Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial

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Summary

Background In patients with coronary artery disease, treated with durable polymer-coated drug-eluting stents, the life-long presence of the polymer might delay arterial healing. Novel very thin strut biodegradable polymer stents, which leave only a bare metal stent after polymer resorption, might improve long-term outcome. We investigated in allcomers the safety and efficacy of three stents eluting either everolimus, sirolimus, or zotarolimus, often clinically used but never compared, of which the biodegradable polymer everolimus-eluting stent was never before assessed in allcomers.

Methods The large-scale, investigator-initiated, multicentre, assessor and patient blinded, three-arm, randomised, BIO-RESORT non-inferiority trial was done at four clinical sites in the Netherlands. All-comer patients were aged 18 years or older, capable of providing informed consent, and required a percutaneous coronary intervention with drug-eluting stent implantation according to clinical guidelines or the operators' judgment. Exclusion criteria were: participation in another randomised drug or device study before reaching the primary endpoint of that study; planned surgery necessitating interruption of dual antiplatelet therapy within the first 6 months; known intolerance to components of the investigational product or medication required; uncertainty about the adherence to follow-up procedures or an assumed life expectancy of less than 1 year; or known pregnancy. Web-based computer-generated allocation sequences randomly assigned patients (1:1:1) to treatment with very thin strut biodegradable polymer everolimus-eluting or sirolimus-eluting stents (which differ substantially in type, amount, distribution, and resorption speed of their respective coating), or thin strut durable polymer zotarolimus-eluting stents. The primary endpoint was a composite of safety (cardiac death or target vessel-related myocardial infarction) and efficacy (target vessel revascularisation) at 12 months of follow up with a very thin strut biodegradable polymer of either everolimus-eluting or sirolimus-eluting stents, compared with durable polymer zotarolimus-eluting stents, analysed by intention to treat (non-inferiority margin 3·5%). This trial was registered with ClinicalTrials.gov, number NCT01674803.

Findings From Dec 21, 2012, to Aug 24, 2015, 3514 patients were enrolled and analysed, of whom 2449 (70%) had acute coronary syndromes, which included 1073 (31%) ST-elevation myocardial infarctions. 12 month follow-up of 3490 (99%) patients (three lost to follow-up; 21 withdrawals) was available. The primary endpoint was met by 55 (5%) of 1172 patients assigned to everolimus-eluting stents, 55 (5%) of 1169 assigned to sirolimus-eluting stents and 63 (5%) of 1173 assigned to zotarolimus-eluting stents. Non-inferiority of the everolimus-eluting stents and sirolimus-eluting stents compared with zotarolimus-eluting stents was confirmed (both –0·7% absolute risk difference, 95% CI –2·4 to 1·1; upper limit of one sided 95% CI 0·8%, $p_{non\text{-}inferiority}<0·0001$). Definite stent thrombosis (defined by the Academic Research Consortium) occurred in four (0·3%) of 1172 patients who were allocated to everolimus-eluting stents, four (0·3%) of 1169 patients who were allocated to sirolimus-eluting stents, and three (0·3%) of 1173 patients who were allocated to zotarolimus-eluting stents (log-rank p=0·70 for both comparisons with zotarolimus-eluting stents).

Interpretation At 12 month follow-up, both very thin strut drug-eluting stents with dissimilar biodegradable polymer coatings (eluting either everolimus or sirolimus) were non-inferior to the durable polymer stent (eluting zotarolimus) in treating allcomers with a high proportion of patients with acute coronary syndromes. The absence of a loss of 1 year safety and efficacy with the use of these two biodegradable polymer-coated stents is a prerequisite before assessing their potential longer-term benefits.

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Research in context

Evidence before this study

We searched PubMed and checked listings of the EuroPCR, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and American College of Cardiology conferences for complete reports of randomised trials comparing the biodegradable polymer everolimus-eluting Synergy or sirolimus-eluting Orsiro stents with the zotarolimus-eluting Resolute Integrity stent or with other stents (we used as search terms "coronary" and "stent" in combination with one or more of the following: "everolimus", "sirolimus", "zotarolimus", "Synergy", "Orsiro", "Resolute Integrity", "randomised", and "randomized", for reports published in English from Sept 15, 2011, to Sept 15, 2016.

Previously, the Synergy stent has been assessed in the EVOLVE first-in-man study and the EVOLVE II trial, which reported non-inferiority of Synergy as compared with a durable polymer everolimus-eluting stent in treating patients with up to moderate risk. The Orsiro stent showed non-inferiority compared with a durable polymer everolimus-eluting stent with respect to a primary angiographical endpoint in BIOFLOW-II, and versus durable polymer everolimus-eluting stents (BIOSCIENCE) and early biodegradable polymer biolimus-eluting stents (SORT OUT VII) in treating all-comers. Yet, no randomised clinical trial has ever compared the Synergy or Orsiro stents with the Resolute Integrity stent. Additionally, the Synergy stent has not yet been assessed in all-comers. Moreover, Synergy and Orsiro stents have never been assessed together in one randomised clinical trial.

Added value of this study

Our analysis shows that treatment with two very thin strut biodegradable polymer stents and the durable polymer zotarolimus-eluting stent was similarly efficacious and safe with excellent 1 year clinical outcomes in a complex population of all-comers. To our knowledge, BIO-RESORT is the first randomised trial to assess the everolimus-eluting platinum chromium stent in all-comers. Moreover, this trial is also the first randomised comparison of two biodegradable, very thin strut, sirolimus-eluting cobalt chromium and everolimus-eluting platinum chromium stents versus thin strut durable polymer zotarolimus-eluting stent.

Implications of all the available evidence

At 12 month follow-up, both very thin strut drug-eluting stents with dissimilar biodegradable polymer coatings were non-inferior to the durable polymer stent in treating all-comers with a high proportion of patients with acute coronary syndromes.

