Novel imaging aspects in the management of patients with acute coronary syndromes

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Quantitative analysis of the impact of total ischemic time on myocardial perfusion and clinical outcome in patients with ST-elevation myocardial infarction

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Abstract

Early reperfusion of the infarct-related coronary artery is an important issue in improvement of outcome after ST-segment elevation myocardial infarction (STEMI). In this study, the clinical significance of total ischemic time on myocardial reperfusion and clinical outcomes was evaluated in patients with STEMI treated with primary percutaneous coronary intervention and thrombus aspiration and additional triple anti-platelet therapy. Total ischemic time was defined as time from symptom onset to first intracoronary therapy (first balloon inflation or thrombus aspiration). All patients with STEMI treated with primary percutaneous coronary intervention with total ischemic times ≥30 minutes and <24 hours from 2005 to 2008 were selected. Ischemic times were available in 1,383 patients, of whom 18.4% presented with total ischemic times ≤2h, 31.2% >2 to 3 hours, 26.8% >3 to 5 hours and 23.5% >5 hours. Increased ischemic time was associated with age, female gender, hypertension, and diabetes. Patients with total ischemic time <5 hours more often had myocardial blush grade 3 (40% to 45% vs 22%, p<0.001) and complete ST-segment resolution (55% to 60% vs 42%; p = 0.002) than their counterparts with total ischemic times >5 hours. In addition, patients with total ischemic times ≤ 5 hours had a lower 30-day mortality (1.5% vs 4.0%; p = 0.032) than patients with total ischemic times >5 hours. In conclusion, in this contemporary cohort of patients with STEMI treated with primary percutaneous coronary intervention, triple anti-platelet therapy, and thrombus aspiration, short ischemic time is associated with better myocardial reperfusion and decreased mortality. After a 5-hour period in which outcomes remain relatively stable, myocardial reperfusion becomes suboptimal and mortality increases.

Introduction

Early reperfusion of the infarct-related coronary artery is an important issue in the improvement of outcomes after ST-elevation myocardial infarction (STEMI). Although the myocardium is damaged during ischemia, it is viable in part early after symptom onset and may be salvaged by rapid reperfusion.[1,2] The presence of microvascular obstruction increases with longer ischemic times, resulting in an increased infarct size.[2,3] In previous studies the best clinical results of reperfusion by primary percutaneous coronary intervention (PCI) have been observed in patients treated within 90 to 120 minutes after symptom onset.[2-5] Pretreatment with aspirin, heparin and clopidogrel before hospital admission and the administration of a glycoprotein IIb/IIIa inhibitor during primary PCI is associated with improvements in myocardial reperfusion and clinical outcomes.[6-8] Furthermore, it has been demonstrated that thrombus aspiration results in an additional improvement of myocardial reperfusion.[9,10] The application of these innovative pharmacologic and intracoronary treatment strategies could influence the time window to obtain optimal reperfusion and clinical outcomes by primary PCI in patients with STEMI. The aim of this study was to evaluate the impact of total ischemic time on myocardial reperfusion and clinical outcomes in a large contemporary cohort of patients with STEMI treated with primary PCI, with thrombus aspiration, and triple anti-platelet therapy.

Methods

We performed an analysis of ischemic time data from consecutive patients with STEMI presenting to the University Medical Center of Groningen from January 2005 to July 2008. Inclusion criteria were symptoms of chest pain suggestive for acute myocardial infarction lasting ≥30 minutes and <24 hours before hospital admission, electrocardiographic findings of ST-segment elevation >0.1 mV in ≥2 leads, and the performance of a primary PCI procedure. Exclusion criteria were the presence of cardiogenic shock and the existence of a life-threatening disease with a life expectancy of <6 months. Patients treated with acute coronary artery bypass grafting after primary PCI were not enrolled. The University Medical Center of Groningen provides 24-hours emergency cardiac care 7 days a week. It is situated in a region with 750,000 inhabitants and has 7 referral hospitals. When acute coronary syndromes are suspected, 12-lead electrocardiography is performed and the results interpreted by the ambulance physician, aided by a computer algorithm and feedback after fax transmission from our coronary care unit. After confirmation of STEMI, the STEMI treatment protocol is initiated. This includes that the coronary care unit of our center is contacted and informed about the arriving patient, and direct activation

of the cardiac catheterization team. The patient is directly transported to the catheterization laboratory, thereby bypassing other regional hospitals. In our region, ambulance transfer times vary, to a maximum of 30 minutes. The STEMI protocol has been initiated in January 2004 and has remained unchanged during the period under study.

