Trends-in-Medicine

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SUMMARY

The pivotal trial of Johnson & Johnson's sirolimus-eluting stent, Cypher, is not expected to be stopped early, but the FDA could make a quick judgment on the product once the trial is complete – provided there are no manufacturing issues. Malapposition and edge effect concerns do not appear to be a big issue, but the FDA is concerned about the deaths in a European in-stent restenosis trial, so it appears that J&J initially may get a somewhat restricted label. Competition continues to heat up, but doctors remain cautious if not dubious about the outlook for paclitaxel. Medtronic is rumored to have struck a deal with Novartis to develop everolimus, and the regulatory path for a non-approved drug appears to have gotten easier, making this a stronger – though late -- potential entrant. Doctors are now suggesting that patients who have had brachytherapy may not be candidates for drug-eluting stents.

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Drug-eluting stents definitely have captured the attention of cardiologists. Excitement was running high at the meeting, and doctors clearly are getting impatient to use them. Brachytherapy is trying to find a role for itself in non-coronary indications (e.g., fem-pop and AV grafts), but the consensus continues to be that drug-eluting stents will reduce brachytherapy to a niche product.

FDA officials are following drug-eluting stent development very closely. An FDA official said, "There is a real concern -- and something the cardiology community has learned well -- that benefits in years one or two don't always translate into five- and ten-year benefits. Short term benefits don't always translate into survival. Almost everything we used in cardiac care 25 years ago was later found to be deleterious, with couple of exceptions. We (at the FDA) intend to be very interactive during development (of drug-eluting stents)…Our performance, on average, is a median time-to-market of one year, but we are working with trade associations on ways to shorten that time frame for products with priority review. We think this is something we can do. Part of this relies on early planning, so modules can and do come in early so we can finish the process early."

Another issue of concern to the FDA has become overlapping stents. A speaker said, "It is true that the FDA asked Cordis (J&J) to test rapamycin at two, three and four times the planned dose on the stent. They couldn't increase the drug time, but they increased the drug level three-fold and did not see any toxic effect. If you combine the ELUTES and ASPECT results on the density of drug (paclitaxel) per mm^2, there is a beautiful dose finding aspect, but you know that somewhere at the end of the dose you will have a toxic effect. With (Guidant's) actinomycin-D it is too early to tell, but certainly it is very powerful with a kind of wedge effect, but (using the) 2.5 µg and 10 µg doses -- which are far away from the toxic effect – should be reassuring. Even if there is an overlap of 10 µg of actinomycin-D with another 10 µg, you are still only at 20 µg, and the toxic effect was seen at 40 µg and 70 µg."

The cost of drug-eluting stents may be an important factor in how extensively they are adopted, particularly in Europe. A European cardiologist said, "Currently, we are paying an average of $700 per stent, and 15% of our patients restenose. If we used a drug-eluting stent in all of these patients – and if they are priced at $2,100 -- it would increase our hospital's cost by $3 million a year."

An expert in cost-effectiveness studies discussed both brachytherapy and drug-eluting stents. He said, "Except for the highest risk populations, brachytherapy is unlikely to pay for itself, even in the long run. But despite a cost of $3,000-$4,000 per patient, it is likely to be reasonably cost effective for certain patients. To be attractive for de novo or focal in-stent restenosis, we need improvements in

efficacy or reductions in cost…(On the other hand) we might want to pay something for patients to be angina-free for a year…For a drug-eluting stent to be cost effective, the additional cost has to be $2,500-$3,000 for the average patient. Diabetic patients could pay more…Whether that is the cost they come in at, we can only hope. The pressure will be intense on payors to suck up the cost to make them a reality."

