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By Lynne Peterson

SUMMARY

The news was mostly good for Johnson & Johnson and Guidant, mixed for Boston Scientific, and too-early-to-tell for Medtronic and Abbott.

√ The preliminary nine-month SIRIUS data showed a 2% in-stent restenosis rate, and a 9.5% in-segment restenosis rate. European cardiologists are anxious to use Cypher stents, but there is little or no reimbursement and that is hampering usage.

√ In the TAXUS trials, restenosis appears to be low, but aneurysms were found, though they are not included in MACE reports due to a lack of clinical effect – yet.

√ Medtronic and Abbott may be trying to convince the FDA to let them skip Phase I and II trials and go directly to a pivotal Phase III trial of ABT-578.

√ The 30-day MACE rate in Guidant's Deliver paclitaxel trial was low, but sources continue to be dubious that this product will be successful.

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EuroPCR: Paris Course on Revascularization May 21-24, 2002

This is the premier interventional cardiology meeting in Europe and one of the leading stent meetings it the world, and drug eluting stents were the hot topic. There were almost more rumors out of this meeting about J&J than news – and most of the rumors were untrue. Among the key rumors circulating were:

Rumor #1: *That the SIRIUS data was so poor that J&J lowered the price of its stents in India and will lower it in the U.S.* Officially and unofficially, J&J officials insisted that this is not accurate. The Cypher will launch in India in June and will be priced less than the U.s. but slightly more than the $2,300 in Europe, they said, pointing out, "There was never a plan to charge U.S. prices in India. Cypher will be priced higher in Indian than in Europe because of different market dynamics there." In the U.S., the price has not been announced but the guidance continues to be above $3,000.

Rumor #2: *That there have been aneurysms in patients treated with a sirolimus-eluting stent.* Again, J&J officials as well as other experts insisted that there have been zero aneurysms in patients treated with a sirolimus-eluting stent, and the doctor in charge of the IVUS core lab for SIRIUS said there were no aneurysms. However, there were three aneurysms with a bare Cypher (BX Velocity) in SIRIUS. This begged the question of whether aneurysms routinely (though rarely) occur with bare stents, and sources were mixed on this, but the consensus was that they occur in 2%-4% of cases, usually as the result of a dissection. Given the length of time BX Velocity has been on the market and the lack of reports of this problem, it would appear that there is no excess aneurysm problem with the bare Cypher.

However, reportedly, there were aneurysms with Guidant's discontinued actinomycin-D, and there have been at least three cases of aneurysms with Boston Scientific's paclitaxel (at least 2 of which were in TAXUS II -- and are thought to have been in the slow release arm). While the aneurysms in the TAXUS trials are real, most doctors at the meeting were surprisingly unconcerned about them. In one case, the angiogram showed large aneurysms at either end of a Nir stent, which a speaker said Boston Scientific preferred to call "pouches" rather than aneurysms. Several experts described these as "pretty nasty." A senior Boston Scientific official said the company is not reporting these pouches/aneurysms as MACE because they were (a) not associated with any clinical events and (b) anecdotal and because no aneurysms "have never been seen in our animal data – at human dose levels." He refused to discuss whether aneurysms have been seen at higher doses.

Rumor #3. *That the Cypher bifurcation registry trial has been halted due to an unacceptably high restenosis rate.* Once, more, J&J officials insisted the trial has not been stopped and is continuing to enroll patients. absolutely insists that this trial has not been stopped and is still ongoing. As of late April, 70 patients had

been enrolled, and by this meeting, the number was up to 86. However, there have been two serious MACE events in this trial:

√ One death that occurred at four months post-procedure in a patient in Italy who was treated with four 18 mm x 2.5 mm Cyphers (small vessels). Three of these stents were placed mid-LAD and one in the second diagonal. At the time of the procedure, the patient was on an anti-arrhythmic, aspirin and clopidogrel. The patient was called at four months and reported feeling fine, but he died of sudden the next day in his office. J&J does not believe that the death was stent-related, but there was no autopsy.

√ The second case was a total occlusion in a patient who got an 18 mm x 2.5 mm Cypher in the LAD and 8 mm x 2.5 mm in the second diagonal side branch. Three days later, the patient presented at the hospital with angina, but was released with nitroglycerin. An angiogram was scheduled and performed, and doctors found a thrombotic event in the LAD by IVUS. The suspicion is that this was an untreated dissection. A source said, "Because it happened so quickly, it would be hard to suggest it was restenosis, but it was a SAT…Bifurcation patients are more complex by nature, and this was a small vessel. The good news is that he was revascularized with balloon and is doing fine."

