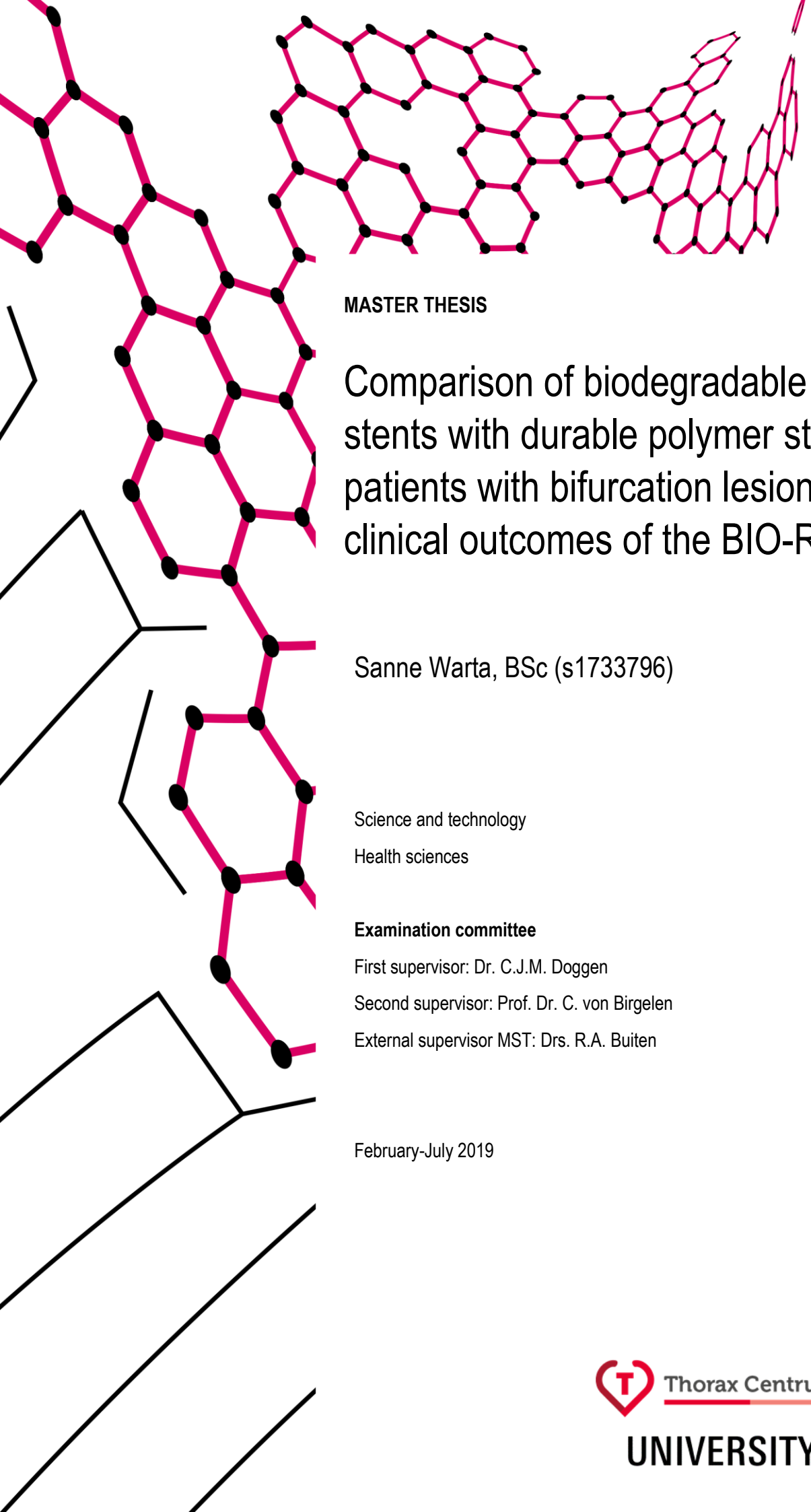

MASTER THESIS

Comparison of biodegradable polymer stents with durable polymer stents in treating patients with bifurcation lesion: three-year clinical outcomes of the BIO-RESORT trial.

Sanne Warta, BSc (s1733796)

Science and technology

Health sciences

Examination committee

First supervisor: Dr. C.J.M. Doggen

Second supervisor: Prof. Dr. C. von Birgelen

External supervisor MST: Drs. R.A. Buiten

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Thorax Centrum Twente

MST

UNIVERSITY OF TWENTE.

Preface

Dear reader,

In front of you lies the thesis entitled: “Comparison of biodegradable polymer stents with durable polymer stents in treating patients with bifurcation lesion: three-year clinical outcomes of the BIO-RESORT trial.” This is my master thesis for the master Health Sciences which has been performed in cooperation with the Thorax Centrum Twente at Medisch Spectrum Twente in Enschede.

I would like to thank my first and second supervisors Dr. C.J.M Doggen and prof.dr. C. von Birgelen for their support and valuable feedback. Second, I would like to thank my external supervisor Drs. R.A. Buiten for thinking along, answering my questions and exchanging thoughts on the content of the thesis on a daily basis. Besides, I would like to thank my colleagues at “Stichting cardiovascular research en educatie Enschede” for the support, the involvement and making writing my thesis more fun.

I hope you enjoy reading this thesis.

Sanne Warta, July 2019

Abstract

Introduction: There are several types of drug eluting stents (DES) that can be used in percutaneous coronary intervention (PCI) to treat patients with coronary artery disease. Stents with thicker struts and durable polymer coatings have been associated with delayed arterial healing, inflammatory responses, restenosis and a higher incidence of adverse clinical events. Novel, thinner strut, biodegradable polymer coated drug eluting stents might reduce these problems. This theoretical benefit may be particularly beneficial in complex lesions like bifurcations. Stenting bifurcation lesions has been associated with an increased clinical adverse event risk due to both anatomical and technical challenges. This sub-study of the randomized BIO-RESORT trial assessed the three-year clinical outcome of patients with bifurcation lesions, treated with very thin strut biodegradable polymer drug eluting stents versus thin strut durable polymer drug-eluting stents. The research question is: *What is the difference in target vessel failure (TVF) when comparing the biodegradable polymer everolimus-eluting stent (EES) and sirolimus-eluting stent (SES) to durable polymer zotarolimus-eluting stents (ZES) in patients with bifurcation lesions?*

Method: The BIO-RESORT trial is a prospective, multicentre, patient-blinded and investigator-initiated randomized clinical trial with three arms, that compares the clinical outcome of 3514 all-comer patients who required PCI with DES implantation. The biodegradable polymer Synergy EES or Orsiro SES and durable polymer Resolute Integrity ZES were randomly assigned to patients in a 1:1:1 ratio. The present sub-study assessed three-year clinical outcome of 1236 BIO-RESORT participants who were treated in at least one bifurcation lesion. The main endpoint was target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization

Results: There was a numeric difference in TVF between Synergy EES versus Resolute Integrity ZES and Orsiro SES versus Resolute Integrity ZES. These differences were statistically not significant for both Synergy EES and Orsiro SES as compared to Resolute Integrity ZES. The individual components of TVF as well as secondary endpoints did not show significant differences between stent groups.

