

## Drug-Eluting Stents: Impact on Management of Coronary Artery Disease

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It is obvious that the implementation of drug-eluting stents has ushered in a new era in cardiovascular technology and care. Restenosis rates originally as high as 40% following percutaneous transluminal coronary angioplasty (PTCA) were reduced to less than 30% with stents and less than 10% with intracoronary brachytherapy. Now, with the development of drug-eluting stents, restenosis rates appear to be in the range of close to 5%. A large amount of research is ongoing in the area of drug-eluting stents, and a session held at the European Society of Cardiology Congress 2002 sought to highlight much of it.

### Are All Drug-Eluting Stents Equal?

**Presenter: E. Grube (Siegburg, GE)**

There are 3 components to a drug-eluting stent system -- stent design, pharmacologic agent, and drug carrier vehicle -- all of which have an impact on clinical outcomes. There are a number of agents currently under investigation (Table 1).

**Table 1. Potential Agents Under Investigation for Drug-Eluting Stent Systems**

<b>Antineoplastic agents</b>	<b>Trial Acronym*</b>
Paclitaxel (taxane)	TAXUS, DELIVER
QP-2	SCORE
Actinomycin D	ACTION
ABT 578	
Vincristine	
Methotrexate	
Angiopeptin	
Antisense c-muy	
<b>Immunosuppressants</b>	
Sirolimus	SIRIUS, RAVEL
Everolimus	FUTURE
Tacrolimus	PRESENT
Tranilast	
Dexamethasone	EMPEROR, STRIDE
Mycophenolic acid	
<b>Migration inhibitors</b>	
Batimastat	
Halofuginone	
<b>Enhanced healing agents</b>	
VEGF	
17-beta-estradiol	
HMG CoA reductase inhibitor	
BCP 671	

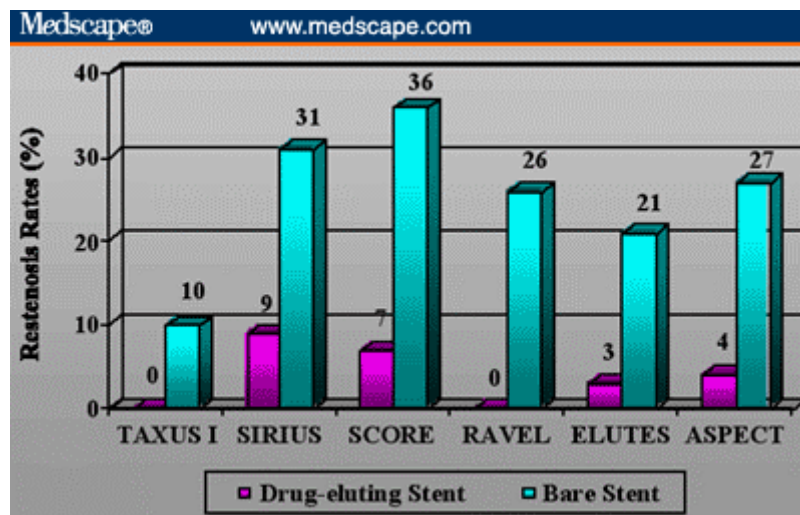
\*See glossary for expanded trial names.

An array of drug-eluting stent systems, each with unique delivery systems, stent platforms, carrier matrices, and agents used, have shown favorable 6-month angiographic follow-up binary restenosis rates (Figure 1, Table 2). The efficacy of the technology is confirmed by the consistent findings of low restenosis rates despite differences in drug-eluting stent systems.

**Table 2. Drug-Eluting Stent Trials: Manufacturer, Device, and Drug Overview**

Study Acronym*	Company	Stent	Drug
ACTION	Guidant	Tetra	Actinomycin D
ASPECT	Cook	Supra	Paclitaxel
DELIVER	Guidant	Penta	Paclitaxel
ELUTES	Cook	V-Flex Plus	Paclitaxel
EVIDENT	Jomed	Jostent	Tacrolimus
PRESENT	Jomed	Jostent	Tacrolimus
RAVEL	Cordis/J&J	Bx Velocity	Sirolimus
SIRIUS	Cordis/J&J	Bx Velocity	Sirolimus
TAXUS I-IV	BSC	Nir/Express	Paclitaxel

\*See glossary for expanded trial names.



**Figure 1.** Binary Restenosis Rates at 6 Months.

Regardless of the type of drug used, the therapeutic benefit vs the local vascular toxicity must always be considered. Concerns surrounding issues related to the drug, stent, lesion, and deployment (Table 3) remain unresolved.

