JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 3, 2017
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.11.007

Comparison of Durable-Polymer Zotarolimus-Eluting and Biodegradable-Polymer Biolimus-Eluting Coronary Stents in Patients With Coronary Artery Disease

3-Year Clinical Outcomes in the Randomized SORT OUT VI Trial

Bent Raungaard, MD, PhD,[a] Evald H. Christiansen, MD, PhD,[b] Hans Erik Bøtker, MD, DMSci,[b] Henrik S. Hansen, MD, DMSci,[c] Jan Ravkilde, MD, DMSci,[a] Leif Thuesen, MD, DMSci,[a] Jens Aarøe, MD,[a] Anton B. Villadsen, MD,[a] Christian J. Terkelsen, MD, DMSci, PhD,[b] Lars R. Krusell, MD,[b] Michael Maeng, MD, PhD,[b] Steen D. Kristensen, MD, DMSci,[b] Karsten T. Veien, MD,[c] Knud N. Hansen, MD,[c] Anders Junker, MD,[c] Morten Madsen, MSc,[d] Søren L. Andersen, MSc, PhD,[d] Svend E. Jensen, MD, PhD,[a] Lisette O. Jensen, MD, DMSci, PhD,[c] for the SORT OUT VI Investigators

ABSTRACT

OBJECTIVES The authors sought to compare the safety and efficacy of the biocompatible durable-polymer zotarolimus-eluting stent with the biodegradable-polymer biolimus-eluting stent in unselected coronary patients.

BACKGROUND Biodegradable-polymer biolimus-eluting stents are superior to first-generation durable-polymer drug-eluting stents in long-term randomized all-comer trials. Long-term data comparing them to second-generation durable-polymer drug-eluting stents are lacking.

METHODS The study was a randomized, multicenter, all-comer, noninferiority trial in patients with chronic stable coronary artery disease or acute coronary syndromes and at least 1 coronary artery lesion requiring treatment with a drug-eluting stent. Endpoints included major adverse cardiac events (MACE), a composite of safety (cardiac death and myocardial infarction not clearly attributable to a non-target lesion) and efficacy (target lesion revascularization); the individual endpoints of MACE; all-cause mortality; any myocardial infarction; target vessel revascularization; and definite or probable stent thrombosis at 36 months.

RESULTS From March 2011 to August 2012, 2,999 patients were randomly assigned (1:1) to receive either the zotarolimus-eluting (1,502 patients) or the biolimus-eluting (1,497 patients) stent. At 3-year follow-up, MACE occurred in 128 (8.6%) patients assigned to the durable-polymer zotarolimus-eluting stent and in 144 (9.6%) assigned to the biodegradable-polymer biolimus-eluting stent ($p = 0.36$). Occurrence of cardiac death (2.7% vs. 3.4%), myocardial infarction not clearly attributable to a non-target lesion (2.7% vs. 2.5%), and target lesion revascularization (5.4% vs. 5.5%) did not differ significantly between the 2 groups. Definite very late stent thrombosis occurred in 6 (0.4%) patients assigned to the durable-polymer zotarolimus-eluting stent and in 10 (0.7%) assigned to the biodegradable-polymer biolimus-eluting stent ($p = 0.33$).

CONCLUSIONS At 3-year follow-up, the durable-polymer zotarolimus-eluting stent and the biodegradable-polymer biolimus-eluting stent were similar in clinical outcome, with no significant difference in safety and efficacy outcomes, including stent thrombosis. (J Am Coll Cardiol Intv 2017;10:255–64) © 2017 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [b]Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark; [c]Department of Cardiology, Odense University Hospital, Odense, Denmark; and the [d]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark. The trial was supported by unrestricted grants from Biosensors Interventional Technologies Pte Ltd. and Medtronic CardioVascular Inc. Dr. Christiansen has received

ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

TLR = target lesion revascularization

TVR = target vessel revascularization

Second-generation drug-eluting stents (DES) have been shown to be superior to bare-metal stents and first-generation DES, with reduced incidences of restenosis, target vessel revascularization (TVR), and stent thrombosis (ST), in particular very late ST occurring after discontinuation of dual antiplatelet therapy (1-5). In first-generation DES, remnants of polymer material after completed drug release have been suggested as triggers of chronic inflammatory responses causing impaired stent strut endothelialization and positive vessel remodeling leading to increasing risk of ST (6,7). Second-generation DES with biodegradable polymers have out-performed the first-generation DES in long-term randomized all-comer trials (8,9). Polymer materials on second-generation durable-polymer DES, however, have been modified to be more biocompatible, with a potential lower risk of inflammation than polymers of first-generation DES. Ex vivo studies (10) supported by meta-analyses of randomized clinical trials (11-13) have suggested that such biocompatible polymers might be less thrombogenic than bare metal. This may reduce the risk of late and very late ST with biocompatible durable-polymer stents.

SEE PAGE 265

The purpose of the SORT OUT (Scandinavian Organization for Randomized Trials with Clinical Outcome) VI trial was to investigate the safety and efficacy of a durable polymer DES versus a biodegradable polymer DES by comparing the highly biocompatible durable-polymer zotarolimus-eluting Resolute Integrity stent (Medtronic CardioVascular, Santa Rosa, California) with the biodegradable-polymer biolimus-eluting BioMatrix Flex stent (Biosensors Interventional Technologies, Singapore) in an all-comer population using registry detection of clinically driven events. At 12 months (14), the durable-polymer zotarolimus-eluting Resolute Integrity stent was noninferior to the biodegradable-polymer biolimus-eluting BioMatrix Flex stent. We report the clinical outcomes at the 3-year follow-up of this trial.

