DUAL ANTIPLATELET THERAPY AFTER STENTING IN ALL-COMERS, ACS PATIENTS AND IN HIGH BLEEDING RISK

Gian Paolo Zocca

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STENTING IN ALL-COMERS, ACS PATIENTS
AND IN HIGH BLEEDING RISK**

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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

GENERAL INTRODUCTION

Coronary artery disease and acute coronary syndrome

Coronary artery disease most often results from a gradual narrowing of the arterial lumen due to the formation of atherosclerotic plaques in the vessel wall that eventually impede coronary blood supply to the myocardium.¹ In general, the disease process progresses slowly over the course of decades. Patients may present with symptoms of stable angina as a result of myocardial ischemia in situations with an increased metabolic demand such as exercise. In addition, stable coronary artery disease may suddenly progress to acute coronary syndromes, which is a spectrum of clinical conditions that include unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction. Common pathophysiological mechanisms of acute coronary syndromes include plaque erosion and, more often, rupture of the thin fibrous cap of the atheromatous plaque.¹ The lipid-rich core of the plaque consists of highly thrombogenic material which, if exposed to blood, causes platelet activation and aggregation, and subsequent thrombus formation.²⁻⁴ These functions of platelets are essential in the context of haemostasis. However, in the vasculature it may result in an acute thrombotic obstruction of the coronary artery, causing transmural ischemia and –if not swiftly resolved – irreversible damage to the myocardial mass that is subtended by the respective coronary artery. Treatment of patients with coronary artery disease generally aims at the reduction of symptoms and may improve life expectancy. In addition, therapeutic measures should aim at preserving as much myocardial tissue as possible and at preventing recurrent ischemic events.⁵⁻⁸ Treatment options to achieve these targets include both, coronary revascularization and antiplatelet therapy.

Aspirin

Aspirin (acetylsalicylic acid) was synthesized in 1899 and currently is one of the most frequently prescribed drugs worldwide. The drug plays an important role in the treatment of patients with coronary artery disease. Willow bark (**Figure 1**), a natural source of salicylic acid, was already used at the time of Hippocrates for treating pain and inflammation. While mucosal bleeding in patients who took salicylic acid was observed as early as in 1891, it was not until the late 1940s that Paul Gibson proposed aspirin for treating coronary thrombosis.⁹ Two decades later, the inhibitory effect on platelet function by preventing prostaglandin synthesis was first described.¹⁰ Aspirin specifically and irreversibly inhibits platelet cyclooxygenase-1 (COX-1), which is involved in platelet aggregation by the production of thromboxanes.¹¹ Thromboxane A₂ is crucial in amplifying the platelet activation process that occurs in reaction to thrombogenic stimuli. Since the 1980s, aspirin is approved for secondary prevention after acute myocardial

infarction, but its role for primary prevention is still debated.¹²⁻¹⁴ Currently, the life-long prescription of aspirin is recommended in patients who suffered from an acute coronary syndrome or underwent a coronary revascularization procedure.

FIGURE 1. Willow (*Salix Alba*) in the botanical garden of the oldest medical school of the world: il Giardino della Minerva, Scuola Medica Salernitana, Salerno, Italy. Photo by P. Zocca, June 22, 2019.

Coronary revascularization and bare metal stents

In order to restore myocardial blood flow, patients were initially treated by cardiothoracic surgeons who performed coronary artery bypass grafting. After the first successful coronary artery bypass operation in humans in 1960,¹⁵ great progress has been made in the field of coronary revascularization. While in current clinical practice many patients are still treated by the hands of surgeons, the majority of patients with symptomatic coronary artery disease is percutaneously treated by interventional cardiologists. Percutaneous transluminal coronary angioplasty, a minimally invasive catheter-based therapy with inflatable balloon catheters that was first performed in 1977,¹⁶ was found to be effective for treating obstructive coronary arterial lesions. However, its success was limited by high rates of lesion recurrence (i.e., restenosis) and major dissection with associated thrombotic complications.¹⁷ Metallic mesh tubes, called bare metal stents (**Figure 2**), were then developed and found to be effective in sealing coronary dissections and in reducing vessel recoil and constrictive vascular remodelling.¹⁸ As a result, coronary stent implantation reduced the incidence of lesion recurrence and the

need for repeat revascularization; however, the formation of neointimal hyperplasia inside the stent emerged as a new major problem.¹⁹ In addition, initially the risk of thrombus formation shortly after stent implantation was very high, which resulted in the use of aggressive anticoagulant regimens that, in turn, were associated with serious bleeding complications.¹⁸ Subsequently, forceful techniques of stent implantation (i.e., larger balloon diameter and higher maximum pressure) and guidance of the intervention with intravascular ultrasound were instrumental in reducing the risk of stent thrombosis and the need for a most aggressive antithrombotic therapy.^{20,21}

FIGURE 2. Bare metal stent, after stent deployment and removal of balloon catheter.

Drug-eluting stents

Drug-eluting stents were developed to overcome the issue of restenosis, as the need for repeat revascularization after the implantation of bare metal stents was still approximately 30%.¹⁷ The main reason for restenosis in bare metal stents was in-stent neointimal hyperplasia which resulted from the stent-induced arterial injury that caused activation, proliferation, and migration of vascular smooth-muscle cells. Consequently, the newly developed devices were composed of a bare metal stent platform, covered by a durable (i.e., permanent) polymer coating that carried and slowly released an anti-proliferative drug into the wall of the coronary artery.²² These drugs inhibit neointimal hyperplasia by either immunosuppressive (inhibitors of mammalian target of rapamycin, such as sirolimus) or cytotoxic (paclitaxel) effects on smooth-muscle cells. The first-generation drug-eluting stents proved to be effective and markedly reduced the incidence of restenosis and the need for repeat revascularization.²³ A few years after the initial success, concerns were raised about long-term safety of first-generation drug-eluting stents, as the rates of very late stent thrombosis (i.e., more than one year after stent implantation) were found to be significantly higher than in bare metal stents.^{24,25} Second-generation drug-eluting stents were developed to resolve this safety issue, which was achieved primarily by improving the biocompatibility of polymer coatings.^{26,27} Other refinements in new-generation drug-eluting stents involved the design of the stent, including a decrease in strut thickness as well as advances in stent flexibility, deliverability, and visibility.²⁸ In addition, in an attempt to reduce the prolonged inflammatory response of the vessel wall to the polymer, drug-eluting stents with biodegradable polymer coatings were developed.²⁹ To assess the safety and efficacy

of new-generation drug-eluting stents, several large-scale randomized clinical trials were performed which included patients and target lesions with various levels of complexity. These “all-comer” trials, which are characterized by very few exclusion criteria, were designed to assess the safety and efficacy of novel stents in study populations that matched “real world” patient populations, treated in routine clinical practice.

Dual antiplatelet therapy

Stent thrombosis (**Figure 3**) is one of the most feared complications after coronary stent implantation, as it is associated with myocardial infarction and death.³⁰ In patients treated with bare metal stents, dual antiplatelet therapy consisting of aspirin and ticlopidine was shown to be superior over conventional anticoagulant therapy and to reduce both ischemic and bleeding events.³¹ In addition, discontinuation of antiplatelet therapy after stenting was found to be associated with an increased risk of stent thrombosis.³² Many randomized clinical trials assessed different combinations of dual antiplatelet therapy in a search for a further decrease in thrombotic complications.^{7,33} In all clinical trials that assessed antiplatelet therapy, aspirin remained a stable factor that was combined with various other antiplatelet agents. Clopidogrel, was found to be safer than ticlopidine, as the latter may cause serious haematological side effects.³⁴ The active metabolite of clopidogrel specifically and irreversibly inhibits the P2Y₁₂ subtype of the adenosine diphosphate (ADP) receptor on platelets; nevertheless, the drug has some shortcomings. First, it requires a two-step oxidation process in the liver by the cytochrome P450 system to produce its active metabolite, and approximately 85% of the prodrug is thereby hydrolysed into inactive substances. Second, the effectivity of clopidogrel was found to be decreased in patients with various genetic polymorphisms.³⁵ Prasugrel, a thienopyridine like ticlopidine and clopidogrel, has a more favourable profile than clopidogrel as it requires only a single step of hepatic oxidation,³⁶ leading to a more prompt, potent, and predictable effect of platelet inhibition. In contrast to clopidogrel and prasugrel, the cyclopentyltriazolo-pyrimidine ticagrelor binds directly and reversibly to the P2Y₁₂ receptor. Prasugrel and ticagrelor were compared with clopidogrel in two large international randomized trials that showed more favourable outcomes for the two newer agents in terms of fewer cardiovascular events.^{37,38}

FIGURE 3. Very late stent thrombosis after first-generation drug-eluting stent implantation in the proximal left anterior descending artery (white arrow), causing large anterior myocardial infarction complicated by out of hospital cardiac arrest (a). Result after percutaneous treatment with thrombus aspiration and new-generation drug-eluting stent implantation (b).

Bleeding

Platelets modulate haemostasis following tissue trauma and vascular injury. Therefore, pharmacological inhibition of platelet aggregation and adhesion results not only in a reduction of thrombotic events, but also in an increase in bleeding risk. In patients treated with percutaneous coronary intervention, the initially high rate of severe bleedings was reduced by the use dual antiplatelet therapy (instead of aspirin plus oral anticoagulation).³¹ In addition to changes in antithrombotic therapy, other factors contributed to the decrease in bleedings. These factors include the preference of radial over femoral arterial access,^{39,40} and the more liberal use of proton pump inhibitors to prevent gastro-intestinal bleedings.⁴¹ Nevertheless, bleedings remained a major issue after percutaneous coronary intervention, and they were associated with an increased mortality and a reduced quality of life.⁴²⁻⁴⁴ Bleeding rates are increased in patients who, instead of clopidogrel, receive the more potent antiplatelet agents prasugrel and ticagrelor.^{37,38,45} These drugs may be particularly harmful in patients with a high bleeding risk. However, patients with a high bleeding risk often also have an increased risk of suffering from ischemic events.⁴⁶ Although in daily practice a substantial proportion of patients who undergo percutaneous coronary intervention are high bleeding risk patients,⁴⁷ data on optimal pharmacological antiplatelet strategy and stent selection in this high-risk group are still scarce.

OUTLINE OF THE THESIS

The general purpose of this thesis was to evaluate the clinical outcome of patients with coronary artery disease, treated with new coronary stents and different regimens of dual antiplatelet therapy. As refinements in the development of coronary stents and new antiplatelet drugs ran in parallel, data on patients treated with both, new-generation drug-eluting stents and dual antiplatelet therapy with a potent P2Y₁₂ inhibitor, are limited. This thesis provides insight into the balance between ischemic and bleeding events in patients with acute coronary syndrome, treated with contemporary stents and ticagrelor-based, instead of clopidogrel-based, dual antiplatelet therapy. A special emphasis will be laid on the treatment of high bleeding risk patients, as they represent a population with highly increased risk of adverse events. In addition, the safety and efficacy of new-generation drug-eluting stents in the treatment of all-comers will be assessed, including follow-up beyond the primary endpoint (i.e., generally at one-year) to assess the performance of stents after the cessation of dual antiplatelet therapy.

Chapter 1 provides a general introduction to this thesis, including background information on acute coronary syndromes, antiplatelet therapy and drug-eluting stents.

The CHANGE DAPT study is described in **chapter 2**. In this study, we evaluate one-year clinical outcome of consecutive acute coronary syndrome patients who were treated with new-generation drug-eluting stents, before and after the change from a primary clopidogrel-based to a primary ticagrelor-based regimen of dual antiplatelet therapy.

Two-year mortality data of the CHANGE DAPT study participants is reported in **chapter 3**.

Chapter 4 evaluates and discusses the clinical outcomes in high bleeding risk patients of CHANGE DAPT.

Chapter 5 evaluates potential benefits of the implantation of two very thin-strut biodegradable polymer drug-eluting stents over thin-strut durable polymer drug-eluting stents in the high bleeding risk patients of the randomized BIO-RESORT (TWENTE III) trial.

Chapter 6 describes the two-year clinical outcome of the multicentre, randomized BIO-RESORT trial in all-comers. It provides insights into the safety and efficacy of contemporary drug-eluting stents beyond the primary endpoint. While the biodegradable polymer coating of the Synergy everolimus-eluting stent will be completely resorbed after no more than 4 months, this process will take up to two years for the Orsiro sirolimus-

CHAPTER 1

eluting stent. Furthermore, dual antiplatelet therapy will generally be discontinued after one year.

The primary one-year outcome of the international, multicentre, randomized BIONYX (TWENTE IV) trial is reported in **chapter 7**. In this trial, we compare two different new-generation drug-eluting stents in all-comers: the thin composite wire strut durable polymer Resolute Onyx zotarolimus-eluting stent and the ultrathin cobalt-chromium strut bioresorbable polymer Orsiro sirolimus-eluting stent.

In **chapter 8**, long-term clinical outcome data of the randomized DUTCH-PEERS (TWENTE II) trial are presented. The study assesses in all-comers the five-year safety and efficacy of thin cobalt chromium strut durable polymer Resolute Integrity zotarolimus-eluting stents versus thin platinum chromium strut durable polymer Promus Element everolimus-eluting stents.

Chapter 9 presents a comment to the five-year clinical outcomes of the randomized BIOSCIENCE trial that elaborates on the importance of long-term follow-up in drug-eluting stent trials.

Chapter 10 contains the general discussion of this thesis and describes research subjects to focus on in the future.

Chapter 11 provides the summary and conclusions of this thesis.

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CLOPIDOGREL OR TICAGRELOR IN ACUTE CORONARY SYNDROME PATIENTS TREATED WITH NEWER- GENERATION DRUG-ELUTING STENTS: CHANGE DAPT

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ABSTRACT

Aims: Acute coronary syndrome (ACS) guidelines have been changed, favouring more potent antiplatelet drugs. We aimed to evaluate the safety and efficacy of a ticagrelor-instead of a clopidogrel-based primary dual antiplatelet (DAPT) regimen in ACS patients treated with newer-generation drug-eluting stents (DES).

Methods and results: CHANGE DAPT (clinicaltrials.gov: NCT03197298) assessed 2,062 consecutive real-world ACS patients, treated by percutaneous coronary intervention (PCI), the primary composite endpoint being net adverse clinical and cerebral events (NACCE: all-cause death, any myocardial infarction, stroke or major bleeding). In the clopidogrel (CP; December 2012-April 2014) and ticagrelor periods (TP; May 2014-August 2015), 1,009 and 1,053 patients were treated, respectively. TP patients were somewhat older, underwent fewer transfemoral procedures, and received fewer glycoprotein IIb/IIIa inhibitors. In the TP, the one-year NACCE rate was higher (5.1% vs. 7.8%; HR 1.53 [95% CI: 1.08-2.17]; $p=0.02$). Assessment of non-inferiority (pre-specified margin: 2.7%) was inconclusive (risk difference: 2.64 [95% CI: 0.52-4.77]; $p_{\text{non-inferiority}}=0.48$). TP patients had more major bleeding (1.2% vs. 2.7%; $p=0.02$) while there was no benefit in ischaemic endpoints. Propensity score-adjusted multivariate analysis confirmed higher NACCE (adj. HR 1.75 [95% CI: 1.20-2.55]; $p=0.003$) and major bleeding risks during TP (adj. HR 2.75 [95% CI: 1.34-5.61]; $p=0.01$).

Conclusions: In this observational study, the guideline-recommended ticagrelor-based primary DAPT regimen was associated with an increased event risk in consecutive ACS patients treated with newer-generation DES.

INTRODUCTION

In patients with acute coronary syndrome (ACS), many of whom require percutaneous coronary intervention (PCI) with implantation of drug-eluting stents (DES), there is an indication for dual antiplatelet therapy (DAPT). Current international guidelines^{1,2} recommend the use of more potent P2Y₁₂ inhibitors, such as ticagrelor or prasugrel, instead of the former standard of clopidogrel and aspirin. The pivotal trial that compared ticagrelor versus clopidogrel showed better clinical outcome for ticagrelor in a moderate to high-risk ACS population that comprised 39% of patients who did not undergo PCI during the index hospitalisation.³ In addition, more than 60% of trial participants treated by PCI received bare metal stents (BMS), and most patients who received DES had first-generation devices.³ Nevertheless, use of this more potent P2Y₁₂ inhibitor was associated with more major bleedings.^{3,4}

Meanwhile, newer-generation DES have become available with thinner stent struts covered by more biocompatible or biodegradable polymer coatings, and improved clinical outcome compared to BMS and first-generation DES.⁵⁻⁷ In clinical practice, most ACS patients are treated with newer-generation DES that showed favourable results with clopidogrel-based DAPT.^{8,9} In the present study, we evaluate the impact of the guideline-recommended change in primary DAPT regimen to ticagrelor on one-year outcome in consecutive ACS patients treated with newer-generation DES at a high-volume PCI centre.

METHODS

Study population and design

At the tertiary PCI centre Thoraxcentrum Twente in the Netherlands we performed an investigator-initiated, prospective observational study that assessed one-year outcome in 2,062 consecutive ACS patients, treated with newer-generation DES (CHANGE DAPT, NCT03197298). Patients were included between 21 December 2012 and 25 August 2015. On 1 May 2014, we followed international guidelines to replace clopidogrel- by ticagrelor-based primary DAPT. Group 1 patients were included before (clopidogrel period [CP]) and group 2 patients after this date (ticagrelor period [TP]). ACS patients ≥ 18 years, treated with newer-generation DES, were included. Exclusion criteria were known pregnancy, life expectancy < 1 year (i.e., no cardiogenic shock or post-resuscitation), planned elective surgery requiring DAPT interruption after < 6 months, and known intolerance to DES components. As guidelines recommend clopidogrel use in patients on oral anticoagulation,² patients with oral anticoagulation at baseline were not included.

This observational study complied with the Declaration of Helsinki. According to Dutch law, and as approved by the Medical Ethics Committee Twente, written informed consent was not required.

Definitions of clinical endpoints

The primary endpoint net adverse clinical and cerebral events (NACCE) is a composite of all-cause death, any myocardial infarction (MI), stroke or major bleeding. Definitions of MI are according to the Academic Research Consortium (ARC).^{10,11} Strokes were a focal loss of neurologic function by an ischaemic or haemorrhagic event, with residual symptoms ≥ 24 hours or leading to death. Bleeding ARC (BARC) and Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria were used.^{12,13} Major bleeding was any BARC class 3 or 5 bleeding and/or all TIMI major bleedings (i.e., coronary artery bypass grafting [CABG] and non-CABG-related).

Secondary endpoints were individual components of the primary composite endpoint, any clinically indicated revascularisation by PCI or CABG, definite or probable stent thrombosis according to ARC,¹⁰ the composite of cardiac death, MI or stroke.

Coronary intervention and medical therapy

Interventional procedures were performed according to local clinical protocols. Unfractionated heparin was administered directly before PCI. Lesion preparation, stent post-dilation and use of glycoprotein IIb/IIIa inhibitors (generally limited to a single bolus of abciximab) were left to the operator's discretion. If patients were not on antiplatelet therapy, loading doses of aspirin (≥ 300 mg) and clopidogrel (600 mg) or ticagrelor (180 mg) were administered before PCI. Timing of drug loading did not change during the study. Maintenance doses were 80-100 mg aspirin and 75 mg clopidogrel daily, and/or 90 mg ticagrelor twice daily. DAPT of patients referred from other hospitals generally remained unchanged. DAPT was generally prescribed for 12 months with the use of statins, beta-blockers, RAS inhibitors, and proton pump inhibitors as appropriate according to guidelines and the physician's judgement. If patients required oral anticoagulation during follow-up, ticagrelor was replaced by clopidogrel, and aspirin was generally stopped one month after PCI.

Clinical follow-up and event assessment

Information on clinical follow-up was obtained at visits to outpatient clinics and/or by mail or telephone. The contract research organisation Cardio Research Enschede (Enschede, the Netherlands) performed the study. During both DAPT periods, similar numbers of patients participated in a DES trial¹⁴ with independent data monitoring. Clinical events

were adjudicated by a committee (three members of the research team), and strokes were assessed by an experienced neurologist.

Statistical analysis

Data were reported as frequencies and percentages or mean±standard deviation. Differences in dichotomous and categorical variables were assessed by chi-square test, while continuous variables were assessed with the Student's t-test. Kaplan-Meier analysis was used to calculate the time to clinical endpoints; the log-rank test was applied for between-group comparisons. Hazard ratios were computed using Cox proportional hazards regression analyses. For adjustment of potential confounders, a propensity score analysis was performed. Propensity scores were estimated using multiple logistic regression analysis. All baseline and procedural variables were used to calculate the propensity score for treatment in the TP; a multivariate Cox regression model was used to adjust for the propensity score.

The primary analyses compared the two treatment periods, CP versus TP. To assess non-inferiority, a NACCE rate of 6.5% was assumed in both periods (i.e., CP and TP), based on the data from the OPTIMIZE, TWENTE and DUTCH PEERS trials.^{8,9,15} With a one-sided alpha level of 0.05 and at least 80% power, a sample size of 1,031 patients in each group was required to demonstrate non-inferiority with a margin of 2.7%, based on the OPTIMIZE trial.¹⁵ Non-inferiority would be achieved if the upper limit of the one-sided 95% confidence interval of the absolute risk difference was less than the non-inferiority margin.

Additional sensitivity analyses were performed, in which patients actually treated with clopidogrel during the CP were compared to patients actually treated with ticagrelor during the TP. Treatment by either clopidogrel or ticagrelor was assessed at discharge or, if a NACCE occurred before discharge, at the time of that in-hospital event.

Except for the non-inferiority analysis, p-values and confidence intervals were two-sided; p-values <0.05 were considered significant. Sample size calculation was performed with PASS (NCSS, Kaysville, UT, USA), and data analysis with SPSS, Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study population

Of all 2,062 patients enrolled, 1,009 (48.9%) were treated during the CP versus 1,053 (51.1%) during the TP (Figure 1). Most patient demographic and clinical characteristics (Table 1) were similar for both periods, including the proportion of STEMI (44.8% vs. 41.2%). TP patients were somewhat older (62.9 ± 11.6 vs. 63.9 ± 12.1 years, $p=0.04$) and less often diagnosed with peripheral artery disease (8.8% vs. 5.5%, $p=0.003$).

FIGURE 1. Flow chart. Exact number of patients not fulfilling inclusion criteria not available.

TABLE 1. Baseline characteristics.

All patients (n=2,062)			
	Clopidogrel Period (CP) n=1,009	Ticagrelor Period (TP) n=1,053	<i>p-value</i>
Age, years	62.9±11.6	63.9±12.1	0.04
Male sex	702 (69.6)	748 (71.0)	0.47
BMI, kg/m² *	27.4±4.3	27.7±4.4	0.13
Clinical history			
Hypertension	428 (42.4)	440 (41.8)	0.77
Hypercholesterolemia	360 (35.7)	384 (36.5)	0.71
Diabetes Mellitus	158 (15.7)	186 (17.7)	0.22
Peripheral artery disease	89 (8.8)	58 (5.5)	0.003
Chronic obstructive pulmonary disease	78 (7.7)	83 (7.9)	0.90
Previous MI	146 (14.5)	151 (14.3)	0.93
Previous PCI	166 (16.5)	174 (16.5)	0.97
Previous CABG	72 (7.1)	63 (6.0)	0.29
Previous stroke	32 (3.2)	31 (2.9)	0.76
Previous gastro-intestinal bleeding	11 (1.1)	15 (1.4)	0.50
Renal insufficiency [†]	40 (4.0)	38 (3.6)	0.67
Dialysis	9 (0.9)	6 (0.6)	0.39
Clinical presentation			
ST-elevation MI	452 (44.8)	434 (41.2)	0.10
Non-ST-elevation MI	256 (25.4)	292 (27.7)	0.23
Unstable angina	301 (29.8)	327 (31.1)	0.55

Values are n (%) or mean±SD. * Out of 1,921 patients. † Defined by creatinine >130 μmol/l (0.15 mg/dL). BMI: body mass index; CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Interventional procedure

Details of PCI and medication are shown in Table 2. Multivessel treatment and stent type did not differ between periods, but transradial access was more common during the TP (17.7% vs. 44.6%, $p<0.001$).

Medication

The use of glycoprotein IIb/IIIa inhibitors decreased from CP to TP (43.7% vs. 24.7%, $p<0.001$) (Table 2). More TP patients were treated with a proton pump inhibitor at discharge (42.6% vs. 55.1%, $p<0.001$).

During the CP, 877/1,009 (86.9%) patients were treated with clopidogrel at discharge, while 132/1,009 (13.1%) were on ticagrelor. At one-year follow-up, 916/1,009 (90.8%) CP patients were still on DAPT: 78.7% used clopidogrel and 12.1% ticagrelor; a combination of oral anticoagulant with P2Y₁₂ inhibitor was prescribed in 42/1,009 (4.2%).

During the TP, 894/1,053 (84.9%) patients were on ticagrelor and 159/1,053 (15.1%) on clopidogrel. At one-year follow-up, 947/1,053 (89.9%) patients were still on DAPT: 17.5% used clopidogrel and 72.5% ticagrelor; an oral anticoagulant plus P2Y₁₂ inhibitor was prescribed in 30/1,053 (2.9%) patients.

Reasons for deviation from the primary DAPT regimen at baseline are presented in Appendix Table 1. The main reason for ticagrelor use during the CP was that DAPT was initiated in referring hospitals. During the TP, clopidogrel was primarily used because of DAPT initiation in referring hospitals or at the discretion of treating physicians (without written motivation).

FIGURE 2. One-year Kaplan-Meier cumulative incidence curves for the primary endpoint NACCE. CI: confidence interval; HR: hazard ratio; NACCE: net adverse clinical and cerebral events.

Clinical outcome

One-year clinical follow-up was available in 2,048/2,062 (99.3%) patients (seven lost in each period). Data of 30-day, and 30-day to one-year outcomes are presented in Appendix Table 2. Table 3 reports one-year outcomes of various clinical endpoints during the CP and TP. The composite primary endpoint NACCE occurred in 51/1,009 (5.1%)

TABLE 2. Procedural characteristics and medication.

All patients (n=2,062)			
	Clopidogrel Period (CP) n=1,009	Ticagrelor Period (TP) n=1,053	p-value
Procedural characteristics			
Arterial access			<0.001
Radial	179 (17.7)	470 (44.6)	
Femoral	830 (82.3)	583 (55.4)	
Vessel disease			0.35
1	550 (54.4)	603 (57.3)	
2	310 (30.7)	294 (27.9)	
3	149 (14.8)	156 (14.8)	
Multivessel treatment	176 (17.4)	181 (17.2)	0.88
Glycoprotein IIb/IIIa-inhibitor	441 (43.7)	260 (24.7)	<0.001
Stent type			0.21
Co-Cr SES	268 (26.6)	290 (27.5)	
Co-Cr ZES	426 (42.2)	455 (43.2)	
Pt-Cr EES	307 (30.4)	306 (29.1)	
Other newer-generation DES	8 (0.8)	2 (0.2)	
Medication at discharge			
Aspirin	1,009 (100)	1,053 (100)	
Clopidogrel	877 (86.9)	159 (15.1)	
Ticagrelor	132 (13.1)	894 (84.9)	
Statin	961 (95.2)	992 (94.2)	0.29
Beta-blocker	749 (74.2)	757 (71.9)	0.23
RAS-blocker	640 (63.4)	698 (66.3)	0.17
NSAID	20 (2.0)	16 (1.5)	0.42
Proton pump inhibitor	430 (42.6)	580 (55.1)	<0.001
Medication at 1-year			
Aspirin	944 (93.6)	982 (93.3)	0.66
DAPT	916 (90.8)	947 (89.9)	0.69
with Clopidogrel	794 (78.7)	184 (17.5)	
with Ticagrelor	122 (12.1)	763 (72.5)	
OAC + P2Y₁₂ inhibitor	42 (4.2)	30 (2.9)	0.20

Values are n (%), or mean±SD. Co-Cr SES: cobalt-chromium sirolimus-eluting stent; Co-Cr ZES: cobalt-chromium zotarolimus-eluting stent; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; NSAID: non-steroidal anti-inflammatory drug; OAC: oral anticoagulant; Pt-Cr EES: platinum-chromium everolimus-eluting stent; RAS-blocker: renin-angiotensin system blocker.

CP patients versus 81/1,053 (7.8%) TP patients (HR 1.53 [95% CI: 1.08-2.17], $p=0.02$). Assessment of non-inferiority of TP versus CP resulted in inconclusive findings (risk difference 2.64 [95% CI: 0.52-4.77], $p_{\text{non-inferiority}}=0.48$). The higher NACCE rate in TP patients was largely caused by a difference in major bleeding (1.2% vs. 2.7%, $p=0.02$). There was no significant difference in the individual endpoints all-cause death, MI, and stroke; the same applied to the composite of cardiac death, MI or stroke (3.7% vs. 4.7%, $p=0.27$). Figure 2 and Figure 3 display the time-to-event curves for the primary endpoint NACCE and its individual components. During the CP and TP, rates of definite (0.3% vs. 0.6%; $p=0.35$) and definite or probable stent thrombosis (0.6% vs. 0.8%; $p=0.65$) were low.

Propensity score-adjusted multivariate analysis confirmed significantly higher rates of NACCE (adjusted HR 1.75, $p=0.003$) and major bleeding (adjusted HR 2.75, $p=0.01$) during the TP (Table 3).

FIGURE 3. One-year Kaplan-Meier cumulative incidence curves for the individual components of the primary endpoint (A) all-cause death, (B) any myocardial infarction, (C) stroke, and (D) major bleeding. CI: confidence interval; HR: hazard ratio.

Sensitivity analysis

Appendix Table 3 and Appendix Table 4 present the baseline characteristics of the study population of the sensitivity analysis; clinical outcomes are presented in Table 4. In clopidogrel-treated patients during the CP versus ticagrelor-treated patients during the TP, the NACCE rate was 5.2% vs. 7.0% (HR 1.33 [95% CI: 0.92-1.99], $p=0.12$); the risk difference was 1.80 [95% CI: -0.43-4.06], $p_{\text{non-inferiority}}=0.21$). There was a significantly higher incidence of major bleeding in ticagrelor-treated patients during the TP (1.1% vs. 2.7%, HR 2.36 [95% CI: 1.13-4.93], $p=0.02$).

After propensity score-adjusted multivariate analysis, this difference in major bleeding was still significant (adjusted HR 2.77 [95% CI: 1.27-6.07], $p=0.01$), while for NACCE the numeric difference did not reach statistical significance (adjusted HR 1.49 [95% CI: 0.99-2.26], $p=0.06$).

DISCUSSION

Patients treated during the TP had significantly higher rates of the primary endpoint NACCE as compared to CP patients, and non-inferiority assessment of the ticagrelor-based primary DAPT regimen (as compared to clopidogrel-based DAPT) showed inconclusive results. During the TP there were significantly more major bleedings. The rates of all-cause death, MI and stroke showed no statistically significant difference between treatment periods. Propensity score-adjusted multivariate analyses demonstrated that treatment during the TP was an independent predictor of NACCE and major bleedings. Patients treated with ticagrelor during the TP had a significantly higher risk of major bleedings than patients treated with clopidogrel during the CP, while there was no difference in ischaemic outcomes.

International guidelines recommend the use of ticagrelor over clopidogrel in all ACS patients merely based on the PLATO (PLATelet Inhibition and Patient Outcomes) trial, in which ticagrelor-treated STEMI and other moderate to high-risk ACS patients had significantly lower rates of vascular death and MI than clopidogrel-treated patients³ In a recent meta-analysis, STEMI patients undergoing PCI were found to have a lower mortality and fewer major adverse cardiac events if ticagrelor-based DAPT was used; however, this was mainly driven by data from PLATO with marginal additional input from a few small-sized studies with short duration (1-3 months) of DAPT and follow-up.¹⁶ In contrast to PLATO, the randomised PHILO trial found non-significantly higher rates of major adverse cardiovascular events and major bleeding in Asian ACS patients treated with ticagrelor versus clopidogrel.¹⁷

able 3. One-year clinical outcome.

All patients (n=2,062)

	Clopidogrel Period (CP) n=1,009	Ticagrelor Period (TP) n=1,053	Unadjusted hazard ratio (95% CI)	p-value	Propensity score- adjusted hazard ratio (95% CI)	p-value
NACCE	51 (5.1)	81 (7.8)	1.53 (1.08-2.17)	0.02	1.75 (1.20-2.55)	0.003
All-cause death	20 (2.0)	30 (2.9)	1.44 (0.82-2.53)	0.21	1.61 (0.88-2.95)	0.12
Any MI	24 (2.4)	29 (2.8)	1.15 (0.67-1.98)	0.60	1.39 (0.78-2.48)	0.26
Stroke						
Ischemic	3 (0.3)	11 (1.1)	3.52 (0.98-12.63)	0.05	2.91 (0.75-11.27)	0.12
Haemorrhagic	3 (0.3)	7 (0.7)				
Other	0 (0.0)	4 (0.4)				
Major bleeding *	12 (1.2)	28 (2.7)	2.24 (1.14-4.41)	0.02	2.75 (1.34-5.61)	0.01
Gastro-intestinal	6 (0.6)	13 (1.2)				
Intracranial	0 (0.0)	4 (0.4)				
Access-site	1 (0.1)	4 (0.4)				
Other	5 (0.5)	9 (0.9)				
Cardiac death, MI, or Stroke	37 (3.7)	49 (4.7)	1.27 (0.83-1.94)	0.27	1.33 (0.84-2.11)	0.22
Any revascularization (PCI or CABG)†	41 (4.2)	56 (5.4)	1.32 (0.88-1.97)	0.18	1.31 (0.85-2.03)	0.22
Any revascularization by PCI	29 (3.0)	42 (4.1)	1.40 (0.87-2.25)	0.16	1.48 (0.89-2.46)	0.13
Any revascularization by CABG	13 (1.3)	15 (1.5)	1.11 (0.53-2.34)	0.78	0.97 (0.43-2.18)	0.95
Definite-or-probable stent thrombosis						
Definite stent thrombosis ‡	6 (0.6)	8 (0.8)	1.28 (0.44-3.69)	0.65	1.03 (0.33-3.27)	0.96
Probable stent thrombosis ‡	3 (0.3)	6 (0.6)	1.92 (0.48-7.67)	0.35	1.64 (0.37-7.34)	0.52

Values are n (%). Analyses based on Kaplan-Meier method, implying that patients who died, withdrew consent or were lost, were censored at exact moments of dropout. Therefore, percentages may slightly differ from results of straightforward calculations. * During TP, two patients had two major bleedings. † One patient in each group underwent PCI and CABG. ‡ CP: 1 acute, 1 subacute and 1 late stent thrombosis; TP: 2 acute, 2 subacute and 2 late stent thrombosis. CABG: coronary artery bypass grafting; MI: myocardial infarction; NACCE: net adverse clinical and cerebral events; PCI: percutaneous coronary intervention.

Randomised controlled trials are considered the gold standard of clinical research, but they only have limited external validity, as trial participants frequently differ from patients in a real-world setting. For instance, participants in randomised trials with unregistered drugs may represent a special category of patients, who are likely to have a better medication adherence than patients in “real-world” registries.^{3,18}

Randomised controlled trials are considered the gold standard of clinical research, but they only have limited external validity, as trial participants frequently differ from patients in a real-world setting. For instance, participants in randomised trials with unregistered drugs may represent a special category of patients, who are likely to have a better medication adherence than patients in “real-world” registries.^{3,18} Therefore, positive findings of randomised controlled trials should be confirmed in broader patient populations, as are examined in large real-world registries, which provide complementary information. In the 45,073 ACS patients of the real-world SWEDEHEART registry, treated with or without PCI, comparable results to PLATO were found with a lower mortality in patients on ticagrelor;¹⁹ however, in SWEDEHEART, ticagrelor was preferentially used in patients at low risk of bleeding and death (indicated by lower CRUSADE and GRACE scores),²⁰ and patients on ticagrelor were significantly more often assessed by coronary angiography and treated by PCI.^{19,20} Furthermore, in the GRAPE registry, which examined ACS patients treated by PCI, ticagrelor- and clopidogrel-treated patients showed similar major adverse cardiac event rates.²¹ These studies suggest that, so far, no equivocal decision can be made on whether ticagrelor is superior in real-world clinical practice.

The main findings of CHANGE DAPT corroborate results of the recent TOPIC trial, which showed no differences in ischaemic outcomes at one-year follow-up between more potent P2Y₁₂ inhibitor-versus clopidogrel-treated ACS patients, and a net clinical benefit for switching to clopidogrel-based DAPT.²² In the TOPIC study, ACS patients treated by PCI were randomised after one month of DAPT with more potent P2Y₁₂ inhibitors, to continued treatment with the potent P2Y₁₂ inhibitor until 12 months, or to switching to clopidogrel. The main outcome consisted of a net clinical benefit for the switched group, primarily driven by a significantly higher bleeding risk in patients with a continued potent P2Y₁₂ inhibitor.²² Furthermore, a preliminary analysis of SCAAR registry data in 12,168 patients from Västra Götaland County, treated for ACS with PCI, also found no mortality benefit for ticagrelor use, but major bleedings were not assessed (Omerovic E. Ticagrelor is not superior to clopidogrel in patients with acute coronary syndrome: a report from SCAAR. Presented at: EuroPCR 2017, Paris, France, 18 May 2017. Available at <https://www.pcronline.com/Cases-resources-images/Resources/Course-videos-slides/2017/Antiplatelet-regimen-after-PCI-an-ongoing-debate> [last visited July 24, 2017]).

The higher rates of major bleedings for ticagrelor-treated patients in the present study are in line with other studies,^{3,19,21} but were not associated with an increased mortality, as observed by others.^{23,24} In CHANGE DAPT, ticagrelor-treated patients had a higher bleeding risk despite more transradial procedures and less glycoprotein IIb/IIIa inhibitor use – two factors known to reduce periprocedural bleedings. Furthermore, during the TP, proton pump inhibitors were more frequently prescribed to prevent gastrointestinal bleedings – the most common type of major bleedings.

