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

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Summary

Background Third-generation, permanent-polymer-based drug-eluting stents with novel, flexible designs might be more easily delivered than previous generations of stents in complex coronary lesions, but might be less longitudinally stable. We aimed to assess the safety and efficacy in all-comer patients of two third-generation stents that are often used clinically, but that have not yet been compared, and one of which has not previously been assessed in a randomised trial.

Methods In this investigator-initiated, single-blind, multicentre, randomised, two-arm, non-inferiority trial, patients aged 18 years and older who required a percutaneous coronary intervention with implantation of a drug-eluting stent were recruited from four study sites in the Netherlands. We randomly assigned patients by independently managed computer-generated allocation sequences in a 1:1 ratio to receive either cobalt-chromium-based zotarolimus-eluting stents (Resolute Integrity, Medtronic, Santa Rosa, CA, USA) or platinum-chromium-based everolimus-eluting stents (Promus Element, Boston Scientific, Natick, MA, USA). Patients and analysts were masked to the allocated stent, but treating clinicians were not. The primary endpoint of target-vessel failure was a composite of safety (cardiac death or target-vessel-related myocardial infarction) and efficacy (target-vessel revascularisation) at 12 months, analysed by intention to treat (with a non-inferiority margin of 3·6%). This trial is registered with ClinicalTrials.gov, number NCT01331707.

Findings Between Nov 25, 2010, and May 24, 2012, 1811 eligible all-comer patients, with 2371 target lesions, were enrolled in the study. 370 (20%) patients presented with ST-elevation myocardial infarction and 447 (25%) with non-ST-elevation myocardial infarction. 906 patients were assigned to receive zotarolimus-eluting stents and 905 to receive everolimus-eluting stents. Ease of stent delivery was shown by very low numbers of patients requiring treatment other than their assigned study treatment (six [1%] in the zotarolimus-eluting stent group *vs* five [1%] in the everolimus-eluting stent group; p=0·22). 12-month follow-up results were available for 1810 patients (one patient in the zotarolimus-eluting stent group withdrew consent). The primary endpoint was met by 55 (6%) of 905 patients in the zotarolimus-eluting stent group and 47 (5%) of 905 in the everolimus-eluting stent group. The zotarolimus-eluting stent was non-inferior to the everolimus-eluting stent (absolute risk difference 0·88%, 95% CI –1·24% to 3·01%; upper limit of one-sided 95% CI 2·69%; non-inferiority p=0·006). We noted no significant between-group differences in individual components of the primary endpoint. Definite stent thrombosis occurred in three (0·3%) patients in the zotarolimus-eluting stent group and six (0·7%) patients in the everolimus-eluting stent group (p=0·34). Longitudinal stent deformation was seen only in the everolimus-eluting stent group (nine [1·0%] of 905 *vs* 0 of 906, p=0·002; nine of 1591 [0·6%] everolimus-eluting stents implanted became deformed), but was not associated with any adverse events.

Interpretation Both stents were similarly efficacious and safe, and provided excellent clinical outcomes, especially in view of the large number of patients who presented with acute myocardial infarctions.

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Introduction

Drug-eluting stents that counteract the development of restenosis by delivering antiproliferative drugs from polymer-based coatings have revolutionised the percutaneous treatment of obstructive coronary artery disease.[1,2] First-generation durable-polymer drug-eluting stents were made from bare-metal stent platforms with little flexibility and fairly plain permanent-polymer coatings, which were associated with an increased risk of late and very late stent thrombosis.[3,4] Second-generation drug-eluting stents with durable coatings that were more biocompatible than those of first-generation stents were then developed. These newer stents showed superior safety profiles in various clinical settings.[5–9]

Most recently, third-generation, durable-polymer-based drug-eluting stents were developed to answer the demand for more flexible and highly deliverable devices that can tackle very challenging coronary lesion and vessel anatomies, as are increasingly encountered in ageing western patient populations. Although the coatings of these stents contain the same established drug and durable polymer combinations as their second-generation counterparts, the design and material of their bare-metal stent platforms have been changed substantially.[10–14] However, such changes might have the trade-off of reducing longitudinal stent stability,[15,16] which would account for the occurrence of longitudinal stent deformation that has been reported after contact between deployed stents and guiding catheters, balloon catheters, or other catheter-based devices.[16–19] Data so far reported about the incidence and clinical significance of longitudinal stent deformation have been conflicting.[16–19]

A cobalt-chromium-based zotarolimus-eluting stent, made from a single sinusoidal-formed wire (Resolute Integrity, Medtronic, Santa Rosa, CA, USA), and a laser-cut platinum-chromium-based everolimus-eluting stent (Promus Element, Boston Scientific, Natick, MA, USA), are two such third-generation drug-eluting stents.[11–14] Although clinical outcome data for the use of the Promus Element stent in patients with mild-to-moderate clinical risk have been reported,[11,19] no such data are available for the Resolute Integrity stent. We aimed to compare clinical outcomes from the use of these two third-generation drug-eluting stents in a broad population of all-comer patients.

Methods

Study design and patients

We undertook a randomised trial entitled DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity (DUTCH PEERS): randomized multicenter trial in all comers population Treated Within Eastern NeThErlands II (TWENTE II) at four Dutch centres (Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede; Rijnstate Hospital, Arnhem; Scheper Hospital, Emmen; and Medisch Centrum Alkmaar, Alkmaar). In this investigator-initiated, single-blind, multicentre, randomised, two-arm, non-inferiority trial,[10] all-comer patients aged 18 years and older, who were capable of providing informed consent and who required a percutaneous coronary intervention with implantation of a drug-eluting stent, were randomly assigned for treatment with one of the two study stents. All coronary syndromes, de-novo and restenotic lesions, and coronary artery or bypass stenoses were permitted (with no limit for lesion length, reference size, or number of lesions or diseased vessels). Exclusion criteria were: participation in another randomised study for a drug or medical device that had not reached its primary endpoint; planned surgery within the next 6 months, unless dual antiplatelet therapy was maintained; known intolerance to a P2Y12 receptor antagonist that would prevent adherence to dual antiplatelet therapy, or intolerance to aspirin, heparin, or components of drug-eluting stents; known pregnancy; and life expectancy of less than 1 year. The study complied with the CONSORT 2010 statement[20] and the Declaration of Helsinki, and was approved by the independent 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 blocks of eight and four in random order by a computer program (block stratified randomisation 5.0, by S Piantadosi). Patients were assigned in a 1:1 ratio to one of the drug-eluting stents. Patients and all analysts were masked to the allocated stent, but treating clinicians were not. The random allocation was implemented by use of sequentially numbered, opaque, sealed envelopes.

