Eligibility for Intravenous Thrombolysis in Suspected Acute Myocardial Infarction

Björn W. Karlson, MD, Johan Herlitz, MD, PhD, Nils Edvardsson, MD, PhD, Håkan Emanuelsson, MD, PhD, Margareta Sjölin, RN, and Åke Hjalmarsen, MD, PhD

Based on the registration of all the 7,157 patients admitted during a 21-month period to the emergency ward of a single hospital in an urban area with chest pain or other symptoms suggestive of acute myocardial infarction, we studied eligibility for intravenous thrombolysis in suspected acute myocardial infarction. We have limited the present analysis to those 1,715 patients with a strong suspicion of myocardial infarction, and for these patients, we have calculated the percentages eligible for thrombolysis when various electrocardiographic and delay time criteria are applied, but we have not considered contraindications to thrombolysis. We have also calculated the proportions of all infarctions in this group that would thereby receive the treatment, and the proportions of patients treated that would develop a confirmed infarction. Using the criteria ST elevation on the initial electrocardiogram and arrival in hospital within 6 hours from onset of symptoms, 18% of patients would have been given early intravenous thrombolysis, 37% of confirmed infarctions would have been treated, and 91% of all treated patients would have developed a confirmed infarction; with a delay time criterion of 12 hours, these percentages would have been 20%, 41%, and 91%, respectively; with a criterion of 24 hours, they would have been 22%, 45%, and 90%, respectively. By not considering the initial electrocardiogram and applying only the criterion of delay time, these percentages would have been 70%, 72%, and 45%, respectively, for a delay time of 6 hours; 83%, 84%, and 45%, respectively, for a delay time of 12 hours; and 91%, 92%, and 44%, respectively, for a delay time of 24 hours. We have also calculated these percentages for two further electrocardiographic criteria, namely, electrocardiogram showing acute ischemia and any form of pathology. We conclude that the percentage of patients with a strong suspicion of myocardial infarction eligible for intravenous thrombolysis varies considerably depending on the electrocardiographic and delay time criteria used. If the delay time is limited to 6 hours and the electrocardiogram is required to show ST elevation, then 37% of patients developing myocardial infarction would receive thrombolytic treatment. (Circulation 1990;82:1140–1146)

The prognosis after development of an acute myocardial infarction is related to its final extent.1,2 In recent years, several large trials have shown a considerable reduction in mortality with thrombolytic treatment given intravenously in the acute phase of infarct development, with only a low rate of severe side effects.3–5 The fact that the treatment is effective, safe, and can be given intravenously makes it practical even in hospitals without catheterization facilities.

However, different criteria for the inclusion of patients have been used in these trials, and different conclusions have been drawn about which patients are suitable for thrombolytic treatment.6 There were also great discrepancies between the numbers of patients evaluated for inclusion and the numbers finally randomized in the three largest trials (Table 1).

Consequently, the beneficial effect of thrombolysis is well established, but the proportion of patients with suspected acute myocardial infarction eligible for such treatment is less clear.

The purpose of this paper is to show how the percentage of patients with strongly suspected or

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Supported by grants from The Swedish Heart Foundation, The Göteborg Society of Medicine, Arbetenmarknadens Försäkringsaktiebolag, The Medical Faculty of the University of Gothenburg, The Swedish Society of Medicine, Roussel Nordiska AB, Trygg Hansa Insurance Co., Skandia Insurance Co., ICY-Pharma AB, Sjukförsäkrings AB Eir's 50-Year Foundation, Leo and Hans Osterman's Fund, Ollie and Elof Ericsson's Foundation.

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Received December 15, 1989; revision accepted May 22, 1990.
TABLE 1. Patients and Inclusion Criteria in Three Large Thrombolytic Studies

<table>
<thead>
<tr>
<th>Study and year</th>
<th>Patients evaluated</th>
<th>Patients randomized</th>
<th>Criteria for inclusion</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI, 1986</td>
<td>31,826</td>
<td>11,806</td>
<td>≤12 hr, ST elevation</td>
<td></td>
</tr>
<tr>
<td>ISIS II, 1988</td>
<td>17,187</td>
<td>5,011</td>
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<td>13,318</td>
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<td>≤5 hr</td>
<td>≤75</td>
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</table>

ECG, electrocardiogram.

confirmed acute myocardial infarction receiving thrombolysis varies according to the treatment criteria used.

