Ischemic events and bleeding complications after primary percutaneous coronary intervention

Kikkert, W.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Introduction and outline of the thesis
INTRODUCTION AND OUTLINE OF THE THESIS

‘A short distance from its origin the left coronary artery was completely obliterated by a red thrombus that had formed at a point of great narrowing.‘

In these words, James Herrick first described the pathological basis of acute myocardial infarction (AMI) in his seminal paper in 1912. He further stated that ‘The hope for the damaged myocardium lies in the direction of securing a supply of blood.’ Although he was referring to establishing collateral blood flow, his novel insights were to form the fundamentals of interventional cardiology more than a century later. Nevertheless, it was not until the late 1970s, when Reimer and colleagues showed that coronary occlusion results in expanding areas of necrosis spreading from the subendocardium to the subepicardium as the occlusion endures, that the merit of reperfusion therapy began to gain belief.

In 1980, De Wood and colleagues first provided angiographic evidence that acute myocardial infarction was the result of a totally occluded or critically stenosed coronary artery. These findings further prompted the development of reperfusion therapy. It is currently well established that ST-segment elevation myocardial infarction (STEMI) is caused by coronary artery occlusion due to rupture of an inflamed thin-capped fibroatheroma containing a lipid-rich necrotic core with superimposed thrombus formation. Lysis of this intracoronary thrombus with fibrinolytic agents was the first reperfusion therapy to emerge in the 1980s. It was shown in large-scale trials involving tens of thousands of patients to result in rapid restoration of coronary perfusion and improved survival. However, in approximately 25% of patients the infarct related artery became reoccluded, resulting in worse long-term prognosis. As a consequence, catheter based mechanical reperfusion of the coronary arteries began to gain interest and in 1983 Hartzler and colleagues first introduced primary percutaneous transluminal coronary angioplasty (primary PTCA) as an alternative to thrombolysis for the treatment of AMI. During PTCA a catheter mounted balloon is advanced through the occlusive thrombus and subsequently inflated causing disruption of the occlusive thrombus and the underlying fissured plaque resulting in recanalization of the infarct related artery (IRA). Mechanical recanalization with PTCA or thrombus aspiration (collectively referred to as primary percutaneous coronary intervention (primary PCI)) is associated with normalisation of antegrade blood flow in the epicardial infarct related artery in 90 to 95% as compared to only 50 to 60% with thrombolytic agents. The improvement in restoration of normal blood flow in the epicardial arteries is associated with a reduction in infarct size and improved short- and long term survival.

Moreover, recurrent myocardial infarction is the second-most-frequent cause of death after reperfusion therapy in STEMI and may provoke infarct expansion, life threatening arrhythmias, and mechanical complications such as rupture of a papillary muscle, the
left ventricular septum or free wall. Unlike thrombolysis, primary PCI also prevents recurrent ischemia and recurrent MI by treating the underlying plaque.

This notwithstanding, adoption of PTCA as standard treatment of AMI was limited by the occurrence of two complications. Reocclusion and restenosis of the IRA caused by dissection and residual luminal narrowing were associated with a marked increase in mortality and morbidity. Coronary artery stents prevented the occurrence of these complications by providing a mechanical scaffold to the vessel wall. Ultimately, multiple randomized controlled trials have demonstrated increased survival and reductions in major adverse cardiovascular events with primary PCI and stenting as compared to thrombolysis. Consequently primary PCI is now the recommended reperfusion modality in patients with AMI.

**Anticoagulation during percutaneous coronary intervention**

Anticoagulation during PCI is directed at minimizing the adverse effects of iatrogenic plaque rupture from balloon angioplasty and stenting and at preventing thrombus formation on intravascular PCI equipment. Injury to the endothelium during PCI results in enhanced release of tissue factor. Tissue factor initiates activation of the coagulation cascade, with subsequent formation of activated factor X (factor Xa). Ultimately, this results in the generation of factor IIa (thrombin), conversion of fibrinogen to fibrin, and thrombus formation. Thrombin additionally directly activates platelets, enhances platelet aggregation, and has proinflammatory properties.

