Clin. Cardiol. 23, 96–102 (2000)

Effects of Early Captopril Therapy after Myocardial Infarction on the Incidence of Late Potentials

JOHN A. CHILADAKIS, M.D., GEORGE KARAPANOS, M.D., GEORGE AGELOPOULOS, M.D., DIMITRIS ALEXOPOULOS, M.D., FACC, FESC, ANTONIS S. MANOLIS, M.D., FACC, FESC

Cardiology Division, Patras University Hospital, Patras University Medical School, Rio, Patras, Greece

Summary

Background: Late potentials (LP) on signal-averaged electrocardiography (SAECG), recorded 6 to 30 days after an acute myocardial infarction (AMI), identify patients at risk for late arrhythmic events. Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce ventricular remodeling and cardiovascular mortality after AMI.

Hypothesis: The aim of this study was to investigate the effect of early (< 24 h) administration of captopril on the presence of LP on Days 6–30 after AMI.

Methods: The study included 117 patients with a first AMI; 63 patients (53 men and 10 women, aged 59 ± 12 years), 35 with an anterior and 28 with an inferior AMI (44 thrombolyzed), received early captopril therapy. The control group consisted of 54 age-matched patients (39 men and 15 women, aged 60 ± 12 years), 19 with an anterior and 35 with an inferior AMI (31 thrombolyzed, p = NS), who did not receive early therapy with an ACE inhibitor. The mean left ventricular ejection fraction was similar in both groups (48 vs. 46%). Time domain analysis of SAECG was performed using a band-pass filter of 40–250 Hz. Late potentials were considered present if any two of three criteria were met: (1) Filtered QRS duration (QRSD) > 114 ms, (2) root-mean-square voltage of the last 40 ms of the QRS complex (RMS) < 20 μV, and (3) duration of low amplitude (< 40 μV) signal of the terminal portion of the QRS (LAS) > 38 ms.

Results: In the two groups of patients there were no differences in mean values of SAECG parameters. No patient was receiving any antiarrhythmic drugs. In the captopril group LPs were present in 9 of 63 patients (14%) and in the control group in 17 of 54 patients (31%) (p = 0.046). There was no difference in the number of patients with a patent infarct-related artery in the two groups (76 vs. 59%).

Conclusion: Captopril treatment early after an AMI reduces the incidence of LPs recorded on Days 6–30 and may thus favorably affect the arrhythmogenic substrate.

Key words: late potentials, signal-averaged electrocardiogram, captopril, arrhythmias, angiotensin-converting enzyme inhibitors

Introduction

Angiotensin-converting enzyme (ACE) inhibitors, added to standard therapy, favorably influence survival of patients with an acute myocardial infarction (AMI) and congestive heart failure or impaired cardiac function.[1–8] Their beneficial effects relate to a reduction in deaths from progressive heart failure due to the attenuation of both infarct expansion and "remodeling" of the heart.[6,8,9] Since reduction in sudden death has been reported in some studies,[7,10] but not in others,[2–6,11] it remains controversial whether the arrhythmogenic substrate is favorably influenced by ACE inhibitors in patients post AMI with or without left ventricular dysfunction.[7,8]

The anatomical and electrophysiologic substrate of ventricular late potentials on the signal-averaged electrocardiogram (SAECG) appears to be fixed relatively early after an AMI, as a marker of electrical instability and potential malignant ventricular reentrant rhythms.[10,12,13] However, there is strong evidence that the prognostic significance of an abnormal SAECG depends on the time of its recording.[14–17] Accordingly, as the late potential activity follows the dynamics of the AMI evolution, most studies reported lack of prognostic association with very early recordings.[14–16] In contrast, an

Presented in part at the 18th Annual Scientific Sessions of NASPE, New Orleans, 1997; XIXth European Congress of Cardiology, Stockholm, 1997

Address for reprints:

Antonis S. Manolis, M.D., FACC, FESC
Professor & Director of Cardiology
41 Kourempana Street
Agios Dimitrios
Athens 173 43, Greece