Stroke rates during the CP were comparable to OPTIMIZE¹⁵ and during the TP similar to PLATO.³ During both DAPT periods, revascularisation and stent thrombosis rates were generally low and did not differ significantly between groups. The low event rates could well be attributed to experienced operators, liberal use of stent post-dilation and use of newer-generation DES only.

Limitations

Inherent to the study design, patients were not randomised. During both DAPT periods, certain patients were treated with the other P2Y₁₂ inhibitor. Although there were only a few differences in baseline characteristics, and propensity score-adjusted multivariate analyses were performed to adjust for potential confounders, residual confounding cannot be excluded. In addition, our study was not powered for detecting differences in clinical outcome with low event rates such as death, stroke, and stent thrombosis.

Despite >99% follow-up in our study, which limits the probability of event underreporting, ischaemic and bleeding events were lower than in previous randomised DAPT trials.³ Nevertheless, this is in line with the low event rates of our randomised stent trials, in which the vast majority of PCI procedures were performed by senior operators with large individual experience.^{9,14} Moreover, the NACCE rate was comparable to OPTIMIZE¹⁵ on which the power calculation of CHANGE DAPT was based. Other contemporary registries in real-world STEMI patients also showed lower event rates than in phase III studies.²⁵ These differences may be partially explained by ascertainment bias and by dissimilarities in study design, endpoint definition, and patient population. The PLATO trial, for instance, comprised ACS patients treated by optimal medical therapy, PCI or bypass surgery; of all the patients treated by PCI, more than 60% received BMS only.³ As BMS use increases major adverse cardiac event risk,^{6,7,26} the exclusive use of newer-generation DES in our study could have lowered the MI and revascularisation rates; the latter may have contributed to the lower bleeding rates observed. CHANGE DAPT findings should not be generalised to ACS patients who undergo non-PCI-based treatment.

TABLE 4. One-year clinical outcome for the sensitivity analysis.

	All patients (n=1,771)				
	Clopidogrel-treated during CP n=877	Ticagrelor-treated during TP n=894	Unadjusted hazard ratio (95% CI)	p-value	Propensity score-adjusted hazard ratio (95% CI)
NACCE	45 (5.2)	62 (7.0)	1.35 (0.92-1.99)	0.12	1.49 (0.99-2.26)
All-cause death	17 (1.9)	18 (2.0)	1.04 (0.53-2.01)	0.92	1.08 (0.53-2.22)
Any MI	22 (2.5)	24 (2.7)	1.07 (0.60-1.90)	0.83	1.30 (0.70-2.43)
Stroke	3 (0.3)	10 (1.1)	3.27 (0.90-11.87)	0.06	1.80 (0.43-7.57)
Ischemic	3 (0.3)	7 (0.8)			
Haemorrhagic	0 (0.0)	3 (0.3)			
Major bleeding *	10 (1.1)	24 (2.7)	2.36 (1.13-4.93)	0.02	2.77 (1.27-6.07)
Gastro-intestinal	5 (0.6)	12 (1.3)			
Intracranial	0 (0.0)	3 (0.3)			
Access site	1 (0.1)	3 (0.3)			
Other	4 (0.5)	8 (0.9)			
Cardiac death, MI or stroke	33 (3.8)	38 (4.3)	1.13 (0.71-1.79)	0.62	1.21 (0.73-2.00)
Any revascularization (PCI or CABG) †	40 (4.6)	49 (5.5)	1.20 (0.79-1.83)	0.39	1.17 (0.74-1.84)
Any revascularization by PCI	28 (3.2)	38 (4.3)	1.33 (0.82-2.17)	0.25	1.38 (0.82-2.35)
Any revascularization by CABG	13 (1.5)	12 (1.3)	0.91 (0.42-1.98)	0.80	0.76 (0.32-1.79)
Definite-or-probable stent thrombosis	6 (0.7)	5 (0.6)	0.82 (0.25-2.68)	0.74	0.64 (0.17-2.35)
Definite stent thrombosis	3 (0.3)	5 (0.6)	1.63 (0.39-6.84)	0.50	1.33 (0.28-6.36)

Values are n (%). * During TP, two patients had two major bleedings. † One patient in each group underwent PCI and CABG. CABG: coronary artery bypass grafting; MI: myocardial infarction; NACCE: net adverse clinical and cerebral events; PCI: percutaneous coronary intervention

CONCLUSIONS

In this observational study, the guideline-recommended primary DAPT regimen was associated with an increased adverse event risk in consecutive ACS patients, treated by PCI with newer-generation DES. The difference in event risk was primarily driven by the rate of major bleeding. Assessment of non-inferiority of ticagrelor-based DAPT for the primary endpoint NACCE was inconclusive.

IMPACT ON DAILY PRACTICE

Based on international guidelines, ticagrelor has largely replaced clopidogrel as a component of DAPT in ACS patients. CHANGE DAPT confirms that treatment with ticagrelor is associated with more major bleedings. This increased bleeding risk should be balanced against benefits in reducing ischaemic events, as previously found in broad populations of ACS patients. Nevertheless, in ACS patients treated by PCI with newer-generation DES, the benefits of ticagrelor in reducing ischaemic events have not yet been demonstrated. In CHANGE DAPT these benefits were not observed, but we cannot exclude that certain subgroups of PCI patients, treated with contemporary DES, may benefit from ticagrelor use.

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CONFLICTS OF INTEREST

P. Zocca has received a lecture fee from AstraZeneca. The other authors have no conflicts of interest to declare.

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CHAPTER 2

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SUPPLEMENTAL MATERIAL

APPENDIX TABLE 1. Reasons for deviation from primary DAPT regimen according to treatment period.

	All patients (n=2,062)	
	Ticagrelor in the Clopidogrel Period (CP) n=132/1,009	Clopidogrel in the Ticagrelor Period (TP) n=159/1,053
Other P2Y ₁₂ inhibitor initiated in another referring hospital	113 (85.6)	61 (38.4)
Discretion of the treating physician without written documentation	6 (4.5)	51 (32.1)
Pre-admission use of the other P2Y ₁₂ inhibitor	0 (0.0)	23 (14.5)
Side effects or allergy	12 (9.1)	6 (3.8)
Comorbidity	0 (0.0)	12 (7.5)
Interaction with pre-admission medication	0 (0.0)	2 (1.3)
To promote medication adherence	0 (0.0)	3 (1.9)
History of stent thrombosis	1 (0.8)	0 (0.0)
History of bleeding	0 (0.0)	1 (0.6)

Values are n (%).

APPENDIX TABLE 2. Clinical outcome at 30 days and 30 days to 1 year.

Clinical Outcome	All patients (n=2,062)					
	Clopidogrel Period (CP) n=1,009	Ticagrelor Period (TP) n=1,053	Unadjusted hazard ratio (95%-CI)	p-value	Propensity score adjusted hazard ratio (95%-CI)	p-value
30 days						
NACCE	30 (3.0)	37 (3.5)	1.18 (0.73-1.91)	0.50	1.37(0.82-2.29)	0.24
All-cause death	6 (0.6)	8 (0.8)	1.28 (0.44-3.68)	0.65	1.25 (0.40-3.92)	0.71
Any MI	22 (2.2)	22 (2.1)	0.95 (0.53-1.72)	0.87	1.08 (0.57-2.05)	0.81
Stroke	1 (0.1)	2 (0.2)	1.92 (0.17-21.12)	0.59	2.46 (0.20-31.16)	0.49
Major bleeding	5 (0.5)	12 (1.1)	2.30 (0.81-6.54)	0.11	3.52 (1.19-10.44)	0.02
30 days – 1 year						
NACCE	21 (2.2)	44 (4.4)	2.03 (1.21-3.42)	0.01	2.29 (1.32-3.99)	0.003
All-cause death	14 (1.4)	21 (2.1)	1.44 (0.73-2.84)	0.28	1.70 (0.82-3.50)	0.15
Any MI	2 (0.2)	7 (0.7)	3.38 (0.70-16.26)	0.11	5.25 (1.03-26.64)	0.045
Stroke	2 (0.2)	8 (0.8)	3.86 (0.82-18.16)	0.07	3.03 (0.59-15.65)	0.19
Major bleeding	6 (0.6)	19 (1.9)	3.06 (1.22-7.66)	0.01	3.30 (1.25-8.69)	0.02

Values are n (%). MI: myocardial infarction; NACCE: net adverse clinical and cerebral events

APPENDIX TABLE 3. Baseline characteristics for the sensitivity analysis.

All patients (n=1,771)			
Characteristics	Clopidogrel-treated during TP n=877	Ticagrelor-treated during TP n=894	p-value
Age, years	62.9 ± 11.7	62.8 ± 11.8	0.83
Male sex	609 (69.4)	664 (72.0)	0.23
BMI, kg/m² *	27.3 ± 4.3	27.7 ± 4.3	0.08
<i>Clinical history</i>			
Hypertension	363 (41.4)	352 (39.4)	0.39
Hypercholesterolemia	307 (35.0)	309 (34.6)	0.85
Diabetes Mellitus	140 (16.0)	137 (15.3)	0.71
Peripheral artery disease	76 (8.7)	45 (5.0)	0.002
Chronic obstructive pulmonary disease	68 (7.8)	54 (6.0)	0.16
Previous MI	124 (14.1)	120 (13.4)	0.66
Previous PCI	143 (16.3)	130 (14.5)	0.30
Previous CABG	63 (7.2)	40 (4.5)	0.02
Previous stroke	28 (3.2)	17 (1.9)	0.08
Previous gastro-intestinal bleeding	10 (1.1)	12 (1.3)	0.70
Renal insufficiency [†]	36 (4.1)	27 (3.0)	0.22
Dialysis	9 (1.0)	3 (0.3)	0.08
<i>Clinical presentation</i>			
ST-elevation MI	407 (46.4)	403 (45.1)	0.57
Non-ST-elevation MI	207 (23.6)	264 (29.5)	0.01
Unstable angina	263 (30.0)	227 (25.4)	0.03

Values are n (%) or mean ± SD. *Out of 1,648 patients. [†] Defined by creatinine >130 µmol/l (0.15 mg/dL). BMI: body mass index; CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention.

APPENDIX TABLE 4. Procedural characteristics and medication for the sensitivity analysis.

All patients (n=1,771)			
Characteristics	Clopidogrel-treated during CP n=877	Ticagrelor-treated during TP n=894	<i>p-value</i>
<i>Procedural characteristics</i>			
Arterial access			<0.001
Radial	145 (16.5)	408 (45.6)	
Femoral	732 (83.5)	486 (54.4)	
Vessel disease			0.34
1	479 (54.6)	519 (58.1)	
2	264 (30.1)	246 (27.5)	
3	134 (15.3)	129 (14.4)	
Multivessel treatment	149 (17.0)	150 (16.8)	0.91
Glycoprotein IIb/IIIa-inhibitor	392 (44.7)	245 (27.4)	<0.001
Stent type			0.10
Co-Cr SES	225 (25.7)	254 (28.4)	
Co-Cr ZES	379 (43.2)	380 (42.5)	
Pt-Cr EES	266 (30.3)	259 (29.0)	
Other newer-generation DES	7 (0.8)	1 (0.1)	
<i>Medication at discharge</i>			
Aspirin + Clopidogrel	877 (100)	0 (0.0)	
Aspirin + Ticagrelor	0 (0.0)	894 (100)	
Statin	836 (95.3)	852 (95.3)	0.98
Beta-blocker	649 (74.0)	632 (70.7)	0.12
RAS-blocker	554 (63.2)	599 (67.0)	0.09
NSAID	18 (2.1)	12 (1.3)	0.25
Proton pump inhibitor	366 (41.7)	485 (54.3)	<0.001
<i>Medication at 1 year</i>			
Aspirin	824 (94.0)	845 (94.5)	0.82
DAPT	800 (91.2)	816 (91.3)	0.99
with Clopidogrel	791 (90.2)	58 (6.5)	
with Ticagrelor	9 (1.0)	758 (84.8)	
OAC + P2Y₁₂ inhibitor	36 (4.1)	20 (2.2)	0.08

Values are n (%) or mean $\pm$ SD. Co-Cr SES: cobalt-chromium sirolimus-eluting stent; Co-Cr ZES: cobalt-chromium zotarolimus-eluting stent; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; NSAID: non-steroidal anti-inflammatory drug; OAC: oral anticoagulant; Pt-Cr EES: platinum-chromium everolimus-eluting stent; RAS-blocker: renin-angiotensin system blocker.

CHANGE DAPT: 2-YEAR
MORTALITY AFTER CLOPIDOGREL
OR TICAGRELOR FOR NEW-
GENERATION DRUG-ELUTING STENT
IMPLANTATION IN ACS

3

Submitted

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ABSTRACT

Aims: In the CHANGE DAPT study, patients with acute coronary syndrome (ACS) and new-generation drug-eluting stent (DES) implantation had an increased 1-year event risk when treated with dual antiplatelet therapy (DAPT) based on ticagrelor compared to clopidogrel. Aim of the current study was to assess *2-year mortality* after percutaneous coronary intervention.

Methods: In the observational CHANGE DAPT study (*clinicaltrials.gov*, number *NCT03197298*), 2,062 consecutive ACS patients were treated with new-generation DES implantation during a clopidogrel-based DAPT period (CP) or a subsequent ticagrelor-based DAPT period (TP). Two-year mortality data was obtained using the Dutch municipal personal records database.

Results: Of all patients, 547 (26.5%) had high bleeding risk (HBR). Two-year mortality data was available in 2,040 of all 2,062 (98.9%) patients. The rates of any death (4.7% vs. 4.3%, $p=0.61$), cardiovascular death (2.4% vs. 2.2%, $p=0.77$), and non-cardiovascular death (2.3% vs. 2.1%, $p=0.66$) were similar for both DAPT periods. Furthermore, there was no significant between-period difference in any death both in HBR (13.6% vs. 10.6%, $p=0.26$) and non-HBR patients (1.8% vs. 1.7%, $p=0.89$). Propensity-score adjusted analyses confirmed these findings.

Conclusions: ACS patients, treated with clopidogrel- and ticagrelor-based DAPT after new-generation DES implantation, showed low and similar 2-year mortality rates.

INTRODUCTION

Ticagrelor-based dual antiplatelet therapy (DAPT) is recommended over clopidogrel-based DAPT for patients presenting with an acute coronary syndrome (ACS), based on findings of the randomized PLATO trial.¹ In contrast, the real-world CHANGE DAPT study recently showed that consecutive ACS patients, treated with percutaneous coronary intervention (PCI) and new-generation drug-eluting stents (DES), had lower 1-year rates of the main composite clinical endpoint when treated during a period that preferred clopidogrel-based DAPT (CP) versus a period that preferred ticagrelor-based DAPT (TP).² This difference was driven by a higher major bleeding rate in the TP, in particular in patients with high bleeding risk (HBR), while no difference in ischemic outcomes was observed.^{2,3} In the present analysis we assessed 2-year mortality in patients treated during the CP versus the TP.

METHODS

The study design and 1-year outcome of the CHANGE DAPT study (*clinicaltrials.gov*, number NCT03197298) have been described previously.^{2,3} Briefly, we included 2,062 consecutive ACS patients treated with PCI and new-generation DES at a tertiary PCI center in the Netherlands. During the CP and the TP, patients were primarily treated with clopidogrel-based DAPT and ticagrelor-based DAPT, respectively. Only few exclusion criteria were applied, the most important being the use of oral anticoagulants.² Patients were classified as HBR based on criteria from previous studies.³⁻⁵ Two-year mortality data was obtained using the Dutch municipal personal records database. For the CHANGE DAPT study written informed consent was not required, as approved by the medical ethics committee. The study complied with the Declaration of Helsinki. The main endpoint of this 2-year analysis was any death. Statistics were performed as previously reported; sensitivity analyses compared patients actually treated with clopidogrel during the CP versus patients actually treated with ticagrelor during the TP.² Additional landmark analyses were performed with the landmark at one year.

RESULTS

Two-year follow-up was available in 2,040 of all 2,062 (98.9%) patients; in each period, 11 patients were lost. Of all CP and TP patients, 48/1,009 (4.7%) and 45/1,053 (4.3%) died (HR 0.90, 95% CI 0.60-1.35, $p=0.61$) (Table 1, Figure 1). During the CP versus the TP, cardiovascular mortality (2.4% vs. 2.2%, $p=0.77$) and non-cardiovascular mortality (2.3% vs. 2.1%, $p=0.66$) were similar. Propensity score-adjusted analysis showed no significant between-group difference (Table 1). In HBR and non-HBR patients, there was no significant difference in mortality between the CP and the TP (Table 1). Landmark analysis showed a higher mortality during the second year in patients treated during the

FIGURE 1. Kaplan-Meier curves for any death in all patients (A), HBR patients (B) and non-HBR patients (C). HBR = high bleeding risk.

CP, which was mainly driven by a difference among HBR patients (Table 1). Furthermore, the findings were confirmed in patients who actually received the ‘preferred’ DAPT regimen (Table 1).

DISCUSSION

In ACS patients treated with PCI and new-generation DES, 2-year mortality was similar during the clopidogrel- versus ticagrelor-based DAPT periods. The findings were consistent in both HBR and non-HBR patients.

CHANGE DAPT patients, in contrast to PLATO trial participants, were treated with new-generation DES which might decrease the need for more potent P2Y₁₂ inhibitors such as ticagrelor to prevent recurrent ischemic events.^{6–8} This may be of interest, as ticagrelor has not only been shown to reduce ischemic risk compared to clopidogrel, but was associated with more bleedings, in particular in HBR patients.^{2,3,9–11} In addition, major bleeding after PCI is associated with worse quality of life and increased mortality.^{12–14} Nevertheless, the current study results show in the ticagrelor-treated PCI patients of CHANGE DAPT that the higher rate of major bleedings did not increase mortality. On the contrary, we noted a signal that mortality might be increased in clopidogrel-treated patients during the second year of follow-up, most particular in the HBR population. A clear explanation for this difference in event rates after the discontinuation of DAPT (i.e., generally 1-year after stent implantation) is lacking. Hypothetically, pleiotropic and antibacterial effects of ticagrelor that have been reported might have contributed to this difference.^{15,16}

Nevertheless, the current study is limited by findings that are hypothesis-generating only, as this observational study was not powered for secondary endpoints. Therefore, future studies should further assess optimal antiplatelet strategies in HBR and non-HBR patients, including prolonged follow-up beyond one year. When doing so, it will be essential for forthcoming trials to use uniform HBR criteria in order to facilitate comparisons among different studies. The recently proposed HBR definition described in a consensus document of the Academic Research Consortium (ARC) for HBR provide a highly suitable definition for future research.¹⁷ For the current analysis, we applied HBR criteria as previously reported;³ in addition, some ARC HBR criteria were unavailable in our database. Other limitations of the current analysis include the unavailability of 2-year outcome data other than mortality and the proportion of patients who continued DAPT beyond 1-year is unknown (although in the Netherlands long-term use of DAPT is rather uncommon).

TABLE 1. Two-year mortality data.

2-year outcome of patients treated during the CP versus the TP							Outcome difference 1-2 years			
All patients (n=2,062)	CP (n=1,009)	TP (n=1,053)	Unadjusted HR (95% CI)	p value	Propensity score- adjusted HR (95% CI)	p value	CP	TP	Difference (95% CI)	p value
Death, any	48 (4.7%)	45 (4.3%)	0.90 (0.60 – 1.35)	0.61	0.88 (0.56 – 1.36)	0.56	28 (2.9%)	15 (1.5%)	-1.4 (-2.7 – -0.1)	0.034
Cardiovascular	24 (2.4%)	23 (2.2%)	0.92 (0.52 – 1.63)	0.77	0.84 (0.45 – 1.56)	0.58	11 (1.1%)	6 (0.6%)	-0.5 (-1.3 – 0.3)	0.20
Non-cardiovascular	24 (2.3%)	22 (2.1%)	0.88 (0.49 – 1.57)	0.66	0.92 (0.49 – 1.71)	0.78	17 (1.7%)	9 (0.9%)	-0.8 (-1.8 – 0.1)	0.10
HBR patients (n=547)	CP (n=245)	TP (n=302)								
Death, any	34 (13.6%)	32 (10.6%)	0.76 (0.47 – 1.23)	0.26	0.72 (0.43 – 1.20)	0.21	20 (8.7%)	9 (3.2%)	-5.5 (-9.5 – -1.4)	0.008
Cardiovascular	18 (7.5%)	18 (6.1%)	0.81 (0.42 – 1.56)	0.52	0.71 (0.35 – 1.43)	0.34	7 (3.1%)	3 (1.1%)	-2.0 (-4.4 – 0.5)	0.11
Non-cardiovascular	16 (6.5%)	14 (4.9%)	0.71 (0.34 – 1.44)	0.34	0.73 (0.34 – 1.57)	0.41	13 (5.7%)	6 (2.2%)	-3.5 (-6.8 – -0.2)	0.038
Non-HBR patients (n=1,515)	CP (n=764)	TP (n=751)								
Death, any	14 (1.8%)	13 (1.7%)	0.95 (0.46 – 2.01)	0.89	1.24 (0.55 – 2.77)	0.60	8 (1.1%)	6 (0.8%)	-0.3 (-1.2 – 0.7)	0.61
Cardiovascular	6 (0.8%)	5 (0.7%)	0.85 (0.26 – 2.78)	0.79	1.20 (0.34 – 4.24)	0.78	4 (0.5%)	3 (0.4%)	-0.1 (-0.8 – 0.6)	0.72
Non-cardiovascular	8 (1.1%)	8 (1.1%)	1.02 (0.38 – 2.71)	0.97	1.26 (0.44 – 3.61)	0.66	4 (0.5%)	3 (0.4%)	-0.1 (-0.8 – 0.6)	0.72

TABLE 1. Continued.

2-year outcome of patients actually treated with 'preferred' DAPT regimen							Outcome difference 1-2 years			
All patients (n=1,771)	CCP (n=877)	TTP (n=894)	Unadjusted HR (95% CI)	<i>p</i> <i>value</i>	Propensity score- adjusted HR (95% CI)	<i>p</i> <i>value</i>	CCP	TTP	Difference (95% CI)	<i>p</i> <i>value</i>
Death, any	41 (4.6%)	29 (3.3%)	0.69 (0.43 – 1.11)	0.12	0.63 (0.37 – 1.06)	0.08	24 (2.8%)	11 (1.3%)	-1.5 (-2.9 – -0.2)	0.023
Cardiovascular	18 (2.1%)	14 (1.6%)	0.76 (0.38 – 1.53)	0.44	0.71 (0.33 – 1.52)	0.38	8 (0.9%)	3 (0.3%)	-0.6 (-1.3 – 0.2)	0.12
Non-cardiovascular	23 (2.6%)	15 (1.7%)	0.6 (0.33 – 1.22)	0.17	0.57 (0.28 – 1.15)	0.12	16 (1.9%)	8 (0.9%)	-1.0 (-2.1 – 0.2)	0.09
HBR patients (n=534)	CCP (n=215)	TTP (n=219)								
Death, any	28 (12.7%)	20 (9.2%)	0.69 (0.39 – 1.23)	0.21	0.62 (0.33 – 1.15)	0.13	17 (8.4%)	6 (2.9%)	-5.5 (-10.0 – -1.0)	0.017
Cardiovascular	13 (6.2%)	11 (5.1%)	0.83 (0.37 – 1.84)	0.64	0.75 (0.32 – 1.78)	0.51	5 (2.5%)	1 (0.5%)	-2.0 (-4.3 – 0.4)	0.10
Non-cardiovascular	15 (6.9%)	9 (4.3%)	0.58 (0.25 – 1.32)	0.19	0.51 (0.21 – 1.23)	0.13	12 (5.9%)	5 (2.5%)	-3.5 (-7.4 – 0.4)	0.08
Non-HBR Patients (n=1,337)	CCP (n=662)	TTP (n=675)								
Death, any	13 (2.0%)	9 (1.3%)	0.68 (0.29 – 1.58)	0.37	0.82 (0.33 – 2.05)	0.67	7 (1.1%)	5 (0.8%)	-0.3 (-1.4 – 0.7)	0.54
Cardiovascular	5 (0.8%)	3 (0.4%)	0.59 (0.14 – 2.46)	0.46	0.82 (0.18 – 3.80)	0.80	3 (0.5%)	2 (0.3%)	-0.2 (-0.8 – 0.5)	0.64
Non-cardiovascular	8 (1.2%)	6 (0.9%)	0.73 (0.25 – 2.11)	0.56	0.81 (0.02 – 10.96)	0.72	4 (0.6%)	3 (0.5%)	-0.2 (-1.0 – 0.6)	0.68

CI = confidence interval; CP = clopidogrel period; CCP = clopidogrel treated during the CP; HBR = high bleeding risk; HR = hazard ratio; TP = ticagrelor period; TTP = ticagrelor treated during the TP.

CONCLUSIONS

ACS patients treated with clopidogrel- and ticagrelor-based DAPT after new-generation DES implantation showed low and similar 2-year mortality rates.

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CONFLICTS OF INTEREST

P.Z. has received a lecture fee (AstraZeneca). All others have no personal conflicts.

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HIGH BLEEDING RISK PATIENTS WITH
ACUTE CORONARY SYNDROMES
TREATED WITH CONTEMPORARY
DRUG-ELUTING STENTS AND
CLOPIDOGREL OR TICAGRELOR:
INSIGHTS FROM CHANGE DAPT

4

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ABSTRACT

Background: The prospective observational CHANGE DAPT study compared clopidogrel versus ticagrelor-based dual antiplatelet (DAPT) regimens in consecutive patients with acute coronary syndrome (ACS), treated with percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DES). During the ticagrelor period (TP, May 2014–August 2015) there were more major bleedings than during the clopidogrel period (CP, December 2012–April 2014).

Methods and results: To evaluate whether the excess of major bleedings during TP may be limited to high bleeding risk (HBR) patients, we performed an explorative analysis of all 2062 CHANGE DAPT participants, of whom 547 (26.5%) were classified as HBR (CP, n=245; TP, n=302). In HBR and non-HBR patients, we assessed the impact of CP versus TP on propensity score-adjusted rates of major bleeding and a pre-defined ischemic endpoint (composite of cardiac death, myocardial infarction, or stroke) at 1-year follow-up. Among HBR patients, the rate of major bleeding was significantly higher during TP (1.7% vs. 5.0%; $HR_{\text{adjusted}} 3.70$ [95% CI 1.18–11.67], $p=0.03$), while there was no significant difference in the ischemic endpoint (6.6% vs. 8.0%, $HR_{\text{adjusted}} 1.23$ [95% CI 0.63–2.42], $p=0.54$). In non-HBR patients, the rates of major bleeding (1.1% vs. 1.7%; $HR_{\text{adjusted}} 2.13$ [95% CI 0.84–5.43], $p=0.11$) and the ischemic endpoint (2.8% vs. 3.4%, $HR_{\text{adjusted}} 1.38$ [95% CI 0.74–2.57], $p=0.32$) were similar between both periods.

Conclusions: Among consecutive ACS patients, the increased risk of major bleeding during ticagrelor-based DAPT was limited to HBR patients. In both HBR and non-HBR patients, ticagrelor-based DAPT did not reduce ischemic outcomes following treatment with contemporary DES implantation.

INTRODUCTION

Ticagrelor, a more potent antiplatelet agent, is recommended over clopidogrel as part of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI).^{1,2} This recommendation is based on the large-scale randomized PLATO trial, in which ticagrelor-treated moderate-to-high risk ACS patients who underwent PCI, surgical, or non-invasive treatment showed a reduction of a composite ischemic endpoint (cardiovascular death, myocardial infarction [MI], or stroke).³ However, this benefit in ischemic outcomes came at the cost of more major bleedings.^{3,4} A more recent prospective real-world registry – the CHANGE DAPT study – compared clopidogrel versus ticagrelor-based DAPT regimens in consecutive low-to-high risk ACS patients who were treated by PCI with contemporary drug-eluting stents (DES), and observed no reduction in ischemic endpoints during the ticagrelor period, but significantly more major bleedings.⁵

The excess in major bleedings in ticagrelor-treated patients may be of particular concern in patients at high bleeding risk (HBR). While the most recent focused update on DAPT from the European Society of Cardiology does not favor clopidogrel over ticagrelor in HBR patients undergoing PCI,⁵ multiple real-world observational studies have shown that complex high-risk ACS patients are more frequently treated with clopidogrel instead of the more potent antiplatelet agents prasugrel and ticagrelor.⁶⁻⁸

As there is a lack of studies comparing DAPT regimens based on different antiplatelet drugs in ACS patients with HBR, we evaluated in the present analysis whether the excess of major bleedings during the ticagrelor-period of CHANGE DAPT was a universal finding or limited to HBR patients only. In addition, as most ACS patients with increased bleeding risk also have an increased risk of ischemic events,⁹ we assessed whether the use of ticagrelor reduced the rates of ischemic events within the HBR population of the CHANGE DAPT study.

METHODS

Study population and design

The study population and design of the CHANGE DAPT study (NCT03197298) has been published before.¹⁰ Briefly, CHANGE DAPT was an investigator-initiated, prospective observational study of 2062 consecutive ACS patients, who were treated with PCI with contemporary DES. The study was performed at the tertiary PCI center Thoraxcentrum Twente in the Netherlands and assessed two successive treatment periods with different

primary DAPT regimens (i.e., the clopidogrel period [CP; December 2012 – April 2014], and the ticagrelor period [TP; May 2014 – August 2015]). Generally, the intended DAPT duration was 1 year. The study did not include patients who were on oral anticoagulation therapy, as international guidelines discourage ticagrelor-based DAPT in such patients.¹ The study complied with the Declaration of Helsinki and was performed by the contract research organization Cardio Research Enschede (Enschede, the Netherlands). Clinical events were adjudicated by a clinical endpoint committee consisting of three members of the research team, and an experienced neurologist assessed all strokes.

Although several specific risk factors for major bleeding have previously been reported and multiple bleeding risk scores have been suggested,¹¹⁻¹³ a generally accepted definition of HBR in ACS patients is currently not available. In the present explorative analysis of the CHANGE DAPT data, we used HBR criteria that followed the criteria of the LEADERS FREE trial.¹⁴ CHANGE DAPT participants were classified at HBR if they fulfilled at least one of the following criteria: 1) age $\geq$ 75 years; 2) hemoglobin <11 g/dl; 3) platelet count $<100.000/\text{mm}^3$; 4) hospital admission for gastro-intestinal bleeding in the previous 12 months; 5) stroke during the previous 12 months; 6) any previous intracranial hemorrhage; 7) creatinine clearance <40 ml/min/1.73m² (calculated from serum creatinine, using the Modification of Diet in Renal Disease [MDRD] equation); 8) cancer (except skin) diagnosed in the previous 3 years; and 9) non-steroidal anti-inflammatory drug use at discharge. As 10) the use of oral anticoagulation at baseline and 11) planned major surgery in the next 6 months after the index PCI had been exclusion criteria of the CHANGE DAPT study,¹⁰ none of the CHANGE DAPT patients fulfilled HBR criteria 10 or 11. In contrast to the LEADERS FREE trial, we did not have information about severe liver disease (e.g. cirrhosis) available in our database and therefore we might have missed some of these HBR patients. However, if patients with severe liver disease had reduced levels of hemoglobin or platelet count, they anyway were classified as HBR.

Definitions of clinical endpoints

The main clinical endpoints of the present study were the 1-year rates of major bleeding and a composite ischemic endpoint of cardiac death, any MI, or stroke. Major bleeding was defined as any Bleeding Academic Research Consortium (BARC) class 3 or 5 bleeding and/or all Thrombolysis in Myocardial Infarction (TIMI) major bleedings (i.e., including CABG-related major bleeding).^{15,16} MI was defined according to the modified Academic Research Consortium criteria, in which creatine kinase with additional creatine kinase myocardial band or troponin were used.^{17,18} Laboratory measurements and definitions of MI did not change during the study. Strokes were defined as a focal loss of neurologic

function by an ischemic or hemorrhagic event, with residual symptoms after ≥ 24 h or leading to death.

Secondary endpoints were Net Adverse Clinical and Cerebral Events (NACCE; a composite of all-cause death, any MI, stroke, or major bleeding); any clinically indicated revascularization, and definite or probable stent thrombosis according to the Academic Research Consortium criteria.¹⁷

Statistical analysis

Patients treated during the CP were compared to patients treated during the TP and stratified for HBR. Additional sensitivity analyses were performed, comparing patients who were actually treated with clopidogrel during the CP versus patients actually treated with ticagrelor during the TP. Treatment with either clopidogrel or ticagrelor was assessed at discharge or, if a NACCE occurred before discharge, at the time of that in-hospital event. Categorical data are reported as numbers and percentages, continuous data as mean $\pm$ standard deviation. Differences are compared using the chi-square test (or Fisher's exact test when appropriate) and Student's t-test, respectively. Time to clinical endpoints was calculated using Kaplan-Meier analyses and the log-rank test was applied for between-group comparisons. Hazard ratios were computed using Cox proportional hazards regression analyses. To adjust for potential confounders, propensity scores were estimated using multiple logistic regression analysis. All baseline and procedural variables of the CHANGE DAPT study were used to calculate the propensity score for treatment during the TP; a multivariate Cox regression model was then used to adjust for the propensity score. All p-values were two-sided and p-values < 0.05 were considered significant. Data analysis was performed with SPSS, Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study population

Between December 21, 2012, and August 25, 2015, a total of 2062 patients were included in the CHANGE DAPT study; 1009 (48.9%) during the CP, and 1053 (51.1%) during the TP (Supplementary Fig. A.1). Of all participants, 547/2062 (26.5%) were at HBR, of which 245 (44.8%) underwent PCI during the CP and 302 (55.2%) during the TP. Of all 1515/2062 (73.5%) non-HBR patients, 764 (50.4%) were treated during the CP and 751 (49.6%) during the TP. HBR patients were significantly older than non-HBR patients, had significantly more comorbidities, presented more often with non-ST-elevation ACS, were more often

TABLE 1. Baseline characteristics stratified for bleeding risk.

	HBR n = 547			Non-HBR n = 1515		
	CP n = 245	TP n = 302	<i>p</i>	CP n = 764	TP n = 751	<i>p</i>
Age (years)	75.4 ± 9.1	76.2 ± 8.7	0.29	58.4 ± 9.3	59.0 ± 9.4	0.75
Male sex	143 (58.4)	172 (57.0)	0.74	559 (72.2)	576 (76.7)	0.11
BMI (kg/m²) *	26.6 ± 4.3	27.1 ± 4.3	0.18	27.6 ± 4.3	27.9 ± 4.3	0.21
Clinical history						
Hypertension	142 (58.0)	156 (51.7)	0.14	286 (37.4)	284 (37.8)	0.88
Hypercholesterolemia	96 (39.2)	104 (34.4)	0.25	264 (34.6)	280 (37.3)	0.27
Diabetes Mellitus	51 (20.8)	76 (25.2)	0.23	107 (14.0)	110 (14.6)	0.72
Peripheral artery disease	40 (16.3)	21 (7.0)	0.001	49 (6.4)	37 (4.9)	0.21
Previous MI	48 (19.6)	54 (17.9)	0.61	98 (12.8)	97 (12.9)	0.96
Previous PCI	49 (20.0)	72 (23.8)	0.28	117 (15.3)	102 (13.6)	0.34
Previous CABG	41 (16.7)	35 (11.6)	0.08	31 (4.1)	28 (3.7)	0.74
Previous stroke	19 (7.8)	20 (6.6)	0.61	13 (1.7)	11 (1.5)	0.71
Clinical presentation						
ST-elevation MI	89 (36.3)	95 (31.5)	0.23	363 (47.5)	339 (45.1)	0.35
Non-ST-elevation MI	78 (31.8)	92 (30.5)	0.73	178 (23.3)	200 (26.6)	0.13
Unstable angina	78 (31.8)	115 (38.1)	0.13	223 (29.2)	212 (28.2)	0.68
HBR criteria						
Age >75 years	183 (74.7)	226 (74.8)	0.97			
Hemoglobin <11 g/dl	36 (14.7)	40 (13.2)	0.97			
Platelet count <100,000/mm ³	5 (2.0)	5 (1.7)	0.74			
Previous GI bleeding <1 year	1 (0.4)	3 (1.0)	0.42			
Previous stroke <1 year	3 (1.2)	4 (1.3)	0.92			
Previous intracranial bleeding	1 (0.4)	3 (1.0)	0.42			
Creatinine clearance <40 ml/min/1.73m ²	24 (9.8)	26 (8.6)	0.63			
Cancer <3 years	21 (8.6)	43 (14.2)	0.04			
NSAID at discharge	22 (9.0)	18 (6.0)	0.18			
Number of HBR criteria			0.87			
1	202 (82.4)	248 (82.1)				
2	36 (14.7)	43 (14.2)				
≥3	7 (2.9)	11 (3.6)				

Values are n (%) or mean ± SD. * Out of 1,921 patients. Abbreviations: BMI: body mass index; CABG: coronary artery bypass grafting; CP: clopidogrel period; GI: gastro-intestinal; HBR: high bleeding risk; MI: myocardial infarction; NSAID: non-steroidal anti-inflammatory drug; PCI: percutaneous coronary intervention; TP: ticagrelor period.

diagnosed with multivessel disease, and were more often treated with clopidogrel-based DAPT at discharge (Supplementary Tables A.1 and A.2).

High bleeding risk patients: characteristics and clinical outcomes

Baseline demographics and HBR criteria are presented in Table 1. Age and comorbidities for HBR patients treated during the CP and TP were similar except for a more frequent diagnosis of peripheral artery disease during the CP (16.3% vs. 7.0%, $p = 0.001$). HBR criteria were comparable between both treatment periods except for more previous cancer in the TP patients (8.6% vs. 14.2%, $p = 0.04$). This difference was mainly driven by the proportion of TP patients with previously diagnosed breast cancer (0.8% vs. 4.3%). Interventional procedural characteristics and medication are presented in Table 2. During the course of the study, i.e., from CP to TP, trans-radial procedures were more often performed (16.3% vs. 37.7%, $p < 0.001$) while the use of glycoprotein IIb/IIIa-inhibitors decreased (33.5% vs. 15.2%, $p < 0.001$).