Introduction

The implantation of a drug-eluting stent is considered the standard approach for percutaneous coronary intervention.[1] The elution of antiproliferative drugs from the stent's polymer coating reduces the risk of lesion recurrence.[1,2] However, the lifelong presence of a durable polymer in a coronary artery might induce vessel wall inflammation, delay arterial healing, and occasionally cause serious complications such as stent thrombosis and myocardial infarction.[3]

Growing awareness of this risk motivated the development of stents with biodegradable coatings that leave only a bare metal stent after polymer resorption.[4–14] Early biodegradable polymer stents had thick stainless steel struts (120 μm) and in a large allcomers trial,[6,7] showed similar efficacy and better long-term safety as compared with early-generation durable polymer stents that also had thick struts. However, in another allcomers trial,[8] similar thick-strut biodegradable polymer stents did not show non-inferiority as compared with early-generation durable polymer stents. Moreover, equivocal results were reported when comparing early biodegradable polymer stents with new-generation durable polymer stents with thin cobalt chromium struts,[11–14] which are in line with previous research showing that thick struts increase the risk of stent thrombosis and lesion recurrence.[15]

Today, novel biodegradable polymer stents are available that have uncoated struts that are up to half as thick as the struts of the early biodegradable polymer stents. These very thin strut (60–81 μm) biodegradable polymer stents have flexible designs and thin, refined coatings.[4] The present trial assesses two stents that share these characteristics, but differ in the type, amount, distribution, and degradation speed of their respective coatings.[16] One device, the everolimus-eluting platinum chromium stent (Synergy, Boston Scientific; Natick, MA, USA),[4,17,18] is the first and currently only biodegradable polymer stent with US Food and Drug Administration approval. While the device has rapidly gained clinical acceptance, there are still no data from a randomised trial with allcomers. The other novel device is a sirolimus-eluting cobalt chromium stent (Orsiro, Biotronik; Bülach, Switzerland) that has shown its usefulness outside of the USA.[19–22]

So far, neither of these stents has been compared with the new-generation, thin-strut durable polymer zotarolimus-eluting stent (Resolute Integrity, Medtronic, Santa Rosa; CA, USA), an established device with excellent clinical outcomes.[12–23] Therefore, the randomised, three-arm, BIO-RESORT non-inferiority trial assessed in allcomers the safety and efficacy of the two novel stents versus the zotarolimus-eluting stent.

Methods

Study design and participants

This randomised trial (BIO-RESORT) was done in an allcomers population, at four clinical centres in the Netherlands (Thoraxcentrum Twente, Medisch Spectrum

Twente, Enschede; Rijnstate Hospital, Arnhem; Haga Hospital, The Hague; and Albert Schweitzer Hospital, Dordrecht). This investigator-initiated study is a three-group trial that assessed two independent non-inferiority hypotheses in allcomers that the 1 year safety and efficacy of the biodegradable polymer everolimus-eluting stent is non-inferior to the durable polymer zotarolimus-eluting stent, and that the 1 year safety and efficacy of the biodegradable polymer sirolimus-eluting stent is non-inferior to the durable polymer zotarolimus-eluting stent. The design of this study has been described previously.[16]

All-comer patients were eligible if they were aged 18 years or older, capable of providing informed consent, and required a percutaneous coronary intervention with drug-eluting stent implantation according to clinical guidelines or the operators' judgment. All coronary syndromes, de-novo and restenotic lesions, and coronary artery or bypass lesions were permitted. There was no limit for lesion length, reference size, number of lesions, or diseased vessels to be treated. The exclusion criteria were: participation in another randomised drug or device study before reaching the primary endpoint of that study; planned surgery necessitating interruption of dual antiplatelet therapy within the first 6 months; known intolerance to components of the investigational product or medication required (eg, intolerance to concomitant anticoagulation or antiplatelet therapy); uncertainty about the adherence to follow-up procedures or an assumed life expectancy of less than a year; or known pregnancy. 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 centres. All patients provided written informed consent.

Randomisation and masking

After guide wire passage or predilation, patients were randomly assigned in a 1:1:1 ratio to one of the three study stents. Web-based randomisation was done with the use of a custom-designed computer program in random block sizes of 6 and 3, stratified according to the presence of diabetes. Patients were blinded to the allocated stent but treating clinicians were not. Assessors such as the angiographic analysts or members of the independent clinical event committee were blinded to the assigned treatment. Blinding was maintained until the independent external event committee had judged all event triggers of the 1 year follow-up.

Procedures

The everolimus stent elutes its drug within 3 months from a 4 μm biodegradable poly(lactic-co-glycolic acid) coating that is located only on the abluminal side of 74 μm (for stent sizes ≤2·5 mm), 79 μm (for 3·0–3·5 mm stents), or 81 μm (for 4·0 mm stents) platinum chromium struts and resorbed within 4 months.[16,17] The sirolimus-eluting stent has 60 μm (for stents ≤3·0 mm) or 80 μm (for stents >3·0 mm) cobalt chromium struts that are circumferentially covered by an asymmetrical hybrid coating that is thicker on the abluminal side (7·4 μm *vs* 3·5 μm).[16] The zotarolimus-eluting stent[16,23] has thin 91 μm cobalt chromium struts, circumferentially covered by a 6 μm zotarolimus-eluting blend of three durable polymers. During study enrolment, everolimus-eluting stents and zotarolimus-eluting stents with diameters of 2·25–4·0 mm and lengths of 8–38 mm were available; sirolimus-eluting stents had the same diameters (2·25–4·0 mm) and similar lengths (9–40 mm).

Coronary interventions were done according to standard techniques. Lesion predilation, direct stenting, and stent postdilation were left to the operator's discretion. Staged procedures with allocated stents were permitted within 6 weeks after the initial percutaneous intervention with coronary stenting (index procedure). Concomitant drugs did not differ from routine treatment; further treatment was given according to medical guidelines and the physician's judgment.[16] Generally, dual antiplatelet therapy (DAPT) was prescribed for 6–12 months. Operators were encouraged to use the assigned stent if additional lesions required treatment during follow-up.

Electrocardiographs were systematically assessed and recommended at routine clinical follow-up. Laboratory tests included systematic assessment of cardiac markers after the intervention and subsequent serial measurements in case of suspected ischaemia. In patients with acute coronary syndromes, cardiac markers were generally also assessed before the intervention. Analysts, blinded for the stent type used, did angiographical analyses and offline quantitative coronary angiographical measurements according to present standards (QAngio XA, version 7.3).

