Drug-Eluting Stents for Emerging Treatment Strategies in Complex Lesions

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The use of drug-eluting stents (DES) has rapidly expanded from lower-risk, single-lesion procedures to include a broad spectrum of high-risk patients and complex lesions. For 4 complex patient subgroups, emerging data suggest that DES might offer an advantage for reducing late clinical restenosis. In ST elevation myocardial infarction, early registry reports are promising, with no evidence to date for an increased incidence of subacute stent thrombosis and significant trends for less restenosis. For chronic total occlusions, early, small clinical series show that DES might have unprecedented long-term patency. Initial registries of DES for in-stent restenosis reveal striking reductions in late loss and restenosis, compared with brachytherapy historical controls. The use of DES in saphenous vein graft lesions is increasing, and early registry results show a very acceptable incidence of thromboembolic complications and major adverse cardiac events. Important data regarding much larger groups of these patient cohorts will emerge over the next year, to help guide the broader application of DES in "real-world" practice.
[Rev Cardiovasc Med. *2005;6(suppl 1):S38-S47*]

Key words: Drug-eluting stents • Sirolimus • Paclitaxel • ST elevation myocardial infarction • Chronic total occlusions • Saphenous vein graft • In-stent restenosis

Drug-eluting stents (DES), both sirolimus-eluting and paclitaxel-eluting, have been shown in randomized clinical trials (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent [SIRIUS], TAXUS IV)[1,2] to dramatically reduce both the need for repeat target vessel revascularization (TVR) and overall major adverse cardiac events (MACE) compared with non–drug-eluting stents. Selected patients with single lesions were studied in these trials, and the reductions

in TVR and MACE were shown across the board in many subsets of patients (eg, in diabetics, in long lesions, and in small vessels). Thus, both the sirolimus-eluting stent (CYPHER®; Cordis, Miami Lakes, FL) and the paclitaxel-eluting stent (TAXUS™; Boston Scientific, Natick, MA) have been approved by the US Food and Drug Administration (FDA) for percutaneous coronary intervention (PCI) in the types of patients included in the randomized trials.

Because of the exciting promise of DES from the SIRIUS and TAXUS IV trials, however, DES are being applied in a wide range of patients, with clinical and lesion characteristics much more complex than in the patients studied in those trials. Over the last 1 to 2 years, emerging clinical trial data have become available in some of these more complex patient subgroups and lesion types through large prospective registries and smaller clinical trials. There is clearly still a need to examine the outcomes of DES in these more complex patients who were excluded from the randomized trials. Lesions for which more data from DES are needed include both large and small vessels, multilesion/multivessel PCI (especially in diabetics), saphenous vein grafts (SVG), diffuse disease (long stented segments or "full metal jackets"), acute ST elevation myocardial infarction (STEMI), chronic total occlusions (CTO), bifurcation lesions, in-stent restenosis (ISR), and the difficult subset of patients with restenosis after previous vascular brachytherapy.

There is clearly still a need to examine the outcomes of drug-eluting stents in the more complex patients who were excluded from the randomized trials.

The purpose of this article is to review new data on the results of DES in patients with acute STEMI, CTO, ISR, and SVG disease.

Emerging DES Registries

To aid in the generation of clinical information on DES outcomes, a number of large prospective registries have been initiated globally. Some of these registries are private-industry initiated and sponsored, and others are independent study groups.

Sirolimus-eluting (CYPHER) stent registries have emerged in Europe and the United States. In Europe there are 2 primary registries: the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry from Rotterdam, The Netherlands, and the e-CYPHER Registry, which is a multinational Internet registry. The RESEARCH Registry compared a pre–sirolimus-eluting-stent (SES) time period (pre-SES phase; from October 16, 2001 to April 16, 2002) with a subsequent consecutive series of SES practice from April 16, 2002 to October 16, 2002 (SES phase).[3,4] The primary goal of the registry was to examine long-term clinical outcomes, such as TVR and MACE, of the SES versus the pre-SES phase. This registry found that more than 60% of patients being treated in the registry would have been excluded from the preceding randomized clinical trials, thus representing a large body of patients in whom DES outcomes were unproven. A total of 663 patients were included in the pre-SES phase and compared with a total of 508 patients in the SES phase. Multivessel stenting was performed in 28% of patients. Other patient groups were as follows: long lesions with stent in-segment lengths greater than 36 mm (18%), acute myocardial infarction (MI) (18%), very small vessels with a 2.25-mm stent (not available in the United States) (15%), bifurcation stenting (11%), CTO (8%), left main artery (4%), and SVG (3%). Overall, the 12-month MACE rate was 14.8% in the pre-SES phase, compared with 9.7% in the SES period, representing a 34% risk reduction (95% confidence interval [CI] 0.44-0.89, $P = .008$). Subgroups of patients within the RESEARCH Registry are currently being evaluated.

