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# A prospective evaluation of the safety and efficacy of TAXUS Element paclitaxel-eluting coronary stent implantation for the treatment of *de novo* coronary artery lesions in small vessels: the PERSEUS Small Vessel trial

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**KEYWORDS**

*Paclitaxel, drug-eluting stents, coronary restenosis, platinum chromium, small vessel, thin-strut*

## Abstract

**Aims:** Small reference vessel diameter predicts adverse outcomes following coronary stenting. TAXUS Express and TAXUS Liberté paclitaxel-eluting stents (PES) reduce restenosis compared to bare metal stents (BMS) in small diameter vessels. TAXUS Element is a novel thin-strut, platinum chromium stent designed to enhance visibility, conformability, and drug delivery in small diameter vessels.

**Methods and results:** The PERSEUS Small Vessel (SV) prospective, single-arm, superiority trial evaluates the TAXUS Element PES in 224 subjects with target lesion length ≤20 mm and vessel diameter ≥2.25 to <2.75 mm, compared to 125 lesion-matched historical Express BMS control subjects from the TAXUS V trial. The primary endpoint was nine-month in-stent late loss. The secondary endpoint was 12-month target lesion failure (TLF) compared to a pre-specified performance goal (PG). Outcomes were analysed with and without propensity-score adjustment. TAXUS Element was superior to the Express BMS for late loss (0.38±0.51 versus 0.80±0.53 mm respectively; $P<0.001$), and TLF (7.3%) was significantly less than the 19.5% PG ($P<0.001$). No differences in mortality, myocardial infarction, or stent thrombosis were observed through 12 months. Results were similar after adjustment.

**Conclusions:** PERSEUS SV supports the efficacy and safety of the platinum chromium, thin-strut TAXUS Element stent in small coronary vessels.

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## Introduction

Small vessel diameter is a predictor of adverse clinical and angiographic outcomes following coronary stenting, particularly with bare metal stents (BMS).[1,2] Prior studies of the first generation TAXUS™ Express™ paclitaxel-eluting stents (PES) (Boston Scientific, Natick, MA, USA) have demonstrated reduced restenosis rates compared with BMS in subgroups of patients with small calibre vessels.[3,4] In the prospective TAXUS ATLAS small vessel trial, the second-generation 2.25 mm TAXUS Liberté™ (Boston Scientific) stent reduced target vessel revascularisation at 12 months compared to historical controls treated with the TAXUS Express (Boston Scientific) (6.1% versus 16.9%, respectively) in vessels 2.2 to 2.5 mm in diameter.[5] Interpretation of these studies has been limited by subgroup analyses involving small numbers of patients.

The third generation TAXUS Element™ (ION™)(1) PES incorporates a novel, thin-strut (81 µm; Figure 1A), platinum chromium alloy platform designed to enhance visibility, conformability, and drug delivery in small calibre vessels.[6] Both strut and polymer thickness of the TAXUS Element stent are reduced compared to prior generation TAXUS Express and TAXUS Liberté PES (Figure 1A) although polymer, drug, and drug release kinetics are similar. Bench testing has demonstrated the platinum chromium alloy to have enhanced radial strength relative to stainless steel and less stent recoil than cobalt chromium.[7] Preclinical testing has supported the vascular compatibility of platinum chromium.[8] In addition, the Element stent was associated with more rapid strut coverage and endothelialisation compared to the Express and Liberté stents in a rabbit model.[9]

The TAXUS PERSEUS Small Vessel (SV) study was designed to evaluate whether the TAXUS Element stent is superior in efficacy to the bare metal Express stent in small coronary vessels and to determine the relative safety of this novel PES platform.

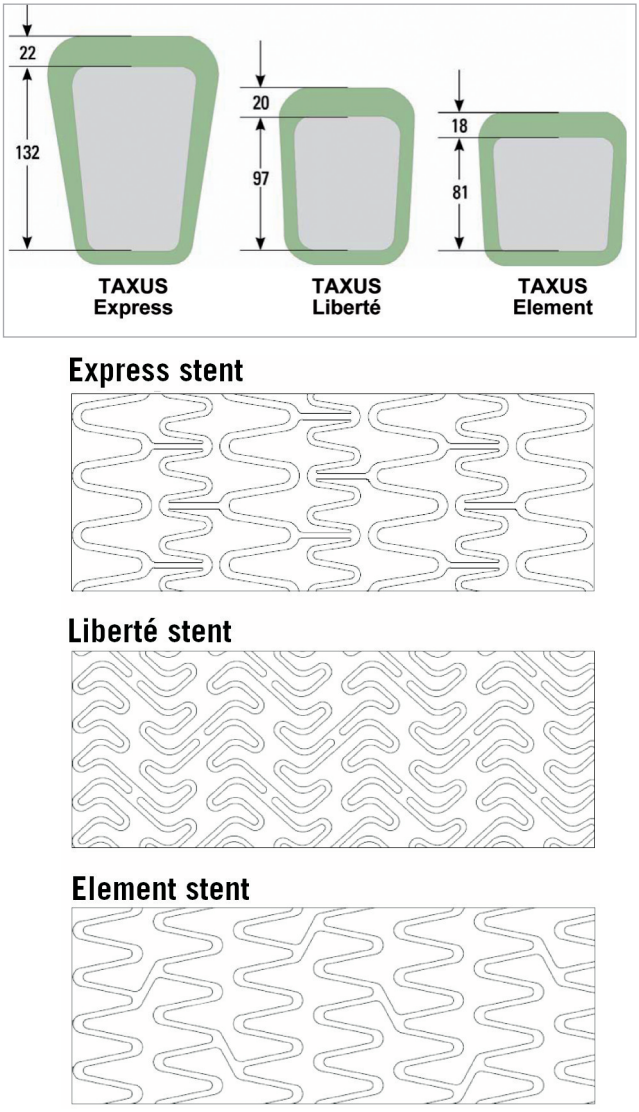


*Figure 1. Stent characteristics. TAXUS Element stent architecture (A) and strut/polymer thickness (in microns) (B), in comparison with previous-generation PES (Reprinted with Permission from Trials[7]).*

## Methods

### Study design

The PERSEUS SV study design has been described previously.[7] Briefly, PERSEUS SV is a prospective, single-arm, open-label trial. Eligible subjects with single, native vessel, *de novo* coronary atherosclerotic lesions of ≥50% to <100% diameter stenosis and ≤20 mm length with reference vessel diameter ≥2.25 to <2.75 mm were eligible for enrolment at 28 United States sites between July 13, 2007 and August 27, 2008.[7] All subjects were required to undergo follow-up angiography at nine months post-enrolment and clinical follow-up at 30 days, nine months, 12 months, 18 months, and annually to five years.

