CHAPTER 10. Summary and concluding remarks

The Captopril And Thrombolysis Study (CATS) investigated the effects of the ACE inhibitor captopril administered during thrombolytic therapy on left ventricular remodeling, neurohumoral activation, and ventricular arrhythmias in 298 patients with a first anterior myocardial infarction. In this thesis, focus was on the relation between dilatation of the left ventricle, activation of neurohumoral systems, and the occurrence of ventricular arrhythmias in the CATS population. These phenomena were assessed using quantitative echocardiography, determination of neurohormones, and ambulatory electrocardiography. Underlying mechanisms were explored more in depth by signal-averaged electrocardiography, body surface mapping and assessment of heart rate variability.

Early observations (within 48 hours after thrombolytic therapy)

The design of CATS was based on a series of experimental studies in which the effect of ACE inhibition during ischemia and reperfusion was investigated. These studies demonstrated that ACE inhibition resulted in limitation of myocardial injury upon reperfusion, reduced release of catecholamines, and a reduction of reperfusion-related ventricular arrhythmias. However, there were considerable differences between these experimental studies and the clinical setting in which CATS was conducted (Table 10.1). First, the experimental studies used animals without preexisting disease, whereas patients participating in CATS all had coronary artery disease. In addition, the duration of ischemia preceding reperfusion was considerably longer in CATS compared to the experimental setting. Furthermore, reperfusion was immediate and complete in the experimental studies compared to gradual restoration of flow during hours to days in 79% of patients, with 21% of study subjects showing no reperfusion at all. This resulted in a different spectrum of ventricular arrhythmias. Ventricular tachycardia and Accelerated IdioVentricular Rhythm (AIVR) were the predominant repetitive ventricular arrhythmias during the first 48 hours after thrombolytic therapy. When an ischemic period of 15-30 minutes is applied in the experimental setting, ventricular fibrillation is the most frequently observed arrhythmia. In contrast to the experimental setting, only five patients (2%) in CATS had ventricular fibrillation early after thrombolytic therapy. Furthermore, the dosage of captopril used in CATS was considerably lower than the dose administered in many experimental studies. Still, this lower dosage did reduce myocardial injury, quantified by $\alpha$-HBDH values (Chapter 7). In parallel to this finding, systemic norepinephrine levels were reduced in patients treated with
captopril. Finally, treatment with captopril resulted in a reduction of early ventricular arrhythmias requiring anti-arrhythmic therapy.

In chapter 9, the characteristics of patients with early ventricular arrhythmias in CATS were investigated. A large enzymatic infarct size and a high wall motion score as a measure of left ventricular dysfunction proved important determinants of patients with early ventricular arrhythmias. This was paralleled by a trend towards a larger end-systolic- and end-diastolic volume. In addition, norepinephrine levels 1 hour after thrombolytic therapy were increased in patients with these arrhythmias. Vice versa, patients with increased cumulative norepinephrine levels up to 96 hours after thrombolytic therapy showed more early ventricular arrhythmias during Holter monitoring in the early phase. However, increased cumulative catecholamine levels did not predict the occurrence of late ventricular arrhythmias (Chapter 5).
Mechanisms by which ACE inhibition may reduce early ventricular arrhythmias

Similar to the preclinical studies, infarct size and norepinephrine levels were reduced by ACE inhibition early after thrombolytic therapy (Chapter 7). A rapid reduction of ACE activity within one hour suggests a reduction of angiotensin II levels, a potentially arrhythmogenic component of the renin-angiotensin system. An effect on left ventricular volume was not detectable at this early stage. In addition, heart rate and blood pressure were not influenced significantly by ACE inhibition in the first hours after randomization. This would lead to the conclu-
sion that the reduction of myocardial injury and neurohumoral activation, rather than possible effects on wall stress and/or myocardial ischemia, appeared to be the mechanisms by which early ventricular arrhythmias were reduced. However, reduction of ischemia by increase of collateral flow as a possible mechanism can not be excluded.

