General introduction and aims of the thesis

Marieke L. Fokkema
Background

Cardiovascular diseases are among the most frequent causes of death in the world, with coronary artery disease as the most common cause.\(^1\) In many European countries age adjusted cardiovascular death rates have decreased over time, but still remain a major cause of death, and contribute to a substantial morbidity.\(^2\)

Coronary artery disease is caused by atherosclerosis, a slow but chronic process developing over a period of many years. Patients with coronary artery disease often only present when they have clinical symptoms of coronary artery disease. Patients may present with symptoms of chest pain starting during exercise, and with relieve by rest or nitroglycerin.\(^3\) As a consequence of a flow limiting stenosis, myocardial ischemia can occur in these patients when myocardial oxygen demand exceeds the oxygen supply by the coronary arteries. This presentation is often called stable angina or stable coronary artery disease. On the other hand, patients can present with symptoms of acute chest pain caused by rupture or erosion of an unstable atheromatous coronary plaque.\(^4,5\) After rupture of a fibrous cap, the highly thrombogenic core is exposed to the arterial lumen, causing platelet aggregation, thrombus formation and embolization of thrombus particles into the microvasculature. Acute coronary syndromes are caused by a temporal, partial or total occlusion of a coronary artery, causing myocardial ischemia. Based on electrocardiographic findings and biomarkers of myocardial damage, acute coronary syndromes are divided in unstable angina, non ST- segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).\(^6\)

Percutaneous coronary intervention

Percutaneous coronary intervention (PCI) is often part of the standard therapy in patients presenting with coronary artery disease, usually consisting of balloon dilatation and stent implantation.\(^7\) During the past decades, technical, procedural and pharmacologic aspects of the PCI procedure have been greatly developed, and have resulted in improvements in clinical outcome and a decrease in mortality.\(^8,9\) In 1964, Dotter and Judkins have been the first who introduced the idea of transluminal recanalisation of atherosclerotic stenoses in patients with severe atherosclerotic obstructions.\(^10\) Later, the first balloon coronary angioplasty was performed by Grüntzig in 1977,\(^11\) followed by the development of the first stent by Palmaz in 1985.\(^12\) The use of stents was introduced in clinical practice as effective treatment of complications and restenoses after balloon angioplasty.\(^13\) Subsequently, it has been demonstrated that treatment with stent implantation resulted in a lower incidence of restenosis and a lower rate of repeat procedures as compared with balloon angioplasty alone in patients with stable coronary artery disease.\(^4,15\) In patients presenting with acute myocardial infarction, stent implantation also resulted in improvement of clinical outcome compared to treatment with thrombolysis,\(^16\) and compared to balloon angioplasty alone.\(^17\) In the last decade, many studies have investigated the effects of bare metal stents compared to drug eluting stents. Drug eluting stents reduce the risk of restenosis, and they are nowadays increasingly used in clinical practice.\(^18\) Besides the improvements in PCI, the use of anticoagulation and anti-platelet agents has greatly evolved and is a cornerstone in current treatment of patients with PCI, in the acute
phase in patients with acute coronary syndromes as well as in secondary prevention. In addition, many other adjunctive pharmacologic and catheter based interventions have been investigated to improve outcome after PCI.

**Aims of the thesis**

Clinical outcome after PCI has been influenced by the development of the PCI procedure, adjunctive therapies, as well as by changes in patient characteristics. 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 STEMI patients. 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 the first part of this thesis, we evaluate clinical outcome in an unselected population with coronary artery disease undergoing PCI. The PCI procedure has evolved over the last decades, however, the risk profile of patients and patient characteristics have also changed over time. Primary PCI is nowadays the preferred treatment in patients with STEMI and it is also recommended in patients presenting in the acute phase of high risk NSTEMI. In addition, PCI is increasingly used in patients with more complex coronary lesions. The changing patient characteristics may influence outcome after PCI, in randomized trials as well as registries. Therefore, it is important to understand the changing PCI population in real world clinical practice. In chapter 2, changes in patient characteristics and clinical outcome after PCI are investigated in an unselected nation-wide PCI population, over the last 2 decades.