At certain doses, drug-eluting stents may have some of the same problems brachytherapy encountered. An expert said, "I'm only predicting, but I think it will take 24-36 months before there is complete healing with drug-eluting stents…In brachytherapy, what we saw in animals occurred exactly the same in humans, so I think that both brachytherapy and drug-eluting stents are dose dependent. Not one dose will work in everyone. How do we determine which dose to give which patients? It is almost impossible to know. It may depend …more on the amount of normal vessel left than the amount of plaque. We should look at five year results, and if we see a benefit at five years, then I'd say this is a good therapy…(but) the benefit is not going to last forever, that is my prediction."

Drug-eluting stents are likely to be available in Europe this year. J&J reportedly filed for a CE Mark for its Cypher stent last fall, Cook and Guidant filed in January 2002 and Boston Scientific officials said they would file soon. A European cardiologist said, "It is my understanding that Cypher will be available in Europe in April (2002), and I expect to be using it before summer."

Drug-Eluting Stent Comparison

Measurement	RAVEL	TAXUS I	ASPECT High dose	ASPECT Low dose
MLD	2.43	2.97	2.85	2.84
MLD at follow-up			2.53	2.28
Late loss	.001	0.35	0.29	0.57
% DS post procedure	0.14	0	4%	4%
% DS at 6 months	15%	13.3%	14%	23%
Binary restenosis	0%	0%	4%	12%
Clinical events at 6 months	2 Q-MI 2 non-Q MI 1 CABG	0	2 non-Q MI	1 death 1 non-Q MI
MACE	3.3%	0%	11.7%	8.6%

The Regulatory Perspective

FDA officials offered some insight into how the agency is thinking about drug-eluting stents. Among the most interesting points they made were:

► **The primary mode of action** determines which FDA center will handle the application. In 2000, FDA officials indicated that a non-approved drug eluted by either an approved or non-approved stent would be treated more like a drug than a device, with the Center for Drug Evaluation and Research (CDER) taking the lead, not theCenter for Devices and Radiologic Health (CDRH). CDER is considered a much tougher and longer regulatory path than CDRH. However, it appears the FDA has changed its mind on this, and now FDA officials are saying that CDRH probably will be the lead center on all drug-eluting stents.

► **Unapproved drugs** eluted by stents will have to show a "no adverse effect level" (NOEL).

► With respect to **cGMP**, drug-eluting stents fall into a sort of gray area. They may be subject to some drug requirements, even if CDRH is the lead. That is, CDER may have GMP requirements in addition to CDRH's requirements.

► **Pitfalls** the agency has encountered so far include:

- → ***Durability of the coating***. An official said, "Spraying a coating on a stent could create a pit or defect, so you need to look at that."
- → ***Incomplete in vitro PK.***
- → ***Lack of sufficient drug chemistry studies***, which include stability protocols/shelf life, sterilization of the finished product, drug distribution on the stent, and residual solvents.

► **Pre-clinical animal evaluations** should explain how rapidly a drug is delivered to the arterial wall.

► **Clinical studies should correlate with in vitro PK studies**, particularly for the hydrophobic drugs (NOTE: paclitaxel is hydrophobic).

► **One and six month preclinical data** is required. Three month data is recommended but still optional. To initiate a human clinical trial, 90-day animal feasibility data at the planned clinical dose plus 3-10 times the clinical dose are necessary. Before initiating a pivotal study, 180-animal data at the same range of doses is required – plus an FDA review of the feasibility data. An official said, "You may have a product that seems highly efficacious and a small study demonstrated efficacy, but you also need an adequate safety database. "

All intended clinical uses should be evaluated, including overlapping stents (with a 4 mm overlap) and pre-existing in-stent restenosis. An official said, "The Wall Street Journal reported a very, very important adverse event with a drug eluting stent when used in arteries previously treated with brachytherapy. So, it is important to look at all intended uses. **We are recommending that all uses be evaluated, or you will get some restrictive labeling when you get approval."** Another official said, "To avoid unfortunate labeling, the agency wants to be convinced the pre-clinical work would account for all the uses, and coronary stents are overlapped…