Late observations (after 48 hours up to one year)

In recent years, it has become clear that an enlarged end-systolic volume assessed 4-8 weeks after myocardial infarction is an important determinant for the occurrence of late ventricular arrhythmias. In Chapter 2, we studied this relation between left ventricular dilatation and ventricular arrhythmias in more detail. Patients who died suddenly, presumably due to ventricular arrhythmias, were characterized not only by a large end-systolic volume at discharge, but also by progressive left ventricular dilatation during follow up. In addition, ongoing dilatation during the first year after myocardial infarction predicted the prevalence of nonsustained ventricular arrhythmias during Holter monitoring at one year independently of end-systolic volume at discharge. This implies that the association between left ventricular dilatation and ventricular arrhythmias is a dynamic one: left ventricular dilatation at discharge is not only associated with even more dilatation, but also leads to an increased incidence of ventricular arrhythmias during follow up. In other words, dilatation begets dilatation, but this in turn also begets late ventricular arrhythmias.

In Chapters 3 and 4, the underlying electrophysiological mechanisms of the relation between dilatation and ventricular arrhythmias were investigated. Previous data suggested that an acute increase in left ventricular volume results in an increased dispersion in refractoriness. However, the effects of chronic dilatation on repolarization characteristics were not well known. Body surface mapping in 78 CATS patients (Chapter 3) revealed that chronic left ventricular dilatation was paralleled by increased nondipolarity of QRST integral maps, a measure of dispersion in refractoriness. In addition, filtered QRS duration, which is also considered an electrical expression of left ventricular dilatation, was prolonged in patients with an increased end-diastolic volume (Chapter 4). However, by means of multiple regression analysis we demonstrated that early dilatation within 24 hours, and not subsequent dilatation during follow up, determined this prolongation of QRS duration. These data suggest that early dilatation, largely determined by acute functional dilatation and expansion of the infarcted area, is associated with a delay in conduction time, whereas late dilatation, occurring in infarcted and noninfarcted areas, contributes to an increased dispersion in refractoriness.
Another factor which may add to the arrhythmogenic effects of a dilated left ventricle is concomitant neurohumoral activation. Sympathovagal imbalance is a well-known risk factor for the occurrence of life-threatening ventricular arrhythmias. This state can be detected indirectly by heart rate variability assessment. In CATS, we measured heart rate variability in 175 CATS patients before discharge, and in a smaller group of 120 patients after three months (Chapter 6). At discharge, end-systolic volume and end-diastolic volume were comparable in patients with and without a reduced heart rate variability. However, during the first year of follow up the increase in end-diastolic and end-systolic volume was more pronounced in patients with a reduced heart rate variability. In addition, patients with left ventricular dilatation were characterized by a reduced heart rate variability at discharge. Surprisingly, heart rate variability was no longer reduced in patients with dilatation after three months of follow up. These data suggest that persistent neurohumoral activation can contribute to left ventricular dilatation in the early phase, when scar tissue formation is incomplete and the infarcted area is still very vulnerable to straining forces. However, this relation between neurohumoral activation and ventricular dilatation does not last until three months, when heart rate variability is no longer different in patients with and without dilatation. Consequently, it is not likely that the late arrhythmogenic effects of left ventricular dilatation can be fully explained by concomitant neurohumoral activation. However, this does not exclude the possibility of a change in local sympathetic activity when the left ventricle is dilated, leading to an increased dispersion in refractoriness. Other studies have recently supplied information to support this hypothesis. Furthermore, in several studies the independent predictive value of a reduced heart rate variability for the occurrence of late ventricular arrhythmias was demonstrated. We only found a trend in this direction (Chapter 6), which may have been caused by the small number of late ventricular arrhythmias observed in this particular group of patients.

Treatment with captopril resulted in a reduction of the number of patients developing left ventricular dilatation (Chapter 8). This was paralleled by a reduction in the proportion of patients developing heart failure. In contrast to the early postinfarction period, ventricular arrhythmias late after myocardial infarction were not reduced in patients treated with ACE inhibition (Chapter 9). Recently, other studies have reported a reduction of late postinfarction ventricular arrhythmias by ACE inhibition. In these studies only patients with a clearly reduced left ventricular function were investigated. It may well be that patients in these studies had a larger infarct size with more left ventricular dilatation and subsequent ventricular arrhythmias. In CATS, approximately one third of patients did not show any dilatation at all, which may explain the low incidence of late ventricular arrhythmias and sudden cardiac death (2%) found in this study.
In fact, when patients with a reduced ejection fraction were selected, we did observe a reduction of nonsustained ventricular arrhythmias in patients treated with captopril.