The e-CYPHER Registry update, presented by Dr. Philip Urban at the EuroPCR meeting in May 2004,[5] showed clinical outcomes of more than 12,000 patients from 275 centers around the world outside the United States. At the time of his presentation, follow-up was available on 4926 patients at 1 year (56% of those eligible). The e-CYPHER patient population, similar to the RESEARCH Registry population, represents a "real-world," more complex patient cohort compared with the previous randomized trials, with 49% of patients being treated for at least one "off label" indication. Lesion lengths averaged more than 18 mm, and vessels less than 2.5 mm in diameter occurred in 30% of patients. Other patient groups included multiple stents (26%), CTO (8.9%), ostial

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(8.4%), left main artery (2.2%), SVG (2%), restenosis lesions (13.1%), and complex B2 or C lesions (86.6%). The overall MACE-free survival rate at 6 months was 97.7%, indicating excellent long-term outcomes in this more complicated patient cohort. Subgroup analysis of the individual complex patients and lesions is ongoing.

The sirolimus-eluting (CYPHER) stent registries in the United States include 1) a Cordis-sponsored post-market surveillance study; 2) the Strategic Transcatheter Evaluation of New Therapies (STENT) Group registry (the first US multicenter registry, beginning in May 2003); 3) the STLLR Registry (DES technique registry); and 4) the DESCOVER Registry (200–300-hospital registry), as well as a number of single-center registries and pharmaceutical company–sponsored registries.

The paclitaxel-eluting (TAXUS) stent global registries include the Milestone II Registry, an observational registry of drug-eluting stent selection and use with data pending, and the WISDOM Registry (Web-Based TAXUS Inter-Continental Observational Data Transitional Registry Program). The WISDOM Registry is an Internet-based data collection of patient outcomes following paclitaxel-eluting stent implantation in nine countries, with 26 sites and 35 physicians worldwide. Enrollment was complete in July 2003, with 778 patients and 992 stents deployed. Type B2 and C lesions occurred in 71%, CTO in 7%; average lesion length was 15.6 mm and reference vessel size 2.9 mm. Multiple lesions were treated in 15% of patients, with SVG in 2% and lesions greater than 20 mm in 14%. The overall MACE rate at 6 months was 4.4%, with TVR in 2.1%. In the United States, the ARRIVE Registry, a peri-approval registry of the TAXUS stent examining long-term clinical outcomes, is ongoing.

The clinical data presented in this article will include results from these important ongoing registries, as well as smaller clinical trials.

ST Elevation Acute Myocardial Infarction

Bare metal stents have proven to be superior to balloon angioplasty alone in STEMI, owing to the reduction of early reocclusion and late clinical restenosis (stent-PAMI, CADILLAC, others), with mortality outcomes similar to percutaneous transluminal coronary angioplasty. Given the suspected delayed endothelial healing of DES compared with bare metal stents, concerns have arisen regarding the risk of acute or subacute thrombosis of DES when implanted in the actively thrombotic environment of the STEMI lesion. In addition, STEMI patients have been categorically excluded from any of the randomized DES trials completed to date.

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Registries and clinical trials with STEMI data include the RESEARCH Registry, the e-CYPHER Registry, the STENT Group Registry, the TYPHOON Trial, and the DESCOVER Registry. The first of these to examine STEMI patients was the RESEARCH Registry from Rotterdam, The Netherlands. The RESEARCH Registry design and overall outcomes are reviewed above, and within this patient population there were 120 patients in the pre-SES phase (October 2001 to April 2002) and 94 patients in the SES phase (April 2002 to October 2002) with STEMI.[3] These patient populations were compared with respect to baseline clinical characteristics and long-term outcome. As shown in Figure 1, the cumulative incidence of death, MI, or TVR at 9 months was 15.8% in the pre-SES phase, compared with 8.5% in the SES phase (95% CI 0.2-1.0, P = .07). There was no increase in the incidence of subacute stent thrombosis during the SES compared with the pre-SES phase. Angiographic follow-up was performed in 60% of the SES patients and showed that for these STEMI lesions, averaging 16.9 mm in length and with a mean vessel diameter of 2.73 mm, the long-term late loss was minimal, with 0% binary restenosis (Table 1). Although the sample size of 94 STEMI patients is rather small, these data from the RESEARCH Registry are highly favorable and indicate that routine SES implantation seemed to be safe for unselected patients with STEMI as compared with patients from the preceding 6 months with bare metal stents. Other emerging clinical data from Europe will include results from the e-CYPHER Registry of 12,108 patients, of whom STEMI occurred in 7.2%.[6]

