Percutaneous coronary interventions of bifurcation lesions

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Chapter 1

General introduction and outline of the thesis

Maik J. Grundeken
GENERAL INTRODUCTION

Ischemic heart disease
Ischemic heart disease (IHD) is the leading cause of death worldwide. IHD encompasses a broad clinical spectrum from stable coronary artery disease (SCAD) to acute coronary syndromes (ACS), including ST-segment elevation myocardial infarction (STEMI).

Clinically, SCAD is most commonly characterized by angina pectoris; chest pain caused by myocardial ischemia secondary to a demand/supply mismatch. In the majority of patients, myocardial ischemia is caused by one or more flow-limiting coronary stenoses, secondary to coronary plaque formation in the vessel wall. In such cases, myocardial ischemia is typically induced by exercise, emotion or other stress; and relieved by rest and/or the use of nitrates. The aim of management of SCAD is two-fold: relief of symptoms and prevention of cardiovascular events. Management of SCAD includes lifestyle modification, controlling of risk factors, evidence-based pharmacological therapy and patient education. In case anginal complaints are refractory to this management, coronary revascularization should be considered to alleviate patient’s symptoms. Revascularization could be achieved by either coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). The choice for CABG or PCI depends on extent of disease, left main involvement, and overall complexity of coronary anatomy.

ACS has a broad clinical spectrum from symptom-free patients at presentation to patients with ongoing ischemic chest pain accompanied with hemodynamic instability including ventricular arrhythmias or cardiac arrest. The pathogenesis of ACS is characterized by plaque rupture or plaque erosion with overlying thrombus formation. Such thrombosis might result in totally occlusion of the coronary artery causing transmural infarction which is recognized on the electrocardiograph (ECG) as persistent ST-segment elevations; or as partly or intermittent thrombus occlusion which is recognized on the ECG as non ST-segment ACS (NSTE-ACS). The cornerstone of STEMI treatment is timely reperfusion by primary PCI. The first step in the management of NSTE-ACS is risk assessment using clinical factors, ECG changes, and cardiac biomarkers. Low-risk patients which are stabilized and symptom-free after start of platelet inhibition, anticoagulants and anti-ischemic treatment do not necessarily need an invasive strategy including coronary angiography (CAG) with or without ad-hoc PCI, while in high-risk patients early (<24 hours) invasive strategy is recommended. CABG could serve as an alternative revascularization strategy for PCI.

A brief history of PCI
As outlined above, PCI is important for the treatment of coronary artery disease, both in SCAD and ACS. Each year, more than 45,000 PCIs are performed in the Netherlands.
Since Andreas Grüntzig performed the first balloon angioplasty in a coronary artery in 1977, the field of percutaneous treatment of coronary artery stenosis underwent an immense development.

Grüntzig used hand-made balloon catheters fabricated at his own kitchen table. These catheters ended with a balloon at their distal end and had a short guide wire attached to the tip. These large catheters were difficult to manoeuvre safely and it was impossible to perform independent movements of the wire and balloon. In 1982, Simpson described for the first time the concept of an ‘over-the-wire’ balloon system with independently movable guide wire with a flexible tip within the balloon catheter. Since then, guide wire technology has advanced rapidly and one of the developments in guide wire technology was coating of the wire with a hydrophilic outer layer, providing a low friction feel inside the vessel which improves trackability of the guide wire.

The metallic stent was initially developed as bailout strategy to treat the complications of balloon angioplasty: acute vessel closure due to coronary dissections and restenosis due to late constrictive recoil. The first stent implantation was performed by Puel in 1986, but its routine use was not widely accepted until the BENESTENT (BELgian NEther-lands STENT) and STRESS (STent REStenosis Study) trials showed superior outcomes of routine stent use compared to POBA in terms of efficacy, as assessed with quantitative coronary angiography (QCA) during follow-up angiography.

QCA was developed in the mid-eighties to overcome the limitations of the human eye to objectively assess coronary lesion severity. QCA software are able to detect lumenal contours, automatically identifying the minimal lumen diameter (MLD). By retracting the MLD at follow-up from the post-procedural MLD, it is possible to calculate the ‘late lumen loss’, which is considered a surrogate for efficacy.

