CARDIOLOGY Rounds®

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# Drug-eluting stents for the treatment of coronary artery disease Part 3: New results from clinical trials

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**Since the first reports of the success of drug-eluting stents for prevention of in-stent restenosis by Sousa et al and Rensing et al in 2001,[1,2] the implantation of drug-eluting stents has become the percutaneous treatment of choice for many coronary lesion subsets. The June/July and August/September 2002 issues of *Cardiology Rounds* presented Part 1 and Part 2 of a review of drug-eluting stents for the treatment of coronary artery disease. In Part 1 of this series, the discussion focused on the rationale behind the development of a stent with a bioactive coating and the early trials using paclitaxel-eluting coatings. Part 2 focused on rapamycin and other cytostatic and cytotoxic drugs that were undergoing clinical evaluation at that time. In the last year, there has been important new information provided by many multicentre clinical studies. Parts 3 and 4 of this series provide an update of the results of trials that were ongoing when Parts 1 and 2 were published last year and summarizes the new clinical data.**

## Clinical trials with sirolimus-eluting stents

Trials examining sirolimus, (rapamycin, Rapamune®) coated devices were among the first to provide concrete evidence that drug-eluting stents had the potential to prevent restenosis. Sirolimus is a natural macrocyclic lactone produced by *Streptomyces hygroscpicus* with potent antiproliferative, anti-inflammatory, and immunosuppressive effects. Because of its lipophilicity, sirolimus easily passes through cell membranes and binds to an intracellular binding protein (immunophilin) known as FK binding protein-12 (FKBP-12). The sirolimus/FKBP-12 complex inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory serine-threonine kinase. The inhibition of mTOR inhibits the translation of a family of mRNAs that code for proteins essential for cell cycle progression and induces the cyclin-dependent kinase inhibitor p27, ultimately causing cell cycle arrest.

### *First studies with the sirolimus-eluting stent*

Results of the first human implantations of sirolimus-eluting (Bx Velocity) stents, the first-in-man (FIM) clinical studies were reported by Sousa et al[1] and Rensing et al.[2] A total of 45 patients with symptomatic coronary artery disease and a single *de novo* lesion were included, 30 patients in São Paolo and 15 in Rotterdam. The study was designed to test the feasibility of implanting sirolimus-eluting Bx Velocity stents. Thirty patients received a slow-release device, while 15 were treated with fast-release stents. Planned endpoints included 1-month, 6-month, and 5-year assessment of major adverse cardiac events (MACE). Four month, 1-year, 2-year, and 4-year quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) analysis were also planned. The follow-up of 30 patients (15 slow-release and 15 fast-release) [1] and the 4-month follow-up of 30 patients[3] was reported by Sousa et al. There was minimal intimal hyperplasia in both groups as determined by:

- IVUS (0.3 ± 0.6 slow-release and 0.3 ± 0.8 fast-release, volume % neointimal hyperplasia; P=NS), or
- QCA, (0.09 ± 0.3 slow-release and -0.1 ± 0.3 fast-release mm in-stent late loss (post-procedural minimal luminal diameter [MLD] minus 4-month follow-up MLD).[1,3]



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Rensing et al reported that there were no adverse cardiac events and no in-stent or edge restenosis (>50% diameter stenosis) observed at the 6-month angiographic follow-up of 13 of their 15-patient slow-release cohort.[2] These favourable results persisted to 12-month follow-up in the patients treated by Sousa as assessed by IVUS (2.3 ± 5.5% slow-release and 2.2 ± 3.4% fast-release, volume % neointimal hyperplasia; P=NS).[3] In-stent neointimal hyperplasia volume, as detected by IVUS, remained minimal after 2 years (fast-release = 6.3 ± 5.5%, slow release = 7.5 ± 7.3%; P=NS).[4] Two-year angiographic follow-up showed that only 1 patient (fast-release group) had a 52% diameter stenosis within the lesion segment that required repeat revascularization. The target-vessel revascularization rate for the entire cohort was 10% (3/30) at 2 years.