Procedures

The third-generation cobalt-chromium-based zotarolimus-eluting Resolute Integrity stent uses a novel, open-cell stent design for increased flexibility and deliverability.[13,14] The stent platform is made from a single, sinusoidal-formed, helically wrapped, locally laser-fused wire (strut thickness 91 μm).[13] It is covered by a 6 μm layer of coating that consists of zotarolimus and the BioLinx polymer system, which have been efficacious in the second-generation Resolute stent (Medtronic).[7,8,21] Zotarolimus-eluting stents were available with stent diameters of 2·25–4·0 mm and lengths of 8–38 mm. The platinum-chromium alloy-based stent platform (minimum strut thickness 81 μm) of the third-generation everolimus-eluting Promus Element stent has a novel, laser-cut, open-cell stent design, consisting of short serpentine rings connected by helically distributed links.[11,12] The stent, which was designed for improved deliverability and visibility (ie, radiopacity), is covered by a 7 μm everolimus-eluting fluoropolymer coating that has been efficacious in the second-generation cobalt-chromium-based everolimus-eluting Xience V/Promus stent (Xience V, Abbott Vascular Devices, Santa Clara, CA, USA; Promus, Boston Scientific, Natick, MA, USA).[5,8] Everolimus-eluting stents were available in diameters of 2·25–4·0 mm and lengths of 8–38 mm.

Interventions were done with standard techniques. Lesion predilation, use of glycoprotein IIb/IIIa receptor antagonists, direct stenting, and stent post-dilation were left to the operator's discretion. Staged procedures with allocated stents were allowed within 6 weeks. Concomitant drugs did not differ from routine treatment; further medical treatment was provided in accordance with medical guidelines and the physician's judgment.[10] Generally, dual antiplatelet therapy was prescribed for 1 year after stent insertion.

Electrocardiographs (ECGs) were systematically assessed before and after the intervention, before discharge, and at suspicion of ischaemia, and were recommended at 12-month follow-up. Laboratory tests included systematic assessment of cardiac markers after the intervention, and subsequent serial measurements in the case of relevant raised markers or chest pain. In patients with acute coronary syndromes, cardiac markers were also assessed before the intervention.[10] Angiographic analysts at Thoraxcentrum Twente, who were masked to the assigned stent type, did subsequent quantitative coronary angiography for study participants from all centres in accordance with present standards, using QAngio XA 7.2 (Medis, Leiden, Netherlands).

Operators were requested to report any evident or suspected longitudinal stent deformation, which was defined as distortion or shortening of an implanted stent in the longitudinal axis after initially successful deployment.[16–18] On angiography, longitudinal stent deformation was identified as a localised change in radiopacity pattern of a stent that occurred between initial deployment and the end of the procedure, after manipulations with the guiding catheter, or after the use of further catheter-based devices (eg, an attempt to recross a deployed stent with a balloon catheter, imaging catheter, or another stent). The angiograms of all patients were reviewed for stent deformation by an analyst, who was masked to reported longitudinal stent deformation and allocated stent type. Measurement of stent length, both final (ie, after completion of the interventional procedure) and immediately after deployment, and calculation of the post-deployment stent length ratio (final stent length divided by stent length after deployment) were done for cases in which longitudinal stent deformation was noted by the operator or identified by the analyst.[19]

Clinical endpoints were defined as proposed by the Academic Research Consortium, including the addendum on myocardial infarction.[10,22,23] The prespecified composite primary endpoint of target-vessel failure assessed both device efficacy and patient safety at 12 months and was composed of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-vessel revascularisation (components listed in hierarchical order by importance). Death was regarded as cardiac unless an unequivocal non-cardiac cause could be established. Myocardial infarction was defined by a creatine kinase concentration of more than double the upper limit of normal with raised confirmatory cardiac biomarkers.[23] A target-vessel-related myocardial infarction was related to the target vessel or could not be related to another vessel; further classification could be based on laboratory, ECG, angiographic, or clinical data.[10,23] Revascularisation procedures were regarded as clinically indicated (ie, there was sufficient objective evidence of a clinically significant lesion) if the angiographic diameter stenosis of the then treated lesion was 50% or more in the presence of ischaemic signs or symptoms, or if the diameter stenosis was 70% or more irrespective of ischaemic signs or symptoms.[23]

Prespecified secondary endpoints included: the separate components of the primary endpoint; all-cause mortality; any myocardial infarction; clinically indicated target-lesion revascularisation; and stent thrombosis.[10,23] Prespecified secondary composite endpoints (components in hierarchical order of importance) were: a composite of target-lesion failure, consisting of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-lesion revascularisation; a composite of major adverse cardiac events, consisting of all-cause mortality, any myocardial infarction, emergent coronary bypass surgery, and clinically indicated target-lesion revascularisation; and a more comprehensive patient-oriented composite, consisting of all-cause mortality, any myocardial infarction, and any coronary

