Left ventricular dilatation and neurohumoral activation as arrhythmogenic factors in myocardial infarction

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CHAPTER 9

Effects of captopril on early and late arrhythmic events in patients with thrombolytic therapy for a first anterior myocardial infarction

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Introduction

In recent years, it has become clear that thrombolytic therapy is one of the few treatments that can significantly reduce the incidence of life-threatening ventricular arrhythmias after myocardial infarction. Combined results of a number of large thrombolysis trials show a nearly 15% reduction of in-hospital VF.[1-5] Sofar, attempts to further reduce life-threatening ventricular arrhythmias in the setting of thrombolytic therapy have not been very successful. Even beta-blockers, agents with powerful (indirect) anti-arrhythmic properties and very successful in the pre-thrombolytic era,[6] do not seem to further reduce the incidence of early life-threatening ventricular arrhythmias when thrombolytic therapy is used.[7,8]

ACE inhibitors may provide an interesting alternative to conventional anti-arrhythmic therapy. Several animal experiments have shown a reduction of ventricular arrhythmias during reperfusion after ligation of a coronary artery.[9-11] Blunting of the neurohumoral response and reduction of infarct size have been suggested as underlying mechanisms.[12-14] Furthermore, ACE inhibitors are known to modulate left ventricular remodeling in the later phases of myocardial infarction.[15-18] Both left ventricular dilatation[19] and ventricular hypertrophy,[20] major components of the remodeling process, are well known arrhythmogenic factors. Thus, modulation of the remodeling process may also result in an indirect reduction of late ventricular arrhythmias. In addition, this anti-arrhythmic effect may be potentiated by modulating effects of ACE inhibitors on electrolyte abnormalities[21] and autonomic imbalance[12] during the later stages of myocardial infarction.

In this study, we tested the hypothesis that treatment with the ACE inhibitor captopril during thrombolysis results in a reduction of clinically relevant ventricular arrhythmias both early and late after myocardial infarction.

Methods

Patients. This study was part of the Captopril And Thrombolysis Study (CATS), in which the effect of captopril treatment, started during thrombolysis, was evaluated in patients with a first anterior myocardial infarction. The patient selection and methods of this study are described elsewhere in detail.[22]

Table 9.1. Early ventricular arrhythmias (within 48 hours)

Nr	Age (y)	M/F	Arrhythmia	Treatment / outcome
1	58	M	VT	Lidocaine
2	60	M	VT	Lidocaine
3	63	M	VT	Lidocaine
4	64	M	VT	Lidocaine
5	60	M	VT	Lidocaine
6	58	M	VT	Lidocaine
7	73	M	VF	Cardioversion, died on day 7 (VT,VF)
8	72	F	VT,VF	Cardioversion
9	70	M	VT	Lidocaine
10	55	F	VT	Lidocaine
11	62	M	VT	Lidocaine
12	74	M	VF	Died, free wall rupture on autopsy
13	54	M	VT	Lidocaine, died day 212, cardiogenic shock
14	69	F	VT,VF	Died, free wall rupture on autopsy
15	74	F	VT	Sotalol
16	60	M	VT	Lidocaine
17	63	M	VF	During rescue PTCA, cardioversion
18	47	M	VT	Lidocaine
19	36	M	VT	Cardioversion

F indicates Female; M, Male; VF, ventricular fibrillation; VT, ventricular tachycardia; Y, years.

In brief, 298 patients were included in 12 hospitals in The Netherlands. Selection criteria included a typical history of chest pain consistent with myocardial infarction with onset of symptoms no longer than 6 hours before admission, and electrocardiographic criteria for acute anterior myocardial infarction. Exclusion criteria included presence of left bundle branch block and severe heart failure (Killip class III or IV). Informed consent was obtained by witnessed oral consent, later confirmed by written informed consent following the acute phase of myocardial infarction.

Infarct size. Enzymatic infarct size was estimated by cumulative alpha-hydroxybutyrate dehydrogenase values over the first 72 hours after myocardial infarction (α-HBDH Q72) as described by van der Laarse et al..[23] This method is not influenced by the presence or absence of reperfusion.

Echocardiography. Regional wall motion abnormalities were evaluated using the wall motion score recommended by the American Society of Echocardiography.[24] In this scoring system the left ventricle is divided into 16 segments,