METHODS

STUDY DESIGN, PATIENTS, AND PROCEDURES. SORT OUT VI has previously been described in detail (14). In brief, SORT OUT VI is an open-label, randomized, multicenter, all-comer, 2-arm, noninferiority trial comparing the durable-polymer zotarolimus-eluting Resolute Integrity stent to the biodegradable-polymer biolimus-eluting BioMatrix Flex stent in treating coronary artery lesions. Study enrollment was performed at 3 university hospitals across western Denmark from March 2011 to August 2012. Patients were eligible if they had stable coronary artery disease or acute coronary syndromes, including myocardial infarction (MI) with or without ST-segment elevation. No restriction was placed on the total number of treated lesions, treated vessels, lesion length, or number of stents implanted. Interventional procedures were performed according to standard techniques and routine clinical protocols. The study complied with the provisions of the Declaration of Helsinki, and the study protocol was approved by the local ethics committee. All patients provided written informed consent for trial participation. Patients were randomly assigned (1:1) to receive the durable-polymer zotarolimus-eluting Resolute Integrity stent or the biodegradable-polymer biolimus-eluting BioMatrix Flex stent.

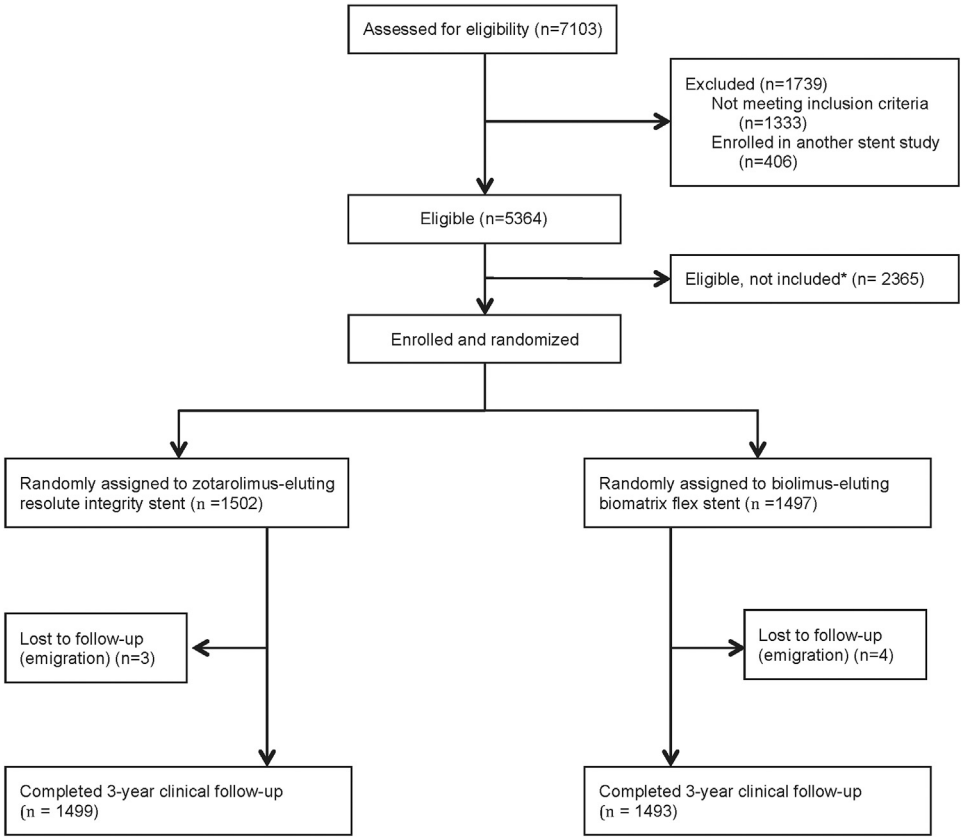
Although second-generation, these stents have considerable variations in polymer, alloy, strut thickness, stent geometry, polymer composition and degradation, and antiproliferative drug that may influence their performance (15-22).

Before stent implantation, patients received at least 75 mg of aspirin, a loading dose of $P2Y_{12}$ platelet inhibitor (600 mg clopidogrel, 180 mg ticagrelor, or 60 mg prasugrel) orally, and unfractionated heparin intravenously (5,000 IU or 70 to 100 IU/kg). Glycoprotein IIb/IIIa inhibitors and/or bivalirudin were used at the operator's discretion. Recommended post-procedure dual antiplatelet regimens were 75 mg aspirin daily lifelong and $P2Y_{12}$ platelet inhibitor (75 mg of clopidogrel once daily in stable coronary artery disease; 90 mg of ticagrelor twice daily or 10 mg of prasugrel once daily in acute coronary syndromes) for 12 months.

unrestricted research grants to his institution from Biosensors and Medtronic. Dr. Maeng has received research grants from Boston Scientific, Biosensors Interventional Technologies, and Volcano Corporation. Dr. L.O. Jensen has received unrestricted research grants to her institution from Terumo, Biotronik, St. Jude Medical, and Biosensors Interventional Technologies. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 18, 2016; revised manuscript received October 17, 2016, accepted November 3, 2016.

FIGURE 1 Trial Profile



*Not all eligible patients were included because some percutaneous coronary intervention operators at participating centers did not want the choice of stent to be decided by a randomization process.