Table 3 and Fig. 1 show the various 1-year clinical outcomes including propensity score-adjusted hazard ratios. Among HBR patients, the rate of major bleeding was significantly higher during the TP (1.7% vs. 5.0%, adjusted HR 3.70 [95% CI 1.18–11.67], $p = 0.03$), while there was no statistically significant difference in the composite ischemic endpoint (6.6% vs. 8.0%, adjusted HR 1.23 [95% CI 0.63–2.42], $p = 0.54$). This resulted in a significantly higher NACCE rate for TP patients (8.2% vs. 13.4%, adjusted HR 1.80 [95% CI 1.02–3.17], $p = 0.04$), while there were no statistically significant between-group differences in all other secondary clinical endpoints.

All HBR patients (i.e. HBR patients treated during CP plus during TP) had significantly higher 1-year rates of major bleeding and a composite ischemic endpoint (cardiac death, MI, or stroke) as compared to all non-HBR patients (Supplementary Table A.3).

Non-high bleeding risk patients: characteristics and clinical outcomes

In non-HBR patients, most baseline demographics, interventional procedural characteristics and medications were similar for patients treated during the CP and TP (Tables 1 and 2). However, TP patients underwent more often trans-radial procedures (18.2% vs. 47.4%, $p < 0.001$), received less glycoprotein IIb/IIIa-inhibitors (47.0% vs. 28.5%, $p < 0.001$), and were more often treated with proton pump inhibitors (37.0% vs. 50.5%, $p < 0.001$).

At 1-year follow-up, non-HBR patients treated during the CP and during the TP had rates of major bleeding (1.1% vs. 1.7%, adjusted HR 2.13 [95% CI 0.84–5.43], $p = 0.11$) and

TABLE 2. Procedural characteristics and medication stratified for bleeding risk.

	HBR n = 547			Non-HBR n = 1515		
	CP n = 245	TP n = 302	p	CP n = 764	TP n = 751	p
<i>Procedural characteristics</i>						
Vascular access			<0.001			<0.001
Radial	40 (16.3)	114 (37.7)		139 (18.2)	356 (47.4)	
Femoral	205 (83.7)	188 (62.3)		625 (81.8)	395 (52.6)	
Multivessel treatment	52 (21.2)	52 (17.2)	0.24	124 (16.2)	129 (17.2)	0.62
Glycoprotein IIb/IIIa-inhibitor	82 (33.5)	46 (15.2)	<0.001	359 (47.0)	214 (28.5)	<0.001
Stent type			0.52			0.42
Co-Cr SES	56 (22.9)	77 (25.5)		212 (27.7)	213 (28.4)	
Co-Cr ZES	112 (45.7)	142 (47.0)		314 (41.1)	313 (41.7)	
Pt-Cr EES	76 (31.0)	83 (27.5)		231 (30.2)	223 (29.7)	
Other DES	1 (0.4)	0 (0.0)		7 (0.9)	2 (0.3)	
<i>Medication at discharge</i>						
Aspirin	100 (100)	100 (100)	-	100 (100)	100 (100)	-
Clopidogrel	215 (87.8)	83 (27.5)	-	662 (86.6)	76 (10.1)	-
Ticagrelor	30 (12.2)	219 (72.5)	-	102 (13.4)	675 (89.9)	-
PPI	147 (60.0)	201 (66.6)	0.11	283 (37.0)	379 (50.5)	<0.001
<i>Medication at 1-year</i>						
Aspirin	212 (86.5)	263 (87.1)	0.53	732 (95.8)	719 (92.5)	0.99
DAPT	204 (83.3)	252 (83.4)	0.69	712 (93.2)	695 (92.5)	0.87
with Clopidogrel	179 (73.1)	79 (26.2)	-	615 (80.5)	105 (14.0)	-
with Ticagrelor	25 (10.2)	173 (57.3)	-	97 (12.7)	590 (78.6)	-
OAC + P2Y₁₂ inhibitor	19 (7.8)	15 (5.0)	0.35	23 (3.0)	15 (2.0)	0.45

Values are n (%) or mean $\pm$ SD. * Out of 1,921 patients. Abbreviations: Co-Cr SES: cobalt-chromium sirolimus-eluting stent; Co-Cr ZES: cobalt-chromium zotarolimus-eluting stent; CP: clopidogrel period; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; HBR: high bleeding risk; OAC: oral anticoagulant; PPI: proton pump inhibitor; Pt-Cr EES: platinum-chromium everolimus-eluting stent; TP: ticagrelor period.

the composite ischemic endpoint (2.8% vs. 3.4%, adjusted HR 1.38 [95% CI 0.74–2.57], $p = 0.32$) that did not differ significantly (Table 3, Fig. 1).

Sensitivity analyses for high bleeding risk and non-high bleeding risk patients

Of the HBR patients, 215/547 (87.8%) were actually treated with clopidogrel during the CP and 219/302 (72.5%) were actually treated with ticagrelor during the TP. Clopidogrel-treated HBR patients during the CP had significantly more comorbidities than ticagrelor-treated HBR patients during the TP (Supplementary Table B.1). In addition, ticagrelor-treated HBR patients during the TP were more often treated via the trans-radial approach (15.3% vs. 38.4%, $p < 0.001$) and less often with glycoprotein IIb/IIIa-inhibitors (34.9% vs. 18.3%, $p < 0.001$) (Supplementary Table B.2). There were no significant between-group differences in HBR criteria, except for more previous cancer in the ticagrelor-treated patients during the TP (7.9% vs. 14.2%, $p = 0.04$). At 1-year follow-up, clopidogrel-treated HBR patients during CP had significantly fewer major bleedings than ticagrelor-treated HBR patients during the TP (1.4% vs. 5.5%, adjusted HR 5.28 [95% CI 1.38–20.29], $p = 0.02$) while the rates of the composite ischemic endpoint were similar (6.6% vs. 7.4%, adjusted HR 1.45 [95% CI 0.66–3.19], $p = 0.35$) (Supplementary Table B.3).

Of the non-HBR patients, 662/764 (86.6%) were treated with clopidogrel during the CP, and 675/751 (89.9%) were treated with ticagrelor during the TP (Supplementary Table B.1). Trans-Radial procedures (16.9% vs. 48.0%, $p < 0.001$) and proton pump inhibitors (36.0% vs. 50.4%, $p < 0.001$) were more often used in ticagrelor-treated non-HBR patients during the TP, while glycoprotein IIb/IIIa inhibitor use was lower in these patients (47.9% vs. 30.4%, $p < 0.001$) (Supplementary Table B.2). There were no statistically significant differences in major bleeding (1.1% vs. 1.8%, adjusted HR 2.56 [95% CI 0.95–6.87], $p = 0.06$) and the composite ischemic endpoint (2.9% vs. 3.3%, adjusted HR 1.25 [95% CI 0.64–2.46], $p = 0.51$) (Supplementary Table B.3). Furthermore, there were no statistically significant between-group differences in other clinical endpoints.

FIGURE 1. One-year major bleeding and ischemic events stratified for HBR and non-HBR patients. Kaplan Meier curves for major bleeding and a composite ischemic endpoint consisting of cardiac death, any MI, or stroke in HBR (A, B) and non-HBR (C, D) patients treated during the clopidogrel period (orange) and the ticagrelor period (blue). Abbreviations: CP: clopidogrel period; HBR: high bleeding risk; MI: myocardial infarction; TP: ticagrelor period.

DISCUSSION

Main results

In the present analysis of 2062 consecutive ACS patients, treated with contemporary DES in the CHANGE DAPT study, approximately one in every four patients was considered to be at HBR, although our study did not assess patients on oral anticoagulation therapy. The main findings were: 1) that treatment during the ticagrelor period was associated with a higher major bleeding risk which was significant in HBR patients only; and 2) that in both HBR and non-HBR patients, ticagrelor-based DAPT was not associated with a benefit in ischemic outcomes.

Treatment of high bleeding risk patients

Major bleeding in ACS patients is associated with an increased mortality and a reduced quality of life, and therefore it is an essential endpoint to account for in studies that evaluate DAPT.¹⁹⁻²² Although several bleeding risk scores have been developed to identify patients at HBR and to tailor DAPT, there is no consensus on the standard use of a particular bleeding risk score. In the present study, when applying criteria based on the LEADERS FREE trial,¹⁴ more than a quarter of all ACS patients (26.5%) was at HBR. This proportion may seem relatively low when compared to the 41.6% HBR patients in another study, using similar HBR criteria in consecutive, percutaneously treated ACS patients,²³ but the difference may be largely explained by the exclusion of patients on oral anticoagulation therapy in CHANGE DAPT.¹⁰ These patients were not assessed since guidelines discourage treatment with ticagrelor in patients on oral anticoagulation therapy due to an excessive bleeding risk.¹

The recently published focused update on DAPT from the European Society of Cardiology is the first guideline to include specific recommendations on which P2Y₁₂ inhibitor to use in HBR patients: both clopidogrel and ticagrelor received a class IIa recommendation.⁵ Since HBR patients, such as the elderly, are frequently under-represented in clinical trials and, therefore, comparative studies assessing different DAPT regimens in these patients are lacking, the recommendation is partly based on expert opinion.⁵ Several studies address the issue of abbreviated DAPT duration in PCI-treated ACS patients at HBR, but to the best of our knowledge the current analysis is the first to evaluate DAPT based on clopidogrel and ticagrelor in this patient population. Our results suggest that the increase in major bleeding in ticagrelor-treated patients can mainly be found in those at HBR. While one may tend to reconsider the use of ticagrelor-based DAPT to avoid major bleedings in HBR patients, just these patients have a higher risk of ischemic events.^{9,24} This was also seen in the present study and is probably related to corresponding risk factors, such as an advanced age. Physicians in both our and other real-world studies tend to treat complex high-risk ACS patients less often with DAPT based on ticagrelor or prasugrel.^{6-8,25} This phenomenon is sometimes called a risk-treatment paradox, since the more potent antiplatelet agents are being withheld from patients at the highest risk of ischemic events. Nevertheless, the results of the present study, which observed an increased rate of major bleedings in ticagrelor-treated patients without a benefit in ischemic outcomes, might reassure clinicians who tend to prefer such a “conservative approach”. In addition, spontaneous ischemic and bleeding events seem equally related to clinical prognosis,^{26,27} and procedure-related bleedings (also assessed in the current study) were previously found to be independently associated with an increased mortality.²⁸ Nevertheless, the optimal approach to balance ischemic and bleeding risks might be a personalized choice of DAPT regimen in individual patients, based on their specific characteristics;²⁹ the use of dedicated risk scores may be very useful in this context.¹¹⁻¹³

TABLE 3. One-year clinical outcome stratified for bleeding risk.

1-year	HBR n = 547				Non-HBR n = 1515						
	CP n = 245	TP n = 302	Unadjusted HR (95% CI)	<i>p</i>	Propensity score- adjusted HR (95% CI)	<i>p</i>	CP n = 764	TP n = 751	Unadjusted HR (95% CI)	<i>p</i>	Propensity score- adjusted HR (95% CI)
Major Bleeding	4 (1.7)	15 (5.0)	3.09 (1.02-9.30)	0.04	3.70 (1.18-11.67)	0.03	8 (1.1)	13 (1.7)	1.65 (0.68-3.98)	0.26	2.13 (0.84-5.43)
Cardiac death, any MI or stroke	16 (6.6)	24 (8.0)	1.21 (0.65-2.29)	0.55	1.23 (0.63-2.42)	0.54	21 (2.8)	25 (3.4)	1.21 (0.68-2.16)	0.52	1.38 (0.74-2.57)
NACCE	20 (8.2)	40 (13.4)	1.65 (0.97-2.83)	0.06	1.80 (1.02-3.17)	0.04	31 (4.1)	41 (5.5)	1.35 (0.84-2.15)	0.21	1.67 (1.01-2.75)
All-cause death	14 (5.8)	23 (7.6)	1.33 (0.69-2.59)	0.40	1.38 (0.68-2.79)	0.38	6 (0.8)	7 (0.9)	1.19 (0.40-3.53)	0.76	1.20 (0.65-6.24)
Cardiac death	10 (4.1)	11 (3.7)	0.89 (0.38-2.09)	0.79	0.76 (0.30-1.91)	0.56	2 (0.3)	1 (0.1)	0.51 (0.05-5.62)	0.57	0.49 (0.04-6.64)
Any MI	6 (2.5)	9 (3.0)	1.21 (0.43-3.39)	0.72	1.60 (0.54-4.76)	0.40	18 (2.4)	20 (2.7)	1.13 (0.60-2.13)	0.71	1.30 (0.66-2.59)

TABLE 3. Continued.

1-year	HBR n = 547				Non-HBR n = 1515			
	CP n = 245	TP n = 302	Unadjusted HR (95% CI)	p	Propensity score- adjusted HR (95% CI)	p	Unadjusted HR (95% CI)	Propensity score- adjusted HR (95% CI)
Stroke	1 (0.4)	5 (1.7)	4.06 (0.47-34.74)	0.17	3.33 (0.36-31.20)	0.29	3.06 (0.62-15.15)	2.62 (0.47-14.54)
Any clinically indicated revascularization	12 (5.1)	14 (4.8)	0.94 (0.44-2.03)	0.88	0.82 (0.36-1.87)	0.63	1.49 (0.93-2.39)	1.57 (0.94-2.61)
Definite-or- probable ST	3 (1.2)	4 (1.3)	1.08 (0.24-4.82)	0.92	0.72 (0.14-3.60)	0.69	1.36 (0.31-6.08)	1.44 (0.29-7.25)
Definite ST	2 (0.8)	2 (0.7)	0.81 (0.11-5.75)	0.83	0.45 (0.06-3.65)	0.45	4.08 (0.46-36.50)	5.11 (0.52-50.03)

Values are n (%). Analyses based on Kaplan-Meier method, implying that patients who died, withdrew consent or were lost were censored at exact moments of dropout. Therefore, percentages may differ slightly from results of straightforward calculations. Abbreviations: CI: confidence interval; CP: clopidogrel period; HBR: high bleeding risk; HR: hazard ratio; MI: myocardial infarction; NACCE: net adverse clinical and cerebral events; ST: stent thrombosis; TP: ticagrelor period.

Treatment with contemporary DES

Several factors may contribute to the lack of benefit in ischemic outcome for ticagrelor-treated HBR and non-HBR patients in CHANGE DAPT. Firstly, in compliance with European guidelines, our study included low-to-high risk ACS patients, while in the PLATO trial moderate-to-high-risk patients were assessed.^{1,3,10,30} Secondly, the side effect profile of ticagrelor may have affected patient compliance³¹ and might have resulted in a somewhat higher risk of interruption of DAPT. Thirdly, all patients were treated with PCI with use of contemporary DES, which has shown to improve clinical outcome with lower ischemic event rates (i.e., target-vessel MI and stent thrombosis), as compared to bare metal, and first-generation drug-eluting stents, which were both used in the PLATO trial.^{3,32}

Previously, patients with HBR were often treated with bare metal stents, as the possibility to shorten DAPT duration was effective in lowering the incidence of bleeding. However, two recent trials showed superior outcomes for PCI with contemporary DES versus bare metal stents in ACS patients at HBR.^{24,33,34} Based on these results, DES are currently recommended over bare metal stents irrespective of the intended DAPT duration.⁵ Since the widespread availability of contemporary DES, there has been an increase in the proportion of patients with HBR who are treated with DES.²³ A significant benefit of ticagrelor over clopidogrel has not been demonstrated in an ACS patient population that was exclusively treated with contemporary DES. Thus, in such patients the need for a more potent P2Y₁₂ inhibitor-based DAPT remains to be demonstrated. The findings of the observational CHANGE DAPT study raise some doubts, but a definite answer will require data from large randomized clinical trials. These future trials should not only assess the optimal duration of DAPT in relation to HBR status, but also evaluate which patient groups truly benefit from a more potent DAPT regimen after PCI with contemporary DES. Such patient groups may be diabetics or patients treated with stenting in left main stems, very long lesions, or small vessels. In addition, it remains to be confirmed whether genotyping³⁵ might play a role in choosing the type of DAPT prior to PCI procedures or downgrading potent DAPT to clopidogrel-based DAPT in ACS patients who underwent PCI.^{36,37}

Minimizing bleeding risk

The impact of different DAPT regimens on the outcome of patients with HBR are currently being assessed by several randomized clinical trials. Studies that randomize clopidogrel versus ticagrelor or prasugrel in the elderly (i.e., the most common HBR criterion),³⁸ and ticagrelor based DAPT versus ticagrelor single antiplatelet therapy in high-risk ACS patients,³⁹ will provide information that may help optimize antiplatelet therapy in the future.

Until the results of these studies are available, the risk of HBR could be lowered by adjusting several factors, as compared to the clinical practice that we observed in CHANGE DAPT: 1) while the CHANGE DAPT patients were treated with an intended DAPT duration of 12 months, an abbreviated treatment with DAPT may be more appropriate and is currently recommended in the presence of HBR by international guidelines;^{5,22} 2) from today's perspective, the use of the trans-radial access was relatively low in our study (28.2%, most likely because the inclusion period was some years ago and the operators then had a large experience in trans-femoral PCI); which could be increased to reduce procedure-related bleedings;^{40,41} 3) the proportion of HBR patients treated with proton pump inhibitors for gastric protection was reasonable (63.6%) but could be further improved. Although during CHANGE DAPT there was a significant improvement from the CP to the TP in the rates of trans-radial access and gastric protection, which theoretically had a lowering effect upon the bleeding risk, a significantly higher incidence of major bleedings was observed during the TP.¹⁰

An alternative approach to lower bleeding risk is to downgrade from DAPT with a more potent P2Y₁₂ inhibitor to clopidogrel-based DAPT. Two recent trials assessed such a step-down approach and showed that switching DAPT 1 or 4 weeks after PCI may lower the bleeding risk without increasing ischemic events.^{36,37}

Limitations

The results of this exploratory study, in particular the findings of the subgroup analysis, should be considered hypothesis generating. Although there are no expected differences between the treatment periods in underreporting events, we cannot exclude that the relatively low adverse event rates may be partly related to ascertainment bias. We performed propensity score-adjusted analyses, but residual confounding cannot be excluded. This could explain the higher rate of previously diagnosed cancer in the TP patients. In the present study, no data of liver disease or expected noncompliance to DAPT were available; nevertheless, both HBR characteristics applied only to few participants in a previous large-scale HBR trial.³³ Other classifications of HBR are valuable alternatives but may require data that were not available for all patients. The present findings cannot be generalized to ACS patients on oral anticoagulation therapy or treated without PCI.

CONCLUSIONS

Among the consecutive ACS patients included in the observational CHANGE DAPT study, the increased major bleeding risk during treatment with ticagrelor-based DAPT was limited to HBR patients. In both HBR and non-HBR patients, ticagrelor-based DAPT did not reduce ischemic events after treatment with contemporary DES as compared to clopidogrel-based DAPT. Further randomized trials are warranted to optimize antiplatelet therapy in ACS patients at HBR who are treated with PCI.

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CONFLICTS OF INTEREST

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SUPPLEMENTAL MATERIAL

SUPPLEMENTARY FIGURE A.1. Study flow chart.

SUPPLEMENTARY TABLE A.1. Baseline characteristics for all HBR and non-HBR patients.

Total population n = 2062			
	HBR n = 547	Non-HBR n = 1515	<i>p</i>
Age(years)	75.5 ± 8.9	58.9 ± 9.3	<0.001
Male sex	315 (57.6)	1,135 (74.9)	<0.001
BMI(kg/m²) *	26.9 ± 4.3	27.7 ± 4.3	0.001
<i>Clinical history</i>			
Hypertension	298 (54.5)	570 (37.6)	<0.001
Hypercholesterolemia	200 (36.6)	544 (35.9)	0.78
Diabetes Mellitus	127 (23.2)	217 (14.3)	<0.001
Peripheral artery disease	61 (11.2)	86 (5.7)	<0.001
Previous MI	102 (18.6)	195 (12.9)	0.001
Previous PCI	121 (22.1)	219 (14.5)	<0.001
Previous CABG	76 (13.9)	59 (3.9)	<0.001
Previous stroke	39 (7.1)	24 (1.6)	<0.001
<i>Clinical presentation</i>			
ST-elevation MI	184 (33.6)	702 (46.3)	<0.001
Non-ST-elevation MI	170 (31.1)	378 (25.0)	<0.01
Unstable angina	193 (35.3)	435 (28.7)	<0.01
<i>HBR criteria</i>			
Age >75 years	409 (74.8)		
Hemoglobin <11 g/dl	76 (13.9)		
Platelet count <100,000/mm ³	10 (1.8)		
Previous GI bleeding <1 year	4 (0.7)		
Previous stroke <1 year	7 (1.3)		
Previous intracranial bleeding	4 (0.7)		
Creatinine clearance <40 ml/min/1.73m ²	50 (9.1)		
Cancer <3 year	64 (11.7)		
NSAID at discharge	40 (7.3)		
<i>Number of HBR criteria</i>			
1	450 (82.3)		
2	79 (14.4)		
≥3	18 (3.3)		

Values are n (%) or mean ± SD. * Out of 1,921 patients. Abbreviations: BMI = body mass index; CABG = coronary artery bypass grafting; CP = clopidogrel period; GI = gastro-intestinal; HBR = high bleeding risk; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; TP = ticagrelor period.

SUPPLEMENTARY TABLE A.2. Interventional procedural characteristics and medication for all HBR and non-HBR patients.

Total population n = 2062			
HBR criteria	HBR n = 547	Non-HBR n = 1515	<i>p</i>
<i>Procedural characteristics</i>			
Vascular access			0.05
Radial	154 (28.2)	495 (32.7)	
Femoral	393 (71.8)	1020 (67.3)	
Multivessel treatment	104 (19.0)	253 (16.7)	0.22
Glycoprotein IIb/IIIa-inhibitor	128 (23.4)	573 (37.8)	<0.001
Stent type			0.11
Co-Cr SES	133 (24.3)	425 (28.1)	
Co-Cr ZES	254 (46.4)	627 (41.4)	
Pt-Cr EES	159 (29.1)	454 (30.0)	
other DES	1 (0.2)	9 (0.6)	
<i>Medication at discharge</i>			
Aspirin	547 (100)	1515 (100)	-
Clopidogrel	298 (54.5)	738 (48.7)	0.02
Ticagrelor	249 (45.5)	777 (51.3)	0.02
PPI	348 (63.6)	662 (43.7)	<0.001
<i>Medication at 1-year</i>			
Aspirin	475 (86.8)	1451 (95.8)	<0.001
DAPT	456 (83.4)	1407 (92.9)	<0.001
with Clopidogrel	258 (47.2)	720 (47.5)	<0.001
with Ticagrelor	198 (36.2)	687 (45.3)	<0.001
OAC + P2Y₁₂ inhibitor	34 (6.2)	38 (2.5)	<0.001

Values are n (%) or mean ± SD. * Out of 1,921 patients. Abbreviations: Co-Cr SES = cobalt-chromium sirolimus-eluting stent; Co-Cr ZES = cobalt-chromium zotarolimus-eluting stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; HBR = high bleeding risk; OAC = oral anticoagulant; PPI = proton pump inhibitor; Pt-Cr EES = platinum-chromium everolimus-eluting stent.

TABLE A.3. One-year clinical outcome for all HBR and non-HBR patients.

Total population n = 2062				
1-year	HBR n = 547	Non-HBR n = 1515	Unadjusted HR (95% CI)	p
Major Bleeding	19 (3.5)	21 (1.4)	2.55 (1.37-4.73)	0.002
Cardiac death, any MI or stroke	40 (7.4)	46 (3.1)	2.44 (1.60-3.73)	<0.001
NACCE	60 (11.1)	72 (4.8)	2.37 (1.68-3.33)	<0.001
All-cause death	37 (6.8)	13 (0.9)	8.08 (4.29-15.20)	<0.001
Cardiac death	21 (3.9)	3 (0.2)	19.73 (5.89-66.14)	<0.001
Any MI	15 (2.8)	38 (2.5)	1.10 (0.61-2.00)	0.75
Stroke	6 (1.1)	8 (0.5)	2.13 (0.74-6.14)	0.15
Any clinically indicated revascularization	26 (5.0)	71 (4.8)	1.05 (0.67-1.64)	0.84
Definite-or-probable ST	7 (1.3)	7 (0.5)	2.82 (0.99-8.03)	0.04
Definite ST	4 (0.7)	5 (0.3)	2.26 (0.61-8.40)	0.21

Values are n (%). Analyses based on Kaplan-Meier method, implying that patients who died, withdrew consent or were lost were censored at exact moments of dropout. Therefore, percentages may differ slightly from results of straightforward calculations. Abbreviations: CI = confidence interval; HBR = high bleeding risk; HR = hazard ratio; MI = myocardial infarction; NACCE = net adverse clinical and cerebral events; ST = stent thrombosis.

TABLE B.1. Baseline characteristics for the sensitivity analysis in HBR and non-HBR patients.

	HBR n = 434			Non-HBR n = 1337		
	Clopidogrel in CP n = 215	Ticagrelor in TP n = 219	p	Clopidogrel in CP n = 662	Ticagrelor in TP n = 675	p
Age (years)	75.2 ± 9.3	75.7 ± 8.5	0.54	58.9 ± 9.3	58.6 ± 9.4	0.52
Male sex	120 (55.8)	129 (58.9)	0.52	489 (73.9)	515 (76.3)	0.30
BMI (kg/m²) *	26.7 ± 4.3	27.5 ± 4.3	0.07	27.5 ± 4.2	27.8 ± 4.3	0.29
Clinical history						
Hypertension	126 (58.6)	107 (48.9)	0.04	237 (35.8)	245 (36.3)	0.85
Hypercholesterolemia	85 (39.5)	65 (29.7)	0.03	222 (33.5)	244 (36.1)	0.32
Diabetes Mellitus	47 (21.9)	49 (22.4)	0.90	93 (14.0)	88 (13.0)	0.59
Peripheral artery disease	34 (15.8)	14 (6.4)	0.002	42 (6.3)	31 (4.6)	0.16
Previous MI	45 (20.9)	39 (17.8)	0.41	79 (11.9)	81 (12.0)	0.97
Previous PCI	44 (20.5)	50 (22.8)	0.55	99 (15.0)	80 (11.9)	0.10
Previous CABG	38 (17.7)	24 (11.0)	0.05	25 (3.8)	16 (2.4)	0.14
Previous stroke	16 (7.4)	9 (4.1)	0.14	12 (1.8)	8 (1.2)	0.35
Clinical presentation						
ST-elevation MI	81 (37.7)	78 (35.6)	0.66	326 (49.2)	325 (48.1)	0.69
Non-ST-elevation MI	65 (30.2)	72 (32.9)	0.55	142 (21.5)	192 (28.4)	0.003
Unstable angina	69 (32.1)	69 (31.5)	0.90	194 (29.3)	158 (23.4)	0.014
HBR criteria						
Age >75 years	160 (74.4)	165 (75.3)	0.82			
Hemoglobin <11 g/dl	33 (15.3)	22 (10.0)	0.10			
Platelet count <100.000/mm ³	5 (2.3)	3 (1.4)	0.50			
Previous GI bleeding <1 year	1 (0.5)	3 (1.4)	0.62			
Previous stroke <1 year	2 (0.9)	1 (0.5)	0.62			
Previous intracranial bleeding	1 (0.5)	2 (0.9)	1.00			
Creatinine clearance <40 ml/ min/1.73m ²	21 (9.8)	13 (5.9)	0.14			
Cancer <3 year	17 (7.9)	31 (14.2)	0.04			
NSAID at baseline	20 (9.3)	13 (5.9)	0.19			
Number of HBR criteria						
1	368 (84.8)					
2	54 (12.4)					
≥3	12 (2.8)					

Values are n (%) or mean ± SD. * Out of 1,921 patients. Abbreviations: BMI = body mass index; CABG = coronary artery bypass grafting; CP = clopidogrel period; GI = gastro-intestinal; HBR = high bleeding risk; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; TP = ticagrelor period.

TABLE B.2. Interventional procedural characteristics and medication for the sensitivity analysis in HBR and non-HBR patients.

	HBR n = 434			Non-HBR n = 1337		
	Clopidogrel in CP n = 215	Ticagrelor in TP n = 219	p	Clopidogrel in CP n = 662	Ticagrelor in TP n = 675	p
<i>Procedural characteristics</i>						
Vascular access			<0.001			<0.001
Radial	33 (15.3)	84 (38.4)		112 (16.9)	324 (48.0)	
Femoral	182 (84.7)	135 (61.6)		550 (83.1)	351 (52.0)	
Multivessel treatment	44 (20.5)	37 (16.9)	0.34	105 (15.9)	113 (16.7)	0.66
Glycoprotein IIb/IIIa-inhibitor	75 (34.9)	40 (18.3)	<0.001	317 (47.9)	205 (30.4)	<0.001
Stent type			0.30			0.26
Co-Cr SES	47 (21.9)	63 (28.8)		178 (26.9)	191 (28.3)	
Co-Cr ZES	99 (46.0)	93 (42.5)		280 (42.3)	287 (42.5)	
Pt-Cr EES	68 (31.6)	63 (28.8)		198 (29.9)	196 (29.0)	
other DES	1 (0.5)	0 (0.0)		6 (0.9)	1 (0.1)	
<i>Medication at discharge</i>						
Aspirin	100 (100)	100 (100)	-	100 (100)	100 (100)	-
Clopidogrel	100 (100)	0 (0.0)	-	100 (100)	0 (0.0)	-
Ticagrelor	0 (0.0)	100 (100)	-	0 (0.0)	100 (100)	-
PPI	128 (59.5)	145 (66.2)	0.15	238 (36.0)	340 (50.4)	<0.001
<i>Medication at 1-year</i>						
Aspirin	188 (87.4)	195 (89.0)	0.52	636 (96.1)	650 (96.3)	0.88
DAPT	180 (83.7)	189 (86.3)	0.44	620 (93.7)	627 (92.9)	0.60
with Clopidogrel	179 (83.3)	20 (9.1)	-	612 (92.4)	38 (5.6)	-
with Ticagrelor	1 (0.5)	169 (77.2)	-	8 (1.2)	589 (87.3)	-
OAC + P2Y₁₂ inhibitor	17 (7.9)	9 (4.1)	0.24	19 (2.9)	11 (1.6)	0.27

Values are n (%) or mean $\pm$ SD. * Out of 1,921 patients. Abbreviations: Co-Cr SES = cobalt-chromium sirolimus-eluting stent; Co-Cr ZES = cobalt-chromium zotarolimus-eluting stent; CP = clopidogrel period; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; HBR = high bleeding risk; OAC = oral anticoagulant; PPI = proton pump inhibitor; Pt-Cr EES = platinum-chromium everolimus-eluting stent; TP = ticagrelor period.

TABLE B.3. One-year clinical outcome for the sensitivity analysis in HBR and non-HBR patients.

1-year	HBR n = 534				Non-HBR n = 1337							
	Clopidogrel in CP n = 215	Ticagrelor in TP n = 219	Unadjusted HR (95% CI)	p	Propensity score- adjusted HR (95% CI)	p	Clopidogrel in CP n = 662	Ticagrelor in TP n = 675	Unadjusted HR (95% CI)	p	Propensity score- adjusted HR (95% CI)	p
Major Bleeding	3 (1.4)	12 (5.5)	3.99 (1.13-14.14)	0.02	5.28 (1.38-20.29)	0.02	7 (1.1)	12 (1.8)	1.67 (0.66-4.25)	0.27	2.56 (0.95-6.87)	0.06
Cardiac death, any MI or stroke	14 (6.6)	16 (7.4)	1.12 (0.54-2.28)	0.77	1.45 (0.66-3.19)	0.35	19 (2.9)	22 (3.3)	1.13 (0.61-2.09)	0.69	1.25 (0.64-2.46)	0.51
NACCE	17 (8.0)	26 (12.0)	1.53 (0.83-2.81)	0.17	1.89 (0.96-3.70)	0.06	28 (4.2)	35 (5.2)	1.22 (0.74-2.01)	0.43	1.57 (0.92-2.68)	0.10
All-cause death	11 (5.2)	14 (6.4)	1.25 (0.57-2.75)	0.58	1.47 (0.62-3.50)	0.39	6 (0.9)	4 (0.6)	0.65 (0.18-2.31)	0.51	1.17 (0.31-4.43)	0.82
Cardiac death	8 (3.7)	7 (3.2)	0.86 (0.31-2.36)	0.76	0.77 (0.26-2.29)	0.64	2 (0.3)	1 (0.1)	0.49 (0.05-5.41)	0.55	0.47 (0.03-6.48)	0.57
Any MI	6 (2.8)	6 (2.8)	0.97 (0.31-3.02)	0.96	1.46 (0.42-5.01)	0.55	16 (2.4)	18 (2.7)	1.10 (0.56-2.16)	0.78	1.27 (0.61-2.66)	0.52

TABLE B.3. Continued.

HBR n = 534				Non-HBR n = 1337									
1-year	Clopidogrel		Ticagrelor	Unadjusted HR (95% CI)	p	Propensity score- adjusted HR (95% CI)	p	Unadjusted HR (95% CI)	p	Propensity score- adjusted HR (95% CI)			
	in CP n = 215	in TP n = 219	Ticagrelor in TP n = 675										
Stroke	1 (0.5)	4 (1.9)		3.92 (0.44-35.08)	0.19	3.80 (0.36-39.62)	0.27	2 (0.3)	4 (0.6)	1.96 (0.36-10.69)	0.43	1.22 (0.18-8.10)	0.84
Any clinically indicated revascularization	12 (5.8)	12 (5.7)		0.97 (0.44-2.17)	0.95	0.78 (0.32-1.91)	0.59	28 (4.3)	37 (5.5)	1.30 (0.80-2.13)	0.29	1.45 (0.85-2.49)	0.17
Definite-or- probable ST	3 (1.4)	2 (0.9)		0.66 (0.11-3.93)	0.64	0.54 (0.07-3.96)	0.55	3 (0.5)	3 (0.4)	0.98 (0.20-4.86)	0.98	1.18 (0.20-6.76)	0.86
Definite ST	2 (0.95)	2 (0.9)		0.98 (0.14- 6.98)	0.99	0.76 (0.09- 6.74)	0.80	1 (0.2)	3 (0.4)	2.94 (0.31- 28.26)	0.33	3.71 (0.34-40.71)	0.28

Values are n (%). Analyses based on Kaplan-Meier method, implying that patients who died, withdrew consent or were lost were censored at exact moments of dropout. Therefore, percentages may differ slightly from results of straightforward calculations. Abbreviations: CI = confidence interval; CP = clotidogrel period; HBR = high bleeding risk; HR = hazard ratio; MI = myocardial infarction; NACCE = net adverse clinical and cerebral events; ST = stent thrombosis; TP = ticagrelor period.

HIGH BLEEDING RISK PATIENTS
TREATED WITH VERY THIN-STRUT
BIODEGRADABLE POLYMER OR
THIN-STRUT DURABLE POLYMER
DRUG-ELUTING STENTS IN
THE BIO-RESORT TRIAL

5

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ABSTRACT

Purpose: Patients with high bleeding risk (HBR) who undergo percutaneous coronary intervention also have an increased risk of ischemic events and represent an overall high-risk population. The coating of durable polymer drug-eluting stents (DP-DES) may induce inflammation and delay arterial healing, which might be reduced by novel biodegradable polymer DES (BP-DES). We aimed to evaluate the safety and efficacy of treating HBR patients with very thin-strut BP-DES versus thin-strut DP-DES.

Methods: Participants in BIO-RESORT (NCT01674803), an investigator-initiated multicenter, randomized all-comers trial, were treated with very thin-strut BP-DES (Synergy or Orsiro) or thin-strut DP-DES (Resolute Integrity). For the present analysis, patients were classified following HBR criteria based on previous trials. The primary endpoint was target vessel failure: a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization at 1 year.

Results: Of all 3514 patients, 1009 (28.7%) had HBR. HBR patients were older ($p < 0.001$) and had more co-morbidities than non-HBR patients ($p < 0.001$). At 1-year follow-up, HBR patients had significantly higher rates of target vessel failure (6.7 vs. 4.2%, $p = 0.003$), cardiac death (1.9 vs. 0.4%, $p < 0.001$), and major bleeding (3.3 vs. 1.5%, $p = 0.001$). Of all 1009 HBR patients, 673 (66.7%) received BP-DES and 336 (33.3%) had DP-DES. The primary endpoint was met by 43/673 (6.5%) patients treated with BP-DES and 24/336 (7.3%) treated with DP-DES (HR 0.88 [95%CI 0.54–1.46], $p = 0.63$). There were no significant between-group differences in the most global patient-oriented clinical endpoint (9.7 vs. 10.5%, HR 0.92 [95%CI 0.61–1.39], $p = 0.69$) and other secondary endpoints.

Conclusions: At 1-year follow-up, very thin-strut BP-DES showed similar safety and efficacy for treating HBR patients as thin-strut DP-DES.

INTRODUCTION

Most patients undergoing percutaneous coronary intervention (PCI) are currently treated with drug-eluting stents (DES) that elute an antiproliferative drug from their coating.^{1,2} But the life-long presence of durable polymers (DP) on the metallic stent struts may induce vessel wall inflammation and delay arterial healing, which can result in adverse clinical events such as stent thrombosis or myocardial infarction (MI).³

Novel very thin-strut biodegradable polymer DES (BP-DES) were designed to overcome these limitations of DP-DES and merely leave a bare metal stent in place after the polymer has been absorbed.^{1,2} International guidelines recommend the use of contemporary DES over first-generation DES and bare metal stents in all patients undergoing PCI.⁴ There is no preference for newer-generation BP-DES over DP-DES, as both DES groups have shown to improve clinical outcome as compared to first-generation DES and bare metal stents. Despite the theoretical advantage of BP-DES, meta-analyses of clinical trials showed no unequivocal benefit of BP-DES over contemporary DP-DES,⁵⁻⁸ but there might still be an advantage for BP-DES in high-risk subgroups. Patients who are at high bleeding risk (HBR) may represent such a patient population.

