Dynamic computer-assisted ST segment monitoring in patients with acute coronary syndromes

Dynamische computerondersteunde ST segment monitoring bij patiënten met acute coronaire syndromen

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Voor Jolanda
Voor Alex, Sandra en Mark

Contents

Chapter 1

Introduction

Since the first recording of the human electrical activity of the heart by Waller in 1887[1] and the invention of the electrocardiograph by Willem Einthoven in 1902[2], the recording of the electrocardiogram (ECG) has evolved into one of the most important noninvasive diagnostic techniques of today-cardiology[3]. In particular, the diagnosis of cardiac arrhythmias, myocardial ischemia and myocardial infarction depends on the use of routine ECG recordings. The development of continuous ECG recording techniques such as long term ambulatory ECG recording (Holter) made it also possible to document less frequently occurring cardiac arrhythmias or ischemic events occurring during daily life.

It has now been well established that long term continuous Holter ST segment recording can identify unstable angina patients with silent myocardial ischemia who are at a high risk of sustaining a major cardiovascular event[4,5]. However, Holter ST recording has the major limitation that it can only provide information on risk prediction using retrospective data (off-line analysis). As such, this technique is not suitable for on-line risk prediction of imminent cardiac events. Over the past 7 years, computer-assisted continuous multilead ECG monitoring techniques have become available for real-time ECG and ST segment monitoring[6]. These techniques have overcome the limitations of earlier ECG technologies as they can record and display the complete 12-lead and / or vector ECG on-line and allow both on-line and retrospective analysis. It offers the possibility of on-line noninvasive monitoring of the vessel status in patients with unstable coronary syndromes, which is becoming increasingly important to monitor the effects of thrombolytics, anti-thrombin and anti-coagulant therapy, platelet inhibitors, and advanced intracoronary intervention.

The present thesis evaluates the usefulness of computer-assisted continuous multilead ECG monitoring techniques for detection and quantitation of myocardial ischemia, prediction of coronary vessel status and for identification of patients at risk of major coronary events.

ECG MONITORING OF VESSEL STATUS IN PATIENTS WITH AN ACUTE MYOCARDIAL INFARCTION RECEIVING REPERFUSION THERAPY

Early reperfusion and sustained patency of the infarct-related coronary artery are important determinants of survival[7]. Thus, more aggressive therapy may be indicated if thrombolytic therapy fails to open up the occluded vessel or if reocclusion of an initially reperfused coronary artery occurs. In contrast, administration of thrombolytic agents might be discontinued to minimize bleeding risk in patients with a rapidly reperfused artery[8]. In this manner, therapy of acute myocardial infarction could be tailored to the status of the infarct-related vessel[9]. In order to guide the therapy, continuous monitoring of the vessel status is mandatory. Coronary angiography is the gold standard to assess patency and (re)occlusion. However, angiography supplies only very momentary information on the status of the infarct-related vessel and this invasive technique is not useful for continuous monitoring.

Noninvasive methods for monitoring of reperfusion of the infarct-related vessel include clinical markers such as resolution of chest pain, electrocardiographic findings such as the occurrence of an accelerated idioventricular rhythm and normalization of the ST segments and monitoring of specific cardiac proteins in plasma[10-13]. Resolution of chest pain is very subjective and may frequently be related to analgesic medication. The occurrence of an accelerated idioventricular rhythm suggesting reperfusion is highly specific but not sufficiently sensitive to predict reperfusion. Thus, monitoring of ST segment normalization seems best suitable for reliable prediction of coronary vessel status. In this overview, the usefulness of the different electrocardiographic techniques for detection of reperfusion and patency of the infarct-related artery is discussed.

The standard 12-lead electrocardiogram for detection of reperfusion and patency

Rapid resolution of ST segment elevation after reperfusion, as documented by coronary angiography, occurs with an almost 5 fold faster time course than the changes associated with the natural evolution of acute myocardial infarction without reperfusion[14-18]. Thus, rapid resolution of ST segment elevation is a marker of reperfusion.

Many studies evaluated the usefulness of ST segment recovery from serial 12-lead ECGs as a marker of reperfusion using coronary angiography as the golden standard[11,19-24]. For proper comparison, the ideal study design should allow for angiographic assessment to be performed immediately after (and not before) the final ECG assessment. Furthermore, assessment of patency is most important during the first few hours following thrombolytic therapy as this may directly influence treatment strategies[9]. Unfortunately, many studies appear invalid because of late angiography[22-24], intercurrent angiography before the final ECG assessment[20,21], or absence of well defined criteria for ST recovery[11]. One of the first studies in this field by Clemmensen *et al.*[19] still appears to be the most valid. This study comprised 53 patients with an acute myocardial infarction treated with thrombolytic therapy. Two serial ECGs were recorded, one on admittance, the other approximately 180 minutes after thrombolytic therapy. Directly following the second ECG, angiographic patency was assessed, using the classification of the Thrombolysis in Myocardial Infarction trial (TIMI) at first injection of contrast[25]. Reduction of the sum ST elevation of ≥ 20%(measured at the J-point) within the pre-defined time interval of 180 minutes rendered sensitivity and specificity of 88 and 80%, respectively, for ECG versus angiographic patency assessment.

Reviewing all the results of the studies on early patency assessment using serial 12-lead ECGs, it appears that a rapid reduction of ST segment elevation or depression of ≥ 20-50% of the highest previous ST value, occurring within 3 hours from start of thrombolytic therapy, is a reasonably accurate predictor of reperfusion. Absence of rapid ST recovery suggests occlusion. Depending on the severity of ST elevation on the initial ECG, the use of either the single lead with maximal ST deviation ("worst lead") or the total ST change of the summated leads may be appropriate. If major ST deviations are present on the initial ECG, the ST recovery applied to the single worst lead is preferable, while the reduction of the summated ST deviation may be more useful in cases of mild ST deviation.

The conflicting results of the studies using serial 12-lead ECG recording for prediction of reperfusion and patency reflect the limitations using this serial method. Coronary reperfusion is a dynamic, rapidly changing process which is often accompanied by intermittent or sustained reocclusion and cyclic flow changes[26,27]. These dynamic changes may remain unrecognized if serial ECG recording is used for monitoring. The time interval between

the serial ECGs may be crucial for accurate detection of reperfusion and interpretation of the coronary status. For example, serial ECG recording may suggest a persistent coronary occlusion if it is taken at the moment of an undetected delayed ST (re-)elevation peak which precedes the moment of ST segment elevation recovery. On the other hand, if an ECG is taken at the moment of a re-elevation episode (reocclusion) that followed the first period of ST recovery, the initial reperfusion following thrombolysis will be missed (Figure 1 and 2). As failed reperfusion and reocclusion may require different treatment strategies (for example rescue PTCA, respectively directed anti-platelet therapy), this time resolution problem may lead to erroneous decision making. Therefore it is more appropriate to use continuous ECG monitoring techniques, in order to avoid less accurate assessments of reperfusion and patency.

Continuous ECG monitoring techniques

Several continuous ECG monitoring techniques have been evaluated for the assessment of reperfusion and patency following reperfusion therapy. Holter ST segment recording was the first technique to monitor the ST segment continuously. However, it has some major limitations. Firstly, only a restricted number of leads can be monitored, which may not always reflect the area with maximal ST deviation. Furthermore, Holter ST monitoring allows for retrospective analysis only. This makes immediate feedback impossible and thus the technique cannot be used for on-line ST segment monitoring and tailoring of reperfusion therapy. This may explain why only few studies are reported evaluating this technique for early patency assessment. The two most representative studies are those from Hohnloser and Krucoff[12,28]. Both studies demonstrate that Holter ST segment recording may be used for ischemia monitoring.

Building on this experience, computer-assisted continuous multilead ECG monitoring techniques have become available for real-time noninvasive patency assessment. These techniques use continuous ECG sampling and averaging techniques, offering a continuous real-time accurate measurement of the QRS complex and ST segment.

Two different approaches for computer-assisted ECG analysis have been developed: continuous multilead ST segment monitoring, based on on-line analysis of the conventional 12-lead ECG, using either measurements of the

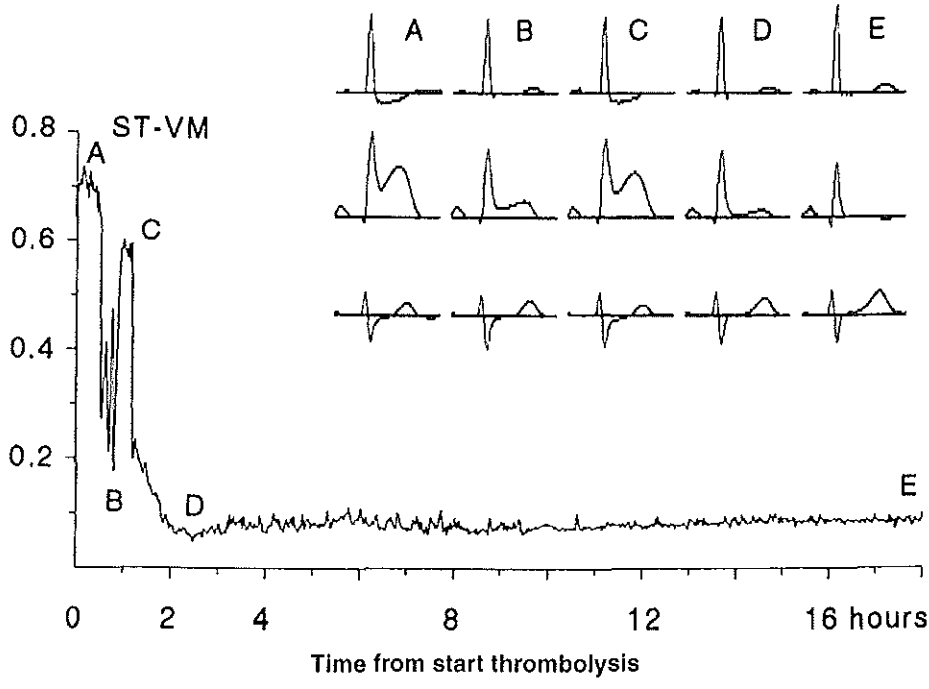

Figure 1. Continuous ECG recording (vector ECG leads X, Y, -Z) in a patient with an inferior wall myocardial infarction. Leads X, Y, -Z more or less resemble V5, II and V2. On admittance, (A) considerable ST elevation is present in lead Y. The ST vectormagnitude (ST VM, magnitude of the sum-vector of the ST deviation in X, Y, Z) decreases as a result of thrombolytic therapy (B), followed by recurrent ST elevation (C). Thereafter, the ST level stabilizes (D-E). Most probably reperfusion (B) and a short episode of "reocclusion" (C) occur, the latter most probably due to a washout and subsequent embolization of thrombus into the distal branches of the culprit coronary artery, followed by a permanent reperfusion of the infarcted area (D-E). Note: if only serial ECG measurements would have been taken, e.g. at moments A and C, the first moment of reperfusion (B) might have been missed, resulting in erroneous interpretation of the myocardial perfusion status.

single leads (Siemens Medical Electronics, Danvers, Massachusetts USA)[29] or the summated ST level (Mortara Instrument, Milwaukee, USA)[30] and continuous vectorcardiographic ECG monitoring, which offers the possibility to study both on-line vectorcardiographic QRS complex and ST segment changes simultaneously (Mida 1000 and Coronet, Ortivus Medical, Täby, Sweden)[31].

Using these continuous digital monitoring techniques, five distinct patterns

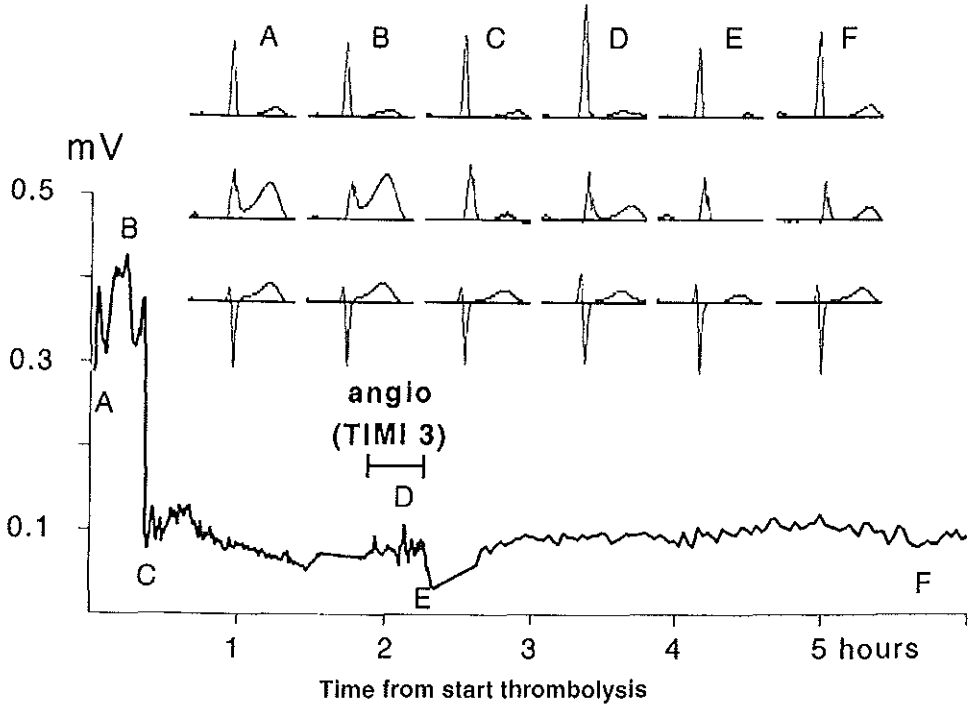

Figure 2. Continuous ECG recording (vector ECG leads X, Y, Z) in a patient with an inferior wall myocardial infarction. After the start of thrombolytic therapy the ST vectormagnitude decreases and increases over time, suggesting fluctuations of impaired myocardial perfusion. Peak ST elevation occurs at moment B, followed by a rapid ST recovery, which is completed at moment C, suggesting myocardial reperfusion. At moment D, coronary angiography is performed. A proximal stenosis of the right coronary artery was found, with TIMI 3 flow at first injection of contrast. The small ST VM peaks reflect injections of contrast.

of ST segment behavior following thrombolysis have been observed[27,31]: (1) rapid ST recovery without re-elevation, (2) rapid ST recovery following a delayed ST elevation peak, (3) persistent ST elevation without a recovery pattern, (4) rapid ST recovery followed by recurrent ST elevation and (5) a delayed ST elevation peak followed by a rapid ST recovery and recurrent ST elevation. The first three patterns may directly point to the status of the infarct-related vessel. Rapid ST recovery without re-elevation or a rapid ST recovery following a delayed ST elevation peak both are highly suggestive of reperfusion of the infarct-related artery. Persistent ST elevation without

Table 1. Continuous ECG monitoring for prediction of coronary reperfusion after thrombolytic therapy.

Study	Technique	Criteria for reperfusion	Interval thrombolysis angiography	No. of pts	% with criteria	Sens. %	Spec. %	Pos/neg. pred. value %	Comment on study
Hohnloser [12]	Holter	≥ 50% ↓ ST el. one of two leads within 90 min. after thr.lysis	60-90 min.	82	48	60	95	97 / 42	only 2 leads short assessment interval
Krucoff [28]	Holter	achievement of ST steady state within 100 min. after thr.lysis	100 min.	36*	56	89	82	85 / 87	less confined criteria selected group of pts.
Krucoff [27]	continuous 12-lead	< 50% ↓ or re-el. single lead or Σ ST at contrast injection	< 6 hrs.	22	?	90**	92**	?	large, not defined assessment interval small study
Krucoff [32]	continuous 12-lead	< 50% ↓ or re-el. single lead or Σ ST at contrast injection	90 min.	144	73	90	64	87 / 71	larger study correct study design short assessment interval
Dellborg [31]	vector-cardiography	QRSVD and STVM qualitative evaluation	at least 15 min.	21	76	94	80	94 / 80	pilot study assessment interval not defined
		QRSVD increase ≥ 0.1 μVs/min, plateau < 2 hrs.		21	86	94	40	83 / 67	
Dellborg [34]	vector-cardiography	QRSVD increase ≥ 0.1 μVs/min, plateau < 2 hrs. STVM decrease ≥ 0.83 μV/min qualitative evaluation	90 min.	96	65	83	73	89 / 61	correct study design short assessment interval

* Totally occluded vessel at initial angio. ** Sensitivity and specificity for assessment of occlusion.
Positive predictive value: predictive value for patency. Negative predictive value: predictive value for occlusion.
QRSVD: QRS Vector Difference. STVM : ST Vector Magnitude. El = elevation. ? = unspecified.

a recovery pattern suggests persistent occlusion, provided that significant ST elevation is present at the start of the monitoring period. Rapid ST recovery followed by recurrent ST elevation or a delayed ST elevation peak followed by a rapid ST recovery and recurrent ST elevation may be less specific and may suggest unstable reperfusion. Patency assessment may then be difficult.

The first representative studies evaluating continuous multilead ECG and vectorcardiographic monitoring are listed in Table 1. Krucoff *et al.* reported on either the presence of one episode of ≥ 50% ST recovery (worst single lead or the sum ST deviation of all 12 leads), its absence, or recurrent ST elevation, using continuous updated 12-lead computer-assisted ST monitoring[27]. Absence of ST recovery or re-elevation at the moment of angiographic assessment predicted occlusion of the infarct-related vessel with sensitivity of 90 and specificity of 92%. However, the time interval between start of thrombolysis and final ECG and angiographic assessment was rather long, up to 6 hours and only 22 patients were studied. Later that year, the same author reported a larger study-population of 144 patients with the moment of ECG assessment and angiographic validation situated at 90 minutes following thrombolysis. Sensitivity and specificity for prediction of occlusion were 64 and 90% respectively with predictive values for reperfusion and occlusion of 87 and 71%[32].

Dellborg *et al.* reported on vectorcardiographic assessment of reperfusion and patency using continuous vectorcardiographic monitoring[31,33,34]. All of his studies used both QRS vector difference and ST vector magnitude changes for prediction of patency. In a pilot study of 21 patients, sensitivity and specificity for patency at angiography were 94% and 80% respectively if a rapid change of both the QRS vector difference and the ST vector magnitude was observed, ending in a steady state. If only the QRS vector difference changes were used, sensitivity remained 94%, but specificity dropped to 40%[33]. In a later study, Dellborg *et al.* studied 96 patients using computer-assisted vectorcardiographic monitoring[34]. More refined criteria were used and the angiographic assessment interval was fixed at 90 minutes as much as possible. Sensitivity and specificity for identification of patency were 83% and 73% respectively.

This thesis reports the results of the GUSTO-I ECG-ischemia monitoring study, a substudy of GUSTO-I (GUSTO = Global Utilization of Streptokinase

and Tissue plasminogen activator for Occluded coronary arteries)[35]. In chapter 2, the usefulness of continuous ST segment monitoring for noninvasive prediction of reperfusion and patency in this well defined large patient series is evaluated. Chapter 3 describes the differences in speed and stability of ST segment recovery in the four treatment groups of this GUSTO-I ECG-ischemia monitoring substudy. Chapter 4 reports on the prognostic significance of ST segment shift early after thrombolytic therapy in this patient group.

ECG MONITORING OF VESSEL STATUS IN PATIENTS WITH UNSTABLE ANGINA

Patients with unstable angina who are treated with intensive medical therapy may still suffer from early unfavorable cardiac events. The identification of these high risk patients mainly depends on the presence of clinical symptoms coinciding with transient ST and T wave changes on the 12-lead ECG. It has been demonstrated that prognosis does not depend on the mere presence of symptoms but rather on the recurrence of either silent or symptomatic myocardial ischemia and the presence of minor myocardial damage or multivessel coronary artery disease[4,5,36,37,38,39]. Immediate relief of the ischemic burden in the early phase of unstable angina either by percutaneous transluminal coronary angioplasty or surgical revascularization may improve clinical outcome and reduce the number of recurrent cardiac events in such patients[40]. Real-time continuous ECG monitoring techniques may help to identify these high risk patients[41-43].

Chapter 5 reports a study in patients with unstable angina and describes a new, on-line method for detection and quantitation of ischemic events using computer-assisted continuous ECG ST recording. The study investigated whether the selection and number of ECG leads used for ST monitoring might influence the detection and quantitation of ischemia. On-line continuous 48-hours "12-lead" (except lead aVR) was compared with 3-lead ST monitoring in 130 unstable angina patients.

The safety and efficacy of efegatran sulphate, a new anti-platelet drug, compared to heparin in patients with unstable angina is assessed in chapter 6. Safety was assessed both clinically and by measurement of clinical laboratory parameters. Efficacy was assessed primarily by measurement of

the number of patients experiencing episode of recurrent ischemia as measured by computer-assisted continuous ECG-ischemia monitoring.

Chapter 7 describes the results of the "CAPTURE" ST segment monitoring substudy (**c**7E3 Fab **A**nti **P**latelet **T**herapy in patients with **U**nstable **RE**fractory angina). The ST monitoring substudy of this large trial investigated if c7E3, now better known as abciximab, reduces recurrent ischemia during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment.

The overall results, therapeutic implications and future directions of dynamic computer-assisted ECG monitoring are discussed in chapter 8.

REFERENCES

1. Waller AD. A demonstration on man of electromotive changes accompanying the heart's beat. J Physiol (Lond) 1887; 8: 229-34.
2. Einthoven W. Galvanometrische registratie van het menschelijk electrocardiogram. In: Herinneringsbundel Professor S. S. Rosenstein. Leiden: Eduard Idjo 1902: 102-7.
3. Fye WB. A history of the origin, evolution and impact of electrocardiography. Am J Card 1994; 73: 937-49.
4. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker of early unfavourable outcomes in patients with unstable angina. N Engl J Med 1986; 314: 1214-9.
5. Gottlieb SO, Gerstenblith G. Assessing the total ischemic burden in the management of unstable angina. Am J Med 1986; 81(4A): 7-11.
6. Dellborg M; Riha M; Swedberg KJ. Dynamic QRS and ST-segment changes in myocardial infarction monitored by continuous on-line vectorcardiography. Electrocardiol 1990; 23 Suppl: 11-9.
7. Simoons ML, Vos J, Tijssen JGP, Vermeer F, Verheugt FWA, Krauss XH, Cats VM. Long term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of The Netherlands. J Am Coll Cardiol 1989; 14: 1609-15.
8. Arnold AER, v. der Vlugt MJ, Boersma H, Barrett MJ, Burgersdijk C, Simoons ML. Tailored thrombolytic therapy for evolving myocardial infarction: stopping alteplase infusion on signs of reperfusion. Eur Heart J 1995; 13 Abstr. Suppl.: 132.
9. Simoons ML, Arnold AER. Tailored thrombolytic therapy. A perspective. Circulation 1993; 88: 2556-64.
10. Califf RM, O'Neill W, Stack RS, Aronson L, Mark DB, Mantell S, George BS, Candela RJ, Kereiakes DJ, Abbottsmith C, Topol EJ. Failure of simple clinical measurements

to predict reperfusion status after intravenous thrombolysis. Ann Intern med 1988; 108: 658-62.
11. Kircher BJ, Topol EJ, O'Neill WW, Pitt B. Prediction of infarct coronary artery recanalization after thrombolytic therapy. Am J Cardiol 1987; 59: 513-5.
12. Hohnloser SH, Zabel M, Kasper W, Meinertz T, Just H. Assessment of coronary artery patency after thrombolytic therapy: accurate prediction utilizing the combined analysis of three noninvasive markers. J Am Coll Card 1991; 18: 44-9.
13. Shah PK, Cercek B, Lew AS, Ganz W. Angiographic validation of bedside markers of reperfusion. J Am Coll Card 1993; 21: 55-61.
14. von Essen R, Merx W, Effert S. Spontaneous course of ST-segment elevation in acute anterior myocardial infarction. Circulation 1979; 59: 105-12.
15. Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. Circulation 1981; 63: 307-15.
16. Anderson JL, Marshall HW, Bray BE, Lutz JR, Frederick PR, Yanowitz FG, Datz FL, Klausner SC, Hagan AD. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N Engl J Med 1983; 308: 1312-8.
17. Blanke H, Scherff F, Karsch KR, Levine RA, Smith H, Rentrop P. Electrocardiographic changes after streptokinase-induced recanalization in patients with acute left anterior descending artery obstruction. Circulation 1983; 68: 406-12.
18. von Essen R, Schmidt W, Uebis R, Edelmann B, Effert S, Silny J, Rau G. Myocardial infarction and thrombolysis. Electrocardiographic short term and long term results using precordial mapping. Br Heart J 1985; 54: 6-10.
19. Clemmensen P, Ohman M, Sevilla DC, Peck S, Wagner NB, Quigley PS, Grande P, Lee KL, Wagner GS. Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. Am J Cardiol 1990; 66: 1407-11.
20. Saran RK, Been M, Furniss SS, Hawkins T, Reid DS. Reduction in ST-segment elevation after thrombolysis predicts either coronary reperfusion or preservation of left ventricular function. Br Heart J 1990; 64: 113-7.
21. Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction: use of the ST segment as a non-invasive marker. Br Heart J 1988; 60: 275-80.
22. Nicolau JC, Lorga AM, Garzon SAC, Jacob JLB, Machado NCS, Bellini AJ, Greco OTG, Marques LAF, Braile DM. Clinical and laboratory signs of reperfusion: are they reliable? Int J Cardiol 1989; 25: 313-20.
23. Barbash GI, Roth A, Hod H, Miller HI, Rath S, Har-Zahav Y, Modan M, Seligson U, Battler A, Kaplinski E, Rabinowitz B, Laniado S. Rapid resolution of ST-elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): results of the Israeli study of early intervention in myocardial infarction. Br Heart J 1990; 64: 241-7.

24. Richardson SG, Morton P, Murtagh JG, Scott ME, O'Keeffe DB. Relation of coronary arterial patency and left ventricular function to electrocardiographic changes after streptokinase treatment during acute myocardial infarction. Am J Card 1988; 61: 961-5.
25. The TIMI Study Group: The Thrombolysis in Myocardial Infarction (TIMI) Trial. N Engl J Med 1985; 312: 932-6.
26. Kwon K, Freedman SB, Wilcox I, Allman K, Madden A, Carter GS, Harris PJ. The unstable ST segment early after thrombolysis for acute infarction and its usefulness as a marker of recurrent coronary occlusion. Am J Card 1991; 67: 109-15.
27. Krucoff MW, Croll MA, Poe JE, Pieper KS, Kanai PM, Granger CB, Veldkamp RF, Wagner BL, Sawchak ST, Califf RM. Continuously updated 12-lead ST-segment recovery analysis for myocardial infarct artery patency assessment and its correlation with multiple simultaneous early angiographic observations. Am J Cardiol 1993; 71: 145-51.
28. Krucoff MW, Green CE, Satler LF, Miller FC, Pallas RS, Kent KM, Del Negro A, Pearle DL, Fletcher RD, Rackley CE. Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. Am J Card 1986; 57: 916-22.
29. Col J, Pirenne B, Decoster O, Payen B, Deligne B, Purnode P, Renkin J. Basic components and patterns of acute ischemia recovery assessed from continuous ST monitoring in acute myocardial infarction treated by thrombolytic therapy. J Electrocardiol 1994; 27 Suppl: 241-8.
30. Krucoff MW, Wagner NB, Pope JE, Mortara DM, Jackson YR, Bottner RK, Wagner GS, Kent KM. The portable programmable microprocessor-driven real-time 12-lead electrocardiographic monitor: a preliminary report of a new device for the noninvasive detection of successful reperfusion or silent reocclusion. Am J Cardiol 1990; 65: 143-8.
31. Dellborg M, Riha M, Swedberg K. Dynamic QRS-complex and ST-segment monitoring in acute myocardial infarction during recombinant tissue-type plasminogen activator therapy. Am J Card 1991; 67: 343-9.
32. Krucoff MW, Croll MA, Pope JE, Granger CB, O'Connor CM, Sigmon KN, Wagner BL, Ryan JA, Lee KL, Kereiakis DJ, Samaha JK, Worley SJ. Continuously 12-lead ST-segment recovery analysis in the TAMI 7 study. Circ 1993; 88: 437-46.
33. Dellborg M, Topol EJ, Swedberg K. Dynamic QRS complex and ST segment vectorcardiographic monitoring can identify vessel patency in patients with acute myocardial infarction treated with reperfusion therapy. Am Heart J 1991; 122,4: 943-8.
34. Dellborg M, Steg PG, Simoons M, Dietz R, Sen S, van den Brand M, Lotze U, Hauck S, van den Wieken R, Himbert D, *et al.* Vectorcardiographic monitoring to assess early vessel patency after reperfusion therapy for acute myocardial infarction. Eur Heart J 1995; 16: 21-9.
35. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673-82.

36. Romeo F, Rosano GM, Martuscelli E, Valente A, Reale A. Unstable angina: role of silent ischemia and total ischemic time (silent plus painful ischemia), a 6-year follow-up. J Am Coll Cardiol 1992; 19: 1173-9.
37. 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. Circulation 1996; 93: 1651-7.
38. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 335: 1342-9.
39. Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell FE Jr, 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: 1333-41.
40. Foley JB, Foley D, Molloy M, Crean PA, Gearty GF, Walsh ML. Acute impact of percutaneous transluminal coronary angioplasty on the ischemic burden in stable and unstable angina. Am Heart J 1993; 126: 705-7.
41. Gerstenblith G. Treatment of unstable angina pectoris. Am J Cardiol 1992; 70: 32G-37G.
42. Dellborg M, Gustaffson G, Riha M, Swedberg K. Dynamic changes of the QRS complex in unstable angina pectoris. Int J Cardiol 1992; 36: 151-62.
43. Lundin P, Erikkson SV, Erhardt L, Strandberg LE, Rehnqvist N, Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology 1992; 81: 145-56.

Chapter 2

Noninvasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial

P. Klootwijk, A. Langer, S. Meij, C. Green, R.F. Veldkamp, A.M. Ross, P.W. Armstrong, M.L. Simoons, for the GUSTO-I ECG-ischemia monitoring substudy

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ABSTRACT

In the GUSTO-I ECG-ischemia monitoring substudy, 1067 patients underwent continuous ST segment monitoring, using vector derived 12-lead (406 patients), 12-lead (373 patients) and 3-lead Holter (288 patients) ECG recording systems. Simultaneous angiograms at 90 or 180 minutes following thrombolytic therapy were performed as a part of the prospective study in 302 patients.

Infarct vessel patency was established as TIMI perfusion grades 2 or 3 and occlusion as TIMI perfusion grades 0 or 1. Coronary artery patency was predicted from ST trends up to the time of angiography. Predictive values at 90 and 180 minutes after the start of thrombolysis were 70% and 82% for patency and 58% and 64% for occlusion, respectively. In retrospect, accuracy appeared greatest (79-100%) in patients with extensive ST segment elevation ($\geq 400\ \mu V$), if both speed of ST recovery and extent of ST segment elevation were taken into account. Although the three recording systems differed considerably in signal processing, no significant difference in accuracy was demonstrated among these systems.

We conclude that continuous ECG monitoring may help select high risk patients without apparent reperfusion who may benefit from additional reperfusion therapy. As ST recovery may occur early after the start of thrombolytics and accuracy of the test is related to peak ST levels, the use of on-line ECG monitoring devices on emergency wards and cardiac care units is recommended.

INTRODUCTION

Early reperfusion and sustained patency of the infarct-related coronary artery are important determinants of survival in patients with myocardial infarction[1-3]. More aggressive therapy may be indicated if thrombolytic therapy fails to open the occluded vessel or if reocclusion of an initially reperfused coronary artery occurs[4]. Thus, continuous monitoring of the degree of ischemia as a marker of vessel (re)perfusion status may help to guide thrombolytic or adjunctive therapy. Noninvasive signs of reperfusion of the infarct-related vessel include resolution of chest pain, the occurrence of accelerated idioventricular rhythm, normalization of the ST segment, or sudden worsening of ST elevation followed by a rapid decline, and measurement of specific cardiac proteins in plasma[5-9]. Continuous monitoring of the ST segment is a promising, readily available, noninvasive technique for assessment of reperfusion and patency[10-12]. Although many attempts have been made to establish criteria that predict reperfusion from serial standard ECGs, only a limited number of studies have prospectively assessed the value of continuous ST segment monitoring for early patency assessment in comparison with angiography[8,13-18]. Therefore, we investigated the ability of continuous ST segment monitoring to predict reperfusion and patency in the context of the angiographic substudy in GUSTO-I (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries)[2,3]. The sensitivity, specificity and predictive value of predefined criteria for prediction of patency were tested in a large group of patients. A secondary objective was to investigate the similarities and differences among the three monitoring systems which were used in this study.

METHODS

Study organization

The GUSTO-I ischemia monitoring substudy mainly involved patients from the GUSTO-I angiographic substudy[2,3] and, to a lesser extent, patients enrolled in the noninvasive part of the main GUSTO-I study. All patients underwent continuous ECG monitoring using either a vector-derived 12-lead ECG recording system, a 12-lead ECG recording system or a 3-lead Holter ECG

recording system, as described below. Patients for this ECG-ischemia monitoring substudy were recruited by a total of 45 participating hospitals, situated in Europe, U.S.A., Canada, Australia and New Zealand. Each site was restricted to using only one type of recording device.

Patient selection

Patients were eligible for enrollment in the GUSTO-I study if they had chest pain lasting for at least 20 minutes, were within 6 hours of onset of symptoms, and had electrocardiographic evidence of evolving myocardial infarction reflected by ≥ 0.1 mV ST segment elevation in two or more limb leads or ≥ 0.2 mV in two or more contiguous precordial leads[2]. At the participating sites, all patients enrolled in the main GUSTO-I trial were considered eligible for the ECG-ischemia monitoring substudy except those with left bundle branch block, third-degree AV block, persistent arrhythmias or pacemakers.

Continuous ST segment monitoring

Eligible patients were monitored by either vector, 12-lead or 3-lead Holter continuous ECG, preferably within 30 minutes of the start of thrombolytic therapy. Continuous ECG recording was performed for at least 18 hours from the start of thrombolytic therapy. The timing of the start of thrombolytic therapy and the moment of angiography were obtained from the study case record forms. An extensive report on the study design and technical considerations was published recently[19].

Dynamic vector-derived 12-lead electrocardiographic recording system (MIDA 1000, Ortivus Medical, Täby, Sweden)

Twelve hospitals in Europe used the MIDA recording equipment. The MIDA system calculates averaged QRS-T complexes from the Frank orthogonal leads X-Y-Z at 1-minute intervals. All averaged complexes were stored on the hard disk and used for calculation of ST trend information. After completion of the recording, 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[15,20]. 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 *et al*[21].

Continuously updated 12-lead ECG recording system (ST 100, Mortara Instrument, Milwaukee, U.S.A.)
The Mortara system, used in 15 hospitals in the U.S.A., calculates median beats of the 12-lead ECG every 15 seconds. These median beats are compared with the patient's baseline ECG in regard to ST segment changes over time in any lead. The system was programmed to store median beats if, in at least four consecutive median complexes, ≥ 200 μV ST change was present in one lead, or if ≥ 100 μV ST change was present in two contiguous leads. If less or no ST change was present, a median ECG complex was stored every 20 minutes. Subsequent editing and analysis were performed at the core laboratory of Duke University, Durham, U.S.A[11,13].

3-lead Holter ECG recording system (Marquette Electronics, Milwaukee, U.S.A.
The Marquette Holter system, which continuously records three bipolar ECG leads, was used in 18 hospitals in Canada, U.S.A., Australia and New Zealand. Special lead configurations were applied to record inferior (left clavicle to left iliac crest), lateral (right clavicle to V5 position), and anterior (spinous process between scapulae to V2 position) ECG leads. The ECG recordings were archived on magnetic tape and sent to the core laboratory of St. Michael's Hospital in Toronto, Canada, for editing and analysis. ST trends of the three leads were generated by the Marquette review station, which averages ST levels from the recorded analogue ECG every 15 seconds[22].

Differences among recording methods of the ECG
As described above, the methods and ECG handling properties of the three systems for generation of the ST trends were different: 1-minute averaging for the vector-derived 12-lead system, 15-second medians for the 12-lead system (requiring a consistent change of ST amplitude during four consecutive median complexes, representing 1 minute) or every 20 minutes and 15-second averaging for the 3-lead Holter system. This implies that the Holter system would be most sensitive to abrupt ST changes and noise. To assess whether this would influence the ST trends, the other two algorithms were simulated using Holter trend data. One-minute averages (simulating the vector system) were obtained by averaging four consecutive Holter ST measurements (each originally representing 15 seconds of data). Similarly, the 12-lead (Mortara)

algorithm was simulated by the requirement that a new measurement would be stored only after 20 minutes and whenever four consecutive measurements exceeded the boundaries as described above.

