Restenosis in clinical practice
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Despite considerable progress, restenosis remains a major limitation of percutaneous coronary intervention (PCI). Restenosis is determined by many factors in which the ‘response to injury’ plays a central role. There are two possible approaches in the prevention of restenosis. Unraveling the complex pathophysiology of this vascular response has lead to a better understanding of its mechanisms and to the identification of numerous risk factors. This has lead to the development of new pharmacological and nonpharmacological treatment options, with more or less success. Another approach is to prevent restenosis mechanically, irrespective of its cause. Today, coronary stents are the cornerstone of mechanical vessel support, thereby also decreasing the restenosis rate in various subsets of patients at increased risk. In chapters 2, 3, and 4 of this thesis, the prognostic value of several “modern” risk factors is described, further unraveling the pathophysiology of restenosis. In chapters 5, 6, 7, and 8 of this thesis, several “mechanical” treatment modalities are tested to prevent restenosis.

Chapter 1: Introduction

Chapter 1 gives a short overview of the pathophysiology of restenosis, which can be divided in elastic recoil, remodeling, and neointima proliferation. Stenting virtually eliminates elastic recoil and remodeling, and in-stent restenosis is mainly caused by neointima proliferation. Furthermore, patient related risk factors and lesion specific angiographic risk factors are described.

Chapter 2: Preprocedural serum levels of acute-phase reactants and prognosis after percutaneous coronary intervention

Circulating inflammatory markers, in particular C-reactive protein (CRP), belong to the most prominent “modern” risk factors of coronary heart disease. In chapter 2 the influence of these acute-phase reactants on prognosis after PCI is described. In a group of 600 patients preprocedural levels of CRP, interleukin-6 (IL-6), lipoprotein(a) (Lp(a)), and fibrinogen were measured. At 8 months follow-up, the occurrence of repeat PCI, coronary artery bypass grafting, myocardial infarction, and death were noted as major adverse clinical events (MACE). Furthermore, the recurrence of angina was noted. CRP levels were significantly higher in patients with repeat angina as compared with patients without recurrent angina (p<0.05). Lp(a) and fibrinogen were both higher in patients with MACE as compared with patients without MACE (p<0.05 and p<0.05, respectively). IL-6 levels were not correlated with MACE or repeat angina.

Conclusion: This study clearly supports the role of inflammation in restenosis after PCI.

Chapter 3: Preprocedural ACE-activity does not predict in-stent restenosis

Chapter 3 describes the correlation between angiotensin converting enzyme (ACE) activity, in plasma as well as in the atherosclerotic plaque, and the occurrence of in-stent restenosis. The ACE activity in peripheral blood was measured in 178 patients before they underwent PCI with stent placement. After 8 months adverse cardiovascular events were counted as a measure of clinical recurrence due to in-stent restenosis, and related to the ACE-activity. In a second group of patients, tissue samples were obtained with an atherectomy catheter before elective stent placement in 13 patients with de novo stenosis. In these samples, the ACE content was determined immunohistologically.
Recatheterisation was performed after 12 months to determine the degree of in-stent restenosis in relation to the amount of ACE in the original plaque.

**Conclusion:** In both substudies, no relation between the amount of preprocedural ACE or ACE-activity and in-stent restenosis could be established.

**Chapter 4: Cytomegalovirus and *Chlamydia pneumoniae* as predictors for major adverse clinical events and angina pectoris after percutaneous coronary intervention**

The development of restenosis is enhanced by several patient related risk factors. Studies investigating the role of microorganisms on restenosis are contradictory. Therefore we investigated the role of two potential candidates: cytomegalovirus (CMV) and *Chlamydia pneumoniae* (CP). We measured preprocedural anti-CMV immunoglobulin G and anti-CP immunoglobulin A (IgA), immunoglobulin M, and immunoglobulin G antibodies in 600 patients. At 8 months follow-up, the occurrence of MACE and angina was noted. We found a higher rate of seropositivity for CP IgA in patients with MACE as compared with patients without MACE (50.9% vs 35.4%, p<0.05). Seropositivity for CMV was not related to adverse events.

**Conclusion:** Preprocedural seropositivity of CP IgA is a risk factor for MACE after PCI.

**Chapter 5: Is Direct Stent Implantation Without Predilatation Safe? Acute and Long-Term Outcome**

The lower the injury, the lower the response. Therefore, stenting without predilatation (SWOP) is likely to result in a lower rate of restenosis. Using the Palmaz-Schatz Crown stent SWOP was attempted in 61 patients who were compared with a control group of provisional stenting. The results of this study are described in chapter 5. In the SWOP group the mean preprocedural minimal luminal diameter (MLD) increased from 0.96±0.47 mm to 3.09±0.54 mm directly after the procedure. At 6 month follow-up the MLD measured 2.32±0.79 mm. In the provisional stenting group the mean MLD increased from 0.92±0.51 to 2.44±0.58 mm and was 1.84±0.70 mm at 6 month follow-up. Restenosis occurred in 8% of the SWOP group compared with 28% in the group of provisional stenting (p<0.001). 

