Reduction of Recurrent Ischemia With Abciximab During Continuous ECG-Ischemia Monitoring in Patients With Unstable Angina Refractory to Standard Treatment (CAPTURE)

Peter Klootwijk, Simon Meij, Rein Melkert, Timo Lenderink and Maarten L. Simoons

Circulation 1998;98;1358-1364
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Reduction of Recurrent Ischemia With Abciximab During Continuous ECG-Ischemia Monitoring in Patients With Unstable Angina Refractory to Standard Treatment (CAPTURE)

Peter Klootwijk, MD; Simon Meij, MS; Rein Melkert, MS; Timo Lenderink, MD; Maarten L. Simoons, MD

Background—In the CAPTURE (c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina) trial, 1265 patients with refractory unstable angina were treated with abciximab or placebo, in addition to standard treatment from 16 to 24 hours preceding coronary intervention through 1 hour after intervention. To investigate the incidence of recurrent ischemia and the ischemic burden, a subset of 332 patients (26%) underwent continuous vector-derived 12-lead ECG-ischemia monitoring.

Methods and Results—Patients were monitored from start of treatment through 6 hours after coronary intervention. Ischemic episodes were detected in 31 (18%) of the 169 abciximab and in 37 (23%) of the 163 placebo patients (NS). Only 9 (5%) of abciximab versus 22 (14%) of placebo patients had ≥2 ST episodes ($P<0.01$). In patients with ischemia, abciximab significantly reduced total ischemic burden ($P<0.02$), which was calculated alternatively as the total duration of ST episodes per patient, the area under the curve of the ST vector magnitude during episodes, or the sum of the areas under the curves of 12 leads during episodes. Twenty-one patients (6%) suffered a myocardial infarction (MI) (18) or died (3) within 5 days of treatment. The presence of asymptomatic and symptomatic ST episodes during the monitoring period preceding coronary intervention was associated with an increased relative risk of these events of 3.2 (95% CI 1.4, 7.4) and 4.1 (95% CI 1.4, 12.2), respectively.

Conclusions—Recurrent ischemia predicts MI or death within 5 days of follow-up. Treatment with abciximab is associated with a reduction of frequent ischemia and a reduction of total ischemic burden in patients with refractory unstable angina. As such, patients with ischemia derive particularly high benefit from abciximab. **(*Circulation*. 1998;98:1358-1364.)**

Key Words: platelet aggregation inhibitors ■ angina ■ ischemia ■ electrocardiography

Computer-assisted continuous ST monitoring is a practical, noninvasive tool for detection and quantification of myocardial ischemia and recognition of myocardial infarction (MI) in patients with unstable coronary syndromes.[1–4] From a recent study using computer-assisted continuous ST monitoring in patients with unstable angina, it appeared that up to 60% of patients exhibited at least one 1 episode of ischemia within the first 24 hours of admission, and only 23% of patients remained free of ST episodes during an ST monitoring period of 48 hours.[4] In unstable angina patients, myocardial ischemia may develop as the result of platelet aggregation and intracoronary thrombosis at the site of plaque fissuring or rupture.[5,6] Recurrent ischemia detected during computer-assisted continuous ST monitoring may thus specifically reflect episodes of platelet aggregation in these patients.

Abciximab, an inhibitor of the platelet glycoprotein IIb/IIIa receptor, has been shown to reduce the rate of complications associated with concurrent PTCA and during follow-up in patients with clinical or angiographic features indicating increased procedural risk.[7–9] In the CAPTURE study (c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina), which was designed to assess the value of treatment with abciximab in patients with refractory unstable angina during 18 to 24 hours preceding PTCA, a major reduction of death, MI, or urgent intervention within 30 days after enrollment was obtained from 15.9% of the placebo group, compared with 11.3% in patients receiving abciximab.[10]

ECG-ischemia monitoring was conducted as a substudy within CAPTURE. The primary objective of this substudy was to investigate the effects of abciximab compared with placebo on the incidence and severity of recurrent ischemia

Received January 13, 1998; revision received May 22, 1998; accepted June 13, 1998.

From the Division of Cardiology, Thoraxcenter, University Hospital Dijkzigt, Erasmus University Rotterdam (P.K., S.M., M.L.S.), The Netherlands, and the Data Processing Center Cardialysis B.V. (R.M., T.L.), Rotterdam, The Netherlands.

Correspondence to A.P.J. Klootwijk, MD, Thoraxcenter Ba 316, Erasmus University Rotterdam, University Hospital Dijkzigt, PO Box 1738, 3000 DR Rotterdam, Netherlands.

during continuous vector-derived 12-lead ECG monitoring in patients with unstable angina refractory to standard drug treatment who were scheduled for PTCA within 24 hours. These effects were studied before, during, and up to 6 hours after PTCA. A secondary objective was to assess the relationship of recurrent ischemia during continuous vector-derived 12-lead ECG monitoring with the clinical events as defined in the main CAPTURE study.

Methods

Study Organization and Patient Selection

This ECG-ischemia monitoring study was conducted as a substudy of CAPTURE. Patients were recruited by 13 hospitals (those that had the availability of ECG-monitoring equipment) of the 69 participating in CAPTURE. All patients underwent continuous ECG monitoring using a vector-derived 12-lead ECG recording system (MIDA 1000, Ortivus Medical), as described below.