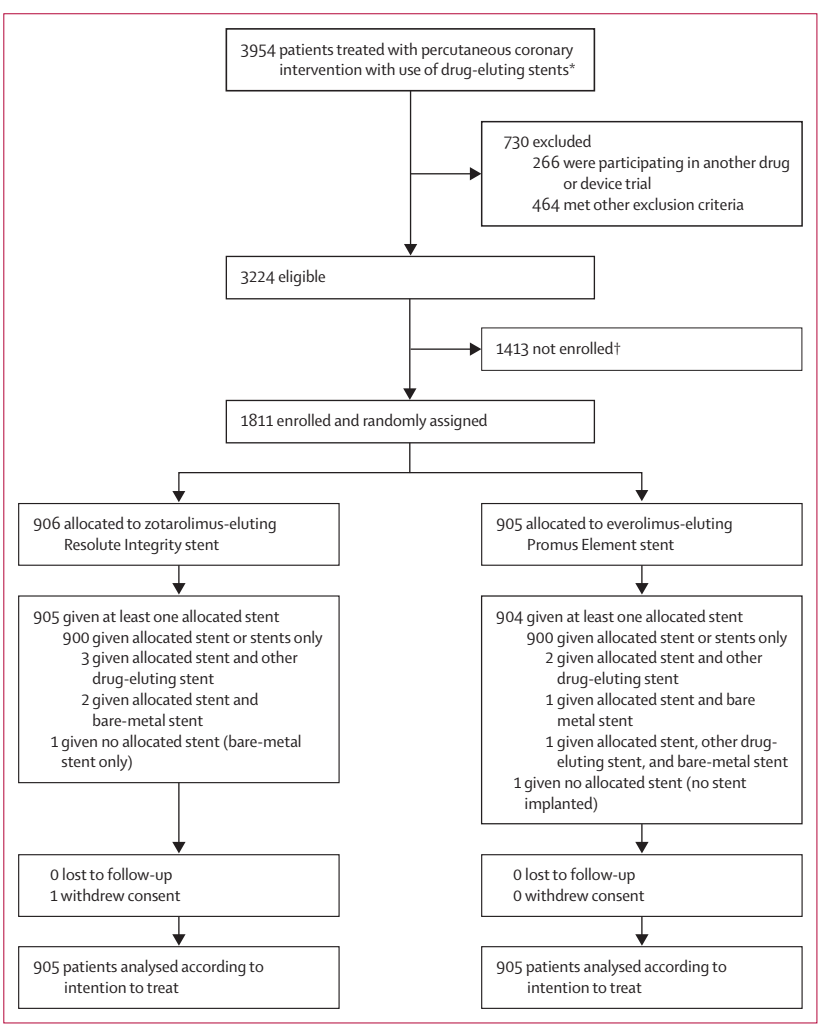

Figure 1: **Trial profile**
*Total number of patients at the four study centres who had percutaneous coronary intervention with use of drug-eluting stents during the study enrolment period, irrespective of inclusion and exclusion criteria. †No reliable data are available for the reasons why eligible patients were not enrolled.

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. We also did a post-hoc exploratory subgroup analysis of the primary endpoint, in line with previous trials.[7,8,21]

The 12-month clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone follow-up, a medical questionnaire, or both (with staff masked to assigned study stents). The contract research organisation (CRO) Cardio Research Enschede (Enschede, Netherlands) coordinated trial and data management, and the regular safety data were reported to the Medical Ethics Committee Twente. The CRO Diagram (Zwolle, Netherlands) did the data monitoring, which consisted of: informed consent and type and size of stent (all patients); all potential clinical events reported by investigators or patients (all event triggers); and further in-depth monitoring of all demographic, procedural, and clinical outcome data (at random in 10% of patients). The CRO Cardialysis (Rotterdam, Netherlands) did the processing of clinical outcome data and clinical event adjudication. The

	Zotarolimus-eluting stent group (n=906 patients)	Everolimus-eluting stent group (n=905 patients)
Age (years)	64 (56–72)	65 (57–72)
Men	665 (73%)	657 (73%)
Body-mass index (kg/m²)*	27·1 (25·0–30·0)	27·2 (24·9–30·5)
Diabetes mellitus (any)	167 (18%)	157 (17%)
Insulin-dependent diabetes mellitus	63 (7%)	50 (6%)
Chronic renal failure†	35 (4%)	28 (3%)
Arterial hypertension	500 (55%)	484 (53%)
Hypercholesterolaemia	418 (46%)	430 (48%)
Current smoker‡	213 (24%)	231 (26%)
Family history of coronary artery disease§	452 (50%)	451 (50%)
Previous myocardial infarction	207 (23%)	190 (21%)
Previous percutaneous coronary intervention	182 (20%)	167 (18%)
Previous coronary bypass surgery	84 (9%)	89 (10%)
Clinical syndrome at presentation		
Stable angina pectoris	372 (41%)	377 (42%)
Unstable angina pectoris	113 (12%)	132 (15%)
Non-ST-elevation myocardial infarction	246 (27%)	201 (22%)
ST-elevation myocardial infarction	175 (19%)	195 (22%)
Acute coronary syndrome (any)	534 (59%)	528 (58%)
Left ventricular ejection fraction <30%¶	15 (2%)	13 (1%)
De-novo coronary lesions only‖	817 (90%)	810 (90%)
At least one chronic total occlusion	38 (4%)	38 (4%)
At least one bifurcation	244 (27%)	221 (24%)
At least one bifurcation with main-vessel stenting only	186 (21%)	174 (19%)
At least one bifurcation with main-vessel and side-branch stenting	54 (6%)	36 (4%)
At least one in-stent restenosis	27 (3%)	28 (3%)
At least one small-vessel (RVD <2·75 mm)	551 (61%)	517 (57%)
At least one lesion length >27 mm	161 (18%)	157 (17%)
Glycoprotein IIb/IIIa antagonist used	262 (29%)	259 (29%)
Number of lesions treated per patient		
One	668 (74%)	688 (76%)
Two	191 (21%)	182 (20%)
Three or more	47 (5%)	35 (4%)

Data are n (%) or median (IQR). Baseline patient characteristics did not differ significantly between treatment arms; p values were greater than 0·10, apart from those for clinical syndrome at presentation (p=0·07) and bifurcation with main-vessel and side-branch stenting (p=0·052). RVD=reference vessel diameter. *Data from 721 patients in the zotarolimus-eluting stent group and 703 patients in the everolimus-eluting stent group. †Chronic renal failure defined by serum creatinine level ≥130 μmol/L. ‡Data from 903 patients in the zotarolimus-eluting stent group and 905 patients in the everolimus-eluting stent group. §Data from 903 patients in the zotarolimus-eluting stent group and 902 patients in the everolimus-eluting stent group. ¶Left ventricular ejection fraction assessed with ultrasound, MRI, or left ventricular angiography; data from 900 patients in the zotarolimus-eluting stent group and 903 patients in the everolimus-eluting stent group. ‖Including chronic total occlusion, but not grafts or in-stent restenosis.

