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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Summary

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%; $p_{non\text{-}inferiority}$=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.

Funding Biotronik and Medtronic.

Lancet 2018; 392: 1235–45

Published **Online** September 22, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32001-4

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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.

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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 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.

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 vessels[18] 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.

See Online for appendix

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,

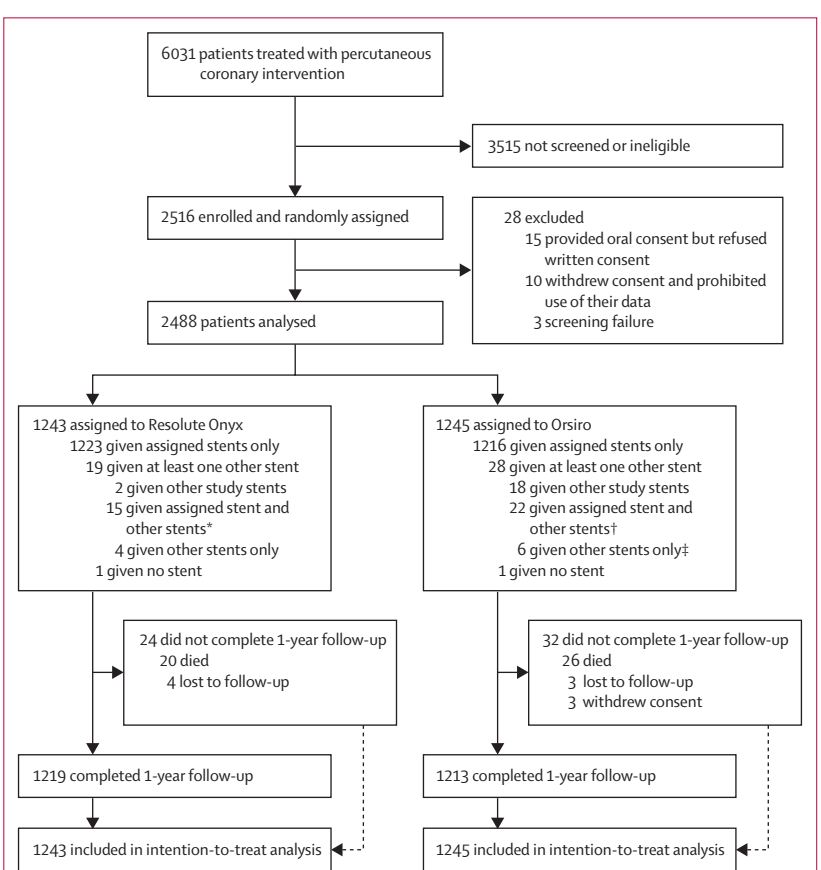

Figure 1: **Trial profile**
*Includes the two patients given other study stents. †14 were given other study stents. ‡Four given other study stents.

	Overall (n=2488)	Resolute Onyx group (n=1243)	Orsiro group (n=1245)
General characteristics			
Age, years	64·0 (11·0)	64·1 (10·9)	63·9 (11·2)
Female sex	594 (23·9%)	297 (23·9%)	297 (23·9%)
White	2370 (95·3%)	1176 (94·6%)	1194 (95·9%)
Body-mass index, kg/m²	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%)
Medically treated diabetes	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%)
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 ischaemia	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%)
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%)
Postdilation	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 μmol/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.

Table 1: **Baseline characteristics**

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 ≥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 bypass surgery, or clinically indicated target lesion 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. 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

	Overall (n=3239)	Resolute Onyx group (n=1646)	Orsiro group (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			
n	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 (15·5%)	247 (15·0%)	255 (16·0%)
In-stent restenosis	75 (2·3%)	47 (2·9%)	28 (1·8%)
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%)
Postdilation	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).

Table 2: **Baseline characteristics of target lesions**

	Resolute Onyx group (n=1243)	Orsiro group (n=1245)	Hazard ratio (95% CI)	Log-rank p value
Death				
Any cause	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
Stent thrombosis				
Definite or probable	1 (0·1%)	9 (0·7%)	0·11 (0·01–0·87)	0·0112
Definite	1 (0·1%)	7 (0·6%)	0·14 (0·02–1·16)	0·0334†
Probable	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).