For an extensive description of the CAPTURE study design, patient selection, and inclusion and exclusion criteria, we refer to the recently reported CAPTURE main trial.[10] In brief, patients were eligible for the CAPTURE study if they had refractory unstable angina, defined as: chest pain at rest with concomitant ECG abnormalities compatible with myocardial ischemia (ST-segment depression, ST-segment elevation, or abnormal T waves) and 1 or more episodes of either typical chest pain and/or ECG abnormalities compatible with myocardial ischemia during therapy with intravenous heparin and nitroglycerin, which started ≥2 hours previously. The most recent episode of ischemia should have occurred within 48 hours preceding enrollment, corresponding to Braunwald class III acute unstable angina.[11,12] All patients had undergone coronary angiography and had significant coronary artery disease with a culprit lesion suitable for PTCA. Patients were enrolled within 24 hours after diagnostic angiography. Before enrollment, all patients gave informed consent.

The exclusion criteria applied for the CAPTURE main trial also applied for the present ECG-ischemia monitoring substudy. For the latter, patients with ECG abnormalities, such as left bundle branch block, left ventricular hypertrophy, or an artificial pacemaker device, rendering ST-segment interpretation unreliable, were also excluded.

After enrollment, patients received a minimal daily dose of 50 mg aspirin. In patients who were not taking aspirin at the time of enrollment, the first dose was a minimum of 250 mg. Heparin was administered before randomization until at least 1 hour after PTCA and adjusted to an activated partial thromboplastin time between 2.0 and 2.5 times normal. All patients received intravenous nitroglycerin. β-Blockers, calcium channel blockers, and other cardiovascular drugs were allowed (Table 1). In addition, patients received an abciximab 0.25 mg/kg bolus followed by a continuous infusion of 10 mg/min or matching placebo for 18 to 24 hours preceding PTCA and continuing for 1 hour after completion of the procedure.

During the hospital stay and 30-day follow-up, all events and medication were recorded, with special attention to recurrent ischemic symptoms.

Study End Points

The incidence and severity of recurrent ischemia were described in different parameters: the number of patients with recurrent ischemia, the number of ischemic episodes in patients with recurrent ischemia, and total ischemic burden across the placebo and abciximab patient groups.

As in the main study, MI during the index hospitalization was defined by CK-MB or CK levels exceeding 3 times the upper limit of normal in 2 samples and increased by 50% over the previous value, or an ECG with new significant Q waves in 2 or more contiguous leads. MI after discharge was defined by CK-MB or CK levels exceeding 2 times the upper limit of normal, or new significant Q waves in ≥2 contiguous ECG leads.

Continuous ST-Segment Monitoring

Continuous ECG monitoring was started preferably before but not later than 1 hour after enrollment. It was continued for at least 24 to 36 hours, including 6 hours after the PTCA procedure. The timing of the start of drug infusion and the moments of angiography and PTCA were obtained from the study case record forms.

Continuous ECG monitoring was performed using the MIDA 1000 vector-cardiographic ECG monitoring device (Ortivus Medical). This system calculates averaged QRS-T complexes from the Frank orthogonal X-Y-Z leads at 1-minute intervals. These averaged complexes were stored on hard disk and used for calculation of ST trend information. After completion of the monitoring period, the averaged ECG data were stored on a floppy diskette and sent to the core laboratory at Cardialysis in Rotterdam, The Netherlands, for subsequent editing and analysis.[4,7]

Editing and Analysis of ECG Data

All averaged X-Y-Z complexes were manually scanned and edited for artifacts, intermittent bundle-branch block, detection or marker errors, and postural changes. Postural changes were defined as a sudden change of the electrical axis or a sudden QRS amplitude shift. After editing, averaged 12-lead ECG complexes and 12-lead ECG trends were generated from the MIDA X-Y-Z leads, using the transformation formulas of Dower.[13] Trends of the ST-segment level measured at J point + 60 ms were generated for each single lead of this derived 12-lead ECG, except aVR.

Definition of ST Episodes

The onset of an ST episode was defined as a change in ST amplitude of at least ±100 μV from the baseline ST level in ≥1 of the 12 derived leads, developing within a 10-minute period and persisting for ≥1 minute. The end of an episode was defined as a return of the ST level within ±100 μV of the baseline ST level, again lasting for at least 1 minute. Episodes had to be separated from each other by ≥1 minute.

If ≥100 μV ST change was present in >1 lead simultaneously, the episode onset was defined by the lead exhibiting the first ST change ≥100 μV. Similarly, the end of an episode was defined by the lead exhibiting the latest return to baseline ST level. If chest pain was present during or within 15 minutes before or after a an ST episode, this ST episode was classified as symptomatic. An example of the ST trend analysis and representative ECG recordings is presented in Figures 1 and 2. An algorithm programmed according to these ST criteria for ischemia, was used for detection of ST episodes, with visual confirmation afterward. The ECG at moments of interest, either detected by the algorithm or by the operator, was documented on hard copy for visual inspection (Figure 2). An extensive report on the method of editing and analysis of ECG data developed and used by our core laboratory has been published recently.[4]

Ischemic Burden

Ischemic burden was calculated in 4 different ways: (1) as the sum of the duration of all episodes per patient; (2) as the sum of the area under the curve of the ST vector magnitude trend of all episodes per patient (Figure 3); (3) as the sum of the area under the ST trend curve of all leads involved in the ST episodes per patient; and (4) as the sum of the area under the ST trend curve of all 12 leads during ST episodes per patient (except aVR).