The first U.S. multicenter data on DES and STEMI come from the STENT Registry and were presented at the Transcatheter Cardiovascular Therapeutics 2004 meeting.[7,8] The STENT registry is a prospective, multicenter "real-world" registry for all PCIs at each of 8 participating cardiovascular centers. The registry began enrolling in May 2003 at the time of FDA approval for the CYPHER stent and includes centers primarily

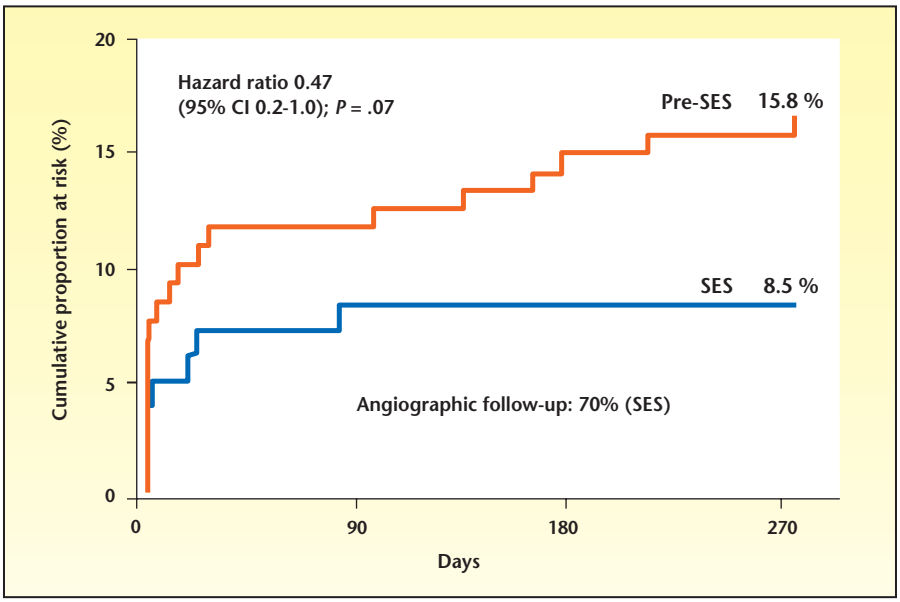


Figure 1. *Acute myocardial infarction (MI) substudy from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study: cumulative incidence of death, MI, or target vessel revascularization. SES, sirolimus-eluting stent.*

in the southeastern United States. As of June 30, 2004, a total of 5506 procedures had been entered in the STENT Registry (85% of all PCIs performed at the participating institutions), with 3-month clinical follow-up completed in 2704 patients (90% of patients eligible at that time) and with 9-month clinical follow-up completed in 798 patients (91% of patients eligible). Of the total procedures entered by June 30, 2004, DES-only procedures constitute 55% of procedures (2852 patients) and DES plus bare metal or other non-stent interventions an additional 12.5% (605 patients). Of the overall patient population, more than 80% of patients in the STENT registry would have been excluded from the previous randomized clinical trials. Multilesion procedures occurred in 30%, multivessel procedures in 12%, SVG in 8%; average lesion length is 15.5 mm, average vessel size 3.0 mm; 81% of lesions were of moderate/high severity (American College of Cardiology definition). STEMI as the primary indication for PCI accounted for 12% of all procedures.

Clinical outcomes of STEMI patients from the STENT Registry are shown in Table 2 for 412 patients with follow-up through March 2004. The results show excellent acute and 3-month outcomes, with no significant difference between DES and bare metal stents for MACE or subacute stent thrombosis. The data also show that bare metal stents are being used in a higher percentage of STEMI patients than DES during this period, and it is too early to determine any difference in rates of TVR.

Two important randomized clinical trials are underway for DES in STEMI. The TYPHOON trial is a multicenter (44 sites), prospective, single-blind, randomized study of the CYPHER stent versus bare metal stent in STEMI. The plan is to enroll 700 STEMI patients in Europe with the primary endpoint of target vessel failure (TVF) at 1 year postprocedure. As of May 2004, 556 of the 700 patients were enrolled; 6-month data will be presented at the 2005 meeting of the American College of Cardiology, and 12-month data will be available at the American Heart Association 2005 meeting.[8] The HORIZONS Trial is a 3400 STEMI patient trial of the TAXUS stent versus bare metal stent. This trial will also examine bi-valirudin versus unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor, as well as the impact of complete revascularization (immediate stenting of all diseased vessels) versus staged stenting.[9]