We learned a lot from the intravascular brachytherapy experience in terms of problems … that could cause late events, etc., and many of these are the same issues we've seen with drug-eluting stents. And we may see even more new safety issues with drug-eluting stents. So…we recommend you include in the pre-clinical animal data the problem of overlapping stents because in normal clinical practice, edge dissections occur 5%-10% of the time. So, we need both preclinical and clinical data on this. We would expect in the clinical protocol that you comment on what you plan to do if there is a drug-eluting stent placed and you have an edge dissection. One would expect you would want to put in another drug-eluting stent next door with some overlap." Another FDA official said, "In the end, the clinical data is the most important. My recommendation is to design preclinical and clinical trials to actively give you the ability to overlap stents. If we don't have preclinical data showing overlapping safety in the IDE we approve, we might limit the label to only bailout situations and that may not give allow you to use them for overlapping when you get device approval."

► **Clinical trials must be nine-months long**, have a primary endpoint that is clinically meaningful (i.e., mortality, MACE, TVR -- not just TLR) and an angiographic secondary endpoint. An IVUS sub-study is strongly encouraged. Five-year, post-market follow-up will also be required.

► The FDA also is concerned about the **antigenicity** of drug-eluting stents. An official said, "It would be devastating if there were circulating antibodies, especially in coronary arteries. The cardiac system is one of the key sites for immune reactions. We are wrestling with this issue. We are aware of it. We don't know how to get a handle on this because animals don't reliably model this."

Sirolimus/Rapamycin: Johnson & Johnson

It now appears that J&J's Cypher (sirolimus-eluting BX Velocity) stent will not be available in the U.S. ahead of schedule. The original target launch date was early 2003, but rumors have been circulating that J&J might file the Cypher with the FDA early – perhaps as soon as February 2002 – based on nine-month data on the first 400 patients in the pivotal SIRIUS trial, rather than waiting until nine-month data on all the patients are available in May 2002.

However, three things make that unlikely: the FDA submission process, deaths in an unrelated trial, and manufacturing issues. A source said, "The (SIRIUS) trial will not be stopped early because all the patients already are enrolled. It is a rolling submission, so the FDA is getting information as it is collected. A decision could come as soon as the last patient is filed, as early as June 2002."

1. Modular FDA submission. J&J has fast-track status and is using a rolling or modular submission. A knowledgeable source explained, "This isn't like a drug trial where it would be inappropriate to continue patients on placebo when a life-saving therapy is available. All of the patients in SIRIUS already have been enrolled, and the company is doing a rolling submission, giving the data to the FDA as it becomes available. So, the FDA could approve this a month after all the data is in."

2. Deaths in a non-pivotal Cypher trial. Until recently, the sirolimus-eluting trials had no deaths and only one case of restenosis, and that was 51%. However, two deaths were reported in early February 2002 in a 40-patient in-stent restenosis trial being conducted in Brazil and the Netherlands. This was a 40 patient, in-stent restenosis trial being conducted in the Netherlands and Brazil. None of the 25 patients in Brazil had any serious complications, but six of the 15 patients in the Netherlands had adverse events, and two of these died. Dr. Patrick Serruys, the investigator in the Netherlands, said, "All the adverse events related to protocol violations… I think these are incidental, peculiar cases. I am not impressed (concerned) by these deaths. We do need to watch patient and respect the protocols. There were some deviations from the protocol in our 15 patients, and if you follow the protocol, I don't think there is a problem. We pushed the envelope and were 'punished' for that, but I am not worried."

The patients treated in the Netherlands were very sick (three had total occlusions, four had previous brachytherapy, etc.). The patients who died were:

► A 79-year-old man with in-stent restenosis got five sirolimus stents (double full metal jacket) and had "spectacular" results at four months but died at nine months. The investigator, Dr. Serruys, said, "Someone stopped the Plavix (clopidogrel) at three months. It should never have been stopped."