Statistical Analysis

Continuous variables are expressed as median and interquartile range (25th and 75th percentiles) and compared using the Mann-Whitney test. Discrete variables are described with percentages and were compared using Fisher's exact test. A two 2-tailed P value of ≤0.05 was considered statistically significant. The Kaplan-Meier method was used for evaluation of the time to a recurrent ST episode and of the time to the next ST episode, with censoring of data. Statistical difference was tested with the log rank test. Relative risks are given as univariate variables with 95% CIs.

TABLE 1. Baseline Data and Concomitant Medication

	ECG-Ischemia Monitoring Substudy		Main Study Patients Not Included in Substudy
	Placebo (n=163)	Abciximab (n=169)	All (n=933)
No. of males, (%)	111 (68.1)	107 (63.3)	702 (75.2)
Mean age, y, (SD)	62 (10)	60 (10)	61 (10)
Anthropometry, mean (SD)			
Weight, kg	77 (13)	77 (13)	75 (12)
Height, cm	172 (10)	171 (9)	169 (9)
Patients with, n (%)			
Angina >7 days previously	90 (56.3)	89 (54.6)	443 (48.2)
Infarction within previous 7 days	16 (9.8)	19 (11.2)	131 (14.0)
Infarction 8–30 days	6 (3.7)	9 (5.3)	81 (8.7)
Infarction >30 days previously	33 (20.2)	33 (19.5)	153 (16.4)
PTCA	24 (14.7)	25 (14.8)	121 (13.0)
CABG	8 (4.9)	3 (1.8)	21 (2.3)
Risk factors, n (%)			
Diabetes	17 (10.5)	19 (11.2)	141 (15.1)
Hypertension	58 (35.8)	65 (38.9)	409 (44.2)
Current smokers	71 (44.4)	66 (39.1)	353 (38.3)
Medication within 7 days before enrollment, n (%)			
Aspirin	143 (89.4)	149 (90.3)	865 (94.2)
Intravenous heparin	162 (99.4)	169 (100)	930 (99.7)
Nitrates	163 (100)	169 (100)	930 (99.9)
β-Blockers	116 (72.5)	125 (75.8)	583 (63.5)
Calcium antagonists	86 (53.8)	82 (49.7)	445 (48.5)
Medication after enrollment, n (%)			
Aspirin	158 (96.9)	164 (97.0)	890 (96.2)
Ticlopidine	4 (2.5)	3 (1.8)	43 (4.6)
Intravenous heparin	158 (100)	160 (100)	909 (100)
Nitrates	160 (98.2)	166 (98.2)	903 (97.6)
β-Blockers	118 (72.4)	122 (72.2)	567 (61.3)
Calcium antagonists	84 (51.5)	86 (50.9)	438 (47.4)

Percentages were calculated only for those patients for whom data was reported.

Results

In the CAPTURE study, a total of 1265 patients were included at 69 sites in 12 countries.[10] Three-hundred ninety-four patients were also enrolled in the ECG-ischemia monitoring substudy. Of these 394 patients, 62 (16%) were excluded from ECG analysis: 38 patients because of a late start of the ECG monitoring (>1 hour after the start of drug infusion or <50% analyzable ECG data), 22 patients because of technical failures due to errors on the part of the investigator, and 2 patients because of a time mismatch of monitoring data and the case record form. Thus, 332 patients (84%) had ECG recordings suitable for final analysis. Most patients (67%) experienced their ischemic episode qualifying for study entry within 12 hours before the start of the study drug, and 39% of the patients had their qualifying episode within 6 hours before enrollment. The majority of patients (193; 58%) had either ST-segment depression or elevation or both of ≥0.1 mV on their 12-lead ECG during the ischemic event, which qualified them for inclusion into the study. Seventy-five patients (23%) had T -wave changes only; and in 64 patients (19%), the entry ECG did not exhibit any ischemic abnormality, although ST-segment changes had been recorded during previous ischemic episodes.

CAPTURE Main Study Versus ECG-Ischemia Monitoring Substudy

Of the 332 patients suitable for ST analysis, 163 patients received placebo and 169 patients abciximab. Baseline data were well balanced among the 2 treatment groups and representative of the baseline data of the CAPTURE main study (Table 1). Death or MI within 5 days occurred in 17 (10.4%) of the placebo patients and 4 (2.4%) of the abciximab patients in the ECG-ischemia monitoring patient group (P=0.006) versus 40 (9.2%) and 23 (5.3%) of the patients

