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

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Background Drug-eluting stents (DES) are increasingly used for the treatment of coronary artery disease. An optimized DES performance is desirable to successfully treat various challenging coronary lesions in a broad population of patients. In response to this demand, third-generation DES with an improved deliverability were developed. Promus Element (Boston Scientific, Natick, MA) and Resolute Integrity (Medtronic Vascular, Santa Rosa, CA) are 2 novel third-generation DES for which limited clinical data are available. Accordingly, we designed the current multicenter study to investigate in an all-comers population whether the clinical outcome is similar after stenting with Promus Element versus Resolute Integrity.

Methods DUTCH PEERS is a multicenter, prospective, single-blinded, randomized trial in a Dutch all-comers population. Patients with all clinical syndromes who require percutaneous coronary interventions with DES implantation are eligible. In these patients, the type of DES implanted will be randomized in a 1:1 ratio between Resolute Integrity versus Promus Element. The trial is powered based on a noninferiority hypothesis. For each stent arm, 894 patients will be enrolled, resulting in a total study population of 1,788 patients. The primary end point is the incidence of target vessel failure at 1-year follow-up.

Summary DUTCH PEERS is the first randomized multicenter trial with a head-to-head comparison of Promus Element and Resolute Integrity to investigate the safety and efficacy of these third-generation DES. (Am Heart J 2012;163:557-62.)

Background

Drug-eluting stents (DES) were developed to improve invasive treatment of coronary artery disease by reducing the rate of restenosis and the need for repeat revascularization. First-generation DES consisted of established bare-metal stent (BMS) platforms and durable polymer coatings that delivered the drug to the vessel wall. Although the early DES studies proved the efficacy of DES to reduce morbidity,[1] these devices had no positive impact on mortality. This was greatly attributed to a somewhat increased incidence of stent thrombosis (compared with BMS).[2-4] Second-generation DES were then developed, aiming at improved biocompatibility of the coatings while maintaining the antiproliferative potential of first-generation DES.[5] Further refinement of DES involved an increase in flexibility of the stent platform, which was realized in third-generation DES. Stent flexibility facilitates both stent delivery in challenging anatomical situations and apposition of DES to the vessel wall with optimal drug delivery.

Resolute Integrity (Medtronic Vascular, Santa Rosa, CA) and Promus Element (Boston Scientific, Natick, MA) are third-generation DES, based on established and previously tested drugs and durable polymer-based coatings[6] in

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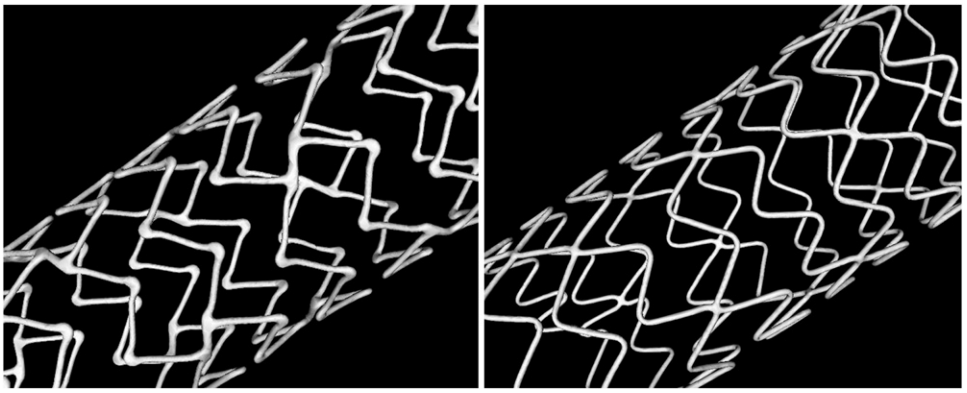
Figure 1



Micro computed tomography images of DES compared in DUTCH PEERS. Promus Element (left panel) and Resolute Integrity (right panel); images from ongoing bench side studies performed by C. von Birgelen and coworkers, University of Twente, Enschede, The Netherlands.

combination with a novel stent design to increase flexibility. DUTCH PEERS is a multicenter trial to evaluate the clinical outcome of these third-generation DES in a real-world, all-comers setting.