The primary endpoint of nine-month in-stent late loss by quantitative coronary angiography (QCA) is designed to assess superiority of TAXUS Element compared with a historical bare metal (Express) stent control. The historical control is comprised of 125 intent-to-treat Express BMS subjects (108 of whom have nine-month QCA follow-up) with target vessel diameter ≥2.25 to <2.75 mm and target lesion length ≤20 mm who were previously enrolled into the TAXUS V *de novo* study between March 7, 2003 and March 5, 2004.[3] The secondary endpoint of 12-month target lesion failure (TLF) compares the TAXUS Element to a pre-specified performance goal (see statistical methods below). TLF is defined as any ischaemia-driven revascularisation of the target lesion (TLR), myocardial infarction (MI) related to the target vessel, or cardiac death related to the target vessel.

Planned use of multiple stents within the target lesion was prohibited, and BMS patients from TAXUS V who had received planned multiple stent deployment during the TAXUS V index procedure were excluded from the PERSEUS historical BMS control group. Additional study stent deployment in the target lesion was allowed only when required for "bailout" indications. Treatment of one lesion in a non-target vessel during the index procedure was allowed prior to treatment of the target lesion, provided that non-target lesion treatment was successful angiographically and did not require additional unplanned stents. Per protocol, the non-target vessel lesion must have been treated with a commercially available TAXUS stent, if

*(1) The TAXUS Element stent will be commercialised as the ION Stent in the United States.*

use of a drug-eluting stent was required (use of an approved BMS or balloon angioplasty were also allowed). Staged PCI procedures or subsequent planned coronary artery bypass graft surgery were not allowed. Myocardial infarction within 72 hours prior to the index PCI procedure was an exclusion criteria for enrolment. Other PERSEUS SV inclusion and exclusion criteria have been reported.[7]

Thienopyridine treatment was required per protocol for at least six months and preferably up to 12 months in subjects not at high risk of bleeding, consistent with the ACC/AHA/SCAI Science Advisory for Percutaneous Coronary Intervention.[10] Aspirin therapy was required indefinitely.

The PERSEUS SV study protocol was approved by all participating ethics review committees and all patients provided written informed consent. An independent clinical events committee adjudicated all reported stent thromboses as well as major adverse cardiac events (MACE) and all angiographic studies were analysed by a central core laboratory (CardioVascular Institute at Beth Israel Deaconess Medical Center, Boston, MA, USA) using qualitative morphologic criteria similar to those used in the TAXUS Express and TAXUS Liberté clinical trials.[4] Both the clinical events committee and angiographic core laboratory were blinded to stent type. An independent data monitoring committee provided oversight of aggregate safety data. Additional PERSEUS study organisation and oversight committee membership have been reported.[7] The PERSEUS SV study is registered on the National Institute of Heath website (www.clinicaltrials.gov) as identifier NCT00489541.

## Statistical methods

A two-sided t-test was used to determine if in-stent late loss at nine months was significantly less in the TAXUS Element group compared to the historical BMS control. For the secondary endpoint, the normal approximation to a 1-sided, single sample binomial test was used to compare the observed 12-month TLF rate in the TAXUS Element group to a pre-specified performance goal of 19.5%, which was based on the 12-month TLF rate from TAXUS Express-treated patients in the TAXUS IV and V clinical studies (approximately 13%) plus a 6.5% margin (preserving approximately half of the observed treatment difference between PES and BMS outcomes in those studies). The performance goal was utilised to provide a comparison between TAXUS Element and TAXUS Express PES outcomes, since a US Food and Drug Administration approved small vessel PES was not commercially available to be used as a comparator at the time of study inception.

Because a non-randomised historical control group was employed, propensity adjustment was performed to correct for differences in baseline characteristics. The propensity score for each patient was estimated using a logistic regression model, with all covariates included as predictors and the treatment as the outcome. Covariates are listed in Online Appendix A. An analysis of covariance (ANCOVA) model was used to compare in-stent late loss (the primary endpoint) between intent-to-treat groups after adjusting for propensity score using a two-sided *P* value. For additional clinical and angiographic outcomes, the entire study analysis set was divided into propensity score quintiles (five equal-size subclasses). Comparisons of the primary and pre-specified endpoints stratified by propensity score subclass were then carried out. SAS System Version 8.2 software or higher (SAS Institute Inc., Cary, NC, USA) was used to develop the model.

Analyses were performed using data pooled across different clinical sites as described in the Online Appendix B.

## Results

A total of 349 patients (125 historical BMS and 224 TAXUS Element) were included in the intent-to-treat analysis set, with 97.4% complete clinical follow-up and 87.4% complete angiographic follow-up (Figure 2).

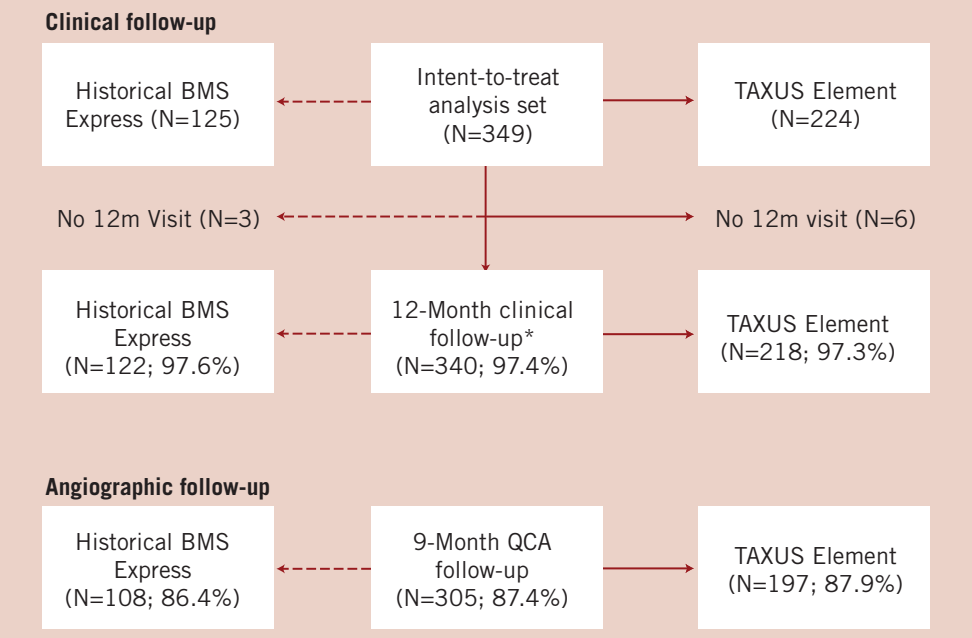


*Figure 2. PERSEUS small vessel study flow. Patients included in the PERSEUS SV clinical and angiographic analysis. *Includes two BMS Express patients and three TAXUS Element patients who died prior to the 12-month follow-up visit.*

Baseline differences between treatment groups included a more frequent history of congestive heart failure and a less frequent history of unstable angina or current smoking among TAXUS Element patients (Table 1). The TAXUS Element cohort had more severe % diameter stenosis, shorter lesion length, and smaller RVD than the BMS-treated group. However, ACC/AHA B2/C lesions and tortuosity were more frequent in the BMS control.