All patients were treated with aspirin (500 mg), heparin (5,000 IU) and clopidogrel (600 mg) after confirmation of ST-segment elevation on the first electrocardiogram, usually obtained in the ambulance before hospital admission. During primary PCI, patients received the glycoprotein IIb/IIIa inhibitor abciximab (0.25 mg/kg intravenously) if not contraindicated. Additional heparin was administered during procedure, guided by the activated clotting time. As the initial step during primary PCI, manual thrombus aspiration was performed in about half of the patients until 2006. After 2006, thrombus aspiration was performed in all patients whenever possible. After restoration of flow through the infarct-related lesion, a stent was implanted. Balloon pre- and postdilatation were used when necessary to achieve visualization of the infarct-related lesion before stent placement or optimal stent deployment. After primary PCI, patients received aspirin, clopidogrel (>1 month), β blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.[11]

Total ischemic time was defined as the time from symptom onset to the first intracoronary therapy (first balloon inflation or thrombus aspiration). Information on the time of symptom onset was systematically collected by asking the patient or his relatives about initiation of continuous chest pain before hospital admission.

Angiographic records before and after primary PCI were evaluated by 2 experienced observers blinded for clinical data. On the initial angiogram and on the final angiogram, Thrombolysis In Myocardial Infarction (TIMI) flow grade, angiographic evidence of thrombus in the infarct-related lesion, and distal embolization were assessed.[12-14] In addition, myocardial blush grade (MBG) was assessed on the angiogram after stenting.[15] The 12-lead electrocardiograms obtained at presentation and 30 to 60 minutes after primary PCI were evaluated by 2 experienced observers blinded to angiographic and clinical data. ST-segment elevation resolution and the presence of Q waves were assessed.[16,17] Aspirated material was collected and analyzed for patients from 2005 to 2006. Thrombus aspiration was defined as effective when atherothrombotic material was present in the aspirated samples.

Follow-up data at 30 days after primary PCI were collected from hospital records, written questionnaires, and telephone interviews. We report all-cause mortality. Reinfarction was defined as the onset of recurrent symptoms of ischemia combined

with new ST-segment elevations and/or a second increase of serum creatine kinase or creatine kinase-MB to ≥2 times the upper limit of the normal range. Target vessel revascularization was defined as PCI or bypass grafting of the infarct-related coronary artery.

The primary end point of our study was optimal myocardial reperfusion, defined as an MBG of 3 and/or ST-segment resolution >70%. Secondary end points were the presence of new Q waves on electrocardiography after primary PCI, enzymatic infarct size as assessed by the maximum creatine kinase-MB level, and mortality, reinfarction and target vessel revascularization at 30 days after primary PCI.

Patients were classified in 4 time categories of whole hours according to total ischemic time, approaching a distribution in quartiles. Categorical variables are presented as frequency values and proportions, and differences between ischemic time categories were evaluated using chi-square or Fisher's exact tests. Continuous variables with normal distributions are presented as mean ± SD, whereas variables with non-normal distribution are presented as medians with interquartile ranges. Differences in continuous variables between ischemic time categories were evaluated using 1-way analysis of variance or the Kruskal-Wallis nonparametric test as appropriate. The cumulative incidence of clinical endpoints was evaluated by the method of Kaplan and Meier, and differences in cumulative event rates according to ischemic time were evaluated using log-rank tests. Univariate and multivariate logistic regression analyses were applied to study the relation between ischemic time and the primary end point, myocardial reperfusion, assessed as MBG of 3 and ST-segment resolution >70%. In multivariate analysis, we adjusted for potential confounders associated with the end points in univariate analysis. We report crude and adjusted odds ratios together with corresponding 95% confidence intervals. For all analyses, 2-sided p values < 0.05 were defined as significant. Statistical analysis was performed using the SPSS version 16.0 (SPSS, Inc., Chicago, Illinois).

