Thrombolysis

Fatal Cardiac Rupture Among Patients Treated With Thrombolytic Agents and Adjunctive Thrombin Antagonists

Observations From the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study

Richard C. Becker, MD,* Judith S. Hochman, MD,† Christopher P. Cannon, MD,‡ Frederick A. Spencer, MD,* Steven P. Ball, RN,* Michael J. Rizzo,§ Elliott M. Antman, MD,‡ for the TIMI 9 Investigators

Worcester, Massachusetts; New York, New York; Boston, Massachusetts, and West Roxbury, Massachusetts

OBJECTIVES

The purpose of this study was to determine the incidence and demographic characteristics of patients experiencing cardiac rupture after thrombolytic and adjunctive anticoagulant therapy and to identify possible associations between the mechanism of thrombin inhibition (indirect, direct) and the intensity of systemic anticoagulation with its occurrence.

BACKGROUND

Cardiac rupture is responsible for nearly 15% of all in-hospital deaths among patients with myocardial infarction (MI) given thrombolytic agents. Little is known about specific patient- and treatment-related risk factors.

METHODS

Patients (n = 3,759) with MI participating in the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9A and B trials received intravenous thrombolytic therapy, aspirin and either heparin (5,000 U bolus, 1,000 to 1,300 U/h infusion) or hirudin (0.1 to 0.6 mg/kg bolus, 0.1 to 0.2 mg/kg/h infusion) for at least 96 h. A diagnosis of cardiac rupture was made clinically in patients with sudden electromechanical dissociation in the absence of preceding congestive heart failure, slowly progressive hemodynamic compromise or malignant ventricular arrhythmias.

RESULTS

A total of 65 rupture events (1.7%) were reported—all were fatal, and a majority occurred within 48 h of treatment. Patients with cardiac rupture were older, of lower body weight and stature and more likely to be female than those without rupture (all p < 0.001). By multivariable analysis, age > 70 years (odds ratio [OR] 3.77; 95% confidence interval [CI] 2.06, 6.91), female gender (OR 2.87; 95% CI 1.44, 5.73) and previous angina (OR 1.82; 95% CI 1.05, 3.16) were independently associated with cardiac rupture. Independent predictors of nonrupture death included age > 70 years (OR 3.68; 95% CI 2.53, 5.35) and prior MI (OR 2.14; 95% CI 1.45, 3.17). There was no association between the type of thrombin inhibition, the intensity of anticoagulation and cardiac rupture.

CONCLUSIONS

Cardiac rupture following thrombolytic therapy tends to occur in older patients and may explain the disproportionately high mortality rate among women in prior clinical trials. Unlike major hemorrhagic complications, there is no evidence that the intensity of anticoagulation associated with heparin or hirudin administration influences the occurrence of rupture. (J Am Coll Cardiol 1999;33:479–87) © 1999 by the American College of Cardiology

Cardiac rupture, most often involving the left ventricular free wall and less frequently the interventricular septum, papillary muscle, right ventricular free wall and atria, is a well recognized complication of acute myocardial infarction (MI) that is responsible for 10% to 15% of all in-hospital deaths. Written descriptions of this predominately fatal event can be traced back several centuries to William Harvey (1647) (1), followed 200 years later by the landmark observations of Malmsten (1861) (2), Winsor (1880) (3), Steven (1884) (4) and Krumhhaar (1925) (5), who linked the occurrence of cardiac rupture to occlusive coronary arterial thrombosis, “softening” of the myocardium and, in a majority of cases, recent MI.

The reperfusion era has heightened an existing interest in cardiac rupture. From a recent evaluation of over 350,000 patients with MI, several observations were made (6). First, the overall incidence of cardiac rupture, although decreased

From the *Cardiovascular Thrombosis Research Center, University of Massachusetts Medical School, Worcester, Massachusetts; †St. Luke’s/Roosevelt Hospital Center, Columbia University, College of Physicians and Surgeons, New York, New York; §Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; ‡TIMI Database and Coordinating Center, Veterans Administration Medical Center, West Roxbury, Massachusetts. Presented, in part, at the American College of Cardiology Meetings in Atlanta, Georgia, March 29–April 1, 1998.