Table 3: **Clinical events during 1-year follow-up**

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% ($p_{non\text{-}inferiority}$=0·0005; $p_{superiority}$=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%; $p_{non\text{-}inferiority}$=0·0012; appendix). Additionally, results for the primary endpoint 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).

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 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

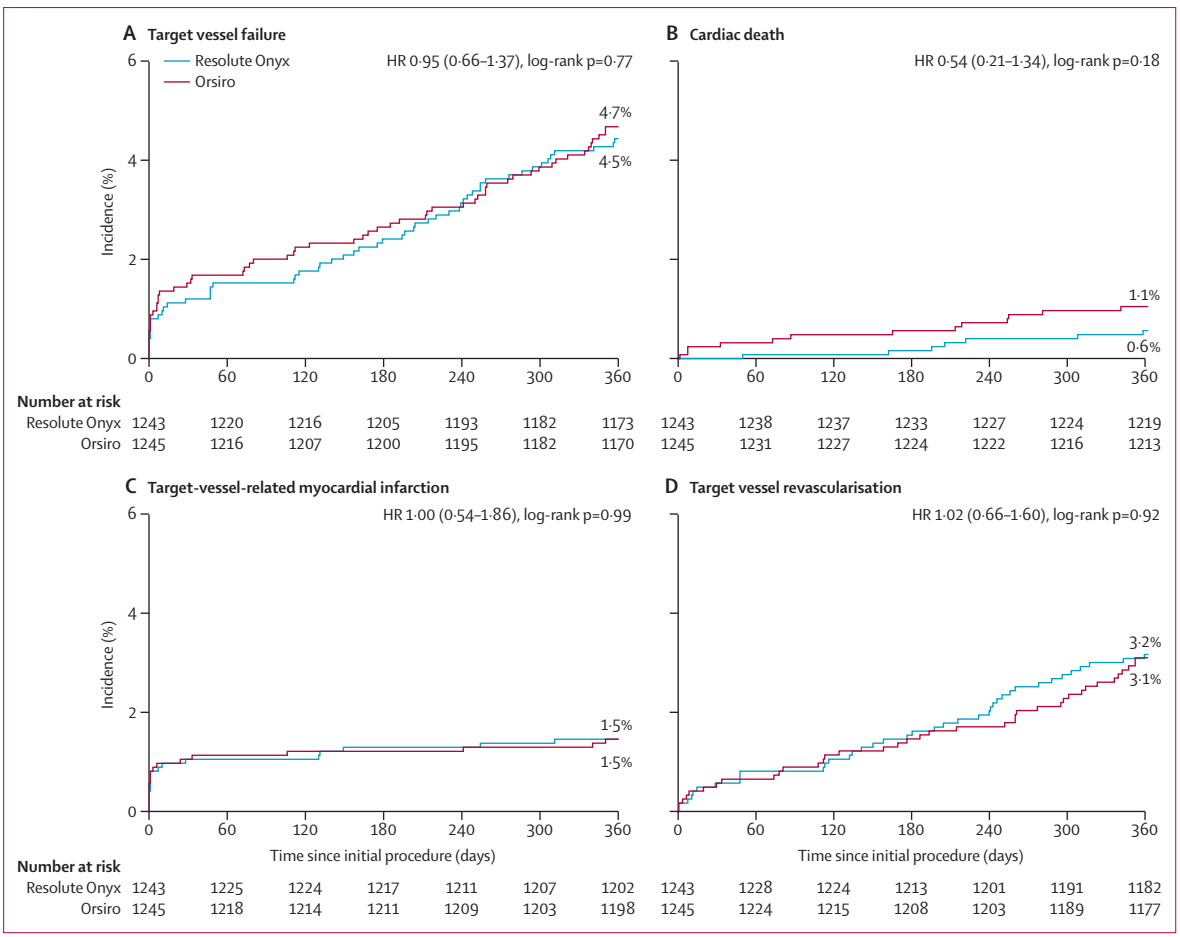

Figure 2: **Kaplan-Meier graphs of cumulative incidence of the composite target vessel failure (A) and its individual components cardiac death (B), target-vessel-related myocardial infarction (C), and target vessel revascularisation (D)**
HR=hazard ratio.

