Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Stent thrombosis was a hot topic, and doctors are keeping an eye on the issue, but most experts do not believe there is enough evidence at this point to prove Boston Scientific's Taxus has a problem. However, Taxus is starting to lose a ***little*** market share to Johnson & Johnson's Cypher, which continues to have supply problems. ♦ Doctors plan to use Medtronic's Endeavor if it gets approved because of the stent's handling, but they predicted it will be a niche product. ♦ Conor's CoStar stent is viewed as credible and probably the technology of the future, but sources insisted the data are still early. ♦ The importance of not stopping Sanofi-Aventis's Plavix too soon – and of continuing aspirin for life – in drug-eluting stent patients is becoming clearer. ♦ A more streamlined regulatory path is needed for modifications to approved drug-eluting stents, but the FDA is unlikely to shorten the process in the near future. ♦ There is a lot of interest in percutaneous valves, but the regulatory hurdles are high, and numerous other issues need to be overcome, making it 5-10 years before they are commonly performed.

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CARDIOVASCULAR REVASCULARIZATION THERAPIES

Washington, DC
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Cardiovascular Revascularization Therapies (CRT), sponsored by the Cardiovascular Research Institute at Washington Hospital Center, is a much smaller meeting than the American College of Cardiology (ACC), but most of the leading experts in the field attend. Because CRT was held only three weeks after ACC, which had been chock full of stent news, there were little new data at CRT – but there was plenty of opportunity to study the data that seemed to fly by too quickly at ACC, including the issue of drug-eluting stent thrombosis. A *Workshop with the FDA* at CRT also provided some good insight into regulatory issues facing the industry.

STENT THROMBOSIS

A key – and repeated – topic at CRT was stent thrombosis. The FDA has no plans for an advisory committee meeting on the stent thrombosis issue with drug-eluting stents. Will the issue cause the FDA to require longer-term data before approving a new drug-eluting stent? A senior FDA official said, "That's the easy answer, but not necessarily the only answer…An FDA official said, "Taxus safety is an issue, but not a crisis."

In Japan, where Cypher is approved and Taxus is awaiting approval, regulators are aware of the issue, but no official statement has been issued yet. However, an official indicated, "The post-marketing division should be able to take some action, but I don't know when." He would not comment on whether this issue would delay Japanese approval of Taxus.

Publicly, opinion leading cardiologists downplayed the significance of what appears to be a slightly higher stent thrombosis rate with Taxus than Cypher, but privately several said the issue is a "concern" that they are watching carefully. However, they stressed, there are no convincing data – yet? – that this is a real phenomenon. If it were to be proven more clearly, they predicted there would likely be a quick and dramatic effect on use of the stent in question.

Among the public comments about stent thrombosis were:

- *Dr. Eduardo Sousa:* "Stent thrombosis is always serious."
- *Dr. Jeff Popma:* "We can't say it (overlapping stents) is a generic drug-polymer problem. It could be, but we won't know until we study them…It could be that…in workhorse lesions, there is not much differentiation (between Taxus and Cypher), but in more complex lesion sets, there may be more differentiation."

- *Dr. Eberhard Grube:* "When we use both stents (Taxus and Cypher), we don't see many differences."
- *Dr. Hans Bonnier:* "Taxus safety is not an issue. I never see stent thrombosis. We've done 2,000 drug-eluting stents at our hospitals, and we've only had one thrombosis. I think it depends on the Plavix (Sanofi-Aventis, clopidogrel) loading dose, etc."

This issue was debated at CRT by Dr. Andrew Farb of the FDA (speaking for himself and not the FDA) and Dr. Eberhard Grube of the Siegburg Heart Center in Germany.

There is a problem. *Dr. Farb noted that:*

- The subacute thrombosis rates with drug-eluting stents appear to be similar to bare metal stents for "vanilla" lesions, but the time window for risk is longer for drug-eluting stents.
- Premature discontinuation of antiplatelet (ATP) therapy clearly increases the risk of thrombosis with drug-eluting stents. He cited one study that found a 29% incidence of thrombosis in patients who stopped ATP early, with death in 44% of these and non-fatal MIs in 48%.
- The thrombosis rate is likely increased for complex lesion subsets such as major side branches, bifurcations, etc. He cited a 178-patient study of bifurcations treated with drug-eluting stents in which the thrombosis rate at six months was 1.9% with Cypher and 4.2% with Taxus. He also mentioned the Italian RECIPE study of overlapping stents in 2,495 patients with 4,578 lesions which found a higher thrombosis rate with Taxus than Cypher. However, he is not convinced there really is a difference between Taxus and Cypher in terms of thrombosis rates, "Nothing I've seen so far separates the two."
- The incidence of hypersensitivity is unknown.
- Drug-eluting stents offer no reduction in mortality or MI rates.
- Continued vigilance for any signal of increased drug-eluting stent thrombosis rates is warranted and prolonged post-marketing studies are needed.
- The incidence of drug-eluting stents-related hypersensitivity is unknown and may be subclinical.