Manuscript received April 28, 1998; revised manuscript received September 10, 1998, accepted October 22, 1998.
with thrombolytic administration, was responsible for a greater proportion of in-hospital fatal events, particularly early deaths, than in patients not given thrombolytic agents. Second, and in contrast to the prereperfusion era (7–9), most cardiac ruptures associated with thrombolytic therapy occurred within 24 to 48 h of infarction rather than later (days 3 to 5) in the hospital course.

Although the nonspecific protease, plasmin, by weakening the collagen-based supporting network in a zone of extensive myocardial necrosis may be an important biochemical/enzymatic contributor, the associated characteristics of a “susceptible” myocardium are largely unknown and the time sequence of cardiac rupture, being similar to major hemorrhagic events, raises questions about the contribution of baseline patient characteristics and systemic features, including coagulation status. Indeed an association between anticoagulant therapy, a common adjunct in current thrombolytic strategies, and cardiac rupture has been considered (6) but not examined in a large-scale clinical trial.

The purpose of our study was to determine the overall incidence and demographic characteristics of patients experiencing cardiac rupture after thrombolytic and adjunctive anticoagulant therapy and to investigate the association between thrombin inhibition, with either heparin or hirudin, and the intensity of systemic anticoagulation with the development of rupture.

METHODS

The Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9 A and B trials have been described in detail previously (10,11). Briefly, to be eligible for enrollment patients were required to have an episode of ischemic myocardial infarction (TIMI 9 A and B trials have been described in detail previously (10,11)). Patients receiving thrombolytic therapy (prior stroke, active bleeding, major surgery within 2 months, confirmed blood pressure >180/110 mm Hg), or if they were <21 years of age, a serum creatinine >2.0 mg/dl, were of childbearing potential, had cardiogenic shock or were therapeu-

**Abbreviations and Acronyms**

- ACE = angiotensin-converting enzyme
- aPTT = activated partial thromboplastin time
- CI = confidence interval
- MI = myocardial infarction
- NRMI-1 = National Registry of Myocardial Infarction
- OR = odds ratio
- TIMI = Thrombolysis and Thrombin Inhibition in Myocardial Infarction
- tPA = tissue plasminogen activator

All patients received thrombolytic therapy in the form of either front-loaded, weight-adjusted tissue plasminogen activator (tPA) (12) (maximum dose 100 mg) or streptokinase (1.5 million U over 60 min). The selection of a thrombolytic agent was at the treating physician’s discretion. Patients received 150 to 325 mg of aspirin immediately and daily thereafter and were then randomized to receive either heparin or hirudin. Other medications including beta-adrenergic blocking agents, nitrates, calcium channel blocking agents, and angiotensin-converting enzyme inhibitors were used at the discretion of the treating physician.

Study drug was administered either before or within 60 min of thrombolysis and was continued for at least 96 h. In TIMI 9A (10) patients received either hirudin (0.6 mg/kg bolus, 0.2 mg/kg/h infusion) or heparin (5,000 U bolus, 1,000 U/h for patients <80 kg or 1,300 U/h for patients ≥80 kg) titrated to target activated partial thromboplastin time (aPTT) of 60 to 90 s. Because the rates of hemorrhage were higher than expected in both treatment arms, randomization was suspended after 757 patients had been enrolled (10). In TIMI 9B the hirudin and heparin dosing was reconfigured as follows: hirudin (5,000 U bolus, followed by a continuous infusion of 1,000 U/h); hirudin (0.1 mg/kg bolus, followed by a continuous infusion of 0.1 mg/kg/h). Neither the bolus nor the infusion of hirudin was permitted to exceed 15 mg (or 15 mg/h). The target aPTT was 55 to 85 s with dose adjustments made for both study drugs according to a standardized nomogram. Samples were obtained at 12 and 24 h after treatment initiation and daily thereafter for aPTT measurement. All measurements were performed by either a hospital-based anticoagulation laboratory or a point-of-care coagulation monitor (CoaguChek Plus; Boehringer-Mannheim Corporation, Indianapolis, IN). Consistency in the method of monitoring was encouraged within the participating centers.

