Editorial Comment

Heparin for Acute Myocardial Infarction: The Controversy Continues*

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The role of anticoagulant agents in managing patients with acute myocardial infarction (MI) has long been controversial. The first clinical trials evaluating anticoagulation for acute MI were published in 1948, and by 1969 the results of some 32 studies involving >12,000 patients had been published (1). In analyzing these studies, Gifford and Feinstein (1) suggested that serious methodologic limitations in the majority of the trials precluded drawing any firm conclusions about the efficacy of anticoagulant therapy.

In 1977, Chalmers et al. (2) again reviewed the studies reported by Gifford and Feinstein (1) and added data from four randomized trials published subsequent to the original analysis. Based primarily on pooled data from six randomized trials involving 3,854 patients, Chalmers et al. (2) concluded that “all patients who present no specific contraindication should receive anticoagulants during hospitalization for infarction.” In retrospect, this conclusion is a bit surprising because there was considerable variability in the design of these trials as well as in the therapeutic regimen utilized. In particular, only the two smallest studies, involving a total of 145 subjects, compared heparin with placebo. In the other studies, oral anticoagulation (phenindione or warfarin), alone or in combination with intravenous or subcutaneous heparin boluses, was compared with placebo or “low dose” anticoagulation. From the perspective of current practice, an even greater limitation of these trials is that none of the patients were treated with aspirin.

In the late 1970s, studies by DeWood et al. (3) and others provided compelling evidence that in situ coronary thrombosis plays a critical role in the pathogenesis of acute MI, and these observations led to intensive investigation of the use of antiplatelet, antithrombotic and fibrinolytic agents in patients with acute coronary ischemia. Some 20 years and an untold number of studies later, we now know that antiplatelet therapy with relatively low doses of aspirin provides substantial benefits across the full spectrum of unstable coronary syndromes, and that fibrinolytic therapy dramatically reduces infarct size and mortality in the subgroup of patients with “transmural” MI. However, the role of antithrombotic therapy in the early stages of MI management, both in patients who are treated with a thrombolytic agent and those who are not, remains uncertain (4–6). The key issue here is not whether early anticoagulation with heparin is superior to placebo in improving MI outcomes (available data suggest that it is), but whether heparin provides additional benefit compared with aspirin alone. In the present context, it is worth pointing out that the potential benefit of heparin is not limited to its effect on mortality, but may include reductions in reinfarctions as well as a host of thromboembolic complications, both venous and arterial. Conversely, any benefits must be weighed against the risk of serious bleeding, including intracranial hemorrhage.

Several recent studies, including Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI-2) (7), Third International Study of Infarct Survival (ISIS-3) (8) and Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-1) (9), have provided insight into the use of heparin in patients with an acute MI treated with a thrombolytic agent. In contrast, there have been no published placebo-controlled trials of early anticoagulation in patients with acute MI treated with aspirin but not receiving a thrombolytic agent. Indeed, the lack of data regarding the use of heparin in this large (60% to 70% of all MIs in the United States) and rather heterogeneous subgroup has resulted in rather ambiguous recommendations from both the American College of Chest Physicians (ACCP) and the American College of Cardiology/American Heart Association (ACC/AHA) Task Force (10,11). Whereas both groups strongly recommend that high risk patients, including those with a large anterior MI, severe left ventricular dysfunction, atrial fibrillation or a history of systemic or pulmonary embolism, be treated with full-dose intravenous heparin, the ACCP suggests that other patients should receive “not less than low-dose heparin therapy (7,500 U subcutaneously every 12 hours)” (10). Similarly, the ACC/AHA Task Force (11) considers the indications for heparin as class IIa and suggests that heparin be given “subcutaneously (7500 U twice daily) (intravenous heparin is an acceptable alternative) in all patients not treated with thrombolytic therapy who do not have a contraindication to heparin.” In discussing this issue, the authors of the Task Force Guidelines note that “in patients who will not be given thrombolytic therapy, there is little evidence about the benefit of heparin in the modern era” (11).

To summarize, currently available data on the use of heparin in patients with an acute MI is inconclusive, and this applies particularly to patients not receiving thrombolytic therapy. Nonetheless, full-dose intravenous heparin is administered to the majority of patients admitted to the hospital with acute MI in the U.S. (12), presumably because most cardiologists believe that it is likely to have a beneficial effect either directly (i.e., at the site of coronary thrombosis), or indirectly.
through the prevention of other thromboembolic complications.

**Myocardial infarction in the elderly.** In 1994, there were 759,000 hospital admissions in the United States with a first-listed discharge diagnosis of acute MI (13). Of these, 59.6% occurred in patients >65 years old (13). Moreover, patients >65 years old account for five of every six hospital deaths from acute MI, and three of every five deaths occur in patients >75 years old (14,15). Thus, although people >65 comprise only 13% of the U.S. population, they account for well over half of all MIs, and the case-fatality rate in this population is extremely high. Furthermore, the proportion of MI patients >65 years old is likely to increase in the decades ahead due to the aging of the population as well as a rightward shift in the age at onset of first coronary events resulting from continued advances in risk factor modification and primary prevention. For these reasons, there is an urgent need to identify therapeutic strategies that are beneficial in older patients and to clarify subgroups of patients who benefit from specific interventions.

One implication of the high acute MI fatality rate in the elderly is that the absolute potential for improving outcomes is greater in older MI patients than in younger ones, simply because event rates are much higher in the elderly. Indeed, recent studies indicate that the beneficial effects of aspirin, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors and fibrinolytic agents are at least as great in the elderly as in younger patients (16). Unfortunately, the converse is also true; that is, older patients are at higher risk for adverse consequences when treated with agents that are lacking in benefit.