A limitation of the metallic stent was the occurrence of in-stent neo-intima hyperplasia (NIH), caused by vascular smooth muscle cells proliferation and migration resulting in growth of scar tissue within the stent. Drug-eluting stents (DES) were developed which were coated with an anti-proliferative drug, inhibiting the proliferation of smooth muscle cells to prevent neo-intima hyperplasia, and the first DES was implanted by Sousa in 1999.

DES proved to be superior to stents without drug-coating (since then referred to as ‘bare-metal stents’ [BMS]) in terms of lower late lumen loss on QCA, resulting in reduced rates of target lesion revascularization (TLR). With these encouraging results, DES was introduced with great enthusiasm in the interventional cardiology community and used on a large scale. This enthusiasm was tempered because major concerns arose on the increased risk of stent thrombosis (ST), with an annual risk ranging from 0.36% to 0.6% per year up to 5 years of follow-up. The pathogenesis of ‘late ST’ (ST >1 year) was multi-factorial, caused by delayed and incomplete endothelialisation, hypersensitivity reactions to the polymer coating (which binds the drug eluted), incomplete apposition,
the occurrence of ‘neo-atherosclerosis’ including plaque ruptures causing intra-stent thrombosis, and thick struts creating peri-strut recirculation zones 32-43.

‘Second generation’ DES were developed to cope with the problem of this excessive late ST risk of the first generation DES. Whereas the first generation DES were made of 316L stainless steel, second generation DES were made from cobalt-chromium (CoCr) or Platinum-chromium (PtCr) alloys, which have superior tensile strength allowing the use of thinner stent struts without losing radial strength. Furthermore, newer generations of DES have biocompatible or even completely biodegradable polymer coatings to prevent hypersensitivity reactions and to promote favourable healing 32. In addition, a DES with endothelial progenitor cell attracting technology has been developed to ensure fast endothelialisation of stent struts which should result in favourable healing with less neo-atherosclerosis at the long-term 44. These improvements led to superior clinical outcomes of second and third generation DES compared to first generation DES and recent data even suggested superiority in terms of ST risk compared to BMS 45-49.

OUTLINE OF THESIS: PERCUTANEOUS CORONARY INTERVENTIONS OF BIFURCATION LESIONS

One of the remaining challenges in PCI: treatment of coronary bifurcation lesions.

Bifurcation lesions accounts for approximately 20% of all PCIs performed 29, 50. The definition of a coronary bifurcation lesion can be somewhat problematic since PCI involving a side branch is not always considered as PCI of a bifurcation lesion. For instance, when PCI is performed with a stent crossing a small side branch of 1mm, this is commonly not referred to as bifurcation lesion treatment. The definition as provided by the ‘European Bifurcation Club’ (EBC) may be helpful and is as follows: a bifurcation lesion is “a lesion occurring at, or adjacent to, a significant division of a major epicardial coronary artery” 51. What should be considered to be a ‘significant’ side branch however is arbitrary. In daily practice, an operator usually considers a side branch as ‘significant’ if he/she does not want ‘to lose’ this branch during PCI, taken into account multiple clinical aspects including patients symptoms and comorbidity, size (diameter and length) of the side branch (which provides you an idea of the myocardium at risk 52), viability of the supplied myocardium, results of functional tests including location of ischemia, collateralization, left ventricular function, and so forth 51.

Although technology in PCI have made impressive advancements over the past decades as outlined above, treatment of bifurcation lesions remains challenging. Historically, in the balloon angioplasty and BMS era, PCI of coronary bifurcation lesions have been associated with a lower procedural success rate, a higher complication rate, and
less favourable clinical outcomes, compared to PCI of non-bifurcation lesions. Even after the introduction of DES, bifurcation PCI remained to be associated with an increased risk of in-stent restenosis and ST.

