Trends in Medicine

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DRUG-ELUTING STENTS:

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SUMMARY

Johnson & Johnson got a huge win with its sirolimus-eluting stent, *Cypher*. The RAVEL data showed zero restenosis at six months. In contrast, a suggestion has been made that paclitaxel-eluting stents are pro-thrombotic, and researchers do not believe any of the other drugs under investigation for use with a stent will be as good as sirolimus. The most interesting agents to watch may be Guidant's actinomycin and Bayer's cerivastatin, as well as oral rapamycin and paclitaxel.

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Johnson & Johnson's sirolimus-eluting *BX Velocity* stent has been named the *Cypher*. The amount of sirolimus (rapamycin, American Home Products *Rapamune*) is equivalent to 3% of a single oral dose (180 µg) of sirolimus. A J&J official said the blood level of the drug will be about 2 µg/ml.

The data on *Cypher* from RAVEL (a 240-patient trial) was outstanding. The 210-day event-free survival was 97.5%, a huge improvement from non-eluting stents, and only slight below CABG. At six months the restenosis rate was zero. The primary investigator, Dr. Patrick Serruys, is continuing to follow the original patients, and so far about 12 have agreed to 18-month or 24-month follow-up IVUS, and he said all of them continue to have zero restenosis, "It is still unchanged. Clearly it is like four-six-twelve months – a clean stent. There is no neointimal hyperplasia."

SurModics has the license to the coating used with J&J's sirolimus stents, and it reportedly will get a royalty on all the *Cyphers* sold. The coating is two polymers in a fixed ratio about 5-10 µ thick. J&J officials would not say how much that royalty would be, and they would not say what they have to pay American Home Products for the sirolimus.

The primary objective was the safety and effectiveness in reducing angiographic in-stent late loss at six month follow-up in de novo lesions with *Cypher* vs. a bare *BX Velocity* stent. Patients were given a protective regimen of Sanofi's *Plavix* (clopidogrel) or *Ticlid* (ticlopidine) for two months, instead of the usual one-month regimen.

The consensus is that, at least initially, European doctors will try to use sirolimus stents only on selected patients for cost reasons, but American doctors are likely to switch almost 100% to drug-eluting stents, in part for medico-legal reasons (fear of lawsuit if they have a bad outcome with a bare stent). The legal aspect gained importance with the litigation activity and lawyer advertising about cerivastatin, sources said. A German cardiologist commented, "At first we will experiment and try to be part of studies. If we can show we can lower the repeat rate at our hospital, then we would go for global budgets for their use. We are trying to discuss that with the insurance companies, and some are willing to discuss it and others aren't."

The worst result in the *Cypher* group was 31.5%, and the researcher said that was due to an incomplete opening of the stent, which compared to 50% worst result with the *BX Velocity*.

RAVEL 6 Month Data

Measurement	*Cypher*	*BX Velocity*
Restenosis	0 *	26%
Late Loss	0.01% *	0.80%
MACE	0	2 deaths
TLR	0	22%
MI – q-wave	2	0
MI- non-q-wave	1	0
Event free survival at 210 days	96.7%	72.9%

p=.0001

Further, *Cypher* showed:

- No edge effect
- No acute thromboses
- No subacute thromboses
- No late occlusion
- No late loss
- No restenosis
- No re-intervention

The restenosis rate appeared a little higher than normal in the control group, but patients with arteries as small at 2.5 mm were treated in this trial. When the control patients with restenosis were examined, researchers found they had smaller arteries and more diabetes, so the rate actually was better than what would be expected in patients with smaller arteries (28.4%).

The moderator of the RAVEL session offered some comments worth repeating:

- Not all polymers are harmless (and the Quanam was cited).
- Stents coated with immobilized heparin have so far failed, though the COAST trial is still ongoing with a heparin-coated *JoStent*.
- "We've never seen results like this in clinical cardiology."

Given these positive findings, J&J reportedly plans to look at applications other than the de novo lesions studied in RAVEL, including:

- Bifurcations
- Long lesions
- Small vessels
- In stent restenosis. J&J already has a pilot study of this underway. An investigator said, "We did one case of diffuse in-stent restenosis with five *Cypher* stents, and the six month results were perfect. That was only one case, but it looks quite promising." A A J&J official said, "The data is very preliminary but looks promising."
- Main stem disease. A speaker described this as "a big target."
- Multivessel disease. RAVEL did not treat multi-vessel disease, but that is an area likely to get attention in the future

The one criticism of this trial that may be valid has to do with patient selection. More of the patients in the control group had diabetes and hypercholesteremia and were smokers.