► A patient from India had been treated for in-stent restenosis in the right coronary artery (but who had diffuse coronary artery disease) died on the street three months post-procedure. He reportedly had very diffuse disease – restenosis in the right coronary artery. A post-mortem was not performed on this patient. Again, the Plavix was stopped early, this time after 60 days. Dr. Serruys said, "We pushed the envelope hard…and when you do that, you have to keep the clopidogrel going for a long period of time."

Cypher In-Stent Restenosis Results

Measurement	Sao Paulo N=25	Netherlands N=15
In-stent Late Loss	0.08	0.233 (.03 with one total occlusion excluded*)
Pre-procedure	62%	71.4%
Post-procedure	16%	2.4%
At 4 months	16%	12.9%

* A patient with 34% post-procedure diameter stenosis

On the other hand, there were no adverse events in the patients done in Brazil. A J&J official suggested this was because Brazilian investigators followed the protocol precisely, while European investigators did not.

Most cardiologists at the meeting were not very concerned about these deaths, and the deaths did not dampen their enthusiasm for Cypher or for other drug-eluting stents. A doctor said, "Things can happen."

The take-away message appeared to be that:

(a) **Brachytherapy patients should be on Plavix long-term** – for 12 months or perhaps even permanently. An Illinois cardiologist said, "When I get home, I'll be calling all my brachytherapy patients and putting them on Plavix for life." However, Dr. Serruys suggested that de novo Cypher patients may need only two months of Plavix, "I'm not afraid of short-term (Plavix) therapy with sirolimus."

(b) **Patients who have had brachytherapy should be excluded from clinical trials of drug-eluting stents.** Several speakers made this point. One said, "Drug-eluting stents may not be able to be combined with brachytherapy." Another said, "If you put a foreign material on a surface that is not healed, it will give you trouble." A BiodivYsio investigator said, "For our in-stent restenosis trial, we are excluding brachytherapy patients." Another expert said, "I caution against using drug-eluting stents for long lesions or brachytherapy patients."

However, it may be the order in which the two therapies are used which is the problem. In a live case from Europe performed during the meeting, a patient who had developed restenosis after a paclitaxel-eluting stent was treated with brachytherapy. An FDA official, asked about this, said, "There are a fair number of safety issues with drug-eluting stents due to some of the compounds used on these stents. That is why there is a need for good on-line monitoring and clearly defined protocols with a real commitment by investigators to follow the protocols carefully."

FDA officials appeared more concerned with the implications of these deaths. They hinted that the label for Cypher (and for other drug-eluting stents) may be restricted to de novo lesions until and unless there is clinical trial data to support a label for in-stent restenosis. An official said, "Drug-eluting stents may have certain applications upon approval. While there is always the practice of medicine issue (off-label use), one would hope that doctors will be cognizant of some of the unusual safety problems that already have been observed with these stents and would proceed carefully and with evidence-based medicine."

Questions also were raised about malapposition of some of the Cypher stents in RAVEL. Dr. Serruys admitted there were 12 cases of malapposition in the 240-patient in-stent restensosis trial (two in the control group and 10 in the drug arm), but he insisted this is not an issue of concern. He emphasized that there were no negative clinical effects from the malappositions, "When you look at the malappositions, you may find a small pouch where you see a few spots where the stent is not exactly against the wall. Competitors and (Wall Street) ad analysts jump on that, which not always useful. We insist today that these 12 cases of malapposition have not had a single event, even though clopidogrel was stopped at two months…and not a single diabetic had a malapposition. So, I think this is very reassuring data…When you quantify the malapposition by volumetric analysis, we are talking about 20 mm^3. Sometimes it is proximal, sometimes middle, sometimes distal. But there was no IVUS at the time of placement. If you look at other stent placements, you find an average of 17% malapposition, so probably some of this malapposition was there (at stent placement), not acquired (later). When we looked at the volume in our 10 patients, it was 14%. And there was not a single clinical event even though patients topped the Plavix after two months."