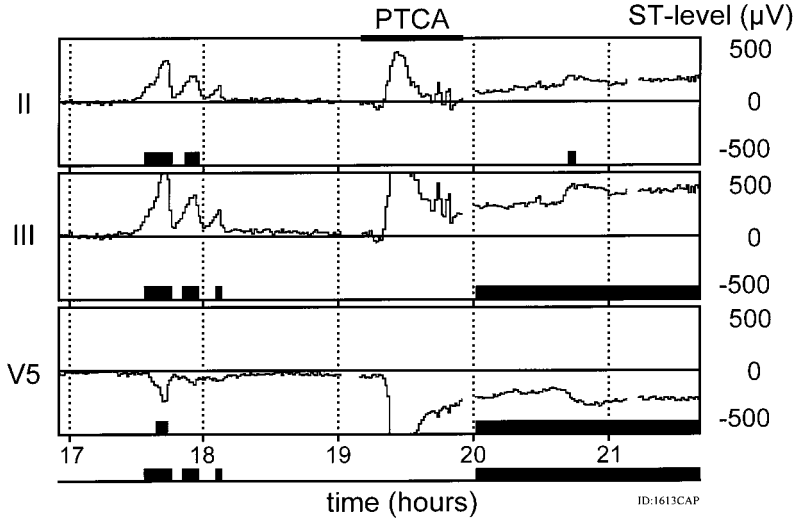

Figure 1. Example of the vector-derived 12-lead ST analysis of a study patient with unstable angina who had an MI as a complication of a PTCA procedure. The ST trends of the relevant leads in which ST episodes occurred and the MI developed are displayed. The black bars in each single-lead ST trend represent the time during which the algorithm detected an ST change ≥100 μV. Note that the number and duration of ST episodes differs across leads. At the bottom of the trend graphs, the black bars indicate the total duration and number of the ST episodes (ischemia), taking into account all leads involved. Before PTCA, 3 ischemic episodes occur around 17:30 and 18:00 hours. During angiography and PTCA, possibly at the moment of first injection of contrast, a sudden, severe ST-segment elevation developed in leads II and III with simultaneous ST-segment depression in lead V5. Subsequently, this ischemic event partially resolved, followed by 2 short peaks of ST-segment elevation/depression, which reflect the inflations of the balloon catheter. After the PTCA procedure, a persistent elevation of the ST segment is observed with depression in lead V5, suggesting a persistent occlusion leading to acute MI. MI in this patient was confirmed by a rise of CK and CK-MB to 4 and 3 times, respectively, the upper limit of normal and the development of Q waves. See also Figure 2.

receiving abciximab or placebo, respectively, who were not included in the ECG-ischemia monitoring substudy ($P=0.04$).

ECG-Ischemia Monitoring Substudy

The duration of the ECG monitoring periods before and after the PTCA procedure did not differ among treatment groups (Table 2).

Recurrent ischemia was detected in 31 (18%) of the 169 abciximab and in 37 (23%) of the 163 placebo patients. This difference was not statistically significant ($P=0.34$, Figure 4A). Yet, repetitive ischemia and total ischemic burden were significantly decreased in patients receiving abciximab, both for the period preceding the PTCA procedure and for the complete monitoring period (Table 3). Excluding the time period of the PTCA and the stay at the catheterization laboratory, only 9 (5%) of abciximab versus 22 (14%) of placebo patients had ≥2 ST episodes ($P=0.01$); only 5 (3%) of abciximab versus 15 (9%) of placebo patients had ≥3 ST episodes ($P=0.02$). Symptomatic episodes occurred in 5 (3%) of abciximab and 13 (8%) of placebo patients ($P=0.05$). These treatment effects were also apparent in the subgroup of 136 patients who exhibited ST-segment depression of ≥0.1 mV on their 12-lead ECG during the ischemic event that qualified them for entry into the study. These patients had more ischemic episodes than patients without ST-segment depression at study entry ($P=0.055$). In this subgroup, only 1 (2%) abciximab versus 9 (12%) placebo patients had ≥3 or more ST episodes ($P=0.02$). Total ischemic burden parameters (as defined by the duration of ischemia per patient, the sum of the area under the curve of the ST vector magnitude during ST episodes, the sum of the area under the ST trend