In clinical practice, a substantial proportion of PCI patients are at HBR.^{9,10} They also have an increased risk of *ischemic* events and thus, represent a population with an **overall high risk** of adverse clinical outcome.¹¹ Comparative studies of HBR patients treated with BP-DES versus DP-DES are lacking, and potential benefits of BP-DES for treating this high-risk subgroup are undetermined. Therefore, in the present study, we analyzed the clinical outcome data at 1-year follow-up of the largescale BIO-RESORT randomized all-comer trial¹² to evaluate in HBR patients the safety and efficacy of PCI with very thin-strut BP-DES versus thin-strut DP-DES.

MATERIALS AND METHODS

Study Design and Population

The present study is an explorative analysis of the BIORESORT trial (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All-Comers Population) [TWENTE III].¹² The study design and population, as well as the main 1-year results have been published previously.^{12,13} In brief, BIORESORT (ClinicalTrials.gov: NCT01674803) is an investigator-initiated, multicenter, randomized controlled trial in 3514 all-comers who were treated with PCI. The study was performed at four clinical sites in the Netherlands (Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede;

Rijnstate Hospital, Arnhem; Haga Hospital, The Hague; Albert Schweitzer Hospital, Dordrecht). Patients were eligible if they were 18 years or older, capable of providing informed consent, and required a PCI with DES implantation according to clinical guidelines or the operators' judgment. All coronary syndromes were permitted and there was no limit for the number of lesions to be treated or for lesion characteristics. Only few exclusion criteria were applied.¹³ Web-based computer-generated allocation sequences randomly assigned study participants in a 1:1:1 fashion to treatment with a very thin-strut, biodegradable polymer everolimus-eluting stent (Synergy; Boston Scientific, Natick, MA, USA), a very thin-strut, biodegradable polymer sirolimus-eluting stent (Orsiro; Biotronik AG, Bülach, Switzerland), or a thin-strut, durable polymer zotarolimus-eluting stent (Resolute Integrity; Medtronic, Santa Rosa, CA, USA). For the present analysis, HBR patients treated with BP-DES (i.e., Synergy and Orsiro) were compared to patients treated with DP-DES (i.e., Resolute Integrity). Dual antiplatelet therapy was generally prescribed for 6–12 months, according to international and local guidelines. The only exception was patients on oral anticoagulation therapy, in whom aspirin was usually discontinued after 1–6 months, while clopidogrel was often prescribed for 1 year. The trial complied with the CONSORT 2010 Statement and Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centers. All trial participants provided written informed consent.

As there is no generally accepted definition of HBR for patients with coronary artery disease who undergo PCI, we applied the vast majority of HBR criteria applied in previous HBR studies,^{10,14,15} using data available in the BIO-RESORT study database. Patients in the present analysis were classified as HBR if they fulfilled at least one of the following criteria: (1) age $\geq$ 75 years; (2) current use of oral anticoagulation therapy; (3) hemoglobin $<$ 11 g/dl; (4) platelet count $<$ 100,000/mm³; (5) previous gastro-intestinal bleeding within last 12 months before the index procedure; (6) previous stroke within 12 months before the index procedure; (7) previous intracranial bleeding; (8) severe renal insufficiency requiring dialysis; (9) current use of nonsteroidal anti-inflammatory drugs. As (10) planned major surgery in the next 6 months after the index PCI had been an exclusion criterion of the BIO-RESORT trial, none of the BIO-RESORT patients fulfilled this criterion. In contrast to the previous HBR trials, we did not have information of previously diagnosed malignancy and severe liver disease (e.g., cirrhosis) available in our database, and therefore, we might have missed some of these HBR patients. However, if patients with severe liver disease had reduced levels of hemoglobin or platelet count, they anyway were classified as HBR.

Follow-Up

One-year clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone or medical questionnaire. Trial coordination and data management were performed by the clinical research organization Cardiovascular Research and Education (CRE, Enschede, the Netherlands). Data monitoring and independent clinical event adjudication were performed by an independent clinical research organization (Diagram, Zwolle, the Netherlands).

Definitions of Clinical Endpoints

All clinical endpoints were pre-specified and defined according to the Academic Research Consortium (ARC) criteria^{16,17} The primary endpoint of this study was the 1-year rate of target vessel failure (TVF), a composite of cardiac death, target vessel-related MI, or clinically indicated target vessel revascularization. Death was considered as cardiac unless an unequivocal non-cardiac cause could be established. Secondary endpoints included any death, any MI, target lesion failure (TLF, a composite of cardiac death, target lesion-related MI, or clinically indicated target lesion revascularization), major adverse cardiac events (MACE, a composite of any death, any MI, emergent coronary bypass revascularization, or clinically indicated target lesion revascularization), the most global patient-oriented composite endpoint (POCE, a composite of any death, any MI, or any revascularization), stent thrombosis, and major bleeding. The latter was defined as any Bleeding Academic Research Consortium (BARC) type 3 or 5 and/or Thrombolysis in Myocardial Infarction (TIMI) major bleeding (i.e., including coronary artery bypass grafting-related major bleeding).^{18,19}

Statistical Analysis

Continuous data are reported as mean $\pm$ standard deviation and categorical data as numbers and percentages. Student's t test and Chi-square test (or Fisher's exact test, as appropriate) were used to compare differences in baseline characteristics. Time to clinical endpoints was calculated using Kaplan-Meier analyses, and the log-rank test was applied for between-group comparisons. Hazard ratios were computed using Cox proportional hazard regression analyses. We used logistic regression for interaction between subgroups and treatment with regard to the primary endpoint in analogy with the BIO-RESORT trial.¹² All p values are two-sided and considered significant if being <0.05 . Data analysis was performed with SPSS, Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Between December 21, 2012 and August 24, 2015, a total of 3514 patients were included in the BIO-RESORT trial. Of all study participants, 1009 (28.7%) were classified as HBR and 2505 (71.3%) as non-HBR (Fig. 1). Follow-up at 1 year was available in 996 (98.8%) of all HBR patients (1 lost to follow-up, 11 consent withdrawals). Outcome data were used until the time of consent withdrawal.

High Bleeding Risk Versus Non-high Bleeding Risk Patients

HBR patients were significantly older than non-HBR and had significantly more comorbidities (Supplementary Table 1). Proportions of all individual HBR criteria are displayed in Table 1. All 1009 HBR patients met a total of 1246 HBR criteria; 798 (79.1%) met 1 HBR criterion, 188 (18.6%) met 2 HBR criteria, and 23 (2.3%) met ≥ 3 HBR criteria. Of all HBR criteria, the most often met criteria were an age ≥ 75 years (50.6%) and the use of oral anticoagulation therapy (30.3%). HBR patients met on average 1.2 HBR criteria. Dual antiplatelet therapy containing aspirin and one of the more potent P2Y₁₂ inhibitors (i.e., ticagrelor or prasugrel) was significantly less often prescribed in HBR patients (Supplementary Table 1).

The Supplementary Table 2 presents the clinical follow-up data for HBR patients versus non-HBR patients. The rate of TVF was significantly higher in HBR patients versus non-HBR patients (6.7 vs. 4.2%, HR 1.59 [95% CI 1.17–2.17], $p = 0.003$). The rates of any death, cardiac death, TLF, MACE, POCE, and major bleeding were also higher in HBR patients (all p values ≤ 0.001). There was no statistically significant difference in the rates of MI, target vessel revascularization, target lesion revascularization, and stent thrombosis.

High Bleeding Risk Patients Stratified for BP-DES Versus DP-DES

Of all 1009 HBR patients, 673 (66.7%) received BPDES, and 336 (33.3%) received DP-DES. There were no significant between-group differences in baseline characteristics for HBR patients treated with BP-DES versus DP-DES, except for a somewhat higher body mass index in the BP-DES group (27.5 vs. 26.8, $p = 0.01$, Table 2). HBR criteria were similar for both stent groups (Table 1), and there was no statistically significant between-group difference in medication at discharge (Table 2). After 1 year, in both groups, similar proportions of patients were on dual antiplatelet therapy or on oral anticoagulation therapy plus P2Y₁₂ inhibitor.

Table 3 presents the clinical outcome data of HBR patients treated with BP-DES versus DP-DES. The primary clinical endpoint TVF was reached in 43/673 (6.5%) HBR patients treated with BP-DES and 24/336 (7.3%) treated with DP-DES (HR 0.88 [95% CI 0.54–

1.46], $p = 0.63$, Fig. 2). The results for the primary endpoint were consistent in various subgroups, except for multivessel treatment (Supplementary Fig. 1). Between BP-DES and DP-DES groups, there was also no significant difference in the following secondary endpoints: any death (3.3 vs. 4.8%, $p = 0.23$); cardiac death (1.8 vs. 2.1%, $p = 0.73$); target vessel MI (2.7 vs. 3.3%, $p = 0.58$); TVR (2.3 vs. 3.0%, $p = 0.46$); TLF (6.1 vs. 5.7%, $p = 0.81$); TLR (2.0 vs. 0.9%, $p = 0.22$); MACE (7.6 vs. 8.1%, $p = 0.77$); POCE (9.7 vs. 10.5%, $p = 0.69$); definite or probable stent thrombosis (0.5 vs. 0.6%, $p = 0.75$); and major bleeding (3.3 vs. 3.1%, $p = 0.84$).

Of all HBR patients in the BP-DES group, 336/673 (49.9%) were treated with Synergy everolimus-eluting stents, and 337/673 (50.1%) were treated with Orsiro sirolimus-eluting stents. Comparison of patients treated with both individual BP-DES versus patients treated with Resolute Integrity DP-DES showed similar results for TVF and all secondary clinical endpoints (Fig. 3, Table 4). In addition, there was no significant difference in clinical outcome between patients treated with Synergy versus Orsiro BP-DES.

FIGURE 1. Study flow chart. Abbreviations: BP-DES = biodegradable polymer drug-eluting stent; DP-DES = durable polymer drug-eluting stent; HBR = high bleeding risk

TABLE 1. HBR criteria for all patients and stratified for patients treated with BP-DES versus DP-DES.

	HBR population N = 1009			
	All HBR patients N = 1009	BP-DES N = 673	DP-DES N = 336	<i>p</i> <i>value</i>
Age ≥ 75 years	631 (62.5)	423 (62.9)	208 (61.9)	0.77
Current use of oral anticoagulation	377 (37.4)	260 (38.6)	117 (34.8)	0.24
Hemoglobin <11 g/dl	91 (9.0)	58 (8.6)	33 (9.8)	0.53
Platelet count <100,000 mm³	11 (1.1)	7 (1.0)	4 (1.2)	0.83
Previous GI-bleeding (within 12 months)	8 (0.8)	4 (0.6)	4 (1.2)	0.31
Previous stroke (within 12 months)	14 (1.4)	9 (1.3)	5 (1.5)	0.85
Previous intracranial hemorrhage (ever)	5 (0.5)	3 (0.4)	2 (0.6)	0.75
Severe renal insufficiency requiring dialysis	10 (1.0)	5 (0.7)	5 (1.5)	0.26
Current use of NSAID	99 (9.8)	58 (8.6)	41 (12.2)	0.07

Values are n (%) or mean ± SD BP-DES biodegradable polymer drug-eluting stent, DP-DES durable polymer drug-eluting stent, GI gastro-intestinal, HBR high bleeding risk, NSAID non-steroidal anti-inflammatory drug.

DISCUSSION

Almost 30% of the PCI all-comers who participated in the BIO-RESORT trial were at HBR. At 1-year follow-up of this large population of HBR patients, PCI with two very thin-strut BP-DES showed similar safety and efficacy as treatment with a contemporary thin-strut DP-DES. There was no significant between-group difference in the rate of the primary composite endpoint TVF and all prespecified secondary clinical endpoints. Many PCI patients have an increased bleeding risk, but the exact proportion depends on the HBR criteria used and may be higher in patients with acute coronary syndromes. A study that applied similar criteria found a HBR in 42% of patients treated for acute coronary syndromes,⁹ a rate that matches quite well with the 29% in BIORESORT, considering that 30% of the BIO-RESORT all-comers had stable coronary disease. Our results confirm the overall high adverse event risk of HBR patients.^{11,15,20}

FIGURE 2. One-year clinical outcomes of HBR patients stratified for treatment with BP-DES versus DP-DES. Kaplan-Meier curves for the primary composite endpoint target vessel failure (a) and the individual components thereof: cardiac death (b), target vessel myocardial infarction (c), and target vessel revascularization (d). Abbreviations: BP-DES = biodegradable polymer drug-eluting stent; DP-DES = durable polymer drug-eluting stent; HBR = high bleeding risk.

So far, no study compared BP-DES and DP-DES specifically in HBR patients. Only two dedicated stent trials assessed HBR patients, comparing polymer-free biolimus A9-coated stent (BioFreedom; Biosensors Europe)¹⁴ or early-generation zotarolimus-eluting DP-DES (Endeavor; Medtronic, USA)¹⁵ with bare metal stents that formerly were used to minimize DAPT duration. The novel stents improved clinical outcome in both trials that applied an abbreviated DAPT regimen of 1 month. Based on these results, guidelines currently recommend DES over bare metal stents in all patients.⁴ In our HBR patients, event rates were lower than in the drug-coated stent arm of LEADERS FREE¹⁴ for: death (all-cause: 3.8 versus 8.0%; cardiac: 1.4 versus 4.2%); MI (any: 2.9 versus 6.1%); revascularization (TLR: 1.6 versus 5.1%; TVR: 2.1 versus 5.8%); stent thrombosis (definite or probable: 0.5 versus 2.2%); and major bleeding (3.3 versus 7.2%).¹⁴ These differences may be explained by dissimilarities in: (1) follow-up duration (360 versus 390 days); (2) MI definitions (extended historical ARC versus third universal definition); (3) DAPT duration (almost two thirds of BIO-RESORT HBR patients still on DAPT after 1 year versus 1 month DAPT in LEADERS FREE); (4) strut thickness (uncoated, 60–91 versus 120 μ m) which might be

TABLE 2. Baseline characteristics of HBR patients stratified for treatment with BP-DES versus DP-DES.

	HBR population N = 1009		
	BP-DES N = 673	DP-DES N = 336	<i>p log- rank</i>
Age (years)	73.7 ± 9.1	73.4 ± 8.9	0.63
Men	414 (61.5)	217 (64.6)	0.34
Body Mass index (kg/m²)	27.5 ± 4.3	26.8 ± 3.7	0.01
Current smoker	104 (16.1)	65 (20.1)	0.13
Family history of coronary artery disease	230 (36.6)	108 (34.0)	0.43
Diabetes Mellitus	159 (23.6)	81 (24.1)	0.87
Hypertension	372 (55.3)	191 (56.8)	0.64
Hypercholesterolemia	259 (38.5)	140 (41.7)	0.33
Previous MI	140 (20.8)	83 (24.7)	0.16
Previous stroke	67 (10.0)	45 (13.4)	0.10
Previous PCI	157 (23.3)	72 (21.4)	0.50
Previous CABG	89 (13.2)	49 (14.6)	0.55
Previous GI-bleeding	19 (2.8)	9 (2.7)	0.90
<i>Clinical presentation</i>			
ST-elevation MI	185 (27.5)	68 (20.2)	0.06
Non-ST-elevation MI	135 (20.1)	84 (25.0)	
Unstable angina	128 (19.0)	70 (20.8)	
Stable angina	225 (33.4)	114 (33.9)	
Acute coronary syndrome	448 (66.6)	222 (66.1)	0.88
Lesion/procedural characteristics			
<i>No. of lesions treated per pt.</i>			
One	488 (72.5)	228 (67.9)	0.13
Two or more	185 (27.5)	108 (32.1)	
<i>Vascular access site</i>			
Radial	229 (44.4)	159 (47.3)	0.38
Femoral	374 (55.6)	177 (52.7)	
<i>Treated coronary vessels</i>			
Right coronary artery	248 (36.8)	144 (42.9)	0.07
Left anterior descending artery	308 (45.8)	153 (45.5)	0.95
Circumflex artery	201 (29.9)	95 (28.3)	0.60
Left main	23 (3.4)	11 (3.3)	0.91
Graft	25 (3.7)	19 (5.7)	0.16
At least one in-stent restenosis	16 (2.4)	13 (3.9)	0.18
At least one small-vessel*	400 (59.4)	187 (55.7)	0.25

TABLE 2. Continued.

	HBR population N = 1009		
	BP-DES N = 673	DP-DES N = 336	<i>p log- rank</i>
At least one lesion length >27 mm	203 (30.2)	107 (31.8)	0.59
Discharge medication			
Dual antiplatelet therapy	618 (91.8)	308 (91.7)	0.93
with clopidogrel	402 (59.7)	209 (62.2)	0.45
with ticagrelor/prasugrel	216 (32.1)	99 (29.5)	0.40
Oral anticoagulation + P2Y₁₂ inhibitor	259 (38.5)	115 (34.2)	0.19
Proton pump inhibitor	490 (72.8)	237 (70.5)	0.49
1-year medication	N = 644	N = 315	
Dual antiplatelet therapy	402 (62.4)	205 (65.1)	0.30
with clopidogrel	231 (35.9)	126 (40.0)	0.21
with ticagrelor/prasugrel	171 (26.6)	79 (25.1)	0.63
Oral anticoagulation + P2Y₁₂ inhibitor	213 (33.1)	92 (29.2)	0.23

Values are n (%) or mean ± SD. *All lesions with a reference vessel-diameter of ≤ 2.75 mm were considered to be small-vessels. CABG coronary artery bypass graft, MI myocardial infarction, PCI percutaneous coronary intervention. Other as in Table 1.

relevant as thicker struts increase stent thrombosis, restenosis, and reintervention risk that theoretically could have contributed to the higher bleeding rate in LEADERS FREE; (5) the number of HBR criteria per patient (1.2 versus 1.7)¹⁴ In addition, in our HBR patients, event rates were lower than in the zotarolimus-eluting DP-DES arm of the ZEUS trial¹⁵ for: death (all-cause: 3.8 versus 15.8%; cardiac: 1.4 versus 11.8%); revascularization (TLR: 1.6 versus 5.2%; TVR: 2.1 versus 5.9%); and stent thrombosis (definite or probable: 0.5 versus 2.6%). These higher event rates may partly be explained by the higher risks of restenosis and repeat revascularization associated with the use of Endeavor as compared to newer-generation DP-DES,^{21,22} while the very high mortality is related to the old age (80.4 years) in ZEUS participants.¹⁵

Based on the two aforementioned trials,^{14,15} the most recent focused update on DAPT of the European Society of Cardiology²³ recommends an abbreviated DAPT duration of 1 to 6 months in HBR. However, it is unclear whether the advantage of such a shortened DAPT regimen in HBR patients may apply to DES other than used in these two trials. Both BioFreedom and Endeavor stents have never been compared to the three DES used in BIO-RESORT. The thin-strut Resolute Integrity DP-DES is a successor of the

Endeavor DP-DES and has shown excellent short- and long-term clinical outcomes.^{5,24,25} The very thin-strut Synergy BP-DES, which in BIO-RESORT was for the first time assessed in allcomers, previously was shown to be non-inferior to durable polymer everolimus-

FIGURE 3. One-year clinical outcomes of HBR patients stratified for treatment with the three individual drug-eluting stents. Kaplan-Meier curves for the primary composite endpoint target vessel failure (a) and the individual components thereof: cardiac death (b), target vessel myocardial infarction (c), and target vessel revascularization (d). Abbreviations: BP-EES = biodegradable polymer everolimus-eluting stent; BP-SES = biodegradable polymer sirolimus-eluting stent; DPZES = durable polymer zotarolimus-eluting stent; HBR = high bleeding risk

eluting stents in the EVOLVE trials.^{26,27} In addition, Synergy was recently studied in patients ≥ 75 years (i.e., the most common HBR criterion) treated with an abbreviated DAPT regimen in the SENIOR trial.²⁸ In that trial, patients treated with Synergy had lower rates of TLR and ischemic events as compared to bare metal stents. The safety of the device is currently being studied in HBR patients who are treated with DAPT for only 1 month (POEM study, NCT03112707) or 3 months (EVOLVE short DAPT study, NCT02605447). The very thin-strut sirolimus-eluting Orsiro BP-DES has recently shown favorable results versus everolimus-eluting DP-DES.^{29,30} In addition, in the SORT-OUT IX trial (NCT02623140), Orsiro is being compared to the BioFreedom stent, which was

TABLE 3. One-year clinical outcome of HBR patients stratified for treatment with BP-DES versus DP-DES.

	HBR population N = 1009		Hazard Ratio (95% CI)	<i>p log-rank</i>
	BP-DES N = 673	DP-DES N = 336		
Death, any	22 (3.3)	16 (4.8)	0.68 (0.36-1.29)	0.23
Cardiac death	12 (1.8)	7 (2.1)	0.85 (0.33-2.15)	0.73
Myocardial infarction, any	18 (2.7)	11 (3.3)	0.81 (0.38-1.72)	0.58
Target vessel myocardial infarction	18 (2.7)	11 (3.3)	0.81 (0.38-1.72)	0.58
Periprocedural myocardial infarction	14 (2.1)	10 (3.0)	0.70 (0.31-1.57)	0.38
Target vessel revascularization	15 (2.3)	10 (3.0)	0.74 (0.33-1.64)	0.46
Target lesion revascularization	13 (2.0)	3 (0.9)	2.14 (0.61-7.53)	0.22
Target vessel failure*	43 (6.5)	24 (7.3)	0.88 (0.54-1.46)	0.63
Target lesion failure	41 (6.1)	19 (5.7)	1.07 (0.62-1.84)	0.81
Major adverse cardiac events	51 (7.6)	27 (8.1)	0.93 (0.59-1.49)	0.77
Patient-oriented composite endpoint	65 (9.7)	35 (10.5)	0.92 (0.61-1.39)	0.69
Definite stent thrombosis	3 (0.45)	0 (0.0)	-	-
Definite or probable stent thrombosis	3 (0.5)	2 (0.6)	1.34 (0.22-8.02)	0.75
Major bleeding	22 (3.3)	10 (3.1)	1.08 (0.51-2.29)	0.84
Fatal	3 (0.4)	0 (0.0)		
Gastrointestinal	10 (1.5)	5 (1.5)		
Intracranial	3 (0.4)	1 (0.3)		
Other	9 (1.3)	4 (1.2)		

The event rates (expressed as no. and %) were calculated with the use of the Kaplan-Meier method. All target-vessel revascularizations were clinically indicated. *Primary endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization. Abbreviations: as in Tables 1 and 2.

previously tested in LEADERS FREE. Upcoming results of some of the abovementioned trials may reveal the safety of using an abbreviated DAPT regimen in HBR patients treated with a DES, used in the present study.

While the absence of durable polymers in BP-DES may reduce inflammation and promote arterial healing, meta-analyses thus far showed no unequivocal benefit in clinical outcome for broad patient populations treated with BP-DES over DP-DES.^{5–8} Our present study adds to the current knowledge that in HBR patients, who have substantially higher event rates than non-HBR patients, there is also no short-term benefit of BP-DES. Nevertheless, the two BP-DES used in our study differ substantially. The polymer of the Synergy BP-DES is completely resorbed in approximately 4 months, while this process takes approximately 18 months in the Orsiro BP-DES.¹³ Therefore, potential benefits of the Orsiro may only be seen later than after 1 year. As a result, the mid- and long-term results of BIO-RESORT will be of considerable interest. This is even more the case, as participants in this trial generally followed a stringent policy of DAPT discontinuation after 12 months.

Limitations

The results of this analysis should be considered hypothesis generating, and the study was not powered to detect differences in rare clinical events such as stent thrombosis. As there is no general HBR definition, we followed criteria applied in previous HBR trials, using data available in the database of the randomized BIO-RESORT trial. In contrast to the previous HBR trials, we had no information of previously diagnosed malignancy and severe liver disease available in our database, and therefore, we might have missed some HBR patients. However, if patients with severe liver disease had reduced levels of hemoglobin or platelet count, they anyway were classified as HBR. Furthermore, we used requirement of dialysis as parameter of severe renal insufficiency rather than a creatinine clearance < 40 cc/min/1.73 m². While this might have lowered the mean number of HBR criteria per patient, many patients with a creatinine clearance below that threshold may have been 75 years or older and, thus, anyway classified as HBR (based on their age). Nevertheless, these minor differences in HBR criteria make it somewhat difficult to compare our results with previous HBR studies. Despite high follow-up rates, and independent monitoring and event adjudication, the event rates were relatively low.

TABLE 4. One-year clinical outcome of HBR patients treated with BP-EES, BP-SES, or DP-ZES.

	HBR population N = 1009			<i>p log-rank</i>		
	BP-EES N = 336	DP-ZES N = 336	BP-SES N = 337	BP-EES vs. DP-ZES	BP-SES vs. DP-ZES	BP-EES vs. BP-SES
Death, any	13 (3.9)	16 (4.8)	9 (2.7)	0.57	0.14	0.36
Cardiac death	7 (2.1)	7 (2.1)	5 (1.5)	0.99	0.54	0.54
Myocardial infarction, any	10 (3.0)	11 (3.3)	8 (2.4)	0.82	0.47	0.63
Target vessel myocardial infarction	10 (3.0)	11 (3.3)	8 (2.4)	0.82	0.47	0.63
Periprocedural myocardial infarction	8 (2.4)	10 (3.0)	6 (1.8)	0.63	0.31	0.59
Target vessel revascularization	7 (2.2)	10 (3.0)	8 (2.4)	0.46	0.59	0.83
Target lesion revascularization	6 (1.8)	3 (0.9)	7 (2.1)	0.32	0.22	0.81
Target vessel failure*	23 (6.9)	24 (7.3)	20 (6.0)	0.87	0.49	0.60
Target lesion failure	22 (6.6)	19 (5.7)	19 (5.7)	0.64	0.95	0.60
Major adverse cardiac events	28 (8.4)	27 (8.1)	23 (6.8)	0.90	0.52	0.44
Patient-oriented composite endpoint	31 (9.3)	35 (10.5)	34 (10.1)	0.61	0.85	0.75
Definite stent thrombosis	2 (0.6)	0 (0.0)	1 (0.3)	0.16	0.32	0.56
Definite or probable stent thrombosis	2 (0.6)	2 (0.6)	1 (0.3)	0.99	0.56	0.56
Any bleeding	14 (4.3)	15 (4.6)	14 (4.2)	0.84	0.80	0.96
Major bleeding	12 (3.7)	10 (3.1)	10 (3.0)	0.68	0.96	0.64
Fatal	3 (0.9)	0 (0.0)	0 (0.0)			
Gastrointestinal	5 (1.5)	5 (1.5)	5 (1.5)			
Intracranial	1 (0.3)	1 (0.3)	2 (0.6)			
Other	6 (1.8)	4 (1.2)	3 (0.9)			

The event rates (expressed as no. and %) were calculated with the use of the Kaplan-Meier method. All target-vessel revascularizations were clinically indicated. *Primary endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization BP-EES biodegradable polymer everolimus-eluting stent, BP-SES biodegradable polymer sirolimus-eluting stent, DP-ZES durable polymer zotarolimus-eluting stent. Other as in Table 1.

CONCLUSIONS

At 1-year follow-up, very thin-strut BP-DES showed similar safety and efficacy for treating HBR patients as thin-strut DP-DES. Further follow-up assessment of these high-risk patients is required to evaluate the presence or absence of long-term benefits of BP-DES over DP-DES.

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CONFLICTS OF INTEREST

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SUPPLEMENTAL MATERIAL

SUPPLEMENTARY FIGURE 1. Subgroup analysis of high bleeding risk patients for the primary endpoint target vessel failure.

SUPPLEMENTARY TABLE 1. Baseline characteristics stratified for HBR and non-HBR patients.

	Total population N = 3514		
	HBR N = 1009	Non-HBR N = 2505	p value
Age (years)	73.6 ± 9.1	60.1 ± 8.8	<0.001
Men	631 (62.5)	1916 (76.5)	<0.001
Body Mass Index (kg/m²)	27.3 ± 4.2	27.5 ± 4.1	0.22
Current smoker	169/969 (17.4)	862/2453 (35.1)	<0.001
Family history of coronary artery disease	338/947 (35.7)	1219/2425 (50.3)	<0.001
Diabetes mellitus	240 (23.8)	384 (15.3)	<0.001
Hypertension	563 (55.8)	1061 (42.4)	<0.001
Hypercholesterolemia	399 (39.5)	936 (37.4)	0.23
Previous MI	223 (22.1)	426 (17.0)	<0.001
Previous stroke	112 (11.1)	119 (4.8)	<0.001
Previous PCI	229 (22.7)	397 (15.8)	<0.001
Previous CABG	138 (13.7)	129 (5.1)	<0.001
Previous GI-bleeding	28 (2.8)	26 (1.0)	<0.001
Clinical presentation			
ST-elevation MI	253 (25.1)	820 (32.7)	<0.001
Non-ST-elevation MI	219 (21.7)	537 (21.4)	
Unstable angina	198 (19.6)	422 (16.8)	
Stable angina	339 (33.6)	726 (29.0)	
Acute coronary syndrome	670 (66.4)	1779 (71.0)	<0.01
Lesion/procedural characteristics			
No. of lesions treated per pt.			
One	716 (71.0)	1864 (74.4)	0.08
Two or more	293 (29.0)	641 (25.6)	
Vascular access site			
Radial	458 (45.4)	1139 (45.5)	0.97
Femoral	551 (54.6)	1366 (54.5)	
Treated coronary vessels			
Right coronary artery	392 (38.9)	945 (37.7)	0.53
Left anterior descending artery	461 (45.7)	1258 (50.2)	0.02
Circumflex artery	296 (29.3)	708 (28.3)	0.52
Left main	34 (3.4)	42 (1.7)	0.002
Graft	44 (4.4)	26 (1.0)	<0.001
At least one in-stent restenosis	29 (2.9)	60 (2.4)	0.41
At least one small-vessel*	587 (58.2)	1491 (59.5)	0.46

SUPPLEMENTARY TABLE 1. Continued.

	Total population N = 3514		
	HBR N = 1009	Non-HBR N = 2505	p value
At least one lesion length > 27mm	310 (30.7)	763 (30.5)	0.88
Randomized Stent			
Orsiro	337 (33.4)	832 (33.2)	0.99
Resolute Integrity	336 (33.3)	837 (33.4)	
Synergy	336 (33.3)	836 (33.4)	
Biodegradable polymer stent	673 (66.7)	1668 (66.6)	0.95
Discharge medication			
Dual antiplatelet therapy	926 (91.8)	2493 (99.5)	<0.001
with clopidogrel	611 (60.6)	1184 (47.3)	<0.001
with ticagrelor/prasugrel	315 (31.2)	1309 (52.3)	<0.001
Oral anticoagulation + P2Y₁₂ inhibitor	374 (37.1)	-	-
Proton pump inhibitor	727 (72.1)	1285 (51.3)	<0.001
1-year medication	N = 959	N = 2473	
Dual antiplatelet therapy	607 (63.3)	2332 (94.3)	<0.001
with clopidogrel	357 (37.2)	1171 (47.4)	<0.001
with ticagrelor/prasugrel	250 (26.1)	1161 (46.9)	<0.001
Oral anticoagulation + P2Y₁₂ inhibitor	305 (31.8)	50 (2.0)	<0.001

Values are n (%) or mean $\pm$ SD. * All lesions with a reference vessel-diameter of $\leq$ 2.75 mm were considered to be small-vessels. Abbreviations: CABG coronary artery bypass grafting; GI gastro-intestinal; HBR high bleeding risk; MI myocardial infarction; PCI percutaneous coronary intervention.

SUPPLEMENTARY TABLE 2. One-year clinical outcome stratified for HBR and non-HBR patients.

	Total population		Hazard Ratio (95% CI)	<i>p</i> log- rank
	HBR N = 1009	Non-HBR N = 2505		
Death, any	38 (3.8)	20 (0.8)	4.82 (2.80-8.28)	<0.001
Cardiac death	19 (1.9)	11 (0.4)	4.36 (2.08-9.16)	<0.001
Myocardial infarction, any	29 (2.9)	56 (2.2)	1.29 (0.82-2.02)	0.26
Target vessel myocardial infarction	29 (2.9)	53 (2.1)	1.36 (0.87-2.14)	0.18
Periprocedural myocardial infarction	24 (2.4)	43 (1.7)	1.38 (0.84-2.28)	0.20
Target vessel revascularization	25 (2.5)	54 (2.1)	1.18 (0.73-1.89)	0.51
Target lesion revascularization	16 (1.6)	36 (1.4)	1.13 (0.63-2.03)	0.69
Target vessel failure*	67 (6.7)	106 (4.2)	1.59 (1.17-2.17)	0.003
Target lesion failure	60 (6.0)	89 (3.6)	1.70 (1.22-2.36)	0.001
Major adverse cardiac events	78 (7.8)	101 (4.0)	1.95 (1.45-2.62)	<0.001
Patient-oriented composite endpoint	100 (10.0)	158 (6.3)	1.60 (1.25-2.06)	<0.001
Definite stent thrombosis	3 (0.3)	8 (0.3)	0.94 (0.25-3.55)	0.93
Definite or probable stent thrombosis	5 (0.5)	11 (0.4)	1.14 (0.40-3.29)	0.81
Major Bleeding	32 (3.3)	37 (1.5)	2.27 (1.41-3.66)	0.001
Fatal	3 (0.3)	1 (<0.1)		

The event rates (expressed as no. and %) were calculated with the use of the Kaplan-Meier method. All target-vessel revascularizations were clinically indicated. * Primary endpoint of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization. Abbreviations: CI confidence interval. HBR high bleeding risk.

TWO-YEAR CLINICAL OUTCOME OF
ALL-COMERS TREATED WITH
THREE HIGHLY DISSIMILAR
CONTEMPORARY CORONARY
DRUG-ELUTING STENTS IN THE
RANDOMISED BIO-RESORT TRIAL

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ABSTRACT

Background: The aim of the study was to evaluate the two-year clinical outcome of all-comer trial participants who were treated with two very different thin-strut biodegradable polymer versus thin-strut durable polymer drug-eluting stents (DES). Prolonged clinical outcome after discontinuation of dual antiplatelet therapy is of particular interest, given the highly dissimilar polymer types, amount, distribution, and degradation speed of both biodegradable polymer DES.

Methods and results: The BIO-RESORT trial (NCT01674803) randomly assigned 3,514 patients to treatment with biodegradable polymer SYNERGY everolimus-eluting stents (EES) or Orsiro sirolimus-eluting stents (SES), or durable polymer Resolute Integrity zotarolimus-eluting stents (ZES). At two-year follow-up (available in 98.8%), the rate of the primary composite endpoint target vessel failure (TVF) was 8.3% in ZES versus 6.8% in EES ($p=0.19$) and 6.6% in SES ($p=0.12$). Landmark analyses at one year revealed differences between SES and ZES in the rates of target lesion revascularisation and target lesion failure (0.6% vs. 1.5%, $p=0.04$, and 1.1% vs. 2.4%, $p=0.02$, respectively) as well as other composite secondary endpoints that reached statistical significance.

Conclusions: At two-year follow-up, there was no significant between-DES difference in the rates of the primary endpoint. Landmark analyses provided a signal that the use of SES versus ZES might reduce the risk of repeat revascularisation after one-year follow-up.

INTRODUCTION

The lifelong presence of durable polymer-coated drug-eluting stents in coronary arteries has been associated with chronic inflammation, delayed arterial healing, and neoatherosclerosis, which may result in late adverse clinical events.¹ New-generation biodegradable polymer DES were designed to overcome these limitations by providing the antiproliferative benefits of durable polymer DES combined with the long-term safety of bare metal stents due to the absence of polymer residues.² The early-generation biodegradable polymer DES had thick struts and, in a large all-comers trial, showed similar efficacy and somewhat better long-term safety as compared to early-generation thick-strut durable polymer DES.^{2,3} Novel biodegradable polymer DES have uncoated struts that are up to half as thick.

These very thin-strut biodegradable polymer DES have flexible designs and thin, refined coatings⁴ to accelerate re-endothelialisation and reduce the risk of ischaemic coronary events. The rapid resorption of the abluminal polymer in SYNERGY™ everolimus-eluting stents (EES) (Boston Scientific, Marlborough, MA, USA) results in a bare metal platform within four months, while the encompassing polymer coating of the Orsiro sirolimus-eluting stent (SES) (Biotronik, Bülach, Switzerland) is slowly degraded within approximately 18 months.⁵ The one-year follow-up of the randomised BIORESORT trial demonstrated non-inferiority of both biodegradable polymer DES versus Resolute Integrity® zotarolimus-eluting stents (ZES) (Medtronic, Santa Rosa, CA, USA) in 3,514 all-comer patients, but there was no short-term advantage.⁶ Nevertheless, biodegradable polymer DES might still improve midterm or long-term outcomes.

Clinical outcome after discontinuation of dual antiplatelet therapy (DAPT) is of particular interest, given the highly dissimilar polymer types, amount, distribution, and degradation speed of the two biodegradable polymer DES tested. In the present study, DAPT was prescribed for 12 months in most patients and then stringently discontinued. Notably, BIO-RESORT is 1) the first randomised trial to assess both the biodegradable polymer SYNERGY and Orsiro stents, and 2) the first randomised trial to test SYNERGY EES in all-comers.⁶ In the present study, we assessed the two-year clinical outcome of the BIO-RESORT allcomers who were treated with EES and SES versus ZES and followed a stringent DAPT discontinuation policy after one year.