Outcomes

Clinical endpoints were prespecified, with definitions according to the Academic Research Consortium (ARC).[16,24,25] The prespecified primary composite endpoint of target vessel failure assessed by device efficacy and patient safety at 1 year follow-up comprised cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularisation (components in hierarchical order). Death was considered as cardiac, unless an unequivocal non-cardiac cause could be established. Myocardial infarction was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated 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 on the basis of laboratory, electrocardiographical, angiographical, or clinical data.[16] Revascularisation procedures were considered clinically indicated if the angiographical percent diameter stenosis of the then treated lesion was

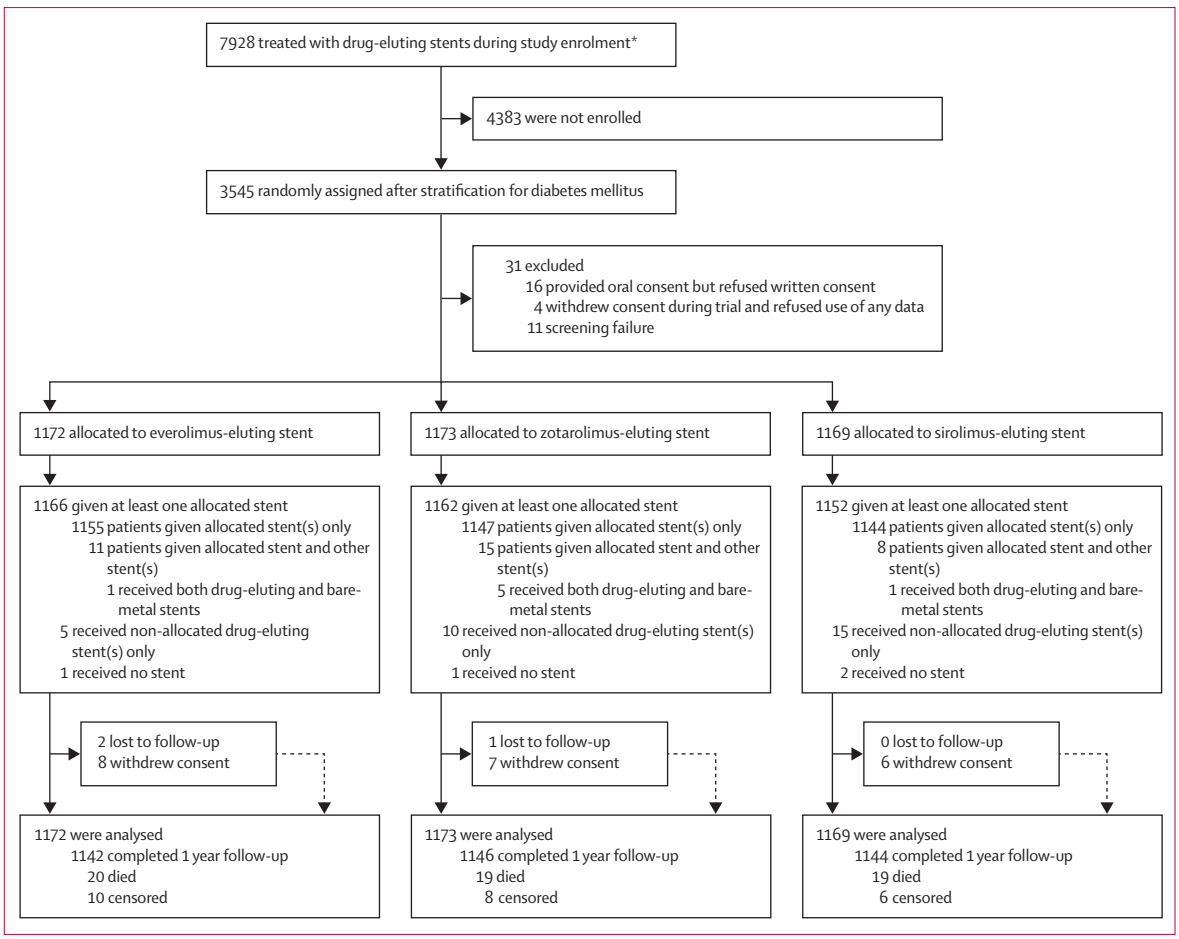

Figure 1: **Trial profile**
*Information on the number of patients treated with drug-eluting stents during the period of study enrolment is given irrespective of whether these patients fulfilled the inclusion and exclusion criteria, as we do not have reliable data on the total number of eligible patients.

50% or higher in the presence of ischaemic signs or symptoms, or if the diameter stenosis was 70% or higher irrespective of ischaemic signs or symptoms.[16,25]

Prespecified secondary endpoints included: all-cause mortality; any myocardial infarction; clinically indicated target lesion revascularisation; and stent thrombosis.[16,24,25] Additional composite endpoints were (components in hierarchical order): a composite endpoint of target lesion failure, consisting of cardiac death, target vessel-related myocardial infarction, or clinically indicated target lesion revascularisation; a composite endpoint of major adverse cardiac events, consisting of all-cause death, any myocardial infarction, emergent coronary bypass surgery, or clinically indicated target lesion revascularisation; and the patient-oriented composite endpoint, consisting of all-cause death, any myocardial infarction, or any coronary revascularisation. A final residual diameter stenosis of less than 50% was defined as device success if achieved with assigned study stents only; lesion success if achieved with any approach; and procedure success if achieved without in-hospital major adverse cardiac events. A predefined subgroup analysis of the primary endpoint was done.

The 1 year clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone follow-up or a medical questionnaire (research staff blinded to assigned stent). There was no routine angiographic follow-up. The clinical research organisation Cardio Research Enschede (Enschede, Netherlands) coordinated trial and data management. A formal data safety monitoring committee reviewed the outcome data periodically. The clinical course of the study population will be assessed per protocol until 5 years from stenting.

Data monitoring, processing of clinical outcome data, and independent clinical event adjudication were done by an independent clinical research organisation (Diagram; Zwolle, Netherlands). Monitoring comprised: informed consent and stent type (all patients); potential clinical events, reported by investigators or patients (all event triggers); and further in-depth monitoring of all demographical, procedural, and clinical outcome data (at random, 10% of

