The merit of radial access, thrombus aspiration, and drug-eluting stents in primary PCI: controversies in the treatment of acute myocardial infarction

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Introduction and outline of this thesis
ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Epidemiology
Traditionally, cardiovascular disease has been the leading cause of mortality in adults and a major burden to health services and society.\(^1\) Of the various diseases that cover cardiovascular disease, patients who suffer from coronary artery disease in particular draw on health care to a great extent. Over 7 million people worldwide die from coronary artery disease each year, and roughly half of all men and one third of all women aged 40 will develop coronary artery disease during life.\(^2\) In more than 50% of patients the sudden event of acute myocardial infarction is the initial manifestation of coronary artery disease.\(^2,3\) Acute myocardial infarction is associated with a high risk of death, as community studies have shown that the 1-month mortality rate of patients with suspected acute myocardial infarction is approximately 50%.\(^4\) Of these deaths roughly half occur within the first 2 hours. Conversely, patients who are hospitalized with the diagnosis of acute myocardial infarction have a fairly high probability of survival. However, despite the gradual improvement of prognosis in the past decades, large registries indicated that 30-day mortality rates of patients hospitalized with acute myocardial infarction currently range from roughly 6 to 10%.\(^5-8\) The improved survival over the past few decades is generally believed to be a result of enhanced primary and secondary prevention as well as progress in reperfusion treatment in the acute phase. This is thought to be specifically on account of the initiation of mechanical reperfusion therapy and treatment with potent antithrombotic medication.\(^6,9\) Nevertheless, every effort to further improve prognosis remains mandatory, since in addition to the mortality risk more than 10% of patients hospitalized with acute myocardial infarction are readmitted to the hospital within 30 days.\(^10\)

Pathophysiology and diagnosis
Acute coronary syndromes are the clinical expression of progressive atherosclerotic coronary artery disease. Atherosclerosis is a chronic inflammatory disease found in major arteries which has its onset as early as in adolescence, usually decades before it becomes clinically manifest.\(^11-13\) The formation of atheroma depends on
arterial endothelial cell dysfunction secondary to various risk factors as smoking, dyslipidemia, diabetes mellitus and hypertension, which causes leukocytes to migrate from the bloodstream into the arterial intima. These leukocytes subsequently induce the vessel wall to maintain a pro-inflammatory state promoting formation of an atheromatous plaque. Coronary atherosclerosis may progress to a flow-limiting stenosis expressed as chronic stable angina, resulting from luminal narrowing of the coronary artery. Alternatively, sudden disruption of the atheromatous plaque may occur, typically caused by rupture or superficial erosion of the fibrous cap overlying a necrotic core. A lesion that is prone to rupture characteristically is a lipid-rich plaque containing macrophages with intracellular lipid accumulation. Particularly these lipid-laden macrophages, which are referred to as ‘foam cells’, generate various precursors of inflammation and coagulation (inflammatory cytokines, proteases, coagulation factors, radicals, and vasoactive molecules). Consequently, once a lipid-rich plaque becomes disrupted it promotes the formation of thrombus by platelet activation and stimulation of the coagulation cascade. The resulting intracoronary thrombosis, frequently accompanied by vasospasm, may cause myocardial cell necrosis by transient or permanent obstruction of the epicardial or distal coronary artery, or it may obstruct microvascular perfusion by embolization of thrombus and/or atheromatous particles. Clinically, this process results in a broad spectrum of acute coronary syndromes ranging from unstable angina to non-ST-segment elevation myocardial infarction and acute ST-segment elevation myocardial infarction (STEMI). Within the spectrum of acute coronary syndromes, STEMI indicates the abrupt closure of an epicardial coronary artery. Within a time span of minutes, the absence of coronary flow causes prolonged myocardial ischemia in the area the coronary artery supplies, ultimately leading to myocardial necrosis which processes in a wave front from the endocardium to the epicardium. The alteration in transmembrane action potential resulting from cell necrosis is typically reflected by an upward shift of the ST-segment recorded on the 12-lead surface electrocardiogram (ECG). If impaired blood supply persists it subsequently leads to chest discomfort. Consequently, the diagnosis of STEMI is made in the presence of ischemic symptoms and persistent ST-segment elevation on the ECG. Alternatively, it may be established as sudden cardiac death due to acute ventricular arrhythmia in a considerable proportion of patients.
Treatment
In the event of an acute ST-segment elevation myocardial infarction, the primary goal of treatment is to achieve prompt and complete reperfusion of the infarct-related coronary artery. Current clinical practice guidelines state that for patients with the clinical presentation of STEMI, early reperfusion should be performed by mechanical or pharmacological therapy, provided that medical contact was sought within 12 hours after symptom onset and the ECG shows persistent ST-segment elevation or a new or presumed new left bundle-branch block. Of the available methods of reperfusion therapy, mechanical opening and dilatation of the coronary artery by primary percutaneous coronary intervention (PCI) has proven to be the treatment of choice, when performed expeditiously in an experienced interventional center and accompanied by the administration of antithrombotic medication. In the early 90s of the past century, the introduction of immediate angioplasty provided a significant improvement of coronary artery patency resulting in increased survival and better preserved left ventricular function, when compared with thrombolytic therapy. Moreover, treatment with urgent angioplasty led to an incremental reduction of subsequent clinical events occurring after STEMI. Subsequently, as opposed to balloon angioplasty alone, additional stenting of the infarct-related lesion proved to further reduce the incidence of cardiac events after STEMI. Therefore, primary PCI nowadays represents the mainstay of the treatment of patients presenting with STEMI.