## *RAVEL*

The remarkably good results from the Phase I clinical trial prompted the initiation of the Phase II trial, RAVEL (**Ra**ndomized Study with the Sirolimus-eluting Bx **Vel**ocity Balloon Expandable Stent).[5] The trial enrolled 238 patients at 19 centres across Europe and Latin America. Patients were randomized to receive either a bare Bx Velocity stent, or a sirolimus-eluting Bx Velocity (Cypher™) stent coated with a 5 µm thick coating of sirolimus-polymer and received 2 months of ticlopidine or clopidogrel post-procedure. At 6-month follow-up, late loss in luminal diameter (primary endpoint) in the cohort treated with the sirolimus-eluting stent was 0.01 compared with 0.80 in the control group (P<0.0001). Binary restenosis rates (>50% diameter stenosis) among the 120 patients who received the drug-eluting device were reported as 0% compared with 26.2% in the group that received the uncoated stent. MACE rates were 3.3% in the treated group and 27.1% in the control group. Subacute stent thrombosis did not occur in either group. At 1-year, no repeat percutaneous transluminal coronary angioplasty (PTCA) of the target lesions were required for the sirolimus-eluting stent (SES) group (n=120), as compared with 13.6% of controls (16 of 118 patients). One bypass procedure was required in the SES group. After up to 2 years, there were no cardiac deaths. A second patient in the SES group required bypass surgery and 1 patient needed repeat PTCA (0.8%). Event-free (death, myocardial infarction [MI], coronary artery bypass graft [CABG], re-PTCA) survival was 90.0% for patients who received the sirolimus stents and was significantly higher than for controls (80.5%). Target lesion revascularization for sirolimus patients was extremely low at 2.5%. Stent thrombosis remained at 0%. Safety profiles were comparable in the two RAVEL arms.

## *SIRIUS*

The U.S. randomized SIRIUS (**Sir**olimus **US** Eluting Stent in De Novo Coronary Lesions) trial – comparing the Cypher device to an uncoated Bx VELOCITY stent – is complete.[6] The SIRIUS trial was a randomized control trial at 53 investigational centres across the US, in 1058 subjects with single *de novo* coronary artery lesions. It was designed to examine the safety and efficacy of sirolimus-coated devices (slow-release, 140 µg sirolimus/cm$^2$) versus placebo. Subjects will be followed for 5 years. At the 8-month angiographic follow-up, sirolimus-treated patients had significantly lower rates of in-stent restenosis (3.2% vs 35.4%, P<0.001). At the 9-month clinical follow-up, the primary endpoint of target vessel failure (cardiac death, MI, target vessel revascularization) was significantly reduced by 59% in sirolimus-treated patients (8.5% vs 21.0%, P<0.001).

## *E-SIRIUS and C-SIRIUS*

The E-SIRIUS (Europe and Latin America) and C-SIRIUS (Canada) clinical trials have recently been completed. These multi-centre, randomized, double-blind clinical trials randomized patients with single *de novo* coronary lesions. The primary endpoint of both trials was the maintenance of in-stent luminal diameter at 8-month follow-up. The E-SIRIUS trial involved 352 patients at 35 centres and was the first drug-eluting stent trial to allow the operators to employ a direct stenting technique (no pre-dilatation of the vessel before stenting).[7,8] Event-free survival in the sirolimus-treated patients was 95.9%, which was significantly better than 78.3% in the bare stent treated group (P<0.001). Binary restenosis rates were 4.0% in the sirolimus group compared with 42.3% in the control arm (P<0.001). There was no difference in outcome between a direct stenting technique and the more traditional technique involving pre-dilatation. The C-SIRIUS trial involved 100 patients at 8 sites. In-stent late loss at 8 months was 0.09 in the sirolimus-treated group and 1.01 in the bare stent group (P<0.0001). Event-free survival was 96.0% in the sirolimus-treated group and 81.7% in the bare stent group (P<0.05). The binary restenosis rate in the sirolimus group was 0% compared with 41.9% in controls (P<0.001).