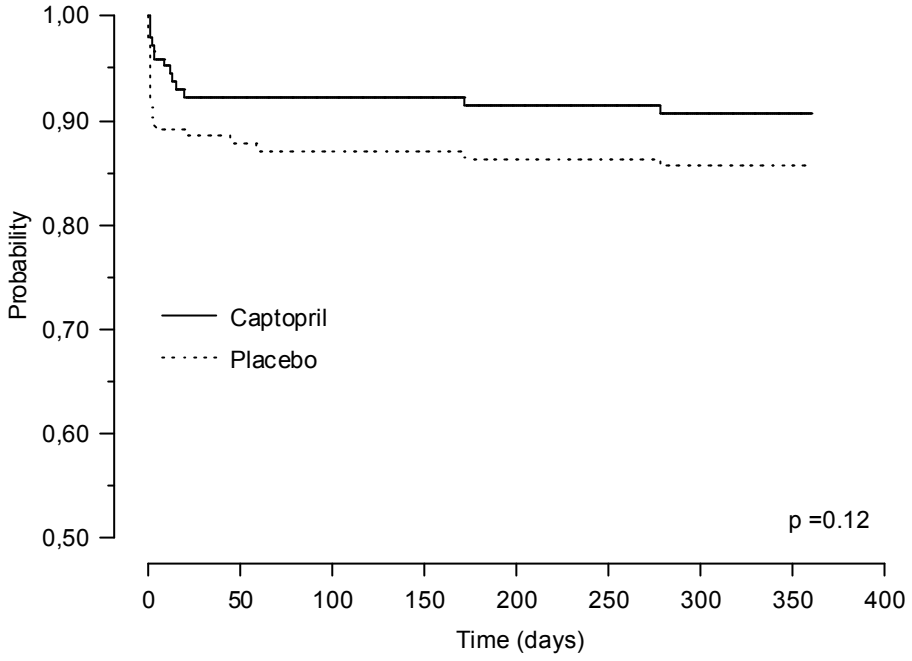

Figure 9.1. The arrhythmia-free survival in patients randomized to captopril or placebo is depicted. Despite a clear difference during the first days after myocardial infarction in f a-vor of captopril, there is no significant difference between the two groups during the first year of follow up.

scoring each segment as 1 for normokinesia, 2 for hypokinesia, 3 for akinesia, 4 for dyskinesia and 5 for an aneurysmal segment. A Wall Motion Score Index (WMSI) was computed as the sum of scores of all segments divided by the number of segments evaluated. Left ventricular end-systolic and end-diastolic volumes were calculated from a two- and four-chamber view using the modified biplane Simpson's rule.[24] From these volume measurements the ejection fraction was calculated.

Measurements were made off-line from end-diastolic and end-systolic still-frames using a Microsonics cardiac analysis system (Nova Microsonics). Left ventricular volumes were indexed for body surface area. Left ventricular dilatation was defined as follows. Left ventricular volumes of all patients with an enzymatic infarct size of α-HBDH Q72 of less than 730 U/l, which represents the

lower tertile of all randomized infarct sizes, were pooled. This group of patients showed no change between first and last echocardiographic evaluation. Mean left ventricular end-diastolic and end-systolic volume index and corresponding standard deviations of this reference group were considered as the normal value for the study population. Subsequently, all individual end-systolic and and-diastolic volume indexes at each time point were compared with this normal value. If a patient showed a left ventricular volume index of more than one standard deviation above normal and end-systolic and end-diastolic volume index were 1.5 standard deviation above normal, the patient was considered to have left ventricular dilatation. This dilatation criterion appeared to be robust since variation of the criterion between 0.5 and 1.5 standard deviation generated comparable results.

Arrhythmic events and Holter monitoring. In this study, ventricular arrhythmias requiring anti-arrhythmic treatment were investigated. These arrhythmias included ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death. Sudden death was defined as death within one hour of symptoms, but also included unwitnessed death in patients who were previously stable. VT was defined as three or more ventricular premature beats with a rate exceeding 100 beats/min. In addition, Holter recordings before discharge, and at three and 12 months were part of the study protocol. Paired ventricular premature beats and VT were defined as high-grade ventricular arrhythmias, corresponding to Lown class 4A and 4B.

Norepinephrine levels. Blood samples were collected for assessment of norepinephrine levels at 0, 1, 12, 24, 48, 72, and 96 hours after the start of study medication, which was at the completion of streptokinase infusion. Norepinephrine was measured using a sensitive assay with electrochemical detection. Cumulative norepinephrine values were calculated following the trapezium rule.[25]

Statistical analysis . Results are presented as means with standard deviation, except when stated otherwise. Differences between groups were examined using the Student's t-test. The Chi-square test was used for discrete data. Fisher's Exact test was used in case of small patient numbers (indicated separately). The Log-Rank test was used in the case of survival analysis.

