Summary

Drug-eluting stents (DES) are widely used as first choice devices in percutaneous coronary interventions (PCI). However, certain concerns are associated with the use of DES, i.e. neo-atherosclerosis, late stent thrombosis and hypersensitivity reactions to the DES polymer. Bioresorbable scaffolds (BRS) such as the Absorb Bioresorbable Vascular Scaffold (BVS) are the next development within the field of PCI, introducing the concept of supporting the natural healing process following initial intervention without leaving any foreign body materials resulting in late adverse events. The first-generation devices have shown encouraging results in multiple studies of selected patients with non-complex lesions up to the point of full bioresorption. It supported the introduction in regular patient care. During its introduction in daily clinical practice outside the previous selected patient groups, a careful approach should be followed in which outcome is continuously monitored. The aim of this thesis was to investigate the safety and efficacy of the Absorb BVS in more complex lesions and higher-risk patients, when treated in a diverse clinical practice.

In Chapter 1, an overview was provided of available studies during that time point (2014/ 2015), demonstrating encouraging results in selected patients and with limited duration of follow-up. Together with a group of early expert users, we set up a Dutch consensus statement for the use of BVS (Chapter 2). We reported that the implantation of a BVS in a *de novo* lesion with a diameter between 2.3 – 2.8 mm and maximum length of 28 mm was indicated as 'Appropriate'. 'Probably appropriate' involved acute coronary syndrome (ACS) patients, long lesions, calcified lesion with proper lesion preparation and provisional bifurcation treatment. Off-label implantation included in-stent restenosis, grafts and vessel with diameter > 4.0 mm. More data needed to be gathered in order create real BVS guidelines.

Part I described the early outcomes of the Absorb BVS using different quantitative techniques. Chapter 3 described the acute angiographic outcomes of BVS when used in a wider range of coronary lesion types such as bifurcation and calcified lesions, chronic total occlusions and long lesions, showing feasible results.

All coronary implant will stretch the natural curvatures in the coronary arteries and reduce the possibility to increase curvatures during cardiac contraction. This alteration in natural morphology does have a known impact on flow patterns and will change shear stress within and at the edges of stents. The longer the lesions and subsequent implants, the more severe the impact will be. In Chapter 4 we compared the conformability of BVS and DES in long lesions (implants of at least 28mm). Due to the difference of materials, the BRS resulted in a non-significant reduction in curvature post-implant while the metallic DES results a significant reduction in curvature of the treated vessel.

Part II reported on the short- and mid-term outcomes of the BVS as investigated in the BVS registries from the Erasmus MC, including a patient population that was more reflective of 'real-world' patients and lesions, such as ACS, bifurcation and calcification.

The BVS Expand registry was the basis for multiple manuscripts, reporting on both angiographic (Chapter 3) and mid-term clinical outcomes (Chapter 5) The BVS Expand registry is an investigator initiated, single-arm, single-centre registry that included patients who presented with non-ST segment elevation myocardial infarction (NSTEMI), unstable angina, stable angina or silent ischemia and who had a *de novo* lesion in vessels with diameter between minimum 2.0 and maximum 3.8 mm by online quantitative coronary analysis (QCA). Main excluding criteria were: previous coronary artery bypass grafting (CABG), presentation with ST elevation myocardial infarction (STEMI) and an expected survival of less than one year. Although advanced age was not an exclusion criterion, BVS were in general reserved for younger patients, and left to operator's interpretation of biological age. We included 249 patients (intention-to-treat population) with mean age of 61.3±10.2 years; 73.5% were male and 18.5% were diabetic. Pre-dilatation was performed in 89.3%, intravascular imaging in 39% and post-dilatation in 53.3%. Device success was 99.2%. Post-procedural reference vessel diameter (RVD) was 2.89±0.42 mm, minimum lumen diameter (MLD) was 2.41±0.41 mm and diameter stenosis (%DS) was 17.6±8.6%. Clinical outcomes at 18 months were acceptable with rate of major adverse cardiac events (MACE) of 6.8% and rate of definite scaffold thrombosis (ScT) of 1.9% (Chapter 5). The BVS STEMI registry was the Erasmus MC's study to investigate the performance of BVS in STEMI patients only. Main exclusion criteria were: known intolerance to contrast medium, uncertain neurological outcome after cardiopulmonary resuscitation, previous PCI with the implantation of a metal stent, left main (LM) disease.