Several theories were suggested by speakers to account for the malapposition, including:

- *Suboptimal stent deployment.* "I suspect there was incomplete apposition in the first place and the stent remains non-opposed. In the placebo (arm), there could be tissue filing the gap in between.
- *Dilution of the drug.*
- *Creation of a void.* "If you oppose your stent in an area of organized thrombus, it is possible the myoblasts can colonize the matrix of the thrombus and you will create a small void."
- *Apoptosis or necrosis.* "Potentially, you could have some apoptosis or necrosis at a certain point."
- *Allergy.* "I wouldn't say the stent is generating allergy, but here are patients with allergy, though usually allergy is shown by growth not necrosis."

The 24-month data on the first sirolimus patients (First in Man) was presented, and it looked good. The 2-year late loss was 0.35 mm. One patient in this group reached 51.5% stenosis, but the investigator (Dr. Eduardo Sousa) said this was because the stent did not cover the entire lesion, "We used only 18 mm stents (in the trial), and that only covered the most severe part of the lesion…For me, this was progression of the lesion, not delayed restenosis. It was a 2 mm lesion at the proximal end of the old lesion/stent. The patient was treated with another rapamycin stent and is doing fine."

First in Man Results

15 Fast release patients *	4 months	12 months	24 months
% obstruction	2.2%	2.3%	4.1%
% DS	4.5	4.0	14.5

*Data on the slow release patients are not yet available.

2. Manufacturing. J&J may not be able to manufacture enough Cypher stents for the U.S. market before the end of 2002, and there were hints from regulatory officials that cGMP approval may take longer than expected.

Combination Sirolimus/Heparin-Eluting Stents.
Apparently at the urging of cardiologists, Johnson & Johnson is investigating the feasibility of combining heparin and sirolimus on the same drug-eluting stent. A speaker said, "You've heard about cases of thrombosis with a drug-eluting stent, and that may be a fine role for these stents -- to reduce this complication should it occur."

The plan right now appears to be for a SurModics-coated sirolimus stent to be topped with heparin embedded in a Carmeda coating. Thus, the sirolimus would elute through the heparin, which has to be on the outside to make contact with the vessel wall. SurModics reportedly would like to do both coatings, but it appears J&J wants to use two different polymers, one for the sirolimus and another for the heparin.

Paclitaxel: Boston Scientific, Cook and Guidant

Experts continue to have mixed opinions about the outlook for paclitaxel-eluting stents. Some continue to believe that it will be impossible to find a dose that is both efficacious and safe, and these sources insisted that Boston Scientific's TAXUS I trial and Cook's ASPECT trial found safe doses but haven't proven efficacy. Other experts believe that paclitaxel will prove efficacious, though probably not with as low restenosis rate as sirolimus/rapamycin. A source said, "I'm not sure it will work either for Cook or for Boston Scientific. There is no real efficacy data yet from either of them."

Safety and efficacy continue to be debated. An expert said, "There is benefit in the two highest doses we tested in rabbits (42 µg and 20.2 µg), but there is more inflammation and more hemorrhage with those higher doses. Medial necrosis is focally present in the high dose, and there is persistent fibrin. At 28 days, there is a benefit, but at 90 days, the benefit is gone once the vessel is fully healed."

Cook and Guidant have taken the lead with their paclitaxel, and that lead may continue to widen. The FDA turned down Boston Scientific's original Phase III trial design, though Boston Scientific has resubmitted its IDE to the FDA for the TAXUS IV trial of a low-dose slow-release paclitaxel. A Boston Scientific official indicated that approval of the IDE is expected in March 2002, with the trial likely to be underway before the Paris Course on Revascularization (PCR) meeting in May 2002.

The role of anti-platelet therapy is being investigated as one of the things that could have contributed to the high thrombosis rate (9%) in SCORE, Quanam's paclitaxel-eluting stent failure, a Boston Scientific official said. Patients from that trial have been advised to remain on lifelong Plavix until the underlying issues are better understood. The official said, "SCORE provided proof of principle that paclitaxel suppresses neointimal response, but that has to be tempered by the safety risk which was unacceptable delayed thrombosis."