41·3% of all patients who were percutaneously 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 trial[11] 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 revascularisation). The frequency of definite stent thrombosis in the Resolute Integrity group

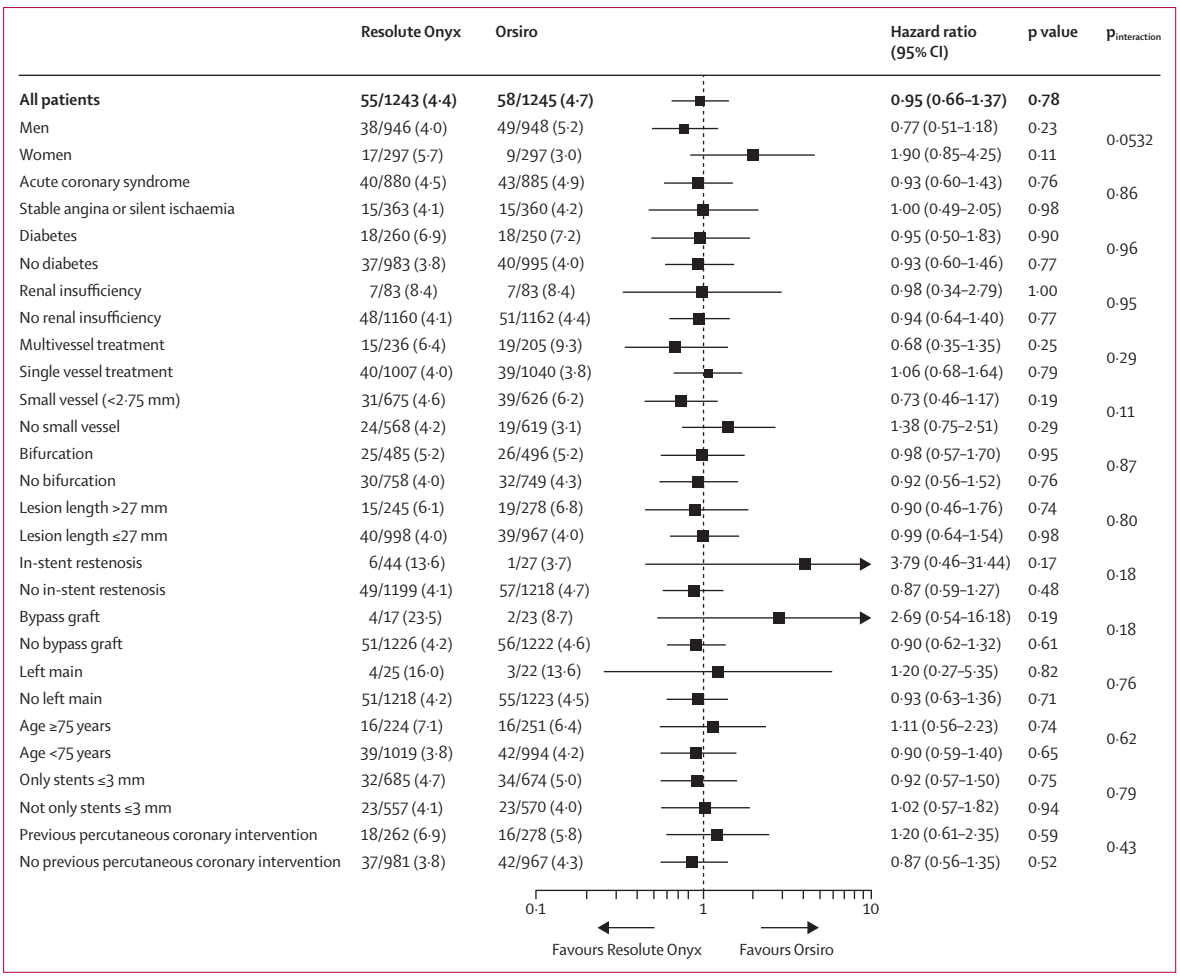

Figure 3: **Subgroup analyses for target vessel failure at 1 year in the Resolute Onyx and Orsiro stent groups**

was 0·6%.[11] The BIOSCIENCE trial[20] 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 trial[12] 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]

