Left Ventricular Thrombus in Anterior Acute Myocardial Infarction After Thrombolysis

A GISSI-2 Connected Study

Carlo Vecchio, MD; Francesco Chiarella, MD; Gabriele Lupi, MD; Paolo Bellotti, MD; and Stefano Domenicucci, MD

Background. Streptokinase reduces the incidence of left ventricular thrombosis after acute myocardial infarction. However, it is unknown whether a similar effect can be obtained with different thrombolytic agents and whether subcutaneous calcium heparin can have an additional efficacy.

Methods and Results. To compare the effects of two different thrombolytic agents combined or not with heparin on the incidence and features of left ventricular thrombi and their related embolic events, we performed a GISSI-2 ancillary echocardiographic study (the first echocardiogram obtained within 48 hours of symptoms onset and the second before hospital discharge) that enrolled 180 consecutive patients (mean age, 63±11 years, 142 men) with a first anterior acute myocardial infarction. Patients were randomized into four groups of treatment: recombinant tissue-type plasminogen activator (rt-PA) (n=47), rt-PA plus heparin (n=45), streptokinase (n=39), and streptokinase plus heparin (n=49). Left ventricular thrombosis was observed in 51 of 180 patients (28%). No significant differences were found concerning the incidence of thrombi in the four treatment groups. Mural shape of left ventricular thrombi was found more frequently than the protruding shape (71% versus 29% at the first examination, 64% versus 36% at the second), particularly in heparin-treated patients (93% versus 7% at first examination, 70% versus 30% at the second). Only one embolic event (0.5%) occurred during the hospitalization.

Conclusions. We conclude that 1) the rate of left ventricular thrombi does not differ in patients with acute myocardial infarction treated either with streptokinase or rt-PA, 2) subcutaneous heparin, when begun 12 hours after intravenous thrombolysis, does not appear to further reduce the occurrence of thrombi but seems to influence the shape of left ventricular thrombi, and 3) during the predischage period, embolic events are rare in patients treated by thrombolysis. (Circulation 1991;84:512–519)

Left ventricular thrombus is common after anterior acute myocardial infarction; in different studies, the incidence of left ventricular thrombi has been reported varying from 28% to 54%,1–9 Because systemic thrombolysis became standard treatment in acute myocardial infarction, few studies reported the effects of thrombolytic agents on ventricular thrombi, showing that thrombolytic therapy reduces their frequency.10–13 However, the impact of different thrombolytic agents on the incidence and anatomic features of left ventricular thrombi remains unknown. Moreover, the effects of heparin given after thrombolysis on left ventricular thrombi are incompletely investigated.

In this study, we evaluated a wide patient population with anterior acute myocardial infarction treated with systemic thrombolysis, and we compared the effect of two different thrombolytic substances, followed or not followed by subcutaneous administration of calcium heparin, on the incidence of left ventricular thrombi and of peripheral embolism.

Methods

This investigation was performed in connection with the GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico) trial, whose protocol has been widely described elsewhere.14 Briefly, every patient admitted to a Coronary Care Unit within 6 hours of the onset of typical chest pain, associated with ST elevation, without
TABLE 1. Randomization of Patients Into the Four Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>SK</th>
<th>SK+H</th>
<th>rt-PA</th>
<th>rt-PA+H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n (%)</td>
<td>39 (22)</td>
<td>49 (27)</td>
<td>47 (26)</td>
<td>45 (25)</td>
<td>180</td>
</tr>
<tr>
<td>Men n (%)</td>
<td>32 (82)</td>
<td>37 (76)</td>
<td>34 (72)</td>
<td>39 (86)</td>
<td>142 (79)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63±10</td>
<td>64±10</td>
<td>63±11</td>
<td>64±11</td>
<td>63±11</td>
</tr>
</tbody>
</table>

SK, streptokinase; H, heparin; rt-PA, recombinant tissue-type plasminogen activator (alteplase).

contraindication to thrombolytic treatment, was considered eligible for the study and was randomized to one of four treatment groups: 1) streptokinase 1,500,000 units i.v. during 1 hour, 2) streptokinase followed by calcium heparin 12,500 units s.c. b.i.d. (heparin), 3) recombinant tissue-type plasminogen activator (rt-PA, alteplase) 100 mg during 3 hours, and 4) rt-PA followed by heparin. Furthermore, in the absence of any contraindication, the protocol suggested the administration of both atenolol 10 mg i.v. upon admission and acetylsalicylic acid (ASA) 325 mg every day. Other treatments such as nitrates, antiarrhythmic drugs, and digitalis were administered according to clinical requirements. If a left ventricular thrombus was detected, no additional anticoagulation was given.

