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CHAPTER 8

This thesis describes outcome after percutaneous coronary intervention (PCI) in patients with different presentations of coronary artery disease. PCI, usually consisting of balloon dilatation and stenting, is often part of the standard therapy in patients presenting with coronary artery disease. During the past decades, important technical, procedural and pharmacologic developments have resulted in improvements in clinical outcome after PCI.

In the first part of this thesis, the aim was to investigate population trends and outcome after PCI in patients with different presentations of coronary artery disease. In the second part, we focused on parameters influencing outcome after primary PCI in patients with ST-elevation myocardial infarction (STEMI). In the third part, the aim was to investigate the cardioprotective and clinical effects of erythropoiesis-stimulating agents (ESAs), as an adjunctive therapy after primary PCI.

Outcome after PCI in patients with coronary artery disease

In chapter 2, we investigated the clinical characteristics of all consecutive patients undergoing a first PCI procedure in Sweden, in an all-comers registry study over a period of 20 years. The PCI population and their risks have substantially changed. The mean age of the PCI treated patients increased, and patients were more often treated for acute coronary syndromes, and less often for stable coronary artery disease over time. This reflects in part the implementation of primary PCI as the recommended therapy in STEMI patients over the years. Unadjusted data showed that the 1-year mortality after PCI increased over time, but after adjustment for age and indication, a modest decrease was shown, mainly in the subgroup of patients with STEMI. This suggests that the treatment for this indication continuously improves. We may conclude that the patient population undergoing PCI has substantially changed, reflecting the establishment of new evidence into real world clinical practice.

In chapter 3, we described clinical outcome for different indications of PCI, in a contemporary unselected population at short- and long term follow-up. The baseline characteristics and risks differed substantially between patients undergoing PCI for stable coronary artery disease, unstable angina, non ST-elevation myocardial infarction (NSTEMI) and STEMI. During the first year after PCI, the mortality risk was highest in patients with STEMI compared to the other indications of PCI. After the first year after PCI, we observed a substantial difference in the adjusted risk of mortality between patients with and without elevated biomarkers of myocardial damage. In addition, NSTEMI and STEMI patients had a higher risk of myocardial infarction and the development of heart failure compared to patients with stable coronary artery disease and unstable angina on short- and long term. The risk of stent thrombosis was highest in STEMI patients, at short as well as long term follow up. These findings suggest that improvements in therapy are needed in the acute phase as well as on long term. Specifically, therapies and strategies to reduce stent thrombosis and the development of heart failure appear to be important for the reduction of mortality in patients presenting with acute coronary syndromes.
Outcome after primary PCI

Chapter 4 examined the influence of time from symptom onset to reperfusion in STEMI patients undergoing primary PCI, in a contemporary cohort treated with thrombus aspiration and triple-anti platelet therapy. Myocardial reperfusion, as assessed by angiography (myocardial blush grade of 3) and electrocardiography (ST-segment resolution > 70%), significantly decreased after 5 hours of total ischemic time. In addition, ischemic time was associated with mortality at 30 days, and mortality rates were nearly 3 times higher after 5 hours of total ischemic time. However, it should be taken into account that patients presenting after 5 hours were older and had more often cardiovascular risk factors. The majority of STEMI patients were treated with PCI in the first 5 hours after symptom onset. We may suggest that all patients should be treated with primary PCI as soon as possible independent of the time of symptom onset, with treatment within the golden hours of 5 hours resulting in better myocardial reperfusion and clinical outcomes.

In chapter 5, we investigated the incidence and clinical consequences of visible distal embolization on the coronary angiogram after primary PCI in a contemporary STEMI population. The incidence of distal embolization was 6.3%, and this is low compared to previous reports. Early administration of aspirin, heparin and clopidogrel before PCI and systematic use of abciximab at the start of the PCI procedure may have contributed to the low incidence of distal embolization. Distal embolization was associated with worse myocardial reperfusion, higher levels of biomarkers of myocardial damage, and a higher incidence of re-infarction at 1 year after primary PCI. In addition, thrombus composition and size were important determinants of the occurrence of distal embolization. No effect of thrombus aspiration, as adjunctive therapy during PCI, was observed on the incidence of distal embolization. This may in part be a consequence of the low incidence of distal embolization, and the presence of distal embolization already on the initial coronary angiogram before PCI. We conclude that in patients treated with triple anti-platelet therapy, the incidence of distal embolization after PCI is low. However, the presence of distal embolization is associated with impaired myocardial reperfusion and poor outcome.