Investigational products

Promus element

Promus Element is a Conformité Européenne and recently Food and Drug Administration–approved DES eluting everolimus as antiproliferative agent from a fluoropolymer coating. It has, at minimum, a strut thickness of 81 μm and a coating thickness of 7 μm. The Promus Element was shown to be highly effective to reduce neointimal proliferation.[7,8] The stent platform is laser cut and made from a platinum chromium alloy. It consists of serpentine rings connected by links (Figure 1) and has been designed for improved deliverability and visibility (ie, higher radiopacity).

Resolute integrity

Resolute Integrity is a Conformité Européenne-certified DES that elutes zotarolimus as antiproliferative agent from the Biolinx (Medtronic Vascular, Santa Rosa, CA) polymer system consisting of a blend of 3 different polymers (hydrophobic C10 polymer, hydrophilic C19 polymer, and polyvinyl pyrrolidinone). This coating is also used in the Resolute DES, which was shown to be highly effective to reduce neointimal proliferation.[9] Resolute Integrity is based on a new flexible stent platform (Fig. 1) made from a cobalt-chromium alloy that increases stent deliverability and conformability. Resolute Integrity has a strut thickness of 91 μm and a coating thickness of 6 μm.

Methods

Study hypothesis/objective and design

The main objective of the DUTCH PEERS (ClinicalTrials.gov no. NCT01331707) is to compare the safety and efficacy of the Resolute Integrity to Promus Element in an all-comers population with complex lesions. The study hypothesis is that Resolute Integrity is not inferior to Promus Element. DUTCH PEERS is a multicenter, prospective, single-blinded, randomized clinical trial in an all-comers population. Randomization will involve the type of DES used. Patients will be blinded as to the type of DES received. It is an investigator-initiated trial, planned and performed by cardiologists of the participating percutaneous coronary intervention (PCI) centers. Boston Scientific and Medtronic provided equal financial support of the entire study.

Study population

A total of 1,788 patients will be studied, which is equal to 894 patients per treatment arm. Patients with a minimum age of 18 years who undergo PCI with DES implantation are eligible for enrollment in the study. All clinical syndromes are permitted, including acute myocardial infarctions (MIs) such as ST-elevation myocardial infarction (STEMI) and non-STEMI.

There are very few exclusion criteria to assess the performance of both DES in a real-world, all-comers setting, as seen in routine clinical practice. Exclusion criteria are (1) participation in another randomized drug or device study before reaching primary end point; (2) planned surgery within 6 months of PCI unless dual antiplatelet therapy is maintained throughout the perisurgical period; (3) intolerance to a P2Y12 receptor antagonist that results in the patient's inability to adhere to dual antiplatelet therapy, or intolerance to aspirin, heparin, or components of the 2 DES examined; (4) known pregnancy; and (5) life expectancy of <1 year. Table I shows an overview of the inclusion and exclusion criteria.

The study complies with the Declaration of Helsinki and was approved by the local ethics committees. All patients provide

Table I. DUTCH PEERS inclusion and exclusion criteria

Inclusion criteria
1. Minimum age of 18 y.
2. Coronary artery disease and lesion(s) eligible for treatment with DES according to clinical guidelines and/or the operators' judgment.
3. Patient is willing and able to cooperate with study procedures and required follow-up visits, and patient has been informed and agrees on the participation by signing an approved written informed consent.
Exclusion criteria
1. Participation in another randomized drug or device study before reaching primary end point.
2. Planned surgery within 6 m of PCI unless dual antiplatelet therapy is maintained throughout the perisurgical period.
3. Intolerance to a P2Y12 receptor antagonist that results in the patient's inability to adhere to dual antiplatelet therapy, or intolerance to aspirin, heparin, or components of the 2 DES examined.
4. Known pregnancy.
5. Life expectancy of <1 y.

written informed consent for participation in the trial. Enrollment takes place at 4 individual study sites in The Netherlands (Thoraxcentrum Twente at Medisch Spectrum Twente, Enschede; Scheper Hospital, Emmen; Hospital Rijnstate, Arnhem; Medisch Centrum Alkmaar, Alkmaar). The first patient was enrolled on November 25, 2010; enrollment is expected to be completed in spring 2012.