Intention-to-treat analyses were performed at 36 months after stent implantation. Endpoints included major adverse cardiac events (MACE), a composite of safety (cardiac death and MI not clearly attributable to a non-target lesion) and efficacy (clinically indicated target lesion revascularization [TLR]); the individual endpoints of MACE; all-cause mortality; any MI; TVR; any clinically indicated revascularization (TVR and non-TVR); and definite or probable ST.

Definitions of all pre-defined clinical endpoints have previously been described in detail (14). Cardiac death was defined as death due to an evident cardiac cause, death related to percutaneous coronary intervention (PCI), unwitnessed death, or death from unknown causes. MI was defined according to the universal definition used by the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation (23). ST was classified as definite or probable according to Academic Research Consortium criteria (24). TVR was defined as repeat revascularization (PCI or coronary bypass surgery) of the target lesion coronary vessel. TLR was defined as repeat revascularization (PCI or coronary bypass surgery) caused by a stenosis within the stent or within a 5-mm border proximal or distal to the stent. Event detection was performed using population-based health care databases as previously described (25). Therefore, all events were clinically driven (i.e., all revascularizations were symptom based). Data on mortality, hospital admissions, coronary angiography, repeat PCI, and coronary bypass surgery were obtained for all randomly allocated patients from the following national Danish administrative and health care registries: the Civil Registration System, the Western Denmark Heart Registry, and the Danish National Registry of Patients (which maintains records for all hospital admissions in Denmark) (25). An independent event committee, masked to treatment

TABLE 1 Baseline Characteristics of the Study Population

	Zotarolimus-Eluting Stent (n = 1,502)	Biolimus-Eluting Stent (n = 1,497)	p Value
Age (yrs)	65.7 ± 10.7	65.8 ± 10.9	0.66
Men	1,144 (76.2)	1,135 (75.8)	0.82
Diabetes mellitus	265/1,502 (17.6)	270/1,497 (18.0)	0.78
Arterial hypertension	872/1,460 (59.7)	850/1,462 (58.1)	0.38
Hypercholesterolemia	871/1,470 (59.3)	867/1,466 (59.1)	0.95
Current smoker	443/1,441 (30.7)	439/1,431 (30.7)	0.97
Body mass index (kg/m^2)	26.9 ± 5.4	26.9 ± 5.5	0.97
Previous myocardial infarction	275/1,468 (18.7)	288/1,464 (19.7)	0.52
Previous percutaneous coronary intervention	277/1,478 (18.7)	324/1,475 (22.0)	0.03
Previous coronary artery bypass grafting	126/1,499 (8.4)	101/1,494 (6.8)	0.09
Indication for percutaneous coronary intervention			0.11
Stable angina	685 (45.6)	670 (44.8)	
Non-ST-segment elevation MI/unstable angina	465 (31.0)	508 (33.9)	
ST-segment elevation MI	295 (19.6)	253 (16.9)	
Other	57 (3.8)	66 (4.4)	
Number of lesions			0.10
1	1,131 (75.3)	1,175 (78.5)	
2	298 (19.8)	270 (18.0)	
3	61 (4.1)	41 (2.7)	
>3	12 (0.8)	11 (0.7)	
Number of lesions per patient	1.3 (0.6)	1.3 (0.5)	0.03
Index lesion			0.66
Stent thrombosis	18 (1.0)	12 (0.7)	
In-stent restenosis	43 (2.3)	45 (2.5)	
Non-in-stent restenosis	13 (0.7)	16 (0.9)	
Target vessel location (%)			0.73
Left main	17 (0.9)	21 (1.2)	
Left anterior descending	758 (40.3)	743 (41.5)	
Left circumflex	447 (23.8)	430 (24.0)	
Right coronary	637 (33.9)	579 (32.3)	
Saphenous vein graft	23 (1.2)	18 (1.0)	
Lesion type			0.28
A	285 (15.2)	289 (16.1)	
B1	544 (28.9)	558 (31.2)	
B2	396 (21.1)	354 (19.8)	
C	656 (34.9)	590 (32.9)	
Chronic total occlusion lesions	82 (4.4)	85 (4.9)	0.55
Bifurcation lesions	226 (12.2)	229 (13.1)	0.44
Lesion length >18 mm	558 (29.7)	491 (27.4)	0.13
Lesion length (mm)	16.0 (12.0–25.0)	15.0 (10.0–25.0)	0.02
Reference vessel size (mm)	3.2 (2.9–3.5)	3.0 (2.8–3.5)	0.11

Values are mean ± SD, n (%), n/N (%), or median (interquartile range). Some of the 2,999 participants' data is missing for some variables (cases/sample size number) because it was not recorded in the Western Denmark Heart Registry.

MI = myocardial infarction.

TABLE 2 Procedure Characteristics

	Zotarolimus-Eluting Stent (n = 1,502)	Biolimus-Eluting Stent (n = 1,497)	p Value
More than 1 stent			
Per patient	534 (35.9)	481 (32.6)	0.057
Per lesion	334 (17.8)	278 (15.6)	0.016
Total stent length (mm)			
Per patient	21.0 (15.0–30.0)	18.0 (14.0–29.0)	0.0007
Per lesion	18.0 (14.0–24.0)	18.0 (14.0–24.0)	0.0021
Direct stenting	277 (14.9)	272 (15.4)	0.67
Stent delivery failure			
Per patient	26 (1.7)	34 (2.3)	0.29
Per lesion	27 (1.4)	30 (1.7)	0.59
Maximum pressure (atm)	16.0 (12.0–18.0)	16.0 (12.0–18.0)	0.19
Length of procedure (min)	22.0 (15.0–36.0)	21.0 (15.0–33.0)	0.057
Contrast (ml)	85.0 (60.0–120.0)	80.0 (60.0–120.0)	0.17
Use of aspirin	1,478 (98.4)	1,458 (97.5)	0.07
Use of clopidogrel	1,099 (73.2)	1,096 (73.6)	0.94
Use of ticagrelor	313 (20.8)	300 (20.0)	0.49
Use of prasugrel	6 (0.4)	10 (0.7)	0.31
Use of glycoprotein IIb/IIIa inhibitors	72 (4.8)	78 (5.2)	0.60