Differences in mortality have been investigated extensively in patients with different presentations of coronary artery disease, especially in NSTEMI and STEMI patients. However, studies have been inconsistent with regard to short- and long term outcome. In the first year after myocardial infarction, both a higher, comparable and lower mortality have been reported in STEMI patients compared to NSTEMI patients. On the long term, some studies have reported a comparable mortality risk in NSTEMI and STEMI patients, while others observed a higher mortality risk among NSTEMI patients. In these studies, various proportions of patients have been treated with PCI as revascularization strategy and the populations have been selected. Therefore, it may be questionable if the previous studies reflect current real world clinical practice. In chapter 3, we evaluate clinical outcome after PCI in patients with different presentations of coronary artery disease in a nation-wide PCI population.

**Outcome after primary PCI**

In the second part of this thesis, we focus on outcome after primary PCI in patients with STEMI. Next to improvements in treatment strategies in STEMI patients, early reperfusion after onset of symptoms is an important issue in the improvement of outcome after primary PCI. During ischemia the myocardium is damaged, but still viable in part early after the onset of symptoms. The myocardium may be salvaged in case of rapid reperfusion of the infarcted myocardium. In previous studies, the best
Clinical results have been observed in patients undergoing PCI within 90 to 120 minutes after symptom onset. Treatment of STEMI patients with aspirin, heparin and clopidogrel before hospital admission, and glycoprotein IIb/IIIa inhibitors during primary PCI, as recommended in guidelines, may influence the time window to obtain optimal reperfusion. Therefore, in chapter 4, we evaluate the impact of the total ischemic time on myocardial reperfusion and clinical outcome in a large contemporary cohort of STEMI patients undergoing PCI.

A significant proportion of patients treated with PCI shows inadequate reperfusion of the infarcted myocardium after primary PCI, resulting in a larger infarct size, and increased mortality. Suboptimal myocardial reperfusion can be caused by microvascular dysfunction, reperfusion injury, myocardial edema or embolization of thrombotic or atherosclerotic particles. In some patients, embolization can be visible on the coronary angiogram as a filling defect with abrupt cut off distal from the infarct related coronary lesion. In chapter 5, we evaluate the consequences of distal embolization in a contemporary STEMI population treated with triple anti-platelet therapy and thrombus aspiration. The aim is to investigate the prevalence and the consequences on myocardial perfusion and clinical outcomes.

Effect of erythropoietin on outcome after primary PCI

In the third part of this thesis, we investigate the effect of ESAs on clinical outcome after primary PCI. Preclinical studies have suggested that ESAs have a cardioprotective effect after myocardial reperfusion. Subsequently, the effect of ESA administration has been investigated in several clinical studies in patients with STEMI undergoing primary PCI to reduce myocardial infarct size and to improve left ventricular function. ESAs did not show a clear effect on left ventricular function or clinical outcome, but some studies suggested an increased risk of thrombo-embolic events.

The HEBE III study was the largest, prospective study randomizing STEMI patients to a single bolus of epoetin alfa or to standard medical care after primary PCI. The single high dose of epoetin alfa did not show an effect on left ventricular function at 6 weeks after primary PCI. However, patients receiving epoetin alfa had a lower incidence of adverse cardiovascular events at 6 weeks after primary PCI. Therefore, in chapter 6, we evaluate the effect of epoetin alfa on clinical outcome during the first year after primary PCI.

Individual clinical trials investigating the effect of ESAs in STEMI patients thus far have been too small to interpret clinical events, as none of the trials have been powered on clinical end points. The current effects of ESAs are based on a small number of events, and no definitive answers with regard to the safety and effectiveness of ESAs are yet available. Previously, Gao et al. have performed a meta-analysis to investigate the effect of ESAs in STEMI patients. However, this meta-analysis was done on study level and without access to individual data. In chapter 7, we present the results of a meta-analysis on individual patient data of all randomized controlled trials investigating the effects of ESAs in STEMI patients, in order to assess the safety and efficacy of these agents.
REFERENCES


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infarction as defined by the ESC/ACC definition (the OPERA registry). Eur Heart J 2007;28:1409-17.


