SUMMARY AND FUTURE PERSPECTIVES
This thesis discusses the occurrence and treatment of acute myocardial infarction with a specific focus on symptom onset time and symptom onset to treatment time.

Symptom onset
Part 1 of this thesis focuses on symptom onset time. Chapter 1 is a review article that describes the epidemiology, circadian variation, and triggers of sudden cardiac death. Sudden cardiac death accounts for over 5% of mortality in the Western World and can be attributed to acute myocardial infarction or chronic coronary artery disease in about 80% of cases. Risk stratification and prevention of sudden cardiac death constitutes a major challenge as 50% of the deaths occur in patients without previously diagnosed heart disease. Sudden cardiac death follows a circadian pattern with an excess incidence in the morning hours of about 30%. This pattern is believed to be the result of morning changes in (neuro)hormonal, hemodynamic, and prothrombotic factors, such as sympathetic tone, heart rate, blood pressure, cortisol levels, and platelet aggregability. Accordingly, the morning hours can be regarded as a trigger for sudden cardiac death in susceptible individuals. Other triggers for sudden cardiac death that have been identified include anger, mental stress, and physical activity.

In chapter 2, we investigated the circadian, weekly, and seasonal pattern of coronary stent thrombosis in the Mayo Clinic Percutaneous Coronary Intervention (PCI) registry. Among 124 patients, we found a predisposition for the occurrence of stent thrombosis in the morning hours. This pattern was absent or less pronounced in late and very late stent thrombosis (>30 days after stent implantation). While we found no weekly pattern, stent thrombosis occurred more often in the summer. In an exploratory analysis, we identified several potential triggers of stent thrombosis, including physical exertion, medication non-compliance, and infections. Most of our findings have now been corroborated by simultaneous,\textsuperscript{1} and subsequent publications.\textsuperscript{2}

The association between symptom onset time and biochemical infarct size among patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI is investigated in chapter 3. In a registry of 2 large PCI-capable centers comprising 6799 patients, we found that infarct size in STEMI patients exhibits a circadian variation of 19% with largest infarct size occurring in patients with symptom onset at night and smallest infarct size in patients with symptom onset in the morning. This pattern was consistent across subgroups, with the exception of patients with prior myocardial infarction, who displayed
an inverse pattern. The association between symptom onset time and infarct size persisted after multivariable adjustment for baseline characteristics and ischemic time. Even so, symptom onset time did not predict mortality at 1-year follow-up. Although the presence of circadian variation in cardiovascular diseases — in particular acute myocardial infarction — is well established, we are only just beginning to understand its pathophysiological basis and potential therapeutic targets. Peripheral molecular clocks consisting of transcriptional-translational feedback loops with a free running period of 24 hours have been identified in numerous human tissues and organs, including the heart. These peripheral molecular clocks can be synchronized by the central circadian clock located in the suprachiasmatic nucleus of the hypothalamus, which itself is synchronized by daylight. Peripheral molecular clocks are probably useful under physiological circumstances where they help to adapt to the different bodily requirements during the day- and nighttime. However, evidence is emerging that peripheral molecular clocks also play a role in disease. Polymorphisms of the Period3 gene, one of the key components of the molecular clock, differ in STEMI patients according to time of symptom onset, suggesting that different clock genotypes might influence the specific timing of onset of STEMI. Furthermore, an experimental study found that time of coronary occlusion greatly influenced infarct size in normal mice, but not in mice that were genetically modified to lack the cardiomyocyte circadian clock. These findings indicate the possibility of circadian dependence of myocardial tolerance to ischemia/reperfusion injury. The results of this thesis reinforce this concept by showing that there is an independent association between symptom onset time and infarct size in human subjects as well. Further elucidation of the genetic and molecular basis of circadian variation in acute myocardial infarction may help to identify specific targets for novel therapies. In the meantime, it is important to highlight some pharmacological implications of circadian variation in myocardial infarction that are often overlooked. In the late 1980’s, beta-blocker use was shown to attenuate circadian variation in the onset of myocardial infarction in the population of the ISAM trial. Similarly, the alternate-day use of aspirin diminished the circadian variation in myocardial infarction in the Physicians’ Health Study. The results of these studies have led some to believe that these drugs completely abolish the circadian variation in acute myocardial infarction. Our current finding of circadian variation in stent thrombosis argues against
this theory, as the vast majority of our study population was on these agents when developing stent thrombosis. In addition, a secondary analysis of the TRITON-TIMI 38 trial showed that the greatest absolute reduction in the incidence of stent thrombosis in patients randomized to prasugrel versus clopidogrel was due to a reduction in early morning events.\textsuperscript{2} Thus, even in patients on both aspirin and clopidogrel, there seems to be a residual risk of thrombotic events in the morning hours. More potent antiplatelet therapy with prasugrel or ticagrelor may reduce this risk. Alternatively, this risk could be lower when antiplatelet therapy is administered in the evening rather than the morning. Another avenue of future interest is the time-dependent efficacy of pharmacological treatment (i.e. \textit{chronotherapy}). In a trial of 2156 hypertensive subjects, patients randomized to ingestion of ≥1 antihypertensive agent in the evening had better blood pressure control and fewer cardiovascular events after a median follow-up of 5.6 years as compared with controls who used all antihypertensive medications in the morning.\textsuperscript{10} This study shows that the simple act of changing the time of medication ingestion might exert an effect on clinical outcome. Along this line of investigation, treatment with the short-acting ACE-inhibitor captopril only benefited cardiac remodeling when it was administered during sleep time as compared with wake time in a mouse model of pressure overload.\textsuperscript{11} If confirmed with different agents and in human subjects, night time administration of short-acting medicine could be particularly useful in patients that currently experience debilitating side-effects from long-acting agents.