Values are n (%) or median (interquartile range).

group assignment, reviewed all endpoints and source documents to adjudicate causes of death, reasons for hospital admission, and diagnosis of MI. Two dedicated PCI operators at each participating center reviewed cine films for the event committee to classify all cases of ST and TVR or TLR. See Online Appendix for the SORT OUT VI Study Group.

Landmark analyses were performed for all endpoints by dividing the entire follow-up period into the initial 12 months and the subsequent 24 months.

STATISTICAL ANALYSIS. Distributions of continuous variables between study groups were compared using the 2-sample Student *t* test (or Cochran test for cases of unequal variance) or the Mann-Whitney *U* test, depending on whether the data followed a normal distribution. Distributions of categorical variables were analyzed using the chi-square test. Intention-to-treat analyses were performed at 36 months after stent implantation. We counted endpoint events occurring during the follow-up period and compared rates for the 2 groups of patients. Follow-up began on the date of the index PCI procedure. In analyses of each outcome, follow-up continued until the date of an endpoint event, death, emigration, or until 36 months after implantation, whichever occurred first. Cumulative incidence curves were constructed based on the cumulative incidence of endpoint events, taking into account the competing risk of death. Further, landmark analyses were performed as previously noted. Differences between groups were estimated using the Cox proportional hazards model. Patients treated with the biodegradable-polymer biolimus-eluting stent were used as the reference

for overall and subgroup analyses. All analyses were performed according to intention-to-treat principles. We computed the hazard ratio of MACE at 36-month follow-up for relevant patient subgroups. A value of $p < 0.05$ was considered as significant. The statistical software used was SAS version 9.4 (SAS Institute, Cary, North Carolina). This trial is registered as NCT01956448.

RESULTS

From March 2011, to August 2012, we randomly assigned 2,999 patients with 3,674 lesions to receive either the durable-polymer zotarolimus-eluting stent (1,502 patients with 1,883 lesions) or the biodegradable-polymer biolimus-eluting stent (1,497 patients with 1,791 lesions) (Figure 1). Of the randomized patients, 3 and 4 in the respective groups had incomplete follow-up due to emigration and were censored on the day of emigration (Figure 1). Complete data were available for 2,992 patients (99.7%).

Baseline demographic and clinical characteristics in the 2 study groups were well balanced (Table 1). A high proportion of patients in both groups had acute coronary syndromes, multivessel disease, and complex lesions (Table 1). Diabetes mellitus was equally distributed and reported in 18% of patients. Previous PCI, number of lesions per patient, and lesion length differed significantly between groups at baseline (Table 1). The proportion of patients having more than 1 lesion and treated with more than 1 stent was higher in the durable-polymer zotarolimus-eluting stent group. Concordantly, the total stent length per patient was significantly longer in the durable-polymer zotarolimus-eluting stent group as compared with the biodegradable-polymer biolimus-eluting stent group (Table 2). Procedural characteristics were otherwise similar in the two study groups, including the use of aspirin, $P2Y_{12}$ platelet inhibitors, and glycoprotein IIb/IIIa inhibitors (Table 2).

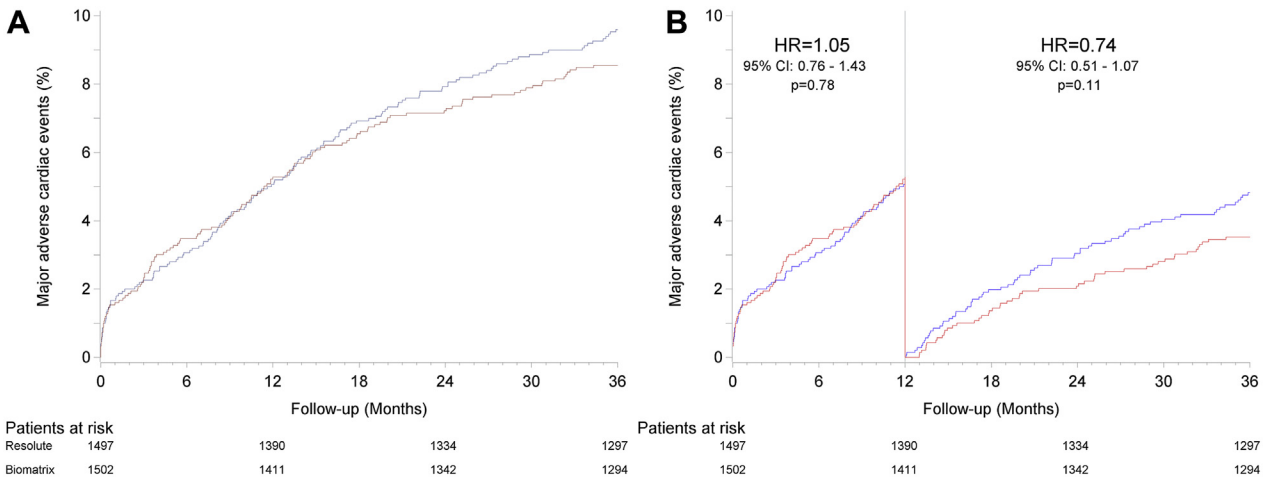
The 3-year clinical outcomes and the landmark analysis of events occurring after year 1 are presented in Table 3 and illustrated for MACE and definite ST in Figures 2 and 3. At 36 months, intention-to-treat analysis showed that MACE occurred in 128 (8.6%) patients who were assigned the durable-polymer zotarolimus-eluting stent and in 144 (9.6%) who were assigned to the biodegradable-polymer biolimus-eluting stent (Figure 2, Table 3). Occurrence of cardiac death (41 [2.7%] vs. 51 [3.4%]), MI not clearly attributable to a non-target lesion (40 [2.7%] vs. 38 [2.5%]), and target lesion revascularization (81 [5.4%] vs. 83 [5.5%]) did not differ significantly between the 2 groups. Definite ST occurred within 36 months in 15 (1.0%) patients in the durable-polymer zotarolimus-eluting stent group and in 17 (1.1%) patients in the biodegradable-polymer biolimus-eluting stent group ($p = 0.44$). Very late definite ST was found in 6 (0.4%) patients in the durable-polymer zotarolimus-eluting stent group and in 10 (0.7%) patients in the biodegradable-polymer biolimus-eluting stent group ($p = 0.33$). At 36 months follow-up, definite or probable ST did not differ significantly between the 2 groups (Table 3). Findings for MACE were consistent across pre-specified subgroups (Figure 4). Adjusting all analyses for differences in baseline and procedural characteristics did not alter the results significantly.