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 VI[11]). 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 registry[29] 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 registry[30] 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]

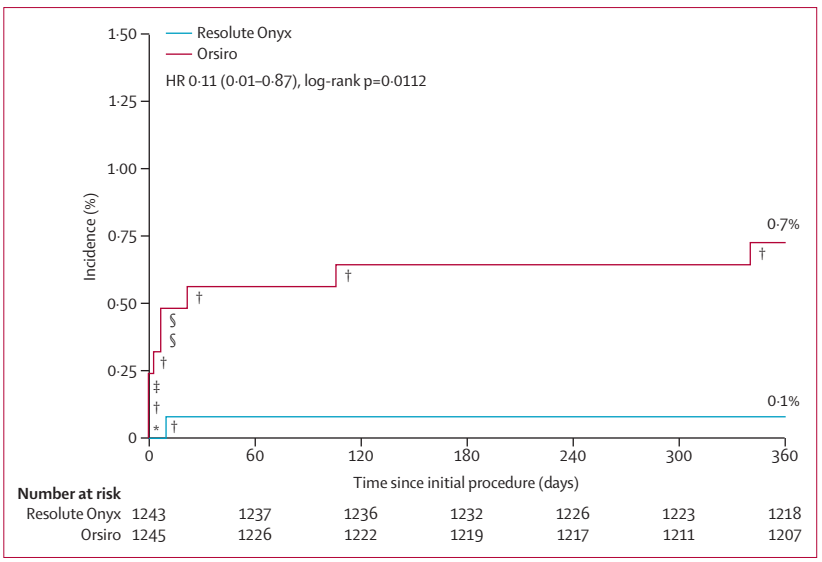

Figure 4: **Cumulative incidence of definite or probable stent thrombosis at 1-year follow-up**
Definite or probable stent thrombosis with clinical consequences. HR=hazard ratio. *Myocardial infarction (definite stent thrombosis). †Target lesion revascularisation plus myocardial infarction (definite stent thrombosis). ‡Target lesion revascularisation, myocardial infarction, and cardiac death (definite stent thrombosis). §Cardiac death (probable stent thrombosis).

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-RESORT[12]) and the more frequent use of radial access (73% *vs* 45% in BIO-RESORT[12]). 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.

Contributors

CvB, GAJJ, CES, AR, PWD, EB, AA, KGvH, MGS, and MH designed the trial. CvB, PZ, and RAB wrote the first draft of the Article. CJMD and MMK also participated in drafting the Article, and all other authors revised the draft for important intellectual content. PZ and RAB gathered the data. PZ, RAB, and CJMD did the statistical analyses. CvB, PZ, RAB, CJMD, and MMK first interpreted the data, then all authors subsequently participated in data interpretation. All authors read and approved the final version of the Article.

Declaration of interests

The research department of Thoraxcentrum Twente, the institution of CvB, PZ, RAB, KGvH, MGS, MH, and MMK, has received institutional research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. CvB is the principal investigator of several randomised clinical trials and registries and has served as an unpaid (formal or informal) consultant to Abbott Vascular, Biotronik, and Medtronic. AR used to be a consultant for Medtronic and has received lecture fees from Biotronik. All other authors declare no competing interests.

Acknowledgments

This trial was equally funded by Biotronik and Medtronic. We thank our patients for their confidence and willingness to participate in this trial, the cardiologists and the staff of the research departments, catheterisation laboratories, wards, and administrative departments of all study sites and referring centres, the patients' general physicians and pharmacists, and Job van der Palen for doing the power calculation and for his expert advice in statistical analyses.

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