ONGOING DEBATES AND ISSUES

Is malapposition a problem with drug-eluting stents. Dr. Patrick Serruys dubbed this "the new enemy," saying it occurs with both paclitaxel and sirolimus stents. Initially, malapposition was thought to be caused by stents not being inflated sufficiently, but this same expert said it also has occurred with properly inflated stents and was due, at least in part, to the drugs. He said, "There has been persistence and incomplete apposition of sirolimus stents (not from SIRIUS) at 18 months. In one case, the EEM (external elastic membrane, a measurement of the circumference of the vessel wall) at six months was 12.9 and increased to 15.8 at 18 months…and (in another case) the angle of malapposition increased." Yet, there have been no clinical events associated with these malappositions – yet.

Other experts (including Fitzgerald) proposed a different theory – that most malapposition is actually incomplete or late apposition. Incomplete apposition is caused by insufficient stent inflation and can either resolve on its own or continue (be preserved). Late apposition, they theorize, occurs when a stent appears initially to be properly apposed, but actually has a thrombus or clot between the stent and the vessel wall which later disintegrates, leaving the stent incompletely apposed. In one major lab, the incidence of incomplete apposition is 9%-13% with bare stents. Some heal on their own and some are preserved (where there is no filling in between the struts and the vessel wall).

One definition of malapposition that appears to be becoming accepted is a stent that was properly apposed to the vessel wall at deployment but later pulls away, leaving it incompletely apposed. In this definition of malapposition, the circumference of the vessel wall expands and can be measured by EEM. In contrast, the dimensions of the vessel wall do not change in a late or incomplete apposition. Thus, incomplete and apposition can be differentiated from malapposition. A paclitaxel researcher said, "The crux of the matter is: Are you getting positive remodeling with these drugs? Is the vessel wall pulling away from the struts? You test that by looking at vessel size, and as we look into it, we find that what is not happening is any of these growing away. None are growing away. It's never been a clinical issue to date. That's not saying it is not important to look at it, but there has been no clinical significance – and the worries in the pig model have not been shown in IVUS data."

There did appear to be agreement among experts that this issue (malapposition or incomplete apposition) can be pretty much resolved by changing operator technique – using longer stents, using less pressure, being sure there is no balloon overhang, etc.

Are closed design stents better for drug-eluting stents than open cell stents? This issue first came up at the American College of Cardiology in March 2002. There was not a lot of discussion of it at EuroPCR, but the issue hasn't gone away. Cypher is a closed-cell stent, Achieve an open-cell stent and the Express somewhere in between.

Is it important for a drug to be hydrophobic? Hydrophobic drugs don't travel very far or move very deep into the blood vessel wall. A speaker said, "If we want drugs to migrate outward, there has to be an evolution in the technology because today's technology may not be sufficient…When drugs pool where they are put, they set up the potential for complications."

Did the preliminary results of the SIRIUS trial lower the bar for J&J's competitors? Sources insisted that, to the contrary, SIRIUS has raised the bar for Cypher competitors. Any problems that have occurred with SIRIUS are worse – or likely to be worse – with competing stents, these experts argue.

Is there a "margin effect" with drug-eluting stents? In SIRIUS, in-segment (the stent plus 5 mm on either end) restenosis was greater than in-stent restenosis, which raised the question of an edge effect. One expert explained, "With radiation, the edges were worse than with bare stents. With sirolimus, the edges are worse than in-stent but better than with bare stents." In other words, sirolimus prevents restenosis in the stent, but there was incomplete suppression in the space just outside the stent, with more restenosis in the proximal edge than the distal edge. The results from TAXUS II were not presented at this meeting, but investigators said

they have seen "a significant" amount of edge effect, indicating the "problem: also has arisen in TAXUS II.

However, experts generally agreed this is not the same edge (or "candy wrapper") effect seen with brachytherapy, which was pro-stenotic. Rather, it is less (or a lack of any) inhibition of restenosis at the edges of the stent. They blamed the SIRIUS and TAXUS "margin effect" on balloon injury. In TAXUS II, for instance, a 16 mm stent was mounted on a 20 mm balloon. A speaker said, "We need to be careful how we place these stents…There is no edge effect, but there can be balloon injury. There is nothing promoting restenosis, but nothing preventing it either (on the edges of the stent)…It may be that you just need to try and be as gentle as you can in delivery." Another speaker said, "The incomplete suppression at the margins led to speculation that collateral balloon injury associated with pre- or post- dilatation or stent delivery remains problematic. So, operator technique and stent delivery changes should be considered, including longer stents, avoidance of gaps between stents, and more IVUS guidance."