Editing and analysis of recorded data

ST trends of all recorded leads were produced at the three core laboratories. The ST segment level was measured at J-point + 60 milliseconds. All ECG recordings and ST trends were manually scanned and edited for artifact, bundle branch block, detection or marker errors, positional changes and data gaps.

Visual patency assessment was performed until the moment of angiography. Patients whose recording began ≥ 1 hour after initiation of thrombolytic therapy or who had an ECG recording gap of ≥ 1 hour before angiography were excluded from the analysis. Patients with low-level ST amplitudes of less than 200 μV during the complete recording were also excluded.

The lead with maximal ST deviation at the onset of recording was selected for final ST analysis and visual patency assessment. If a 12-lead ECG prior to the start of the recording was available, this was used for selection of the lead with maximal ST deviation. For the Holter group, the most comparable lead of the three bipolar leads was chosen. As a consequence, the ST value of the first available ECG was considered to be the first ST value of the ST trend.

A visual analysis of the ST trend, validated by inspection of the actual ECG, was performed until the start of angiography. ST recovery criteria derived from previous studies were used for prediction of vessel status (Table 1)[8,11,19,23,24]. If ≥ 50% ST recovery from the first peak ST level was present immediately before angiography, the infarct-related vessel was predicted to be patent at angiography (Figure 1A). In the absence of ≥ 50% ST recovery before angiography, the vessel was predicted to be non-patent (Figure 1D). Similarly, the vessel was predicted to be non-patent if ≥ 50% ST recovery was followed by re-elevation of ≥ 100 μV occurring within a 10-minute time interval and lasting until the start of angiography (recurrent ischemia, Figure 1C). If before angiography, a transient ST segment re-elevation fell below 50% of its own peak ST level or decreased within 100 μV of the previous baseline ST level, the vessel was again predicted to be patent (Figure 1B). All visual readings were done blinded to angiographic characteristics.

Table 1. ECG criteria for prediction of vessel status at angiography.

ECG criteria for prediction of vessel status	Expected vessel status at angiography
≥ 50% ST recovery from first peak ST level, no re-elevation ≥ 100 μV	'patent' TIMI flow 2–3
≥ 50% ST recovery from first peak ST level, followed by transient re-elevation ≥ 100 μV, recovering before moment of angiography	
Absence of ≥ 50% ST recovery before angiography	'occluded' TIMI flow 0–1
≥ 50% ST recovery from first peak ST level, followed by re-elevation ≥ 100 μV, persisting until moment of angiography	

As it was expected that patency prediction would be influenced by peak ST levels and speed of ST recovery, retrospectively, four ST patterns related to pre-angiogram peak ST levels were studied for ability to predict vessel status at angiography: fast ≥ 50% ST recovery within 45 minutes following thrombolysis or, compared to the previous study entry ECG, ≥ 50% ST recovery already present at the start of the recording; ≥ 50% ST recovery occurring within 45-90 minutes following thrombolysis; absent or late ≥ 50% ST recovery (later than 90 minutes following thrombolysis); and persistently high or increasing ST levels. In the absence of ST re-elevation as described before, the first two patterns were regarded as predicting patency at angiography. The latter two were thought to predict a non-patent vessel.

Coronary angiography and angiographic analysis

In the GUSTO-I angiographic substudy, coronary angiography was performed according to stratified randomization at 90 minutes, 180 minutes, 24 hours or one week after start of thrombolytic therapy[3]. Only patients with 90- and 180- minutes angiography were selected for early electrocardiographic patency assessment. The coronary angiograms were sent to the core laboratory at the George Washington University, Washington, D.C.. Angiographic assessments were made by experienced angiographers without knowledge

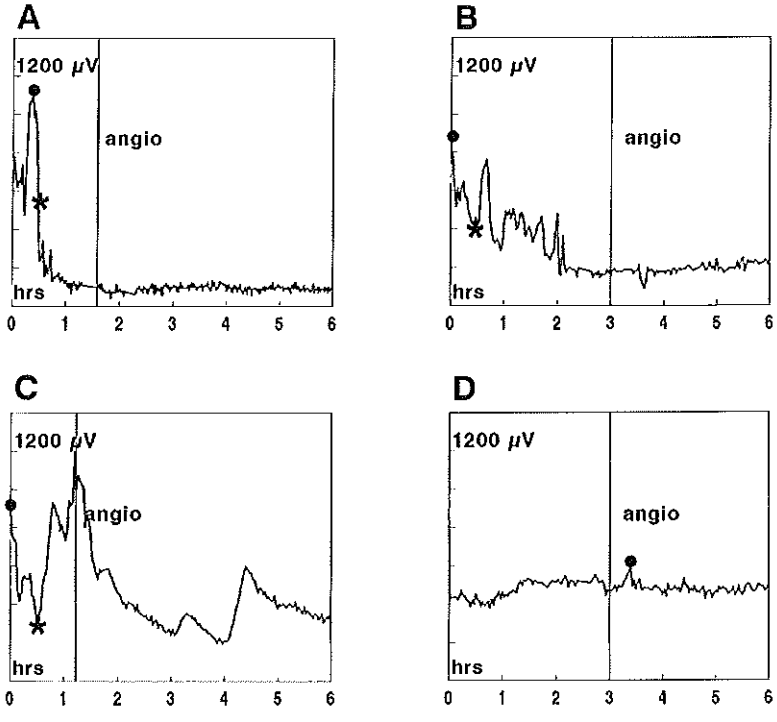

Figure 1. Assessment of patency from ST trend graphs. Visual analysis was performed until the moment of angiography (vertical line). • = peak ST level; * = first moment of 50% ST recovery from peak ST level. (A) ST recovery within 45 minutes from start of thrombolytic therapy. No recurrent ST elevation. The vessel is predicted to be patent at the moment of angiography. (B) ST recovery within 45 minutes from start of thrombolytic therapy. Recurrent ST elevation episodes are present, but not on the moment of angiography. The vessel is predicted to be patent at the moment of angiography. (C) ST recovery followed by recurrent ST elevation, still present at the moment of angiography. The vessel is predicted to be non-patent at the moment of angiography. (D) Persistently high ST levels, no 50% ST recovery.

of the electrocardiographic data[3]. The angiograms were evaluated for flow in the infarct-related segment using the classifications of the Thrombolysis in Myocardial Infarction trial (TIMI) at first injection of contrast[25]. TIMI perfusion grade 0-1 indicated an occluded coronary artery, TIMI perfusion grade 2-3 an open artery. Collateral flow was graded as none or minimal and moderate or large.

Data management

The edited and analyzed data and final patency assessment scores were forwarded from the other core laboratories to the Ischemia Monitoring Laboratory at Duke University, Durham, N.C., U.S.A., for data entry, generation of queries for missing or inconsistent data, and final data-analysis. Subsequently, all data were returned to the other two core laboratories.

RESULTS

A total of 1067 patients were included in the ECG-ischemia monitoring substudy. Four hundred and six patients were monitored with the vector-derived 12-lead, 373 with the 12-lead system and 288 with the 3-lead Holter system. Four hundred and fourteen patients (39%) were excluded from analysis, mainly because of technical failures due to error on the part of the investigator (143 patients) or because the recording started more than 60 minutes after initiation of thrombolytic therapy (139 patients). Sixty-three patients were excluded because of missing ECG and ST trend data for more than 1 hour prior to the start of angiography. Sixty-nine patients had low-level ST amplitudes less than 200 μV during the complete recording. Thus, 653 patients had ECG recordings suitable for further study and determination of the moment of first 50% ST recovery. Within the design of the GUSTO-I angiographic substudy, 302 of those patients also underwent angiography at 90 (224 patients) or 180 minutes (78 patients) after initiation of thrombolytic therapy. This group of 302 patients was used for assessment of ECG prediction of vessel status. The infarct-related vessel was the left anterior descending artery in 137 patients, the right coronary artery in 121 and the left circumflex artery in 36.

Time to 50% ST recovery

Seventy-five percent of the 653 patients had 50% ST recovery within 90 minutes of initiation of thrombolytic therapy. Median times (25%, 75%) from initiation of thrombolytic therapy to 50% ST recovery were 50 (25, 107), 52 (25, 105) and 33 (15, 54) minutes for vector-derived 12-lead, 12-lead and 3-lead Holter, respectively (Figure 2). The Holter system identified the moment of 50% ST recovery significantly earlier than either the vector-derived

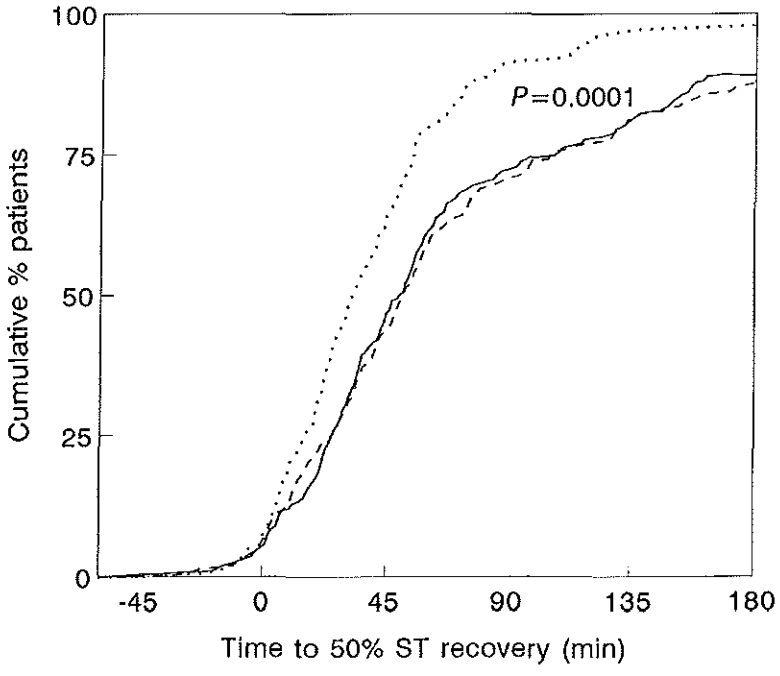

Figure 2. Cumulative percentage of patients exhibiting ST recovery plotted against the time from initiation of thrombolytic therapy to the first moment of 50% ST recovery for each ST monitoring system. •••• = Holter (145 patients); —— = vector (282 patients); – – – = 12-lead (226 patients).

12-lead or the 12-lead system (P=0.0001). The 12-lead entry ECG contributed to the determination of the moment of 50% ST recovery in 37%, 35% and 53% for vector-derived 12-lead, 12-lead and 3-lead Holter, respectively. If these patients were excluded from the analysis, the differences in median time from initiation of thrombolytic therapy to 50% ST recovery persisted: 63 (35, 134), 58 (33, 126) and 47 (28, 71) minutes, respectively (P=0.002). To assess whether this effect could be attributed to the differences among the algorithms used by the three recording devices, the ECG sampling algorithms of the vector-derived 12-lead and 12-lead ECG recording systems were simulated using the Holter ST trend data as the source data. Figure 3 illustrates a shift in detection of the moment of first 50% ST recovery that may occur when the original data of a Holter ST trend are transformed into a simulated vector-derived 12-lead and 12-lead ECG ST trend. Transformation

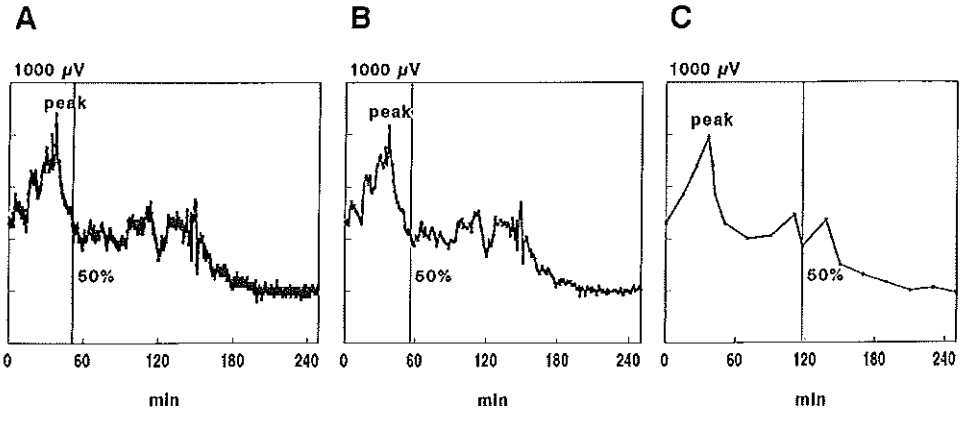

Figure 3. Effects of different algorithms on the moment of 50% ST recovery. (A) Example of a Holter ST trend recording using original 15-second averaged ST data. The first moment of 50% ST recovery occurs at 51 minutes from the start of the recording. (B) Simulated vector-derived 12-lead ECG ST trend of (A), using 1-minute averaged ST data. The first moment of 50% ST recovery occurs at 56 minutes from the start of the recording. (C) Simulated 12-lead ECG ST trend of (A), using either 15-second intervals, in the case of consistent 100 μV changes of ST amplitude, or 20-minute intervals. The first moment of 50% ST recovery occurs at 110 minutes from the start of the recording.

of ST trend data from 145 Holter recordings confirmed that 50% ST recovery was present earliest in the Holter and later in the simulated vector-derived 12-lead and 12-lead ST trends: 33 (15, 54), 37 (19, 66) and 49 (23, 90) minutes, respectively.

Visual patency assessment

Within the design of the GUSTO-I angiographic substudy, 302 patients underwent early angiography at either 90 (224 patients) or 180 minutes (78 patients) after initiation of thrombolytic therapy. A patent artery at first injection of contrast was present in 139 (62%) of the 224 patients with angiography at 90 minutes and in 58 (74%) of the 78 patients with angiography at 180 minutes following thrombolytic therapy.

Overall accuracy and predictive values for visual assessment of patency from the pre-angiogram ST trends of these 302 patients are presented in Table 2. Patency predictive value using the predefined criterion of 50% recovery was 74% against non-patency predictive value of 59%. Overall

Table 2. Predictive values from pre-angiography ST trends.

Time of angiogram (min)	Device (n)		Patency predictive value (%)	Occlusion predictive value (%)	Overall accuracy (%)
90	Vector	(122)	71	48	65
	12-lead	(57)	73	63	70
	Holter	(45)	63	73	67
	All	**(224)**	**70**	**58**	**67**
	No collaterals	(193)	76	53	69
180	Vector	(45)	89	67	84
	12 lead	(15)	75	67	73
	Holter	(18)	75	67	73
	All	**(78)**	**82**	**64**	**79**
	No collaterals	(69)	89	50	84
90 or 180	Vector	(167)	76	52	70
	12-lead	(72)	74	63	71
	Holter	(63)	67	71	68
	All	**(302)**	**74**	**59**	**70**
	No collaterals	(262)	80	52	73

Patency predictive value = number of true ECG predictions of a patent artery at angiography divided by the number of true + false ECG predictions of a patent artery. *Occlusion predictive value* = number of true ECG predictions of an occluded artery at angiography divided by the number of true + false ECG predictions of an occluded artery. *Overall accuracy* = number of true ECG predictions of vessel status at angiography divided by the number of true + false ECG predictions of vessel status at angiography.

accuracy was 70%. If patients with collateral filling of the infarct-related vessel were excluded (40 patients), patency predictive value increased to 80%, but non-patency predictive value decreased to 52% and overall accuracy remained almost unchanged. The 95 percent confidence limits of predictive values and accuracies of the three recording devices were wide, and no significant differences among the three systems were demonstrated.

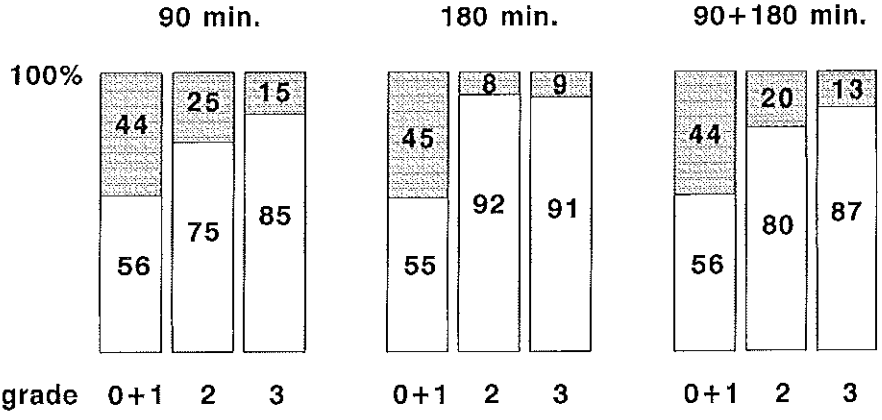

Figure 4. Visual assessment of patency from pre-angiogram ST trends and relation to TIMI flow grade at either 90 or 180 minutes following thrombolytic therapy. The white parts and shaded parts of the bars represent the percentage of patients with ECG indications of patent and non-patent vessels, respectively.

The visual patency assessment appeared correct in 75-92% of patients with TIMI grade 2 or 3 flow (sensitivity, Figure 4). A small, non-significant difference between assessment of TIMI grade 2 and 3 flow was observed in the 90-minute angiography group. ECG assessment correctly predicted TIMI grade 0 and 1 flow in 44-45% of patients (specificity). ECG prediction of TIMI grade 0 and 1 flow was slightly better for the left circumflex artery and for the left anterior descending artery than for the right coronary artery. However, no significant differences could be demonstrated between the site of the infarct-related artery and the prediction of vessel status.

Pre-angiography ST levels and ST patterns

The peak ST level, speed of ST recovery and ≥ 50% ST recovery with transient re-elevation before angiography affected the accuracy of prediction of vessel status. A peak ST level of ≥ 400 μV was present in 116 patients (38%). Patency predictive value, non-patency predictive value and overall predictive accuracy of this group were 79%, 64% and 75% respectively, which were slightly better than those of patients with lower ST levels: 67%, 41% and 61% respectively (ns). As a retrospective observation, it appeared that if both ≥ 400 μV peak ST elevation and ≥ 50% ST recovery with transient re-elevation within 90 minutes from start of thrombolytic therapy were present

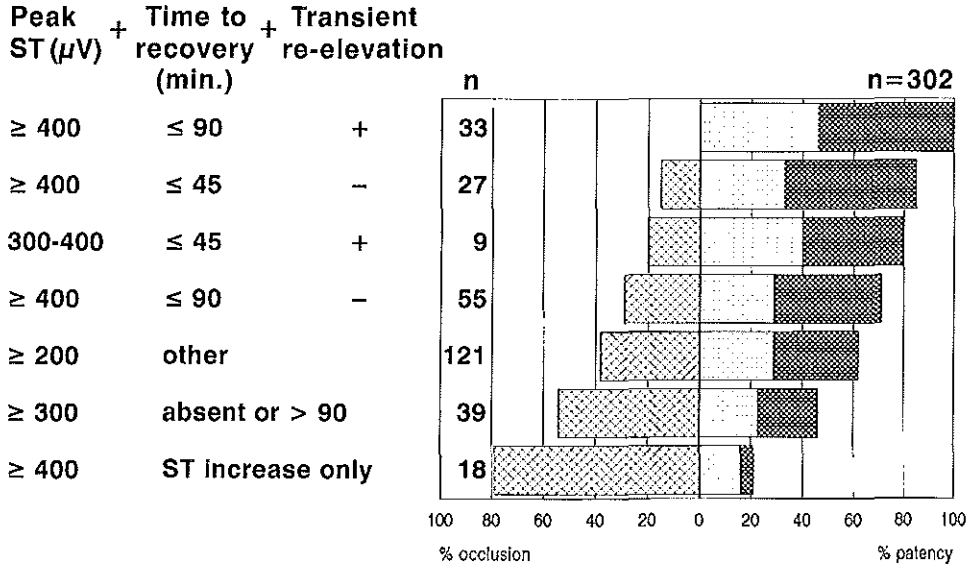

Figure 5. Predictive value of ST patterns and peak ST levels in relation to the speed of ST recovery and the presence or absence of transient re-elevation before angiography. The cross-hatched, dotted and dark parts of the bars represent the percentage of patients with TIMI grade 0-1 flow, TIMI grade 2 flow and TIMI grade 3 flow, respectively.

before angiography, the predictive value for TIMI grade 2-3 flow was 100% (33 patients, Figure 5). Similarly, a predictive value of 79% was found for TIMI grade 0-1 flow if both ≥ 400 μV ST elevation and a pattern of persistently high or increasing ST levels were present (18 patients). Thus, by the combination of peak ST levels, speed of ST recovery and ST recovery with transient ST re-elevation before angiography, prediction of vessel status was 79-100% accurate in a subgroup corresponding to 29% of all angiographic patients studied.

DISCUSSION

The present report is part of the GUSTO-I ECG-ischemia monitoring substudy and represents the largest series comparing ST recovery analysis and early angiography during thrombolytic therapy. The purposes of the GUSTO-I

ECG-ischemia monitoring substudy were (1) to compare the speed and stability of ST segment recovery across the four treatment arms of the GUSTO-I study, (2) to compare noninvasive patency assessment with simultaneous angiographic assessment and (3) to investigate whether different ECG recording techniques would give equal and comparable results. The present report focuses on the latter two objectives. The comparison among the four GUSTO-I treatment arms has been described recently in a separate report. In contrast to the results of the GUSTO-I main trial, this study did not demonstrate a difference in ST recovery and recurrent ischemia across treatment arms[38].

Many smaller studies have been conducted to determine the value of ECG monitoring for noninvasive prediction of vessel status after thrombolytic therapy for acute myocardial infarction[7,8,11-18,23,24,26-31]. The total numbers of patients reported in the literature who were studied via early angiography plus serial ECG, Holter, or continuous ECG monitoring are 171, 118 and 261, respectively[7,8,14-18,24,28]. The present study used simple, objective and unequivocally defined ST recovery criteria, derived from previous studies[8,11,23,24]. The study design and the relatively large number of patients allowed us to study noninvasive patency assessment at both 90 minutes and 180 minutes following thrombolytic therapy. The study demonstrates that noninvasive patency prediction using continuous ECG recording techniques is possible and may be used in clinical practice. The technique appears better for prediction of patency (70-82%) than for occlusion (58-64%), depending on the extent of the initial ST segment elevation. Prediction of vessel status appeared 79-100% accurate in the subgroup of patients with initially-high ST levels, which is the group of patients with the highest risk of adverse cardiac events and receiving the greatest benefits of reperfusion therapy[4,32].

ST analysis criteria

The criteria for ST segment recovery used in this study were a simplification of ST criteria published previously[8,11,23,24]. This simplification was applied to facilitate the use of three ST monitoring systems with different ECG handling properties and to allow uniform analysis of the ST trends by the three core laboratories.

The presence of 50% ST recovery before either 90- or 180-minute

angiography was taken as a sign of reperfusion, absence of 50% recovery was considered to predict a non-patent vessel, recurrence of ST elevation was considered to represent reocclusion or re-ischemia. The speed and stability of ST recovery were not taken into account in this primary assessment, as ECG sampling intervals were different for the three recording systems. Moreover, for the sake of uniformity of this study, only single-lead ST trend analysis was performed. Thus, these "simplified" ST recovery criteria may have resulted in less accurate patency assessment. The additional use of more refined analysis criteria, which also took into account initial peak ST levels, the time to 50% ST recovery and the various ST recovery patterns, substantially improved predictive accuracy of vessel status in a subgroup of patients. Indeed, the ≥ 50% ST recovery criterion reflects reperfusion only if it occurs early, preferably within a time interval of 90 minutes following the start of thrombolysis. Otherwise a non-patent infarct-related vessel should be suspected.

Time intervals and technical limitations

Assessment of patency is relevant mainly during the first hours following thrombolytic therapy. The longer the time from onset of chest pain to start of the recording, the less the ST segment deviation at the start of the recording. As our study demonstrated, the amount of ST elevation present during the recording is a major determinant of the accuracy of patency prediction: less ST deviation at the start of the recording and during subsequent recording may result in less accurate prediction of vessel status. The same is true for the delay from start of thrombolytic therapy to start of the recording. The time from initiation of thrombolytic therapy to first evidence of 50% ST recovery was less than 90 minutes in 75% of patients. Thus, in order to detect ST recovery, the recording should be started early, preferably before the start of thrombolytic therapy. If the start of the recording is delayed and thrombolytic therapy has already been effective, the first moment of 50% ST recovery may not be properly recorded, which would result in false assessment of vessel status.

Finally, the results of this study were limited by the use of three different ECG recording devices, which demanded adaptation of ST analysis criteria, and by the relative inexperience of participating centers in using these devices

in the setting of acute myocardial infarction. The number of technical problems should decrease if continuous multilead ECG-ischemia monitoring systems become integrated in emergency wards and coronary care units.

Differences among recording methods of the ECG

The ST criteria were simplified to facilitate uniform ST recovery analysis across the three ECG systems. Thus, additional benefits of individual devices, such as the use of the QRS vector difference for vector[14], the summated ST deviation for 12-lead[16], and continuous rhythm documentation for 3-lead Holter[33], were not taken into account.

The use of the 12-lead study-entry ECG to select the lead with maximal ST deviation may have contributed to a less accurate assessment of the moment of 50% ST recovery in some instances. This may especially have been the case with the 3-lead Holter system, as one of only three bipolar leads was selected for comparison with the 12-lead entry ECG.

Optimal comparison would monitor all three devices simultaneously and a report on such a comparison during PTCA-induced transient occlusion and reperfusion has been published recently[34]. However, significant differences in time to 50% ST recovery were apparent among the three systems (Figure 2). The Holter system appeared to detect 50% ST recovery earliest. If ECG recordings were excluded in which the 50% ST recovery moment was determined by the entry ECG, this difference persisted, which confirms that the moment of 50% ST recovery is indeed dependent on the sampling algorithms used for generation of ST trends. Recalculation of Holter ST trend data into vector-derived 12-lead or 12-lead ST trend data confirmed that the earlier detection of 50% ST recovery was related to the short (Holter) averaging interval of 15 seconds. In fact, such shorter recording intervals will both facilitate early detection of rapid changes in the ST amplitude and be more sensitive to noise. Thus, adaptation of ST analysis criteria to the characteristics of each device may result in an improvement of predictive performance of these devices and of subsequent study results. It should be emphasized that in spite of the major differences in technologies, the reliability for prediction of vessel status appeared similar across the three recording devices. Nevertheless, the users of different systems must be aware of the technical features of these systems for correct interpretation of the signal[35].

Coronary angiography

Coronary angiography was used to validate ST monitoring of vessel status. This technique is regarded as the "gold standard" for assessment of patency and (re)occlusion. However, its limitations may have influenced the accuracy and predictive values of electrocardiographic patency assessment in a negative manner. It should be appreciated that angiography supplies only very momentary information on the status of the infarct-related vessel. As such, the rapidly changing dynamics of coronary blood flow in an injured vessel through active thrombus formation, clot lysis, vasoconstriction and vasodilatation, cannot be assessed properly by this technique. Moreover, Ito *et al.* demonstrated that restoration of epicardial bloodflow, as visualized by angiography, does not always correlate with restoration of perfusion at the cellular level[36]. Thus, angiographically successful reflow cannot be equated with achievement of myocardial reperfusion and oxygenation, and it may well be that continuous ECG monitoring reflects the oxygenation status of the myocardium at risk more accurately than the "gold standard" of angiography itself.

The lack of precision of registration of the first contrast injection in relation to the ECG recordings may also have negatively influenced ECG prediction outcome. The ECG recordings were analyzed until the start of the procedure in the catheterization laboratory. Accordingly, the status of the infarct-related vessel may have altered in some patients between the time of ECG assessment and actual angiography. Inaccurate tracking of the exact time of the start of thrombolytic therapy, the start of the ECG recording, or the first injection of contrast in the present multicenter study may have contributed to incorrect ECG patency assessment. In addition, the recording system (vector) sometimes had to be disconnected during transportation from the coronary care unit to the angiography room. The resulting ST trend data gaps between the moment of ECG assessment of patency and the start of angiography may also have resulted in less accurate prediction of vessel status, particularly for the vectorcardiographic system.

CONCLUSIONS

The present large study confirms the results of previous small studies that continuous ST segment monitoring techniques may become clinically useful for prediction of reperfusion, patency and reocclusion during thrombolytic therapy.

Ellis *et al.* demonstrated that rescue PTCA after failed thrombolysis may improve clinical outcome, reflected by a reduction of combined heart failure and death (P=0.055) and an increase of left ventricular ejection fraction during exercise (P=0.04), within 30 days from the onset of myocardial infarction[37]. This strongly points towards tailoring of reperfusion therapy[4]. In this respect, continuous ECG monitoring techniques may assist the clinician in decision-making and may help to select patients who may benefit from additional reperfusion therapy.

The simple ST recovery criteria used in this study resulted in a correct prediction of vessel patency in 70-82% of patients with ST recovery, but apparently persistent ST elevation predicted a non-patent vessel in only 58-64% of patients. However, if speed of ST recovery, stability of ST recovery and recognition of ST patterns that suggested either complete reperfusion, unstable reperfusion, occlusion or reocclusion were taken into account, prediction of vessel status appeared 79-100% accurate for those patients having high initial ST levels. This subset of patients is at the highest risk of adverse cardiac events[32] and will benefit most from additional "rescue" procedures for failed reperfusion. Dynamic trend analysis and adaptation of ST analysis criteria to each recording method may yield even better results. Further study of the ECG and ST trends in the GUSTO-I database may help establish more refined ST recovery criteria for each recording method.

Finally, as the prediction of vessel status is most accurate in patients with high initial ST levels, the usefulness of continuous ECG monitoring systems may be greatly improved if the recording is begun as soon as the patient is admitted. Therefore, the use of on-line ECG monitoring devices may be recommended in emergency wards and coronary care units in order to avoid delay and to improve the clinical usefulness of noninvasive patency assessment.

REFERENCES

1. Simoons ML, Vos J, Tijssen JGP, Vermeer F, Verheugt FWA, Krauss XH, Cats VM. Long term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of The Netherlands. J Am Coll Cardiol 1989; 14: 1609-15.
2. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673-82.
3. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329(22): 1615-22.
4. Simoons ML, Arnold AE. Tailored thrombolytic therapy. A perspective. *Circulation* 1993; 88(6): 2556-64.
5. Steg PG, Dellborg M, van den Brand M, Simoons ML. Transient exacerbation of ST segment elevation upon reperfusion in acute myocardial infarction. Eur Heart J 1993; 14(Abstr Suppl): 473.
6. Califf RM, O'Neill W, Stack RS, Aronson L, Mark DB, Mantell S *et al.* Failure of simple clinical measurements to predict reperfusion status after intravenous thrombolysis. Ann Intern Med 1988;108: 658-62.
7. Kircher BJ, Topol EJ, O'Neill WW, Pitt B. Prediction of infarct coronary artery recanalization after thrombolytic therapy. Am J Cardiol 1987;59:513-15.
8. Hohnloser SH, Zabel M, Kasper W, Meinertz T, Just H. Assessment of coronary artery patency after thrombolytic therapy: accurate prediction utilizing the combined analysis of three noninvasive markers. J Am Coll Cardiol 1991;18:44-9.
9. Shah PK, Cercek B, Lew AS, Ganz W. Angiographic validation of bedside markers of reperfusion. J Am Coll Cardiol 1993;21:55-61.
10. Hackett D, Davies G, Chiercha S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction: value of combined thrombolytic and vasodilator therapy. N Engl J Med 1984;311:1488-92.
11. Krucoff MW, Croll MA, Pope JE, Pieper KS, Kanai PM, Granger CB *et al.* Continuously updated 12-lead ST segment recovery analysis for myocardial infarct artery patency assessment and its correlation with multiple simultaneous early angiographic observations. Am J Cardiol 1993;71:145-51.
12. Dellborg M, Riha M, Swedberg K. Dynamic QRS-complex and ST segment monitoring in acute myocardial infarction during recombinant tissue-type plasminogen activator therapy. Am J Cardiol 1991; 67: 343-9.
13. Krucoff MW, Wagner NB, Pope JE, Mortara DM, Jackson YR, Bottner RK *et al.* The portable programmable microprocessor-driven real-time 12-lead electrocardiographic monitor: a preliminary report of a new device for the noninvasive detection of successful reperfusion or silent reocclusion. Am J Cardiol 1990; 65: 143-8.
14. Dellborg M, Topol EJ, Swedberg K. Dynamic QRS complex and ST segment vectorcardiographic monitoring can identify vessel patency in patients with acute

myocardial infarction treated with reperfusion therapy. Am Heart J 1991; 122(4): 943-8.
15. Dellborg M, Steg PG, Simoons M, Dietz R, van den Brand M, Lotze U, *et al.* Vectorcardiographic monitoring to assess early vessel patency after reperfusion therapy for acute myocardial infarction. Eur Heart J 1995; 16: 21-9.
16. Krucoff MW, Croll MA, Pope JE, Granger CB, O'Connor CM, Sigmon KN *et al.* Continuously 12-lead ST segment recovery analysis in the TAMI 7 study. Circulation 1993; 88: 437-46.
17. Krucoff MW, Green CE, Satler LF, Miller FC, Pallas RS, Kent KM *et al.* Noninvasive detection of coronary artery patency using continuous ST segment monitoring. Am J Cardiol 1986; 57: 916-22.
18. Dellborg M, Riha M, Swedberg K. Dynamic QRS-complex and ST segment monitoring in acute myocardial infarction during recombinant tissue-type plasminogen activator therapy. Am J Cardiol 1991; 67: 343-9.
19. Krucoff MW, Green CL, Langer A, Klootwijk P, Trollinger KM, Sawchek ST *et al.* Global utilization of streptokinase and tPA for occluded arteries (GUSTO) ECG-monitoring substudy. Study design and technical considerations. J Electrocardiol 1993; 26(suppl): 249-55.
20. Simoons ML, de Boer MJ, van den Brand MJBM, van Miltenburg AJM, Hoorntje JCA, Heyndrickx GR *et al.* Randomized trial of a IIB/IIIA platelet receptor blocker in refractory unstable angina. Circulation 1994; 89: 596-603.
21. Dower GE, Machado HB, Osborne JA. On deriving the electrocardiogram from vectorcardiographic leads. Clin Cardiol 1980; 3: 87-95.
22. 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.
23. Clemmensen P, Ohman M, Sevilla DC, Peck S, Wagner NB, Quigley PS *et al.* Changes in standard electrocardiographic ST segment elevation predictive of successful reperfusion in acute myocardial infarction. Am J Cardiol 1990; 66: 1407-11.
24. Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction: use of the ST segment as a non-invasive marker. Br Heart J 1988; 60: 275-80.
25. The TIMI Study Group: The Thrombolysis in Myocardial Infarction (TIMI) Trial. N Engl J Med 1985; 312: 932-6.
26. Blanke H, Scherff F, Karsch KR, Levine RA, Smith H, Rentrop P. Electrocardiographic changes after streptokinase-induced recanalization in patients with acute left anterior descending artery obstruction. Circulation 1983; 68: 406-12.
27. von Essen R, Schmidt W, Uebis R, Edelmann B, Effert S, Silny J *et al.* Myocardial infarction and thrombolysis. Electrocardiographic short term and long term results using precordial mapping. Br Heart J 1985; 54: 6-10.
28. Saran RK, Been M, Furniss SS, Hawkins T, Reid DS. Reduction in ST segment elevation

after thrombolysis predicts either coronary reperfusion or preservation of left ventricular function. Br Heart J 1990; 64: 113-17.
29. Nicolau JC, Lorga AM, Garzon SAC, Jacob JLB, Machado NCS, Bellini AJ *et al.* Clinical and laboratory signs of reperfusion: are they reliable? Int J Cardiol 1989; 25: 313-20.
30. Barbash GI, Roth A, Hod H, Miller HI, Rath S, Har-Zahav Y *et al.* Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): results of the Israeli study of early intervention in myocardial infarction. Br Heart J 1990; 64: 241-7.
31. Richardson SG, Morton P, Murtagh JG, Scott ME, O'Keeffe DB. Relation of coronary arterial patency and left ventricular function to electrocardiographic changes after streptokinase treatment during acute myocardial infarction. Am J Cardiol 1988; 61: 961-5.
32. Willems JL, Willems RJ, Willems GM, Arnold AE, Van de Werf F, Verstraete M. Significance of initial ST segment elevation and depression for the management of thrombolytic therapy in acute myocardial infarction. European Cooperative Study Group for Recombinant Tissue-Type Plasminogen Activator. Circulation 1990; 82(4): 1147-58.
33. Gressin V, Gorgels A, Louvard Y, Lardoux H, Bigelow R. ST segment normalization time and ventricular arrhythmias as electrocardiographic markers of reperfusion during intravenous thrombolysis for acute myocardial infarction. Am J Cardiol 1993; 71(16): 1436-9.
34. Krucoff MW, Crater SW, Green CL, Loeffler KK, Pope JE, Langer A *et al.* Simultaneous Holter, VCG, and ECG ST monitoring during transient occlusion and reperfusion: implications for comparing or combining data sets. Circulation 1993; 88(Supp I):I-306.
35. Simoons ML, Hugenholtz PG, Ascoop CA, Distelbrink CA, de Land PA, Vinke RVM. Quantitation of exercise electrocardiography. Circulation 1981;63(3):471-5.
36. Ito H, Tomooka T, Sakai N, Yu H, Higashino Y, Fujii K *et al.* Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992; 85(5): 1699-1705.
37. Ellis SG, da Silva ER, Heyndrikx G, Talley JD, Cernigliaro C, Steg G, *et al.* Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. Circulation 1994; 90(5): 2280-4.
38. Langer A, Krucoff MW, Klootwijk P, Veldkamp R, Simoons ML, Granger C, Califf RM, Armstrong PW. Noninvasive assessment of speed and stability of infarct-related artery reperfusion: results of the GUSTO ST segment monitoring study. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1995; 25(7): 1552-7.