TABLE 3 Three-Year Clinical Outcomes

	Zotarolimus-Eluting Stent (n = 1,502)	Biolimus-Eluting Stent (n = 1,497)	Hazard Ratio (95% CI)	p Value
0–36 months				
Major adverse cardiac events*	128 (8.6)	144 (9.6)	0.90 (0.71–1.14)	0.36
Death	114 (7.6)	114 (7.6)	1.01 (0.78–1.30)	0.96
Cardiac death	41 (2.7)	51 (3.4)	0.81 (0.54–1.22)	0.31
Myocardial infarction	62 (4.1)	70 (4.7)	0.89 (0.63–1.25)	0.49
Target myocardial infarction†	40 (2.7)	38 (2.5)	1.06 (0.68–1.65)	0.80
Any revascularization	239 (16.0)	249 (16.6)	0.96 (0.80–1.14)	0.63
Target vessel revascularization	115 (7.7)	121 (8.1)	0.95 (0.74–1.23)	0.70
Target lesion revascularization	81 (5.4)	83 (5.5)	0.98 (0.72–1.33)	0.90
Definite or probable stent thrombosis‡	19 (1.3)	18 (1.2)	1.06 (0.56–2.02)	0.86
Definite stent thrombosis‡	15 (1.0)	17 (1.1)	0.89 (0.44–1.77)	0.73
Early (<30 days)	5 (0.3)	1 (0.1)		
Late (31 days to 12 months)	4 (0.3)	6 (0.4)		
Very late (12–36 months)	6 (0.4)	10 (0.7)		
12–36 months				
Major adverse cardiac events*	50 (3.6)	68 (4.8)	0.74 (0.51–1.07)	0.11
Death	64 (4.4)	74 (5.1)	0.87 (0.62–1.22)	0.42
Cardiac death	19 (1.3)	25 (1.7)	0.77 (0.42–1.39)	0.38
Myocardial infarction	31 (2.1)	39 (2.7)	0.79 (0.49–1.27)	0.33
Target myocardial infarction†	18 (1.2)	23 (1.5)	0.79 (0.42–1.45)	0.44
Any revascularization	85 (6.3)	77 (5.8)	1.09 (0.80–1.49)	0.56
Target vessel revascularization	50 (3.5)	50 (3.5)	1.00 (0.68–1.48)	1.00
Target lesion revascularization	30 (2.1)	36 (2.5)	0.84 (0.52–1.36)	0.48
Definite or probable stent thrombosis‡	7 (0.5)	10 (0.7)	0.70 (0.27–1.85)	0.48
Definite stent thrombosis‡	6 (0.4)	10 (0.7)	0.60 (0.22–1.66)	0.33

Values are n (%) unless otherwise indicated. Two-sided confidence intervals have been used for all endpoints. *Cardiac death, myocardial infarction not clearly attributable to a non-target lesion, and clinically indicated target lesion revascularization. †Myocardial infarction not clearly attributable to a non-target lesion. ‡Academic Research Consortium definition.