Are there any new regulatory issues? An FDA official said:

a. Manufacturing approval is still an issue for J&J, which needs approvals for each of the 3 plants making parts of the Cypher.

b. CDRH will continue to be the lead agency for drug-eluting stents, including those with non-approved drugs, but CDER is consulting with CDRH, and non-approved drugs will face a tougher approval process.

Is reimbursement holding back adoption of drug-eluting stents in Europe? The answer was a resounding Yes! Cypher costs $2,300 across Europe, while the bare BX Velocity price varies by country, averaging about $850. European doctors said very few Cypher stents are being put in patients because there currently is little or no reimbursement in most countries, and no improvement in reimbursement is in sight for about six months, at the earliest. A J&J official said 50% of Cypher use in Europe so far has been off-label. Fewer than 300 hospitals in Europe currently are using Cyphers, and several sources said many of the patients currently being done at European centers are Americans who have flown over to get them, sometimes bringing their own interventional cardiologist.

- **Germany** is not increasing its angioplasty reimbursement to give any extra money for drug-eluting stents. Hospitals get $1,050 for the procedure, including stents, and stents are available in Germany for about $200. Thus, hospitals have to absorb the cost of any Cypher stents they use.

- There is strong use already in the **Netherlands**, where a bare stent costs about $670, and a Cypher $2,300. A speaker said, "The price is relatively high in the Netherlands, but Cypher offers value for the money."

- The **U.K.** may be a bright spot, but it is one of the smallest stent markets in Europe. An official from NICE suggested that drug-eluting stents appear cost-effective, and that raises the hope that they will be reimbursed in the U.K.

- **Luxembourg** and **Switzerland** will start full reimbursement in a few months, a speaker reported.

- In **France**, the No. 2 European stent market, a reimbursement decision is expected in September of October 2002. Currently, there is no reimbursement. A Cypher investigator predicted that she would use the stents in 60%-70% of her patients if there were reimbursement, but right now she said she is only using them for high risk patients, "The CE Mark was approved on the RAVEL indication. We practice evidence-based medicine. With the CE mark, about 60% of patients are appropriate for a Cypher. It won't be approved for left main use, for instance…and I think reimbursement will be limited to indications."

- An **Italian** cardiologist (Colombo) said his choice of patients for Cypher is based on insurance: "Patients who have good insurance, get a drug-eluting stent, which means I try to place a drug-eluting stent in every lesion (in those patients)." He reportedly isn't using any Cypher stents for public hospital patients.

In this environment, some experts are recommending that drug-eluting stents be reserved for specific patient subgroups. An Italian cardiologist said, "I've been looking at the data (here) over the last couple of days, and I'm reconsidering (using a drug-eluting stent in every patient). If you a have a relatively short lesion in a 3.2 mm (diameter) vessel, the benefit is really marginal. If you have a 9-10 mm lesion in a vessel that is 3.2 by QCA, then I think you are wasting your money by placing a drug-eluting stent, especially at a public hospital, so maybe some kind of stratification needs to be done – unless patients are willing to pay. But in a public hospital, where you are using the public's money, you need to be a little discriminating."

Their recommendations are:

- Do not use a drug-eluting stent for:

  > Unstable angina. A speaker said, "This is not, by itself, a reason for using a drug-eluting stent."

  > Benestent-like lesions. A speaker said, "These should use plain old bare stents (POBS). Their restenosis rate is highly predictable by vessel size. There is a change of the restenosis rate that can be expected with each vessel length and diameter, and we should encourage its use."

- Do use a drug-eluting stent for:
  - > Diabetics. A speaker said, "Diabetics should be on the top of the list for use, especially insulin-dependent diabetics and those with small vessels. We probably could even consider putting plain old bare stents (POBS) in diabetics with large vessels."
  - > Left main disease. A speaker aid, "I don't say we should stent all these now that we have drug-eluting stents, but when we do, we should use drug-eluting stents."
  - > Long lesions, where restenosis is very difficult to treat.
  - > Bifurcation lesions.
  - > Small vessels –not truly small vessels (which can be treated with a balloon and possibly a POBS) but pseudo small vessels.
  - > Chronic total occlusions – only if they are in the very proximal LAD but not in smaller vessels where the prognosis of the patient does not rely on the patency of this vessel.
  - > Proximal LADs – big ones – only if the lesions are not relatively short and Type A (where a POBS should be considered).
  - > Possibly saphenous vein grafts (SVGs).
  - > Multi-vessel disease. A speaker noted, "Drug-eluting stents will increase the number of patients in whom multi-vessel stenting could be proposed instead of CABG, but it will decrease the number of patients in whom we can afford multi-vessel stenting."