METHODS

Study design and patients

The investigator-initiated, multicentre randomised BIO-RESORT trial (TWENTE III) enrolled all-comers requiring percutaneous coronary intervention (PCI) with DES at four sites in the Netherlands (Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede; Rijnstate Hospital, Arnhem; Haga Hospital, The Hague; Albert Schweitzer Hospital, Dordrecht).^{5,6} In this three-arm clinical trial (ClinicalTrials.gov Identifier: NCT01674803), patients were randomly (1:1:1) assigned to either a platinum-chromium EES (SYNERGY), a cobalt-chromium SES (Orsiro), or a new-generation thin-strut ZES (Resolute Integrity). All coronary syndromes, de novo and restenotic lesions, and coronary or bypass lesions were permitted. There was no limit for lesion length, reference vessel size, and number of lesions or vessels to be treated. The study design has been described previously.^{5,6}

The trial complied with the CONSORT 2010 Statement and the Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centres. All patients provided written informed consent.

Procedures and follow-up

Treatment was performed according to current medical guidelines and the physician's judgement.⁶ Lesion predilation, direct stenting and stent post-dilation were left to the operator's discretion. The SYNERGY stent elutes everolimus within three months from a 4 µm biodegradable PLGA (poly[lactic-co-glycolic acid]) coating that is located only on the abluminal side of 74 µm/79 µm/81 µm platinum-chromium struts (for stent sizes ≤2.5 mm/3.0-3.5 mm/4.0 mm, respectively) and resorbed within four months^{5,7}. The sirolimus-eluting Orsiro stent has 60 µm or 80 µm (for stents ≤3.0 mm or >3.0 mm) cobalt-chromium struts that are circumferentially covered by an asymmetrical hybrid coating that is thicker on the abluminal side (7.4/3.5 µm).⁵ Its biodegradable PLLA (poly[L-lactide] acid) elutes the drug within three months, is fully resorbed within 18 months, and covers a thin passive coating of amorphous silicon carbide.⁵ The zotarolimus-eluting Resolute Integrity stent has thin 91 µm cobalt-chromium struts, covered by a 6 µm zotarolimus-eluting blend of three durable polymers.

Clinical follow-up was obtained at visits to outpatient clinics or, if not feasible, by telephone follow-up or medical questionnaire. A clinical research organisation (Cardiovascular Research and Education, Enschede, the Netherlands) coordinated trial and data management.

Clinical endpoints were pre-specified, using definitions of the Academic Research Consortium.^{5,8} The primary composite endpoint of target vessel failure (TVF) assessed device efficacy and patient safety and consisted of cardiac death, target vessel-related myocardial infarction (MI), or clinically indicated target vessel revascularisation. Secondary endpoints included: target lesion revascularisation (TLR), target lesion failure (TLF, a composite of cardiac death, any MI not clearly attributable to a non-target vessel, or clinically driven TLR), major adverse cardiac events (MACE, a composite of all-cause death, any MI, or emergent coronary bypass surgery, or repeat clinically indicated TLR), the most global patient-oriented composite endpoint (POCE, a composite of all-cause death, any MI, or any repeat coronary revascularisation), and definite-or-probable stent thrombosis.

Data monitoring, processing of clinical outcome data, and independent clinical event adjudication were performed by an independent clinical research organisation (Diagram, Zwolle, the Netherlands).

Statistical analysis

Categorical variables were assessed with the chi-square or Fisher's exact test, as appropriate, while continuous variables were assessed with the Student's t-test. The time to primary endpoint and components thereof was assessed according to Kaplan-Meier methods; the log-rank test was applied for between-group comparisons. Hazard ratios were computed using Cox proportional hazards regressions analysis. We performed landmark analyses of the primary endpoint and all secondary endpoints by using the one-year landmark. P-values <0.05 were considered significant. P-values and confidence intervals were two-sided. Statistical analyses were performed with SPSS, Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

From December 2012 to August 2015, a total of 3,514 patients were randomised and assessed at four clinical sites in the Netherlands, of whom 3,472 (98.8%) completed two-year follow-up or had died. Eleven (0.3%) patients were lost to follow-up, and 31 (0.9%) withdrew their consent (censored at the moment of dropout).

Table 1 presents the baseline characteristics of the trial participants, stratified for assigned treatment arms. Most patients presented with acute coronary syndromes (69.7%) and 79.2% of patients had ≥ 1 complex target lesion. At two years, DAPT rates

were low (Table 2). Between stent arms, there were no statistically significant differences in the use of antiplatelet agents and oral anticoagulation therapy.

TABLE 1. Clinical characteristics of patients, lesions, and procedures.

	All patients N=3,514	EES N=1,172	ZES N=1,173	SES N=1,169
Age, yrs	63.9 ± 10.8	64.0 ± 10.7	63.6 ± 10.9	64.2 ± 10.7
Male	2,547 (72.5)	845 (72.1)	848 (72.3)	854 (73.1)
Body mass index (kg/m²)	27.4 ± 4.2	27.6 ± 4.2	27.3 ± 4.0	27.4 ± 4.2
Current smoker—no. (%)	1,031/3,422 (30.1)	336/1,135 (29.6)	354/1,143 (31.0)	341/1,144 (29.8)
Family history of coronary artery disease	1,557/3,372 (46.2)	512/1,114 (46.0)	529/1,138 (46.5)	516/1,120 (46.1)
Diabetes mellitus, medically treated	624 (17.8)	203 (17.3)	210 (17.9)	211 (18.0)
Hypertension	1,624 (46.2)	520 (44.4)	554 (47.2)	550 (47.0)
Hypercholesterolemia	1,335 (38.0)	422 (36.0)	450 (38.4)	463 (39.6)
Previous myocardial infarction	649 (18.5)	192 (16.4)	248 (21.1)	209 (17.9)
Previous stroke	231 (6.6)	74 (6.3)	81 (6.9)	76 (6.5)
Renal insufficiency†	108 (3.1)	29 (2.5)	33 (2.8)	46 (3.9)
Previous percutaneous coronary intervention	626 (17.8)	214 (18.3)	198 (16.9)	214 (18.3)
Previous coronary artery bypass grafting	267 (7.6)	91 (7.8)	96 (8.2)	80 (6.8)
Clinical presentation				
Acute coronary syndrome	2,449 (69.7)	816 (69.6)	815 (69.5)	818 (70.0)
Stable angina	1,065 (30.3)	356 (30.4)	358 (30.5)	351 (30.0)
Lesion characteristics‡				
At least one complex lesion	2,783 (79.2)	903 (77.0)	938 (80.0)	942 (80.6)
At least one bifurcation lesion	1,236 (35.2)	415 (35.4)	409 (34.9)	412 (35.2)
At least one chronic total occlusion	139 (4.0)	44 (3.8)	48 (4.1)	47 (4.0)
At least one bypass graft lesion	70 (2.0)	18 (1.5)	30 (2.6)	22 (1.9)
At least one ostial lesion	252 (7.2)	97 (8.3)	81 (6.9)	74 (6.3)
At least one severely calcified lesion	783 (22.3)	252 (21.5)	265 (22.6)	266 (22.8)

TABLE 1. Continued.

	All patients	EES	ZES	SES
	N=3,514	N=1,172	N=1,173	N=1,169
Procedural characteristics				
Implantation of assigned stents only	3,446 (98.1)	1,155 (98.5)	1,147 (97.8)	1,144 (97.9)
Total stent length per patient—mm	31 (20-50)	32 (20-48)	30 (22-52)	30 (18-49)
Direct stenting	589 (16.8)	208 (17.7)	174 (14.8)	207 (17.7)
Postdilatation	2,833 (80.6)	960 (81.9)	927 (79.0)	946 (80.9)
Multivessel treatment	640 (18.2)	201 (17.2)	220 (18.8)	219 (18.7)
Radial approach	1,597 (45.4)	523 (44.6)	544 (46.4)	530 (45.3)
Fractional Flow Reserve Use	440 (12.5)	147 (12.5)	155 (13.2)	138 (11.8)

Data are n (%) or median (IQR), plus-minus values are means $\pm$ SD. ¶ Defined as an estimated glomerular filtration rate of <30 ml/min/1.73 m² or the need for dialysis. ‡Definitions of lesion characteristics have been reported previously.⁶ EES: everolimus-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

The two-year clinical outcome data are presented in Table 3. At two-year follow-up, the primary endpoint TVF occurred in 79/1,172 (6.8%) patients assigned to EES, 76/1,169 (6.6%) patients assigned to SES, and 96/1,173 (8.3%) patients assigned to ZES. These differences were statistically non-significant for both EES and SES versus ZES ($p=0.19$, and $p=0.12$, respectively). The event rates of TVF and its individual components are displayed in Figure 1. The event rates for the primary endpoint were consistent across subgroups, except for patients who were treated for bypass grafts (Supplementary Table 1A, Supplementary Table 1B). Definite stent thrombosis was an infrequent event that occurred in 7 (0.6%), 5 (0.4%) and 6 (0.5%) patients, respectively. Definite-or-probable stent thrombosis rates were similar among treatment groups (11 [1.0%], 7 [0.6%], and 9 [0.8%], respectively; $p=0.65$ and $p=0.62$) (Table 3, Figure 2).

In landmark analyses between one- and two-year follow-up, patients assigned to SES had, compared to patients assigned to ZES, significantly lower rates of TLR (0.6% vs. 1.5%, $p=0.04$) and TLF (1.1% vs. 2.4%, $p=0.02$) (Table 4, Figure 3). In addition, the rates of the composite endpoints MACE and POCE were significantly lower in SES versus ZES (0.8% vs. 2.2% and 3.2% vs. 5.3%, respectively, both $p=0.01$), while the TVF rate was 1.9% versus 3.0% ($p=0.10$). TLR as well as non-cardiovascular death contributed to the differences in MACE and POCE. A detailed description of the TLR cases is presented in Supplementary Table 2. Landmark analyses between one and two years for TVF and secondary endpoints showed no statistically significant differences for EES versus ZES (Table 4).

TABLE 2. Medication at 1- and 2-year follow-up.

	All patients	EES	ZES	SES	<i>p-value</i>
Medication at 1 year	N=3,432	N=1,142	N=1,146	N=1,144	
Dual antiplatelet therapy	2,939 (85.6)	976 (85.5)	989 (86.3)	974 (85.1)	0.72
with clopidogrel	1,528 (44.5)	500 (43.8)	517 (45.1)	511 (44.7)	0.81
with ticagrelor or prasugrel	1,411 (41.1)	476 (41.7)	472 (41.2)	463 (40.5)	0.84
OAC with P2Y₁₂ inhibitor	355 (10.3)	123 (10.8)	112 (9.8)	120 (10.5)	0.72
Medication at 2 years	N=3,399	N=1,131	N=1,132	N=1,136	
Dual antiplatelet therapy	267 (7.9)	87 (7.7)	103 (9.1)	77 (6.8)	0.12
with clopidogrel	158 (4.6)	51 (4.5)	62 (5.5)	45 (4.0)	0.22
with ticagrelor or prasugrel	109 (3.2)	36 (3.2)	41 (3.6)	32 (2.8)	0.55
OAC with P2Y₁₂ inhibitor	45 (1.3)	20 (1.8)	14 (1.2)	11 (1.0)	0.24

EES: everolimus-eluting stent; OAC: oral anticoagulation therapy; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

DISCUSSION

The present analysis shows that, at two-year follow-up, the rate of the primary endpoint TVF is similar in both very thin-strut biodegradable polymer DES and the reference durable polymer DES. This supports the concept in PCI all-comers that the combination of very thin struts with biodegradable polymers is associated with safety and efficacy which, during the first two years from implantation, are similar to DES with durable polymer coatings.

Landmark analyses revealed lower rates of TLR and several secondary composite endpoints (TLF, MACE, and POCE) in SES versus ZES during the second year of follow-up. This signal of a potentially lower long-term risk of target lesion recurrence following treatment with SES is of interest but should be interpreted cautiously. During the second year of follow-up, the sirolimus has already been eluted for >9 months, while the process of polymer resorption is just finishing. Clinical data suggest that this very slow polymer degradation might be advantageous, potentially by minimising vascular inflammation. In addition, the very high rate of stent post-dilation in >80% of patients could have resulted

in a deeper embedding of the very thin stent struts, which might have contributed to the overall favourable event rates.

FIGURE 1. Kaplan-Meier cumulative event curves for the primary endpoint target vessel failure and its individual components at two-year follow-up. The primary endpoint target vessel failure (A), a composite of cardiac death (B), target vessel-related myocardial infarction (C), or clinically indicated target vessel revascularisation (D).

Potential benefits of the biodegradable polymer DES might be seen no earlier than after several years.^{3,9,10} Clinical event rates after discontinuation of DAPT are of particular interest, given the highly dissimilar polymer types, amount, distribution, and degradation speed of SYNERGY and Orsiro tested in the BIO-RESORT trial. In our study, DAPT was prescribed for 12 months in most patients and then stringently discontinued, as is common practice in the Netherlands. At two-year follow-up, DAPT use was 8%, while in another large-scale randomised DES trial that studied SYNERGY EES the DAPT rate was 47% (Kereiakes DJ et al. Late clinical outcomes after bioresorbable or permanent polymer everolimus-eluting stents: 2-year results from the EVOLVE II randomized trial. Presented at ACC 2017, Washington DC, USA, 17 March 2017).

FIGURE 2. Incidence of definite or probable stent thrombosis at two-year follow-up. Symbols indicate the adverse events associated with stent thrombosis.

Randomised DES studies with Synergy and Orsiro

BIO-RESORT is the first randomised study to examine both SYNERGY and Orsiro biodegradable polymer DES, and the first randomised trial to assess SYNERGY EES in all-comers. This and other randomised trials have demonstrated the short-term safety and efficacy of both novel biodegradable polymer DES, which were found to be similar to established new-generation durable polymer DES.^{6,11} The large-scale EVOLVE II trial examined 1,684 patients with up to moderate clinical risk, treated with SYNERGY EES versus durable polymer platinum-chromium EES, and demonstrated non-inferiority of SYNERGY at one-year follow-up.⁷ The two-year outcome showed similar safety and efficacy outcomes for both devices. Theoretically, the rapid polymer resorption in the SYNERGY may justify an abbreviated DAPT regime, which may be most advantageous in patients with an increased bleeding risk. In the randomised SYNERGY II Senior trial, elderly patients, treated with one or six months of DAPT after PCI, showed superior outcomes after PCI with SYNERGY EES versus bare metal stents.¹²

The biodegradable polymer Orsiro stent was previously tested against other DES in large randomised studies, which ascertained the safety and efficacy of Orsiro in greatly unrestricted patient populations.¹³⁻¹⁵ The SORT OUT VII trial studied 2,525 PCI patients, randomly assigned to the sirolimus-eluting Orsiro versus thick-strut biolimus-eluting biodegradable polymer DES and showed similar two-year clinical outcomes.¹⁶ In addition, the two-year clinical outcome of the randomised BIOSCIENCE trial in 2,119 patients

was similar for patients treated with Orsiro versus durable polymer XIENCE EES.¹⁷ In the BIOFLOW V randomised trial, Orsiro outperformed the durable polymer EES in a complex patient population, mainly based on a lower incidence of in-hospital MI, which did not translate into a difference in mortality.¹⁸

FIGURE 3. Kaplan-Meier cumulative event curves and landmark analyses for target lesion revascularisation and target lesion failure. Target lesion failure is a composite of cardiac death, target lesion-related myocardial infarction, or clinically driven target lesion revascularisation.

TABLE 3. Clinical events until 2-year follow-up.

All patients N=3,514						
	EES N=1,172	ZES N=1,173	SES N=1,169	Hazard ratio (95% CI) EES vs. ZES	P-logrank	Hazard ratio (95% CI) SES vs. ZES
Death, any	35 (3.0)	38 (3.3)	30 (2.6)	0.92 (0.58–1.46)	0.73	0.79 (0.49–1.28)
Cardiac death	17 (1.5)	17 (1.5)	15 (1.3)	1.00 (0.51–1.96)	1.00	0.88 (0.44–1.77)
Myocardial infarction, any	34 (2.9)	42 (3.6)	36 (3.1)	0.81 (0.51–1.27)	0.35	0.86 (0.55–1.34)
Target vessel myocardial infarction	30 (2.6)	38 (3.3)	30 (2.6)	0.79 (0.49–1.27)	0.33	0.79 (0.49–1.28)
Coronary revascularisation, any	71 (6.1)	94 (8.1)	75 (6.4)	0.75 (0.55–1.02)	0.07	0.80 (0.59–1.08)
Target vessel revascularisation	39 (3.4)	56 (4.8)	43 (3.7)	0.70 (0.46–1.05)	0.08	0.77 (0.51–1.40)
Target lesion revascularisation	27 (2.4)	34 (3.0)	25 (2.2)	0.80 (0.48–1.32)	0.37	0.74 (0.44–1.23)
Non-target vessel revascularisation	36 (3.1)	39 (3.4)	34 (3.0)	0.92 (0.59–1.45)	0.73	0.88 (0.55–1.39)
Target vessel failure*	79 (6.8)	96 (8.3)	76 (6.6)	0.82 (0.61–1.10)	0.19	0.79 (0.58–1.07)
Target lesion failure	67 (5.8)	79 (6.8)	59 (5.1)	0.85 (0.61–1.17)	0.31	0.75 (0.53–1.04)
Major adverse cardiac events	76 (6.5)	85 (7.3)	68 (5.8)	0.89 (0.66–1.22)	0.47	0.80 (0.58–1.10)
Patient-oriented composite endpoint	125 (10.6)	147 (12.5)	121 (10.3)	0.85 (0.67–1.07)	0.17	0.82 (0.65–1.05)
Definite-or-probable stent thrombosis	11 (1.0)	9 (0.8)	7 (0.6)	1.23 (0.51–2.96)	0.65	0.78 (0.29–2.10)
Definite stent thrombosis	7 (0.6)	6 (0.5)	5 (0.4)	1.17 (0.39–3.48)	0.78	0.84 (0.26–2.74)
Probable stent thrombosis	4 (0.3)	3 (0.3)	2 (0.2)	1.34 (0.30–5.97)	0.70	0.67 (0.11–4.00)

The event rates, expressed as n (%), were calculated with the use of the Kaplan-Meier method. *Primary endpoint. EES: everolimus-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

TABLE 4. Outcome difference between 1 and 2 years.

	EES	ZES	SES	Difference (95% CI) EES vs. ZES	P-logrank	Difference (95% CI) SES vs. ZES	P-logrank
Death, any	15 (1.3)	19 (1.7)	11 (1.0)	-0.3 (-1.3–0.6)	0.50	-0.7 (-1.6–0.2)	0.14
Cardiac death	7 (0.6)	7 (0.6)	5 (0.4)	0.0 (-0.6–0.6)	>0.99	-0.2 (-0.8–0.4)	0.57
Myocardial infarction, any	9 (0.8)	11 (1.0)	7 (0.6)	-0.2 (-1.0–0.6)	0.65	-0.4 (-1.1–0.4)	0.35
Target vessel myocardial infarction	5 (0.4)	7 (0.6)	4 (0.4)	-0.2 (-0.8–0.4)	0.56	-0.3 (-0.8–0.3)	0.36
Coronary revascularisation, any	31 (2.8)	42 (3.8)	26 (2.4)	-1.0 (-2.5–0.4)	0.18	-1.5 (-2.9–0.0)	0.049
Target vessel revascularisation	16 (1.4)	26 (2.3)	17 (1.5)	-0.9 (-2.0–0.2)	0.12	-0.8 (-1.9–0.3)	0.17
Target lesion revascularisation	10 (0.9)	17 (1.5)	7 (0.6)	-0.6 (-1.5–0.3)	0.18	-0.9 (-1.7–0.0)	0.04
Non-target vessel revascularisation	19 (1.7)	18 (1.6)	10 (0.9)	0.1 (-1.0–1.1)	0.87	-0.7 (-1.6–0.2)	0.13
Target vessel failure	24 (2.2)	33 (3.0)	21 (1.9)	-0.8 (-2.2–0.5)	0.22	-1.1 (-2.4–0.2)	0.10
Target lesion failure	18 (1.6)	26 (2.4)	12 (1.1)	-0.7 (-1.9–0.4)	0.22	-1.3 (-2.4– -0.2)	0.02
Major adverse cardiac events	17 (1.5)	24 (2.2)	9 (0.8)	-0.6 (-1.8–0.5)	0.27	-1.4 (-2.4– -0.3)	0.01
Patient-oriented composite endpoint	44 (4.1)	57 (5.3)	34 (3.2)	-1.2 (-3.0–0.6)	0.18	-2.1 (-3.8– -0.4)	0.01
Definite-or-probable stent thrombosis	6 (0.5)	3 (0.3)	2 (0.2)	0.3 (-0.3–0.8)	0.31	-0.1 (-0.5–0.3)	0.66
Definite stent thrombosis	3 (0.3)	3 (0.3)	1 (0.1)	0.0 (-0.4–0.4)	>0.99	-0.2 (-0.5–0.2)	0.32
Probable stent thrombosis	3 (0.3)	0 (0.0)	1 (0.1)	0.3 (0.0–0.6)	0.08	0.1 (-0.1–0.3)	0.32

EES: everolimus-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent

Biodegradable polymer DES

The struts of the novel biodegradable polymer stents are substantially thinner than those of the early biodegradable polymer stents.² These very thin struts may have the advantage of reducing the incidence of side branch occlusion and periprocedural MI. A recent meta-analysis confirmed low MI rates after PCI with these devices but observed no benefit in clinically driven TLR versus other contemporary DES.¹⁵ The reduction in strut thickness needs to be balanced against a decrease in radial strength, which can be achieved by modifications in stent design or the use of metal alloys with a higher strength. In addition, a potential disadvantage of the thin stent struts is their inferior radiographic visibility that is more marked in cobalt-chromium devices than in platinum-chromium stents;¹⁹ theoretically, a lower visibility increases the risk of geometrical miss and related adverse cardiovascular events. Our current analysis, obtained in a broad population of PCI all-comers, shows no signal of increased adverse event risk for both very-thin strut biodegradable polymer DES but excellent outcomes until two-year follow-up.

The type and pharmacokinetic release profile of the antiproliferative drug as well as the reproducibility of drug elution varies across different biodegradable polymer DES.^{3,20-22} Variance in polymer formulation and properties, such as polymer chain length and hydrophobicity, determines the course and products of polymer degradation.¹⁸ All of the above may have an effect on the biological response of the coronary vessel, the speed of endothelialisation, the required minimum DAPT duration, and finally clinical outcome. Therefore, the various types of biodegradable polymer DES should not be considered a homogeneous class of devices. As a matter of fact, it is of the utmost importance to assess all individual biodegradable polymer DES carefully with a longer-term follow-up and to report clinical findings of the specific devices with their highly unique features in stent design, metal backbone, polymer type, composition of polymer and drug, and profiles of drug elution and polymer resorption.

Limitations

The findings of the landmark analyses should be considered hypothesis-generating. In addition, this study is not powered for reliable assessment of secondary clinical endpoints and, in particular, adverse events with a low incidence such as stent thrombosis. Despite high follow-up rates, systematic assessment of biomarkers, electrocardiographs and independent monitoring, the clinical event rates of the present study were low.⁶

CONCLUSIONS

Two years after stenting, the biodegradable polymer EES and SES showed favourable clinical outcomes that were comparable to the reference durable polymer ZES in a broad all-comers population, including many patients with acute coronary syndromes. Long-term follow-up will be of interest, as landmark analyses provided a signal that the use of SES might reduce the risk of repeat revascularisation after the first year of follow-up.

IMPACT ON DAILY PRACTICE

Novel DES with very thin-strut biodegradable polymers may have advantages over stents with thin-strut durable polymers. The current two-year outcome data of the randomised BIORESORT trial show no statistically significant difference in adverse event rates between each of two novel very thin-strut biodegradable polymer DES and a thin-strut durable polymer reference DES. However, we found a signal that the biodegradable polymer sirolimus-eluting stent might be associated with a lower repeat revascularisation risk beyond one-year follow-up. Further long-term follow-up assessment is warranted and certainly of interest.

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CONFLICTS OF INTEREST

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CHAPTER 6

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLE 1A. Subgroup analyses for the 2-year rates of Target Vessel Failure: EES versus ZES.

	EES	ZES	Forestplot	Hazard ratio [95% CI]	<i>P</i> interaction
Men	58/845 (6.9)	69/848 (8.1)		0.84 (0.59 - 1.19)	0.82
Women	21/327 (6.4)	27/325 (8.3)		0.78 (0.44 - 1.37)	
Acute coronary syndrome	49/816 (6.0)	59/815 (7.2)		0.83 (0.57 - 1.21)	0.96
Stable angina	30/356 (8.4)	37/358 (10.3)		0.81 (0.50 - 1.32)	
Multivessel treatment	19/201 (9.5)	26/220 (11.8)		0.80 (0.44 - 1.44)	0.88
Single vessel treatment	60/971 (6.2)	70/953 (7.3)		0.84 (0.59 - 1.19)	
Diabetes	20/203 (9.9)	26/210 (12.4)		0.78 (0.44 - 1.40)	0.84
No diabetes	59/969 (6.1)	70/963 (7.3)		0.84 (0.59 - 1.18)	
Only stents ≤3 mm	56/757 (7.4)	71/797 (8.9)		0.83 (0.58 - 1.17)	0.99
Not only stents ≤3 mm	23/415 (5.5)	25/376 (6.6)		0.83 (0.47 - 1.47)	
Small vessel <2.75 mm	51/680 (7.5)	67/667 (10.0)		0.74 (0.51 - 1.06)	0.36
No small vessel treatment	28/492 (5.7)	29/506 (5.7)		1.00 (0.59 - 1.67)	
Bifurcation lesion	31/415 (7.5)	45/409 (11.0)		0.67 (0.42 - 1.05)	0.24
No bifurcation lesion	48/757 (6.3)	51/764 (6.7)		0.95 (0.64 - 1.42)	
Lesion length >27 mm	27/353 (7.6)	40/369 (10.8)		0.69 (0.43 - 1.13)	0.38
Lesion length ≤ 27 mm	52/819 (6.3)	56/804 (7.0)		0.92 (0.63 - 1.33)	
In-stent restenosis	2/28 (7.1)	4/31 (12.9)		0.53 (0.10 - 2.90)	0.61
No in-stent restenosis	77/1,144 (6.7)	92/1,142 (8.1)		0.83 (0.62 - 1.13)	
Renal insufficiency	4/29 (13.8)	8/33 (24.2)		0.54 (0.16 - 1.79)	0.45
No renal insufficiency	75/1,143 (6.6)	88/1,140 (7.7)		0.85 (0.62 - 1.16)	
Bypass graft treated	6/18 (33.3)	3/30 (10.0)		3.73 (0.93 - 14.93)	0.03
No bypass graft treated	73/1,154 (6.3)	93/1,143 (8.1)		0.77 (0.57 - 1.05)	
Left main treated	3/25 (12.0)	5/28 (17.9)		0.66 (0.16 - 2.76)	0.72
No left main treated	76/1,147 (6.6)	91/1,145 (7.9)		0.83 (0.61 - 1.13)	

SUPPLEMENTAL TABLE 1B. Subgroup analyses for the 2-year rates of Target Vessel Failure: SES versus ZES.

SUPPLEMENTAL TABLE 2. Circumstances and consequences of TLR between 1 and 2 years.

Randomised stent	Gender (age)	Clinical presentation	Treated vessel	Total number of stents /total stent length	Pre/post dilation performed	Clinical presentation and angiographic findings	Treatment
Everolimus-eluting stent	Male (79)	Stable angina	Graft	1/12	Yes/Yes	Acute MI, CK max 213 U/l Definite ST*	Re-PCI
	Male (49)	Stable angina	LM, LAD, RCX	5/134	Yes/Yes	Stable angina In-stent restenosis	Re-PCI
	Male (57)	Unstable angina	LAD	2/28	Yes/Yes	Stable angina In-stent restenosis	Re-PCI
	Male (63)	NSTEMI	RCA	2/44	Yes/Yes	Stable angina Diffuse in-stent restenosis	Re-PCI
	Male (57)	Stable angina	RCX, RCA	2/24	Yes/No	Stable angina Mild in-stent hyperplasia and new stenosis just outside stents	Re-PCI
	Male (69)	Stable angina	LAD, RCX	2/40	Yes/No	NSTEMI Stenosis just proximal of stent RCX	Re-PCI
	Male (67)	NSTEMI	LAD, RCA	3/68	Yes/Yes	Silent ischemia Diffuse in-stent restenosis	Re-PCI

SUPPLEMENTAL TABLE 2. Continued.

Randomised stent	Index PCI			Event			
	Gender (age)	Clinical presentation	Treated vessel	Total number of stents /total stent length	Pre/post dilation performed	Clinical presentation and angiographic findings	Treatment
	Female (62)	Stable angina	LAD	2/28	Yes/Yes	Unstable angina In-stent restenosis	Re-PCI
	Female (67)	STEMI	RCA	2/58	No/Yes	Acute MI, CK max 250 U/l Definite ST **	Re-PCI
	Male (67)	NSTEMI	LAD	2/38	Yes/Yes	Stable angina In-stent restenosis	Re-PCI
	Male (54)	Stable angina	LAD	2/48	Yes/Yes	Stable angina In-stent restenosis	Re-PCI
Zotarolimus-eluting stent	Male (73)	Stable angina	RCX	2/24	Yes/Yes	Stable angina In-stent restenosis	Re-PCI
	Male (86)	NSTEMI	Graft	1/18	No/No	Acute MI, CK max 733 U/l In-stent restenosis	Re-PCI
	Male (56)	Stable angina	RCA	3/82	Yes/Yes	Unstable angina In-stent restenosis	Re-PCI
	Female (60)	NSTEMI	LAD	4/100	Yes/Yes	NSTEMI Ostial in-stent restenosis	CABG

SUPPLEMENTAL TABLE 2. Continued.

Randomised stent						
Gender (age)	Clinical presentation	Treated vessel	Total number of stents /total stent length	Pre/post dilation performed	Clinical presentation and angiographic findings	Treatment
Female (62)	Unstable angina	LAD, RCX	2/34	Yes/Yes	Stable angina Mid and distal in-stent restenosis	Re-PCI
Male (44)	NSTEMI	LAD	2/38	Yes/Yes	Acute MI, CK max 540 U/l Definite ST**	Re-PCI
Female (70)	STEMI	RCX	2/48	Yes/Yes	Stable angina Stenosis just distal of stent	Re-PCI
Male (64)	Stable angina	LAD, RCA	4/105	Yes/Yes	Acute MI, CK max 185 U/l Definite ST***	Re-PCI
Female (76)	NSTEMI	RCA	4/65	Yes/Yes	Stable angina In-stent restenosis	Re-PCI
Female (69)	Stable angina	RCA	2/27	Yes/Yes	Unstable angina Ostial in-stent restenosis	Re-PCI
Male (53)	STEMI	RCX	1/15	No/Yes	Stable angina In-stent restenosis	Re-PCI

SUPPLEMENTAL TABLE 2. Continued.

Randomised stent	Gender (age)	Clinical presentation	Treated vessel	Total number of stents /total stent length	Pre/post dilation performed	Clinical presentation and angiographic findings	Treatment
	Male (62)	Stable angina	LAD, RCX, RCA	3/48	Yes/No	Stable angina Chronic in-stent occlusion	Re-PCI
	Male (69)	Unstable angina	RCA	2/60	Yes/Yes	Unstable angina Chronic in-stent occlusion	Re-PCI
	Male (56)	NSTEMI	RCA	1/30	Yes/Yes	Acute MI, CK max 540 U/l Plaque rupture of stenosis just proximal of stent	Re-PCI
	Male (52)	STEMI	LAD, RCX	3/60	Yes/Yes	Acute MI, CK max 2460 U/l Definite ST**	Re-PCI
Sirolimus-eluting stent	Female (72)	Unstable angina	LAD	1/8	Yes/No	Stable angina In-stent restenosis	Re-PCI
	Male (35)	Unstable angina	LAD	1/40	Yes/Yes	Acute MI, CK max 348 U/l Definite ST**	Re-PCI
	Male (70)	Unstable angina	RCA	1/40	Yes/Yes	Stable angina Chronic occlusion just proximal of stent	CABG

SUPPLEMENTAL TABLE 2. Continued.

Randomised stent							
Gender (age)	Clinical presentation	Treated vessel	Total number of stents /total stent length	Pre/post dilation performed	Clinical presentation and angiographic findings	Treatment	
Female (69)	Stable angina	LM, RCX	1/22	Yes/Yes	Unstable angina In-stent restenosis	Re-PCI	
Male (42)	STEMI	LAD	2/41	Yes/Yes	Acute MI, CK max 500 U/l Stenosis distal stent edge	Re-PCI	
Male (54)	STEMI	LAD	1/30	Yes/Yes	Acute MI, CK max 449 U/l In-stent restenosis	Re-PCI	
Male (65)	Unstable angina	LAD	1/30	Yes/No	NSTEMI In-stent restenosis	Re-PCI	
Female (62)	Stable angina	LAD, RCX	2/43	Yes/Yes	Unstable angina Stenosis just distal of stent	Re-PCI	

All index PCI were performed for de novo lesions except for 2 patients in the zotarolimus-eluting stent group. Abbreviations: CK = creatine kinase; LAD = left anterior descending artery; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; RCX = ramus circumflex artery; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TLR = target lesion revascularisation.

* on clopidogrel-based dual antiplatelet therapy; ** on aspirin single antiplatelet therapy, *** on oral anticoagulation therapy

THIN COMPOSITE WIRE STRUT,
DURABLE POLYMER-COATED (RESOLUTE
ONYX) VERSUS ULTRATHIN COBALT-
CHROMIUM STRUT, BIORESORBABLE
POLYMER-COATED (ORSIRO) DRUG-
ELUTING STENTS IN ALLCOMERS WITH
CORONARY ARTERY DISEASE (BIONYX):
AN INTERNATIONAL, SINGLE-BLIND,
RANDOMISED NON-INFERIORITY TRIAL

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ABSTRACT

Background: During the past decade, many patients had zotarolimus-eluting stents implanted, which had circular shape cobalt-chromium struts with limited radiographic visibility. The Resolute Onyx stent was developed to improve visibility while reducing strut thickness, which was achieved by using a novel composite wire with a dense platinum-iridium core and an outer cobalt-chromium layer. We did the first randomised clinical trial to assess the safety and efficacy of this often-used stent compared with the Orsiro stent, which consists of ultrathin cobalt-chromium struts.

Methods: We did an investigator-initiated, assessor-blinded and patient-blinded, randomised non-inferiority trial in an allcomers population at seven independently monitored centres in Belgium, Israel, and the Netherlands. Eligible participants were aged 18 years or older and required percutaneous coronary intervention with drug-eluting stents. After guide wire passage with or without predilation, members of the catheterisation laboratory team used web-based computer-generated allocation sequences to randomly assign patients (1:1) to either the Resolute Onyx or the Orsiro stent. Randomisation was stratified by sex and diabetes status. Patients and assessors were masked to allocated stents, but treating clinicians were not. The primary endpoint was target vessel failure at 1 year, a composite of cardiac death, target-vessel-related myocardial infarction, and target vessel revascularisation, and was assessed by intention to treat (non-inferiority margin 2.5%) on the basis of outcomes adjudicated by an independent event committee. This trial is registered with ClinicalTrials.gov, number NCT02508714.

Findings: Between Oct 7, 2015, and Dec 23, 2016, 2516 patients were enrolled, 2488 of whom were included in the intention-to-treat analysis (28 withdrawals or screening failures). 1243 participants were assigned to the Resolute Onyx group, and 1245 to the Orsiro group. Overall, 1765 (70.9%) participants presented with acute coronary syndromes and 1275 (51.2%) had myocardial infarctions. 1-year follow-up was available for 2478 (99.6%) patients. The primary endpoint was met by 55 (4.5%) patients in the Resolute Onyx group and 58 (4.7%) in the Orsiro group. Non-inferiority of Resolute Onyx to Orsiro was thus established (absolute risk difference -0.2% [95% CI -1.9 to 1.4]; upper limit of the one-sided 95% CI 1.1% ; $p_{\text{non-inferiority}} = 0.0005$). Definite or probable stent thrombosis occurred in one (0.1%) participant in the Resolute Onyx group and nine (0.7%) in the Orsiro group (hazard ratio 0.11 [95% CI 0.01 – 0.87]; $p = 0.0112$).

Interpretation: The Resolute Onyx stent was non-inferior to Orsiro for a combined safety and efficacy endpoint at 1-year follow-up in allcomers. The low event rate in both groups suggests that both stents are safe, and the very low rate of stent thrombosis in the Resolute Onyx group warrants further clinical investigation.

INTRODUCTION

First-generation drug-eluting stents were associated with an increased risk of stent thrombosis,^{1,2} and were thus replaced by newer devices that deliver antiproliferative drugs from more biocompatible coatings.^{3–6} These newer-generation drug-eluting stents are as efficacious as first-generation stents in prevention of lesion recurrence after percutaneous coronary intervention and have better safety profiles in broad patient populations.⁷ Most contemporary stents have platforms made from a cobalt–chromium alloy, which permits the creation of fine mesh tubes with satisfactory radial force but has poor radiographic visibility. Suboptimal radiographic visibility can be challenging in patients who are obese, when treating bifurcated or calcified coronary lesions, or when assessing stent expansion.

The Resolute Onyx stent (Medtronic, Santa Rosa, CA, USA) was developed in response to the demand for stents with improved radiographic visibility. It has a novel thin strut composite wire stent platform that is covered with the same zotarolimus-eluting durable polymer coating as its predecessors.^{8–13} The metallic stent platform consists of a composite wire made from a dense platinum–iridium core, which makes the struts radiopaque, and an outer layer of cobalt–chromium alloy. The dense core also allows for reduced strut thickness, which might be associated with a decreased risk of stent thrombosis.^{14,15} A wide range of stent diameters are available.^{16,17} The availability of well fitted stents could help to prevent suboptimal stent expansion in very small vessels¹⁸ and to avoid incomplete stent apposition in large vessels—both of which are risk factors for stent thrombosis.¹⁹ Resolute Onyx is used to treat all types of patients and lesion anatomies, but no randomised clinical trial has ever been done to assess its performance in an allcomers population.