Patient Selection in RAVEL

Demographics	Sirolimus n=120	Control n=118
Male	70%	81%
Mean age	62	60
Previous MI	38%	34%
Previous revascularization	21%	19%
Diabetes	16%	21%
Hypercholesteremia treated	38%	43%
Hypertension treated	62%	61%
Current smoker	27%	33%

Is there any downside to *Cypher*? This is what researchers warned should be watched:

1. Incidence of "stentocarditis" due to impaired local immune response.

2. Late thrombosis. There were three cases of MI in RAVEL. The RAVEL principal investigator explained why these were not considered adverse events, "In all angioplasty there is a risk of MI, and this level of 3% is relatively new. Two of these patients had an angiogram, and there was no stent occlusion, and the other had a 600 CK elevation after the procedure and no pain, so that was probably due to side branch occlusion during the procedure. There is no data that can make us suspect stent thrombosis ."

3. Delayed restenosis. In animals there was some indication of loss of efficacy long-term, though 18 and 24 month data in the first few patients has shown no problems. RAVEL patients will be followed for five years, just in case.

4. The Unknown. A speaker said, "Every new interventional technique so far has had its unique disadvantage. It is very hard to predict what it will be. I'm quite sure a couple of years from now we will have at least one unique sirolimus adverse event. I hope it will be mild."

According to a J&J official, the company has had preliminary discussions with the FDA and CMS (HCFA) "for quite a while. We are involved in collecting health economic data upfront, trying to accelerate the process. There is no agreement for an accelerated process, but there is an understanding by HCFA that this has real potential for patients. The FDA has indicated it is willing to talk about some accelerated review in contrast to the standard review time, but we've had no formal discussions, and we don't have an agreement."

At a press conference following the presentation of the data, J&J officials indicated *Cypher* is on the following regulatory track: CE Mark by 2Q2002 and FDA approval by 1Q2003. In Europe, a J&J official admitted that the company will need both drug review and CE Mark approval, and other sources said this could delay availability in Europe. The pivotal U.S. SIRIUS trial was fully enrolled (1,100 patients) in mid-August 2001 and requires nine month follow-up, so the trial will end in mid-May 2002, and the company plans to submit its application to the FDA a couple of months later.

The consensus is that European doctors will try to use sirolimus stents only on selected patients for cost reasons, but American doctors are likely to switch almost 100% to drug-eluting stents, in part for medico-legal reasons (fear of lawsuit). A J&J official said the company estimated its market at 500,000 stents in Europe and said, "That is what we are producing."

Pricing in the U.S. has been $3,000-$3,200 in RAVEL, but J&J officials said this is being re-evaluated, hinting that the final figure may be lower. Doctors questioned about how they intend to handle the increased cost of these stents said they are going home to figure out where to cut. One of the areas likely to face cuts: IIb/IIIa use, especially in light of the PCI-CURE data indicating that Sanofi/Bristol-Myers Squibb's *Plavix* may be a viable substitute.

A researcher predicted that *Cypher* would reduce the number of patients having CABG, making them PCI candidates instead. However, she noted that there also will be fewer cases of restenosis, so overall there may be fewer PCI procedures done in the future than now.

Additional New Data:

- At the American Heart Association (AHA) meeting in November 2001, Dr. Eduardo Sousa will present RAVEL data on: MACE at 1 and 6 months (though patients will be followed out to 5 years), TLR and TVR.
- At AHA, there also is supposed to be data on the use of *Cypher* to treat in-stent restenosis.

Other Drug Eluting Stents

Several questions remain with respect to all drug-eluting stents, including:

- Will one single magic bullet win out?
- Should local therapy be applied to all patients or only to patients at higher risk of restenosis?
- Should we really use a cancer strategy against a healing process?

Many companies are racing to find a drug-eluting stent to compete with *Cypher*. Several feasible polymers have been found; it is the drug that is proving to be the problem. There currently are at least 29 drugs being tested. A researcher said, "Many coatings work. We have made major progress in this. In the past, coatings were not expanding with the stents and were not sterilizable. Today's coated stents have solved this problem."

Sources insisted that these competitors are further behind J&J than is commonly believed. An expert predicted that none of these competitors will be prove as good as sirolimus, though some may gain regulatory approval. A J&J researcher said, "The competitors are far behind. What is important for me as a doctor, with this drug (sirolimus), I am very confident. It looks very safe which is not the case with some of the drugs. I am never afraid to propose *Cypher* to my patients. I don't want to enter some trials because of concerns about safety. Restenosis is a very big problem, and we have to discuss it with all our (PCI) patients, but it is not life-threatening, and taking an anti-cancer treatment for a non-life threatening disease may be too much."

