# Value of Admission Electrocardiogram in Predicting Outcome of Thrombolytic Therapy in Acute Myocardial Infarction

## A Randomized Trial Conducted by The Netherlands Interuniversity Cardiology Institute

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**To determine the value of the admission 12-lead electrocardiogram to predict infarct size limitation by thrombolytic therapy, data were analyzed in 488 of 533 patients with acute myocardial infarction (AMI) from a randomized multicenter study. All patients had typical electrocardiographic changes diagnostic for an AMI and were admitted within 4 hours after the onset of chest pain; 245 patients were allocated to thrombolytic treatment and 243 to conventional treatment. Cumulative 72-hour release into plasma of myocardial $\alpha$-hydroxybutyrate dehydrogenase (HBDH) was used as a measure of infarct size. In general, the amount of infarct limitation due to thrombolytic therapy was proportional to the size of the area at risk. Patients with new Q waves, high QRS score and high ST-segment elevation or depression had the largest enzymatic infarct size in both treatment groups, irrespective of location of the AMI. Compared with conventionally treated patients, patients with anterior AMI treated with streptokinase had significant infarct size limitation (480 U/liter HBDH, 37%), and limitation was most prominent in those with Q waves (820 U/liter HBDH) or high ST elevation (750 U/liter HBDH). Infarct size limitation in inferior AMI was less impressive (330 U/liter HBDH, 33%) and patients with high ST-segment elevation (460 U/liter HBDH) or marked contralateral ST-segment depression (430 U/liter HBDH) had the most notable infarct limitation. Independent of interval between onset of chest pain and admission, in both types of AMI no significant infarct limitation was seen in patients with low ST elevation in the absence of Q waves, while in those with high ST elevation, in the presence but especially in the absence of Q waves, thrombolytic therapy was effective. Thus, thrombolytic therapy is most potent in patients with AMI admitted early after onset of chest pain who have electrocardiographically a large infarcted or ischemic area.**

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Data from the study conducted by the Netherlands Interuniversity Cardiology Institute and by others indicate that in patients treated with streptokinase, reduction of the mortality rate[1–5] and preservation of left ventricular function[4–7] is related to limitation of enzymatic infarct size, which was estimated to be 30%.[8] However, such treatment carries a risk of bleeding and increased need for blood transfusion.[9] It would be of great clinical value to be able to identify patients with acute myocardial infarction (AMI) most likely to benefit from thrombolytic therapy at the time of admission using the 12-lead electrocardiogram and time

of onset of chest pain. In a retrospective manner the present analysis was done to define such subgroups of patients.

## Methods

**Study design:** The study design has been described.[3] Briefly, patients admitted to the coronary care unit with an AMI were randomized to conventional treatment (control subjects) or thrombolytic therapy. Inclusion criteria were: age 70 years or younger; typical chest pain for more than 20 minutes; admission to the coronary care unit within 4 hours of onset of symptoms; no contraindications to streptokinase therapy; and electrocardiographic changes diagnostic of AMI (≥0.1 mV of ST-segment elevation at the J point in ≥1 extremity lead or ≥0.2 mV in ≥1 precordial lead, or ≥0.2 mV of ST-segment depression in ≥1 precordial lead, indicating posterior wall infarction).

Informed consent was sought from patients allocated to thrombolytic therapy only.[10] Conventional therapy was given to patients in the control group. This included, in all patients, Thalamonal® (droperidol, fentanyl) and heparin followed by acenocoumarol (Sintrom®) administration until hospital discharge. Other drugs were given when indicated.[11] Patients who received thrombolytic therapy but who refused consent were treated according to the conventional treatment protocol, but evaluated according to their original treatment allocation (intention to treat).[10] At first, patients who received thrombolytic therapy were treated with intracoronary streptokinase only. In later patients a combination of intravenous and intracoronary streptokinase was given because thrombolytic therapy appeared to be delayed by approximately 1 hour, which was needed for preparation of the catheterization. Furthermore, other studies[12,13] suggested that the initial patency rate would increase to approximately 50% of patients. Intravenous streptokinase was given immediately after informed consent in a dosage of 500,000 U infused within 20 minutes. In patients in whom the infarct-related vessel was occluded or the open artery contained thrombus, intracoronary streptokinase was given up to a maximal dosage of 250,000 U in 1 hour.

**Electrocardiographic criteria used for QRS pathology and ST-segment changes:** For the present analysis 2 sets of criteria for QRS pathology were used. Further, the sum of ST-segment elevation and the sum of ST-segment depression were studied. QRS complexes were judged abnormal by the following criteria: (1) Extremity leads—Q wave more than 25% of the R wave or width of Q at least 0.04 second (lead III is excluded). (2) Lead $V_1$—Q wave was diagnosed if a Q/R complex was seen. An isolated QS complex in lead $V_1$ was interpreted as normal. (3) In leads $V_2$ to $V_3$—a Q wave was always interpreted as abnormal. (4) Lead $V_4$—the Q wave was abnormal when it was more than 0.1 mV deep or the Q in lead $V_4$ was larger than in $V_5$, or the Q was at least 0.02 second wide. (5) In lead $V_5$—the Q wave was considered abnormal if more than 25% of the R wave, larger than the Q wave in $V_6$ or at least 0.04 second wide. (6) Lead $V_6$—Q wave more than 25% of the R wave or Q wave at least 0.04 second wide.