Methods

Sahlgrenska Hospital in Gothenburg serves a population of about 230,000. Between February 15, 1986, and November 9, 1987, all patients admitted to the emergency ward with chest pain or other symptoms suggestive of an acute myocardial infarction were evaluated and prospectively classified into four categories, based on history, clinical examination, and electrocardiogram in the emergency ward. These categories were 1) obvious myocardial infarction, which included typical symptoms and ST elevation with or without Q waves on the initial 12-lead electrocardiogram, 2) strong suspicion of myocardial infarction, which included subcategories: a) typical symptoms, but an electrocardiogram without ST elevation or Q waves, b) atypical symptoms, but ST-T changes or Q waves on the electrocardiogram, c) sudden onset of severe congestive heart failure without ST elevation on the electrocardiogram, and d) unstable angina pectoris regardless of electrocardiogram, 3) vague suspicion of myocardial infarction: difficulties in the interpretation of the symptoms and no signs of acute ischemia on the electrocardiogram, and 4) no suspicion of myocardial infarction, but with the subcategories of a) no suspicion of ischemic heart disease and b) stable angina pectoris.

For the diagnosis of acute myocardial infarction, two of the following criteria had to be fulfilled: 1) chest pain with a duration of at least 15 minutes, 2) serum aspartate aminotransferase above the normal range in samples from at least two different days, and 3) appearance of new Q waves in at least two leads in a 12-lead standard electrocardiogram.

Among the factors that are usually considered in the evaluation of patients for intravenous thrombolysis are the strength of the suspicion of myocardial infarction, age, contraindications to treatment, the delay time from onset of symptoms until arrival in hospital, and the electrocardiographic pattern in the emergency ward. With regard to the first two factors, we have limited the present analysis to patients in categories 1 and 2 as described above (obvious and strongly suspected myocardial infarction), but we have not used any age limit. Contraindications are reported in various frequencies in different patient materials considered for thrombolysis. We have chosen to present our results (Figures 2–4) without exclusion of any patients for contraindications because the exact number of patients with contraindications cannot be given in our material. The delay times we have used in this analysis are 3 hours or less, 6 hours or less, 12 hours or less, and 24 hours or less. As for the initial electrocardiogram, we have analyzed the effects of using the following criteria: 1) ST elevation (≥2 mm in leads V₁-V₄, ≥1 mm in leads V₅-V₆, aVL, I, II, III, and aVF); 2) acute ischemia (ST elevation, ST depression ≥ 1 mm, T wave inversion or Q wave ≥ 2 mm deep); 3) pathological electrocardiogram (including acute ischemia or other abnormalities such as previous infarction, bundle branch block, nonspecific ST-T changes); and 4) electrocardiogram not considered (that is, thrombolysis to be given regardless of the electrocardiographic pattern). The acute ischemic changes had to be found in two or more leads.

Results

During the 21-month registration period, 7,157 patients were admitted to the emergency ward with chest pain or other symptoms suggestive of an acute myocardial infarction. Of these patients, 921 (13%) developed a confirmed infarction during the first 3 days in the hospital. The percentages of all patients in the four categories of suspicion were as follows: category 1, 4%; category 2, 20%; category 3, 35%; and category 4, 41%.

Table 2 shows the numbers of patients and confirmed infarctions in total and in patients with an initially strong suspicion of myocardial infarction (that is, in categories 1 and 2). The patients with a strong suspicion of infarction made up only 24% of the unselected population, but 79% of all infarctions developed in this group.

Table 3 shows the characteristics of the 1,715 patients with a strong suspicion of myocardial infarction. Figure 1 shows the same patients divided into groups according to initial electrocardiographic pattern and the numbers of confirmed infarctions in each such group. It should be noted that the electrocardiographic patterns used in Figure 1 are not the

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ECG, electrocardiogram.