Table 1: **Baseline characteristics of patients**

	Zotarolimus-eluting stent group (n=1205 lesions)	Everolimus-eluting stent group (n=1166 lesions)
Left main stem	19 (2%)	21 (2%)
Left anterior descending artery	493 (41%)	469 (40%)
Left circumflex artery	304 (25%)	280 (24%)
Right coronary artery	378 (31%)	379 (33%)
Bypass graft	30 (2%)	35 (3%)
ACC/AHA lesion class		
A	73 (6%)	70 (6%)
B1	339 (28%)	331 (28%)
B2	432 (36%)	412 (35%)
C	361 (30%)	353 (30%)
De-novo lesion*	1147 (95%)	1103 (95%)
Chronic total occlusion	38 (3%)	39 (3%)
In-stent restenosis	28 (2%)	28 (2%)
Aorto-ostial lesion	59 (5%)	65 (6%)
Severe calcification	221 (18%)	251 (22%)
Bifurcated lesion	282 (23%)	249 (21%)
Thrombus present†	165 (14%)	174 (15%)
Total occlusion	167 (14%)	153 (13%)
Lesion length (mm)	13·63 (9·58–20·41)	13·46 (9·56–20·68)
Diameter of reference vessel (mm)	2·64 (2·25–3·06)	2·66 (2·27–3·07)
Minimum lumen diameter (mm)	0·88 (0·63–1·18)	0·88 (0·61–1·23)
Lumen diameter stenosis (%)	65·25 (53·83–75·84)	64·48 (53·92–76·17)
Preprocedural TIMI flow grade		
0	175 (15%)	155 (13%)
1	40 (3%)	39 (3%)
2	128 (11%)	125 (11%)
3	862 (72%)	847 (73%)

Data are n (%) or median (IQR). Baseline lesion characteristics did not differ significantly between treatment arms; p values were greater than 0·10, apart from that for severe calcification (p=0·052). ACC/AHA=American College of Cardiology/American Heart Association. TIMI=thrombolysis in myocardial infarction. *Including chronic total occlusion, but not grafts or in-stent restenosis. †Only thrombi that triggered use of a thrombus aspiration catheter were counted.

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

clinical event committee in Rotterdam, which was masked to the assigned treatment, adjudicated all clinical endpoints, with the only exception being the secondary endpoint of non-target-vessel revascularisation, which was adjudicated by Cardio Research Enschede. Members of the clinical event committee are listed at the end of the report.

Statistical analysis

The main outcome was the difference in primary endpoint at 12 months between patients assigned to treatment with zotarolimus-eluting or everolimus-eluting stents, analysed by the χ^2 test with at least 80% power to detect non-inferiority at a one-sided type I error of 0·05.[24] We applied a non-inferiority margin of 3·6%, with the expectation of 10% events (on the basis of results from the RESOLUTE All Comers trial[7]). With a maximum loss to follow-up of 3%, a minimum of 1788 patients was needed. All analyses were based on the intention-to-treat principle. We also did a per-protocol analysis of the primary endpoint.

Categorical variables were assessed with the χ^2 test, whereas continuous variables were assessed with the Student's *t* test or the Wilcoxon rank-sum test, as appropriate. The time to primary endpoint and the components thereof were assessed by Kaplan-Meier analysis;[25] the log-rank test was applied to compare groups. We calculated relative risk using the log-binomial method and hazard ratios (HRs) using Cox proportional hazards regression analysis. To account for intra-patient correlation (due to inter-lesion dependence), we did an additional lesion-based analysis using the generalised estimating equation method. We used logistic regression to test for interaction between subgroups and stent type with respect to the primary endpoint.

A p value of less than 0·05 was regarded as significant. All p values and CIs were two-sided, except those for non-inferiority testing of the primary endpoint. After non-inferiority was assessed, we calculated regular two-sided 95% CIs and two-sided p values to allow conventional interpretation of results (as for superiority trial design). Since it is unnecessary to compare baseline characteristics statistically in randomised trials,[26] we do not report individual p values for these data. We used SPSS 15.0 (SPSS, Chicago, IL, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA) for all statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT01331707.

Role of the funding source

The sponsors of the study had no role in study design, data collection and monitoring, data analysis, data interpretation, or writing of the report. They had no access to the clinical trial database. The authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Nov 25, 2010, and May 24, 2012, 1811 eligible all-comer patients, aged 21–91 years, with 2371 target lesions, were enrolled and randomly assigned to treatment with third-generation zotarolimus-eluting Resolute Integrity stents (906 patients, 1205 lesions) or everolimus-eluting Promus Element stents (905 patients, 1166 lesions; figure 1). One patient from the zotarolimus-eluting stent group withdrew consent after 1 day; therefore, baseline data and interventional results are reported for 1811 patients and follow-up results for 1810 patients. We obtained 12-month follow-up data for all 1810 remaining trial participants, which were used for clinical endpoint analysis.

We recorded no significant differences in baseline patient and preprocedural lesion characteristics between the study groups (tables 1, 2). Patients often presented with ST-elevation or non-ST-elevation myocardial infarction, which contributed to the overall high proportion of acute coronary syndromes at presentation (1062 patients [59%]). Most patients (1068 [59%]) were treated for at least one lesion in a small vessel, and many patients underwent treatment for bifurcation lesions (table 1). Of all coronary lesions, most (1558 [66%]) were complex, with lesion class B2 or C, and many lesions had severe plaque calcification (table 2).

More than 99% of patients were successfully treated with the assigned study stents only, across both groups

	Zotarolimus-eluting stent group (n=1205 lesions)	Everolimus-eluting stent group (n=1166 lesions)	p value
Implantation of assigned stents only	1195 (99%)	1161 (100%)	0·22
Number of stents per patient*	1·80 (1·08)	1·76 (1·10)	0·41
Number of stents per lesion	1·35 (0·68)	1·36 (0·70)	0·70
Total stent length per patient (mm)*	30 (18–50)	28 (20–48)	0·64
Total stent length per lesion (mm)	22 (18–36)	24 (16–38)	0·10
Maximum nominal stent diameter per lesion (mm)†	3·00 (2·50–3·50)	3·00 (2·50–3·50)	0·09
Direct stenting	352 (29%)	326 (28%)	0·50
Stent post-dilation	887 (74%)	920 (79%)	0·002
Device success‡	1194 (99%)	1158 (99%)	0·54
Lesion success§	1203 (100%)	1162 (100%)	0·39
Procedure success*¶	884 (98%)	890 (98%)	0·25
Post-procedure minimum lumen diameter (mm)†	2·22 (1·80–2·64)	2·15 (1·78–2·58)	0·06
Post-procedure minimum lumen diameter stenosis (%)†	15·07 (10·58–21·17)	15·73 (10·86–21·63)	0·24
Acute lumen gain in segment (mm)†	1·27 (0·85–1·78)	1·24 (0·79–1·77)	0·38

Data are mean (SD), median (IQR), or n (%). *Data are per patient (906 patients in the zotarolimus-eluting stent group and 905 patients in the everolimus-eluting stent group). †Data from 1204 lesions in the zotarolimus-eluting stent group and 1165 lesions in the everolimus-eluting stent group. ‡Device success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50% with only the assigned study device. §Lesion success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50% by any percutaneous method. ¶Procedure success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50%, together with the absence of any in-hospital major adverse cardiac events.