In addition, the QRS scoring system proposed by Wagner et al[14] was applied. Patients with complete right bundle branch block or left axis deviation were not excluded. In these cases points attributed to height of the R wave in leads $V_1$ and $V_2$ or the S wave in leads $V_4$-$V_6$ were neglected. Patients with a QRS score of 2 or less according to the criteria were not considered to have Q signs of AMI. Patients with previous AMI were excluded when presence or absence of Q waves and height of QRS score was determined because these electrocardiographic abnormalities have no relation to the current AMI.

ST-segment elevation and depression were measured at the J point. We calculated sum of the elevations and depressions in the anterior and inferior leads (Table I). Leads I, aVL, $V_5$ and $V_6$ were assigned to the inferior leads in case of inferior or posterior AMI, provided that anterior infarction was absent[15]; otherwise these 4 leads were combined with the anterior leads. Based upon location of the ST-segment elevation on the electrocardiogram at the time of randomization, we separated our patients into 2 categories: those with anterior AMI (n = 220) and those with inferior AMI (n = 268) (Table I). For practical reasons degree of elevation or depression was measured in millimeters instead of millivolts (10 mm = 1 mV) (Fig. 1).

Sum of ST-segment elevation and depression was separated into 2 categories of equal size: In anterior AMI, ST-segment elevation was ≤12 mm or >12 mm and ST-segment depression ≤2 mm or >2 mm. In inferior AMI, ST elevation was ≤6 mm or >6 mm and ST depression in ≤4 mm or >4 mm. Electrocardiograms were read independently by 2 experienced electrocardiographers. In case of differences in interpretation,

**TABLE I Location of Anterior and Inferior Electrocardiographic Abnormalities**

| | Anterior Leads | Inferior Leads |
|---|---|---|
| ST elevation | $V_1$-$V_4$ —if ST elevation $V_1$-$V_4$ —if no ST abnormalities in other leads | II,III,aVF —if ST elevation II,III,aVF —if ST depression $V_1$-$V_4$ |
| Sum (mm) determined in leads | $V_1$-$V_4$ (I,aVL,$V_5$,$V_6$) | II,III,aVF (I,aVL,$V_5$$V_6$) |
| Contralateral ST depression | $V_1$-$V_6$ | II,III,aVF |
| Sum (mm) determined in leads | $V_1$-$V_6$ | II,III,aVF |
| Q wave | $V_1$-$V_4$ (I,aVL,$V_5$,$V_6$) | II,aVF (I,aVL,$V_5$,$V_6$) |

I,AVL,V5,V6

Anterior infarct: ST elevation in 1 or more of the leads $V_1$-$V_4$, and I, aVL, $V_5$, $V_6$ (if ST elevation in $V_1$-$V_4$ or no ST abnormalities in other leads).

Inferior infarct: ST elevation in 1 or more of the leads II, III, aVF and I, aVL, $V_5$, $V_6$ (if ST elevation II, III, aVF or ST depression $V_1$-$V_4$).