Periprocedural platelet GPIIb/IIIa inhibitors were more frequently administered in the BMS versus TAXUS Element groups (35.2% vs. 13.8% respectively; *P*<0.001). Both periprocedural and discharge treatment with aspirin and/or clopidogrel were similar between BMS and TAXUS Element groups as was the administration of statin therapy at hospital discharge. Technical success (successful delivery and deployment of the study stent without balloon rupture or stent embolisation) was comparable between treatment groups (Table 2). Deployment balloon withdrawal resistance was not observed in the TAXUS Element group. There were no stent fractures[11] observed by the angiographic core laboratory in TAXUS Element treated patients. Stent fractures were not assessed in the TAXUS V historical control group.

Although the planned use of multiple stents was prohibited in both treatment arms, multiple stents were implanted for bailout purposes in 8.0% (10/125) of the historical BMS group and 8.0% (18/224) of the TAXUS Element group.

Although aspirin compliance at one year was similar between treatment groups (98.3% BMS control versus 96.7% TAXUS Element; *P*=0.50), thienopyridine compliance was more frequent in TAXUS Element (93.5%) compared with the Express BMS historical control (65.0%, *P*<0.001). Based on guidelines at the time of

**Table 1. Baseline patient demographics and lesion characteristics.**

| | Historical BMS control (N=125) | TAXUS Element (N=224) | *P* value |
|---|---|---|---|
| Demographics, cardiac history, and risk factors | | | |
| Age, years | 64.2±10.9 (125) | 64.7±10.3 (224) | 0.64 |
| Male | 60.8 (76/125) | 63.8 (143/224) | 0.57 |
| Stable angina | 56.0 (70/125) | 60.7 (136/224) | 0.39 |
| Unstable angina | 29.6 (37/125) | 20.1 (45/224) | 0.04 |
| Silent ischaemia | 15.3 (18/118) | 19.2 (43/224) | 0.37 |
| Ejection fraction | 55.0±9.2 (123) | 57.9±9.4 (223) | 0.006 |
| Prior percutaneous intervention | 33.9 (42/124) | 41.3 (92/223) | 0.18 |
| Prior coronary artery bypass graft | 19.5 (24/123) | 18.4 (41/223) | 0.80 |
| Prior myocardial infarction | 29.0 (36/124) | 25.8 (57/221) | 0.52 |
| Prior congestive heart failure | 2.4 (3/124) | 8.1 (18/222) | 0.03 |
| Smoker (current) | 22.2 (26/117) | 13.6 (30/220) | 0.04 |
| Caucasian race | 92.0 (115/125) | 91.1 (204/224) | 0.77 |
| Medically treated diabetes | 32.0 (40/125) | 36.6 (82/224) | 0.39 |
| Insulin requiring | 12.0 (15/125) | 16.5 (37/224) | 0.26 |
| Hyperlipidaemia* | 77.6 (97/125) | 85.7 (191/223) | 0.06 |
| Hypertension* | 80.0 (100/125) | 80.8 (181/224) | 0.86 |
| Target lesion characteristics by QCA | | | |
| LAD target vessel | 42.4 (53/125) | 37.9 (85/224) | 0.41 |
| LCx target vessel | 36.0 (45/125) | 41.5 (93/224) | 0.31 |
| RCA target vessel | 21.6 (27/125) | 20.5 (46/224) | 0.81 |
| Reference vessel diameter | 2.19±0.35 (125) | 2.08±0.28 (224) | <0.001 |
| Minimum lumen diameter | 0.62±0.24 (125) | 0.55±0.23 (224) | 0.007 |
| % Diameter stenosis | 71.5±10.4 (125) | 73.5±10.2 (224) | 0.08 |
| Target lesion length, mm | 12.9±5.1 (125) | 11.7±5.1 (224) | 0.04 |
| Modified ACC/AHA B2 or C | 77.6 (97/125) | 58.0 (130/224) | <0.001 |
| Tortuosity (moderate or severe) | 18.4 (23/125) | 8.9 (20/224) | 0.01 |
| Calcification (moderate or severe) | 20.8 (26/125) | 13.4 (30/224) | 0.07 |

Numbers are % (n/N) or mean±standard deviation (n); * History of hypertension/ hyperlipidaemia requiring medication; ACC/AHA: American College of Cardiology/ American Heart Association; LAD: left anterior descending artery; QCA: quantitative coronary angiography

**Table 2. Technical and procedural performance.**

| Stent-based technical performance in all attempted study stents (per stent) | Historical BMS Control (N=125 patients, 137 stents) | TAXUS Element (N=224 patients, 241 stents) | *P* value |
|---|---|---|---|
| Technical success (per stent)* | 99.3 (136/137) | 99.6 (240/241) | >0.99 |
| Technical failure (per stent) | 0.7 (1/137) | 0.4 (1/241) | >0.99 |
| Unable to cross lesion | 0.7 (1/137) | 0.4 (1/241) | >0.99 |
| Balloon rupture | 0.0 (0/137) | 0.0 (0/241) | – |
| Stent embolisation | 0.0 (0/137) | 0.0 (0/241) | – |
| Other | 0.0 (0/137) | 0.0 (0/241) | – |
| Withdrawal resistance | unknown¶ | 0.0 (0/240) | – |
| Other delivery system failure | 0.0 (0/136) | 0.0 (0/240) | – |
| **Clinical procedural performance (per patient)** | **Historical BMS Control (N=125)** | **TAXUS Element (N=224)** | ***P* value** |
| Clinical procedural success‡ | 97.6 (122/125) | 99.6 (223/224) | 0.13 |
| Clinical procedural failure | 2.4 (3/125) | 0.4 (1/224) | 0.13 |
| In-hospital MACE | 1.6 (2/125) | 0.0 (0/224) | 0.13 |
| Post-procedure % diameter Stenosis ±30% | 0.0 (0/125) | 0.0 (0/224) | – |
| Post-procedure TIMI <3 | 0.8 (1/125) | 0.4 (1/224) | >0.99 |
| Post-procedure outcomes | | | |
| Post-procedure MLD (QCA), mm | | | |
| Analysis segment | 1.76±0.38 (108) | 1.70±0.29 (197) | 0.18 |
| In-stent | 2.09±0.30 (108) | 2.11±0.21 (197) | 0.50 |
| Acute gain (QCA), mm | | | |
| Analysis segment | 1.14±0.39 (108) | 1.16±0.30 (197) | 0.55 |
| In-stent | 1.47±0.33 (108) | 1.57±0.27 (197) | 0.007 |