Eleven of the institutions participating in the GISSI-2 trial contributed to the recruitment of patients (see Appendix).

Study Population

All the patients of the present study were also included in the GISSI-2 trial. In two centers, the enrollment of patients started with the beginning of the GISSI 2; the remaining nine institutions began to enroll from December 1988 on. In total, we studied 180 patients (142 men and 38 women; aged 40–79 years; mean, 63±11 years) with diagnosis of anterior wall acute myocardial infarction, which was assessed by ST segment elevation in at least two continuous precordial leads and no history of previous myocardial infarction, treated with systemic thrombolysis within 6 hours of symptom onset.

As shown in Table 1, 39 of 180 (22%) were assigned to the streptokinase group, 49 of 180 (27%) to the streptokinase plus heparin group, 47 of 180 (26%) to the rt-PA group, and 45 of 180 (25%) to the rt-PA plus heparin group. Overall, 88 of 180 (49%) patients were treated with streptokinase; 92 of 180 (51%) were treated with rt-PA; and in 94 of 180 (52%), the thrombolytic treatment was followed by heparin. The four groups were matched in age, sex, and Killip class. In 88 of 180 (49%), atenolol was administered upon admission; moreover, 150 of 180 (83%) received ASA during hospitalization.

Echocardiography

Two-dimensional echocardiographic examinations were performed with commercially available ultrasound machines with 2.5- or 3.5-MHz transducer; a standard VHS video format was used to record the echocardiograms. In each patient, at least two ultrasonic evaluations were obtained: the first within 48 hours of symptom onset and the second at the hospital discharge (12±5 days after the first examination). The diagnosis of left ventricular thrombus was made in each of the 11 centers by experienced operators, who were unaware of the treatment group.

In all centers, echocardiographic examinations were performed according to criteria for visualizing the left ventricular apex and for searching for thrombi, as previously described. To assess the reproducibility in the diagnosis of left ventricular thrombi, three members of the Coordination and Data Center, who were unaware of the sequence, the treatment, and the clinical data of the patients, independently reviewed 40 randomly chosen videotaped examinations: Agreement in the diagnosis of left ventricular thrombi was 95%.

Left Ventricular Thrombi

The diagnosis of ventricular thrombosis was based on the criteria suggested by Asinger et al1: detection of an echodense mass with definite margins, adjacent to asynergic myocardium, distinguishable from chordal structure, muscle trabeculation, or false mass resulting from technical artifacts; doubtful cases were always considered as negative.

With regard to the shape, a thrombus was defined as mural when its free margin was concave and followed the curvature of the adjacent ventricular wall and was defined as protruding when its free margin showed an opposite curvature to that of the left ventricular wall, projecting into the cavity. In two cases of autopsy diagnosis, the thrombus shape was decided on the anatomic finding. A thrombus was defined as mobile when it showed a pattern of motion independent of that of the adjacent myocardium.

Left Ventricular Wall Motion

Analysis of left ventricular wall motion was performed according to the criteria proposed by Edwards, partially modified, as suggested by the GISSI Scientific Committee. The left ventricle was divided into 11 segments; each left ventricular segment was assigned a score (0, normal; 1, hypokinetic; 2, akinetic; and 3, dyskinetic), and a global wall motion score was obtained by the addition of each segment score.

Autopsy

In 10 of the 12 patients who died within the hospital stay, autopsy examination was performed. Particular attention was given to determining the presence of left ventricular thrombi.

Statistical Analysis

Continuous data are expressed as mean±SD. Differences between two means were assessed with the Student’s t test for unpaired data. Differences be-
tween more than two means were assessed by the one-way analysis of variance. Differences between proportions were analyzed with the \( \chi^2 \) test, corrected for small sample sizes when necessary by Fisher’s exact test. Differences were considered significant for probability values less than 0.05.

Results

Diagnosis of Left Ventricular Thrombi

Within the whole study population, left ventricular thrombi were detected in 51 of 180 (28%) patients. Diagnosis of ventricular thrombi was made in 49 patients by means of echocardiography, whereas in two patients, it was obtained by autopsy examination; in fact, of the 10 patients who were submitted to anatomic examination, the autopsy showed the presence of left ventricular thrombus in one patient who died before the first echocardiogram was obtained and in one other in whom the thrombus was not detectable on the first echocardiogram. In the remaining eight patients, the autopsy confirmed the echocardiographic findings.

