JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 7, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.01.033

Clinical Events and Patient-Reported Chest Pain in All-Comers Treated With Resolute Integrity and Promus Element Stents

2-Year Follow-Up of the DUTCH PEERS (DUrable Polymer-Based STent CHallenge of Promus ElemEnt Versus ReSolute Integrity) Randomized Trial (TWENTE II)

Hanim Sen, MD, PhD,* Ming Kai Lam, MD,* Marije M. Löwik, PhD,* Peter W. Danse, MD, PhD,† Gillian A.J. Jessurun, MD, PhD,‡ K. Gert van Houwelingen, MD,* Rutger L. Anthonio, MD, PhD,‡ R. Melvyn Tjon Joe Gin, MD,† Raymond W.M. Hautvast, MD, PhD,§ J. (Hans) W. Louwerenburg, MD,* Frits H.A.F. de Man, MD, PhD,* Martin G. Stoel, MD, PhD,* Liefke C. van der Heijden, MD,* Gerard C.M. Linssen, MD, PhD,‖ Maarten J. IJzerman, PhD,¶ Kenneth Tandjung, MD, PhD,* Carine J.M. Doggen, PhD,¶ Clemens von Birgelen, MD, PhD*†

ABSTRACT

OBJECTIVES This study assessed clinical events and patient-reported chest pain 2 years after treatment of all-comers with Resolute Integrity zotarolimus-eluting stents (Medtronic Vascular, Santa Rosa, California) and Promus Element everolimus-eluting stents (Boston Scientific, Natick, Massachusetts).

BACKGROUND For both drug-eluting stents (DES), no all-comer outcome data from >12 months of follow-up have been published. Although there is increasing interest in patient-reported chest pain following stenting, data with novel DES are scarce.

METHODS The DUTCH PEERS multicenter trial (TWENTE II) (DUrable Polymer-Based STent CHallenge of Promus ElemEnt Versus ReSolute Integrity) Randomized Trial [TWENTE II]) randomized 1,811 all-comer patients to treatment with 1 type of DES. Monitoring and event adjudication were performed by independent contract research organizations.

RESULTS The 2-year follow-up of 1,810 patients (99.9%) was available. The primary composite endpoint target vessel failure occurred in 8.6% and 7.8% of patients treated with zotarolimus- and everolimus-eluting stents, respectively ($p = 0.55$). Rates of components of target vessel failure were: cardiac death (2.4% vs. 1.9%, $p = 0.42$); target vessel-related myocardial infarction (2.4% vs. 1.8%, $p = 0.33$); clinically-indicated target vessel revascularization (4.6% vs. 4.9%, $p = 0.83$). At 1- and 2-year follow-up, >80% of patients were free from chest pain (no between-stent difference). In addition, >87% of patients were either free from chest pain or experienced pain only at maximal physical exertion, but not during normal daily activities. Patients with chest pain after 12 months at no more than moderate physical effort had a higher risk of target vessel revascularization during the following year (hazard ratio: 1.89 [95% confidence interval: 1.05 to 3.39], $p = 0.03$).

CONCLUSIONS During the second year of follow-up, the incidence of adverse clinical endpoints remained similar and low for both DES. The vast majority of patients were free from chest pain. (J Am Coll Cardiol Intv 2015;8:889–99)

From the *Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands; †Department of Cardiology, Rijnstate Hospital, Arnhem, the Netherlands; ‡Department of Cardiology, Scheper Hospital, Emmen, the Netherlands; §Department of Cardiology, Medical Center Alkmaar, Alkmaar, the Netherlands; ‖Department of Cardiology, Hospital Group Twente, Almelo and Hengelo, the Netherlands; and the ¶Department of Health Technology and Services Research, University of Twente, Enschede, the Netherlands. This investigator-initiated study was equally supported by Boston Scientific and Medtronic. Dr. von Birgelen has been a consultant to and has received lecture fees or travel expenses from Abbott Vascular, Boston Scientific, and

ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TLR = target lesion revascularization

TVF = target vessel failure

TVR = target vessel revascularization

ZES = zotarolimus-eluting stent(s)

Drug-eluting stents (DES) have revolutionized the treatment of obstructive coronary disease. Since their introduction, these devices have undergone major improvements (1). These include an increase in biocompatibility of their durable polymer-based coatings in the second-generation DES (2,3) and an improvement in flexibility and deliverability of their metallic stent platforms in the more recent generation of DES, using the same coatings (4–6).

The cobalt-chromium-based Resolute Integrity zotarolimus-eluting stent (ZES) (Medtronic, Santa Rosa, California) and the platinum-chromium-based Promus Element everolimus-eluting stent (EES) (Promus Element, Boston Scientific, Natick, Massachusetts) are 2 such novel, highly-flexible DES, which have recently been compared in the randomized, multicenter DUTCH PEERS trial (DUrable Polymer-Based STent CHallenge of Promus ElemEnt Versus ReSolute Integrity) Randomized Trial [TWENTE II]) in all-comers (4). DUTCH PEERS is the first randomized trial that reports outcome data of Resolute Integrity ZES and the first trial to provide a head-to-head comparison of the 2 durable coating-based DES, showing low clinical event rates at 1 year (4). Follow-up information after the cessation of dual-antiplatelet therapy (DAPT) at 1 year is of interest to demonstrate or exclude any potential late catch-up in adverse events.

In the presence of very low rates of traditional clinical endpoints following percutaneous coronary interventions (PCIs) with novel DES (4–6), there is growing interest in the assessment of patient-reported chest pain—the principal anginal symptom and main trigger of repeat cardiac assessment despite a successful PCI (7,8). Moreover, long-lasting absence of chest pain determines to a great extent the "patient satisfaction" with PCI. Therefore, in the present 2-year analysis of the DUTCH PEERS all-comers population, we investigated both clinical event rates and patient-reported chest pain following treatment with Resolute Integrity ZES and Promus Element EES.

METHODS

STUDY DESIGN, PATIENTS, AND PROCEDURES. The DUTCH PEERS trial has previously been described in detail (4). In brief, DUTCH PEERS is a multicenter, prospective, randomized, single-blinded, investigator-initiated trial in an all-comers patient population. Study enrollment was performed between November 25, 2010, and May 24, 2012. There was no limit for lesion length, reference size, and number of lesions or diseased vessels to be treated. Interventional procedures were performed according to standard techniques and routine clinical protocols. The study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centers. All patients provided written informed consent. Patients were randomly assigned, in a 1:1 fashion, to treatment with 1 of the 2 study stents.