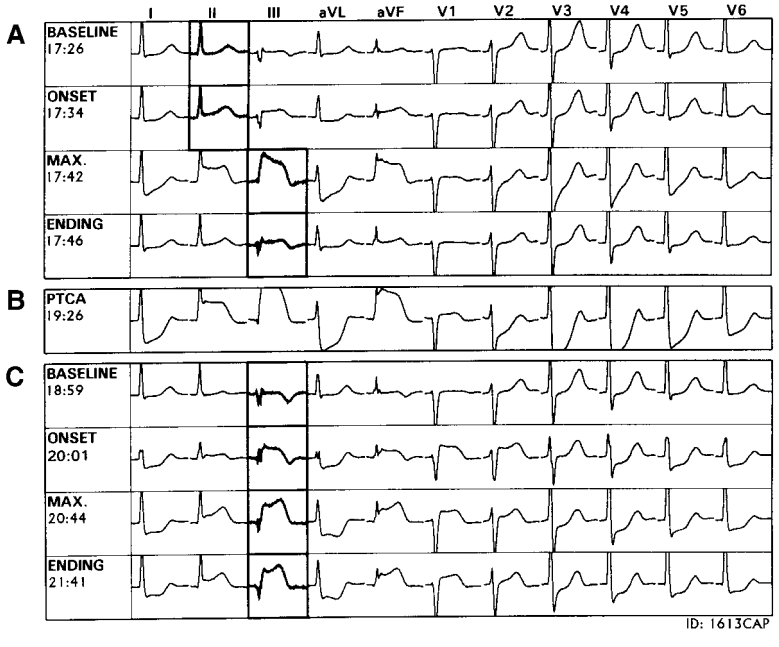

Figure 2. Samples of the computer assisted 12-lead ECG recording of the patient in Figure 1. A, Ischemic episode before PTCA, detected by the algorithm. The upper ECG row (17:26 hours) demonstrates the baseline "nonischemic" 12-lead ECG (except aVR). The ECG rows directly below demonstrate the time (17:34 hours) and ECG lead (indicated in bold) in which the ST episode occurred. ST changes are present in multiple leads, but the first ST change is detected in lead II. However, the maximum (MAX.) and ending of the episode are detected in lead III (17:46). B, ECG sample during PTCA. Note the severe ST-segment elevations in the inferior leads with simultaneous ST-segment depressions in leads V3 to V6. C, After PTCA, ST-segment elevations persist in the same area as during the procedure, suggesting an acute MI. As the ST measurements during the PTCA procedure were not included in the analysis, the algorithm used the last ECG template before PTCA as the reference "nonischemic" ECG (18:59). As such, the onset of ischemia is again detected directly after the procedure (20:01).

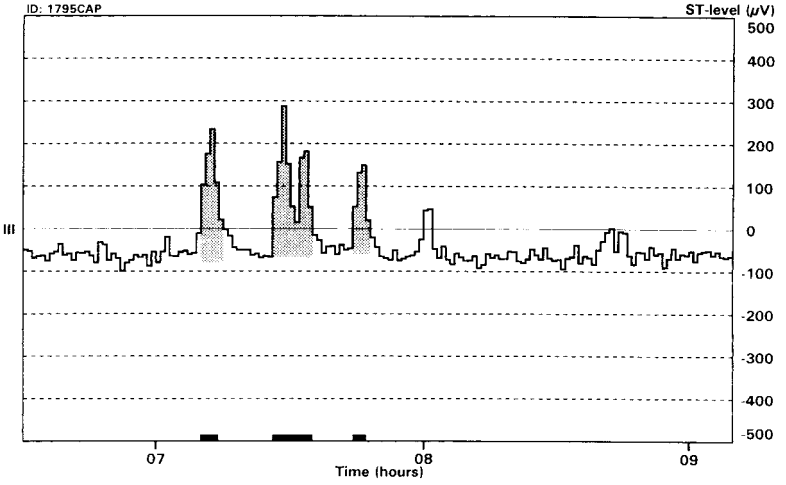

Figure 3. Measurement of the ischemic burden. For simplification, only a magnification of the ST trend of a single lead is displayed. Three ST episodes ≥100 μV are detected between 07:10 and 07:50 hours. The ST-segment elevations around 08:00 and 08:50 hours do not reach the threshold of 100 μV and are not classified as ST episodes. The area under the trend curve of the episodes is measured from the baseline ST level that is present at the moment of the beginning of the episode. These ST measurements are repeated for all 12 leads except aVR. Subsequently these values are summated, thus reflecting the total area under the curve for all leads involved. The same procedure is followed for the ST vector magnitude, but in this case the onset and ending of episodes remain defined by the ST onset and ending measurements taken from the vector-derived 12-lead ECG.

curve of all leads involved, or the sum of the area under the curve of all 12 leads during ST episodes) were reduced in favor of abciximab (Table 3). Thus, patients receiving abciximab had significantly less frequent and fewer severe ischemic episodes. Both the probabilities to remain free from a second ischemic episode after the start of monitoring and to remain free from a second ischemic episode after the first were significantly higher for patients receiving abciximab ($P=0.01$ and 0.02, respectively, Figure 4B and 4C).

The majority of clinical events occurred during and within 24 hours after PTCA. Eighteen patients had an MI, and 3 died within 5 days of treatment. Eventually, 24 patients developed MI or died within 30 days of follow-up (7.2%). The presence of chest pain without concomitant ST episodes during the monitoring period preceding the PTCA procedure was not related to an increased relative risk of subsequent events. However, the presence of any ST episode and especially of any symptomatic ST episode was associated with an increased relative risk of 3.2 (95% CI 1.4, 7.4; absolute risk 15%) and 4.1 (95% CI 1.4, 12.2; absolute risk 23%), respectively. This association also remained apparent for the occurrence of MI or death within 30 days.

Discussion

In the CAPTURE study, treatment with abciximab (c7E3 Fab, ReoPro) resulted in a 50% reduction in MI and 29% reduction in the primary composite end point of death, MI, or urgent (re)intervention in patients with refractory unstable angina.[10] The results of the present ECG-ischemia monitoring substudy, which included 332 of the 1264 patients of CAPTURE are consistent with these findings. Compared with placebo, treatment with abciximab resulted in a greater reduction of frequent ischemia and symptomatic ischemic episodes during continuous ECG-ischemia monitoring; it also resulted in a major reduction of ischemic burden in patients with ischemia. This extends the observation in CAPTURE that treatment with abciximab reduced the occurrence of MI during the 16- to 24-hour period of treatment before PTCA was performed. It is likely that the reduction of recurrent ischemia reflected stabilization of the plaque, resolution of thrombus, and prevention of recurrent thrombosis by abciximab, which led to the reduction of clinical events. This is supported by the observation that the presence of recurrent ischemia during the ST monitoring period before PTCA appeared strongly predictive of MI and death within the next 5 days; this is in concordance with previous studies using Holter ST monitoring, demonstrating that ischemic ST episodes relate to clinical outcome in patients with unstable angina.[14–17]