A diagnosis of cardiac rupture was made (by the on-site investigator) at the time of death in patients with electromechanical dissociation or sudden cardiac death in the absence of preceding congestive heart failure, slowly progressive hemodynamic compromise or malignant ventricular arrhythmias. All major efficacy and safety end points, including serious adverse events, were reviewed and classified by the Morbidity and Mortality Classification Committee, which was unaware of treatment assignment.

**Statistical methods.** The frequency of cardiac rupture events was analyzed using the chi-square statistical method. Comparisons were then made between heparin- and hirudin-treated patients. The time to rupture- and non–rupture-related death was analyzed using survival analysis methods.

A logistic regression analysis was used to test the relationship between cardiac rupture (and nonrupture death)
and clinical variables or covariates (age, gender, height, weight, past history of angina, MI or hypertension, time to treatment, thrombolytic agent, anticoagulant [heparin or hirudin], site of infarction, pretreatment blood pressure, initial pulse, serial aPTT measurements, in-hospital procedures and medications before treatment and during the study drug infusion). For multivariable analyses, the significance of each regression variable was adjusted for other variables used in the model.

**RESULTS**

**Baseline characteristics.** A total of 3,759 patients were enrolled in the TIMI 9A and 9B studies. There were no significant differences in age, cardiac risk factors, site of infarction, prior MI, thrombolytic agent or time from symptom onset to the treatment between patients allocated to heparin and those allocated to hirudin. The assigned study drug was received by 97.2% of patients randomized (9,10).

There were a total of 65 (1.7%) cardiac rupture events reported in TIMI 9—all were fatal. Fifteen (1.9%) were reported in TIMI 9A and 50 (1.6%) in TIMI 9B. Patients with rupture were older, on average by 10 years, of lower body weight and stature and more likely to be female than patients without rupture (all \( p = 0.001 \)). They were also more likely to have a history of hypertension, be nonsmokers and receive treatment later. An anterior site of infarction was documented more often than other sites in patients with rupture, and although Q waves were present on the electrocardiogram in a majority of cases, nearly one out of every three patients did not develop Q waves prior to the event. The admission heart rate was higher in patients who subsequently experienced cardiac rupture; however, there were no differences in the presenting systolic and diastolic blood pressures. The prereandomization use of ACE inhibitors, aspirin, beta-blockers and either oral or intravenous anticoagulants did not differ between patients with cardiac rupture and those without rupture.

Table 1 summarizes the baseline characteristics for patients with cardiac rupture, those with death from non–cardiac rupture–related causes and patients surviving to 30 days after infarction. Patients dying, whether from cardiac rupture or another cause, were older, of lower body weight and stature, received treatment later, experienced prior angina, had a history of hypertension, were nonsmokers and had a higher initial heart rate than patients surviving their infarction. A majority of deaths (90%) occurred within the first 5 days. Patients dying from non–rupture–related causes when compared to survivors were more likely to be diabetic and have experienced a prior MI. In addition, their initial blood pressure (systolic and diastolic) was lower, and their heart rate was higher.

A comparison of patients dying from rupture– and non–rupture–related events identified female gender and shorter stature as being particularly prevalent in the former. A multivariable linear regression analysis was performed to identify potential predictors of cardiac rupture (Fig. 1). Age >70 years (odds ratio [OR] 3.77; 95% confidence interval [CI] 2.06, 6.91), female gender (OR 2.87; 95% CI 1.44, 5.73) and prior angina (OR 1.82; 95% CI 1.05, 3.16) were independently associated with rupture. A separate analysis was performed to determine the predictors of nonrupture death at 30 days (Fig. 2). Age >70 years (OR 3.68; 95% CI 2.53, 5.35), initial pulse >100 beats per minute (OR 3.08; 95% CI 2.02, 4.70) and prior MI (OR 2.14; 55% CI 1.45, 3.17) were independently associated with death not related to cardiac rupture.