Incidence and Time of Appearance of Left Ventricular Thrombi

Table 2 shows the incidence of left ventricular thrombi in the four treatment groups. Thrombi developed in 10 of 39 (26%) of the streptokinase group, in 12 of 49 (24%) of the streptokinase plus heparin group, in 16 of 47 (34%) of the rt-PA group, and in 13 of 45 (29%) of the rt-PA plus heparin group. None of the differences among the four groups was significant. In particular, no difference in the incidence of thrombi was found either between patients who received streptokinase and those who received rt-PA, independently of the heparin therapy (22 of 88, 25%, versus 29 of 92, 32%) or between those who received heparin after thrombolysis and those who did not (25 of 94, 27%, versus 26 of 86, 30%).

Table 3 shows the presence of left ventricular thrombi in the four treatment groups at the time of the first and the second echocardiographic examination, respectively.

In 34 patients (19% of the total study population, 65% of the patients with left ventricular thrombi), a thrombus developed within 48 hours of acute myocardial infarction; at the time of the second echocardiogram, thrombosis was present in 44 patients (26% of the total study population, 86% of the patients with left ventricular thrombi). No significant difference in the incidence of thrombi was detected between the first and second echocardiographic examinations among the four treatment groups.

Table 4 shows the left ventricular thromb appearance and disappearance upon the second echocardiographic examination. During the hospital period, we observed the new appearance of 17 thrombi (33% of the total thrombi observed and 13% of the patients who were free of thrombi at the first echocardiographic examination); on the other hand, seven of the 34 thrombi (21%), detected upon the first echocardiographic examination, were not detectable on the second. No difference in the rate of new appearance and disappearance of left ventricular thrombi was noted among the four treatment groups or between heparin-treated and untreated patients.

Atenolol, ASA, and Left Ventricular Thrombi

Of the 88 patients who received intravenous administration of atenolol on hospital admission, 28 (32%) showed a ventricular thrombus compared with 23 (25%) in the group of 92 patients who did not receive atenolol (\( p=NS \)).

The occurrence, time of appearance, and disappearance of left ventricular thrombi were similar in patients treated and not treated with ASA (Table 5).

### Table 2. Overall Incidence of Left Ventricular Thrombi in the Four Randomized Groups

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>No H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>SK</td>
<td>12</td>
<td>24</td>
<td>10/39</td>
</tr>
<tr>
<td>rt-PA</td>
<td>13</td>
<td>45</td>
<td>16/47</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>94</td>
<td>26/86</td>
</tr>
</tbody>
</table>

H, heparin; SK, streptokinase; rt-PA, recombinant tissue-type plasminogen activator (alteplase).

### Table 3. Left Ventricular Thrombi in the Four Groups on the First and Second Echocardiographic Examination

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>No H</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>First examination: LV thrombi presence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td>6</td>
<td>49</td>
<td>6/39</td>
</tr>
<tr>
<td>rt-PA</td>
<td>9</td>
<td>45</td>
<td>13/47</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>94</td>
<td>19/86</td>
</tr>
<tr>
<td>Second examination: LV thrombi presence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td>10</td>
<td>48</td>
<td>9/35</td>
</tr>
<tr>
<td>rt-PA</td>
<td>10</td>
<td>41</td>
<td>15/44</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>89</td>
<td>24/79</td>
</tr>
</tbody>
</table>

*12 patients died.

H, heparin; LV, left ventricular; SK, streptokinase; rt-PA, recombinant tissue-type plasminogen activator (alteplase).
Shape and Mobility of Left Ventricular Thrombi

Table 6 shows the distribution of shape of left ventricular thrombi in the four randomized groups.

With regard to the shape, the first echocardiogram showed that 24 of 34 (71%) thrombi were mural and 10 of 34 (29%) were protruding. The second echocardiogram showed that 28 of 44 (64%) thrombi were mural and 16 of 44 (36%) were protruding.

Of the 27 ventricular thrombi observed in both echocardiographic examinations, 24 showed unchanged shape (17 mural and seven protruding), whereas three thrombi showed changed shape, all demonstrating the variation from mural to protruding shape. No changes from protruding to mural shape were noted.