Results

From January 2005 to July 2008 1,731 consecutive patients with STEMI were treated with primary PCI at our hospital (Figure 1). Ischemic time was available in 1,383 patients, (79.9%) of all 1,731 STEMI patients. Of these, 255 patients (18.4%) had ischemic times ≤2hours, 432 patients (31.2%) had times >2 to 3 hours, 371 patients (26.8%) had times >3 to 5 hours and 325 patients (23.5%) had times >5 hours. The median ischemic time was 3.1 hours (interquartile range 2.3 to 4.8). As listed in Table 1, prolonged ischemic time was associated with age, female gender, hypertension, diabetes, and smoking status. Angiographic and procedural characteristics are listed

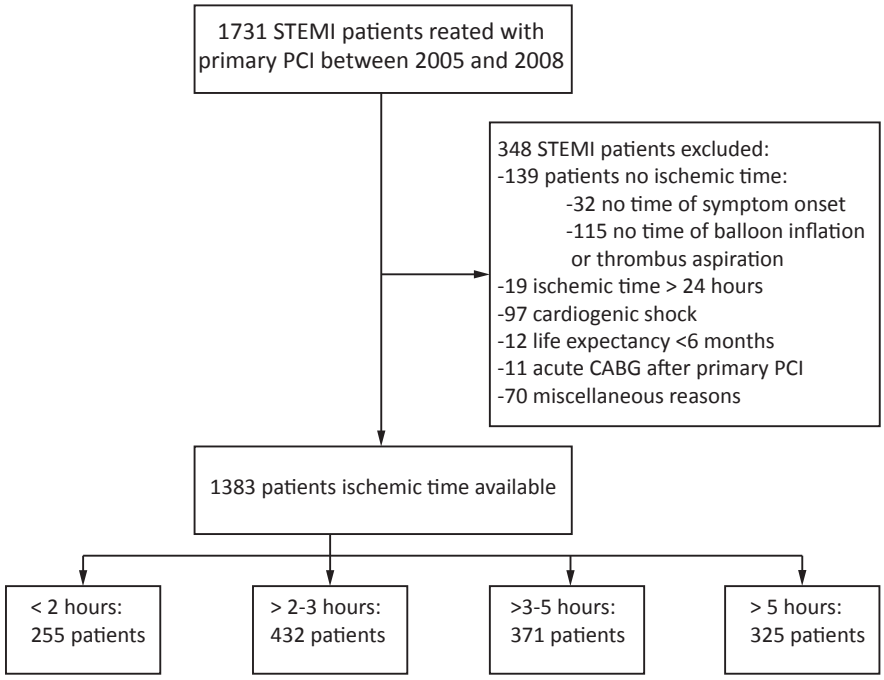


Figure 1. Flow diagram. Flow diagram of the inclusion of STEMI patients with primary PCI

in Table 2. Ischemic time was associated with multivessel disease, the presence of collateral arteries, the use of glycoprotein IIb/IIIa inhibitors, balloon dilatation, and stent implantation. The incidence of TIMI grade 3 flow decreased from 93.3% to 79.9% after 5 hours ($p<0.001$).

MBG was analyzed in 1,358 patients (98.2%) after primary PCI. In the first 5 hours of ischemic time, MBG of 3 varied from 44.6% and 40.1%, but decreased to 22.3% after 5 hours ($p<0.001$; Table 3, Figure 2). ST-segment resolution could be analyzed in 1,243 patients (89.9%). Complete ST-segment resolution varied from 54.5% and 59.8% in the first 5 hours but decreased to 42.4% after 5 hours ($p<0.001$; Table 3, Figure 2). Multivariate analysis showed that after correction for predictive baseline and procedural variables in the univariate analysis, ischemic time was a significant predictor of MBG of 3 and ST-segment resolution >70% (Table 4). In addition, the presence of Q waves and the maximum value of creatine kinase-MB were associated with prolonged total ischemic time (Table 3, Figure 2). A total of 29 patients (2.1%) had died at 30 days after primary PCI. Mortality was about 1.5% up to 5 hours of ischemic time and increased to 4.0% after 5 hours ($p = 0.032$; Table 3). Figure 3 shows differences in cumulative rates of mortality at 30 days ($p = 0.05$).