	All patients (n=3514)	Everolimus-eluting stents (n=1172)	Zotarolimus-eluting stents (n=1173)	Sirolimus-eluting stents (n=1169)
General characteristics				
Age, years	63·9 (10·8)	64·0 (10·7)	63·6 (10·9)	64·2 (10·7)
Men	2547 (72%)	845 (72%)	848 (72%)	854 (73%)
Women	967 (28%)	327 (28%)	325 (28%)	315 (27%)
Body-mass index	27·4 (4·2)	27·6 (4·2)	27·3 (4·0)	27·4 (4·2)
Current smoker	1031/3422 (30%)	336/1135 (30%)	354/1143 (31%)	341/1144 (30%)
Medical history				
Family history of coronary artery disease	1557/3372 (46%)	512/1114 (46%)	529/1138 (47%)	516/1120 (46%)
Diabetes, medically treated	624 (18%)	203 (17%)	210 (18%)	211 (18%)
Hypertension	1624 (46%)	520 (44%)	554 (47%)	550 (47%)
Hypercholesterolaemia	1335 (38%)	422 (36%)	450 (38%)	463 (40%)
Previous myocardial infarction	649 (19%)	192 (16%)	248 (21%)	209 (18%)
Previous stroke	231 (7%)	74 (6%)	81 (7%)	76 (7%)
Renal insufficiency*	108 (3%)	29 (3%)	33 (3%)	46 (4%)
Previous percutaneous coronary intervention	626 (18%)	214 (18%)	198 (17%)	214 (18%)
Previous coronary artery bypass grafting	267 (8%)	91 (8%)	96 (8%)	80 (7%)
Clinical presentation				
ST elevation myocardial infarction	1073 (31%)	377 (32%)	326 (28%)	370 (32%)
Non-ST elevation myocardial infarction	756 (22%)	247 (21%)	270 (23%)	239 (20%)
Unstable angina	620 (18%)	192 (16%)	219 (19%)	209 (18%)
Stable angina	1065 (30%)	356 (30%)	358 (31%)	351 (30%)
Lesion characteristics†				
At least one complex lesion	2783 (79%)	903 (77%)	938 (80%)	942 (81%)
At least one bifurcation lesion	1236 (35%)	415 (35%)	409 (35%)	412 (35%)
At least one chronic total occlusion	139 (4%)	44 (4%)	48 (4%)	47 (4%)
At least one bypass graft lesion	70 (2%)	18 (2%)	30 (3%)	22 (2%)
At least one ostial lesion	252 (7%)	97 (8%)	81 (7%)	74 (6%)
At least one severely calcified lesion	783 (22%)	252 (22%)	265 (23%)	266 (23%)
Procedural characteristics				
Implantation of assigned stents only	3446 (98%)	1155 (99%)	1147 (98%)	1144 (98%)
Total stent length per patient (mm)	31 (20–50)	32 (20–48)	30 (22–52)	30 (18–49)
Direct stenting	589 (17%)	208 (18%)	174 (15%)	207 (18%)
Postdilation	2833 (81%)	960 (82%)	927 (79%)	946 (81%)
Multivessel treatment	640 (18%)	201 (17%)	220 (19%)	219 (19%)
Radial approach	1597 (45%)	523 (45%)	544 (46%)	530 (45%)
Fractional flow reserve use	440 (13%)	147 (13%)	155 (13%)	138 (12%)

Data are n (%), means (SD), or median (IQR). *Renal insufficiency was defined as an estimated glomerular filtration rate of less than 30 mL per min per 1·73 m² of body-surface area or the need for dialysis. †Definitions of lesion characteristics are provided in the appendix. Lesion-based analysis corrected for intrapatient correlation with generalised estimating equations are available in the appendix.

Table 1: **Characteristics of patients and procedures**

patients). The independent clinical event committee was at all times blinded to the assigned treatment.

Statistical analysis

For both main comparisons, we did non-inferiority analyses[26] for the primary endpoint at 12 months. The time to primary endpoint and associated components were assessed according to Kaplan-Meier methods; the log-rank test was applied for between-group comparisons. Assuming a proportion of target vessel failure of 8·5%, based on the early 2012 available outcome data of the RESOLUTE All comers[27] and TWENTE trials[28] and the assumed enrolment of substantially more patients with ST-elevation myocardial infarction, we estimated that 3540 patients would provide a power of 85% or higher to show non-inferiority with a margin of 3·5%, with a one-sided α level of 2·5% and 3·0% loss to follow-up. We calculated the sample size with PASS software (version 11.0.8). Analyses were based on the intention-to-treat principle. For the primary endpoint, we also did a per-protocol analysis. Pearson's χ^2 test or Fisher's exact test were used to compare categorical variables and the *t* test was done to compare continuous variables. Hazard ratios (HRs) were

	All patients (n=4663)	Patients with everolimus-eluting stents (n=1532)	Patients with zotarolimus-eluting stents (n=1580)	Patients with sirolimus-eluting stents (n=1551)
Left main stem	76 (2%)	25 (2%)	28 (2%)	23 (2%)
Left anterior descending artery	1883 (40%)	616 (40%)	588 (37%)	679 (44%)
Left circumflex artery	1091 (23%)	358 (23%)	395 (25%)	338 (22%)
Right coronary artery	1530 (33%)	510 (33%)	535 (34%)	485 (31%)
Bypass graft	86 (2%)	23 (2%)	34 (2%)	29 (2%)
ACC/AHA lesion class	4645	1527	1573	1545
A	225 (5%)	82 (5%)	68 (4%)	75 (5%)
B1	1063 (23%)	361 (24%)	370 (24%)	332 (22%)
B2	1826 (39%)	578 (38%)	624 (40%)	624 (40%)
C	1531 (33%)	506 (33%)	511 (33%)	514 (33%)
Chronic total occlusion	151 (3%)	50 (3%)	49 (3%)	52 (3%)
In-stent restenosis	93 (2%)	30 (2%)	33 (2%)	30 (2%)
Bifurcated lesion	1327 (29%)	446 (29%)	438 (28%)	443 (29%)
Severely calcified lesion	940 (20%)	296 (19%)	327 (21%)	317 (20%)
Preprocedural*				
Median lesion length (mm)	14·67 (10·53–22·02)	14·59 (10·34–21·95)	14·74 (10·65–21·92)	14·63 (10·59–22·30)
Median minimum lumen diameter (mm)	0·71 (0·38–1·02)	0·71 (0·36–1·02)	0·70 (0·42–1·02)	0·71 (0·37–1·01)
Mean reference vessel diameter (mm)	2·76 (0·57)	2·76 (0·56)	2·76 (0·59)	2·75 (0·56)
Median lumen diameter stenosis (%)	73·0 (62·4–85·3)	73·8 (62·7–86·3)	72·5 (62·5–84·1)	72·8 (62·2–86·3)
Postprocedural†				
Median minimum lumen diameter (mm)	2·20 (1·83–2·59)	2·23 (1·84–2·60)	2·20 (1·84–2·59)	2·18 (1·83–2·57)
Median lumen diameter stenosis (%)	17·3 (13·3–22·9)	17·4 (13·4–22·9)	17·3 (13·3–23·0)	17·4 (13·3–22·9)
Median acute lumen gain in segment (mm)	1·47 (1·03–1·96)	1·50 (1·06–1·99)	1·45 (1·04–1·95)	1·46 (1·01–1·95)

Data are n (%), mean (SD), or median (IQR), unless otherwise stated. Lesion-based analysis corrected for intrapatient correlation with generalised estimating equations are available in the appendix. ACC=American College of Cardiology. AHA=American Heart Association. *Data for 1527 lesions in the everolimus-eluting stent group, 1573 lesions in the zotarolimus-eluting stent group, and 1545 lesions in the sirolimus-eluting stent group. †Data for 1526 lesions in the everolimus-eluting stent group, 1574 lesions in the zotarolimus-eluting stent group, and 1547 lesions in the sirolimus-eluting stent group.