\textbf{Symptom onset to treatment} Part 2 of this thesis discusses symptom onset to treatment time. In chapter 4, we validated patient-reported symptom onset time with biochemical onset time in 607 STEMI patients undergoing primary PCI. Biochemical onset time was estimated by backward modeling of serial rising cardiac troponin T measurements. We found that reported symptom onset time is typically later than biochemical onset time, with a median difference of 4.2 hours. This phenomenon was especially pronounced in the elderly, patients with a lower body mass index, patients without a history of PCI, and patients with residual flow in the culprit coronary artery. When reported symptom onset time was used to determine ischemic time, no association with biochemical infarct size or 1-year mortality was found. However, recalculation of ischemic time with biochemical onset time greatly enhanced its association with both infarct size and mortality. These results indicate that reported time of
symptom onset does not necessarily reflect the true time of coronary occlusion and that this phenomenon can compromise the prognostic value of conventional ischemic time (i.e. symptom onset to treatment time). This finding is in accordance with prior studies that have also noted that more objective measures of delay, such as first medical contact to treatment time\textsuperscript{12,13} and the presence of Q waves on the baseline electrocardiogram (ECG)\textsuperscript{14} outperform ischemic time as prognostic markers. When considering these studies, it is important to realize that the limited prognostic value of ischemic time most likely reflects an artifact that is induced by the subjectivity of (recollection of) symptom onset time and that minimization of ischemic time should remain a key goal in STEMI care.