Although novel anticoagulants have emerged over the past decade, unfractionated heparin (UFH) has traditionally been the agent of choice during PCI. UFH is a heterogeneous mixture of glycosaminoglycans of varying molecule weights. It is an indirect anticoagulant requiring binding to a cofactor: antithrombin (AT). It exerts its main anticoagulant effect by inhibiting thrombin and activated factor Xa. Approximately one third of heparin molecules contain a high-affinity pentasaccharide sequence required for binding to AT. The remaining two thirds of heparin molecules exhibit little anticoagulant effect. Inhibition of thrombin requires binding of heparin to both thrombin and AT, whereas binding to factor Xa is not necessary for inhibition of factor Xa (this occurs by AT itself). Molecules of heparin consisting of less than 18 saccharides lack the chain length to bridge between thrombin and AT and therefore are unable to inhibit thrombin. Because unfractionated heparin consists of a mixture of molecules of varying size, it has a variable anticoagulant effect. Therefore, it requires monitoring with activated clotting time (ACT) or activated partial thromboplastin time (aPTT). During prolonged UFH treatment, it is recommended to keep the activated partial thromboplastin time (aPTT) between 50 and 70 seconds. This ‘therapeutic range’ is based on post hoc analyses from thrombolysis trials, in which aPTT values between 50 and 70 seconds were associated with the lowest risk of recurrent ischemic events.
Antiplatelet therapy during and after coronary stenting

Coronary atherothrombosis is not only mediated by activation of the coagulation cascade, but also by activation and aggregation of platelets. Spontaneous and iatrogenic plaque rupture promote adhesion of platelets to the vessel wall, followed by activation and aggregation of platelets ultimately resulting in arterial thrombosis.\(^{37}\) Although stent implantation during PCI prevents abrupt vessel closure by providing outward radial forces on the vessel wall, up to 1.9 percent of STEMI survivors develop a recurrent myocardial infarction of the non-culprit lesion in the year following PPCI.\(^{38}\) Moreover, the stainless steel or cobalt chrome platform of stents provokes platelet adhesion and activation with subsequent thrombosis within the stent. Owing to the release of cytostatic drugs, drug-eluting stents impair endothelialisation of the stent struts and are therefore associated with prolonged risk of stent thrombosis.\(^{39}\) As a consequence, antiplatelet medication is essential in the prevention of stent thrombosis and recurrent ischemic events such as myocardial infarction and stroke, both in the acute phase, as well as in the year following stent implantation. Dual antiplatelet therapy with both aspirin, a COX-1 inhibitor, and a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) is currently recommended for up to 12 months after PPCI.\(^{40}\)

Bleeding complications after primary PCI for STEMI

Before the introduction of dual antiplatelet therapy for PCI, stent thrombosis and reinfarction were frequent complications after PCI, occurring in up to 24% of patients. Improvements in interventional techniques coupled with potent antithrombotic therapy have led to significant reductions in recurrent ischemic events. Unfortunately however, the combination of arterial puncture in concert with aggressive antithrombotic treatment, has introduced a major challenge in interventional cardiology: iatrogenic hemorrhagic complications. Bleeding complications have been associated with adverse outcome and have been a major focus in research in the past decade. However, the prognostic implications of bleeding complications after PCI are poorly understood. This thesis aims to provide further understanding into the determinants and outcome after hemorrhagic complications after percutaneous coronary intervention for myocardial infarction.

Section 1 of this thesis addresses anticoagulant therapy during primary PCI. In chapter 2 we investigate current antithrombotic treatment preferences of Dutch cardiologists in the treatment of patients with acute coronary syndromes. In chapter 3 we investigate the prognostic impact of activated partial thromboplastin time (aPTT) on recurrent ischemic events and bleeding after PPCI in patients with STEMI. We hypothesized that short coagulation times would predispose to an increase in recurrent ischemic events and prolonged coagulation times would result in an increased tendency for hemorrhagic complications.
Patients with chronic kidney disease (CKD) have been shown to be prone for hemorrhagic complications and worse outcome after PCI for STEMI, in part as a result of excess dosing of antithrombotic treatment. In chapter 4 we investigate if altered pharmacokinetic properties of UFH in patients with CKD might contribute to an increased bleeding risk among patients with CKD. The binding of anion drugs to plasma proteins in patients with renal failure is reduced. Thus, the free fraction of unfractionated heparin, an anion drug, might be enhanced in patients with renal failure. This might result in prolonged aPTTs. In addition, UFH has been shown to be cleared by the kidneys in high doses. Therefore, accumulation of UFH might occur in patients with CKD. In chapter 4 we investigate if, and at which bolus dose UFH, aPTT prolongation occurs in STEMI patients with chronic kidney disease undergoing PPCI.