Our study demonstrates that ischemia, detected during vector-derived multilead ECG-ischemia monitoring, can be used as a study end point in patients with unstable coronary syndromes. The prevalence of ischemia using Holter ST monitoring or continuous ECG-ischemia monitoring techniques in patients with unstable angina has been reported as 50% to 70%.[4,14–17] This is in contrast to the lower percentage of patients (21%) exhibiting ischemia in the present study. It may be explained by the intensive therapy of these patients before enrollment in CAPTURE, which included aspirin, heparin, nitroglycerin, and β-blockers in most patients. It

TABLE 2. Duration of ST Monitoring Periods

	Placebo	Abciximab	All Patients
Patients, n	163	169	332
Total monitoring time, h*	28 (26, 29)	27 (26, 29)	28 (26, 29)
Duration of stay at cath-lab, h*	1.3 (1.0, 1.7)	1.3 (1.0, 1.7)	1.3 (1.0, 1.7)
Total analyzable monitoring time, h*	27 (24, 28)	26 (25, 28)	26 (25, 28)
Start study until PTCA, h*	20 (18, 21)	19 (18, 21)	20 (18, 21)
End PTCA until end monitoring, h*	6 (6, 7)	6 (6, 7)	6 (6, 7)
ECG data loss, %*	2 (1, 7)	2 (1, 5)	2 (1, 6)

*Median (25th, 75th percentiles).

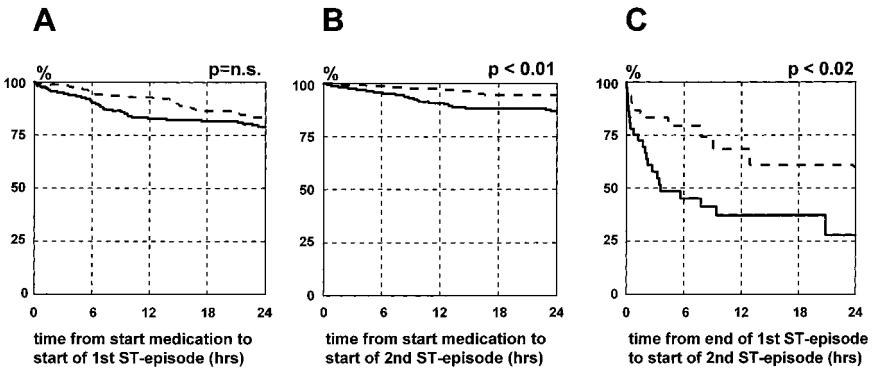

Figure 4. Kaplan-Meier estimate of the probability to remain free of an ST episode during the course of the monitoring period. A, Probability to remain free from a recurrent ST episode from the start of medication. The continuous curve represents the patients treated with placebo (163) and the dashed curve the patients treated with abciximab (169). B, Probability to remain free from a second ST episode from the start of medication. C, Probability to remain free from a second ST episode after the first one has ended. The continuous curve represents the patients with at least 1 ST episode treated with placebo (37) and the dashed curve the patients with at least 1 ST episode treated with abciximab (31). Both the probability to remain free from a second ischemic episode after the start of medication and the probability to remain free from a second ischemic episode after the first one appear significantly better for patients treated with abciximab.

suggests that some of these patients may already have been stabilized by this intensive therapy.

In patients without recurrent ischemia, as in patients without elevated troponin T levels,[18–20] the risk of MI and death is low, particularly when treated with a glycoprotein IIb/IIIa receptor blocker. Thus it may be questioned whether early PTCA is necessary. In patients who appear to have been stabilized through medical therapy (eg, abciximab), a PTCA procedure could possibly be deferred to a later time to allow further stabilization of the unstable plaque. On the other hand, patients with recurrent ischemia during ECG monitoring (as well as patients with elevated troponin T levels) exhibited a higher risk of MI or death.[20] This suggests that those patients who remain unstable will benefit from immediate or urgent invasive therapy and may benefit from treatment with abciximab both before and during PTCA. If urgent intervention is not possible, these patients should be stabilized with a platelet glycoprotein IIb/IIIa receptor blocker.

Conclusions

The present ECG-ischemia monitoring study, which was conducted as a substudy of CAPTURE,[10] demonstrates that treatment with abciximab versus placebo is associated with a reduction of frequent ischemia and a reduction of total ischemic burden in patients with refractory unstable angina both before (thus stabilizing patients) and after PTCA. The incidence of recurrent ischemia appeared lower than observed in patients with unstable angina studied shortly after hospital admission.[4,14–17] This indicates that, most patients tend to stabilize over time, particularly when treated with abciximab.

The presence of recurrent ischemia predicts MI or death both within 5 days' and at 30 days' follow-up. As such, continuous vector-derived 12-lead ECG monitoring appears to be a useful noninvasive tool for further risk stratification and selection of high risk unstable patients who may require invasive intervention and/or platelet glycoprotein IIb/IIIa receptor blocker therapy.