One of the principal strategies to reduce ischemic time in STEMI patients is 12-lead ECG based prehospital diagnosis and direct referral to a primary PCI-capable center. In 2004, a prehospital triage protocol was implemented in the northeastern part of the Netherlands to facilitate this. In chapter 5, we assessed the coverage of this STEMI network by evaluating the incidence, predictors, and clinical impact of interhospital transfer for primary PCI after initial referral to a non-PCI-capable center due to a failed prehospital STEMI diagnosis. Among 846 consecutive STEMI patients undergoing primary PCI, the incidence of interhospital transfer after failed prehospital diagnosis was still 15\% and occurred more often in women, diabetics, patients with a history of myocardial infarction, and patients with STEMI onset at a greater distance of the PCI-capable center. Interhospital transfer was independently associated with a 47\% increase in ischemic time, which was mainly the result of a relatively long door-in to door-out time at the non-PCI-capable center. One-year mortality was higher among patients undergoing interhospital transfer, although this was at least in part due to a more high-risk baseline profile. With first medical contact to treatment times ≤120 minutes in 90\% of patients with a prehospital STEMI diagnosis, our prehospital triage protocol shows excellent performance that is comparable with other highly developed STEMI networks.\textsuperscript{15} Therefore, efforts to further increase the proportion of STEMI patients included in these networks are more likely to improve outcome than attempts to further reduce delays among patients already diagnosed in the prehospital setting. This could, for instance, be done by lowering the threshold to include patients with suspected acute coronary syndrome and indeterminate ECG patterns. Delays in these patients are generally long, whereas they are at high risk of adverse outcome.\textsuperscript{16,17} While STEMI patients require rapid
reperfusion therapy, preferably by means of primary PCI, time to treatment is more complex in patients with non-ST-elevation myocardial infarction (NSTEMI). Chapter 6 summarizes current evidence on the role and timing of coronary intervention in patients with NSTEMI. These patients require a risk assessment upon admission, ideally by means of a validated risk score such as the Global Registry of Acute Coronary Events (GRACE) score. Patients with a low baseline risk may be treated conservatively with an anticoagulant and dual antiplatelet therapy. Initial invasive management is usually preferred in patients with a higher baseline risk. These patients undergo coronary angiography and possible subsequent revascularization by PCI or coronary artery bypass grafting (CABG) after a pharmacological pretreatment regimen that is similar to that of the conservative group. In patients with non-ST-elevation acute coronary syndromes (NSTE-ACS; unstable angina or NSTEMI) selected for an initial invasive strategy, the optimal timing of coronary angiography has been the subject of several randomized trials. In chapter 7, we performed a meta-analysis of 8 published trials randomizing 5904 NSTE-ACS patients to early versus delayed invasive management to assess the relationship between timing of intervention and clinical outcome in NSTE-ACS patients. A U-shaped relationship between delay to intervention and the occurrence of myocardial infarction was found, with an optimal time window between 20 and 40 hours after admission. Earlier invasive management probably increases the risk of periprocedural myocardial infarction, while delays beyond 40 hours increase the risk of spontaneous myocardial infarction in high-risk patients. While NSTE-ACS patients do not require the “time is muscle” approach that is generally accepted in STEMI patients, early diagnosis and initiation of pharmacological pretreatment is clearly indicated. The first steps towards prehospital risk stratification of NSTE-ACS patients with point of care high-sensitivity troponin T assays are currently being undertaken. If proven to be feasible, paramedics may identify high-risk NSTE-ACS patients that are likely to benefit from initial invasive management in the prehospital phase, thereby allowing for direct initiation of medical pretreatment and transportation to a PCI-capable center. This would diminish the need for interhospital transfer, which still causes delays to intervention beyond 40 hours in >50% of NSTE-ACS patients selected for an initial invasive approach.

**Treatment**

Inhospital treatment is investigated in part 3. In chapter 8, we studied the
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The impact of thrombus aspiration before primary PCI on myocardial reperfusion and clinical outcome in 113 patients with coronary stent thrombosis. The use of thrombus aspiration was found to be independently associated with improved epicardial and microvascular myocardial reperfusion. Furthermore, fewer balloon dilatations were required in patients treated with thrombus aspiration and the rate of procedural complications such as distal embolization and side branch occlusions was lower. No significant differences were seen in 1-year mortality, although numeric mortality was lower in patients treated with thrombus aspiration in this small observational study. The publication of the TASTE trial has cast doubts on the clinical benefit of routine use of thrombus aspiration in patients with STEMI, as no reduction in 30-day mortality was found. The results of the ongoing TOTAL trial (NCT01149044) may help to definitively determine the usefulness of thrombus aspiration in STEMI. For now, it is reasonable to perform thrombus aspiration in selected patients. Due to their high thrombus load, patients with stent thrombosis seem to be suitable candidates for thrombus aspiration. This is evidenced by the results of our study as well as studies that have subsequently been published. However, it is important to note that evidence regarding the efficacy of thrombus aspiration in stent thrombosis is – and will most likely remain – non-randomized. The incidence of stent thrombosis is already low and will probably drop even further due to the uptake of new-generation drug-eluting stents and more potent antiplatelet therapy, thus making it extremely challenging to conduct a trial in these patients.