**Timing of cardiac rupture.** Patients with cardiac rupture died earlier in the hospital course than patients dying from non–rupture–related causes (median 1.5 [range 0 to 15] days

---

**Table 1.** Baseline Characteristics (TIMI 9A and TIMI 9B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cardiac Rupture/EMD (n = 65)</th>
<th>Death Without Cardiac Rupture/EMD (n = 171)</th>
<th>Alive Without Cardiac Rupture (n = 3523)</th>
<th>( p ) Value*</th>
<th>( p ) Value†</th>
<th>( p ) Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>70.9 ± 1.1</td>
<td>70.6 ± 0.8</td>
<td>59.8 ± 0.2</td>
<td>0.986</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>39 (69%)</td>
<td>65 (38%)</td>
<td>871 (25%)</td>
<td>0.003</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.8 ± 1.7</td>
<td>74.6 ± 1.2</td>
<td>79.8 ± 0.3</td>
<td>0.297</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.3 ± 1.3</td>
<td>168.1 ± 0.8</td>
<td>170.4 ± 0.2</td>
<td>0.090</td>
<td>0.0001</td>
<td>0.0015</td>
</tr>
<tr>
<td>Time to treatment (h)</td>
<td>3.92 ± 0.34</td>
<td>3.77 ± 0.25</td>
<td>3.38 ± 0.05</td>
<td>0.701</td>
<td>0.045</td>
<td>0.011</td>
</tr>
<tr>
<td>Prior angina</td>
<td>29 (45%)</td>
<td>58 (34%)</td>
<td>1004 (29%)</td>
<td>0.173</td>
<td>0.005</td>
<td>0.096</td>
</tr>
<tr>
<td>Prior MI</td>
<td>11 (17%)</td>
<td>51 (30%)</td>
<td>572 (16%)</td>
<td>0.047</td>
<td>0.863</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (49%)</td>
<td>93 (54%)</td>
<td>1188 (34%)</td>
<td>0.557</td>
<td>0.011</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (15%)</td>
<td>39 (23%)</td>
<td>544 (15%)</td>
<td>0.280</td>
<td>1.000</td>
<td>0.013</td>
</tr>
<tr>
<td>Current smoker</td>
<td>18 (28%)</td>
<td>52 (30%)</td>
<td>1580 (45%)</td>
<td>0.701</td>
<td>0.045</td>
<td>0.011</td>
</tr>
<tr>
<td>Initial systolic BP</td>
<td>132.95 ± 2.52</td>
<td>122.48 ± 1.67</td>
<td>130.01 ± 0.36</td>
<td>0.001</td>
<td>0.430</td>
<td>0.0001</td>
</tr>
<tr>
<td>Initial diastolic BP</td>
<td>78.98 ± 1.70</td>
<td>74.52 ± 1.08</td>
<td>78.21 ± 0.23</td>
<td>0.018</td>
<td>0.541</td>
<td>0.0003</td>
</tr>
<tr>
<td>Initial pulse</td>
<td>80.05 ± 1.80</td>
<td>84.39 ± 1.58</td>
<td>75.53 ± 0.27</td>
<td>0.171</td>
<td>0.015</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Cardiac rupture/EMD versus death without cardiac rupture/EMD. †Cardiac rupture/EMD versus patients alive without cardiac rupture. ‡Death without cardiac rupture/EMD versus patients alive without cardiac rupture.

\( BP \) = blood pressure (mm Hg); EMD = electromechanical dissociation; MI = myocardial infarction.
Cardiac rupture was analyzed separately after dividing events into those occurring within 24 h of treatment initiation and those occurring after 24 h of treatment. There were no significant differences in the timing of rupture based on clinical features, initial clinical assessment, site of infarction, thrombolytic agent, time to treatment, thrombin antagonist (heparin, hirudin) or the combination of thrombolytic and thrombin antagonist (data not shown).