A head-to-head comparison of the Resolute Onyx stent and the bioresorbable polymer-coated sirolimus-eluting Orsiro stent (Biotronik, Bülach, Switzerland) would be of interest, because the Orsiro stent, with its ultrathin cobalt–chromium strut platform,^{6,17} has shown excellent efficacy and safety outcomes in several randomised trials.^{12,20–22} Most recently, in the randomised BIOFLOW V trial,²² Orsiro outperformed a fluoropolymer-coated cobalt–chromium everolimus-eluting stent at 1-year follow-up. In the BIONYX trial, we compared the safety and efficacy of the Resolute Onyx and Orsiro stents in an allcomers population at 1-year follow-up.

METHODS

Study design and participants

We did a randomised, prospective, investigator- initiated, patient-blinded and assessor-blinded study at seven specialised cardiac centres with expertise in percutaneous coronary intervention in the Netherlands, Belgium, and Israel (appendix). The trial design has been previously reported.²³ Eligible patients were aged 18 years or older and required percutaneous coronary intervention. All types of coronary syndromes, coronary artery and bypass lesions, and de-novo and restenotic lesions were eligible for inclusion, and there was no limit for lesion length, reference size, and number of lesions or diseased vessels to be treated, as long as all lesions were suitable for treatment with both stent types according to the operator's judgment. Exclusion criteria are in the appendix.²³ All patients provided written informed consent. The study complied with the CONSORT 2010 Statement and Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centres.

Randomisation and masking

Participants were enrolled in the catheterisation laboratory by the operators who did the interventional procedure. After guide wire passage with or without predilation, patients were randomly assigned (1:1) to Resolute Onyx or Orsiro stents. Web-based randomisation was independently managed and done by members of the catheterisation laboratory team, who used a custom- designed program that generated random block sizes of eight and four, stratified by sex and diabetes. Patients and assessors were masked to allocated stents (letters and reports generally blinded to stent type), but treating clinicians were not. Masking was maintained until the independent external clinical event committee had judged all adverse event triggers.

Procedures

The stent platform of the Resolute Onyx is made from a single-strand, swaged shape composite wire that is manufactured into a sinusoidal waveform and automatically welded at predefined connection sites. The Resolute Onyx's struts are thinner (81 μm uncoated strut thickness in stents with diameters ≤ 4.00 mm) than its predecessor's (91 μm). The struts are circumferentially covered with a 5.6 μm layer of the BioLinX durable polymer that elutes zotarolimus (an antiproliferative agent) for 6 months and consists of a blend of three different polymers, which help to control drug release and support biocompatibility. The increased radiopacity together with a larger strut width-to-thickness ratio are intended to improve visibility and deliverability while maintaining longitudinal and radial strength. The Orsiro stent has ultrathin cobalt–chromium struts

with a thickness of 60 μm (in stents ≤ 3.00 mm) or 80 μm (in stents ≥ 3.50 mm), and has been previously described.²³ The available stent diameters ranged from 2.00 mm to 5.00 mm for Resolute Onyx stents, and from 2.25 mm to 4.00 mm for Orsiro stents.

Coronary interventions were done according to standard techniques. The use of lesion predilation and stent postdilation was at the operator's discretion. Treatment within a single procedure was encouraged if safe and reasonable. Planned staged procedures were permitted within 6 weeks of the index procedure. Operators were encouraged to use assigned stents if additional lesions in the same patient required treatment. Concomitant drug therapy did not differ from routine treatment. In general, dual antiplatelet therapy was prescribed for at least 6 months in clinically stable patients and for 12 months after acute coronary syndromes. Choice of P2Y₁₂ inhibitors besides aspirin was based on international guidelines and local protocols. In patients who required oral anticoagulation, aspirin was generally discontinued after 1–6 months.

Electrocardiographs were recommended at routine clinical follow-up and systematically assessed. Laboratory tests included systematic assessment of cardiac biomarkers after the intervention and subsequent serial measurements in case of suspected ischaemia. In patients with acute coronary syndromes, cardiac biomarkers were generally also assessed before intervention. Angiographic analyses and offline quantitative coronary angiographic measurements were done by analysts at an angiographic core laboratory according to current standards (QAngio XA version 7.3).

At 1 year, clinical follow-up was done at patient visits to outpatient clinics or, if not feasible, by telephone follow-up or medical questionnaire (research staff were masked). No routine angiographic follow-up was done. The clinical research organisation the Foundation for Cardiovascular Research and Education Enschede (Enschede, Netherlands) coordinated trial and data management. A formal data safety monitoring board reviewed outcome data periodically.

Data monitoring and processing of clinical outcome data were done by an independent clinical research organisation (Diagram, Zwolle, Netherlands). Monitoring included informed consent and stent type (all patients); potential clinical events reported by investigators, other physicians, or patients; and further in-depth monitoring of all demographic, procedural, and clinical outcome data (in a random 10% of patients). All potential adverse clinical events were adjudicated by an independent, blinded clinical event committee that consisted of cardiologists of the University of Amsterdam

(Amsterdam, Netherlands) with long experience in interventional cardiology and event adjudicating for stent trials.

Outcomes

Clinical endpoints were prespecified and defined according to the Academic Research Consortium.^{24,25} The primary endpoint was target vessel failure at 1-year follow-up—a composite of cardiac death, target-vessel-related myocardial infarction, or clinically indicated target vessel revascularisation, representing device efficacy and patient safety. Death was judged to be cardiac unless an unequivocal non-cardiac cause could be established (appendix). As in all previous TWENTE trials,^{9,10,12} myocardial infarction was defined as any creatine kinase concentration of more than double the upper limit of normal associated with increased confirmatory cardiac biomarkers.²⁵ Target-vessel-related myocardial infarction was related to the target vessel or could not be related to another vessel; further classification was based on laboratory, electrocardiographic, angiographic, and clinical data.²³ Revascularisation procedures were judged to be clinically indicated if angiographic percentage diameter stenoses of the then-treated lesion were 50% or greater in the presence of ischaemic signs or symptoms, or if diameter stenoses were $\geq 70\%$.^{23,25}

Secondary endpoints at 1-year follow-up included individual components of the primary endpoint; all-cause death; any myocardial infarction; clinically indicated target lesion revascularisation; major bleeding; and stent thrombosis. Additional composite endpoints were target lesion failure (cardiac death, target-vessel-related myocardial infarction, or clinically indicated target lesion revascularisation) major adverse cardiac events (all-cause death, any myocardial infarction, emergent coronary or bypass clinically indicated target lesion surgery, revascularisation), and the patient-oriented composite endpoint (all-cause death, any myocardial infarction, or any coronary revascularisation). A prespecified subgroup analysis of the primary endpoint was done in analogy with previous trials.^{10,12}

Statistical analysis

The trial was designed to assess non-inferiority of the primary endpoint at 1-year follow-up. Assuming a target vessel failure rate of 6.0% on the basis of DUTCH PEERS trial data,¹⁰ we estimated that 2470 patients would provide 80% power to show non-inferiority with a margin of 2.5%, an upper one-sided α of 0.05, and allowing for at least 3.0% loss to follow-up. Sample size calculation was done with PASS software (version 11.0.8). Analyses were by intention to treat. A two-sided 90% CI (ie, a 5% one-sided significance level) was created for the between-group difference in probabilities of the primary endpoint. If non-inferiority were established, an additional superiority analysis

would be done. Pearson's χ^2 test or Fisher's exact test were used to compare categorical variables, and the t test was used to compare continuous variables. Time to endpoints was assessed by the Kaplan-Meier method; the log-rank test was applied for between-group comparisons. Hazard ratios (HRs) were computed by Cox proportional hazards analysis. For the primary endpoint, additional per-protocol and sensitivity analyses (ie, adjusted for the stratification factors sex and diabetes with a Cox model) were done. To account for intra-patient correlation (because of inter-lesion dependence), additional lesion-based analyses were done with the generalised estimating equations method. Logistic regression was done to test for interaction between subgroups and treatment with regard to the primary endpoint. p values less than 0.05 were deemed to be significant. p values and CIs were two-sided, except for the non-inferiority testing (primary endpoint). Statistical analyses were done in SPSS (version 22.0). This trial is registered with ClinicalTrials.gov, number NCT02508714.

Role of the funding source

The study funders provided equal financial support, but had no roles in study design; data collection, analysis, or interpretation; or writing of the report. CvB, PZ, RAB, CJMD, and MMK had full access to all study data, and CvB, the corresponding author, had final responsibility for the decision to submit for publication.

RESULTS

Between Oct 7, 2015, and Dec 23, 2016, we randomly assigned 2516 patients, after stratification for sex and diabetes, to one of the trial stents (figure 1). 28 randomly assigned patients fulfilled an exclusion criterion, so 2488 trial participants (3239 target lesions) were included in the intention-to-treat analysis, 1243 in the Resolute Onyx group (1646 lesions) and 1245 in the Orsiro group (1593 lesions; figure 1). 2432 (97.7%) patients completed 1-year follow-up and 46 (1.8%) died; thus outcome data were available for 2478 (99.6%) patients. Seven (0.3%) patients were lost to follow-up, and three (0.1%) withdrew consent (figure 1).

Participants were aged 30–96 years (mean 64.0 [SD 11.0]), 594 (23.9%) were women, 2370 (95.3%) were white, 1765 (70.9%) presented with acute coronary syndromes, and 1275 (51.2%) presented with acute myocardial infarctions (table 1). Of all 3239 assessable target lesions, 2255 (69.6%) were complex—ie, American College of Cardiology and American Heart Association lesion class B2 or C (table 2). A reference vessel size (assessed by quantitative coronary angiography) less than 2.00 mm was present in 218 (8.8%), whereas a reference vessel size greater than 4.00 mm was recorded in 71 (2.9%) patients.

TABLE 1. Baseline characteristics.

	All patients (n=2488)	Resolute Onyx (n=1243)	Orsiro (n=1245)
General characteristics			
Age, years	64.0 (11.0)	64.1 (10.9)	63.9 (11.2)
Women	594 (23.9%)	297 (23.9%)	297 (23.9%)
Caucasian	2370 (95.3%)	1176 (94.6%)	1194 (95.9%)
Body-mass index (kg/m ²)	27.9 (4.4)	27.9 (4.4)	28.0 (4.4)
Current smoker	741/2418 (30.6%)	371/1214 (30.6%)	370/1204 (30.7%)
Medical history			
Family history of coronary artery disease	1038/2385 (43.5%)	533/1193 (44.7%)	505/1192 (42.2%)
Diabetes, medically treated	510 (20.5%)	260 (20.9%)	250 (20.1%)
Hypertension	1262/2451 (51.5%)	611/1228 (49.8%)	651/1223 (53.2%)
Hypercholesterolaemia	1114/2427 (45.9%)	552/1215 (45.4%)	562/1212 (46.4%)
Previous myocardial infarction	400 (16.1%)	194 (15.6%)	206 (16.5%)
Previous stroke	190 (7.6%)	97 (7.8%)	93 (7.5%)
Renal insufficiency*	166 (6.7%)	83 (6.7%)	83 (6.7%)
Previous percutaneous coronary intervention	540 (21.7%)	262 (21.1%)	278 (22.3%)
P Previous coronary artery bypass grafting	176 (7.1%)	79 (6.4%)	97 (7.8%)
Clinical presentation			
Acute coronary syndrome	1765 (70.9%)	880 (70.8%)	885 (71.1%)
Acute myocardial infarction	1275 (51.2%)	626 (50.4%)	649 (52.1%)
ST elevation myocardial infarction	621 (25.0%)	282 (22.7%)	339 (27.2%)
Non-ST elevation myocardial infarction	654 (26.3%)	344 (27.7%)	310 (24.9%)
Unstable angina	490 (19.7%)	254 (20.4%)	236 (19.0%)
Stable angina or silent ischemia	723 (29.1%)	363 (29.2%)	360 (28.9%)
Lesion characteristics[†]			
At least one complex lesion	1873 (75.3%)	936 (75.3%)	937 (75.3%)
At least one bifurcation lesion [‡]	981 (39.4%)	485 (39.0%)	496 (39.8%)
At least one chronic total occlusion	112 (4.5%)	50 (4.0%)	62 (5.0%)
At least one bypass graft lesion	40 (1.6%)	17 (1.4%)	23 (1.8%)
At least one severely calcified lesion	423 (17.0%)	200 (16.1%)	223 (17.9%)
Procedural characteristics			
Radial approach	1818 (73.1%)	914 (73.5%)	904 (72.6%)
Fractional flow reserve use [§]	268 (10.8%)	125 (10.1%)	143 (11.5%)
IVUS or OCT use	29 (1.2%)	16 (1.3%)	13 (1.0%)
Thrombus aspiration	172 (6.9%)	70 (5.6%)	102 (8.2%)
Glycoprotein inhibitor	554 (22.3%)	254 (20.4%)	300 (24.1%)

TABLE 1. Continued.

	All patients (n=2488)	Resolute Onyx (n=1243)	Orsiro (n=1245)
Bivalirudin	126 (5.1%)	63 (5.1%)	63 (5.1%)
Implantation of assigned stents only	2439 (98.0%)	1223 (98.4%)	1216 (97.7%)
Total stent length per patient (mm)	30 (18-48)	30 (18-49)	30 (18-48)
At least one stent <2.75 mm	923/2483 (37.2%)	481/1240 (38.8%)	442/1243 (35.6%)
Direct stenting	590 (23.7%)	284 (22.8%)	306 (24.6%)
Postdilatation	1721 (69.2%)	859 (69.1%)	862 (69.2%)
Multivessel treatment	441 (17.7%)	236 (19.0%)	205 (16.5%)

Data are n (%), n/N (%), mean (SD), or median (IQR). IVUS=intravascular ultrasonography. OCT=optical coherence tomography. *Defined as previous renal failure, creatinine ≥ 130 $\mu\text{mol/L}$, or the need for dialysis. †Lesion characteristics are defined in the appendix. ‡Target lesions were classified as bifurcated if a side branch ≥ 1.5 mm originated from them. §The cutoff for a significant fractional flow reserve value was 0.80.

FIGURE 1. Trial profile. *Includes the two patients given other study stents. †14 were given other study stents. ‡Four given other study stents.

CHAPTER 7

In 3194 (98.6%) of all 3239 lesions, at least one randomly assigned stent was implanted, and 3184 (98.3%) lesions were treated with assigned stents only. Of all 2125 implanted stents in the Resolute Onyx group, 30 (1.4%) had a diameter of 2.00 mm and 13 (0.6%) had a diameter of 4.50 mm or greater. Eight (0.4%) of 2055 implanted stents in the Orsiro group measured 2.00 mm and four (0.2%) measured 4.50 mm or greater (crossover). More than one vessel was treated in 441 (17.7%) of all 2488 patients. Direct stenting was done in 590 (23.7%) patients, and stents were postdilated in 1721 (69.2%), without noticeable between-group difference (table 1).

At 1-year follow-up, the primary endpoint, target vessel failure, was met by 55 (4.5%) of 1243 patients in the Resolute Onyx group and 58 (4.7%) of 1245 in the Orsiro group (table 3). Non-inferiority of Resolute Onyx compared with Orsiro was established with an absolute risk difference of −0.2% (95% CI −1.9 to 1.4) and an upper limit of the one-sided 95% CI of 1.1% ($p_{\text{non-inferiority}}=0.0005$; $p_{\text{superiority}}=0.77$; figure 2A). A per-protocol analysis to account for the possibility that deviation from the assigned stent might have affected the primary outcome had similar results (absolute risk difference −0.03% [95% CI −1.7 to 1.6]; upper limit of one-sided 95% CI 1.4%; $p_{\text{non-inferiority}}=0.0012$; appendix). Additionally, results for the primary end point were consistent in the sensitivity analysis (HR 0.9 [95% CI 0.7 to 1.4]; $p=0.74$) and across various subgroups (figure 3). The frequencies of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target vessel revascularisation (ie, the individual components of the primary endpoint) were low and similar in both groups (figure 2B–D; table 3).

TABLE 2. Baseline characteristics of target lesions.

	All lesions (n=3239)	Resolute Onyx (n=1646)	Orsiro (n=1593)
Left main	47 (1.5%)	25 (1.5%)	22 (1.4%)
Left anterior descending artery	1340 (41.4%)	678 (41.2%)	662 (41.6%)
Left circumflex artery	772 (23.8%)	400 (24.3%)	372 (23.4%)
Right coronary artery	1071 (33.1%)	541 (32.9%)	530 (33.3%)
Bypass graft	44 (1.4%)	19 (1.2%)	25 (1.6%)
ACC/AHA lesion class	3235	1644	1591
A	159 (4.9%)	75 (4.6%)	84 (5.3%)
B1	821 (25.3%)	425 (25.9%)	396 (24.9%)
B2	1112 (34.3%)	580 (35.3%)	532 (33.4%)
C	1143 (35.3%)	564 (34.3%)	579 (36.4%)
Bifurcation	1033 (31.9%)	515 (31.3%)	518 (32.5%)
Severe calcification	502 (15.4%)	247 (15.0%)	255 (16.0%)
In-stent restenosis	75 (2.3%)	47 (2.9%)	28 (1.8%)

TABLE 2. Continued.

	All lesions (n=3239)	Resolute Onyx (n=1646)	Orsiro (n=1593)
Chronic total occlusion	114 (3.5%)	51 (3.1%)	63 (4.0%)
Before procedure*			
Lesion length, mm	15.4 (11.0 - 23.2)	15.3 (10.9 - 22.9)	15.6 (11.2 - 23.7)
Minimum lumen diameter, mm	0.75 (0.46 - 1.05)	0.75 (0.48 - 1.04)	0.74 (0.43 - 1.06)
Reference vessel diameter, mm	2.81 (0.56)	2.79 (0.57)	2.83 (0.56)
Lumen diameter stenosis, %	72.3 (61.5 - 83.0)	72.0 (61.2 - 82.1)	72.7 (61.8 - 84.4)
After procedure†			
Minimum lumen diameter, mm	2.41 (0.53)	2.41 (0.54)	2.41 (0.52)
Reference vessel diameter, mm	2.78 (0.55)	2.77 (0.56)	2.79 (0.54)
Lumen diameter stenosis, %	12.7 (8.2 - 18.3)	12.4 (8.1 - 17.8)	13.0 (8.5 - 18.9)
Acute lumen gain in segment, mm	1.67 (0.63)	1.65 (0.62)	1.68 (0.64)
Number of stents per lesion	1.26 (0.56)	1.27 (0.55)	1.26 (0.57)
Implantation of assigned stents only	3184 (98.3%)	1623 (98.6)	1561 (98.0%)
Lesion success‡	3217 (99.7%)	1638 (99.7)	1579 (99.6%)
Device success§	3166 (98.1%)	1616 (98.4)	1550 (97.8%)
Postdilatation	2065 (64.0%)	1042 (63.5%)	1023 (64.5%)

Data are n (%), mean (SD), or median (IQR). Lesions were classified as bifurcated on the basis of quantitative coronary angiographic data and the bifurcation definition of the Syntax Score. Lesion-based analysis corrected for intra-patient correlation with generalised estimating equations are available in the appendix. ACC=American College of Cardiology. AHA=American Heart Association. *Data available for at least 1638 lesions in the Resolute Onyx group and 1589 lesions in the Orsiro group. †Data available for at least 1641 lesions in the Resolute Onyx group and 1585 lesions in the Orsiro group. ‡Lesion success was defined as <50% residual stenosis after percutaneous coronary intervention; N=3228 (1643 in the Resolute Onyx group and 1585 in the Orsiro group). §Device success was defined as <50% residual stenosis after percutaneous coronary intervention with assigned stents only; N=3228 (1643 in the Resolute Onyx group and 1585 in the Orsiro group).

At hospital discharge after the index procedure, 1214 (97.7%) of 1243 patients in the Resolute Onyx group, and 1209 (97.1%) of 1245 in the Orsiro group were treated with dual antiplatelet therapy ($p=0.38$). We noted no between-group differences in P2Y₁₂ inhibitors or other drugs prescribed (appendix). At 1-year follow-up, 2067 (85.0%) patients were still on dual antiplatelet therapy, without any between-group differences (appendix). Definite-or-probable stent thrombosis occurred in one (0.1%) patient in the Resolute Onyx group and nine (0.7%) in the Orsiro group (HR 0.11 [95% CI 0.01–0.87]; $p=0.0112$; figure 4). Definite stent thrombosis occurred in one (0.1%) in the Resolute Onyx group and seven (0.6%) in the

FIGURE 2. Kaplan-Meier graphs of cumulative incidence of the composite target vessel failure (A) and its individual components cardiac death (B), target-vessel-related myocardial infarction (C), and target vessel revascularisation (D). HR=hazard ratio.

Orsiro group (table 3). One patient in the Resolute Onyx group developed a subacute, non-fatal, definite stent thrombosis after self-discontinuation of aspirin and had an acute myocardial infarction with cardiogenic shock that required urgent revascularisation. Of the seven definite stent thromboses in the Orsiro group, three were acute, two were subacute, and two were late; all seven patients presented with acute myocardial infarctions while taking dual antiplatelet therapy. Two patients in the Orsiro group died suddenly 7 days after the index procedure, and these events were classified as probable stent thrombosis. None of the stent thromboses occurred in devices with the smallest diameter available (ie, 2.00 mm; appendix).

DISCUSSION

In this large-scale, international, randomly assigned allcomers trial, we noted no difference between stent groups in the incidence of the composite primary endpoint of target vessel failure at 1 year. Thus, the Resolute Onyx stent met the criterion of non-inferiority compared with the Orsiro stent. The frequencies of the individual components of the primary endpoint were similar and quite low in both groups, which could be perceived as a positive signal of safety for both devices. Although the frequency of stent thrombosis was also low in both groups, the risk was particularly low in the Resolute Onyx group, which is noteworthy in view of the complexity of the trial participants and coronary lesions treated. The only stent thrombosis in a patient in the Resolute Onyx group occurred subacutely in a vessel treated with four stents along more than 10 cm, after the patient's self-discontinuation of dual antiplatelet therapy. A previous study showed that interruption of dual antiplatelet therapy within 1 month of stent implantation was associated with an increased risk of stent thrombosis,²⁶ but none of the seven patients in the Orsiro group who developed a definite stent thrombosis was off dual antiplatelet therapy. However, three of the seven patients had at least three stents implanted with a total stent length of more than 9 cm. Additionally, preclinical studies showed that thrombogenicity of the coating on the Orsiro stent is low.²⁷ The use of dual antiplatelet therapy at discharge (97.4%) or 1-year follow-up (85.0%) did not differ between groups. We noted no significant between-group difference in the rate of any target lesion revascularisation (2.5% vs 2.0%), and the small between-group difference in target lesion revascularisation by coronary artery bypass surgery (0.9% vs 0.2%; appendix) is probably chance.

The BIONYX trial is the first randomised study of Resolute Onyx, the first assessment of the stent's safety and efficacy in allcomers, and the first comparison of the stent with Orsiro. The study population represents 41.3% of all patients who were percutaneously

FIGURE 3. Subgroup analyses for target vessel failure at 1 year in the Resolute Onyx and Orsiro stent groups

treated (irrespective of inclusion or exclusion criteria; figure 1) and included many patients with increased clinical, lesion-related, or procedural risk. 1765 (70.9%) trial participants were treated for acute coronary syndromes and 1275 (51.2%) for acute myocardial infarction. The clinical presentation of trial participants was challenging and similar to that of participants in the complex allcomers population of the BIO-RESORT trial,¹² suggesting that the assessed study population represents patients treated in routine clinical practice. The age range of trial participants—30–96 years— reflects the non-discriminating nature of our study. Similar to previous trials^{10–12,20} in allcomers undergoing percutaneous coronary intervention, almost a quarter of all participants in BIONYX were women. More than 98% of all patients were exclusively treated with randomly assigned stents, and outcome data were available for 99.6% of patients.

Despite the different durable and bioresorbable polymer coatings and strut thicknesses of the two study stents, we noted no advantages for one stent over the other. The rates of the primary endpoint were low despite the overall high complexity of patients and target lesions, independent monitoring of all potential event triggers, and almost complete follow-up. These event rates were quite similar to the rates of the primary composite endpoints reported in previous allcomers trials of Resolute Integrity (ie, the predecessor of Resolute Onyx) versus bioresorbable polymer-coated stents,^{11,12} or of the Orsiro stent versus a durable polymer-coated stent.^{12,20} In the SORT OUT VI trial¹¹ of 2999 allcomers, the Resolute Integrity stent was non-inferior to a bioresorbable polymer-coated biolimus-eluting stent (BioMatrix Flex, Biosensors Interventional Technologies, Singapore, Singapore) in terms of the primary composite endpoint of safety and efficacy at 1-year follow-up (5.3% vs 5.0%), with no significant between-group differences in the individual components of the primary endpoint (ie, cardiac death, target vessel-related myocardial infarction, and target lesion re vascularisation). The frequency of definite stent thrombosis in the Resolute Integrity group was 0.6%.¹¹ The BIOSCIENCE trial²⁰ of 2119 allcomers showed that the Orsiro stent was non-inferior to a durable polymer-coated everolimus-eluting stent (Xience Prime/Xpedition, Abbott, Abbott Park, IL, USA) for the primary composite endpoint of target lesion failure at 1-year follow-up (6.5% vs 6.6%), and no significant differences were noted between the groups for various secondary endpoints. In BIOSCIENCE, the frequency of definite stent thrombosis in the Orsiro group was 0.9%,²⁰ which is similar to that in the BIONYX trial (0.6%). The BIO-RESORT allcomers trial¹² showed the non-inferiority of the Orsiro stent (in 1169 patients) and a bioresorbable polymer-coated everolimus-eluting platinum–chromium- based stent (Synergy, Boston Scientific, Natick, MA, USA; in 1172 patients) to the Resolute Integrity stent (in 1173 patients) for the primary composite endpoint of target vessel failure at 1 year (4.7% and 4.7% vs 5.4%), and no significant between-stent differences

were noted in any secondary clinical endpoint. In that trial, the frequency of definite stent thrombosis at 1 year was 0.3% in all stent groups.¹²

TABLE 3. Clinical events during 1-year follow-up.

	All patients (n=2488)			
	Resolute Onyx (n=1243)	Orsiro (n=1245)	Hazard ratio (95% CI)	Log- rank p value
Death, any	20 (1.6%)	26 (2.1%)	0.77 (0.43 - 1.37)	0.37
Cardiac death	7 (0.6%)	13 (1.1%)	0.54 (0.21 - 1.34)	0.18
Myocardial infarction, any	20 (1.6%)	20 (1.6%)	1.00 (0.54 - 1.86)	0.97
Target vessel myocardial infarction	18 (1.5%)	18 (1.5%)	1.00 (0.52 - 1.92)	1.00
Periprocedural myocardial infarction	11 (0.9%)	12 (1.0%)	0.92 (0.41 - 2.08)	0.84
Coronary revascularisation, any	65 (5.3%)	70 (5.7%)	0.92 (0.66 - 1.29)	0.64
Target vessel revascularisation	39 (3.2%)	38 (3.1%)	1.02 (0.66 - 1.60)	0.92
Target lesion revascularisation	31 (2.5%)	24 (2.0%)	1.29 (0.76 - 2.20)	0.35
Target vessel failure*	55 (4.5%)	58 (4.7%)	0.95 (0.66 - 1.37)	0.77
Target lesion failure	48 (3.9%)	44 (3.6%)	1.09 (0.72 - 1.64)	0.68
Major adverse cardiac events	61 (4.9%)	57 (4.6%)	1.07 (0.75 - 1.54)	0.71
Patient-oriented composite endpoint	91 (7.3%)	102 (8.2%)	0.89 (0.67 - 1.18)	0.41
Definite-or-probable stent thrombosis	1 (0.1%)	9 (0.7%)	0.11 (0.01 - 0.87)	0.0112
Definite stent thrombosis	1 (0.1%)	7 (0.6%)	0.14 (0.02 - 1.16)	0.0334 [†]
Probable stent thrombosis	0 (0.0%)	2 (0.2%)	0.02 (0.00 - 1327.44)	0.16

Event rates are expressed as n (%) and were calculated with the Kaplan-Meier method. All target vessel revascularisations were clinically indicated. *Primary clinical endpoint of cardiac death, target-vessel-related myocardial infarction, or clinically indicated target vessel revascularisation; other composite endpoints are defined in the appendix. †Because the log-rank p value is based on χ^2 , it does not correspond with the 95% CI because of the very low event rate in the Resolute Onyx group (p value based on Wald test: 0.0682).

The incidence of definite-or-probable stent thrombosis in the Orsiro group in our trial (0.7%) is similar to that in several previous randomised allcomer trials of the stent, such as BIO-RESORT (0.4%)¹² and SORT OUT VII (0.9%).²¹ In the Resolute Onyx group of our trial, the incidence of definite-or-probable stent thrombosis was very low (0.1%). In previous randomised allcomers trials of Resolute Integrity, the frequency of definite- or-probable stent thrombosis was somewhat higher (0.5% in BIO-RESORT,¹² 0.6% in DUTCH PEERS,¹⁰ and 0.8% in SORT OUT VI¹¹). Additionally, in BIONYX, the rate of definite stent thrombosis

with Resolute Onyx stents (0.1%) was below those with Resolute Integrity in previous allcomers stent trials (0.3%–0.6%).^{10–12}

The improved radiographic visibility of Resolute Onyx could facilitate the recognition of stents that are not yet well expanded or incompletely apposed to the arterial wall. Theoretically, reduction of the occurrence of these scenarios, which are both associated with stent thrombosis,²⁸ could have contributed to the particularly low frequency of stent thrombosis in the Resolute Onyx group. However, the frequency of additional balloon dilations (inside implanted stents) did not differ between groups (69.1% vs 69.2%). This finding suggests that, on average, there was no difference between groups in operators' effort to optimise procedural results. Additionally, the quantitative coronary angiographic analysis showed that lumen gain and final minimum lumen diameter did not differ significantly between groups. Nonetheless, the detection of only a few (otherwise perhaps unnoticed) suboptimally deployed Resolute Onyx stents could have contributed to the low rate of stent thrombosis. Additionally, the use of the swaged shape wire has lowered strut thickness by 10 µm compared with the stent's predecessor, and lowering strut thickness reduces thrombogenicity.¹⁴

38 of the smallest stents (2.00 mm), which were exclusively Resolute Onyx, were implanted (30 in the Resolute Onyx group and eight in the Orsiro group because of crossover). No stent thrombosis occurred in these very small stents, which can be used to treat side branches or the most distal coronary segments. However, such lesions are generally treated with antianginal drugs rather than invasive revascularisation. Nonetheless, after stenting of large (main) vessels, the very small stents could occasionally be helpful to keep open smaller side branches that remain collapsed despite balloon dilatations in the main vessel to open the struts. This technique could help to avoid some (probably minor) periprocedural myocardial infarctions. In our study, in both stent groups the event rates for periprocedural myocardial infarction (11 [0.9%] in the Resolute Onyx group vs 12 [1.0%] in the Orsiro group) and any target vessel myocardial infarction (18 [1.4%] vs 18 [1.4%]) were nearly identical.

The very low rate of stent thrombosis in the Resolute Onyx group supports the findings of a prospective registry²⁹ of 101 patients with up to moderate risk, in whom no definite-or-probable stent thromboses were recorded within 12 months after implantation of 2.00 mm Resolute Onyx stents. Furthermore, in a registry³⁰ of 402 patients with myocardial infarction who had Resolute Onyx stents implanted, the frequency of definite-or-probable stent thrombosis was 0.2%. Finally, in an angiographic endpoint study,³¹ one

(1%) of 75 patients implanted with Resolute Onyx stents developed an acute definite stent thrombosis during 8 months of follow-up.

The Promus Element durable polymer-coated everolimus-eluting platinum-chromium stent (Boston Scientific, Natick, MA, USA) also has high radiographic visibility.^{10,16} In the DUTCH PEERS trial,¹⁰ Promus Element stents were postdilated significantly more often than the less visible Resolute Integrity stents. These findings appear to contrast with those of BIONYX, in which the frequency of postdilation did not differ noticeably between groups. However, factors other than visibility could affect the frequency of stent postdilation. Although Promus Element and Resolute Onyx have high radiopacity in common, they differ in many other characteristics (eg, strut materials, design of platforms, the balloon catheters on which they are mounted).^{16,17} These device features affect the spatial stent geometry after deployment and, thus, the need for stent optimisation. Additionally, the operators involved play a part: some interventional cardiologists postdilate stents irrespective of angiographic appearance after deployment.^{10,12}

FIGURE 4. Cumulative incidence of definite or probable stent thrombosis at 1-year follow-up. Definite or probable stent thrombosis with clinical consequences. HR=hazard ratio.

Our study has some limitations. The incidence of the primary endpoint was lower than assumed, but the expected event rate was in line with outcomes in other randomised allcomers stent trials.^{10,11} The lower-than-expected rates of the primary endpoint affect the robustness of the results, particularly the results of subgroup analyses. The non-inferiority margin (2.5%) was lower than that in most other stent trials in allcomers,^{10,12,13,20,22,32} but because of the low incidence of the primary endpoint that margin represented more than half of the recorded primary endpoint rate. Similar to other randomised trials, we cannot exclude a certain degree of under-reporting of events. Nonetheless, substantial under-reporting seems unlikely, in view of the systematic postprocedural assessment of cardiac biomarkers and electrocardiograms, the high follow-up rate, and the use of independent monitoring and event adjudication. Additionally, several other stent trials also had lower-than-expected event rates.^{10,12,32,33} We cannot exclude the possibility that the event rates in our study might be more representative of the outcome of present coronary interventions, as opposed to when our trial was designed, and that the choice of study centres with many highly experienced operators could have favourably affected outcomes. Additional factors could have lowered event rates in our trial, such as the frequent use of more potent P2Y₁₂ inhibitors (55% vs 48% in BIO-RESORT¹²) and the more frequent use of radial access (73% vs 45% in BIO-RESORT¹²). Our study was not adequately powered to reliably assess very rare clinical events, such as stent thrombosis, and therefore stent thrombosis data should be considered hypothesis generating. However, stent thrombosis is such an important adverse event that our findings should not be ignored—particularly because Resolute Onyx is a novel stent that has never previously been assessed in a randomised trial or in allcomers. Centres that treat a low proportion of patients with acute coronary syndromes might have different event rates, because thrombus management and type, timing, and duration of dual antiplatelet therapy could be the most important factors in treatment of acute coronary syndrome. 2-year follow-up will be of particular interest, because most patients will stop dual antiplatelet therapy after 1 year, which can be associated with an inherent increase in the risk of stent thrombosis. Finally, we do not have reliable data for the operators' motivation for using stents other than that assigned. We did not formally restrict target vessel size but left decisions about the treatability of lesions (with both stent types) to the operators to reflect clinical practice, in which implantation pressures can be adjusted to the vessel size and stents can be overstretched by postdilations with large balloons. Data for the use of dedicated techniques for magnification and boosting of stents in radiographic images were not collected.

In conclusion, the novel Resolute Onyx stent was non-inferior to the reference Orsiro stent for a combined safety and efficacy endpoint at 1-year follow-up in an allcomers

population with a high proportion of patients with acute coronary syndromes. Other outcomes were also favourable, and suggested that both stents are safe. The very low frequency of stent thrombosis noted with Resolute Onyx warrants further clinical investigation.

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CONFLICTS OF INTEREST

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed with the terms “coronary” AND “stent” in combination with one or more of “sirolimus”, “zotarolimus”, “Resolute Onyx”, “Orsiro”, “randomised”, and “randomized” for complete reports of randomised trials comparing the durable polymer-coated zotarolimus-eluting Resolute Onyx stent with the bioresorbable polymer-coated sirolimus-eluting Orsiro stent or with other stents, published in any language up to July 18, 2018. We also checked the listings of the EuroPCR, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and American College of Cardiology Conferences. Previously, the Resolute Onyx stent had been assessed in an angiographic endpoint study of 75 patients with 8 months of follow-up and in two registry studies, one of which examined 101 US and Japanese patients with up to the moderate risk who were treated with 2.00 mm Resolute Onyx stents, and the other of which examined 402 Korean patients with acute myocardial infarction. In previous studies, the Orsiro stent was non-inferior to a durable polymer-coated everolimus-eluting stent with respect to a primary angiographical endpoint (BIOFLOW-II), and to a durable polymer-coated everolimus-eluting stent (BIOSCIENCE), an early biodegradable polymer-coated biolimus-eluting stent (SORT OUT VII), and durable polymer-coated zotarolimus-eluting cobalt-chromium stents (BIO-RESORT) in treating allcomers. In a randomised clinical trial in most-comers (BIOFLOW V), Orsiro outperformed (in terms of the primary endpoint, target lesion failure) a durable polymer-coated cobalt–chromium everolimus-eluting stent at 1-year follow-up. Resolute Onyx and Orsiro stents have not previously been compared in a randomised trial. Additionally, the Resolute Onyx stent has not been assessed in allcomers or been compared with any other drug-eluting stent.

Added value of this study

Our analysis shows that treatment with the Resolute Onyx stent and the Orsiro stent was similarly efficacious and safe, with excellent 1-year clinical outcomes in an allcomer population. BIONYX is the first randomised trial of the Resolute Onyx stent and the first assessment of this stent in allcomers. Additionally, this trial is the first randomised comparison of the Resolute Onyx and Orsiro stents.

Implications of all the available evidence

The Resolute Onyx stent was non-inferior to Orsiro for the combined safety and efficacy endpoint at 1-year follow-up in a complex allcomer patient population. The preliminary observation of a low incidence of stent thrombosis with Resolute Onyx warrants further investigation.