Table 3: **Interventional procedure and results**

(table 3); the proportion of patients with deviation from the assigned treatment was low and similar for both groups (six [1%] of 906 patients in the zotarolimus-eluting stent group *vs* five [1%] of 905 patients in the everolimus-eluting stent group; p=0·76; figure 1). Stenting without predilation (direct stenting) was done in 678 (29%) of the 2371 lesions (table 3). The frequency of stent post-dilation was high and differed between lesions treated with zotarolimus-eluting and everolimus-eluting stents (table 3). We recorded no significant difference between groups for any of the other procedure-related parameters (table 3). An additional lesion-based analysis of procedural details and results (with analyses corrected for intra-patient correlation with generalised estimating equations) did not change the overall findings (appendix p 1). At coronary intervention, 521 (29%) patients were treated with a glycoprotein IIb/IIIa antagonist (table 1), whereas only two patients (<1%) were treated with bivalirudin. At discharge, most (1790 [99%] of 1810) patients were treated with an antiplatelet therapy that included clopidogrel and aspirin; only three patients (<1%) received ticagrelor and 18 (1%) received prasugrel.

See Online for appendix

Table 4 shows clinical outcome at 12 months. The primary endpoint of target-vessel failure was met by 55 (6%) of 905 patients in zotarolimus-eluting stent group and 47 (5%) of 905 patients in the everolimus-eluting stent group. The zotarolimus-eluting Resolute Integrity stent was non-inferior to the everolimus-eluting Promus Element stent, with an absolute risk difference of 0·88% (95% CI –1·24 to 3·01) and an upper limit of the one-sided 95% CI of 2·69% (non-inferiority p=0·006). We noted no significant between-group differences in individual components of the primary endpoint (figure 2) or in the secondary clinical endpoints (table 4). HRs (with 95% CIs) and log-rank p values for the clinical outcomes at 1 year are reported in the appendix (pp 2–3). An exploratory subgroup

	Total patients (n=1810)	Zotarolimus-eluting stent group (n=905 patients)	Everolimus-eluting stent group (n=905 patients)	Relative risk (95% CI)	p value
Target-vessel failure (primary endpoint)*	102 (6%)	55 (6%)	47 (5%)	1·17 (0·80–1·71)	0·42
Death					
Any cause	34 (2%)	22 (2%)	12 (1%)	1·83 (0·91–3·68)	0·08
Cardiac cause	25 (1%)	15 (2%)	10 (1%)	1·50 (0·67–3·32)	0·31
Non-cardiac cause	9 (<1%)	7 (1%)	2 (<1%)	3·50 (0·73–16·80)	0·18
Target vessel-related myocardial infarction					
Any	32 (2%)	20 (2%)	12 (1%)	1·67 (0·82–3·39)	0·15
Q-wave	5 (<1%)	3 (<1%)	2 (<1%)	1·50 (0·25–8·96)	0·65
Non-Q-wave	27 (1%)	17 (2%)	10 (1%)	1·70 (0·78–3·69)	0·18
Periprocedural (≤48 h from index procedure)	30 (2%)	19 (2%)	11 (1%)	1·74 (0·83–3·61)	0·14
Non-periprocedural (>48 h from index procedure)	2 (<1%)	1 (<1%)	1 (<1%)	1·00 (0·06–15·96)	1·00
Any target-vessel revascularisation	53 (3%)	26 (3%)	27 (3%)	0·96 (0·57–1·64)	0·89
Clinically indicated target-vessel revascularisation	50 (3%)	24 (3%)	26 (3%)	0·92 (0·53–1·60)	0·77
Clinically indicated target-lesion revascularisation	40 (2%)	20 (2%)	20 (2%)	1·00 (0·54–1·85)	1·00
Death from cardiac cause or target-vessel-related myocardial infarction	56 (3%)	34 (4%)	22 (2%)	1·55 (0·91–2·62)	0·10
Target-lesion failure†	92 (5%)	51 (6%)	41 (5%)	1·24 (0·83–1·86)	0·29
Major adverse cardiac events‡	102 (6%)	58 (6%)	44 (5%)	1·32 (0·90–1·93)	0·15
Patient-oriented composite endpoint§	156 (9%)	84 (9%)	72 (8%)	1·17 (0·86–1·58)	0·32
Stent thrombosis (0–360 days)					
Definite, any (0–360 days)	9 (<1%)	3 (<1%)	6 (1%)	0·50 (0·13–2·00)	0·51
Definite, acute (0–1 days)	3 (<1%)	2 (<1%)	1 (<1%)	2·00 (0·18–22·02)	0·56
Definite, subacute (2–30 days)	3 (<1%)	0	3 (<1%)	<0·001	0·08
Definite, late (31–360 days)	3 (<1%)	1 (<1%)	2 (<1%)	0·50 (0·05–5·50)	0·56
Definite or probable, any (0–360 days)	13 (1%)	5 (1%)	8 (1%)	0·63 (0·21–1·90)	0·40
Possible, any (0–360 days)	14 (1%)	8 (1%)	6 (1%)	1·33 (0·50–3·83)	0·59
Definite, probable, or possible, any (0–360 days)	27 (1%)	13 (1%)	14 (2%)	0·93 (0·44–1·96)	0·85

Data are n (%), unless otherwise indicated. *The primary endpoint of target-vessel failure is a composite of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-vessel revascularisation. †Target-lesion failure is a composite of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-lesion revascularisation. ‡Major adverse cardiac events is a composite of all-cause death, any myocardial infarction, emergent coronary-artery bypass surgery, and clinically indicated target-lesion revascularisation. §The patient-oriented composite endpoint is a composite of all-cause death, any myocardial infarction, and any revascularisation.