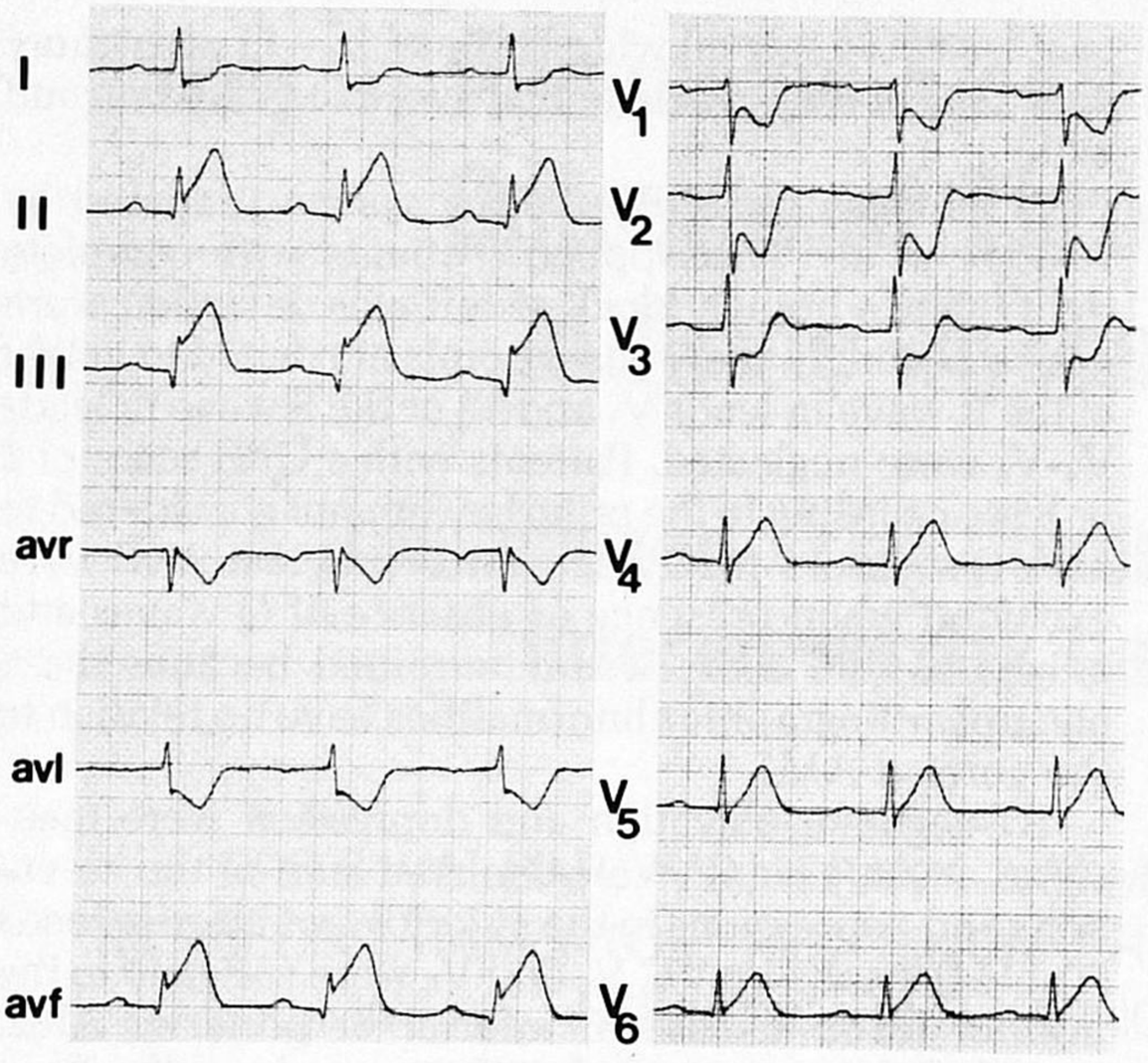


**FIGURE 1. Twelve-lead electrocardiogram of a patient having an acute inferoposterior infarct (1 mV = 10 mm). The Q wave in lead II is approximately 40 ms, while the Q in lead aVF is more than 25% of the R wave. According to the QRS scoring system the Q wave in lead II is ≥30 ms, the Q wave in lead aVF is ≥40 ms and the R-wave duration in lead $V_1$ is ≥40 ms and in lead $V_2$ ≥50 ms, resulting in 5 points. ST segment elevation—lead II, 2 mm; III, 4 mm; aVF, 3 mm; $V_6$, 1 mm; sum ST elevation, 10 mm; contralateral ST depression: lead $V_1$, 3 mm; $V_2$, 5 mm; $V_3$, 3 mm; sum ST depression, 11 mm.**

they agreed after discussion. Adequate electrocardiographic tracings were available in 488 of 533 patients. Forty-five patients were excluded from the present analysis as explained in the Results section.

**Enzymatic infarct size determination:** Myocardial α-hydroxybutyrate dehydrogenase (HBDH) levels were measured on admission, every 12 hours during the first 2 days and then once daily up to the fifth day after admission. Enzymatic infarct size was determined from the cumulative release of HBDH within 72 hours after onset of symptoms, which reflects at least 95% of the total HBDH release.[8,16] Missing values for HBDH release were substituted on the basis of clinical data (death) or other enzymatic data as described elsewhere.[8]

**Left ventricular function:** Radionuclide left ventricular ejection fraction was measured before hospital discharge. If radionuclide angiographic ejection fraction before discharge was missing, earlier or later nuclear studies or angiographic left ventricular ejection fraction was used, as described before.[5] Patients with previous AMI were excluded from analysis.

**Statistical analysis:** Because missing data on enzymatic infarct size were arbitrarily set at 6,000 or 40 U/liter, nonparametric tests were used for analysis. Differences between groups were tested with the Fisher exact test or the Mann-Whitney rank sum test when appropriate. Two-sided p values are reported. Multivariate linear regession analysis was performed to predict the effect of thrombolytic therapy on enzymatic infarct size and left ventricular ejection fraction.

## Results

One hundred fifty-two of the first 302 patients were randomized to intracoronary streptokinase therapy and 150 patients to conventional treatment. Of the next 231 patients, 117 were assigned to intravenous and intracoronary streptokinase therapy. Gender (83% men), age (mean 55 years) and a history of infarction (22%) were equally distributed between control and thrombolysis groups.

Median interval between onset of symptoms and hospital admission was 90 minutes. Randomization was done at 115 minutes and patients receiving streptokinase arrived in the catheterization laboratory 165 minutes after symptom onset. Infusion of intracoronary streptokinase was initiated 195 minutes (range 55 to 375) after the onset of chest pain. In patients in whom the occluded vessel reopened during the intervention, recanalization was achieved after a median of 30 minutes.[3]

The electrocardiogram at the time of randomization was suitable for the present analysis in 488 of 533 patients. Forty-five patients were excluded: The reviewers judged the electrocardiograms of 40 patients inadequate for the present analysis, although the physician who admitted the patient to the trial interpreted the electrocardiogram as typical of AMI; the electrocardiographic diagnosis "true posterior infarct" depended on subjective interpretation. Therefore, 6 patients with ST-segment depression in leads $V_1$-$V_2$ only were excluded. Also, 4 patients were excluded because of complete left bundle branch block, Wolff-Parkinson-White syndrome or third-degree atrioventricular block with ventricular escape rhythm. In 30 patients the electrocardiogram did not fulfill the criteria of ST-segment elevation. The electrocardiogram of 5 patients could not be retrieved.