Study protocol, patient demographics, and medical data

Patient demographics and baseline data are collected by the investigators and entered in a database at Thoraxcentrum Twente in Enschede. Laboratory tests will be performed in the local laboratories of the participating centers as part of their clinical routine practice. In all patients, cardiac biomarkers measurement will be scheduled before PCI and 6 to 18 hours after PCI, with subsequent serial measurements in case of relevant biomarker elevation or complaints until the peak elevation has been measured.

Percutaneous coronary intervention procedures are performed according to routine clinical practice. The use of predilatation or postdilatation and intravascular ultrasound or optical coherence tomography is left to the operator's discretion. If an operator is unable to insert the study stent despite various measures, crossover to a nonstudy stent of choice is permitted (BMS or DES). It is preferred to treat all significant coronary lesions within a single PCI procedure; however, staged procedures (defined as procedures planned at the time of the index procedure and performed within 6 weeks with the allocated type DES) are permitted. In case of unplanned revascularization procedures requiring stent implantation, it is recommended that physicians use the allocated type of DES. Coronary angiographic imaging is performed according to current guidelines to obtain high-quality angiographic images that permit reliable quantitative analyses with quantitative coronary angiography.

Medical therapy during PCI does not differ from current routine medical treatment; the use of glycoprotein IIb/IIIa inhibitors is left at the operator's discretion. Patients who are not on oral aspirin therapy will receive a loading dose of at least 300 mg before PCI. A loading dose of clopidogrel will be given before PCI (at least 300 mg); if prasugrel is used, patients will receive a loading dose of 60 mg. After the index PCI procedure, patients are generally maintained on aspirin ≥80 mg daily. In addition, clopidogrel 75mg daily is generally prescribed for a period of 1 year. If patients require oral anticoagulation therapy (eg, for atrial fibrillation), clopidogrel is prescribed for 1 year, and aspirin ≥80 mg daily for at least 1 month. Further medical treatment is performed according to current medical guidelines, clinical standards, and the judgment of the referring physicians.

Follow-up data collection

Follow-up data will be collected during routine visits to the outpatient clinic, or if not feasible, by telephone follow-up and/or a medical questionnaire. Staff, blinded to the allocated treatment arm, will conduct the telephone calls during follow-up. During outpatient visits or telephone calls, patients will be interviewed regarding rehospitalizations, revascularization procedures, and MIs during follow-up. In case of death, information will be obtained from the patient's medical chart, general practitioner, and/or cardiologist. Follow-up data after 1 month, 12 (±1) months, and 24 (±1) months will be collected.

Clinical end points and definitions

The primary end point of the study will be target vessel failure (TVF) at 12 months as defined by the Academic Research Consortium (ARC).[10] Target vessel failure is a composite end point to assess device efficacy as well as patient safety. Components of the primary end point are cardiac death, target vessel–related MI, and clinically indicated repeated target vessel revascularization.

Cardiac death is defined as any death caused by proximate cardiac cause (eg, MI, low-output failure, or fatal arrhythmia), unwitnessed death, death of unknown cause, and all procedure-related deaths, including those related to concomitant therapy. In brief, all deaths are considered cardiac, unless an unequivocal noncardiac cause can be established. Target vessel–related MI (Q-wave or non–Q-wave MI) is defined as an MI that can be related to the target vessel or cannot be related to another vessel. Myocardial infarction is defined according to the revised ARC definition of MI, including periprocedural MI.[11] Clinically indicated repeated target vessel revascularization includes revascularization procedures by means of coronary artery bypass graft or PCI.

Secondary end points will include all-cause death, target-lesion failure (TLF) (a composite of cardiac death, target vessel MI, and clinically indicated target lesion revascularization), a patient-oriented composite end point (a composite of all-cause death, any MI, any revascularization), and stent thrombosis, which will be assessed according to the ARC.[10]

Sample size calculation

The main outcome parameter is the difference in TVF between the 2 treatment arms after 12 months, analyzed by χ^2 test. We applied a noninferiority margin of 3.6%, expecting an event rate of 10%, based on data of the RESOLUTE All Comers

and TWENTE trial.[12,13] If the upper limit of the 1-sided 95% CI of the difference in the primary end point is less than the prespecified noninferiority margin 3.6%, Resolute Integrity will be considered noninferior to Promus Element. Considering the aforementioned parameters, 894 patients per group (total study population, 1788 patients) would allow to demonstrate noninferiority, taking into account a maximum loss to follow-up of 3%. The power to detect a true difference will be at least 80%,[14] and statistical significance is set at 5%.