Table 4: **Clinical outcomes at 1 year**

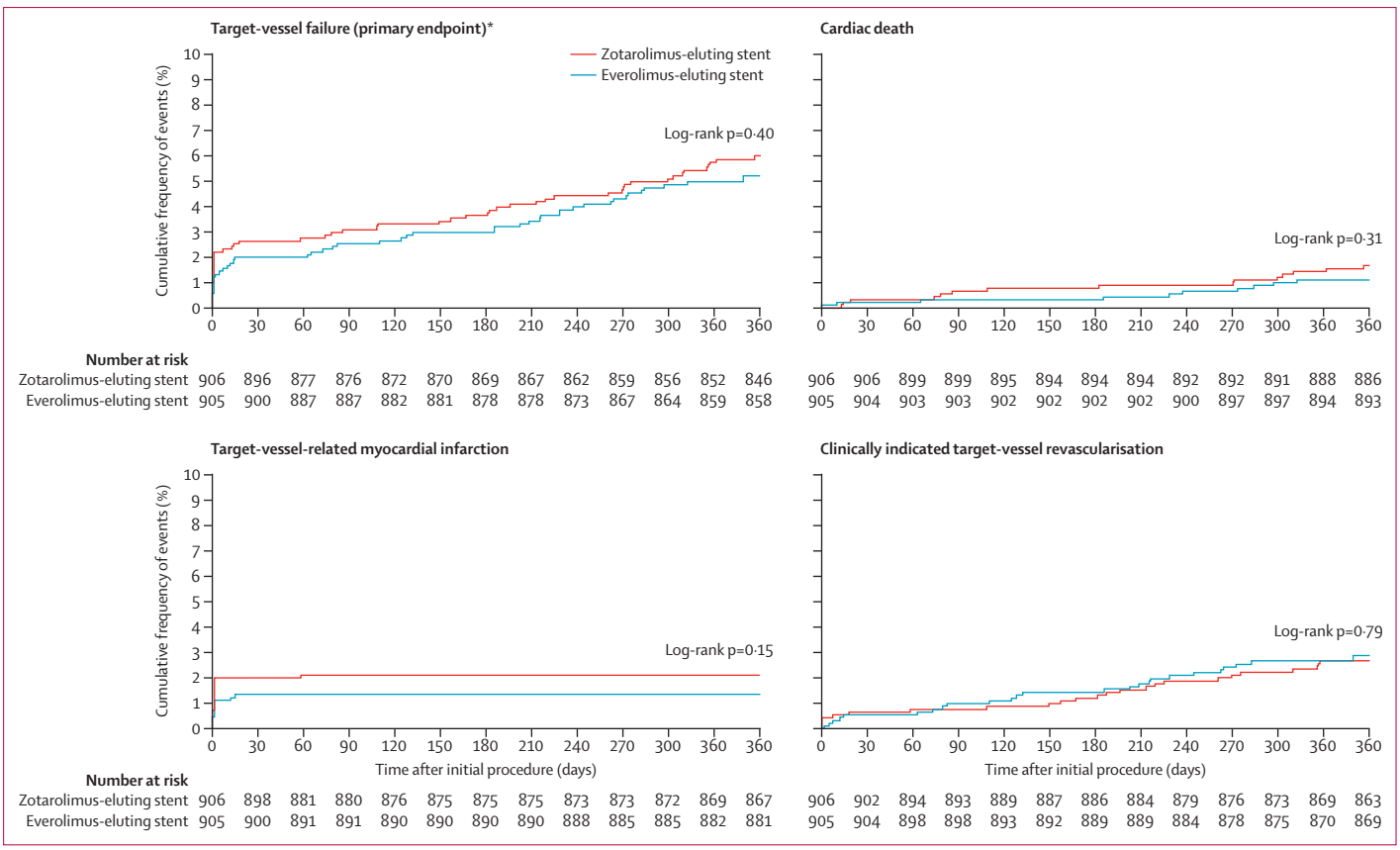

Figure 2: **Kaplan-Meier cumulative event curves for the primary combined safety and efficacy endpoint and its individual components at 12 months**
*The primary endpoint of target-vessel failure is a composite of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-vessel revascularisation.

analysis revealed no significant between-group difference in the primary endpoint across the various subgroups (appendix p 4).

In both stent groups, frequencies of definite and definite-or-probable stent thrombosis were low (table 4). No definite stent thrombosis occurred beyond 3 months after stenting. Figure 3 shows the time-to-event curve of definite-or-probable stent thrombosis and information about corresponding clinical events.

Longitudinal stent deformation during the index procedure was seen only in patients assigned to treatment with everolimus-eluting stents (nine [1·0%] of 905 *vs* 0 of 906 patients; p=0·002). With respect to the number of stents implanted, nine (0·6%) of 1591 everolimus-eluting stents became deformed. However, none of the patients with longitudinal stent deformation had any adverse clinical events as a result (appendix p 5).

To account for the possibility that deviation from the assigned stent might have affected the primary outcome, we also did a per-protocol analysis of the primary endpoint, which gave a similar result to the intention-to-treat analysis. The primary endpoint of target-vessel failure was met by 53 (6%) of 899 patients treated with zotarolimus-eluting stents and 45 (5%) of 900 patients treated with everolimus-eluting stents. The zotarolimus-eluting stent remained non-inferior, with an absolute risk difference of 0·90% (95% CI −1·20 to 3·00) and an upper limit of the one-sided 95% CI of 2·66% (non-inferiority p=0·006).

Discussion

DUTCH PEERS is the first randomised comparison of the third-generation zotarolimus-eluting Resolute Integrity and everolimus-eluting Promus Element stents. It is also the first trial ever to investigate the Resolute Integrity stent. In this all-comer patient population, no significant difference was seen between stent groups in the primary endpoint of target-vessel failure at 12-month follow-up. As a result, the zotarolimus-eluting Resolute Integrity stent met the criterion of non-inferiority compared with the everolimus-eluting Promus Element stent (panel). No significant differences were seen in the individual components of the primary endpoint (cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-vessel revascularisation). Stent thrombosis was rare in both groups, and no definite stent thrombosis occurred beyond 3 months from stenting.

