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Extent of Early ST-Segment Elevation Resolution Correlates with Myocardial Salvage Assessed by Tc 99m Sestamibi Scintigraphy in Patients with Acute Myocardial Infarction after Mechanical or Thrombolytic Reperfusion Therapy

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Abbreviations

ACE	Angiotensin-Converting Enzyme
ACVB	Aortocoronary Venous Bypass
AMI	Acute Myocardial Infarction
APSAC	Acylated Plasminogen Streptokinase Activator Complex
CHF	Congestive Heart Failure
CK	Creatine Kinase
CK-MB	Creatine Kinase-MB fraction
ECG	Electrocardiogram
IRA	Infarct-related Artery
LV	Left Ventricle
MCE	Myocardial Contrast Echocardiography
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
rt-PA	recombinant tissue-Plasminogen Activator
SST	Sum of ST-segment elevation
STEMI	ST Elevation Myocardial Infarction
SK	Streptokinase
SPECT	Single Photo Emission Computed Tomography
PCI	Percutaneous Coronary Intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
TIMI	Thrombolysis in Myocardial Infarction
tPA	Tissue-type Plasminogen Activator

1. Introduction

1.1. Historical overview of ST-segment elevation resolution monitoring

In 1969 Braunwald and his coworkers demonstrated that myocardial ischemic injury after coronary artery occlusion is not fixed but can be influenced profoundly by altering the balance between supply and demand of myocardial oxygen (9). In dogs with occluded coronary arteries, the magnitude of ST-segment elevation correlated well with subsequent depression of myocardial creatine kinase activity (71) and with evidence of myocardial necrosis on histologic examination (71, 72). The height of the ST-segment on epicardial electrocardiograms (ECG) was, therefore, utilized as an index of the severity of ischemic injury. In considering how this approach could be utilized clinically, extension from the epicardial to the surface ECG was considered, and a close correspondence between the precordial and epicardial ECG was described (72, 80) (Fig. 1-1).

In the dog with coronary occlusion, myocardial reperfusion was accompanied by rapid normalization of ST-segment elevation (73). A decade later, with the clinical development of thrombolytic therapy for acute myocardial infarction (AMI), similar observations were made in humans (38). ST-segment resolution was subsequently evaluated in a number of studies to determine its accuracy for predicting patency of the infarct-related artery (IRA) (17, 7, 108, 13, 65), but no clear consensus was reached on the utility of this measurement. Thus, coronary angiography has remained the "gold standard" for identifying promising reperfusion regimens that merit evaluation in large phase III trials.

In the last decade, several observations have led to a reappraisal of the utility of ST-segment monitoring after ST elevation myocardial infarction (STEMI). First, Schröder and colleagues (103, 104) showed that ST-segment resolution can predict accurately the risk for death and congestive heart failure (CHF) in patients treated with fibrinolytic therapy. Subsequent studies (105, 2) confirmed a remarkably consistent relationship between the degree of ST segment resolution and subsequent mortality (Fig. 1-2). Second, Ito et al. (60, 58) demonstrated that restoration of normal epicardial blood flow is not sufficient to ensure adequate myocardial reperfusion; the latter requires perfusion at the level of the coronary microcirculation and myocytes.

Novel reperfusion regimens have been developed that incorporate both fibrinolytic and antiplatelet therapies (89, 6, 116), and these therapies may be particularly effective in the coronary microcirculation (85, 20). Resolution of ST-segment elevation is now being used with increasing frequency in clinical trials and patient management as a tool for assessing the efficacy of reperfusion therapy (24).

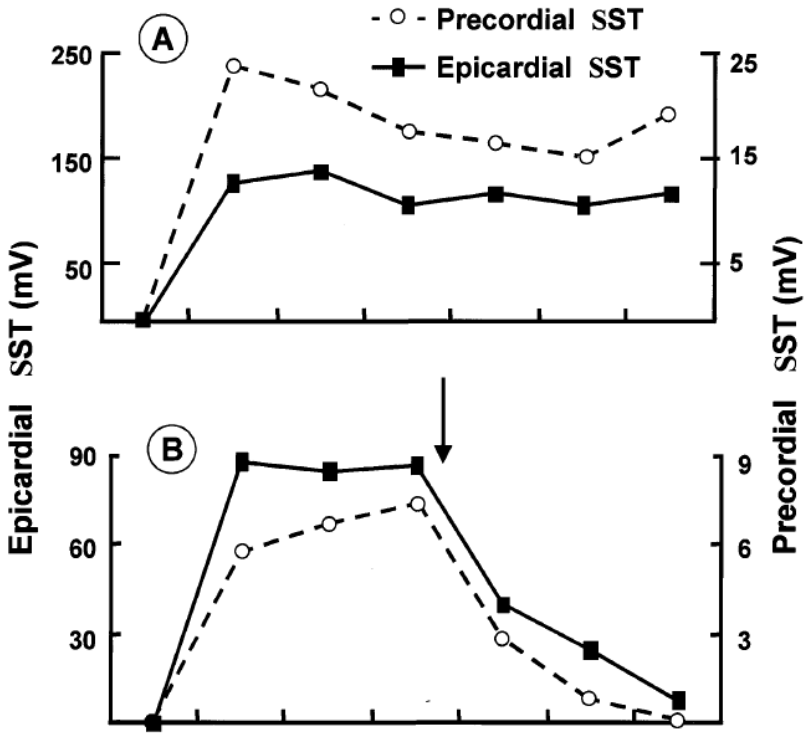

Figure 1-1. Examples of the correspondence between the sum of ST-segment elevations (SST) from epicardial leads and the SST from precordial leads at 5-min intervals after experimental coronary artery occlusion. (A) Correlation between epicardial SST and precordial SST when the occlusion was maintained. (B) Correlation between epicardial SST and precordial SST when one of the two occlusions was release at 15 min (**arrow**). Note the market fall in both epicardial and precordial SST after reperfusion of the larger of the two vessels. Adapted from reference 80.

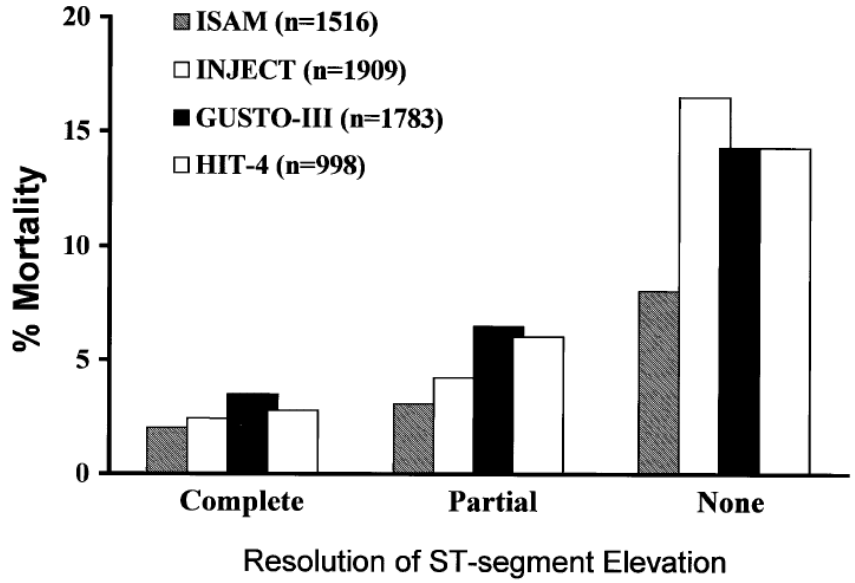

Figure 1-2. ST-segment resolution 180 min after administration of therapy and mortality (at time points between 21 to 35 days) in four trials of thrombolytic therapy in acute myocardial infarction. All studies found statistically significant mortality differences between the three groups of ST resolution. GUSTO-III = Global Use of Strategies to Open Occluded Coronary Arteries III study; HIT-4 = Hirudin for Improvement of Thrombolysis 4 study; INJECT = International Joint Efficacy Comparison of Thrombolytics study; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction. Data abstracted from references 103, 104, 105, 2.

1.2. Background and objectives of the present study

In patients evolving myocardial infarction (MI), the primary goal of various reperfusion strategies is to save the jeopardized myocardium and achieve maximum myocardial salvage. Single photo emission computed tomographic (SPECT) imaging with ^{99m}Tc-sestamibi is considered as the best available measurement tool for infarction size (42). Treatment efficacy, myocardial salvage, can be assessed by performing sequential SPECT imaging with ^{99m}Tc-sestamibi. However, SPECT imaging with ^{99m}Tc-sestamibi is expensive and not universally available. ST-segment elevation resolution has been demonstrated to be a simple and useful means to predict

infarction size, left ventricular function and clinical outcomes after both thrombolytic and coronary interventional approaches (103, 104, 7, 16, 75). Most recently, in the Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI) trial, Angeja et al. (4) showed the association between ST-segment resolution and final infarction size as assessed by SPECT imaging with ^{99m}Tc-sestamibi. However, whether this correlation is the expression of the degree of myocardial salvage achieved with reperfusion therapy remains unclear. In addition, in several studies ST-segment elevation resolution was used to compare the efficacy of different thrombolytic regimens (103, 104). However, there is no study comparing the extent of early ST-segment resolution between primary percutaneous coronary intervention (PCI) and thrombolysis in patients with AMI.

The Stent versus Thrombolysis for Occluded Coronary Arteries with Acute Myocardial Infarction (STOPAMI) 1 and 2 trial (100, 62) have been accomplished in our institute. The STOPAMI 1 trial was designed to assess whether primary coronary stenting combined with the blockade of platelet glycoprotein receptor (abciximab) produces a greater degree of myocardial salvage determined by SPECT imaging with ^{99m}Tc-sestamibi and better clinical outcomes than fibrinolysis with full-dose alteplase. In the trial of STOPAMI 2, 2 reperfusion strategies, primary coronary stenting and fibrinolysis with half-dose alteplase, both combined with abciximab, were compared in patients with AMI with respect to their ability to salvage myocardium determined by SPECT imaging with ^{99m}Tc-sestamibi and clinical outcomes. These 2 reperfusion trials enable us to investigate the unclear issues mentioned above. Accordingly we undertook the present analysis in patients enrolled in the STOPAMI 1 and 2 trials

(1) to evaluate the correlation between extent of early ST-segment resolution and myocardial salvage assessed by SPECT imaging with ^{99m}Tc-sestamibi in patients with AMI after thrombolysis or primary coronary stenting;
(2) to evaluate the association between extent of early ST-segment resolution and mortality;
(3) to compare the extent of early ST resolution between thrombolysis and primary coronary stenting.

2. Methods

2.1. STOPAMI trials

Details of the rationale, design and the main results of the STOPAMI trials were available in the original reports (100, 62). In short, between December 1997 and February 2001, 302 patients with AMI were randomized to receive either primary coronary stenting or thrombolysis in the context of the STOPAMI 1 and 2 trials (100, 62). Primary coronary stenting was accompanied by abciximab as an adjunct therapy (both STOPAMI 1 and STOPAMI 2 trial) and thrombolysis was applied as full-dose alteplase alone (STOPAMI 1 trial) or as half-dose alteplase plus abciximab (STOPAMI 2 trial). The inclusion criteria for the 2 STOPAMI trials were the same: patients presented within 12 hours after the onset of symptoms, had chest pain for at least 20 minutes, and had ST-segment elevation of at least 0.1 mV in two or more limb leads or at least 0.2 mV in two or more contiguous precordial leads on the surface ECG. Patients with contraindications against thrombolytic therapy were excluded in the STOPAMI trials.

Totally 152 patients (71 patients in STOPAMI1 trial, 81 patients in STOPAMI2 trial) were assigned to undergo primary coronary stenting. Placement of coronary stents was carried out according to our previously described method (101). In both trials, the stent implanted was the Multi-link stent (Guidant, Advanced Cardiovascular Systems, Santa Clara, Calif.). In STOPAMI1 trial, during the intervention the patients received abciximab (ReoPro, Lilly Deutschland, Bad Homburg, Germany), given as a bolus of 0.25 mg/Kg followed by a continuous infusion at a rate of 10 μg/minute for 12 hours. In STOPAMI2 trial, before randomization all patients received abciximab given as a bolus of 0.25 mg/Kg of body weight followed by a continuous infusion of 0.125 μg/Kg/minute (up to a maximal dose of 10 μg/minute) for 12 hours.

In STOPAMI1 trial, patients assigned to full-dose alteplase (69 patients) received a bolus dose of 15 mg alteplase (Actilyse, Boehringer Ingelheim, Ingelheim, Germany) followed by a 90-minute infusion in which 0.75 mg/Kg of body weight (maximum dose, 50 mg) was given over a period of 30 minutes, followed by 0.5 mg/kg (maximum dose, 35 mg) over a period of 60 minutes. In STOPAMI2 trial, patients assigned to half-dose alteplase plus abciximab (79 patients) received a bolus dose of

15 mg alteplase followed by an infusion of 35mg over the next 60 minutes. As mentioned above, these patients also received abciximab infusion before randomization. Figure 2-1 and Figure 2-2 illustrated the study protocol of the 2 STOPAMI trials.

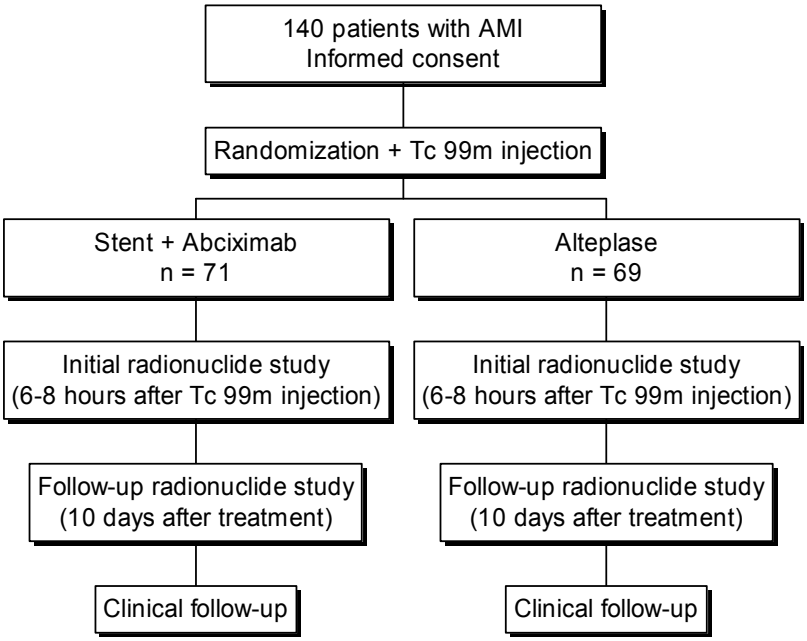

Figure 2-1. The study protocol of the STOPAMI1 trial. AMI, acute myocardial infarction.