Chapter 3

Noninvasive assessment of speed and stability of infarct-related artery reperfusion: results of the GUSTO ST segment monitoring study

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ABSTRACT

Objectives. The ST segment monitoring substudy of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial compared the speed and stability of ST segment recovery among four thrombolytic strategies for acute myocardial infarction.
Background. Rapid resolution of ST segment elevation has been suggested as a noninvasive marker of infarct-related artery patency. We expected that patients treated with accelerated recombinant tissue-type plasminogen activator (rt-PA) would show a quicker recovery than that of other patients but that those treated with streptokinase would show greater stability of recovery.
Methods. ST segment monitoring was initiated in 1,067 patients within 30 minutes of the start of thrombolysis and continued for >18 hours with the use of a three-channel continuous vectorcardiographic monitor, a 12-lead continuous electrocardiographic (ECG) monitor or a three-channel (V2, V5, aVF) Holter ambulatory ECG monitor.
Results. Time to 50% recovery could be assessed in 618 patients and was similar in the four treatment groups: median 45 minutes with streptokinase/subcutaneous heparin, 45 minutes with streptokinase/intravenous heparin, 42 minutes with accelerated rt-PA and 47 minutes with combination therapy (P=0.7). No significant difference among the thrombolytic regimens was shown with the three monitors used. Time to initiation of ST segment monitoring was directly related to the time to 50% recovery (P=0.0001) and was its best predictor in a multiple regression model. ST segment elevation recurred equally in each treatment group (~36%, P=0.9) but was significantly more common in patients with a patent infarct-related artery (P=0.033) or a low ejection fraction (P=0.001)
Conclusions. The greater 90 minute patency seen with accelerated rt-PA in the angiographic substudy did not correlate with a shorter time to 50% ST segment recovery, possibly because of technical limitations and study design. The similar rates of recurrent ischemia (as assessed by ST elevation) among the regimens support the similar infarction and reocclusion rates seen in the main trial and angiographic substudy.

INTRODUCTION

Rapid resolution of ST segment elevation has been related to early arterial patency in patients with acute myocardial infarction[1-6] and can be used as a simple and readily available marker for assessment of thrombolytic efficacy[7]. The recently reported GUSTO-I trial (Global Utilization of Streptokinase and t-PA for Occluded coronary arteries)[8] and its angiographic substudy[9] have demonstrated improved clinical outcomes and arterial patency in patients treated with an accelerated regimen of tissue-type plasminogen activator (rt-PA) as compared with findings in patients treated with streptokinase. The goal of the GUSTO ST segment monitoring substudy was to provide a noninvasive assessment of the speed and stability of reperfusion. The primary hypotheses were (1) that resolution of ST segment elevation as measured by time to 50% ST segment recovery would be faster in patients treated with regimens of accelerated rt-PA than in patients treated with streptokinase, and (2) that recurrent ST elevation, reflecting early reocclusion, would occur less frequently in patients treated with streptokinase than in those treated with rt-PA.

METHODS

The protocol and the results of the GUSTO trial have been published previously[8]. Eligible patients presented to a participating hospital < 6 hours after the onset of symptoms with chest pain lasting at least 20 minutes, accompanied by electrocardiographic (ECG) signs of ≥ 0.1 mV ST segment elevation in two or more limb leads or ≥ 0.2 mV elevation in two or more contiguous precordial leads. Exclusion criteria were those conventionally used for administration of thrombolytic therapy[8]. Eligible patients were randomized to receive one of four regimens: 1) streptokinase, 1.5 million U over 60 minutes, with subcutaneous heparin in a dose of 12.500 U twice daily, beginning 4 hours after the start of thrombolytic therapy; 2) streptokinase, 1.5 million U over 60 minutes, with an intravenous heparin bolus of 5,000 U then 1,000 U per hour; 3) accelerated rt-PA bolus of 15 mg, 0.75 mg/kg body weight over 30 minutes and 0.5 mg/kg over the next 60 minutes with the same intravenous heparin regimen; or 4) the combination

of intravenous rt-PA (1.0 mg/kg over 60 minutes, not to exceed 90 mg, with 10% given as a bolus) and streptokinase (1.0 million U over 60 minutes) given simultaneously with the same intravenous heparin. All patients received chewable aspirin, ≥ 160 mg, followed by a dose of 160-325 mg/day. Patients without a contraindication to beta-adrenergic blockade received intravenous atenolol, 5 mg, given in two divided doses, followed by oral therapy of 50-200 mg daily. All other medications were prescribed at the discretion of the attending physician.

The majority of patients who underwent continuous ST segment monitoring as part of this substudy were also participants in the angiographic substudy[9] in which patients were randomly assigned to coronary angiography after thrombolytic therapy at 90 minutes, 180 minutes, 24 hours or 5 to 7 days. Half of the patients were assigned to the 90-minute and 5- to 7-day follow-up angiographic study to allow analysis of reocclusion and ventricular function[9].

ST segment monitoring was begun preferably within 30 minutes of the start of thrombolytic treatment and continued for at least 18 hours. To allow a universal evaluation of ST segment response, one of three ST segment monitoring devices was used: a three-channel (Franks orthogonal X,Y,Z leads) continuous vectorcardiographic monitor (MIDA 1000, Ortivus Medical, Stockholm, Sweden), a 12-lead continuous ECG monitor (ST-100, Mortara Instrument, Milwaukee, USA) or a three-channel (bipolar modified V2, V5, AVF) Holter ambulatory ECG monitor (Marquette 8000 Holter Scanner, Marquette Electronics, Milwaukee, USA). ST segment analysis was first performed with all personnel unaware of treatment assignment and angiographic outcome in three core laboratories. Electrocardiographic editing and interpretation were performed by an experienced operator using a computer-assisted device. The technical details of the ST segment analysis for the three monitoring devices have been summarized elsewhere[10].

Comparison across the four treatment groups was carried out with respect to two endpoints: (1) resolution of ST segment elevation, defined as time to 50% ST recovery observed in the lead with the greatest baseline ST segment shift identified from either the monitoring device or the admission 12-lead ECG; (2) episodes of recurrent ST segment elevation in the same lead, defined as ≥ 0.1 mV shift from baseline after 50% resolution had occurred, lasting ≥ 1 minute and separated from other episodes by ≥ 1 minute.

Patients were excluded from analysis of time to 50% recovery because of

time delay of ≥ 1 hour in initiating recording from the time of onset of thrombolytic therapy; inadequate (< 0.2 mV) peak ST segment elevation to allow detection of ST segment elevation recovery; or a significant data gap (absence of data or inability to interpret ST segments) for ≥ 1 hour during the first 3 hours of recording. Excluded from analysis of recurrent ST elevation were patients with < 18 hours of effective monitoring time or a data gap of > 50% of monitoring time and patients without 50% recovery. To exclude ST segment shift in response to contrast injection or mechanical revascularization, ST segment analysis was not performed during the time of the coronary angiogram.

Statistical Analysis

The primary endpoints of time to 50% recovery and recurrent ST segment elevation were not distributed normally and are therefore described using median, 25th and 75th percentiles. Comparisons for the primary endpoints between the predefined rt-PA-containing and streptokinase combined groups were performed with a Wilcoxon test and all four treatment groups were compared by using the Kruskal-Wallis test. The distribution of the primary endpoints was normalized by means of log transformation, and a multiple regression model was employed to define the best predictors of time to 50% recovery of ST segment elevation and recurrent episodes of ST elevation. Because three monitoring devices were used for ST segment analysis, time to 50% recovery of ST segment elevation was compared among the four thrombolytic regimens by a two-way analysis of variance.

Baseline clinical characteristics of patients in the four treatment groups were compared by analysis of variance (for continuous variables distributed normally) and chi-square analysis (for discrete variables).

RESULTS

Of 1,067 patients who underwent ST segment monitoring with one of the three devices, the data of 97 were technically not analyzable. With respect to assessment of time to recovery, 176 patients were excluded because of time to monitor hookup ≥ 1 hour after initiation of thrombolytic therapy, 94 because of peak ST elevation < 0.2 mV, 60 because of a data gap and

Table 1. Baseline clinical characteristics of the four treatment groups.

	SK + Sc Heparin (n=169)	SK + IV Heparin (n=144)	Accel rt-PA (n=152)	rt-PA + SK (n=153)	*P* value
Age (yr)	60 (52,69)	62 (51,70)	61 (50,70)	59 (53,70)	1.0
Gender (M/F)	112/40	109/35	118/35	132/37	0.8
History of hypertension (%)	56 (33%)	55 (38%)	57 (38%)	66 (43%)	0.3
Diabetes Mellitus (%)	21 (12%)	15 (10%)	19 (12%)	27 (18%)	0.3
History of Smoking (%)	126 (75%)	95 (67%)	96 (64%)	102 (72%)	0.15
Previous MI	23 (26%)	19 (21%)	22 (25%)	25 (28%)	0.9
Admission heart rate (bpm)	72 (62,84)	75 (65,85)	70 (60,84)	73 (61,86)	0.3
Admission systolic BP (mmHg)	126(110,140)	130(114,142)	130(115,145)	130(115,143)	0.5
Admission diastolic BP (mmHg)	78 (70,85)	80 (70,90)	80 (70,90)	80 (70,90)	0.5
Killip class					
I	151	128	138	129	
II	15	14	11	20	0.9
III	2	1	2	3	
IV	1	1	1	1	
MI Location Anterior	73	53	62	61	
Inferior	90	84	87	90	0.5
Other	6	7	3	2	
Ejection Fraction (%)	60 (51,70)	59 (49,71)	60 (47,70)	60 (48,67)	0.6
In-hospital deaths	7 (4%)	10 (7%)	6 (4%)	9 (6%)	0.6

Continuous variables shown are median values, with 25th and 75th percentiles in parentheses.
Accel rt-PA = accelerated tissue plasminogen activator; BP = blood pressure; F = female; IV = intravenous; M = male; MI = myocardial infarction; Sc = subcutaneous; SK = streptokinase.

22 because of data entry problems that precluded adequate assessment of the relation between initiation of thrombolytic therapy and onset of monitoring. In the remaining 618 patients assessment of 50% ST recovery was possible.

Comparison of the baseline features and in-hospital mortality for these 618 patients among the four treatment groups (Table 1) revealed no significant differences and showed similarity to the overall population of the GUSTO trial[8]. Comparison of the baseline characteristics and in-hospital mortality of patients who were and were not included in this study did not show significant differences. With respect to detection of recurrent ST segment elevation, 171 patients were excluded because of a monitoring time < 18 hours,

65 because of a > 50% data gap during monitoring and 49 because of an absence of resolution of ST segment elevation ≥ 50%. Thus there were 694 patients for whom assessment of recurrent ST elevation was possible. Again, these patients had characteristics similar to those of the other GUSTO patient groups.

Speed of reperfusion

Time to 50% recovery of ST segment elevation (as a marker of reperfusion) was similar in patients receiving rt-PA-containing regimens (accelerated rt-PA and combination group) and those who received streptokinase only

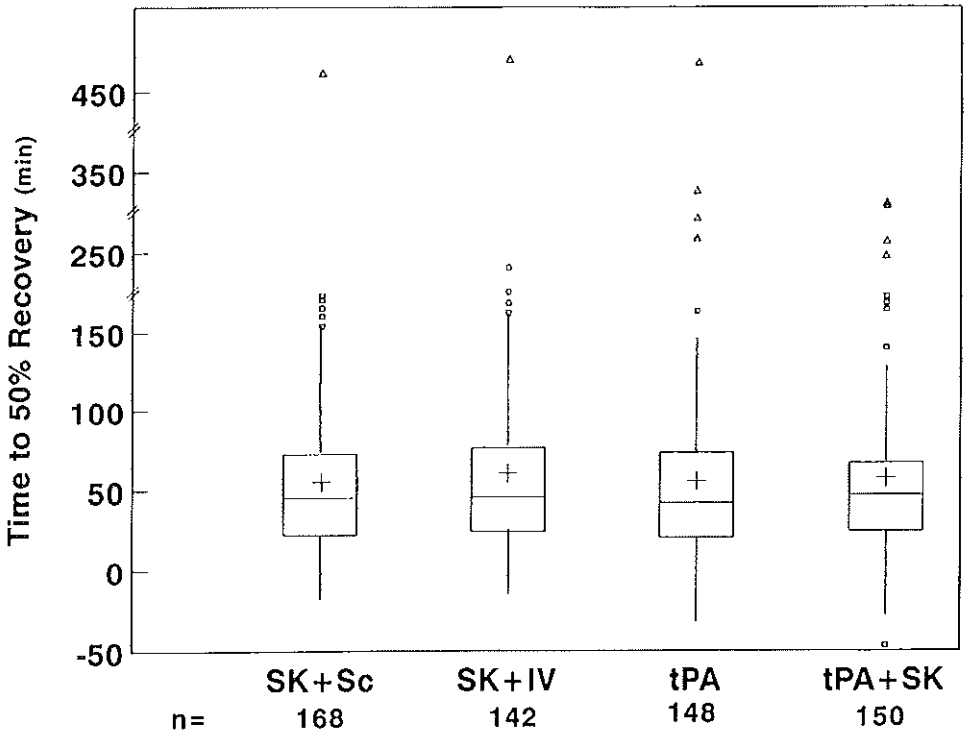

Figure 1. Boxplot summary statistics for time to 50% recovery of ST segment elevation in the four treatment groups. Median values are shown by **lines** and mean values by **plus signs** within the boxes; the length of each box is bounded by 25th and 75th percentiles. Outliers are shown by **small squares** (> 1.5 to < 3 interquartile ranges above the 75th percentile) and **triangles** (> 3 interquartile ranges above the 75th percentile). IV = intravenous; Sc = subcutaneous; SK = streptokinase; Time 0 = start of thrombolytic therapy.

Table 2. Time to thrombolytic therapy, monitoring and 50% ST segment recovery in the four treatment groups.

	SK + Sc Heparin (n=169)	SK + IV Heparin (n=144)	Accel rt-PA (n=152)	rt-PA + SK (n=153)	*P* value
Pain onset to therapy (min)	156 (110,232)	161 (109,224)	160 (120,200)	175 (128,251)	0.10
Qualifying ECG to therapy (min)	43 (28,57)	41 (28,63)	46 (32,68)	49 (36,70)	0.004
Therapy to monitor hookup (min)	5 (-3,59)	6 (-6,21)	7 (-7,22)	11 (-5,22)	0.9
Therapy to 50% ST segment recovery (min)	45 (22,73)	45 (24,76)	42 (20,72)	47 (24,66)	0.7

Times (min) shown are median values, with 25th and 75th percentiles in parentheses.
ECG = electrocardiogram; other abbreviations as in Table 1.

(median 45 [25th and 75th percentiles 22, 68] minutes vs. 45 [23, 75] minutes, P=0.4). The distribution of time from initiation of thrombolytic therapy to 50% recovery of ST segment elevation (Figure 1) also revealed no significant difference among treatment groups. All but 10 of the 618 patients had 50% recovery of ST segment elevation within the first 24 hours (of these 10 patients, 1 received streptokinase with subcutaneous heparin, 2 received streptokinase with intravenous heparin, 4 received accelerated rt-PA and 3 received combination rt-PA and streptokinase). Comparison of time intervals from the onset of pain to the initiation of thrombolytic therapy and from the initiation of thrombolytic therapy to the commencement of ST segment monitoring revealed no significant differences, although a trend toward a longer time to thrombolytic therapy in the combination arm was evident (Table 2).

Time to 50% recovery of ST segment elevation from the onset of thrombolytic therapy as detected by each of the three monitoring devices also did not differ significantly among the four thrombolytic regimens (Figure 2). Two-way analysis of variance using four thrombolytic regimens and three monitoring devices revealed no significant interaction between these two classes of variables (F=0.79, P=0.58) and no difference among four thrombolytic regimens (F=0.19, P=0.90); however, the difference among the monitoring devices was significant (F=4.38, P=0.013), with time to 50% resolution being the shortest for Holter monitoring and longest for continuous 12-lead ECG monitoring.

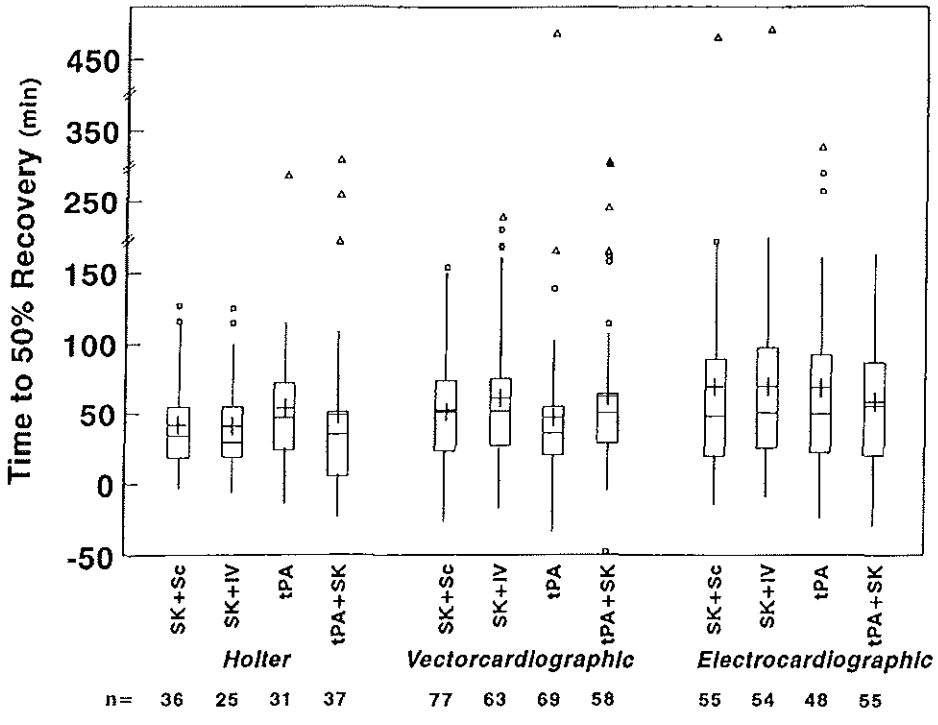

Figure 2. Boxplot summary statistics for time to 50% recovery of ST segment elevation in the four treatment groups as assessed by the three monitoring devices. Format and abbreviations as in Figure 1.

A multiple regression model revealed that time to initiation of ST segment monitoring (F=54.87, *P*=0.0001) and type of monitoring device used (F=9.88, *P*=0.0001) were the best predictors of time to 50% recovery of ST segment elevation, whereas time to initiation of thrombolytic therapy (F=3.35, *P*=0.07) and thrombolytic regimen (F=0.63, *P*=0.59) did not significantly predict time to 50% of ST segment recovery.

Stability of reperfusion

Comparison of recurrent ST segment elevation (an indicator of reocclusion) revealed no difference between patients treated with streptokinase-containing regimens (streptokinase with intravenous or subcutaneous heparin and

combination group) and those who received accelerated rt-PA (median 0 [25th and 75th percentiles 0, 1] episodes vs. 0 [0, 1] episodes, P=0.6). Recurrent ST segment elevation was equally frequent (P=0.9) in patients treated with streptokinase with either subcutaneous (36%) or intravenous (36%) heparin and similar to that in patients receiving accelerated rt-PA (37%) or the combination treatment (34%). No difference in the frequency of recurrent ST elevation in the four treatment groups was evident with the use of any one of the three monitoring devices. Nevertheless, the frequency of recurrent ST elevation detected by Holter monitoring (55%) was greater (P=0.0001) than that seen with either continuous vectorcardiography (28%) or electrocardiography (33%).

Recurrent ST segment elevation showed a weak trend in a relation with patency of infarct-related vessel (r=-0.10, P=0.033) and ejection fraction (r=-0.16, P=0.001).

DISCUSSION

The principal findings of this study are a similarity in time to 50% recovery of ST segment elevation and similarity in the frequency of recurrent ST segment elevation among the four thrombolytic regimens used in the GUSTO trial. Comparison of the patients enrolled in the main GUSTO trial and those participating in the ST segment monitoring substudy revealed no difference in baseline clinical characteristics and outcome. The difference in mortality in the ST monitoring substudy between patients treated with accelerated rt-PA (4.0%) and those receiving streptokinase (5.4%), although not statistically significant, was directionally similar to findings in the main trial[8]. This observation indicates that the sample of patients participating in the substudy was a representative subset of GUSTO patients. The inability to demonstrate a difference in time to 50% recovery, a presumed noninvasive surrogate measure of infarct-related artery patency, is somewhat surprising considering that the main GUSTO trial[8] and the angiographic substudy[9] revealed greater patency at 90 minutes and better outcomes in patients treated with accelerated rt-PA than in those treated with streptokinase.

Several possible explanations for the observed results deserve consideration.

First, there may be no differences in time to reperfusion among the treatment regimens. Second, our ability to demonstrate a difference in time to 50% recovery of ST elevation may have been hampered by uncontrolled and variable time to initiation of ST segment monitoring or by differences among the devices, such as the algorithms used to detect and evaluate ST segment shift[10]. These concerns are supported by the regression model that revealed that time to initiation of ST segment monitoring was the most significant factor associated with time to 50% recovery, followed closely by the type of ST segment monitoring device used. The inability to meet technical requirements in > 40% of patients reduced the power to detect differences, although we found no evidence of bias introduced by technical failure. Finally, the choice of the endpoint was based on the presumption that time to 50% recovery would represent the most sensitive measure of the effect of the thrombolytic agent in achieving reperfusion. This endpoint has not been validated as the best measure related to patient outcome or to coronary angiographic outcome, and subsequent analyses[11] have suggested that other endpoints representing the time to stable evidence of ST segment recovery may be better. These factors notwithstanding, the current study represents a large prospective assessment in the rapidly evolving field of the study of the speed and stability of methods of achieving coronary reperfusion.

Recurrent ischemia as measured by episodes of recurrent ST segment elevation occurred in approximately one third of the patients and was similar in the four treatment groups; however, significant differences existed among monitoring devices. It remains unclear whether differences in ST segment monitoring algorithms[10], patient selection, intervention rates or continuity of monitoring may explain the more frequent detection of ST elevation with Holter monitoring.

Recurrent ST segment elevation was more frequent than the observed rates[8,9] of reocclusion (4.9% to 6.4%), reinfarction (3.4% to 4.0%) or even clinically determined recurrent ischemia (18.8% to 19.9%). Our findings of a similar frequency of recurrent ST elevation across four treatment groups supports the previous findings[8,9] of similar rates of reocclusion and reinfarction. The greater frequency of ST elevation than of angiographic reocclusion may be partly related to differences in the assessment of myocardial perfusion and recurrent ischemia as detected by continuous ST segment monitoring versus

a single determination of patency with coronary angiography. Our findings of a weak relation between recurrent ST segment elevation and patency of the infarct-related vessel and ejection fraction extend our previous observations of the prognostic significance of ST segment depression on Holter monitoring after acute myocardial infarction in relation to severity of stenosis of the culprit lesion and lack of improvement in left ventricular function[12].

CONCLUSIONS

ST segment monitoring for detection of myocardial reperfusion and recurrent ischemia after thrombolytic therapy as defined in this GUSTO substudy did not demonstrate a difference among patients treated with accelerated rt-PA, streptokinase with intravenous or subcutaneous heparin, or combination rt-PA and streptokinase. The technical and study design limitations resulted in diminished sensitivity to detect differences in time to 50% recovery of ST segment elevation among the four treatment groups. Although assessment of the frequency of recurrent ischemia was related to the type of monitoring device, the lack of difference in this primary endpoint among treatments supports the observations of similar reocclusion and reinfarction rates in the main GUSTO trial and angiographic substudy. Further insight regarding the pathophysiology of myocardial perfusion early after thrombolysis based on ST segment monitoring may come from additional post hoc analyses of these data. Nevertheless, ST segment monitoring may be used to compare different reperfusion strategies in the future, provided that the methodology of monitoring is improved.

REFERENCES

1. Hackett D, Davies G, Chiercha S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction: value of combined thrombolytic and vasodilator therapy. N Engl J Med 1984; 311: 1055-9.
2. Krucoff MW, Wagner NB, Pope JE, Mortara DM, Jackson YR, Bottner RK, Wagner GS, Kent KM. The portable programme microprocessor-driven real-time 12-lead electrocardiographic monitor: a preliminary report of a new device for the noninvasive detection of successful reperfusion or silent reocclusion. Am J Cardiol 1990; 65: 143-8.

3. Clemmensen P, Ohman M. Sevilla DC, Peck S, Wagner NB, Quigley PS, Grande P, Lee KL, Wagner GS. Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. Am J Cardiol 1990; 66: 1407-11.
4. Dellborg M. Topol EJ, Swedberg K. Dynamic QRS complex and ST-segment vectorcardiographic monitoring can identify vessel patency in patients with acute myocardial infarction treated with reperfusion therapy. Am Heart J 1991; 122: 943-8.
5. Dellborg M, Riha M. Swedberg K. Dynamic QRS-complex and ST-segment monitoring in acute myocardial infarction during recombinant tissue-type plasminogen activator therapy. Am J Cardiol 1991; 67: 343-9.
6. Krucoff MW, Cross MA, Poe JE, Pieper KS, Kanai PM, Granger CB, Veldkamp RF, Wagner BL, Sawchak ST, Califf RM. Continuously updated 12-lead ST-segment recovery analysis for myocardial infarct artery patency assessment and its correlation with multiple simultaneous early angiographic observations. Am J Cardiol 1993; 71: 145-51.
7. Simoons ML, Arnold AER. Tailored thrombolytic therapy. A perspective. Circulation 1993; 88: 2556-64.
8. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673-82.
9. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329: 1615-22.
10. Krucoff MW, Green CL, Langer A, Klootwijk LJP, Trollinger KM, Sawchak ST, Wilderman NM, Veldkamp RF, Pope JE, Simoons ML, Granger CB, Armstrong PW. Global utilization of streptokinase and tPA for occluded arteries (GUSTO) ECG-monitoring substudy. J Electrocard 1994; 26 Suppl: 249-55.
11. Krucoff MW, Green CL, Trollinger KM, Sawchak ST, Wilderman NM, Shah A, Granger CB, O'Connor CM, Pope JE. Univariate relationships between mortality and parameters of continuous 12-lead ST-segment deviation and recovery after thrombolytic therapy for acute infarction. Circulation 1994; 90 Suppl I: I-501A.
12. Langer A, Minkowitz J, Dorian P, Casella L, Harris L, Morgan C, Armstrong PW for the TPAT Study Group. The Pathophysiology and Prognostic Significance of Holter Detected ST-segment Depression After Myocardial Infarction. J Am Coll Cardiol 1992; 20: 1313-7.

Chapter 4

Prognostic significance of ST segment shift early after resolution of ST elevation in patients with myocardial infarction treated with thrombolytic therapy: the GUSTO-I ST Segment Monitoring Substudy

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ABSTRACT

Objectives. We sought to study the relation between recurrent ST segment shift within 6 to 24 hours of initial resolution of ST elevation after thrombolytic therapy and 30-day and 1-year mortality.

Background. Rapid and stable resolution of ST segment elevation in relation to thrombolytic therapy in patients with acute myocardial infarction is an indicator of culprit artery patency. Whether recurrence of ST segment shift during continuous ST monitoring after initial resolution is related to poor prognosis has not been studied.

Methods. ST segment monitoring was performed within 30 minutes after thrombolytic therapy for acute myocardial infarction. The predictive value of a new ST segment shift (assessed as ≥ 0.1 mV deviation from the baseline) 6 to 24 hours after thrombolytic therapy was studied with respect to 30-day and one-year mortality.

Results. Of 734 patients, 243 had a new ST segment shift (33%). The 30-day mortality rate in patients with an ST shift (7.8%) was significantly higher than that in patients without an ST shift (2.25%, P=0.001), as was the 1-year mortality rate (10.3% versus 5.7%, respectively, P=0.025). Multivariable analysis revealed an independent predictive value of ST shift with respect to 30-day mortality (P=0.008), even after consideration of multiple clinical risk factors in the overall Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I mortality model (P=0.0001). Moreover, the duration of the ST shift bore a direct relation with 1-year mortality (P=0.008).

Conclusions. Detection of ST segment shift early after thrombolytic therapy for acute myocardial infarction is a simple, noninvasive means of identifying patients at high risk and is superior to other commonly assessed clinical risk factors. Thus, patients with a new ST shift after the first 6 hours, but within 24 hours, represent a high risk group that may benefit from more aggressive intervention, whereas patients without evidence of an ST shift represent a low risk subgroup.

INTRODUCTION

In the setting of acute ischemic syndromes, continuous ST segment monitoring can be used for the detection of culprit vessel reperfusion on the basis of rapid and stable resolution of ST segment elevation[1-9]. There is also evidence of a more frequent unfavorable outcome among patients with an ST segment shift on continuous monitoring after presentation with unstable angina[10-15] or after myocardial infarction[16-22]. Although recurrent symptoms and the admission electrocardiogram (ECG) have predictive value[23,24], several studies have found that continuous ST segment monitoring has additional prognostic value[14], independent of such prognostic indicators as left ventricular dysfunction or angiographic extent of coronary artery disease[15]. Thus, ST segment shift reflects a variety of adverse underlying pathophysiological processes in patients with acute ischemic syndromes and has been related not only to angiographic detection of thrombus[25] but also to cardiac adrenergic dysfunction[26] and cycles of thrombosis and thrombolysis.[27].

The recently reported Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial[28] and its angiographic substudy[29] showed improved clinical outcomes and angiographic patency in patients treated with an accelerated regimen of rt-TPA versus streptokinase. The primary goal of the GUSTO-I ST segment monitoring substudy was to provide a noninvasive assessment of the speed and stability of reperfusion[9]. The prognostic significance of recurrent ST shift after initial resolution of ST segment elevation in patients presenting with ST elevation and acute myocardial infarction has not been studied. Thus, we studied the relation between recurrent ST shift 6 to 24 hours subacutely after initial resolution of ST elevation after thrombolytic therapy and 30-day and 1-year mortality.

METHODS

Patients

The protocol and results of the GUSTO-I trial have been published elsewhere[28]. Eligible patients were randomized to receive streptokinase with subcutaneous

or intravenous heparin, accelerated rt-PA with intravenous heparin or the combination of intravenous rt-PA and streptokinase with intravenous heparin.

ST segment monitoring

The details of ST segment monitoring have been reported previously[9,30]. We aimed to start ST segment recording within 30 minutes of thrombolytic treatment, and monitoring continued for 24 hours. The GUSTO-I ECG monitoring substudy was a collaborative effort[30] of three core laboratories, which used one of three ST segment monitoring devices: a three-channel (Franks orthogonal X, Y, Z leads) continuous vectorcardiographic monitor (MIDA 1000, Ortivus Medical, Stockholm, Sweden); a 12-lead continuous electrocardiographic monitor (ST-100, Mortara Instrument, Milwaukee, USA); or a three-channel (bipolar modified V2, V5, and aVF leads) Holter monitor (Marquette Electronics, Milwaukee, USA). ST segment analysis was first performed in blinded manner as to treatment assignment at the three core laboratories. ECG editing and interpretation were performed by an experienced operator with a computer-assisted device. The technical details of ST segment analysis for the three monitoring devices have been summarized elsewhere[30]. The three core laboratories provided edited ST segment trends as a data stream containing the ST segment level at 60 ms after the J-point, which was used for this analysis.

We evaluated new ST segment shift after resolution of initial ST elevation within 6 hours of thrombolytic therapy (Figure 1) on the basis of the following criteria: (1) $\geq$ 50% resolution of initial ST shift (elevation or depression) in the lead with maximal ST deviation at the initiation of monitoring[6,9] or if maximal ST deviation was not detected, for example, because of a late hook-up of the ST monitoring device, an ST segment level within 6 hours of thrombolysis $<$ 0.2 mV (elevation or depression); otherwise, the resolution of initial ST elevation was not thought to have occurred; (2) duration of $\geq$ 50% resolution of $\geq$ 10 minutes within 6 hours of thrombolysis; and (3) new ST segment elevation or depression, defined as $\geq$ 0.1 mV from the average ST segment baseline $>$ 6 hours after thrombolysis and lasting $\geq$ 1 minute. The average ST segment baseline value was calculated from all ST segment data points for the duration of monitoring beyond the initial 6 hours. Thus, ST shift as discussed here represents a recurrent ST shift $>$ 6 hours from the time of thrombolytic therapy. Because the duration of monitoring varied among

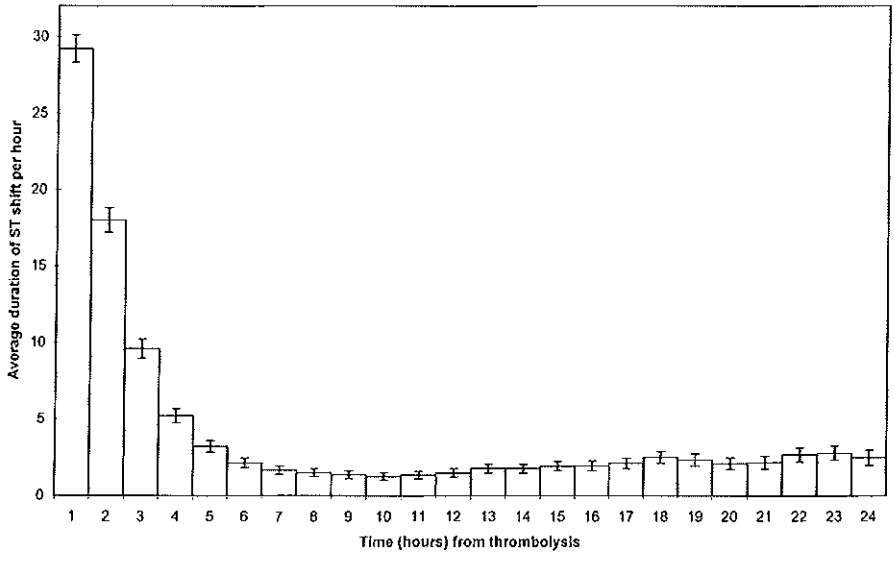

Figure 1. Average duration of ST shift per hour (min) for all patients from the time of thrombolysis. **Vertical lines** indicate standard deviation.

patients, the duration of the ST segment shift for each patient was normalized for 24 hours: Normalized duration of ST segment shift = (actual ST segment shift duration/Hours of monitoring) × 24 hours. Total ischemic burden (total ST shift) consisted of ST depression and ST elevation duration. If both ST segment depression and elevation were seen in different leads at the same time, the ST shift with greatest ST deviation magnitude was chosen. Excluded from analysis were patients with < 12 hours of effective monitoring time or a data gap of > 50% of monitoring time or those in whom recurrence of ST shift could not be assessed. Many patients who underwent continuous ST segment monitoring as part of this substudy also participated in the angiographic substudy[29]. ST segment analysis was not performed during coronary angiography to exclude ST segment shift in response to contrast injection or mechanical revascularization.