The 488 patients available for analysis had baseline characteristics similar to those of the total group of 533 patients. Two hundred forty-five patients were allocated to thrombolysis and 243 to conventional treatment. In 212 of the 245 patients allocated to streptokinase therapy, acute coronary angiography was performed. Thirty-three patients refused the intervention or were subsequently found to have a contraindication. At the end of the procedure patency was 85% after intracoronary and 86% after intravenous plus intracoronary streptokinase therapy.

**Infarct size and electrocardiogram:** Patients treated with intracoronary streptokinase and those treated with intravenous plus intracoronary streptokinase showed no significant differences in enzymatic infarct size (Table II). Also, location of AMI was equally distributed. Therefore, we present results as from 1 group. Median enzymatic infarct size (cumulative HBDH release in 72 hours) was significantly smaller in the thrombolysis group for both anterior and inferior AMI than in the conventionally treated group (Table II). Overall, infarct size was smaller with inferior AMI than with anterior AMI.

Streptokinase treatment resulted in significant limitation of infarct size irrespective of electrocardiographic findings (Fig. 2). However, enzymatic infarct

**TABLE II Treatment Allocation, Location of Myocardial Infarction and Cumulative Enzyme Release (Median HBDH U/liter)**

| | Thrombolysis | | Control | | |
|---|---|---|---|---|---|
| | n | HBDH | n | HBDH | p Value |
| All | 245 | 760 | 243 | 1,170 | 0.0001 |
| IC group | 133 | 760 | 134 | 1,100 | 0.0001 |
| IV + IC group | 112 | 770 | 109 | 1,270 | 0.0001 |
| Anterior infarct | 115 | 820 | 105 | 1,300 | 0.0001 |
| Inferior infarct | 130 | 670 | 138 | 1,000 | 0.0001 |

HBDH = $\alpha$-hydroxybutyrate dehydrogenase; IC = intracoronary; IV = intravenous; n = number of patients.

size was largest in patients with Q waves, a QRS score above 2, high ST-segment elevation and high ST depression, independent of infarct location. Of all subsets of patients with anterior infarction, the most notable enzymatic infarct size limitation was achieved when the electrocardiogram showed Q waves (820 U/liter) or high ST-segment elevation (750 U/liter). In contrast to patients with anterior AMI, myocardial salvage by streptokinase was less striking in patients with inferior AMI; infarct limitation was highest in the presence of high ST-segment elevation (460 U/liter) or depression (430 U/liter).

In anterior AMI the combination of 2 electrocardiographic criteria (ST-segment elevation and Q waves) showed only very minor infarct limitation as a result of streptokinase treatment in patients with little ST elevation in the absence of Q waves (Fig. 3). The other combinations yielded statistically significant lower enzyme levels in the thrombolysis than the control group. In inferior AMI all 4 combinations had lower infarct size in the treated group; however, differences were not statistically significant.

**Infarct size and left ventricular ejection fraction relative to electrocardiogram and interval between onset of pain and admission:** To assess left ventricular function, radionuclide or contrast angiographic ejection fraction was determined in 460 patients.[5] Median left ventricular ejection fraction was 43% in the conventionally treated group and 50% in the thrombolysis group ($p = 0.0001$).

In univariate analysis the effects of thrombolytic therapy appeared to be related to degree of ST elevation, presence or absence of Q waves (Fig. 2) and delay between onset of symptoms and admission.[4,5] Multivariate linear regression analysis was performed. The results of the linear regression on enzymatic infarct size and left ventricular ejection fraction are presented in Table III. In patients with anterior AMI the effects of thrombolytic therapy were modified by the