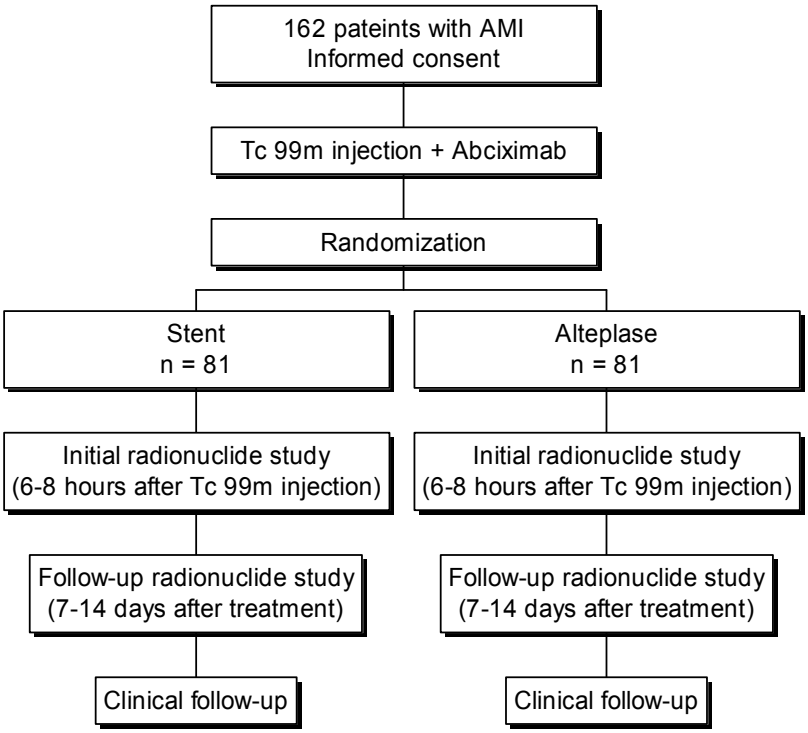

Figure 2-2. The study protocol of the STOPAMI2 trial. AMI, acute myocardial infarction.

In both trials the primary end point was myocardial salvage index assessed by SPECT imaging with ^{99m}Tc-sestamibi. It was found that myocardial salvage index was significantly greater in the stent groups than in the thrombolysis groups (0.57 [0.35, 0.69] vs. 0.26 [0.09, 0.61], $p < 0.001$ for STOPAMI1; 0.60 [0.37, 0.82] vs. 0.41 [0.13, 0.58], $p = 0.001$ for STOPAMI2). In STOPAMI1, the cumulative incidence of death, reinfarction, or stroke at 6 months was lower in the stent group than in the full-dose alteplase group (8.5% vs. 23.2%, $p = 0.02$). In STOPAMI2, the combined incidence of death, recurrent myocardial infarction or stroke at 30 days was lower in the stent group than in the half-dose alteplase plus abciximab group (3.7% vs. 12.3%, $p = 0.04$). It was concluded that in patients with AMI primary coronary stenting plus abciximab leads to a greater myocardial salvage and a better clinical outcome compared to fibrinolysis with or without combination of abciximab.

2.2. Study population of the present analysis

The ST-segment resolution analysis was added to the protocol in September 1998, after the enrollment of the first 37 patients of the overall 302 patients recruited in the 2 STOPAMI trials. Of the 265 patients, 22 were excluded from the present analysis: 7 patients without complete ECG data; 15 patients without interpretable ECG (10 patients had left bundle branch block, 5 patients with idioventricular rhythm). Therefore, 243 patients who underwent either primary coronary stenting (122 patents) or thrombolysis (121 patients: 50 patients without and 71 patients with abciximab infusion) formed the population for the present analysis (Fig. 2-3). Patients with right bundle branch block and ischemic ST-segment elevation were included in the analysis. A 6-month visit to the outpatient clinic was carried out in all eligible patients.

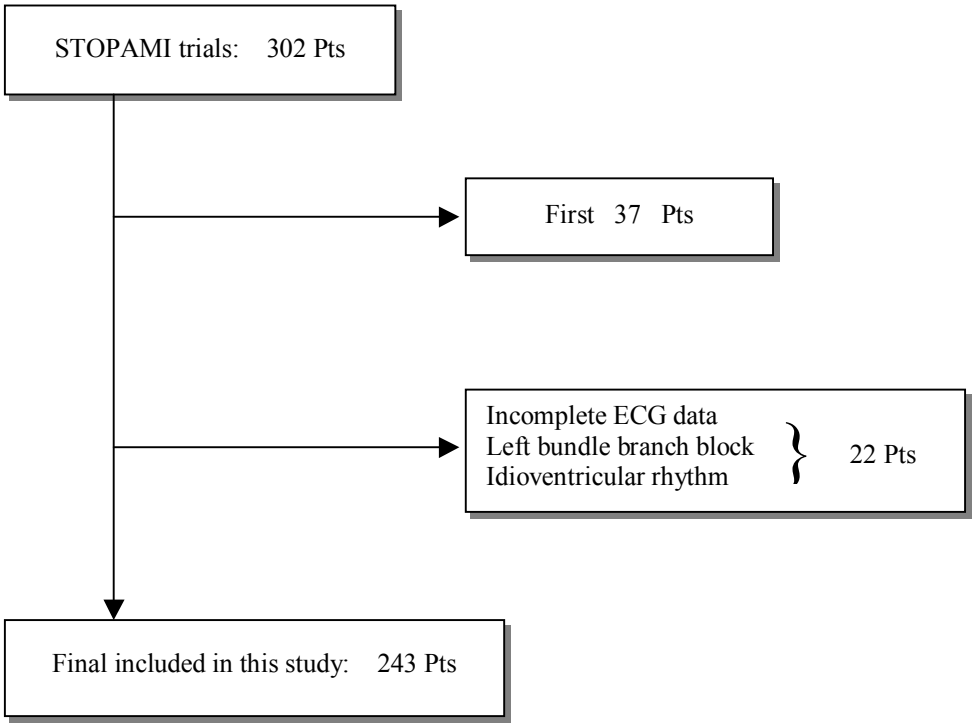

Figure 2-3. Disposition of patients. Pts, patients.

2.3. Electrocardiographic analysis

Standard 12-lead ECGs (i.e. speed 50 mm/sec, scale 1mV = 10 mm) were collected by trained study personnel before and 90 minutes after initiation of reperfusion therapy.

The amount of ST-segment deviation (elevation and/or depression) was measured manually to the nearest 0.05 mV, 20 ms after the J point (end of the ORS complex), with the PR segment as reference baseline for all 12 standard ECG leads (Fig. 2-4). ST-segment elevation was characterized with positive values, whereas ST-segment depression with negative values. The scale was calibrated so that 10 mm was equivalent to 1.0 mV. ST-segment deviation was expressed in mm.

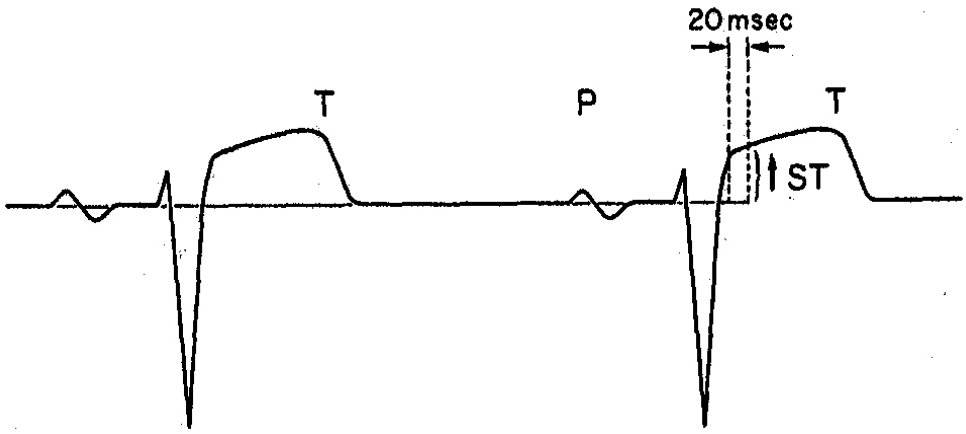

Figure 2-4. Measurement of ST Segment Elevation

As in comparable studies (103, 104, 125), the sum of ST-segment elevation was measured in leads I, aVL, and V1-V6 for anterior, and leads II, III, aVF, and V5-V6 for inferior infarction. Anterior infarction was defined as ST-segment elevation in 2 of the following leads: V1 to V6, I, and aVL. Inferior infarction was defined as ST-segment elevation in 2 of the following leads: II, III, and aVF. If ST-segment elevation was confined to leads V5, V6, I, and aVL, the infarction was defined as anterior unless concomitant ST-segment elevation was also present in leads II, III, or aVF.

ST-segment elevation resolution was expressed by the reduction of the sum of ST-segment elevation between the first ECG and the second ECG, as the percentage of the initial ST-segment elevation (Equation 2-1).

$$STR = \frac{SST1 - SST2}{SST1} \times 100\%$$

STR, ST-segment resolution;
SST1, sum of ST-segment elevation in the first ECG;
SST2, sum of ST-segment elevation in the second ECG.

Equation 2-1. Calculation of ST-segment elevation resolution.

Two most commonly used cutoff points of ST-segment elevation resolution (70% and 30%) were applied. Three groups of ST-segment elevation resolution were defined as complete (≥ 70%), partial (< 70% to 30%) and no resolution (< 30%).

All the measurements were completed by cardiologists who were not aware of assigned treatment and clinical results, using a hand-held caliper with the help of a magnified lens.

2.4. Tc-99m Scintigraphy

Patients received an intravenous injection of 27mCi (1000 MBq) of technetium Tc 99m sestamibi before the initiation of reperfusion therapy. SPECT was performed within 6 to 8 hours after the injection of the radionuclide. A follow-up scintigraphy was performed 7-14 days after treatment. Multihead camera systems with low-energy, high-resolution collimators were used for the radionuclide studies. Images were acquired in a 64-by-64 matrix with an acquisition time of 40 seconds per image. Dedicated software was used to generate transverse slices. A volumetric sampling tool was applied to create polar maps of the relative distribution of activity throughout the left ventricle (81). Each polar map was adjusted for its own maximal value. The size of the defect was calculated with the use of a threshold of 50 percent, which was derived from studies that used a phantom, according to previously described methods (43, 88). This method allowed us to calculate the following three parameters: initial perfusion defect (expressed as a percentage of the left ventricle); final infarction size (perfusion defect at follow-up studies, also expressed as a percentage of the left ventricle); and myocardial salvage index, calculated as the proportion of the initial perfusion defect that was salvaged (initial perfusion defect minus finial infarction size divided by initial perfusion defect) (Equation 2-2).

$$Myocardial\ salvage\ index = \frac{Initial\ perfusion\ defect - Final\ infarction\ size}{Initial\ perfusion\ defect}$$

Equation 2-2. Calculation of myocardial salvage index.

All the measurements were conducted in the scintigraphic core laboratory by investigators who were blind to the reperfusion therapy received and clinical outcomes. The mean (± SD) intraobserver and interobsever variation in the measurement of the size of the defect in this laboratory were 2 ± 3 percent and 2 ± 3 percent of the left ventricle, respectively.

2.5. Statistical Analysis

Descriptive statistics were summarized as mean ± SD for continuous variables, and one-way analysis of variance (ANOVA) was used for comparison of different groups. For categorical variables, the data were summarized as counts or percentages, and Pearson chi square test or Fisher's exact test was used to assess group differences.

Survival curves for different ST-segment resolution groups were estimated according to Kaplan-Meier method; comparisons were made by means of the log-rank test. Thirty-day and 6-month mortality data were 100% complete.

The relations between ST-segment resolution as a continuous variable and final infarction size and myocardial salvage index were assessed by using linear regression analysis. The relation between ST-segment resolution as a continuous variable and 6-month survival was assessed by conducting the Cox regression analysis. The independence of the main relation of this study between ST-segment resolution and myocardial salvage index was checked after adjustment for other factors by using multiple linear regression analysis.

Differences were significant if the two-tailed p value was < 0.05. All analyses were performed with the use of SPSS (version 10.0.1).

3. Results

3.1. Baseline characteristics and mortality in the population of the overall STOPAMI trials and the present analysis

Of the 302 patients enrolled in the STOPAMI trials (100, 62), 243 (80%) were included to the present analysis. The overall STOPAMI trials population and those included in the present analysis are similar in terms of baseline characteristics, 30-day mortality, and 6-month mortality (Tab. 3-1).

Characteristics	STOPAMI trials (N = 302)	Present analysis (N = 243)
Age (yr)	61 ± 13	60 ± 13
Female	76 (25)	59 (24)
Previous MI	38 (13)	29 (12)
Previous ACVB	13 (4.3)	11 (4.5)
Current smoker	147 (49)	118 (49)
Diabetes mellitus	58 (19)	49 (20)
Hypercholesterolemia	211 (70)	181 (75)
Hypertension	189 (63)	154 (63)
Killip class > 2	18 (6)	15 (6.2)
Anterior infarction	147 (49)	121 (50)
Peak CK (IU/ml)	1039 ± 1111	1057 ± 1117
Form of reperfusion regimen Thrombolysis Primary coronary stenting	 150 (50) 152 (50)	 121 (50) 122 (50)
Symptom onset to treatment (min)	258 ± 164	252 ± 160
Initial perfusion defect (% of left ventricle)	31 ± 20	31 ± 20
No. of death at 30 days	15 (5)	10 (4.1)
No. of death at 6 months	23 (7.6)	17 (7.0)

Table 3-1. Baseline characteristics and mortality in the population of the overall STOPAMI trials and the present analysis. Data presented as mean ± SD or number (%) of patients. MI, myocardial infarction; ACVB, aortocoronary venous bypass.

3.2. Baseline characteristics in ST resolution groups

The baseline characteristics of the three ST segment resolution groups are shown in table 3-2. Of the 243 study patients eligible for the present analysis, complete resolution (≥ 70%) was present in 85 (35%) patients, partial resolution (< 70% to 30%) in 80 (33%) patients, and no resolution (< 30%) in 78 (32%) patients on the ECG recorded 90 minutes after initiation of reperfusion therapy.

The three ST-segment resolution groups did not differ in terms of age, female gender, previous MI, previous ACVB, hypercholesterolemia, hypertension, Killip class > 2 at admission, level of peak CK.

Infarction location was unevenly distributed. There were about two-thirds of patients with anterior infarction in no ST-segment resolution group, whereas one-fourth of patients in complete ST-segment resolution group suffered from anterior infarction ($P < 0.001$).

It was noteworthy that the distribution of form of reperfusion regimen was significantly different among the three ST-segment resolution groups ($P < 0.001$). In complete ST-segment resolution group, about two-thirds of patients underwent coronary stenting, and one-third thrombolysis; in no ST-segment resolution group, the situation was reversed.

There was a significant difference among the three ST-segment resolution groups with respect to initial perfusion defect. Compared with patients with complete ST-segment resolution, patients with partial or no ST-segment resolution had significant larger initial perfusion defects ($P = 0.04$).

There was a nonsignificant trend that patients present late were more likely to have partial or no ST-segment resolution.

Characteristics	Complete resolution (N = 85)	Partial resolution (N = 80)	No resolution (N = 78)	P Value
Age (yr)	60 ± 11	61 ± 14	60 ± 13	0.83
Female	22 (26)	20 (25)	17 (22)	0.82
Previous MI	10 (12)	8 (10)	11 (14)	0.73
Previous ACVB	5 (5.9)	2 (2.5)	4 (5.1)	0.55
Current smoker	48 (56)	49 (49)	31 (40)	0.10
Diabetes mellitus	12 (14)	22 (27)	15 (19)	0.10
Hypercholesterolemia	66 (78)	62 (78)	53 (68)	0.27
Arterial hypertension	53 (62)	52 (65)	49 (63)	0.93
Killip class > 2	6 (7.1)	7 (8.8)	2 (2.6)	0.51
Anterior infarction	20 (24)	47 (59)	48 (62)	<0.001
Peak CK (IU/ml)	1069 ± 1393	1104 ± 918	997 ± 966	0.83
Form of reperfusion regimen				< 0.001
Thrombolysis	28 (33)	41 (51)	52 (67)	
Primary coronary stenting	57 (67)	39 (49)	26 (33)	
Symptom onset to treatment (min)	220 ± 131	266 ± 170	272 ± 174	0.07
Initial perfusion defect (% of left ventricle)	27 ± 17	34 ± 20	34 ± 22	0.04

Table 3-2. Baseline characteristics in the three ST-segment resolution groups in the population of the present analysis. Data presented as mean ± SD or number (%) of patients. MI, myocardial infarction; ACVB, aortocoronary venous bypass.