Discussion: At three-year follow up, this sub-study found no significant difference in the main endpoint TVF in patients with bifurcation lesions treated with biodegradable polymer Synergy EES or Orsiro SES versus durable polymer Resolute Integrity ZES. The safety and efficacy of the three stents in bifurcation lesions appears to be comparable.

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Introduction

In atherosclerosis there is an accumulation of cholesterol containing low-density lipoprotein particles in the arterial wall, called an atherosclerotic plaque, which causes a chronic inflammatory process. This can cause an atherosclerotic lesion which is a thickening of the intima.[1] Atherosclerosis in the coronary arteries is referred to as coronary artery disease, which may cause a variety of symptoms. If the plaque is stable but partly occludes one of the coronary arteries and leads to significant decrease in blood flow, the patient experiences chest pain only during exertion. If the plaque is unstable, complaints can get worse, even with minimal exertion or at rest. In this case the clinical syndrome is referred to as unstable angina or as non-ST segment elevation myocardial infarction (NSTEMI). In the latter, there is acute ischemia of the myocardium but no complete occlusion of the coronary. If there is a complete occlusion, the patient will have symptoms at rest and the electrocardiogram (ECG) shows ST segment elevation, hence the name ST segment elevation myocardial infarction (STEMI) in which urgent medical treatment is required to open the occluded vessel.[2]

To restore blood flow, obstructive lesions can be treated with percutaneous coronary intervention (PCI). PCI refers to various procedures that reopen obstructed coronary arteries, often including the placement of a stent, with the goal to improve myocardial perfusion and reduce the patient's symptoms.[3] Several types of stents have been developed. The first stents were bare metal stents, after which drug eluting stents (DES) were developed that resulted in a lower need for repeat revascularisation.[4] A DES generally consists of a metallic stent platform and a polymer coating that releases an antiproliferative agent. Several kinds of drugs can be released like sirolimus, everolimus or zotarolimus.[5] The platform material and the strut thickness differ between stents, as well as the polymer coating which can be durable or biodegradable. A durable polymer coating stays on the stent platform after drug release and is associated with delayed arterial healing and inflammatory responses. To prevent these problems, biodegradable polymer coatings, which degrade after drug release, were developed.[6] Furthermore, the strut thickness matters because thinner strut DES may reduce restenosis as compared to thicker strut DES[7, 8]. Therefore, newer DES with more flexible, thin-strut stent platforms and biodegradable polymer coating, such as the Synergy everolimus eluting stent (EES) and Orsiro sirolimus eluting stent (SES), were developed. The flexible design also improves deliverability, which means that it is easier to place the stent on the intended place[9]. These DES have been studied in all-comer patients, which means that there were few inclusion and exclusion criteria in the study. In all-comer patients these newer DES showed safety and efficacy that were comparable to durable polymer DES[10, 11].

Thicker struts and durable polymer coated stents have been associated with delayed arterial healing, inflammatory responses and restenosis[6-8], and theoretically the newer DES might reduce

these problems. The theoretical benefits of these newer stents may particularly be of interest in complex lesions like small vessels[12] and bifurcation lesions[9]. In general, patients with bifurcation lesions have a higher risk of myocardial infarction (MI) or repeated revascularisation, than patients without bifurcation lesions. [13, 14]. Therefore, these newer, thinner strut stents with biodegradable polymers might improve clinical outcomes for patients with bifurcation lesions.

Bifurcation lesion

Off all PCI procedures, about 15-20% are performed in patients with coronary bifurcations. Coronary bifurcation anatomy is a complex vessel structure, consisting of a proximal main vessel, a distal main vessel and a side branch that are connected through the bifurcation core segment.[15]

A common method to classify bifurcations is the Medina classification, as shown in appendix 1. It indicates which part of the coronary bifurcation segment has a significant stenosis. This is done in a fixed order: the proximal main vessel, the distal main branch and the side branch. Each branch will get a 1 or a 0 to indicate the presence of disease, and then the numbers are separated by a comma. A "1" indicates a significant stenosis (i.e. angiographic diameter of stenosis is more than 50%) and a "0" indicates a non-significant stenosis. For example, when there is significant stenosis in the proximal main vessel and the side branch, the Medina classification of that lesion is 1,0,1.[15]

When treating a bifurcation lesion (with DES), there are several stenting techniques that can be used. These techniques are classified in the Main, Across, Distal, Side (MADS) classification, as shown in appendix 2. This classification indicates which branch is stented first, whether a proximal optimization technique is used and how many stents are used.[16] The standard technique is provisional stenting of the main branch using a single stent. Consideration of a second stent depends on the characteristics of the lesion, accessibility towards the most distal strut, how important (i.e. large) the side branch is and the level of residual side branch stenosis. In general, a second stent is needed in 5 to 25% of the cases.[17]

Stenting bifurcation lesions has been associated with an increased clinical adverse event risk due to both anatomical and technical challenges[15]. A single-stent technique is associated with a lower long-term mortality as compared to a dual stenting technique,[18, 19] but with a single stenting technique there is a risk of losing the side branch by accidental closure during the procedure[15]. A two-stent technique is complex and can increase the risk of peri-procedural MI and the risk of long-term adverse effects such as restenosis and stent thrombosis.[15]

Due to this complexity of bifurcation lesions and the higher risk of clinical adverse events, during or after PCI, newer DES might be advantageous in this complex patient population.

Drug eluting stents in bifurcation

Several studies have compared new-generation DES in patients with bifurcation lesions. These studies found similar clinical outcomes for biodegradable polymer DES as compared to durable polymer DES[20-22]. But there are also some studies that found lower rates of target vessel and target lesion revascularisation (TLR) in biodegradable polymer DES as compared to durable polymer DES[23-25]. However, data on the newest biodegradable polymer DES in bifurcations is scarce and more studies on biodegradable polymer-coated DES are needed to define their role in the treatment of bifurcations[15].

This thesis is a sub-study of the BIO-RESORT trial that examined two of the newest biodegradable polymer-coated DES. The BIO-RESORT trial is a large, prospective, randomised, multicentre trial with three stent arms that uses data of 3514 all-comer patients that required PCI with DES implantation. The biodegradable polymer Synergy EES and Orsiro SES are compared with the durable polymer Resolute Integrity zotarolimus eluting stent (ZES). The goal of this trial is to evaluate the efficacy and safety of these stents, with a maximum follow-up of five years. The BIO-RESORT trial is the first trial that compares the biodegradable polymer Synergy EES and Orsiro SES with the durable polymer Resolute Integrity ZES simultaneously.[26]

At one-year follow-up, the BIO-RESORT study showed that in all-comers the biodegradable polymer EES and SES are non-inferior to the durable polymer ZES[27]. Clinical outcome in EES and SES were comparable to ZES at two- and three-year follow-up.[28]

However, the Synergy EES and Orsiro SES and Resolute Integrity ZES have not yet been compared with each other in bifurcation lesions. The aim of this sub-study is to compare the biodegradable polymer Synergy EES and biodegradable polymer Orsiro SES with the durable polymer Resolute Integrity ZES regarding several clinical endpoints in patients with bifurcation lesions. It is important to compare these stents to provide information on whether one stent might provide better clinical outcomes than the other stent. This might facilitate decision making on which stent should be used in patients with bifurcation lesions.