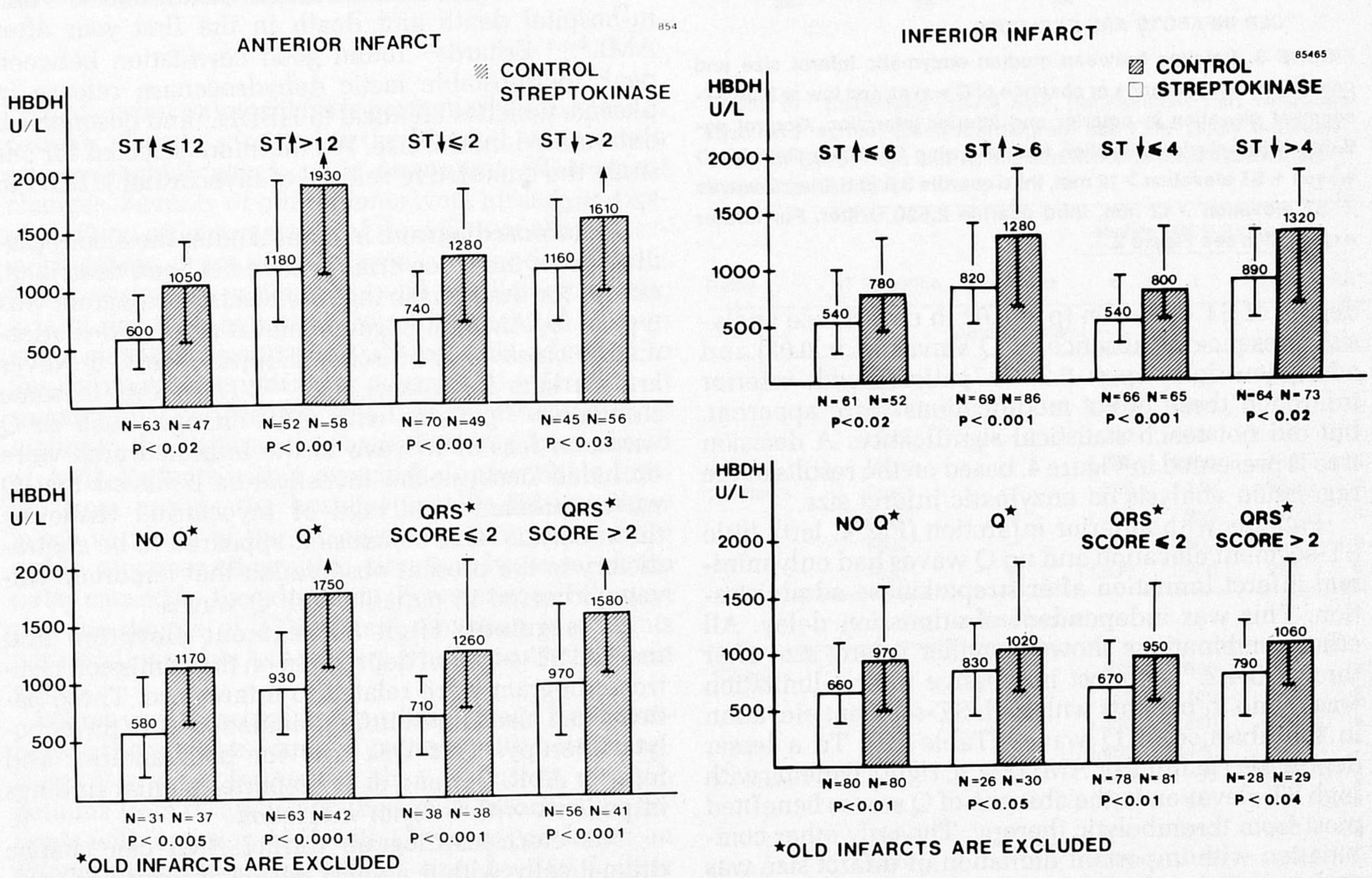


**FIGURE 2. Relation between median enzymatic infarct size (HBDH) and the electrocardiographic findings in patients with an anterior infarction (*left*) and an inferior infarction (*right*). Numbers of patients, median HBDH values and p value of differences in infarct size between conventionally treated patients and those treated with thrombolysis are given. *Vertical lines* in the *bars* represent first and third quartiles. Third quartile of control patients having anterior infarct: ST-segment elevation >12 mm, 3,270 U/liter; ST-segment depression >2 mm, 2,400 U/liter; Q waves: 2,420 U/liter; and QRS score >2, 2,530 U/liter.**