3.3. Myocardial salvage and ST-segment resolution

Of the 243 patients enrolled in the ECG substudy, 217 (89%) underwent both initial and follow-up Tc 99m sestamibi scintigraphy. There was no significant difference among the three ST-segment resolution groups regarding the proportion of patients with paired scintigraphy (94%, 86% and 87% for complete, partial and no ST resolution group, respectively; P = 0.2). Analyses of myocardial salvage were confined to these 217 patients with paired scintigraphy.

3.3.1. Final infarction size

Linear regression analysis revealed that ST-segment resolution as a continuous variable correlated significantly with final infarction size: the larger the extent of ST-segment resolution, the smaller the final infarction size (P < 0.001).

As shown in Figure 3-1, final infarction size was 13% ± 12% of the left ventricle in the group with complete ST-segment resolution, 20% ± 14% in the group with partial ST-segment resolution and 23% ± 19% in the group with no resolution (P < 0.001).

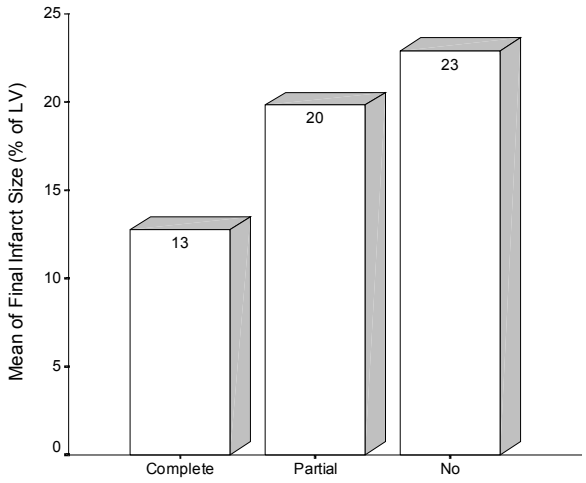

Figure 3-1. Final Infarction size in the three ST-segment resolution groups (P < 0.001). LV, left ventricle.

3.3.2. Myocardial salvage index

There was a correlation between extent of ST-segment resolution as a continuous variable and myocardial salvage index: the larger the extent of ST-segment resolution,

the greater the myocardial salvage index (P = 0.008). Myocardial salvage index was 0.54 ± 0.32 in the group with complete ST-segment resolution, 0.39 ± 0.36 in the group with partial ST-segment resolution and 0.33 ± 0.60 in the group with no resolution (P = 0.01) (Fig. 3-2).

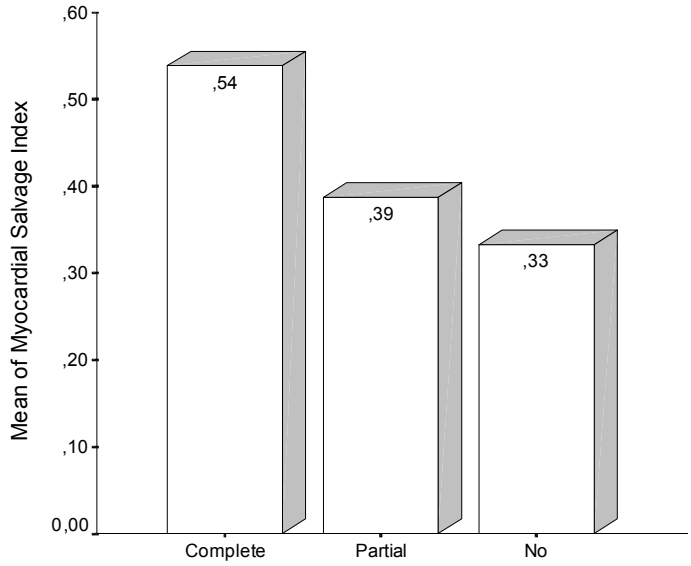

Figure 3-2. Myocardial salvage index in the three ST-segment resolution groups (P = 0.01).

The relation between ST-segment resolution and myocardial salvage index was also assessed in a multivariate model including all baseline characteristics listed in Table 3-2. This model demonstrated that ST-segment resolution was the second strongest predictor of salvage index (P = 0.006) after the form of reperfusion regimen, stenting or thrombolysis (P = 0.002) (Tab. 3-3).

	Coefficient	P Value
Form of reperfusion regimen	0.19	0.002
ST-segment resolution	0.11	0.006
Previous MI	-0.23	0.014
Anterior Infarction	0.15	0.041
Peak CK	-0.0001	0.045

Table 3-3. Predictors for myocardial salvage index. MI, myocardial infarction.

3.4. Mortality and ST-segment resolution

3.4.1. Thirty-day Mortality

During the follow-up of 30 days, no patients died in the complete ST-segment resolution group, whereas 4 patients and 6 patients died in the partial ST-segment resolution and no ST-segment resolution group. As shown in Figure 3-3, 30-day mortality was 0% in the group with complete ST-segment resolution, 5% in the group with partial ST-segment resolution and 7.7% in the group with no ST-segment resolution (P = 0.042). Kaplan-Meier survival curves showed significant mortality differences among the three ST-segment resolution groups with 30-day follow-up (p = 0.044, Fig. 3-4).

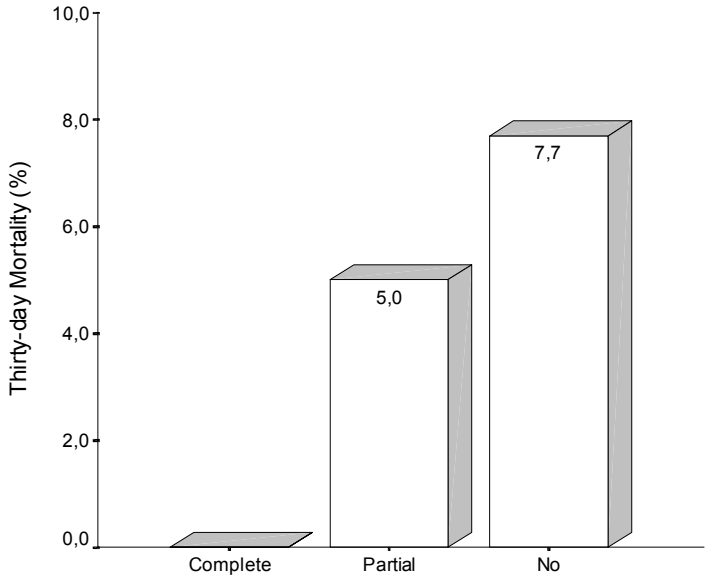

Figure 3-3. Thirty-day mortality in the three ST-segment resolution groups (P = 0.042).

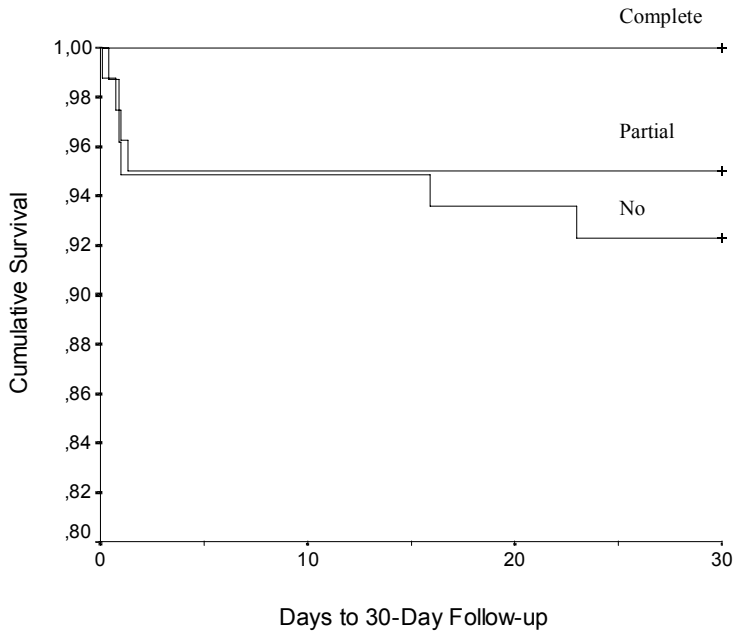

Figure 3-4. Kaplan-Meier survival curves for the three ST-segment resolution groups (P = 0.044).

3.4.2. Six-month Mortality

Cox regression analysis found that ST-segment resolution as a continuous variable correlated significantly with 6-month mortality (P = 0.03). During 6 months follow-up, the number of death was 2, 5, and 10 for complete resolution group, partial resolution group and no resolution group, respectively. Thus, 6-month mortality was 2.4% in the group with complete ST-segment resolution, 6.2% in the group with partial ST-segment resolution and 12.8% in the group with no ST-segment resolution (P = 0.031, Fig. 3-5). Kaplan-Meier survival curves showed significant mortality differences among the three ST-segment resolution groups with 6-month follow-up (P = 0.032, Fig. 3-6).

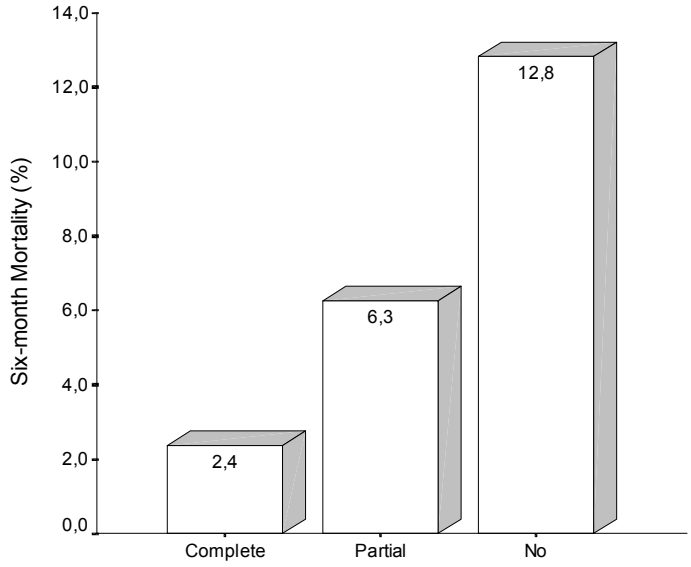

Figure 3-5. Six-month mortality in the three ST-segment resolution groups (P = 0.031).

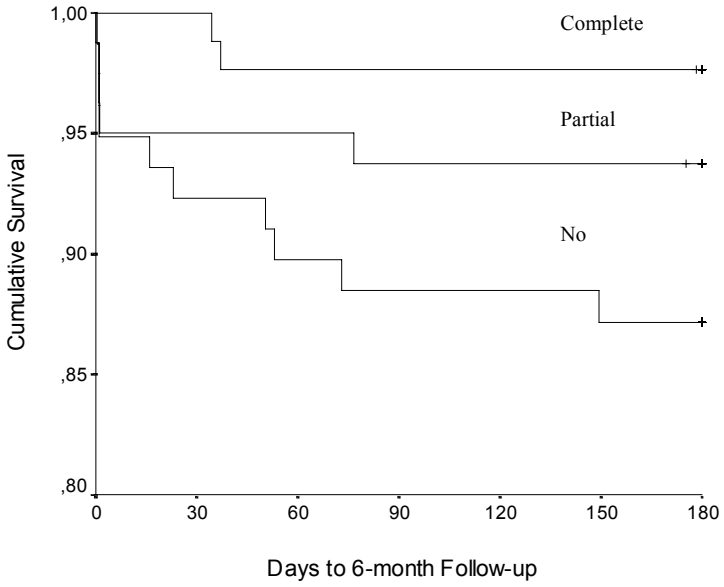

Figure 3-6. Kaplan-Meier survival curves for the three ST-segment resolution groups (P = 0.032).

3.5. Reperfusion strategy and ST-segment resolution

3.5.1. Comparison of baseline Characteristics between thrombolysis and coronary stenting (Tab. 3-4)

Among the 243 patients eligible for ST-segment resolution analysis, 121 patients underwent thrombolysis and 122 patients underwent primary coronary stenting. The interval from symptom onset to treatment was significantly longer in stenting patients than in thrombolysis patients. There was a nonsignificant trend that patients who underwent primary coronary stenting were more likely to suffer from hypercholesterolemia and have heart failure at admission.

There were no significant differences in age, female gender, distribution of infarct location, previous MI, diabetes mellitus, hypertension, and initial perfusion defect between coronary stenting and thrombolysis.

Characteristics	Thrombolysis (N = 121)	Coronary Stenting (N = 122)	P Value
Age (yr)	61 ± 12	60 ± 13	0.480
Female	30 (25)	29 (24)	0.852
Previous MI	18 (15)	11 (9.0)	0.159
Previous ACVB	7 (5.8)	4 (3.3)	0.347
Present smoker	53 (44)	65 (53)	0.139
Diabetes mellitus	23 (19)	26 (21)	0.655
Hypercholesterolemia	84 (70)	97 (80)	0.071
Hypertension	78 (65)	76 (62)	0.726
Killip class > 2	4 (3.3)	11 (9.0)	0.064
Anterior infarction	63 (52)	58 (48)	0.481
Peak CK (IU/ml)	1052 ± 986	1063 ± 1237	0.937
Symptom onset to treatment (min)	224 ± 153	280 ± 163	0.006
Initial perfusion defect (% of LV)	33 ± 20	31 ± 19	0.663

Table 3-4. Baseline characteristics in the two therapeutic groups. Data presented as mean ± SD or number (%) of patients. MI, myocardial infarction; ACVB, aortocoronary venous bypass.

3.5.2. Distribution of ST-segment resolution in reperfusion strategies

As a continuous variable, ST-segment resolution was significantly higher in patients treated with primary coronary stenting than those treated with thrombolysis (53% ± 46% vs. 31% ± 55%, P = 0.001) (Fig. 3-7). Stent-treated patients were more likely to achieve complete ST-segment resolution in comparison of thrombolysis-treated patients (47% vs. 23%, P < 0.001), whereas a significantly higher proportion of patients in thrombolysis group had no ST-segment resolution as compared with patients treated with primary coronary stenting (43% vs. 21%, P < 0.001) (Fig. 3-8).

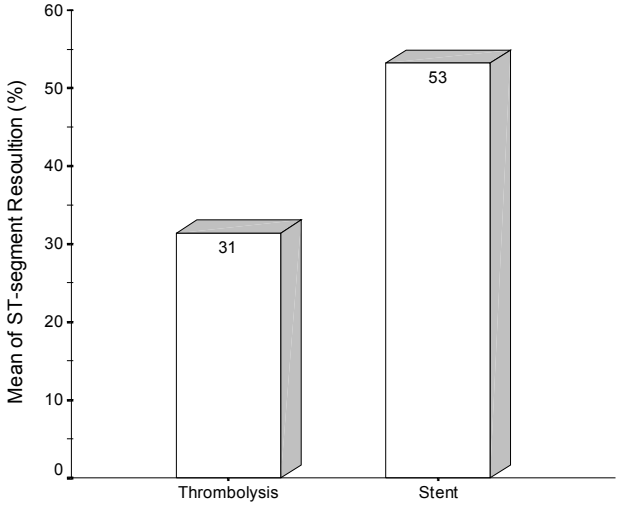

Figure 3-7. Comparison of extent of ST-segment resolution between patients treated with thrombolysis and primary coronary stenting (P = 0.001).