Some of the concerns expressed by speakers about paclitaxel include:

- *Disadvantageous remodeling* at higher doses.
- *Fibrin deposition*, even at low dose. A speaker said, "In pigs, at six months, there was a dramatic inhibition of collagen formation and a delay of healing, but fibrin was present…Fibrin was intensely present even 90 days post-implantation at high doses. At low doses, it was there at 28-days but not 90 days."
- *Vascular dilation*. In pigs at 90 days, high doses cause significant vascular dilation, with the vessel pulling away from the stent. Recoil should be 5%-10%, but in high dose paclitaxel, there was no recoil, and the vessel was slightly larger than before the stent implantation."
- *A delay in endothelial growth*, which occurs markedly at high doses.
- *Late animal death*, which a speaker said is almost always due to late thrombosis and rarely due to bare or polymer coated stents, reportedly was 23% in animals given high-dose/fast release paclitaxel. The speaker said, "The presumption is that they died due to thrombosis."
- *Stent design*. This is particularly important with paclitaxel, which is extremely lipophylic (hydrophobic). The greater the number of stent struts in contact with the vessel wall, the better the deposition in the vessel wall. A speaker explained, "There are drug concentrations around the struts and valleys between the struts where there is no drug. It is very hard to get the drug where there is no strut. When struts are not spaced evenly, you run the risk of pooling the drug and isolating sites with no drug, and that might explain the low dose/high dose paclitaxel problem."
- *Overlapping stents* could be an issue – but this may be true of other drugs eluted by stents.
- *Hemorrhage*. A speaker said this has occurred "mostly in patients where the drug was most effective – in the two higher doses (40 µg and 70 µg)."
- *Medial necrosis* – at 20.2 µg and 42 µg.

Actinomycin: Guidant

There wasn't a lot of information on this agent, but a few interesting comments were made:

- 10 µg dose reportedly has the best drug-release profile.
- The 40 µg and 70 µg doses are considered to toxic for development. A speaker said, "At 70 µg, we see holes and gaps in the endothelial lining with platelets and leukocytes and other cellular manifestations. So, upfront the 70 µg dose was excluded, and (another expert) recommended excluding 40 µg. So, the trial was designed with 2.5 µg and 10 µg doses."

Guidant has taken a slightly different approach to its coating by doing that itself, purchasing the polymer and doing the coating in house.

Restn-NG (AVI-4126, Antisense): Medtronic

Among the interesting comments a speaker made about this agent were:

- "It was tried with a variety of delivery vehicles, and all but one was positive."
- "The clinical application remains limited by a relative lack of specificity and slow uptake across the cell membrane."
- Enrollment in the AVAIL trial has been "challenging because of the learning curve required for the Infiltrator balloon."

Everolimus (Certican, RAD): Novartis and Medtronic?

Rumor were flying at the meeting that:

1. Medtronic has licensed this analog of rapamycin from Novartis.
2. Medtronic is about to begin a large animal trial of an everolimus-eluting stent. J&J officials appeared to have their fingers crossed that American Home Products' patents on sirolimus would prevent commercialization of an everolimus-eluting stent.
3. SurModics will provide the polymer for the stent. SurModics had previously announced that it had signed a new customer, and this may be Medtronic and everolimus. J&J officials did not appear upset about this idea.

The regulatory path for an everolimus-eluting stent may be easier than previously thought, given the apparent change in attitude of the FDA toward the use of non-approved drugs on stents.