Received: December 15, 1998
Accepted with revision: May 3, 1999

abnormal SAECG recorded 6 to 30 days and possibly 6 to 14 days after infarction has the highest predictive accuracy for arrhythmic events in the first postinfarction year.[17]

Apart from a substudy of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) II trial of early enalapril treatment in AMI, evidence supporting the association of a lower incidence of late potentials with the beneficial impact of ACE inhibition on the remodeling process is lacking.[18] Thus, the aim of this prospectively designed study was to examine whether early captopril treatment, added to standard therapy in patients with an AMI might influence the arrhythmogenic substrate, as reflected by the presence of late potentials on the SAECG. Secondary objectives included the investigation of the effects of captopril on left ventricular function, as well as the safety of its early administration in patients with AMI.

Patients and Methods

Patient Population

Eligible patients were assigned to oral captopril treatment if they had been admitted to our hospital within 24 h of symptom onset of a first documented AMI (Table I). Patients who were referred to our hospital later, but within the first postinfarction month, were included in the study as the comparison group, if they had not received previous ACE inhibitor treatment, based on a decision made by their referring physicians. All patients admitted to our hospital with an AMI and clinical evidence of heart failure (pulmonary venous congestion on chest radiograph and/or auscultatory evidence of a third heart sound with persistent tachycardia) and/or a depressed (< 0.40) left ventricular ejection fraction as evaluated by echocardiography, received captopril therapy and were included in the study if this treatment could be started within the first 24 h. Only patients with a first AMI, as evidenced by new pathologic Q waves on the 12-lead ECG (anterior-lateral and inferior-posterior) and abnormal cardiac enzymes were included.[19]

Patients were ineligible if they had atrial fibrillation, bundle-branch block, manifest ventricular preexcitation, long QT interval, ventricular pacing on the ECG; received digoxin, antiarrhythmic drugs, steroids or anti-inflammatory agents; or presented with persistent hypotension (< 95 mmHg), serum creatinine > 2.5mg/dl, or had a history of bilateral stenosis of the renal arteries or documented allergy to ACE inhibitors. Conventional adjuvant treatment for both captopril-allocated and control group patients consisted of beta blockers, nitrates, diuretics, and oral acetylsalicylic acid. Metoprolol, both alone or in combination with captopril, was started routinely in all patients the first day of AMI, unless signs of heart failure were present. Calcium antagonists were not given during the initial

TABLE I Patients' demographic and clinical characteristics

	Captopril group (n = 63)	Control group (n = 54)	p Value
Mean age (years)	59 ± 12	60 ± 12	NS
No. of men (%)	53 (84)	39 (72)	NS
Infarct location (%)			
Anterolateral (%)	35 (55)	19 (35)	NS
Inferoposterior (%)	28 (44)	35 (65)	NS
Thrombolysis (%)	44 (70)	30 (55)	NS
Anterolateral (%)	24 (68)	12 (63)	NS
Inferoposterior (%)	20 (71)	18 (51)	NS
Peak CK level (U/l)	1932 ± 1026	2128 ± 1127	NS
CHF (%)	17 (27)	12 (22)	NS
Beta blocker (%)	46 (73)	42 (78)	NS
LVEDVI (ml/m^2)	55.8 ± 2.4	55.9 ± 2.6	NS
LVESVI (ml/m^2)	34.5 ± 3.3	35.1 ± 3.0	NS
PE / PA	1.2 ± 0.3	1.1 ± 0.3	NS
Ejection fraction (%)	48.5 ± 10	46.1 ± 8	NS
> 40% (%)	49/63 (77)	41/54 (76)	NS
Coronary angiography (%)	51 (81)	44 (81)	NS
CAD single-vessel (%)	24 (47)	17 (38)	NS
CAD double-vessel (%)	13 (25)	14 (31)	NS
CAD triple-vessel (%)	14 (27)	13 (29)	NS
Patent IRA (%)	39/51 (76)	26/44 (59)	NS

Values are expressed as mean ± standard deviation.