OUTLINE OF THIS THESIS
At the present time, three major concerns in primary PCI exist that may adversely affect outcome. First, concurrent treatment with potent antithrombotic medication involves a substantial risk of bleeding, of which a considerable part is access site bleeding. Procedure-related bleeding is associated with poor outcome and therefore measures should be taken to minimize bleeding as much as possible. PCI through the radial artery as an alternative to the femoral artery is associated with a reduced incidence of vascular complications but may be unattractive in the emergency setting.
of STEMI. Second, patients treated with primary PCI are frequently confronted with impairment of microvascular perfusion immediately after epicardial coronary patency has been restored. Distal embolization of atherothrombotic debris from the infarct-related lesion is thought to contribute to this phenomenon. The removal of thrombus and debris prior to primary PCI has been suggested to reduce distal embolization and thereby preserve myocardial salvage. Finally, the implantation of an intracoronary stent will result in vessel wall damage with subsequent neointimal tissue proliferation. This may cause recurrent stenosis of the coronary artery, which entails an essential disadvantage of stenting because it may necessitate additional revascularization. Stents that carry anti-proliferative drugs have shown to reduce the extent of restenosis in elective PCI. Hence, these drug-eluting stents have been proposed to further reduce events occurring after primary PCI.

This thesis addresses three different concepts in the treatment of STEMI that may favorably affect clinical outcome but are subject to debate. The transradial approach, thrombus aspiration, and the use of drug-eluting stents in primary PCI may reduce bleeding risk, distal atherothrombotic embolization, or restenosis, respectively.

PART I  RADIAL ACCESS IN PRIMARY PCI

In the first part of this thesis the unique approach of using the radial artery as arterial access site in primary PCI is described. It is well-known that vascular and bleeding complications impair clinical outcome. With the use of currently available potent anti-thrombotic medication, the extent of bleeding complications may theoretically be reduced by more than one-third of cases, as the occurrence of access-site related bleeding is rather common. In elective PCI for stable coronary artery disease, the transradial approach proved to be efficacious and safe, as compared with the transfemoral approach. Meanwhile, though, this approach is regularly avoided in primary PCI, mainly because of the operator’s fear of delay in restoration of coronary flow. A large, randomized controlled trial recently confirmed the safety and efficacy of using this access site
in acute coronary syndromes including STEMI. Nevertheless, little is known about the procedural success rates of the transradial approach in a real-world situation. To evaluate vascular access and procedural success rates, chapter 2 illustrates the impact of the routine strategy of transradial primary PCI in an observational study.

PART II THROMBUS ASPIRATION IN PRIMARY PCI

In the second part of this thesis the value of catheter aspiration of intracoronary thrombus in adjunct to coronary stenting during primary PCI is investigated. Although in primary PCI timely intervention and the accomplishment of complete restoration of epicardial flow is achieved in the majority of cases, myocardial salvage after primary PCI is frequently hampered by impaired microvascular reperfusion. Diminished myocardial perfusion at the tissue level may be present in up to 20% of cases, depending on the method of assessment of this phenomenon, and has been associated with larger infarct size and poor prognosis. Adjoining mechanisms that are thought to contribute to this phenomenon are microvascular dysfunction and reperfusion injury. Microvascular dysfunction is multifactorial and considered to result from vasospasm, inflammation, and embolization of thrombus and/or atheroma from the disrupted plaque prior or during intervention. Reperfusion injury reflects post-ischemic injury to the myocardium. It may occur immediately after blood flow is restored to ischemic myocardial tissue. At the time of reperfusion of the coronary microcirculation, oxygen free radicals and pro-inflammatory mediators may be released when post-ischemic myocardium is reached. In addition, reperfusion may lead to intracellular accumulation of Ca++ resulting in myocyte cell swelling and ultimately cell death. Although apparent in many different animal models, interventions aimed at the reduction of reperfusion injury in humans have not convincingly shown to be effective.