A survey of European cardiologists on the last day of the meeting, produced these results on the outlook for drug-eluting stent use:

- 29.5% said drug-eluting stents are not yet available in their country
- 32.9% plan to restrict drug-eluting stents to subsets of patients
- 14.5% will use drug-eluting stents for off-label indications
- 13.3% do not believe there is enough evidence to support use of drug-eluting stents, and they will wait and see before adopting them
- 5.8% will adhere to RAVEL and SIRIUS criteria in the use of drug-eluting stents
- 4.0% will give a drug-eluting stent to every patient

What is the value of a drug-eluting stent in in-stent restenosis (ISR)? The value is obvious in straightforward, de novo lesions, but in total occlusions and in-stent restenosis experts still are not sure they are beneficial. The issue may be answered by the SECURE registry in U.S., but so far results have not been spectacular (yet) with drug-eluting stents:

> Cook's paclitaxel had an event rate of 22%.

> TAXUS III reported a 25% MACE rate.

> There were two deaths in a small J&J in-stent restenosis registry trial, though those were extremely complex patients and probably protocol violations.

Among the unanswered questions about drug-eluting stents:

- What stent lengths should be used for lesions >15 mm?
- Should the stented segment be longer than the lesion length or should only the more severe part of the lesion be covered?
- Does the eluted drug have upstream or downstream effect on the healing process of a proximal or distal dissection?
- What are the consequences of an over dilatation?
- What happens with high pressure dilatation for a calcified lesion?
- What happens with overlapped stents? (TAXUS VI and DELIVER do not allow overlapped stents.)

SPECIFIC COMPANIES

Boston Scientific

The TAXUS program uses paclitaxel in a polymer coating at a dose of 1 μg/mm^2, for a total stent load of 4,000 μg/mm^2 on a 16 mm stent. A researcher said, "The importance of the polymer is: precise dose control, surface integrity and versatility. With a polymer, the drug can concentrate in pockets of the stent and will not have a uniform delivery…The moderate release is the one most clinically suitable and will be the platform for most of the clinical trials…The only difference (between slow and moderate release) is in the first 48 hours. The moderate release gives a much higher dose in the first 48 hours compared to the slow release." The exception to this, of course, is the TAXUS IV ongoing now in the U.S., where the FDA limited the trial to the slow release formulation.

Neither Guidant nor Cook have shown electronic microscopic images of their non-polymer stents coated with paclitaxel, but a TAXUS speaker showed one. That picture depicted bare spots and pools of drug – not even, consistent drug coating.

Antiplatelet therapy should be continued for at least three months with paclitaxel, a speaker said.

Trial results:
In the 61-patient TAXUS I trial, the TLR was 0 at six months and continued to be 0 at 12 months, but there was no 12-month angiographic follow-up. There was a cumulative 3% MACE rate, all TVR. Two stents were used – the Nir and the NirX, and there were no significant differences between the two.

There was no data presented from the 532-patient TAXUS II trial, but the principal investigator said that there is a

"significant edge effect" – worse than in SIRIUS – and probably due to balloon overhang from the use of 16 mm stent on a 20 mm balloon. A investigator said, "Is the higher edge effect in TAXUS II due to a primitive delivery system? The evidence is in the proximal margin. I wonder how many (operators) did the old technique that is likely to cause an edge effect – deploying with low pressure, deflating the balloon, pulling back and then inflating again? It's easy to correct that." Another investigator said, "I see more dissections with the proximal edge. It is an interesting phenomenon, and we should look at it. It is just something we have to deal with even though the drug works."

The safety data from the 30-patient TAXUS III in-stent restenosis trial was presented at the American College of Cardiology in March 2002, showing a 25.1% MACE rate, but about 25% of patients were lost to follow-up. Among the patients with TLR were:

- 2 patients with a gap between two NirX stents
- 1 patient with restenosis in a bare stent next to two NirX stents
- 2 patients with TLR on IVUS due to incomplete expansion of the stent
- 1 patient with anginal complaints and a small MLD

Boston Scientific's **Symbiott** stent for SVGs got a lot of positive attention at the meeting, and a few days after PCR, it received a CE Mark. Symbiott is a self-expanding nintinol stent encased in a thin, porous ePTFE polymer membrane. Positive 30-day results were reported at the meeting from the prospective, non-randomized, 77-patient SYMBIOTT II trial. SYMBIOTT III, a randomized U.S. trial of up to 700 patients is currently underway, and a U.S. launch is expected in early 2004.