The benefit of sirolimus-eluting stents in patients for the treatment of recurrent in-stent restenosis has also been demonstrated. Degertekin et al reported the results of the implantation of one or more Bx Velocity sirolimus-eluting stents in 16 patients with in-stent restenosis in a native coronary artery and objective evidence of ischemia.[9] Quantitative angiographic and IVUS follow-up was performed at 4 months, and clinical follow-up at 9 months. Four patients had recurrent restenosis following brachytherapy and 3 patients had totally occluded vessels pre-procedure. At the 4-month follow-up, 1 patient had died and 3 patients had angiographic evidence of restenosis (1 in-stent and 2 in-lesion). At 9 months clinical follow-up, 3 patients had experienced 4 major adverse cardiac events (2 deaths and 1 acute MI necessitating repeat target vessel angioplasty). Twenty-five patients with in-stent restenosis were successfully treated with implantation of 1 or 2 sirolimus-eluting Bx Velocity stents in Sao Paulo, Brazil.[10] Quantitative angiographic and IVUS follow-up was performed at 4 and 12 months. All vessels were patent at the time of 12-month angiography. Angiographic late loss averaged 0.07 ± 0.2 mm in-stent and -0.05 ± 0.3 mm in-lesion at 4 months, and 0.36 ± -0.46 mm in-stent and 0.16 ± -0.42 mm in-lesion after 12 months. No patient had in-stent or stent margin restenosis at 4 months and only one patient developed in-stent restenosis at 1-year follow-up. Percent volume obstruction by 3-dimensional IVUS was 0.81 ± 1.7% at 4 months and 1.76 ± 3.4% after 1 year. There were no deaths, stent thromboses, or repeat revascularizations reported.

### *RESEARCH Registry*

The impact of the implantation of sirolumus-eluting stents on the occurrence of early adverse events (30 days) in a consecutive series of unselected "real-world" patients was evaluated in the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. A total of 508 patients were enrolled in the RESEARCH registry over a 6-month period. Additionally, a control group was formed by all patients treated with percutaneous interventions in the 6-month period immediately before this study. Therefore, the control and the RESEARCH groups were constituted by 2 sequential cohorts, primarily defined by the interventional strategy applied (conventional bare stent or sirolimus-eluting stent implantation, respectively). The post-procedural antiplatelet regimen consisted of lifelong aspirin and clopidogrel 75 mg/day for 3 months in patients treated with sirolimus-eluting stents. Prolonged clopidogrel prescription (6 months) was recommended for patients treated with sirloimus-eluting stents and at least 1 of the following characteristics: multiple drug-eluting stents (>3 stents), total stented length >36 mm, chronic total occlusion, bifurcations, and in-stent restenosis. The 30-day incidence of MACE (death, nonfatal MI, or re-intervention) in those patients with unstable angina or acute MI treated with sirolimus-eluting stents (198 consecutive patients) have been reported.[11] Compared with control patients, patients treated with sirolimus-eluting stents had more bifurcation stenting (16% vs. 8%; P < 0.01), less previous MI (30% vs. 40%; P < 0.01), and less glycoprotein IIb/IIIa inhibitor utilization (19% vs. 33%; P < 0.01). The 30-day MACE rate was similar between both groups (sirolimus 3.0% vs. control patients 4.2%; P = 0.3), with most complications occurring during the first week. Stent thrombosis occurred in 0.4% of patients treated with drug-eluting stents and in 1.6% of control patients (P = 0.4). The one-year cumulative risk of MACE was significantly reduced in the sirolumus-eluting stent group (9.7 versus 14.8%, hazard ratio 0.62 [95% CI, 0.44-0.89]; P=0.008). The results of the RESEARCH registry indicated that sirolimus-eluting stent implantation in "real-world" patients is safe and effective in reducing both repeat revascularization and major adverse cardiac events at one year compared to bare stent implantation.

## Clinical trials with paclitaxel-eluting stents

Paclitaxel (Taxol) is a potent antiproliferative agent that stabilizes the intracellular microtubules thereby inhibiting cell replication, motility, shape, and intracellular transport. Cook stents (V-Flex-Plus, Logic PTX, Supra G; Cook Inc., Bloomington, IN, USA), coated with paclitaxel using a proprietary polymer-free technology, have been examined in several clinical trials.