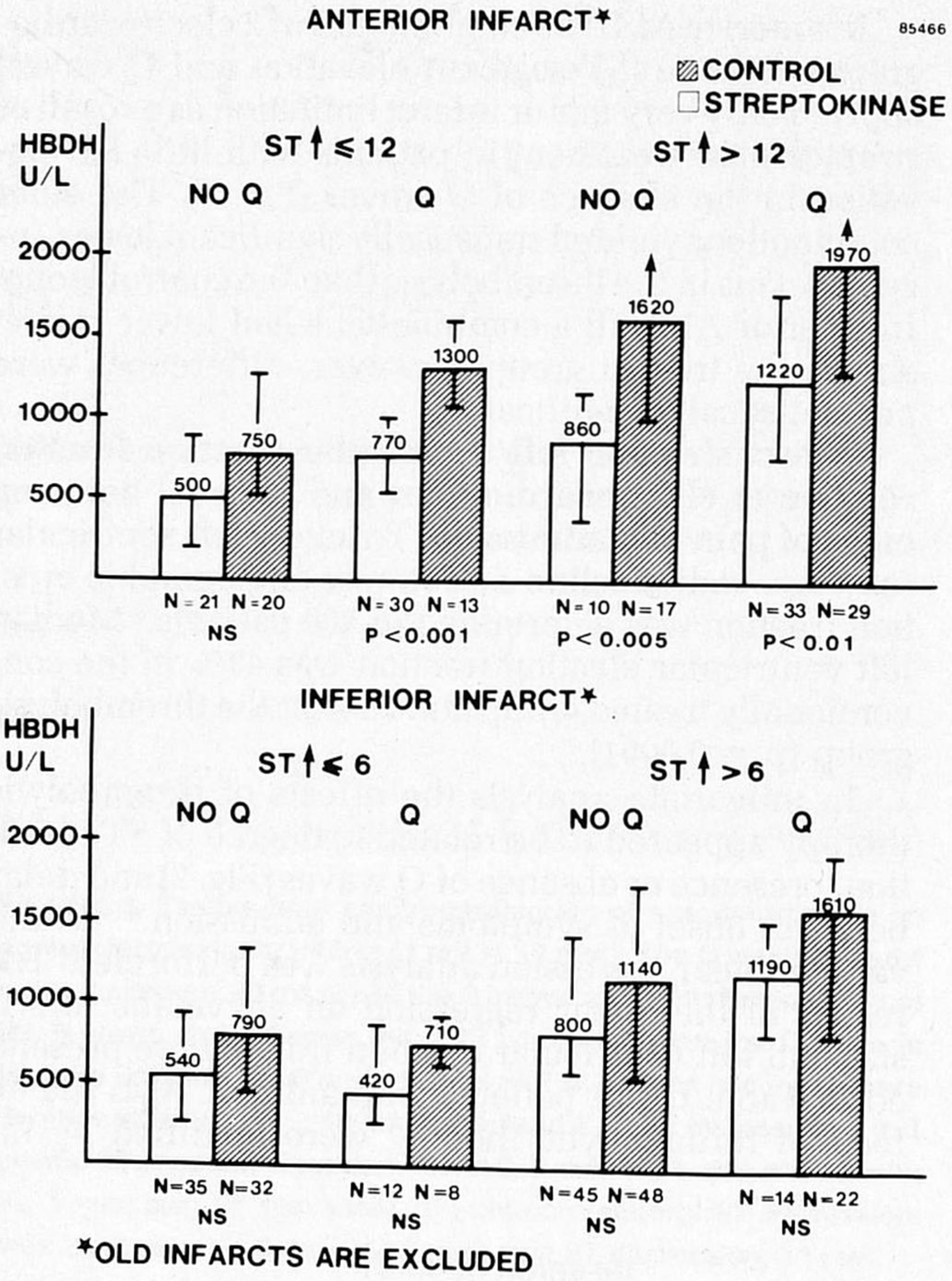


**FIGURE 3. Relation between median enzymatic infarct size and combination of presence or absence of Q waves and low or high ST-segment elevation in anterior and inferior infarction. Control patients with anterior infarction had following third quartiles: No Q waves + ST elevation >12 mm, third quartile 3,310 U/liter; Q waves + ST elevation >12 mm, third quartile 2,630 U/liter. For further explanation see Figure 2.**

degree of ST elevation ($p = 0.02$ in covariance analysis), presence or absence of Q waves ($p = 0.02$) and admission delay ($p = 0.2$). In patients with inferior infarction these effect modifications were apparent, but did not reach statistical significance. A decision tree is presented in Figure 4, based on the results of the regression analysis on enzymatic infarct size.

Patients with anterior infarction (Fig. 4, left), little ST-segment elevation and no Q waves had only minimal infarct limitation after streptokinase administration. This was independent of admission delay. All other combinations showed smaller infarct size after thrombolysis. The most impressive infarct limitation was found in patients with high ST-segment elevation in the absence of Q waves (Table III). To a lesser degree also in inferior AMI (Fig. 4, right), patients with high ST elevation in the absence of Q waves benefited most from thrombolytic therapy. The only other combination with important limitation of infarct size was early admission, high ST elevation and Q waves. All other comparisons yielded only small differences in enzyme levels between patients treated with thrombolysis and those treated conventionally.

## Discussion

The present analysis of data shows that thrombolytic therapy is most effective in terms of infarct size limitation in a subset of patients admitted early after onset of chest pain with signs of a large infarction (development of Q waves) or extensive ischemic area (high ST-segment elevation or marked ST depression). These observations are relevant for the clinical decision as to whether the patient should or should not receive thrombolytic treatment. Such an analysis has not been undertaken. Results of some studies[1,2,17–19] of streptokinase therapy in patients with AMI agree with our results[3–7] that thrombolytic therapy preserves left ventricular function or reduces mortality, but Rentrop et al[20] could not show a positive effect of this type of treatment. The disparities in outcome of thrombolytic therapy can partially be explained by the small number of patients in most studies.

**Enzymatic infarct size:** In most trials peak CK-MB or lactic dehydrogenase enzyme levels for determination of infarct size were used[1,20] This is another reason for the discrepancy in outcome of streptokinase trials. As pointed out by van den Laarse et al and others,[8,16,21] peak enzyme levels cannot be used for that purpose. In contrast, cumulative HBDH release in the first 72 hours correlates well with left ventricular ejection fraction, development of heart failure, arrhythmias and intraventricular conduction disturbances,[16] and in-hospital death and death in the first year after AMI.[4–6,8] Erhardt[22] found good correlation between peak thermostable lactic dehydrogenase release in plasma, which is identical to HBDH,[8] and postmortem determined infarct size. We therefore selected for our study the cumulative release of myocardial HBDH in 72 hours.

**Electrocardiogram:** In many studies the electrocardiographic inclusion criteria have not been described, except for the remark that the electrocardiogram was typical for AMI. ST-segment elevation provides information on severity of ischemic injury, while Q waves are markers for infarct size.[14,23] Therefore, in some studies,[1,17,20] patients with QRS changes such as Q waves or loss of R wave in the infarcted area were excluded because the investigators believed that Q waves precluded salvage of myocardial tissue by thrombolysis. This conclusion appeared to be contradictory to the present observation that important salvage occurred in patients with Q waves.

**ST segment:** High ST-segment elevation and marked ST-segment depression on the admission electrocardiogram were related to infarct size. These patients had also largest infarct limitation after thrombolytic therapy. This was true for both anterior and inferior AMI. Berland et al[24] reported similar findings in patients with inferior infarction.