**Conclusion:** The acute and long-term results of SWOP are better as compared with provisional stenting.

**Chapter 6: Stenting for Restenotic Lesions with the BARD XT Stent**

A history of restenosis after balloon angioplasty is among the most important and relatively frequent occurring risk factors for recurrent restenosis. Many treatment modalities have been investigated for the treatment of restenotic lesions. In chapter 6 the immediate and 6-month clinical and angiographic results of stenting for restenosis are described. One-hundred patients with restenosis after conventional balloon angioplasty were stented using the BARD XT stent. The mean MLD increased from 1.09±0.57mm to 2.70±0.44mm. The procedural success rate was 99%. The mean MLD at follow-up was 1.74±0.67mm with a mean diameter stenosis of 41±20%. Residual anginal complaints were reported in 29% of patients. In-stent restenosis occurred in 18% of the patients.

**Conclusion:** Coronary stenting for restenotic lesions results in a good immediate result and yields a favorable long-term outcome.
Chapter 7: Cutting Balloon for in-stent restenosis: acute and long-term results

The long-term success of stenting is limited by the occurrence of in-stent restenosis. Repeat balloon angioplasty shows good immediate results, but the rate of recurrent in-stent restenosis is high. In-stent restenotic tissue, which is mainly composed of smooth muscle cells, is not as compressible as compared with an atherosclerotic plaque. Chapter 7 describes the results of the cutting balloon for in-stent restenosis. The incisions made by the blades of the cutting balloon decrease the radial force of the restenotic tissue and facilitate dilatation. In this study 100 consecutive patients with in-stent restenosis were treated with the Barath cutting balloon. The mean inflation pressure was 8.7±2.0 (range 6.0-18.0) atm. Before the procedure the mean MLD was 0.95±0.45mm. Immediately after the procedure the mean MLD was 2.42±0.54 mm. At 8 month follow-up 26 patients (26%) reported to have anginal complaints CCS class 2 to 4 of whom 16 (16%) needed target lesion revascularization.

Conclusion: angioplasty for in-stent restenosis using a cutting balloon has good immediate results and a low need for repeated target lesion revascularization.

Chapter 8: Primary Stenting of Occluded Native Coronary Arteries: Final Results of the PRISON Study

Chronic total coronary occlusions have long been considered to be an indication for coronary artery bypass graft surgery because of the low success rate of balloon angioplasty. Coronary stent implantation is expected to improve the outcome of PCI for chronic total occlusions. Chapter 8 describes the results of the Primary Stenting of Occluded Native Coronary Arteries (PRISON) study. In this randomized study, the results of stent implantation are compared with balloon angioplasty in 200 patients. After the procedure the mean MLD in the balloon group was 2.34±0.46 mm versus 2.90±0.41 mm in the stented group (p<0.0001). The 6-month angiographic follow-up showed a mean MLD of 1.57±0.74 mm in the conventional group versus 1.93±0.85mm in the stented group (p<0.01). Angiographic restenosis was seen in 33% in the conventional group versus 22% in the stented group (p=0.14). The reocclusion rates were 7.3% and 8.2% respectively (p=1.0). At 12 month follow-up, the rate of target lesion revascularization was significantly higher in the balloon group (29% versus 13%, p<0.0001).

Conclusion: Stenting of chronic total occlusions is superior to balloon angioplasty alone.

Chapter 9: Primary Stenting of Occluded Native Coronary Arteries II: Rationale and design of the PRISON II study

A randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of chronic total coronary occlusions.

Although chapter 8 showed that coronary stenting using bare metal stents is superior to balloon angioplasty in chronic total occlusions, restenosis continues to pose a problem to the interventionalist and the patient. During the past few years, studies evaluating stents coated with sirolimus (rapamycin) have shown promise at reducing restenosis rates in selected groups of patients. Chapter 9 describes the rationale and design of the Primary Stenting of Occluded Native Coronary Arteries II (PRISON II) study. This randomized study will investigate the results of sirolimus-eluting stent implantation as compared with bare metal stent implantation in chronic total occlusions. A total of 200 patients will be followed for 5 years, with angiographic follow-up at 6 months.