Statistical analysis

The primary endpoint was death at 30 days, with a secondary endpoint of death at one year. A comparison of baseline clinical characteristics of patients in and excluded from this study as well as patients with and without ST

segment shift was performed with chi-square analysis or an unpaired *t* test (mean value ± SD for continuous variables). The variable of ST duration was normalized with the logarithmic transformation. The relation between ST segment shift and death was studied with univariate logistical regression analysis. The variable "ST segment shift" was then added to the multivariable model containing the overall 30-day GUSTO-I mortality model[31]. One-year survival analysis based on the presence of ST shift was performed with Kaplan-Meier curves. To study the relation between duration of ST shift and death, 30-minute increments of ST shift duration were chosen on the basis of previous observations[11,12,14,32].

RESULTS

Patient characteristics

Of 1,067 patients who underwent ST segment monitoring with one of the three devices, 333 were excluded because of a monitoring time < 12 hours, a data gap duration > 50% of monitoring time, or other technical difficulties. An additional 41 patients were excluded because resolution of initial ST shift was not achieved. Patients who were excluded from the study (n=333) were significantly older, more frequently had an anterior myocardial infarction, received thrombolytic therapy later and had a higher mortality rate at 30 days and 1 year than those included in the study. Among 734 patients evaluated in this study, 243 (32%) had an ST segment shift, whereas 491 (67%) patients did not. Among patients with an ST shift, the median duration of the ST shift was 30 minutes, with 25th and 75th percentile of 7 and 110 minutes, respectively; the average duration of the ST shift is shown in Figure 1.

A Comparison of baseline clinical and presenting characteristics of patients with and without ST segment shift is shown in Table 1; patients with ST shift were older and more frequently had diabetes mellitus. There was a trend for a more frequent history of anterior infarction and cerebrovascular disease, as well as elevated systolic blood pressure on admission. No differences were seen in the frequency of administration of various thrombolytic regimens or in time to treatment (Table 1).

Table 1. Clinical Characteristics.

	No ST shift (n = 491)	ST shift (n = 243)	*P* value
Age (yr) *	60±12	62±12	0.005
Male	75.2%	76.5%	0.68
Weight, (kg) *	80±16	79±16	0.38
Height (cm) *	172±9	171±10	0.45
Smoking history *	68%	71%	0.47
Family history	46%	42%	0.31
Hypercholesterolemia	36%	31%	0.15
Hypertension *	36%	41%	0.26
Systolic blood pressure (mm Hg) *	128±20	131±24	0.09
Diastolic blood pressure (mm Hg) *	78±14	79±15	0.21
Heart rate (beats/min) *	74±16	74±17	0.92
Previous bypass surgery *	4.7%	4.5%	0.92
Previous angina	40%	35%	0.22
Previous myocardial infarction *	12%	15%	0.26
Previous cerebrovascular accident *	0.6%	2.1%	0.08
Diabetes *	11%	17%	0.03
Killip Class *			0.72
I	89%	89%	
II	10%	10%	
III	0.8%	1.7%	
IV	0.2%	0.4%	
Site of myocardial infarction *			0.07
Anterior	33%	42%	
Inferior	62%	55%	
Other	5%	3%	
Time to treatment (hours) *	3.0±1.5	3.0±1.6	0.91
Treatment *			0.55
Accelerated rt-PA	25%	23%	
Streptokinase + IV heparin	21%	26%	
Streptokinase + Sc heparin	26%	24%	
rt-PA + Streptokinase	28%	28%	
Peak creatine kinase-MB (IU/liter)	162±162	191±165	0.10

* included in GUSTO-I mortality model[31]. Data presented are mean value ± SD or percent of patients. IV = intravenous; Sc = subcutaneous.

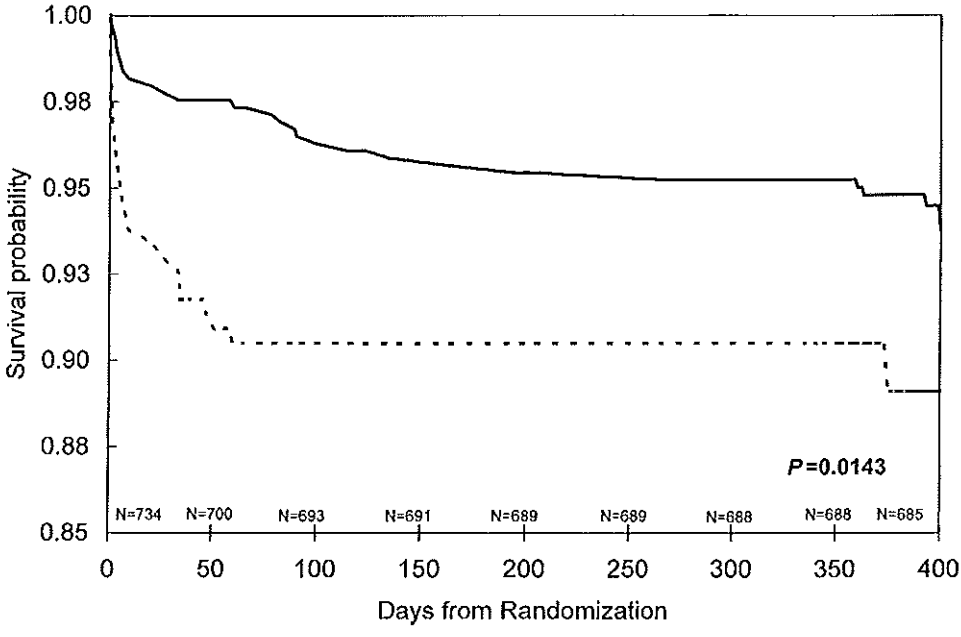

Figure 2. Kaplan-Meier survival curves for patients with ST shift **(dashed line)** and those without ST shift **(solid line)** demonstrating a significant difference in 1-year mortality rates. Overall number of patients available for follow-up at each point in time is also shown.

Recurrent ST segment shift and death

The survival disadvantage in patients with versus those without an ST segment shift can be appreciated early and persists for up to one year (Figure 2). The mortality rate at 30 days (7.8% vs. 2.25%, odds ratio [OR] 3.7, 95% confidence interval [CI] 1.7 to 7.9, P=0.008) and at 1 year (10.3% vs. 5.7%, OR 1.9, 95% CI 1.1 to 3.3, P=0.025) was higher in patients with than those without an ST segment shift, respectively. After adjustment for significant baseline inequalities (Table 1), there continued to be greater mortality in patients with an ST shift at 30 days (P=0.015).

To further define the prognostic significance of ST shift, this variable was added to the overall 30-day GUSTO-I mortality model[31].When ST shift was added to the overall mortality model (OR for the model 2.65, 95% CI 1.9 to 3.7) the duration of the ST shift had an independent and significant incremental value when considered with 1- or 30- minute interval increases (OR 1.13,

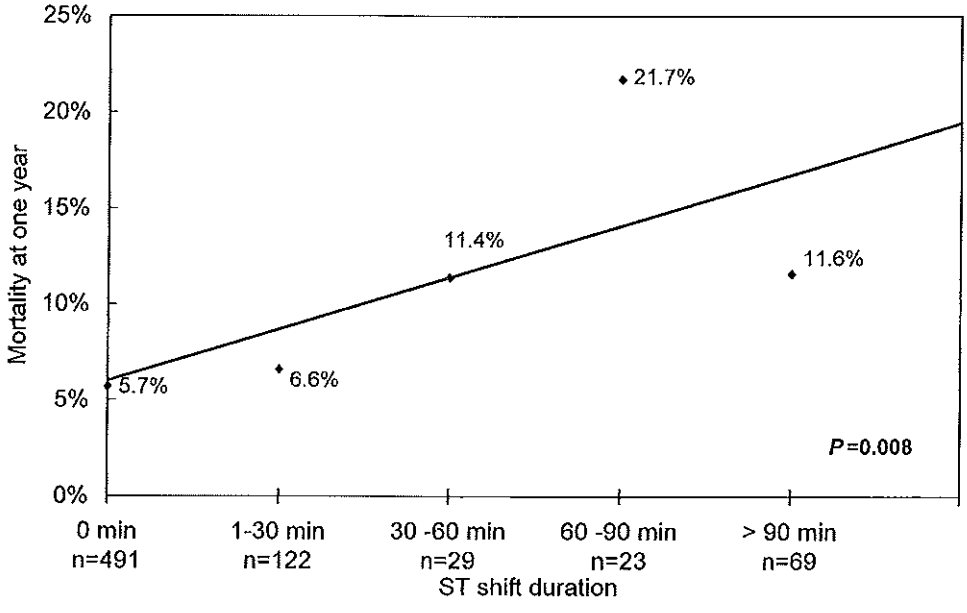

Figure 3. Relation between duration of ST shift within the first 24 hours after myocardial infarction and 1-year mortality rates (r=0.88). Duration of ST shift was grouped on the basis of 30-minute intervals and plotted against the respective mortality (average) rate for each group of patients. Significance level is based on univariate analysis of ST shift.

95% CI 1.03 to 1.24, *P*=0.008). To examine whether a continuous relation existed between the duration of the ST shift and 1-year mortality rates, we partitioned the ST shift duration into 30-minute intervals. As shown in Figure 3, a good direct relation existed between duration of ST shift and 1-year mortality (r=0.88, *P*=0.008).

Direction of ST segment shift

Among patients with an ST shift, 92 (38%) had ST depression, and 151 (62%) had ST elevation. Compared with patients without an ST shift, there was an increase in the 30-day mortality rate both among those with ST depression (9.78% vs. 2.25%, *P*=0.0009, OR 4.71, 95% CI 1.89 to 11.72) and those with ST elevation (6.62% vs. 2.25%, *P*=0.012, OR 1.76, 95% CI 1.13 to 2.72). The relation with higher mortality was maintained after adjustment with the GUSTO-I mortality model[31] in patients with ST depression

(OR 3.64, 95% CI 1.38 to 9.61, *P*=0.009) or ST elevation (OR 2.43, 95% CI 0.96 to 6.12, *P*=0.06).

Similarly, there was an increase in 1-year mortality rates among patients with ST segment depression compared with those without an ST shift (11.96% vs. 5.7%, *P*=0.03, OR 2.25, 95% CI 1.08 to 4.69) and ST elevation (9.3% vs. 5.7%, *P* 0.13, OR 1.30, 95% CI 0.93 to 1.82).

The 30-day prognostic significance of ST depression and elevation persisted after the elimination of two deaths that occurred within the first 24 hours.

DISCUSSION

The principal novel finding of this study is that a recurrent ST segment shift detected within 6 to 24 hours of thrombolytic therapy and after the initial resolution of ST elevation is an independent predictor of 30-day mortality in patients with an acute myocardial infarction. We also found a direct relation between the duration of the ST shift and 1-year mortality. Previous studies[16-22] have related poor outcome to recurrent ischemia detected beyond the first day. Our study extends those findings of prognostic significance by demonstrating the importance of early (i.e., within the first 24 hours) detection of ischemia when other noninvasive modalities such as stress testing are not applicable and within a time frame in which therapeutic intervention is feasible.

Multiple studies have demonstrated that rapid and stable resolution of ST elevation in patients with acute an myocardial infarction is related to patency of an infarct-related artery[1-9]. Our goal in this respect was to study early risk stratification beyond the initial 6 hours when patency status has been established. We were interested in ST segment monitoring beyond this point to identify high risk patients beyond the time frame for immediate intervention, such as rescue angioplasty.

ST segment elevation

We observed a higher mortality rate in patients with recurrent ST segment elevation than in those without an ST segment shift; however, the pathophysiology and specificity of ST segment elevation for identifying recurrent ischemia could not be determined from our analysis and remain uncertain. Recurrent ST elevation is thought to reflect a culprit vessel

occlusion[6,33-35]. Thus, recurrent ST elevation in our analysis may have been indicative of recurrent thrombosis in the infarct-related artery; alternatively, mechanical changes in left ventricular geometry in response to transient alterations in loading conditions, for example, may account for the recurrent ST elevation[6-38].

ST segment depression

The pathophysiology of ST segment depression after myocardial infarction is related to the severity of culprit lesion stenosis and the dynamic aspects of the culprit lesion activity, including thrombosis and vasospasm; these result in more frequent recurrent ischemia, persistent left ventricular dysfunction, electrical instability and poor outcome[16,19-22,39]. Based on our observations, ST segment depression appears to have a stronger relation to mortality than does ST segment elevation, especially after adjustment for other variables with the GUSTO-I mortality model[31]. This may suggest that recurrent ST segment depression is a more specific marker of recurrent ischemia than ST segment elevation.

Total ischemic burden

We demonstrated the prognostic significance of ST segment depression and ST segment elevation with respect to 30-day or 1-year mortality, suggesting that the measure of overall ST segment shift can be used for prognostic risk stratification, at least when acquired within the first 24 hours after acute myocardial infarction. Further insight into the mechanism of our findings would have been provided by concurrent measures of infarct size and ventricular function as well as the status of the culprit vessel.

With acute ischemic syndromes, ST segment shift may be a marker of myocardial ischemia or necrosis depending on the underlying pathophysiology, which can include intracoronary thrombosis, vasoconstriction, distal embolization and microvascular injury. Dynamic changes in ST segments on continuous monitoring have been related to angiographic detection of intracoronary thrombosis[25], cardiac adrenergic dysfunction[26] and thrombus-mediated cycles in coronary flow[27]. Thus, ST segment shift represents a convenient surrogate measure of underlying pathophysiology because it is readily available, can be continuously updated, quantitatively relates to the extent of myocardial cell injury in real time and bears a relation to prognosis.

The relation of ST segment monitoring to other markers of higher risk patients[40,41] requires further evaluation.

In this era of fiscal restraint and diminishing access to more intense therapy, our findings provide support for the use of this noninvasive and universally available marker of recurrent ischemia for risk stratification. Studies have shown a lack of benefit from the indiscriminate use of target lesion angioplasty in patients early after myocardial infarction[42-51]. Our study provides support for the triage of patients with ST shift who represent a high risk group; this increased risk may be mediated by reocclusion of the infarct-related artery or recurrent ischemia. This approach is further supported by the findings of a continuous relation between the duration of ST segment shift and death (Figure 3) and by the independent predictive nature of ST shift in multivariable analysis, which included the GUSTO-I 30-day mortality model[31].

Study limitation

The main limitation of our study relates to the arbitrary selection of a 6-hour cut off period for detection of recurrent ST shift after thrombolysis. This choice was supported by three considerations: (1) Resolution of the initial ST shift was rapid (Figure 1), with an apparent "shoulder" at 6 hours. (2) Insight from concurrent participation in the angiographic substudy[35] indicated that by 3 hours, up to 80% of patients experienced ≥ 50% resolution of initial maximal ST shift; only a few patients underwent angiography beyond 3 hours in the first day[29], precluding further assessment of patency in relation to recurrent ST shift. (3) We wished to study the prognostic significance of ST shift beyond the initial period of thrombolysis and related instability. Approximately one third of patients initially enrolled into this substudy were excluded for technical reasons, which limits the generalizability of our findings. The observation of higher mortality rates in the excluded patients than in the included patients may have resulted in the dilution of the relation between the new ST shift and death. It should also be noted that the relationship of ST shift to death was independent of clinical variables and risk factors documented at the time of randomization. However, we did not study ST shift in relation to symptomatic recurrence of ischemia or heart failure or in relation to a particular QRS configuration (e.g., the development of Q waves). Although the accuracy of ST shift detection may have been limited by the

use of three different techniques, the concurrence of our findings within each of the technologies facilitates the generalizability of the results.

CONCLUSION

Recurrent ST shift at 6 to 24 hours after thrombolytic therapy for acute myocardial infarction is related to increased mortality at 30 days and 1 year. This simple, noninvasive monitoring technique may be of additional prognostic value in the early period after acute myocardial infarction when rapid decision making pertaining to the management of these patients is required. Patients with a recurrent ST shift within the first 24 hours represent a high risk group that may benefit from more aggressive intervention. Patients without a recurrent ST shift represent a low risk subgroup that, in the absence of other high risk features, may be suitable for early discharge.

REFERENCES

1. Hackett D, Davies G, Chiercha S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction: value of combined thrombolytic and vasodilator therapy. N Engl J Med 1987; 317: 1055-9.
2. Krucoff MW, Wagner NB, Pope JE, Mortara DM, Jackson YR, Bottner RK, Wagner GS, Kent KM. The portable programmable microprocessor-driven real-time 12-lead electrocardiographic monitor: a preliminary report of a new device for the noninvasive detection of successful reperfusion or silent reocclusion. Am J Cardiol. 1990; 65: 143-8.
3. Clemmensen P, Ohman M, Sevilla DC, Peck S, Wagner NB, Quigley PS, Grande P, Lee KL, Wagner GS. Changes in standard electrocardiographic ST segment elevation predictive of successful reperfusion in acute myocardial infarction. Am J Cardiol 1990; 66: 1407-11.
4. Dellborg M, Topol EJ, Swedberg K. Dynamic QRS complex and ST segment vectorcardiographic monitoring can identify vessel patency in patients with acute myocardial infarction treated with reperfusion therapy. Am Heart J 1991; 122: 943-8.
5. Dellborg M, Riha M, Swedberg K. Dynamic QRS complex and ST segment monitoring in acute myocardial infarction during recombinant tissue-type plasminogen activator therapy. Am J Cardiol 1991; 67: 343-9.
6. Krucoff MW, Cross MA, Pope JE, Pieper KS, Kanai PM, Granger CB, Veldkamp RF, Wagner BL, Sawchak ST, Califf RM. Continuously updated 12-lead ST segment recovery

analysis for myocardial infarct artery patency assessment and its correlation with multiple simultaneous early angiographic observations. Am J Cardiol 1993; 71: 145-51.
7. Shah PK, Cercek B, Lew AS, Ganz W. Angiographic validation of bedside markers of reperfusion. J Am Coll Cardiol 1993; 21: 55-61.
8. Kondo M, Tamura K, Tanio H, Shimono Y. Is ST segment re-elevation associated with reperfusion an indicator of marked myocardial damage after thrombolysis? J Am Coll Cardiol 1993; 21: 62-7.
9. Langer A, Krucoff MW, Klootwijk P, Veldkamp R, Simoons ML, Granger C, Califf RM, Armstrong PW, for the GUSTO Investigators. Noninvasive assessment of speed and stability of infarct-related artery reperfusion: results of the GUSTO ST segment monitoring study. J Am Coll Cardiol 1995; 25: 1552-7.
10. von Arnim T, Gerbig HW, Krawietz W, Hofling B. Prognostic implications of transient - predominantly silent - ischaemia in patients with unstable angina pectoris. Eur Heart J 1988; 9: 435-40.
11. Nademanee K, Intarachot V, Josephson MA, Rieders D, Mody FV, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. J Am Coll Cardiol 1987; 10: 1-9.
12. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death during 2 year follow-up of unstable angina. J Am Coll Cardiol 1987; 10: 756-60.
13. Johnson SM, Mauritson DR, Winniford MD, Willerson JT, Firth BG, Cary JR, Hillis LD. Continuous electrocardiographic monitoring in patients with unstable angina pectoris: identification of high-risk subgroup with severe coronary disease, variant angina, and/or impaired early prognosis. Am Heart J 1982; 103: 4-12.
14. 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.
15. Langer A, Singh N, Freeman MR, Tibshirani R, Armstrong PW. Detection of silent ischemia adds to the prognostic value of coronary anatomy and left ventricular function in predicting outcome in unstable angina patients. Can J Cardiol 1995; 11: 117-22.
16. Ouyang P, Chandra NC, Gottlieb SO. Frequency and importance of silent myocardial ischemia identified with ambulatory electrocardiographic monitoring in the early in-hospital period after acute myocardial infarction. Am J Cardiol 1990; 65: 267-70.
17. Gottlieb SO, Gottlieb SH, Achuff SE, Baumgardner R, Mellits ED, Weisfeldt ML, Gerstenblith G. Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. JAMA 1988; 259: 1030-5.
18. Tzivoni D, Gavish A, Zin D, Gottlieb S, Moriel M, Keren A, Banai S, Stern S. Prognostic significance of ischemic episodes in patients with previous myocardial infarction. Am J Cardiol 1988; 62: 661-4.
19. Langer A, Minkowitz J, Dorian P, Casella L, Harris L, Morgan CD, Armstrong PW, for the Tissue Plasminogen Activator: Toronto (T-PAT) Study Group. Pathophysiology

and prognostic significance of Holter-detected ST segment depression after myocardial infarction. J Am Coll Cardiol. 1992; 20: 1313-7.
20. Solimene MC, Ramires JA, Gruppi CJ, Alfieri RG, de Oliveira SF, Da Luz PL, Pileggi F. Prognostic significance of silent myocardial ischemia after a first uncomplicated myocardial infarction. Int J Cardiol 1993; 38: 41-7.
21. Silva P, Galli M, Campolo L, for the IRES (Ischemia Residua) Study Group. Prognostic significance of early ischemia after acute myocardial infarction in low-risk patients. Am J Cardiol 1993; 71: 1142-7.
22. Gill JB, Cairns JA, Roberts, RS, Tech M, Costantini L, Sealey BJ, Fallen ER, Tomlinson CW, Gent M. Prognostic importance of myocardial ischemia detected by ambulatory monitoring early after acute myocardial infarction. N Engl J Med 1996; 334: 65-70.
23. Betriu A, Heras M, Cohen M, Fuster V. Unstable angina: outcome according to clinical presentation. J Am Coll Cardiol 1992; 19: 1659-63.
24. Cohen M, Hawkins L, Greenberg S, Fuster V. Usefulness of ST segment changes in greater than or equal to 2 leads on the emergency room electrocardiogram in either unstable angina pectoris or non-Q wave myocardial infarction in predicting outcome. Am J Cardiol 1991; 67: 1368-73.
25. Langer A, Freeman MR, Armstrong PW. Relation to angiographic detected intracoronary thrombus and silent myocardial ischemia in unstable angina pectoris. Am J Cardiol 1990; 66: 1381-2.
26. Serneri GGN, Boddi M, Arata L, Rostagno C, Dabizzi P, Coppo M, Bini M, Lazzerini S, Dagianti A, Gensini GF. Silent ischemia in unstable angina is related to an altered cardiac norepinephrine handling. Circulation 1993; 87: 1928-37.
27. Gurfinkel E, Altman R, Scazziota A, Rouvier J, Mautner B. Importance of thrombosis and thrombolysis in silent ischaemia: comparison of patients with acute myocardial infarction and unstable angina. Br Heart J 1994; 71: 151-5.
28. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673-82.
29. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329: 1615-22.
30. Krucoff MW, Green CL, Langer A, Klootwijk LJP, Trollinger KM, Sawchak ST, Wildermann NM, Veldkamp RF, Pope JE, Simoons ML, Granger CB, Armstrong PW. Global utilization of streptokinase and t-PA for occluded arteries (GUSTO) ECG monitoring substudy. J Electrocardiol 1994; 26: 249-55.
31. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM, for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. Circulation 1995; 91: 1659-68.
32. Pepine CJ. Is silent ischemia a treatable risk factor in patients with angina pectoris? Circulation 1990; 82 (Suppl II): II-135-142.
33. Fernandez AR, Sequeira RF, Chakko S, Correa LF, de Marchena EJ, Chahine RA,

Franceour A, Myerburg RJ. ST segment tracking for rapid determination of patency of the infarct-related artery in acute myocardial infarction. J Am Coll Cardiol 1995; 26: 675-83.
34. Timmis GC. ST segment analysis for determining the dynamic status of reperfusion therapy. J Am Coll Cardiol 1995; 25: 684-7.
35. Klootwijk P, Langer A, Meij S, Green C, Veldkamp RF, Ross AM, Armstrong PW, Simoons ML. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial. Eur Heart J 1996; 17: 689-98.
36. Fox KM, Jonathan A, Selwin A. Significant of exercise-induced ST segment elevation in patients with previoius myocardial infarction. Br Heart J 1983; 49: 15-9.
37. Coma-Canella I, Gomez MV, Terol I, Rodrigo F, Castro JM. Radionuclide studies in patients with stress-induced ST segment elevation after acute myocardial infarction. Am Heart J 1994; 128: 459-65.
38. Elhendy A, Fioretti PM. Stress-induced ST segment elevation after a recent myocardial infarction: Myocardial necrosis, viability or both? Eur Heart J 1996; 17: 975-7.
39. Dorian P, Langer A, Morgan C, Casella L, Harris L, Armstrong P. Importance of ST segment depression as a determinant of ventricular premature complex frequency after thrombolysis for acute myocardial infarction. Am J Cardiol 1994; 74: 419-23.
40. 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: 1333-41.
41. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 335: 1342-9.
42. Topol EJ, Califf RM, George BS, Kereiakes DJ, Abbottsmith CW, Candela RJ, Lee KL, Pitt B, Stack RS, O'Neill WW, and the Thrombolysis and Angioplasty in Myocardial Infarction Study Group. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987; 317: 581-8.
43. Guerci AD, Gerstenblith G, Brinker JA, Chandra NC, Gottlieb SO, Bahr RD, Weiss JL, Shapiro EP, Flaherty JT, Bush DE, Chew PH, Gottlieb SH, Halperin HR, Ouyang P, Walford GD, Bell WR, Fatterpaker AK, Llewellyn M, Topol E, Healy B, Siu CO, Becker LC, Weisfeldt ML. A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. N Engl J Med 1987; 317: 1613-8.
44. Simoons ML, Betriu A, Col J, von Essen R, Lubsen J, Michel PL, Rutsch W, Schmidt W, Thery C, Vahanian A, Willems GM, Arnold AER, De Bono DP, Dougherty FC, Lambertz H, Meier B, Raynaud P, Sanz GA, Serruys PW, Uebis R, Van De Werf F, Wood D, Verstraete M. Thrombolysis with tissue plasminogen activator in acute

myocardial infarction: no additional benefit from immediate percutaneous coronary angiolasty. Lancet 1988; 1: 197-203.

45. The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. JAMA 1988; 260: 2849-58.
46. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. N Engl J Med 1989; 320: 618-27.
47. Rogers WJ, Baim DS, Gore JM, Brown G, Roberts R, Williams DO, Chesebro JH, Babb JD, Sheehan FH, Wackers RJ, Zaret BL, Robertson TL, Passamani ER, Ross R, Knatterud GL, Braunwald E, for the TIMI II-A Investigators. Comparison of immediate invasive, delayed invasive, and conservative strategies after tissue-type plasminogen activator. Results of the Thrombolysis in Myocardial Infarction (TIMI) phase II-A Trial. Circulation 1990; 81: 1457-76.
48. Barbash GI, Roth A, Hod H, Modan M, Miller HI, Rath S, Zahav YH, Keren G, Motro M, Shachar A, Basan S, Agranat O, Rabinowitz B, Laniado S, KaPlinsky E. Randomized controlled trial of late in-hospital angiography and angioplasty versus conservative management after treatment with recombinant tissue-type plasminogen activator in acute myocardial infarction. Am J Cardiol. 1990; 66: 538-45.
49. SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group. SWIFT Trial of delayed elective intervention vs conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. Br Med J 1991; 302: 555-60.
50. Topol E, Califf RM, Vandormael M, Grines CL, George BX, Sanz ML, Wall T, O'Brien M, Schwaiger M, Aguirre FV, Young S, Popma JJ, Sigmon KN, Lee KL, Ellis SG, and the Thrombolysis and Angioplasty in Myocardial Infarction-6 Study Group. A randomized trial of late reperfusion therapy for acute myocardial infarction. Circulation 1992; 85: 2090-9.
51. Ellis SG, Mooney MR, George BS, Ribeiro de Silva EE, Talley D, Flanagan WH, Topol EJ, for the Treatment of PoST Thrombolytic Stenosis (TOPS) Study Group. Randomized trial of late elective angioplasty versus conservative management for patients with residual stenosis after thrombolytic treatment of myocardial infarction. Circulation 1992; 86: 1400-6.

Chapter 5

Comparison of usefulness of computer-assisted continuous 48-hours 3-lead with 12-lead ECG-ischemia monitoring for detection and quantitation of ischemia in patients with unstable angina

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ABSTRACT

Aims. The selection of ECG leads used for ST monitoring may influence detection and quantitation of ischemia.
Methods. We compared on-line continuous 48-hours 12-lead against 3-lead ST monitoring in 130 eunstable angina patients (Mortara, ELI-100). Onset and offset of ST episodes were defined by the lead with the first ≥ 100 μV ST change relative to baseline and the lead with the latest return to baseline ST level, respectively. ST episodes were calculated for 12 leads and 3 leads (V2, V5, III) separately.
Results. ST episodes were detected in 88 patients (77%) by 12-lead and in 71 patients (62%) by 3-lead ST monitoring ($P<0.02$). The median number (25, 75%) of episodes/patient was 1 (0, 3) for 3-lead and 2 (1, 6) for 12-lead ($P<0.0001$). The total duration of ischemia detected during 12-lead far exceeded 3-lead monitoring: 12.3 (1, 58.2) and 1.7 (0, 23.3) minutes respectively ($P<0.0001$). The probability of recurrent ischemia declined most during the first 24 hours of monitoring. After a period without ST changes of 1, 12, 24 and 36 hours, the probabilities of recurrent ischemia were 63, 31, 14 and 9%, respectively.
Conclusions. Continuous 12-lead ST monitoring increases detection rate and duration of ST episodes compared to 3-lead ST monitoring. The use of continuous 12-lead ECG monitoring devices on emergency wards and coronary care units is recommended.

INTRODUCTION

Patients with unstable angina may suffer from early unfavorable cardiac events in spite of intensive medical therapy. Prognosis is defined primarily by the recurrence and severity of silent or symptomatic myocardial ischemia and by the presence of multivessel coronary artery disease[1-7]. The assessment of the total ischemic burden and the identification of patients at risk should preferably be based on continuous ECG monitoring techniques. Continuous ST monitoring, whether on-line or by Holter recording with subsequent off-line analysis, has been limited by a restricted number of 2 or 3 ECG leads. Recently, new systems have been introduced for continuous on-line analysis of 12-leads or orthogonal vector lead ECGs, which have overcome the limitations of these earlier technologies[8-12]. However, the additional value of 12-lead ECG analysis over 2 or 3 leads or single lead analysis in patients with unstable angina is not reported. Comparative studies of different lead systems have been performed to address the value of multilead exercise electrocardiography[13-15]. These results, however, may not be applicable to patients with unstable angina, since the pathophysiology of unstable angina differs from the pathophysiology of stable angina (plaque rupture and coronary thrombosis vs. fixed stenosis with ischemia due to increased myocardial oxygen consumption).

The aim of the present study was to compare continuous 12-lead ST monitoring with more conventional 3-lead ST monitoring for detection and quantitation of ischemia in patients with unstable angina, and to investigate which leads most frequently contribute to the detection of ST episodes. A new algorithm for detection and quantitation of ischemic events is presented, which takes into account all 12 ECG leads simultaneously.

METHODS

Study patients

One hundred and thirty patients, who were hospitalized for unstable angina and who participated in a dose-finding study of a new anti-thrombin agent, underwent continuous 12-lead ST monitoring in 18 hospitals (see appendix)[16,17]. Patients were eligible for the study if an episode of chest

pain was accompanied by dynamic ST and / or T wave changes indicative of myocardial ischemia. Patients with ECG abnormalities such as left bundle branch block, left ventricular hypertrophy or artificial pacemaker device, making ST segment interpretation unreliable, were excluded, as were patients with a recent myocardial infarction.

Continuous ST monitoring

Continuous ECG monitoring was performed using the ELI-100 continuously updated 12-lead ECG monitoring system (Mortara Instruments, Milwaukee, U.S.A.), which automatically calculates median ECG complexes of the 12 ECG leads every 15 seconds. The system was programmed to store median ECG complexes every 20 seconds if $\geq$ 100 μV ST segment shift was present in one lead relative to the baseline ECG of that patient, or if $\geq$ 50 μV ST shift was present in any two leads of the 12-lead ECG. If less or no ST change was present, a baseline median ECG was stored every 20 minutes.

Median ECG complexes and ST trend data were stored on a removable hard disk or floppy disk. After completion of the recording, this disk was sent to the Cardialysis core laboratory (Rotterdam, The Netherlands) for subsequent editing and analysis.

Editing and analysis of recorded data

Before editing, the 12-lead ECG templates at the start of the continuous ECG recording were compared with the study entry 12-lead ECGs in order to verify proper lead placement. In the case of discordance, the recording was rejected.

All median QRST templates were manually scanned and edited for artifacts, intermittent bundle branch block, detection or marker errors and postural changes. The latter was defined as a sudden change of the frontal QRS axis and / or a sudden QRS amplitude change from V1 to V6 or vise versa. After editing, the trends of the ST segment level measured at the J-point + 60 mseconds were generated for each single lead of the 12-lead ECG, except aVR.

Reference ECG

At study entry, an attempt was made to document both a standard 12-lead ECG during chest pain and a 12-lead ECG without chest pain. These ECGs were used to define a reference "non-ischemic" (without chest pain) median ECG complex during the continuous ECG recording. If the median ECG complex at the start of the recording was similar to the study entry non-ischemic 12-lead ECG, this ECG complex was used as the reference "non-ischemic" continuous ECG complex. If the first ECG complex was not similar to the study entry non-ischemic 12-lead ECG, attempts were made to identify the most comparable "non-ischemic" ECG complex of the continuous ECG recording. Subsequently, this ECG complex was used as the reference "non-ischemic" ECG.

Definition of ST episodes

The onset of an ST episode was defined as a change of ST amplitude in one or more leads of at least ± 100 μV from the baseline ST level, developing within a 10 minute period and persisting for at least 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 one minute. Episodes had to be separated from each other by at least one minute. If ≥ 100 μV ST change was present in more than one lead simultaneously, the episode onset was defined by the lead exhibiting the first significant ST change. Similarly, the end of an episode was defined by the lead exhibiting the latest return to baseline ST level. An example of the ST trend analysis and representative ECG recordings is presented in Figures 1 and 2.

Automated detection of ST segment changes ≥ 100 μV

An algorithm programmed according to the previously described ST criteria for ischemia, was applied to each single lead ST trend, in order to detect both the time and ST values of onset and offset of an ST episode and its peak ST level. In order to prevent a reversal of baseline with a real ST episode (or false detection of an untrue ST episode), the algorithm was programmed to skip episodes of which the onset ST value was closer to the initial reference ST level than the baseline ST level during the predefined 10 minutes window. In such an instance, the ST value was used as baseline update for the detection of a possible next episode.

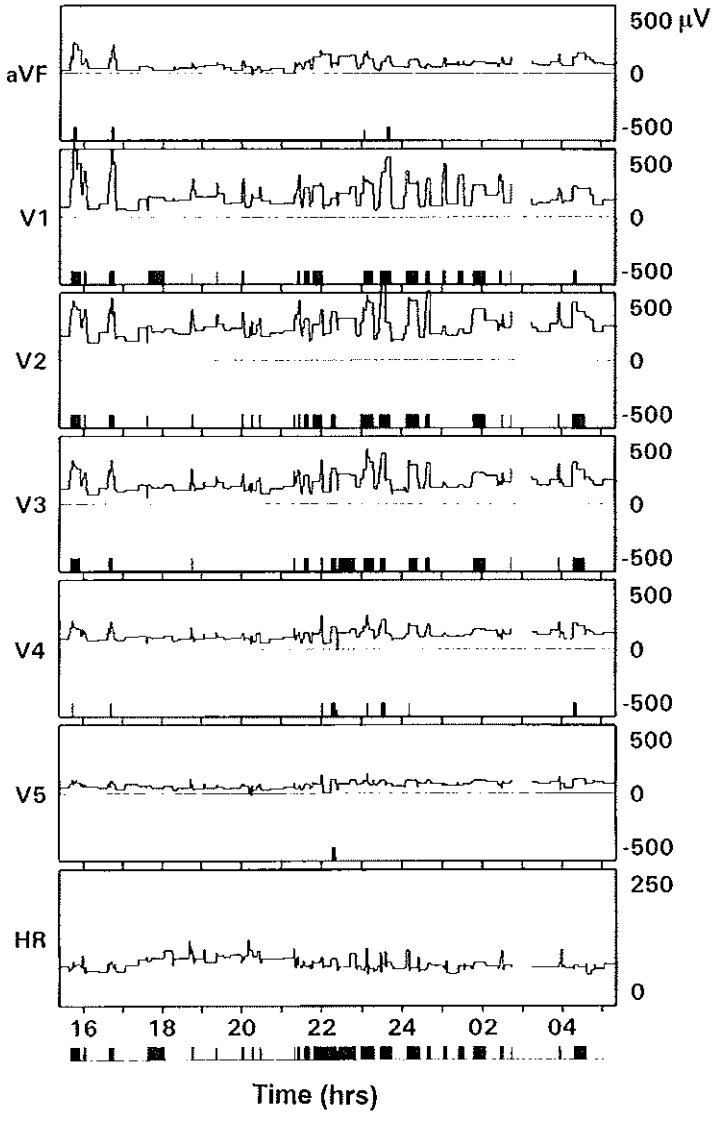

Figure 1. Twelve-lead ST analysis in a patient with unstable angina. The ST trends of those leads in which ST episodes occurred are displayed, together with the heart rate trend (bottom trend curve). The black bars in each single lead ST trend represent the time during which the algorithm detected a ≥ 100 µV ST change. At the bottom of the trend graphs, the black bars indicate the total ST episode duration (ischemia), taking into account all leads involved.