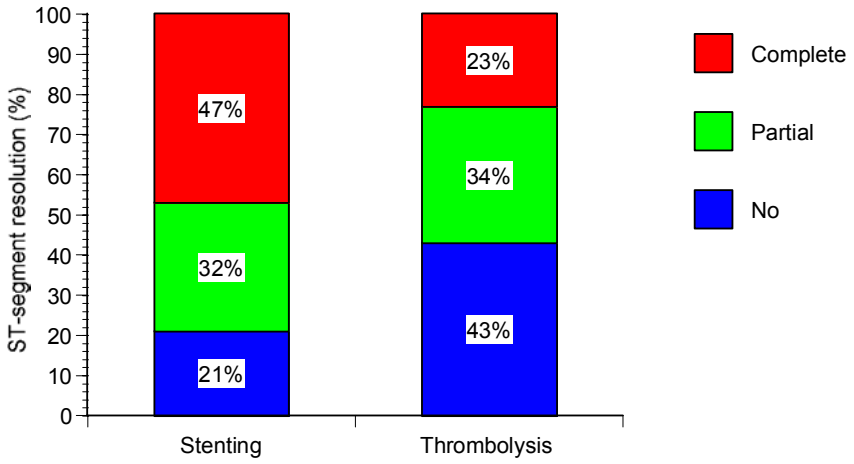

Figure 3-8. Distribution of ST-segment resolution in stenting and thrombolysis patients (P < 0.001)

When the thrombolysis group was further divided into alteplase alone and alteplase plus abciximab, the difference in ST-segment resolution as a continuous variable between these 2 subgroups was not significant (28% ± 60% vs. 33% ± 51%, P = 0.62) (Fig. 3-9). However, there was a nonsignificant trend that patents treated with alteplase plus abciximab was more likely to achieve complete ST-segment resolution than those treated with alteplase alone (28% vs. 16%, P = 0.099) (Fig. 3-10).

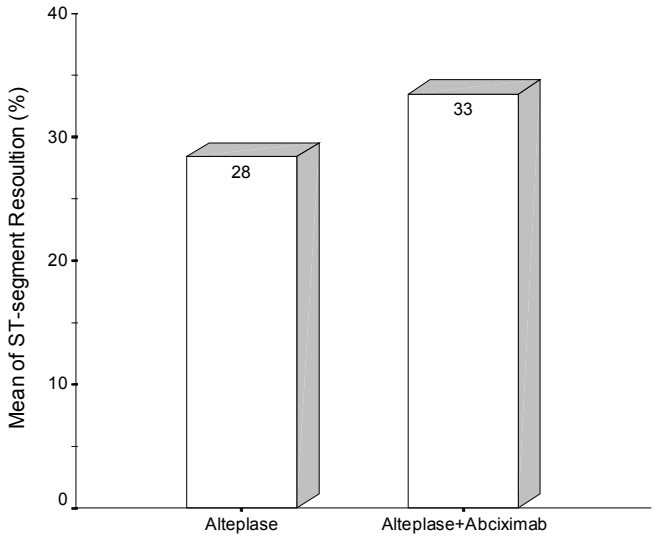

Figure 3-9. Comparison of ST-segment resolution between patients treated with alteplase alone and alteplase plus abciximab (P = 0.62).

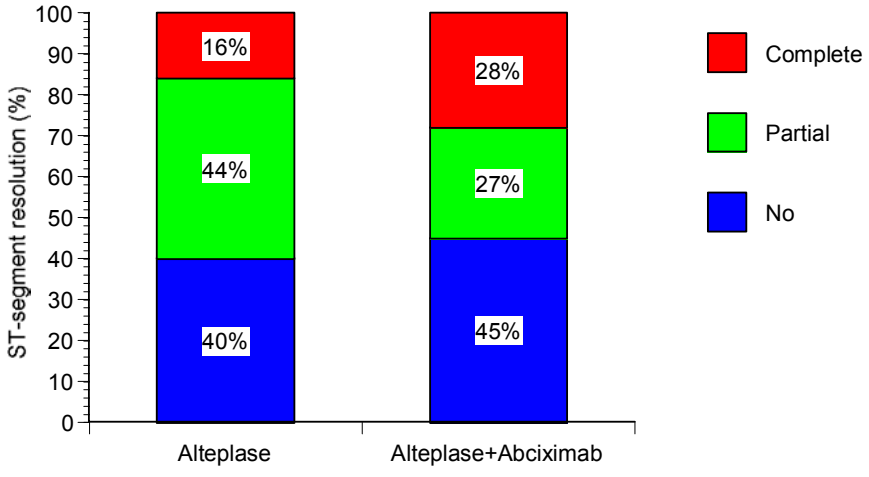

Figure 3-10. Comparison of distribution of ST-segment resolution between alteplase alone and alteplase plus abciximab (P = 0.099).

3.5.3. Myocardial salvage and reperfusion strategy

Compared with thrombolysis, primary coronary stenting was associated with smaller final infarction size (14% ± 12% vs. 22% ± 18% of the left ventricle, P < 0.001) (Fig. 3-11), greater myocardial salvage index (0.54 ± 0.31 vs. 0.30 ± 0.53, P < 0.001) (Fig. 3-12), although there was no significant difference in the initial perfusion defect (Tab. 3-4).

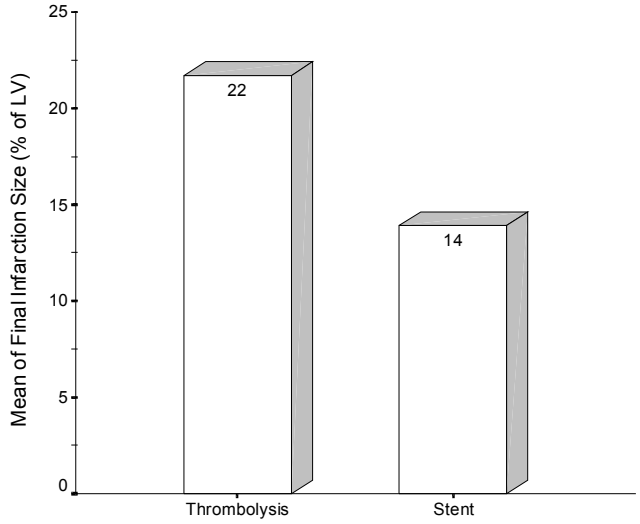

Figure 3-11. Final infarction size in thrombolysis-treated and stent-treated patients (P < 0.001). LV, left ventricle.

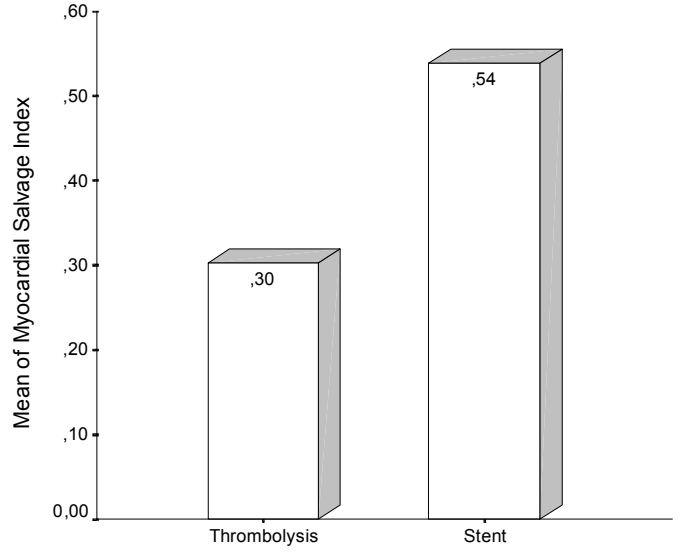

Figure 3-12. Myocardial salvage index in thrombolysis-treated and stent-treated patients (P < 0.001).

Within the group of patients who received thrombolysis, there were no significant differences in initial perfusion defect, final infarction size, and myocardial salvage index associated with administration of abciximab (Tab. 3-5).

	Alteplase (n = 50)	alteplase plus abciximab (n = 71)	P Value
Initial perfusion defect (% of left ventricle)	36 ± 19	31 ± 21	0.280
Final infarct size (% of left ventricle)	25 ± 19	21 ± 18	0.236
Myocardial salvage index	0.25 ± 0.57	0.34 ± 0.51	0.422

Table 3-5. Comparison of myocardial salvage between alteplase and alteplase plus abciximab.

3.5.4. Mortality and reperfusion strategy

The 30-day mortality for thrombolysis patients and for coronary stenting patients was 6.6% and 1.6%, respectively (p = 0.06) (Fig. 3-13). After 6 months follow-up, coronary stenting was associated with a significantly lower mortality as compared with thrombolysis (3.3% vs. 10.7%, P = 0.023) (Fig. 3-14). Kaplan-Meier survival curves showed significant mortality differences among the three ST-segment resolution groups with 6-month follow-up (P = 0.022) (Fig. 3-15).

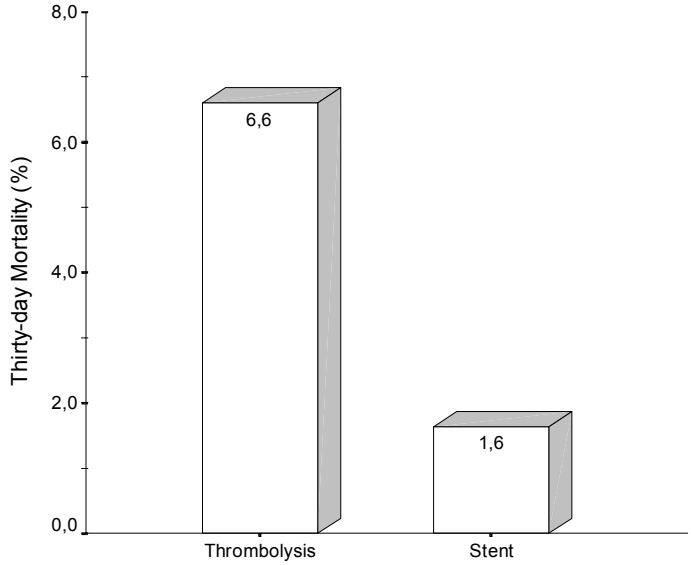

Figure 3-13. Thirty-day mortality in thrombolysis and stent patients (P = 0.06).

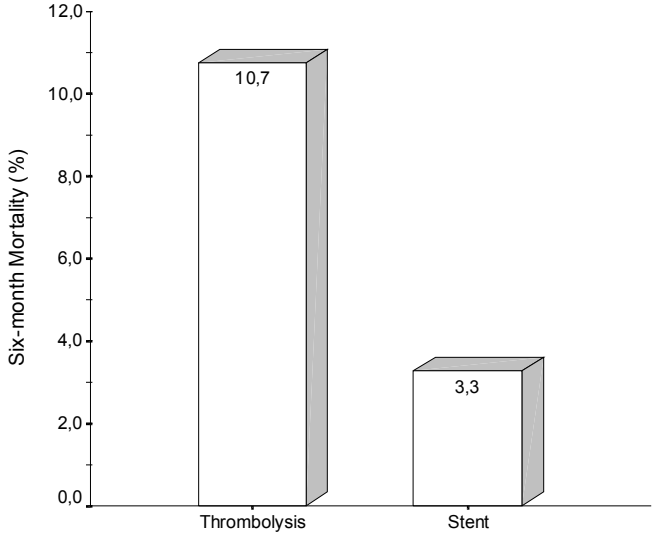

Figure 3-14. Six-month mortality in thrombolysis and stent patients (P = 0.023).

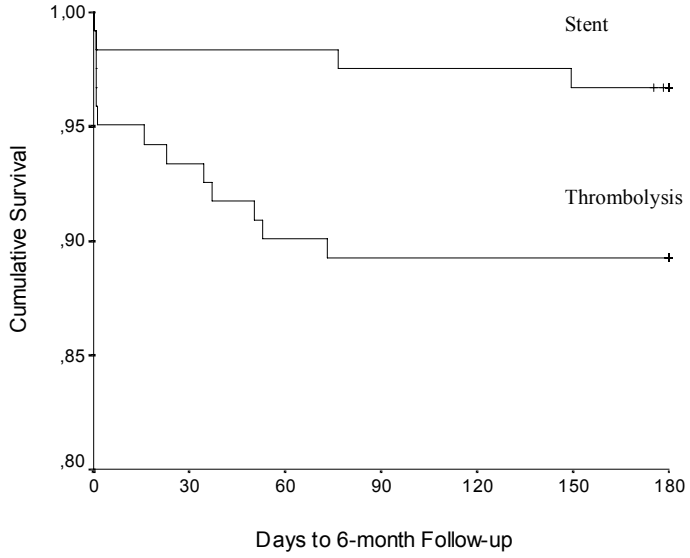

Figure 3-15. Kaplan-Meier survival curves for the two reperfusion groups (P = 0.022).

The analyses were repeated after further dividing thrombolysis patients into alteplase alone and alteplase plus abciximab. No significant differences were found in terms of 30-day and 6-month mortality between these 2 subgroups (Tab. 3-6).

	Alteplase (n = 50)	Alteplase plus abciximab (n = 71)	P Value
30-day mortality	3 (6%)	5 (7%)	1
6-month mortality	6 (12%)	7 (9.9%)	0.708

Table 3-6. Comparison of 30-day and 6-month mortality between alteplase and alteplase plus abciximab.

4. Discussion

4.1. Main findings in the present analysis

To the best of authors' knowledge, the present analysis is the first study to investigate the correlation between extent of ST-segment resolution and degree of myocardial salvage determined by SPECT imaging with ^{99m}Tc-sestamibi in patients with AMI after reperfusion therapy. In this study we found patients with larger extent of ST-segment resolution were more likely to achieve greater degree of myocardial salvage and, consequently, better survival at 30 days and 6 months. In addition, primary coronary stenting was associated with larger extent of ST-segment resolution as compared with thrombolysis. The extent of ST-segment resolution was a sensitive parameter to identify the superiority of stenting over thrombolysis as a reperfusion strategy in patients with AMI.

4.2. ST-segment resolution in assessing the efficacy of reperfusion therapy

4.2.1. Historical background of reperfusion therapy

The first clinical description of acute coronary thrombosis as the cause for AMI was published by Herrick in 1912 (54). Over the next few decades, controversy raged as to whether the clot formed after death and was merely a postmortem finding. In the late 1970s De Wood and colleagues reported that a thrombus was observed in the IRA in nearly 90% of patients undergoing acute coronary artery surgery in the first few hours after the onset of AMI (27). Thereafter acute thrombosis of a major epicardial coronary artery as the cause of AMI was widely accepted. Restoring flow by either thrombolysis or mechanically, with so called primary PTCA or stenting is referred to as recanalization of the IRA. In the past decade, key advances in the treatment of AMI have arisen from the "open artery theory" that timely, complete reperfusion of IRA is a major determinant of outcome (10).

4.2.1.1. Thrombolysis

The first use of intravenous thrombolytic therapy in patients with AMI was reported in 1958 (35). Over the next 25 years, 24 randomized studies of intravenous thrombolytic therapy in AMI were conducted, using primarily regimens with 12- to 24-hour infusions of streptokinase (133). The results varied from statistically

significant benefit to no suggestion of benefit. By modern standards these trials had major design flaws, including low doses of streptokinase and inclusion of patients up to 72 hours after symptom onset. As a result of these discouraging studies, thrombolytic therapy was rarely used in clinical practice. In the late 1970s, there was a reawakening of interest in thrombolytic therapy for AMI, initially directed at intracoronary administration. Chazov et al. (14) were the first to demonstrate angiographically the clot lysing effect of intracoronary thrombolytic therapy in patients with AMI and occluded infarct vessels. These findings were confirmed by Rentrop and coworkers in Göttingen (94). Since the concept of intracoronary application of thrombolysis requires a catheter laboratory, which is not available in most hospitals, intravenous thrombolysis was reevaluated using short-term administration of high-dose streptokinase (82, 102). It could be angiographically demonstrated that intravenous streptokinase was effective in the restoration of bloodflow in occluded infarct vessels.

