Towards a tailored approach in Percutaneous Coronary Interventions
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Chapter 10

Summary and future perspectives
Summary

The aim of this thesis, as formulated in chapter 1, is to investigate the role of new diagnostic and treatment modalities for interventional cardiologists in routine clinical practice.

Identifying patients at risk of Clinical Recurrence after PCI

In chapter 2, the effect of eight specific functional gene polymorphisms of the angiotensin pathway and one polymorphism of the heme oxygenase-1 (HO-1) gene on restenosis was examined in a large population of consecutive patients undergoing Percutaneous Coronary Intervention (PCI). The renin-angiotensin system (RAS) is thought to play a major role in the pathophysiology underlying both de novo restenotic lesions and in-stent restenosis after PCI. HO-1 is thought to counteract Angiotensin-II and beneficially influence these processes. The genetic determinants of restenosis (gender) project is a multicenter prospective follow-up study, that aimed to investigate the influence of genetics on the occurrence of restenosis after PCI. A total of 3,146 patients was included and had a successful PCI. Genotyping in these patients was performed for the ACE gene insertion/deletion polymorphism, the angiotensinogen 235Met/Thr gene, T174M and A(-6)G polymorphisms, the 1166A/C and the T810A polymorphism of the angiotensin-II type-1 receptor (AT1R), the 1675G/A and 3123A polymorphisms of the angiotensin-II type-2 receptor (AT2R) and the length polymorphism in the HO-1 promoter region.

A total of 3,104 patients were followed for 10±2 months and in 2,975 patients at least one of the nine genotypes could be determined. Of these patients, 2,216 (71%) were male, 453 (15%) had diabetes and 1,432 (46%) had multivessel disease. The majority was treated for stable angina. Stenting was performed in 2,309 (74%) patients. Target vessel revascularization (TVR) after the first month by either Coronary Artery Bypass Grafting or PCI was necessary in 304 patients (9/12 month event-rates: 9.3%/10.8%) after follow-up. In addition, patients were checked for clinical restenosis, which consisted of TVR, myocardial infarction and death. The AT1R 1166 CC genotype showed a significant association with TVR (RR=1.85, 95%CI; 1.28-2.66, p=0.002), where the other polymorphisms did not. There was no association between the use of RAS-inhibitory drugs and the incidence of TVR. The authors found an interesting trend, as patients with the ACE insertion/insertion polymorphism seemed to have a better outcome if they had a short number of repeats in the HO-1 promoter. This relationship was inversely present in carriers of the ACE deletion/deletion polymorphism. The described study indicates that the AT1R 1166 A/C polymorphism plays a role in the occurrence of restenosis after PCI. However, a gene-gene interaction was also suggested for the ACE gene and the HO-1 promoter.

In chapter 3, the influence of a previous clinical recurrence after PCI on outcome after a subsequent PCI is described. To select patients who benefit most from Drug Eluting Stents (DES), it is important to identify patients at high-risk for restenosis. In this study, the authors hypothesized that a history of Clinical Recurrence (CR) after PCI increases the risk of getting CR after treat-
ment of a de novo lesion in another coronary artery. To test this hypothesis, all patients who underwent PCI between 1993 and 2004 were retrospectively analyzed and patients with at least 2 interventions in 2 different native vessels were selected. Included patients were divided into patients without CR and with CR after the first PCI. A total of 1,010 patients were met the inclusion criteria and were entered into the final analysis: 727 without CR after PCI 1 and 283 with CR after PCI 1. No significant difference in major risk factors was found between both groups. Patients with CR after their first PCI had a much higher risk of getting CR after a second PCI (Odds ratio: 3.4, 95% Confidence Interval: 2.3 to 4.9) than patients without CR after PCI 1. This effect was even more pronounced when patients were checked for a third PCI and data from the first two PCI’s were taken into account. This study is important, as it is the first study to suggest that patients with a history of clinical recurrence after a previous PCI are more prone to develop long-term complications when treated for a second lesion. Although these data should be confirmed by other studies, they suggest that patients with restenosis after a previous PCI might benefit most from Drug Eluting Stents, as they are at high-risk for developing restenosis again.