Table 1. Baseline characteristics

Variable	Myocardial Ischemic Time (hours)				p Value
	≤2 h (n = 255)	>2-3 h (n = 432)	>3-5 h (n = 371)	> 5 h (n = 325)	
Ischemic time (hours)	1.83 (1.50-1.92)	2.50 (2.25-2.75)	3.75 (3.33-4.25)	7.25 (5.87-10.58)	<0.001
Age (years)	61.6 ± 12.0	61.9 ± 12.2	62.5 ± 13.0	65.2 ± 12.6	0.001
Men	193/255 (75.7%)	321/432 (74.3%)	266/371 (71.7%)	215/325 (66.2)	0.006
Hypertension	84/249 (33.7%)	143/411 (34.8%)	118/364 (32.4%)	139/316 (44.0)	0.022
Hypercholesterolemia	66/217 (30.4%)	98/357 (27.5%)	88/315 (27.9%)	80/280 (28.6)	0.763
Diabetes mellitus	18/254 (7.1%)	44/426 (10.3%)	34/368 (9.2%)	50/323 (15.5)	0.003
Myocardial infarction	18/254 (7.1%)	42/426 (9.9%)	36/368 (9.8%)	31/323 (9.6)	0.392
Previous PCI	18/254 (7.1%)	28/427 (6.6%)	25/366 (6.8%)	20/322 (6.2)	0.735
Previous CABG	4/255 (1.6%)	9/427 (2.1%)	15/368 (4.1%)	10/323 (3.1)	0.115
Current smoker	135/231 (58.4%)	199/397 (50.1%)	175/337 (51.9%)	133/293 (45.4)	0.011

Data are expressed as median (interquartile range), as mean ± SD, or as number (percentages)
CABG = coronary artery bypass grafting

Discussion

In this contemporary cohort of patients with STEMI treated with primary PCI, thrombus aspiration, and triple anti-platelet therapy, myocardial reperfusion, as assessed by angiography (MBG of 3) and electrocardiography (ST-segment resolution >70%), was better in patients with total ischemic times ≤5 hours than in those with longer ischemic times. Interestingly, if ischemic times can be limited to ≤5 hours, the duration of the ischemia seems to only modestly influence myocardial reperfusion. Most patients with STEMI could be treated with primary PCI in the first 5 hours after symptom onset. Treatment within these golden hours of primary PCI results in better myocardial reperfusion and clinical outcomes.

Our findings confirm the observation in various previous studies that prolonged total ischemic time is associated with impaired myocardial reperfusion.[18,19] Recent studies have also confirmed that time to reperfusion is associated with infarct size as assessed using technetium sestamibi imaging and magnetic resonance imaging,[2,3,5] with treatment benefit especially in patients who were treated within <90 to 120 minutes after symptom onset.[2,5] In addition, microvascular obstruction increased over time.[2,3]

A relation between treatment delay and mortality was clearly described by Boersma et al,[20] showing that in patients with STEMI treated with fibrinolytic therapy, relative as well as absolute mortality reduction was significantly higher when fibrinolysis was performed in the first 2 hours after symptom onset than after that time. In patients treated with primary PCI, this observation was confirmed, often showing that patients treated within the first 2 hours had a better prognosis than patients treated after 2 hours.[4,18,19,21] However, these studies did not systematically use triple anti-platelet therapy and did not perform thrombus aspiration in addition to primary