Abbreviations: CAD = coronary artery disease, CHF = congestive heart failure, CK = creatine kinase, IRA = infarct-related artery, LVEDVI = left ventricular end-diastolic volume index, LVESVI = left ventricular end-systolic volume index, NS = not significant, PE/PA = Doppler E- to A-wave transmitral ratio.

phase of AMI. Patients initially received a titration dose of 6.25 mg of captopril; this dose was gradually increased, as tolerated, to a target total dose of 150 mg daily given in three divided doses.

Diagnostic Procedures

Before hospital discharge, patients were examined by echocardiography using Hewlett-Packard Sonos 1000 (Hewlett-Packard, Andover, Mass., USA) ultrasound equipment with a 3.5 MHz transducer. End-diastolic and end-systolic left ventricular frames before initial coaptation of the mitral valve were obtained, and the mean of three consecutive measurements was used to estimate left ventricular end-diastolic volume index (LVEDVI, ml/m^2) and left ventricular end-systolic volume index (LVESVI, ml/m^2) using the body surface area. Ventricular diastolic dysfunction was reflected by the assessment of the transmitral Doppler E- to A-wave flow; this was obtained from the apical four-chamber view between the mitral leaflets by using pulsed-wave Doppler echocardiography to calculate the ratio between early and atrial peak flow velocities (PE/PA). Planimetric volume measurements of apical left ventricular 4- and 2- chamber views were analyzed for ejection fraction calculation, using the disc-summation method (modified Simpson's rule).[20] Only patients with clear visualization of the endocardium in systole and diastole were entered into the study.

Before discharge, patients underwent an exercise test according to the modified Bruce protocol, and those with a positive exercise test underwent coronary arteriography before discharge from the hospital. Coronary angiography was also performed in patients with recurrent angina or any other standard indication. Patients with > 70% narrowing of the luminal diameter of a major epicardial artery were judged to have significant disease, and were identified as having single-, double-, or triple-vessel coronary artery disease. The infarct-related artery was identified on the basis of the location of the infarction as determined by ECG and/or by the pattern of regional dysfunction. The infarct-related artery was characterized as patent if it had a normal, TIMI grade 3, anterograde flow.[21]

Signal-Averaged Electrocardiogram

An SAECG, using the Marquette Case 15 system (Marquette Electronics, Milwaukee, Wisc., USA), was usually performed at hospital discharge, after the sixth postinfarction day or within the first month after AMI. The standard XYZ bipolar orthogonal bipolar electrode lead system was used. For time-domain analysis, the bi-directionally filtered QRS signals were averaged at frequencies of 40 to 250 Hz as the root mean square method of $X^2+Y^2+Z^2$. For each recording, 250 beats were averaged and accepted only if the noise level was < 0.7 μV. According to the established standards for data acquisition and analysis of SAECG, using a 40 Hz high-pass bi-directional filter, the following parameters were considered normal: (1) A filtered QRS duration (QRSD) of < 114 ms, (2) duration of the terminal filtered QRS signal < 40 μV (LAS) of < 38 ms, and (3) root-mean-square voltage of the terminal 40 ms of the filtered QRS complex (RMS) of > 20 μV.[22] An SAECG tracing was defined as positive for the presence of late potentials when two or more of these parameters were abnormal.

Statistical Analysis

Results are presented as mean ± standard deviation (SD). Mean values were compared by using the Student's *t*-test. Comparison of proportions were made with the use of Z-statistic. A two-tailed p value of < 0.05 was considered to indicate a significant difference.

Results

Baseline Evaluation

In all, 117 patients were eligible for enrollment. The baseline demographic, clinical, electrocardiographic, echocardiographic, and angiographic profile of the 63 patients receiving captopril therapy and of the 54 patients receiving conventional treatment alone is presented in Table I. The two groups were well matched for age and gender and did not differ significantly with respect to clinical characteristics, infarction location, peak of creatine kinase level, LVEDVI, LVESVI, PE/PA, extent of coronary artery disease, left ventricular ejection fraction, and the adjuvant treatment applied. A similar percentage of patients in both groups received beta-blocker and thrombolytic therapy, and among those having coronary angiography, a comparable proportion of patients in each group had a patent infarct-related artery (Table I).