Resolute Integrity ZES releases zotarolimus from the 6 μm BioLinx conformal, permanent polymer system (blend of 3 polymers), which has been highly effective on Resolute stents (2,3,9), and uses the novel, sinusoid-shaped, single cobalt-chromium wire-based, open-cell design Integrity stent platform (91-μm round struts) (4) with slightly more strut connections in close vicinity to its proximal and distal ends. Promus Element EES releases everolimus from a 7-μm conformal, permanent fluoropolymer coating that recently demonstrated its efficacy in other patient populations (2,3,9–12) and uses the novel, laser-cut, platinum-chromium alloy (highly radiopaque), open-cell design (serpentine rings connected by links) Element stent platform (81-μm struts) for improved deliverability (4,13,14). Novel flexible, highly-deliverable stents may be less longitudinally stable, which can sometimes result in a distortion or shortening of an initially successfully-implanted stent in the longitudinal axis; differences in stent design and radiographic visibility may explain between-stent differences. In DUTCH PEERS, a dedicated angiographic analysis confirmed the presence of longitudinal stent deformations in 1% of patients treated with Promus Element (no clinical consequences up to 1-year follow-up) and in none of the patients treated with Resolute Integrity (4).

Medtronic; has served on the advisory boards of Boston Scientific and Medtronic; has received lecture fees from Boston Scientific, Medtronic, and Merck Sharp & Dohme; and his institution has received research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. Dr. IJzerman is a consultant to PANAXEA b.v.; and he has received payments for lectures from Roche, Pfizer, and Sanofi. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 22, 2014; accepted January 1, 2015.

Interventions were performed according to standard techniques. Patients were pre-treated with acetylsalicylic acid and clopidogrel. Lesion pre-dilation, use of glycoprotein IIb/IIIa receptor antagonists, direct stenting, and stent post-dilation were left to the operator's discretion. Operators were requested to report evident (or suspected) longitudinal stent deformation, defined as distortion or shortening of initially successfully-implanted stents in the longitudinal axis (15,16). In general, dual-antiplatelet therapy was prescribed for 1 year. Systematic laboratory and electrocardiographic testing were performed as previously described (4) to identify periprocedural myocardial infarction (MI).

The follow-up procedures of the study have previously been reported (4,17). At 1- and 2-year follow-up, research nurses and analysts who were blinded to the assigned stent type obtained information on chest pain by use of a medical questionnaire or, in the absence of a response, a telephone follow-up that used the same questions.

Angiographic analysts, blinded to the stent type used, performed off-line quantitative coronary angiography according to current standards (QAngio XA 7.2, Medis, Leiden, the Netherlands). The CRO Cardio Research Enschede (Enschede, the Netherlands) coordinated the trial and data management. Regular safety data were reported to the independent Medical Ethics Committee Twente. Data monitoring was performed by the independent contract research organization Diagram (Zwolle, the Netherlands). Processing of clinical outcome data and clinical event adjudication were performed by the independent contract research organization Cardialysis (Rotterdam, the Netherlands).

DEFINITION OF CLINICAL ENDPOINTS. Definitions of all pre-defined clinical endpoints have previously been described in detail (4,17). Clinical endpoints were defined according to the Academic Research Consortium, including the addendum on MI (4,17–19). In brief, *target vessel failure* (TVF), the primary endpoint of DUTCH PEERS, is a composite of cardiac death, target vessel-related MI, or clinically-indicated target vessel revascularization (TVR). Death was considered cardiac unless an unequivocal noncardiac cause could be established. MI was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated confirmatory cardiac biomarkers. A target vessel–related MI was related to the target vessel or could not be related to another vessel. TVR and target lesion revascularization (TLR) were considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms. Stent thrombosis was classified according to the Academic Research Consortium definitions (19,20).

Pre-defined secondary endpoints included the components of the primary endpoint, all-cause mortality, any MI, clinically-indicated TLR, stent thrombosis, and longitudinal stent deformation. Other composite parameters were (in hierarchical order): *target lesion failure*, a composite of cardiac death, target vessel–related MI, or clinically-indicated TLR; *major adverse cardiac events*, a composite of all-cause death, any MI, emergent coronary bypass surgery, or clinically-indicated TLR; and *patient-oriented composite endpoint*, a composite of all-cause death, any MI, or any coronary revascularization. An exploratory subgroup analysis of the primary endpoint was performed in line with previous trials (2,3).

Patient-reported chest pain, the principal symptom of angina pectoris and a surrogate for myocardial ischemia, was classified into 4 scores: 0 = no chest pain at all; 1 = chest pain only during most severe physical exertion; 2 = chest pain at moderate physical effort (during moderate/normal daily activities); and 3 = chest pain at mild physical effort or at rest.

STATISTICAL ANALYSIS. Data were reported as frequencies and percents for dichotomous and categorical variables and as mean ± SD for continuous variables. Differences in dichotomous and categorical variables were assessed with the chi-square or Fisher exact tests, whereas continuous variables were assessed with the Student *t* test or the Wilcoxon rank sum test, as appropriate. The Kaplan-Meier analysis was used to calculate the time to clinical endpoints, and the log-rank test was applied to compare between-group differences. A landmark analysis was performed at 1 year for various adverse clinical events expressed as a difference in proportion and 95% confidence interval (CI) (21). The Cox proportional-hazards regression analysis was performed to test for interaction between subgroups and stent type with regard to the clinical endpoint TVF. All p values and CIs were 2-sided, and a p value <0.05 was considered significant. Data analysis was performed with SPSS version 17 (SPSS Inc., Chicago, Illinois) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 1,811 patients were randomly assigned to treatment with the Resolute Integrity ZES (n = 906) or Promus Element EES (n = 905). The main clinical, procedural, and angiographic characteristics of both

TABLE 1 Characteristics of Patients, Target Lesions, and Interventional Procedures