Optimal percutaneous treatment of bifurcation lesions has been a topic of numerous clinical trials. Multiple randomized trials comparing a systematic two-stent strategy with the ‘provisional’ strategy (i.e. single stenting of the main branch with additional side branch treatment only when necessary) have shown comparable efficacy between the two treatment strategies. However, a systematic two-stent approach resulted in an increased risk of (peri-procedural) MI, higher amounts of contrast use, higher X-ray doses and longer procedural time. The lack of benefit with the two-stent approach, together with the coinciding higher procedural complexity including an increased risk of peri-procedural MI, have resulted in recommendations by the European Bifurcation Club (EBC) and the American combined ACCF/AHA/SCAI guideline for PCI to use the provisional approach as default strategy for the treatment of bifurcation lesions. However, there is also consensus that an (upfront) two-stent approach is reasonable to consider if a large side branch is involved, if the side branch is extensively diseased, if side branch occlusion is likely to occur, or if re-wiring is foreseen to be difficult.

**Remaining challenges in the provisional (single-stenting) approach**

One of the factors influencing the risk of in-stent restenosis and ST after PCI of bifurcations is the occurrence of jailed side branch struts after treatment. These jailed struts, also referred to as non-apposed side branch struts (NASB), have been shown to result in delayed and incomplete endothelialisation, leaving the thrombogenic stent struts exposed to blood, potentially precipitating ST. On the long-term, jailed side branch struts, especially when side branch post-dilatation is not performed after main branch stenting, may contribute to the occurrence of late restenosis of the side branch ostium. The amount of jailed side branch struts could be minimized by performing a side branch dilatation. However, side branch (re-)wiring, necessary to perform side branch dilatation, may be technically challenging and time-consuming, and may lead to an increase in fluroscopy time and contrast use. Furthermore, side branch dilatation may lead to stent deformities, especially when re-wiring is performed through a proximal (instead of distal) cell. Another challenge in bifurcation treatment is appropriate stent sizing. Due to the fractal geometry of the coronary tree, there is a natural ‘step-down’ in diameter at each branching point, per definition resulting in differences in proximal and distal diameters. When stents are sized according to the proximal main branch diameter, they are per definition oversized relative to the distal branch, which may lead to the phenomenon of ‘carina shift’, resulting in a ‘pinched’ side branch ostium post-procedural. The above described stent distortions (stent distortions after proximal cell recrossing and carina shift) could be corrected by performing final kissing balloon...
inflation (FBKI), although on itself FKBI may create elliptical-shaped stent deformities in the proximal main branch \(^65\). These proximal stent deformities can be corrected by the proximal optimization technique (often referred to as 'POT') \(^66\). All these refinements and improvements in provisional stenting may have resulted in improved clinical outcomes as suggested by data from the Institut Cardiovasculaire de Paris Sud (ICPS) registry on provisional stenting \(^67\). However, technical challenges with provisional single stenting remain, including difficulties to re-wire, difficulties to properly size the stent when there is a large difference in proximal an distal diameters, and difficulties with the final kissing balloon inflation technique \(^68\).

**Remaining challenges in the two-stent approach**

A variety of two-stent strategies have been described, of which the ‘culotte’, the (double-kissing) ‘crush’ and the ‘T-stenting’ are the most often used. A limitation of the two-stent approach is that they are in general technically challenging. As described above, there is a general consensus that most bifurcations should be treated according to the provisional approach and only a minority of bifurcations may be considered to be treated with an upfront two-stent approach. Only 20% of all PCIs involve a bifurcation lesions, and the vast majority of these bifurcation lesions should be treated with the provisional strategy. If we assume that 80% should be treated with the provisional approach, this means that only ~5% of all PCIs will be a bifurcation lesion treatment which will need an upfront two-stent approach. So it will be a challenge to gain enough experience to master one or more of these techniques. Furthermore, there are potential drawbacks of the two-stent approach which are inherent to conventional stent design. One example is the limited stent expansion of the second stent caused by the cell size of the first deployed stent in the culotte technique (the so-called ‘napkin ring’ effect) \(^69,70\). A limitation of the Crush technique is the three layers of stent struts at the lateral side branch wall, opposite to the carina, resulting in delayed endothelialization, requiring final kissing balloon inflation \(^71,72\). Another limitation of the two-stents approach might be the increased risk of ST. Pathology studies have demonstrated delayed endothelialisation with fibrin deposition at the carina site where flow divides and were shear stresses are highest, especially when two DES were used \(^73\). Indeed, a meta-analysis comparing the two-stent approach with the single-stent approach using DES has shown an increased risk of ST in the two-stent approach \(^74\).