Results

Early ventricular arrhythmias

In the first 48 hours after thrombolytic therapy, 19 patients (6%) had ventricular arrhythmias requiring anti-arrhythmic treatment (Table 9.1). Fourteen patients had

Table 9.2. Characteristics of patients with- and without early ventricular arrhythmias

	Arrhythmias	N	No arrhythmias	N	p-value
Demographics					
Age (years)	62 ± 10	19	59 ± 10	279	0.300
Male (%)	79	19	75	279	0.905
Onset (hours)	3.0 ± 1.0	19	3.5 ± 1.3	278	0.112
Laboratory					
α-HBDH Q72 (U/l)	2240 ± 1526	16	1215 ± 935	242	< 0.001
Potassium (mmol/l)	4.1 ± 0.3	17	4.1 ± 0.4	261	0.415
Norepinephrine (pg/ml)					
at 1 hour	1409 ± 1230	15	965 ± 648	235	0.017
cumulative (96 hours)	731 ± 297	10	796 ± 435	207	0.639
Echocardiography					
WMSI	2.2 ± 0.3	11	1.9 ± 0.4	222	0.004
LVESVI (ml/m^2)	32 ± 14	7	25 ± 10	174	0.102
LVEDVI (ml/m^2)	65 ± 19	7	55 ± 13	174	0.073
LVEF (%)	52 ± 11	7	55 ± 10	174	0.383
LV aneurysm (%)	18	17	10	241	0.597
Dilatation (%)	83	12	50	224	0.047
Hemodynamics					
Heart rate (beats/min)	79 ± 14	16	83 ± 17	196	0.453
Blood pressure(mmHg)					
systolic	131 ± 20	15	126 ± 21	204	0.345
diastolic	85 ± 12	15	78 ± 15	204	0.109
Rate-pressure product	10162 ± 2214	15	10471 ± 2966	195	0.694
Medication					
ACE inhibitor (%)					
randomized	21	19		279	0.018
open label	12	17	52	272	0.007
Diuretics (%)	18	17	1	272	0.735
Beta-blocker (%)	18	17	12	272	0.471
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Digoxin (%)	6	17	5	272	0.706

α-HBDH Q72 indicates cumulative alpha-hydroxy butyrate dehydrogenase over the first 72 hours after myocardial infarction; LVESVI, left ventricular end-systolic volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; onset, time from onset of symptoms to randomization; WMSI, wall motion score index. Hemodynamics were assessed 8 hours after randomization.

VT, one of whom needed DC cardioversion (case 19); the other patients were treated with mostly class I anti-arrythmic agents. Patient 13 was treated with lidocaine and also needed temporary pacemaker support for subsequent bradycardia. This patient died at day 212 due to progressive heart failure. Patient 8 and 14 had VT degenerating into VF. Patient 8 had successful DC cardioversion. However, patient 14 did not recover and was shown to have a free wall rupture on autopsy. Patients 7, 12 and 17 had primary ventricular fibrillation. Patient 7 initially recovered after DC cardioversion and was treated with amiodarone. However, despite this therapy the patient had several episodes of VT and died on day 7 due to untreatable VF. Autopsy was performed, and a dilated left ventricle was found with a 90% stenosis in the left anterior descending artery, and a significant stenosis in the ramus circumflexus. Patient 12 died after failure of a CPR procedure; a free wall rupture was found on autopsy. Patient 17 had VF during a PTCA procedure, and recovered after cardioversion without further complications. Thus, four of the 19 patients (21%) with early ventricular arrhythmias requiring therapy died during the first year of follow up, three of whom died during the first week. Coronary angiography was performed in another 5 patients (case 6, 7, 11, 13 and 16) within 20 days. All of these patients had a patent infarct-related (left anterior descending) artery.

In Table 9.2, other characteristics of patients with and without early ventricular arrhythmias are given. On average, patients with early ventricular arrhythmias received thrombolytic therapy and subsequent study medication 0.5 hours earlier than patients without these arrhythmias (difference not significant). In addition, these patients were characterized by a significantly larger enzymatic infarct size (α-HBDH Q72), a higher wall motion score, and a trend towards a larger end-diastolic volume. At one hour after thrombolytic therapy, this was paralleled by increased norepinephrine levels. However, cumulative levels of norepinephrine over 96 hours did not differ significantly between patients with- and without early ventricular arrhythmias. During follow up, more left ventricular dilatation was seen in the group with early ventricular arrhythmias. Heart rate and blood pressure did not differ significantly between both groups, although there was a trend towards a higher diastolic blood pressure in patients with early ventricular arrhythmias. Finally, a significant treatment effect of captopril on early ventricular arrhythmias was observed, since of patients randomized to captopril, 3% had early ventricular arrhythmas compared to 10% in patients allocated to placebo, reflecting a relative risk of 0.27 (95% CI 0.09 - 0.78).

Table 9.3. Late ventricular arrhythmias (after 48 hours, up to one year)

Nr	Age (y)	M/F	Arrhyth-mia	Days	Treatment / outcome
1	72	M	VF	2	During coronary angiography
2	54	M	VT	3	Procainamide
3	58	M	VT	3	Lidocaine
4	73	M	VT,VF	7	Died
5	67	M	VF	8	Cardioversion
6	62	M	VF	11	Cardioversion, lidocaine
7	55	M	VT	11	Sotalol. Died day 143 (CHF/VT)
8	58	M	VT	12	Mexiletine
9	69	M	VT,VF	14	Cardioversion
10	64	M	VT	14	Amiodarone
11	68	M	VT	14	Propafenon
12	55	M	VT	19	Lidocaine
13	67	M	SCD	26	Unwitnessed
14	54	M	VF	44	Reinfarction
15	62	M	SCD	58	Data not available
16	63	M	VT	63	Lidocaine
17	61	F	SCD	171	Unwitnessed
18	70	M	SCD	171	Unwitnessed
19	53	M	SCD	277	Unwitnessed
20	64	M	SCD	277	VF registered

CHF indicates congestive heart failure; SCD, sudden cardiac death. Other abbrevations as in Table 9.1.