Numbers are % (n/N) or mean±standard deviation (n); * Technical success is defined as successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolisation; ¶ Information not collected; ‡ Mean lesion diameter stenosis <30% in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of in-hospital MACE; BMS: bare metal stent; MACE: major adverse cardiac events (target-vessel related MI, Cardiac Death, or TVR); MLD: minimum lumen diameter; QCA: quantitative coronary angiography; TIMI: thrombolysis in myocardial infarction

subject enrolment, the TAXUS V protocol mandated only six months of thienopyridine use.

In-stent late loss by QCA at nine months, the study primary endpoint, was significantly reduced by TAXUS Element compared with the Express BMS control (Figure 3A). The superiority of TAXUS Element (versus bare metal Express) was maintained after propensity adjustment for differences in baseline clinical and angiographic characteristics between the two non-randomised treatment groups (Figure 3B). The key secondary endpoint of 12-month TLF was significantly lower in the TAXUS Element cohort when compared to the pre-specified 19.5% performance goal (Figure 3C). Cumulative frequency of TLF to 12 months versus the BMS control group is shown in Figure 4. Following propensity adjustment, TLF was significantly reduced in the TAXUS Element group compared to the historical BMS control group (Table 3). Significant predictors of increased TLF to 12 months by multivariate analysis included LAD target lesion and non-Caucasian race (Online Appendix C).

Additional unadjusted and propensity adjusted clinical outcomes (12 months) are shown in Table 3 and angiographic outcomes (nine

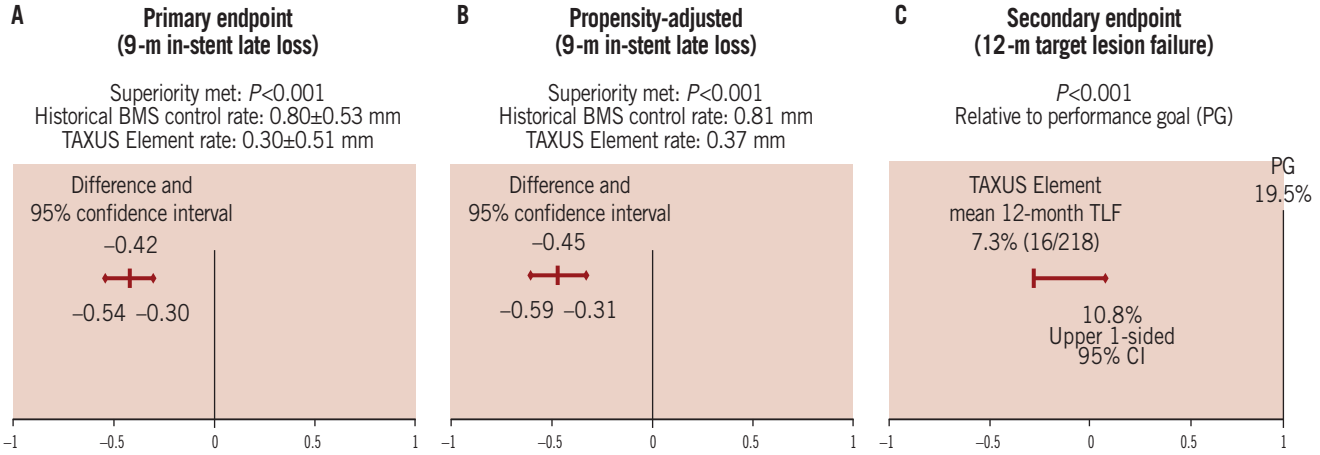


*Figure 3. PERSEUS SV primary and secondary endpoints and propensity adjustment. (A) PERSEUS SV primary endpoint was met: unadjusted nine-month in-stent late loss was significantly lower (P<0.001) in the TAXUS Element group than in the historical BMS control group. (B) Propensity-adjusted nine-month in-stent late loss using an analysis of covariance (ANCOVA) model to compare the nine-month in-stent late loss between the treatment groups based on the intent-to-treat analysis set after adjusting for the propensity score using a 2-sided P value. (C) PERSEUS SV secondary endpoint was met: the unadjusted 12-month TLF rate in the TAXUS Element group was significantly lower (P<0.001) than the pre-specified performance goal of 19.5%.*

**Table 3. Clinical outcomes at 12 months.**

| | Unadjusted results | | | Propensity adjusted results | | |
|---|---|---|---|---|---|---|
| | Historical BMS control (N=125) | TAXUS Element (N=224) | *P* value | Historical BMS control (N=125) | TAXUS Element (N=224) | *P* value |
| TLF* | 22.3 (27/121) | 7.3 (16/218) | <0.001 | 20.5 | 6.6 | 0.01 |
| MACE¶ | 27.3 (33/121) | 12.4 (27/218) | <0.001 | 30.4 | 10.5 | 0.002 |
| Cardiac death or MI | 3.3 (4/121) | 2.3 (5/218) | 0.73 | 2.9 | 2.5 | 0.83 |
| Cardiac death | 0.8 (1/121) | 1.4 (3/218) | >0.99 | 0.4 | 1.8 | 0.26 |
| MI‡ | 2.5 (3/121) | 0.9 (2/218) | 0.35 | 2.5 | 0.6 | 0.26 |
| Q-wave MI | 0.0 (0/121) | 0.5 (1/218) | >0.99 | 0.0 | 0.3 | 0.31 |
| Non-Q-wave MI§ | 2.5 (3/121) | 0.5 (1/218) | 0.13 | 2.5 | 0.3 | 0.18 |
| TVR, overall | 24.8 (30/121) | 11.5 (25/218) | 0.001 | 28.1 | 8.9 | 0.002 |
| TLR | 20.7 (25/121) | 6.0 (13/218) | <0.001 | 19.7 | 4.7 | 0.006 |
| Non-TLR | 7.4 (9/121) | 7.8 (17/218) | 0.91 | 10.6 | 6.0 | 0.35 |
| All-cause mortality | 1.7 (2/121) | 1.4 (3/218) | >0.99 | 1.0 | 1.8 | 0.56 |
| Stent thrombosis‖ | 0.8 (1/119) | 0.5 (1/215) | >0.99 | 0.6 | 0.3 | 0.65 |