The main endpoint of this sub-study is the composite endpoint target vessel failure (TVF), which consists of cardiac death, target vessel-related MI, or clinically indicated target vessel revascularisation (TVR).

The research question is: *What is the difference in target vessel failure when comparing the biodegradable polymer EES and SES to durable polymer ZES in patients with bifurcation lesions?*

Moreover, safety and efficacy of the DES will be assessed. Safety is important because the newer stents itself should not increase the risk of adverse events. Safety is assessed with cardiac death, target vessel MI and stent thrombosis. Efficacy is important because it assesses to what extent the stents are doing what they are designed for, which is keeping the lesion and vessel open. Efficacy is assessed with the endpoints TVR and TLR. Furthermore, a patient-oriented composite endpoint (POCE) will be assessed, which consists of any death, any MI, or any revascularisation, as for patients it does not matter what the cause of death is or which of the coronary vessels requires treatment.

This resulted in the following sub-questions:

- What is the efficacy of biodegradable polymer EES and SES as compared to durable polymer ZES?
- What is the safety of biodegradable polymer EES and SES as compared to durable polymer ZES?
- What is the difference in the patient oriented composite endpoint when comparing the biodegradable polymer SES and EES to the durable polymer ZES?

Methods

Study design

This study is a quantitative study that used data collected in the BIO-RESORT trial. No additional collection of data outside the BIO-RESORT trial took place. The BIO-RESORT trial is a prospective, randomised clinical trial. The study is a patient-blinded, investigator-initiated, multicentre three-arm trial, with 3514 all-comer patients who required PCI with DES implantation.[26]

Study population

The BIO-RESORT trail collects data from patients of four clinical centres in the Netherlands which are Thorax centrum Twente at Medisch Spectrum Twente (Enschede), Rijnstate Hospital (Arnhem), Albert Schweitzer Hospital (Dordrecht) and Haga Hospital (The Hague). The study population in the BIO-RESORT trial is an all-comer patient population, which means that there were few inclusion and exclusion criteria. These all-comers had DES implanted for various clinical syndromes. Table 1 presents inclusion and exclusion criteria for the all-comers study population of the BIO-RESORT trial.[26]

Inclusion criteria	**Exclusion criteria**
The patient is 18 years or older.	The patient is participating in another randomised drug or device trial before reaching its primary endpoint.
The patient is able provide informed consent.	Pregnancy is known.
The patient is able and willing to cooperate with the follow-up and study procedures.	The patient is intolerant to components of an investigational product, or to antithrombotic or anticoagulant medication, preventing adherence to dual antiplatelet therapy.
According to clinical guidelines and/or the operators' judgement, there is/are (a) coronary artery or bypass graft lesion(s) that require(s) PCI with DES implementation.	Planned elective surgical procedure during the first 6 months after randomisation, necessitating the interruption of dual antiplatelet therapy.
	Adherence to the scheduled follow-up is uncertain and/or the life expectancy is lower than 1 year.

Table 1: Inclusion and exclusion criteria of the BIO-RESORT trial[26]

Of all 3514 BIO-RESORT participants, 1236 (35%) were treated for at least one bifurcation lesion. These patients treated for bifurcation lesion represent the study population of the present study.

Stent specifications

The very thin strut Synergy EES is a platinum-chromium stent with a strut thickness (depending on the stent diameter) of 74 µm (for ≤2,5 mm), 79 µm (for 3,0–3,5 mm), or 81 µm (for 4,0 mm stents). The coating is a 4 µm thick biodegradable poly-lactic co-glycolic acid (PLGA) coating and elutes

everolimus. Only the abluminal side is coated to minimize the amount of polymer and the coating is resorbed within 4 months.[4, 26] The very thin strut Orsiro SES is a cobalt-chromium stent and has a strut thickness of 60 µm for stents with a nominal diameter ≤ 3,0 mm or a strut thickness of 80 µm for stents with a nominal diameter > 3,0 mm. The coating is biodegradable and consists of an active and passive component. The active component is the BIOlute coating that elutes sirolimus. The passive component is the PROBIO coating which reduces the interaction of the surrounding tissue and blood with the metallic surface to prevent corrosion of the stent. The coating is circumferential and asymmetrical. On the abluminal side it is thicker (7,4 µm) than on the luminal side (3,5 µm), and it is degraded within two years.[26] The thin strut Resolute Integrity ZES has cobalt-chromium struts of 91 µm thick. The coating is a durable polymer coating called a BioLinx polymer system, which is a blend of 3 polymers. The hydrophobic C10 polymer is used to control drug release of zotarolimus. The biocompatibility is supported by the hydrophilic C19 polymer, and the polyvinyl pyro-lidinone improves the elution rate and initial drug burst. The coating is 6 µm thick and circumfencial.[26]

Randomisation and blinding

The three DES were randomly assigned to patients in a 1:1:1 ratio after guide wire passage with or without predilation using a custom designed computer program. Random blocks of 6 and 3 were used for randomisation and stratified on the prevalence of medically treated diabetes mellitus. Treating clinicians were not blinded to the allocated stent. Patients were blinded as well as staff collecting data at follow-up and assessors such as angiographic analysts or members of the independent clinical event committee.[26]

Procedure

In the trial, PCI was performed following standard techniques and the operators decided on lesion predilation, direct stenting and stent postdilation. After PCI, dual antiplatelet therapy (DAPT) was prescribed for 6 to 12 months, depending on the clinical syndrome at index procedure. Drugs were the same as in routine clinical care, and other treatment was in accordance with medical guidelines and the physician's judgement. When additional lesions needed treatment during follow-up, it was preferred that the same stent as the study stent was used. It was encouraged to treat all target lesions in one PCI, but if needed staged procedures with the allocated stents were permitted within 6 weeks after the index procedure.[26]

Follow-up

The follow-up data for each individual patient was collected within a period of three years. Follow-up data was collected when patients visited outpatient clinics or, if this was not feasible, by telephone or questionnaire. Information was gathered regarding clinical adverse events. Information on survival was collected through the municipal population register. When a patient died, information needed for follow-up, like occurrence of MI or repeat hospitalizations, was obtained from the patient's medical charts, the cardiologist or the general practitioner.[26]

Clinical endpoints

Clinical endpoints were defined according to definitions of the Academic Research Consortium[29]. The main endpoint was the composite endpoint TVF, consisting of cardiac death, target vessel MI or clinically driven TVR. These components were individually assessed as well. The other endpoints were the POCE (consisting of: all-cause death, any MI or any repeat revascularisation), target lesion failure (TLF) (composite endpoint consisting of cardiac death, target vessel MI or clinically driven TLR), TLR, and definite or probable stent thrombosis.

Statistical analysis

According to the BIO-RESORT study protocol, Synergy EES and Orsiro SES were compared to the reference device Resolute Integrity ZES. The Synergy EES and Orsiro SES were not compared with each other. To compare baseline characteristics, differences in categorical variables were assessed with the Chi Square test. The Fishers exact test was used when the expected amount in one or more cells was lower than 5. To compare continuous variables, for a normal distribution the Students T-test was used and for a non-normal distribution, the Wilcoxon Rank-Sum test was used. The Kaplan Meier method was used to assess the time to the events and the log rank test was used to compare the three DES groups. Hazard Ratios were generated with Cox Regression. Potential confounders were identified if, in univariate analysis for comparing the baseline characteristics, a p-value <0.15 was found. Multivariate analysis was then performed using a Cox regression model; the first model included all potential confounders and with backwards selection only true confounding factors were kept in the model. A p-value is considered significant when it is lower than 0,05. The p-values and confidence intervals were two-sided. Statistical analyses were performed in SPSS, Version 25.0 (IBM).