Widespread acceptance of thrombolysis was reached after the demonstration of reduced mortality after intravenous application of thrombolysis in the large randomized trials (Fig. 4-1), in particular the GISSI-1 and ISIS-2 trials (5, 56). However, there remained doubts about which agent was the most effective. A comparison of Streptokinase and alteplase (the Italian GISSI-2 study (51)), showed post-MI mortality of 8.5% with Streptokinase and 8.9% with alteplase; the ISIS-3 study (57) suggested there was no important difference between the effects of Streptokinase, anistreplase, or alteplase. However, doubts about whether heparin had been used in the most effective regimen in GISSI-2 and ISIS-3, as well as a change in the dosing regimen for alteplase, led to the GUSTO I study, which showed alteplase to be the most effective agent (120). In addition to development of newer thrombolytic agents that result in higher rates of early coronary arterial patency and lower rates of bleeding complication, reduced-dose thrombolytic therapy in combination with administration of a glycoprotein IIb/IIIa inhibitor was shown to be able to restore antegrade flow as effectively as full-dose thrombolytic therapy but is associated with lower rates of reocclusion and reinfarction (123).

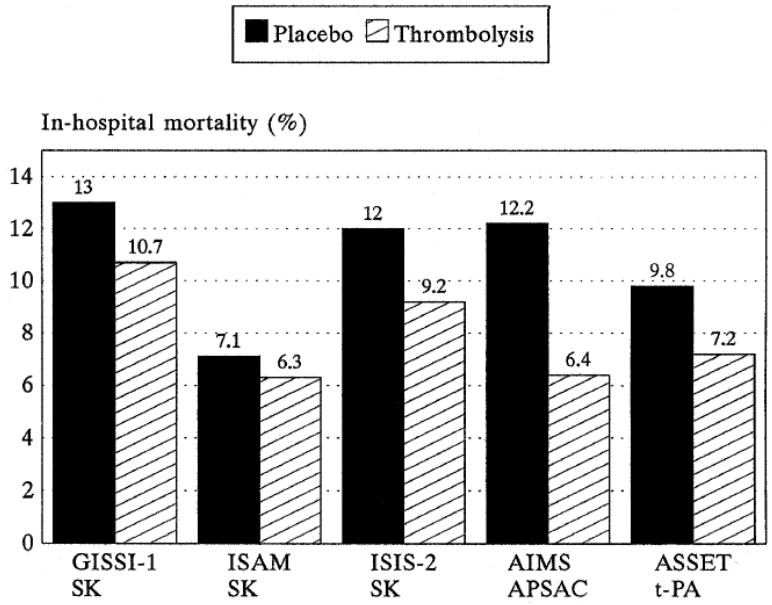

Figure 4-1. In-hospital mortality in patients with acute myocardial infarction treated with thrombolysis (SK = streptokinase, t-PA = tissue-type plasminogen activator, APSAC = acylated plasminogen streptokinase activator complex) or placebo in randomized trials.

4.2.1.2. Primary PTCA or stenting

The first large series of patients treated with primary angioplasty for AMI were published in the early 1980s (53). The rationale of primary PTCA was to increase the patency rate of IRA, reduce the incidence of reocclusion, and avoid the risk of severe bleeding complications associated with thrombolysis. It was introduced as routine clinical practice in many interventional departments worldwide after three papers on direct angioplasty appeared in a 1993 issue of the New England Journal of Medicine (50, 135, 41). A more "real world" view of primary PTCA derives from large registries, e.g., the Direct-PTCA Registry of the Arbeitsgemeinschaft Leitender Kardiologishcer Krankenhausärzte (ALKK) (127). The registry contains 4,280 primary PTCA procedures performed in 80 centers in Germany between July 1994 and October 1998. The success rate of PTCA, as defined by TIMI-3 patency of the infarct vessel, was 87%, the in-hospital mortality was 10.2% and the reinfarction-rate was 2.6%. The most powerful predictors of death were cardiogenic shock present in 14.6% of whom 47% died, and failed PTCA with a mortality of 32%. The success rates are clearly below those of early randomized studies reporting up to 97% TIMI 3 flow. The results of the ALKK registry are similar to the data of the GUSTO-2

angioplasty substudy (119) and the registry of the MITI group (30), based on a diverse range of hospitals like the ALKK registry.

As compared with thrombolytic reperfusion in AMI, primary PTCA increases the rates of patency of the IRA, improve survival rates, and reduces the rates of reinfarction and stroke (130, 136, 87). However, dissection and residual luminal narrowing after PTCA may result in early or late reocclusion or restenosis (114). In this regard, the mechanical scaffolding properties of coronary stents (106, 34) may be expected to enhance outcomes. Most recently, the controlled abciximab and device investigation to lower late angioplasty complication (CADILLAC) investigators (115) demonstrated that as compared with primary PTCA, the placement of one or more stents in patients with AMI does not reduce the likelihood of early adverse events (death, reinfarction, or the need for urgent revascularization), even if a glycoprotein IIb/IIIa inhibitors is given concomitantly, but it does diminish the likelihood that restenosis will develop within the next 6 months, necessitating another revascularization procedure.

4.2.2. Assessment of efficacy of reperfusion therapy

Successful reperfusion after AMI has traditionally been considered to be restoration of epicardial patency, but increasing evidence suggests that disordered microvascular function and inadequate myocardial tissue perfusion are often present despite infarct vessel patency. Thus, optimal reperfusion is being redefined to include intact microvascular flow and restored myocardial perfusion, as well as sustained epicardial patency (95). Therefore, assessment of efficacy of reperfusion strategy includes 2 levels: epicardial reperfusion and myocardial reperfusion.

4.2.2.1. Assessment of epicardial reperfusion

4.2.2.1.1. TIMI-flow grading

The gold standard for the assessment of epicardial reperfusion is clearly direct angiographic visualization of the IRA. The TIMI-flow grading (122) has been the generally accepted measure to describe the quality of antegrade flow beyond the infarct related lesion, and it has been shown to be closely correlated to survival in

several thousands of patients (32). TIMI 0 flow signifies no penetration of contrast beyond the clot in the IRA; TIMI 1 flow refers to flow of contrast past the vessel occlusion, but no contrast fills the terminal portion of the vessel (penetration without perfusion); TIMI 2 flow signifies contrast filling of the IRA to the full length, but slower than adjacent vessels (inadequate perfusion); and TIMI 3 is normal filling of IRA in comparison with adjacent vessels. Initially TIMI 0 and 1 flow were deemed to be failure of reperfusion, while TIMI 2 and 3 were considered to be similar and denote successful reperfusion. Subsequently, clinical trials have proven this interpretation to be misleading. Despite restoring some tissue-level perfusion, mortality outcome for patients with TIMI 2 flow at 90-min angiography was found to be intermediate between TIMI 0 or 1 flow and TIMI 3 flow (but closer to TIMI 0/1) (69, 48, 110).

A major draw back of angiography is the invasive nature of the method precluding its routine use both because it is unavailable for most patients and because of an increased risk of bleeding during thrombolytic treatment. Other indices of reperfusion such as the rate of enzyme rise and the resolution of ST-segment elevation have, therefore, been extensively investigated (13).

4.2.2.1.2. Rate of enzyme rise

The sensitivity and specificity of enzyme kinetics for the prediction of early and complete reperfusion in the individual patient, however, are very limited, and their predictive value can be improved only to a limited extent by inclusion of symptom relief. Furthermore, the release of most enzymes apart from myoglobin is too slow to help for decision making with regard to reperfusion strategies. The most widely used CK-MB takes up to 14 hours to reach its peak serum level in case of early reperfusion, and even more when the infarct artery remains occluded. Similar rates of rise are observed for troponins, which make these enzymes clearly unsuitable for an assessment of early reperfusion.

4.2.2.1.3. ST-segment elevation resolution

Because ST-segment elevation resolution can be readily obtained in all patients with ST-segment elevation, it has been extensively evaluated for assessment of epicardial reperfusion after reperfusion therapy (17, 7, 108, 13, 65). Early studies were limited by small size, the use of different measurement techniques and definitions for ST-segment resolution, varying time points for ECG and angiographic measurements and the retrospective definition of thresholds for ST-segment resolution. Despite these

important methodologic differences, the aforementioned studies yielded remarkably similar results, suggesting that ST-segment resolution is a highly accurate predictor of infarct artery patency (positive predictive value ≥ 90%) but inaccurate for predicting IRA occlusion (negative predictive value approximately 50%) (13, 65, 66, 55, 90).

In the largest studies comparing angiographic measures of reperfusion with simultaneous measurements of ST resolution, a significant stepwise correlation has been observed between greater ST-segment resolution and higher rates of IRA patency and TIMI grade 3 flow (134, 21)(Fig. 4-2). After tissue plasminogen activator (tPA), 35% to 40% of patients achieve complete (≥ 70%) ST-segment resolution 90 min after therapy, as defined using Schröder's criteria (20, 84); in contrast, after streptokinase, only approximately 25% of patients achieve complete ST-segment resolution at 90 min (105). By 180 min, differences between the two agents are no longer apparent, as tPA and streptokinase each achieve complete ST-segment resolution in approximately 59% of patients (84, 105).

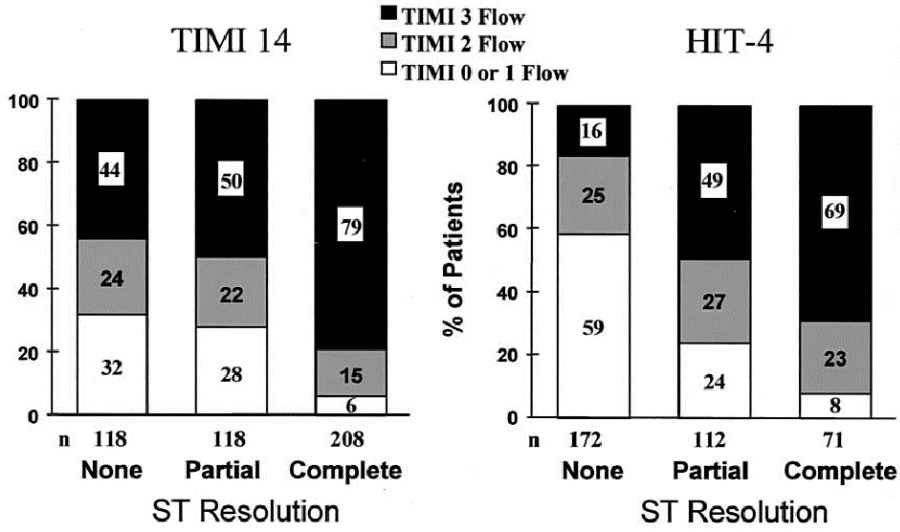

Figure 4-2. ST-segment resolution versus Thrombolysis In Myocardial Infarction (TIMI) flow grade. The reperfusion regimens used in the TIMI-14 substudy were tissue plasminogen activator (tPA) and combinations of abciximab plus reduced-dose tPA, whereas the fibrinolytic agent used in Hirudin for Improvement of Thrombolysis study (HIT-4) was streptokinase. $P < 0.001$ for the correlation between ST-segment resolution and TIMI 3 flow; $p < 0.001$ for correlation between ST-segment resolution and infarct-related artery patency (TIMI 2 + 3 flow). Adapted from references 134, 21.

Despite differences between tPA and streptokinase in the proportion of patients who achieve complete ST-segment resolution 90 min after therapy, the correlation between ST-segment resolution and epicardial blood flow at 90 min is similar for the two drugs (Fig. 4-2). Patients with complete ST-segment resolution at 90 min have a 92% to 94% likelihood of IRA patency and a 70% to 80% probability of TIMI grade 3 flow (134, 21). However, the absence of ST-segment resolution dose not accurately predict an occluded IRA in that approximately 50% of patinas with no (< 30%) ST-segment resolution still have a patent IRA (134, 21). Previously, the absence of ST-segment resolution despite a patent IRA had been considered to be a false positive of the 12-lead ECG. As will be discussed in the following text, in such patients, the ECG, rather than the angiogram, may better reflect the adequacy of myocardial reperfusion.

Patients with TIMI grade 3 flow demonstrate significantly greater ST-segment resolution than patients with TIMI grade 2 flow (90, 134, 21, 61) (Fig. 4-3). Yet, among patients with complete (≥ 70%) ST-segment resolution, the probability of TIMI grade 3 flow is only 70% to 80% (vs. an approximately 95% probability of TIMI grade 2 + 3 flow). Thus, while "complete" ST-segment resolution confirms that the infarct artery is patient, it does not confirm that TIMI grade 3 flow is present with > 80% accuracy (90, 134) (Fig. 4-2). However mortality appears to be similar between patients with TIMI grade 2 flow and TIMI grade 3 flow if they have similar degrees of ST-segment resolution (21).

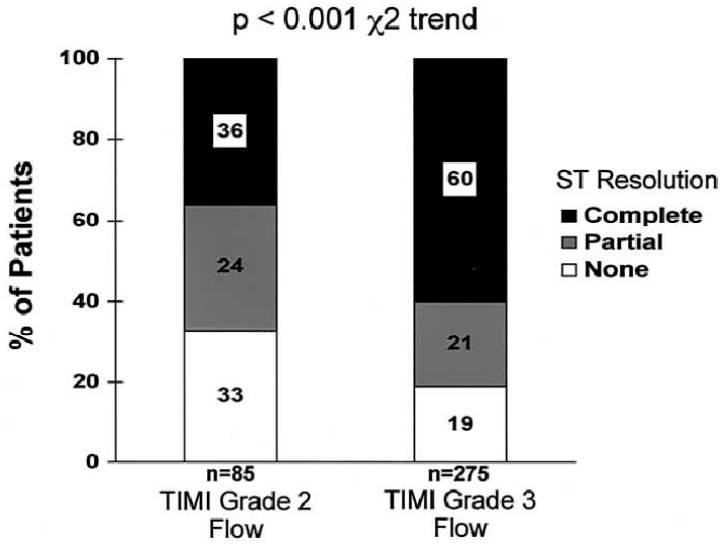

Figure 4-3. Differences in ST-segment resolution between patients with Thrombolysis In Myocardial Infarction (TIMI) grade 2 and TIMI grade 3 epicardial blood flow. Adapted from reference 21.

4.2.2.2. Assessment of myocardial reperfusion

Although restoration of TIMI flow grade 3 has been used as the gold standard for reperfusion success, distal coronary flow can vary considerably despite flow grade 3 in the epicardial vessel (46). Approximately 25% of patients with restoration of normal antegrade flow in the epicardial IRA, however, do not have reperfusion of the myocardium at the tissue level (60). Using myocardial contrast echocardiography (MCE), it has been demonstrated that many patients with successful epicardial reperfusion have "no reflow" at the level of the coronary microcirculation and myocardium (60). Patients with TIMI grade 3 flow in the infarct artery, but no-reflow at the tissue level, have poor recovery of left ventricular function after AMI and are at high risk for the development of congestive heart failure (CHF) and death (60). Promising diagnostic tests that focus on the identification of patients with microvascular dysfunction after epicardial reperfusion may complement TIMI flow grading. Techniques now available that are sensitive to microcirculatory flow and have been validated will be discussed in the following text.