As shown in Table 6, in the group of patients treated with heparin, at the first echocardiographic examination, a significantly lower occurrence of protruding shape was observed (one of 15 versus nine of 18, p < 0.01); however, a significant difference was not detectable at the second echocardiographic examination. No left ventricular thrombus was noted to be mobile at the first echocardiographic examination, whereas mobility was noted in one case (one of 44, 2%) at the second.

Left Ventricular Wall Motion

The wall motion score was calculated in 168 patients at the time of the first echocardiographic examination and in 150 patients at the time of the second (Table 7).

No differences in wall motion score were found among the four randomized treatment groups at the first and second echocardiographic evaluation.

Patients who developed left ventricular thrombi showed a mean wall motion score of 7.8 ± 3.7 at the time of the first echocardiographic examination and 7.6 ± 4 at the time of the second. These values are significantly higher than those of patients who did not develop left ventricular thrombi (6 ± 4.2 and 5.6 ± 4, p < 0.05 and p < 0.01, respectively).

Table 4. Left Ventricular Thrombi Appearance and Disappearance on the Second Echocardiographic Examination

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>%</th>
<th>No H</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV thrombi appearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td>6/48</td>
<td>12.5</td>
<td>4/35</td>
<td>11</td>
<td>10/83</td>
<td>12</td>
</tr>
<tr>
<td>rt-PA</td>
<td>4/41</td>
<td>10</td>
<td>3/44</td>
<td>7</td>
<td>7/85</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>10/89</td>
<td>11</td>
<td>7/79</td>
<td>9</td>
<td>17/168</td>
<td>10</td>
</tr>
<tr>
<td>LV thrombi disappearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td>2/6</td>
<td>33</td>
<td>1/6</td>
<td>17</td>
<td>3/12</td>
<td>25</td>
</tr>
<tr>
<td>rt-PA</td>
<td>3/9</td>
<td>33</td>
<td>1/13</td>
<td>7</td>
<td>4/22</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>5/15</td>
<td>33</td>
<td>2/19</td>
<td>11</td>
<td>7/34</td>
<td>21</td>
</tr>
</tbody>
</table>

LV thrombi appearance, left ventricular thrombi that are absent at the first examination and present at the second; LV thrombi disappearance, LV thrombi that are present at the first examination and absent at the second; H, heparin; SK, streptokinase; rt-PA, recombinant tissue-type plasminogen activator (alteplase).

Table 5. Influence of Treatment With Acetylsalicylic Acid on Left Ventricular Thrombi: Occurrence, Time of Appearance, and Disappearance

<table>
<thead>
<tr>
<th></th>
<th>ASA</th>
<th>No ASA</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>LV thrombi total</td>
<td>43/150</td>
<td>29</td>
<td>8/30</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV thrombi &lt;48 hr</td>
<td>29/150</td>
<td>19</td>
<td>5/30</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV thrombi &gt;48 hr</td>
<td>14/134</td>
<td>10</td>
<td>3/32</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disappearance</td>
<td>5/32</td>
<td>16</td>
<td>2/5</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASA, acetylsalicylic acid; LV, left ventricular; LV thrombi <48 hr, LV thrombi appearance at the first echocardiographic examination; LV thrombi >48 hr, LV thrombi appearance at the second examination; Disappearance, LV thrombi disappearance at the second examination.

Table 6. Left Ventricular Thrombi Shape in the Four Randomized Groups

<table>
<thead>
<tr>
<th></th>
<th>Mural (n)</th>
<th></th>
<th>Protruding (n)</th>
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<tbody>
<tr>
<td></td>
<td>H</td>
<td>No H</td>
<td>Subtotal</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>First examination</td>
<td>24/34 (71%)</td>
<td></td>
<td>9/12</td>
<td>0/6</td>
</tr>
<tr>
<td>SK</td>
<td>6/6</td>
<td>3/6</td>
<td>9/12</td>
<td>0/6</td>
</tr>
<tr>
<td>rt-PA</td>
<td>8/9</td>
<td>7/13</td>
<td>15/22</td>
<td>1/9</td>
</tr>
<tr>
<td>Subtotal</td>
<td>14/15*</td>
<td>10/19*</td>
<td>24/34</td>
<td>1/15*</td>
</tr>
<tr>
<td>Second examination</td>
<td>28/44 (64%)</td>
<td></td>
<td>11/9</td>
<td>5/10</td>
</tr>
<tr>
<td>SK</td>
<td>5/10</td>
<td>6/9</td>
<td>11/9</td>
<td>5/10</td>
</tr>
<tr>
<td>rt-PA</td>
<td>9/10</td>
<td>8/15</td>
<td>17/25</td>
<td>1/10</td>
</tr>
<tr>
<td>Subtotal</td>
<td>14/20</td>
<td>14/24</td>
<td>28/44</td>
<td>6/20</td>
</tr>
</tbody>
</table>