Ethical considerations

The BIO-RESORT trial was approved by the Medical Ethics Committee Twente (request number 190151) and the institutional review boards of all participating centres. Patients provided written informed consent for participation in the BIO-RESORT trial. This sub-study was approved by the Ethics Committee of the faculty of Behavioural, Management and Social Sciences at the University of Twente. Patient data is coded and only accessible at computers in the MST for the researchers of the BIO-RESORT trial.

Results

Of all 3514 BIO-RESORT participants, 1236 were treated in at least one bifurcation. Of these patients, 409 were treated with Resolute Integrity ZES, 415 with Synergy EES and 412 with Orsiro SES. Three-year follow-up was available in 1200 (97,1%) patients; 19 patients withdrew consent and 17 patients were lost to follow-up.

Patient characteristics

Table 1 presents the patient characteristics. The average age of the study population was 64 years, ranging between 35 and 88 years, and the majority of patients were men (78,0%). Most patients presented with stable angina pectoris (33,7%). All characteristics were equally distributed among the stent groups, except for previous MI. Of all patients treated with Resolute Integrity ZES 101/409 (24,7%) had a previous MI, while 56/415 (13,5%) patients treated with Synergy EES (p: <0,001) and 70/412 (17,0%) patients with Orsiro SES (p: 0,007) had a previous MI.

Lesion and procedural characteristics

In Table 2, the lesion and procedural characteristics of the patient groups are shown. Most patients had de novo lesions (97,1%) and small vessels were involved in the majority of the patients (69,3%). Bifurcations with the Medina classification 1,1,0 were most commonly (39,8%) treated. Medina classification (39,8%). In almost every patient (97,7%) the assigned stent was the only type of DES implemented. The mean number of stents implanted was 2,02 (SD: 1,23) and the mean of the total stent length was 44,38 (SD: 30,17) mm. In the SES group, there were significantly more patients with small vessels involved than in the ZES group (p=0,04), while all other characteristics were equally distributed among the three stent groups. Most patients with bifurcation lesions received a single stent (85,8%) instead of 2 stents or more. T-stenting was the two-stent technique that was used most frequently (63,4%) in patients who received two stents.

Clinical outcomes

The clinical outcomes are shown in Table 3 and Figure 1. The main endpoint TVF occurred in 40/415 (9,8%) patients treated with the Synergy EES, in 42/412 (10,3%) patients treated with the Orsiro SES and 49/409 (12,1%) patients treated with Resolute Integrity ZES. These differences were statistically not significant for both Synergy EES and Orsiro SES as compared to Resolute Integrity ZES (HR 0,79, 95% CI 0,52-1,20, p= 0,26 and HR 0,84, 95% CI 0,56-1,27, p= 0,40, respectively).

No significant differences occurred in the individual components of TVF. Cardiac death rates were 7/415 (1,7%) for patients treated with Synergy EES, 42/412 (10,3%) for Orsiro SES and 49/409

(12,1%) for Resolute Integrity ZES (EES vs. ZES p=0,44 and SES vs. ZES p=0,62). Target vessel MI rates for Synergy EES, Orsiro SES and Resolute Integrity ZES were respectively 15/415 (3,7%), 19/412 (4,7%) and 20/409 (4,9%) (EES vs. ZES p=0,36 and SES vs. ZES p=0,84). The TVR rate was 23/415 (5,7%) for Synergy EES, 24/412 (5,9%) for Orsiro SES and 26/409 (6,5%) for Resolute Integrity ZES (EES vs. ZES p=0,60 and SES vs. ZES p=0,73)

In addition, the composite endpoint TLF was met by 35/415 (8,5%) of the patients with Synergy EES, 34/412 (8,4%) of the patients with Orsiro SES and 43/409 (10,6%) of the patients with Resolute Integrity ZES. The numeric differences, as compared to Resolute Integrity ZES were not significant for both Synergy EES (p= 0,29) and Orsiro SES (p= 0,26). TLR rates for Synergy EES, Orsiro SES and Resolute Integrity ZES were respectively 16/415 (3,9%), 18/412 (4,5%) and 14/409 (3,4%) (EES vs. ZES p=0,68 and SES vs. ZES p=0,45). The POCE endpoint rate was 58/415 (14,1%) for Synergy EES, 66/412 (16,2%) for Orsiro SES and 67/409 (16,5%) for Resolute Integrity ZES, and numeric differences were not significant (EES vs. ZES p=0,31 and SES vs. ZES p= 0,81). Definite or probable stent thrombosis occurred in Synergy EES in 5/415 (1,2%) patients, in Orsiro SES in 4/412 (1,0%) and in Resolute Integrity ZES in 6/409 (1,5%). Numerical differences were statistically not significant (EES vs. ZES p= 0,74 and SES vs. ZES p= 0,51).

Multivariate analysis for Synergy EES versus Resolute Integrity ZES resulted after adjustment for confounders (the total number of stents) in an adjusted HR of 0,82 (95% CI 0,54-1,25) for TVF at 3 years. For Orsiro SES versus Resolute Integrity ZES, the confounding factors were a history of previous MI and having renal insufficiency, which resulted in an adjusted HR of 0,85 (95% CI 0,56-1,30) for TVF at 3-year follow-up.

Table 1: Patient characteristics and clinical presentation of patients with bifurcation lesion (n=1236)

	Total N= 1236	EES N= 415	ZES N= 409	SES N= 412	p (EES vs. ZES)	p (SES vs. ZES)
Patient characteristics						
Men	964 (78,0%)	321 (77,3%)	313 (76,5%)	330 (80,1%)	0,78	0,22
Age (years)	64,07 (10,11)	63,96 (10,15)	63,97 (9,90)	64,29 (10,29)	>0,99	0,65
BMI (kg/m2)	27,38 (3,92)	27,44 (3,87)	27,63 (4,02)	27,08 (3,85)	0,50	0,05
Smoking	300/1207 (24,9%)	104/401 (25,9%)	92/402 (22,9%)	104/404 (25,7%)	0,31	0,34
Diabetes Mellitus	236 (19,1%)	75 (18,1%)	87 (21,3%)	74 (18,0%)	0,25	0,23
Hypertension	579 (46,8%)	184 (44,3%)	202 (49,4%)	193 (46,8%)	0,15	0,47
Hypercholesterolaemia	460 (37,2%)	150 (36,1%)	151 (36,9%)	159 (38,6%)	0,82	0,62
Family history of CAD[a]	556/1190 (46,7%)	182/395 (46,1%)	190/401 (47,4%)	184/394 (46,7%)	0,71	0,85
Previous myocardial infarction	227 (18,4%)	56 (13,5%)	101 (24,7%)	70 (17,0%)	<0,001	0,007
Previous heart failure	24 (1,9%)	7 (1,7%)	8 (2,0%)	9 (2,2%)	0,77	0,82
Previous PCI	216 (17,5%)	72 (17,3%)	64 (15,6%)	80 (19,4%)	0,51	0,16
Previous CABG[a]	78 (6,3%)	29 (7,0%)	22 (5,4%)	27 (6,6%)	0,34	0,48
Renal insufficiency	39 (3,2%)	6 (1,4%)	12 (2,9%)	21 (5,1%)	0,14	0,12
Clinical presentation						
Stable angina pectoris	416 (33,7%)	140 (33,7%)	133 (32,5%)	143 (34,7%)		
Unstable angina pectoris	239 (19,3%)	71 (17,1%)	87 (21,3%)	81 (19,7%)		
Non-ST-elevation myocardial infarction	270 (21,8%)	93 (22,4%)	90 (22,0%)	87 (21,1%)	0,48	0,89
ST-elevation myocardial infarction	311 (25,2%)	111 (26,7%)	99 (24,2%)	101 (24,5%)		