Table 2. Angiographic and procedural characteristics

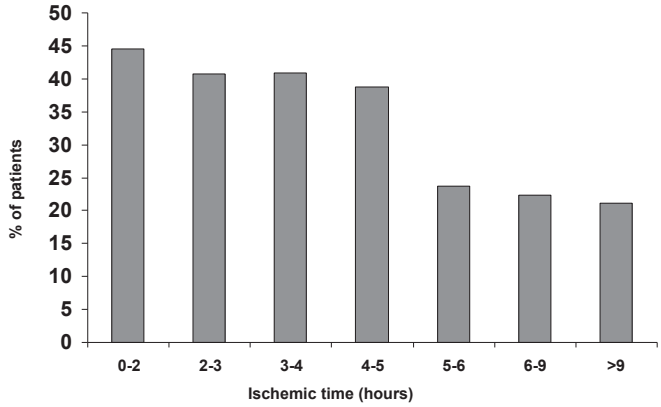
Variable	Myocardial Ischemic Time (hours)				p Value
	≤2 h (n = 255)	>2-3 h (n = 432)	>3-5 h (n = 371)	> 5 h (n = 325)	
Pre-PCI angiography					
Anterior infarction	113/255 (44.3%)	184/432 (42.6%)	152/371 (41.0%)	141/325 (43.4%)	0.763
Multivessel disease	156/254 (61.4%)	275/431 (63.8%)	240/371 (64.7%)	226/324 (69.8%)	0.036
Collateral arteries	65/252 (25.8%)	95/420 (22.6%)	91/362 (25.1%)	108/320 (33.8%)	0.011
Thrombus before PCI	141/252 (56.0%)	236/425 (55.5%)	211/364 (58.0%)	181/321 (56.4%)	0.787
TIMI grade 0 or 1 flow before PCI	152/253 (60.1%)	244/428 (57.0%)	221/369 (59.9%)	211/323 (65.3%)	0.096
Procedural					
Thrombus aspiration	149/252 (59.1%)	265/431 (61.5%)	218/366 (59.6%)	189/324 (58.3%)	0.648
Effective Glycoprotein IIb/IIIa inhibitor	60/80 (75.0%)	116/158 (73.4%)	108/153 (70.6%)	86/122 (70.5%)	0.401
Balloon dilatation	239/253 (94.5%)	402/430 (93.5%)	343/369 (93.0%)	291/325 (89.5%)	0.022
Stent implantation	123/243 (50.65%)	216/415 (52.0%)	203/352 (57.7%)	211/312 (67.6%)	<0.001
Intra-aortic balloon pump	231/243 (95.1%)	397/419 (94.7%)	330/352 (93.8%)	284/311 (91.3%)	0.047
Post-PCI angiography	6/150 (4.0%)	14/288 (4.9%)	14/261 (5.4%)	15/216 (6.9%)	0.199
TIMI grade 3flow after PCI	236/253 (93.3%)	385/430 (89.5%)	321/370 (86.8%)	259/324 (79.9%)	<0.001
Distal embolization after PCI	15/233 (6.4%)	33/389 (8.5%)	21/348 (6.0%)	23/300 (7.7%)	0.925
Thrombus post PCI	3/253 (1.2%)	6/431 (1.4%)	10/370 (2.7%)	9/323 (2.8%)	0.082

Data are expressed as number (percentages).

PCI. In addition, patients with prolonged ischemic time (12 to 24 hours) were often not included, but may still benefit from primary PCI.[22]

In the present study, myocardial reperfusion decreased after 5 hours of total ischemic time, which was a considerably longer ischemic time than reported in previous studies. First, it could be suggested that the administration of aspirin, heparin and clopidogrel before hospital admission has a favourable effect on reperfusion. Because they are already administered during the ischemic time period, an open infarct-related artery may be present in a considerable portion of patients before primary PCI.[23] Second, the administration of glycoptroteïn IIb/IIIa inhibitors during primary PCI may result in reduced platelet aggregation and microthrombi, which otherwise would increase as total ischemic time prolongs. Third, the performance of thrombus aspiration may have improved myocardial reperfusion, because it is still feasible and effective when total ischemic time increases. In the first 5 hours, the duration of ischemia seems to only modestly influence myocardial reperfusion. However, we suggest that all patients should be treated with primary PCI as soon as possible, independent of time of symptom onset. First, this will lower the median total ischemic time and decreases the number of patients treated after 5 hours. Second, it shortens the time interval during which life-threatening arrhythmias and cardiogenic shock can develop.

A



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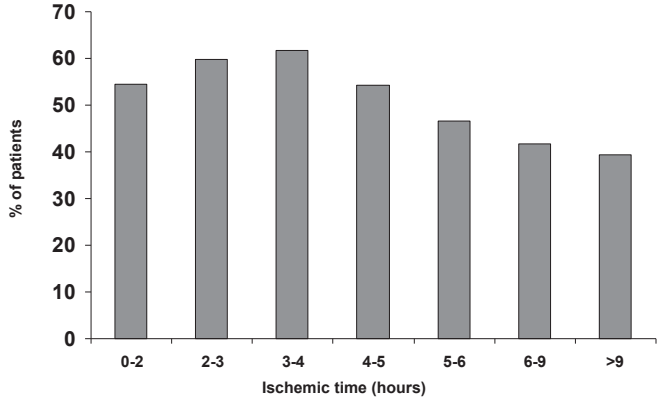