Invasive and non-invasive assessment of coronary stenoses

In Chapter 4, the use of a non-invasive visualizing technique for coronary arteries, 16-slice Multi-Detector Computed Tomography (MDCT), was evaluated. Although this technique has already been shown to be accurate in diagnosing anatomical significant coronary stenoses, its relation with functional severity of coronary artery disease (CAD) had not yet been investigated. Therefore, the authors sought to investigate the relation between the anatomical severity of coronary artery disease detected by MDCT and functional severity measured by fractional flow reserve (FFR).

Fifty-three patients (39 men and 14 women) with single-vessel disease scheduled for PCI were included. All patients underwent MDCT scanning one day prior to PCI and FFR was measured before PCI in the target vessel. In addition, Quantitative Coronary Angiography (QCA) was performed in the vessel of interest to be compared with MDCT visual analysis and lesion measurements. No significant relation could be found between MDCT and QCA degrees of stenosis. The mean FFR in all patients was 0.67 ± 0.18 and a relation of r = -0.46 (p = 0.0006) between QCA and FFR was found. In contrast, no relation between MDCT and FFR could be demonstrated. Furthermore, a high incidence of false positive and false negative findings compared to FFR was present in both imaging modalities. Therefore, the authors conclude that, although MDCT is a useful tool in screening patients for anatomical significant CAD, functional assessment of coronary artery disease remains mandatory for clinical decision making. Chapter 5, which was published as a letter, emphasized this statement as no clear relation between anatomical and functional severity of CAD as defined by MDCT or conventional angiography and FFR can be found.
Chapter 6 further elaborates on functional assessment of CAD and specifically intracoronary flow and pressure measurements. These techniques can be used for evaluating intermediate lesions. Furthermore, PCI can be deferred when a sufficient coronary flow \((\text{CFR} \geq 2.0)\) or pressure \((\text{FFR} \geq 0.75)\) is found. However, long-term results of this deferral strategy were not available, and so the authors assessed the long-term safety and clinical implications of decision making for intermediate coronary stenosis based on intra-coronary hemodynamic measurements in a group of 61 patients for a period of 5.5 years. Patients were included in the period of January 1994 to December 1998 and had either coronary flow reserve or fractional flow reserve measurements. Both database analysis and telephone questionnaires were used to check for target vessel revascularization, myocardial infarction, unstable angina, cerebrovascular accident and death as major adverse cardiac events \((\text{MACE})\). Although patients presented with complaints, only 19.7\% experienced a MACE in the follow-up period. This is comparable to outcome after PCI in patients from that time period. Therefore, this study suggests that intracoronary measurements of CFR and FFR can be routinely used for justified clinical decision making in intermediate coronary stenoses. The 5-year event rate supports conservative treatment strategy when cut-off values are implemented.

Adjuvant pharmacological therapy and PCI

Chapter 7 and chapter 8 focus on the effect of abciximab, a Glycoprotein \((\text{GP})\) IIb/IIIa-antagonist, administration on the occurrence of restenosis after PCI of complex lesions. The American College of Cardiology/American Heart Association Task Force lesion complexity system was used to divide lesions into simple (type A and type B1) and complex (type B2 and type C). Two studies were conducted. In the first, the combination of a silicon-carboid coated stent and periprocedural administration of abciximab in patients with type B2/C lesions was evaluated. In this single-center study, a prospective cohort of 44 patients that underwent elective PCI was included. All had type B2/C lesions characteristics and most were relatively small, tortuous and calcified. All involved vessel segments were stented with silicon carbide-coated stents. The main outcome measures of MACE was checked after 6 months of follow-up. Only four patients had a MACE. Three patients had undergone target vessel revascularization and one patient had suffered from a cerebrovascular accident. Sixteen patients underwent re-angiography 6 months after the initial procedure. The mean diameter stenosis at 6 months was 15\% with a minimal lumen diameter of 2.4 mm. A low major adverse cardiac event rate of 9\% and a target vessel revascularization rate of 7\% at 6 months was recorded. However, further investigation on the use of this specific treatment combination is warranted, as this was only a single-center study in a selected patient group.