Values are n (%) or mean (SD)

[a]Abbreviations: CAD: coronary artery disease, CABG: coronary artery bypass grafting

Table 2: Lesion and procedural characteristics of patients with bifurcation lesion (n=1236)

	Total N= 1236	EES N= 415	ZES N= 409	SES N= 412	p (EES vs. ZES)	p (SES vs. ZES)
Lesion characteristics						
Medina classification					0,47	0,31
0,0,1	104 (8,4%)	39 (9,4%)	38 (9,3%)	27 (6,6%)		
0,1,0	191 (15,5%)	58 (14,0%)	55 (13,4%)	78 (18,9%)		
0,1,1	59 (4,8%)	17 (4,1%)	21 (5,1%)	21 (5,1%)		
1,0,0	64 (5,2%)	29 (7,0%)	18 (4,4%)	17 (4,1%)		
1,0,1	46 (3,7%)	20 (4,8%)	13 (3,2%)	13 (3,2%)		
1,1,0	492 (39,8%)	162 (39,1%)	162 (39,5%)	168 (40,8%)		
1,1,1	280 (22,7%)	89 (21,5%)	103 (25,1%)	88 (21,4%)		
De novo lesion	1200 (97,1%)	406 (97,8%)	395 (96,6%)	399 (96,8%)	0,27	0,83
At least one severe calcification[a]	327 (26,5%)	100 (24,1%)	112 (27,4%)	115 (27,9%)	0,28	0,87
At least one chronic total occlusion[a]	56 (4,5%)	20 (4,8%)	21 (5,1%)	15 (3,6%)	0,84	0,30
At least one in stent restenosis	33 (2,7%)	7 (1,7%)	13 (3,2%)	13 (3,2%)	0,16	0,99
At least one small vessel (<2.75 mm)	856 (69,3%)	280 (67,5%)	274 (67,0%)	302 (73,3%)	0,88	0,05
Procedural characteristics						
Implantation of assigned stent only	1209 (97,8%)	405 (97,6%)	401 (98,0%)	403 (97,8%)	0,66	0,82
Multivessel treatment	365 (29,5%)	114 (27,5%)	124 (30,3%)	127 (30,8%)	0,37	0,88
Number of stents per patient	2,01 (1,23)	1,93 (1,22)	2,09 (1,23)	2,01 (1,28)	0,06	0,39
Total stent length per patient (mm)	44,45 (30,29)	42,60 (29,25)	45,60 (30,30)	44,99 (31,29)	0,13	0,84
Predilation	1077 (87,1%)	361 (87,0%)	364 (89,0%)	352 (85,4%)	0,37	0,13
Postdilation	1062 (85,9%)	353 (85,1%)	353 (86,3%)	356 (86,4%)	0,61	0,97
Stenting approach[b]					0,81	0,35
1-stent technique	1060 (85,8%)	353 (85,5%)	348 (84,9%)	359 (87,1%)		
2-stent techniques[c]	175 (14,2%)	60 (14,5%)	62 (15,1%)	53 (12,9%)		
T-stenting[d]	111 (63,4%)	39 (65,0%)	43 (69,4%)	29 (54,7%)		
Culotte	7 (4,0%)	1 (1,6%)	4 (6,3%)	2 (3,8%)		
Crush	39 (22,3%)	15 (25,0%)	9 (14,5%)	15 (28,3%)		
Other	18 (10,3%)	5 (8,3%)	6 (9,7%)	7 (13,2%)		

Values are n (%) or mean (SD)

[a] Definitions can be found in appendix 3.

[b] One patient did not receive a stent, the stent technique was marked as missing.

[c] Contains 3-stent techniques as well.

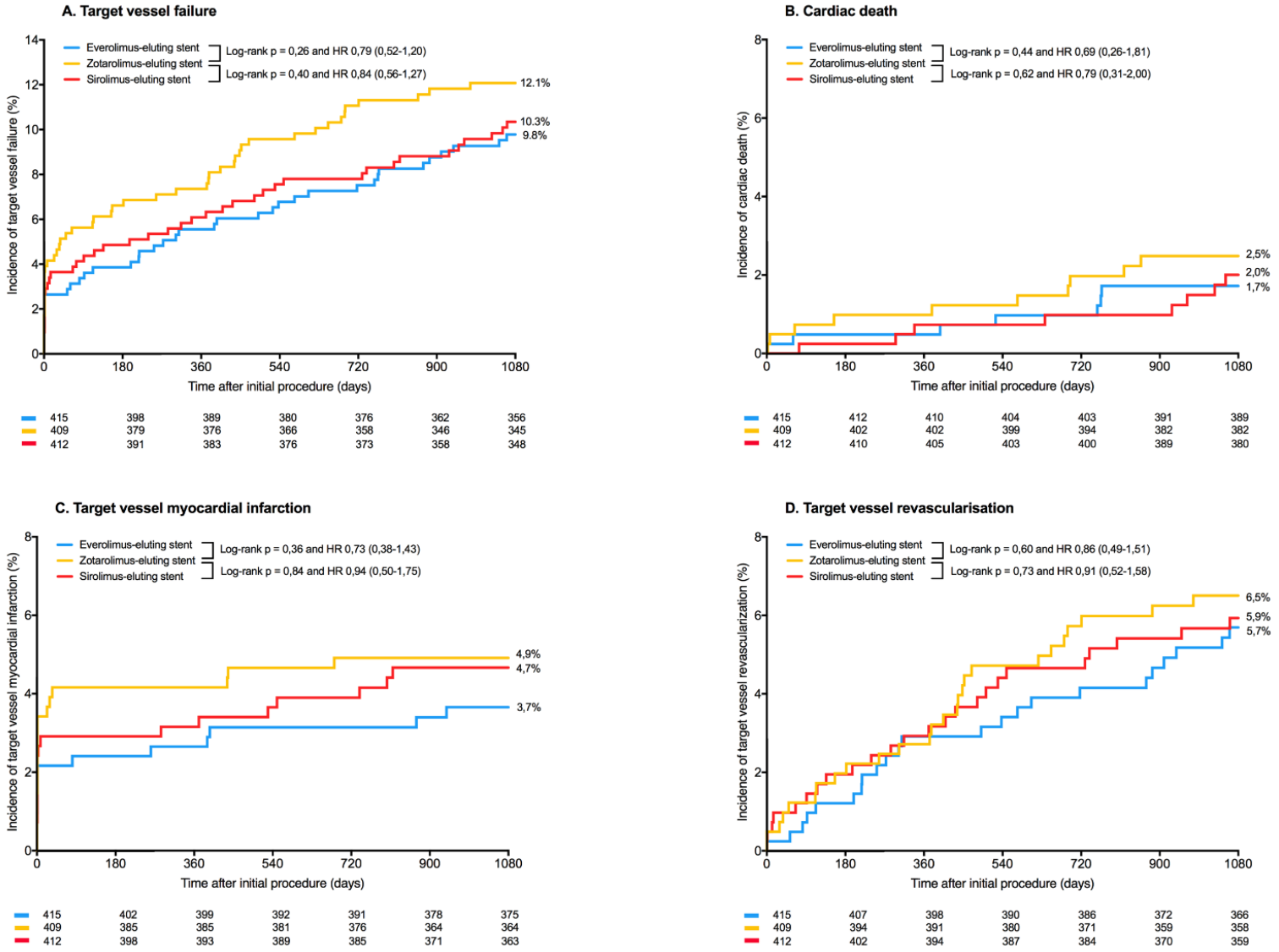
[d] The % values are based on patients with a 2-stent technique (and not the whole study population).