In previous studies, many of the pathways that cause microvascular dysfunction have been the objective of therapy. Of these mechanisms, the occurrence of distal embolization has been proposed to be mitigated by the removal of thrombus from the epicardial culprit lesion prior to stent implantation. Early reports of manual
and mechanical thrombus aspiration devices have indeed shown that their use was beneficial to microvascular perfusion as assessed by angiographic measures of coronary flow or the extent of ST-segment resolution.\textsuperscript{42-44} In the clinical trials that were conducted subsequently, however, the impact of thrombus aspiration on clinical outcome appeared somewhat disappointing, although one study showed a significant benefit of routine thrombus aspiration on mortality.\textsuperscript{45-49}

In chapter 3 the results of a prospective, randomized comparison of manual versus mechanical thrombus aspiration in primary PCI are presented. In chapter 4 the use of thrombus aspiration is evaluated in a post-hoc analysis of the PASSION (Paclitaxel-Eluting versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial. To conclude this section, chapter 5 describes a study in which procedural and clinical factors that may contribute to failure of thrombus aspiration were identified. In addition, the influence of failure to aspirate on prognosis was evaluated.

**PART III  DRUG-ELUTING STENTS IN PRIMARY PCI**

Whereas in elective PCI balloon angioplasty alone is associated with an angiographic restenosis rate of approximately 50%, the implantation of a stent, depending on vessel size, lesion length and lesion complexity, demonstrated to reduce the occurrence of clinical restenosis to 10-20\%.\textsuperscript{50} Accordingly, a significant reduction in clinical restenosis was found using stents in STEMI, when compared with balloon angioplasty.\textsuperscript{51} Still, the risk of developing restenosis remained the major disadvantage of stenting a coronary artery. Restenosis is a complex process secondary to trauma to the arterial wall consisting of thrombosis, inflammation, cellular proliferation, and extracellular matrix production.\textsuperscript{50} Three subsequent stages contributing to restenosis after balloon angioplasty were found to be early and late elastic recoil, late vascular remodelling, and neointima proliferation. Stenting with bare-metal stents (BMS) proved to prevent restenosis specifically by providing a metallic scaffold to the artery, which led to a reduction in elastic recoil and vessel remodelling when compared with balloon angioplasty alone. However, cell proliferation inducing neointimal hyperplasia continued to be a challenging issue.
In the beginning of this century a new type of stents was introduced that carried a drug (sirolimus or paclitaxel) with an anti-proliferative profile inhibiting neointimal hyperplasia. Various randomized controlled trials demonstrated that the use of drug-eluting stents (DES) in the setting of elective PCI was indeed superior to conventional BMS. The major advantage was a further decrease of restenosis clinically expressed by a reduction of repeat revascularization.

As from 2005, the use of drug-eluting stents in the setting of STEMI was examined in several randomized controlled trials. The majority of the earliest trials showed a moderate advantage of DES over BMS in primary PCI by a reduction in repeat revascularization. Long-term follow-up, however, proved to be mandatory since in 2006 it emerged that the implantation of these “first generation” drug-eluting stents was related to serious cardiac events resulting from stent thrombosis, an event that could occur even several years after implantation. Specifically stents implanted in patients with an acute coronary syndrome appeared to be at risk for acute thrombotic occlusion. Another concern that obligates long-term analysis of DES is the possible occurrence of restenosis beyond 6 to 9 months after implantation.

This may be due to biological, mechanical or technical mechanisms secondary to the use of these type of stents. A delayed pattern of restenosis could thereby thwart the initial advantage of DES, although currently only limited data are available regarding the extent of this phenomenon.

We conducted a prospective, randomized controlled trial (PASSION trial) in which we compared paclitaxel-eluting stents with conventional uncoated stents in STEMI. In Chapter 6 the two-year clinical results of this trial are presented. Chapter 7 is the final report of this trial with 5-year results of safety and efficacy. Finally, chapter 8 describes coronary artery patency of paclitaxel-eluting stents as compared with BMS, as assessed by follow-up angiography very late after implantation in STEMI.
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