### *ELUTES*

The ELUTES (**E**uropean Eva**lu**ation of Pacli**t**axel **E**luting **S**tent) trial examined the safety, efficacy, and dosing of paclitaxel-coated V-Flex Plus stents (V-Flex Plus PTX).[12] One hundred and ninety-two patients were divided into 5 groups; 4 groups received a 16 mm long V-Flex Plus PTX stent at 4 different doses of paclitaxel (0.2 µg/mm$^3$, 0.7 µg/mm$^3$, 1.4 µg/mm$^3$, 2.7 µg/mm$^3$) and the fifth received a non-coated stent as control. All patients had a single, *de novo* lesion in one artery. The primary endpoint of the study was effectiveness, assessed by the per cent diameter stenosis and late loss at 6 months follow-up after implantation. Safety was determined by assessing major adverse cardiac events at 1 and 6 months. The high-dose paclitaxel group showed significant reduction in diameter stenosis (14% vs 34% [P<0.01]). Although there was no difference between the treated groups in terms of benefit, a dose response curve was seen. Late loss was also significantly lower in the high-dose group compared to controls (0.10 mm vs. 0.73 mm, P<0.005), with no difference between treated groups. Only 3% of high-dose patients versus 31% of controls experienced binary in-stent restenosis (>50% diameter stenosis, P=0.055). There were no significant adverse events at 1 month, with a nearly 100% event-free rate in all arms. At 6 months event rates were still low among all treated groups, with between 89% and 97% of patients remaining event-free. Based on the results of the ELUTES trial, Cook Inc. received CE Mark approval to market its paclitaxel-coated V-Flex™ Plus PTX Coronary Stent System in the European Union.

A Belgian group has shown that V-Flex Plus PTX stents (Cook) are also effective for the prevention of recurrent in-stent restenosis.[13] In their study, 21 patients who had been treated a minimum of 4 times for recurring in-stent restenosis received a 16-mm Cook V-Flex Plus PTX coronary stent coated with a cytostatic dose of paclitaxel. After 6 months, no patient in the study exhibited restenosis in the portion of the target vessel where the paclitaxel-coated stent was placed.

### *ASPECT*

The double-blind ASPECT (**As**ian **P**aclitaxel-Coated **St**ent **C**linical **T**rial) randomized 177 patients to control or 1 of 2 paclitaxel dose groups, high dose (3.1 µg/mm$^3$), and low dose (1.3 µg/mm$^3$) delivered using Cook's coated Supra-G stent system, that implements a polymer-free technology to that of the V-Flex Plus PTX.[14] At 6-month follow-up, a significant dose-dependent reduction in binary restenosis rates (high dose; 4%, low dose; 12%, control; 27%) and late loss (high dose; 0.29 ± 0.72 mm, low dose; 0.57 ± 0.71 mm, control; 1.04 ± 0.83 mm) were seen in the paclitaxel arms, compared to the control group. In ASPECT, enrollees treated with conventional antiplatelet therapy (aspirin and a thienopyridine), no thrombotic complications were noted following stent implantation. In a breech of protocol, however, 37 patients were treated with aspirin and cilostazol rather than a thienopyridine following stenting. Of this group, there were thrombotic complications in 3 of the 12 patients who received a high-dose stent, 1 of the 15 patients who received a low-dose stent, and none of the 10 patients who received a bare stent. These results indicate that locally-delivered paclitaxel exhibits an important anti-restenotic effect, but likely delays wound healing in a manner that may increase the risk of stent thrombosis unless conventional antiplatelet therapy is prescribed.

## *DELIVER I and II*

Under a partnership agreement, Cook Inc. and Guidant Corp. have developed the paclitaxel-coated Achieve stent using the Cook proprietary polymer-free coating technology on a Guidant Multilink coronary stent platform. The efficacy of the Achieve device, coated with 3 μg/mm$^2$ of paclitaxel, was tested in the DELIVER-I (The RX Achieve **D**rug-**E**luting Coronary Stent System **i**n the Treatment of Patients With *De Novo* Native Coronary Lesions-I) Trial. In this prospective, randomized, single-blind, multicentre trial, 1043 patients were enrolled at 61 US centres. The primary endpoint of a 40% reduction in target vessel failure at 270 days for the Achieve drug-eluting stent compared to the Penta stent was not met in the DELIVER-I trial.