FIGURE 2 Time-to-Event Curves for MACE



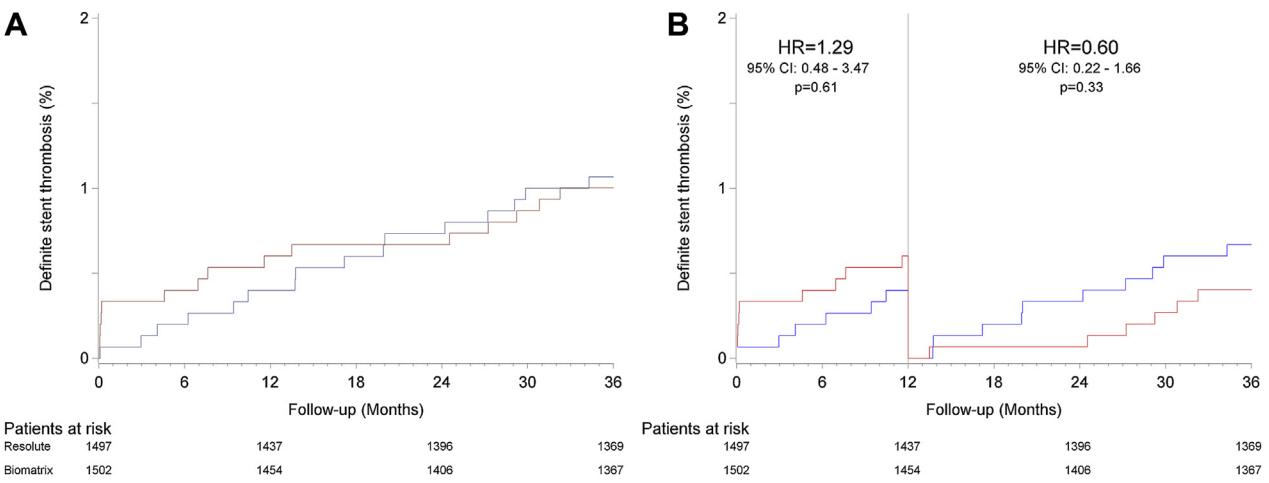
Event rates of major adverse cardiac event(s) (MACE), a composite of cardiac death, myocardial infarction not clearly attributable to a non-target lesion, and target lesion revascularization in the zotarolimus-eluting **(red lines)** versus biolimus-eluting **(blue lines)** stent groups. **(A)** Event rates during the 3-year follow-up. **(B)** A landmark analysis of events occurring after year 1. CI = confidence interval; HR = hazard ratio.

DISCUSSION

The SORT OUT VI trial directly compared the performance of a biocompatible, durable-polymer and a biodegradable-polymer DES in an all-comer population over an extended follow-up period. The main finding of the present study is that at 3-year follow-up, the durable-polymer zotarolimus-eluting Resolute Integrity stent and the biodegradable-polymer biolimus-eluting BioMatrix Flex stent were similar in clinical outcome with no significant differences in safety and efficacy outcomes, including ST, despite variations in alloy, strut thickness, stent geometry, polymer composition and degradation, and antiproliferative drug.

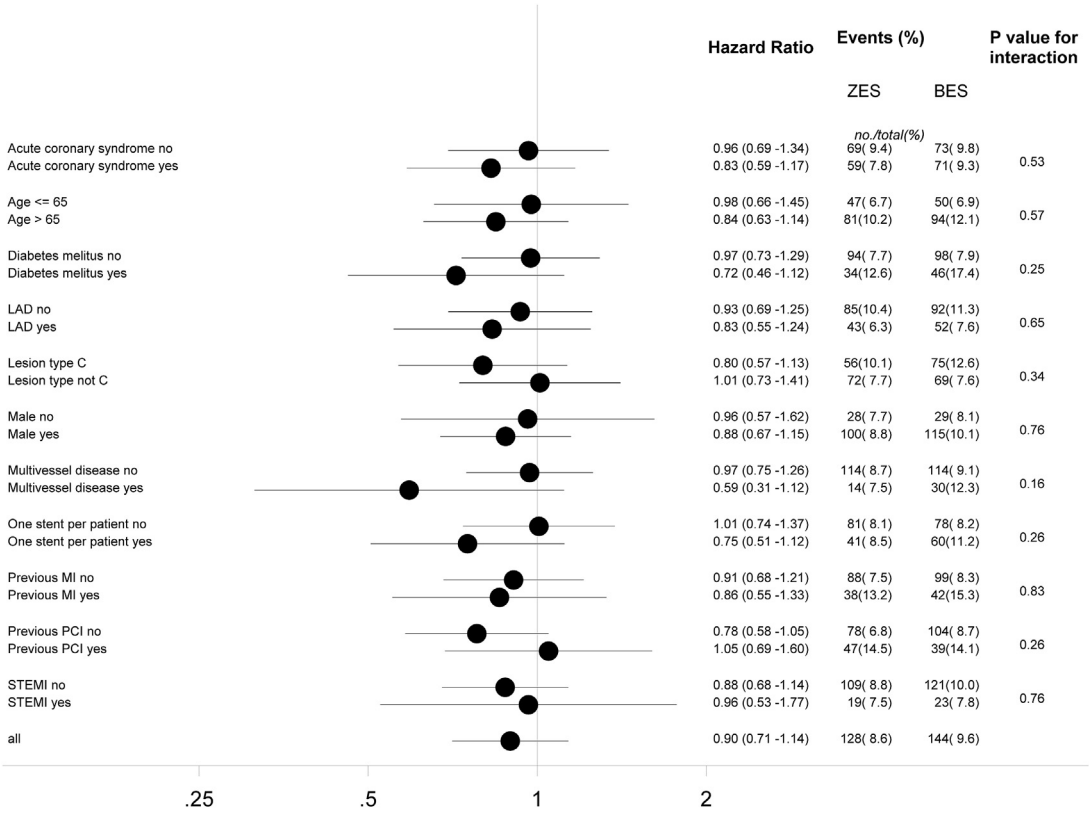
Our low event rates for components of target lesion failure for the durable-polymer zotarolimus-eluting Resolute Integrity stent group were in accordance

FIGURE 3 Time-to-Event Curves for Definite ST



Event rates of definite stent thrombosis (ST) in the zotarolimus-eluting **(red lines)** versus biolimus-eluting **(blue lines)** stent groups. **(A)** Event rates during the 3-year follow-up. **(B)** A landmark analysis of events occurring after year 1. Abbreviations as in Figure 2.