A comparison of rupture events either within or after 24 h of treatment according to medications received prior to hospital admission identified a trend toward reduced pre-hospital aspirin use among patients experiencing rupture within 24 h (10%) as compared to those experiencing rupture after 24 h (24%) (p = 0.19); however, there were no differences in the use of beta-blockers, ACE inhibitors, nitrates or calcium channel blockers. In contrast, patients experiencing early rupture (≤24 h) were less likely to have been given aspirin (84% vs. 97%; p = 0.09), oral beta-blockers (3.2% vs. 35.4%; p < 0.001) and ACE inhibitors (6.5% vs. 18.5%; p = 0.02) during the study drug infusion compared to those experiencing rupture at a later time (>24 h). Compared with patients who survived their MI, patients experiencing cardiac rupture received beta-blockers, ACE inhibitors or both less often during the 96-h study drug infusion. The difference was most notable for patients with cardiac rupture during the initial 24 h, in whom ACE inhibitors and beta-blockers were administered to 6.5% and 3.2% of patients, respectively. From a total of 31 rupture events that were recorded, no patient had received both an ACE inhibitor and beta-blocker. Patients dying from any cause (rupture and non–rupture related), were less likely to have received a beta-blocker or an ACE inhibitor than those surviving their infarction. By multivariable analysis ACE inhibitor or beta-blocker use were inversely associated with cardiac rupture (OR 0.27; 95% CI 0.16, 0.46; p < 0.001).

Figure 1. Multivariable analysis of patients experiencing cardiac rupture or electromechanical dissociation (EMD) identified age ≥70 years, female gender and prior angina as independent predictors of an in-hospital event.

Figure 2. Multivariable analysis of patients with non–rupture-related death. Female gender was not independently associated with non–cardiac rupture death.
Thrombin antagonist and intensity of anticoagulation. Patients experiencing death from rupture- and non–rupture-related causes based on randomization to either heparin or hirudin are summarized in Table 2. There was no difference in the overall incidence of cardiac rupture death between heparin- and hirudin-treated patients. The intensity of anticoagulation, as determined by the aPTT at 12 and 24 h, did not differ between patients with cardiac rupture and non–rupture-related death. Similarly, the corresponding aPTT values at baseline, 12 h, 24 h, 48 h and 72 h for patients with and those without cardiac rupture did not differ (Fig. 3).

By multivariable analysis neither heparin, hirudin nor an aPTT greater than 90 s at any time point was independently associated with cardiac rupture.

DISCUSSION

Cardiac rupture is an early and predominantly fatal complication of acute MI that occurs in approximately 1% of patients but is responsible for nearly 15% of all deaths. Thrombolytic therapy accelerates the occurrence of rupture to within 24 to 48 h of treatment. Despite an early clustering of events that could potentially be interpreted as representing a major bleeding complication, our study including over 3,700 patients treated with thrombolytics, aspirin and adjunctive thrombin antagonists failed to identify an association between cardiac rupture, the mechanism of thrombin inhibition and the intensity of systemic anticoagulation. We were able to show, however, that cardiac...
rupture as a cause for early death is particularly common in women and the elderly, providing a mechanistic basis for the higher mortality among women with MI compared to men that has been reported previously in large-scale thrombolytic trials and registries. Lastly, our findings suggest that early ACE inhibitor and/or beta-blocker administration may reduce the occurrence of cardiac rupture after thrombolytic therapy.

**Early mortality and cardiac rupture in women.** Several investigative groups have reported higher mortality rates for women compared to men with acute MI receiving thrombolytic therapy (13–19). In TIMI 2 (13), the 6-week mortality was 9% for women and 4% for men (adjusted relative risk 1.54). Overall, women were older and had a greater prevalence of prior congestive heart failure, systemic hypertension and diabetes mellitus than men suffering an infarction. However, mortality was higher among women than men in all age strata and persisted after adjustment for differences in baseline characteristics. The National Registry of Myocardial Infarction (NRMI-1) reported a higher in-hospital mortality in women than in men (6.8 vs. 3.0%) even after adjusting for age. Lower body weight (<70 kg) was also independently associated with in-hospital mortality (20).

