹³ the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-2 (GISSI-2),¹⁴ and the International Study Group¹⁵ trials, which randomized over 60,000 thrombolytic-treated patients to therapy with aspirin and delayed subcutaneous heparin (12,500 U twice daily) versus aspirin alone. This heparin regimen was not associated with a clear reduction in 35-day mortality or in the incidence of reinfarction or postinfarction angina. Post hoc analysis did suggest that mortality may be reduced during the heparin treatment period, but the absolute benefit was small (only about 5 fewer deaths/1,000 patients). However, there were significantly in-

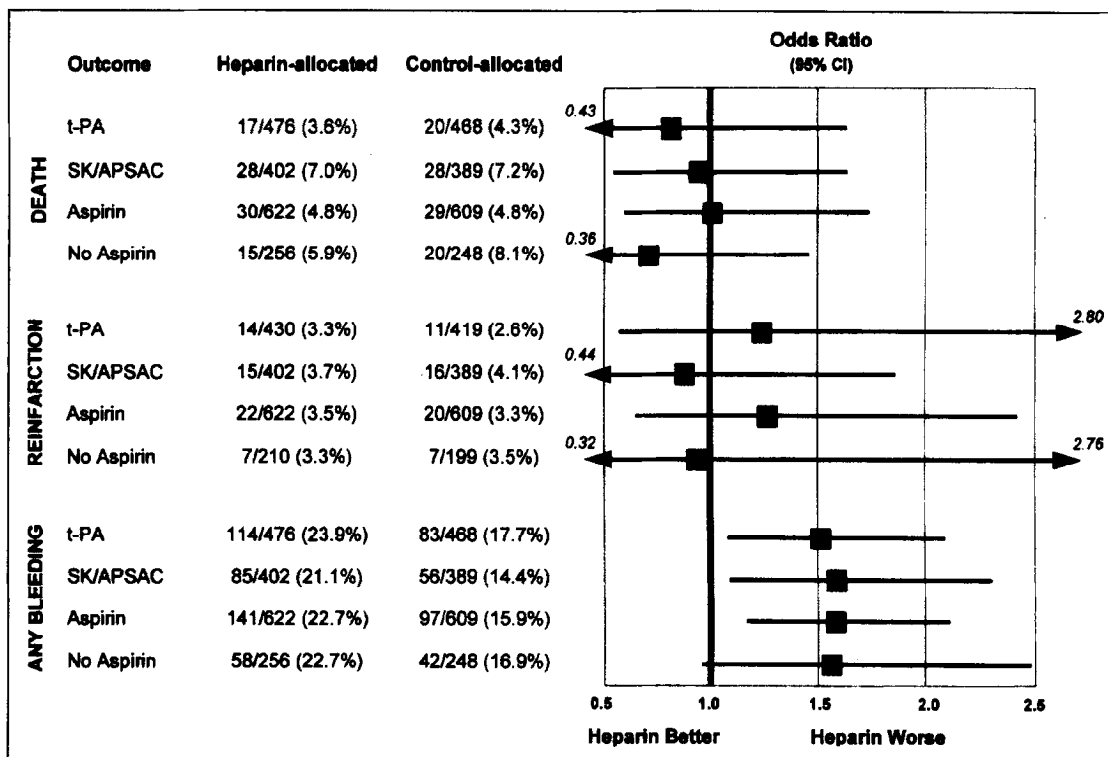


FIGURE 2. Odds ratios and 95% confidence intervals (CI) for intravenous heparin compared with no heparin for selected major clinical outcome events subdivided by type of treatment. APSAC = anisoylated plasminogen streptokinase activator complex; SK = streptokinase; t-PA = tissue-type plasminogen activator.

creased rates of bleeding in patients allocated to heparin in these trials.

Controversy has ensued for some time regarding the lack of a demonstrated significant survival benefit from subcutaneous heparin. Although the use of subcutaneous heparin and the delay in heparin initiation in GISSI-2 and ISIS-3 may have resulted in suboptimal anticoagulation, intravenous heparin in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I)¹⁶ trial was not shown to be superior to delayed subcutaneous heparin in patients allocated to streptokinase, with no apparent difference in 24-hour, 30-day, or 1-year mortality.¹⁷ Somewhat surprisingly, there was an increase in reinfarction among patients given intravenous heparin.

The lack of a demonstrated benefit of intravenous heparin on survival in this overview may be due to suboptimal levels of anticoagulation with the regimens used. The HART investigators¹⁸ reported that only 42% of patients allocated a 5,000 U intravenous bolus of heparin followed by 1,000 U/hour had activated partial thromboplastin times (aPTTs) >60 seconds at both 8 and 12 hours after initiation of therapy. More importantly, patients with aPTTs <45 seconds at both 8 and 12 hours had a 45% infarct-artery Thrombolysis in Myocardial Infarction trial (TIMI) 2 or 3 patency rate compared with 99% for patients with aPTTs >60 seconds. In apparent contrast, the GUSTO-I trial showed that aPTT values higher than 60 to 70 seconds were associated with an increased incidence of adverse events, including

mortality.¹⁹ Moreover, increasing the heparin infusion to 1,300 U/hour in GUSTO-IIA²⁰ and TIMI-9A²¹ trials appeared to be associated with higher serious bleeding rates.

Improved in-hospital infarct-artery patency has been associated with intravenous heparin therapy,³⁻⁷ and it has been shown that there is a relation between improved early patency and improved survival.²² However, cardiac catheterization provides information about arterial patency only at one particular point in time in a continually changing environment in the infarct vessel. Ohman et al²³ reported data on 90-minute and 7-day angiograms in patients with acute myocardial infarction treated with reperfusion therapy which indicated that 42% of patients with reocclusion had no clinical signs or symptoms.

An initial benefit of heparin anticoagulation on arterial patency in the first few days after acute myocardial infarction may be lost with the discontinuation of anticoagulation treatment and subsequent arterial reocclusion. A clustering of reinfarctions in the early hours following cessation of intravenous heparin after thrombolytic therapy has been described.¹⁹ A rebound phenomenon in thrombin activity was recently demonstrated by transient elevations in fibrinopeptide A and prothrombin fragment 1.2 after cessation of heparin infusions.²⁴ This may help explain the seemingly paradoxical findings of this overview that there was a tendency, although small, toward a higher incidence of reinfarction and recurrent ischemia in heparin-allocated patients.

Although this overview contains all the available data from randomized trials of adjunctive intrave-

nous heparin in patients with acute myocardial infarction treated with thrombolysis, the results are inconclusive. However, these findings demonstrate the absence of definitive outcome data to support the common practice in the United States of routine administration of intravenous heparin therapy in addition to aspirin and thrombolysis in patients with acute myocardial infarction. The results cannot refute a worthwhile benefit associated with intravenous heparin, and emphasize the need for continued investigation of heparin and of newer antithrombotic agents in large-scale clinical trials.

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