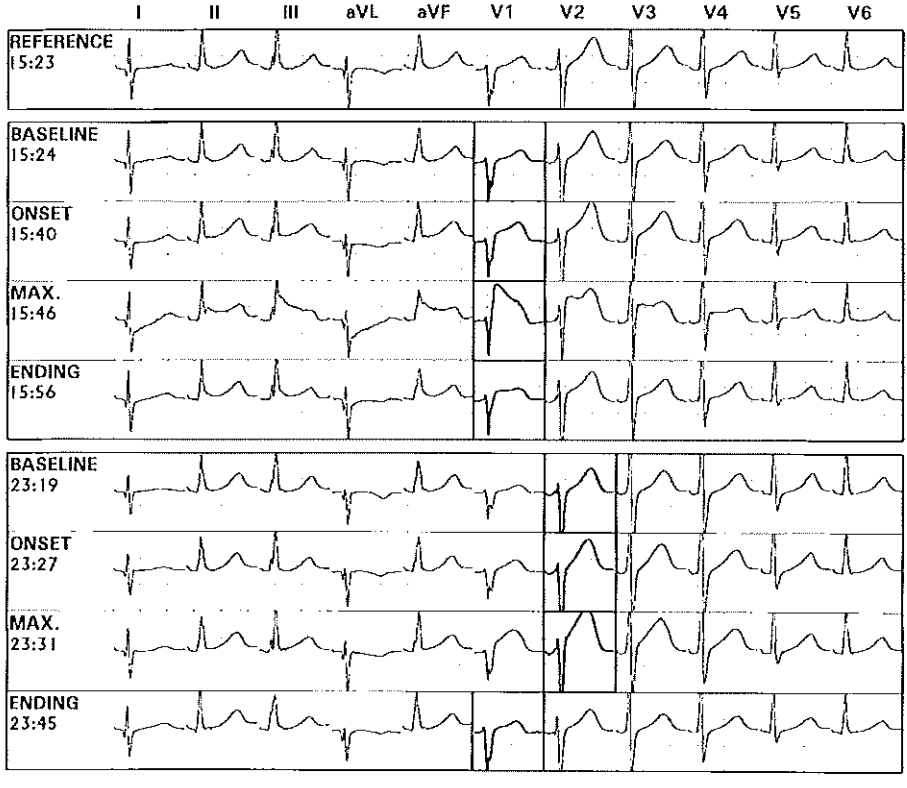

Figure 2. Samples of the computer-assisted 12-lead ECG recording of the patient in Figure 1. The upper ECG row demonstrates the 12-lead ECG (except aVR) which has been selected as the reference, "non-ischemic" ECG. The ECG rows directly below demonstrate the time and ECG lead (indicated in bold) in which the ST episode occurred. In the upper panel, ST changes are present in multiple leads, but the ST changes of V1 appear dominant. Thus the onset, maximum and ending of the episode is detected in this lead. However, in another episode shown in the lower panel, the onset and maximum of the ST episode is detected in lead V2, but the end of this combined episode is detected in lead V1.

Subsequently, the digital trend analysis was confirmed by a second visual analysis of the real-time ECG, thus double checking template quality and excluding false-positive or false-negative automated ST measurements. 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).

ST episodes based on 12-lead and 3-lead ST trends

As a final summary analysis, the total number of ST episodes was calculated based on both the combination of either 3 leads III, V2 and V5 or the combination of all 12 leads (except aVR).

Statistical analysis

Continuous variables are expressed as median and interquartile range (25th and 75th percentiles). Unpaired variables were compared using the Mann-Whitney test. Wilcoxon signed rank test was used for paired variables. Discrete variables are described with percentages and were compared using the chi-square test. The number of episodes per patient during 3-lead and 12-lead ST monitoring might differ in two directions, since both more and less frequent ST episodes might be detected by 12 leads compared with 3 leads. The latter might be due to combining of multiple short episodes in one long episode. This would result in fewer episodes but a longer ischemic duration. Therefore, a two-tailed P value was calculated in all instances. A P value of ≤ 0.05 was considered statistically significant. The Kaplan-Meier method was used for the evaluation of the time to the occurrence of a first ST episode and the possibility of a recurrent ST episode, with censoring of data. Statistical difference was tested with the log rank test.

RESULTS

ECG monitoring was initiated in 130 patients. Good quality recordings were eventually obtained in 114 patients (88%). The median (25, 75 percentiles) total ECG monitoring time was 53 (49, 55) hours. Total analyzable ECG monitoring time was 44 (38, 48) hours. Twelve-lead ST monitoring detected 515 ST episodes suggestive of transient ischemia against 311 for 3-lead ST monitoring, respectively (Table 1, $P<0.0001$). This resulted in detection of ischemia by 12-lead ST monitoring in 88 patients (77%) vs. 71 patients (62%) by 3-lead ST monitoring ($P=0.02$). Sixty-four of the 88 patients with ST episodes during 12-lead monitoring had more than one ST episode (73%), against 46 (65%) of the 71 patients during 3-lead monitoring ($P=0.02$).

Several other observations support the greater sensitivity for detection of ST segment changes of 12-lead monitoring over 3 leads. For example, the

Table 1. Summary of ST analysis parameters. Comparison of computer assisted 3-lead against 12-lead ST monitoring in 114 patients with unstable angina.

N=114	3-lead ST monitoring	12-lead ST monitoring	*P* value
ST episodes present (pts)	71 (62%)	88 (77%)	0.02
> 1 ST episode present (pts)	46	64	0.02
total number of episodes	311	515	<0.0001
patients with symptomatic ST episodes	10 (9%)	10 (9%)	n.s.
number of episodes/pt*	1 (0, 3)	2 (1, 6)	<0.0001
total duration (min) of ST shift/pt*	1.7 (0, 23.3)	12.3 (1, 58.2)	<0.0001
duration of ST episode (min)**	5 (1.3, 17.7)	7 (1.3, 20)	<0.0001
mean duration of episode/pt (min)**	7.7 (1.8, 14.4)	10.2 (2.6, 15.2)	0.03
time to first episode (hrs)**	12.7 (5.8, 28.4)	9.9 (4.0, 21.2)	<0.0001

* median, 25, 75 percentiles, including patients without ischemia
** median, 25, 75 percentiles, patients with ischemia only

Table 2. Number of leads involved per ST episode. Comparison of computer-assisted 3-lead and 12-lead ST monitoring.

Lead selection	Number of leads involved per ST episode (%)						Total number of ST episodes
	1	2	3	4	5	> 5	
3 leads	252 (81)	47 (15)	12 (4)	-	-	-	311
12 leads	283 (55)	97 (19)	63(12)	24 (5)	14 (3)	34 (7)	515

first ST episode during monitoring was detected earlier by 12 leads (Table 1 and Figure 3), and the duration of ischemia detected by 12 leads exceeded the duration in 3 leads (Figure 4). Furthermore, the number of leads involved per ST episode was higher for 12-lead than for 3-lead ST monitoring (Table 2).

For 12-lead ST monitoring, episodes with precordial lead involvement only were far more frequently present than episodes with only standard or augmented lead involvement (77% against 11% respectively, $P<0.0001$). Simultaneous involvement of both the standard or augmented leads and the precordial leads

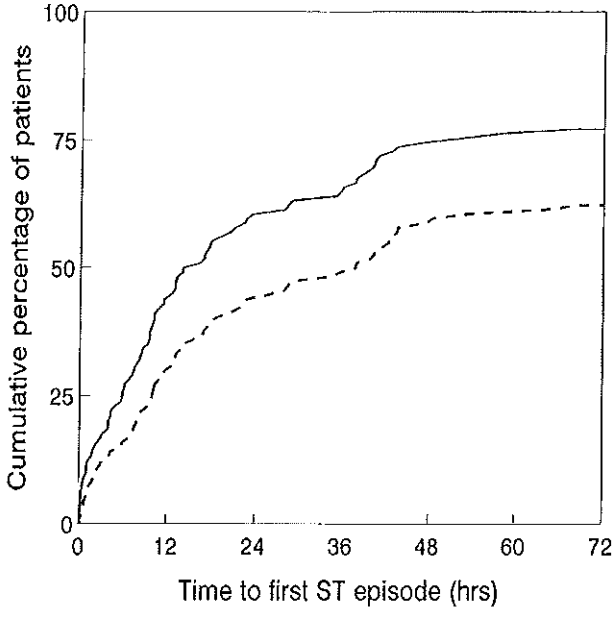

Figure 3. Time to the occurrence of the first ST episode after the start of ST monitoring plotted against the cumulative percentage of patients. — = 12-lead; – – – = 3-lead.

was present in 60 out of 515 ST episodes (12%). A shift of ST episodes from either the standard or augmented leads to the precordial leads or vise versa occurred in 20 (31%) of the 64 patients who had more than one ST episode during 12-lead ST monitoring. For 3-lead ST monitoring, the single lead episodes of V2 contributed most to the detection of the onset of ST episodes (Figure 5, panel B, $P<0.0001$), while V2, V3 and V4 were equally sensitive in the 12-lead analysis (Figure 5, panel A).

Figure 6 shows a Kaplan-Meier "survival" analysis with censoring of data of the probability to remain free of a new ST episode during the course of the monitoring period using 12 leads. The probability of a recurrent ST episode declined most during the first 24 hours of monitoring. There was no difference between the probability of occurrence of a new ST episode after the start of the ECG monitoring period or the probability of recurrence of a second ST episode after the first, or a third after the second episode.

Forty-five patients (39%) had at least one episode of chest pain during

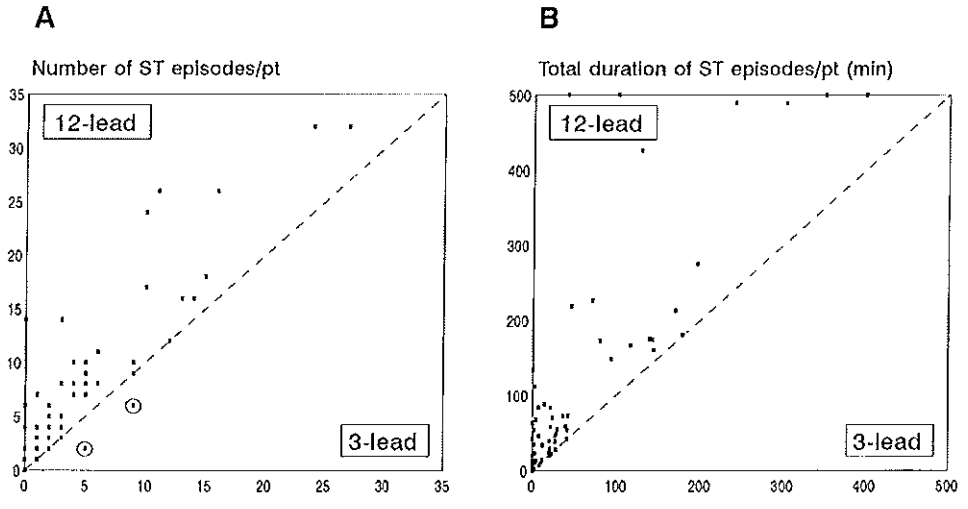

Figure 4. Comparison of 12-lead and 3-lead ST monitoring. (A) Demonstrates the number of episodes per patient for both techniques. (B) The total duration of the ST episodes per patient. Note: Single dots may represent more than one patient. The encircled patients in (A) show more episodes during 3-lead than 12-lead ST monitoring. In these patients, several isolated 3-lead ST episodes appeared to be part of one, longer lasting 12-lead ST episode, depending on the leads involved.

ECG monitoring. However, ST changes of $\geq$ 100 µV were present during those episodes in 10 patients only (22%), during both 3- and 12-lead ECGs. If additional less prominent ST and T wave changes similar to the study entry ECG were also taken into account, ECG signs of ischemia were present during chest pain in 26 patients (58%). There was no significant difference between the number of ST episodes in patients with and without episodes of chest pain.

Nineteen patients (17%) suffered from an in-hospital cardiac event and / or underwent emergency angiography within the first seven days of admittance to hospital. There were no cardiac deaths. Clinical events occurred more frequently in patients with chest pain during the monitoring period and in patients with chest pain and concomitant ST episodes compared to those without recurrent ischemia (Table 3). These observations were, however, not statistically significant in this small series of patients.

Table 3. Correlation of in-hospital cardiac events within 7 days from admission to hospital with the presence of chest pain and / or ST episodes during the ECG monitoring period.

During recording	Number of pts	Myocardial infarction	PTCA/CABG	Any clinical event (%)	No clinical event (%)
Chest pain	45	5	7	11 (24)	34 (76)
No chest pain	69	7	1	8 (12)	61 (88)
chest pain + ST episode(s)	37	4	7	9 (24)	28 (76)
chest pain + corr. ST episode	10	0	3	3 (30)	7 (70)
no chest pain, no ST episodes	18	2	0	2 (11)	16 (88)
12 lead, ST episodes present	88	9	8	16 (18)	72 (82)
12 lead, no ST episodes	26	3	0	3 (12)	23 (88)
3 lead, ST episodes present	71	7	7	13 (18)	58 (82)
3 lead, no ST episodes	43	5	1	6 (14)	37 (80)

DISCUSSION

Recently, computer-assisted continuous 12-lead ECG monitoring techniques have become available for real-time ECG and ST segment monitoring in patients with acute coronary syndromes[8,9,18]. These techniques have outgrown the limitations of serial ECG recording, which provides snapshot information only, and Holter ST recording, which is limited by a restricted number of leads and allows for retrospective off-line analysis only.

In patients with an acute myocardial infarction receiving thrombolytic therapy, computer-assisted continuous ECG monitoring has proven to be of clinical value for prediction of vessel status and identification of high risk patients[10-12]. However, so far, no systematic studies have been conducted to evaluate the usefulness of computer-assisted continuous 12-lead ECG monitoring techniques in patients with unstable angina. To our knowledge, this study is the first to demonstrate the relationship between detection and quantitation of ischemia and ECG monitoring technology in these patients. Twelve lead ST monitoring appeared to be more sensitive than the more generally applied 3-lead technology. When only three leads were used for ST monitoring, ischemia was detected in 62% of patients, which is comparable to studies using Holter ST monitoring in patients with unstable angina[1,19].

Table 4. Differences of ST analysis in patients with acute myocardial infarction and unstable angina.

Acute myocardial infarction	Unstable angina
ST monitoring of single lead with greatest ST shift will suffice in most instances	multilead ST monitoring necessary, as the ischemic area may vary in time. Scanning of different leads for earliest onset, highest peak and latest end of ST episodes is necessary
baseline ST level is defined by the moment of ST recovery and ST steady state	baseline ST level is not defined, a reference ECG is necessary
recurrent ischemia is reflected by ST re-elevation instead of ST depression in most instances	ischemia may be reflected by both ST elevation, ST depression and T wave changes, which makes automated analysis using computer algorithms difficult
gradual T wave changes only	minor ST segment and T wave changes may reflect ischemia, which makes accurate quantitation of ischemia difficult

With 12-lead ST monitoring, ischemia was detected in an additional 15% of patients. Both the number and duration of ischemic episodes far increased using 12-lead compared to 3-lead ST monitoring.

The ST changes were found to disperse and shift among different leads in time in at least 31% of patients with more than one ST episode during the monitoring period. This may depend on the flow balance of the coronary system, the degree of vessel injury and the duration and severity of ischemia. Thus, instead of monitoring the lead with maximal ST deviation or sum ST deviation in patients with myocardial infarction[20,21], full 12-lead ST monitoring should be preferred for detection and quantitation of ischemia in patients with unstable angina. The major differences between ST monitoring of unstable angina patients vs. ST monitoring of acute myocardial infarction patients are listed in Table 4.

ST episodes were most frequently present in the leads V2, V3 and V4. In addition, these leads also contributed most to the detection of the onset of ST episodes if all involved leads were taken into account. This is in contrast to previous studies on body surface mapping and optimal lead placement during exercise electrocardiography in patients with coronary artery disease[13-15]. These studies demonstrated that the single lead with the greatest

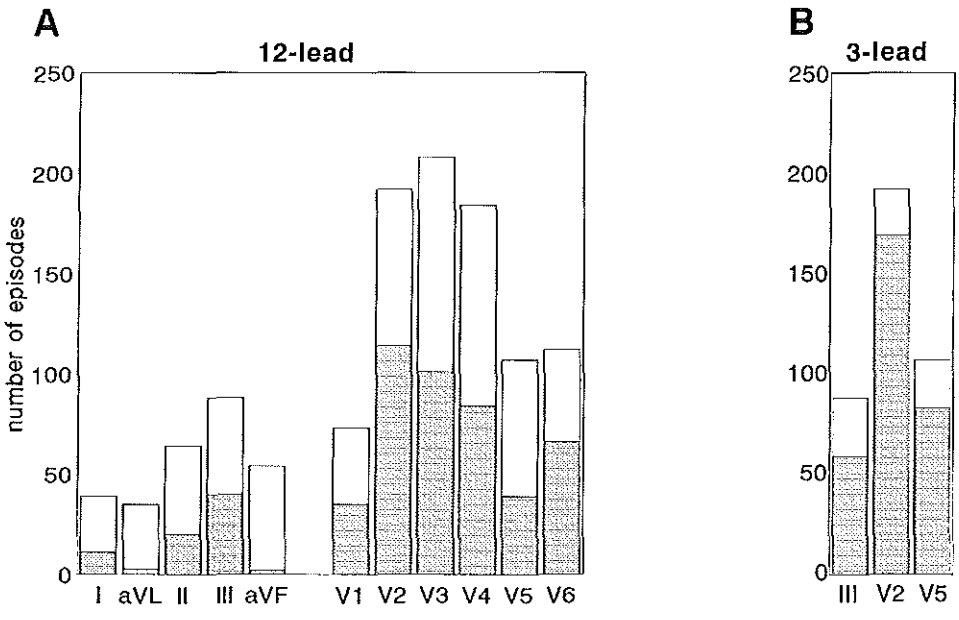

Figure 5. Number of single ST episodes per lead and detection of earliest ST episode onset if all leads involved are taken into account. The bars represent the number of ST episodes detected in each single lead. The tinted areas represent the number of episodes which detected the earliest episode onset. (A) Detection of onset of ST episodes when using 12-lead ST monitoring. (B) Detection of onset of ST episodes when using leads III, V2 and V5 only.

sensitivity for detecting ST segment shift was between the right infraclavicular region area and the V5 position, which is in fact a bipolar V5 lead. Our data do not support these findings and suggest that studies on lead placement and ST shift during exercise testing in patients with stable angina may not be applicable to patients with unstable angina in whom both the underlying pathophysiological mechanism and the extent and area of ischemia is different[22]. In addition, our results indicate that ST episodes with only standard lead involvement are rare. As such, it is conceivable that the applied cut-off value of $\geq$ 100 μV ST change is not adequate for standard lead monitoring in general practice.

Previous studies on patients with unstable angina demonstrated that recurrent ischemia occurs most frequently in the first 24-48 hours of admission to hospital[22,23]. This is in concordance with our finding that the majority of

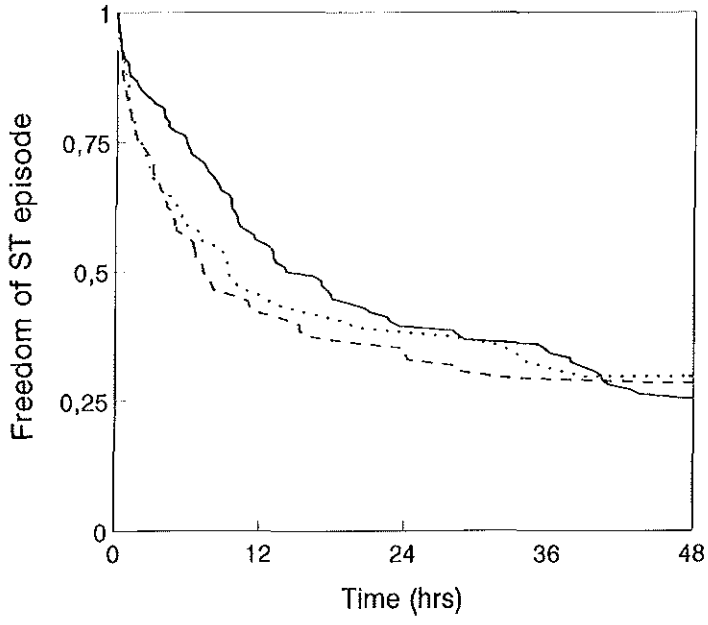

Figure 6. Kaplan-Meier event free survival estimate. The curves indicate the probability of remaining free of an ST episode during the course of the monitoring period: (1) from start of the monitoring period (— , median time 15.3 hours), (2) from the end of the first ST episode until the second (– – –, median time 7.4 hours) and (3) from the end of the second ST episode until the third (• • • •, median time 9.6 hours), using 12-lead ST monitoring. The curves virtually overlap, suggesting similar pathophysiology for the different episodes. Plaques apparently become quiescent after a period without ischemia of approximately 24 hours.

patients exhibited a recurrence of ischemia within the first 15 hours of ST monitoring, with only 23% of patients remaining free of an ST episode during the total monitoring period (Figure 3). In addition, Figure 6 demonstrates that the distribution of the occurrence of an ST episode over time was similar for the first interval since the start of the ST monitoring period, as well as for the occurrence of a second episode after the first and a third after the second. This suggests similar underlying pathophysiological mechanisms of these episodes[23]. Apparently, plaques stabilize and become "quiescent" after a period without recurrent ischemia of approximately 24 hours.

In agreement with Holter ST studies in patients with unstable angina, ST changes of ≥ 100 μV during moments of chest pain were infrequently present, occurring in only 22% of the patients with chest pain during the monitoring

period[19,24,25]. This may be due to at least three factors: (1) complaints may not always be ischemic of origin, (2) the time of occurrence of complaints may not always have been correctly indicated by the patient or annotated in the case record forms, (3) the generally accepted ≥ 100 μV ST change criterion for detection of ischemia may be too insensitive to pick up minor ischemic ECG changes that may occur in these unstable patients. The latter assumption is supported by the fact that minor ST and T wave changes, similar to the study entry ECG during pain were present during pain in 58% of all patients who had episodes of chest pain during the recording. This implies that not only ST changes of ≥ 100 μV but also smaller ST and T wave changes should be taken into account as signs of ischemia in these patients. Until recently, the standardization and automated detection and quantitation of these minor ST and T wave changes was hampered by the limitations of earlier ECG technologies such as Holter, because of baseline drift and restriction of number of leads. In contrast, the high quality ECG signals provided by computer-assisted ECG monitoring technologies have overcome these limitations and may challenge us to develop new ischemia standards and algorithms for its automated detection and quantitation.

Finally, in contrast to other studies using Holter ST recording techniques[1,19], we did not demonstrate a significant difference in the occurrence of in-hospital cardiac events within the first week from admittance between patients with and without ST episodes, although trends were similar to previous studies (Table 3). This may be due to the small number of patients who suffered from an in-hospital clinical event.

We conclude that computer-assisted 12-lead ECG monitoring can be used for on-line ECG-ischemia monitoring of unstable angina patients both for clinical purposes and for quantitation of myocardial ischemia in studies. The use of continuous 12-lead ST monitoring significantly increased the detection rate of ST episodes as compared to more conventional continuous 3-lead ST monitoring. Furthermore 12-lead ST monitoring yields more episodes and longer duration of ischemia. Whether this also relates to a better specificity for prediction of impending clinical events could not be established from the small subset of patients who actually suffered an in-hospital clinical event during this study. Computer-assisted 12-lead ECG monitoring systems are recommended on emergency wards and coronary care units, not only for

monitoring of patients with an acute myocardial infarction receiving thrombolytic therapy, but also for monitoring of unstable angina patients.

REFERENCES

1. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker of early unfavourable outcomes in patients with unstable angina. N Engl J Med 1986; 314: 1214-9.
2. Gottlieb SO, Gerstenblith G. Assessing the total ischemic burden in the management of unstable angina. Am J Med 1986; 81(4A): 7-11.
3. Romeo F, Rosano GM, Martuscelli E, Valente A, Reale A. Unstable angina: role of silent ischemia and total ischemic time (silent plus painful ischemia), a 6-year follow-up. J Am Coll Cardiol 1992; 19(6): 1173-9.
4. Nademanee K, Intarachot V, Josephson MA, Reiders D, Mody Vaghaiwalla F, Sigh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. J Am Coll Cardiol 1987; 10: 1-9.
5. Sharma GVRK, Deupree RH, Luchi RJ, Scott SM and the participants of the Veterans Administration Cooperative Study No. 28. Identification of unstable angina patients who have favourable outcome with medical or surgical therapy (eight-year follow-up of the Veterans Administration Cooperative Study. Am J Cardiol 1994; 74:454-8.
6. Sclarowski S, Davidson E, Lewin RF, Strasberg B, Arditti A, Agmon J. Unstable angina evolving to acute myocardial infarction: Significance of ST changes during chest pain. Am Heart J 1986; 112: 459-62.
7. Foley JB, Foley D, Molloy M, Crean PA, Gearty GF, Walsh ML. Acute impact of percutaneous transluminal coronary angioplasty on the ischemic burden in stable and unstable angina. Am Heart J 1993; 126: 705-7.
8. Dellborg M, Gustaffson G, Riha M, Swedberg K. Dynamic changes of the QRS complex in unstable angina pectoris. Int J Cardiol 1992; 36: 151-62.
9. Lundin P, Eriksson SV, Erhardt L, Strandberg LE, Rehnqvist N. Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology 1992; 81: 145-56.
10. Krucoff MW, Croll MA, Pope JE *et al.* Continuously 12-lead ST-segment recovery analysis in the TAMI 7 study. Circulation 1993; 88: 437-46.
11. Dellborg M, Steg PG, Simoons M *et al.* Vectorcardiographic monitoring to assess early vessel patency after reperfusion therapy for acute myocardial infarction. Eur Heart J 1995; 16: 21-9.
12. Klootwijk P, Langer A, Meij S, *et al.*, for the GUSTO-I ECG-ischemia 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: 689-98.

13. Simoons ML, Block P. Toward the optimal lead system and optimal criteria for exercise electrocardiography. Am J Cardiol 1981; 47: 1366-74.
14. Phibbs BP, Buckels LJ. Comparative yield of ECG leads in multistage stress testing. Am Heart J 1975; 90: 275-6.
15. Chaitman BR, Bourassa MG, Wagniart P, Corbara F, Ferguson RJ. Improved efficiency of treadmill exercise testing using a multiple lead ECG system and basic hemodynamic exercise response. Circulation 1978; 57: 71-9.
16. Simoons ML, van Miltenburg A, Scheffer MG *et al.* Anticoagulant properties of efegatran, a direct thrombin inhibitor in patients with unstable angina. Eur Heart J 1994;15 (Abstr Suppl):757.
17. Simoons M, Lenderink T, Scheffer M *et al.* Efegatran, a new direct thrombin inhibitor: safety and dose response in patients with unstable angina. Circulation 1994;90;4 (Abstr Suppl 2):1241.
18. Gerstenblith G. Treatment of unstable angina pectoris. Am J Cardiol 1992; 70: 32G-37G.
19. 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.
20. Clemmensen P, Ohman M, Sevilla DC *et al.* Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. Am J Cardiol 1990; 66: 1407-11.
21. Klootwijk P, Cobbaert C, Fioretti P, Kint PP, Simoons ML. Noninvasive assessment of reperfusion and reocclusion after thrombolysis in acute myocardial infarction. Am J Cardiol 1993; 72: 75G-84G.
22. Braunwald E. Unstable angina. A classification. Circulation 1989; 80: 410-4.
23. Miltenburg-van Zijl AJM. Management policies and prognosis in unstable angina pectoris. Use of coronary angiography in different practice settings. Erasmus University Rotterdam. Thesis 1992.
24. Biagini A, Mazzei MG, Carpeggiani C *et al.* Vasospastic ischemic mechanism of frequent asymptomatic transient ST-T changes during continuous electrocardiographic monitoring in selected unstable angina patients. Am Heart J 1982; 103: 13-20.
25. Amanullah AM, Lindvall K. Prevalence and significance of transient -predominantly asymptomatic- myocardial ischemia on Holter monitoring in unstable angina pectoris, and correlation with exercise test and Thallium-201 myocardial perfusion imaging. Am J Cardiol 1993; 72: 144-8.

APPENDIX

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Chapter 6

Anticoagulant properties, clinical efficacy and safety of efegatran, a direct thrombin inhibitor, in patients with unstable angina

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ABSTRACT

Aims. Thrombin plays a key role in the clinical syndrome of unstable angina. We investigated the safety and efficacy of 5 dose levels of efegatran sulphate, a direct thrombin inhibitor, compared to heparin in patients with unstable angina.

Methods. 432 patients with unstable angina were enrolled. Five dose levels of efegatran were studied sequentially, ranging from 0.105 mg/kg/hr to 1.2 mg/kg/hr. during 48 hours. Safety was assessed clinically, with reference to bleeding and by measurement of clinical laboratory parameters. Efficacy was assessed by the number of patients experiencing any episode of recurrent ischemia as measured by computer-assisted continuous ECG-ischemia monitoring. Clinical endpoints were: episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA or CABG), and death.

Results. Efegatran demonstrated a dose dependent anticoagulant activity with the highest dose level of 1.2 mg/kg/hr. resulting in steady state mean APTT values of approximately 3 times baseline. Thrombin time was also increased. Neither of the doses of efegatran studied were able to suppress myocardial ischemia during continuous ECG-ischemia monitoring to a greater extent than that seen with heparin. There were no statistically significant differences in clinical outcome or major bleeding between the efegatran and heparin groups. Minor bleeding and thrombophlebitis occurred more frequently in the efegatran treated patients.

Conclusions. Administration of efegatran sulphate at levels of at least 0.63mg/kg/hour provided a level of thrombin inhibition which is at least comparable to APTT adjusted heparin infusion. There was no excess of major bleeding. The level of thrombin inhibition by efegatran, appeared to be more stable than with heparin. Thus, like other thrombin inhibitors, efegatran sulphate is easier to administer than heparin. However, no clinical benefits of efegatran over heparin were apparent.

INTRODUCTION

Acute coronary ischemic syndromes are usually the result of a ruptured atherosclerotic plaque, followed by platelet aggregation, often in combination with increased vasomotor tone, leading to sudden increase of the pre-existing stenosis[1,2]. This process may result in one or more episodes of impaired flow without myocardial necrosis and the syndrome of unstable angina[3], or progress into total coronary occlusion and myocardial infarction. Thrombin plays a key role in this process. It causes fibrin formation through proteolytic cleavage of plasma fibrinogen, and it induces platelet activation and aggregation[4,5]. Thus, drugs which directly inhibit thrombin, such as efegatran sulphate, have been considered for the treatment of unstable angina, in order to prevent recurrent ischemic episodes and progression into myocardial infarction.

Efegatran sulphate is a tripeptide, direct acting thrombin inhibitor. Unlike heparin it has the capacity to bind directly to thrombin, and to inactivate both circulating and clot-bound thrombin[6]. Efegatran sulphate also inhibits thrombin induced platelet aggregation. The primary objective of the present study was to assess the safety and efficacy of different doses of efegatran sulphate compared to heparin in patients with unstable angina. Safety was assessed clinically with particular reference to bleeding occurrences and by measurement of clinical laboratory parameters. Efficacy was assessed by comparison of the number of patients experiencing any episode of recurrent ischemia as measured by computer-assisted continuous ECG-ischemia monitoring during different treatment regimens[7]. Furthermore, the incidences of clinical ischemic episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA or CABG), and death were evaluated. The first stage of this study was a dose ranging program to assess the anticoagulant effect and the bleeding risk associated with administration of five dose regimens of efegatran sulphate in 132 patients with unstable angina, compared to heparin. These results were used for selection of two dose levels of efegatran sulphate which were compared to heparin in a subsequent study of 300 patients.

PATIENTS AND METHODS

Study patients

Patients between 21 years and 75 years old with a clinical diagnosis of unstable angina were eligible for the study. For inclusion, patients should exhibit at least one episode of angina at rest or minimal exertion and have concomitant transient ST and / or T wave changes on their ECG, either at admission, or during observation in-hospital. Patients were excluded for any of the following reasons: ECG abnormalities making ST-T segment interpretation unreliable, such as left bundle branch block, left ventricular hypertrophy or artificial pacemaker rhythm; recent myocardial infarction (within the hospitalization period), unless creatinekinase (CK) had returned to less than twice the normal upper limit; heparin treatment since the most recent episode of ischemia prior to study enrollment; known aspirin-allergy or other contraindication for aspirin; concurrent use of oral anticoagulants (coumarins) at the time of study entry, or anticipated need for oral anticoagulants during the study period; recent administration of a thrombolytic agent, unless fibrinogen values had returned to more than 50% of the normal lower limit; APTT and PT values exceeding the normal upper limits, within the past 24 hours prior to study enrollment; active internal bleeding or peptic ulcer disease; bleeding risk factors such as recent surgery, major trauma, gastro-intestinal or genito-urinary bleeding, puncture of noncompressible vessels or organ biopsy in a 3 months period prior to enrollment; a history of cerebrovascular accident, transient ischemic attack, cranial or intraspinal surgery; underlying medical conditions such as persistent hypertension despite treatment, history of hemorrhagic diathesis, or a platelet count of less than 100×10^9 / liter within the 24 hours prior to the study; known, or suspected major hepatic or renal disease and known hemostatic defects, including those secondary to hepatic, or renal insufficiency, or a bleeding time $\geq$ 8 minutes (Ivy method), or $\geq$ 20 minutes (Simplate method) while receiving aspirin; women with childbearing potential.

Study design

A single blind randomized multicenter comparison of different dose levels of efegatran sulphate versus heparin was performed in patients with unstable angina. The study consisted of a dose ranging phase, where five doses of efegatran were assessed in a sequential manner, followed by a parallel phase

in which two doses of efegatran (chosen following review of the data generated in the first phase) were compared to heparin.

Study drug regimens

In the dose ranging phase, the patients of dosage groups 1-4 received efegatran sulphate as an initial loading i.v. bolus of 0.1 mg/kg over 15 minutes, followed by continuous infusion of either 0.105, 0.32, 0.63 or 0.84 mg/kg/hr. In the 5th dosage group, an i.v. loading bolus of 0.3 mg/kg over 1 minute was given, followed by continuous infusion of 1.2 mg/kg/hr. The infusions were continued for 48 ± 10 hours. The parallel design phase compared group 3 (loading dose of 0.1 mg/kg over 15 minutes followed by continuous infusion of 0.63 mg/kg/hr), and group 5 (loading dose of 0.3 mg/kg over 1 minute followed by 1.2 mg/kg/hr) from the dose ranging phase with heparin.

Control patients were treated with a bolus injection of 5000 IU heparin, followed by a continuous infusion of 1000 IU/hr heparin for 48 ± 10 hours. After this period, treatment could be continued with heparin at the discretion of the treating physician. Throughout any heparin infusion, the heparin dosage was adjusted to a APTT ratio of 2.0 to 2.5 times normal, based on local laboratory APTT values. Heparin treatment was not allowed before the start of the study, nor during the infusion of efegatran sulphate. After termination of the efegatran sulphate infusion, heparin could be the initiated for treatment of recurrent, or continuing ischemia, at the discretion of the treating physician.

All patients were concomitantly treated with aspirin. If the patient was on aspirin treatment prior to the start of study treatment, aspirin was continued at a dose of 80 mg once daily for the first four days. If a patient was not on aspirin, the initial dose was a minimum of 250 mg chewed, or intravenously, followed by an oral dose of 80 mg aspirin once daily during the first four days. After day four, aspirin was continued at the discretion of the physician. Nitroglycerin, beta-blockers, calcium channel blockers and other cardiovascular drugs were allowed.