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CHAPTER 7

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SUPPLEMENTAL DATA

APPENDIX TABLE 1. Extended baseline characteristics

	All patients (n=2488)	Resolute Onyx (n=1243)	Orsiro (n=1245)
Medical history			
Peripheral artery disease	211/2475 (8.5%)	109/1236 (8.8%)	102/1239 (8.2%)
Left ventricular ejection fraction <30 %	38/2467 (1.5%)	19/1233 (1.5%)	19/1234 (1.5%)
Heart failure	58/2485 (2.3%)	28/1242 (2.3%)	30/1243 (2.4%)
Previous stroke or TIA	190 (7.6%)	97 (7.8%)	93 (7.5%)
Previous stroke	86 (3.5%)	42 (3.4%)	44 (3.5%)
Previous gastro-intestinal bleeding	18 (0.7%)	10 (0.8%)	8 (0.6%)
Previous malignancy	205 (8.3%)	111 (9.0%)	94 (7.6%)
Chronic obstructive pulmonary disease	227 (9.1%)	116 (9.3%)	111 (8.9%)
Lesion characteristics			
At least one in-stent restenosis	71 (2.9%)	44 (3.5%)	27 (2.2%)
At least one small vessel (<2.75 mm)	1301 (52.3%)	675 (54.3%)	626 (50.3%)
At least one very small vessel (≤2.00 mm)	218 (8.8%)	121 (9.7%)	97 (7.8%)
At least one large vessel (>4.00 mm)	71 (2.9%)	41 (3.3%)	30 (2.4%)
At least one lesion length >27 mm	523 (21.0%)	245 (19.7%)	278 (22.3%)
Number of lesions treated per patient			
One	1870 (75.2%)	913 (73.5%)	957 (76.9%)
Two	501 (20.1%)	263 (21.2%)	238 (19.1%)
Three or more	117 (4.7%)	67 (5.4%)	50 (4.0%)
Left main	47 (1.9%)	25 (2.0%)	22 (1.8%)
Left anterior descending artery	1224 (49.2%)	612 (49.2%)	612 (49.2%)
Left circumflex artery	723 (29.1%)	374 (30.1%)	349 (28.0%)
Right coronary artery	946 (38.0%)	476 (38.3%)	470 (37.8%)
Bypass graft	40 (1.6%)	16 (1.3%)	24 (1.9%)
Procedural characteristics			
Guiding catheter expansion	179 (7.2%)	79 (6.4%)	100 (8.0%)
Thrombus present	237 (9.5%)	106 (8.5%)	131 (10.5%)
Rotablation	29 (1.2%)	13 (1.0%)	16 (1.3%)
Cutting balloon	30 (1.2%)	12 (1.0%)	18 (1.4%)

Data are n (%), mean (SD), or median (IQR). TIA=transient ischemic attack.

APPENDIX TABLE 2. Lesion-based interventional procedure data (analyses corrected for intra-patient correlation with generalized estimating equations)

	All lesions (n=3239)	Resolute Onyx (n=1646)	Orsiro (n=1593)	<i>p-value</i>
Complex lesion	2255 (69.7)	1144 (69.6)	1111 (69.6)	0.78
Bifurcation	1033 (31.9)	515 (31.3)	518 (32.5)	0.52
Chronic total occlusion	114 (3.5)	51 (3.1)	63 (4.0)	0.24
Bypass graft	44 (1.4)	19 (1.2)	25 (1.6)	0.29
Severely calcified lesion	502 (15.4)	247 (15.0)	255 (16.0)	0.30
Implantation of assigned stents only	3184 (98.3)	1623 (98.6)	1561 (98.0)	0.13
Number of stents per lesion	1.26 (0.56)	1.27 (0.55)	1.26 (0.57)	0.88
Postdilation	2065 (64.0)	1042 (63.5%)	1023 (64.5)	0.60
Lesion success	3217 (99.7)	1638 (99.7)	1579 (99.6)	0.60
Device success	3166 (98.1)	1616 (98.4)	1550 (97.8)	0.14
Preprocedural*				
Lesion length, mm	15.4 (11.0 - 23.2)	15.3 (10.9 - 22.9)	15.6 (11.2 - 23.7)	0.0504
Minimum lumen diameter, mm	0.75 (0.46 - 1.05)	0.75 (0.48 - 1.04)	0.74 (0.43 - 1.06)	0.17
Reference vessel diameter, mm	2.81 (0.56)	2.79 (0.57)	2.83 (0.56)	0.07
Lumen diameter stenosis, %	72.3 (61.5 - 83.0)	72.0 (61.2 - 82.1)	72.7 (61.8 - 84.4)	0.06
Postprocedural†				
Minimum lumen diameter, mm	2.41 (0.53)	2.41 (0.54)	2.41 (0.52)	0.95
Reference vessel diameter, mm	2.78 (0.55)	2.77 (0.56)	2.79 (0.54)	0.0482
Lumen diameter stenosis, %	12.7 (8.2 - 18.3)	12.4 (8.1 - 17.8)	13.0 (8.5 - 18.9)	0.24
Acute lumen gain in segment, mm	1.67 (0.63)	1.65 (0.62)	1.68 (0.64)	0.27

Data are n (%), means (SD) or median (IQR). All lesion-based analyses were corrected for intra-patient correlation with generalized estimating equations. There were no significant differences between the groups except for reference vessel diameter post-procedural. Definitions of lesion characteristics are on page 7. * Data for at least 1638 lesions in the Resolute Onyx group, and 1589 lesions in the Orsiro group. † Data for at least 1641 lesions in the Resolute Onyx group, and 1585 lesions in the Orsiro group.

APPENDIX TABLE 3. Extended clinical outcome

	All patients (n = 2488)		Hazard ratio (95% CI)	Log- rank p value
	Resolute Onyx (n=1243)	Orsiro (n=1245)		
Vascular death	2 (0.2%)	5 (0.4%)	0.40 (0.08 – 2.05)	0.25
Non-cardiovascular death	11 (0.9%)	8 (0.7%)	1.37 (0.55 – 3.40)	0.50
Non-target vessel myocardial infarction	3 (0.2%)	2 (0.2%)	1.49 (0.25 – 8.93)	0.66
Any revascularisation by PCI	50 (4.1%)	63 (5.1%)	0.79 (0.54 – 1.14)	0.20
Any revascularisation by CABG	16 (1.3%)	9 (0.7%)	1.78 (0.78 – 4.02)	0.16
Target vessel revascularisation by PCI	27 (2.2%)	32 (2.6%)	0.84 (0.50 – 1.40)	0.50
Target vessel revascularisation by CABG	13 (1.1%)	6 (0.5%)	2.16 (0.82 – 5.69)	0.11
Target lesion revascularisation by PCI	21 (1.7%)	21 (1.7%)	1.00 (0.54 – 1.82)	0.99
Target lesion revascularisation by CABG	11 (0.9%)	3 (0.2%)	3.66 (1.02 – 13.13)	0.0327
Any non-target vessel revascularisation	35 (2.8%)	47 (3.8%)	0.74 (0.48 – 1.14)	0.17
Non-target vessel revascularisation by PCI	25 (2.0%)	40 (3.3%)	0.62 (0.38 – 1.02)	0.0564
Non-target vessel revascularisation by CABG	10 (0.8%)	7 (0.6%)	1.42 (0.54 – 3.73)	0.47
Major bleeding*	31 (2.5%)	33 (2.7%)	0.94 (0.57 – 1.53)	0.79

The event rates (expressed as n and %) were calculated with the use of the Kaplan-Meier method. All target vessel revascularisations were clinically indicated. * Major bleeding was defined by bleeding academic research consortium (BARC) class class 3 or 5, or any thrombolysis in myocardial infarction (TIMI) major bleeding (i.e. CABG or non-CABG related). CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.

APPENDIX TABLE 4. Use of and adherence to antithrombotic medication

	All Patients	Resolute Onyx	Orsiro	<i>p-value</i>
At discharge	n=2488	n=1243	n=1245	
Aspirin	2425 (97.5%)	1216 (97.8%)	1209 (97.1%)	0.25
P2Y ₁₂ inhibitor	2485 (99.9%)	1241 (99.8%)	1244 (99.9%)	0.56
DAPT	2423 (97.4%)	1214 (97.7%)	1209 (97.1%)	0.38
with clopidogrel	1044 (42.0%)	524 (42.2%)	520 (41.8%)	0.84
with prasugrel or ticagrelor	1379 (55.4%)	690 (55.5%)	689 (55.3%)	0.93
Oral anticoagulation	254 (10.2%)	128 (10.3%)	126 (10.1%)	0.88
Vitamin K antagonist	172 (6.9%)	86 (6.9%)	86 (6.9%)	0.99
NOAC	82 (3.3%)	42 (3.4%)	40 (3.2%)	0.82
Oral anticoagulation with P2Y ₁₂ inhibitor	253 (10.2%)	128 (10.3%)	125 (10.0%)	0.83
Triple therapy*	200 (8.0%)	103 (8.3%)	97 (7.8%)	0.65
At 1-year follow-up	n=2432	n=1219	n=1213	
Aspirin	2134 (87.7%)	1078 (88.4%)	1056 (87.1%)	0.30
P2Y ₁₂ inhibitor	2347 (96.5%)	1174 (96.3%)	1173 (96.7%)	0.60
DAPT	2067 (85.0%)	1043 (85.6%)	1024 (84.4%)	0.43
with clopidogrel	847 (34.8%)	441 (36.2%)	406 (33.5%)	0.16
with prasugrel or ticagrelor	1220 (50.2%)	602 (49.4%)	618 (50.9%)	0.44
Oral anticoagulation	290 (11.9%)	146 (12.0%)	144 (11.9%)	0.94
Vitamin K antagonist	175 (7.2%)	86 (7.1%)	89 (7.3%)	0.79
NOAC	115 (4.7%)	60 (4.9%)	55 (4.5%)	0.65
Oral anticoagulation with P2Y ₁₂ inhibitor	271 (11.1%)	136 (11.2%)	135 (11.1%)	0.98
Triple therapy*	19 (0.8%)	14 (1.1%)	5 (0.4%)	0.0379

* Triple therapy consists of aspirin, a P2Y₁₂ inhibitor, and oral anticoagulation. DAPT=dual antiplatelet therapy. NOAC=non-vitamin K oral anticoagulant. VKA=vitamin K antagonist.

APPENDIX TABLE 5. Circumstances and consequences of stent thrombosis

Stent thrombosis (days) Definite Probable	Sex (age in years)	Clinical presentation (index PCI)	Lesion class*	Min stent diameter / total stent length	Stent overlap	Post dilatation	Clinical consequences	Antithrombotic medication	
Resolute Onyx									
10	-	Male (81)	Stable angina	C	2.5 / 101	Yes	Yes	Acute MI with cardiogenic shock; TLR	Clopidogrel, VKA [†]
Orsiro									
0	-	Male (50)	Unstable angina	C	3.0 / 100	Yes	Yes	No-reflow during initial procedure; Acute MI	Aspirin, Clopidogrel
0	-	Male (78)	Unstable angina	B2	2.25 / 26	No	Yes	Acute MI after PCI; TLR	Aspirin, Ticagrelor
0	-	Male (63)	STEMI	B2	3.5 / 18	N/A	Yes	Acute MI after PCI; TLR	Aspirin, Ticagrelor
3	-	Male (72)	STEMI	C	2.5 / 18	N/A	No	Acute MI; TLR; Cardiac death after mitral valve surgery because of ischemic MR	Aspirin, Ticagrelor
22	-	Female (64)	NSTEMI	C (CTO)	2.0 / 136 [†]	Yes	Yes	Acute MI; TLR	Aspirin, Ticagrelor
106	-	Male (57)	Stable angina	C	3.0 / 26	N/A	No	Acute MI; TLR	Aspirin, Ticagrelor
340	-	Male (69)	Stable angina	C (CTO)	2.5 / 91	Yes	Yes	Acute MI; TLR	Aspirin, Clopidogrel
-	7	Male (67)	NSTEMI	C (SVG)	3.5 / 9	N/A	Yes	Sudden death (no autopsy)	Aspirin, Ticagrelor
-	7	Male (64)	STEMI	C	3.0 / 43	Yes	Yes	Sudden death (no autopsy)	Aspirin, Ticagrelor

Stent thromboses occurred following interventions in 4 study sites without any abnormal clustering. Only one of the patients had a non-assigned stent implanted, but the non-assigned stent was not the stent in which stent thrombosis occurred. [‡] The minimal stent diameter of 2.0 mm concerns a cross-over stent but stent thrombosis occurred in an assigned stent (one of five assigned stents implanted). * Lesion classification according to the American College of Cardiology/American Heart Association. [†] Patient stopped aspirin because he was out of medication. CTO=chronic total occlusion, MI=myocardial infarction, MR=mitral regurgitation; NSTEMI=non-ST elevation myocardial infarction, PCI=percutaneous coronary intervention, STEMI=ST elevation myocardial infarction, SVG=Saphenous vein graft, TLR=target lesion revascularisation, VKA=vitamin K antagonist.

5-YEAR OUTCOME FOLLOWING
RANDOMIZED TREATMENT OF
ALL-COMERS WITH ZOTAROLIMUS-
ELUTING RESOLUTE INTEGRITY AND
EVEROLIMUS-ELUTING PROMUS
ELEMENT CORONARY STENTS:
FINAL REPORT OF THE
DUTCH PEERS (TWENTE II) TRIAL

8

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ABSTRACT

Objectives: The study sought to evaluate for the first time the 5-year outcomes after treating an all-comers population with newer-generation cobalt chromium-based Resolute Integrity zotarolimus-eluting stents (ZES) (Medtronic, Santa Rosa, California) versus platinum chromium-based PROMUS Element everolimus eluting stents (EES) (Boston Scientific, Natick, Massachusetts).

Background: The DUTCH PEERS (TWENTE II) (DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity: TWENTE II) trial is a randomized, multicenter, single-blinded, investigator-initiated all-comers trial that found at its main analysis similar 1-year safety and efficacy for both drug-eluting stents. It is the first randomized trial ever to investigate the Resolute Integrity ZES and the first trial to compare both devices.

Methods: In total, 1,811 patients were 1:1 randomized to ZES versus EES. We performed a pre-specified assessment of the 5-year clinical outcomes in terms of safety and efficacy. The main endpoint target vessel failure (TVF) is a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization. Secondary endpoints included the individual components of TVF, and stent thrombosis. The study was independently monitored, and adverse clinical events were independently adjudicated.

Results: Five-year clinical follow-up data was available in 1,798 (99.3%) patients. The ZES and EES groups showed favorable outcomes, with similar 5-year incidence of TVF (13.2% vs. 14.2%; $p_{\log\text{-rank}} = 0.62$) and its individual components: cardiac death (4.5% vs. 4.9%; $p_{\log\text{-rank}} = 0.69$), target vessel-related myocardial infarction (3.1% vs. 2.6%; $p_{\log\text{-rank}} = 0.47$), and target vessel revascularization (7.6% vs. 8.6%; $p_{\log\text{-rank}} = 0.46$). The 5-year incidence of definite or probable stent thrombosis was similar (1.5% vs. 1.3%; $p_{\log\text{-rank}} = 0.83$).

Conclusions: At 5-year follow-up, the Resolute Integrity ZES and PROMUS Element EES showed similar and sustained results in terms of safety and efficacy for treating a broad population of all-comers.

INTRODUCTION

Second-generation metallic drug-eluting stents (DES) have resolved the issue of late and very late coronary stent thrombosis, which occurred with first generation DES in the late post-implantation period, by improvements in stent design and polymer coatings, and the use of newer antiproliferative drugs.¹ The cobalt-chromium-based Resolute Integrity zotarolimus-eluting stent (ZES) (Medtronic, Santa Rosa, California) and the platinum chromium-based PROMUS Element everolimus-eluting stent (EES) (Boston Scientific, Natick, Massachusetts) are examples of newer-generation DES that were developed to facilitate deliverability and improve DES apposition while maintaining the same durable polymer coatings and antiproliferative drugs as used in the second-generation DES.²⁻⁴ Both DES were compared for the first time in the randomized DUTCH PEERS (Durable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity) trial, which demonstrated in 1,811 all-comer patients noninferiority of ZES versus EES for the primary endpoint target vessel failure (TVF) at 1-year follow-up (6.1% vs. 5.2%; noninferiority $p=0.006$).²

Long-term data from comparative clinical DES trials are of significant interest as certain between-stent differences, such as late restenosis and very late stent thrombosis, may only be discovered after several years. However, published reports of long-term clinical outcome data are limited and not yet available for the 2 aforementioned DES. In this final report of the DUTCH PEERS trial we present the 5-year assessment of safety and efficacy of treating a broad population of all-comers by percutaneous coronary interventions (PCIs) with these newer-generation DES.

METHODS

Study design and patient populations

The design of the DUTCH PEERS trial has previously been reported.⁵ In short, this multicenter, patient-blinded, investigator-initiated, randomized clinical trial (NCT01331707) enrolled 1,811 patients between November 2010 and May 2012 at 4 PCI centers in the Netherlands (Thoraxcentrum Twente, Enschede; Rijnstate Hospital, Arnhem; Treant Zorggroep, Emmen; Alkmaar Medical Center, Alkmaar). Patients 18 years of age and older and capable of providing informed consent with an indication for PCI with DES were randomized in a 1:1 fashion for treatment with Resolute Integrity ZES or PROMUS Element EES. Exclusion criteria were limited and all coronary syndromes, de novo and restenotic lesions, and coronary artery or bypass stenosis were permitted. There was no limit for lesion length, reference size, or number of lesions to be treated.²

Generally, dual antiplatelet therapy consisted of aspirin and clopidogrel and was prescribed in patients without anticoagulation therapy for 1 year. In patients on oral anticoagulation, triple therapy was generally prescribed for 1 to 3 months, followed by a period with clopidogrel as a single antiplatelet agent.

The contract research organization CardioResearch Enschede (Enschede, the Netherlands) coordinated the trial and data management. Follow-up data were obtained by the treating physician or cardiologist or dedicated research nurses every 12 months during routine visits to outpatient clinics (if they coincided with the time of follow-up) or by telephone call or medical questionnaire. Clinical outcome monitoring and event adjudication was performed by the independent external CRO Diagram (Zwolle, the Netherlands). The DUTCH PEERS trial complied with the CONSORT 2010 statement⁶ and the Declaration of Helsinki, and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centers. All patients provided written informed consent. The clinical outcome of the DUTCH PEERS trial has not been reported beyond the 3-year follow-up.⁷

Clinical endpoints

Clinical endpoints were defined according to the Academic Research Consortium, including the addendum on definition of myocardial infarction (MI).^{8,9} The main endpoint was TVF at 5-year follow-up, a composite of cardiac death, target vessel-related MI or clinically indicated target vessel revascularization. Pre-specified secondary endpoints included the individual components of TVF, all-cause mortality, and definite or probable stent thrombosis. Further composite clinical endpoints were: target lesion failure (TLF) (cardiac death, any MI which was not clearly attributable to a nontarget vessel, or clinically indicated target lesion revascularization), major adverse cardiac events (MACE) (all-cause death, any MI, emergent coronary artery bypass surgery, or repeat clinically indicated target lesion revascularization), and a more global patient-oriented composite endpoint (all-cause death, any MI, or any coronary revascularization).

Besides this, we assessed very late clinical adverse events in all patients who had stents implanted with longitudinal stent deformation during the index procedure.² Of all cases of longitudinal stent deformation, 6 of 9 (66.7%) cases were detected by angiography (i.e., no intracoronary imaging modalities were used) by the operator whereas all 9 cases were detected post-procedurally by the analysts. All stent deformations were located in the proximal stent entrance; additional proximal stents were implanted in 7 of 9 (77.8%) cases and post-dilation was performed in 8 of 9 (88.9%) cases. Death was regarded as cardiac unless an unequivocal noncardiac cause could be established. MI was defined

by creatine kinase concentrations of more than double the upper limit of normal with raised confirmatory cardiac biomarkers. Revascularization procedures were regarded as clinically indicated if the angiographic diameter stenosis of the then treated lesion was 50% or more in the presence of ischemic signs or symptoms, or if the diameter stenosis was 70% or more irrespective of ischemic signs or symptoms.⁹

Statistical analysis

Categorical variables were assessed with the chi-square test, whereas continuous variables were assessed with the Student t test or the Wilcoxon rank sum test, as appropriate. The time to clinical endpoints was assessed by Kaplan-Meier analyses and the log-rank test was applied to compare groups. Hazard ratios were calculated using Cox proportional hazards regression analysis. The p values and confidence intervals were 2-sided and p values < 0.05 were considered significant. Further details on statistical methods have been reported previously (2). SPSS version 22.0 (IBM Corporation, Armonk, New York) was used.

RESULTS

Out of all 1,811 patients, 5-year clinical follow-up data were available in 1,798 patients (99.3% follow-up: 3 patients were lost to follow-up and 10 withdrew consent) (Figure 1). As previously reported, there were no differences in baseline clinical and lesion characteristics between patients randomized to treatment with ZES versus EES (Table 1).² In both groups, large proportions of patients with acute MI presentation (46.5% vs. 43.7%) were included. Target lesion and interventional characteristics were also similar for both groups, including high rates of complex coronary lesions (American College of Cardiology/American Heart Association class B2 or C: 65.8% vs. 65.6%), with the only exception of more frequent stent postdilation in EES (73.6% vs. 78.9%; p = 0.002) (Table 2). This is probably related to the excellent radiographic visibility of the PROMUS Element EES and has been reported in other trials.⁴

At discharge, most patients (99%) were treated with antiplatelet therapy that included aspirin and clopidogrel; only 18 (1%) patients received prasugrel and 3 (<1%) patients received ticagrelor in addition to aspirin. Information regarding medication use at 5-year follow-up was available in ≥93.9% of all patients. In both DES groups, there was no statistically significant difference in the use of aspirin (78.7% vs. 81.3%; p = 0.17), P2Y₁₂ receptor inhibitors (12.1% vs. 10.2%; p = 0.22), dual antiplatelet therapy (6.6% vs. 6.4%; p = 0.88), oral anticoagulant agents (15.8% vs. 15.8%; p = 0.85), or statins (86.4% vs. 85.0%; p = 0.42).

FIGURE 1. Study flow chart.
Study flow chart of the DUTCH PEERS (Durable polymer-based stent Challenge of Promus ElemEnt versus Resolute integrity) trial. EES = everolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

The 5-year incidence of the main clinical endpoint TVF was favorable and similar for the ZES and EES groups (13.2% vs. 14.2%; log-rank $p = 0.62$) (Table 3, Figure 2 and 3). The rates of the individual components of TVF were also similar for both stent arms: cardiac death (4.5% vs. 4.9%; log-rank $p = 0.69$); target vessel-related MI (3.1% vs. 2.6%; log-rank $p = 0.47$); and target vessel revascularization (7.6% vs. 8.6%; log-rank $p = 0.46$), respectively (Figure 2). In addition, the rates of the composite endpoints TLF (12.0% vs. 12.5%; log-rank $p = 0.86$), MACE (17.0% vs. 17.2%; log-rank $p = 0.97$), and the patient-oriented composite endpoint (22.8% vs. 23.3%; log-rank $p = 0.86$) were similar for both groups (Table 3).

As shown in Table 3, the rates of definite or probable stent thrombosis were low for patients treated with ZES and EES (1.5% vs. 1.3%; log-rank $p = 0.83$). Due to an apparent dissimilarity between the Resolute Integrity ZES and PROMUS Element EES groups in the course of their time-to-event curves for definite or probable stent thrombosis, an additional post hoc landmark analysis at 12-month follow-up is displayed in Figure 4, Table 3. Definite or probable stent thrombosis occurred in 0.6% versus 0.9% (log-rank $p = 0.41$) of patients during the first year and in 0.9% vs. 0.5% ($p = 0.24$) during the second to fifth years.

Longitudinal stent deformation during the index procedure was observed in 9 of the patients treated with EES and in none of the patients treated with ZES. Between 1- and 5-year follow-up, 1 of these EES patients died from progressive heart failure (unrelated to the implanted study stent) whereas all other patients experienced no adverse event.

DISCUSSION

Main results

The present study reports the final 5-year clinical outcome of the randomized DUTCH PEERS trial, which assessed the safety and efficacy of the Resolute Integrity ZES versus PROMUS Element EES in treating all-comer patients.² The rates of the main clinical endpoint TVF (13.2% vs. 14.2%) were relatively low and similar for both stent groups. There was also no significant between-group difference in the individual components of TVF (i.e., cardiac death, target vessel related MI, and clinically driven target vessel revascularization). Very late stent thrombosis was rare, and the 5-year incidence of stent thrombosis was low and comparable in both groups (definite or probable, 1.5% vs. 1.3%). The present 5-year results are consistent with the main outcome of DUTCH PEERS trial at 1-year follow-up, which demonstrated noninferiority of ZES versus EES.² Furthermore,

TABLE 1. Baseline demographics

	Resolute Integrity ZES (n=906)	PROMUS Element EES (n=905)	<i>p</i> value
Age, years	63.9 ± 10.6	63.9 ± 11.0	0.97
Men	665 (73.4)	657 (72.6)	0.70
Body-mass index (kg/m²)*	28.1 ± 4.8	27.8 ± 4.6	0.39
Diabetes Mellitus (any)	167 (18.4)	157 (17.3)	0.55
Chronic renal failure†	35 (3.9)	28 (3.1)	0.37
Arterial hypertension	500 (55.2)	484 (53.5)	0.47
Hypercholesterolemia	418 (46.1)	430 (47.5)	0.56
Current smoker‡	213 (23.6)	231 (25.5)	0.32
Family history of coronary artery disease§	452 (50.1)	451 (49.9)	0.98
Previous myocardial infarction	207 (22.8)	190 (21.0)	0.34
Previous percutaneous coronary intervention	182 (20.1)	167 (18.5)	0.38
Previous coronary bypass surgery	84 (9.3)	89 (9.8)	0.68
Clinical syndrome at presentation			0.07
Stable angina	372 (41.1)	377 (41.7)	
Unstable angina	113 (12.5)	132 (14.6)	
Non-ST-elevation myocardial infarction	246 (27.2)	201 (22.2)	
ST-elevation myocardial infarction	175 (19.3)	195 (21.5)	
Acute coronary syndrome (any)	534 (58.9)	528 (58.3)	0.80
Left ventricular ejection fraction <30%	15 (1.7)	13 (1.4)	0.71
De-novo coronary lesions only	817 (90.2)	810 (89.5)	0.64
At least one chronic total occlusion	38 (4.2)	38 (4.2)	0.99
At least one bifurcation	244 (26.9)	221 (24.4)	0.22
At least one in-stent restenosis	27 (3.0)	28 (3.1)	0.89
At least one small-vessel (RVD <2.75 mm)	551 (60.8)	517 (57.1)	0.11
At least one lesion length > 27 mm	161 (17.8)	157 (17.3)	0.81
Glycoprotein IIb/IIIa antagonist	262 (28.9)	259 (28.6)	0.89
Number of lesions treated per patient			0.32
One	668 (73.7)	668 (76.0)	
Two	191 (21.1)	182 (20.1)	
Three or more	47 (5.2)	35 (3.9)	

Values are mean ± SD or n (%). *Data from 721 patients in the zotarolimus-eluting stent(s) (ZES) group and 703 patients in the everolimus-eluting stent(s) (EES) group. †Chronic renal failure defined by serum creatinine level ≥130 mmol/l. ‡Data from 903 patients in the ZES group and 905 patients in the EES group. §Data from 903 patients in the ZES group and 902 patients in the EES group. RVD = reference vessel diameter.

landmark analyses at 1-year showed for all endpoints no statistically significant difference between the stent groups.

Previous studies

A meta-analysis of randomized trials, comparing different types of ZES versus EES, showed comparable safety and efficacy at short-term to midterm follow-up.¹⁰ The same meta-analysis suggested that in real-world observational studies EES may be more safe and efficacious, a finding that was greatly driven by the outcome of studies that compared EES versus the no longer available Endeavor ZES, which was known to have a higher repeat revascularization risk.^{10,11} This underlines the importance of obtaining long-term outcome data from large-scale randomized all-comer trials to evaluate the clinical value of modified stents that may be considered to be derivatives. However, 5-year long-term outcomes of all-comers, treated either with Resolute Integrity ZES or with PROMUS Element EES, have not been reported yet.¹

The SORT OUT VI (Scandinavian Organization for Randomized Trials with Clinical Outcome VI) trial is the only other large-scale randomized trial that assessed the Resolute Integrity in all-comers.³ That study compared 1,502 patients treated with Resolute Integrity ZES versus 1,497 patients treated with biodegradable polymer-based biolimus-eluting Bio-Matrix Flex stents (Biosensors, Singapore) and showed at 3-year follow-up for both stents similar rates of the primary endpoint MACE (8.6% vs. 9.6%; $p = 0.36$) and all secondary endpoints, including definite or probable stent thrombosis (1.3% vs. 1.2%; $p = 0.86$).¹² In addition, some previous randomized studies compared the predecessor of the Resolute Integrity ZES (i.e., the Resolute ZES) with EES in broad patient populations and showed favorable 5-year outcomes for both devices.¹³⁻¹⁵

So far, the PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial is the only large-scale randomized study besides the DUTCH PEERS trial that has published 3-year follow-up data of PROMUS Element EES.¹³ In the PLATINUM trial, 758 patients treated with the platinum-chromium PROMUS Element EES were compared to 749 patients treated with the cobalt-chromium Xience V EES (Abbott Vascular, Santa Clara, California).⁴ The study showed a favorable safety and efficacy for both stent groups: the TLF rate was 5.9% versus 7.1% ($p = 0.40$); the rate of a composite endpoint of all-cause death, MI, or target vessel revascularization was 11.4% versus 12.7% ($p = 0.48$); and the incidence of definite or probable stent thrombosis was low and comparable in both treatment arms (0.7% vs. 0.5%; $p = 0.76$).⁴ Nevertheless, the PLATINUM trial did not assess allcomers but rather a population of

low- to medium-risk patients who experienced stable or unstable angina and required PCI for up to 2 de novo coronary lesions in vessels with a diameter of at least 2.5 mm. The present 5-year follow-up of the DUTCH PEERS trial supports the favorable 3-year findings of the PLATINUM trial in a much broader patient population. Besides this, our results are consistent with long-term outcomes in the COMPARE II (Abtimal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent) trial, which compared the predecessor of the PROMUS Element (i.e., the PROMUS EES) or Xience V EES to a biodegradable-polymer biolimus-eluting stent.¹⁴

FIGURE 2. Kaplan-Meier curves for target vessel failure and the individual components thereof. Kaplan-Meier curves for (A) target vessel failure, (B) cardiac death, (C) target vessel-related myocardial infarction, and (D) target vessel revascularization for patients treated with the Resolute Integrity ZES (yellow) versus PROMUS Element EES (gray). Abbreviations as in **FIGURE 1**.

TABLE 2. Target lesion characteristics and interventional procedure

	Resolute Integrity ZES (n=1,205 lesions)	PROMUS Element EES (n=1,166 lesions)	<i>p</i> value
De novo lesion*	1,147 (95.2)	1103 (94.6)	0.51
ACC/AHA lesion class B2/C	793 (65.8)	765 (65.6)	0.92
Reference vessel diameter (mm)	2.68 ± 0.59	2.70 ± 0.59	0.32
Implantation of assigned stents only	1,195 (99.2)	1,161 (99.6)	0.22
Number of stents per lesion	1.35 ± 0.68	1.36 ± 0.70	0.70
Total stent length per lesion (mm)	28.60 ± 18.51	29.71 ± 19.11	0.15
Direct stenting	352 (29.2)	326 (28.0)	0.50
Stent post dilation	887 (73.6)	920 (78.9)	0.002

Value are n (%) or mean ± SD. Details of lesion characteristics and interventional procedure have previously been reported. *Including chronic total occlusion, but not grafts or in-stent restenosis. ACC/AHA = American College of Cardiology/American Heart Association; other abbreviations as in Table 1.

Stent thrombosis

Although the risk of very late stent thrombosis is attenuated with the introduction of second-generation DES,¹⁵⁻¹⁸ each individual case represents an important adverse event that can result in a large MI or death. A recent study in 64 patients with very late DES thrombosis, assessed by optical coherence tomography, revealed a median time from DES implantation until very late stent thrombosis of 4.7 years (interquartile range: 3.1 to 7.5 years).¹⁹ This emphasizes the need for a prolonged follow-up of clinical DES trials. It is reassuring that the rate of very late stent thrombosis is low in the present 5-year analysis of the DUTCH PEERS trial, as well as in other studies with 5-year follow-up.^{14,20-22}

Longitudinal stent deformation

Longitudinal stent deformation has been identified as a potential trade-off of newer-generation DES due to a decreased longitudinal stability caused by thinner stent struts and a reduced number of connectors.^{23,24} However, in the DUTCH PEERS trial, longitudinal stent deformation was observed only in 0.6% of the implanted PROMUS Element EES and in none of the Resolute Integrity ZES.² A recent meta-analysis of randomized trials showed a higher risk of observing longitudinal stent deformation in PROMUS Element EES than in other newer-generation DES that was not associated with worse clinical outcome at 1-year follow-up.²⁵ The findings of the present analysis of the DUTCH PEERS

TABLE 3. Clinical outcomes at 5-year follow-up

	Resolute Integrity ZES	PROMUS Element EES	Hazard ratio (95% CI)	P _{log-rank}	Resolute Integrity ZES	PROMUS Element EES	Difference (95% CI)	p value
Target vessel failure	118 (13.2)	127 (14.2)	0.94 (0.73 – 1.21)	0.62	63 (7.5)	80 (9.3)	-1.9 (-4.5 – 0.8)	0.17
Death (any)	86 (9.5)	82 (9.1)	1.06 (0.78 – 1.43)	0.72	64 (7.2)	70 (7.8)	-0.6 (-3.1 – 1.9)	0.64
Cardiac death	40 (4.5)	44 (4.9)	0.92 (0.60 – 1.41)	0.69	25 (2.8)	34 (3.8)	-1.0 (-2.6 – 0.7)	0.25
Target vessel myocardial infarction	28 (3.1)	23 (2.6)	1.23 (0.71 – 2.13)	0.47	8 (0.9)	11 (1.2)	-0.3 (-1.3 – 0.7)	0.52
Target vessel revascularization	66 (7.6)	75 (8.6)	0.88 (0.64 – 1.23)	0.46	42 (4.9)	49 (5.7)	-0.8 (-2.9 – 1.3)	0.48
Target lesion failure	109 (12.0)	113 (12.5)	0.98 (0.75 – 1.27)	0.86	58 (6.8)	72 (8.4)	-1.5 (-4.0 – 1.0)	0.24
Major adverse cardiac events	154 (17.0)	156 (17.2)	1.00 (0.80-1.25)	0.97	96 (11.3)	112 (13.0)	-1.7 (-4.8 – 1.4)	0.29
Patient-oriented composite endpoint	207 (22.8)	211 (23.3)	0.98 (0.81-1.19)	0.86	125 (15.2)	137 (16.5)	-1.3 (-4.8 – 2.2)	0.47
Definite-or-probable stent thrombosis	13 (1.5)	12 (1.3)	1.09 (0.50 – 2.39)	0.83	8 (0.9)	4 (0.5)	0.4 (-0.3 – 1.2)	0.24
Definite stent thrombosis	10 (1.1)	10 (1.1)	1.00 (0.42 – 2.41)	0.99	7 (0.8)	4 (0.5)	0.3 (-0.4 – 1.1)	0.36

Values are n (%). CI = confidence interval; other abbreviations as in Table 1.

trial extend our knowledge, as they show that longitudinal stent deformation, which was recognized and directly managed by the operator in the majority of cases, was not associated with very late adverse clinical events.

FIGURE 3. Kaplan-Meier curves for target vessel failure. Kaplan-Meier curves for target vessel failure for patients treated with Resolute Integrity zotarolimus-eluting (yellow) versus PROMUS Element everolimus-eluting stents (gray).

Study limitations

This analysis of the 5-year follow-up was pre-specified but the findings should be considered hypothesis generating. The high 5-year follow-up rate (>99%) and the independent monitoring and adjudication support the validity of the data, but our study is not powered to assess low-incidence adverse events. Nevertheless, in the absence of long-term data from other or even larger randomized all-comer studies to compare both DES, we believe that these data are of interest. From baseline to 5-year follow-up there was an increase in the proportion of patients on oral anticoagulation from 8.8% to 15.8%, which may be most likely related to an increase in the prevalence of atrial fibrillation during this study with long-term follow-up; the latter remains hypothetical, as we did not assess reasons for starting oral anticoagulation. We cannot exclude some degree of selection during enrollment, as 56.2% of all eligible patients were enrolled.² Nevertheless, it may be fair to state that this enrollment rate is relatively high for an all-comer DES trial, and the high proportion of patients who underwent the index PCI

for an acute MI (45.1%) underlines that this trial provides information that is relevant to routine clinical practice.

FIGURE 4. Landmark analysis for definite or probable stent thrombosis. Kaplan-Meier curve of stent thrombosis for patients treated with the Resolute Integrity ZES (yellow) versus the PROMUS Element EES (gray). Dual antiplatelet therapy (DAPT) means acetylsalicylic acid plus P2Y₁₂ receptor antagonist. Abbreviations as in **FIGURE 1**.

CONCLUSIONS

At 5-year follow-up, the Resolute Integrity ZES and PROMUS Element EES showed similar and sustained results in terms of safety and efficacy for treating a broad population of all-comers.

PERSPECTIVES

WHAT IS KNOWN? Newer-generation DES are superior to first-generation DES. The DUTCH PEERS randomized trial has shown low rates of adverse clinical events, such as target vessel MI, repeat target vessel revascularization, and stent thrombosis for 2 newer-generation DES: the Resolute Integrity ZES and the PROMUS Element EES. However, data on the 5-year safety and efficacy of both stents are not available yet.

WHAT IS NEW? The present long-term results of the DUTCH PEERS trial provide a strong signal of similar and sustained safety and efficacy of both metallic DES after 5 years of follow-up in a broad population of all-comer patients.

WHAT IS NEXT? These data are useful to interpret the long-term outcome of novel DES and to put the long-term clinical outcome after treatment with bioresorbable vascular scaffolds into perspective.

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CONFLICTS OF INTEREST

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LATE CLINICAL OUTCOME
OF STENT TRIALS:
A MATTER OF LIFE OR DEATH?