TABLE 3. ST Monitoring Results

	Period From Start of Study Until Balloon Angioplasty			Period Following Balloon Angioplasty			Total Monitoring Period		
	Placebo	Abciximab	*P*	Placebo	Abciximab	*P*	Placebo	Abciximab	*P*
Patients, n	163	169		155	162		163	169	
ST-episodes, n (%)									
≥1	29 (18)	24 (14)	NS	16 (10)	9 (6)	NS	37 (23)	31 (18)	NS
≥2	18 (11)	9 (5)	0.07	15 (10)	8 (5)	NS	22 (14)	9 (5)	0.01
≥3	12 (7)	3 (2)	0.02	2 (1)	0 (0)	NS	15 (9)	5 (3)	0.02
Symptomatic episodes	9 (6)	4 (2)	NS	6 (4)	1 (1)	0.06	13 (8)	5 (3)	0.05
Ischemic burden*									
Total duration per patient, min	12	6	NS	61	9	0.10	38	8	0.02
ST-VM, $\mu V \cdot min$	1293	677	NS	7084	796	0.06	4819	796	0.01
12-lead ST area, $\mu V \cdot min$	8832	4682	NS	45 599	3876	0.10	29 392	5376	0.01
ST area of leads ≥100 μV, $\mu V \cdot min$	2394	1383	NS	27 026	1858	NS	8558	1858	0.03

The number of ST episodes were compared using Fisher's exact test. Ischemic burden variables are given as medians and were compared using the Mann-Whitney test. A 2-tailed *P* value of ≤0.05 was considered statistically significant. Borderline-significant *P* values ≤0.10 are also indicated.

*Patients with ischemia only. Total duration indicates the sum of the duration of all episodes per patient; ST-VM, the sum of the area under the curve of the ST vector magnitude trend of all ST episodes per patient; 12-lead ST-area, the sum of the area under the ST trend curve of all 12 leads during ST episodes per patient (except a VR); and ST area of leads ≥100 μV, the sum of the area under the ST trend curve of all leads involved in the ST episodes per patient (except a VR).

Appendix

CAPTURE Study Organization

Steering Committee

M.L. Simoons (Chairman, The Netherlands); W. Rutsch (Co-Chairman, Germany); A. Vahanian (France); J. Adgey (United Kingdom); A. Maseri and C. Vassanelli (Italy); J. Col (Belgium); A. Adelman (Canada); C. Macaya (Spain); H. Miller (Israel); M.J. de Boer (The Netherlands); and R. McCloskey and H. Weisman (United States).

Clinical Endpoint Committee

The Netherlands: F. Bär (Chairman), Maastricht; J.W. Deckers, Rotterdam; J.J. Piek, Amsterdam; A.P.J. Klootwijk, Rotterdam; V. Manger Cats, Leiden; W. Bruggeling, Oosterhout; F. Jonkman, Rotterdam; P. van der Meer, Rotterdam; V. Umans, Alkmaar; D. Foley, Rotterdam; T. Ansink, Rotterdam; D. Keane, Rotterdam; D. Sane, Rotterdam (thrombocytopenia review); P. Koudstaal, Rotterdam (stroke review, Rotterdam). Belgium: P. Block, Brussels.

Angiography Committee

M.J.B.M. van den Brand (Chairman, The Netherlands); G.J. Laarman (The Netherlands); G. Hendrickx (Belgium); I. de Scheerder, (Belgium); P.G. Steg (France); K. Beat (United Kingdom).

Coordinating Centers

M. Hoynck van Papendrecht, M. Daniëls, T. Poulussen, J. de Graaf (Centocor, The Netherlands); T. Lenderink (Cardialysis, The Netherlands); T. de Craen (Academic Medical Center, Amsterdam, The Netherlands); S. Cabacowic (EuroBiopharm, The Netherlands); T. Schaible, K. Anderson, A. Wang, S. FitzPatrick (Centocor, United States); S. Malbrain, J. Paul, M. Dijkhuizen, K. Verhamme, I. Nelissen, (Besselaar, Belgium); M. Gibbs (Besselaar, United Kingdom); S. Marron (Besselaar, Ireland); S. Lochu, C. Guiot (Besselaar, France); P. Ferrari, A. Vizzotto, (Besselaar, Italy); A. Alémany, E. Mahillo (Besselaar, Spain); S. Hoffmann (Besselaar, Germany); L. Stahl (Besselaar, Sweden); and D. Kafka (Besselaar, Israel).

Study Centers, Principal Investigators, and Study Coordinators Participating in the ECG-Ischemia Monitoring Substudy

The Netherlands

Ziekenhuis De Weezenlanden, Zwolle (M.J. de Boer, H. Suryapranata, A.L. Liem, G. Velsink); Onze Lieve Vrouwe Gasthuis, Amsterdam (G.J. Laarman, R. van der Wieken, J.P. Ezechiëls, S. Zonneveld); Thoraxcentrum Erasmus Universiteit en Academisch Ziekenhuis Rotterdam-Dijkzigt (M.L. Simoons, M. van den Brand, C. van der Zwaan, P.P. Kint); Catharina Ziekenhuis, Eindhoven (R.M. Michels, P. Van der Voort, I. van de Kerkhof, C. Hanekamp); Academisch Ziekenhuis Groningen (J. Peels, L. Drok, P. den Heijer); and St Antonius Ziekenhuis, Nieuwegein (T. Plokker, E.G. Mast, K. Marquez).