In this thesis, we will evaluate current technologies used in bifurcation lesions, investigate the potential role of a dedicated bifurcation stent to improve the two-stent strategy, examine the use of QCA in bifurcation lesions, and explore the use of a bioresorbable scaffold in complex lesions including bifurcations.
Part A: Current treatment of coronary bifurcation lesions

In chapter 2, we will evaluate differences in clinical outcomes between bifurcation and non-bifurcation lesions in the DES era and how second generation DES with bioresorbable polymer might improve clinical outcomes compared to a first generation DES. In chapter 3, we will investigate the occurrence of detachment and subsequent embolization of hydrophilic coating material from hydrophilic coronary guide wires, which are often used during percutaneous treatment of coronary bifurcation lesions.

Part B: Use of a dedicated bifurcation stent

In chapter 4, we will introduce the design and technical specifications of the Tryton Side Branch Stent; a dedicated bifurcation stent developed to improve clinical outcomes after PCI of bifurcations lesions. In chapter 5, we will evaluate clinical outcomes after use of this device in a single-center registry performed at the Academic Medical Center (AMC) in Amsterdam. In chapter 6, data from intravascular imaging using optical coherence tomography (OCT) will be presented from ten patients treated with the Tryton Side Branch Stent in the AMC. To explore whether clinical findings after Tryton stent use were reproducible outside a single-center registry, we will present a patient-level pooled analysis including 925 patients in chapter 7. The role of final kissing balloon inflation after Tryton stent implantation will be investigated in chapter 8. A randomized comparison of the Tryton stent against the provisional (single-stent) strategy will be presented in chapter 9. In chapter 10, the final chapter of this part of the thesis, we will present a substudy of the randomized trial presented in chapter 9, investigating luminal dimensions at follow-up using intravascular ultrasound (IVUS) and three-dimensional bifurcation QCA.

Part C: Dedicated bifurcation quantitative coronary angiography

In chapter 11, we will discuss why single-vessel QCA software is inaccurate in bifurcation lesions. In chapter 12, we will present a validation study using a bifurcation phantom model to quantify the inaccuracy of single-vessel software in bifurcation lesions and to validate different bifurcation QCA software. In chapter 13, we will investigate the reproducibility of bifurcation QCA, even if the same angiographies are analyzed by two different ‘core laboratories’ across the Atlantic. In chapter 14, we will explore the impact of the use of the different modalities (visual estimation, single-vessel QCA and bifurcation QCA) on bifurcation lesion severity estimation.

Part D: The use of bioresorbable vascular scaffolds: from simple lesions to bifurcations

In chapter 15, we will first evaluate the performance of bioresorbable vascular scaffolds (BVS) in relative simple lesions. In this chapter, we will present the procedural and 1 year
clinical outcomes of the randomized ABSORB II trial, comparing the use of the Absorb BVS with the Xience metallic DES for the treatment of de novo coronary lesions in patients presenting with SCAD. In chapter 16 we will subsequently investigate whether clinical results are similar in more complex lesions by using clinical data from 135 patients who were treated with Absorb BVS in the AMC (the AMC registry). In chapter 17, we will explore procedural outcomes, acute angiographic results using QCA, side branch ostium appearance using three-dimensional OCT and mid-term clinical outcomes of a subset of patients included in the AMC registry with a bifurcation lesion treated with Tryton in combination with Absorb BVS in the main branch. In chapter 18, we will investigate the fate of Absorb BVS jailed side branch struts over time by serial assessment (up to 5 years) using three-dimensional OCT.
REFERENCES