Laboratory tests

The effect of efegatran sulphate and heparin on markers of thrombosis and hemostasis was assessed by measuring bleeding time (Ivy, Simplate, Surgicut and Duke method, local laboratory, dose-ranging part only), the activated partial thromboplastin time (local, and central laboratory), prothrombin time

(local, and central laboratory) and fibrinogen levels (central laboratory). Levels of fibrinogen were measured using both the ACL and the Clauss method. Levels of the activation markers β-thromboglobulin, platelet factor 4, prothrombin fragment 1.2, fibrinopeptide A, thrombin-antithrombin complexes, and fibrin degradation products were measured in the dose finding phase only (central laboratory). Furthermore, general hematology (local laboratory); chemistry (central laboratory) and urinanalysis (local laboratory) were performed.

Efficacy criteria

The efficacy of efegatran sulphate as compared with heparin was assessed by its effect on the percentage of patients experiencing any episodes of recurrent ischemia, measured by computer-assisted continuous ECG-ischemia monitoring, as described below. Clinical ischemic episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA wit balloon or other devices, CABG) and death were also evaluated from the moment of randomization until 30 days follow-up.

Definition of a myocardial infarction required either documentation of an increase in CK or CK-MB levels, or electrocardiographic changes. CK or CK-MB levels should exceed two times the upper limit of normal (in 2 samples collected at different sampling times) and increase by at least 50% over the baseline value. If both CK and CK-MB values were available CK-MB took preference. Electrocardiographic changes were defined as new significant Q waves of ≥ 0.04 seconds duration or having an amplitude of at least one-fourth of the corresponding R wave amplitude in two or more contiguous leads. The onset of a myocardial infarction was derived from the occurrence of chest pain of at least 30 minutes duration. In the absence of chest pain, the time of measurement of the trough CK (-MB) level immediately preceding CK (-MB) rise was taken as the moment of onset of myocardial infarction, unless the time interval between these two samples was greater than 6 hours.

Each patient was carefully observed for signs or symptoms of bleeding. Bleeding was classified as major, or minor. Major bleeding was defined as clinically overt, and accompanied by either transfusion of two or more units of blood, surgery for treatment of the bleeding, or intracranial location of the bleeding. Bleeding was defined as minor if it was clinically overt but did not meet the other criteria for major bleeding.

Computer-assisted continuous ECG-ischemia monitoring

Continuous ECG monitoring was performed using the ELI-100 continuously updated 12-lead ECG monitoring system (Mortara Instruments, Milwaukee, U.S.A). ECG monitoring was started preferably before the start of study-drug and continued for at least 6 hours following the termination of study-drug infusion.

The system was programmed to store median ECG complexes of the 12 ECG leads every 20 seconds if ≥ 100 μV ST segment shift was present in one lead relative to the baseline ECG of that patient, or if ≥ 50 μV ST shift was present in any 2 leads of the 12-lead ECG. If less or no ST change was present, a baseline median ECG was stored every 20 minutes. Median ECG complexes and ST trend data were stored on a removable hard disk or floppy disk. After completion of the recording, this disk was sent to the central ECG core laboratory of Cardialysis Rotterdam, The Netherlands for subsequent editing and analysis. ST changes were evaluated in a blinded fashion and considered indicative of ischemia if greater than 100 μV for more than one minute duration.

The method of editing and analysis of the recorded data has recently been described in detail[8]. In brief, the onset of an ST episode was defined as a change of ST amplitude in one or more leads of at least ± 100 μV from the baseline ST level, developing within a 10 minute period and persisting during at least 1 minute. The end was defined as a return of the ST level within ± 100 μV of the baseline ST level, again lasting for at least one minute. Episodes had to be separated from each other by at least one minute. If ≥ 100 μV ST change was present in more than one lead simultaneously, the episode onset was defined by the lead exhibiting the first significant ST change. Similarly, the end of an episode was defined by the lead exhibiting the latest return to baseline ST level.

Statistical analysis

Continuous variables are expressed as median and interquartile range (25th and 75th percentiles). Unpaired variables were compared using the Mann-Whitney test. Discrete variables are described with percentages and were compared using Fischer's exact test. A two-tailed *P* value was calculated in all instances. A *P* value of ≤ 0.05 was considered statistically significant. The Kaplan-Meier method was used for the evaluation of the time to the

Table 1. Baseline data.

	Efegatran 0.105 (n=10)	Efegatran 0.32 (n=25)	Efegatran 0.63 (n=122)	Efegatran 0.84 (n=24)	Efegatran 1.2 (n=128)	Heparin (n=123)	All (n=432)
Male	5 (50%)	17 (68%)	83 (68%)	19 (79%)	100 (78%)	77 (63%)	301 (70%)
Mean (SD) age in years	60 (9)	60 (10)	62 (10)	59 (10)	60 (10)	61 (10)	61 (10)
Anthropometry: mean (SD)							
Weight (kg, SD)	75 (9)	77 (12)	77 (12)	79 (10)	82 (13)	77 (12)	79 (12)
Height (cm, SD)	170 (11)	171 (10)	172 (9)	173 (7)	175 (9)	172 (9)	173 (9)
Number of patients with							
previous myocardial Infarction	7 (70%)	10 (40%)	41 (34%)	11 (46%)	38 (30%)	43 (35%)	150 (35%)
PTCA	0 (0%)	0 (0%)	15 (13%)	0 (0%)	13 (10%)	14 (11%)	42 (10%)
CABG	0 (0%)	2 (8%)	15 (12%)	2 (8%)	13 (10%)	14 (11%)	46 (11%)
Risk factors							
Diabetes	0 (0%)	2 (8%)	12 (10%)	3 (13%)	14 (11%)	10 (8%)	41 (10%)
Hypercholesterolemia	5 (50%)	9 (36%)	45 (37%)	12 (50%)	56 (44%)	51 (42%)	178 (42%)
Hypertension	2 (20%)	1 (4%)	14 (12%)	0 (0%)	11 (9%)	12 (10%)	40 (9%)
Current smokers	4 (40%)	11 (44%)	42 (34%)	9 (38%)	58 (45%)	44 (36%)	168 (39%)

Percentages only calculated for those patients in whom data were reported

Table 2. Clinical events from randomization until seven days of follow-up or discharge.

	Efegatran 0.105 (n=10)	Efegatran 0.32 (n=25)	Efegatran 0.63 (n=122)	Efegatran 0.84 (n=24)	Efegatran 1.2 (n=128)	Heparin (n=123)	All (n=432)
Composite endpoint reached *	7 (70%)	13 (52%)	77 (63%)	17 (71%)	84 (66%)	87 (71%)	285 (66%)
Death	-	-	2 (1.6%)	-	-	-	2 (0.5%)
Myocardial infarction / reinfarction	-	-	3 (2.5%)	-	3 (2.3%)	3(2.4%)	9 (2.1%)
Recurrent or refractory ischemia	6 (60%)	13 (52%)	76 (62%)	17 (71%)	84 (66%)	85 (69%)	282 (65%)
PTCA	-	-	11 (9%)	-	10 (8%)	5 (4%)	26 (6%)
CABG	1 (10%)	-	1 (0.8%)	-	3 (2.3%)	4(3.3%)	9 (2.1%)

*Composite endpoint defined as the occurrence of either death, myocardial infarction, recurrent or refractory ischemia or need for revascularization

occurrence of a first ST episode or a recurrent ST episode, with censoring of data. Statistical difference was tested with the log rank test.

RESULTS

A total of 432 patients were included: 132 patients in the dose finding phase and another 300 patients in the parallel phase. Baseline patient characteristics are summarized in Table 1. The mean age of the patients was 60 years, 70% were male, and almost all were Caucasian (98%). There were no differences in the prevalence of previous myocardial infarction, diabetes mellitus, hypertension or a smoking history among the treatment groups. Fifty-eight patients (13.4%) were enrolled as having unstable angina, but actually had a myocardial infarction at presentation which became evident from subsequent CK elevation.

Markers of coagulation and bleeding time

Infusion of efegatran was associated with an increase of both the activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT), which rapidly resolved following cessation of therapy (Figure 1). The APTT increase appeared to be dose dependent. The increase in APTT associated with 1.2 mg/kg/hr efegatran was comparable to that observed with heparin (P=0.89). APTT levels were more stable with efegatran than with heparin.

With respect to the three major treatment groups, PT was mildly increased following administration of efegatran, with a significant difference between the 1.2 mg/kg/hr efegatran and heparin group (P=0.006). PT returned rapidly to normal after discontinuation of therapy (Figure 1B). TT was influenced in a strong and dose dependent manner by efegatran, while administration of heparin did not modify TT (Figure 1C). Efegatran 0.63 mg/kg/hr was associated with an increase of TT levels of approximately 40%, while TT values doubled following the administration of efegatran 1.2 mg/kg/hr. These differences were all highly significant (P=0.0007). TT levels returned to normal rapidly after cessation of efegatran.

Fibrinogen levels decreased following administration of efegatran, and

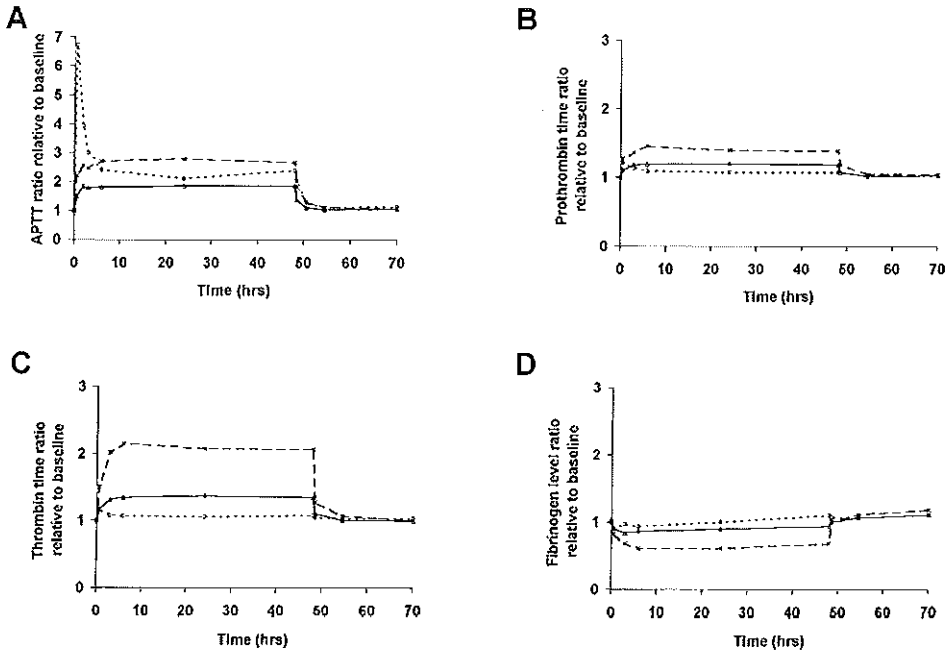

Figure 1. Activated partial thromboplastin times, prothrombin times, thrombin times and fibrinogen levels of the three major treatment groups. —, efegatran 0.63 mg/kg/hr; – – –, efegatran 1.2 mg/kg/hr; ••••, heparin. (A) ratio of median activated partial thromboplastin times relative to baseline value. (B) Ratio of median prothrombin times relative to baseline. (C) Ratio of median thrombin times relative to baseline. (D) Ratio of median fibrinogen levels relative to baseline levels.

returned to baseline levels immediately following discontinuation of therapy (Figure 1D). The concentration of fibrinogen did not change under heparin.

Different methods were employed to measure bleeding times. Local measurements were abnormal at baseline in 9.1% of the patients. The number of abnormal values increased slightly during infusion of heparin and efegatran, but no consistent pattern emerged across the different treatment groups.

Markers of coagulation activation

Levels of activation markers were measured in the dose finding phase group only and were therefore available in a limited number of patients. It should be appreciated that the concentrations of all these parameters, with the exception

of the fibrin degradation products, could have been affected artificially as a result of a traumatic vein puncture, although it was attempted to avoid this.

Levels of β-thromboglobulin and platelet factor 4 showed wide variability at baseline, during treatment with heparin and efegatran, and following discontinuation of medication. No consistent changes were observed, and no differences between the treatment groups could be established. Also fibrinopeptide A, prothrombin fragment 1.2, thrombin-antithrombin complexes and fibrin degradation products did not change significantly during treatment with heparin or efegatran.

Clinical outcomes

Recurrent ischemia was frequent in all groups, but only 2.1% and 0.5% of patients experienced a myocardial infarction or death within 7 days, respectively (Table 2). The percentage of patients that reached the composite endpoint (recurrent or refractory angina, myocardial infarction, ischemia driven coronary intervention or death) at seven days or discharge ranged from 52% to 71% in the efegatran treatment groups and was 71% in patients treated with heparin. No significant differences were observed among the treatment groups.

At 30 days follow-up, the percentage of patients that reached the composite endpoint (parallel dose selection population only) was 62% and 67% in the efegatran treatment groups, and 68% in those treated with heparin. Only 2.7% and 2.0% of patients experienced a myocardial infarction or death at 30 days follow-up, respectively.

Recurrent ischemia during computer-assisted continuous ECG-ischemia monitoring

Good quality ECG recordings were obtained in 405 patients (93%). Hundred-fourteen patients were randomized to one of the six treatment groups in the dose finding phase, and 291 patients to one of the three treatment groups of the parallel design phase.

For all patients, the median (25-75 percentiles) total ECG monitoring time from the start of study drug until the end of monitoring was 51 (46-54) hours. Total analyzable ECG monitoring time was 46 (39-50) hours and did not differ across treatment groups. The median ECG recording data loss was 6 % (2-6).

Table 3. Number and duration of ischemic episodes.

	Efegatran 0.105		Efegatran 0.32		Efegatran 0.63		Efegatran 0.84		Efegatran 1.2		Heparin		All	
Patients	7		21		115		18		124		120		405	
Ischemic episodes*														
≥ 1 ST episode	5	(71%)	17	(81%)	68	(59%)	10	(56%)	80	(65%)	77	(64%)	257	(64%)
≥ 2 ST episodes	4	(57%)	10	(48%)	53	(46%)	7	(39%)	55	(44%)	55	(46%)	184	(45%)
≥ 3 ST episodes	2	(29%)	7	(33%)	37	(32%)	5	(28%)	34	(27%)	34	(28%)	130	(32%)
pts. with ≥ 30 min. of ischemia*	2	(29%)	7	(33%)	31	(27%)	2	(11%)	28	(23%)	39	(33%)	109	(27%)
Total duration / pt (min)**	11	(6, 14)	11	(4, 16)	8	(3, 16)	11	(3, 13)	8	(3, 16)	12	(5, 20)	10	(4, 17)
Time to first episode (hrs)**	13.7(2.1, 22.1)		9.2 (4.0, 37.5)		9.1 (1.8, 21.5)		9.0(2.9, 20.6)		10.9(2.3, 20.4)		7.5(1.9, 21.6)		9.2(2.2, 21.3)	

* normalized to 24 hours of recording
** median, 25, 75 percentiles, patients with ischemia only

Table 4. Bleeding events.

	Efegatran 0.105 (n=10)		Efegatran 0.32 (n=25)		Efegatran 0.63 (n=122)		Efegatran 0.84 (n=24)		Efegatran 1.2 (n=128)		Heparin (n=123)		All (n=432)	
Major bleeding (total)	-		-		1	(0.8%)	-		-		2	(1.6%)	3	(0.69%)
hematoma at puncture site	-		-		1	(0.8%)	-		-		-		1	(0.2%)
gastro-intestinal bleeding	-		-		-		-		-		1	(0.8%)	1	(0.2%)
m. psoas bleeding	-		-		-		-		-		1	(0.8%)	1	(0.2%)
Minor bleeding (total)	2	(20%)	8	(32%)	35	(29%)	4	(17%)	39	(31%)	13	(11%)	101	(23%)
hematoma at puncture site	1	(10%)	5	(20%)	16	(13%)	2	(8%)	17	(13%)	4	(3%)	45	(10%)
other	1	(10%)	3	(12%)	19	(16%)	2	(9%)	22	(18%)	9	(8%)	56	(13%)

Recurrent ischemic episodes were observed in 64% of all patients. Symptomatic episodes occurred in 14% of patients. The median number of episodes (25-75 percentiles) per patient (normalized to 24 hours) was 0.6 (0-3.4) and the total duration of ischemic episodes per patient in those patients having ischemia was 10 (4-17) minutes (Table 3). Ischemia of ≥ 30 minutes duration was present in 27% of all patients. There was no significant difference between the number of patients with recurrent ischemia or the number or duration of ischemic episodes among the treatment groups, although there was a trend towards less prolonged ischemia with the higher doses of efegatran compared to heparin (P=0.068).

Figure 2 demonstrates Kaplan-Meier estimates of the probability to remain free of recurrent ischemia during the course of the monitoring period for the three largest groups. Overall, the median time to the first episode in patients with recurrent ischemia was 9.2 hours. The risk of a first, second or third recurrent ischemic episode was comparable among the three treatment groups. There was no evidence of a rebound of ischemia following cessation of efegatran nor heparin administration (data not shown).

The relationship of ischemic episodes during treatment with subsequent death and myocardial infarction was explored but the number of these complications was too low for a meaningful assessment of such an association.

Adverse events and bleedings

Patients receiving efegatran often developed a superficial thrombophlebitis that seemed to increase, although not significantly, in severity in the higher dose groups, the incidence ranging from 7.7% to 20%, which was significantly higher than with heparin (P=0.0001). For this reason the infusion rate in the highest dose group during the dose ranging phase was increased from 4 ml/hr to 40 ml/hr with a subsequent decrease in the concentration of efegatran administered. This regimen was also used for the subsequent phases of the study, and did reduce the severity of the events. However, it did not reduce the overall occurrence of phlebitis. In the second phase of the study, the number of patients with phlebitis in the 0.63 mg/kg/hr dose group was 13%, compared to 25% in the 1.2 mg/kg/hr dose group and 2% in the patients treated with heparin. In the great majority of patients, the severity of the phlebitis was only mild.

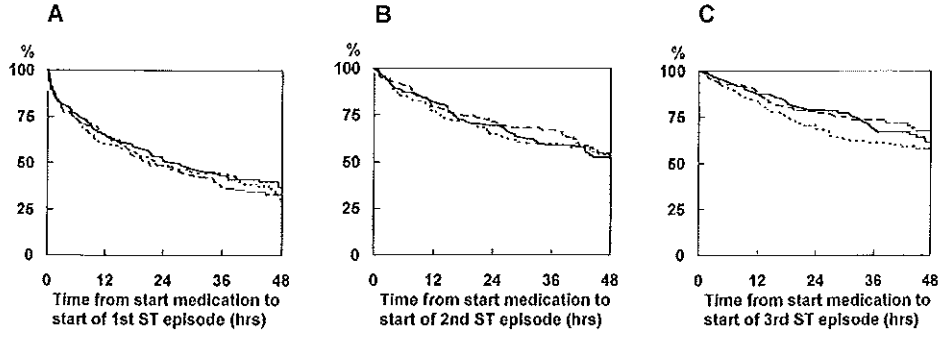

Figure 2. Kaplan-Meier estimate of the probability to remain free of a ST episode during the course of the monitoring period. (A) Probability to remain free from a recurrent ST episode from the start of medication. —, patients treated with efegatran 0.63 mg/kg/hr (115); – – –, patients treated with efegatran 1.2 mg/kg/hr (124); ••••, patients with treated with heparin (120). (B) Probability to remain free from a second ST episode from the start of medication. (C) Probability to remain free from a third ST episode from the start of medication.

The incidence of minor bleeding events was significantly higher in patients treated with efegatran (P=0.001) ranging from 17% to 32%, against 11% in patients under heparin (Table 4). There were three major bleedings, 2 of which occurred in patients treated with heparin. Spontaneous gross hematuria was equally distributed and observed in three patients (0.7%). Most minor bleedings were associated with a previous puncture site, and did not require specific measures. There were no strokes associated with administration of trial medication.

DISCUSSION

In this multicenter single-blind dose finding study, the anti-thrombotic effects of the direct acting thrombin inhibitor efegatran sulfate were compared with heparin in patients with unstable angina. At similar levels of anticoagulation, APTT levels were more stable for the thrombin inhibitor. However, no clinical advantages for efegatran were apparent, while mild or moderate bleeding and thrombophlebitis were more frequent.

Anticoagulant effects

A dose dependent anticoagulant activity of efegatran was demonstrated, with the highest dose level of 1.2 mg/kg/hr resulting in a steady state APTT value of about 3 times baseline. Furthermore, administration of efegatran was associated with a pronounced increase in thrombin time, suggesting this test to be the most sensitive for measuring the level of thrombin inhibition by efegatran. Fibrinogen levels decreased in patients treated with efegatran. However, there were no demonstrable effects on the levels of coagulation activation markers nor on the concentration of thrombin-antithrombin complexes.

The level of thrombin inhibition by efegatran appeared to be more stable than with heparin especially during the first hours following initiation of therapy, during which APTT guided dose adjustments were made in the heparin treated patients. Similar observations have been reported for other direct thrombin inhibitors[9-13].

The incidence of minor bleeding was higher in patients treated with efegatran compared to patients treated with heparin. However, there was no excess in major bleeding for either dose of efegatran and there were no strokes associated with trial treatment. These results are similar to other studies in patients with unstable angina receiving anti-thrombin therapy, which reported no, or only a modest increase in minor bleeding events compared to heparin[12,13,16]. A higher incidence of bleeding events was reported using thrombin inhibitors in combination with thrombolytic agents[10,11,14,15,17]. This lead to interruption of three trials studying the effects of hirudin in patients with an acute myocardial infarction or acute coronary syndromes[14,15,17]. Two of these (TIMI 9b and GUSTO IIb) were restarted at lower doses of hirudin, with APTT guided dosing regimens[10,11]. In GUSTO IIb, 25% of patients received concomitant thrombolytic therapy. Compared to heparin, the administration of low dose hirudin appeared to be associated with an increased major bleeding rate (7.9% vs. 6.9%, P=0.03), with an excess of intracranial hemorrhages in patients without ST elevation, who had not received concomitant thrombolytic therapy (0.2% vs. 0.02%, P=0.06). In TIMI 9b, all patients received concomitant thrombolytic therapy, and similar bleeding rates were observed for hirudin and heparin treated patients.

Clinical outcome

Neither dose of efegatran studied did suppress myocardial ischemia to a greater extent than that seen with heparin, and there were no differences in clinical outcome between the efegatran and heparin groups. The composite clinical endpoint (death, myocardial infarction, recurrent or refractory ischemia or need for revascularization) was reached by 62% and 67% of the patients treated with efegatran, compared to 68% in patients on heparin. Of note was the high incidence of patients with a myocardial infarction at the time of enrollment (58 patients, 13.4%) and the subsequent low incidence after enrollment into the study (14 patients, 3.2%). This was due to the selection process since the majority of patients was enrolled directly after admission to hospital, without knowledge of possibly elevated CK and CK-MB enzyme levels.

These data confirm the results of other studies on direct thrombin inhibitors, which reported only equivalent or slightly improved outcome compared to heparin, sometimes at cost of a higher incidence of bleeding[10-18]. Of all studies with direct thrombin inhibitors, only the OASIS study reported superiority of hirudin over heparin in preventing both short (7 days) and long term (180 days) ischemic outcome in patients with unstable angina and patients with a myocardial infarction without ST segment elevation[16]. As in our study, there was no significant increase of major bleedings, while the incidence of minor bleeding events was higher for hirudin compared with heparin. In the HELVETICA study, treatment with hirudin peri-PTCA was associated with fewer early cardiac events during the first month, without an increased risk of bleeding, but no apparent benefit was present at 7 months follow-up[18,19]. A similar study of hirulog versus heparin showed a reduction in immediate (in-hospital) ischemic complications in a predefined group of patients with post-infarction angina only[13]. Again, this difference was no longer apparent after 6 months follow-up.

In the TIMI 9B and GUSTO IIb study, the effects of hirudin in patients with an acute myocardial infarction or acute coronary syndrome were investigated[10,11]. Clinical benefits were modest or absent, with only GUSTO IIb showing a reduction of myocardial infarction or death within 24 and 48 hours from the start of treatment and a borderline effect at 30 days follow up (P=0.06) at the cost of more major bleedings. In another study, hirulog appeared to be more effective than heparin in promoting early patency in patients with an acute myocardial infarction treated with streptokinase and

aspirin, without increasing the risk of major bleeding. However, no benefit on cardiac events could be demonstrated (HERO)[12]. Finally, studies with another thrombin inhibitor, argatroban, have not shown any beneficial effect over heparin in patients with an acute myocardial infarction[20].

The high expectations of direct thrombin inhibitors have not been confirmed by clinical trials so far. Dosing regimens and duration of treatment of both heparin and anti-thrombins varied widely across these studies, making comparisons difficult. As only one study demonstrated a persisting beneficial effect of these agents, it may be questioned whether the duration of treatment (24 hours to five days maximum) may have been too short for obtaining long term clinical benefit. Rebound effects may also have influenced long term outcome, although such were not observed in the present study[16]. The lack of clinical benefit may be related to the mechanism of action direct anti-thrombins, which have a greater ability to decrease thrombin activity (also clot-bound thrombin) than heparin, while the latter has a greater ability to decrease thrombin generation, as it inhibits earlier steps in the coagulation cascade, which are not affected by direct thrombin inhibitors[21]. Such combined inhibition of both thrombin generation and thrombin activity may in fact be advantageous.

CONCLUSIONS

We compared the effect of efegatran, a direct thrombin inhibitor with heparin. Administration of efegatran sulphate at levels of at least 0.63mg/kg/hour provided a pronounced increase in thrombin time, reflecting a level of thrombin inhibition which is at least comparable to APTT adjusted heparin infusion. The level of thrombin inhibition by efegatran, as reflected by the APTT, appeared to be more stable than with heparin, especially during the first few hours following initiation of therapy. This may reflect a more predictable dose response, suggesting that efegatran sulphate is probably easier to administer than heparin.

As thrombin plays a key role in the coagulation cascade it was expected that the direct effects of efegatran would result in a more potent anticoagulant effect compared to heparin, which acts indirectly, requiring antithrombin III as a cofactor. However, no clinical benefit of efegatran over heparin was

apparent whereas minor bleeding was more frequent. Our findings are in concert with other studies investigating direct thrombin inhibitors.

REFERENCES

1. Davies MJ, Thomas AC. Plaque fissuring-the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985; 53: 363-73.
2. Rehr R, Disciascio G, Vertovec G, Crowley M. Angiographic morphology of coronary artery stenoses in prolonged rest angina: evidence of intracoronary thrombosis. J Am Coll Cardiol 1989; 14: 1429-37.
3. Gorlin R, Fuster V, Ambrose JA. Anatomic-physiologic links between acute coronary syndromes. Circulation 1986; 74: 6-9.
4. Coller BS. Activation affects access to the platelet receptor for adhesive glycoproteins. J Cell Biol 1986; 103: 451-6.
5. Weiss HJ, Hawiger J, Ruggeri ZM, Turitto VT; Thiagarajan P; Hoffmann T. Fibrinogen-independent platelet adhesion, and thrombus formation on subendothelium mediated by glycoprotein IIb-IIIa complex at high shear rate. J Clin Invest 1989; 83: 288-97.
6. Verstraete M, Zoldhelyi P. Novel antithrombotic drugs in development. Drugs 1995; 49: 856-84.
7. Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). Circulation 1998, in press.
8. Klootwijk P, Meij S, v. Es GA, Müller EJ, Umans VAWM, 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: 931-40.
9. Zoldhelyi P, Webster MW, Fuster V, Grill DE, Gaspar D, Edwards SJ, Cabot CF, Chesebro JH Recombinant hirudin in patients with chronic, stable coronary artery disease. Safety, half-life, and effect on coagulation parameters. Circulation 1993; 88: 2015-22.
10. Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. Circulation 1996; 94: 911-21.
11. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996; 12; 335: 775-82.
12. White HD, Aylward PE, Frey MJ, Adgey AA, Nair R, Hillis WS, Shalev Y, Brown MA, French JK, Collins R, Maraganore J, Adelman B. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. Circulation 1997; 96: 2155-61.
13. Bittl JA, Adelman B, Deutsch E, Maraganore J, Chaitman BR, Meckel CR, Ahmed

WH, Brinker JA, Strony J, for the Hirulog Angioplasty Study Investigators. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. N Engl J Med 1995; 333: 764-9.
14. Neuhaus KL, von Essen R, Tebbe U, Jessel A, Heinrichs H, Maurer W, Doring W, Harmjanz D, Kotter V, Kalhammer E, *et al.* Safety observations from the pilot phase of the randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) study. Circulation 1994; 90: 1638-42.
15. Antman EM, for the TIMI 9A investigators. Hirudin in acute myocardial infarction. Safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A Trial. Circulation 1994; 90: 1624-30.
16. Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: a pilot study. Circulation 1997; 96: 769-77.
17. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. Circulation 1994; 90: 1631-7.
18. Serruys PW, Herrman JP, Simon R, Rutsch W, Bode C, Laarman GJ, van Dijk R, van den Bos AA, Umans VA, Fox KA, Close P, Deckers JW, for the Helvetica Investigators. A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. Helvetica Investigators. N Engl J Med 1995; 333: 757-63.
19. Simoons ML. Prevention and management of thrombotic complications during coronary interventions. Foreword. Eur Heart J 1995; 16 (suppl L): 1-2.
20. Vermeer F, Vahanian A, Fels PW, Besse P, Radzik D, Simoons ML. Intravenous argatroban versus heparin as co-medication to alteplase in the treatment of acute myocardial infarction; preliminary results of the ARGAMI pilot study. J Am Coll Cardiol 1997;29:185-6 (abstract).
21. Zoldhelyi P, Janssens S, Lefevre G, Collen D, Van de Werf F, for the GUSTO-2A Investigators. Effects of heparin and hirudin (CGP39393) on thrombin generation during thrombolysis for acute myocardial infarction. Circulation 1995; 92: I-740.

Appendix

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Chapter 7

Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE)

P. Klootwijk, S. Meij, R. Melkert, T. Lenderink, M.L. Simoons

Circulation: in press

ABSTRACT

Background. In the CAPTURE trial, 1265 patients with refractory unstable angina were treated with abciximab or placebo, in addition to standard treatment from 16-24 hours preceding coronary intervention through 1 hour post intervention. In order 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 post 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 abciximab patients (5%) vs. 22 placebo patients (14%) had ≥ 2 ST episodes ($P<0.01$). In patients with ischemia, abciximab significantly reduced total ischemic burden ($P<0.02$), which was calculated alternately as either the total duration of ST episodes per patient, or 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 (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 myocardial infarction or death within 5 day 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.

INTRODUCTION

Computer-assisted continuous ST monitoring is a practical noninvasive tool for detection and quantitation of myocardial ischemia and recognition of myocardial infarction 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 exhibit at least one episode of ischemia within the first 24 hours of admission, with only 23% of patients remaining free of ST episodes during an ST monitoring period of 48 hour[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 percutaneous transluminal coronary angioplasty (PTCA) as well as during follow-up in patients with clinical or angiographic features indicating increased procedural risk[7-9]. In the **CAPTURE** study (**c**7E3 Fab **A**nti **P**latelet **T**herapy in **U**nstable **RE**fractory angina), which was designed to assess the value of treatment with abciximab in patients with refractory unstable angina during 18-24 hours preceding PTCA, a major reduction of death, myocardial infarction or urgent intervention within 30 days after enrollment was obtained from 15.9% in the placebo group to 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 to placebo on the incidence and severity of recurrent ischemia during continuous vector-derived 12-lead ECG monitoring in patients with unstable angina refractory to standard drug-treatment, scheduled for PTCA within 24 hours. These effects were studied both before, during and up to 6 hours post 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, which had the availability of ECG monitoring equipment, out of 69 hospitals participating in CAPTURE. All patients underwent continuous ECG monitoring using a vector-derived 12-lead ECG recording system (MIDA 1000, Ortivus Medical, Täby, Sweden), 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 one or more episodes of either typical chest pain and/or ECG abnormalities compatible with myocardial ischemia during therapy with heparin i.v. and nitroglycerin, started at least 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 following 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, making ST segment interpretation unreliable, were also excluded.

After enrollment, patients received a minimal daily dose of 50 mg aspirin. In patients not yet on aspirin, the first dose was a minimum of 250 mg. Heparin was administered prior to randomization until at least 1 hour after PTCA and adjusted to an APTT between 2.0 and 2.5 times normal. All patients received nitroglycerin i.v.. Beta-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

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)
Male	111 (68.1%)	107 (63.3%)	702 (75.2%)
Mean (SD) age in years	62 (10)	60 (10)	61 (10)
Anthropometry: mean (SD)			
Weight (kg, SD)	77 (13)	77 (13)	75 (12)
Height (cm, SD)	172 (10)	171 (9)	169 (9)
Number of patients with			
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			
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			
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%)
ß-blockers	116 (72.5%)	125 (75.8%)	583 (63.5%)
Calcium antagonists	86 (53.8%)	82 (49.7%)	445 (48.5%)
Medication after enrollment			
Aspirin	158 (96.9%)	164 (97.0%)	890 (96.2%)
Ticlopidin	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%)
ß-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 were reported.

10 mg/min or matching placebo for 18-24 hours preceding PTCA and continuing for one 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 endpoints

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, myocardial infarction 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 two or more contiguous leads. Myocardial infarction following discharge was defined by CK-MB or CK levels exceeding 2 times the upper limit of normal, or new significant Q waves in two or more 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 24-36 hours, including 6 hours following 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, Täby, Sweden). This system calculates averaged QRS-T complexes from the Frank orthogonal X-Y-Z leads at 1-minute intervals. These averaged complexes are stored on the 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 mseconds 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 of ST amplitude of at least ± 100 μV from the baseline ST level in one or more of the 12 derived leads, developing within a 10 minute period and persisting during at least 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 one minute. Episodes had to be separated from each other by at least one minute.

If ≥ 100 μV ST change was present in more than one lead simultaneously, the episode onset was defined by the lead exhibiting the first ≥ 100 μV ST change. 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 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 afterwards. 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 four different ways: (1) the sum of the duration of all episodes per patient; (2) the sum of the area under the curve of the ST vector magnitude trend of all episodes per patient (Figure 3); (3) the sum of the area under the ST trend curve of all leads involved in the ST episodes per patient; (4) the sum of the area under the ST trend curve of all 12 leads during ST episodes per patient (except aVR).

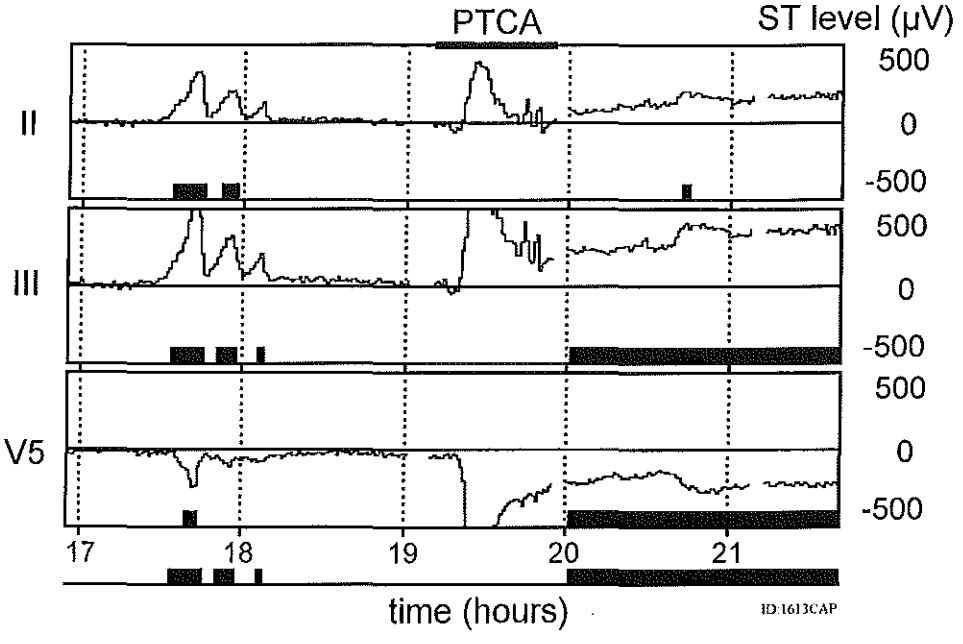

Figure 1. Example of the vector derived 12-lead ST analysis of a study patient with unstable angina who suffered from a myocardial infarction as a complication of a PTCA procedure. The ST trends of the relevant leads in which ST episodes occurred and in which the myocardial infarction developed are displayed. The black bars in each single lead ST trend represent the time during which the algorithm detected a ≥ 100 μV ST change. 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 hrs. and 18:00 hrs. During angiography and PTCA, possibly at the moment of first injection of contrast, a sudden severe ST elevation develops in leads II and III with simultaneous ST depression in lead V5. Subsequently, this ischemic event partially resolves, followed by 2 short peaks of ST elevation / depression, which reflect the inflations of the balloon catheter. Following the PTCA procedure, a persistent elevation of the ST segment is observed with depression in lead V5, suggesting a persistent occlusion leading to acute myocardial infarction. Myocardial infarction in this patient was confirmed by a rise of CK and CK-MB to 4 and 3 times the upper limit of normal, respectively, and the development of Q waves. See also Figure 2.