Table 3: Clinical outcomes at three-year follow up of patient with bifurcation lesion (n=1236)

	Synergy EES n=415	Resolute Integrity ZES n=409	Orsiro SES n=412	EES vs. ZES		SES vs. ZES	
	Event rates			Hazard ratio (95%CI)	p-log rank	Hazard ratio (95%CI)	p-log rank
Target vessel failure	40 (9,8%)	49 (12,1%)	42 (10,3%)	0,79 (0,52-1,20)	0,26	0,84 (0,56-1,27)	0,40
Cardiac death	7 (1,7%)	10 (2,5%)	8 (2,0%)	0,69 (0,26-1,81)	0,44	0,79 (0,31-2,00)	0,62
Target vessel MI	15 (3,7%)	20 (4,9%)	19 (4,7%)	0,73 (0,38-1,43)	0,36	0,94 (0,50-1,75)	0,84
Target vessel revascularisation	23 (5,7%)	26 (6,5%)	24 (5,9%)	0,86 (0,49-1,51)	0,60	0,91 (0,52-1,58)	0,73
Target lesion failure	35 (8,5%)	43 (10,6%)	34 (8,4%)	0,79 (0,50-1,23)	0,29	0,77 (0,49-1,21)	0,26
Target lesion revascularisation	16 (3,9%)	18 (4,5%)	14 (3,4%)	0,87 (0,44-1,70)	0,68	0,77 (0,38-1,54)	0,45
Patient oriented composite endpoint	58 (14,1%)	67 (16,5%)	66 (16,2%)	0,84 (0,59-1,19)	0,32	0,96 (0,68-1,35)	0,81
Definite or probable stent thrombosis	5 (1,2%)	6 (1,5%)	4 (1,0%)	0,82 (0,25-2,69)	0,74	0,66 (0,19-2,34)	0,52
Definite stent thrombosis	3 (0,70%)	4 (1,00%)	3 (0,70%)	0,737 (0,165-3,295)	0,69	0,74 (0,17-3,32)	0,70

Values are n (%)

Figure 1: Kaplan Meier curves for target vessel failure (A), cardiac death (B), target vessel MI (C) and target vessel revascularisation (D).



Discussion

Main findings

At three-year follow up, this sub-study in 1236 patients with treatment of bifurcation lesions found no statistically significant difference in the main endpoint TVF between patients treated with biodegradable polymer Synergy EES or Orsiro SES versus durable polymer Resolute Integrity ZES. The individual components of TVF showed no significant differences as well as other endpoints, including POCE. Thus, safety and efficacy of biodegradable polymer EES and SES were comparable to the durable polymer ZES.

Thick struts and durable polymer stent coatings are associated with delayed arterial healing, inflammatory responses and restenosis[6-8]. So, in theory the use of biodegradable polymer DES with very thin struts might reduce these problems in bifurcation lesions. Although some clinical outcomes showed a numeric difference in favour of the biodegradable polymer coated DES, the theoretical benefits did not translate into a statistically significant differences.

Previous studies

The role of biodegradable polymer stents in bifurcations has been investigated in several studies, which will be described and compared to the present analysis below. An overview of the studies and the results are shown in appendix 4.

The stents of the present analysis were assessed in several previous studies. The DUTCH PEERS trial, with a comparable study design as the BIO-RESORT trial, assessed the durable polymer Resolute Integrity ZES in 1811 all-comer patients, and compared it to the durable polymer Promus Element EES. There were 465 patients treated in at least one bifurcation lesion. At two-year follow-up, clinical adverse event rates (TVF in ZES: 9,8%) were slightly lower than the current study at three-year follow-up, which does not surprise due to the difference in duration of follow-up.[14]

The biodegradable polymer Orsiro SES was assessed in a pilot study in which the nano-crush stenting technique was evaluated in Medina 1,1,1 or 0,1,1 lesions which were stented with the Orsiro SES. At one-year follow-up no clinical adverse events occurred.[30] These extremely low event rates might be explained by the low number of participants that comprised 52 patients.

The CELTIC Bifurcation study is a randomised trial that compares the biodegradable polymer Synergy EES with the durable polymer Xience EES in 170 patients with de novo coronary disease in true bifurcation lesions (Medina 1,1,1 lesion). All patients underwent bifurcation stenting using the culotte technique, and the follow-up period was quite short (9 months).[22] No significant difference in various clinical and angiographic endpoints occurred, which is similar to the present study. However,

the follow-up period of the CELTIC trial might be too short to measure any potential advantage of one stent over the other, because it is likely that patients will experience adverse events after more than 9 months.

Other studies assessed different types of biodegradable polymer and durable polymer DES. A retrospective non-randomised study of Costopoulos et al. compared biodegradable polymer BES (Nobori or Biomatrix) with a durable polymer EES (Xience Prime or Xience V) in 223 patients with bifurcation lesions[20]. After two-year follow-up, clinical outcomes were similar between both stent groups.[20] Our findings corroborate the findings of this non-randomised study. However, in the non-randomised study of Costopoulos et al. the revascularisation rates at two-years were higher (BES 5,8% and EES 7,8%) than the corresponding rates in the present study at three-year follow-up. This might be explained by the difference in strut thickness between the used DES. The strut thickness of the biodegradable polymer BES is 120 µm, which is thicker than the struts of the DES used in the BIO-RESORT trial, and thinner struts are associated with lower restenosis rates as compared to thicker struts[7, 8]. Therefore, the thicker strut BES might be related to higher event rates. In addition, two-stent techniques were more frequently (BES 34,2% and EES 43,3%) used in the study of Costopoulos et al. than in the present study. This might partly explain the higher event rates because the use of a two-stent technique in bifurcation lesions is associated with a higher risk of TLR[15]**.**

A sub-study of the randomised CENTURY II trial compared the use of biodegradable polymer Ultimaster SES with the durable polymer Xience EES in 194 patients with non-left main bifurcation lesions from 58 study sites in 13 countries. At two-year follow-up, the study showed a numerically lower incidence of TVF in the biodegradable polymer SES (SES 6,3% vs. EES 10,1%, p= 0,34) . This difference was statistically not significant which might be related to the low number of patients.[21]