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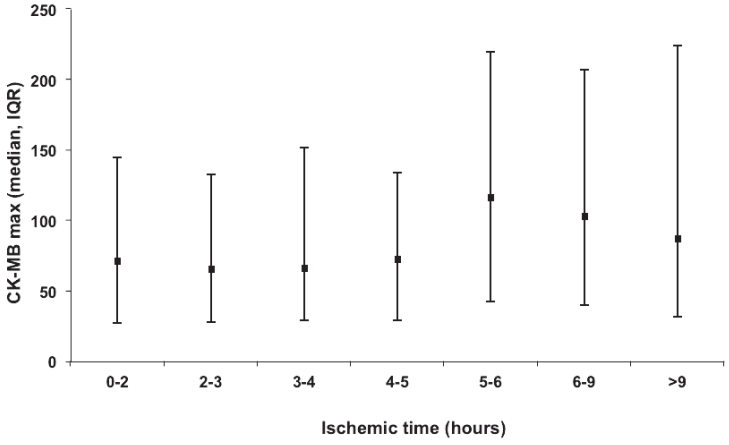

Figure 2A. **Myocardial blush grade 3 after primary PCI** Myocardial reperfusion as assessed by myocardial blush grade 3. B. **ST-segment resolution >70% after primary PCI.** Myocardial reperfusion as assessed by complete ST-segment resolution. C. **CK-MB maximum after primary PCI** Infarct size as assessed by CK-MB maximum.

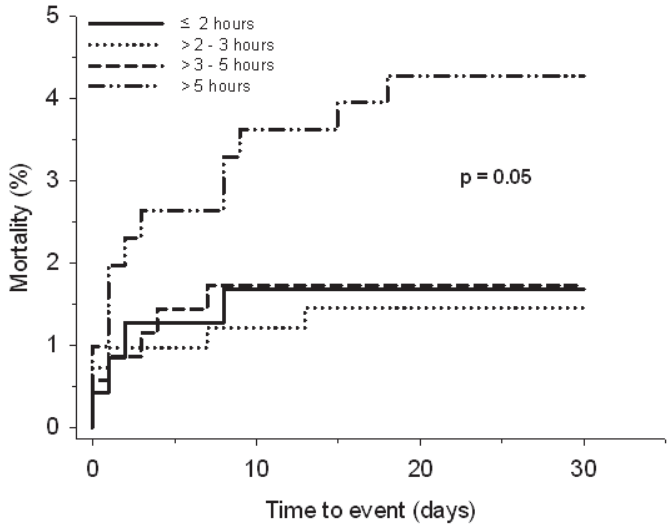

Figure 3. **Kaplan Meier curve 30 day mortality** Kaplan Meier curve for 30 day mortality for the 4 intervals of ischemic time.

Total ischemic time was associated with mortality at 30 days after primary PCI, and mortality rates were nearly 3 times higher in patients with an ischemic time >5 hours than in patients presenting in the first 5 hours. However, it should be considered that patients presenting late were older, more often had cardiovascular risk factors, more often had multivessel disease, less often were administered glycoprotein IIb/IIIa inhibitors, more often underwent balloon dilatation, and less often underwent stent implantation. These differences in patient baseline characteristics may in part explain the increased mortality after 30 days.

As total ischemic time increases, platelet aggregation continues, and blood stagnation causes occlusion of the coronary artery.[24] Although the prevalence of total coronary occlusion did not significantly increase with prolonged ischemic time, balloon dilatation was more often performed in patients with increased ischemic time. The additional use of balloon dilatation may have contributed to fragmentation of thrombus material and a higher incidence of embolization into the microvasculature.

In this contemporary cohort patients with STEMI were treated with aspirin, heparin and clopidogrel, the glycoprotein IIb/IIIa inhibitor abciximab, and thrombus aspiration. In recent years, new antithrombin treatments and new glycoprotein IIb/IIIa inhibitors have been developed. The use of bivalirudin has been investigated, with promising results, especially on bleeding complications.[25,26] The glycoprotein IIb/IIIa inhibitor eptifibatide was suggested to be as effective as abciximab in restoring myocardial perfusion.[27] In addition, 2 new thienopyridines, prasugrel and ticagrelor, have become available, causing a more rapid and higher level of platelet inhibition and