**Table 3. Unresolved Concerns About Drug-Eluting Stents**

<b>Drug-related</b>	Type of drug
	Polymer
	Tissue interaction
	Value of animal trials
	Diffusion characteristics
	Edge effect

	Aneurysms
<b>Stent-related</b>	Stent-to-lesion ratio
	Stent design
	Stent apposition/malapposition/incomplete
	Late thrombosis
	Restenosis rate (peri-stent and in-stent)
	Geographical miss
<b>Lesion-related</b>	Lesion length
	Tortuosity
	Ostial lesions
	Plaque burden
	Morphology
	Plaque and artery anatomy
<b>Deployment-related</b>	Pressure of balloon inflation
	Injury outside the boundaries of the stent

Ultimately, interactions between all components of the stent system yield the potential for complications, and unfortunately, it is still a matter of trial and error until the exact definitions of treatment are determined. Ideally, an optimal stent system will include excellent delivery with good scaffolding properties and low restenosis rates. Other factors that would comprise an "optimal" drug-eluting stent include:

- MRI friendly, nonferromagnetic
- Improved drug loading patterns
- Pharmacokinetic diversity
- High deliverability
- Biodegradable properties

### Conclusions

While there are a lot of reasons to be optimistic about drug-eluting stents, caution is warranted, since plenty of work remains unaccomplished and many of the aforementioned issues still require resolution. As new trials develop and results accumulate, the true extent of the benefits of this revolutionary change in interventional cardiology will emerge.

### A New Trial Comparing Drug-Eluting Stents vs Surgery. Is It Feasible? Is It Needed?

Presenter: P.W. Serruys (Rotterdam, NL)

Stents have had a major impact on coronary artery revascularization. For instance, the Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI)<sup>[1]</sup> study demonstrated that patients treated with coronary artery bypass grafting (CABG) had fewer major adverse cardiac events (MACE) than patients randomized to PTCA (difference of 32%). The recently completed Arterial Revascularization Therapeutics Study (ARTS) trial,<sup>[2]</sup> which involved the use of stents, narrowed the gap between CABG and PTCA to 14%. The 2 most recent trials, ARTS and Stent or Surgery (SoS),<sup>[3]</sup> which compared percutaneous coronary intervention (PCI) to CABG, yielded similar rates of MACE in favor of PCI (Table 4).

**Table 4. MACE in SoS and ARTS**

	<b>SoS</b>	<b>ARTS</b>
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	PCI (n = 488)	CABG (n = 500)	PCI (n = 600)	CABG (n = 605)
Death (%)	2.5	0.8	2.5	2.8
Stroke (%)	1.0	1.6	1.7	2.0
Myocardial infarction (%)	4.1	6.6	5.3	4.0
Revascularization (CABG) (%)	5.9	0.4	4.7	0.5
Revascularization (PCI) (%)	8.6	2.8	12.2	3.0
Total MACE (%)	22.1	12.2	26.2	12.2
Difference $\Delta$	$\Delta$ 9.9%		$\Delta$ 14%	

While positive in a general sense, when examining high-risk subsets of ARTS patients -- including those with 3-vessel disease (n = 402), a lesion in the proximal LAD (n = 477), and unstable angina (n = 407) -- CABG appeared to confer lower rates of MACE compared with PCI (Figure 2).

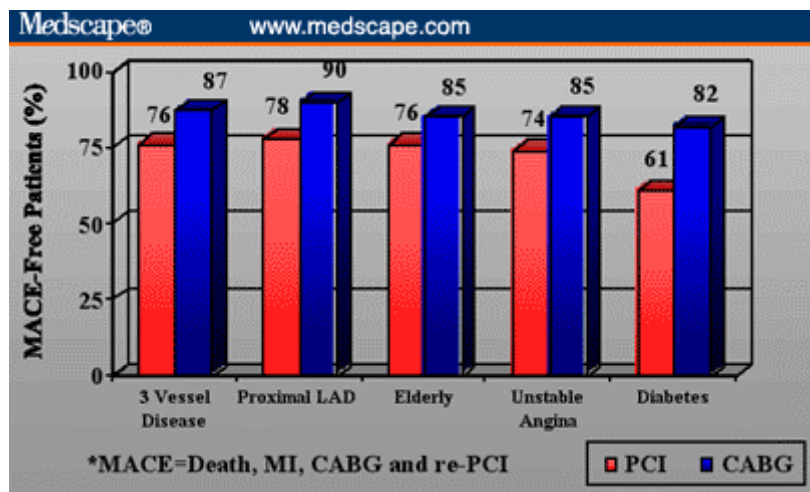
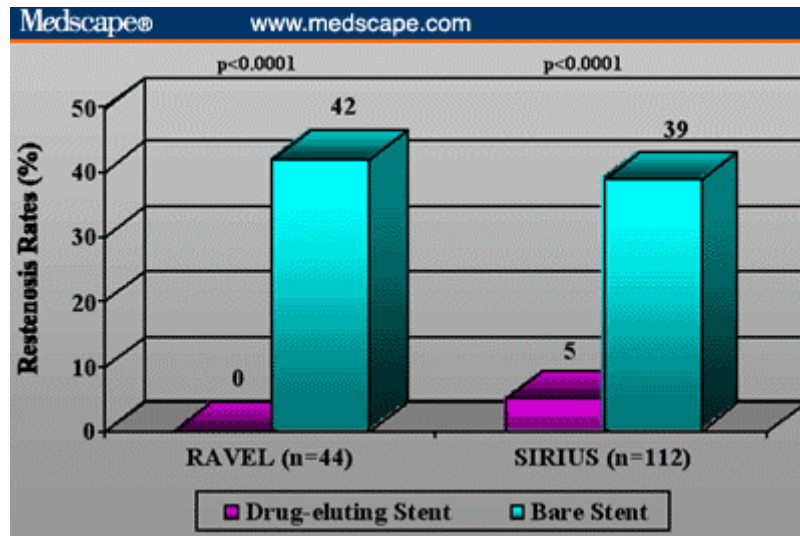