Chronic Total Occlusions

CTOs have historically met with lower primary procedural success

Table 1
The RESEARCH Registry: 6-Month Angiographic Follow-Up for Acute STEMI Population

	Preprocedure	Postprocedure	Follow-Up
RD (mm ± SD)	2.73 ± 0.59	2.80 ± 0.47	3.04 ± 0.49
MLD (mm ± SD)	0.34 ± 0.50	2.54 ± 1.31	2.59 ± 0.42
DS (% ± SD)	86 ± 21	14 ± 12	15 ± 11
Length (mm ± SD)	16.90 ± 9.93		
Late loss (mm ± SD)			-0.04 ± 0.25
Binary restenosis (%)			0

Mean (± SD) values related to 62 patients (70% of those eligible) with 6-month angiographic follow-up. RESEARCH, Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital; RD, reference diameter; MLD, minimal lumen diameter; DS, diameter stenosis.

rates and high restenosis rates.[10,11] CTO procedures involve increased procedural time and cost, increased radiation exposure, and 95% of procedure failures are due to inability to cross the lesion with a guidewire or a balloon. With the advent of new CTO devices enhancing the ability to successfully cross these lesions, tremendous interest has arisen in the ability of drug-eluting stents to reduce the long-term restenosis rate (historically as high as 35%–50% with bare metal stents). The rationale for opening CTOs comes from numerous studies reporting improved survival in patients with successful angioplasty of CTO lesions compared with patients with failed procedures. The largest series of long-term follow-up is that of Suero and associates,[12] in which 2007 CTO patients treated at the Mid-America Heart Institute were followed for 10 years. Comparison was made between successful and failed CTO procedures as well as between CTO patients and a matched cohort of non-CTO patients. The results showed that the rate of in-hospital MACE was 3.8% for CTO patients and that there was a 10-year survival advantage for successful versus failed CTO procedures (73.5% for successful vs 65.1% for failed procedures, $P = .0001$). In addition, it was found that there was no survival difference between successful CTO procedures and non-CTO procedures. Thus, there is an important need for data from the use of DES in CTO procedures to 1) assess the safety of placing stents in these often longer and more complex lesions to rule out the possibility of higher thrombosis rates; and 2) to document that long-term TVR is indeed reduced with DES in this setting.

Table 2
STENT Registry STEMI Results: Nonadjusted Event Rates for STEMI Procedures with Drug-Eluting Stent (DES) or Bare Metal Stent (BMS) to 3 Months Follow-Up

	DES	BMS	*P*
In hospital	n = 137	n = 203	
Death	3 (2.2)	18 (8.9)	.01
Reinfarction	1 (0.7)	5 (2.5)	NS
Stroke	1 (0.7)	4 (2.0)	NS
TVR	0	2 (1.0)	
Stent thrombosis	0	2 (1.0)	
At 3 months	n = 68	n = 119	
Death	1 (1.5)	4 (3.4)	.4
Reinfarction	0	4 (3.4)	
Stroke	0	0	
TVR	1 (1.5)	1 (0.8)	1.0
Stent thrombosis	0	2 (1.7)	NS

Data are presented as n (%). Values are not risk-adjusted for comparisons owing to the small number of events. Risk adjustments for mortality show no significant difference between DES and BMS STEMI. STENT, Strategic Transcatheter Evaluation of New Therapies; STEMI, ST elevation myocardial infarction; TVR, target vessel revascularization; NS, nonsignificant. Reproduced with permission from Gupta et al.[7]

The rationale for opening CTOs comes from numerous studies reporting improved survival in patients with successful angioplasty of CTO lesions compared with patients with failed procedures.

The first series of patients to be studied in a consecutive fashion, entitled the CYPHER Sirolimus-Eluting Stent in Chronic Total Occlusion study (SICTO Study), was presented at the 2004 EuroPCR meeting by Dr. Chaim Lotan.[13] The study design included a multicenter, prospective, nonrandomized series of patients to assess the feasibility and restenosis/reocclusion rate of coronary stenting with the CYPHER stent in chronic total occlusions. A total of 25 patients were treated with the CYPHER stent after successful balloon angioplasty and intravascular ultrasound (IVUS) examination. Clinical follow-up was planned at 30 days and 6, 12, 18, and 24 months, with repeat angiography and IVUS performed at 6 months. The baseline angiographic characteristics showed a mean lesion length of 30.2 mm and reference vessel diameter of 2.6 mm (Table 3). Vessels treated included the left anterior descending artery in 40%, right coronary artery in 32%, and circumflex in 28%. The angiographic follow-up results of SICTO are shown in Table 3. The immediate postprocedure in-stent percent stenosis was 15.7%, compared with a 6-month follow-up stenosis of 19.3%. The in-stent late loss was –0.1 mm. The clinical events to 6 months are shown in Table 4. There were no MACE, and TVR was observed in only 2 patients (8%). One patient had proximal and