The Captopril Group

There were 63 patients, 35 (55%) with an anterior and 28 (44%) with an inferior AMI, who received captopril at a mean dose of 97 ± 25 mg daily. On admission, 17 (27%) patients showed signs of heart failure and 44 (69%) received thrombolytic therapy. Adverse events leading to a dose reduction but not to withdrawal of captopril were seen in four patients. These included cough in two, hypotension in one, and renal dysfunction in another case. Coronary angiography was performed in 51 patients (81%): 24 had single-vessel coronary artery disease, 13 had double-vessel disease, and 14 had triple-vessel disease; 39 of these (76%) had a patent and 12 (23%) had an occluded infarct-related artery. No patient underwent elective coronary angioplasty or coronary bypass surgery before recording an SAECG.

The Control Group

Of the 54 patients who received conventional treatment, 19 (35%) had an anterior and 35 (65%) an inferior AMI. Twelve patients (22%) had heart failure and 31 (57%) were treated with thrombolysis. Coronary angiography was performed

in 44 patients (81%): 17 had single-vessel disease, 4 had double-vessel disease, and 13 had triple-vessel disease; 26 of these (59%) had a patent and 18 (41%) had an occluded infarct-related artery.

Effects of Captopril Treatment on Signal-Averaged Electrocardiogram

The median time to record the SAECG was 11 days in the captopril group and 14 days in the control group. There was a significant difference in the incidence of an abnormal SAECG between the two groups of patients; in the captopril group, 9 of 63 patients (14%) had evidence of an abnormal SAECG, compared with 17 of the 54 patients (31%) who did not receive captopril ($p = 0.046$) (Table I). This difference was ascribed to a beneficial effect of captopril and could not be attributed to either a difference in AMI location, number of patients receiving thrombolysis or having a patent infarct-related artery, or a difference in left ventricular function in the two groups, as these parameters were similar in the two groups (Table I).

Of the nine patients with an abnormal SAECG in the captopril group, eight had an increased QRSD of 128 ± 8 ms, eight had an increased LAS of 48 ± 8 ms, and seven had a decreased RMS of 10 ± 5 μV. Of the 17 patients in the control group with an abnormal SAECG, 15 had a prolonged QRSD of 126 ± 6 ms, 15 had an increased LAS of 48 ± 8 ms, and 14 had a decreased RMS of 12 ± 4 μV. Captopril treatment did not preferentially influence any single SAECG parameter, and there were no significant differences between the two groups with respect to the mean values of the individual LP parameters. However, among those with abnormal SAECG, the individual QRSD parameter was abnormal in 89% in the captopril group and in 88% in the control group, and thus was the major contributor in defining positive late potentials.

Among all patients of both groups, thrombolytic therapy was associated with a reduction trend in the incidence of late potentials (12 of 74 patients, 16%, vs. 14 of 43 patients, 33%; $p = 0.06$), but not within each group. However, among those catheterized there was a clear association between late potentials and patency of the infarct-related artery, with 6 of 65 (9%) of patients with a patent artery and an abnormal SAECG, compared with 20 of 30 (67%) of patients with an occluded artery and an abnormal SAECG ($p = 0.001$). This difference was also significant within each group (8% for patent arteries vs. 50% for occluded arteries in the captopril group, $p = 0.004$; 12% for patent vs. 78% for occluded arteries in the control group, $p = 0.001$). With regard to infarct location, 5 of 54 (9%) of patients with an anterior AMI had positive late potentials, and 21 of 63 (33%) of patients with an inferior AMI had positive late potentials ($p = 0.004$). A similar difference was apparent in the control group (11% incidence of late potentials in anterior AMI vs. 43% in inferior AMI, $p = 0.035$), but not in the captopril group (9 vs. 21%, respectively).