Miscellaneous

Among the other drug-eluting approaches on the horizon are:

- **A monoclonal antibody on a stent**. A speaker said, "That may be science fiction now, but that is the way to go." Another speaker said, "The idea is that the hemato-poeitic stem cell or progenitor cells will be attracted by the structures on the struts of the stent, and the antibody will be used to attract and promote the cells."
- **Terumo has been investigating statins**, particularly simvastatin and cerivastatin.
- **Biocompatibles' batimastat**.
- **Jomed's tacrolimus-eluting stent**. This agent had been thought not to be a viable agent for drug-eluting stents, but it is getting new attention. Biologically, it is very different from sirolimus. An expert said, "It is 50-times less potent than sirolimus, but the dose can be increased. It has been tested in 14 patients so far."
- **Igaki-Tamai's tranilast-eluting stent**.

A variety of other drugs are being investigated as possible agents to be eluted by stent, including: Interferon gamma 1b, leflunomide, OP-2 and ABT-578.

Oral Rapamune (rapamycin): American Home Products

An investigator-sponsored trial of low dose, oral rapamycin is underway, with data expected at the European Society of Cardiology meeting in 2002. Most experts were dubious about the outlook for oral rapamycin. However, a normally conservative source thought an oral agent may work, "I think if you release a drug only seven days, you will have a benefit at 28 days, but I think you will then have to follow with another dose of the drug. We've done early work with oral paclitaxel, repeating the dose at 30 days and sacrificing the animals at 90 days, and we seem to have benefit if we repeat the dose, but not if we don't." Another speaker said, "I am encouraged that a systemic approach will be effective, but there are issues with practicality, cost and side effects that may not be present with drug-eluting stents."

Polymers for Drug-Eluting Stents

Experts agree that there are several good polymers today for drug-eluting stents. However, it does not appear that anyone has a drug-eluting stent with a biodegradable polymer in development.

Drug-Eluting Stent Trials

Company	Data
Johnson & Johnson (sirolimus)	
N/A (Combination with heparin)	Still pre-clinical
Secondary Prevention of Restenosis ***(ISR)***	Data at ACC 2002
SIRIUS pivotal	Trial will be complete in about May 2002. Data possible at ESC 2002.
RAVEL	12 month data at ACC 2002
First in MAN	Data already presented on 6, 12 and 24 month follow-up.
Cook-Guidant (paclitaxel)	
ASPECT	Presented: 4% restenosis with high dose 12% with low dose
PATENCY	Ongoing (Pivotal US)
DELIVER	First patient enrolled in Nov 2001. About 570 patients are now enrolled and enrollment expected to end soon (Pivotal)
ELUTES –ISR	N/A
ELUTES	3.1% (p=.055)
Guidant (actinomycin-D)	
ACTION	6 mo efficacy/ safety data at PCR 2002 or ESC 2002. Enrollment completed in Nov 2001. Company does not plan to release the 30-day safety data, which it has. (Pivotal OUS)
N/A	(Pivotal US)
AVAIL-US	N/A
AVAIL-OUS	N/A
Novartis possibly with Medtronic (everolimus)	
N/A	Animal study expected to start in first quarter of 2002
Boston Scientific	
TAXUS I	0% at 6 months, not statistically significant because of small number of patients.
TAXUS II	Finished enrollment February 2002. There has been 1 peri-procedural death and 2 thromboses (one peri-procedural and another an angiographic filling defect with no clinical consequences)
TAXUS III	Partial data expected at ACC2002, full at PCR2002. This is a registry in Germany and Netherlands of in-stent restenosis.
TAXUS IV Pivotal	IDE has been submitted to FDA, company hopes to start enrollment by PCR (May 2002)
TAXUS V	This will be conducted only after TAXUS IV, if FDA approves.
TAXUS VI	This will not start until **after** TAXUS IV is complete
SCORE	STOPPED for excess thrombosis.
American Home Products	
ORBIT -I	1 patient with elevated CKMB, one discontinued for bleeding gums, 5 diarrhea that resolved upon discontinuation. No repeat PTCA required for any patients.
ORBIT-IIa	Trial was due to start in mid-Feb 2002
ORBIT-IIb	Six-month data expected at ESC2002
Biocompatibles	
DESCEND	N/A
STRIDE	Final data will be available at ACC 2002.
BRILLIANT	N/A
BATMAN-II	N/A
DISTINCT	N/A