distal stenosis outside the stent and one patient had a distal dissection at the index procedure, which was treated at follow-up. The SICTO study shows that in this feasibility phase, the CYPHER stent was very effective in the treatment of CTO, with very low rates of TVR and MACE compared with historical data from bare metal stents. In addition, the IVUS data showed that the CYPHER stent significantly reduced luminal hyperplasia within the stents at long-term follow-up, with minimum luminal area only 0.3 mm^2 less at follow-up compared with immediately after the procedure.

To date, the STENT Registry includes a total of 158 CTO procedures (3.3% of all procedures, with a range across centers of 1.4%–5.9%). Of these, 61 patients received DES alone for a CTO. Acute, 3-month, and 9-month MACE and TVR rates are being examined.[14] These are the first emerging, multicenter, long-term data concerning DES for CTO in the United States.

Table 3
SICTO Study: Angiographic Data at 6-Month Follow-Up

	Postprocedure	6-Mo Follow-up
RVD (mm)	2.6 ± 0.5	2.8 ± 0.6
MLD (mm)	1.9 ± 0.6	2.0 ± 0.7
In-stent % stenosis	15.7 ± 8.6	19.3 ± 11.0
In-stent late loss (postprocedure – follow-up)	NA	–0.1 ± 0.3

Data are presented as mean ± SD. SICTO, CYPHER Sirolimus-Eluting Stent in Chronic Total Occlusion; RVD, reference vessel diameter; MLD, minimal lumen diameter.

In-Stent Restenosis

Clinically driven ISR occurs in 15% to 20% of patients after placement of bare metal stents. Thus, at present, given the continued use of bare metal stents in a significant proportion of patients, these lesions will continue to arise and create a demanding subset of patients for interventional therapies. Vascular brachytherapy has been shown to significantly reduce the incidence of repeat restenosis after PCI of ISR. However, as shown in Figure 2, the initial reduction in MACE produced by gamma brachytherapy in the GAMMA I trial seems to be lost by the time of 4-year follow-up owing to late "catch-up" in the treated patients.[15] Long-term follow-up of the patients from the GAMMA I Trial shows that the significant reduction in MACE at 270 days after gamma brachytherapy versus placebo for ISR is reduced to a nonsignificant difference by the third and fourth years of follow-up, owing to continued catch-up of TVR events in the treated group. Although not as dramatic, similar findings are apparent in WRIST (the Washington Restenosis In-Stent Trial), which examined gamma brachytherapy for ISR[16] (Figure 3). In WRIST, target lesion revascularization was 24% at 1 year and increased to 32% by 4 years. In addition, the efficacy of brachytherapy for ISR in diabetics has been less favorable, with binary restenosis of 32.8% in the Stents and Radiation Therapy (START) Trial[17] (beta radiation) and 36.1% in the GAMMA I Trial (gamma radiation). Interestingly, in the START Trial, although there was a trend toward reduced restenosis with beta radiation, this did not reach statistical significance for diabetics. Because of the relatively high target lesion revascularization (TLR) rates after brachytherapy for ISR, there has been an interest in applying DES to this patient population.

Because of the relatively high target lesion revascularization rates after brachytherapy for in-stent restenosis, there has been an interest in applying drug-eluting stents to this patient population.

Initial clinical data on DES for ISR has come from small feasibility studies. The first reported experience includes combined series of sirolimus for ISR from Rotterdam, The Netherlands and Sao Paulo,

Table 4
SICTO Study: Events to 6 Months

Event	n (%)
MACE (overall)	0
Death	0
MI	0
Emergency CABG	0
Target lesion PTCA	0
TVR	2* (8)
Acute/subacute thrombosis	0

N = 25. SICTO: CYPHER Sirolimus-Eluting Stent in Chronic Total Occlusion; MACE, major adverse cardiac events; MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; TVR, target vessel revascularization.
*1 patient proximal and distal stenosis outside stent; 1 patient distal dissection at index procedure, treated at follow-up.