TABLE 2. Patients and Myocardial Infarctions

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<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Myocardial infarctions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7,157 (100%)</td>
<td>921 (100%)</td>
</tr>
<tr>
<td>Strong suspicion of infarction</td>
<td>1,715 (24%)</td>
<td>723 (79%)</td>
</tr>
</tbody>
</table>
TABLE 3. Characteristics of 1,715 Patients With a Strong Suspi-
    cion of Myocardial Infarction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Med. 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 34–101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men/women</td>
<td>65%/35%</td>
<td></td>
</tr>
<tr>
<td>Previous infarction*</td>
<td>(9)</td>
<td>37%</td>
</tr>
<tr>
<td>Angina pectoris*</td>
<td>(19)</td>
<td>54%</td>
</tr>
<tr>
<td>Heart failure*</td>
<td>(5)</td>
<td>26%</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>(6)</td>
<td>35%</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>(8)</td>
<td>13%</td>
</tr>
<tr>
<td>Smokers</td>
<td>(150)</td>
<td>31%</td>
</tr>
</tbody>
</table>

*Diagnosed before this admission.

The number in parenthesis gives the number of patients for each variable in which the information was missing.

The percentages of treated patients, among 1,715 patients with a strong suspicion of myocardial infarction, developing a confirmed myocardial infarction are as follows. Figure 3 shows that, depending on the electrocardiographic and delay time criteria used, between 44% and 91% of the patients considered eligible for treatment would actually have developed a confirmed infarction.

The percentages of 723 patients with an initially strong suspicion of myocardial infarction, and who subsequently developed a confirmed myocardial infarction, who would have been eligible for thrombolytic treatment are as follows. As shown in Figure 4, depending on the electrocardiographic and delay time criteria used, between 28% and 92% of the patients who developed a myocardial infarction would have been treated with intravenous thrombolysis.

In most of the subgroups in Figures 2 and 4, about 50–60% of those considered eligible for thrombolysis were transported to hospital by ambulance. Thus, eligibility for prehospital thrombolysis in each subgroup can be roughly calculated by dividing the percentage values given in Figures 2 and 4 by two.

**Discussion**

Because most myocardial infarctions appear to be caused by an occlusive thrombus in the infarct-related coronary vessel,8 intense attempts have been made with intracoronary and intravenous thrombolytic agents to dissolve such thrombi. Large randomized trials have shown that it is possible to limit infarct size9–12 and to reduce mortality considerably3–5 by early intervention with intravenous thrombolysis in myocardial infarction, and the frequency of serious side effects seems to be reasonably low.

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**Figure 1.** Bar graph of development of myocardial infarction in relation to electrocardiogram in 1,715 patients with a strong suspicion of myocardial infarction. Each column shows the total number of patients and the number of patients who developed an infarction. Information about electrocardiogram was missing in five patients, none of whom developed an infarction.
In the studies that have evaluated thrombolytic treatment, varying inclusion criteria have been used, and some discrepancies have been observed in terms of outcome in subgroup analyses.

In this study we have included patients with sudden onset of heart failure and unstable angina pectoris, regardless of the electrocardiogram. The reason for this is that we wanted to include as many patients with development of infarction as possible in the material, and it is impossible to exclude infarct development in these patients in the emergency room.

Regarding the time from onset of symptoms, maximal durations of 5, 12, and 24 hours, respectively, were stated in the protocols of the three largest trials3-5 (Table 1). Based on the results of the GISSI trial, it was suggested that little benefit was observed if thrombolysis was started more than 6 hours after the onset of symptoms and that the greatest benefit was observed if treatment was started within 3

**Figure 2.** Bar graph of percentages of 1,715 patients with a strong suspicion of myocardial infarction who would have been eligible for thrombolytic treatment depending on the electrocardiographic and delay time criteria applied. Information about delay time or electrocardiogram was missing in 100 patients.

**Figure 3.** Bar graph showing how the percentage of treated patients who develop a confirmed myocardial infarction varies with the electrocardiographic and delay time criteria applied in 1,715 patients with a strong suspicion of myocardial infarction.
hours. In the ISIS-2 trial, it was, however, shown that intravenous thrombolysis can favorably affect outcome up to 24 hours after onset of symptoms, even if early treatment gave the best results.

Delay times in suspected acute myocardial infarction vary somewhat between countries. For the patients in the present study, the median delay time was 3 hours. This figure is fairly similar to those found in many other countries, but one hopes that delay times will be reduced in the future.

