General Introduction

Cardiovascular diseases (CVD), with coronary artery disease (CAD) being the most common type, are the leading cause of death globally. After numerous experiments on animals[1], coronary bypass grafting (CABG) was developed as treatment option for stenosed or completely occluded coronary. A German surgeon named Robert Goetz performed a CABG (IMA to LAD) on a human in a New York hospital in 1960, using a non-suture technique. The first suture technique based CABG procedure took place in 1964 by the Russian Vasilli Kolesov. Unfortunately, rate of mortality was high in these days, yet technology accelerated and improvements were made, which reduced the one-year mortality rate to approximately 3%. [2]

Andreas Gruentzig performed his first successful coronary angioplasty in 1977.[3] However, still in these early days many patients died or needed surgery the same day. Since then, numerous important developments have taken place within the field of interventional cardiology with a subsequent decrease in event rates. From the mid-eighties, the use of bare metal stents (BMS) reduced the high rate of acute recoil seen with classical angioplasty [4] but they went along with the frequent (up to 25%) occurrence of in-stent restenosis (ISR) within the first year after implant due to neointimal hyperplasia. [5] This phenomenon was contested by the introduction of metallic drug-eluting coronary stent (DES) in 1999 which subsequently, reduced the 1- and 2-year rates of restenosis and repeated revascularizations below 10% and soon, they became the gold standard for the treatment of CAD. However, DES were not devoid of limitations such as chronic inflammation, neoatherosclerosis, stent fracture, incomplete endothelization, loss of normal vessel geometry and vasomotion. Re-intervention rate using DES beyond 1 year post-implant, is on average 1 - 2% per year. [6, 7]

The mean age of patients treated with PCI is approximately 65 years. While treatment of ischemic heart disease improves and patients become older, the PCI population has quite some years to live after their first stent implant and the long-term risk of adverse events can be up to 20%. Therefore, new technologies have to be developed with the aim of improving outcomes beyond one year and envision 10 to 20 year durability of PCI. As mechanical support is most important to prevent acute recoil and preserving the lumen during the subsequent vascular healing process in the next three months, a temporary supportive device should be sufficient. This would eliminate the late response to the permanent metallic devices mentioned above.

Up to this moment, five bioresorbable scaffolds (BRS) received "Conformité Européene" (CE) mark: 1) the DESolve novolimus-eluting bioresorbable coronary scaffold system (Elixir Medical Corporation, Sunnyvale, California, USA), made of poly-L-lactic acid; [8] ; 2) ART Pure (Terumo Corporation, Tokio, Japan and Arterial Remodeling Technologies S.A. [ART], Noisy le Roi, France), a scaffold made of poly-D, L-lactic acid without any drug-elution; 3) the Magmaris scaffold (previously known as DREAMS, Biotronik AG, Bülach, Switzerland), a sirolimus-eluting and magnesium based scaffold. [9]; 4) Fantom (REVA

Medical, San Diego, California, USA), a sirolimus-eluting poly-tyrosine–derived polycarbonate scaffold. [10] 5) the everolimus-eluting Absorb bioresorbable vascular scaffold (BVS, Abbott Vascular, Santa Clara, California, USA), made of poly-L-lactide. Hypothesized advantages of the BVS over DES are late lumen enlargement, restored vasomotion, no interference with non-invasive imaging and complete resorption in approximately three years, leaving nothing behind. [11, 12]

The first iteration of the BVS (1.0) was tested in the ABSORB Cohort A in 2006. This study included only low-risk patients with simple lesions, with late lumen loss (LLL) as primary endpoint. [13] A second iteration of the device was developed with improvement in mechanical integrity and was tested in the ABSORB cohort B trial, revealing good results, with LLL of 0.19±0.18 mm at six months. Multiple randomized controlled trials (RCTs), mainly designed for regulatory approval in different countries which compare BVS with the best-in-class everolimus DES (Xience, Abbott Vascular, Santa Clara, California, USA), reported comparable results on the short-term (one year). [14-17] However, complex patients (acute myocardial infarction) and lesions (bifurcation, heavy calcification, chronic total inclusion [CTO]) were excluded. Because of the limited in- and exclusion criteria used in RCTs, patients included in registries are more representative of usual practise. Therefore, registry-based results are important and have a higher generalizability.

At the Absorb BVS's clinical introduction in September 2012, the Erasmus Medical Centre started two prospective, single-arm, investigator-initiated registries as a structured program, aiming at hospital quality control and an increase in knowledge to share with the interventional cardiology community through scientific publications. Up to this day, there is still a lack of data concerning the implementation of this new technology in 'real-world' patients, consisting of more complex subsets such as ACS patients, calcified and bifurcation lesions and with a longer duration of follow-up.

Scope of this thesis

The aim of this thesis is to investigate the early and mid-term performance of the Absorb BVS in more complex lesions and higher-risk patients, when treated in a diverse clinical practice.

Also, the purpose is to identify potential factors that could influence these outcomes to optimize patient and lesion selection, procedural strategies and post-procedural pharmaceutical treatment. Lastly, more information is necessary regarding the mechanisms of scaffold failure (both scaffold thrombosis and restenosis) and to develop this treatment further and treatment options are provided.

The early outcomes of this new device in will be investigated in Part I, using different quantitative techniques in different clinical scenarios. We will use early proven surrogate endpoints and look at short-term outcomes.