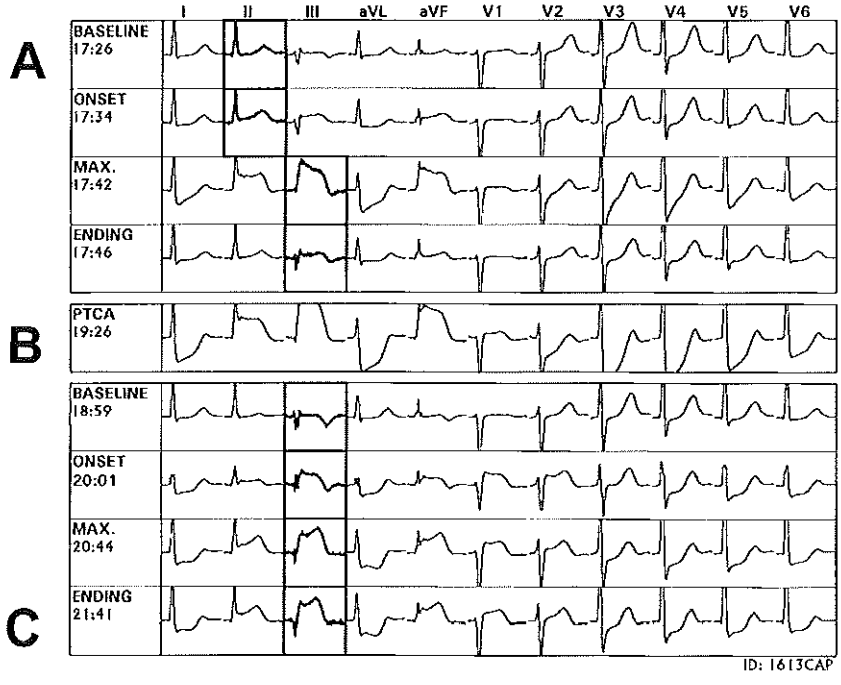

Figure 2. Samples of the computer-assisted 12-lead ECG recording of the patient in Figure 1. (A) Ischemic episode before PTCA, detected by the algorithm. The upper ECG row (17:26 hrs) demonstrates the baseline "non-ischemic" 12-lead ECG (except aVR). The ECG rows directly below demonstrate the time (17:34 hrs) 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 and ending of the episode are detected in lead III (17:46 hrs). (B) ECG sample during PTCA. Note the severe ST elevations in the inferior leads with simultaneous ST depressions in leads V3 to V6. (C) Following PTCA, ST elevations persist in the same area as during the procedure, suggesting an acute myocardial infarction. 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 "non-ischemic" ECG (18:59 hrs). As such, the "onset" of ischemia is again detected directly after the procedure (20:01 hrs).

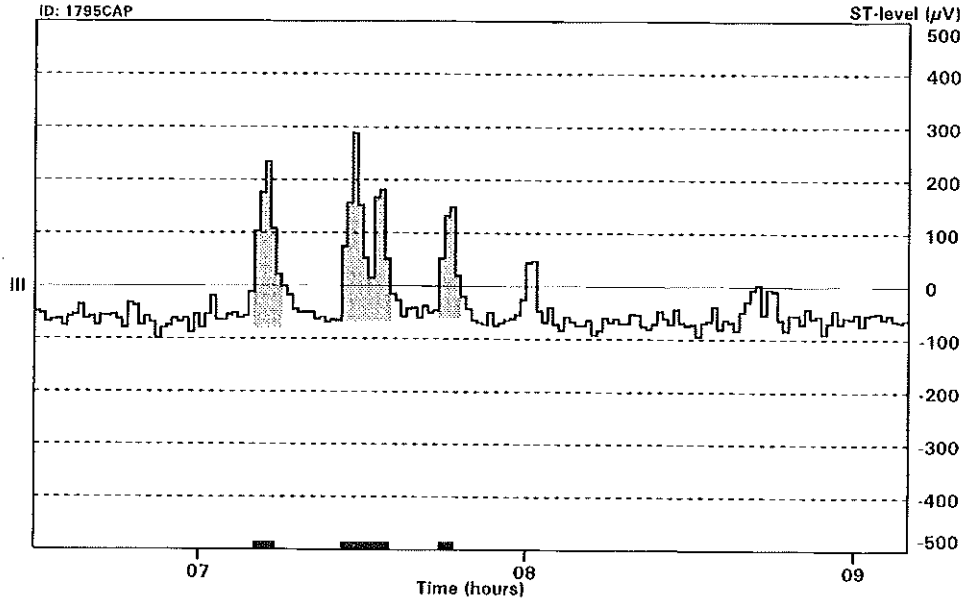

Figure 3. Measurement of the ischemic burden. For simplification, only a magnification of the ST trend of a single lead is displayed. Three ST episodes ≥ 100 μV are detected between 07:10 and 7:50 hrs. The ST elevations around 08:00 hrs and 08:50 hrs do not reach the threshold of 100 μV and are not classified as ST episodes. The area under the trendcurve of the episodes is measured from the baseline ST level which 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.

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-tailed P value of ≤ 0.05 was considered statistically significant. The Kaplan-Meier method was used for the 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% confidence intervals.

RESULTS

In the CAPTURE study, a total of 1265 patients were included at 69 sites in 12 countries[10]. Three-hundred and 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 (later than 1 hour after the start of drug-infusion or less than 50% analyzable ECG data), 22 patients because of technical failures due to errors on 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, with 39% patients having their qualifying episode within 6 hours before enrollment. The majority of patients (193, 58%) had either ST depression, elevation or both of at least 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 two treatment groups and representative of the baseline data of the CAPTURE main study (Table 1). Death or myocardial infarction within 5 days occurred in 17 (10.4%) of the placebo patients and in 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 receiving abciximab or placebo 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 the 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

Table 2. Duration of ST monitoring periods.

	placebo		abciximab		all patients	
Patients	163		169		332	
total monitoring time (hrs)*	28	(26, 29)	27	(26, 29)	28	(26, 29)
duration of stay at cath-lab (hrs)*	1.3	(1.0,1.7)	1.3	(1.0, 1.7)	1.3	(1.0, 1.7)
total analyzable monitoring time (hrs)*	27	(24, 28)	26	(25, 28)	26	(25, 28)
start study -> PTCA (hrs)*	20	(18, 21)	19	(18, 21)	20	(18, 21)
end PTCA -> end monitoring (hrs)*	6	(6, 7)	6	(6, 7)	6	(6, 7)
ECG data loss (%)*	2	(1, 7)	2	(1, 5)	2	(1, 6)

* median (25, 75 percentiles)

burden were significantly decreased in patients receiving abciximab, both for the period preceding the PTCA procedure and the complete monitoring period (Table 3). Excluding the time period of the PTCA and the stay at the catheterization laboratory, only 9 abciximab patients (5%) versus 22 placebo patients (14%) had 2 or more ST episodes (P=0.01) and only 5 abciximab (3%) versus 15 placebo patients (9%) had 3 or more ST episodes (P=0.02). Symptomatic episodes occurred in 5 abciximab (3%) and in 13 (8%) placebo patients (P=0.05). These treatment effects were also apparent in the subgroup of 136 patients who exhibited ST depression of $\geq$ 0.1 mV on their 12-lead ECG during the ischemic event which qualified them for entry into the study. The latter patients had more ischemic episodes than patients without ST depression at study entry (P=0.055). In this subgroup, only 1 abciximab patient (2%) versus 9 placebo patients (12%) had 3 or more ST episodes (P=0.02). Total ischemic burden parameters as defined by either the duration of ischemia per patient or 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 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 one were significantly higher for abciximab (P=0.01 and 0.02, respectively, Figure 4B and 4C).

Table 3. ST monitoring results.

	period from start of study until balloon angioplasty					period following balloon angioplasty					total monitoring period				
	placebo	%	abciximab	%	*P* value	placebo	%	abciximab	%	*P* value	placebo	%	abciximab	%	*P* value
Patients	163		169			155		162			163		169		
ST episodes															
≥ 1	29	18	24	14	n.s.	16	10	9	6	n.s.	37	23	31	18	n.s.
≥ 2	18	11	9	5	0.07	15	10	8	5	n.s.	22	14	9	5	0.01
≥ 3	12	7	3		0.02	2	1	0	0	n.s.	15	9	5	3	0.02
symptomatic episodes	9	6	4	2	n.s.	6	4	1	1	0.06	13	8	5	3	0.05
Ischemic burden *															
total duration / pt (min)	12		6		n.s.	61		9		0.10	38		8		0.02
ST VM (mV.min)	1293		677		n.s.	7084		796		0.06	4819		796		0.01
12-lead ST area (mV.min)	8832		4682		n.s.	45599		3876		0.10	29392		5376		0.01
ST area of leads ≥100 mV (mV.min)	2394		1383		n.s.	27026		1858		n.s.	8558		1858		0.03

The number of ST episodes was compared using Fisher's exact test. Ischemic burden variables are given as medians and were compared using the Mann-Whitney test. A two-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=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 aVR); ST area of leads ≥ 100 mV=the sum of the area under the ST trend curve of all leads involved in the ST episodes per patient (except aVR).

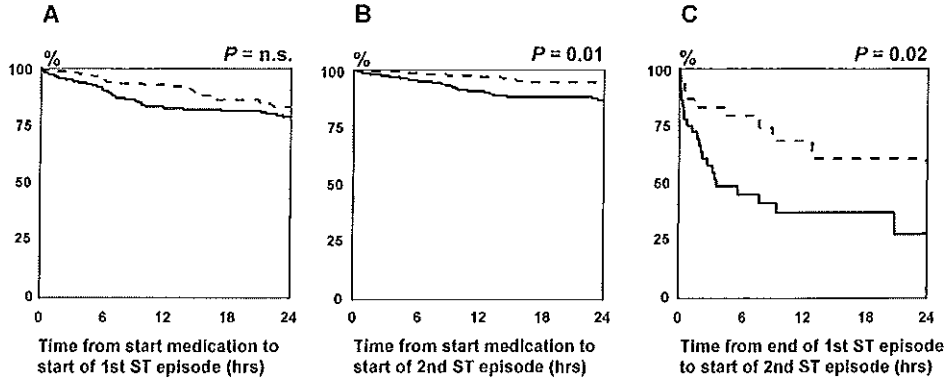

Figure 4. Kaplan-Meier estimate of the probability to remain free of a ST episode during the course of the monitoring period. (A) Probability to remain free from a recurrent ST episode from the start of medication. — = patients treated with placebo (163); – – – = the patients treated with abciximab (169). (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. — = patients with at least one ST episode treated with placebo (37); – – – = patients with at least one 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 abciximab.

The majority of clinical events occurred during and within 24 hours following PTCA. Eighteen patients suffered from a myocardial infarction and three died within 5 days of treatment. Eventually, twenty-four patients developed a myocardial infarction 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% confidence interval 1.4, 7.4; absolute risk 15%) and 4.1 (95% confidence intervals 1.4, 12.2; absolute risk 23%), respectively. This association also remained apparent for the occurrence of myocardial infarction or death within 30 days.

DISCUSSION

In the CAPTURE study, treatment with abciximab (c7E3 Fab, ReoPro) resulted in a 50% reduction of myocardial infarction and 29% reduction in the primary composite endpoint of death, myocardial infarction or urgent (re-)intervention in patients with refractory unstable angina[10]. The results of the present ECG-ischemia monitoring substudy including 332 out of the 1264 patients of CAPTURE are consistent with these findings. Compared to placebo, treatment with abciximab resulted in a reduction of frequent ischemia and symptomatic ischemic episodes during continuous ECG-ischemia monitoring, and 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 myocardial infarction during the 16 to 24 hours 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 lead 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 myocardial infarction and death within the next 5 days, which 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 endpoint 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 50-70%[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 suggests that a part 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 myocardial infarction 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 stabilized on medical therapy (e.g. abciximab), a PTCA procedure could possibly be deferred to a later moment in order 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 myocardial infarction 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, compared to placebo, is associated with a reduction of frequent ischemia and a reduction of total ischemic burden in patients with refractory unstable angina both before PTCA (thus stabilizing patients) and post PTCA. The incidence of recurrent ischemia appeared lower than observed in patients with unstable angina studied shortly after hospital admission[4,14-17]. Thus, most patients tend to stabilize over time, particularly when treated with abciximab.

The presence of recurrent ischemia predicts myocardial infarction 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.

REFERENCES

1. Krucoff MW, Croll MA, Pope JE, Granger CB, O'Connor CM, Sigmon KN, Wagner BL, Ryan JA, Lee KL, Kereiakes DJ. Continuously 12-lead ST-segment recovery analysis in the TAMI 7 study. Circulation 1993; 88: 437-46.
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: 21-9.
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: 689-98.
4. Klootwijk P, Meij S, v. 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: 931-40.
5. Davies MJ, Thomas AC. Plaque fissuring - the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985; 53: 363-73.
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, Boer MJ de, Brand MJBM van den, Miltenburg AJM, Hoorntje JCA, Heyndrickx GR, wieken LR van der, De Bono D, Rutsch W, Schaible TF, weisman HF, Klootwijk P, Nijssen K, Stibbe J, Feyter PJ de 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: 956-61.
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: 881-6.
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: 1429-35.
11. Braunwald E. Unstable angina. A classification. Circulation 1989; 80:410-4.
12. Miltenburg AJM van, Simoons ML, Veerhoek RJ, Bossuyt PMM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. J Am Coll Cardiol 1995; 25: 1286-92.
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: 1214-9.
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(6): 1173-9.
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. Circulation 1996; 93: 1651-7.
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: 1333-41.
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.

APPENDIX

CAPTURE study organization

Steering Committee: ML 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); MJ de Boer (The Netherlands); R McCloskey and H Weisman (Centocor, U.S.A.). *Clinical Endpoint Committee:* The Netherlands: F Bär (Chairman) Maastricht; JW Deckers, Rotterdam; JJ Piek, Amsterdam; APJ 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:* MJBM van den Brand (Chairman, The Netherlands), GJ Laarman (The Netherlands), G Hendrickx, I de Scheerder (Belgium), PG Steg (Paris), K Beat (United Kingdom). *Coordinating Center:* 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 (Euro-Biopharm, The Netherlands);); T Schaible, K Anderson, A Wang, S FitzPatrick (Centocor, U.S.A.); 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); D Kafka (Besselaar, Israel).

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Chapter 8

Summary and conclusions

With the ongoing development of new reperfusion regimens, new anti-coagulants and anti-platelet agents as well as intracoronary intervention, the monitoring of the perfusion status of the myocardium in patients with acute coronary syndromes (unstable angina and myocardial infarction) is becoming increasingly important. The easiest noninvasive method for monitoring the perfusion status of the myocardium is recording of the ST segment of the electrocardiogram. Computer-assisted continuous real-time vectorcardiographic or multilead ECG-ischemia monitoring techniques are nowadays available and have outgrown the limitations of earlier ECG technologies as they can record and display the complete 12-lead ECG or vector lead ECG on-line and store the data for retrospective analysis (full disclosure).

In this thesis the application of computer-assisted continuous vectorcardiographic and multilead ECG monitoring techniques for detection and quantitation of myocardial ischemia, prediction of coronary vessel status and for identification of patients at risk of major coronary events is evaluated.

CONTINUOUS ECG-ISCHEMIA MONITORING IN PATIENTS WITH AN ACUTE MYOCARDIAL INFARCTION RECEIVING REPERFUSION THERAPY (GUSTO-I ECG-ISCHEMIA MONITORING SUBSTUDY).

In chapters 2, 3 and 4, the results of the GUSTO-I ECG-ischemia monitoring substudy are reported (GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries). One thousand and sixty four patients underwent continuous ST segment monitoring, using vector-derived 12-lead (406 patients), 12-lead (373 patients) and 3-lead Holter (288 patients) ECG recording systems. Chapter 2 evaluates these three different monitoring techniques for on-line prediction of the perfusion status of the infarct-related vessel in 302 GUSTO-I patients who underwent angiography at either 90 or 180 minutes after the start of thrombolysis. This study demonstrates that noninvasive patency prediction using continuous ECG recording techniques is feasible and can be used in clinical practice, particularly in patients with extensive initial ST segment elevation. Prediction of vessel status appeared 79-100% accurate in the subgroup of patients with initially high ST levels, which is the group of patients having the greatest risk of adverse cardiac events and benefiting most from reperfusion therapy. Although the three recording systems differed considerably in signal processing, no significant difference in accuracy was demonstrated among these systems. The study demonstrates that tailoring of therapeutic strategies guided by computer-assisted continuous ECG monitoring techniques is feasible in patients with acute myocardial infarction.

In Chapter 3, the speed and stability of ST segment recovery is compared among the 4 different thrombolytic strategies for acute myocardial infarction studied in GUSTO-I[1]. It was expected that patients treated with accelerated rt-PA would exhibit a faster ST recovery than patients receiving the other regimens, and that those treated with streptokinase would show greater stability of recovery. Although the angiographic substudy of GUSTO-I indeed demonstrated a greater 90 minutes patency with accelerated r-tPA[2], we were not able to correlate this finding with a shorter time to 50% ST segment recovery, mainly because of technical limitations and the use of three different ECG monitoring techniques. Recurrent ST segment shift (mainly ST elevation),

suggestive of reocclusion of the infarct-related vessel was present in approximately 36% of patients.

As a consequence, chapter 4 addresses the question whether those patients with recurrent ST segment shift after an initial ST recovery suggestive of successful reperfusion exhibit a higher mortality compared to those patients without. Indeed, both 30 days and 1 year mortality in patients with recurrent ST segment shift is higher than in patients without such ST segment shift. The presence of either recurrent ST elevation or ST depression 6-24 hours after the initial 50% ST recovery following thrombolytic treatment was an independent prognostic predictor of mortality at 30 days, even after adjustment for multiple clinical risk factors derived from the overall GUSTO-I mortality model[3]. The duration of the ST segment shift appeared directly related to subsequent mortality. Thus, continuous ECG-ischemia monitoring is useful not only for selection of high risk non-reperfused patients, but also for selection of high risk patients who reperfused but subsequently exhibit recurrences of ischemia and / or reocclusion.

ECG-ISCHEMIA MONITORING IN PATIENTS WITH UNSTABLE ANGINA

ECG-ischemia monitoring in patients with unstable angina is more complex than in patients with evolving myocardial infarction. The latter most commonly have ischemic ST shifts (ST elevation) at the start of ST monitoring and normalization of the ST segment after ST recovery. In contrast, patients with unstable angina may exhibit very different patterns. Ischemia may be reflected by both ST elevation, ST depression and T wave changes, making automated analysis using computer algorithms difficult. Some patients have abnormal non-ischemic ECGs with ST shift and T wave inversions at baseline and pseudo-normalization during ischemia. Thus, when monitoring patients with unstable angina, a baseline ST level (without ischemia) should be defined first, which requires the selection of a reference (non-ischemic) ECG. ST monitoring of the single lead with the greatest initial ST shift is sufficient in many patients with myocardial infarction, but may not be appropriate in patients with unstable angina, as ischemia may shift from one lead to another (see below).

IMPACT OF THE NUMBER OF LEADS AND LEAD SELECTION FOR DETECTION AND QUANTITATION OF ISCHEMIA IN PATIENTS WITH UNSTABLE ANGINA

In chapters 2-4, we demonstrated that computer-assisted continuous ECG monitoring in patients with an acute myocardial infarction is of clinical value for prediction of vessel status and for identification of high risk patients. For monitoring and patency assessment we had selected the ECG lead with the greatest ST shift at the onset of monitoring as it was assumed that this lead would optimally reflect the area which was injured by the occlusion of the culprit coronary vessel. In contrast, in patients with unstable angina the site of the ischemic area may vary, depending on the flow balance of the coronary system, the degree of vessel injury and the duration and severity of ischemia. Thus, the selection and number of ECG leads used for ST monitoring may influence detection and quantitation of ischemia in patients with unstable angina. As such, standard 12-lead ST monitoring might be preferred. In order to validate this assumption, we compared on-line continuous 48-hours 12-lead (except aVR) with 3-lead ST monitoring in 130 unstable angina patients (chapter 5).

Twelve lead ST monitoring appeared to be more sensitive than the 3-lead technology more generally applied at cardiac care units. With three leads, ischemia was detected in 62% of patients, which was comparable to studies using Holter ST monitoring in patients with unstable angina[4,5]. With 12-lead ST monitoring, ischemia was detected in an additional 15% of patients. Also the number and duration of ischemic episodes increased using 12-lead compared to 3-lead ST monitoring. Most importantly, the ST changes were found to disperse and shift among different leads in time in at least 31% of patients with more than one ST episode during the monitoring period, confirming that the use of multiple leads (8-12 standard leads) or vectorcardiographic leads is mandatory in these patients.

RISK ASSESSMENT AND ASSESSMENT OF THERAPEUTIC EFFICACY IN PATIENTS WITH UNSTABLE ANGINA USING ECG-ISCHEMIA MONITORING

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[6,7]. Recurrent ischemia detected during computer-assisted continuous ST monitoring may thus specifically reflect episodes of platelet aggregation in these patients. We conducted two studies with continuous ECG-ischemia monitoring in patients with unstable angina, evaluating the therapeutic efficacy of efegatran, a direct anti-thrombin (chapter 6), and abciximab, a platelet glycoprotein IIb-IIIa receptor blocker (chapter 7).

Efegatran was studied in 432 patients with unstable angina. Five dose levels of efegatran sulphate were investigated and compared to heparin. Efficacy was assessed by measurement of the number of patients with recurrent ischemia, the number of episodes and the duration of episodes. Clinical endpoints were: episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA or CABG), and death. Neither of the doses of efegatran studied were able to suppress myocardial ischemia during continuous ECG-ischemia monitoring to a greater extent than that seen with heparin. The study was hampered by the fact that a high number of patients with a myocardial infarction at the time of enrollment had been included into the study (13.4%). This was due to the fact that the majority of patients was enrolled directly after admission to hospital without knowledge of possibly elevated CK and CK-MB enzyme levels. The incidence of subsequent infarction after enrollment into the study was low (3.2%). No significant difference between the efegatran and heparin treated groups was apparent with respect to clinical outcome. Furthermore, no relation could be demonstrated between clinical outcome and the presence of ischemic episodes or the ischemic burden detected during ECG-ischemia monitoring.

Abciximab was studied in the CAPTURE trial (**c**7E3 Fab **A**nti **P**latelet **T**herapy in **U**nstable **RE**fractory angina)[8], in which 1265 patients with refractory unstable angina were treated with abciximab (c7E3 Fab, ReoPro) or placebo, on top of standard treatment from 16-24 hours preceding coronary intervention through 1 hour post intervention. Treatment with abciximab resulted in a 50% reduction of myocardial infarction (from 8.2% to 4.1%)

and 29% reduction in the primary composite endpoint of death, myocardial infarction or urgent (re-)intervention in patients with refractory unstable angina (from 15.9% to 11.3%) at 30 days.

In order 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. Although the incidence of ischemia in this substudy was less than expected in this group of refractory unstable patients (21%), it could be demonstrated that treatment with abciximab was associated with a reduction of frequent ischemia and a reduction of total ischemic burden. Patients with recurrent ischemia during the ST monitoring period before PTCA had a greater probability to develop myocardial infarction or death within 5 days follow-up. This association also remained apparent at 30 days follow-up.

The results of this ECG-ischemia monitoring substudy extended the observation in the CAPTURE main trial that treatment with abciximab reduced the occurrence of myocardial infarction during the 16 to 24 hours medical treatment period before PTCA was performed. It is likely that the reduction of recurrent ischemia reflected resolution of thrombus and prevention of recurrent thrombosis by abciximab with possible stabilization of the plaque, which lead 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 myocardial infarction and death.

The latter study demonstrates that ischemia, detected during vector-derived multilead ECG-ischemia monitoring, can be used for risk assessment in patients with unstable coronary syndromes and as a study endpoint in phase II trials.

Recently we completed the ECG-ischemia monitoring substudy of the PURSUIT trial (**P**latelet IIb-IIIa in **U**nstable angina: **R**eceptor **S**uppression **U**sing **I**ntegrilin **T**herapy)[9]. In this trial, 9461 patients with refractory unstable angina or evolving myocardial infarction without ST elevation were treated with eptifibatide, (a platelet glycoprotein IIb-IIIa receptor blocker) or placebo during 3-4 days. Eptifibatide reduced the event rate of death or (re)infarction at 30 days from 15.7% to 14.2% (p 0.042). A subset of 216 patients (2.3%) underwent continuous standard 12-lead ECG-ischemia monitoring (Mortara system) from start of treatment until 24 hours later. There was no demonstrable effect of eptifibatide on ischemic burden. At 7 days, 30 days and 6 months

follow-up, death or myocardial infarction occurred in 21, 33, and 38 patients respectively. These patients had significantly more frequent recurrent ischemic episodes and a higher ischemic burden compared with those without events. Significance was greatest at 6 months follow-up. This study confirmed our results of the CAPTURE ECG-ischemia monitoring substudy, that recurrent ischemia and ischemic burden quantified by continuous 12-lead ECG-monitoring are significant predictors of both death and myocardial infarction.

TECHNICAL ASPECTS OF COMPUTER-ASSISTED CONTINUOUS ECG-ISCHEMIA MONITORING

Computer-assisted continuous multilead and vectorcardiographic ECG-ischemia monitoring use continuous ECG sampling and averaging techniques, which offer an accurate continuous real-time measurement of the QRS complex and ST segments. This has resulted in a major improvement in the quality of the analysis compared to conventional ECG recording- and monitoring techniques. However, the user should appreciate the differences that exist between conventional ECG recording techniques and the various computer-assisted systems. Conventional techniques (e.g. Holter) measure the ST level from individual beats of the real-time ECG and subsequently average these measurements over fixed time intervals (generally 15 seconds to 1 minute). In contrast, computer-assisted techniques average a number of ECG complexes in a preset time interval and subsequently calculate the ST level. Proper beat selection with exclusion of noisy beats can be done before averaging, resulting in more robust and accurate measurements. Conventional techniques will be more sensitive to abrupt ST changes, thus more easily triggering on minor ECG variations. In a noisy ECG environment, such technique will also be most sensitive to noise. This is illustrated by the results of GUSTO-I ECG-ischemia monitoring substudy (chapter 2). Holter ECG recording detected the moment of 50% ST recovery earlier (but not more accurately) than vectorcardiographic or 12-lead ECG-ischemia monitoring. It also detected more recurrent ST episodes (in 55% versus 33% of patients, chapter 3). Thus, for correct interpretation of the signal, users should be aware of the characteristics of the device used. Adaptation of the ST analysis criteria to the individual characteristics of each device and to the demands of the user and the site of

monitoring may result in optimal predictive performance and clinical usefulness.

In general, computer-assisted ECG-ischemia monitoring systems will render good quality ECG recordings and analyses at a preset time interval of 1 minute averaging. However, in some situations, such as ECG-ischemia monitoring during coronary angiography or PTCA, this time interval will be too long for detection of procedure related short episodes of ischemia. Fifteen seconds averaging may then be preferred. If the sampling time interval of a computer-assisted system is set at a too long interval (e.g. 5 minutes instead of 1), the system will "overlook" shorter episodes of ischemia, resulting in less accurate detection of ischemic burden.

THERAPEUTIC IMPLICATIONS AND FUTURE DIRECTIONS

Continuous computer-assisted ECG-ischemia monitoring has become a mature noninvasive method to monitor of the perfusion status of the myocardium in patients with acute coronary syndromes. The technique may help to select patients at high risk for clinical events and assist the clinician to select optimal treatment. Such treatment should focus on rapid achievement of reperfusion or resolution of ischemia and should be tailored to the optimal risk benefit ratio in the individual patient.

In patients with evolving myocardial infarction, ECG-ischemia monitoring can help discriminate patients with stable reperfusion from those who do not exhibit any signs of reperfusion or patients who reperfused but develop early re-ischemia, often caused by reocclusion. In the patients who have stable reperfusion early after initiation of thrombolytic therapy, it may be decided to stop infusion of the thrombolytic in order to reduce the hazard of intracranial bleeding and to save costs[10,11]. Those patients with persistent occlusion may benefit from subsequent rescue PTCA, although this has not been proven definitely. Finally, patients with re-ischemia following initial reperfusion may benefit from subsequent treatment with a platelet glycoprotein IIb-IIIa receptor blocker such as abciximab, and from immediate or early angiography and PTCA[12].

Patients with unstable angina who exhibit recurrent ischemia during continuous ECG-ischemia monitoring may benefit from additional treatment with abciximab or other IIb-IIIa receptor blockers, followed by early PTCA.

In patients without recurrent ischemia, coronary angiography and / or PTCA may not be necessary, or may be deferred in order to allow for further plaque stabilization with subsequent reduction of procedural risk.

The following case example illustrates the clinical power of continuous ECG-ischemia monitoring in a patient with an acute coronary syndrome[13]:

Patient history

A 48-year-old man was admitted to our cardiac care unit following a resuscitation procedure. An accompanying friend informed us that complaints of chest pain had been present for approximately 4 hours. The patient intended to visit our outpatient clinic but suddenly collapsed on his way to the reception desk. He was successfully resuscitated from ventricular fibrillation and subsequently intubated because of respiratory arrest. The 12-lead ECG demonstrated ST elevations both in the inferior leads and in V1, V2, and V3, suggesting acute inferior wall myocardial infarction with right ventricular involvement.

On admission to the coronary care unit, the patient was still unconscious and not breathing spontaneously, rendering respiration support necessary. The hemodynamic situation was not compromised. Subsequently, thrombolytic therapy with rt-PA was initiated and the patient was connected to a continuous vectorcardiographic ECG monitoring system (Coronet, Ortivus Medical, Täby, Sweden).

One hour later, the patient again needed resuscitation, because of episodes of recurrent ventricular fibrillation (Figure 1). Until the moment of recurrence of ventricular fibrillation, the continuous ECG recording had not shown any ST segment recovery (Figure 2, ECG B). However, following resuscitation the ECG improved dramatically, with almost complete ST segment recovery of all involved leads, suggesting that reperfusion actually had occurred on the moment of recurrent ventricular fibrillation (Figure 2, ECG C). Unfortunately, this reperfusion period only lasted for a few minutes. Thereafter the ST segment re-elevated, with more pronounced involvement of leads V2 and V3, and lead V4 showing ST elevation instead of depression (Figure 2, ECG D). Subsequently angiography was performed with the intention to perform PTCA if possible.

At coronary angiography, a proximally occluded right coronary artery was found, which opened up immediately at first injection of contrast. As the vessel

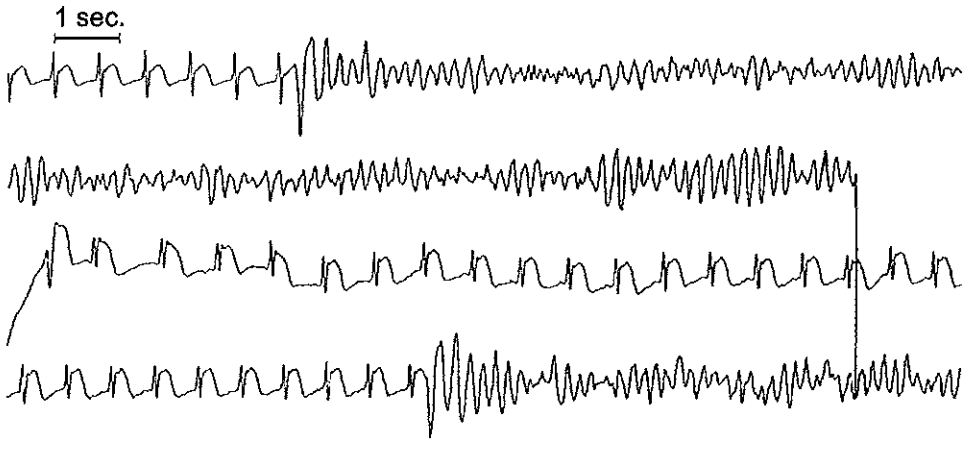

Figure 1. ECG monitoring strip, recorded during the second resuscitation procedure, one hour following initiation of thrombolytic therapy (see case report). Sinus rhythm is present with a sudden occurrence of ventricular fibrillation, terminated by DC shock. Subsequently a new episode of ventricular fibrillation occurs, again terminated by DC shock (the latter not shown).

appeared to be diffusely narrowed and TIMI 2 flow was obtained (which was considered adequate at that time in 1994), no further balloon dilatation was performed. The left descending coronary artery demonstrated a 50-90% luminal narrowing directly following the first diagonal branch, which also had a 90-99% narrowing. The left circumflex artery did not show any significant obstructions.

Upon return to the cardiac care unit, the ECG had recovered completely (Figure 2, ECG E). However, 10 minutes later ST elevation occurred again, accompanied by hypotension and low left ventricular filling pressures. Because of the diffuse two vessel coronary artery disease, it was decided not to undertake a new invasive procedure. The patient was successfully treated with additional intravenous heparin, nitroglycerin and fluid-loading (Figure 2, ECG G). The next morning, the patient appeared alert and hemodynamically and electrocardiographically stable. He was successfully weaned from the respirator and extubated. No signs of post-anoxic cerebral dysfunction were noted, and the patient was feeling well. Maximal serum cardiac protein indices for creatine kinase, αHbDH and ASAT were 4100, 337 and 179 U/L, respectively.

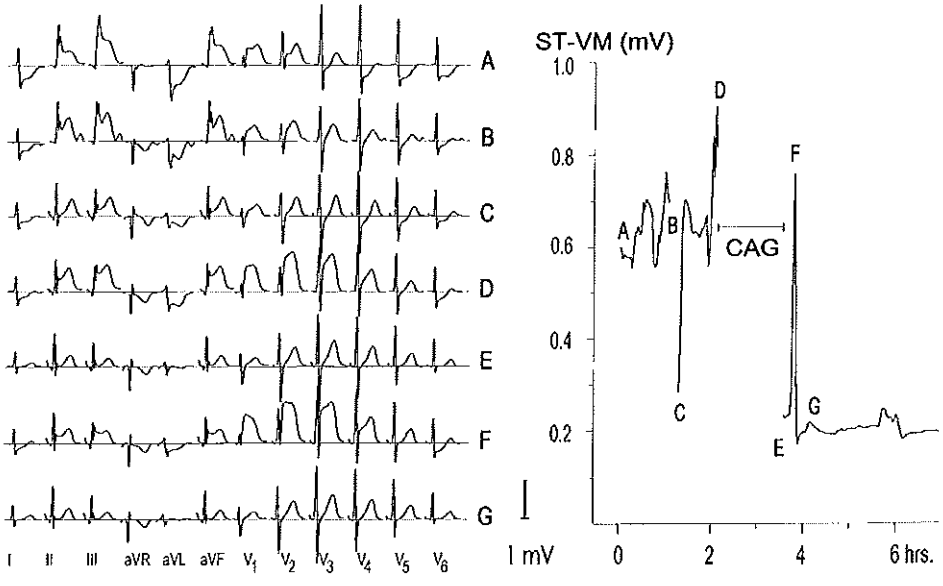

Figure 2. ST vector-magnitude trend (ST-VM) of the patient described. The ST vector-magnitude is the magnitude of the sum ST vector, calculated from Frank's orthogonal X, Y and Z leads. Letters A-G indicate the moments of interest with actual 12-lead ECG. For further explanation, see text.

Three days later, the patient again experienced anginal pain. The continuous ECG recording demonstrated recurrent ST segment elevation in the precordial leads, but not inferior. The patient was treated with intravenous rt-PA. Subsequently, the pain subsided and the ECG normalized, suggesting that stable reperfusion had been obtained. Following this recurrence of coronary reocclusion, the patient was referred for coronary artery bypass surgery, which was successfully performed the next day.

This case history clearly illustrates the clinical power of computer-assisted continuous ECG monitoring techniques for tailoring of therapeutic strategies in patients with acute myocardial infarction. It also demonstrates the limitations of other noninvasive markers such as chest pain and reperfusion arrhythmias. As the patient was connected to a respirator, the monitoring of presence or absence of residual chest pain was impossible. Complaints would have been difficult to interpret anyhow, because of additional complaints caused by the

resuscitation procedure. The occurrence of ventricular fibrillation in the setting of acute coronary (re)occlusion has almost certainly been the cause of the first collapse of this patient at our outpatient clinic. The second period of ventricular fibrillation however, resulted from reperfusion of the infarct-related artery. This is supported by the fact that complete ST recovery was present directly following this episode. Thus, both (re)occlusion and reperfusion induced ventricular fibrillation in this patient.