	Resolute Integrity ZES	Promus Element EES	p Value
Patient Data			
n	906	905	
Age, yrs	63.9 ± 10.6	63.9 ± 11.0	0.97
Men	665 (73.4)	675 (72.6)	0.70
Diabetes mellitus (any)	167 (18.4)	157 (17.3)	0.55
Arterial hypertension	500 (55.2)	484 (53.5)	0.47
Hypercholesterolemia	418 (46.1)	430 (47.5)	0.56
Current smoker*	213 (23.6)	231 (25.5)	0.34
Family history of CAD†	452 (50.0)	451 (50.0)	0.98
Previous myocardial infarction	207 (22.8)	190 (21.0)	0.34
Previous percutaneous coronary intervention	182 (20.1)	167 (18.5)	0.38
Previous coronary bypass surgery	84 (9.3)	89 (9.8)	0.68
Clinical syndrome at presentation			0.07
Stable angina pectoris	372 (41.1)	377 (41.7)	
Unstable angina pectoris	113 (12.5)	132 (14.6)	
Non-ST-segment elevation myocardial infarction	246 (27.2)	201 (22.2)	
ST-segment elevation myocardial infarction	175 (19.3)	195 (21.5)	
At least 1 small vessel (RVD <2.75 mm)	551 (60.8)	517 (57.1)	0.11
At least 1 lesion length >27 mm	161 (17.8)	157 (17.3)	0.81
At least 1 chronic total occlusion	38 (4.2)	38 (4.2)	1.00
Glycoprotein IIb/IIIa antagonist	262 (28.9)	259 (28.6)	0.89
Number of lesions treated per patient			0.32
1 lesion treated	668 (73.7)	688 (76.0)	
2 lesions treated	191 (21.1)	182 (20.1)	
3 or more lesions treated	47 (5.2)	35 (3.9)	
Lesions and Interventional Procedures Data			
Lesions, n	1,205	1,166	
ACC/AHA lesion class B2/C	793 (65.8)	765 (65.6)	0.92
De novo lesion‡	1,147 (95.2)	1,103 (94.6)	0.51
Reference vessel diameter, mm	2.68 ± 0.59	2.70 ± 0.59	0.32
Implantation of assigned stents only	1,195 (99.2)	1,161 (99.6)	0.22
Number of stents per lesion	1.35 ± 0.68	1.36 ± 0.70	0.70
Total stent length per lesion, mm	28.60 ± 18.51	29.71 ± 19.11	0.15
Direct stenting	352 (29.2)	326 (28.0)	0.50
Stent post-dilation	887 (73.6)	920 (78.9)	<0.01

Values are n, mean ± SD, or n (%). *Of 903 patients in the zotarolimus-eluting stent group and 905 patients in the everolimus-eluting stent group. †Of 903 patients in the zotarolimus-eluting stent group and 902 patients in the everolimus-eluting stent group. ‡Including chronic total occlusion, but not grafts or in-stent restenosis.

ACC/AHA = American College of Cardiology/American Heart Association; CAD = coronary artery disease; EES = everolimus-eluting stent(s); RVD = reference vessel diameter; ZES = zotarolimus-eluting stent(s).

study groups are summarized in Table 1. The 2-year follow-up data was obtained from all but 1 patient, who withdrew consent (Online Figure 1 shows trial consort diagram).

RATES OF ADVERSE CLINICAL EVENTS. At 2-year follow-up, the composite primary endpoint TVF occurred in 78 patients (8.6%) treated with Resolute Integrity ZES and in 71 patients (7.8%) treated with Promus Element EES (p = 0.55) (Table 2, Figure 1). The incidence of the individual components of TVF was similar for both stent arms: cardiac death (2.4% vs. 1.9%, p = 0.42); target vessel-related MI (2.4% vs. 1.8%, p = 0.33); and clinically-indicated TVR (4.6% vs. 4.9%, p = 0.83).

An exploratory subgroup analysis revealed no significant between-stent difference in TVF at 2 years across various subgroups (Figure 2). In addition, there was also no significant difference in various event rates between 1- and 2-year follow-up (Table 3). None of the 9 patients who had developed longitudinal stent deformation in Promus Element EES during the index PCI procedure experienced an adverse clinical event during the second year of follow-up, although DAPT was discontinued after 12 months in all but 1 patient, who continued DAPT at physician discretion (Online Table 1).

The incidence of definite-or-probable stent thrombosis was 1.1% for both DES at 2-year follow-up (Figure 3), and the rate of definite stent thrombosis was similar in patients treated with Resolute Integrity ZES and Promus Element EES (0.8% vs. 0.9%, p = 0.80) (Table 2). Very late definite stent thrombosis occurred in 4 (0.4%) versus 2 (0.2%) patients, respectively. At 2-year follow-up, 8.9% (78 of 872) and 9.0% (79 of 881) of the (surviving) patients in both stent arms were still on DAPT (Online Table 2).

PATIENT-REPORTED CHEST PAIN. At 1-year follow-up, 1,647 (92.7%) of all 1,776 surviving patients provided information about the presence or absence of chest pain (Figure 4A). Most of these patients had no chest pain at all, and there was no difference between stent arms (81.6% vs. 81.0%, p = 0.96). In addition, 88.2% and 87.4% of patients in both stent arms had either no chest pain at all or chest pain only during maximal exertion (p = 0.96). Patients with a chest pain score of 2 or 3 at 1-year follow-up had an almost 2-fold increase in risk of clinically-indicated TVR during the second year of follow-up (hazard ratio: 1.89 [95% CI: 1.05 to 3.39], p = 0.03) compared with those with a chest pain score of 0 or 1.