France

Hôpital Tenon, Paris (A. Vahanian, E. Garbarz, O. Nallet, B. Farrah); and Hôpital Bichat, Paris (J.J.M. Juliard, P.G. Steg).

Belgium

Onze Lieve Vrouwe Ziekenhuis, Aalst (G. Heyndricks, F. Staelens, B. de Bruyne); and Hôpital St Luc, Brussels (J. Col, K. al-Schwafi).

Germany

Universitätsklinikum Rudolf Virchow, Berlin-Buch (D. Gulba, R. Dechend, S. Christow); Universitätsklinikum Charitéb, Berlin (W. Rutsch, C. Brunckhorst); and Klinikum der Christian Albrechts Universität, Kiel (R. Simon, N. Al Mokthari).

References

1. Krucoff MW, Croll MA, Pope JE, Granger CB, O'Connor CM, Sigmon KN, Wagner BL, Ryan JA, Lee KL, Kereiakes DJ. Continuous 12-lead ST-segment recovery analysis in the TAMI 7 study: performance of a noninvasive method for real-time detection of failed myocardial reperfusion. *Circulation*. 1993;88:437–446.
2. Dellborg M, Steg PG, Simoons M, Dietz R, Sen S, van den Brand M, Lotze U, Hauck S, van den Wieken R, Himbert D. Vectorcardiographic monitoring to assess early vessel patency after reperfusion therapy for acute myocardial infarction. *Eur Heart J*. 1995;16:21–29.
3. Klootwijk P, Langer A, Meij S, Green C, Veldkamp RF, Ross AM, Armstrong PW, Simoons ML, for the GUSTO-I ECG-ischaemia monitoring substudy. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST-segment monitoring in the GUSTO-I trial. *Eur Heart J*. 1996;17:689–698.
4. Klootwijk P, Meij S, von Es GA, Muller EJ, Umans VA, Lenderink T, Simoons ML. Comparison of usefulness of computer assisted continuous 48-hours 3-lead with 12-lead ECG ischaemia monitoring for detection and quantitation of ischaemia in patients with unstable angina. *Eur Heart J*. 1997;18:931–940.
5. Davies MJ, Thomas AC. Plaque fissuring: the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J*. 1985;53:363–373.
6. Falk E. Unstable angina pectoris with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation*. 1985;71:699–705.
7. Simoons ML, de Boer MJ, van den Brand MJBM, van Miltenburg AJM, Hoorntje JCA, Heyndrickx GR, van der Wieken LR, de Bono D, Rutsch W, Schaible TF, Weisman HF, Klootwijk P, Nijssen K, Stibbe J, de Feyter PJ, and the European Cooperative Study Group. Randomized trial of a GPIIb/IIIa platelet receptor blocker in refractory unstable angina. *Circulation*. 1994;89:596–603.
8. EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk coronary angioplasty. *N Engl J Med*. 1994; 330:956–961.
9. Topol EJ, Califf RM, Weisman HF, Ellis SG, Tcheng JE, Worley S, Ivanhoe R, George BS, Fintel D, Weston M, on behalf of the EPIC Investigators. Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet*. 1994;343:881–886.
10. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet*. 1997;349:1429–1435.
11. Braunwald E. Unstable angina: a classification. *Circulation*. 1989;80: 410–414.
12. van Miltenburg AJM, Simoons ML, Veerhoek RJ, Bossuyt PMM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. *J Am Coll Cardiol*. 1995;25:1286–1292.
13. Dower GE, Machado HB, Osborne JA. On deriving the electrocardiogram from vectorcardiographic leads. *Clin Cardiol*. 1980;3:87–95.
14. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischaemia as a marker of early unfavourable outcomes in patients with unstable angina. *N Engl J Med*. 1986;314:1214–1219.
15. Romeo F, Rosano GM, Martuscelli E, Valente A, Reale A. Unstable angina: role of silent ischaemia and total ischaemic time (silent plus painful ischaemia), a 6-year follow-up. *J Am Coll Cardiol*. 1992;19: 1173–1179.
16. Nademanee K, Intarachot V, Josephson MA, Reiders D, Mody Vaghaiwalla F, Sigh BN. Prognostic significance of silent myocardial ischaemia in patients with unstable angina. *J Am Coll Cardiol*. 1987; 10:1–9.
17. Langer A, Freeman MR, Armstrong PW. ST-segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. *J Am Coll Cardiol*. 1989;13:1495–1502.
18. Lindahl B, Venge P, Wallentin L, for the FRISC Study Group. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease: The FRISC study group. *Circulation*. 1996;93: 1651–1657.
19. Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell FE, Califf RM, Topol EJ, for the GUSTO -IIa Investigators. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med*. 1996;335:1333–1341.
20. Hamm CW, Heeschen C, Goldmann BU, Barnathan E, Simoons ML, for the CAPTURE Investigators. Value of troponins in predicting therapeutic efficacy of abciximab in patients with unstable angina. *J Am Coll Cardiol*. 1998;31:185A. Abstract.