While some experts believe that polymers are key to drug delivery, others suggested that polymers will not be needed the future. Conor Medsystems, for instance, is working on a non-polymer system that might allow delivery of higher drug doses (four to 60 times the dose that can be delivered by polymeric-coated stents). A speaker said, "It is likely that we will ultimately move away from polymeric material-coated stents…Further development will lead away from polymers." Another speaker said, "The Conor stent could allow delivery of multiple, compartmentalized drugs. So, it could have something early for in-stent restenosis, and something late for progression of disease."

Interestingly, SurModics apparently won't be the only company providing a polymer for J&J's sirolimus-eluting stents. A speaker commented that a higher dose of sirolimus would require a different polymer than the one currently being used on the Cypher. In addition, a J&J official also confirmed that the company is not using the SurModics coating for its non-coronary drug-eluting stents. He explained, "There are limitations to the expandability of the SurModics coating, and stents for non-coronary uses need to expand further than coronary stents."

Brachytherapy

The success of drug-eluting stents has caused many experts to predict that brachytherapy is a transient technology that will not be around much longer. One said, "In 2000 I warned that brachytherapy could fade from the scene if later technology worked. That statement basically was true…I think we will keep alive, artificially, a brachytherapy program until drug eluting stent price come down. In the future, (both) de novo and in-stent restenosis patients will get drug-eluting stents, and the reservoir for brachytherapy will shrink. Is brachytherapy transient? Yes. Will it stay? No, except transiently until the price of drug-eluting stents settles down."

Several speakers warned that brachytherapy probably should be a contraindication for participation in drug-eluting stent trials in the future, and some sources believe this may make cardiologists reluctant to use brachytherapy because it could preclude patients from getting drug-eluting stents in the future. This concern is likely to become a more critical issue as the availability of drug-eluting stents gets closer.

The brachytherapy companies – Johnson & Johnson, Novoste and the newest entrant, Guidant – **may** see the writing on the wall. A Novoste official, during a company presentation, painted a picture of the future in non-coronary areas.

However, the deaths in the Cypher in-stent restenosis trial actually may extend the life of brachytherapy systems – at least for a short time in the U.S. -- if the FDA puts a warning about use for in-stent restenosis in the label for drug-eluting stents. And many of the concerns about brachytherapy that were discussed in the past – geographic miss, edge effect, logistics, safety – have been resolved, though cost remains an issue, especially in Europe. Dr. Serruys commented, "Brachytherapy did achieve its goal. Trials for in-stent restenosis have shown it works, reducing MACE 24%-68%, so there is no doubt that brachytherapy is the way to go if you want to achieve something for in-stent restenosis. The missed opportunity with brachytherapy is the treatment of de novo lesions without stenting." A Novoste investigator said, "We are moving to off-label use (for de novo lesions)…but in high-risk patients (e.g., diabetics), we need more definitive data before we use brachytherapy. There are still some issues about what is truly going on at the edges, etc." Sources and FDA officials did not appear optimistic that brachytherapy will gain approval soon for de novo lesions.

The uptake of brachytherapy in Europe appears to have slowed somewhat. An Austrian cardiologist said there currently are 150 sites doing brachytherapy in Europe, and the companies hope by the end of 2002 to have a combined total of 200 sites doing 6,000 procedures annually. Right now the number of sites by country is: Germany 65, Belgium 15, Italy 12, Switzerland 8, U.K. 7, Nordic countries 7, France 5, Netherlands 4, and Austria 2.

In terms of competition, Novoste has the market lead because of its ease of use, but Guidant's new, automated machine is capturing attention and market share. There also are still advocates and users of J&J's gamma system. A speaker said, "The Guidant system is preferable because the computer control is more refined." ♦