There were no statistically significant differences between the two groups with respect to the total mean values of SAECG parameters, QRSD, RMS, and LAS (Table II).

Discussion

Angiotensin-converting enzyme inhibitors have been shown to reduce mortality after AMI, particularly in patients

TABLE II Signal-averaged electrocardiographic data

	Captopril group (n = 63)	Control group (n = 54)	p Value
Median days to SAECG	11 (range 6–17)	14 (range 6–28)	NS
Total QRS duration (ms)	91.5 ± 8.7	91.8 ± 8.4	NS
Filtered QRS duration (ms)	112.6 ± 11.4	112.6 ± 10.7	NS
RMS voltage (μV)	33.6 ± 17.3	33.7 ± 21.6	NS
LAS duration (ms)	31.8 ± 12.4	33.8 ± 12	NS
Abnormal 2 SAECG parameters (%)	9/63 (14)	17/54 (31)	0.046
Anterolateral MI (%)	3/35 (9)	2/19 (11)	NS
Inferoposterior MI (%)	6/28 (21)	15/35 (43)	NS
P value	NS	0.035	
Thrombolyzed MI (%)	4/44 (9)	8/30 (27)	NS
Non-thrombolyzed MI (%)	5/19 (26)	9/24 (38)	NS
P value	NS	NS	
Patent IRA (%)	3/39 (8)	3/26 (12)	NS
Occluded IRA (%)	6/12 (50)	14/18 (78)	NS
P value	0.004	0.001	
LVEF > 40% (%)	5/49 (8)	15/41 (37)	0.002
LVEF < 40% (%)	4/14 (29)	2/13 (15)	NS
P value	NS	NS	

Values are means ± standard deviation.

Abbreviations: MI = myocardial infarction, SAECG = signal-averaged electrocardiogram, IRA = infarct-related artery, LAS = low-amplitude signal, LVEF = left ventricular ejection fraction, NS = not significant, RMS = root-mean-square.

with heart failure or left ventricular dysfunction (ejection fraction < 40%).[2–6, 10] The issue of administering ACE inhibitors to all patients with an AMI remains controversial, although it is conceivable that their beneficial effects on neurohormonal modulation as well as on cardiovascular structure with attenuation of the remodeling process[23–25] might prolong survival in every patient after infarction. With regard to the timing of initiation of ACE inhibitor therapy after AMI, all trials in which oral ACE inhibitors were used early (within 24 h) showed a benefit in mortality. Only when intravenous therapy was employed (CONSENSUS II trial), no benefit was shown.[11] Angiotensin-converting enzyme inhibitors are also useful in patients who have recovered from the acute phase of AMI; they prolong long-term survival in these patients.[2, 6]

As in most trials of ACE-inhibitor therapy in patients with congestive heart failure, the mortality reduction noted with ACE inhibitors after AMI pertains to all-cause and /or cardiac mortality in most studies, and there is very limited information on their effect on arrhythmic mortality. Apart from the cautiously interpreted data from V-HeFT II trial in patients with heart failure, which showed a benefit of enalapril on sudden death mortality, there are only the results of the Trandolapril Cardiac Evaluation (TRACE) study in patients with AMI and reduced left ventricular function, showing a significant reduction of arrhythmic mortality with the use of trandolapril.[7, 8] Of note, there are also two recent studies which suggested a beneficial effect of captopril on the number of ventricular arrhythmias during the acute phase of AMI, especially in patients with left ventricular dysfunction.[26, 27] Thus, apart from the neurohormonal modulation by ACE inhibitors and the indirect antiarrhythmic influence that this may incur, there is no clear evidence of any direct electrophysiologic effects of ACE inhibitors on the arrhythmogenic substrate. However, based on the limited data reported in the above few studies regarding potential antiarrhythmic effects of ACE inhibitors, a hypothesis of their beneficial effect on arrhythmogenesis following AMI might be formulated as based on improved loading conditions, as well as on potential attenuation of structural changes and adverse ventricular remodeling.[28] This concept of interplay between ventricular remodeling, arrhythmogenesis, and the use of ACE inhibitors could be indirectly exposed by the presence of late potentials.