These considerations are particularly germane to the use of heparin. If heparin is indeed beneficial, then older patients might be expected to reap the greatest benefits. If, on the other hand, heparin is not beneficial, bleeding complications, hemorrhagic strokes and possibly heparin-induced thrombocytopenia may be more prone to occur in older patients. The problem is that no prospective, randomized trials of heparin versus no heparin have been conducted in the modern era in patients not receiving fibrinolytic therapy; therefore, we must rely on alternative data sources to aid in clinical decision making.

**The current study.** In this issue of the Journal, Krumholz et al. (17) describe the results of a retrospective cohort study involving 6,935 patients ≥65 years old admitted to the hospital with an acute MI from June 1992 to February 1993 in one of four states. Medical records data were analyzed to determine the frequency of full-dose intravenous heparin utilization in patients not undergoing reperfusion therapy. Patients were excluded from the analysis if they had a contraindication to heparin or a noncardiac terminal illness. The average age of the study population was 76 years, and 52% were male.

Overall, 47% of the study population received full-dose intravenous heparin within the first 2 days of hospital admission. This proportion is similar to that reported by Weaver et al. (18) in the Myocardial Infarction Triage and Intervention (MITI) project (48% among 1,842 patients ≥65 years old) and by the National Registry of Myocardial Infarction (NRMl) investigators (56% among patients not receiving thrombolytic therapy) (12). As evidence that the dose of heparin used was effective in achieving an appropriate level of anticoagulation, the authors reported that 88% of patients given heparin had a documented activated partial thromboplastin time >46 s within the first 24 h of initiation of therapy.

The unadjusted 30-day mortality rate in patients receiving heparin was 13.4% compared with 18.6% in patients not receiving heparin (odds ratio 0.67, p < 0.001). However, there were substantial baseline demographic and clinical differences between the heparin and nonheparin groups, such that the heparin-treated patients comprised a relatively low risk subgroup of the total population. In addition, the use of “proven” MI therapies, including aspirin and beta-blockers, occurred more frequently in the heparin cohort. To adjust for these differences, the authors performed a series of multivariable logistic regressions and found that these baseline differences accounted for all apparent mortality differences between groups. Thus, in the final model the odds ratio for 30-day mortality was 1.02 (95% confidence interval 0.87 to 1.18) for heparin-treated versus nonheparin-treated patients. Furthermore, multiple subgroup analyses based on age, presence of diabetes or heart failure, previous MI and aspirin use failed to identify any subgroup that appeared to benefit from intravenous heparin.

In contrast to the “negative” findings with respect to mortality, heparin-treated patients experienced a twofold greater incidence of major hemorrhage and need for transfusion. The number of strokes was also higher in the heparin group, although not significantly so, and in a restricted cohort of the study sample, heparin-treated patients had an increased length of hospital stay compared with nonheparin-treated patients (10.6 vs. 9.3 days, p < 0.001; Krumholz HM, personal communication, 1997). This difference, which persisted after adjustment for baseline demographic and clinical factors, may reflect the increased incidence of bleeding complications that occurred in the heparin group.

The authors concluded that in this large cohort of older MI patients not undergoing reperfusion therapy, there was no evidence of a significant mortality benefit attributable to intravenous heparin (17).

**Strengths and limitations.** Because of the study’s large sample size, meticulous data collection by experienced chart reviewers and sophisticated statistical analysis, the findings are quite robust, and it is unlikely that even a small benefit attributable to heparin was missed (type II error). In addition,
because the data are representative of practice patterns at all acute care hospitals in four states, the study avoids the selection bias that may occur in studies confined to academic or other referral centers.

As the authors point out, the major limitation of their study is the lack of random allocation of heparin therapy. In addition, data were collected retrospectively by chart review, and there is thus no way to verify the accuracy of the data. It is possible, for example, that major bleeding episodes were documented more consistently in patients receiving heparin, or that heparin-treated patients were more likely to undergo cardiac catheterization and angioplasty, both of which could increase the risk of bleeding unrelated to heparin therapy. Similarly, these additional procedures could have contributed to the increased length of stay in the heparin cohort. Also, no data are provided on the incidence of nonfatal thromboembolic complications, which may occur less frequently in heparin-treated patients (10,11). Finally, the fact that data were collected 5 years ago may represent an additional limitation because the current, more prevalent use of weight-based heparin dosing nomograms may result in greater efficacy and fewer bleeding complications (19,20).

**Clinical implications.** Despite these limitations, the results of the present study, which are generally concordant with previous reports, provide additional evidence that routine heparinization is unlikely to favorably influence mortality in patients with an MI receiving standard therapy with aspirin. Moreover, as in virtually all previous studies, the incidence of major bleeding complications is increased in patients treated with heparin. These findings clearly suggest that the risk/benefit ratio of full-dose intravenous heparin may be unfavorable, particularly in the large cohort of older patients not undergoing primary reperfusion therapy. Therefore, routine use of intravenous heparin in these patients cannot be recommended at this time. However, the findings of this study do not negate the value of heparin in selected patients with well-defined indications for its use, as outlined in the ACCP and ACC/AHA guidelines (10,11).

**The future.** Clearly, the only way to resolve the heparin debate is to conduct a prospective, randomized trial of sufficient size to detect clinically meaningful differences in outcomes. Alternatively, conventional antithrombotic therapy with heparin may be rendered obsolete by newer agents, such as the low molecular weight heparins and glycoprotein IIb/IIIa inhibitors (21,22). Large randomized trials evaluating these classes of drugs are currently underway, but it may be several years before the results of these studies are available. In the meantime, it seems likely that the heparin controversy will continue unabated.

**References**