The electrocardiogram during AMI can change dramatically within a short period. Because ST-segment abnormalities may vary considerably over time, in some patients the classification of the sum of ST elevation or depression would have been different if the electrocardiogram of randomization had been re-

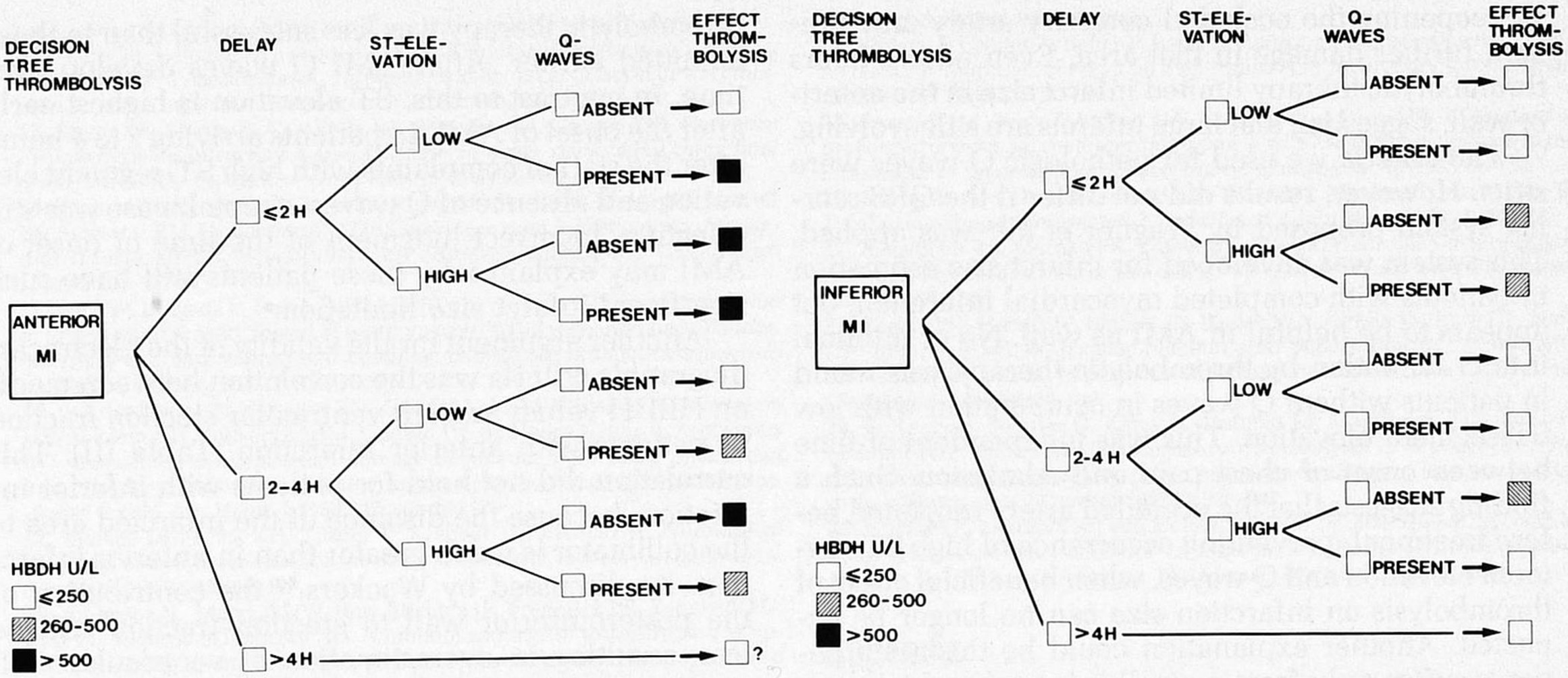


**FIGURE 4. Decision trees for anterior myocardial infarction (MI) (*left*) and inferior infarction (*right*). Patients are categorized according to time between onset of chest pain and admission (delay) and 2 electrocardiographic findings (degree of ST elevation and presence or absence of Q waves). Differences in enzymatic infarct size between the conventionally treated patients and those who received thrombolytic therapy are expressed in 3 groups: <250 U/liter, 260 to 500 U/liter, and >500 U/liter. Patients with anterior infarction treated with streptokinase have significantly lower enzyme levels, except for those with low ST elevation and absence of Q waves. Patients with high ST elevation and absence of Q waves benefit most. Patients with inferior infarction have similar findings. Patients admitted early, with high ST elevation and Q waves also have significantly lower enzyme levels in the thrombolysis group. Finally, thrombolysis is more effective in patients with a short admission delay.**

corded earlier or later. This is particularly important in patients already admitted to the hospital, who have a severe anginal attack with prominent ST-segment changes. Seventy of our patients were already in hospital. Even after correction of the effect of short interval between onset of chest pain and randomization, this group of 70 patients showed smaller enzymatic infarct size than expected from the height of ST-segment elevation, compared with patients admitted to the coronary care unit after myocardial infarction. It suggests that the degree of ST-segment elevation is higher in the hyperacute phase than in a later period of AMI. Patients with a myocardial infarction admitted from outside the hospital usually did not show much variation of the ST segments, being in a more stable electrocardiographic situation because of the delay caused by the admission. Foerster et al[25] showed that the degree of ST-segment elevation in patients with AMI is stable 1 to 4 hours after the onset of chest pain.