Clinical outcomes were excellent for both stent groups, especially in view of the large proportion of patients with complex lesions and acute myocardial infarction at

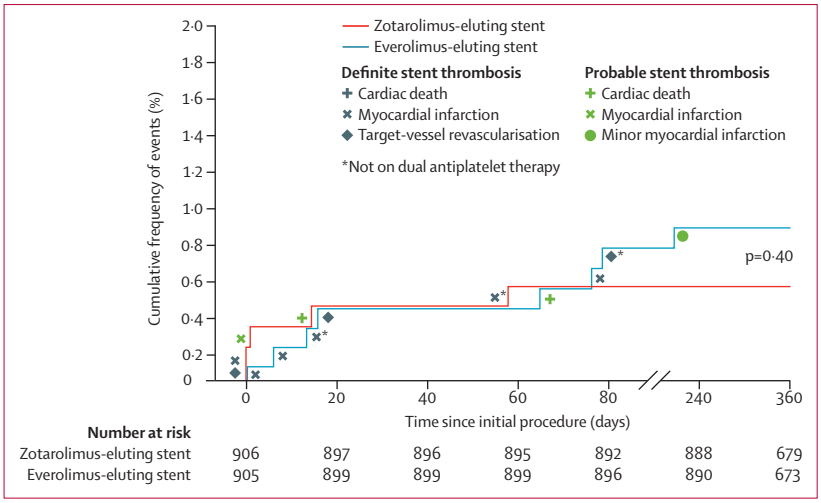

Figure 3: **Cumulative incidence of definite or probable stent thrombosis**
Symbols indicate the hierarchically most important adverse events associated with stent thromboses. Dark grey symbols signify definite stent thromboses, of which none were fatal. Green symbols signify probable stent thromboses. In patients treated with zotarolimus-eluting stents, only one late, definite stent thrombosis occurred in a patient who was not on dual antiplatelet therapy. In patients treated with everolimus-eluting stents, beyond 3 months no definite and only one probable stent thrombosis occurred; the one probable case was related to a minor myocardial infarction (clinically significant increase in cardiac troponin concentration, but no clinically significant increase in creatine kinase concentration). Dual antiplatelet therapy consisted of aspirin (≥80 mg daily) and an adequate dose of a P2Y12 receptor antagonist (usually clopidogrel 75 mg daily). Reasons for not being on dual antiplatelet therapy were: clopidogrel was stopped without substitution because of a novel allergic reaction (myocardial infarction on day 12); non-compliance to the prescribed drug treatment (myocardial infarction on day 58); and per-protocol cessation of aspirin after 1 month of dual antiplatelet therapy because of chronic oral anticoagulation therapy (target-vessel revascularisation on day 79).

presentation. Our findings showed favourable event rates in a population in which most patients had advanced cardiovascular disease. Therefore, these data might serve as an important reference for future stent trials. Our study assessed many patients with increased clinical, lesion-related, or procedural risk. The proportions of patients with acute coronary syndrome and, in particular, ST-elevation myocardial infarction, were among the highest of all randomised, multicentre trials of drug-eluting stents in an all-comers population.[7,19,27–29] The proportions of patients with complex type B2 or C coronary lesions and bifurcation lesions were also high compared with other trials.[6–8,19,28,29]

Very few patients deviated from their assigned stents in this trial, which suggests excellent deliverability and similar feasibility for both devices. In fact, deviation from the assigned stents was much higher in the permanent-polymer-based drug-eluting stent groups of various other randomised trials, such as TWENTE,[8] RESOLUTE All Comers,[7] COMPARE II,[30] and LEADERS,[27] across which treatment of 1·6–5·3% of patients deviated from the assigned stents.

Up to now, the third-generation Promus Element stent has only been compared with second-generation drug-eluting stents.[11,19] In the PLATINUM trial,[11] which enrolled patients at low-to-moderate risk of adverse cardiovascular events, the Promus Element stent was shown to be non-inferior to the second-generation cobalt-chromium-based everolimus-eluting Xience V/Promus stent, and only a small proportion of patients (4·2%) met the target-vessel-related composite endpoint.[11] Our findings show excellent results for the Promus Element stent in an all-comers population with a much higher risk profile than that of the PLATINUM trial.

The HOST-ASSURE trial[19] has compared the Promus Element stent with the second-generation zotarolimus-eluting Resolute stent in an all-comers population in South Korea (patients with a reference vessel diameter less than 2·5 mm or heart failure were excluded). The investigators attributed the very low frequencies of clinical endpoints to the excellent device characteristics and generally lower clinical event frequencies in east Asian populations.[19] DUTCH PEERS provides the first randomised assessment of Promus Element stents in an all-comer population of European patients. Besides this difference in ethnic background, the patient population of DUTCH PEERS differed from the HOST-ASSURE patients in its much higher proportion of acute ST-elevation myocardial infarctions at presentation (20% *vs* 11%), treatment of more complex target lesions (class B2 or C, 66% *vs* 51%), and treatment of more lesions in small vessels (by not excluding patients with a reference vessel diameter of less than 2·5 mm).

Moreover, investigators of a very small randomised study[31] from Spain also reported favourable outcome data for 150 patients treated with Promus Element stents, but this study did not permit a meaningful between-stent comparison. Compared with the second-generation everolimus-eluting stent in the TWENTE[8] and RESOLUTE All Comers[7] trials, which recruited broad patient populations, the Promus Element stent group in our trial showed lower frequencies of both target-vessel-related (5·2% *vs* 8·1–9·6%) and target-lesion-related composite endpoint events (4·5% *vs* 6·8–8·3%).

Only a small-scale, first-in-man study has reported data for the bare-metal stent platform that is used in the third-generation zotarolimus-eluting Resolute Integrity stent.[14] Our trial is the first clinical study to investigate this particular stent, and has shown it to have a favourable outcome in a broad patient population. The frequencies of target-vessel-related composite endpoint events and the number of definite stent thromboses were much lower than reported for its second-generation counterpart in the randomised TWENTE[8] and RESOLUTE All Comers[7] trials (target-vessel-related composite endpoint: 6·1% *vs* 8·2–9·0%; definite stent thromboses: 0·3% *vs* 0·6–1·2%).