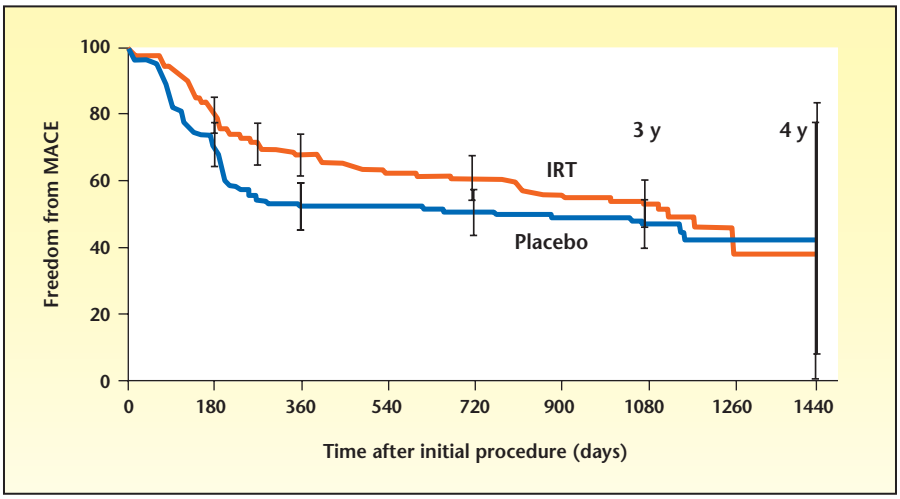


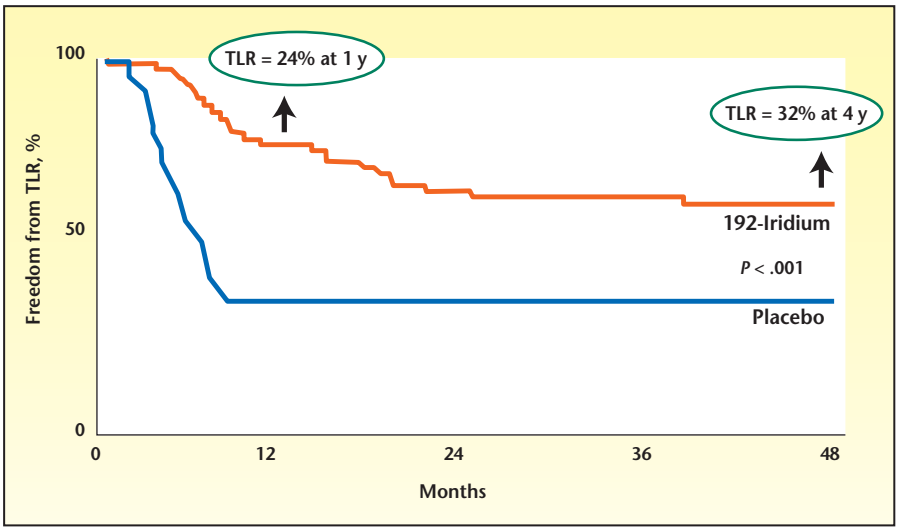
Figure 2. *Major adverse cardiac event (MACE)-free survival (at 4 years) in patients from the GAMMA I Study: late "catch-up." There is no difference between brachytherapy (intracoronary radiation therapy [IRT]) and placebo at 3 to 4 years.*

Brazil.[8] In this feasibility study, 41 patients (25 from Sao Paulo, 16 from Rotterdam) with ISR were treated with the sirolimus stent. Vessel sizes ranged from 2.5 mm to 3.5 mm and included one or two 18-mm CYPHER stents. Aspirin and clopidogrel were used for 60 days. ISR lesion patterns included focal in 40%, diffuse in 32%, and proliferative in 28%. The angiographic late loss was shown to be 0.17 mm in the Sao Paulo patients and 0.51 mm (owing to 2 total occlusions) in the Rotterdam patients. At 1 year, restenosis occurred in 3 patients (7.3%), with 1 MI and 2 deaths. These early results suggested that acute complications might arise in very complex diffuse ISR lesions (such as those with previous brachytherapy) but that very low long-term restenosis is possible in selected patients. The TAXUS III feasibility trial examined the TAXUS stent for ISR in a total of 30 patients. MACE occurred at 1 year in 28.6%, with TLR in 21.4%. MI occurred in 3.6%. There was no stent thrombosis or mortality in this series.