Section 2 of this thesis focuses on biomarkers in risk prediction in STEMI. Improvements in interventional techniques and adjunctive pharmacotherapy have substantially improved the prognosis of STEMI patients. Despite these improvements however, mortality and morbidity remains high in specific subsets of STEMI patients. Identification of these patient subsets might be of utility, as high risk patients might derive most benefit of additional interventional and pharmacological treatment. In addition, risk stratification allows a tailored approach and improves clinical therapeutic decision making and potentially improves outcomes. By using different risk scores for recurrent ischemic events and bleeding, physicians are able to distinguish patients at high risk of recurrent ischemic events from patients at high risk of bleeding. Given the differential safety and efficacy profiles of the different antithrombotic agents currently available, physicians can adopt a tailored approach, providing patients at high risk of recurrent ischemic events with potent antithrombotic agents and those at high risk of bleeding with less potent antithrombotic agents.

Patient, treatment and procedural characteristics associated with an increased risk of bleeding have been previously identified, but whether new biomarkers are of incremental value to further define the patient at risk of bleeding has not been investigated. For this purpose, in chapter 5 we investigate the relationship between 26 biomarkers and the risk of bleeding in a sample of the large scale pivotal HORIZONS-AMI study. In chapter 6, we further focus on one of the 26 previously mentioned biomarkers, and investigate the association between D-dimer levels and subsequent recurrent ischemic and hemorrhagic events after PPCI.

In section 3 we investigate the determinants and outcome after ischemic and hemorrhagic events after primary percutaneous coronary intervention. In chapter 7 we investigate the prognostic value of bleeding complications for one year mortality and we compare the prognostic value of bleeding complications defined according to a novel bleeding classification with existing bleeding classifications. Chapter 8 compares the relative prognostic value and temporal mortality pattern after recurrent myocardial
infarction and severe bleeding after STEMI. In chapter 9 we determine predictors and outcome after recurrent myocardial infarction after primary PCI and stenting in STEMI patients. As a result of aggressive antithrombotic therapy during treatment of STEMI in conjunction with the arterial puncture required for transluminal balloon angioplasty, hemorrhage at the arterial access site represents a frequent complication in STEMI patients. Approximately half of all bleeding complications however, originate at a site not related to the arterial access site (so called non-access site bleedings). In chapter 10, we investigate if outcome after bleeding is dependent on the source of the bleeding: access site related versus non-access site related. Of the non-access site bleedings, gastrointestinal bleeding represent the most frequent source and has been associated with the ulcerogenic effects of aspirin. In chapter 11 we further focus on predictors and outcome after gastrointestinal bleeding after primary PCI. Finally, chapter 12 focusses on a special patient subset at high risk of both ischemic and hemorrhagic complications after primary PCI: the elderly.
REFERENCES

19. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrino-
20. Widimsky P, Budesinsky T, Vorac D, et al. Long distance transport for primary angioplasty vs im-
21. Rao SV, Ohman EM. Anticoagulant Therapy for Percutaneous Coronary Intervention. Circulation:
22. Davie EW. Biochemical and molecular aspects of the coagulation cascade. Thrombosis and hae-
24. Andersson LO, Barrowcliffe TW, Holmer E, Johnson EA, Sims GE. Anticoagulant properties of
heparin fractionated by affinity chromatography on matrix-bound antithrombin iii and by gel
25. Johnson EA, Mulloy B. The molecular-weight range of mucosal-heparin preparations. Carbohy-
26. Lam LH, Silbert JE, Rosenberg RD. The separation of active and inactive forms of heparin. Bio-
chemical and biophysical research communications 1976; 69(2): 570-7.
27. Lane DA, Denton J, Flynn AM, Thunberg L, Lindahl U. Anticoagulant activities of heparin oligo-
saccharides and their neutralization by platelet factor 4. The Biochemical journal 1984; 218(3):
725-32.
variability of the antithrombin-binding sequence in heparin. The Journal of biological chemistry
1984; 259(20): 12368-76.
29. Nesheim ME. A simple rate law that describes the kinetics of the heparin-catalyzed reaction be-
30. Oosta GM, Gardner WT, Beeler DL, Rosenberg RD. Multiple functional domains of the heparin
78(2): 829-33.
31. Camilleri JF, Bonnet JL, Bouvier JL, et al. [Intravenous thrombolysis in myocardial infarction. Influ-
ence of the quality of the anticoagulation on the early recurrence rate of angina or infarction].
32. Kaplan K, Davison R, Parker M, Mayberry B, Feiereisel P, Salinger M. Role of heparin after intrave-
thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. Circulation
34. Cheng S, Morrow DA, Sloan S, Antman EM, Sabatine MS. Predictors of Initial Nontherapeutic
Anticoagulation With Unfractionated Heparin in ST-Segment Elevation Myocardial Infarction.
35. Anand SS, Yusuf S, Pogue J, Ginsberg JS, Hirsh J, Investigators oBotOtASfIS. Relationship of
Activated Partial Thromboplastin Time to Coronary Events and Bleeding in Patients With Acute