Numbers are % (n/N). Propensity adjustment by logistic regression model; * TLF is defined as any ischaemia-driven revascularisation of the target lesion (TLR), myocardial infarction (MI) related to the target vessel, or cardiac death related to the target vessel; ¶MACE (major adverse cardiac events) is defined MI, TVR, or cardiac death; ‡Myocardial infarction is defined as Q-wave MI (*de novo* Q-waves in 2 or more leads lasting ≥0.04 seconds, with elevated CK-MB) or non-Q-wave MI (*de novo* elevation of CK >2.0x upper limit of normal without new Q-waves, or positive CK-MB); § Non-Q-wave MI timing: Events occurred at days 0, 8, and 187 post-procedure in the historical BMS control group and at day 218 post-procedure in the TAXUS Element group; ‖Stent thrombosis was adjudicated by the CEC according to the Academic Research Consortium (ARC) definite/probable definition12 and does not exclude events occurring before or after TLRs. Stent thrombosis occurred between 2 and 30 days in the historical BMS group and between 31 and 365 days in the TAXUS Element Group; ARC: Academic Research Consortium; MI: myocardial infarction; TLF: target vessel failure; TLR: target lesion revascularisation; TVR: target vessel revascularisation

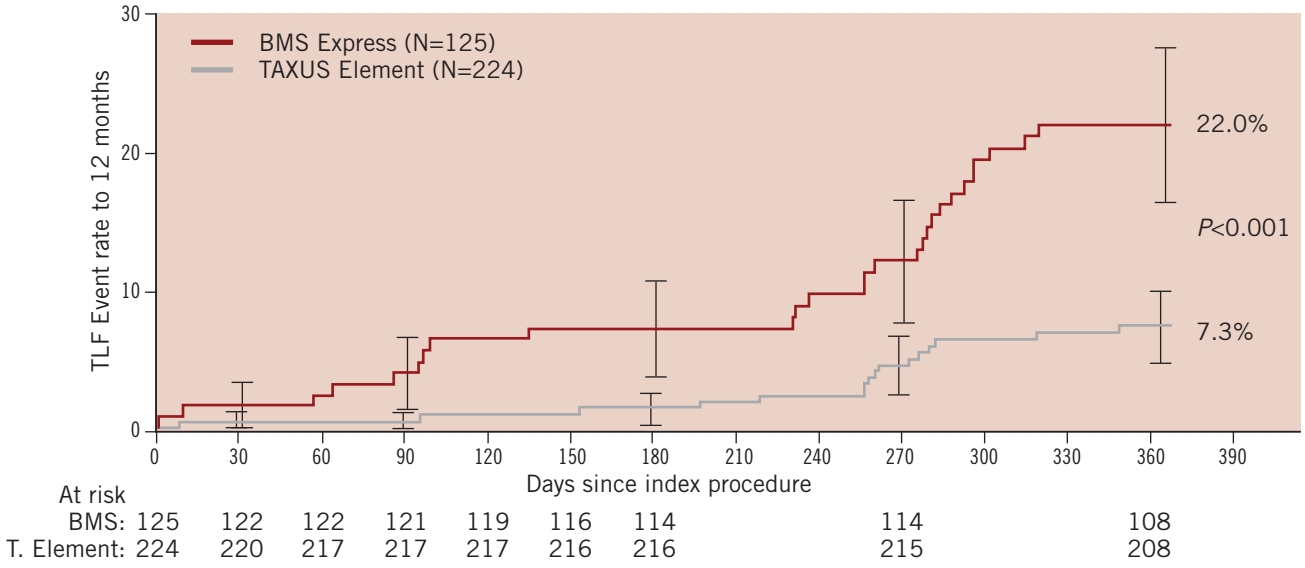


*Figure 4. Target lesion failure to 12 months, unadjusted outcomes. Cumulative rate of target lesion failure to 12 months, event rate ±1.5 standard error, all intent-to-treat patients (N=349).*

months) are shown in Table 4. Compared with the historical BMS control, TAXUS Element-treated patients had a significant reduction in MACE, primarily driven by less frequent TLR, which was accompanied by reductions in angiographic measures of restenosis. The relative improvement in outcomes following TAXUS Element deployment was maintained after propensity adjustment. Predictors of increased in-stent late loss at nine months by multivariate analysis included hyperlipidaemia requiring medication, smaller baseline RVD, and longer target lesion length (Online Appendix C).

Non-Q-wave MI was numerically less frequent in the TAXUS Element group. A single stent thrombosis (Academic Research Consortium [ARC] definitions)[12] event was observed in each treatment arm (subacute thrombosis [eight days post-index procedure] in the historical BMS arm and late stent thrombosis [152 days post-index procedure] in the TAXUS Element arm).

## Discussion

The TAXUS PERSEUS SV study was designed to evaluate the relative efficacy of the TAXUS Element PES when compared with a historical Express BMS treated control. The principal finding of this study was that TAXUS Element is superior to Express BMS with respect to late lumen loss in-stent as measured by QCA nine

**Table 4. QCA outcomes at nine months (paired lesion analyses).**

| | Unadjusted results | | | Adjusted results* | | |
|---|---|---|---|---|---|---|
| | Historical BMS control (N=108) | TAXUS Element (N=197) | *P* value | Historical BMS control (N=108) | TAXUS Element (N=197) | *P* value |
| Minimum lumen diameter, mm | | | | | | |
| Analysis segment* | 1.22±0.50 (108) | 1.50±0.48 (197) | <0.001 | 1.19 | 1.52 | <0.001 |
| In-stent | 1.29±0.55 (108) | 1.73±0.53 (197) | <0.001 | 1.28 | 1.76 | <0.001 |
| % Diameter stenosis | | | | | | |
| Analysis segment¶ | 43.85±21.44 (108) | 29.82±19.82 (197) | <0.001 | 44.25 | 29.81 | <0.001 |
| In-stent | 40.72±23.64 (108) | 18.48±23.31 (197) | <0.001 | 40.03 | 18.59 | <0.001 |
| Binary restenosis, % | | | <0.001 | | | |
| Analysis segment¶ | 38.0 (41/108) | 13.7 (27/197) | <0.001 | 39.8 | 13.8 | <0.001 |
| In-stent | 34.3 (37/108) | 11.7 (23/197) | <0.001 | 32.4 | 11.9 | 0.002 |
| In-stent restenosis characteristics§ | | | | | | |
| Focal | 18.9 (7/37) | 52.2 (12/23) | 0.007 | Propensity adjustment not conducted due to small sample size | | |
| Diffuse | 48.6 (18/37) | 21.7 (5/23) | 0.04 | | | |
| Proliferative | 27.0 (10/37) | 8.7 (2/23) | 0.11 | | | |
| Total occlusion | 5.4 (2/37) | 17.4 (4/23) | 0.19 | | | |
| ISR length, mm | 14.4±5.8 (36) | 12.0±6.9 (23) | 0.14 | | | |