Our data demonstrate that in patients post AMI, early captopril treatment may attenuate the arrhythmogenic substrate, as evidenced by a lower incidence of late potentials (14%) in patients who received early captopril therapy, than in those who did not (31%, $p = 0.046$). Since captopril treatment failed to correlate with selective changes of any single LP parameter, no specific SAECG parameter appears to be useful in predicting drug efficacy. The probable beneficial effect of captopril treatment on the electrical stability appears to correlate with slowing global ventricular activation that can be quantified by the SAECG, attributed to the improved wound healing response.

Our results are consistent with those of the previously reported CONSENSUS II subtrial which showed a significantly reduced presence of late potentials after early enalapril treatment, both at discharge and after 3 to 6 months.[18] Taking it a step further, in our study we considered the effect of thrombolytic therapy in all patients; this therapy is known to be associated with a decreased incidence of late potentials when compared with patients who do not receive thrombolysis, attributable to a higher number of patent infarct-related arteries in thrombolyzed patients.[29–31] Indeed, the number of thrombolyzed patients and the number of patent infarct-related arteries were comparable in the two groups, and therefore this cannot account for the lower incidence of late potentials in the captopril group. Surely, the overall incidence of late potentials among all patients of both groups was lower in those with a patent infarct-related artery.

In an important study, late potentials independent of their primary use as reliable predictors of arrhythmic events were recorded during the first postinfarction week in patients with anterior AMI and were also found to serve as determinants of subsequent ventricular dilatation.[32] Thus, late potentials could be used as a screening test for identifying the patient at risk for developing cardiac dilatation. Indeed, following the results of the decreased left ventricular volumes in the ACE-inhibitor-allocated subgroups of patients from the Survival and Ventricular Enlargement (SAVE) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) trials, a recent CONSENSUS II subtrial reported improved left ventricular wall motion index after 3 to 6 months of enalapril treatment related to significantly reduced presence of late potentials.[2, 3, 33] In our study, the lack of a positive association between early post-AMI captopril therapy and decreased left ventricular volume and/or improved left ventricular function on discharge, is in agreement with reports showing a gradual improvement of the dysfunctioning myocardium, if it exists, rather than a short-term effect.[2, 33–35] Captopril treatment started within 24 h from the onset of symptoms of AMI has proved to be safe, and it could be continued over a longer period of time not only in patients with clinically large AMI and/or current or previous left ventricular failure, but also in the subset of patients with smaller infarcts and positive late potentials, thereby offering possible protection from left ventricular dysfunction.

A major limitation of our study is the lack of randomization of therapy in the two groups, but this may not be ethically possible any longer in the future in light of recent compelling evidence in favor of ACE-inhibitor use early after AMI, at least for patients with heart failure or left ventricular dysfunction. Despite this limitation, our groups were well matched for most demographic and clinical parameters. Other potential criticisms of the present study might concern the timing of SAECG recording and the limited patient follow-up. However, most agree that the arrhythmogenic substrate related to late potentials rather stabilizes after Day 6 post AMI and that few major changes occur after the first month;[17] this time period was selected for recording an SAECG in our patients. It is obvious that because of lack of follow-up data, any long-term effects that captopril might have had on the SAECG could not be detected in our study.