4.2.2.2.1. Myocardial contrast echocardiography

Using MCE, contrast injections before establishing patency of the IRA can define the area of myocardium at risk and establish a baseline for determining the adequacy or extent of myocardial reperfusion. MCE perfusion patterns have been correlated with TIMI flow grades. Ito et al. (59) showed that 18 of 18 patients with TIMI 2 flow after IRA recanalization displayed reduced myocardial perfusion on MCE, as defined by a ration of contrast defect area (postcanalization to precanalization) > 25%. More importantly, 11 of the 68 patients (16%), despite having TIMI 3 flow by angiography, showed reduced myocardial reperfusion. Patients with TIMI 3 epicardial flow but reduced myocardial perfusion on MCE had a reduced wall motion score and ejection fraction at 28 days as compared with patients with normal myocardial perfusion by MCE. Importantly, such patients had clinical outcomes similar to patients with TIMI 2 flow. Other studies (93, 60) have confirmed these findings, and demonstrated that not only is there dissociation between epicardial flow and myocardial perfusion but there is also significant correlation with myocardial perfusion and resultant left ventricular function. Until recently, a major limitation to the routine use of MCE was that intracoronary injections of echo contrast were needed. New contrast agents that can be injected intravenously are being developed, but have not been adequately tested in a large cohort of patients with acute MI (92, 91).

4.2.2.2.2. Coronary Doppler flow wires

Coronary Doppler flow wires can be used to measure coronary flow velocity and coronary flow reserve after epicardial reperfusion in order to estimate the degree of microvascular dysfunction in the infarct zone. Disruption of coronary flow velocity and reserve after successful epicardial reperfusion appears to predict recovery of regional left ventricular function and contractile reserve (124, 117). Myocardial tissue perfusion cannot be assessed directly with coronary Doppler flow wires, however, coronary angiography is required, and the reproducibility of this technique has not been studied.

4.2.2.2.3. Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) appears to be one of the most comprehensive imaging techniques used to evaluate microvascular dysfunction, because it can be used to assess coronary flow, myocardial tissue perfusion, left ventricular volumes and regional and global left ventricular function (132, 12). However, high costs, long procedure times and the inability to accommodate unstable patients are significant limitations of cardiac MRI.

4.2.2.2.4. TIMI myocardial perfusion

TIMI myocardial perfusion is an angiographic method that assesses the filling and clearance of contrast in the myocardium (47). TIMI myocardial perfusion grades are defined as follows: (1) grade 0 is defined as no apparent tissue-level perfusion (no ground glass appearance of blush or opacification of myocardium) in the distribution of the culprit artery; (2) grade 1 indicates presence of myocardial blush but no clearance from the microvasculature (blush or stain is present on the next injection); (3) grade 2 blush clears slowly (blush is strongly persistent and diminishes minimally or not at all during 3 cardiac cycles of the washout phase); and (4) grade 3 indicates blush begins to clear during washout (blush is minimally persistent after 3 cardiac cycles of washout). Gibson et al. (47) founded that even among patients with epicardial TIMI 3 flow, TIMI myocardial perfusion grade had prognostic significance with highest mortality in the TIMI myocardial perfusion grade 0 patients and lowest in patients with TIMI myocardial perfusion grade 3. Therefore, refinement of the angiographic characterization of reperfusion has emphasized the importance of restored myocardial tissue perfusion in determining the ultimate success of reperfusion strategies (18) (Fig. 4-4). However, angiography is a “snapshot”

technique that may not adequately assess the continuum of reperfusion; it is also expensive and cannot be performed early at most hospitals (70).

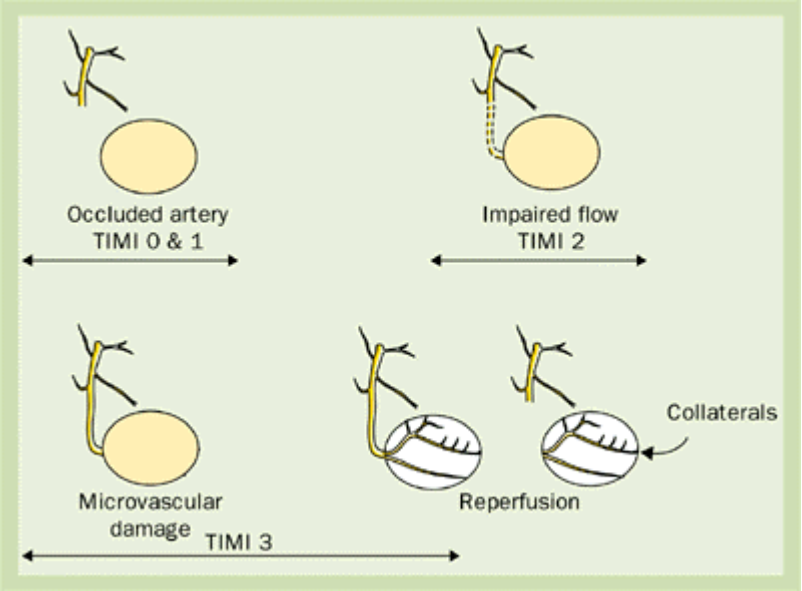

Figure 4-4. Stages of successful reperfusion depicted with angiographic techniques. As epicardial patency is re-established, tissue perfusion is restored if microvascular damage is not present. Adapted from reference 18.

4.2.2.2.5. Technetium-99m-sestamibi SPECT

During the early hours of acute myocardial infarction, evaluation of myocardial perfusion is of interest in patients who have reperfusion therapy. Serial myocardial perfusion imaging can demonstrate a decrease in myocardial perfusion defect size over time in patients who had successful reperfusion. Imaging with 201Tl is not practical in this setting. Because of 201Tl redistribution, myocardial imaging has to be performed before initiation of therapy. This would cause a clinically unacceptable delay in treatment. A more practical approach is the use of 99mTc-sestamibi. Because of the lack of significant redistribution, this imaging agent can be injected before initiation of reperfusion therapy, and imaging of myocardial perfusion can be performed later using SPECT imaging in the nuclear cardiology laboratory (43, 128, 97, 19, 8, 31). Gibbons et al. (43) and Wackers et al. (128) showed that successful

thrombolysis of the infarct artery can be predicted by a decrease of the size of myocardial perfusion defects on serial 99mTc-sestamibi imaging.

The noninvasive demonstration of successful myocardial reperfusion by thrombolysis could be useful in defining management of individual patients. For example, patients who apparently had failure of thrombolytic therapy (i.e., no change in myocardial perfusion defect) may be candidates for a more aggressive and invasive approach, whereas patients who had apparently successful reperfusion, as demonstrated by improvement of myocardial perfusion, may be more appropriate candidates for conservative management.

Serial myocardial perfusion imaging with sestamibi has provided new insights on the pathophysiology of acute human myocardial infarction. Gibbons et al. conducted a series of important clinical studies with sestamibi in patients with acute infarction. Their experience can be summarized as follows. The myocardial area at risk varies greatly in individual patients (43, 128). Little correlation exists between extent of the risk area as demonstrated with sestamibi imaging and the anatomic site of occlusion of the infarct artery, i.e., distal or proximal (45). The area at risk in acute anterior myocardial infarction is usually larger than that in acute inferior infarction (15). Patients with collateral coronary circulation to the infarct artery have smaller ultimate infarct size than patients without collateral vessels (15).

Serial myocardial perfusion imaging with 99mTc-labeled myocardial perfusion imaging agents is now recognized as a potentially useful clinical research tool to assess the efficacy of various reperfusion strategies in acute myocardial infarction (40). The patient serves as his own control, and fewer patients needed to be recruited for a clinical trial. In a comparative trial of primary angioplasty versus thrombolysis for acute myocardial infarction, Gibbons et al. (41) demonstrated with acute sestamibi imaging that the area at risk in both patient groups was the same.

Although cumulative infarct size measurement with ^{99m}Tc-sestamibi SPECT appears to be a promising technique to determine left ventricular damage and the amount of myocardial salvage after reperfusion therapy (78, 42), it is not commonly available and much technically demanding. In addition, initial ^{99m}Tc-sestamibi SPECT imaging is sometimes difficult to perform while treating AMI.

4.2.2.2.6. ST-segment resolution — a bedside marker of myocardial and microvascular reperfusion

ST-segment resolution appears to reflect restoration of myocardial tissue perfusion, not just epicardial flow. Rapid ST-segment resolution within 30 to 60 min of successful primary angioplasty (patent IRA with TIMI flow grade 3) predicts greater improvement in ejection fraction, reduced infarction size and improved survival as compared with delayed ST-segment resolution (75, 16, 96, 125). Microvascular dysfunction may explain these findings because rapid ST segment resolution after successful primary angioplasty correlates with microvascular reflow into the infarction region as measured by MCE (98). Studies using angiographic "blush" scores have shown that, among patients with normal epicardial blood flow, persistent ST-segment elevation is usually indicative of impaired tissue and microvascular perfusion (126, 26). Using technetium-99m tetrofosmin SPECT, Watanabe et al. demonstrated that persistent ST-segment elevation 30 min after successful PTCA is a highly specific electrocardiographic marker of impaired microvascular reperfusion in patients with AMI (129).

Since none of the aforementioned imaging tests is readily available to the clinician at the bedside, ST-segment resolution has re-emerged as a simple and universally available means of assessing tissue-level reperfusion. In the TIMI 14 trial, ST-segment resolution was used as an index of myocardial reperfusion to assess the efficacy of combination therapy with abciximab and reduced-dose tPA (20). By evaluation of the resolution of ST-segment elevation, Claeys et al. (16) investigated microvascular reperfusion injury after successful PTAC in patients with AMI.

4.2.3. ST-segment resolution and myocardial salvage

Myocardial salvage is the principal mechanism by which patients with AMI benefit from various reperfusion therapies (11, Fig. 4-5). As discussed in the preceding text, ST-segment resolution is a simple and useful index of not only epicardial reperfusion but also microvascular and myocardial tissue reperfusion after reperfusion strategies. Thus, it could be speculated that ST-segment resolution might be useful to predict myocardial salvage, which reflects the efficacy of reperfusion therapy. Moreover, previous studies in patients treated with thrombolysis or primary PCI for AMI showed that the extent of the early ST-segment resolution correlates with the angiographic

flow to the infarction area (125, 20, 3, 25, 36), the enzymatic and scintigraphic final infarction size (103, 104, 4) and subsequent left ventricular function (103, 125). These results imply that early ST-segment resolution might be used to evaluate degree of myocardial salvage after reperfusion therapy.

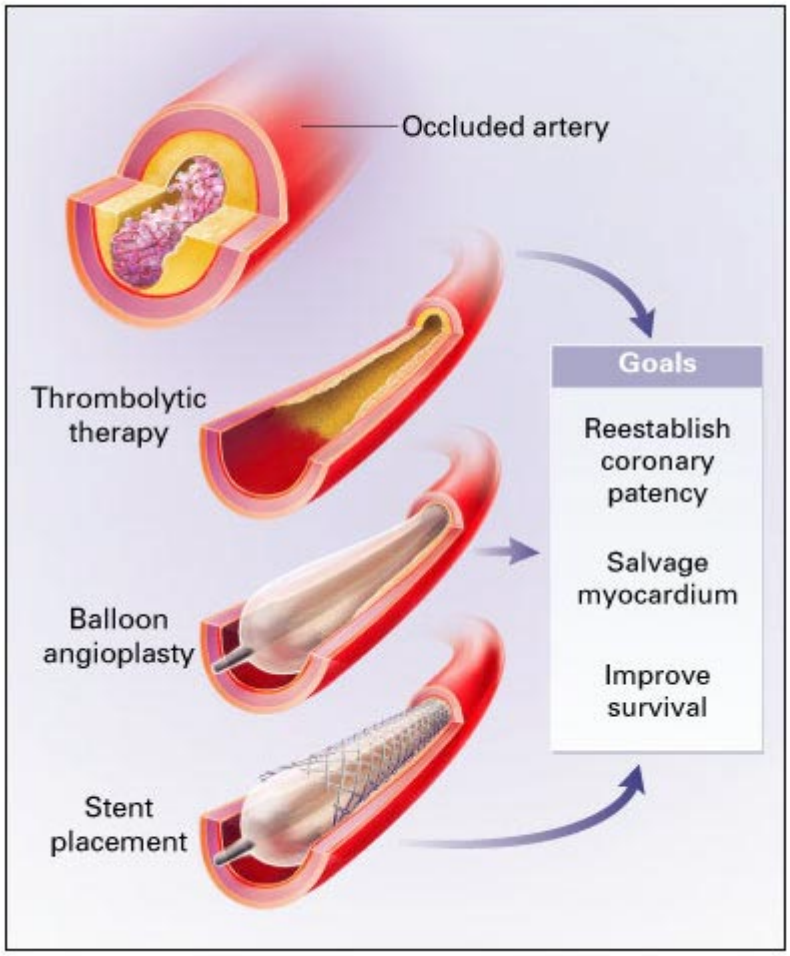

Figure 4-5. Goals of reperfusion strategies in patients with acute myocardial infarction.

Most recently, in the Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial infarction (LIMIT AMI) trial of lytic monotherapy versus lytic plus rhuMAb CD18, Angeja et al. (4) demonstrated that final infarction size assessed by Tc 99m sestamibi scintigraphy was larger in patients with no ST-segment resolution (median 15%) or partial resolution (median 11%) than in those with complete resolution (median 6%, overall P = 0.0001). In the present study, we also found a good correlation between a greater ST-segment resolution and smaller scintigraphic final infarct size. However, it may be speculated that this is the result of a smaller area

of myocardium at risk (i.e., initial perfusion defect) rather than of a higher reperfusion efficacy. In fact, we found that the group of patients with a greater extent of ST-segment resolution had a lower proportion of anterior infarction and a smaller initial scintigraphic perfusion defect when compared to the other groups with less ST-segment resolution. The finding of less ST-segment resolution in anterior infarctions has been reported previously (103, 104, 85). As discussed previously, the myocardial area at risk varies greatly in individual patients and little correlation exists between extent of the area of myocardium at risk as demonstrated with sestamibi imaging and the anatomic site of occlusion of the infarct artery. Moreover, using intracoronary injections of ^{99m}TC-macroaggregated albumin and gated planar imaging, Feiring et al. (33) showed that the amount of myocardium at risk during AMI is highly variable, even when the coronary occlusion occurs in a similar location. On the basis of these findings, they suggested that the determination of the amount of myocardium at risk was therefore crucial in the assessment of acute intervention in myocardial infarction.

In the present study, myocardial salvage was assessed by paired ^{99m}Tc-sestamibi SPECT imaging, which is regarded as the best available measurement tool for infarction size and a measure of the efficacy of therapy in AMI with the capability of taking myocardium at risk into consideration (42). The minimal redistribution of Tc 99m sestamibi makes it ideal for the measurement of myocardium at risk (44). Tc 99m sestamibi can be injected before the reperfusion treatment and imaging can be postponed until after the treatment, avoiding any delay in the treatment of patients with AMI. The accuracy of this method for the assessment of both the size of the initial defect and the size of infarction after reperfusion has been validated in several studies (43, 111). The using of myocardial salvage as an end point in reperfusion trials is being advocated because of its potential prognostic value (42, 40). In fact, it has been used as an primary end point in the 2 STOPAMI trials to compare the efficacy between thrombolysis and primary coronary stenting and the benefit of myocardial salvage was showed to be translated to better clinical outcomes (100, 62).

Consequently, we found that a larger extent of ST-segment resolution correlates with a greater myocardial salvage index and this correlation is independent of baseline characteristics including myocardium at risk, infarction location, and reperfusion strategy. Although these results were entirely expected, our data highlight that early ST-segment resolution analysis may be used as a surrogate for myocardial salvage

achieved with reperfusion therapy and this finding has implications for design of future reperfusion trials.