H, heparin; SK, streptokinase; rt-PA, recombinant tissue-type plasminogen activator (alteplase).
* p < 0.01 H vs. no H.
Patients who were treated with atenolol showed a significantly lesser wall motion score compared with patients who were not treated (5.4±3.9 versus 7.3±4.2, p<0.01). This difference was expected, considering criteria for administration of the drug that excluded patients with heart failure.

**Clinical Events, Embolisms, and Left Ventricular Thrombi**

On admission, 123 of 176 (70%) patients were in Killip class I, 41 (23%) in class II, nine (5%) in class III, and three (2%) in class IV.

Left ventricular thrombi developed in 18 of 123 (15%) of patients admitted in Killip class I, in 13 of 41 (32%) in class II, in three of nine (33%) in class III, and in one of three (33%) in class IV.

During hospitalization, 12 (6.7%) patients died; no difference was noted in the mortality rate between patients with (nine of 139, 6.5%) and without left ventricular thrombi (three of 51, 6%).

Clinical signs of embolism were observed in one patient (0.5%) treated with rt-PA. In this patient, who suffered from a nonfatal ischemic stroke 13 days after acute myocardial infarction, a protruding thrombus was detected at the first echocardiographic examination. No patient had major hemorrhagic complications.

**Discussion**

In recent years, left ventricular thrombosis has been widely studied with ultrasound by many investigators. A prospective investigation on patients receiving no antithrombotic drugs allowed the description of the natural history of left ventricular thrombi.\(^8\)

The use of anticoagulant and, more recently, of thrombolytic drugs, has modified the incidence and the evolution of the thrombi.\(^12\) Intravenous infusion of fibrinolytic drugs within the first hours after symptom onset has proved to be a very effective therapy for acute myocardial infarction,\(^14\) and thrombolytic agents with different pharmacological profiles are now available.\(^26\) However, to date, no randomized study comparing the effects of different thrombolytic agents on left ventricular thrombi has been performed. Moreover, the possible additional action on thrombi of heparin treatment after thrombolytic treatment has not been investigated. Therefore, we assessed the incidence and the features of left ventricular thrombi in a population of patients with anterior acute myocardial infarction enrolled in a large trial designed to compare the efficacy of rt-PA and streptokinase administered within 6 hours of symptom onset followed or not followed by heparin therapy. The four treatment groups were comparable and well balanced; the whole sample size, even if relatively small, is the largest population to date of patients with anterior acute myocardial infarction treated with different thrombolytic drugs who were included in a study of left ventricular thrombi.

**Incidence of Left Ventricular Thrombi**

The overall incidence of left ventricular thrombi in this population treated with thrombolytic agents was 28%. Some investigators have reported an incidence of thrombi of more than 45% in patients who received no antithrombotic drugs,\(^8,12,17,27\) whereas other investigators studying patients who were treated with anticoagulants have reported a lower occurrence.\(^6,28,29\) Previous investigations, performed in smaller populations, demonstrated a reduction of left ventricular thrombi incidence in patients treated with streptokinase compared with those receiving conventional therapy.\(^10,12,13\) Our study shows that the choice of the thrombolytic agent, either streptokinase or rt-PA, does not further influence the incidence of left ventricular thrombi. Also, heparin treatment does not induce substantial modifications to left ventricular thrombi formation: In fact, after thrombolytic therapy, the administration of heparin did not further reduce their occurrence, and the proportion of thrombi in patients treated or not treated with heparin was similar (27% versus 30%). However, some limitations regarding the modality of administration of heparin must be pointed out. As established in the GISSI-2 protocol, heparin was not begun until 12 hours after thrombolytic treatment and was given subcutaneously; this modality of administration may further delay the onset of effective anticoagulation, leaving the patient unprotected from ongoing thrombosis, especially when the lytic effects have worn off. Recently, two different studies, one performed by Turpie et al\(^30\) and another by the SCATI group,\(^31\) both presented data on the effect of heparin administration (12,500 units