Among 350,755 patients enrolled in NRMI-1, 122,243 received thrombolytic therapy. Although cardiogenic shock (pump failure) was the most common cause of death, cardiac rupture was responsible for 12.1% of deaths compared to 6.1% in patients with MI not receiving thrombolytic therapy. By multivariable analysis thrombolytic agents, prior MI, advancing age and female gender were independently associated with cardiac rupture (9). The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico-2 investigators also found a strong association between female gender, increasing age and death due to cardiac rupture (21). Patients greater than 70 years of age who died and underwent autopsy (84 patients) were found to have cardiac rupture nearly 90% of the time.

Our group is the first to provide data showing that the increased risk of death for women experiencing MI may be attributable to cardiac rupture. By multivariable analysis, female gender was independently associated with rupture death; however, it was not an independent predictor of death due to non–rupture-related causes. The predisposition of women with MI who receive thrombolytic therapy to early cardiac rupture may be attributable to a susceptible collagen framework within the infarcted myocardium. Plasmin–mediated collagen degradation (22–26) and early metalloprotease activation (27), by weakening the supportive connective tissue matrix, undoubtedly contribute to the process of rupture. Plasmin generation is increased among patients of low body weight (even with weight-adjusted dosing) (28) and the collagen matrix itself is thought to differ between women and men (29), particularly with advancing age (30).

**Thrombin inhibition, intensity of anticoagulation and cardiac rupture.** Hemorrhagic infarction, defined grossly as visible blood within the myocardium, is a pathologic feature that coexists with areas of extensive coagulative necrosis (the end product of severe, persistent ischemia found commonly within the center of the infarct zone). Although recognized by pathologists for decades, hemorrhagic infarction has become a more common occurrence with the advent of thrombolytic therapy (31), and some have suggested that cardiac rupture is the direct result of myocardial hemorrhage extending through planes of necrotic and nonnecrotic myocardium (32). If myocardial hemorrhage is a prerequisite for cardiac rupture, the concomitant administration of anticoagulant therapy, particularly in high doses, could have a facilitatory effect among patients with transmural necrosis (33–43).

There is no evidence from either experimental models or clinical trials that anticoagulation exerts a direct effect on the myocardium after infarction (44). In our study of over 3,700 patients with acute MI given thrombolytics, aspirin and adjunctive anticoagulant therapy we were unable to identify an association between the mechanism of thrombin inhibition (indirect via antithrombin-mediated neutralization or direct), intensity of anticoagulation and cardiac rupture. To the best of our knowledge this is the first study in the reperfusion era to investigate the potential effect of anticoagulation on rupture events among patients receiving thrombolytic therapy. Despite a clear association between the intensity of anticoagulation and major hemorrhage as reported in several clinical trials (45,46), we did not uncover a similar relationship with cardiac rupture even with doses of heparin and hirudin that lead to a marked increase of bleeding events. Although several studies performed in the prereperfusion era reached a different conclusion, most were nonrandomized retrospective analyses, the level of anticoagulation was excessive and poorly regulated by current standards and the focus was on hemorrhagic pericardial effusions rather than cardiac rupture (34,35,38,39). Thus, we conclude that cardiac rupture, as a pathologic event involving the myocardium, is not a hemorrhagic complication directly related to antithrombotic therapy.

**Concomitant pharmacologic therapy and cardiac rupture.** In TIMI 9, patients experiencing early cardiac rupture (within 24 h of treatment) were less likely to have received oral beta-blockers and ACE inhibitors during the drug infusion study period than patients who had late rupture. Further, patients with rupture (at any time) were treated less often with ACE inhibitors and beta-blockers than patients who survived their infarction. Zones of extensive myocardial necrosis are characterized by a marked reduction in collagen fibers (22,26); a process that begins within hours of infarction (47). Early infarct expansion and thinning developing within these areas predispose to both cardiac rupture, as an early manifestation of extensive collagen loss, and chamber
dilation with or without aneurysm formation, as a late feature of a weakened collagen supportive framework.