Conclusion

The rationale for the use of ACE inhibitors following AMI is established among patients with low ejection fraction and/or signs or symptoms of left ventricular dysfunction. Since late potentials may serve as predictors of both arrhythmic events and ventricular dilatation, SAECG recording in the patient post AMI has major potential diagnostic and therapeutic implications. The ability of early captopril treatment after an AMI to reduce the prevalence of late potentials argues in favor of expanding the drug's use in unselected patients with AMI regardless of left ventricular function status. This will offer greater protection against the development of an arrhythmogenic substrate and possible subsequent cardiac dilatation, and it is hoped that this will translate into an arrhythmic mortality reduction. Indeed, the beneficial effect of captopril in the present study was apparent in patients with left ventricular ejection fraction > 40% (8% incidence of late potentials in the captopril group vs. 37% in the control group, $p = 0.002$) (Table II). Finally, in patients with AMI and positive late potentials, early or even late captopril therapy might possibly offer some antiarrhythmic benefit due to its effect on remodeling, a hypothesis that needs to be explored further in future studies.

References

1. The SOLVD Investigators: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685–691
2. Pfeffer M, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rutherford J, Wertheimer JH, Hawkins CM: The SAVE Investigators: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669–677
3. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico: GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343: 1115–1122
4. ISIS Collaborative Group: ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669–685
5. Kingma JH, van Gilst WH, Peels CH, Dambrink JHE, Verheugt FWA, Wielenga RP: Acute intervention with captopril during thrombolysis in patients with first anterior myocardial infarction: Results from the Captopril and Thrombolysis study (CATS). *Eur Heart J* 1994;15:898–907
6. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators: Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821–828
7. Koeber L, Torp-Pedersen C, Carlsen JA, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole D, Auglert L, Pavly NC, Alliot E, Person S, Camm AJ, for the Trandolapril Cardiac Evaluation (TRACE) Study Group: A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333: 1670–1676
8. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman B, Loeb H, Wong M, Bhat G, Goldman S, Fletcher RD, Doherty J, Hughes CV, Carson P, Cintron G, Shabeti R, Haakenson C: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303–310
9. Ertl G, Kloner RA, Alexander RA, Braunwald E: Limitation of experimental infarct size by an angiotensin-converting enzyme inhibitor. *Circulation* 1982;65:40–48
10. Ambrosini E, Borghi C, Magnani B, for the Survival of Myocardial Infarction Long-term Evaluation (SMILE) Study Investigators: The effect of the angiotensin-converting enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995;332:80–85
11. Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H, for the CONSENSUS II Study Group: Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. *N Engl J Med* 1992;327:678–684
12. Kloner RA, Przyklenk K: Cardioprotection with angiotensin-converting enzyme inhibitors: Redefined for the 1990s. *Clin Cardiol* 1992;15:95–103
13. Denniss AR, Ross DL, Richards DA, Uther JB: Changes in ventricular activation time on the signal-averaged-electrocardiogram in the first year after acute myocardial infarction. *Am J Cardiol* 1987; 60:580–583
14. Kuchar DL, Thorburn CW, Sammel NL: Prediction of serious arrhythmic events after myocardial infarction: Signal-averaged electrocardiogram, Holter monitoring and radionuclide ventriculography. *J Am Coll Cardiol* 1987;9:531–538
15. Grimm M, Billhart RA, Mayerhofer KE, Denes P: Prognostic significance of signal-averaged ECGs during acute myocardial infarction: A preliminary report. *J Electrophysiol* 1988;21:283–288
16. Lewis SJ, Lander PT, Taylor PA, Chamberlain DA, Vincent R: Evolution of late potential activity in the first six weeks after acute myocardial infarction. *Am J Cardiol* 1989;63:647–651
17. El-Sherif N, Ursell SN, Bekheit S, Fontaine J, Turitto G, Henkin R, Caref EB: Prognostic significance of the signal-averaged ECG depends on the time of recording in the postinfarction period. *Am Heart J* 1989;118:256–264
18. Junker A, Ahlquist P, Thayssen P, Angelo-Nielsen K, Mickley H, Moeller M: Ventricular late potentials after early enalapril treatment in acute myocardial infarction. *Am J Cardiol* 1995;76:1300–1302
19. Greenberg H, Gillespie J, Dwyer EM, and the Multicenter Post-Infarction Research Group: A new electrocardiographic classification for post-myocardial infarction clinical trials. *Am J Cardiol* 1987;59:1057–1063
20. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Grugesell H, Reicheck N, Sahn D, Schnittger I, Silverman NH, Tajik J: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echo* 1989;2:358–367
21. Chesebro JH, Knatterud G, Roberts R, Boger J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E: Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase: Clinical findings through hospital discharge. *Circulation* 1987;76:142–154
22. Breithardt G, Cain ME, El-Sherif N, Flowers N, Hombach V, Janse M, Simson MB, Steinbeck G: Standards for analysis of ventricular late potentials using high resolution or signal-averaged electrocardiography. *Circulation* 1991;83:1481–1486
23. van Gilst WH, de Graeff PA, Wesseling H, de Langen CDJ: Reduction of reperfusion arrhythmias in the ischemic isolated rat heart by angiotensin converting enzyme inhibitors: A comparison of captopril, enalapril, and HOE 498. *J Cardiovasc Pharmacol* 1986;8:722–728