Table 2: **Characteristics of target lesions**

computed with Cox proportional hazards regressions analysis. To account for intrapatient correlation (due to interlesion dependence), additional lesion-based analyses were done with the generalised estimating equations method. Logistic regression was used to test for interaction between subgroups and treatment with regard to the primary endpoint. p values of less than 0·05 were considered significant. p values and confidence intervals were two sided, except those for non-inferiority testing of the primary endpoint. Data analysts remained blinded to the assigned treatment until the evaluation of 12 month follow-up was finished. No interim analysis was done. SPSS (version 22) was used for the statistical analysis. This trial is registered with ClinicalTrials.gov, number NCT01674803.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CvB, MMK, LCvdH, and MML had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Dec 21, 2012, to Aug 24, 2015, 3514 patients with 4663 target lesions were randomly assigned and assessed at four clinical sites, representing 44% of all 7928 patients who underwent percutaneous coronary interventions with drug-eluting stent implantation during the sites' participation in the trial (irrespective of inclusion and exclusion criteria; we have no reliable data for the total number of eligible patients; figure 1). Of these allcomers aged 32–93 years, most (2449 [70%] of 3514) were treated for acute coronary syndromes (table 1). The proportion of patients with ST elevation myocardial infarction was very high (1073 [31%] of 3514). Of all coronary lesions treated, 3357 (72%) of 4663 were complex (American College of Cardiology and American Heart Association lesion class B2 or C; table 2). In almost all patients (3480 [99%] of 3514), at least one assigned stent was implanted. Of the 3514 patients, 30 (<1%) received only non-assigned stents and four (<1%) received no stent (figure 1). Deviation from the assigned stent did not differ significantly between treatment groups (p=0·33). Assignment to treatment was balanced among the participating research

	All patients (n=3514)			Everolimus *vs* zotarolimus		Sirolimus *vs* zotarolimus	
	Everolimus-eluting stent (n=1172)	Zotarolimus-eluting stent (n=1173)	Sirolimus-eluting stent (n=1169)	Hazard ratio (95% CI)	Log-rank p value	Hazard ratio (95% CI)	Log-rank p value
Death, any	20 (2%)	19 (2%)	19 (2%)	1·06 (0·56–1·98)	0·87	1·00 (0·53–1·89)	0·99
Cardiac death	10 (1%)	10 (1%)	10 (1%)	1·00 (0·42–2·41)	1·00	1·00 (0·42–2·41)	1·00
Myocardial infarction, any	25 (2%)	31 (3%)	29 (3%)	0·81 (0·48–1·36)	0·42	0·94 (0·57–1·56)	0·80
Target vessel myocardial infarction	25 (2%)	31 (3%)	26 (2%)	0·81 (0·48–1·36)	0·42	0·84 (0·50–1·42)	0·51
Periprocedural myocardial infarction	21 (2%)	25 (2%)	21 (2%)	0·84 (0·47–1·50)	0·55	0·84 (0·47–1·50)	0·56
Coronary revascularisation, any	40 (4%)	52 (5%)	49 (4%)	0·77 (0·51–1·16)	0·21	0·95 (0·64–1·40)	0·79
Target vessel revascularisation	23 (2%)	30 (3%)	26 (2%)	0·77 (0·45–1·32)	0·34	0·87 (0·51–1·47)	0·60
Target lesion revascularisation	17 (2%)	17 (2%)	18 (2%)	1·00 (0·51–1·97)	0·99	1·06 (0·55–2·06)	0·86
Target vessel failure*	55 (5%)	63 (5%)	55 (5%)	0·87 (0·61–1·25)	0·45	0·87 (0·61–1·25)	0·46
Target lesion failure	49 (4%)	53 (5%)	47 (4%)	0·92 (0·63–1·36)	0·69	0·89 (0·60–1·31)	0·55
Major adverse cardiac events	59 (5%)	61 (5%)	59 (5%)	0·97 (0·68–1·38)	0·85	0·97 (0·68–1·39)	0·86
Patient-oriented composite endpoint	81 (7%)	90 (8%)	87 (8%)	0·90 (0·67–1·21)	0·49	0·97 (0·72–1·30)	0·84
Definite or probable stent thrombosis	5 (<1%)	6 (<1%)	5 (<1%)	0·84 (0·26–2·74)	0·77	0·84 (0·26–2·74)	0·77
Definite stent thrombosis	4 (<1%)	3 (<1%)	4 (<1%)	1·34 (0·30–5·97)	0·70	1·34 (0·30–5·98)	0·70
Probable stent thrombosis	1 (<1%)	3 (<1%)	1 (<1%)	0·33 (0·04–3·21)	0·32	0·33 (0·04–3·21)	0·32

The event rates (expressed as n and %) were calculated with the use of 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.

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

centres (p=0·94). Overall, direct stent implantation (ie, without predilation of the lesion) was done in 589 (17%) of 3514 patients, and stent postdilation was done in 2833 (81%) of 3514 patients (table 1); no significant difference between stent arms. Postprocedural cardiac biomarkers were available in 3412 (97%) of 3514 patients (no significant difference between stent arms). A total of 3490 (99%) of 3514 patients completed the 12 month follow-up or had died. Very few patients (three [<0·1%] of 3514 patients) were lost to follow-up, and 21 (<1·0%) of 3514 patients withdrew consent during the trial (censored; outcome data were used until time of withdrawal).