Randomization

Patients will be randomized by a computer program (block stratified randomization V5.0 by S. Piantadosi) after diagnostic catheterization. The randomization will be performed in blocks of 8 and 4 in random order. Patients will be assigned either a Resolute Integrity stent or Promus Element stent on a 1:1 basis.

Statistical considerations

Baseline characteristics will be reported as mean ± SD or as percentage for categorical and dichotomous variables. If variables are not normally distributed, values are reported as median with corresponding range. Between-group differences in TVF rate at 12 months will be analyzed by means of χ^2 tests. In addition, the primary end point will be analyzed by the log-rank test by comparing the time to the primary end point using the Kaplan-Meier method. Subgroup analyses will be performed for, but will not be limited to, diabetes mellitus, age, gender, recent MI, in-stent restenosis, known renal insufficiency, bifurcation lesion, left main stenting, bypass graft lesion treated, multivessel stenting, number of implanted stents, lesion length, small vessels, and number of treated lesions in which the primary and secondary end points will be analyzed. The subgroup analyses will be performed to assess consistency of treatment effect across different subsets and are considered hypothesis generating. We will perform even more detailed analyses in important subgroups such as patients with STEMI and diabetics. The principal analyses will be performed based on the principles of intention to treat.

Trial organization

Trial coordination and data management will be performed by Cardio Research Enschede, Enschede, The Netherlands. Study monitoring will be carried out by an independent external contract research organization (Diagram, Zwolle, The Netherlands). An independent clinical events committee (Cardialysis, Rotterdam, The Netherlands) will adjudicate all adverse clinical events.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. Stent-manufacturing companies will have no access to the study database and are not involved in the interpretation of data or manuscript preparation.

Discussion

The use of DES in daily clinical practice has gradually been extended to so-called "off-label indications," including its use in angiographically complex coronary lesions. This is supported by data that demonstrated similar safety and efficacy of DES (compared with BMS) for off-label indications[15] such as STEMI,[16-18] bifurcations,[19,20] left main lesions,[21] long lesions,[22] small vessels,[23] bypass grafts,[24-26] and chronic total occlusions.[27] Although officially reported data on the penetration of DES in clinical practice is scarce, current estimates of the mean DES penetration vary from 64% in the United Kingdom to 80% in the United States.[28-30]

So far, very few data are available on the clinical performance of third-generation Promus Element and Resolute Integrity DES. Other DES, which have major similarities using the same coating and polymer but different stent platforms, are the second-generation Xience V (Abbott Vascular, Santa Clara, CA) and Resolute. Several randomized trials demonstrated a superior outcome after PCI with these second-generation DES compared with first-generations DES.[31-33] An example may be SPIRIT IV, which provided interesting insights into the safety and efficacy of Xience V compared with Taxus Liberté (Boston Scientific, Natick, MA).[32] In the Xience V study arm, the primary end point TLF at 1-year follow-up (a composite of cardiac death, target vessel MI, and target lesion revascularization) occurred 38% less often compared with Taxus Liberté (4.2% vs 6.8%, P = .001). In addition, rates of definite-or-probable stent thrombosis according to ARC were lower in Xience V than in Taxus (0.3% vs 1.1%, P = .004).

Similar to DUTCH PEERS, some recent randomized comparative DES trials were "all-comers studies" that comprised a significant proportion of challenging lesions in complex patients with various clinical syndromes including STEMI. The results of such trials are particularly valuable, as they reflect the performance of DES in routine clinical practice. As a consequence, their results may be generalizable to most PCI centers. The COMPARE trial and RESOLUTE All Comers trial are such studies, which examined Xience V and Resolute in an all-comer patient population.[12,31]

In the COMPARE trial, superiority of Xience V over Taxus Liberté was shown.[31] In this prospective, randomized, controlled single-center trial, the primary end point—a composite of all-cause mortality, nonfatal MI, and target vessel revascularization at 1 year—occurred in 6.2% in the Xience V arm as compared with 9.1% in the Taxus Liberté arm (P = .02). Lower rates of definite-or-probable stent thrombosis (0.7% vs 2.5%) contributed to this difference.