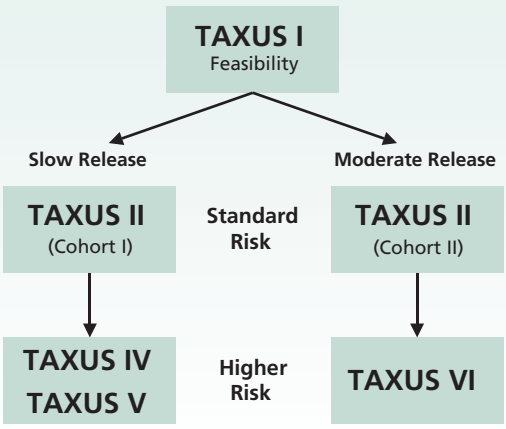
The DELIVER-II clinical study was a prospective, nonrandomized, multicentre study designed to evaluate the benefit of the Achieve drug-eluting stent in patients with complex coronary lesions with a high risk of revascularization. The study enrolled 1533 patients at 86 sites in Europe, the Middle East, and South Africa. All patients received the Achieve stent platform. The primary endpoint of the study was to elucidate the rate of target lesion revascularization (TLR) at 6 months and to identify the factors that led to an increased relative risk of revascularization in patients with complex lesions such as long lesions, small vessels, multi-vessels, chronic total/subtotal occlusions, bifurcations, or restenotic (including in-stent restenosis) lesions treated with a non-polymeric paclitaxel eluting stent. Secondary endpoints included 6-month target vessel failure and MACE rates at 30 days, 6 months, and 1 year (in a subset of 500 patients).

At 6 months, the TVR rate in the overall population was 10.5% and the hierarchical MACE rate (death, Q-wave MI, non-Q-wave MI and TVR) was 15.7%. Univariate analysis identified a history of angina and the number of diseased vessels as risk factors for worsened prognosis at 6 months. The specific characteristics identified as risk factors for TLR by multivariate analysis included:

- lesions in the left anterior descending (LAD) artery
- restenotic lesions
- post-procedural minimal lumen diameter
- total stent length
- number of diseased vessels (P<0.05).

The only conclusions that could be made from the results of DELIVER II were that the TLR rate in the high-risk population was low and that a number of multivariate patient/lesion risk factors contributed to the increased risk of TLR. As the study was not randomized, efficacy of the Achieve device could not be evaluated. However, based on the results of the DELIVER-I trial, questions were raised concerning the durability of the coating and how much drug was actually delivered. Early loss of paclitaxel may have occurred during insertion, or there may have been variability in dose from stent to stent. Based on the disappointing results of the DELIVER-I trial, it was decided that the Achieve stent would not be further developed.

**Figure 1: Scheme outlining the Boston Scientific TAXUS paclitaxel-eluting stent clinical trials.**




## *The TAXUS Program*

The TAXUS program, which began in 1997, is a series of clinical studies being performed by Boston Scientific (Natick, MA, USA) to collect data on their proprietary paclitaxel-eluting stent technology on 2 of its stent platforms: the NIR stent (NIRx) and the Express stent (TAXUS stents) (Figure 1). The devices employed by Boston Scientific differ from those developed by Guidant/Cook in that Boston Scientific uses a polymer coating to hold and release the drug, while the Cook system involves application to the stent without a polymeric coating.