4.3. ST-segment resolution and prognosis

4.3.1. Prognostic markers in AMI in the era of reperfusion therapy

In recent decades, new therapies such as thrombolytic agents, aspirin, angiotensin-converting enzyme (ACE) inhibitors, ß blockers, and glycoprotein IIb/IIIa inhibitors have vastly improved the outcome of patients with AMI. These and other advances have reduced in-hospital and post-hospital AMI morbidity and mortality rates by promoting reperfusion, limiting infarct size, relieving ischemia, improving left ventricular function, or preventing arrhythmia. Interactions among these treatments, as well as a strong international initiative to decrease coronary artery disease mortality rates, have complicated our identification of the factors that best predict the outcome of AMI in this modern era. As traditional predictors are being reappraised, new lines of investigation are identifying prognostic indicators that promise greater clinical relevance.

4.3.1.1. Traditional prognostic markers

The prognostic value of traditional risk factors in AMI patients is being reassessed in this era of thrombolytic therapy. In a study by Miller et al. (79), the predictive relevance of thallium-201 exercise treadmill testing, performed at a mean of 9.6 days after AMI patients received thrombolytic therapy alone (n = 131) or in conjunction with coronary angioplasty (n = 79), was examined in a cohort of patients followed for 2 years. A total of 139 patients (66%) were classified as having “high-risk for adverse outcome” based on thallium scan findings showing redistribution in at least 1 segment outside the infarct zone or increased lung uptake of thallium-201. Early revascularization (before discharge) was required because of symptoms in 36 patients, most of whom were in the high-risk group. Of the remaining 174 patients, 30 had cardiac events (cardiac death, nonfatal reinfarction, or revascularization > 3 months after the thallium study). Interestingly, 2-year, event-free survival rates were not significantly different in patients with high-risk scans as opposed to low-risk scans: 86% versus 80%, respectively. Multivariate analysis identified no single thallium-201

exercise variable that predicted outcome. These findings typify the trend of recent reports from the reperfusion era.

Another provocative report focused on a subanalysis of the European Cooperative Study (68). Determinants of 5-year survival were assessed in 923 patients randomly assigned to treatment with recombinant tissue-plasminogen activator (rt-PA) (with or without angioplasty) or placebo following hospitalization for AMI. Based on multivariate analysis, significant determinants of survival were enzymatic infarct size, indicators of residual left ventricular function (such as ejection fraction or clinical heart failure), number of diseased vessels, and TIMI perfusion grade at discharge.

Other insights emerged from a Canadian Multicenter study (49) of continuous, ambulatory electrocardiographic monitoring in the early post-MI period. In this trial, reported by Gill et al. (49), 406 patients (55% of whom received thrombolytic therapy) underwent 48-hour ECG monitoring between the fifth and seventh post-MI days. Ischemia was identified on ambulatory ECG monitoring in 23% of patients. The presence of ischemia, compared with no ischemia, was associated with significantly higher 1-year mortality (11.6% vs. 3.9%, respectively; $P = 0.009$); death or MI (23.2% vs. 9.6%, respectively; $P = 0.001$); and death, MI, or hospitalization for unstable angina (44.2% Vs 19%, respectively; $P < 0.001$).

Post-AMI heart failure and male gender were important predictors of death, whereas age $\geq$ 65 years was of borderline significance ($P < 0.065$) (49). The presence of ischemia on ambulatory ECG, But not a positive exercise test or a low ejection fraction, were additional factors providing prognostic information to predict death or nonfatal AMI. Although age $\geq$ 65 years was of borderline significance as an indicator of mortality in this study, other large-scale trials have found that age remains a reliable indicator of increase risk (1). Thus, these data illustrate that the clinical variables of post-MI heart failure, male gender, age, and signs of ambulatory ischemia appear to provide the most reliable post-MI prognostic information.

Gill et al. (49) found that, in an analysis of the combined endpoint of hospitalization for unstable angina, nonfatal MI, or death, the strongest clinical predictors were anterior MI, post-AMI angina, and male gender. Again, the presence of ambulatory ischemia was a highly significant predictor, whereas neither a positive exercise test or a lower ejection fraction provide meaningful prognostic information.

4.3.1.2. Newer electrocardiographic predictors — ST-segment resolution

Ideally, an early prognostic indicator in patients with AMI should be simple, quick, noninvasive and easy to be used in all patients. An assessment by ECG criteria would fulfill all of these claims. Recent attention has focused on evaluation the degree of ST-segment elevation on repeated ECG monitoring following reperfusion therapy as a prognostic marker for post-MI outcome.

Different thresholds have been proposed as indictors of poor prognosis. Saran et al. (99) suggested that persistent coronary occlusion and lower ejection fraction can be predicted by < 30% ST-segment resolution at 3 hours. Barbash et al. proposed that < 50% resolution at 1 hour is predictive of less preservation of left ventricular function, higher morbidity, and higher short- and long-term mortality. In the second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico trial (GISSI-2), a large substudy (7426 patients) showed that two-thirds of patients had ≥ 50% ST-segment resolution 4 hours after thrombolysis; these patients had a 30-day mortality rate of 3.5% versus 7.4% in the patients with < 50% ST-segment resolution (76).

Dissmann et al. (29) and Schröder et al. (103) took this concept a step further by using a three-component definition for resolution of the sum of ST-segment elevation 180 min after fibrinolysis. Complete resolution was defined as ≥ 70%, partial resolution as 30% to 70%, and no resolution as < 30%. Using this technique, Schröder and colleagues have demonstrated a strong, stepwise correlation between the degree of ST-segment resolution at 180 min and subsequent mortality in a series of large fibrinolytic trials (103, 104, 105) (Fig. 1-2).

Two recent studies showed both 60- and 90-min determinations of ST-segment resolution provide excellent discrimination of the risk for death and CHF in patients receiving tPA-based fibrinolytic regimens (22, 23) (Tab. 4-6). Furthermore, it appears that patients who develop complete ST-segment resolution by 60 min are at even lower risk for death and heart failure than those who develop complete ST-segment resolution by 90 min (23). Because of the slower onset of fibrinolytic activity with streptokinase, 180 min rather than 90 min may be a more appropriate time to assess the efficacy of reperfusion with this agent (105). In contrast to analyze early ST-segment resolution, most recently, Fu et al. (37) demonstrated that ST-segment resolution at 24-36 hours after fibrinolysis still had prognostic value in patients with AMI.

Outcome	ST Resolution			p Trend
	Complete (≥70%)	Partial (30% to <70%)	None (<30%)	
60 min ST resolution:				
n	295 (33%)	268 (30%)	337 (37%)	
Death, 30 days (%)	1.7	4.5	7.7	0.002
Death, 1 year (%)	2.7	7.5	10.7	0.0005
CHF, 30 days (%)	7.1	13.8	17.2	0.0007
90 min ST resolution:				
n	318 (41%)	243 (32%)	203 (27%)	
Death, 30 days (%)	3.1	5.3	8.9	0.02
Death, 1 year (%)	4.7	7.4	11.3	0.02
CHF, 30 days (%)	8.5	12.8	15.3	0.05

Table 4-6. Comparison of 60- and 90-min measurement of ST-segment resolution. CHF, congestive heart failure. Adapted from reference 23.

In addition to its ability to predict mortality, the degree of ST-segment resolution also predicts the development of left ventricular dysfunction and clinical CHF. More complete ST-segment resolution consistently has been associated with smaller infarction size and improved left ventricular function (7, 74, 75, 99). Similar to mortality, the probability of CHF decreases in a stepwise fashion with greater degrees of ST-segment resolution (103, 104, 74, 22, 23, 107, 3).

Of particular importance is the observation that the prognostic power of ST-segment resolution persists even after accounting for the effects of epicardial blood flow. In the TIMI 14 substudy mentioned earlier, among patients with a patent infarct artery (TIMI 2 or 3 flow) 90 min after thrombolysis, those with < 70% ST-segment resolution had a tenfold increase in 30-day mortality versus those with complete (≥ 70%) ST-segment resolution (5.9% vs. 4.2%, P = 0.01) (21). Interestingly, when patients were characterized as to whether they had complete (≥ 70%) or incomplete (< 70%) ST-segment resolution, there was no difference in 30-day mortality between patients with TIMI grade 2 flow and TIMI grade 3 flow (21). Using continuous ST-segment monitoring, the Hirulog Early Reperfusion/Occlusion-1 investigators have shown that patients with early, stable ST-segment recovery have improved infarction zone wall motion, independent of TIMI flow grade (3). In a substudy from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI)-7 and the Global

Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-1 trials, ST-segment resolution, but not TIMI flow grade, was an independent predictor of mortality and CHF (107).

Additional support for the independent prognostic value of ST-segment resolution comes from the experience with primary PCI for STEMI. After successful primary PCI, in which TIMI grade 3 flow is established in the infarct artery, persistent ST-segment elevation is associated with poor recovery of left ventricular function and increased mortality (75, 113, 16, 125). Patients with an increase in ST-segment elevation after PCI (ST-segment re-elevation) appear to be at even higher risk for the development of death and heart failure due to extensive infarction, distal embolization or reperfusion injury (113, 28, 67, 77).

Taken together, these studies support the conclusion that the extent of ST-segment resolution early after reperfusion therapy is a strong, reliable, and noninvasive predictor of clinical outcome.

4.3.2. Correlation between ST-segment resolution and mortality in the present analysis

Consistent with previous studies (103, 104, 105), in the present analysis the 2nd ECG were recorded 90 minutes after initiation of reperfusion therapy and 2 cutoff points (70% and 30%) were used to define three ST resolution groups after reperfusion therapy: complete (≥ 70%), partial (<70% to 30%) and no resolution (<30%). Analyses were performed to investigate the correlation between ST-segment resolution and mortality. Consequently we found the stepwise correlation between the extent of ST-segment resolution and 30-day and 6-month mortality: a higher ST-segment resolution was associated with a better survival at 30 days and 6 months. ST-segment resolution as a continuous variable also correlates with 6-month mortality. Thus, our findings confirmed the results from other investigators (103, 104, 75, 125). Given the number of patients who died during 6-month follow-up is small, the independence of the relation between ST-segment resolution and mortality could not be checked.

Taken together, our data support the hypothesis that ST-segment resolution is a surrogate of efficacy of reperfusion therapy. When “complete” ST-segment resolution is seen after reperfusion therapy, successful reperfusion has occurred at both the

epicardial and microvascular level, greater myocardial salvage is achieved, and the prognosis is excellent. Persistent ST-segment elevation, on the other hand, appears to be indicative of either an occluded IRA or a patient artery with failure of myocardial and microvascular reperfusion which translates into less myocardial salvage and bad prognosis. In this sense, the main finding of the present analysis, ST-segment resolution correlates with degree of myocardial salvage, provides the explanation for the favorable prognostic value of the ST-segment resolution.

4.4. ST-segment resolution in comparing different reperfusion therapies

4.4.1. Current problems in comparison of efficacy in reperfusion trials

Multiple end points, including global left ventricular function (64), regional left ventricular function (109), early arterial patency (112), and clinical outcomes (131), have been used in various randomized trials as measures of the efficacy of reperfusion therapy in AMI. Clearly, the most important clinical outcome is mortality, which has formed the basis for multiple megatrials comparing thrombolytic agents with placebo and with each other. However, use of mortality as an end point requires increasing large sample size (Fig. 4-7) to test advances compared with existing therapy, which is already highly effective. A “head-on” comparative trial aiming to show a difference such as 1% between fatality rates in the different groups would need to include 20,000 or 30,000 patients. Such a very large sample size limits the number of new therapies that can be tested and imposes prohibitive financial barriers on the early testing of potentially promising therapies. End points that are potential “surrogates” for both early and late mortality are therefore attractive for several purpose: (1) to conduct very early pilot studies to demonstrate potential efficacy of a new agent, (2) to serve as end points for dose-ranging studies to select the “best dose” of a new agent, and (3) to indicate a possible late mortality benefit for a new therapy that my be “equivalent” to existing therapy with respect to early mortality.

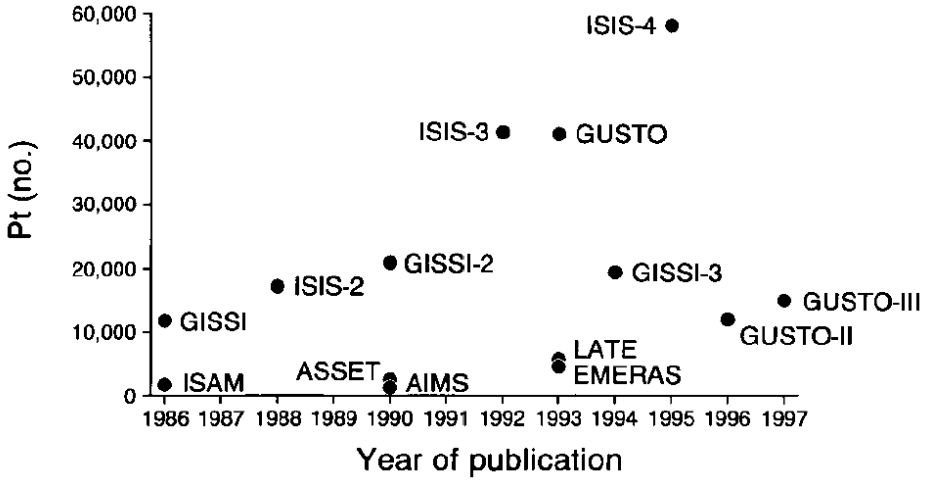

Figure 4-7. Total patient (Pt) enrollment in selected major randomized therapeutic trials in acute myocardial infarction displayed by year of publication. GISSI, GISSI-2, and GISSI-3 indicate Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico I, II, and III; ISAM, Intravenous Streptokinase in Acute Myocardial infarction; ISIS-2, ISIS-3, and ISIS-4, International Study of Infarct Survival 2, 3, and 4; ASSET, Anglo-Scandanavian Study of Early Thrombolysis; AIMS, APSAC intervention Mortality Study; LATE, Late Assessment of Thrombolytic Efficacy; EMERAS, Estudio Multicéntrico Estreptoquinasa Repúblicas de Américas del Sur; and GUSTO, GUSTO-II, and GUSTO-III, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arterial, Global Use of Strategies To Open occluded arteries, and Global Use of Strategies To Open occluded coronary arteries.

As existing therapy improves, the third possibility may become more likely. It will be increasingly difficult to demonstrate an advantage in early mortality, even if one really exits, because of the decreasing mortality with existing therapy and the distinct possibility that the deaths that still occur in AMI may be related to phenomena that cannot be altered by reperfusion therapy. For example, some patients may die of embolic complications (cerebral or pulmonary) that are unrelated to therapy. Thus, at least a portion of the existing low mortality with reperfusion therapy may reflect an "irreducible foundation" of early mortality that is unlikely to be prevented with any new therapy.

4.4.2. ST-segment resolution as a surrogate efficacy measure in reperfusion trials

As discussed previously, ST-segment resolution has been demonstrated as a powerful predictor of mortality in patients with AMI treated with all kinds of reperfusion strategies. Due to its ease of use and universal availability, ST-segment resolution has long been considered as a potential useful means of comparing different reperfusion therapies for STEMI. In a retrospective analysis of data from the Intravenous Streptokinase in Acute Myocardial Infarction trials, Schröder et al. (103) found greater ST-segment resolution among patients who received streptokinase than among those who received placebo; in the overall trial, there was a similar trend in mortality favoring streptokinase. Similar observations were made in the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial, in which reteplase was associated with greater ST-segment resolution and a trend towards lower mortality than streptokinase (104). Other small trials, not powered for mortality, have incorporated ST-segment analysis into composite assessments of clinical efficacy (89, 121, 83).