The Resolute All Comers trial compared the clinical performance of Resolute and Xience V stents.[12] In this pivotal, prospective, randomized, controlled multicenter trial, Resolute proved to be noninferior to Xience V with similar safety and efficacy of both DES. The primary end point TLF at 12 months was 8.2% and 8.3% for Resolute and Xience V, respectively ($P_{\text{noninferiority}} < .001$). In

addition, TVF rates at 12 months were nonsignificantly different (9.0% vs 9.6%) with stent thrombosis rates of 1.6% and 0.7% for both DES. Noninferiority of Resolute versus Xience V was maintained at 2-year follow-up.[5] The randomized TWENTE trial recently confirmed noninferiority of Resolute versus Xience V in a patient population with minimal exclusion criteria and with most complex lesions and "off-label" indications for DES use.[13]

Although second-generation DES use novel coatings, aiming at increased biocompatibility, third-generation DES make use of stent platforms that were designed specifically for use in DES. Advantages of such platforms may be an improved stent flexibility and conformability, a more homogeneous drug delivery to the vessel wall, and/or an improved visibility of the stent. However, for both Resolute Integrity and Promus Element, there are only limited data available from large randomized multicenter trials in third-generation DES on more complex lesions and clinical end points. Recently, the PLATINUM trial showed noninferiority of the third-generation Promus Element stent compared with the second-generation Xience V stent.[8] In that study, patients with stable angina, unstable angina, and silent ischemia with 1 or 2 de novo lesions were examined, revealing for Promus Element and Xience V at 1-year follow-up TLF rates of 3.5% and 3.2% and TVF rates of 4.2% and 4.0%, respectively. Definite-or-probable stent thrombosis occurred in 0.4% in each group. Promus Element is the first third-generation DES that was approved for clinical use in the United States. So far, for the third-generation Resolute Integrity stent, no information is available from randomized comparative trials, but clinical performance is generally assumed to be at least similar to that of Resolute. Nevertheless, Promus Element will be considered as the reference device in DUTCH PEERS because (1) more clinical data have been reported on its clinical performance, (2) it was recently shown to be noninferior to the second-generation Xience V stent in the PLATINUM trial,[8] and (3) it recently received approval by the US Food and Drug Administration.

It will be interesting to investigate whether changes in stent platform made in third-generation DES will affect clinical outcome in diabetic patients. The question whether there is a clear relation between DES type and clinical outcome in the presence of diabetes mellitus has not been definitely answered yet. A pooled analysis showed an interaction between diabetes and DES type.[34] Everolimus-eluting stents may be less effective in diabetic patients in reducing neointimal formation than in nondiabetics. Because zotarolimus is also a rapamycin analogue, Resolute Integrity theoretically could have the same interaction with diabetes mellitus. In fact, in the RESOLUTE All Comers trial, Xience V showed no significant difference compared with Resolute in patients with diabetes (P = .25), and there was no substantial difference between the 2 DES types in inhibiting neointima.[12] Because the DUTCH PEERS trial will include a significant number of diabetic patients, the subanalysis of diabetic patients may provide more insight in this matter. Nevertheless, as in many other randomized stent trials, subgroup analyses may be considered as hypothesis generating only because they are often not powered to draw sound conclusions.

Because both devices share (different) changes in stent platform for improved flexibility and conformability, this study may not be able to assess a potential negative impact of these design changes in clinical practice. A major safety issue of one of both devices is likely to be detected in DUTCH PEERS. However, the assessment of small between-device differences in certain rare events may require pooling of data from more than 1 randomized trial. Nevertheless, the great acceptance of both devices in clinical practice and the fact that, worldwide, many operators use these stents as their "workhorse" stent(s) make the comparison of DUTCH PEERS clinically interesting and relevant.

Thus, Resolute Integrity and Promus Element are third-generation DES of which so far no head-to-head comparison has been performed. In the randomized DUTCH PEERS multicenter trial, we therefore compare both devices with regard to safety and efficacy in a large all-comers population, assuming noninferiority of Resolute Integrity compared with Promus Element.

Disclosures

CvB is consultant to and has received lecture fees or travel expenses from Boston Scientific, Medtronic, and Abbott Vascular; he received lecture fees from Merck, Sharp & Dohme. All other authors declare that they have no conflict of interest.

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