**The TAXUS-I study** was a prospective, randomized, double-blind, clinical trial designed to evaluate the feasibility and safety of low-dose paclitaxel-eluting stents (NIRx) used for the treatment of *de novo* and restenotic lesions.[15] The coated stents were seven cell, 15 mm long NIR stents containing 1 μg paclitaxel/mm$^2$ (85 μg/stent) and uncoated NIR stents served as controls. The trial was performed at 3 centres in Germany and included 61 patients. The primary endpoint was the incidence of MACE at 30 days. There were no adverse events reported in either group at 30 days and no stent thromboses were reported up to 12 months. The 6-month binary restenosis rate (>50% diameter stenosis) was 10% in the bare control stent group compared with "zero" restenosis in the paclitaxel-coated stent group (P=NS). At 12 months, the MACE rate was 3% in the paclitaxel treated group and 10% in the control group (P=NS).

**TAXUS II** was a 536-patient, 15-country, randomized, double-blind, controlled study of the safety and efficacy of the NIRx paclitaxel-eluting coronary stent, in which 2 sequential cohorts of patients with standard risk, *de novo* coronary artery lesions were treated with different dose formulations. The primary endpoint of the trial was

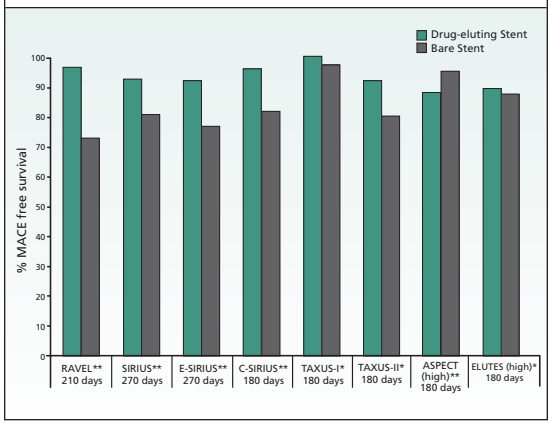
the reduction of mean percent in-stent net volume obstruction at 6 months as measured by IVUS. The slow-release formulation (NIRx SR stent, 1 μg/mm$^2$) cohort showed a significant 66% reduction in in-stent volume obstruction as measured by IVUS at 6-month follow-up (7.9% vs 23.2%, NIRx SR stent vs control, P<0.0001). The slow-release cohort reported an 8.5% MACE rate at 6 months compared with 19.5% in the control group (P=0.013). Binary restenosis rates were 2.3% for the NIRx SR group compared with 17.9% in the control group (P<0.0002). The moderate-release formulation (NIRx MR stent, 1 μg/mm$^2$) cohort reported a significant 62% reduction in in-stent volume obstruction at 6-month follow-up (7.8% vs 20.5%, NIRx SR stent vs control, P<0.0001). The moderate-release cohort reported a 7.8% MACE rate at 6 months compared with 20.0% in the control group (P=0.006). Binary restenosis rates were 4.7% for the NIRx MR group compared with 20.2% in the control group (P<0.0001).

**TAXUS III** was a single-arm, 28-patient registry study that examined the feasibility and safety of the paclitaxel slow-release formulation on a NIRx platform for treatment of in-stent restenosis. No subacute stent thrombosis occurred up to 12 months, but there was one late chronic total occlusion and an additional 3 patients showed angiographic restenosis.[16] The mean late loss was 0.54 mm. The MACE rate was 29%.

**The TAXUS IV** trial was a prospective, randomized, double-blind study designed to assess the safety and efficacy of a slow-release dose formulation paclitaxel-eluting TAXUS Express stent system in patients with a single *de novo* lesion up to 28 mm long and 3.75 mm in diameter amenable to treatment with a single stent. A total of 1326 patients were randomized, with a primary endpoint of TVR at 9 months. Treatment with clopidogrel was given for 6 months post-procedure. At 9 months, the TVR rate in the control stent group was 12.0% compared with 4.7% in those treated with paclitaxel-eluting stents (P<0.0001). Sub-group analysis revealed that the devices were equally effective for the reduction in restenosis rates in diabetics treated with oral hypoglycemic medications (TLR rates of 17.4% in patients receiving a bare stainless-steel stent compared with 4.8% in those treated with a TAXUS drug-eluting stent, P = 0.004); however, a similar benefit was not documented in insulin-treated diabetic patients (TLR rate of 13% in control patients compared with 5.9% in those receiving a paclitaxel-eluting stent. The results of TAXUS-IV support the effectiveness of the slow-release paclitaxel-eluting TAXUS stent for the reduction of restenosis in a wide range of complex patients and lesions, including small vessels, long lesions, and patients with diabetes.