The clinical outcome data are presented in table 3. The primary composite endpoint of target vessel failure at 1 year was met by 55 (5%) of 1172 patients assigned to everolimus-eluting stents, 55 (5%) of 1169 patients assigned to sirolimus-eluting stents and 63 (5%) of 1173 assigned to zotarolimus-eluting stents. Non-inferiority of the everolimus-eluting stent versus zotarolimus-eluting stent was confirmed with an absolute risk difference of –0·7% (95% CI –2·4 to 1·1) and an upper limit of the one sided 95% CI of 0·8% ($p_{non\text{-}inferiority}$<0·0001; figure 2A). Moreover, non-inferiority of the sirolimus-eluting stent versus zotarolimus-eluting stent was confirmed with an absolute risk difference of –0·7% (95% CI –2·4 to 1·1) and an upper limit of the one sided 95% CI of 0·8% ($p_{non\text{-}inferiority}$<0·0001; figure 2A). For these two main comparisons, the results for the primary endpoint were consistent across subgroups (appendix).

Figure 2 also shows the event rates of the individual components of the primary endpoint, which were low for all treatment groups. Various other adverse events and composite clinical endpoints are reported in table 3. Further lesion-based results are provided in the appendix. To account for the possibility that deviation from the assigned stent might have affected the primary outcome, we also performed a per-protocol analysis of the primary endpoint, which gave results similar to the intention-to-treat analyses (appendix).

3419 (97%) of 3514 patients at discharge and 2939 (86%) of 3432 patients at 1 year follow-up were on DAPT, without any difference in DAPT rate or use of more potent P2Y12 inhibitors among the treatment groups (appendix). Among the three treatment groups, definite stent thrombosis was an infrequent event that occurred in four (0·3%) of 1172, four (0·3%) of 1169, and three (0·3%) of 1173 patients (log-rank p=0·70 for both comparisons with zotarolimus-eluting stents). Moreover, the 1 year rate of definite or probable stent thrombosis was similar among the treatment groups (log-rank p=0·77; table 3, figure 3). In patients treated with everolimus-eluting stents, there were two non-fatal, late, definite stent thromboses in patients who were on DAPT. In patients treated with sirolimus-eluting stents, there was one, non-fatal, late, definite stent thrombosis in a patient who was not on DAPT. In patients treated with zotarolimus-eluting stents, there was one non-fatal, late, definite stent thrombosis in a patient on DAPT; there was also one fatal, late, probable stent thrombosis in a patient on DAPT (figure 3). Further information on circumstances and clinical consequences of patients who developed a stent thrombosis is provided in the appendix.

See Online for appendix

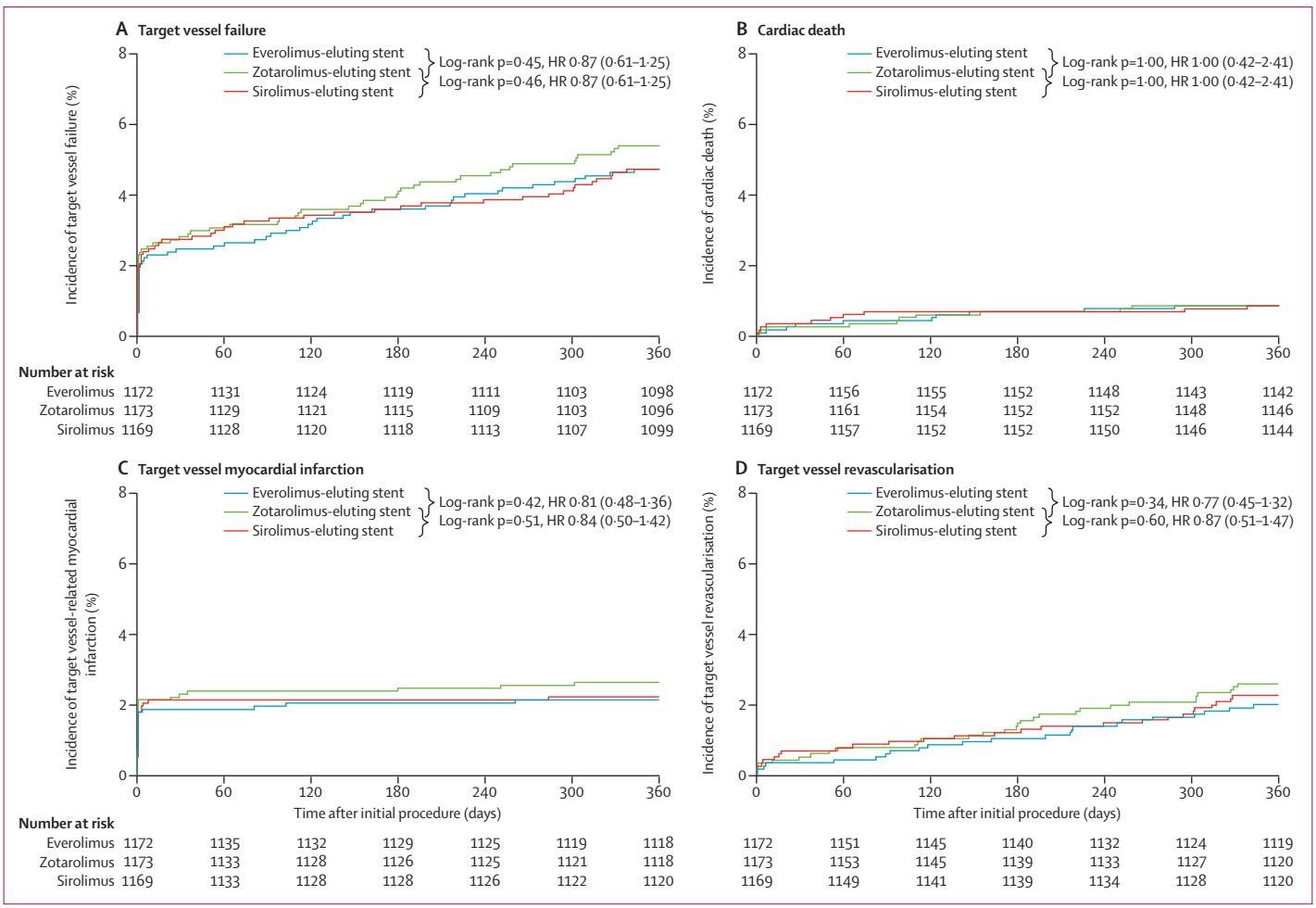

Figure 2: **Kaplan-Meier for the primary endpoint target vessel failure and its individual components at 1 year follow-up**
(A) Target vessel failure, comprising cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularisation. The individual components are (B) cardiac death, (C) target vessel-related myocardial infarction, and (D) target vessel revascularisation.