Numbers are % (n/N) or mean±standard deviation (n); *Logistic regression model; ¶The analysis segment consists of the proximal edge, the stent, and the distal edge, where each edge segment contains up to 5 mm immediately outside the stent; §Among patients with in-stent restenosis; BMS: bare metal stent; ISR: in-stent restenosis; QCA: quantitative coronary angiography

months following stent deployment. The relative benefit of TAXUS Element (for reduction in late loss) remains superior to Express BMS even after propensity adjustment for 28 clinical and angiographic variables. Similarly, clinical endpoints reflective of restenosis including TLF and MACE were also significantly reduced following TAXUS Element (versus Express BMS) after propensity adjustment. The secondary endpoint, 12-month TLF, was lower (7.3%, $P<0.001$) compared with a pre-specified performance goal (19.5%) derived from a historical cohort of paclitaxel-eluting TAXUS Express-treated patients.

Furthermore, no safety concerns were observed with respect to the occurrence of death (cardiac or all-cause), MI, or stent thrombosis through 1-year follow-up. Although risk for stent thrombosis may be increased following small vessel stenting, the low incidence of propensity-adjusted or unadjusted definite or probable stent thrombosis (ARC definition)[12] observed following TAXUS Element PES deployment in the present study (0.3%) is noteworthy. Finally, although no stent strut fractures were observed by QCA following TAXUS Element treatment, neither intravascular ultrasound nor optical coherence tomography (more sensitive techniques for detection) were performed.

Although the PERSEUS SV trial demonstrates reduced revascularisation rates following the TAXUS Element compared to the Express stent, the relative impact of strut thickness (81 µm versus 132 µm respectively) when comparing the PES to a BMS cannot be determined.

## Study limitations

A limitation of PERSEUS SV is that the TAXUS Element PES is compared with a non-randomised Express BMS historical control group as there were no commercially available small vessel PES in the US at the time of study inception. After the completion of PERSEUS SV enrolment, two dedicated small vessel PES (TAXUS Express Atom and TAXUS Liberté Atom) were approved for use by the US Food and Drug Administration.[3,5] Although propensity score adjustment was performed using both clinical and angiographic variables, unmeasured covariate imbalance may still confound the conclusions drawn. Furthermore, practice patterns and adjunctive pharmacotherapies (including statin use, oral clopidogrel loading, and compliance with dual antiplatelet therapy) may differ between the study time frames analysed (TAXUS V versus PERSEUS SV) and may not be accounted for.

While caution must be exercised when comparing results across separate studies, the outcomes observed from the PERSEUS SV TAXUS Element cohort appear favourable in the context of previously published event rates following deployment of either the TAXUS Express or TAXUS Liberté PES in small calibre vessels.[3,5]

In addition, in lieu of a prospective PES comparator for PERSEUS SV, we performed a post-hoc patient-level analysis of 12-month clinical and angiographic outcomes from 555 TAXUS Liberté and 437 TAXUS Element treated subjects with baseline RVD <3.0 mm from the TAXUS ATLAS[5,13] and PERSEUS trials (including both PERSEUS SV and PERSEUS Workhorse studies[14]) respectively and used multivariable regression to adjust for baseline differences between these non-randomised groups. TAXUS Element subjects had numerically less frequent TLR (5.7% versus 7.9 TAXUS Liberté, $P=0.39$), and significantly fewer non-Q-wave MI events (0.6% versus 1.9% TAXUS Liberté, $P=0.03$), suggesting improvement in clinical outcomes following TAXUS Element deployment (unpublished results). Furthermore, PERSEUS SV demonstrated a reduction in 12-month TLF following TAXUS Element treatment compared to a performance goal based on TAXUS Express PES outcomes. Although these observations suggest that the TAXUS Element PES may be associated with improved clinical outcomes (reduction in revascularisation and non-Q-wave MI) in small calibre vessels when compared to past generation PES, an adequately powered, randomised trial would be required to prove this hypothesis.

## Conclusions

The PERSEUS SV study supports the efficacy and safety of the novel thin-strut, platinum chromium TAXUS Element stent when compared to the Express BMS in small calibre coronary vessels. Further studies are required to determine the relative advantages provided by this novel stent design when compared to more contemporary PES following deployment in small calibre vessels and more complex lesions.

## Acknowledgements

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## Conflict of interest

Dr. Cannon serves on the Advisory Board or Speakers Bureau for Medtronic, Abbott, Boston Scientific, and holds equity in Boston Scientific, Medtronic, and BioStar Ventures. Dr. Kereiakes received research grants from Boston Scientific, Cordis, Medtronic, and Abbott Vascular, and serves on the Advisory Boards for Boston Scientific and Abbott Vascular. Dr. Popma has received personal and institutional research grants from Cordis Corporation, and institutional research grants from Boston Scientific and Abbott Vascular. Dr. Mooney serves on the Medical Advisory Boards for Medtronic, Boston Scientific, and Cordis and has received research grants (institutional) and honoraria from Medivance. Dr. Mishkel serves on the Medical Advisory Board for Boston Scientific, has received honoraria from Boston Scientific, and has received travel funds for Boston Scientific Advisory Board meetings. Dr. Lee serves as a consultant to and has received grants, travel funds, and honoraria from Boston Scientific. Dr. Wilson serves as a consultant to Boston Scientific and serves on the Speaker's Bureau for Medtronic. Dr. Stuckey serves on the Medical Advisory Board and Speaker's Bureau for Boston Scientific, and has received travel funds for educational presentations. Dr. Ring serves on the Advisory Boards for Boston Scientific and Abbott Vascular. Dr. Kellett has received research grant support from Boston Scientific.

Dr. Underwood and Dr. Dawkins are full-time employees and stockholders of Boston Scientific Corporation. Drs. Orlow, Mann, and McGarry report no financial conflicts of interest. The PERSEUS Small Vessel study is funded by Boston Scientific Corporation, Natick, MA.

## References

1. Akiyama T, Moussa I, Reimers B, Ferraro M, Kobayashi Y, Blengino S, Di Francesco L, Finci L, Di Mario C, Colombo A. Angiographic and clinical outcome following coronary stenting of small vessels: a comparison with coronary stenting of large vessels. *J Am Coll Cardiol.* 1998;32:1610-8.