In Chapter 6, using pooled data from both the Expand and STEMI registry, our group described outcomes in ACS patients and non-ACS patients, demonstrating similar one year clinical outcomes. Acute angiographic outcomes such as post-procedural MLD and %DS appeared to be better in the ACS group. But of note, stable patients were older, had more risk factors and often presented with more complex lesions (higher rates of bifurcation, calcification and chronic total occlusions [CTO]). MACE rate and rate of ScT was comparable between groups but the latter represented with a different distribution in time: early ScT (< 30 days) occurred mainly in ACS patients whereas in the stable group, all cases of ScT were clustered between 30 days and 1 year (late ScT).

Our group was the first to describe acute outcomes of the BVS in a small group of STEMI patients, showing excellent expansion, low malapposition and small in-stent protruding masses. [1] Subsequently, we investigated the 18-months clinical outcomes of almost 150 patients, propensity matched with a metallic DES group (Chapter 7). Procedural and angiographic results were similar between groups. However, clinical events rates were higher for the BVS groups. Most events occurred in the first 30 days after implantation and mainly in cases without post-dilatation. This might suggest that the optimisation of the implantation technique in the acute clinical setting is of paramount importance

for optimal short and mid-term outcomes. Performance of the BVS in different lesion subtypes such as bifurcation and calcified lesions was investigated in Chapters 8 and 9. In Chapter 8, 102 patients (107 lesions) with a bifurcation lesion, originating from both BVS Expand and BVS STEMI, were investigated to report performance of BVS in this type of lesion. The focus was on side branch impairment. Patients were included with at least one *de novo* bifurcation lesion involving a side branch ≥ 2.0 mm by visual estimation and treated with at least one BVS. Most patients were treated by T-provisional strategy showing good acute angiographic outcomes. Device and procedural success were 99.1% and 94.3% respectively and side branch impairment during the procedure occurred in 12.1%. One-year results were good with rate of MACE of 5.5% and definite ScT of 2.2%. Chapter 9 studied the effect of calcium on acute procedural and clinical outcomes in patients treated with BVS. Patients with a calcified lesion were older, had more often hypertension and kidney insufficiency and presented less likely with one-vessel disease. Also, the calcified group included more complex lesion types: higher rate of AHA/ ACC type B2/C lesions, bifurcation, total occlusions, longer lesions and with smaller RVD than in the non-calcified group. Device success rate was 99.1% with no significant differences between the groups. The calcified group showed more aggressive lesion preparation and post-dilatation than the non-calcified group. However, acute lumen gain was significantly less in calcified lesions (1.50 ±0.66 mm vs 1.62 ±0.69 mm, p= 0.040) and with lower final MLD (2.28± 0.41 mm vs 2.36±0.43, p=0.046). There were no significant differences in all-cause mortality, definite ScT, TLR and MI between the groups. Late ScT occurred more frequently in the calcified group compared to non-calcified group (2.1% vs 0%, p=0.02).

These results demonstrated that implantation of a BVS in a more complex patient and lesion subset may be feasible and associated with acceptable rate of adverse events. These observations were also reported in other studies.

Chapter 10 described the performance of BVS when investigated by multislice computed tomography (CT) in a BVS Expand sub cohort. Mid-term performance of BVS, when assessed by computed tomography coronary angiogram (CTCA) was good and CTCA as non-invasive investigation was feasible to evaluate scaffold patency and in-scaffold stenosis.

Part III described the implications of failed cases for future applications. Chapter 11 reported pilot imaging observations in 'real-world' patients with BVS thrombosis. Suboptimal implantation with underexpansion, malapposition, and incomplete lesion coverage, often in combination with dual antiplatelet therapy (DAPT) discontinuation appeared to be the major substrate both for acute and late events.

In Chapter 12 both pathophysiology and treatment of BRS failure are discussed. Chapter 13 describes three cases of very late ScT and their possible relationship with DAPT termination before 18 months. In Chapter 14 we report on the impact of DAPT termina-

tion before 18 months on ScT. Data of three Dutch centres were pooled to investigate the impact of DAPT termination on the occurrence of very late ScT. The incidence of ScT was most notable in the first month after DAPT termination.

Chapter 15 was a systematic review and meta-analysis comparing the mid-term (weighted follow-up duration of 30.6 months) clinical outcomes of the BVS with second-generation DES, including seven randomized controlled trials and three observational propensity matched studies. The use of BVS was associated with an increased risk of adverse events (target lesion failure, myocardial infarction, target lesion revascularization and device thrombosis, especially the risk of very late (> 1 year) device thrombosis. However, this did not result in an increased risk of all-cause mortality.

REFERENCES

1. Diletti, R., et al., Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction: BVS STEMI first study. Eur Heart J, 2014. 35(12): p. 777-86.