Implications for clinical practice

The findings of CATS are confirmed by much larger studies like GISSI-3 and ISIS-4, in which it is shown that ACE inhibition can safely be applied early after acute myocardial infarction in patients without severe heart failure, hypotension, or renal failure. Data from our study suggest that the early reduction of mortality observed in these large trials may well be based on a reduction of ventricular arrhythmias, at least in patients with anterior wall myocardial infarction. After the early phase of myocardial infarction, patients with moderate-sized infarcts are most likely to benefit from ACE inhibition, since in these patients left ventricular dilatation and the occurrence of heart failure were significantly reduced by treatment with captopril. In addition, in this group of patients an effect on non-sustained ventricular arrhythmias, and possibly also on sustained ventricular arrhythmias, may be expected.

These findings support a treatment strategy in which all patients with anterior myocardial infarction, and without signs of severe heart failure, hypotension, or renal failure receive an ACE inhibitor during thrombolytic therapy or at least within 24 hours after onset of symptoms. When no left ventricular dilatation is observed, left ventricular function is (close to) normal, and there are no signs of persistent neurohumoral activation (e.g., increased heart rate, reduced heart rate variability), the likelihood of benefit is low and treatment can be stopped. Conversely, in patients showing left ventricular dilatation and/or neurohumoral activation, a beneficial effect on left ventricular remodeling and accompanying ventricular arrhythmias may be expected.

Indications for future research

Many clinical studies have demonstrated a beneficial effect of ACE inhibition on left ventricular remodeling. In CATS, an effect on infarct size, one of the major determinants of remodeling, was also observed. Since the treatment effect observed was not very large, and limited mostly to patients with large infarcts, this result needs further investigation. Furthermore, some studies suggest that the incidence of ventricular fibrillation is increased after very early thrombolytic
therapy (i.e., within one hour after onset of symptoms). Since experimental evidence of an anti-arrhythmic effect of ACE inhibition was especially observed after a short duration of ischemia, ACE inhibition during this very early phase may help to reduce the high incidence of life-threatening arrhythmias in this period. In addition, immediate and complete reperfusion, as opposed to gradual reperfusion, may also reduce the threshold for ventricular arrhythmias. This mode of reperfusion is typical for coronary angioplasty (PTCA), a procedure which is increasingly used in the acute phase of myocardial infarction without preceding thrombolytic therapy. Some studies have already reported an increased incidence of ventricular fibrillation after direct angioplasty for acute myocardial infarction. It should be investigated whether ACE inhibition may further increase the safety of this procedure when used in the setting of acute myocardial infarction.

Final conclusions

Neurohumoral activation is still a major determinant of early ventricular arrhythmias in the setting of thrombolytic therapy for acute myocardial infarction. Increased sympathetic activity and early activation of the renin-angiotensin system after myocardial infarction are modulated significantly within one hour after administration of the ACE inhibitor captopril. Together with the observed reduction of infarct size after captopril treatment, these effects may explain the observed reduction of early postinfarction ventricular arrhythmias.

Progressive dilatation of the left ventricle proves an important determinant of late ventricular arrhythmias after thrombolytic therapy. Left ventricular dilatation may be promoted by persistant neurohumoral activation, and is associated with distinctive changes in electrophysiology, which include prolonged QRS duration and increased dispersion in refractoriness. Treatment with captopril results in a reduction of left ventricular dilatation and accompanying signs of heart failure, especially in patients with moderate-sized infarcts. A reduction of late ventricular arrhythmias is observed only in patients with significant left ventricular dysfunction.

These clinical observations confirm results from experimental studies and support the early use of ACE inhibition during thrombolytic therapy in patients with anterior myocardial infarction. In the later phases of myocardial infarction, patients with moderate but not severe left ventricular dysfunction are most likely to benefit from this treatment.