Late ventricular arrhythmias

In Table 9.3, patients with late ventricular arrhythmias (after 48 hours up to one year after myocardial infarction) are listed. Approximately half of these late arrhythmic events occurred before hospital discharge (cases 1 to 9, 45%). Thus, including the early ventricular arrhythmias, 28 of all 39 arrhythmic events in this study (72%) occurred before hospital discharge.

Of all patients with late ventricular arrhythmias, eight had VT, treated with anti-arrhythmic medication as listed. Patient 7 had VT during exercise and was treated with sotalol. This patient experienced a second myocardial infarction on day 143 and died due to progressive heart failure and untreatable VT. The other seven patients with VT survived up to one year without further events. Two

other patients had VT degenerating into VF. Patient 9 was successfully cardioverted, but patient 4 did not survive despite a CPR procedure. (This patient is the same as case nr. 7 listed under early ventricular arrhythmias).

Table 9.4. Characteristics of patients with and without late ventricular arrhythmias

	Arrhythmias	N	No arrhyth-mias	N	p-value
Demographics					
Age (years)	62 ± 10	19	59 ± 10	279	0.312
Male (%)	95	19	74	279	0.077
Laboratory					
α-HBDH Q72 (U/l)	1725 ± 949	18	1245 ± 1007	240	0.051
Potassium (mmol/l)	4.4 ± 0.5	12	4.5 ± 0.4	191	0.496
Echocardiography					
WMSI	2.03 ± 0.47	14	1.81 ± 0.42	224	0.063
LVESVI (ml/m^2)	33 ± 13	12	27 ± 12	176	0.076
LVEDVI (ml/m^2)	61 ± 11	12	59 ± 15	176	0.655
LVEF (%)	47 ± 14	12	56 ± 10	176	0.003
LV aneurysm (%)	12	17	11	240	0.740
Dilatation (%)	73	11	50	225	0.250
Exercise testing					
Exercise duration (s)	421 ± 113	16	428 ± 368	229	0.939
Positive for ischemia (%)	25	16	26	229	0.873
Functional class					
NYHA (%)					
I	50	9	67	176	0.209
II	44	8	28	72	0.208
III	6	1	4	10	0.793
IV	0	0	1	3	0.469
≥ II	50	18	13	261	< 0.001
Medication					
ACE inhibitor (%)					
randomized	47	19	50	279	1.000
open label	6	18	2	253	0.866
Diuretics (%)	50	18	19	253	0.004
Beta-blocker (%)	29	18	32	253	0.884
Digoxin (%)	17	18	9	253	0.479

NYHA indicates New York Heart Association class, other abbrevations as in Table 9.2. Assessments were performed before hospital discharge. Potassium levels were measured at six months.

Four patients had VF after 48 hours. Patient 1 had VF during coronary angiography and was successfully cardioverted. Patient 5 had VF and was car-

dioverted successfully; however, this patient died suddenly at day 26 (case 5 and 13 represent the same patient). Patient 6 had VF and was cardioverted and treated with lidocaine. Patient 14 had VF during a second infarction on day 44 and was cardioverted successfully. There were six cases of sudden death after hospital discharge (2% of all patients). In only one patient, case 20, an arrhythmia (VF) was documented. Patient 15 had an unsuccessful CPR attempt in a hospital not participating in CATS; data on (the type of) arrhythmias were not obtained. The other four patients (cases 13,17,18,19) died unwitnessed. Coronary angiography was performed in 12 patients with late ventricular arrhythmias up to 136 days after myocardial infarction. Five patients had an occluded LAD (42%) compared to 30 out of 151 patients (20%) without these arrhythmas (p=0.160).

In Table 9.4, other characteristics of patients with late ventricular arrhythmias are listed. Similar to patients with early ventricular arrhythmias, those with late ventricular arrythmias were characterized by a relatively large enzymatic infarct size. There was also a trend towards more wall motion abnormalities and a larger end-systolic volume before hospital discharge. This resulted in a clearly reduced ejection fraction in patients with late ventricular arrhythmias. Left ventricular dilatation was not seen more frequent in the late arrhythmia group, although all patients who died suddenly during follow up showed some degree of dilatation (data previously published).[26] The reduction in ejection fraction was paralleled by more symptoms of heart failure: half of those with late ventricular arrhythmias were in NYHA class II or higher, compared to 13% of patients without these arrhythmias. There was no clear treatment effect of captopril, since the fraction of patients randomized to captopril were comparable between patients with- and without late ventricular arrhythmias. There were no clear differences in the use of open label ACE inhibitors or digoxin, but patients with late ventricular arrhythmias did use significantly more diuretics at discharge.