Effect of erythropoietin on outcome after primary PCI

In chapter 6, we evaluated the long term effects of epoetin alfa administration in STEMI patients undergoing primary PCI. We performed a follow-up study of the HEBE III trial, in which STEMI patients were randomized to standard medical treatment or an additional high dose bolus of epoetin alfa after primary PCI. At 1 year after primary PCI, there was no significant difference in the composite end point of all-cause mortality, re-infarction, target vessel revascularization, stroke and heart failure between patients randomized to standard medical treatment or an additional bolus of epoetin alfa. These results are in contrast with the results of many animal models of acute myocardial infarction, reporting a cardioprotective effect of ESAs after myocardial ischemia. We can conclude that the administration of epoetin alfa in STEMI patients did not result in a reduction of cardiovascular events at 1 year after primary PCI. However, a higher incidence of thrombo-embolic complications, as observed in some previous studies, was not observed in patients receiving epoetin alfa in this study. Whether ESAs
administration in STEMI patients is safe and effective should be further investigated in an adequately powered trial on clinical end points.

In chapter 7, we described the results of a meta-analysis on individual patient data of randomized clinical trials investigating the effect of ESAs administration in patients undergoing primary PCI for STEMI. Individual patient data were obtained from 10 out of 11 identified trials, including 97.3% of all patients randomized to control or to ESAs administration. Baseline clinical characteristics were well balanced between the treatment allocations. We observed no effect of ESAs administration on the composite end point of all-cause mortality, myocardial infarction and in-stent thrombosis. There was a trend towards a lower incidence of mortality in the ESAs group compared to the control group, but the number of events was low. No difference in the risk of thromboembolic events was found between the treatment allocations. As non-significant differences may be caused by low event rates, uncertainty about the positive effect of ESAs administration remains. Current ongoing clinical trials are needed to further clarify the clinical effects of ESAs in STEMI patients.

**Future perspectives**

During the last 2 decades, the characteristics and risks of patients undergoing PCI have changed. In addition, important developments in the PCI procedure have resulted in a continuous decrease in age adjusted mortality over time, especially in STEMI patients. Current knowledge may be translated to suggestions for future clinical trials and interesting fields of research, which may contribute to further improvements.

First, in chapter 2 we suggested that the decrease in mortality in STEMI patients over time may in part be caused by the developments in pre-treatment with antithrombotic and anti-platelet therapies, as recommended nowadays in current guidelines. In chapter 3, we suggested that patients presenting with myocardial damage (NSTEMI and STEMI patients) have a higher risk of mortality compared to patients without myocardial damage (stable coronary artery disease and unstable angina). Myocardial damage should be limited as much as possible. Future improvements might focus on pharmacologic therapies that continue to improve myocardial reperfusion. So far, treatment with ESAs failed, but other adjunctive therapies need to be investigated to reduce myocardial infarct size and heart failure after PCI. On the other hand, delays to treatment should be limited, for example by patient awareness of symptoms of acute coronary syndromes, and thorough pre-hospital logistics and STEMI treatment protocols.

Second, we concluded in chapter 2 that the patient population undergoing PCI has substantially changed over time. As a consequence, the changing PCI population should be taken into account in the design of future clinical trials. The exclusion of high risk subgroups, which may benefit, should be prevented. In registries of patients with acute coronary syndromes or PCI, approximately 30% of patients ages \( \geq 75 \). It may therefore be questioned if elderly patients should be excluded in future randomized clinical trials.

On the other hand, it can be questioned how much new invasive treatment strategies and adjunctive pharmacologic therapies can contribute to a further decrease in adverse clinical events after PCI in the future. The mortality has greatly decreased over time,
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with 1 year incidences in randomized clinical trials often below 5% in patients with acute coronary syndromes undergoing PCI.\textsuperscript{4,5} As a consequence of the decrease in hard clinical end points, the number of included patients should increase in order to perform an adequately powered study. As a solution, surrogate end points, for example myocardial infarct size or measures of myocardial reperfusion, may be chosen as the primary end point of a study. However, another solution may be the performance of a randomized clinical trial based on national health registries. In the concept of a randomized clinical registry trial, first introduced in the TASTE trial, present registries and databases are used as the basis of the clinical trial.\textsuperscript{6} Baseline information that is routinely registered during PCI can be used as clinical report form, which reduces the additional work associated with inclusion.\textsuperscript{7} In addition, clinical end points can be obtained by merging with national health registries. In this setting, patients can be included in a short period. In addition, as costs reduce, it may be possible to investigate important health issues in treatment areas with less commercial interest.

Next to the improvements in treatment strategies of PCI, improvements in outcome should focus on the implementation of evidence based strategies in real world clinical practice. In STEMI patients, it has been described that an increase in the use of evidence based treatments is associated with a reduction in mortality.\textsuperscript{8} Registries have been introduced to improve the quality of care and monitor the implementation of evidence based treatments.\textsuperscript{7,9,10} For further improvements in outcome after PCI, it may become increasingly recommended to monitor the adherence to guidelines in clinical practice, preferably by nation-wide, web based registries.

REFERENCES