Chest pain data at 2-year follow-up was available from 1,606 of 1,753 (91.6%) of the surviving patients with pain scores that were similar to 1-year follow-up (Figure 4B). At 2-year follow-up, new-onset (as compared to 1-year) chest pain was reported by 8.8% of patients. Between 1- and 2-year follow-up, 77.9% (of the 1,572 patients who were alive at 2 years and answered the chest pain questionnaire at both 1 and 2 years) in both stent arms showed no change in chest pain score (Figure 4C), whereas only 10.6% and 12.2% of patients in the respective stent

TABLE 2 2-Year Clinical Outcome in Treatment Arms

	Total Patients (n = 1,810)	Resolute Integrity ZES (n = 905)	Promus Element EES (n = 905)	Relative Risk (95% CI)	p Value
Death					
Any cause	57 (3.1)	33 (3.6)	24 (2.7)	1.38 (0.82–2.31)	0.23
Cardiac cause	39 (2.2)	22 (2.4)	17 (1.9)	1.29 (0.69–2.42)	0.42
Target vessel–related myocardial infarction					
Any	38 (2.1)	22 (2.4)	16 (1.8)	1.38 (0.73–2.60)	0.33
Q-wave	10 (0.6)	5 (0.6)	5 (0.6)	1.00 (0.29–3.44)	1.00
Non-Q-wave	28 (1.5)	17 (1.9)	11 (1.2)	1.55 (0.73–3.28)	0.34
Periprocedural (<48 h from index procedure)	30 (1.7)	19 (2.1)	11 (1.2)	1.74 (0.83–3.61)	0.14
Target vessel revascularization					
Any	88 (4.9)	43 (4.8)	45 (5.0)	0.96 (0.64–1.44)	0.83
Clinically indicated	86 (4.8)	42 (4.6)	44 (4.9)	0.96 (0.63–1.44)	0.83
Target lesion revascularization, clinically indicated	66 (3.6)	34 (3.8)	32 (3.5)	1.06 (0.66–1.71)	0.80
Target vessel failure*	149 (8.2)	78 (8.6)	71 (7.8)	1.10 (0.81–1.50)	0.55
Target lesion failure†	131 (7.2)	71 (7.8)	60 (6.6)	1.18 (0.85–1.65)	0.32
Major adverse cardiac events‡	156 (8.6)	83 (9.2)	73 (8.1)	1.14 (0.84–1.54)	0.40
Patient-oriented composite endpoint§	228 (12.6)	114 (12.6)	114 (12.6)	1.00 (0.78–1.27)	0.99
Stent thrombosis					
Definite, any (0–720 days)	15 (0.8)	7 (0.8)	8 (0.9)	0.88 (0.32–2.40)	0.80
Definite, very late (360–720 days)	6 (0.3)	4 (0.4)	2 (0.2)	2.00 (0.37–10.89)	0.69
Definite or probable, any (0–720 days)	20 (1.1)	10 (1.1)	10 (1.1)	1.00 (0.42–2.39)	1.00
Definite or probable, very late (360–720 days)	7 (0.4)	5 (0.6)	2 (0.2)	2.50 (0.49–12.85)	0.45
Definite, probable, or possible, any (0–720 days)	46 (2.5)	23 (2.5)	23 (2.5)	1.00 (0.57–1.77)	1.00

Values are n (%). *Primary target vessel failure is a composite of cardiac death, target vessel–related myocardial infarction, or clinically-indicated target vessel revascularization. †Target lesion failure is a composite of cardiac death, target vessel–related myocardial infarction, or clinically-indicated target lesion revascularization. ‡Major adverse cardiac events is a composite endpoint of all-cause death, any myocardial infarction, emergent coronary artery bypass surgery, or clinically-indicated target lesion revascularization. §Patient-oriented composite endpoint is a composite of all-cause death, any myocardial infarction, or any revascularization.

CI = confidence interval; other abbreviations as in Table 1.

arms reported an increase and 11.6% and 9.9% a decrease (p = 0.30). Restricting the analysis of chest pain score at 1 and 2 years to patients who provided *chest pain information at both times* (Online Figure 2) led to results that were similar to findings in all responding patients at the individual times of follow-up (**Figures 4A and 4B**).