Effects of captopril

Table 9.5 shows some of the other effects of captopril, documented in CATS. Already one hour after the first dose of captopril (6.25 mg) a significant 11% reduction of ACE activity was observed in patients allocated to captopril. This was paralleled by a significant 15% reduction of norepinephrine levels compared to baseline in the captopril group. At 8 hours after the start of study medication, after a third dose of 6.25 mg, there were still no differences in heart rate, blood pressure or rate-pressure product. Peak α-HBDH and cumulative α-HBDH over 72 hours in large infarcts were significantly reduced by captopril. At day 3, there was no difference in potassium levels between patients random-

ized to placebo or captopril. However, six months after randomization, potassium levels were significantly higher in patients allocated to captopril. Although no significant differences were found in left ventricular end-diastolic and end-systolic volume, these dimensions were consistently larger in the placebo group during the first months of follow up.[22] Moreover, captopril was shown to prevent left ventricular dilatation, especially in patients with moderately sized infarcts.

In Figure 9.1, the arrhythmia-free survival in patients treated with captopril or placebo is depicted during the first year of follow up. It is shown that early after myocardial infarction ventricular arrhythmias were more frequent in the placebo group. However, after the first few days, no additional difference in the incidence of ventricular arrhythmias was observed, resulting in a non-significant difference for the complete observation period of one year.

Holter monitoring performed before hospital discharge and after three and 12 months showed no differences in high-grade ventricular arrhythmias (Lown class 4A and 4B). However, when patients were divided into two subgroups separated by the median ejection fraction, the following was observed. In patients with an ejection fraction above the median of the population (56%), the prevalence of high-grade ventricular arrhythmias were similar (Figure 9.2A). However, in patients with a reduced ejection fraction, high-grade ventricular arrhythmias were consistently reduced in patients allocated to captopril, with a difference reaching statistical difference at 12 months (Figure 9.2B). Patients with an ejection fraction above the median were characterized by the absence of left ventricular dilatation, whereas a significant increase in end-diastolic volume was seen in those with a reduced ejection fraction.

Discussion

In this double-blind, placebo-controlled study a reduction of early postinfarction arrhythmic events was observed in patients randomized to the ACE inhibitor captopril. No effect was found on late arrhythmic events, although high-grade ventricular ectopy during Holter monitoring was reduced in a subgroup of patients with pronounced left ventricular dysfunction. These effects may be explained by a reduction of enzymatic infarct size, early blunting of the neurohumoral response, beneficial effects on potassium levels, and reduction of left ventricular dilatation during follow up.