Table 3. Outcome characteristics

Variable	Myocardial Ischemic Time (hours)				p Value
	≤2 h (n = 255)	>2-3 h (n = 432)	>3-5 h (n = 371)	> 5 h (n = 325)	
Myocardial reperfusion					
MBG 3	112/251 (44.6%)	173/425 (40.7%)	146/364 (40.1%)	71/318 (22.3%)	<0.001
ST-segment resolution > 70%	126/231 (54.5%)	234/391 (59.8%)	197/333 (59.2%)	122/288 (42.4%)	0.002
Measures of infarct size					
Q waves	186/238 (78.2%)	315/403 (78.2%)	268/343 (78.1%)	251/295 (85.1%)	0.047
Creatine kinase -MB maximum (U/L)	71.0 (26.9-145.0)	65.5 (28.0-132.8)	68.9 (29.1-147.7)	98.2 (36.0-222.3)	<0.001
Clinical outcome at 30 days					
Mortality	4/255 (1.6%)	6/430 (1.4%)	6/371 (1.6%)	13/325 (4.0%)	0.032
Reinfarction	4/255 (1.6%)	3/430 (0.7%)	6/371 (1.6%)	5/325 (1.5%)	0.647
Target vessel revascularization	11/255 (4.3%)	14/430 (3.3%)	22/371 (5.9%)	19/325 (5.8%)	0.134

Data are expressed as number (percentages) or as median (interquartile range).

improving clinical outcome.[28,29] When they are added to or replaced by clopidogrel in the prehospital treatment, it could be suspected that these thienopyridines lead to more intitial patency of the infarct-related vessel.

Several limitations should be considered. This was a single-center study, and therefore data can not automatically be extrapolated to other PCI centers, although with the inclusion of 80% of all patients with STEMI, this patient cohort does reflect a real-world clinical practice. However, it should be mentioned that patients presenting with cardiogenic shock were excluded in our analysis, which may have influenced our results. In patients with cardiogenic shock it was often not possible to assess the onset of ischemic time. Ischemic time data were not available for all patients because of missing times of symptom onset, thrombus aspiration or balloon inflation. The exclusion of these patients may have influenced our results, although the baseline characteristics of the included and excluded patients were similar. Furthermore, thrombus aspiration was performed in only 60% of patients. However, the incidence of thrombus aspiration did not differ between the ischemic time groups. In addition, ST- segment resolution could only be analyzed in 90% of patients, because the electrocardiograms at presentation or after primary PCI were not available, or because of the occurrence of an intraventricular conduction delay. Furthermore, maximum creatine kinase-MB levels were measured only during the stay in our hospital. Because some patients were transferred to a regional hospital 1 day after primary PCI, maximum measured creatine kinase-MB may have been too low.

Table 4. Univariable and multivariable analysis between total ischemic time and myocardial reperfusion, assessed by myocardial blush grade 3 and ST-segment resolution >70%.

Variable	Univariate analysis		Multivariate analysis	
	OR*	95% CI	OR*	95% CI
MBG 3				
Ischemic time ≤ 2 hours	2.80	1.95-4.03	2.66	1.76-4.03
Ischemic time 2-3 hours	2.39	1.72-3.31	2.33	1.60-3.38
Ischemic time 3-5 hours	2.33	1.66-3.26	2.31	1.57-3.39
Age	0.97	9.96-0.98	0.98	0.97-0.99
Current smoker	1.35	1.07-1.70	1.10	0.85-1.43
Multivessel disease	0.79	0.63-0.99	1.10	0.85-1.44
Collateral ateries	0.66	0.49-0.89	0.80	0.60-1.08
Glycoprotein IIb/IIIa inhibitor	1.65	1.04-2.60	1.08	0.62-1.87
Balloon dilatation	0.41	0.33-0.52	0.48	0.37-0.61
ST-segment resolution > 70%				
Ischemic time ≤ 2 hours	1.63	1.15-2.31	1.14	0.77-1.68
Ischemic time 2-3 hours	2.03	1.49-2.76	1.68	1.19-2.38
Ischemic time 3-5 hours	1.97	1.43-2.71	1.71	1.20-2.44
Age	0.98	0.97-0.99	0.99	0.98-1.00
Diabetes	0.56	0.39-0.81	0.64	0.42-0.98
Current smoker	1.30	1.03-1.65	1.19	0.92-1.54
Multivessel disease	0.71	0.56-0.90	0.83	0.63-1.08
Collateral arteries	0.69	0.54-0.89	0.80	0.60-1.06
Balloon dilatation	0.58	0.46-0.74	0.64	0.50-0.83
Stent implantation	1.62	1.01-2.59	1.39	0.82-2.36

CI = confidence interval; OR = odds ratio.
* For total ischemic time, the reference categoriy was ischemic time group >5 hours.

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