The most recent multicenter data on ISR come from the Treatment of Patients With an In-stent Restenotic Native Coronary Artery Lesion (TROPICAL) Study, presented at the EuroPCR 2004 meeting by Dr. Franz-Josef Neumann.[18] TROPICAL is a multicenter, nonrandomized study of the CYPHER stent in the treatment of patients with ISR. The objective of the study was to compare the CYPHER stent in ISR of native coronary lesions with the historical group of the combined GAMMA I and II Trials. A total of 162 patients with ISR were consecutively treated with the CYPHER stent. Angiographic follow-up was planned in all patients. The primary endpoint was in-lesion late loss and was shown to be 0.08 mm for the CYPHER-treated patients, compared with 0.68 mm in the historical control group from the GAMMA I/II Trials. The clinical outcomes at 180 days for the TROPICAL Study are shown in Figure 4. The results show 4.9% MACE, 0.6% deaths, 1.8% MI, 2.5% TLR, and 0.6% late stent thrombosis. This compared favorably with the historical control group of the GAMMA I/II Trials, particularly in relation to the rate of TLR (2.5% vs 14%, $P < .001$). This study demonstrated that sirolimus-eluting stents were highly effective in ISR, with an average in-lesion late loss of less than 0.1 mm, which translated into a very low restenosis rate when compared with historical results of brachytherapy.

Presently, there is an ongoing randomized trial of sirolimus-eluting stents versus brachytherapy for ISR, entitled the SISR Trial (Sirolimus-Eluting BX Velocity Balloon Expandable Stent vs Intracoronary

Figure 3. *Freedom from target lesion revascularization (TLR) at 4 years in the Washington Restenosis In-Stent Trial (gamma brachytherapy vs placebo).*



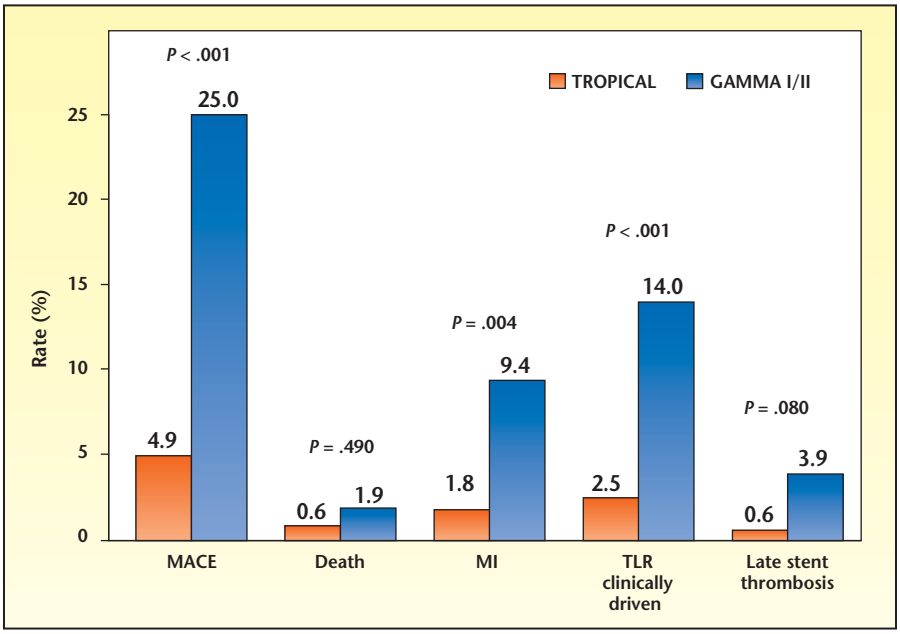


Figure 4. *Clinical outcomes at 180 days from the Treatment of Patients With an In-stent Restenotic Native Coronary Artery Lesion (TROPICAL) Study, compared with historical data from the GAMMA I and II Trials. MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization.*

Brachytherapy in the Treatment of Patients with In-Stent Restenotic Coronary Artery Lesions). This is a multicenter (26 sites, 400 patients), randomized study (2:1) of CYPHER stent versus brachytherapy. The primary endpoint is target vessel failure at 9 months postprocedure, and efficacy results are expected by mid-2005. Despite the lack of randomized trial data at this time, the initial results of the TROPICAL Study and emerging data from other registries suggest very favorable results of DES for the treatment of ISR. Clearly, however, additional data are needed from larger registries and prospective clinical series in the future.

SVG Lesions

Bare metal stents have shown superiority over balloon angioplasty for SVG lesions, owing to improved late clinical outcomes (Reduced Anticoagulation Vein Graft Stent Trial)[19] and have become the standard of care for the treatment of SVG disease in conjunction with distal protection devices. The application of DES to SVG lesions has not been systematically studied to date, and there are theoretic concerns about the efficacy of DES in these lesions, because of the expected delay in endothelial healing after DES placement, perhaps increasing the risk of thrombosis. However, this group of patients experiences higher clinical restenosis rates than patients with de novo lesions and are an important group in whom DES might have an impact on long-term outcomes. It will be essential, however, to document that DES for SVG disease is not associated with a higher subacute stent thrombosis rate or with thromboembolic complications and to document the impact on late restenosis. Registries that will soon have data on DES for SVG lesions include the RESEARCH Registry (SVG lesions in 3% of patients), the e-CYPHER Registry (2% SVGs), and the STENT Registry (8% of patients).