SYMBIOTT II Results

Measurement	Symbiott	Control
MACE	5.2%	13.5%
Death	0	0
Q-wave MI	0	0
Non-Q-wave MI	3.8%	N/A
Late loss	0.3	1.1
% DS	15%	N/A
TVF	14%	29%

Guidant

Everolimus (SDZ, RAD): There is no human data from this rapamycin-analog program yet; it is still in the preclinical stage. A researcher said the company is pursuing two (animal) dosages: fast release (282 µg/cm^2) and slow release (205 µg/cm^2), noting, "Everolimus inhibits smooth muscle cell similar to rapamycin."

Paclitaxel. Guidant approach to the drug-eluting stent competition is: It's the combination of drug and delivery system that matters. And Guidant's newest stent, the MultiLink Zeta, which was launched in May 2002, has a low restenosis rate: 17.5%. Guidant officials said they intend to offer all their stent platforms with drug-elution.

Guidant filed for a CE mark for its Achieve stent coated with paclitaxel – based on the data from Cook's ELUTES trial of paclitaxel on a Cook stent. It might seem unlikely that one drug-eluting stent could be approved based on data from another, even though the drug is the same, but a regulatory official who spoke at the meeting insisted it is possible, particularly if the European country in which the submission was made was one of the "friendlier, looser" countries, like Belgium. He said, "That is a loophole people are trying to close." However, Guidant filed in the U.K., so it is still impossible to predict the outcome of this submission.

Experts continue to predict that the Cook/Guidant paclitaxel effort eventually will fail. They adamantly insist that non-polymer paclitaxel-eluting stents will not work. Doctors involved in DELIVER explained that the protocol calls for replacing any stents not deployed within 90 seconds, raising a concern that too much of the drug will be "washed" off during delivery.

DELIVER and TAXUS IV may compare favorably to SIRIUS because, a source suggested, the inclusion criteria in those trials are not as broad as in SIRIUS. This expert recommended looking at the percent reduction – not absolute reduction – in restenosis to compare the trials, "any improvement greater than 50%, and doctors will use it. A 70% improvement is great."

So far, however, DELIVER appears to be going well. The 30-day safety data from DELIVER showed no significant problems, though eight patients had a total of 14 events. Those events included Q-wave MI and non-Q-wave MIs (defined as 3xCPK plus the presence of MB), SATs, TLRs and a death, with the most events occurring in Group A, but the death in Group B. However, the trial is still blinded, so it is not known which group is the drug arm of the trial.

DELIVER 30-Day Safety Results

Measurement	Group A n=524	Group B n=519
MACE (primary endpoint)	1.2%	0.4% *
Q-wave MI	0.2% (1 SAT)	0
Non-Q wave MI	0.6% (3 patients)	0.2% (1)
TLR		
CABG	0.2% (1 patient)	0
PCI	0	0
Death	.2% (1 patient)	.2% (1 SAT)

* p=.287

DELIVER adverse events: Eight patients experienced a total of 14 cardiac events. These included:

Group A:

- Three periprocedural non-Q-wave MIs, one of who had a spiral dissection and bailout procedure
- One TLR who could not be adequately pre-dilated and went to CABG
- One subacute thrombosis (SAT) on Day 12 who had another PCI
- One Q-wave MI with SAT and TLR

Group B:

- One non-Q-wave MI with TLR and PCI
- One Q-wave MI who had an SAT and died

DELIVER was not supposed to have overlapping stents, and investigators reported that <10% of patients got multiple stents. An investigator said, "Doctors are trying to abut the stents instead of overlapping them." Another doctor said, "There was a 27% overlap rate in SIRIUS, but I don't think there is a need for that much overlapping."

Cook

A speaker said, "With ELUTES, we got the dose right. There was re-endothelialization beyond three months, and three months of clopidogrel was enough…There was a wonderful dose response curve."

ELUTES 12-month Results

Measurement	2.7 µg	Control
6-month results		
Late loss	0.1	0.73
Restenosis	3%	21%
Death	0	1
% DS	14%	34%
SAT	1 patient*	1 patient
TLR	3 patients	1 patient
12-month results		
TLR	5%	16%
SAT	0	0
In-stent restenosis	3%	21%

* a proximal edge dissection on day 8 that was successfully treated with PCI.

Johnson & Johnson

A preliminary analysis of the 8-month angiographic and IVUS results plus 9-month clinical results from the first 400 patients in the 1,101-patient SIRIUS trial was presented. A speaker said, "This stuff really works! And I still believe it will transform the landscape of intravascular intervention."