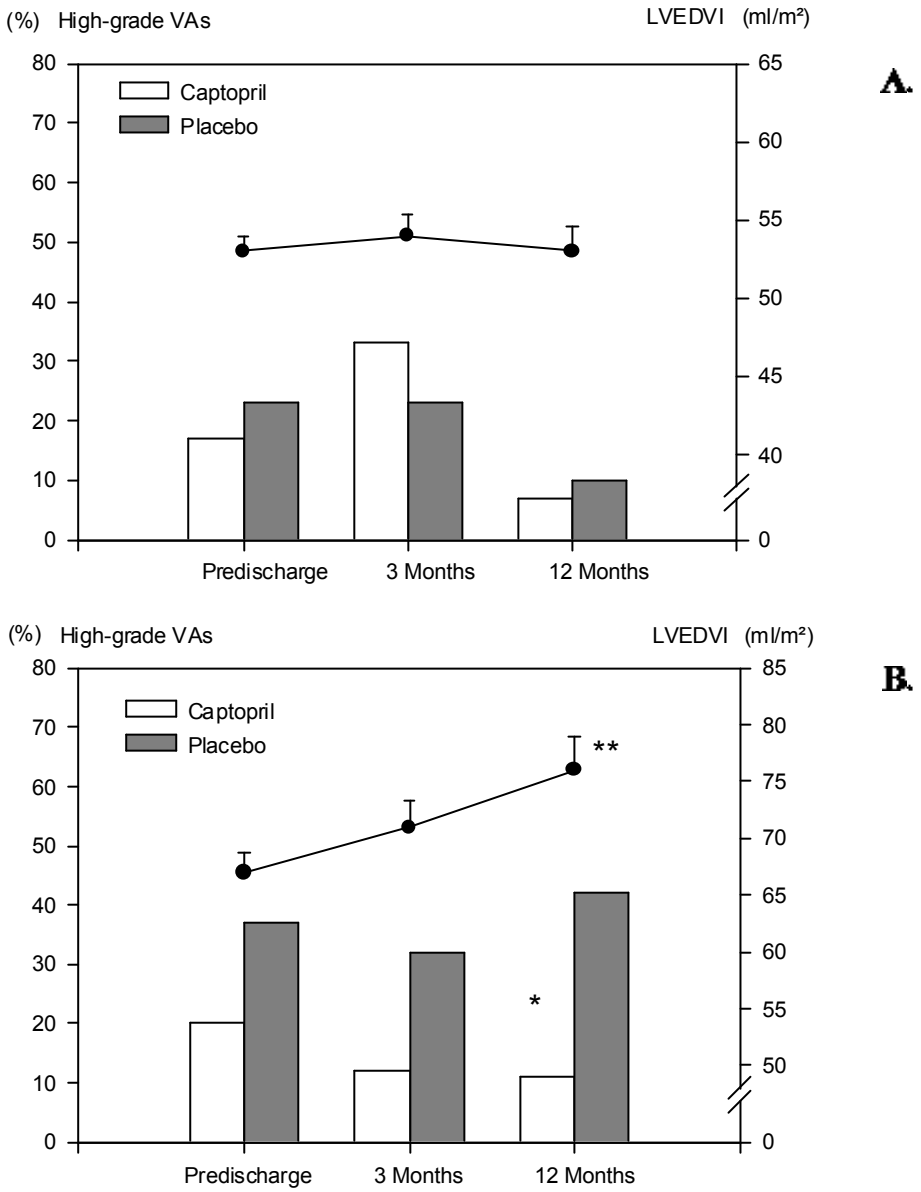

Figure 9.2. Effect of captopril on high-grade ventricular arrhythmias in subgroups of preserved (panel A) and reduced (panel B) ejection fraction. For explanation, see text. LVEDVI, left ventricular end-diastolic volume index; VAs, ventricular arrhythmias. $^{*}p=0.039$, $^{**}p=0.001$.

Early ventricular arrhythmias - previous studies

A limited number of studies have investigated the effects of ACE inhibition on ventricular arrhythmias early after myocardial infarction. Ray et al.[27] studied the effect of captopril, administered a mean of 15 hours after the onset of symptoms in 99 patients with acute myocardial infarction. None of the patients received thrombolytic therapy; patients with small infarcts were excluded. There was no difference in the incidence of ventricular arrhythmias during the first 24 hours. Pipilis et al.[28] investigated the effects of ACE inhibition 13 hours after onset of symptoms in 100 patients, 92 of whom received thrombolytic therapy (ISIS-4 pilot study). There was a non-significant reduction of VT and AIVR after captopril treatment. Bussman et al.[29] found a significant reduction of ventricular arrhythmias after captopril during the first 48 hours of Holter monitoring in 49 patients (50% received thrombolytic therapy). None of the patients in the captopril group had VF during this period, compared to seven patients in the placebo group. Study medication was given intravenously a mean of 10 hours after the onset of symptoms. In the present study, study medication was administered during thrombolytic therapy at a mean of 3.5 hours after onset of symptoms. A significant reduction of early ventricular arrhythmias requiring therapy was observed (3% vs 10%, p=0.018). These data suggest that the time of administration may be an important determinant of the anti-arrhythmic effect of ACE inhibitors, with a more pronounced effect when ACE inhibition is applied earlier. Di Pasquale et al.[30] addressed this issue using a randomized design. In their study, captopril treatment started before thrombolytic therapy was compared to treatment initiated several days later. Early treatment resulted in significantly less ventricular arrhythmias compared to late treatment. This may be caused by the fact that the incidence of ventricular arrhythmias drops rapidly beyond 12 hours after the start of symptoms.[31] When the incidence of arrhythmias is low, a treatment effect may be difficult to detect and clinically less relevant. In addition, potentially anti-arrhythmic effects of ACE inhibitors may be especially operative during the early stages of myocardial infarction.

How do ACE inhibitors reduce early ventricular arrhythmias ?

It is generally accepted that ACE inhibitors do not have direct anti-arrhythmic effects.[32] Despite this, substantial reductions in the incidence and duration of VF upon reperfusion have been reported in experimental studies.[9-11] In these studies, this was attributed to the observed limitation of myocardial injury and reduction of catecholamine overflow. This beneficial effect on ventricular ar-

rhythmias, infarct size and norepinephrine levels was abolished by indomethacin, suggesting a prostaglandin-mediated mechanism.[10] In contrast to these experimental studies, where rapid and complete reperfusion was accomplished after a short episode of ischemia (minutes), thrombolysis in man provides gradual reperfusion several hours after the onset of ischemia. After one hour or more of ischemia, AIVR and nonsustained VT become the dominating reperfusion arrhythmias,[33] both of which are considered relatively harmless. Still, life-threatening ventricular arrhythmias requiring therapy did occur in the early stages after thrombolytic therapy (Table 9.1), and these arrhythmias appeared to be reduced by ACE inhibition. This may be explained by modulation of several arrhythmogenic factors.