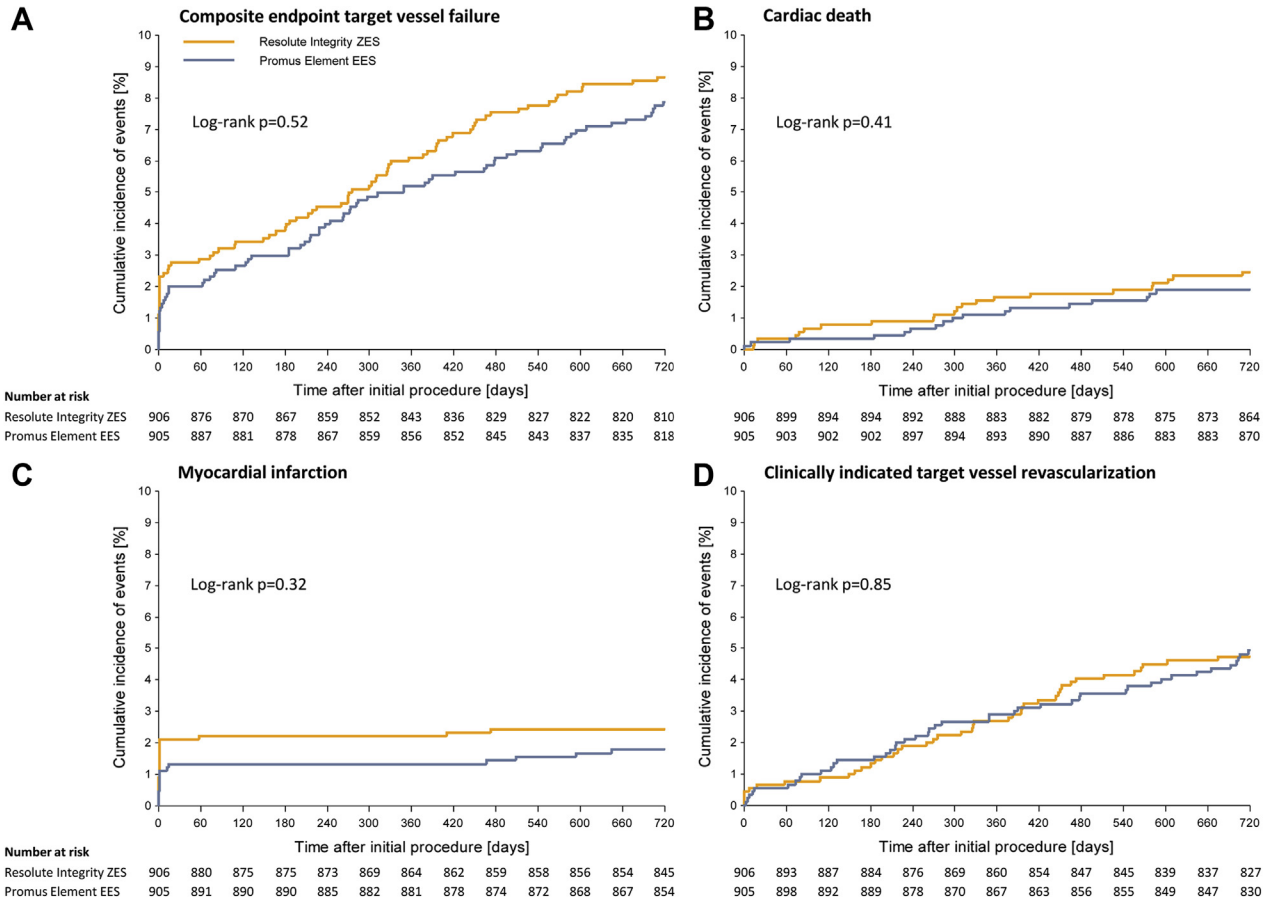
DISCUSSION

At 2-year follow-up of the DUTCH PEERS trial, the incidence of the primary endpoint TVF was low and similar in both stent arms. The rates of cardiac death, target vessel–related MI, and clinically-indicated TVR (i.e., the individual components of TVF), were also low and similar. In addition, despite enrollment of an all-comers population that included many high-risk patients and complex lesions, the incidence of very late stent thrombosis was extremely low. None of the few patients who initially had developed longitudinal stent deformation in Promus Element arm experienced a very late clinical event after cessation of DAPT.

At 1- and 2-year follow-up, >80% of patients in both stent arms were free from chest pain. In addition, >87% were either symptom-free or experienced chest pain only at the very maximal level of physical exertion, in that the pain did not limit the daily activities of this large group of patients.

PREVIOUS DES TRIALS WITH THE EXAMINED STENTS. The present analysis from the DUTCH PEERS randomized trial is the first report of 2-year clinical outcome data in all-comers treated with the Resolute Integrity or Promus Element stents. The PLATINUM trial (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions trial), which assessed patients with low-to-moderate cardiovascular event risk, has previously demonstrated noninferiority of the Promus Element stent as compared with the second-generation Xience V/Promus stent (Abbott Vascular/Boston Scientific) (13), showing a favorable rate of the primary endpoint target lesion failure (5.9%) for Promus Element after 3 years (14). The HOST-ASSURE trial (Harmonizing

FIGURE 1 Kaplan-Meier Curves for TVF and the Individual Components at 2-Year Follow-Up

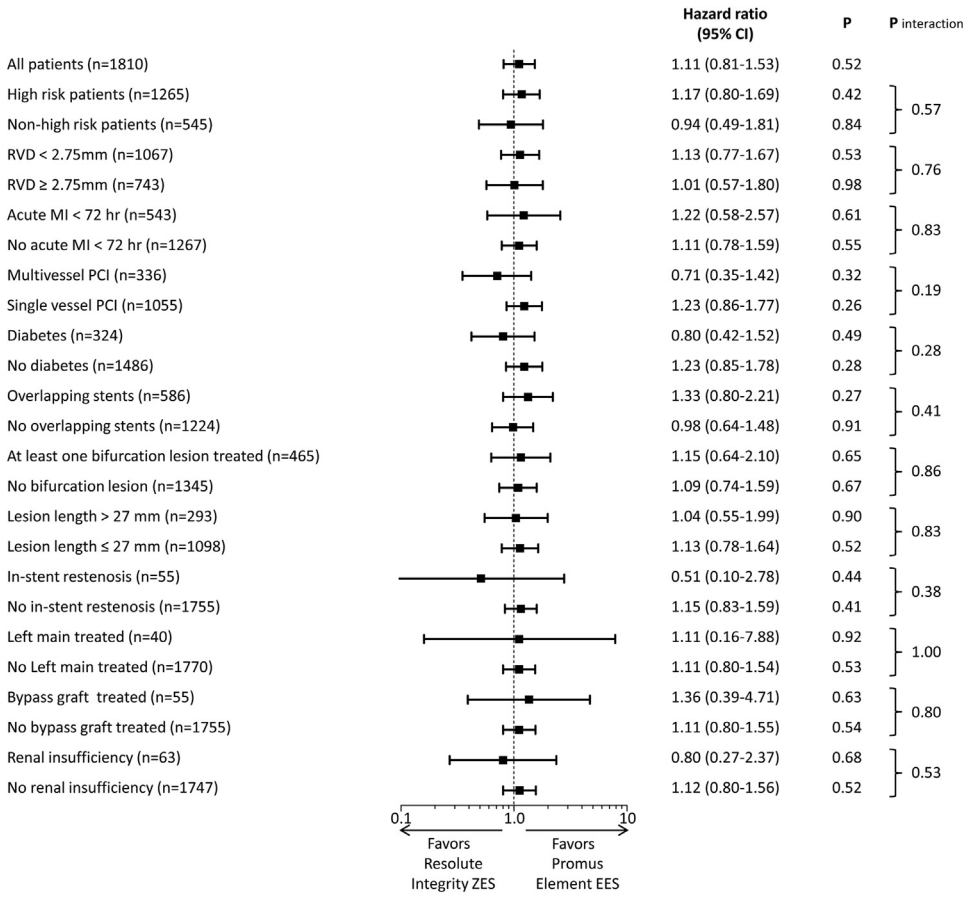


Kaplan-Meier cumulative incidence curves for: **(A)** the primary endpoint target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization; **(B)** cardiac death; **(C)** target vessel–related myocardial infarction; and **(D)** target vessel revascularization for patients treated with Resolute Integrity zotarolimus-eluting stents (ZES) or Promus Element everolimus-eluting stents (EES).

Optimal Strategy for Treatment of coronary artery stenosis - sAfety & effectiveneSS of drug-elUting stents & antiplatelet REgimen trial) has compared Promus Element with the second-generation Resolute stent in South Korean patients in coronary vessels >2.5 mm in diameter, showing a similar clinical performance of both stents at 1 year (5). So far, the SORT-OUT VI all-comers trial (Scandinavian Organization for Randomized Trials with clinical OUTcome VI trial) is the only other randomized study that has also examined the Resolute Integrity stent, showing at 1 year an incidence of the primary endpoint of major adverse cardiac events that was similar to the comparator, the bioresorbable coating-based BioMatrix Flex stent (Biosensors, Singapore) (5.3% vs. 5.1%) (6).