In hemodynamically stable STEMI patients with multivessel disease, there is an ongoing debate about the optimal treatment strategy of non-culprit lesions after primary PCI of the infarct related artery. If amenable for PCI, these lesions may be treated during the initial PCI procedure (multivessel PCI), during subsequent procedures (staged PCI), or only if clinically indicated during follow-up (culprit only PCI). In chapter 9, we conducted a network meta-analysis of prospective and retrospective studies that reported on clinical outcome with at least 2 of the 3 strategies. A total of 18 studies with a cumulative sample size of 40,280 patients were included. The framework of a network meta-analysis allowed us to consider both direct and indirect evidence. We found that staged PCI was associated with the lowest short- and long-term mortality rates, followed by culprit only PCI, and multivessel PCI, respectively. Although staged PCI is now the guideline-recommended approach in STEMI patients with multivessel disease, evidence is surprisingly limited. Our
analysis only included 4 prospective studies,\textsuperscript{26-29} three of which were small randomized clinical trials.\textsuperscript{26-28} Recently, the PRAMI trial has been published, showing a significant reduction in the composite of cardiac death, myocardial infarction, and refractory angina with multivessel PCI as compared with culprit only PCI after a mean follow-up of 23 months.\textsuperscript{30} With a sample size of only 465 patients, this trial is larger than all previous randomized trials on this topic combined. But where does it leave us? Although the finding of a benefit of multivessel PCI over culprit only PCI appears compelling, this trial did not consider the currently recommended strategy of staged PCI. The CvLPRIT trial is in the late stages and will provide more insight into the impact of multivessel PCI versus culprit only PCI on clinical outcome in STEMI patients.\textsuperscript{31} In addition, larger studies are underway that will assess the role of fractional flow reserve guided multivessel PCI versus culprit only PCI (CompareAcute; NCT01399736) and staged PCI versus culprit only PCI (COMPLETE; NCT01740479).

Finally, in chapter 10, we hypothesized that event rates are commonly lower than expected in randomized clinical trials, which may compromise the statistical power to draw firm conclusions from the observed results. We selected the latest randomized trials on 10 preselected topics in the field of cardiovascular interventions and devices and assessed the observed and estimated event rate in the control group, as this is not affected by the uncertain efficacy of the experimental treatment. Twenty six trials, randomizing 19,029 patients were included. Event rates in the control group were lower than estimated in 73% of the trials. The observed event rate was on average 23% lower than estimated and an even greater lack of events was seen in randomized trials evaluating biodegradable polymer drug-eluting coronary stents and renal artery stenting. Due to this lack of events, 79% of the superiority trials with non-significant results were actually “inconclusive” rather than “truly negative” as they could not exclude the possibility of a clinically relevant treatment effect. The results of our study will hopefully fuel the ongoing debate about the ethical justification of conducting underpowered clinical trials.\textsuperscript{32} From a methodological standpoint, there is nothing in the way of conducting a blinded interim sample size recalculation to arrive at a sample size that suits the clinical question the investigators are seeking to answer.\textsuperscript{33} National and international collaborations should be stimulated, to even allow for an appropriate sample size when patient recruitment and event rates are low and to ensure that budgetary restrictions do not prevent promising new therapies from being tested. In addition, novel methods to
reduce the costs associated with trial conduction, such as nesting a trial in existing registries and using factorial designs, should be further explored.\textsuperscript{20,34} The future of evidence based medicine lies in large randomized trials to demonstrate moderate benefits that may translate into substantial health gain on a population level. This has been recognized more than 15 years ago and is probably even more true today.\textsuperscript{35}
REFERENCES


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