Myocardial ischemia is a major causative factor of early ventricular arrhythmias.[34] It has been shown that patients with early VF are characterized by more extensive coronary artery disease.[35] A reduction of myocardial ischemia may be accomplished by a reduction of blood pressure and/or heart rate after ACE inhibition. However, in CATS there were no significant differences in blood pressure, heart rate or rate-pressure product between patients allocated to captopril or placebo during the first few days after myocardial infarction, although hypotension occurred somewhat more frequent in patients randomized to captopril.[22] Another mechanism by which ACE inhibition could reduce ischemia may be an increase in collateral flow to the area at risk, as demonstrated by Ertl et al..[36] In this experimental study in dogs, this resulted in a significant reduction of infarct size. Similarly, treatment with captopril in the present study resulted in a reduced enzymatic infarct size, especially in patients with large infarcts. This may indicate that after captopril treatment collateral flow to the area at risk is increased, although the evidence supporting this hypothesis is indirect.

Neurohumoral activation. Denervating the heart before ligation of a coronary artery almost completely prevents the occurrence of subsequent ventricular arrhythmias.[37,38] Pharmacological reduction of sympathetic imput may also result in an anti-arrhythmic effect. As stated before, a reduction of norepinephrine levels after ACE inhibition has been described in animal experiments.[9-11] This reduction was paralleled by a clear-cut reduction of ventricular arrhythmias. In the present study, a modest but significant reduction of norepinephrine levels was observed one hour after the start of captopril. It should be noted that these values represent systemic catecholamine levels, whereas noreprinephrine outflow in the mentioned animal experiments was measured locally in the coronary effluent. Thus, a small reduction in systemic norepinephrine levels may represent a much larger reduction at the site of reperfusion.

Angiotensin II, which is increased in the setting of acute myocardial infarction,[39] also has documented pro-arrhythmic effects.[40] Although this component

of the renin-angiotensin system was not measured directly in CATS, a rapid reduction in angiotensin II levels is likely since ACE activity was already significantly reduced one hour after the first dose of study medication (6.25 mg captopril). So far, the pro-arrhythmic effects of angiotensin II have not been documented in man. Still, the reduction of this peptide may add to the anti-arrhythmic effect of ACE inhibitors.

Electrolytes. Potassium is also important determinant of early ventricular arrhythmias.[41] Although clear effects of ACE inhibition on potassium levels have been reported,[42] no effect was seen three days after start of captopril. However, we did observe a significant increase of potassium levels after six months of treatment.

In conclusion, the reduction of early ventricular arrhythmias is most likely precipitated by a reduction of the ischemic area, resulting in a smaller infarct size, and beneficial effects on norepinephrine and angiotensin II levels.

Late ventricular arrhythmias - previous studies

Most information concerning the effect of ACE inhibition on late ventricular arrhythmias originates from patients with heart failure. Many of these studies have reported a beneficial effect on total mortality.[43-47] In addition, some[45-47] but not all investigators[43,44] have reported an effect on sudden cardiac death. This may be explained by differences in the severity of heart failure, design of the study, and definition of heart failure. Recently, the SAVE investigators[48] reported on the effect of captopril in patients without heart failure, but with significant left ventricular dysfunction (ejection fraction of 40% or less) after myocardial infarction. In this study, total mortality was reduced by 19%. In addition, sudden cardiac death was also reduced by 19%.[49] Additional Holter recordings showed a reduction of VT in the captopril group after one year, compared to a relative increase in the placebo group relative to baseline.[49]

In the present study, late ventricular arrhythmias were not reduced after captopril treatment. In addition, no effect was seen on high-grade ventricular arrhythmias (Lown 4A and B) during Holter monitoring. The differences between CATS and SAVE are substantial: patients in CATS were not selected, and all received thrombolytic therapy, resulting in a median ejection fraction of 56% before hospital discharge. In contrast, in SAVE only patients with an ejection fraction of ≤ 40% were included. Thus, a certain degree of left ventricular dysfunction may be required for ACE inhibitors to produce an effect on late life-threatening ventricular arrhythmias. Søgaard et al.[50] described the effect of captopril on the incidence of ventricular arrhythmias during the first six months

Table 9.5. Early and late effects of captopril

	Captopril	Placebo	p-value
Heart rate (beats/min)	83 ± 17	82 ± 15	0.474
Systolic RR (mmHg)	126 ± 21	126 ± 20	0.773
Rate-pressure product	10547 ± 3151	10352 ± 2676	0.631
α-HBDH (U/l)			
peak	669 ± 454	876 ± 720	0.019
Q72 all infarcts	1166 ± 886	1390 ± 1109	0.077
Q72 large infarcts	1873 ± 738	2193 ± 1035	0.045
Norepinephrine after 1 hour (% reduction)	15	8	< 0.001*
ACE activity after 1 hour (% reduction)	11	3	0.001*
Potassium (mmol/l)			
day 3	4.1 ± 0.4	4.1 ± 0.4	0.660
six months	4.6 ± 0.4	4.4 ± 0.4	0.008
Dilatation (%)			
small infarcts	30	19	0.354
medium size	63	40	0.036
large infarcts	87	85	0.955
LV aneurysm (%)			
up to 12 months	19	20	0.960

α-HBDH Q72 indicates cumulative alpha-hydroxybutyrate hydrogenase over the first 72 hours after myocardial infarction; RR, blood pressure. *Significant differences in the captopril group compared to baseline, no differences in placebo group (paired t-test).

after myocardial infarction in patients with left ventricular dysfunction (EF ≤ 45%).