CHEST PAIN FOLLOWING PCI. Chest pain, the principal symptom of angina pectoris, is the main trigger for patients to consult medical professionals following a successful PCI procedure, and it is frequently associated with further cardiac assessment and increased costs (8). The prevalence and recurrence of angina pectoris after coronary revascularization had previously been investigated in randomized studies that compared balloon angioplasty with coronary bypass surgery (22,23) or with PCI, using bare-metal stents (24,25). However, randomized trials with DES were mostly focused on device-oriented endpoints (26). Nowadays, there is a growing interest in the assessment of angina pectoris following the implantation of novel DES and bioresorbable scaffolds (7). But so far, there is a lack of published data

FIGURE 2 Subgroup Analysis: TVF at 2-Year Follow-Up



Target vessel failure (TVF) is a composite of cardiac death, target vessel-related myocardial infarction, and clinically-indicated target vessel revascularization. CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; other abbreviations as in Figure 1.

about this matter regarding treatment with newer-generation DES.

In the DUTCH PEERS trial, there was no difference in chest pain between the 2 stent arms at both 1- and 2-year follow-up. More than 80% of our patients were entirely free from chest pain. This rate is similar to or higher than the prevalence of angina in several studies with bare-metal stents or DES, reporting 66% to 79% of the patients to be angina-free at 1 year (7,27-30). However, none of these studies applied the highly-deliverable DES that were used in DUTCH PEERS. A substudy of the FREEDOM trial (the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease trial), which assessed diabetic patients with multivessel disease being treated with PCI or CABG, found 79.5% and 81.0% of patients to be free from angina at 1- and 2-year follow-up after PCI with first-generation sirolimus-eluting stents (27), but this excellent result may be partly attributed to the general lower incidence of angina in diabetic patients. In the SYNTAX trial (The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery trial), which assessed angina after PCI for the treatment of 3-vessel or left-main coronary disease with first-generation paclitaxel-eluting stents, 71.6% of patients were free from angina at 1-year follow-up (28).

The 2 aforementioned studies used the Seattle Angina Questionnaire, which is a validated method to assess anginal stability and frequency, physical limitation, treatment satisfaction, and disease perception by use of a list of standardized questions (31). This approach requires patients to answer a considerable

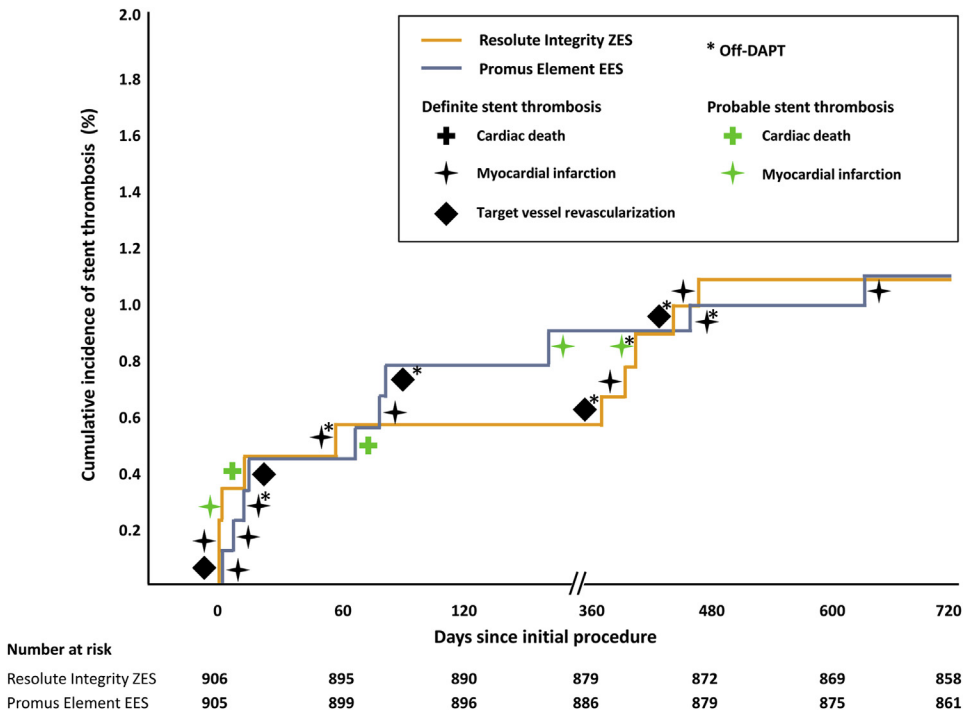
TABLE 3 Outcome Differences Between 1- and 2-Year Follow-Up

	Resolute Integrity ZES	Promus Element EES	Difference (95% CI)	p Value
Death				
Any cause	1.2 (11/883)	1.3 (12/893)	−0.10 (−1.03 to 1.23)	0.86
Cardiac cause	0.8 (7/893)	0.8 (7/883)	−0.01 (−0.91 to 0.94)	0.98
Target vessel-related myocardial infarction	0.2 (2/864)	0.5 (4/881)	−0.22 (−0.45 to 0.95)	0.69
Target vessel revascularization, clinically indicated	2.1 (18/860)	2.1 (18/867)	0.02 (−1.43 to 1.39)	0.98
Target lesion revascularization, clinically indicated	1.6 (14/864)	1.4 (12/873)	0.25 (−1.48 to 0.96)	0.67
Target lesion failure*	2.4 (20/847)	2.2 (19/862)	0.16 (−1.64 to 1.31)	0.83
Target vessel failure†	2.7 (23/843)	2.8 (24/856)	−0.08 (−1.54 to 1.69)	0.93
Major adverse cardiac events‡	3.0 (25/847)	3.4 (29/861)	−0.42 (−1.29 to 2.13)	0.62
Patient-oriented composite endpoint§	3.7 (30/821)	5.0 (42/833)	−1.39 (−0.60 to 3.41)	0.17
Stent thrombosis				
Definite	0.5 (4/880)	0.2 (2/887)	0.23 (−0.96 to 0.43)	0.41
Definite or probable	0.6 (5/879)	0.2 (2/886)	0.34 (−1.12 to 0.33)	0.29

Values are % (n/N) or % difference (95% CI). Analyses were performed among survivors of the first year of follow-up who did not experience the respective adverse event during 1-year follow-up. *Target lesion failure is a composite of cardiac death, target vessel–related myocardial infarction, or clinically-indicated target lesion revascularization. †Primary endpoint target vessel failure is a composite of cardiac death, target vessel–related myocardial infarction, or clinically-indicated target vessel revascularization. ‡Major adverse cardiac events is a composite of all-cause death, any myocardial infarction, emergent coronary artery bypass surgery, or clinically-indicated target lesion revascularization. §Patient-oriented composite endpoint is a composite of all-cause death, any myocardial infarction, or any revascularization.