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**Table 7. Wall Motion Score in the Four Randomized Treatment Groups**

<table>
<thead>
<tr>
<th></th>
<th>H</th>
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<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>mean±SD</td>
<td>n</td>
<td>mean±SD</td>
</tr>
<tr>
<td>First examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td>7.1±4.8</td>
<td>47</td>
<td>5.8±3.8</td>
</tr>
<tr>
<td>rt-PA</td>
<td>6.6±4.3</td>
<td>41</td>
<td>5.7±3.7</td>
</tr>
<tr>
<td>Total</td>
<td>6.8±4.7</td>
<td>88</td>
<td>5.7±3.7</td>
</tr>
<tr>
<td>Second examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td>6.8±4.9</td>
<td>40</td>
<td>5.9±3.6</td>
</tr>
<tr>
<td>rt-PA</td>
<td>6.2±4.3</td>
<td>38</td>
<td>5.4±3.4</td>
</tr>
<tr>
<td>Total</td>
<td>6.5±4.7</td>
<td>78</td>
<td>5.7±3.4</td>
</tr>
</tbody>
</table>

H, heparin; SK, streptokinase; rt-PA, recombinant tissue-type plasminogen activator (alteplase).
s.c. every 12 hours) on postinfarction thrombosis that are different from the data in the present study. Turpie et al observed left ventricular thrombi only in 10 of 95 patients (11%), whereas the SCATI group observed that the incidence of thrombus at the time of the predischarge examination was significantly lower in the heparin-treated group than in the control group.29

However, these studies are hardly comparable with ours because of differences concerning the study population and protocol. Turpie et al30 evaluated nonthrombolized patients. Moreover, these investigators performed only one echocardiographic examination on the tenth day after myocardial infarction; this may have lead to an underestimation of thrombus incidence. With regard to the SCATI study, about one third of the patients did not undergo thrombolytic treatment in the acute phase of myocardial infarction.

Time of Appearance

In our investigation, 66% of the left ventricular thrombi were detected within 48 hours of acute myocardial infarction. This finding is in agreement with observations on the early presence of ventricular thrombi in the prethrombolytic era.7,8 Time of appearance of thrombi was not significantly different in the four treatment groups. However, at the first echocardiographic examination, the percentage of patients who developed left ventricular thrombi was higher in the rt-PA than in the streptokinase group (left ventricular thrombi: 22 of 92, 24%, versus 12 of 88, 14%), but the difference was not significant. A more sustained activity of streptokinase might have played a role in provoking this trend. Concerning the effects of heparin treatment, our data do not confirm the lower rate of left ventricular thrombi development previously reported by the SCATI study31 at the time of the predischarge echocardiographic examination in heparin-treated patients who were free of left ventricular thrombi at the first examination.

Disappearance of Left Ventricular Thrombi

Seven of the 34 (21%) left ventricular thrombi detected at the first echocardiographic examination disappeared during the study period. It is conceivable that the small number of patients in each treatment group did not allow us to detect a possible difference in the incidence of thrombus resolution that was attributable either to the type of thrombolytic drug or to heparin treatment.

β-Blocker, ASA, and Left Ventricular Thrombi

We observed the same rate of left ventricular thrombi in both patients who received or did not receive atenolol on admission. Previous studies reported a higher frequency of thrombus development in patients treated with β-blockers. In particular, Johannessen et al32 noted that the prolonged administration of timolol induced a significantly higher occurrence of left ventricular thrombi. Recently, Turpie et al30 reported similar results after treatment with β-blockers in a large population of patients with acute myocardial infarction.

The difference with our results may be explained by the different protocol of β-blocker administration: In fact, in the GISSI-2 study, β-blockers were not given in a randomized fashion, but β-blocker treatment was recommended. Moreover, our patients received only a single dose of atenolol on hospital admission.

ASA did not modify the occurrence of left ventricular thrombi in our study. The present study confirms the data reported by Kupper et al,33 who investigated, in a randomized trial, the effects of ASA (100 mg) on ventricular thrombi and demonstrated no difference between treated and untreated patients. Thus, ASA does not appear to be effective in modifying postinfarction thrombi.