Unlike the present analysis, some previous studies found a significant difference between biodegradable polymer DES and durable polymer DES for treating bifurcation lesions. One of these studies is the randomised LEADERS trial that compared the biodegradable polymer Biomatrix Flex BES with the early-generation durable polymer Cypher Select SES. A bifurcation sub-study was done in 497 patients and reported one-year and five-years of follow-up data. The safety endpoints of the stent groups were comparable, but there was a difference in efficacy in favour of the BES. The TVR and TLR rates were significantly lower in the BES than in the SES groups (TLR in BES 3,5% vs. SES 9,6%, p= 0,005 and TVR in BES 4,3% vs. SES 11,3%, p=0,004).[23, 24] Remarkably, in the LEADERS bifurcation study the one-year adverse event rates of MI, TVR and TLR were higher than the three-year adverse event rates in the present bifurcation analysis of BIO-RESORT.[23, 24] This might be

attributed to several factors. First, the thicker struts of the DES in the LEADERS trial may play a role since the Cypher SES and the Biomatrix Flex BES have a strut thickness of 140 µm and 120 µm, respectively, and thicker struts are associated with higher restenosis rates [7, 8]. Second, the LEADERS trial does not distinguish target vessel MI from any MI, which can partly explain the higher rate if MI reported in the LEADERS trial.

A study of Chen et al. combined the data of the randomised DKCRUSH-I and DKCRUSH-II trials. The early-generation durable polymer TAXUS paclitaxal-eluting stent (PES) was compared with the biodegradable polymer Excel SES. The study included 275 patients with bifurcation target lesions and reported one-year follow-up data. Patients treated with the biodegradable polymer SES had lower TVR, TLR and MACE rates than patients treated with the durable polymer PES. Compared to the present analysis at three years, the one-year TVR and TLR rates in the DKCRUSH study were high. Especially the event rates of the durable polymer PES (TVR: 14,4%, TLR 12,2%) were high.[25] The higher revascularisation rates might be partly related to the strut thickness because both devices had thicker struts (Excel SES 119 µm and Taxus PES 132 µm). In addition, the patient population differed substantially between the trials. All patients in the DKCRUSH study had true bifurcations, and true bifurcations are known to be associated with higher event rates[31]. Furthermore, patients were stented with a two-stent technique (DK crush), whereas most of the BIO-RESORT trial participants were treated with a one-stent technique. And a two-stent technique is associated with higher TLR rates, which can also explain the higher event rates in the DKCRUSH study[15].

In summary, the findings of the present bifurcation analysis corroborate the findings of some previous studies that did not find a significant difference in outcomes between biodegradable or durable polymer coated DES. Two previous studies that assessed early-generation DES did find a significant difference in TVR and TLR in favour of biodegradable polymer DES. Overall, the event rates of the BIO-RESORT trial in bifurcations are low as compared to other previous studies that assessed biodegradable polymer DES and durable polymer DES in bifurcation lesions treatment.

Strengths and limitations

Strengths

This study is the first study to compare the Synergy EES and Orsiro SES with the Resolute Integrity ZES in bifurcations and therefore provides new information on the use of these stents. The three-year follow-up rate of the study is high (97,1%). In addition, the present study included 1236 patients with bifurcation lesions, which is a larger patient population than assessed in previous bifurcation

studies. The previous studies as well as the current study are not powered for the comparison of DES in bifurcation lesions, and more patients adds power to the analysis.

Limitations

The findings should be considered hypothesis generating because of the post hoc nature of the present analysis. Besides, the present study assessed the occurrence of various clinical endpoints but does not consider the patient's quality of life after PCI. Therefore, this study may provide an incomplete perspective on the use of DES for PCI in bifurcation lesions.

Conclusion

At three-year follow-up, no significant between-stent differences occurred in various clinical safety and efficacy outcomes, when comparing treatment with biodegradable polymer Synergy EES and Orsiro SES versus durable polymer Resolute Integrity ZES. All three DES appear safe and efficient for stenting patients with bifurcation lesions.

Recommendations

Data on newer generation, thinner strut, biodegradable polymer DES, as investigated in the present analysis, is scarce. Previous studies often investigated thicker strut, biodegradable polymer DES, included a relatively low number of patients and were not powered for the assessment of bifurcation lesions. To provide more reliable information on the usage of newer DES in bifurcations, dedicated well-powered studies are needed, preferably randomised controlled clinical trials.

In addition, it is important to take the patient perspective into account. For patients it is important whether physical and psychological symptoms may occur, what these symptoms are, and how symptoms may influence the quality of life[32]. However, many studies only focus on the occurrence of events. Studies on the patient perspective are useful to provide insight in whether the new DES are effective in improving quality of life after PCI and whether they meet the patient's needs. This can be investigated with interviews and Patient Reported Outcomes (PRO) can be assessed by questionnaires like the SF-36 questionnaire, which is one of the most commonly used questionnaires for the evaluation of quality of life in patients undergoing treatment in cardiology and cardiac surgeries[33].