Figure 2. ARTS: MACE\*-Free Survival.

The difference in outcome between the general population and those at high-risk was not due to irreversible events. For instance, the rates of death, stroke, and myocardial infarction (MI) were similar for patients who were randomized to the stent arm and those randomized to CABG (90.5% vs 91.2%, respectively). Rather, the differences can be attributed to the variance in rate of revascularization procedures between the groups. After 1 year, the MACE gap between patients randomized to stents vs CABG was 14%; at 2 years it widened to 15%, and at 3 years, it reached 18%.

Perhaps one way to resolve this issue is to use a combination of drug-eluting stents, glycoprotein IIb/IIIa inhibitors, and statins. Looking at the restenosis rates reported in the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions (RAVEL),<sup>[4]</sup> the event-free survival of patients with diabetes treated with a drug-eluting stent was 94%, compared with 70.7% in patients randomized to a bare stent. Similar results were obtained in the Sirolimus-coated VELOCITY stent in treatment of patients with de novo coronary artery lesions (SIRIUS) trial in the United States (unpublished). Figure 3 shows a comparison of the restenosis rates among the diabetic patients treated with drug-eluting stents in the RAVEL and SIRIUS trials.



**Figure 3.** Binary Restenosis Rates in Diabetic Patients.

On the basis of recent data obtained from the Lescol Intervention Prevention Study (LIPS)<sup>[5]</sup> trial (fluvastatin vs placebo in patients undergoing PCI), it is hypothesized that a MACE rate at 1 year of 11% could be obtained when combining a drug-eluting stent and a statin -- the same rate obtained in the surgical arm of ARTS. Still, not all questions have been answered regarding the use of drug-eluting stents, particularly in high-risk populations. Some issues that remain outstanding include the impact that drug-eluting stents will have on:

- Lesion length
- Small vessels
- Chronic total occlusions
- Bifurcation lesions
- Main stem lesions
- Diabetes
- Renal insufficiency

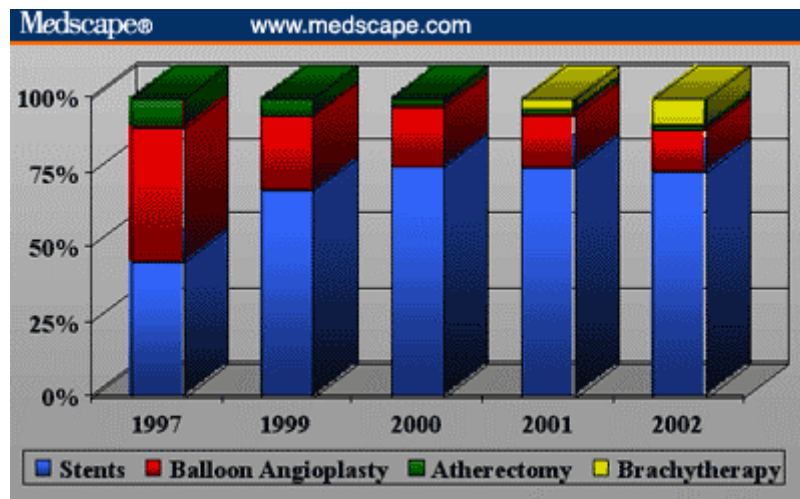
### Conclusions

Physicians strive to implement minimally invasive treatments -- which explains the need for percutaneous interventions; however, physicians, particularly surgeons, will only be convinced of the superiority or inferiority of a system through evidence-based medicine, and in the absence of such proof, entrenched surgical practice will continue. Randomized trials are needed to prove the worth of drug-eluting stents over surgery, but, according to Dr. Serruys, as time passes, finding patients willing to accept the randomization process may become increasingly difficult. Moreover, Dr. Serruys believes that if the high costs of drug-eluting stents preclude the treatment for financial reasons, such as for those with multivessel disease, CABG procedures will continue; however, its continuation will be primarily for economic reasons as opposed to medical purposes. Therefore, he concludes, researchers should now act within the window of opportunity to create randomized trials comparing CABG vs PCI (with drug-eluting stents).