Shape and Mobility

A previous study8 on the natural history of the shape of thrombi in patients not receiving antithrombotic drugs showed that during the first month of acute myocardial infarction in the absence of antithrombotic treatment the protruding configuration is more frequent than the mural one. Also, during hospitalization, a high occurrence of mobility patterns has been described. Conversely, we observed an extremely low percentage of mobility pattern, and moreover, the mural thrombi were more frequently found than the protruding thrombi (first examination: 71% versus 29%, p<0.01; second examination: 64% versus 36%, p=NS). Heparin seems to play an important additional role in determining the shape of the thrombi. In fact, in patients treated with this agent, the mural shape was significantly more frequent at the first echocardiographic examination, and a similar trend was observed at the second. On the other hand, in patients untreated with heparin, the proportions of mural and protruding thrombi are similar in both echocardiographic evaluations. This suggests that the combination of thrombolytic and heparin treatments modifies the spontaneous evolution of thrombus anatomy.

Previous studies indicated that patients with a protruding or mobile thrombus are at higher risk of embolism than those with a mural, nonmobile thrombus.34–36 Clinically evident embolism was infrequent in our patients compared with large trials dealing with thrombolytic treatment.25,31,38,39 It is conceivable that the higher incidence of mural and the lower one of protruding and mobile thrombi observed in our patients was linked to the lower incidence of embolism.

Study Limitations

Because left ventricular thrombosis is a dynamic phenomenon characterized by multiple changes, it would be highly advisable to obtain a higher number of echocardiograms to observe left ventricular thrombus evolution during hospitalization. However, this
approach would have made the protocol too complex for GISSI-2 participating centers.

In our study, streptokinase-treated patients tended to have a lower incidence of thrombi during the first echocardiographic evaluation: streptokinase, 12 of 88 (14%) versus rt-PA 22 of 92 (24%), p < 0.08. A larger number of patients might have made this difference significant.

Neither the plasma concentration of heparin, started 12 hours after thrombolysis, nor activated partial thromboplastin time could be monitored to know whether the administration of heparin reached its maximal efficacy (as carried out by Turpie et al\(^{16}\)). However, the doses administered are now considered part of standardized treatment.

**Conclusions**

Our study shows that in the thrombolytic era, postinfarction left ventricular thrombosis continues to be a frequent event, for it is identified in 28% of patients. Furthermore, the type of thrombolytic drugs (streptokinase or rt-PA) and the combination with subcutaneous heparin treatment 12 hours after thrombolysis does not seem to produce significant differences in the incidence of left ventricular thrombi. A protruding shape and mobility pattern, recognized as markers of embolic risk,\(^{34}\) are observed in a low percentage, particularly when heparin treatment follows thrombolytic treatment during the pre-discharge period. This fact may account for the low incidence of peripheral embolization (0.5%) observed during hospitalization.

**Appendix**

**Italian Multicenter Left Ventricular Thrombosis Study Group**

Chairman: Carlo Vecchio, MD; Divisione di Cardiologia, EO Ospedale Galliera, Genova.

Coordinating and Data Center: F. Chiarella, MD; P. Bellotti, MD; S. Domenicucci, MD; Divisione di Cardiologia, EO Ospedale Galliera, Genova.

Participating Cardiology Divisions and Investigators: Belluno: P. Pellegrini, MD; G. Soravia, MD; A. Brida, MD. Bergamo: P. Invernizzi, MD; M. Tespili, MD. Cittadella: P. Maiolino, MD; M. Rossi, MD. Firenze: P.F. Fazzini, MD; D. Antonucci, MD. Genova: C. Vecchio, MD; F. Chiarella, MD; P. Bellotti, MD; S. Domenicucci, MD; G. Lupi, MD. Lavagna: A. Bertulla, MD; P. Rosselli, MD; R. Bollini, MD. Lucca: G. Masini, MD; M. Masini, MD. Milano: C. Belli, MD; D. Nassiacos, MD; S. Meloni, MD. Milano: A. Lotto, MD; F. Nador, MD; U. La Marchesina, MD. Reggio Emilia: G. Casali, MD; M. Bottone, MD. Varese: G. Binaghi, MD; M. Santarone, MD; P. Ambrosetti, MD; G. Macchi, MD.

First-mentioned physicians at the participating divisions were administratively responsible for the trial at their institutions.

**References**


Key Words • myocardial infarction • thrombosis, left ventricular • thrombolysis • echocardiography • GISSI 2 • heparin • streptokinase • plasminogen activator, recombinant tissue-type
Left ventricular thrombus in anterior acute myocardial infarction after thrombolysis. A GISSI-2 connected study.
C Vecchio, F Chiarella, G Lupi, P Bellotti and S Domenicucci