9

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Clemens von Birgelen
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Millions of patients with obstructive coronary artery disease worldwide are treated with metallic stents each year. Since the first stent implantation in a human in 1986, stents have undergone substantial refinements that have involved numerous innovations and extensive clinical research.¹ Over three decades, various problems were faced and solved or minimised. Among them were the frequent acute and sub-acute thrombotic occlusions of the very first stents, the recurrence of difficult-to treat lesions within bare metal stents (typically within the first 6 months after implantation), and the late (1–12 months after implantation) and very late (>1 year after implantation) formation of thrombi in the first generation of drug-eluting stents.² New-generation drug-eluting stents with more biocompatible polymer coatings reduce the risk of stent thrombosis compared with first-generation drug-eluting stents, and have a similar low risk of lesion recurrence and need for reintervention. These good safety and efficacy outcomes were found in studies^{3–7} assessing patients with only few exclusion criteria (so-called all-comers) undergoing percutaneous coronary intervention. As a result, these studies included many patients with complex clinical characteristics (eg, acute myocardial infarction, diabetes, or multivessel disease) and target lesions (eg, with a total occlusion or thrombi).

Randomised clinical trials are designed so that the study population, the primary outcome, and the time at which the primary outcome is assessed reflect clinically relevant challenges. Several stent studies^{3–11} reported not only primary outcomes — generally at 1-year follow-up — but also provided information about longer-term safety and efficacy. It is of particular interest to gain insight into the thrombosis risk of new stents after cessation of dual antiplatelet therapy; such information will generally be obtained during the second year of follow-up because most all-comers are treated for acute coronary syndromes with a recommended dual antiplatelet therapy for 12 months. However, given that most patients live for many years or even decades after percutaneous coronary intervention, data from even longer-term follow-up are also needed.

In *The Lancet*, Thomas Pilgrim and colleagues¹² report 5-year outcome data of BIOSCIENCE, a large-scale, randomised trial in patients with chronic stable coronary artery disease or acute coronary syndromes from Switzerland. In that study, 1063 patients treated with ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents had a similar cumulative incidence of the primary composite outcome, target lesion failure (consisting of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation), as did 1056 patients treated with thin-strut, durable-polymer, everolimus-eluting stents (20.2% with the biodegradable polymer vs 18.8% with the durable polymer; rate ratio [RR] 1.07, 95% CI 0.88–1.31; $p=0.49$). These event

rates were higher than those in other large-scale trials^{8–10} in all-comers that compared two new-generation drug-eluting stents and reported 5-year outcomes (11.5–17.0%).

Pilgrim and colleagues also found that the incidence of important safety endpoints, cardiac death, target vessel myocardial infarction, and definite stent thrombosis, were similar in both stent groups. In fact, the incidence of all-cause death was the only one of 20 outcome parameters to differ significantly between stents (14.1% in the biodegradable-polymer group vs 10.3% in the durable-polymer group; RR 1.36, 95% CI 1.06–1.75; $p=0.017$), driven by a difference between groups in the incidence of death secondary to different types of cancer. Based on existing knowledge and the results of other trials that assessed sirolimus-eluting stents, play of chance might be the most plausible explanation for this difference. Nevertheless, given that age is directly related to an increased risk of both cancer development and death, it might be relevant that the average age of the study population (around 66 years) was the highest of all previous trials^{3–6,8–10} in all-comers that reported 5-year outcomes (62.9–65.1 years). In BIOSCIENCE, the difference in all-cause mortality emerged within 2 years of stent implantation. By contrast, in the BIO-RESORT trial,¹³ all-cause mortality at 2 years was low (2.6%) for patients treated with the same sirolimus-eluting stent as in the BIOSCIENCE trial, and was numerically but not significantly lower in these patients than in patients treated with durable-polymer, zotarolimus eluting stents (3.3%). Similarly, in the 5-year follow-up of the TWENTE trial,¹¹ all-cause mortality was 2.6% lower in patients treated with zotarolimus-eluting stents than in those treated with everolimus-eluting stents (9.0% vs 11.6%; $p=0.12$).

The event rates reported in various clinical trials are affected by a multitude of factors, such as the composition of the study population, the use of non-invasive tests to diagnose myocardial ischaemia, the frequency of invasive physiological assessments to ascertain the haemodynamic significance of intermediate coronary stenoses, the complexity of target lesions, the exact type and duration of dual antiplatelet therapy (and other drugs), endpoint definitions, and follow-up procedures. Additionally, human factors and region-specific or country-specific characteristics might be relevant. For example, there might be differences in patient compliance and how patients cope with symptoms, the ease and frequency at which health-care providers can be contacted, the coverage of costs by health-care insurance, and how interventional procedures are performed. Procedures might differ in use of fractional flow reserve measurements and stent post dilation and in staging of multivessel procedures, which in some countries might be related to reimbursement practices.

These considerations and the long-term results of BIOSCIENCE suggest that it is desirable to obtain outcome data for novel coronary stents from more than one randomised clinical trial. Ideally, these trials should originate from different countries so as to increase diversity in study populations. Ultimately, late follow-up of clinical trials might be a matter of life or death.

CONFLICTS OF INTEREST

CvB's research department of Thorax Centrum Twente reports institutional research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic.

CvB is the principal investigator of several randomised clinical trials and registries; he has been an unpaid consultant for Abbott Vascular, Biotronik, and Medtronic, outside the area of work commented on here. PZ declares no competing interests.

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CHAPTER 9

12. Pilgrim T, Piccolo R, Heg D, et al. Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial. *Lancet* 2018;published online Aug 28. [http://dx.doi.org/10.1016/S0140-6736\(18\)31715-X](http://dx.doi.org/10.1016/S0140-6736(18)31715-X).
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GENERAL DISCUSSION
AND FUTURE PERSPECTIVES

10

GENERAL DISCUSSION

Dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor has been shown to reduce the risk of stent thrombosis and myocardial infarction after percutaneous coronary intervention with coronary stent implantation.¹ The balloon- and stent-related injury of the arterial intima and media increases the risk of thrombus formation, and atherosclerotic disease remote from the site of coronary intervention may be a source of ischemic events as well. After the implantation of coronary stents, clopidogrel-based dual antiplatelet therapy has been the standard of care for many years.^{2,3} In addition, clopidogrel is still recommended in patients with stable angina who undergo coronary stenting.⁴ In patients with acute coronary syndromes, who have a higher risk of intracoronary thrombosis and recurrent myocardial infarction, clopidogrel has largely been replaced by prasugrel and ticagrelor, since clinical trials have shown further reduction of cardiovascular events with these newer drugs.^{5,6} Notably, these trials were performed in an era in which bare metal and of first-generation drug-eluting stents were primarily used.

In current clinical practice, all patients undergoing percutaneous coronary intervention generally are treated with new-generation drug-eluting stents that have shown superior outcomes over bare metal stents and first-generation drug-eluting stents in numerous studies.⁷⁻⁹ In the ‘real world’ CHANGE DAPT observational study (**Chapter 2**) that exclusively assessed patients who were treated with contemporary drug-eluting stents, the use of ticagrelor was associated with a higher adverse event risk than the use of clopidogrel. In the CHANGE DAPT study, ticagrelor-based dual antiplatelet therapy did not reduce ischemic events, but as expected, it increased the risk of major bleeding. Nevertheless, extended follow-up showed no difference in mortality between the clopidogrel and ticagrelor groups at two years from stenting (**Chapter 3**).

Both ischemic and bleeding events affect the prognosis of patients with coronary artery disease.¹⁰⁻¹² In patients on dual antiplatelet therapy some bleeding complications may be expected, as platelet function plays an important role in achieving haemostasis. An in-depth analysis of the CHANGE DAPT study showed that high bleeding risk patients suffer most from the increased risk of major bleeding, associated with ticagrelor-based dual antiplatelet therapy (**Chapter 4**). Nevertheless, high bleeding risk patients may theoretically also benefit from ticagrelor-based dual antiplatelet therapy. Intuitively this might seem contradictory, but high bleeding risk patients also have an increased risk of recurrent ischemic events.¹³ Still, the use of ticagrelor did not reduce ischemic endpoints in participants in the CHANGE DAPT observational study, compared to the use of clopidogrel.

Major bleedings are associated with mortality and a reduced quality of life.^{12,14,15} Consequently, every effort should be made to minimize bleeding risk. To achieve this, bare metal stents were frequently used in high bleeding risk patients, even after the introduction of drug-eluting stents.¹⁶ Endothelialization of bare metal stents will largely be completed within a month,¹⁷ and so the P2Y₁₂ inhibitor of dual antiplatelet therapy may be discontinued after that period. This brief duration of dual antiplatelet therapy is associated with a lower risk of bleeding-related death following percutaneous coronary intervention.¹⁵ On the contrary, after concerns about the increased risk of very late stent thrombosis in patients treated with first-generation drug-eluting stents,¹⁸ twelve months of dual antiplatelet therapy was usually recommended. Current guidelines still generally recommend at least six and twelve months of dual antiplatelet therapy after drug-eluting stent implantation in patients with stable angina and acute coronary syndrome, respectively.⁴ The lifelong presence of the durable polymer-coating of drug-eluting stents has been associated with chronic vascular inflammation, delayed arterial healing, and neoatherosclerosis, which may result in late adverse clinical events.¹⁹ The risk of stent thrombosis declined after the introduction of second-generation drug-eluting stents,⁸ which had more biocompatible polymer coatings than the first-generation devices and other refinements in stent design, such as a lower strut thickness, enhanced stent flexibility, and improved visibility (of some devices). Despite these improvements in stent design, the advice on the optimal duration dual antiplatelet therapy remained greatly unchanged.²⁰

Besides innovations in polymer-coated drug-eluting stents, polymer-free drug-coated stents were developed and proved to be safer and more efficient than bare metal stents in high bleeding risk patients who were treated with one month of dual antiplatelet therapy.^{21,22} Nevertheless, the use of polymer-free drug-coated stents is not commonly adapted in clinical practice, as clinical trial results in broader patient populations and comparative data against contemporary drug-eluting stents are lacking.²³ An observational study that examined polymer-free drug-coated stents in a real-world cohort of all-comer patients suggested a higher rate of re-stenosis as compared to durable polymer-coated drug-eluting stents.²⁴ Another approach to prevent long-term presence of a polymer inside the coronary vessel is the use of drug-eluting stents with biodegradable polymer coatings, which may provide the antiproliferative benefits of durable polymer drug-eluting stents combined with the long-term safety of bare metal stents.²⁵ In the high bleeding risk patients of the randomized BIO-RESORT trial, the use of two novel but otherwise dissimilar biodegradable polymer-coated drug-eluting stents proved to be safe and efficacious as compared to a reference durable polymer-coated drug-eluting stent (**Chapter 5**).

The two biodegradable polymer drug-eluting stents, examined in BIO-RESORT, have different polymer degradation times. While the polymer of the everolimus-eluting Synergy stent resolves within four months, this process takes approximately two years for the sirolimus-eluting Orsiro stent. Therefore, follow-up beyond the date of the primary endpoint and after the cessation of the P2Y₁₂ inhibitor component of dual antiplatelet therapy (i.e., generally one year after stenting for both) is of particular interest. Two-year follow-up of the all-comer patients included in the BIO-RESORT trial showed no significant difference in the primary composite endpoint target vessel failure between the two biodegradable polymer-coated and the reference durable polymer-coated stents (**Chapter 6**). Interestingly, landmark analysis showed a lower rate of target lesion revascularization for the Orsiro stent during the second year after percutaneous coronary intervention. This may be related to the use of ultrathin stent struts, which in a large meta-analysis were found to be associated with an improved clinical outcome.²⁶

The novel durable polymer-coated zotarolimus-eluting Resolute Onyx stent has thinner, somewhat differently shaped stent struts than its predecessor. In the international randomized controlled BIONYX all-comers trial, the Resolute Onyx stent was found to be non-inferior to the reference biodegradable polymer-coated everolimus-eluting Orsiro stent regarding the primary endpoint target vessel failure at one year (**Chapter 7**). Notably, the one-year rate of stent thrombosis in all-comer patients treated with Resolute Onyx was only 0.1%. The Resolute Onyx stent is currently being investigated by others in high bleeding risk patients who are treated with one month of dual antiplatelet therapy.²⁷

Long-term outcome of the predecessor of Resolute Onyx –the zotarolimus-eluting Resolute Integrity stent– was compared versus the everolimus-eluting Promus Element stents in the randomized DUTCH PEERS trial in all-comers. In this trial, the vast majority of patients was treated with dual antiplatelet therapy for the duration of one year.²⁸ Five-year follow-up showed for both stent groups low and similar rates of target vessel failure and stent thrombosis (**Chapter 8**). The prolonged clinical outcome of participants in randomized stent trials is of great interest given that after the intervention most patients live on for a period of many years or even decades (**Chapter 9**).

FUTURE PERSPECTIVES

During the last decades, innovations in stent technology have led to an impressive lowering of adverse event rates after percutaneous coronary intervention. Therefore, it will become increasingly difficult to demonstrate that a novel treatment is better than the established therapeutic approach. This is true for novel metallic drug-eluting stents but even more for devices that may provide a theoretical long-term advantage but that may not yet be refined. For example, bioabsorbable vascular scaffolds are, for the time being, no longer used in clinical practice because of safety issues as compared to current generation drug-eluting stents.²⁹ Scaffold technology could improve in the same way as metallic stents did, but it will be very difficult to outperform the low stent thrombosis rates of the latest metallic drug-eluting stents.

Yet, it is our obligation to strive for lowering the risk of adverse events as much as possible. Notably, nowadays the most important risk factor for stent thrombosis is not stent-related but related to the procedure itself. Therefore, fellows in interventional cardiology should be carefully trained in optimizing the result of coronary stenting. In addition, it is important to treat only patients and lesions that actually require an intervention. In this context, the (routine) use of intracoronary hemodynamic assessment and, to some extent, intracoronary imaging is of great importance.³⁰⁻³²

Pharmacological treatment before, during, and after the intervention is another field that may still offer room for improvement. New antithrombotic drug trials investigate several different strategies such as a de-escalation of dual antiplatelet therapy,^{33,34} the use of P2Y₁₂ inhibitor single antiplatelet therapy,³⁵ combinations of new oral anticoagulants with antiplatelet agents, and, as previously, shorter duration of dual antiplatelet therapy –but now after treatment with contemporary drug-eluting stents.³⁶ Future research should focus on tailored antithrombotic therapy, considering patient- and procedure-related factors and possibly using a pharmacogenomic approach,³⁷ to balance between the risks of bleeding and recurrent ischemic events.

The current thesis suggests that newer therapies should not necessarily replace already available and often less expensive therapies. There are still a lot of research questions to be answered, in particular about how to optimize therapy for specific subgroups of patient and how to ultimately achieve an entirely patient-tailored medical treatment.

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CHAPTER 10

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SUMMARY AND CONCLUSIONS
SAMENVATTING EN CONCLUSIES

SUMMARY

There is an ongoing search for the optimal medical treatment of patients with symptomatic coronary artery disease. Dual antiplatelet therapy has emerged as an effective treatment in patients undergoing percutaneous coronary intervention with stent implantation, and it has reduced the incidence of worrying adverse events such as stent thrombosis and myocardial infarction. Compared to the long-established drug clopidogrel (besides aspirin), newer and more potent antiplatelet drugs have been introduced with promising results in randomized clinical trials that showed a reduction in ischemic events in patients with acute coronary syndromes. However, the favourable study effects were at least partly counterbalanced by some undesirable (side) effects, especially by an increase in the risk of major bleeding. Furthermore, clinical trial participants represent a somewhat “selected” patient population and therefore, “real world” studies remain essential to assess the effects of new drugs in patients who are treated in daily clinical practice. This may be even more important as ongoing refinement and new development of medical therapy may soon outdate the findings of previous studies. Notably, drug-eluting stents have been constantly improved to enhance the safety and efficacy of percutaneous coronary intervention. As a result of this progress in stent technology, the favourable effects of newer antiplatelet agents may be less obvious after treatment with new-generation drug-eluting stents, but in clinical practice the undesirable side effects do remain.

While physicians rely on clinical trial results and treat most of their patients accordingly, specific patient subgroups may benefit from a different treatment strategy that is tailored to their needs and risk profile. This includes high bleeding risk patients who have a particularly high risk of both, major bleedings and (recurrent) ischemic events.

This thesis assessed patients with acute coronary syndromes, who underwent percutaneous treatment with contemporary drug-eluting stents, in order to evaluate the impact of a guideline-recommended change in dual antiplatelet therapy from clopidogrel- to ticagrelor-based dual antiplatelet therapy. A special focus has been laid on the clinical outcome of high bleeding risk patients, a subgroup of patients that is currently underreported. In addition, the safety and efficacy of new-generation drug-eluting stents was assessed with particular attention to clinical outcome beyond the first year after stenting, as Dutch cardiologists generally discontinue dual antiplatelet therapy after 12 months from a percutaneous coronary intervention.

Chapter 1 provides background information on coronary artery disease and acute coronary syndrome, together with a brief outline on the evolution of coronary stents and the development of antiplatelet therapy with the associated risk of bleeding complications.

Chapter 2 presents the primary outcome of the “real world” CHANGE DAPT study. A total of 2,062 consecutive acute coronary syndrome patients, who had contemporary drug-eluting stent implantation, were included during two subsequent periods of this study. Patients were treated with primarily clopidogrel-based dual antiplatelet therapy (first period) or with primarily ticagrelor-based dual antiplatelet therapy (second period). The guideline-recommended ticagrelor-based regimen was associated with an increased adverse event risk (net adverse clinical and cerebral events: 5.1% vs. 7.8%). This difference in event risk was primarily driven by the rate of major bleeding (1.2% vs. 2.7%), while no significant difference in ischemic endpoints was observed.

In **Chapter 3**, two-year outcome of CHANGE DAPT participants is described. The results showed low and similar mortality rates (4.7% vs. 4.3%). The findings were consistent in both high bleeding risk (13.6% vs. 10.6%) and non-high bleeding risk patients (1.8% vs. 1.7%).

Chapter 4 addresses clinical outcome of the high bleeding risk population of CHANGE DAPT, representing 26.5% of all study participants. During primarily clopidogrel-based versus ticagrelor-based dual antiplatelet therapy, one-year major bleeding rate was similar in non-high bleeding risk patients (1.1% vs 1.7%). But in high bleeding risk patients there was a higher rate during the second period (1.7% vs. 5.0%). Thus, the higher major bleeding risk of the ticagrelor-based treatment in CHANGE DAPT was limited to high bleeding risk patients. In addition, the ticagrelor-based therapy did not reduce ischemic event, as compared to clopidogrel-based dual antiplatelet therapy, in both high bleeding risk and non-high bleeding risk patients.

In **Chapter 5**, we assessed the safety and efficacy of very thin strut biodegradable polymer drug-eluting stents versus thin strut durable polymer drug-eluting stents in the high bleeding risk patients of the randomized BIO-RESORT trial. Almost 30% of the 3,514 all-comers who participated in the BIO-RESORT trial were at high bleeding risk. At one-year follow-up, both stent groups showed similar safety and efficacy. There was no significant between-group difference in the rate of the primary composite endpoint target vessel failure (6.5% vs. 7.3%) and all prespecified secondary clinical endpoints.

Chapter 6 describes the two-year outcome of the 3,514 BIO-RESORT trial participants. In BIO-RESORT, all-comer patients were randomized to treatment with two very thin-strut biodegradable polymer drug-eluting stents (the sirolimus-eluting Orsiro and the everolimus-eluting Synergy), versus a thin strut durable polymer drug-eluting stent (the zotarolimus-eluting Resolute Integrity) and followed a stringent policy of discontinuing dual antiplatelet therapy after one year. At two-year follow-up, the safety and efficacy of the two biodegradable polymer stents were comparable to the reference durable polymer stent. Landmark analyses suggested that the use of the Orsiro stent might reduce the risk of repeat revascularisation during the second year as compared to the Resolute Integrity stent.

Chapter 7 reports the primary one-year outcome of the international, multicentre, randomized BIONYX trial. In BIONYX, 2,488 all-comer patients, of whom a high proportion presented with acute coronary syndromes, were randomly assigned to treatment with novel thin composite wire strut durable polymer drug-eluting stents (the zotarolimus-eluting Resolute Onyx) versus ultrathin cobalt-chromium strut bioresorbable polymer-coated drug-eluting stents (the sirolimus-eluting Orsiro). The novel Resolute Onyx stent was for the first time assessed in a randomized clinical study and was shown to be non-inferior to the reference Orsiro stent for the primary endpoint of safety and efficacy (target vessel failure: 4.5% vs. 4.7%). Particularly low rates of stent thrombosis were found in patients treated with Resolute Onyx stents (0.1 vs. 0.7%).

Chapter 8 presents the long-term outcome of 1,811 all-comer patients who were assessed in the DUTCH-PEERS trial. Trial participants were randomized to treatment with thin cobalt-chromium strut durable polymer drug-eluting stents (the zotarolimus-eluting Resolute Integrity) or thin platinum-chromium strut durable polymer stents (the everolimus-eluting Promus Element). Five years after stent implantation, both stents showed similar and sustained results in terms of safety and efficacy. The rates of target vessel failure (13.2% vs. 14.2%) and definite or probable stent thrombosis (1.5% vs. 1.3%) were comparable.

In **Chapter 9**, we illustrate the importance of long-term follow-up of coronary stent trials in a comment about the five-year outcomes of the randomized BIOSCIENCE trial.

Chapter 10 presents the general discussion of the findings of this thesis, together with a discussion of the future perspectives.

CONCLUSIONS

The treatment of patients with coronary artery disease has greatly evolved. Currently, almost all percutaneous coronary interventions are performed with the implantation of drug-eluting stents that have proven to be highly effective in reducing the incidence of lesion recurrence. In addition, we found contemporary drug-eluting stents to be safe with a low risk of cardiac death and myocardial infarction, as well as favourable stent thrombosis rates that can be as low as 0.1% after one year. Furthermore, we found that the safety and efficacy of these devices are maintained at long-term follow-up.

In parallel with the innovation in drug-eluting stents, there has been a progress in the strategy of antithrombotic treatment, both in patients with acute coronary syndromes and in patients treated with coronary stents. Dual antiplatelet strategies with different agents (besides aspirin) were examined. In randomized clinical trials, more potent antiplatelet agents, such as ticagrelor, were found to reduce the incidence of ischemic events, as compared to clopidogrel. However, these trials had been performed in patients who were not always treated with a percutaneous coronary intervention, and mostly early-generation stents were used. Our own research suggested that the need for such more potent antiplatelet agents might be reduced in patients treated with contemporary drug-eluting stents.

This may especially apply to patients with acute coronary syndromes who have a high bleeding risk. Although these patients also have an increased risk of recurrent ischemic events, our study showed that this high-risk subgroup mainly suffered from major bleedings, associated with the more potent dual antiplatelet therapy. The observations of our studies and the findings of other research groups should motivate physicians to identify subjects with high bleeding risk among their patients with acute coronary syndromes, treated with coronary stenting. In this way, each individual patient can receive the optimal treatment strategy that balances the risks of both, recurrent ischemic events and bleeding complications. Ongoing research on new antithrombotic strategies, such as de-escalation of P2Y₁₂ inhibitors or the application of a pharmacogenomic approach, might soon be added to the decision making about the optimal antithrombotic treatment.

SAMENVATTING

Er is voortdurend onderzoek gaande naar de optimale medische behandeling van patiënten met symptomatisch coronairlijden. In de afgelopen decennia is gebleken dat duale antiplaatjes therapie (d.w.z. een combinatie van aspirine en een andere plaatjesremmer) effectief is bij de behandeling van patiënten die een percutane coronaire interventie met stent implantatie ondergaan. Deze therapie heeft geleid tot een vermindering van nadelige uitkomsten zoals een stent trombose of myocardinfarct. De introductie van nieuwe medicijnen met krachtigere plaatjesremming ten opzichte van het lang gebruikte middel clopidogrel heeft geleid tot veelbelovende resultaten in gerandomiseerde klinische trials. In deze studies, uitgevoerd bij patiënten die behandeld werden voor een acuut coronair syndroom, werd met de krachtigere antiplaatjes therapie een reductie gezien in ischemische eindpunten. Deze gunstige studieresultaten moeten echter in perspectief worden geplaatst. Enerzijds werden de positieve effecten deels tenietgedaan door ongewenste bijwerkingen; zo bleken patiënten die behandeld werden met de nieuwe medicijnen een verhoogd risico te hebben op het optreden van ernstige bloedingen. Daarnaast valt op te merken dat patiënten in klinische trials een geselecteerde groep betreft welke niet altijd representatief hoeft te zijn voor de patiënt uit de dagelijkse praktijk. Om deze redenen is het noodzakelijk de effecten van nieuwe medicijnen separaat te onderzoeken in patiënten die behandeld worden in de dagelijkse praktijk. Dit wordt gedaan in zogenaemde *real world* studies.

Naast de introductie van nieuwe medicijnen kan parallelle ontwikkeling op het gebied van medische hulpmiddelen ervoor zorgen dat eerdere studieresultaten al snel verouderd raken en daarmee niet meer bruikbaar zijn voor in de kliniek. In de afgelopen jaren is er een belangrijke ontwikkeling geweest in de verbetering van medicijn-afgevend coronaire stents waardoor de effectiviteit en veiligheid van een percutane coronaire interventie zijn toegenomen. Het resultaat van deze progressie in stent technologie zou ertoe kunnen leiden dat de eerder gevonden voordelen van de nieuwere plaatjesremmers niet of nauwelijks aanwezig zijn in patiënten die behandeld worden met nieuwe generatie medicijn-afgevend stents. De nadelige effecten van de nieuwe krachtige plaatjesremmers blijven echter wel bestaan.

Artsen zullen patiënten zoveel mogelijk behandelen op basis van beschikbare data uit wetenschappelijke klinische studies. Bepaalde subgroepen van patiënten zouden baat kunnen hebben bij een meer op maat gesneden behandeling, rekening houdend met het individuele risicoprofiel en de behoeften van een specifieke patiënt. Eén van deze subgroepen betreft patiënten met coronairlijden en een hoog bloedingsrisico. Deze groep

bevat patiënten met een bijzonder hoog risico op ernstige bloedingen maar ook op recidiverende ischemische complicaties.

In dit proefschrift worden patiënten met een acuut coronair syndroom onderzocht die een percutane coronaire interventie ondergaan met implantatie van huidige generatie medicijn-afgevend stents. Op deze manier wordt de impact van de aanbevelingen uit internationale richtlijnen onderzocht die de afgelopen jaren gewijzigd zijn en tegenwoordig duale antiplaatjes therapie met ticagrelor aanraden in plaats van met clopidogrel (naast aspirine). Speciale aandacht wordt besteed aan de klinische uitkomsten van patiënten met een hoog bloedingsrisico, aangezien deze belangrijke subgroep onderbelicht is in veel klinische studies. Daarnaast worden de effectiviteit en veiligheid van huidige medicijn-afgevend stents onderzocht in gerandomiseerde klinische studies met zeer beperkte exclusiecriteria, zogenoemde *all-comers* studies. Hierbij ligt de nadruk op de klinische uitkomsten na het eerste jaar na stent implantatie aangezien Nederlandse cardiologen in het algemeen de duale antiplaatjes therapie stoppen na één jaar en vervolgens alleen de aspirine continueren.

Hoofdstuk 1 geeft achtergrondinformatie over coronaire hartziekten en het acuut coronair syndroom. Daarnaast wordt een korte uiteenzetting gegeven over de ontwikkeling van coronaire stents en de ontwikkeling van antiplaatjes therapie met het daarbij samengaande risico op bloedingscomplicaties.

Hoofdstuk 2 presenteert de primaire uitkomsten van de *real world* CHANGE DAPT studie. Er werden 2.062 patiënten geïnccludeerd die behandeld werden voor een acuut coronair syndroom met de huidige generatie medicijn-afgevend stents. Inclusie vond plaats gedurende twee opeenvolgende studieperiodes. Patiënten werden tijdens de eerste periode primair behandeld met duale antiplaatjes therapie bestaande uit aspirine en clopidogrel en in de tweede periode met duale antiplaatjes therapie bestaande uit aspirine en ticagrelor. Het door de nieuwe richtlijnen aanbevolen ticagrelor bleek geassocieerd met hogere risico's, wat werd teruggezien in het primaire eindpunt *net adverse clinical and cerebral events* (5.1% vs. 7.8%). Het verschil in dit gecombineerde eindpunt werd voornamelijk gedreven door het aantal ernstige bloedingen (1.2% vs. 2.7%), terwijl er geen significant verschil werd gevonden in ischemische eindpunten.

Hoofdstuk 3 beschrijft de mortaliteit van de CHANGE DAPT deelnemers twee jaar na stent implantatie. De resultaten tonen lage sterftcijfers in de clopidogrel groep (4.7%) en in de ticagrelor groep (4.3%) zonder significante verschillen tussen beide groepen. De

bevindingen bleken consistent in zowel patiënten met een hoog bloedingsrisico (13.6% vs. 10.6%) als in patiënten zonder hoog bloedingsrisico (1.8% vs. 1.7%).

Hoofdstuk 4 richt zich op de patiënten met een hoog bloedingsrisico in de CHANGE DAPT studie. Van alle deelnemers had 26.5% een hoog bloedingsrisico. In deze populatie bleek dat, ten opzichte van patiënten in de clopidogrel groep, patiënten in de ticagrelor groep een significant hoger risico hebben op het krijgen van een ernstige bloeding (1.7% vs. 5.0%). Het risico op een ernstige bloeding in patiënten zonder hoog bloedingsrisico bleek na één jaar gelijk te zijn voor patiënten behandeld in de clopidogrel groep en in de ticagrelor groep (1.1% vs. 1.7%). Er werd geen verschil gevonden in ischemische eindpunten tussen de clopidogrel groep en de ticagrelor groep voor zowel patiënten met een hoog als een niet-hoog bloedingsrisico.

In **hoofdstuk 5** onderzoeken we de effectiviteit en veiligheid van medicijn-afgevend stents met verschillende soorten polymeren in de behandeling van patiënten met een hoog bloedingsrisico die deelnamen aan de BIO-RESORT trial. Patiënten ondergingen een percutane coronaire interventie met implantatie van stents met een biologisch afbreekbare polymeer of stents met een permanente polymeer. Bij ongeveer 30% van de 3.514 *all-comers* in BIO-RESORT bleek er sprake van een hoog bloedingsrisico. Beide stentgroepen bleken vergelijkbaar te presteren op het gebied van effectiviteit en veiligheid één jaar na stent implantatie. Er werd geen significant verschil gevonden tussen de stentgroepen met betrekking tot het primaire samengestelde eindpunt *target vessel failure* (6.5% vs. 7.3%) en alle vooraf gespecificeerde secundaire klinische eindpunten.

Hoofdstuk 6 beschrijft de klinische uitkomsten van alle 3.514 patiënten die deelnamen aan de BIO-RESORT trial twee jaar na stent implantatie. In deze studie werden *all-comers* gerandomiseerd naar behandeling met één van twee soorten medicijn-afgevend stents met een biologisch afbreekbare polymeer (de Orsiro stent of de Synergy stent) of een medicijn-afgevend stent met een permanente polymeer (de Resolute Integrity stent). Deelnemende patiënten volgden een strikt beleid omtrent het stoppen met duale antiplaatjes therapie één jaar na de percutane interventie. De effectiviteit en veiligheid van beide stents met een biologisch afbreekbare polymeer was twee jaar na interventie vergelijkbaar met de stent met een permanente polymeer. Een landmark analyse suggereerde dat de Orsiro stent het risico op een herhaalde revascularisatie gedurende het tweede jaar reduceert ten opzichte van de Resolute Integrity stent.

Hoofdstuk 7 rapporteert het primaire eindpunt van de internationale, gerandomiseerde BIONYX trial. In BIONYX werden 2.488 *all-comer* patiënten gerandomiseerd naar

behandeling met medicijn-afgevend stents bestaande uit samengesteld metaal met een permanente polymeer (de Resolute Onyx stent) of met medicijn-afgevend stents bestaande uit kobalt-chroom met een biologisch afbreekbare polymeer (de Orsiro stent). De nieuwe Resolute Onyx stent werd hiermee voor het eerst in een gerandomiseerde klinische studie vergeleken met een andere stent en bleek niet inferieur ten opzichte van de Orsiro stent ten aanzien van het primaire gecombineerde eindpunt *target vessel failure* (4.5% vs. 4.7%). Een opvallende bevinding was het erg lage aantal gevallen van stent trombose in patiënten die behandeld werden met de Resolute Onyx stent (0.1% vs. 0.7%).

Hoofdstuk 8 presenteert de lange termijn uitkomsten van de 1.811 *all-comer* patiënten die deelnamen aan de DUTCH-PEERS studie. Deelnemers aan deze studie werden gerandomiseerd naar behandeling met medicijn-afgevend stents bestaande uit kobalt-chroom met een permanente polymeer (de Resolute Integrity stent) of medicijn-afgevend stents bestaande uit platina-chroom met een permanente polymeer (de Promus Element stent). Vijf jaar na implantatie lieten beide stents vergelijkbare resultaten zien met betrekking tot effectiviteit en veiligheid. Het aantal gevallen van *target vessel failure* (13.2% vs. 14.2%) en stent trombose (1.5% vs. 1.3%) bleek vergelijkbaar.

In **hoofdstuk 9** illustreren we het belang van lange termijn follow-up van patiënten die zijn geïncludeerd in coronaire stent studies in een commentaar op de vijf jaar uitkomsten van de gerandomiseerde BIOSCIENCE trial.

Hoofdstuk 10 presenteert de algemene discussie van de bevindingen van dit proefschrift. Daarnaast wordt een visie gegeven op te verrichten onderzoeken in de toekomst.

CONCLUSIES

Er heeft een indrukwekkende ontwikkeling plaats gevonden in de behandeling van patiënten met coronaire hartziekten. Tegenwoordig worden vrijwel alle percutane coronaire interventies uitgevoerd met het plaatsen van medicijn-afgevende stents. Deze stents zijn bewezen effectief gebleken in het reduceren van de incidentie van nieuwe vernauwingen ter plaatse van de initiële laesie. Daarnaast is aangetoond dat de huidige generatie medicijn-afgevende stents veilig zijn met een laag risico op cardiale dood en een zeer laag risico op stent trombose na één jaar. Tevens blijkt uit onze resultaten dat de effectiviteit en veiligheid van deze stents ook op lange termijn behouden blijft.

Simultaan aan de innovatie in medicijn-afgevende stents heeft er een ontwikkeling plaats gevonden in de antitrombotische behandeling van patiënten met een acuut coronair syndroom en na coronaire stent implantatie. Duale antiplaatjes strategieën met verschillende medicijnen (naast aspirine) werden onderzocht. Uit gerandomiseerde klinische studies is gebleken dat krachtige antiplaatjes medicijnen zoals ticagrelor het risico op ischemische uitkomsten verlagen ten opzichte van behandeling met clopidogrel. Deze studies werden echter uitgevoerd in patiënten die niet altijd behandeld werden met een percutane interventie en bij de patiënten die wel een percutane interventie ondergingen werden voornamelijk oudere generatie stents gebruikt. Ons eigen onderzoek suggereert dat de noodzaak tot krachtige antiplaatjes therapie minder noodzakelijk is in patiënten die behandeld worden met de huidige generatie medicijn-afgevende stents.

Deze resultaten kunnen van groot belang zijn voor patiënten met een acuut coronair syndroom die een verhoogd bloedingsrisico hebben. Ondanks dat deze patiënten ook een verhoogd risico lopen op recidiverende ischemische complicaties laat ons onderzoek zien dat deze hoog risico subgroep voornamelijk te lijden heeft van ernstige bloedingen welke geassocieerd zijn met de krachtige antiplaatjes therapie. De huidige observaties van onze studies, in combinatie met de bevindingen van anderen, zal artsen motiveren om patiënten met een verhoogd risico te identificeren. Op deze manier kan iedere individuele patiënt de optimale behandelingsstrategie krijgen waarbij een balans wordt gezocht tussen enerzijds het risico op ischemische complicaties en anderzijds het risico op bloedingen. Resultaten van voortschrijdend onderzoek naar nieuwe antitrombotische strategieën zoals de-escalatie van krachtige naar minder krachtige plaatjesremmers of een farmaco-genetische benadering zouden in de toekomst gebruikt kunnen worden bij de besluitvorming ten aanzien van de optimale medicamenteuze behandeling van iedere individuele patiënt.

LIST OF PUBLICATIONS
DANKWOORD
CURRICULUM VITAE

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Mijn familie: Anneke en Marco; Marjolein, Lars, Amber en Mika; Wouter, Hanneke, Matteo en Isabel; Trudy en Koen (ook familie inmiddels); ooms, tantes, neven en nichten. Dank jullie wel voor alle interesse maar ook dat jullie de afronding van dit traject samen

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CURRICULUM VITAE

Gian Paolo Zocca werd op 21 juni 1984 geboren te Enschede. Na afronding van het Atheneum aan het Stedelijk Lyceum Zuid volgde hij vanaf 2002 de opleiding Geneeskunde aan de Rijksuniversiteit Groningen. Ter afronding van zijn coschappen volgde hij een keuze stage cardiologie in het Ospedale SS. Annunziata in Cento (Italië) onder begeleiding van dr. M. Dinelli en dr. P. Alboni. Na het behalen van het artsexamen in 2009 was hij een jaar werkzaam als arts-assistent cardiologie om vervolgens de opleiding tot cardioloog te volgen in het Medisch Spectrum Twente onder begeleiding van de opleiders dr. P.M.J. Verhorst en dr. M.F. Scholten. Een jaar van de opleiding werd gevolgd in het Deventer Ziekenhuis onder supervisie van dr. J. van Wijngaarden. Na afronding van de opleiding tot cardioloog eind 2016, werd begin 2017 een start gemaakt met wetenschappelijk onderzoek bij prof. dr. C. von Birgelen. Dit heeft geresulteerd in het huidige proefschrift. Vanaf 2018 is hij werkzaam als fellow interventiecardiologie. Paolo is in 2017 getrouwd met Lotte.