The initial electrocardiographic pattern seems to be related to prognosis in myocardial infarction. Thus, patients having pathological changes on the admission electrocardiogram have a higher mortality than patients having no such changes. In many of the studies evaluating the effect of early thrombolysis, only patients having ST segment elevation on the electrocardiogram were included. In the ISIS-2 and ASSET studies, patients were included regardless of the pattern on the initial electrocardiogram. Even if most of the included patients had, in fact, signs of ischemia on the electrocardiogram, these studies did not indicate that treatment should be given only to patients with initial ST elevation. In the GISSI and ISIS-2 studies, however, no beneficial effect was observed in patients having ST depression only, and in the ASSET study, this issue was not evaluated.

When thrombolytic treatment is used in suspected acute myocardial infarction, some patients without infarction will receive treatment. These patients are exposed to the risk of side effects but will probably have no benefit from the treatment. The number of such patients is greatly influenced by the electrocardiographic criteria used (Figure 3).

The upper age limit for thrombolysis has not been defined. The GISSI and ISIS-2 studies had no upper age limit, whereas the ASSET study set a limit at 75 years. In the GISSI trial, there was no significant reduction in mortality among patients above 65 years of age, whereas in the other two trials there was, in fact, a somewhat greater benefit among the older patients. However, only 10–20% of the patients included in the GISSI and ISIS-2 studies were older than 70–75 years of age. Severe complications from thrombolytic treatment have been reported, in a minor study, to be more common in older patients. Although it is most likely that many old patients will benefit from treatment, a clear definition of these patients in higher ages is lacking.

The contraindications to treatment are mainly dictated by the risk of hemorrhage. In some randomized trials, the percentages of patients with contraindications leading to exclusion have been reported, for example, as 9%, 13%, and 35%. In a randomized trial, performed in Göteborg during the same period of time as this one, we found contraindications in 17% of the patients, a rate we think is correct to use at our hospital. Thus, we have to reduce the percentage in Figures 2 and 4 by 17% to get the appropriate percentages. Every reader has to do the same kind of calculation, from the rate of contraindications that can be established or is probable at his hospital.

In the GISSI and ASSET studies, only about 35% of the admitted patients were randomized. Murray et al have reported that only 9% of evaluated patients were recruited to a study with intravenous streptokinase at their hospital and concluded that such treatment can be used in only a small proportion of patients. Other studies have also reported high rates of exclusion, for example 48%, 49%, and 63%. The only exception is 20% in the GISSI 2 study.
However, these percentages were found in randomized studies, where the criteria for randomization often differ from the criteria for treatment in everyday clinical practice. For example, some criteria for exclusion in randomized studies are of an administrative nature. Furthermore, the populations from which patients in these large trials were recruited have not been adequately described, and thus, it is difficult to draw firm conclusions from the results. Therefore, from a totally unselected population of consecutive patients with a strong suspicion of acute myocardial infarction in the emergency ward, we have tried to calculate the proportions of patients eligible for intravenous thrombolysis when various electrocardiographic and delay time criteria are applied. Depending of the criteria chosen, between 13% and 91% of such patients are eligible for treatment (Figure 2); between 28% and 92% of such patients who actually develop a confirmed infarction would receive thrombolytic treatment (Figure 4); and between 44% and 91% of such patients found to be eligible for treatment would actually develop a confirmed myocardial infarction (Figure 3).

In another evaluation of eligibility for thrombolytic treatment, which used the criteria age 75 years or less, electrocardiogram suggestive of infarction, and time from onset of symptoms 4–6 hours, 23–25% of infarct patients were eligible before contraindications were considered.

One could argue that the number of patients actually developing myocardial infarction may be related to whether thrombolyis is given or not because in theory thrombolyis may prevent infarct development if given very early. This hypothesis has, however, not been confirmed in clinical trials, and our own experience does not indicate that very early thrombolysis prevents infarct development.

In conclusion, from large randomized studies, it is unclear what proportion of patients is eligible for treatment with thrombolytic agents. We find that, depending on the electrocardiographic and delay time criteria used, the proportion of patients eligible for thrombolysis varies widely as does the proportion of confirmed infarctions that will receive treatment and the proportion of patients treated who actually develop an infarction. The proportions of treated patients actually developing a confirmed infarction seem to be mainly influenced by the electrocardiographic criteria used.

Acknowledgment

We thank Peter Nicol, MD, Köping, Sweden, for help in the preparation of the manuscript.

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**KEY WORDS** • thrombolysis • acute myocardial infarction • delay time • electrocardiogram
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*Circulation* 1990;82:1140-1146
doi: 10.1161/01.CIR.82.4.1140

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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