In the second study, the administration of abciximab in relation to lesion complexity and periprocedural complications was evaluated. Although abciximab administration has been suggested for all patients, the costs are high and therefore administration in all patients may not be possible due to budget restraints. A total of 357 patients with 435 de novo lesions were included.
in this study. The administration was left to the discretion of the operator, and so abciximab was given mainly to patients with unstable complex lesions and simple lesions with a periprocedural unstable complicated course. The overall incidence of MACE during the 9-month follow-up period was 17.0%. Patients treated with abciximab had more high-risk characteristics, such as higher lesion complexity, more dissections, more stents, and more vessels involved. Also, a higher angina NYHA class, lower TIMI flow prior to stenting, and a longer total inflation time were found in the abciximab group, indicating that overall the coronary artery disease was more severe in patients that were treated with abciximab. Despite these clinical differences, the occurrence of MACE within the abciximab group was slightly less than in the group without abciximab (16.2% and 17.3%, respectively). Lesion complexity was directly related to MACE in the group that did not receive abciximab, while in subjects treated with abciximab, lesion complexity was not related to a higher incidence of MACE.

**Beyond PCI: induction of angiogenesis**

In Chapter 9, the effect of gene therapy with Vascular Endothelial Growth Factor (VEGF) on endothelial function was described. VEGF is a potent angiogenic factor and VEGF gene therapy improves perfusion of ischemic myocardium in experimental models and possibly in patients with end-stage coronary artery disease. In addition to its proliferative and migratory effect on endothelial cells, it also activates and up-regulates endothelial nitric oxide synthase (eNOS). Nitric oxide (NO) release by the endothelium results in vasodilatation in normal arteries. Therefore, the authors investigated coronary endothelium-dependent vasodilatation in patients before and after VEGF gene therapy. To assess the effect of VEGF on the endothelium, the influence of intracoronary acetylcholine infusion on coronary diameter was investigated. In normal coronary arteries, acetylcholine facilitates NO release by the endothelium and subsequent vasodilatation. However, in diseased coronary arteries, NO is released and infusion of acetylcholine directly results in vasoconstriction. Thus, reactions to acetylcholine infusion at baseline and after 3 months follow-up in patients with end-stage coronary artery disease treated with VEGF gene and in controls scheduled for elective PCI was evaluated.

Five out of six VEGF patients experienced a reduction in anginal complaints. Angiographic evidence for improved collateral filling was evident in two out of six patients. The vasoconstrictive response to acetylcholine was partly converted into dilatation. In contrast, the acetylcholine response in control patients remained vasoconstrictive. Therefore, VEGF gene therapy could facilitate a beneficial effect on the functional characteristics of the myocardial vascular network.

**Future perspectives**

New techniques for diagnosing and treating coronary artery disease are being developed rapidly. In optimizing patient treatment as well as comfort, decisions have to be made on whether new
techniques are applicable in routine clinical practice or if these new modalities should be used in selected patient groups only.

Research on the influence of genetics on disease has just begun. Although many polymorphisms have been identified and relations of some polymorphisms to specific diseases have been shown, there is still a paucity of conclusive data on the role of genetics in common diseases such as coronary artery disease. Furthermore, specific treatment strategies focusing on genetics have to be developed and evaluated. Therefore, it will take time to see if this knowledge will be useful in routine clinical practice.

As for new imaging techniques, such as MDCT angiography and magnetic resonance angiography (MRA); they will have to prove their additive value in clinical practice. As anatomy will never be able to reflect coronary function, coronary catheterization (and subsequent intracoronary hemodynamic measurements) will remain necessary to make final decisions on optimal treatment in the individual patient. However, MDCT and MRA could become essential in screening patients suspected of coronary artery disease, without the need for invasive procedures. Therefore, research should focus on the clinical relevance of stenoses diagnosed on MDCT and MRA and their relation to the need for subsequent revascularization therapy.

Although many important breakthroughs have been achieved throughout the last two decades, restenosis still is the major challenge in coronary intervention. Multiple risk factors, both in patient and lesion characteristics, have been assessed and the effects of different treatment options in specific patient groups have been thoroughly elaborated. Therefore, the focus of new investigations should not only be on identifying new risk factors, but moreover on how to implement all the current data into a model that focuses on the individual patient. In addition, as is apparent from the studies presented in this thesis, every new diagnostic or treatment modality has to be put in perspective of the daily clinical routine in the catheterization laboratory. Not only do logistics have to adapt to new techniques such as MDCT, but also budget restraints may limit the opportunities to use expensive resources. Therefore, although this might well be an impossible mission, a risk stratification chart for patients scheduled for PCI could prove to be a practical tool for identifying which patients will benefit from more expensive treatments such as drug eluting stents and GP IIb/IIIa-antagonists.