Part II will examine the mid-term outcomes in relation to complex lesion and patient subtypes and clinical presentations to identify predictors of potential unfavourable

results. This was done in a more general population and in specific higher-risk groups such ACS patients, calcified and bifurcation lesions.

Part III will report on late events, occurring during the resorption phase. It will focus on scaffold thrombosis and restenosis and concerns results from cases with poor outcome. Also, we will provide some suggestions for how to handle these.

In the final section (Discussion), observations from this research will be discussed while integrating these with the current international literature to an updated statement on the use of this first-generation bioresorbable vascular scaffold and directions for improvement in outcome.

REFERENCES

1. Carrel A. VIII. On the Experimental Surgery of the Thoracic Aorta and Heart. Ann Surg 1910;**52**(1):83-95.
2. Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: Part 1--the evolution over the first 50 years. Eur Heart J 2013;**34**(37):2862-72.
3. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;**1**(8058):263.
4. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;**316**(12):701-6.
5. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;**331**(8):489-95.
6. Simsek C, Magro M, Boersma E, Onuma Y, Nauta S, Daemen J, Gaspersz M, van Geuns RJ, van der Giessen W, van Domburg R, Serruys P. Comparison of six-year clinical outcome of sirolimus- and paclitaxel-eluting stents to bare-metal stents in patients with ST-segment elevation myocardial infarction: an analysis of the RESEARCH (rapamycin-eluting stent evaluated at Rotterdam cardiology hospital) and T-SEARCH (taxus stent evaluated at Rotterdam cardiology hospital) registries. J Invasive Cardiol 2011;**23**(8):336-41.
7. Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, Cutlip DE, Sudhir K, Hou L, Koo K, Stone GW. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). JACC Cardiovasc Interv 2013;**6**(12):1263-6.
8. Verheye S, Ormiston JA, Stewart J, Webster M, Sanidas E, Costa R, Costa JR, Jr., Chamie D, Abizaid AS, Pinto I, Morrison L, Toyloy S, Bhat V, Yan J, Abizaid A. A next-generation bioresorbable coronary scaffold system: from bench to first clinical evaluation: 6- and 12-month clinical and multimodality imaging results. JACC Cardiovasc Interv 2014;**7**(1):89-99.
9. Haude M, Ince H, Abizaid A, Toelg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Neumann FJ, Kaiser C, Eeckhout E, Lim ST, Escaned J, Onuma Y, Garcia-Garcia HM, Waksman R. Sustained safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de novo coronary lesions: 12-month clinical results and angiographic findings of the BIOSOLVE-II first-in-man trial. Eur Heart J 2016.
10. Abizaid A, Carrie D, Frey N, Lutz M, Weber-Albers J, Dudek D, Chevalier B, Weng SC, Costa RA, Anderson J, Stone GW, Investigators FIC. 6-Month Clinical and Angiographic Outcomes of a Novel Radiopaque Sirolimus-Eluting Bioresorbable Vascular Scaffold: The FANTOM II Study. JACC Cardiovasc Interv 2017;**10**(18):1832-1838.
11. Karanasos A, Simsek C, Gnanadesigan M, van Ditzhuijzen NS, Freire R, Dijkstra J, Tu S, Van Mieghem N, van Soest G, de Jaegere P, Serruys PW, Zijlstra F, van Geuns RJ, Regar E. OCT assessment of the long-term vascular healing response 5 years after everolimus-eluting bioresorbable vascular scaffold. J Am Coll Cardiol 2014;**64**(22):2343-56.
12. Simsek C, Karanasos A, Magro M, Garcia-Garcia HM, Onuma Y, Regar E, Boersma E, Serruys PW, van Geuns RJ. Long-term invasive follow-up of the everolimus-eluting bioresorbable vascular scaffold: five-year results of multiple invasive imaging modalities. EuroIntervention 2016;**11**(9):996-1003.

13. Dudek D, Onuma Y, Ormiston JA, Thuesen L, Miquel-Hebert K, Serruys PW. Four-year clinical follow-up of the ABSORB everolimus-eluting bioresorbable vascular scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2012;**7**(9):1060-1.
14. Serruys PW, Chevalier B, Dudek D, Cequier A, Carrie D, Iniguez A, Dominici M, van der Schaaf RJ, Haude M, Wasungu L, Veldhof S, Peng L, Staehr P, Grundeken MJ, Ishibashi Y, Garcia-Garcia HM, Onuma Y. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet 2015;**385**(9962):43-54.
15. Ellis SG, Kereiakes J, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, Litt MR, Kini A, Kabour A, Marx SO, Popma JJ, McGreevy R, Zhang Z, Simonton C, Stone GW, Investigators AI. Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease. N Engl J Med 2015.
16. Gao R, Yang Y, Han Y, Huo Y, Chen J, Yu B, Su X, Li L, Kuo HC, Ying SW, Cheong WF, Zhang Y, Su X, Xu B, Popma JJ, Stone GW, Investigators AC. Bioresorbable Vascular Scaffolds Versus Metallic Stents in Patients with Coronary Artery Disease: ABSORB China trial. J Am Coll Cardiol 2015.
17. Kimura T, Kozuma K, Tanabe K, Nakamura S, Yamane M, Muramatsu T, Saito S, Yajima J, Hagiwara N, Mitsudo K, Popma JJ, Serruys PW, Onuma Y, Ying S, Cao S, Staehr P, Cheong WF, Kusano H, Stone GW, Investigators AJ. A randomized trial evaluating everolimus-eluting Absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan. Eur Heart J 2015;**36**(47):3332-42.