They found a consistent reduction of ventricular arrhythmias in patients treated with captopril. The authors attributed this result to a reduction of left ventricular dilatation and ischemia in the treated group. This further demonstrates the effect of ACE inhibition on ventricular arrhythmias in patients with significant left ventricular dysfunction. In fact, when patients in CATS were divided into two groups separated by an ejection fraction of 56% (median value), a significant effect of ACE inhibition on high-grade ventricular arrhythmias was observed (Figure 9.2, panel B). In conclusion, it appears that ACE inhibition reduces repetitive forms of ventricular ectopy during Holter monitoring in patients with significant left ventricular dysfunction. This may also result in a reduction of sudden cardiac death, although at present the evidence is not conclusive.

How does captopril reduce late ventricular arrhythmias ?

Left ventricular dilatation. In this study, patients with late ventricular arrhythmias were characterized by a reduced ejection fraction, a significantly higher NYHA class, and more frequent use of diuretics (see Table 9.4). This group of patients with left ventricular dysfunction is characterized by progressive left ventricular dilatation (Figure 9.2, panel B). Left ventricular dilatation in the first few weeks after myocardial infarction is a powerful predictor of life-threatening ventricular arrhythmias during follow up.[19] In addition, ongoing dilatation after discharge increases the incidence of ventricular arrhythmias even more.[26] In CATS, left ventricular dilatation was prevented in patients with moderate-sized infarcts (Table 9.5) by treatment with captopril. However, this did not result in a reduction of late arrhythmic events. Still, high-grade ventricular ectopy during Holter monitoring was reduced by captopril in patients with a reduced ejection fraction, a group of patients characterized by progressive dilatation.

Anti-thrombotic effects. Most cases of sudden cardiac death after myocardial infarction are not related to ischemia.[51] In addition, in the present study patients with late ventricular arrhythmia did not show more exercise-induced ischemia compared to other patients (Table 9.4). However, recurrent coronary thrombosis may result in life-threatening ventricular arrhythmias late after myocardial infarction.[52] For instance, in the present study patient 14 (Table II) had VF at day 44, and proved to have a second myocardial infarction. ACE inhibition may also have a beneficial effect on late ventricular arrhythmias related to recurrences of angina pectoris or myocardial infarction. Recent evidence suggests that angiotensin II increases levels of plasminogen activator inhibitor-1, the most important physiological inhibitor of tissue-type plasminogen activator (tPA).[53] This implies that in patients with an activated renin-angiotensin system the risk for recurrent myocardial infarction (and accompanying ventricular arrhythmias) may be increased. Furthermore, ACE inhibition may reduce the incidence of these thrombotic events. In the SAVE trial,[48] the incidence of reinfarction was reduced significantly in patients treated with captopril. The SOLVD investigators also reported a (nonsignificant) reduction of death due to myocardial infarction in patients with heart failure.[44] In CATS, no effect on thrombotic events or thrombosis-related ventricular arrhythmias was observed. This may be due to the small number of patients studied and the relatively short duration of follow up. In addition, the renin-angiotensin system may have been activated in

only a limited number of patients, since 50% of the patients had an ejection fraction of more than 56% at discharge.

Potassium. Most of the anti-arrhythmic effect of ACE inhibitors in patients with heart failure has been attributed to the potassium-sparing effect of these agents.[54] In the present study, potassium was significantly increased in patients treated with captopril after six months. However, patients with late ventricular arrhythmias requiring treatment were not characterized by low potassium levels (Table 9.4). Still, since these patients are frequent users of diuretics compared to patients without late ventricular arrhythmias (50 vs 19%, p=0.004), hypokalemia is more likely to occur in these patients, which may result in more arrhythmic events.

Conclusions

In this study, ventricular arrhythmias requiring therapy early after myocardial infarction were reduced by captopril administered during thrombolysis. An increase of collateral flow to the infarcted area may be the predominant mechanism, since heart rate and blood pressure were not reduced after ACE inhibition, and ischemia is known to be the predominant cause of these arrhythmias. In addition, a reduction of norepinephrine levels and ACE activity, presumably leading to lower angiotensin II levels, may add to the anti-arrhythmic effect. Late ventricular arrhytmias that were life-threatening or required treatment were not reduced by captopril. This lack of effect may be caused by the relatively well-preserved left ventricular function in CATS patients. This was supported by the finding that high-grade ventricular ectopy during Holter monitoring was reduced in a subgroup of patients with a reduced ejection fraction.

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