Preliminary SIRIUS Results

Measurement	Cypher with sirolimus N=190	Control (bare stents) n=210
In-stent		
Restenosis	2%	31.2%
MLD	2.47	1.79
% DS	9.2%	37.0%
Late loss	0.14	0.92
Loss index	0.06	0.55
In-segment		
Restenosis	9.2%	32.3%
MLD	2.10	1.69
%DS	23.9	40.5
Late loss	0.25	0.75
Loss Index	0.15	0.46
Proximal margin		
late loss	0.16	0.26 *
Restenosis	0.57	0.58
Distal margin late loss		
late loss	0.04	0.19
Restenosis	2.0%	5.5%
Restenosis by vessel size:		
Small vessels	1.7%	32.7%
Medium vessels	1.9%	37.5%
Large vessels	2.4%	25.0%

SIRIUS Adverse Events

Measurement	Cypher with Sirolimus	Control
MACE	5.3%	18.1%
TVR	7.9%	20.5%
TLR	4.7%	16.7%
In hospital MI	3.7%*	1.0%
Out of hospital MI	0	1.9%
Out of hospital death	0.5%	0.5%
Acute thrombosis ≤24 hours	0	0
SAT (1-30 days)	0	0.5%
Late thrombosis (31-270 days)	0	0
Total thrombosis	0	0.5%
TVF (primary endpoint)	6.8%	19.0%
Survival free from TVF	89%	79.6%
Aneurysms	0	1.8% (3)

*nss

J&J received a CE mark for Cypher in mid-April 2002, and reportedly filed Cypher with the FDA in early May 2002. Sales throughout Europe started April 15, but sources indicated sales are starting out slowly due to reimbursement issues.

In Europe, J&J currently offers Cypher in only 12 of its 56 different BX Velocity SKUs. An official said the company will continue to increase the number of different stents available with sirolimus and predicted that by the time Cypher is launched in the U.S. every length and width will be available with sirolimus.

Other details on these SIRIUS results include:

√ The 7.3% late incomplete apposition (4 patients) was not statistically significantly different from control. The explanation was that these patients were not really complete appositions at deployment, that there was some thrombus or clot behind a strut that made it appear to be good apposition, but that clot dissolved leaving a gap. By EEM measurement, the artery wall measurement in these patients did not increase, did not stretch out, which is what it does if it is malapposition (defined as a pulling away of the wall from the stent).

SIRIUS Apposition

Measurement	Distal edge	Proximal edge
Baseline incomplete apposition	12.1%	9%
Resolved	2.4%	5.5%
Persistent	9.7%	3.6%
Late incomplete apposition	0	7.3%
Malapposition	0	0

√ The Cypher failures were carefully analyzed, and an investigator claimed they were due to operator error or undersizing stents.

√ There was a relatively high restenosis rate (31.2%)in the control arm of SIRIUS, which led some doctors to suggest that the bare BX Velocity stent may be inferior to some other stents on the market.

√ In all of SIRIUS, 28% of patients had diabetes.

Diabetic Patients in SIRIUS
Preliminary Results

Measurement	Cypher N=53	Control n=49
Restenosis	5.1%	39.0%
Late Loss	0.24	1.13

√ The Cypher in-segment restenosis rate varied by vessel size: 14.5% in small vessels, 7.5% in medium vessels; 2.4% in large vessels.

√ SIRIUS lesions were supposed to be 15-30 mm long, but the average turned out to be 14.3 mm. An expert said, "The core lab uses a fixed definition of lesion length, but doctors use a visual estimate." A tercile analysis of lesion length did not find (as has been reported with regular stents) a gradient of late loss related to stent length: "The in-stent restenosis is independent of stent length, which means that the incremental benefit is greater for longer lesions."

√ 27% of patients got overlapping stents, which may give J&J enough data to justify this indication to the FDA.

Currently, J&J has 18 different Cypher trials underway or planned. These include:

- SIROCCO, a six-month, 36-patient, randomized, double-blind trial comparing Cypher to the SMART stent in SFA. Data is due in early 2003, and the PI is Dr. Duda in Germany.
- Results of the Cypher bifurcation study are expected in 2003. The primary endpoint is %DS in the stented branch at six months by QCA, and the PI is Dr. Antonio Colombo (Italy).
- E-SIRIUS, a 353-patient trial of 15 mm -32 mm lesions with direct stenting, should have results at ACC 2003.
- C-SIRIUS, a 100-patient trial. The primary endpoint is MLD at eight months by QCA, and the PI is Dr. Schampaert. Preliminary results will be presented at European Cardiology 2002, with final results in 1Q03.
- Unprotected Left Main trial of 100 patients in the U.S. and Europe, with a primary endpoint of restenosis at 12 months, should be reported in 2003.
- Chronic total occlusions, the 25-patient SICTO trial, will have results in 3Q03. The primary endpoint is in-stent late loss at six months by QCA, and the PI is Dr. Haim Lotan (Israel).
- The 160-patient TROPICAL in-stent restenosis trial should have results by the end of 2003. The PI is Prof. Neumann (Germany).
- ARTS II, a study of drug-eluting stents in multivessel disease, should have results in 1Q2005. This is an open-label, non-randomized trial of 600 patients, and Dr. Patrick Serruys is the PI. It will compare drug-eluting stent results to the bypass arm of ARTS I (a historical control). The primary endpoint is absence of MACCE at one year post-procedure. This trial is about to start.
- FREEDOM is a 1,600-patient trial comparing Cypher to CABG with LIMA to the LAD, with five-year clinical follow-up. The primary endpoint is MACCE at 12 months. This trial is funded in part by the NHLBI and is due to start in 1Q03. A speaker predicted, "Drug-eluting stents may entirely change the diabetes landscape, but CABG remains the best choice for diffuse disease."
- E-CYPHER, a registry of Cypher stents implanted after the CE mark was granted in April 2002.

Jomed

Jomed's tacrolimus is in trouble if not dead. A speaker declared the PRESENT trial a failure, but a Jomed official said this is not true. So far, two of 22 patients have returned for angiography, and both had proximal lesions (one was clearly distinct from the stent), though there was no in-stent restenosis. Thus, the TVR so far is 10% -- or 100%, depending on how you look at it. Jomed's take on this is that the dose needs to be increased, and they are doing that. An official said, "The good thing was that we learned early on that we need to increase the dose."

The European EVIDENT trial of tacrolimus in SVG is still ongoing.

Medinol

Medinol launched its next-generation, closed-cell design NIRflex stent in Europe during the meeting. The NIRflex and the NIRflex Royal received a CE mark in March 2002 and are in clinical trials in the U.S.

Medtronic/Abbott

Through a licensing agreement, both Abbott and Medtronic are developing stents that elute ABT-578, but neither is in human clinical trials yet. A human trial is expected to begin by the end of 2002, but the companies have not yet decided whether this will be a European or U.S. trial. However, neither company has an IDE yet.

Two sources said that Abbott (and perhaps Medtronic) is trying to convince the FDA to permit it to start its human program with a pivotal trial, skipping any Phase I or II trials. A source said, "This is a risky strategy, but the companies are anxious to jumpstart their (drug-eluting stent) program."

Terumo

Terumo is working on a statin-coated stent. Early work was on cerivastatin, but the company is now focusing on simvastatin. An official said, "We are using simvastatin now, but we still could change the statin. Working with the statins and finding a polymer that works have proven to be much more difficult than we expected. We are still in the preclinical stage, and we hope to have data at the European Cardiology 2002 meeting or at TCT 2002."

MISCELLANEOUS

Brachytherapy. Some experts have already rung the death knell for brachytherapy, but a few speakers suggested it will continue to have at least a small role. One said, "Brachytherapy in de novo lesions may have been an opportunity missed. All the problems that appeared in the pivotal trial are being solved – late loss, geographic miss, edge effect, etc. We found that patients needed prolonged antiplatelet therapy…For intent restenosis, brachytherapy is the gold standard and remains as such." Another speaker said, "I suspect brachytherapy will continue as a niche product perhaps as a treatment for failed drug-eluting stents."

Distal protection. There is a huge difference between the attitude toward this technology in Europe and in the U.S. A European cardiologist predicted, "Distal protection devices will not justify their cost." Another European cardiologist said, "One of the issues in Europe is reimbursement." A U.S. cardiologist said, "That is totally opposite from the U.S., where we think it is essential to use distal protection." Another U.S. cardiologist said, "U.S. doctors accept the fact that distal protection lowers complications."

Among doctors in the audience at one lecture, 54.1% said they never use distal protection in SVG, and 73% use distal protection for fewer than 2% of these cases. When a distal protection device is used in SVG procedures, the preference is:

- 31.4% Percusurge
- 29.1% Angioguard
- 7.0% Medtronic AVE
- 32.6% Filter wire EX (EPI)

Interestingly, Kensey Nash's TriActive, which recently got a CE Mark was not mentioned in this or any of the talks or included in any of the lists of distal protection devices available. A Kensey Nash official had no explanation for this and admitted it will make marketing the product in Europe more difficult.