24. Raya TE, Gay RG, Aguirre M, Goldman S: Importance of venodilatation in prevention of left ventricular dialatation after chronic large myocardial infarction in rats: A comparison of captopril and hydralazine. *Circ Res* 1989;64:330–337
25. Oldroyd KG, Pye MP, Ray SG, Christie J, Ford I, Cobbe SM, Dargie HJ: Effects of early captopril administration on infarct expansion, left ventricular remodelling and exercise capacity after AMI. *Am J Cardiol* 1991;68:713–718
26. Sogaard P, Gotzsche CO, Ravkilde J, Norgaard A, Thygesen K: Ventricular arrhythmias in the acute and chronic phases after acute myocardial infarction. Effect of intervention with captopril. *Circulation* 1994;90:101–107
27. Budaj A, Cybulski J, Cedro K, Karczmarewicz S, Maciejewicz J, Wisniewski M, Ceremuzynski L: Effects of captopril on ventricular arrhythmias in the early and late phase of suspected acute myocardial infarction. *Eur Heart J* 1996;17:1506–1510
28. Hemsworth PD, Pallandi RT, Campbell TJ: Cardiac electrophysiological actions of captopril: Lack of direct antiarrhythmic effects. *Br J Pharmacol* 1989;98:192–196
29. Gang ES, Lew AS, Hong M, Wang FZ, Siebert CA, Peter T: Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1989;321:712–716
30. Lange RA, Cigarroa RG, Wells PJ, Kremers MS, Hillis LD: Influence of anterograde flow in the infarct artery on the incidence of late potentials after acute myocardial infarction. *Am J Cardiol* 1990;65:554–558
31. Denes P, El-Sherif N, Katz R, Capone R, Carlson M, Mitchell B, Ledingham R, for the Cardiac Arrhythmia Suppression Trial (CAST) SAECG substudy investigators: Prognostic significance of signal-averaged electrocardiogram after thrombolytic therapy and/or angioplasty during acute myocardial infarction (CAST substudy). *Am J Cardiol* 1994;74:216–220
32. Zaman AG, Morris JL, Smyllie JH, Cowan JC: Late potentials and ventricular enlargement after myocardial infarction. A new role for high-resolution electrocardiography? *Circulation* 1993;88:905–914
33. Bonarjee VVS, Carstensen S, Caidahl K, Nilsen DWI, Edner M, Berning J, on behalf of the CONSENSUS II multi-echo study group: Attenuation of left ventricular dilatation after acute myocardial infarction by early initiation of enalapril therapy. *Am J Cardiol* 1993;72:1004–1009
34. Sogaard P, Gotzsche CO, Ravkilde J, Thygesen K: Effects of captopril on ischemia and dysfunction of the left ventricle after myocardial infarction. *Circulation* 1993;87:1093–1099
35. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moyé LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S, Manapace FJ, Parker JO, Lewis S, Sestier F, Gordon DF, McEwan P, Bernstein V, Braunwald E, for the SAVE Investigators: Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction: The protective effects of captopril. *Circulation* 1994;89:68–75