Several factors have increased interest in using ST-segment resolution as a surrogate efficacy measure in reperfusion trials. First, although angiographic studies are regarded as the most important complements to mortality, they are inevitably somewhat hazardous and not universally available because of its invasive nature. ST-segment resolution, a bedside and noninvasive measure, which has been demonstrated as a marker of epicardial and myocardial reperfusion and a predictor of outcome, might serve as a surrogate end point of efficacy after reperfusion therapy. Second, measurement of epicardial flow using coronary angiography, the "gold standard" used to identify promising reperfusion regimens for testing in large mortality trials, has proven disappointing in its ability to distinguish different reperfusion regimens and doses. For example, a phase II trial (112) found a higher rate of TIMI grade 3 flow with reteplase than with alteplase, but this agent was not associated with a lower mortality than alteplase in a large phase III study (118). Third, as discussed above, ST-segment resolution has been shown to provide prognostic information independent of epicardial blood flow because it also reflects tissue and microvascular perfusion. As such, it may be a better surrogate marker than epicardial blood flow (107) and, at the very least, appears to provide complementary information for assessing therapeutic efficacy. Finally, certain therapies may be particularly beneficial in the

coronary microcirculation. For example, Neumann et al. (85) demonstrated that, among patients undergoing PCI for AMI, Doppler peak flow velocity (a measure of microvascular function) was improved over 14 days in patients who received adjunctive therapy with the platelet GP IIb/IIIa inhibitor abciximab. This finding was accompanied with improved regional and global left ventricular function.

ST-segment resolution has been used to evaluate newer reperfusion regimens that incorporate combinations of GP IIb/IIIa inhibitors and fibrinolytic. In the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-Acute Myocardial Infarction study (IMPACT-AMI), combination therapy with eptifibatide and alteplase improved the time to steady state ST-segment recovery versus alteplase alone (89) (Fig. 4-8). Similarly, in the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction trial (PARADIGM), lamifiban improved ST-segment resolution when given in combination with fibrinolytic therapy (121) (Fig. 4-8). The TIMI 14 trial compared the combination of abciximab and reduced doses of fibrinolytics with full-dose fibrinolytics alone. In the primary outcome analysis of the study, the combination of abciximab and reduced-dose alteplase (tPA) resulted in a significant improvement in epicardial flow (increased TIMI grade 3 flow rates and lower TIMI frame counts at 60 an 90 min) when compared with tPA alone (6). All 346 patients with interpretable baseline and 90 min ECGs treated with either tPA alone or abciximab plus reduced-dose tPA (combination therapy) were included in an ST-segment resolution substudy (20). Patients who received combination therapy had a higher probability of complete ST-segment resolution than those receiving tPA alone (59% vs. 37%; $p < 0.0001$) (Fig. 4-8). Even after controlling for differences in epicardial blood flow, patients receiving combination therapy had significant greater ST-segment resolution than those receiving tPA alone (Fig. 4-8). This benefit appeared to be present regardless of the fibrinolytic agent and dose used, suggesting that this effect was due to abciximab rather than the fibrinolytic agent. It was concluded that combination therapy with abciximab and reduced-dose fibrinolytic therapy improved myocardial perfusion in addition to epicardial flow (20). The promising findings with combination reperfusion therapy were confirmed in two companion studies, which evaluated abciximab with reduced-dose reteplase instead of alteplase (116, 5). A large phase III trial, GUSTO-V, recently reported 30-day safety and efficacy outcomes for this reperfusion strategy. Patients randomized to receive combination therapy with abciximab and reduced-dose

reteplase had a nonsignificant 0.3% reduction in 30-day mortality versus patients randomized to reteplase alone (123). The results of long-term follow-up in this study, as well as the results of other ongoing trials evaluating different combination of GP IIb/IIIa inhibitors and fibrinolytics, are eagerly awaited.

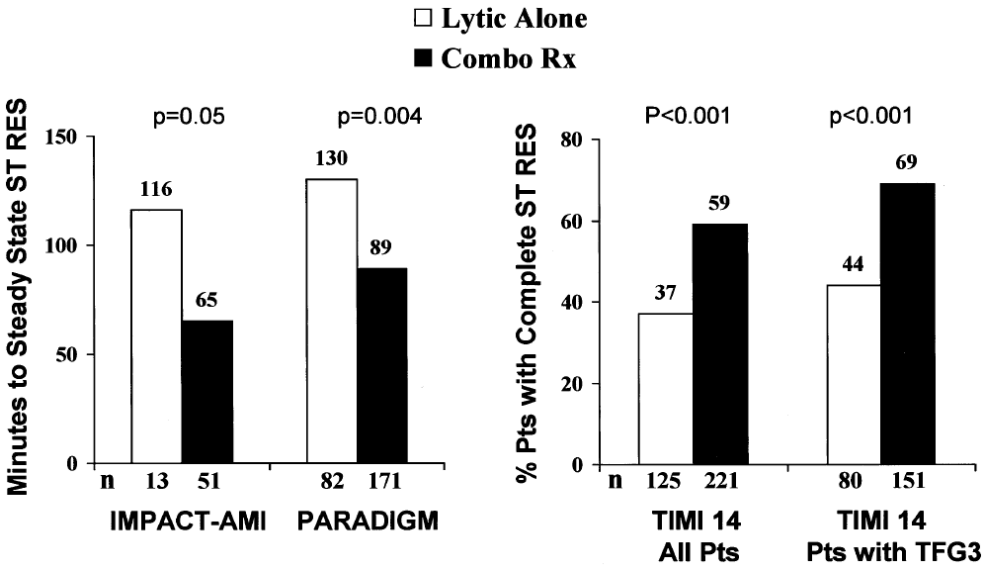

Figure 4-8. Overview of studies using ST-segment resolution (ST RES) to compare standard fibrinolytic therapy with reperfusion regimens containing glycoprotein IIb/IIIa inhibitors and reduced doses of fibrinolytics (combination therapy). Pts = patients; TFG3 = TIMI grade 3 flow. Adapted from references 16, 20 and 83.

In a related analysis from the TIMI 14 study, the extent of ST-segment resolution after early adjunctive PCI was determined. Among patients who underwent adjunctive PCI between 90 and 180 min after fibrinolysis, those who had initially been treated with a combination regimen containing abciximab had significantly greater ST-segment resolution after PCI and lower likelihood of ST-segment re-elevation than patients who had been treated with a fibrinolytic agent alone (25). Furthermore, the percutaneous procedure itself was associated with enhanced ST-segment resolution among patients who had received abciximab but not those who had received a fibrinolytic alone (25) (Fig. 4-9). These findings suggest that abciximab may prevent the microvascular injury that frequently occurs when adjunctive PCI is performed early after the administration of fibrinolytic therapy.

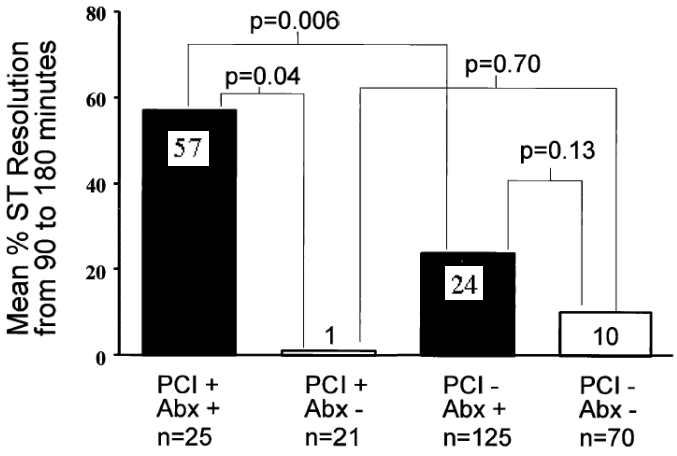

Figure 4-9. Subset of patients from the Thrombolysis In Myocardial Infarction (TIMI) 14 trial with TIMI grade 3 flow in the infarct artery at 90 min. Comparison of mean percent ST-segment resolution from 90 to 180 min between patients who did and did not undergo early adjunctive percutaneous coronary intervention (PCI) between 90 to 180 min after fibrinolysis. Patients are further separated into those who received and did not receive abciximab (Abx) as part of the reperfusion regimen. In the presence of Abx pretreatment, early adjunctive PCI was associated with greater ST-segment resolution, whereas in the absence of Abx pretreatment, ST-segment resolution tended to be worse in patients who underwent PCI. Adapted from reference 25.

4.4.3. ST-segment resolution in coronary stenting and thrombolysis

The previous discussion addressed that ST-segment resolution has been used as a surrogate end point to compare the efficacy of different thrombolytic regimens. However, there is no study comparing the extent of early ST-segment resolution between primary PCI and thrombolysis in patients with AMI. Are they really incomparable because of their distinct principles? As discussed above, early ST-segment resolution has been considered as a marker of myocardial reperfusion after both thrombolytic and coronary intervention approaches. Therefore, it is reasonable to speculate that the comparison could be performed. However, ST-segment resolution should be analyzed within the window of time when an intervention can affect outcome. That window is likely the first 1-2 hours of reperfusion, when a significant amount of microvascular obstruction can be attributable to platelet

microemboli/thrombi (39). In the present study, the second ECG was performed 90 minutes after initiation of reperfusion therapy.

Consequently we found patients treated with primary coronary stenting were more prone to achieve greater extent of early ST-segment resolution than those treated with thrombolysis though stenting patients had significant longer time interval from symptom onset to treatment. This result is not surprising. It was shown that primary coronary stenting is highly effective to restore epicardial flow by restoration the patency of IRA in patients with AMI (63, 86). The latter is important to subsequent myocardial reperfusion. In addition, observation from the TIMI 14 trial showed abciximab improves both epicardial flow and myocardial reperfusion in STEMI (20). Neumann et al. (85) demonstrated that abciximab improved coronary microcirculation in patients with AMI treated with primary coronary stenting. Although the present analysis is not powered to compare the efficacy of coronary stenting with thrombolysis, paralleling with larger ST-segment resolution, greater myocardial salvage and better clinical outcomes were observed in patients after stenting than those after thrombolysis. These findings confirmed the superiority of primary coronary stenting over thrombolysis, which has been demonstrated in the primary analysis of the 2 STOPAMI trials (100, 62).

In addition, the extent of early ST-segment resolution was compared in the present analysis between patients who received combination with half-dose alteplase and abciximab and those receiving full-dose alteplase alone. We found that combination with half-dose alteplase and abciximab tends to have higher probability to achieve complete ST-segment resolution than full-dose alteplase alone (28% versus 16%, $p = 0.099$). However, the difference did not reach statistical significance. Besides, there were no significant differences in mortality between these two thrombolytic regimens. These results partially coincide with two aforementioned studies in which the extent of early ST-segment resolution and clinical outcomes were compared in a prospective fashion between these two thrombolytic regimens (20, 123). In the two previous studies (20, 123) with larger study population (346 patients and 16,588 patients), combination therapy of half-dose tPA and abciximab was associated with higher percentage of complete ST-segment resolution (59% vs. 37%, $P < 0.001$), nonsignificant lower 30-day mortality (5.6% vs. 5.9%, $P = 0.43$) than full-dose tPA alone. The distinct study design and study population may contribute to the discrepancy.

Taken together, the evidences from present analysis and previous studies suggest early ST-segment resolution may be considered as a surrogate end point in comparing the efficacy of different reperfusion strategies.

4.5. Study limitations

The present study has some limitations. First, patients included in this study were those within 12 hours from symptom onset to admission. This duration is doubled compared with most of the previous studies investigating the prognostic value of ST-segment resolution (103, 104, 105, 125). The predictive power of ST-segment resolution might be limited because patients presenting later had already had a spontaneous reduction in their initial ST-segment elevation. However in a substudy of INJECT trial, Schröder et al. (104) found the prognostic value of ST-segment resolution remain the same after including all patients within 12 hours from symptom onset to admission for analysis. Moreover, most (85%) of the patients included in this analysis presented less than 6 hours after symptom onset. Second, although pooling both stenting patients and thrombolysis patients into analysis enabled us to compare the extent of ST-segment resolution in these two distinct reperfusion therapies, that also introduced more confounding factors in correlating ST-segment resolution with degree of myocardial salvage. However the statistical method performed in the present study, multiple linear regression analysis, facilitated us to achieve the 'purer' contribution of ST-segment resolution to the corresponding myocardial salvage by taking account of these confounding variables, such as form of reperfusion regimen, infarction location, previous myocardial infarction. Finally, this study comprised 243 patients with AMI treated with coronary stenting or thrombolysis. The sample size is relatively small, as preventing us from performing further subset analysis and checking the independence of the correlation between ST-segment resolution and subsequent mortality.

5. Summary

The extent of early ST-segment elevation resolution has been demonstrated to be a simple and useful means to predict final infarction size and clinical outcomes in patients with AMI after reperfusion therapy. However, whether this is the expression of initial infarction characteristics or degree of myocardial salvage achieved with reperfusion therapy remains unclear. In addiction, there is no study comparing the extent of early ST-segment resolution between primary PCI and thrombolysis.

We prospectively Included 243 patients (60 ± 13 y, 59 females) with AMI treated with either primary coronary stenting (122 patients) or thrombolysis (121 patients), who were enrolled in 2 reperfusion trials. Serial 12-lead electrocardiograms were performed at baseline and 90 minutes after initiation of reperfusion therapy. Three groups of ST-segment resolution were defined as complete (≥ 70%), partial (< 70% to 30%) and no resolution (< 30%). Myocardial salvage was assessed by paired SPECT imaging with ^{99m}Tc-sestamibi.

ST-segment resolution as a continuous variable correlated significantly with myocardial salvage index (P = 0.008), final infarction size (P < 0.001) and mortality at 6 months (P = 0.03). In the groups with complete, partial and no resolution, myocardial salvage index was 0.54 ± 0.32, 0.39 ± 0.36 and 0.33 ± 0.60, respectively (P = 0.01); final infarction size was 12.5% ± 12.0%, 20.0% ± 13.9% and 22.7% ± 19.4% of the left ventricle, respectively (P < 0.001); 6-month mortality was 2.4%, 6.2% and 12.8%, respectively (P = 0.03). After adjustment for baseline characteristics, ST-segment resolution was the second strongest predictor of myocardial salvage index (P = 0.006) after the form of reperfusion regimen, coronary stenting or thrombolysis (P = 0.002).

ST-segment resolution as a continuous variable was significantly higher in patients treated with primary coronary stenting than those treated with thrombolysis (53% ± 46% vs. 31% ± 55%, P = 0.001). Stent-treated patients were more likely to achieve complete ST-segment resolution in comparison of thrombolysis-treated patients (47% vs. 23%, P < 0.001), whereas a significantly higher proportion of patients treated with thrombolysis had no ST-segment resolution as compared with those treated with coronary stenting (43% vs. 21%, P < 0.001). Parallel to this finding, coronary stenting

was associated with significantly greater myocardial salvage index, smaller final infarction size, and lower 6-month mortality compared with thrombolysis.

In conclusion, extent of early ST-segment elevation resolution in surface ECG correlates with degree of myocardial salvage in scintigraphy in patients with AMI after reperfusion therapy and coronary stenting is associated with greater extent of early ST-segment resolution than thrombolysis. These data provide the explanation for the favorable prognostic value of the ST-segment resolution and support the use of this means to compare the efficacy of different reperfusion strategies.

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7. Appendix

7.1. Resume

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Publications:

1. **Dong J**, Ndrepepa G, Schmitt C, Mehilli J, Schmieder S, Schwaiger M, Schoemig A, Kastrati A.
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