Other current cardiology practices and attitudes.
Among doctors participating in interactive sessions:

- 47.3% are not using any IVUS with PCI, and 87.3% use IVUS for ≤25% of cases.
- 72.5% already have performed a left main stent.
- 63.6% prefer balloon expandable stents to covered stents for SVGs.

A speaker offered these messages for cardiologists:

> Lytics should be used less and angioplasty more. A speaker said, "We can save 2.5 lives per 100 patients by using intervention and avoiding lytics. PCI saves more lives than lytics…The lytic companies realize this, so they are starting trials as lytic supportive therapy."

> Interventional cardiologists need to identify and refer more patients post-MI for an ICD, especially after the MADIT I and II and MUSTT findings.

> Chest pain centers of excellence should be established using the trauma center model for primary angioplasty. These should have formal certification, training, volume requirements, and a 24 hour commitment. Ambulances also should selectively transfer patients to MI centers within 95 miles.

> More post-MI patients should be receiving ACE inhibitors, statins and clopidogrel (Sanofi's Plavix). ♦

New Technology Worth Watching

- Ocular coherence tomography
- Catheter-based MRI
- Stereotactic interventional procedures
- Gene, tissue and cell injection therapy
- Anastomoses devices
- Conor Medsystems stent. This non-polymer system may allow delivery of higher drug doses (four to 60 times the dose that can be delivered by polymeric-coated stents), and it is continuing to attract attention.

Comparison of Drug Eluting Trials

Measure-ment	SIRIUS	RAVEL	Cypher in-stent restenosis	DELIVER	TAXUS III	TAXUS II	TAXUS I	ELUTES	ASPECT	
Results timeframe	9 months	12 months	9 months	30-days	6 months	30 days	12 months	6 months	30 days	
Company	J&J	J&J	J&J	Guidant	Boston Sci	Boston Sci	Boston Sci	Cook	Cook	
Drug	Sirolimus	Sirolimus	Sirolimus	Paclitaxel 3 µg/mm^2 (no polymer)	Paclitaxel 1 µg/mm^2 slow release	Paclitaxel 1 µg/mm^2 slow/moderate release	Paclitaxel slow release	Paclitaxel (no polymer) high dose =2.7µg/mm^2	Paclitaxel (no polymer)	
Stent	BX Velocity (Cypher)	BX Velocity (Cypher)	BX Velocity (Cypher)	Penta (Achieve)	Nir Conformer	Nir Conformer (NIRx)	Nir Conformer (NIRx)	V-Flex Plus	SupraG	
Number patients	400	238	40	Group A 524 Group B 519	30 (25% lost to follow-up)	532 (no control)	61	190	140 high dose	low dose
Patients in drug arm(s)	190	120	40	Either 519 or 524	30	266 slow 266 moderate	31	152 (32 high dose)	48	43
Late loss	0.14	-0.001	0.08 Brazil 0.23 Netherlands	N/A	0.44	N/A	0.35	0.1	0.29	0.57
% DS at follow-up	9.5%	15%	N/A	N/A	15%	N/A	13.3%	10%	14%	23%
Binary restenosis	2% (in-stent) 9.5% (in-segment	0%	12.9% Brazil 16.9% Netherlands	N/A	16%	N/A but margin effect expected	0%	3.1%	4%	12%
Clinical events at follow-up	TLR, TVR, 1 death, in-hospital MI	2 Q-MI 2 non-Q MI 1 CABG 2 deaths	Brazil= 0 Netherlands = 6 events (2 deaths, 1 total occlusion)	Group A: 1 death, 4 MI (3 non-Q-wave), 1 SAT Group B: 1 Q-wave MI (died), 1 non-Q-wave MI	2 TLR, 1 angina, 1 Q-wave	No deaths **Slow:** SAT, MI, CABG, **Mod:** MI	N/A	1 SAT and 1 TLR at high dose, total of 4 TLRs in other doses	2 non-Q MI, 3 SAT	1 death, 1 non-Q MI, 1 SAT
MACE	5.3%	5.8%	2 deaths	A=1.2% B=0.4%	25.1%	4.1% slow 1.9% mod.	3.2%	N/A	11.7%	8.6%
TLR	4.7%	0	N/A	A=0.2% B=0	21.4%	0	0	5%	2%	5%
TVR	7.9% TVF: 6.8%	0.8%	N/A	N/A	N/A	.4% slow 0 moderate	3.2%	N/A	0	0
Event-free survival	89%	94.2%	N/A	N/A	N/A	N/A	100%	89% high dose	96% (75%-98%)	95% (87%-100%)