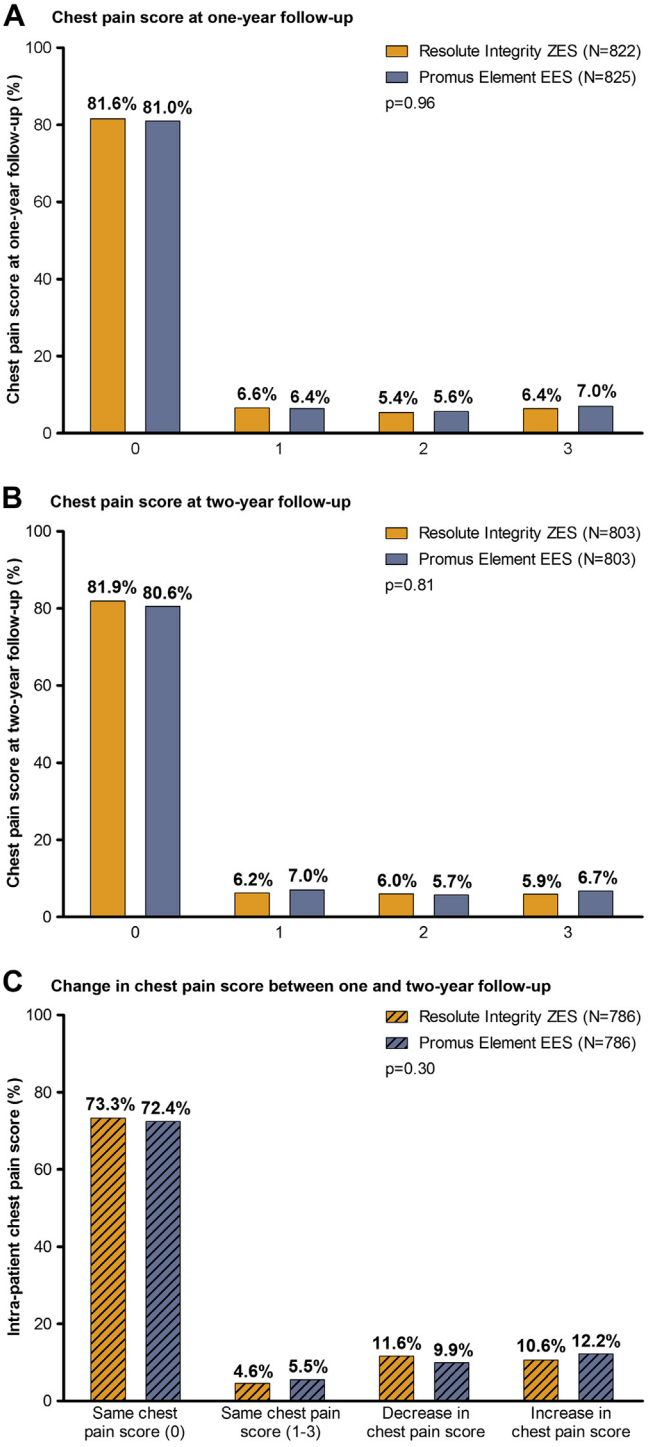
Abbreviations as in Tables 1 and 2.

FIGURE 3 Cumulative Incidence of Definite or Probable Stent Thrombosis



The symbols indicate the hierarchically highest adverse events associated with stent thrombosis. **Black symbols** signify definite stent thrombosis. **Green symbols** signify probable stent thrombosis. *Off-DAPT indicates stent thrombosis in patients not on dual antiplatelet therapy (DAPT), which consisted of aspirin ≥80 mg daily and an adequate dose of a $P2Y_{12}$ receptor antagonist (generally clopidogrel 75 mg daily). Abbreviations as in Figure 1.

FIGURE 4 **Patient-Reported Chest Pain at 1 and 2 Years**



Patient-reported chest pain was classified into 4 scores: 0 = no chest pain at all; 1 = chest pain only during most severe physical exertion; 2 = chest pain at moderate physical effort (during moderate/normal daily activities); and 3 = chest pain during mild physical exertion or at rest. **(A and B)** Information about the presence and extent (i.e., pain score) of chest pain at 1- and 2-year follow-up in all (surviving) patients who provided chest pain information at the 2 individual time points (n = 1,647 and n = 1,606 patients, respectively). **(C)** *Change* in chest pain score between 1- and 2-year follow-up in 1,572 patients who were alive at 2-year follow-up and answered the chest pain questionnaire both times.

number of questions, which might sometimes have a negative effect on the overall response rate of a study (32).

In the present study, we did not assess angina, but we scored the patient-reported chest pain in relation to the individual range of physical activities of a patient. Although this approach does not attempt to distinguish between angina and atypical chest pain, it tackles the key issue of "patient satisfaction," which is greatly independent of the classification of chest pain into angina or atypical chest pain (26). We assessed *whether an individual patient felt chest pain during (individually graded) levels of physical activity*, as this will generally determine whether a patient seeks further medical advice and/or repeat cardiac assessment. Notably, we found a significant relation between chest pain at 1-year follow-up and repeat clinically-indicated TVR during the second year of follow-up.