FIGURE 4 Pre-Specified Subgroup Analysis for the Composite Endpoint at 3 Years



Data are number of events (% of patients). Composite endpoint: cardiac death, myocardial infarction not clearly attributable to a non-target lesion, and target lesion revascularization. BES = biolimus-eluting stent; LAD = left anterior descending coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; ZES = zotarolimus-eluting stent.

with those reported in the 2-year follow-up of the DUTCH PEERS (DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity) trial (26). Also the RESOLUTE All Comers (Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents) trial (17) had similar 2-year rates of cardiac death for the Resolute Integrity stent, but had higher rates for target vessel-related MI and TVR than in our and the DUTCH PEERS trial. This may partly be attributed to higher rates of patient-related and stent-independent comorbidities (diabetes mellitus, hypertension, hyperlipidemia, and previous MI) in the RESOLUTE All Comers trial (17), as such comorbidities exacerbate the underlying coronary artery disease over time.

The LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial (20) showed an increasing divergence in outcomes in favor of the biodegradable-polymer biolimus-eluting BioMatrix Flex stent over the durable-polymer sirolimus-eluting Cypher over 4 years. The event rates for the biodegradable-polymer biolimus-eluting stent were comparable to our 3-year event rates. Additionally, in the COMPARE II (Abluminal biodegradable-polymer biolimus-eluting stent versus durable-polymer everolimus-eluting stent) trial (9), 3-year event rates for the biodegradable-polymer biolimus-eluting Nobori stent were comparable to our results.

ST is a serious clinical event resulting in ST-segment elevation MI in the majority of cases (27-29), and mortality rates may be as high as 17% (29). A recent systematic review of randomized trials with DES reported a median incidence of definite late ST of 0.61% (30). Current clinical registries and large randomized trials with broad inclusion criteria show annual rates of very late ST at ~0.1% to 0.4% (9,17,20,26). With the introduction of new-generation DES with altered stent designs and polymers, overall rates of late and very late ST have halved compared with first-generation DES (31,32), but with an unchanged high mortality (32).

Late and very late ST may be dependent on stent type-related factors. First-generation DES were associated with a steadily increasing risk of very late ST compared with bare-metal stents during long-term follow-up (33-36), a difference that was most obvious in complex patients, such as those with acute MI, multivessel disease, diabetes, and bifurcation lesions (37-39). Intrinsic characteristics of durable polymers of first-generation DES seemed to be related to a variety of pathophysiological mechanisms, which in turn might result in very late ST (6,40-43). Polymer materials on second-generation durable-polymer DES, however, have been modified to be more biocompatible with potential lower risk of inflammation than polymers of first-generation DES. The favorable ST rate for the second-generation durable-polymer DES has been confirmed in several longer-term follow-up randomized studies. In the COMPARE (44), SORT OUT III (45), and SORT OUT IV (46) trials, an increasing divergence in ST event rates between first-generation and the second-generation stents was found in favor of the second-generation stent.

Biodegradable-polymer DES designed to diminish long-term adverse events related to the persistence of durable polymers after completion of drug-release have also demonstrated favorable ST event rates during long-term follow-up compared with first-generation DES (20,47-48). However, data on the safety and efficacy of DES coated with biodegradable polymers have not been consistent when compared with first-generation DES as shown by 3-year follow-up in the SORT OUT V trial (49).

STUDY LIMITATIONS. The power of the primary endpoint in our study was target lesion failure at 12 months. The composite endpoint at 3 years was a nonpowered, but pre-specified, secondary endpoint. A limitation of the present study was that data regarding duration of dual antiplatelet therapy were not collected. However, since 2002, all patients treated with coronary stent implantation in Denmark have been recommended to receive 12 months dual antiplatelet therapy, and all our patients in this study received reimbursement of costs related to $P2Y_{12}$ platelet inhibitor treatment for 12 months. We therefore find it unlikely that the duration of dual antiplatelet therapy differed between the groups. We used broad inclusion criteria to include routine clinical care patients, but the SORT OUT VI trial included only 56% of eligible patients in western Denmark. This abridged inclusion rate, however, was mainly caused by a few nonparticipating operators.

CONCLUSIONS

The 3-year results from the SORT OUT VI all-comer randomized trial show that both the durable-polymer zotarolimus-eluting Resolute Integrity stent and the biodegradable-polymer biolimus-eluting BioMatrix Flex stent had a similar and excellent long-term safety and efficacy profile. These data indicate that a durable-polymer stent can be as safe and efficacious as a biodegradable-polymer stent.

ACKNOWLEDGMENT The authors are thankful to Helle Bargsteen for her efficient help with all aspects of the trial.

ADDRESS FOR CORRESPONDENCE: Dr. Bent Raungaard, Department of Cardiology, Aalborg University Hospital, Hobrovej 18-22, DK-9000, Aalborg, Denmark. E-mail: b.raungaard@rn.dk.

PERSPECTIVES

WHAT IS KNOWN? Stent thrombosis is a very serious clinical event with high mortality rates. Our study shows that at 3 years, the durable-polymer zotarolimus-eluting Resolute Integrity stent is remarkably efficacious and safe.

WHAT IS NEW? The Resolute Integrity stent is noninferior to the biodegradable-polymer biolimus-eluting BioMatrix Flex stent.