**The TAXUS V** trial is an extension of TAXUS IV, and it is studying higher risk patients, including those with smaller vessels, as well as those with longer lesions requiring overlapping stents. TAXUS V is currently underway with a planned enrollment of 1108 patients.

**Figure 2: Major adverse clinical events (MACE)-free survival (MACE) of the various drug-eluting stent trials at < 1 year.**



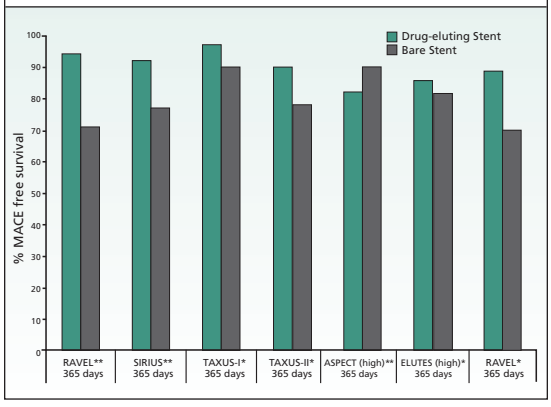

* MACE includes target lesion revascularization for all reasons.
** MACE includes only clinically driven target lesion revascularization.

TAXUS VI is a prospective, randomized, double-blind trial studying the efficacy of the implantation of a moderate-release paclitaxel-eluting stent in patients with long lesions. Inclusion criteria in this trial included single or sequential lesions which could be completely covered by up to two study stents (maximum stent length 48 mm). The planned enrollment of 448 patients is complete and final results will soon be available.

The main results of the drug-eluting stent trials are shown in Figures 2, 3, and 4.

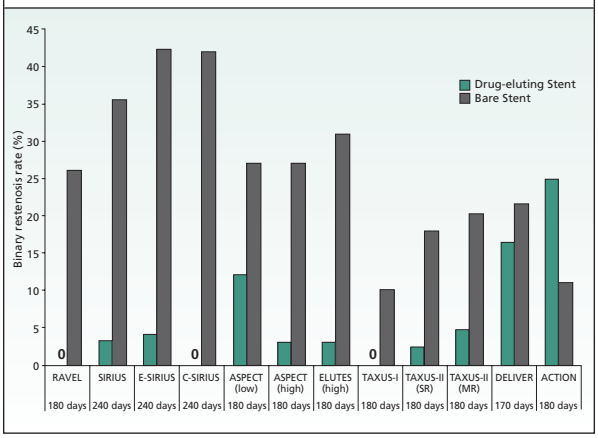
In the December issue of *Cardiology Rounds*, this review of clinical trials of drug-eluting stents continues with the examination of QP-2, actinomycin D, phosphorylcholine, everolimus, and 17ß-estradiol loaded BiodivYsio Matrix LO–eluting stents, as well as a review of biodegradable stents. Thoughts on the future of this rapidly evolving treatment and new approaches for its use in the treatment of coronary artery disease will also be discussed.

**Figure 3: MACE-free survival of the various drug-eluting stent trials at ≥ 1 year.**




* MACE includes target lesion revascularization for all reasons.
** MACE includes only clinically driven target lesion revascularization.

**Figure 4: In-stent binary restenosis rates (>50% diameter stenosis as measured by quantitative coronary angiography) of the major drug-eluting stent trials.**





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## Upcoming meetings

5-7 February 2004
**29th International Stroke Conference**
San Diego, CA
CONTACT: AHA National Center
Tel: 214-706-1543
Fax: 214-706-5262
E-Mail: strokeconference@heart.org

26-28 February 2004
**Cardiovascular Topics at Johns Hopkins**
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**53rd Annual Scientific Session of the American College of Cardiology**
New Orleans, LA
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Tel: 800-253-4636, ext. 694 / 301-897-5400
Fax: 301-897-9745
E-Mail: resource@acc.org

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