Discussion

To our knowledge, BIO-RESORT is the first randomised trial to compare the very thin strut biodegradable polymer everolimus-eluting or sirolimus-eluting stents with the durable polymer zotarolimus-eluting stent, to assess the everolimus-eluting stent in allcomers; and to assess more than one novel very thin strut biodegradable polymer stent. Between stent groups, there was no difference in the 12 month incidence of the composite primary endpoint. As a result, both the everolimus-eluting stent and the sirolimus-eluting stent met the criterion of non-inferiority compared with the zotarolimus-eluting stent. Moreover, in all three treatment groups the rates of individual components of the primary endpoint were relatively low.

The study population represents 44% of all potentially eligible patients (irrespective of inclusion and exclusion criteria). Additionally, 70% of all 3514 allcomers were treated for acute coronary syndromes, and the enrolment rate of 31% patients with acute ST elevation myocardial infarction was much higher than in previous stent trials in allcomers.[6,8,11,12,21–23,27,28] The fact that BIO-RESORT has such very high percentages of patients with these disorders suggests that the present study population might be a true representation of the full range of patients treated in routine clinical practice. Almost all patients (99%) received the assigned stent. Moreover, postprocedural cardiac biomarkers were available in 97% of all patients, and the 1 year follow-up rate of 99% was very high. Considering the complex study population in BIO-RESORT, which included many patients with increased clinical, lesion-related, or procedural risk, the event rates were remarkably low and represent at 1 year an excellent safety signal for the stents assessed.

It has been suggested that the absence of a permanent polymer in the coronary artery might reduce vascular inflammation, which has been connected to delayed arterial healing, incomplete endothelial strut coverage, neoatherosclerosis, and potentially fatal complications such as (very) late stent thrombosis and myocardial infarction.[3,29] So far, some clinical trials reported

encouraging outcome data for biodegradable polymer stents.[3,7,10] But comprehensive clinical proof is still pending to show that the theoretical advantages of biodegradable polymer stents translate into long-term clinical outcomes that are significantly better than with new-generation, durable polymer stents.[13,30] Nevertheless, a substantial proportion of operators support the concept of biodegradable polymer stents and use them in routine clinical practice. However, evidence from clinical and experimental research has shown that specific durable polymer coatings might lower the risk of stent thrombosis as compared with biodegradable polymer coatings,[13,31] but these durable polymer stents might still develop in-stent neoatherosclerosis and stent thrombosis.[13,32]

The potential benefits (or disadvantages) of biodegradable polymer stents might be noted later than after a year.[7–9] But before consideration of potential long-term benefits of biodegradable polymer stents, the short-term usefulness of these devices should be determined—preferably in a complex allcomers population. BIO-RESORT shows that the 1 year efficacy and safety of the two novel biodegradable polymer stents are non-inferior to that of an established new-generation, durable polymer stent. The mid-term and long-term clinical outcome of these patients will also be of great interest.

The clinical results of the everolimus-eluting stent group in our present all-comer trial represent an important addition to scientific knowledge about this device. Previously, the EVOLVE II[18] randomised trial assessed 1684 patients with up to moderate complexity, treated with Synergy biodegradable polymer versus durable polymer everolimus-eluting platinum chromium stents, and reported non-inferiority of the biodegradable polymer stent.

The outcome of the sirolimus-eluting Orsiro stent group of our trial corroborates the results of two previous multicentre trials that compared this device with an everolimus-eluting, durable polymer stent in 2119 allcomers of the BIOSCIENCE trial[21] and versus a biolimus-eluting, early biodegradable polymer stent in 2525 allcomers from the SORT OUT VII trial.[22] Both trials reported non-inferiority of the sirolimus-eluting stent compared with the respective comparator stent.[21,22]

The durable fluoropolymer coating of newer-generation everolimus-eluting stents has been shown to reduce the risk of thrombus formation as compared with bare metal stents,[15] which corroborates clinical data that showed a particularly low risk of stent thrombosis in durable fluoropolymer stents.[33] Resolute-type durable polymer (ie, blend of three durable polymers) zotarolimus-eluting stents, as used in the present trial, were previously shown to also have a highly favourable safety profile with relatively low stent thrombosis rates.[30] Recent data suggested that biodegradable polymer stents, of which many have a polymer coating on the abluminal surface only, might be less thromboresistant than fluoropolymer-coated stents.[31] Nevertheless, in the present study, both biodegradable polymer stents showed excellent clinical outcomes and low stent thrombosis rates. This finding might be related to their low strut thickness, because the overall surface that requires re-endothelialisation is much smaller in thin strut stents. Additionally, preclinical research has shown that thin struts reduced both thrombus formation and intimal proliferation.[15] Consequently, the use of thinner struts might lower the risk of potentially fatal complications, such as stent thrombosis and myocardial infarction, as well as the risk of lesion recurrence.[15]

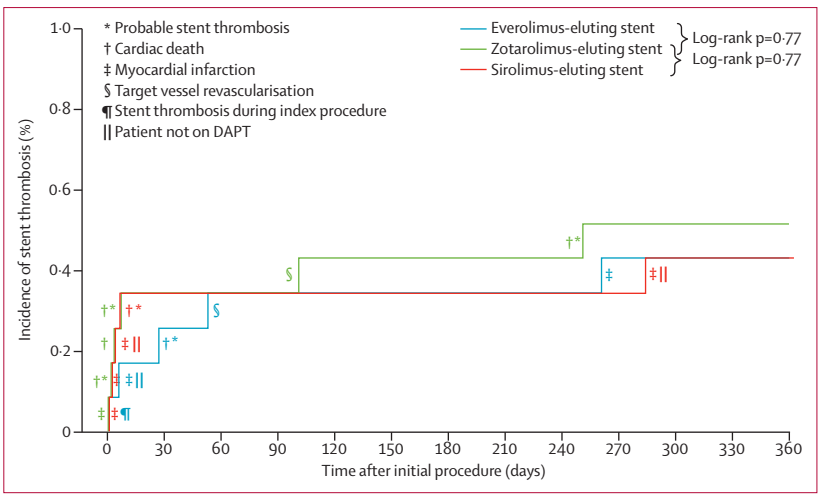

Figure 3: **Incidence of definite or probable stent thrombosis up to 1 year**
Symbols indicate the hierarchically highest adverse events associated with stent thromboses. Probable stent thromboses had five fatal events; all other events represent definite stent thromboses (one fatal event). DAPT consisted of aspirin 80 mg or more daily and an adequate dose of a P2Y12 receptor antagonist. DAPT=dual antiplatelet therapy.