**Q wave:** Important myocardial salvage by thrombolytic therapy was found in patients with new pathologic Q waves, indicating that exclusion of such patients from thrombolytic therapy is incorrect. In patients with anterior AMI with Q waves, we found an important limitation of infarct size, by 820 U/liter HBDH (47%). Early Q waves may not indicate definite loss of myocardial tissue because patients with extensive ischemia can show transient Q waves because of conduction delay in that zone.[26] Cessation of ischemia

**TABLE III Enzymatic Infarct Size, Radionuclide Left Ventricular Ejection Fraction, Electrocardiogram and Time Delay Between Onset of Chest Pain and Admission: Results from Multivariate Regression Analysis**

| Delay | ST Elevation | Q Waves | Median HBDH (U/liter) C | T | Diff | EF* |
|---|---|---|---|---|---|---|
| **Anterior Infarct** | | | | | | |
| <2 hours | Low | − | 970 | 740 | 230 | 4 |
| | Low | + | 1,410 | 590 | 820 | 16 |
| | High | − | 1,940 | 720 | 1,220 | 17 |
| | High | + | 2,070 | 1,330 | 740 | 15 |
| 2-4 hours | Low | − | 880 | 1,110 | −230 | −4 |
| | Low | + | 1,330 | 960 | 370 | 8 |
| | High | − | 1,860 | 1,090 | 770 | 9 |
| | High | + | 1,990 | 1,700 | 290 | 6 |
| **Inferior Infarct** | | | | | | |
| <2 hours | Low | − | 830 | 580 | 250 | 4 |
| | Low | + | 720 | 480 | 240 | 8 |
| | High | − | 1,330 | 860 | 470 | 6 |
| | High | + | 1,450 | 1,110 | 340 | 7 |
| 2-4 hours | Low | − | 860 | 750 | 110 | 5 |
| | Low | + | 750 | 650 | 100 | 8 |
| | High | − | 1,360 | 1,030 | 330 | 6 |
| | High | + | 1,480 | 1,310 | 170 | 8 |

*Differences between thrombolysis and control group.

C = conventionally treated; Diff = difference between conventional and thrombolysis group; EF = left ventricular ejection fraction; HBDH = α-hydroxybutyrate dehydrogenase.

by reopening the occluded coronary artery may prevent further damage in that area. Even after 2 hours thrombolytic therapy limited infarct size in the anterior wall, suggesting that large infarcts are still evolving.

The criteria we used for pathologic Q waves were strict. However, results did not differ if the QRS scoring system proposed by Wagner et al[14] was applied. This system was developed for infarct size estimation in patients with completed myocardial infarction, but appears to be helpful in AMI as well. No or minimal infarct limitation by thrombolytic therapy was found in patients without Q waves in combination with low ST-segment elevation. This was independent of time between onset of chest pain and admission. Such a finding suggests that the occluded artery reopened before treatment, preventing occurrence of high ST-segment elevation and Q waves, when beneficial effect of thrombolysis on infarction size can no longer be expected. Another explanation could be that such patients suffer only from a small infarct, in which case the effect of thrombolytic therapy is minor and not statistically significant.

**Importance of time between onset of chest pain and admission:** In the reported studies[1-3,17-20] interval from onset of chest pain to intervention varied from 3 to 18 hours. An inverse relation between duration of occlusion and subsequent ventricular function has been shown in animal experiments.[27] In humans, this relation was not always found.[19,28] Most studies reported, however, that reperfusion within 4 hours after the onset of symptoms resulted in improvement of left ventricular function[18,29] or a decrease in mortality rate, as shown in the GISSI trial.[2] In the present trial, thrombolysis was started relatively early after onset of symptoms (median 195 minutes), while recanalization was achieved within 4 hours in most patients. This is probably the most important explanation as to why, in our study, streptokinase had such a beneficial effect. As expected from animal studies,[27] we found prominent infarct size limitation in most patients arriving at the hospital within 2 hours after onset of chest pain. As shown by Simoons et al,[4] in patients allocated to conventional treatment, HBDH release was independent of the interval between onset of symptoms and hospital admission. On the other hand, infarct size was reduced with 51% in thrombolysis patients admitted within 1 hour, 31% in those admitted between 1 and 2 hours, and only 13% in those arriving 2 to 4 hours after the start of complaints. In the patients coming to the coronary care unit between 2 and 4 hours after onset of chest pain, subgroups could be identified that did not show limitation of infarct size even after successful reperfusion. This indicates that a time limit of 4 hours is too long for some patients. Although it was apparent that time after onset of chest pain is an important determinant of the outcome of successful thrombolytic therapy, the exact time of onset of pain may be difficult to define. Especially in patients with several attacks of pain, time of onset of myocardial infarction cannot be determined accurately. Accepting these uncertainties, we found that in patients arriving at the coronary care unit between 2 and 4 hours after onset of chest pain, thrombolytic therapy was less successful than in those admitted earlier. After AMI Q waves develop over time. In contrast to this, ST elevation is highest early after the onset of AMI. In patients arriving 2 to 4 hours after the start of complaints with high ST-segment elevation and absence of Q waves, streptokinase was still effective. Incorrect judgment of the time of onset of AMI may explain why these patients still have such significant infarct size limitation.

Another argument for the validity of the electrocardiographic criteria was the correlation between median HBDH values and left ventricular ejection fraction in patients with anterior infarction (Table III). This correlation did not hold for patients with inferior infarction, because the distance of the infarcted area to the collimator is much greater than in anterior infarction. As discussed by Wackers,[30] the contribution of the posteroinferior wall to ejection fraction will be less, resulting in overestimation of ventricular wall motion.

It was mentioned earlier that 33 of 245 patients refused the intervention or were subsequently found to have a contraindication for thrombolysis. They were evaluated according to their original treatment allocation.[10] These 33 patients influence negatively the results of thrombolysis. If they would have been excluded, therapeutic success in terms of infarct size limitation would be greater.

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## Appendix

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