Preliminary results of the ongoing follow-up of SVG procedures in the STENT Registry are shown in Table 5 and include 125 patients enrolled from May 2003 through March 2004, representing 8% of all procedures.[7] The results show a very acceptable

Table 5
Saphenous Vein Graft Stent Results from the STENT Registry

Event	n (%)
In hospital (n = 125)	
Death	0
Emergency CABG/Re-PCI TV	0
MI (ST + NST)	4 (3.2)
MACE (Death, MI, TVR)	4 (3.2)
At 3 months (n = 52)	
Death	1 (2)
CABG TV	0
Re-PCI TV	0
MI	2 (4)
MACE (Death, MI, TVR)	2 (4)

STENT, Strategic Transcatheter Evaluation of New Therapies; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TV, target vessel; MI, myocardial infarction; MACE, major cardiac adverse events; TVR, target vessel revascularization.

incidence of thromboembolic complications and MACE for DES in SVG lesions. Adverse event rates are too low to risk-adjust for outcomes of DES versus bare metal stents until greater numbers are collected.

Conclusions

Owing to the tremendous promise demonstrated in lower-risk, single-lesion procedures in randomized trials, the use of DES has rapidly expanded to include a broad spectrum of high-risk patients and complex lesions. Thus, clinical practice has raced quickly ahead of the results of clinical research trials, which have yet to document the safety and efficacy of DES in these more complex patients and lesions. The emerging data discussed above, therefore, will increasingly aid in directing clinical practice for these more complex lesions.

For the 4 complex patient subgroups discussed above, the emerging data suggest that DES might offer an important new advantage for reducing late clinical restenosis. Specifically, in STEMI, early registry reports are promising, with no evidence to date for an increased incidence of subacute stent thrombosis and significant trends for less restenosis. Important randomized clinical trials for DES and STEMI (TYPHOON and HORIZONS) are underway. The early, small clinical series of DES and CTO lesions (longer and more complex lesion morphologies) show that DES might have unprecedented long-term patency. Larger registries are needed in this patient population and will be forthcoming in the United States within the next 12 months. Initial registries of DES for ISR reveal striking reductions in late loss and restenosis compared with brachytherapy historical controls, with a key randomized trial pending (SISR). The use of DES in SVGs is increasing, and in most registries might approach 50% of all SVG procedures. Early results from the STENT Registry indicate no increase in thromboembolic or MACE rates with DES and a trend toward a reduction in target vessel revascularization. Over the next 12 months, important data will emerge regarding much larger groups of these patient cohorts and will help to guide the application of DES for the much broader patient population of "real-world" practice. ■

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Main Points

- Because of the exciting promise of drug-eluting stents (DES) from the SIRIUS and TAXUS IV trials, DES are being applied in a wide range of patients, with clinical and lesion characteristics much more complex than in the patients studied in those trials; preliminary clinical trial data have become available regarding some of these more complex patient subgroups and lesion types.
- For unselected patients with ST elevation myocardial infarction (STEMI), data from the RESEARCH Registry indicated that routine sirolimus-eluting stent implantation seemed to be safe, as compared with treatment with bare metal stents.
- In the STENT Registry, STEMI as the primary indication for percutaneous coronary intervention accounted for 12% of all procedures; acute and 3-month outcomes were excellent, with no significant difference between DES and bare metal stents for major adverse cardiac events (MACE) or subacute stent thrombosis.
- Chronic total occlusions (CTOs) have historically met with lower primary procedural success rates and high restenosis rates; in the feasibility phase of the SICTO study, the sirolimus-eluting stent was very effective in the treatment of CTO, with very low rates of target vessel revascularization and MACE, compared with historical data from bare metal stents.
- Because of the relatively high target lesion revascularization rates after brachytherapy for in-stent restenosis (ISR), there has been an interest in applying DES to this patient population; the TROPICAL study demonstrated that sirolimus-eluting stents were highly effective in ISR, with a very low restenosis rate when compared with historical results of brachytherapy.
- Patients with saphenous vein graft (SVG) lesions experience higher clinical restenosis rates than do patients with de novo lesions and are a group in whom DES might have an impact on long-term outcomes; preliminary results of the ongoing follow-up of SVG procedures in the STENT Registry show a very acceptable incidence of thromboembolic complications and MACE for DES in SVG lesions.

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