### Is There a Future for Other Devices: Plain Balloon, Atherectomy Devices, Noncoated Stents, Brachytherapy?

**Presenter: R. Waksman (Washington, DC)**

A shift, clearly reflected by the experience at the Washington Hospital Center, Washington, DC, USA (Figure 4), has occurred over the years in interventional cardiology. For instance, 5 years ago, operators were using atherectomy devices in approximately 10% of all patients; however, since then, the number has significantly decreased.



**Figure 4.** Device Use at the Washington Hospital Center.

**How should atherectomy devices be used in the present era?** Dr. Waksman explained that there is still a role for debulking devices, specifically for complex (calcified, ostial, bifurcated, eccentric, and bulky) lesions. Other appropriate instances include:

- Facilitating delivery of balloons and stents
- Improving acute outcomes
- Administering prior to brachytherapy
- Reducing the incidence of late restenosis
- Treating failed drug-eluting stent outcomes

There is still substantial controversy regarding these devices, as several trials have shown conflicting results. Some have shown a definitive benefit of atherectomy devices prior to stenting, while others have shown benefit only in patients with bifurcated lesions. With respect to the excimer laser, new findings have shown a benefit in saphenous vein graft lesions, for diffuse in-stent restenosis, for recanalization of chronic total occlusions, and for the dissolution of thrombus in patients with acute MI.

**Is there a place for bare stents?** According to Dr. Waksman, yes, there is -- especially since it is known that there is a direct correlation between vessel size and restenosis. The results from a SIRIUS interim analysis showed a > 9.2% restenosis rate, and when analyzed by target vessel failure, the rate of restenosis was 10.5% vs 19.5% in the control group, which corresponds to a difference of 9%, meaning that 1 out of 10 patients would benefit from the sirolimus stent. These data are not much different from data obtained with the new generation of bare stents. Furthermore, there is insufficient experience with drug-eluting stents, and there are initial reports of vessel toxicity, late thrombosis, malapposition, and aneurysm formation, to the extent that the studies with paclitaxel, batimastat, and actinomycin D were halted indefinitely.

The data of drug-eluting stents for patients with in-stent restenosis are still unclear. From the Rotterdam experience with 16 patients, there were 2 deaths (1 due to late thrombosis), 1 non Q-wave MI, 1 total occlusion at 4 months, and 2 patients with in-stent restenosis, which translates to a 36% restenosis rate.

**What about brachytherapy?** Dr. Waksman believes that the high acceptance rate of vascular brachytherapy will continue to gain momentum, particularly since it is used in over 500 catheterization labs around the world, and the technology is expected to treat over 40,000 patients during the course of 2002. Early reports have shown that late thrombosis has been well controlled with prolonged antiplatelet therapy; edge effect is controlled with long radiation sources; reimbursement is in effect for both the device and the cardiologist; new guidelines from the European Society for Therapeutic Radiology and Oncology (ESTRO) and the National Regulatory Commission (NRC) do not require the presence of the radiation oncologist; and most important of all, efficacy has been demonstrated with more than 5 years of follow-up in de novo and restenosis lesions.

**Economics.** The economics of utilizing widespread technology are always an issue, particularly in light of the rapid advancements in the field. A simple analysis of a catheterization lab that does 1000

interventions a year with an average of 1.5 stents per patient at a \$1000 price tag for each stent shows a total cost of \$1.5 million. Accounting for target vessel failure in 20% of cases that then requires PCI and brachytherapy adds another \$2 million, bringing the total to \$3.5 million a year. Adding a drug-eluting stent into the equation, the price tag for the stents alone would be \$4.5 million, and the likely 10% target vessel failure requiring PCI and brachytherapy would add another \$1 million for a grand total of \$5.5 million, which amounts to a loss of \$2 million per year.

## **Conclusions**

1. While drug-eluting stents may have a great future, there are still many unknowns. The problems that may emerge as these stents go through the regulatory and clinical process remain unknown. Most likely, there will be a place for both intracoronary brachytherapy and drug-eluting stents in the fight against restenosis.
2. Bare stents have the potential to sustain a role in the management of patients, particularly if new advancements can yield similar low rates of restenosis.
3. Atherectomy devices, laser, and cutting balloons will be available for plaque modification to prepare the vessel for either a bare stent or a drug-eluting stent.
4. Brachytherapy will continue to be an effective tool for refractory restenosis.
5. Before they can be used as first-line treatment for PCI, drug-eluting stents will have to become less expensive and the incidence of vessel toxicity must be reduced