WHAT IS NEXT? These results support the concept that a durable-polymer stent can be as safe and efficacious as a biodegradable-polymer stent.

REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.

2. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.

3. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.

4. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.

5. Jensen LO, Tilsted HH, Thayssen P, et al. Paclitaxel and sirolimus eluting stents versus bare metal stents: long-term risk of stent thrombosis and other outcomes. From the Western Denmark Heart Registry. EuroIntervention 2010;5:898–905.

6. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.

7. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5.

8. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, non-inferiority trial. J Am Coll Cardiol Intv 2013;6:777–89.

9. Vlachojannis GJ, Smits PC, Hofma SH, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with coronary artery disease: three-year follow-up of the COMPARE II (Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent) trial. EuroIntervention 2015;11:272–9.

10. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011;123:1400–9.

11. Bangalore S, Toklu B, Amoroso N, et al. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. BMJ 2013;347:f6625.

12. Navarese EP, Tandjung K, Claessen B, et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. BMJ 2013;347:f6530.

13. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2014;63:299–307.

14. Raungaard B, Jensen LO, Tilsted HH, et al. Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. Lancet 2015;385:1527–35.

15. Banerjee S. The resolute™ integrity zotarolimus-eluting stent in coronary artery disease: a review. Cardiol Ther 2013;2:17–25.

16. Garg S, Serruys PW. Coronary stents. looking forward. J Am Coll Cardiol 2010;56 Suppl S:S43–78.

17. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136–46.

18. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350–61.

19. Yeung AC, Leon MB, Jain A, et al. Clinical evaluation of the resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. J Am Coll Cardiol 2011;57:1778–83.

20. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.

21. Grube E, Buellesfeld L. BioMatrix Biolimus A9-eluting coronary stent: a next-generation drug-eluting stent for coronary artery disease. Expert Rev Med Devices 2006;3:731–41.

22. Ormiston JA, Webber B, Ubod B, White J, Webster MW. Stent longitudinal strength assessed using point compression: insights from a second-generation, clinically related bench test. Circ Cardiovasc Interv 2014;7:62–9.

23. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525–38.

24. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

25. Thuesen L, Jensen LO, Tilsted HH, et al. Event detection using population-based health care databases in randomized clinical trials: a novel research tool in interventional cardiology. Clin Epidemiol 2013;5:357–61.

26. von Birgelen C, Sen H, Lam MK, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet 2013;383:413–23.

27. Kimura T, Morimoto T, Kozuma K, et al. Comparisons of baseline demographics, clinical presentation, and long-term out- come among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation 2010;122:52–61.

28. Armstrong EJ, Feldman DN, Wang TY, et al. Clinical presentation, management, and outcomes of angiographically documented early, late, and very late stent thrombosis. J Am Coll Cardiol Intv 2012;5:131–40.

29. Thayssen P, Jensen LO, Lassen JF, et al. The risk and prognostic impact of definite stent thrombosis or in-stent restenosis after coronary stent implantation. EuroIntervention 2012;8:591–8.

30. Byrne RA, Serruys PW, Baumbach A, et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. Eur Heart J 2015;36:2608–20.

31. Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. J Am Coll Cardiol Intv 2013;6:1267–74.

32. Philip F, Stewart S, Southard JA. Very late stent thrombosis with second generation drug eluting stents compared to bare metal stents: network meta-analysis of randomized primary percutaneous coronary intervention trials. Catheter Cardiovasc Interv 2016;88:38–48.

33. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice: 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.

34. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.

35. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.

36. Dibra A, Kastrati A, Alfonso F, et al. Effectiveness of drug-eluting stents in patients with bare-metal in-stent restenosis. Meta-analysis of randomized trials. J Am Coll Cardiol 2007;49:616–23.

37. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007;297:2001–9.

38. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA 2007;297:1992–2000.

39. Marroquin OC, Selzer F, Mulukutla SR, et al. A comparison of bare-metal and drug-eluting stents for off-label indications. N Engl J Med 2008;358:342–52.

40. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.

41. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391–9.

42. Wilson GJ, Nakazawa G, Schwartz RS, et al. Comparison of inflammatory response after implantation of sirolimus- and paclitaxel-eluting

stents in porcine coronary arteries. Circulation 2009;120:141–9.

43. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.

44. Smits PC, Vlachojannis GJ, McFadden EP, et al. Final 5-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice: the COMPARE trial (A Trial of Everolimus-Eluting Stents and Paclitaxel Stents for Coronary Revascularization in Daily Practice). J Am Coll Cardiol Intv 2015;8:1157–65.

45. Maeng M, Tilsted HH, Jensen LO, et al. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. Lancet 2014;383:2047–56.

46. Jensen LO, Thayssen P, Christiansen EH, et al. Safety and efficacy of everolimus- versus sirolimus-eluting stents: 5-year results from SORT OUT IV. J Am Coll Cardiol 2016;67:751–62.

47. Kufner S, Byrne RA, Valeskini M, et al. Five-year outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease: final results from the ISAR-TEST 4 randomised trial. EuroIntervention 2016;11:1372–9.

48. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012;33:1214–22.

49. Christiansen E, Jensen LO, Thayssen P, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving PCI (SORT OUT V): 3-year outcome. Paper presented at: EuroPCR 2014; May 21, 2014; Paris, France.

KEY WORDS **biolimus, drug-eluting, polymer, randomized clinical trial, stent, zotarolimus**

APPENDIX **For an expanded list of the SORT OUT VI trial investigators, please see the online version of this article.**