2. Kereiakes DJ. Coronary small-vessel stenting in the era of drug elution. *Rev Cardiovasc Med.* 2004;5 Suppl 2:S34-45.

3. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA.* 2005;294:1215-23.

4. Ellis SG, Stone GW, Cox DA, Hermiller J, O'Shaughnessy C, Mann T, Turco M, Caputo R, Bergin PJ, Bowman TS, Baim DS. Long-Term Safety and Efficacy With Paclitaxel-Eluting Stents: 5-Year Final Results of the TAXUS IV Clinical Trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). *J Am Coll Cardiol Intv.* 2009;2:1248-59.

5. Turco MA, Ormiston JA, Popma JJ, Hall JJ, Mann T, Cannon LA, Webster MWI, Mishkel GJ, O'Shaughnessy CD, McGarry TF, Mandinov L, Dawkins KD, Baim DS. Reduced Risk of Restenosis in Small Vessels and Reduced Risk of Myocardial Infarction in Long Lesions With the New Thin-Strut TAXUS Liberté Stent: 1-Year Results From the TAXUS ATLAS Program. *J Am Coll Cardiol Intv.* 2008;1:699-709.

6. O'Brien BJ, Stinson JS, Larsen SR, Eppihimer MJ, Carroll WM. A platinum-chromium steel for cardiovascular stents. *Biomaterials.* 2010;31:3755-61.

7. Allocco DJ, Cannon LA, Britt A, Heil JE, Nersesov A, Wehrenberg S, Dawkins KD, Kereiakes DJ. A prospective evaluation of the safety and efficacy of the TAXUS Element paclitaxel-eluting coronary stent system for the treatment of de novo coronary artery lesions: Design and statistical methods of the PERSEUS clinical program. *Trials.* 2010;11:1.

8. Wilson GJ, Huibregtse BA, Stejskal EA, Crary J, Starzyk RM, Dawkins KD, Barry JJ. Vascular Response to a Third Generation Everolimus-Eluting Stent. *EuroIntervention.* 2010;6:512-519.

9. Soucy NV, Feygin JM, Tunstall R, Casey MA, Pennington DE, Huibregtse BA, Barry JJ. Strut tissue coverage and endothelial cell coverage: a comparison between bare metal stent platforms and platinum chromium stents with and without everolimus-eluting coating. *EuroIntervention.* 2010;6:630-637.

10. King SB, 3rd, Smith SC, Jr., Hirshfeld JW, Jr., Jacobs AK, Morrison DA, Williams DO, Feldman TE, Kern MJ, O'Neill WW, Schaff HV, Whitlow PL, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. *Circulation.* 2008;117:261-95.

11. Nakazawa G, Finn AV, Vorpahl M, Ladich E, Kutys R, Balazs I, Kolodgie FD, Virmani R. Incidence and predictors of drug-eluting stent fracture in human coronary artery a pathologic analysis. *J Am Coll Cardiol.* 2009;54:1924-31.

12. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

13. Turco MA, Ormiston JA, Popma JJ, Mandinov L, O'Shaughnessy CD, Mann T, McGarry TF, Wu CJ, Chan C, Webster MW, Hall JJ, Mishkel GJ, Cannon LA, Baim DS, Koglin J. Polymer-based, paclitaxel-eluting TAXUS Liberte stent in de novo lesions: The Pivotal TAXUS ATLAS Trial. *J Am Coll Cardiol.* 2007;49:1676-83.

14. Kereiakes DJ, Cannon LA, Feldman RL, Magorien R, Whitbourn R, Dauber IM, Rabinowitz AC, Ball MW, Bertolet B, Kabour A, Foster MC, Wang JC, Underwood P, Dawkins KD. Clinical and Angiographic Outcomes After Treatment of de novo Coronary Stenoses with a Novel Platinum Chromium Thin-Strut Stent: Primary Results of the PERSEUS (Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System) Trial. *J Am Coll Cardiol.* 2010;56:264-71.

## Appendix A. Propensity adjustment – PERSEUS SV

**Variables included in PERSEUS SV propensity adjustment.**

| | |
|---|---|
| Demographics | Gender, age, race (Caucasian vs non-Caucasian) |
| CAD risk factors and medical history | Previous CABG, previous PCI, previous MI, medication for hyperlipidemia, medication for hypertension, congestive heart failure, peripheral vascular disease, angina class 3/4, arrhythmia, previous TIA or CVA, medically treated diabetes, current smoking at baseline, LVEF |
| QCA Baseline measurements | Coronary artery location (LAD), pre-procedure reference vessel diameter (RVD), lesion length, pre-procedure percent diameter stenosis, pre-procedure minimum lumen diameter (MLD), calcification, bend, vessel tortuosity, American College of Cardiology/American Heart Association classification (B2 or C), thrombus, aneurysmal appearance |
| Peri-procedural medication use | GPIIb/IIIa inhibitor use. |

## Appendix B. Pooling analysis

Poolability across sites was assessed for the primary endpoint both for (1) the sites that enrolled patients in PERSEUS SV (i.e., TAXUS Element group) alone and (2) the sites with patients both in the historical control and PERSEUS SV (i.e., common sites). Poolability was also assessed for PERSEUS SV sites for the secondary endpoint. In the assessment of all PERSEUS SV sites, Analysis of Variance (ANOVA) with site as the main effect indicated a significant site effect on in-stent late loss ($P$=0.003); Fisher exact test with Monte Carlo estimation did not show a significant site effect on 12-month TLF ($P$=0.45). Investigation into the site effect on late loss yielded 2 influential sites and patients with potential outlier values. Assessment of poolability with the potential outlier values (N=7) removed resulted a loss of the significant site effect, i.e., no site effect ($P$=0.12), and assessment of poolability with the two influential sites removed also showed no site effect ($P$=0.16). The analysis of poolability across common sites, including 152 patients, showed a significant site-by-treatment interaction for in-stent late loss ($P$=0.003). Exploration in to the site-by-treatment interaction identified one site with results that were divergent from all other sites. Assessment of poolability across common sites with this one influential site removed (N=146) resulted in no significant site-by-treatment interaction ($P$=0.14).

Superiority analysis of the primary endpoint (1) excluding the TAXUS Element potential outliers (N=7), (2) excluding the two influential PERSEUS SV sites, and (3) removing the one influential common site all produced results consistent with those reported below (which *do not* exclude any outliers), supporting the robustness of the primary analysis and conclusion of superiority.