A potential trade-off of the novel, flexible designs of third-generation drug-eluting stents might be a reduced longitudinal stability.[15,16] Since the introduction of the Promus Element stent, longitudinal stent deformation has been reported much more frequently.[18] Retrospective analyses[16,17] have shown longitudinal deformation to occur at a frequency of 0·3–0·9% per Promus Element

stent implanted, although such deformations are associated with a mostly benign clinical course. In the HOST-ASSURE trial,[19] longitudinal deformation of the Promus Element stent was noted in seven (0·2%) of 2938 patients, but was not associated with future adverse events.[19] In our study, visually assessed longitudinal stent deformation was noted only in the everolimus-eluting Promus Element stents, with a frequency of 0·6% per stent implanted, but without clinical sequelae. Quantitative coronary angiographic assessment of longitudinal stent deformation was not done systematically, but was restricted to cases with visually determined stent deformation. Investigators of two previous studies[19,32] did systematic, quantitative, coronary angiography-derived measurement of post-deployment stent length compared with the nominal stent length and showed the absence of a systematic shortening of this stent platform. The excellent radiographic visibility of the Promus Element stent might have contributed to the more frequent recognition of longitudinal stent deformation and the slightly higher frequency of stent post-dilation compared with the Resolute Integrity stent.

Although the use of the highly device-oriented composite of target-lesion failure has been advocated as primary endpoint,[22] DUTCH PEERS used the composite of target-vessel failure.[10] Target-vessel failure is also very appropriate and has been used as primary endpoint by other trials of drug-eluting stents in all-comers.[27–29] Both composite endpoints have advantages and disadvantages. Target-lesion failure includes only target-vessel revascularisations for lesions inside the original target-lesion segment, whereas target-vessel failure also includes revascularisation procedures for lesions at other sites of the target-vessel (ie, inside and outside the target-lesion segment). Target-vessel failure, therefore, avoids the sometimes difficult discussion about whether the target lesion segment is touched by a stenosis or restenosis, or not. Additionally, target-vessel failure would cover the progression of lesions that are initially not clinically significant to stenoses that require interventional treatment, which might sometimes be caused by the intracoronary use of a bulky device.

Our trial has some limitations. The lower-than-expected frequencies of primary endpoint events affect the robustness of the results, particularly the results of the post-hoc subgroup analysis. When designing the DUTCH PEERS trial, we assumed that the tested devices would have an event risk that was in the range of their second-generation counterparts tested in the RESOLUTE All Comers trial,[7] and that enrolment of more patients with ST-elevation myocardial infarction (who have an inherently increased risk of adverse outcome) would slightly increase the frequency of events. However, although we succeeded in enrolling more patients with ST-elevation myocardial infarction than did the RESOLUTE All Comers trial,[7] event frequencies were lower. Underreporting of events in our study is very unlikely, in view of the systematic post-procedural assessment, the complete 12-month follow-up, and the independent monitoring used.

Other randomised trials of stents in all-comers[19,30] have also had low event frequencies, suggesting that our findings are actually more representative of the present outcomes of percutaneous coronary interventions than of those from when the trial was designed. Nevertheless, even with a more conservative non-inferiority margin of 2·7% (to compensate for the lower-than-expected event frequency), the primary outcome of non-inferiority of the Resolute Integrity stent compared with the Promus Element stent was unchanged. A one-sided α of 0·05, which is also used by other trials of drug-eluting stents in all-comers,[7,29,30] is less conservative in establishing non-inferiority of two treatments, but the use of a one-sided α of 0·025 would not have had an effect on the outcome of our study (ie, the upper limit of the 97·5% CI of the difference is 3·01%, which is below our prespecified non-inferiority margin).

Two final issues should also be mentioned, relating to our subgroup analysis of the primary endpoint and the definition of third-generation drug-eluting stents used. On the first point, because the subgroup analysis done for the primary endpoint of target-vessel failure was not prespecified, we applied subgroup definitions from previous trials[7,8] to avoid a subjective post-hoc selection. On the second, although the term third-generation drug-eluting stents is sometimes used for a broader spectrum of novel stents, we have used the term to refer specifically to the more flexible, highly deliverable durable-polymer stents that followed the second-generation durable-polymer stents.

***Panel:* Research in context**

Systematic review

We searched PubMed for reports with an abstract in English published up to Aug 26, 2013, and checked the listings of the EuroPCR, Transcatheter Cardiovascular Therapeutics, and American College of Cardiology conferences (from 2009 onwards) for reports of randomised trials that compared the zotarolimus-eluting Resolute Integrity stent or the everolimus-eluting Promus Element stent with another drug-eluting stent. We used as search terms "coronary" and "stent" in combination with one or more of "zotarolimus", "everolimus", "Resolute Integrity", "Promus Element", "platinum", "randomised", and "randomized". The third-generation Resolute Integrity stent had not yet been assessed in a randomised trial. The Promus Element stent had been assessed in two randomised clinical trials.[11,19] In the PLATINUM trial,[11] Promus Element was non-inferior to the cobalt-chromium-based Xience V stent in patients at low-to-moderate risk of adverse cardiovascular events. Preliminary data from the HOST-ASSURE trial[19] in allcomer patients in South Korea showed very low event frequencies for both the Promus Element and the second-generation Resolute stent.

Interpretation

DUTCH PEERS was the first randomised trial to investigate the Resolute Integrity stent. The third-generation, permanent-polymer zotarolimus-eluting (Resolute Integrity) and everolimus-eluting (Promus Element) stents were similarly efficacious and safe, with excellent clinical outcomes in a real all-comer patient population.

In conclusion, both stents were similarly efficacious and safe, and provided excellent clinical outcomes, especially in view of the large number of patients who presented with acute myocardial infarctions.

Contributors

CvB, KT, and MWZB designed the trial. CvB, PWD, and GAJJ were the trial steering committee. CvB wrote the first draft of the report, with the participation of KT, HS, MKL, MGS, MML, and GCML. RWMH, GKvH, ARS, RMTJG, JWL, FHAFdM, SAMS, MBN, and PMJV revised the draft for important intellectual content. HS, MKL, MML, and KT gathered and analysed data. KT and CJMD did the statistical analyses. CvB, HS, MKL, MML, CJMD, and KT interpreted the data. All authors read and approved the final submitted version of the report.

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Conflicts of interest

The research department of Thoraxcentrum Twente has received educational and research grants funded by Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. CvB is a consultant to Abbott Vascular, Boston Scientific, and Medtronic, and has received a travel grant from Biotronik and lecture fees from Biotronik and MSD. All other authors declare that they have no conflicts of interest.

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