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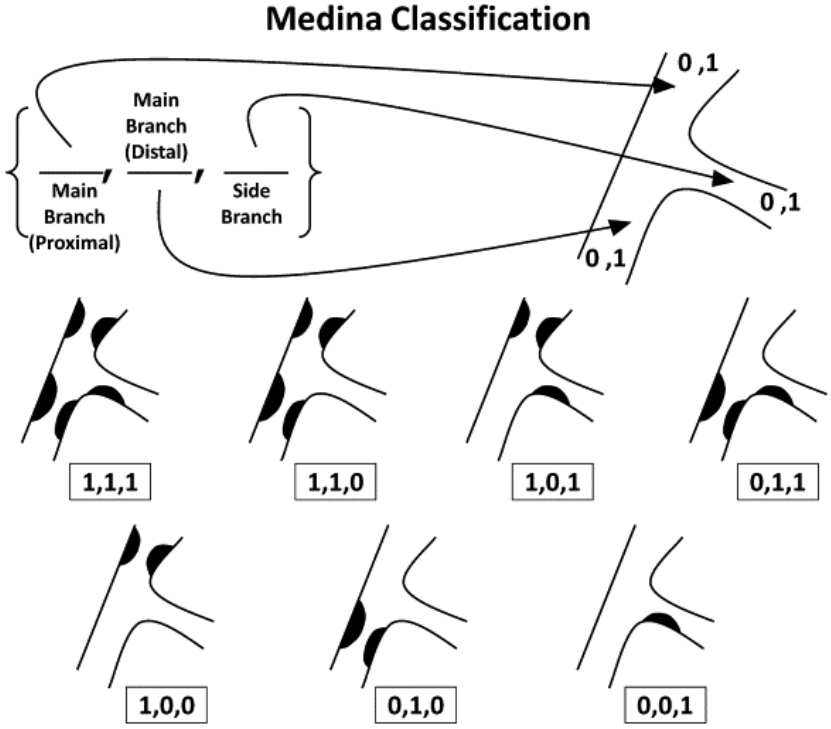
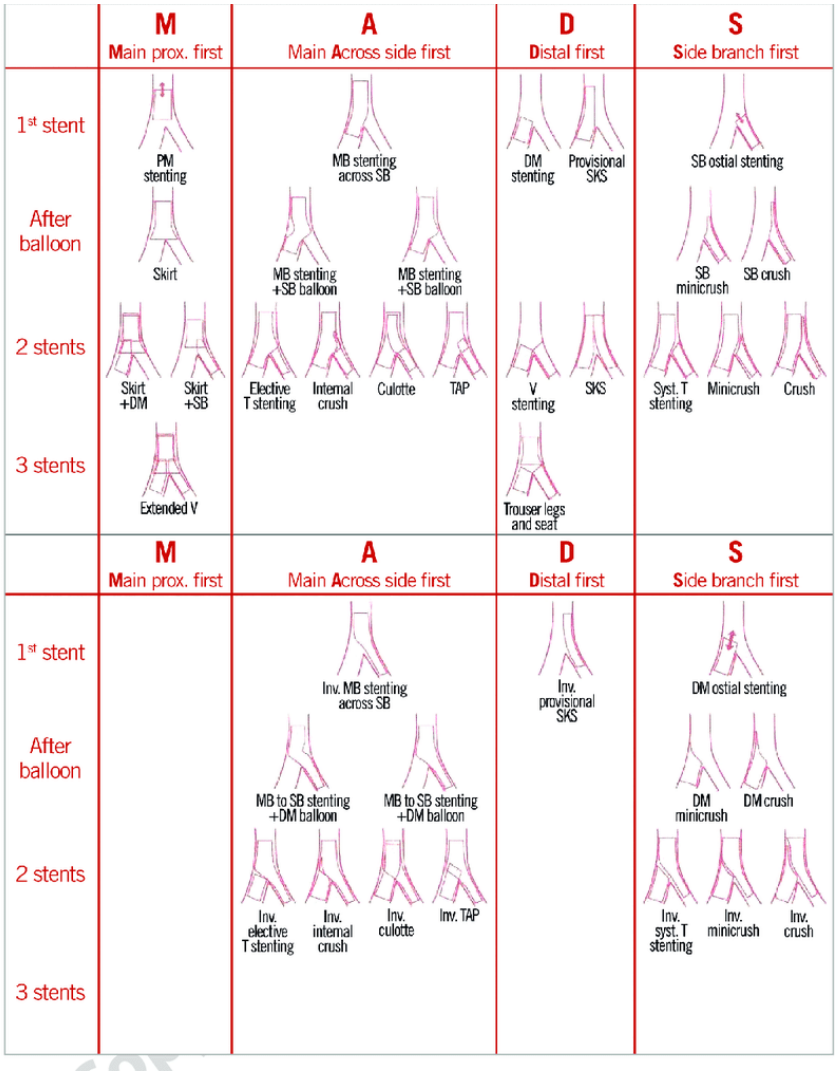
Appendix

Appendix 1: Medina classification



Reference: Zlotnick, D. M., Ramanath, V. S., Brown, J. R. & Kaplan, A. V. Classification and treatment of coronary artery bifurcation lesions: putting the Medina classification to the test. Cardiovascular revascularization medicine : including molecular interventions 13, 228-233, doi:10.1016/j.carrev.2012.04.002 (2012).

Appendix 2: MADS classification



Reference: Lassen, J. F. et al. Percutaneous coronary intervention for coronary bifurcation disease: consensus from the first 10 years of the European Bifurcation Club meetings. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 10, 545-560, doi:10.4244/eijv10i5a97 (2014).

Appendix 3: definitions baseline

The definitions of severe calcification and a chronic total occlusion, applied in the BIO-RESORT trial, are as following:

- Severe calcification: readily apparent densities or x-ray absorbing mases, noted within the apparent vascular wall at site of the target lesion prior to any contrast injection; in addition, severe target lesion calcification was noted without cardiac motion before contrast injection and generally compromised both sides of the arterial wall.
- Chronic total occlusion: a total occlusion for more than 3 months.

Appendix 4: results of previous studies

	BIORESORT	CELTIC	CENTRUY II	Costoupolos et al.	DKCRUSH-I + DKCRUSH-II	DUTCH PEERS	LEADERS trial	Rigatelli et al.
Type of study	RCT	RCT	Sub-study of all-comers RCT	Non-randomised, retrospective study	Substudy of RCT	RCT	Substudy of all-comers RCT	Pilot study
Follow-up period	Three-years	Nine months	Two-years	Two-years	One-year	Two-years	One-year	One-year
Number of patients included	1236	170	194	223	275	465	497	52
Stents used	Biodegradable polymer Synergy EES vs. durable polymer Resolute Integrity EES vs. biodegradable polymer Orsiro SES	Biodegradable polymer Synergy EES vs. durable polymer Xience EES	Biodegradable polymer SES vs. durable polymer EES	Biodegradable polymer BES vs.durable polymer EES vs.	Biodegradable polymer Excel SES vs. durable polymer Taxus PES	Durable polymer Resolute Integrity ZES	Durable polymer Cypher SES vs biodegradable polymer Biomatrix Flex BES	Biodegradable polymer Orsiro
Results								
Target vessel failure	9,8% vs. 12,1% vs 10,3%	1,4% vs. 0% (p=0,47)	6,3% vs. 10,1% (p= 0,34)	-	-	9,8%	-	-
Cardiac death	1,7% vs. 2,5% vs. 2,0%	2,4% vs. 0% (p= 0,25)	0% vs. 4% (p=0,04)	2,9% vs. 1,9% (p= 0,66)	2,9% vs. 1,9% (p=0,598)	1,6%	2,7% vs. 2,9% (p= 1,00)	0
Target vessel MI*	3,7% vs. 4,9% vs. 4,7%	4,9% vs. 1,2% (p= 0,20)	1,1% vs. 2,0% (p= 0,96)	2,9% vs. 5,2% (p= 0,44)	2,9% vs. 5,2% (p= 0,35)	3,7%	8,9% vs. 5,4% (p= 0,17)	0
Target vessel revascularisation	5,7% vs. 6,5% vs. 5,9%	-	4,2% vs. 4,0% (p= 0,95)	5,8% vs. 7,8% (p= 0,60)	5,8% vs. 7,8% (p=0,02)	4,9%	4,3% vs. 11,3% (p= 0,004)	-
Target lesion failure	8,5% vs. 10,6% vs. 8,4%	-	5,3% vs. 9,1% (p= 0,30)	-	-	9,0%	-	-
Target lesion revascularisation	3,9% vs. 4,5% vs. 3,4%	-	3,2% vs. 3,0% (p= 0,96)	4,3% vs. 6,5% (p=0,53)	4,3% vs 6,5% (p= 0,01)	4,1%	3,5% vs. 9,6% (p= 0,005)	-
The patient oriented composite endpoint	14,1% vs. 16,5% vs. 16,2%	-	-	-	-	13,5%	-	-
Definite stent thrombosis**	0,7% vs 1,0% vs 0,7%	0% vs 1,2% (p= >0,99)	1,1% vs 2,0% (p= 0,58)	0% vs 0%	2,2% vs 5,6% (p= 0,16)	0,4%	1,9% vs 2,5% (p= 0,77)	-

*The CELTIC study, Costoupolos et al., DKCRUSH and LEADERS trial only measured any MI and not target vessel MI.

** The CENTURY II trial only measured total stent thrombosis not definitie stent thrombosis