Finally, this case report also demonstrates that predictive accuracy of continuous ECG monitoring is very accurate if high initial ST levels are encountered. Continuous ECG-ischemia monitoring may thus lead to selection of specific reperfusion and anti-ischemic strategies. As such, continuous computer-assisted ECG-ischemia monitoring should be an integrated part of the treatment protocols at emergency wards and coronary care units. The technique may also become of substantial value for the peri-operative monitoring of patients undergoing coronary bypass surgery or major peripheral vascular surgery[14].

Early risk assessment in patients with chest pain

Evaluation of patients admitted with acute chest pain is time consuming and expensive, while a substantial proportion of these patients do not really suffer from an acute coronary syndrome[15]. Van Miltenburg reported on a study of 417 patients consecutively admitted for chest pain suggestive of an acute coronary syndrome. Thirty-eight of these patients (9%) eventually appeared to have a myocardial infarction, 270 patients (65%) had unstable angina and 109 (26%) had non-cardiac or non-specific chest pain. The first two groups represent patients with an acute coronary syndrome who are at risk for an adverse cardiac event, thus requiring high care treatment (74%), whereas the third group (26%) includes patients at low risk for cardiac events who might be discharged after appropriate risk stratification. Early risk stratification may thus both improve patient care and reduce costs.

Such early risk stratification can be achieved through different bedside methods, including assessment of the clinical status and complaints of the patient, information obtained from the admission ECG, and bedside essays of chemical markers of myocardial damage such as creatine-kinase MB or troponin T and I[16-21]. Bedside tests for detection of these cardiac-specific

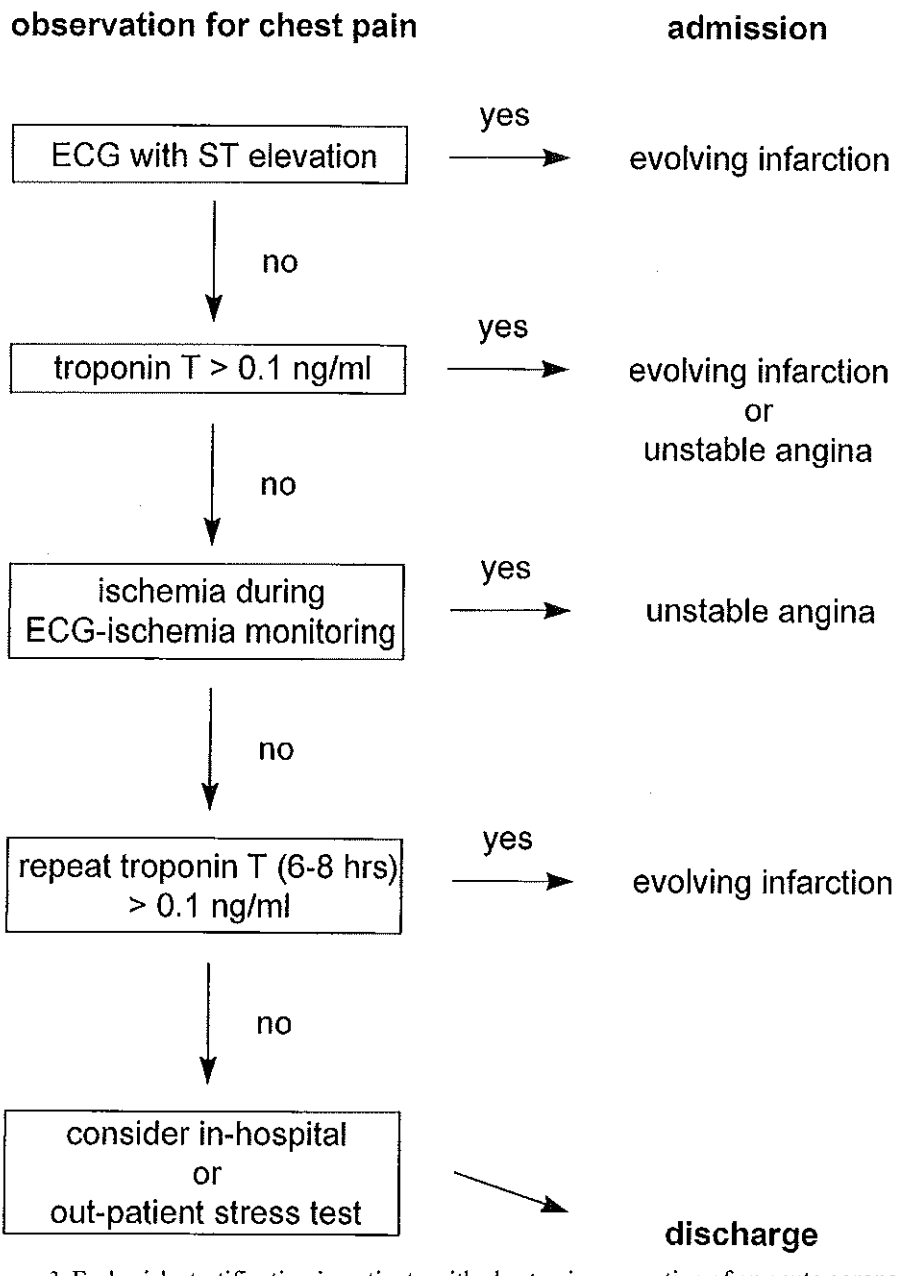

Figure 3. Early risk stratification in patients with chest pain suggestive of an acute coronary syndrome.

Table 1. Prognostic value of the admission ECG for early risk stratification in 12.142 patients with an acute coronary syndrome. Death and (re)infarction at 30 days follow-up (GUSTO IIb trial)[23].

	ST-elev. +ST-depr.	ST-elevation	ST-depression	T-wave inversion	P-value
% of patients	15%	28%	35%	23%	
acute infarction on admission	87%	81%	47%	31%	< 0.0001
death (%)	6.8%	5.0%	5.0%	1.8%	< 0.001
(re-)infarction (%)	6.9%	5.1%	6.7%	4.3%	< 0.001

troponins appear highly sensitive for the early detection of minimal myocardial cell injury in acute coronary syndromes[16,18,21]. Patients with unstable angina who present with elevated troponin T / I levels on admission have a worse short and long term prognosis[18,20]. In contrast, negative troponin test results on admission and 6 hours later in patients with chest pain without ST elevation are associated with low risk of adverse cardiac events and may allow safe and early discharge of these patients[19]. Recently, also early dobutamine-atropine stress echocardiography has been suggested for early risk assessment[22].

The standard 12-lead admission ECG does provide direct prognostic information. In patients with an acute coronary syndrome, the presence of ST elevation with or without concomitant ST depression most commonly reflects evolving myocardial infarction (87%, Table 1) having the highest rate of mortality within 30 days (6.8%)[23,24]. Patients with isolated ST depression end up with mortality rates of 5.0% and almost half of them (47%) have an evolving myocardial infarction on admission. In patients with unstable angina without evidence of an acute myocardial infarction, ST segment depression on the admission ECG (regardless its severity) is highly predictive of an in-hospital adverse cardiac outcome, while the presence of isolated T wave inversion indicates a favorable prognosis, as well as a normal admission ECG[25,26].

In patients who present with chest pain suggestive of an acute coronary syndrome, the presence of transient ischemia during continuous ECG-ischemia monitoring after an initially inconclusive admission ECG may provide important additional information for risk stratification (chapter 7). Continuous

ECG-ischemia monitoring can easily be combined with simultaneous serial creatine kinase MB and / or troponin T or I measurements. Recently, an emergency department protocol for rapidly ruling out myocardial ischemia in patients admitted with chest pain has been proposed (Figure 3)[22]. Patients with negative findings of the different tests have a low risk profile and may thus be discharged from hospital within 12 hours following admission. If one of the tests is positive for ischemia, an acute coronary syndrome is diagnosed. The latter patients should receive intensive treatment with continuation of ECG-ischemia monitoring. Patients who subsequently appear to stabilize on medical therapy, not having recurrences of ischemia, as well as patients without elevated troponin T levels[18,20], have a low risk of myocardial infarction and death, particularly when treated with a glycoprotein IIb-IIIa receptor blocker[27-29]. It is questionable whether early angiography and PTCA is necessary in these patients[30]. In contrast, patients with recurrent ischemia during ECG-ischemia monitoring (as well as patients with elevated troponin T levels) exhibit a higher risk of myocardial infarction or death (chapter 7)[27]. This suggests that such patients will benefit from immediate or urgent invasive therapy.

Future study and systematic application of the combined use of ECG-ischemia monitoring, serial measurement of troponin T levels and early dobutamine-atropine stress echocardiography may help to improve the early care of patients with a suspected acute coronary syndrome.

CONCLUSIONS

Continuous ECG-ischemia monitoring should become an integrated part of the standard care protocols at emergency wards, pre-coronary care or chest pain units and coronary care units. The technique is of use for early diagnosis and risk assessment in patients with chest pain suggestive of an acute coronary syndrome and for subsequent identification of low and high risk patients with an acute coronary syndrome. It may guide medical and invasive therapy in these patients.

The accuracy of continuous ECG-ischemia monitoring to predict vessel status in patients with evolving myocardial infarction is best if high initial

ST elevation is present and an "ischemic reference ECG" can be obtained. Thus, continuous ECG monitoring should be started as soon as possible, preferably before the initiation of thrombolytic therapy (myocardial infarction) or at the moment of ischemia (unstable angina), although it should not delay the onset of therapy. Full integration of continuous ECG-ischemia monitoring in emergency wards and coronary care units will greatly enhance further clinical usefulness, predictive performance and monitoring possibilities of these systems.

REFERENCES

1. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673-82.
2. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329(22): 1615-22.
3. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. Circulation 1995; 91(6): 1659-68.
4. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker of early unfavourable outcomes in patients with unstable angina. N Engl J Med 1986; 314: 1214-9.
5. 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.
6. Davies MJ, Thomas AC. Plaque fissuring - the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985; 53: 363-73.
7. 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.
8. The CAPTURE investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-35.
9. Klootwijk P, Krucoff MW, Akkerhuis M, Maas A, Meij S, Melkert R, Califf RM, Simoons ML. Recurrent ischemia in patients with unstable angina or myocardial infarction without ST-elevation treated with eptifibatide predicts mortality and (re)infarction. A report from the PURSUIT study. Eur Heart J 1998; 19, suppl (abstract): 3419.

10. Arnold AER, van der Vlugt MJ, Boersma H, Barrett MJ, Burgersdijk C, Simoons ML. Tailored thrombolytic therapy for evolving myocardial infarction: stopping alteplase infusion on signs of reperfusion. Eur Heart J 1995; 16, suppl (abstract): 132.
11. Simoons ML, Arnold AE. Tailored thrombolytic therapy. A perspective. Circulation 1993; 88(6): 2556-64.
12. Madsen JK, Grande P, Saunamaki K, Thayssen P, Kassis E, Eriksen U, Rasmussen K, Haunso S, Nielsen TT, Haghfelt T, Fritz-Hansen P, Hjelms E, Paulsen PK, Alstrup P, Arendrup H, Niebuhr-Jorgensen U, Andersen LI. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). DANish trial in Acute Myocardial Infarction. Circulation 1997; 96(3): 748-55.
13. Klootwijk APJ, Kint PP. Dynamic computer assisted ECG monitoring of the coronary artery status in acute myocardial infarction. The Thoraxcentre Journal 1994; 6(3):28-30.
14. Poldermans D, Meij S, Klootwijk P, Peterse AM, van de Ven LMM, Boersma E, Leendertse K, van Sambeek M, van Urk H, Simoons ML. Correlation between pre- and peri-operative myocardial ischaemia detected in patients undergoing major vascular surgery by dobutamine stress echocardiography and continuous 12-lead electrocardiography. Eur Heart J 1998; 19, suppl (abstract): P2260.
15. v. Miltenburg-van Zijl. Management policies and prognosis in unstable angina pectoris: use of coronary angiography in different practice settings. Thesis, Rotterdam, The Netherlands 1992: 33-57.
16. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P; Peheim E, Ljungdahl L, Goldmann B, Katus HA. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992; 327(3): 146-50.
17. Antman EM, Braunwald E, Cannon CP, McCabe CH, Rifai N, Sacks DB. Time to positivity of a rapid bedside assay for cardiac-specific troponin T predicts prognosis in acute coronary syndromes: a Thrombolysis in Myocardial Infarction (TIMI) 11A substudy. J Am Coll Cardiol 1998; 31(2): 326-30.
18. Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. Circulation 1996;93(9): 1651-7.
19. Hamm CW, Meinertz T, Berger J, Kreymann G, Heeschen C, Goldmann BU. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997; 337 (23): 1648-53.
20. Ohman EM, Topol EJ, Califf RM, Harrell FE Jr, Kleiman NS, Wagner GS, O'Hanesian MA, Hamm CW, Katus HA, Granger CB, Christenson RH, Armstrong PW., for the GUSTO IIA Investigators. Cardiac troponin T levels for risk stratification in acute myocardial ischemia.. N Engl J Med 1996; 335(18): 1333-41.
21. Antman EM, Braunwald E, Wybenga D, Thompson C, Fung AY, Fischer GA, Cannon CP, McCabe CH, Schactman M, Thompson B, Tanasijevic MJ. Cardiac-specific troponin

I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 335(18): 1342-9.
22. Geleijnse ML, Elhendy A, Kasprzak JD, Rambaldi R, van Domburg RT, Cornel JH, Klootwijk APJ, Fioretti PM, Roelandt JRTC, Simoons ML. Safety and prognostic value of early dobutamine-atropine stress echocardiography in patients with spontaneous chest pain and a nondiagnostic electrocardiogram. Submitted.
23. Savonitto S, Ardissino D, Ottani F, Prando M, Mafrici A, Merlini PA, Vahanian A, Van de Werf F, Granger C, Thompson T, Califf R, Topol EJ, on behalf of GUSTO-IIb Investigators. Prognostic value of the admission electrocardiogram in acute coronary syndromes. Results from the GUSTO-IIb trial. Eur Heart J 1997; 18, suppl (abstract): 812.
24. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996; 12; 335: 775-82.
25. Patel DJ, Holdright DR, Knight CJ, Mulcahy D, Thakrar B, Wright C, Sparrow J, Wicks M, Hubbard W, Thomas R, Sutton GC, Hendry G, Purcell H, Fox K. Early continuous ST segment monitoring in unstable angina: prognostic value additional to the clinical characteristics and the admission electrocardiogram. Heart 1996; 75(3): 222-8.
26. Patel DJ, Knight CJ, Holdright DR, Mulcahy D, Clarke D, Wright C, Purcell H, Fox KM. Long-term prognosis in unstable angina. The importance of early risk stratification using continuous ST segment monitoring. Eur Heart J 1998; 19(2): 240-9.
27. 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.
28. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998; 338: 1488-97.
29. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338: 1498-1505.
30. Boden WE, Dai H, on behalf of the VANQWISH Trial Investigators. Long-term outcomes in non-Q-wave infarction patients randomized to an "invasive" versus "conservative" strategy: results of the multicentre VA non-Q-wave infarction strategies in-hospital (VANQWISH) trial. Eur Heart J 1997; 18, suppl (abstract): 1967.

Samenvatting

Hoofdstuk 1
Gezien de mogelijkheden voor behandeling met thrombolyse en intracoronaire interventie bij patiënten met acute coronaire syndromen, is het voor de keuze en aanpassing van de therapie belangrijk om geïnformeerd te worden over de status van het betrokken coronair vat en de mate van myocard perfusie. Het ECG en met name het vervolgen van het ST segment in de tijd is hiervoor een eenvoudige methode. Continue computerondersteunde (digitale) multilead ECG monitoring technieken hebben inmiddels de beperkingen van eerdere ECG technieken overwonnen. Dit promotieonderzoek bestudeert de technische mogelijkheden (en beperkingen) alsook de klinische bruikbaarheid van deze nieuwe ECG systemen.

Hoofdstuk 2
Als onderdeel van de GUSTO-I studie (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries), waarin vier verschillende thrombolytische regimes werden vergeleken bij patiënten met een acuut hartinfarct, ondergingen 1064 patiënten continue ECG monitoring: 406 patiënten met een vectorafgeleid 12-afleidingen ECG systeem, 373 patiënten met een 12-afleidingen systeem en 288 patiënten met een 3-afleidingen Holter systeem. Hiervan ondergingen 302 patiënten 90 of 180 minuten na het starten van thrombolytische behandeling een coronair angiografie. In dit hoofdstuk wordt aangetoond dat een snelle afname van de ST segment elevatie of depressie tijdens continue ECG monitoring een goede voorspeller is van reperfusie van het infarct gerelateerde coronair vat. Afwezigheid van herstel of laat herstel van het ST segment suggereert persisterende occlusie. Continue ECG-ischemie monitoring is vooral informatief bij patiënten met uitgebreide ST segment elevaties bij aanvang van de monitoring periode. Bij deze patiëntengroep, die het grootste risico heeft op cardiale complicaties en het meeste baat heeft van reperfusie therapie, bleek de voorspelling van de toestand van het betrokken coronair vat in 79-100% correct. Alhoewel de drie ECG systemen aanzienlijk verschilden in signaal bewerking werden geen belangrijke verschillen tussen betrouwbaarheid van de systemen aangetoond. De studie laat zien dat het

mogelijk is om bij patiënten met een acuut hartinfarct de keuze en de intensiteit van de reperfusie behandeling te bepalen op geleide van de bevindingen van continue ECG-ischemie monitoring.

Hoofdstuk 3
In dit hoofdstuk wordt de snelheid en de stabiliteit van het herstel van het ST segment tijdens continue ECG monitoring vergeleken bij de vier verschillende thrombolytische strategieën in de GUSTO-I studie. De verwachting was dat patiënten die werden behandeld volgens het protocol van versnelde rt-PA toediening een sneller herstel van het ST segment zouden laten zien dan de patiënten die werden behandeld volgens de andere protocollen. Van de patiënten die werden behandeld met streptokinase werd een stabieler herstel van het ST segment verwacht. Alhoewel de angiografische substudie van GUSTO-I inderdaad aantoonde dat versnelde rt-PA toediening resulteerde in een snellere opening van het infarct gerelateerde coronair vat, konden we deze bevinding niet correleren met een sneller herstel van het ST segment in deze patiëntengroep. Dit werd voornamelijk veroorzaakt door technische beperkingen en het gebruik van drie verschillende ECG monitoring technieken.

Hoofdstuk 4
In ongeveer 36% van de GUSTO-I ST monitoring substudie patiënten ontstonden tijdens continue ECG monitoring na een initieel herstel van het ST segment opnieuw ST segment veranderingen (voornamelijk ST elevatie) suggestief voor re-ischemie of re-occlusie van het infarct gerelateerde coronair vat. In dit hoofdstuk werd onderzocht of deze patiënten een grotere kans hebben om te overlijden in vergelijking met patiënten zonder re-ischemie of re-occlusie. Het bleek dat bij patiënten met een initieel herstel van het ST segment (reperfusie), de sterftekans zowel na 30 dagen als na 1 jaar het grootst was als er opnieuw ST segment veranderingen waren opgetreden suggestief voor re-ischemie of re-occlusie. De duur van de ST segment verandering bleek direct gerelateerd aan de sterftekans. Continue ECG monitoring is derhalve niet alleen bruikbaar voor de selectie van hoog risico patiënten die geen tekenen van reperfusie vertonen, maar ook voor de selectie van hoog risico patiënten met tekenen van reperfusie en vervolgens aanwijzingen voor re-ischemie en / of re-occlusie.

Hoofdstuk 5

Bij patiënten met onstabiele angina pectoris kan de plaats van het ischemische gebied variëren, afhankelijk van de verdeling van de doorstroming van het coronair systeem, de mate van de coronaire vaatwand beschadiging en de duur en ernst van de ischemie. Omdat het aantal en de keuze van de ECG afleidingen tijdens continue ECG monitoring de detectie en kwantificering van ischemie kunnen beïnvloeden werd onderzocht in hoeverre 12 afleidingen ECG monitoring bij deze patiëntengroep de voorkeur verdient. Continue 48-uurs 12 afleidingen ECG monitoring (zonder aVR) werd bij 130 patiënten met onstabiele angina pectoris vergeleken met de frequenter gebruikte 3 afleidingen ECG monitoring.

Twaalf afleidingen ECG monitoring bleek gevoeliger dan de 3 afleidingen technologie, die over het algemeen wordt gebruikt op hartbewakings- en intensive care afdelingen. Met 3 afleidingen werd in 62% van de patiënten ischemie gedetecteerd, terwijl dit met 12 afleidingen in 77% van de patiënten het geval was. Ook het aantal en de duur van de ischemische episodes nam toe bij het gebruik van 12 afleidingen. Van belang was dat de ST veranderingen verspreid over de afleidingen optraden en in de tijd verschoven naar andere afleidingen bij ten minste 31% van de patiënten die ST episodes hadden. Dit bevestigde de noodzaak voor registratie van zoveel mogelijk afleidingen (of vectorcardiografische afleidingen) bij patiënten met onstabiele angina pectoris.

Hoofdstuk 6

Bij patiënten met onstabiele angina pectoris kan myocard ischemie ontstaan ten gevolge van bloedplaatjes aggregatie en intracoronaire thrombose ter plaatse van een fissuur of ruptuur van een plaque in een coronair arterie. Re-ischemie tijdens continue ECG monitoring zou derhalve episodes van bloedplaatjes aggregatie kunnen reflecteren. In dit en het volgende hoofdstuk worden twee studies met continue ECG monitoring beschreven bij patiënten met onstabiele angina. In de eerste studie wordt de therapeutische effectiviteit van efegatran, een direct anti-thrombine, vergeleken met heparine, en in de tweede studie de effectiviteit van abciximab, een glycoproteïne IIb-IIIa bloedplaatjes receptor blokker (hoofdstuk 7).

Efegatran werd geëvalueerd in 432 patiënten met onstabiele angina.

Klinische eindpunten waren: nieuwe episodes van angina, hartinfarct, coronaire interventie (PTCA of CABG), en dood. Er bleek geen aantoonbaar verschil in cardiovasculaire of bloedingscomplicaties te bestaan tussen de met efegatran en heparine behandelde patiënten. Ook was er vergeleken met heparine geen reductie van myocard ischemie tijdens continue ECG monitoring. De studie werd beperkt door het grote aantal patiënten met een hartinfarct op het moment van inclusie in de studie (13.4%). Het optreden van een hartinfarct na inclusie was vervolgens laag (3.2%). Een relatie tussen klinische eindpunten en de aanwezigheid van ischemie of de ernst van de ischemie ("ischemic burden") tijdens ECG monitoring kon niet worden aangetoond.

Hoofdstuk 7

In the CAPTURE trial (c7E3 Fab Anti Platelet Therapy in Unstable REfractory angina) werden 1265 patiënten met refractaire onstabiele angina pectoris behandeld met abciximab (c7E3 Fab, ReoPro) of placebo (toegevoegd aan de standaard behandeling) van 16-24 uur voorafgaand aan een coronaire interventie (PTCA of stent implantatie) tot 1 uur er na. Behandeling met abciximab resulteerde in 50% reductie van het aantal patiënten met een hartinfarct (van 8.2% naar 4.1%) en 29% reductie van het primaire samengestelde eindpunt van dood, hartinfarct of urgente (re-)interventie 30 dagen later (van 15.9% naar 11.3%).

Driehonderdtweeëndertig van deze 1265 patiënten (26%) ondergingen continue vectorafgeleide 12-afleidingen ECG monitoring. Het bleek dat behandeling met abciximab resulteerde in een reductie van frequente ischemie en een reductie van de totale ischemische last ("ischemic burden"). Patiënten met re-ischemie tijdens de ST monitoring periode voorafgaand aan de PTCA hadden een grotere kans om binnen 5 dagen te overlijden of een hartinfarct te krijgen. Ook na 30 dagen follow-up bleek deze kans nog steeds verhoogd.

Deze studie laat zien dat ischemie, gedetecteerd door middel van vectorafgeleide 12-afleidingen ECG monitoring kan worden gebruikt voor risico stratificatie bij patiënten met onstabiele coronaire syndromen en als een studie eindpunt in fase II studies.

Hoofdstuk 8

In dit hoofdstuk worden de conclusies van het proefschrift samengevat. Continue ECG monitoring is bruikbaar voor snelle diagnose en risico stratificatie

bij patiënten met pijn op de borst en voor identificatie van laag en hoog risico patiënten met een acuut coronair syndroom. Continue ECG monitoring dient derhalve onderdeel te zijn van de behandelprotocollen op spoedeisende hulp afdelingen, pre-coronary care en coronary care units. Volledige integratie van continue ECG monitoring systemen op deze afdelingen zal de klinische bruikbaarheid en de toepassingen van deze systemen aanzienlijk doen toenemen.

Dankwoord

Old paint on canvas, as it ages, sometimes becomes transparent. When that happens it is possible, in some pictures, to see the original lines: a tree will show through a woman's dress, a child makes way for a dog, a large boat is no longer on an open sea. This is where the painter "repainted", changed his mind. Perhaps it would be as well to say that the old conception, replaced by a later choice, is a way of seeing and then seeing again.

Lillian Hellman

Als de tekst van dit proefschrift "transparant" zou zijn en de originele lijnen zichtbaar, dan zouden de bijdragen van de vele mensen die direct of indirect betrokken waren bij de totstandkoming ervan nog goed te zien zijn. Maar de "verf" van dit proefschrift is vers en *"The old conceptions are replaced by a later choice"*: de veranderingen en toevoegingen die in de loop der tijd plaats vonden zijn veelal niet meer zichtbaar en gingen op in het geheel. Met dit gevoel en zonder volledig te kunnen zijn, wil ik graag een aantal mensen in het bijzonder bedanken:

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Curriculum vitae

Peter Klootwijk was born on February 3, 1951 in Rotterdam, The Netherlands. He completed his preparatory academic education in 1969 at the Christelijk Lyceum "De Populier" (Gymnasium ß division) in The Hague and started his medical training at the Erasmus University in Rotterdam that same year. In 1976 he passed his final examinations in medicine and became a fellow of Internal Medicine at the St. Franciscus Gasthuis in Rotterdam (supervisor dr. M. de Jong). In 1979 he started his training in cardiology at the Thoraxcentre of the University Hospital Dijkzigt in Rotterdam under Professor P.G. Hugenholtz. In 1982 he received his certificate as a cardiologist from the Committee for the Registration of Specialists of the Royal Netherlands Medical Association.

Since 1982 until present, the author works as a staffmember of the Department of Cardiology at the Thoraxcentre of the University Hospital Dijkzigt in Rotterdam, with special interest in the field of electrocardiography. He also supervises the central ambulatory Holter ECG scanning service of Cardiolab and the ECG core-laboratory of Cardialysis Rotterdam.

The author is happily married to Jolanda Ruchti and together they have three children, Mark, Sandra and Alex, and a big black dog named Bobo.

Publications

Roelandt J, *Klootwijk P.* Holter electrocardiografie. Cordiaal 1981; 2: 27-32.

Klootwijk APJ, Roelandt JRTC. ECG registratie per telefoon voor de beoordeling van patienten met klachten verdacht voor ritmestoornissen. Ned Tijdschr Geneesk 1983; 127: 545-9.

Roelandt J, *Klootwijk P*, Lubsen J, Janse MJ. Sudden death during longterm ambulatory monitoring. Eur Heart J. 1984; 5: 7-20.

Roelandt J, *Klootwijk P*, Lubsen J. Documentazione della morte improvvisa cardiaca mediante elettrocardiografia di Holter. Le nuove frontiere delle aritmie. Padova 1984: 667-74.

Klootwijk P, Roelandt J, Telefonische ECG-registratie bij klachten verdacht voor ritmestoornissen. In: Roelandt en Lubsen, Ambulante 24-uurs electrocardiografie. 1985; 31-6.

Klootwijk P, Leenders CM, Roelandt J. Usefulness of transtelephonic documentation of the electrocardiogram during sporadic symptoms suggestive of cardiac arrhythmias. Int. J. Card 1986; 13: 155-61.

Koudstaal PJ, v. Gijn J, *Klootwijk APJ*, v. der Meché FGA, Kapelle LJ. Holter monitoring in patients with transient and focal ischemic attacks of the brain. Stroke 1986; 17(2): 192-5.

Klootwijk APJ, Simoons ML. Medicamenteuze behandeling van angina pectoris. Geneesmiddelenbulletin 1987, 21(4) (28 maart 1987).

Klootwijk APJ. Quarterly Holter: Solving clinical problems with longterm ambulatory ecg recordings. The Thoraxcentre Journal 1990; 2(1): 26-7.

Klootwijk APJ. Quarterly holter: Solving clinical problems with transtelephonic ecg recordings. The Thoraxcentre Journal 1990; 2(2): 24-5.

Klootwijk APJ. Quarterly holter: Symptoms and cardiac arrhythmias, correlation or coincidence? The Thoraxcentre Journal 1990; 2(3): 22-3.

Klootwijk APJ. Quarterly Holter: Sudden cardiac death during longterm ambulatory ECG monitoring. The Thoraxcentre Journal 1990; 2: 18-20.

Klootwijk APJ. Quarterly Holter: Drug-induced Torsade de Pointes documented during ambulatory ECG recording. The Thoraxcentre Journal 1991; 3: 15-7.

Klootwijk APJ. Quarterly Holter: Sick sinus syndrome, documented during long-term ambulatory ECG recording. The Thoraxcentre Journal 1991; 3: 18-9.

Klootwijk APJ. Quarterly Holter: Long term ambulatory continuous ST recording in a patient with atypical chest pain. The Thoraxcentre Journal 1991; 3: 10-2.

Klootwijk APJ. Quarterly Holter: Cardiac arrhythmias and topical drug application: the "overlooked" eye-drops. The Thoraxcentre Journal 1991; 3: 16-8.

Klootwijk APJ, Circadiaanse ritmen van cardiovasculaire aandoeningen. Cardiovisie Nederland, Excerpta Medica 1991; 8: 1-2.

Klootwijk APJ. Quarterly Holter: Cardiac arrhythmias as the first manifestation of heart disease. The Thoraxcentre Journal 1992; 4: 8-9.

Klootwijk APJ. Quarterly Holter: A coachman who dropped dead from his coach. Physical training and cardiac arrhythmias. The Thoraxcentre Journal 1992; 4: 47-49.

Klootwijk APJ. Quarterly Holter: Asymptomatic WPW syndrome becomes symptomatic during physical activities. The Thoraxcentre Journal 1992; 4: 102-4.

Klootwijk APJ. Arrhythmia special: Caffeine and arrhythmias. The Thoraxcentre Journal 1993; 5: 38-9,41.

Klootwijk APJ, Roelandt JRTC. Systemische bijwerkingen van oogdruppels: een onopvallende oorzaak van hartritmestoornissen. Ned Tijdschr. Cardiol 1992; 6: 145-8.

Klootwijk P, Cobbaert C, Fioretti P, Kint PP, Simoons ML. Noninvasive assessment of reperfusion and reocclusion after thrombolysis in acute myocardial infarction. Am J Cardiol 1993; 72: 75G-84G.

Krucoff MW, Green CL, Langer A, *Klootwijk P*, Trollinger KM, Sawchek ST *et al.* Global utilization of streptokinase and tPA for occluded arteries (GUSTO) ECG-monitoring substudy. Study design and technical considerations. J Electrocardiol 1993; 26(suppl): 249-55.

Luyten HE, *Klootwijk APJ.* Syncope and repeated non-diagnostic ambulatory electrocardiographic recordings. The Thoraxcentre Journal 1993/1994; 6: 15-6.

Klootwijk APJ, Kint PP. ECG special: Dynamic computer assisted ECG monitoring of the coronary artery status in acute myocardial infarction. The Thoraxcentre Journal 1994; 6: 28-30.

Meij SH, *Klootwijk P*, Arends J, Roelandt JRTC. An algorithm for automatic beat-to-beat measurement of the QT-interval. Computers in Cardiology Proceedings 1994.

Simoons ML, de Boer MJ, van den Brand MJBM, van Miltenburg AJM, Hoorntje JCA, Heyndrickx GR, v.der Wieken LR, de Bono D, Rutsch W, Schaible TF, Weisman HF, *Klootwijk P*, Nijssen KM, Stibbe J, de Feyter PJ, and the European Cooperative Study Group. Randomized trial of a IIB/IIIA platelet receptor blocker in refractory unstable angina. Circulation 1994; 89: 596-603.

Meij SH, *Klootwijk P*, van der Putten N, Laclé C, Arends J. Computer-aided analysis of ambulatory electrocardiograms. Cardiologie 1995; 11: 409-13.

Dekker JM, Schouten EG, *Klootwijk P*, Pool J, Kromhout D. Association between QT interval and coronary heartdisease in middle-aged and elderly men. The Zutphen Study. Circulation 1994;90(2):779-85. Comment in: Circulation 1995; 91: 564-65.

Dekker JM, Schouten EG, *Klootwijk P*, Pool J, Kromhout D. ST and T-wave characteristics as indicators of coronary heart disease risk. The Zutphen Study. J Am Coll Cardiol 1995; 25: 1321-6.

Dekker JM, Schouten EG, Kromhout D, *Klootwijk P*, Pool J. The Cardiac Infarction Injury Score and coronary heart disease in middle-aged and elderly men: the Zutphen Study. J Clin Epidemiol 1995; 48: 833-40.

Langer A, Krucoff MW, *Klootwijk P*, Veldkamp R, Simoons ML, Granger C, Califf RM, Armstrong PW. Noninvasive assessment of speed and stability

of infarct-related artery reperfusion: results of the GUSTO ST segment monitoring study. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1995; 25: 1552-7.

Nelwan S, Meij S, van Dam T, *Klootwijk P*, Simoons ML. A new ST ischemia monitoring system. The Thoraxcentre Journal 1996; 8: 23-7.

Dekker JM, Schouten EG, Pool J, *Klootwijk P*, Kromhout D. Het electrocardiogram en het risico op toekomstige coronarire hartziekten. Hart Bull 1996; 27: 57-60.

Dekker JM, Feskens EJ, Schouten EG, *Klootwijk P*, Pool J, Kromhout D. QTc duration is associated with levels of insulin and glucose intolerance. The Zutphen Elderly Study. Diabetes 1996; 45: 376-80.

Klootwijk P, Langer A,Meij S, Green C, Veldkamp RF, Ross AM, Armstrong PW,. Simoons ML, for the GUSTO-I ECG-ischemia 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: 689-98. Erratum in Eur Heart J 1996; 17: 1451; Comment in Eur Heart J 1997; 18: 348.

Klootwijk P, Meij S, v. Es GA, Müller EJ, Umans VAWM, Lenderink T, Simoons ML. Comparison of usefulness of computer assisted continuous 48-h 3-lead with 12-lead ECG-ischemia monitoring for detection and quantitation of ischaemia in patients with unstable angina. Eur Heart J 1997; 18: 931-40.

Klootwijk P, Kint PP. Dynamische computerondersteunde ECG ST-bewaking. Cordiaal 1997; 18: 83-5.

Dekker JM; Schouten EG; *Klootwijk P*; Pool J; Swenne CA; Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. Am J Epidemiol 1997; 145: 899-908.

Cobbaert C, Hermens WT, Kint PP, *Klootwijk PJ*, Van de Werf F, Simoons ML. Thrombolysis-induced coronary reperfusion causes acute and massive interstitial release of cardiac muscle cell proteins. Cardiovasc Res 1997; 33: 147-55.

Langer A, Krucoff MW, *Klootwijk P*, Simoons ML, Granger CB, Barr A, Califf RM, Armstrong PW. Prognostic significance of ST-segment shift early after resolution of ST elevation in patients with myocardial infarction treated with thrombolytic therapy: the GUSTO-I ST Segment Monitoring Substudy. J Am Coll Cardiol 1998; 31: 783-9.

van Domburg RT, *Klootwijk P*, Deckers JW, van Bergen PFMM, Jonker JJC, Simoons ML. The Cardiac Infarction Injury Score as a predictor for long-term mortality in survivors of a myocardial Infarction. Eur Heart J 1998; 19: 1034-41.

Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). Circulation 1998; in press.

Moons KGM, *Klootwijk P*, Meij S, van Es, Baardman T, Lenderink T, van den Brand M, Habbema JDF, Grobbee DE, Simoons ML. Continuous ST-segment monitoring for prediction of infarct size and left ventricular function. Submitted.

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