STUDY LIMITATIONS. We did not pre-specify the analysis of the primary endpoint TVF across the various subgroups; to avoid subjectivity, we applied subgroup definitions of previous DES trials (2,3). Rigorous embracing of the principle of ischemia-driven PCI may have contributed to the relatively low rate of residual chest pain following PCI with novel newer-generation DES in DUTCH PEERS. Knowledge on the completeness of coronary revascularization would have facilitated the interpretation of the chest pain data, but similar to most other all-comer DES trials, DUTCH PEERS did not assess this matter. It is desirable that future randomized clinical trials prospectively address this issue.

CONCLUSIONS

During the second year of follow-up, the incidence of adverse clinical endpoints remained similar and low for both DES. The vast majority of patients were free from chest pain after 1 and 2 years.

ACKNOWLEDGMENTS The authors would like to thank Mrs. Ilona Valkenburg for performing QCA measurements and for her great commitment during the collection of follow-up data; Mrs. Jacqueline C. Jonge Poerink for performing QCA measurements; and Mrs. Renate E. van der Leest for her great commitment during the collection of follow-up data (all from Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands).

REPRINT REQUESTS AND CORRESPONDENCE: Prof. Clemens von Birgelen, Department of Cardiology, Thoraxcentrum Twente, Haaksbergerstraat 55, 7513ER Enschede, the Netherlands. E-mail: c.vonbirgelen@mst.nl.

PERSPECTIVES

WHAT IS KNOWN? For Resolute Integrity and Promus Element stents, no outcome data beyond 1-year were available from a randomized clinical trial in all-comers.

WHAT IS NEW? The present 2-year results of the DUTCH PEERS (TWENTE II) trial provide a safety signal, as treatment with these drug-eluting stents showed no late catch-up in adverse events (e.g., stent thrombosis or repeat revascularization), despite the cessation of dual-antiplatelet therapy after 12 months in the vast majority of patients. As patient satisfaction after coronary revascularization is closely related to the achievement of a lasting absence of chest pain, we assessed patient-reported chest pain and found that 2 years after interventions with the study stents almost 9 of 10 patients were not limited by chest pain in their daily activities.

WHAT IS NEXT? Long-term follow-up of the DUTCH PEERS trial will not only monitor and carefully assess very late adverse clinical events after the implantation of these modern durable polymer-coated stents, but will also help to build a standard of comparison with the clinical results of biodegradable vascular scaffolds, which at present require >1 year for complete resorption.

REFERENCES

1. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254–65.

2. 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.

3. 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.

4. 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 2014;383:413–23.

5. Park KW, Kang SH, Kang HJ, et al. A randomized comparison of platinum chromium-based everolimus-eluting stents versus cobalt chromium-based zotarolimus-eluting stents in all-comers receiving percutaneous coronary intervention: HOST-ASSURE (Harmonizing Optimal Strategy

for Treatment of Coronary Artery Stenosis-Safety & Effectiveness of Drug-Eluting Stents & Anti-Platelet Regimen), a randomized, controlled, noninferiority trial. J Am Coll Cardiol 2014;63:2805–16.

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

7. Stone GW. Demonstration of clinical superiority with a bioresorbable vascular scaffold: The ABSORB III + IV Clinical Trial Program. Paper presented at: EuroPCR; May 20, 2014; Paris, France.

8. Jaworski R, Jankowska EA, Ponikowski P, Banasiak W. Costs of management of patients with coronary artery disease in Poland: the multicenter RECENT study. Pol Arch Med Wewn 2012;122:599–607.

9. 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.

10. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.

11. Jensen LO, Thayssen P, Hansen HS, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials With Clinical Outcome IV (SORT OUT IV). Circulation 2012;125:1246–55.

12. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.

13. Stone GW, Teirstein PS, Meredith IT, et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: The PLATINUM (a prospective, randomized, multicenter trial to assess an everolimus-eluting coronary stent system [PROMUS element] for the treatment of up to two de novo coronary artery lesions) trial. J Am Coll Cardiol 2011;57:1700–8.

14. Meredith IT, Teirstein PS, Bouchard A, et al. Three-year results comparing platinum-chromium PROMUS element and cobalt-chromium XIENCE V everolimus-eluting stents in de novo coronary artery narrowing (from the PLATINUM trial). Am J Cardiol 2014;113:1117–23.

15. Williams PD, Mamas MA, Morgan KP, et al. Longitudinal stent deformation: a retrospective analysis of frequency and mechanisms. EuroIntervention 2012;8:267–74.

16. Mamas MA, Williams PD. Longitudinal stent deformation: Insights on mechanisms, treatments and outcomes from the food and drug administration manufacturer and user facility device experience database. EuroIntervention 2012;8:196–204.

17. Tandjung K, Basalus MW, Sen H, et al. DUrable polymer-based sTent CHallenge of promus ElemEnt versus ReSolute integrity (DUTCH PEERS): rationale and study design of a randomized multicenter trial in a dutch all-comers population. Am Heart J 2012;163:557–62.

18. Tandjung K, Sen H, Lam MK, et al. Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE trial. J Am Coll Cardiol 2013;61:2406–16.

19. 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.

20. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871–4.

21. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873–90.

22. Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. Lancet 1995;346:1184–9.

23. Sculpher MJ, Seed P, Henderson RA, et al. Health service costs of coronary angioplasty and coronary artery bypass surgery: the randomised intervention treatment of angina (RITA) trial. Lancet 1994;344:927–30.

24. Serruys PW, de Jaegere P, Kiemeneij F, et al., Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–95.

25. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496–501.

26. Hill R, Bagust A, Bakhai A, et al. Coronary artery stents: A rapid systematic review and economic evaluation. Health Technol Assess 2004;8:iii, iv, 1–242.

27. Abdallah MS, Wang K, Magnuson EA, et al. Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. JAMA 2013;310:1581–90.

28. Cohen DJ, Van Hout B, Serruys PW, et al. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. N Engl J Med 2011;364:1016–26.

29. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.

30. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: A collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190–7.

31. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle angina questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333–41.

32. Edwards PJ, Roberts I, Clarke MJ, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev 2009;(3):MR000008.

KEY WORDS all-comer/all-comers, DES, drug-eluting-stents, EES, percutaneous coronary intervention, Promus Element platinum-chromium everolimus-eluting stent, randomized clinical trial, Resolute Integrity cobalt-chromium zotarolimus-eluting stent, ZES

APPENDIX For supplemental figures and tables, please see the online version of this article.