The struts of the novel biodegradable polymer stents are substantially thinner (60–81 μm) than those of the early biodegradable polymer stents (120 μm). We use the term very thin strut stents to characterise the novel devices and to emphasise this difference.

The minimum stent strut thickness required to ensure sufficient radial force to prevent elastic recoil of the dilated vessel depends on the stent material and design. The two novel biodegradable polymer stents use platinum chromium and cobalt chromium alloys, which permit the construction of stents with very thin struts and flexible designs.[4] Such stent designs reduce the thrombogenicity by lowering the incidence of strut malapposition, a well-known cause of coronary flow disturbance and thrombus formation.[15] However, very thin struts might also have disadvantages. Theoretically, the inferior radiographical visibility of thin stent struts, which is more marked in cobalt chromium stents than in platinum chromium stents,[17,18] might increase the risk of geometrical miss and could have resulted in higher event rates. Nevertheless, our present study shows for both novel devices that there is no loss of 1 year efficacy and safety. Longer-term follow-up of the present and future studies will be required to assess potential long-term benefits of these devices.

In the BIO-RESORT trial, the substantial differences in type, amount, distribution, and resorption speed of the polymer coating between the everolimus-eluting and sirolimus-eluting stent did not result in a significant between-stent difference in 1 year clinical outcome. Theoretically, the rapid polymer resorption in the everolimus-eluting stent might have justified a shorter DAPT in this treatment arm. Nevertheless, most patients in all three stent groups remained on DAPT for 12 months, and the use of the more potent P2Y12 inhibitors ticagrelor or prasugel did not differ between treatment groups. Shortening DAPT after drug-eluting stent implantation might be most advantageous in patients with increased bleeding risk. Yet, in the present trial, almost 70% of patients were treated for acute coronary syndromes, where shortening DAPT is generally not considered.

The present study has some limitations. When designing the BIO-RESORT trial in early 2012, the expected incidence of the primary endpoint was based on results of previous studies done in high-volume centres.[27,28] At that time, no data were available about the clinical outcome after treatment of allcomers with the specific type of thin-strut durable polymer zotarolimus-eluting stent used in the present trial; these data were later reported by the DUTCH PEERS trial[23] and the SORT OUT VI trial.[12] We assumed that BIO-RESORT would enrol a complex allcomers population with a substantially higher proportion of patients with ST-elevation myocardial infarction than enrolled in the RESOLUTE All Comers trial[27] and that this increase in patient complexity might result in a slightly higher event rate. As a result, we assumed a target vessel failure rate of 8·5% was reasonable. Moreover, the choice of a non-inferiority margin of 3·5% was in line with previous stent trials in allcomers that used non-inferiority margins of 3·5–4·0%.[6,11,23,27]

While BIO-RESORT succeeded in enrolling 31% of patients with ST-elevation myocardial infarction, the actual event proportion of the primary endpoint target vessel failure was lower than expected. As in other randomised trials, under-reporting of adverse events cannot be completely excluded. Nevertheless, considering the systematic postprocedural assessment of biomarkers and electrocardiograph, high follow-up rates, and independent monitoring and event adjudication, under-reporting might not have been substantial. Other randomised stent trials also have found lower than expected event rates;[11,18,21–23,34] which suggests that the event rates of the present study are actually more representative of the outcome of present percutaneous coronary interventions, as opposed to when this trial was designed. Besides the improvement in stent systems, balloon catheters, and other equipment to facilitate interventional procedures, other aspects might also have contributed to the low event rates: wider use of the more potent P2Y12 antagonists (in 48% of patients receiving DAPT) as compared with our previous trials;[23,28] more frequent use of the radial access route (in 45% in this trial); and wider implementation of fractional flow reserve measurements (13% of patients in this trial) to identify clinically relevant target lesions and defer haemodynamically non-significant lesions. Moreover, in patients with acute coronary syndromes (70% in BIO-RESORT) the probability of observing periprocedural myocardial infarction is reduced, which might have contributed to the low rates of target vessel myocardial infarction and various composite endpoints, including the primary endpoint.

Although the present trial is a large-scale study, it is not powered to reliably assess very rare adverse clinical events, for instance, stent thrombosis. However, stent thrombosis is an event that is too important to be ignored, in particular as one of the two novel stents was never before assessed in an allcomers trial. These data are no more than hypothesis generating. Future studies might assess the potential of novel biodegradable polymer stents to be treated with short-term DAPT.

In conclusion, the two very thin strut drug-eluting stents with highly dissimilar biodegradable polymer coatings were non-inferior to the durable polymer stent in treating a complex allcomers population with a high proportion of patients with acute coronary syndromes. The absence of a loss of 1 year safety and efficacy with the use of these biodegradable polymer-coated stents is a prerequisite before assessing their potential longer-term benefits.

Contributors

CvB, MH, KGvH, J(H)WL, FHAFdM, MGS, PWD, CES, and MS designed the trial. CvB, MMK, LCvdH wrote the first draft of the report. JvdP, CJMD, and MML participated in drafting the report; and all other authors revised the draft for important intellectual content. MMK, LCvdH, PZ, and MML gathered the data. LCvdH, MMK, JvdP, and CJMD did the statistical analyses. CvB, MMK, LCvdH, JvdP, CJMD, and MML first interpreted the data and had full access to the data. All authors participated in the interpretation of data. All authors read and approved the final version of the manuscript. CvB, the principal investigator and corresponding author, had final responsibility for the decision to submit for publication.

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Monitoring and independent clinical event committee

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Elvin Kedhi (chair), Marjolein Brusse-Keizer (statistician), and Gianclaudio Mecozzi (member).

Declaration of interests

The research department of Thoraxcentrum Twente has received research grants from AstraZeneca, Biotronik, Boston Scientific, and Medtronic. CvB was a consultant to device-manufacturing companies, among them Abbott, Boston Scientific, and Medtronic; he has received travel expenses from Biotronik and speakers honoraria from AstraZeneca and MSD. All other authors declare no competing interests.

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