Therapies to prevent early infarct expansion have focused predominantly on ACE inhibitor use in various patient subsets, including those with or without clinical signs and symptoms of congestive heart failure (48,49) when started within (50) or after (51,52) 24 h of infarction. Our findings are consistent with those from a previously reported clinical trial (50); however, confirmation of the apparent protective role of ACE inhibitors in patients receiving thrombolytic therapy will require further investigation. Whether women (particularly those greater than 70 years of age) and men derive similar or differing degrees of benefit must also be studied. The impact of beta-blocker therapy will be more difficult to elucidate with one early trial suggesting a protective effect (53) and a more recent study (54) showing no difference in the incidence of cardiac rupture between patients given beta-blockers early versus those treated later. Unfortunately, the small number of events in TIMI 9 does not permit us to draw firm conclusions.

Study limitations. The diagnosis of cardiac rupture was based on clinical rather than strict pathologic (necropsy) findings. It is possible that the number of events was overestimated; however, prior large-scale clinical trials with autopsy-confirmed cases have shown that a clinical diagnosis of cardiac rupture can be accurate (55), particularly when patients with evidence of early pump failure who subsequently experience electromechanical dissociation and death are excluded (56). Our analyses focused on fatal cardiac rupture, which is most often caused by disruption of the myocardial free wall. Regardless, this potential limitation is unlikely to have influenced comparative event rates between treatment groups, varying levels of anticoagulation or genders.

The absence of standardized or normalized methods for aPTT measurement is a limitation for all large-scale clinical trials attempting to investigate an association between coagulation status and clinical events. The method for aPTT determination was kept constant within participating centers, and a consistent formulation of porcine heparin was used throughout the trial. The aPTT is a standard method of coagulation monitoring in the United States and has been proven to be a useful measure for predicting patients at increased risk for hemorrhagic events (45,46). Accordingly, we did not evaluate other laboratory measurements of anticoagulation.

Cardiac rupture typically occurs within 24 to 48 h of treatment; therefore, we may have excluded patients dying before the initial aPTT measurement in whom high aPTT values may have been achieved within the first few hours after thrombolytic therapy and study drug administration. It is also possible that early hemorrhagic events or excessive levels of anticoagulation could have prompted a decrease or “down-titration” of the study drug infusion, causing lower aPTT values at subsequent time points prior to rupture. Although it is likely that most fatal events occur suddenly, it is possible that type I ruptures (small slit-like tears) progress over several hours, making both the duration and the intensity of anticoagulation important rather than one or two isolated readings. These factors may have limited our ability to determine the association between aPTT and cardiac rupture but should not have influenced our analysis comparing heparin and hirudin. It is likely that the overall low cardiac rupture event rate in TIMI 9 limited our ability to detect modest influences attributable to thrombin inhibition and/or the intensity of anticoagulation.

The apparent protective effect derived from ACE inhibitors and oral beta-blockers may also have been influenced by the time sequence of cardiac rupture. Patients experiencing rupture within the initial 24 h had less time to have been treated, and their rapid decline in hemodynamic status may have influenced management decisions. The use of ACE inhibitors and beta-blockers was not randomized, and therefore firm conclusions should not be drawn.

Lastly, in our study, all reported ruptures were fatal. It is possible that this led to an underestimation of the number of events and the overall impact of anticoagulation (57). Although cardiac rupture is predominantly fatal, clinicians must remain aware that subacute cardiac rupture with tamponade if diagnosed early is potentially treatable.

Conclusions. Women with MI who receive thrombolytic therapy appear to be at increased risk for early cardiac rupture, providing a mechanistic explanation for their higher mortality when compared with men. Despite a recognized association between adjunctive anticoagulant therapy and hemorrhagic complications, the available evidence suggests that thrombin inhibition and the overall intensity of systemic anticoagulation do not directly influence the occurrence of rupture. The early protective effects of ACE inhibitors and beta-blockers warrant further investigation.

Reprint requests and correspondence: Richard C. Becker, MD, Cardiovascular Thrombosis Research Center, University of Massachusetts Medical School, Worcester, Massachusetts 01655-0214. E-mail: Becker@Banyan.Ummed.edu.

REFERENCES