## Appendix C. Multivariate modeling – PERSEUS SV

Univariate and multivariate analyses were performed to assess the effect of possible predictors on the primary and secondary endpoints of 9-month in-stent late loss and 12-month TLF. All possible predictors were modeled univariately on each outcome, as well as multivariately using a stepwise procedure in an appropriate regression model. The significance level thresholds for entry and exit of independent variables were set at 0.10.

Variables considered:

**Variables included in PERSEUS SV univariate and multivariate modeling.**

| | |
|---|---|
| Demographics | Gender, age, race (Caucasian vs non-Caucasian) |
| Baseline characteristics | Previous CABG, prior PCI, hyperlipidemia requiring medication, previous MI, peripheral vascular disease, CCS class 3/4, arrhythmia, previous TIA or CVA, medically treated diabetes, hypertension requiring medication, current smoking at baseline, LVEF |
| Angiographic lesion characteristics | Target lesion location in LAD, lesion length, calcification, thrombus, moderate/severe vessel tortuosity, lesion angulation, aneurysmal appearance |
| Quantitative angiographic variables | RVD, MLD (pre- and post-procedure*), maximum balloon-to-artery ratio |
| Periprocedural variables | Use of unplanned stents, total number of lesions treated during the procedure, 1 versus 2 vessel treatment, GPIIb/IIIa inhibitor use, Clinical procedural success (ignoring in-hospital MACE)** |

*MLD post-procedure was not included in the models for late loss because MLD post-procedure is a part of calculation for late loss; **Mean post-stent lesion diameter stenosis <30% in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician

Outcomes. Multivariate predictors are shown below.

**Multivariate analysis of predictors of 9-month in-stent late loss, All TAXUS Element patients (N=224).**

| Variable | Coefficient | Standard error | t-Statistic | *P* value |
|---|---|---|---|---|
| Non-caucasian race | –0.35 | 0.12 | –2.94 | 0.004 |
| Hyperlipidemia requiring medication | 0.24 | 0.10 | 2.40 | 0.02 |
| Baseline RVD | –0.27 | 0.13 | –2.12 | 0.04 |
| Lesion length (mm) | 0.01 | 0.01 | 1.93 | 0.05 |

**Multivariate analysis of predictors of 12-month TLF, All TAXUS Element patients (N=224).**

| Variable | Coefficient | Standard error | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|
| Coronary Artery Location (LAD) | 1.99 | 0.70 | 7.35 (1.86, 29.07) | 0.005 |
| Non-caucasian race | –1.59 | 0.77 | 0.20 (0.04, 0.93) | 0.04 |

## Appendix D. PERSEUS SV sites, principal investigators, and study coordinators

The authors wish to thank the following sites, investigators, and study coordinators for their contribution to the PERSEUS Small Vessel study. This research would not be possible without their efforts. Additional study committee membership has been published (Allocco et al., *Trials* 2010;11:1).

| Clinical site | City, state, country | Investigator | Current study coordinator(s) |
|---|---|---|---|
| Abbott Northwestern Hospital | Minneapolis, MN, USA | Mooney, Michael | Morgan, Jill |
| Bakersfield Memorial Hospital | Bakersfield, CA, USA | Lee, Tommy | Marsh, Jenny |
| Carolinas Medical Center | Charlotte, NC, USA | Wilson, Bryan | Schwarz, Gale |
| Christiana Hospital | Newark, DE, USA | Hopkins, James | Huntley, Jacqueline Jones, Sandra Laucirica, Jacqueline Veasey, Jennifer |
| Columbia University Medical Center | New York, NY, USA | Moses, Jeffrey | Hidalgo, Ariel |
| LeBauer Cardiovascular Research Foundation | Greensboro, NC, USA | Stuckey, Thomas | Gettinger, Debbie |
| Lenox Hill Hospital | New York,NY, USA | Cohen, Howard | Mathew, Staicy |
| Lutheran Hospital of Indiana | Fort Wayne, IN, USA | Orlow, Steven | Johnson, Jacqueline |
| Main Line Health Heart Center | Bryn Mawr, PA, USA | Pratsos, Antonis | Pensyl, Catherine |
| Maine Medical Center | Portland, ME, USA | Kellett, Mirle | Berg, Claire Burgess, Joanne Gallant, |
| Medical Center East | Birmingham, AL, USA | Foster, Robert | Jeannie Hall, Shelly Hall, Wanda |
| Mediquest Research at Munroe | Ocala, FL, USA | Feldman, Robert | Crouch, Elizabeth Grubbs, Rhonda Luby, |
| Regional Medical Center | | | Susan McIntyre, Deb |
| Methodist DeBakey Heart Center | Houston, TX, USA | Raizner, Albert | Joseph, Jane |
| Nebraska Heart Hospital | Lincoln, NE, USA | Martin, Steven | Godfrey, Corey Krenk, Susan |
| Northern Michigan Hospital | Petoskey, MI, USA | Cannon, Louis | Haderer, JoAnn LaLonde, Jennifer Witucki, Cindy |
| Oklahoma Foundation for Cardiovascular Research | Oklahoma City, OK, USA | McGarry, Thomas | Hanes, Stacie |
| Providence Sacred Heart Medical Center | Spokane, WA, USA | Ring, Michael | Degelia, Amber Fisher, Marian Meyer, Gae |
| Riverside Methodist Hospital | Columbus, OH, USA | Yakubov, Steven | Terry, Tammy |
| Sarasota Memorial Hospital | Sarasota, FL, USA | Yaryura, Ricardo | Bradley, Mary Miller, Amanda |
| Scripps Clinic | La Jolla, CA, USA | Teirstein, Paul | Tyler, MaryBeth Ernst, Alissa |
| St. John's Hospital | Springfield, IL, USA | Mishkel, Gregory | Harden, Michelle Hubbard, Paula |
| St. Joseph's Hospital Health Center | Liverpool, NY, USA | Caputo, Ronald | Riley, Jan |
| St. Mary's Medical Center | Huntington, WV, USA | Studeny, Mark | Marcum, Melissa Monway, Tammy |
| Swedish Medical Center | Seattle, WA, USA | Desai, Amish | Braam, Lauren |
| TexSan Heart Hospital | San Antonio, TX, USA | Rabinowitz, Abram | Addington, Jodie Jones, Rebecca |
| The Christ Hospital | Cincinnati, OH, USA | Kereiakes, Dean | Howard, Wendy |
| Wake Forest University School of Medicine | Winston-Salem, NC, USA | Kutcher, Michael | Young, Teresa |
| Wake Medical Center | Raleigh, NC, USA | Mann, Tift | Allen, Brittany Saylors, Elizabeth |