A J&J official, asked what evidence there is that stents that elute a cancer drug are dangerous, responded, "There is data in the literature about stents that elute paclitaxel that clearly show a narrow therapeutic window through which it works, and in human trial doses, there was incomplete healing, delayed re-endothelialization, and in the worst case, necrosis. It's similar to radiation. One (paclitaxel) trial was stopped prematurely for safety reasons – patients were having MIs, and there was a death due to treatment."

An expert said the ideal drug for stent delivery is anti-inflammatory and specific.

Properties of Drugs in Development for Stents

Anti-Inflammatory	Migration Inhibitor	Healing Promotion
Sirolimus	Batimastat	VEGF
Actinomycin		BCP671
Statins		Estrogen
ABT-578		
BCP678		

The strength of the RAVEL data, and the promise of using drug-eluting stents to treat in-stent restenosis, spell:

❖ **Doom for brachytherapy.** A speaker said, "Europe has had a slow take-up of this technology. In our experience in Switzerland, the late thrombosis has been 12.2%, but adding prolonged antiplatelet therapy has dropped that to 1%. This will continue to have limited use in Europe." Another speaker said, "Next year, cardiologists won't be able to avoid drug-eluting stents. They will be a tidal wave, and in that environment, brachytherapy won't be relevant."

- **A limited role for sonotherapy** (ultrasound delivered by catheter), though the technology looks promising.

- **Uncertainty for**:
  - Soft x-rays, down to almost 1 mm in size.
  - Ultraviolet (UV) light, which has not yet made it to clinic.
  - "Cold lasers" (600-800 nm) with a photo sensitizer.
  - Temperature (heat or cold) has been tried in animal models, and cold is moving to the clinical arena.

Following are comments on some of the key drug-eluting stents under investigation:

Paclitaxel (Boston Scientific and Cook/Guidant). Paclitaxel may have serious problems, including pro-thrombotic activity. An article came out in the journal *Heart* in early September 2001 that reportedly makes a case for the pro-thrombotic theory. Another researcher said, "This is an honest concern from people who showed this experimental data. The *Heart* article shows thrombogenesis in paclitaxel either by local delivery or by stent delivery. We may have underestimated

the toxicity of this drug. Maybe the cell won't die, but the function will be strongly altered, and I think we should definitely pay attention to that." Another researcher said, "It is fairly likely that the action is on the endothelium, so I think it is exactly like radiation."

Cook's paclitaxel data from the ELUTE trial will be presented at the AHA in November 2001, and it is expected to be "okay" but not zero restenosis. Asked why Guidant got involved with Cook and paclitaxel, a researcher commented, "It was just an insurance policy in case it works. It got Guidant some positive publicity now, and helped give its stock a run up." Even a Bristol-Myers Squibb researcher was dubious that paclitaxel will work.

Actinomycin (Guidant). A key researcher said he is starting work with this because "I don't want a monopoly in drug-eluting stents. A monopoly is not good." However, he does not expect actinomycin to prove as effective as sirolimus. That is, it may have a low restenosis rate, but probably not zero. It also reportedly is too toxic at a dose of 70 mcg, so the dose will have to be kept lower than that.

Tranilast. Interest in biodegradable stents is still low, but increasing. There were several favorable mentions of the Igaki-Tamai stent, but the tranilast-eluting Igaki-Tamai stent failed. A researcher said, "It is safe and feasible. The percent stenosis could be better, but it is okay. The concept of a 'permanent stent' may be worn out."

Antisense. Medtronic is working on this with AVI BioPharma. Reportedly, antisense, when delivered directly by balloon catheter, "has no effect." A researcher suggested this may be becaue the dose was too low.

Novartis' *Certican* (everolimus, RAD), an analog of rapamycin. Sources were not aware of any actual development plans for this agent.

The biggest threats to *Cypher* appear to be:

Orals. Perhaps the biggest threat to *Cypher* would be if an oral therapy was proven to work. The FDA has given approval for a trial of oral rapamycin to begin this month, and a trial of oral *Taxo*l (paclitaxel) also reportedly will be getting underway soon.

Statins. Cerivastatin is even more powerful than sirolimus and was described by a researcher as "the most powerful of the statins." If it works eluted on a stent and doesn't cause rhabdomyolysis, it has potential. Reportedly, a Japanese company is initiating a trial of a cerivastatin-eluting stent.

Estrogen. BiodivYsio is working on using its DD stent to elute estradiol at a low dose of 67µg and a high dose of 240 µg. In pigs, an intracoronary infusion of estrogen reduced restenosis by approximately 40%, and there was no negative effect on re-endothelialization. Doctors in the audience where this was discussed questioned whether this would work equally in men and women (the majority of the pigs tested were female).

Actinomycin. While this is not expected to be as effective as sirolimus, it has the marketing power of Guidant behind it, and it would offer doctors an alternative to *Cypher*.

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