Stent thrombosis is *not* a problem. *Dr. Grube said:*

- "I don't think the stent thrombosis issue should be taken lightly, and it is important to talk about it...but, quite frankly, I don't think stent thrombosis is a problem…If we go by the numbers, I don't think we can say there is a real issue with stent thrombosis…but we have to look at it…The long-lasting effect is something we have to look at out two, three, four, five years…I obviously look at all drug-eluting stents very carefully, and if I had a single doubt – proven by a trial – of one stent having a safety issue, I would discontinue that stent, given the option of having another stent."
- "Personally, I believe there is not a safety issue (with Taxus). In REALITY, there was no statistically significant difference between Taxus and Cypher by intent-to-treat (p=.072), and the difference was borderline by treatment received. You need to beware of post-hoc analyses and alpha error…If you put in more Taxus, you may see more Taxus events."
- The factors contributing to stent thrombosis include:
  - Stent thrombogenicity (material, designs, surface coating, adjunctive therapeutic agent, etc.). But this has improved with better dosing and release kinetics.
  - Procedure-related factors (under expansion, etc.). This has improved with better procedure handling, balloon pressures, and IVUS.
  - Patient/lesion factors (vessel size, increasing length, plaque characteristics, etc.). This has improved with better ATP.
- Major trials such as SIRIUS and REALITY have not shown an increased risk.

Stent Thrombosis in Major Clinical Trials

Trial	Drug-eluting stent	Bare stent control
SIRIUS – stent thrombosis	0.4% Cypher	0.8%
SIRIUS – late stent thrombosis	0.2% Cypher	0.6%
TAXUS-IV – stent thrombosis	0.5% Taxus	0.2%
TAXUS-IV – total thrombosis	1.1% Taxus	0.7%
TAXUS-VI – stent thrombosis <30 days	0.5% Taxus	0.9%
REALITY – subacute + acute stent thrombosis <30 days by ITT	0.6% Cypher 1.6% Taxus	---
REALITY – subacute + acute stent thrombosis <30 days by actually treated	0.4% Cypher 1.8% Taxus	---

ANTIPLATELET THERAPY

Doctors in the audience at CRT repeatedly asked speakers for advice on antiplatelet therapy following use of a drug-eluting stent, especially in light of the questions raised about stent thrombosis. Dr. Antonio Colombo described a patient of his who stopped Plavix after three years of therapy and within days dropped dead of an MI. Experts varied on how long they would continue ATP post-implantation, and when they would use a bare metal stent instead, but they generally agreed that aspirin should be continued forever. An expert recommended, "Even if you discontinue Plavix at one year, keep the aspirin going." Another expert said, "Right now, I'd give aspirin indefinitely."

- **For a patient who *plans* hip or knee replacement surgery.** Experts advised using a bare metal stent instead. One expert said, "I wouldn't put a drug-eluting stent into a patient with elective surgery…If I know a patient has to have surgery, I use a bare metal stent." Another expert said, "If you know a patient has to undergo surgery, it is safer to put in a

bare metal stent. If a patient has to go to surgery a month after a drug-eluting stent, that is not good, so you should not do elective surgery close to a drug-eluting stent."

➢ **For a patient who got a drug-eluting stent and then needs non-elective surgery.** An expert said, "If it is an emergency, we can't do much about it. At this point in time, we don't have data on when it is safe to stop Plavix. Personally, I believe there is something in a given patient we don't understand on why and when he develops stent thrombosis. I think we need to identify those patients at high risk. Until then, I can't give any indication. I think it is safe (to stop Plavix) after six months, but I can't be sure." Another expert said, "Often, you can find surgeons who will operate on Plavix. That is one approach you can take…If you have to stop Plavix, tell (the other) physician to re-institute the Plavix immediately after the surgery is completed. The patient or the physician may forget to resume the Plavix…We tell patients that even if the Pope tells you in the middle of the night to stop Plavix, to call us first."

➢ **For patients who develop a GI bleed.** An expert said, "This is an important question because the GI people are seeing more bleeds now, and they tell us there is more gastric bleeding with aspirin+Plavix, which we don't see as cardiologists. This is a very different situation. I would discontinue the Plavix and the aspirin." Another expert said, "If a patient is bleeding, we have to stop (Plavix)."

➢ **Would a heparin-coated stent be better for elective surgery?** An expert said, "We don't have them on the shelf any more. The truth is the clinical trials didn't show it worked …I think it (heparin) is more a marketing gig than science."

➢ **For patients with an aspirin allergy or hypersensitivity to Plavix.** One expert said, "I would wonder if those patients should get a drug-eluting stent. But we do give Plavix without aspirin. Or, you can use ticlopidine, but cilastazol (Otsuka American Pharmaceutical's Pletal) is not a substitute, in my opinion."

Specific Drug-Eluting Stents

Abbott Laboratories' ZoMaxx

Shortly after CRT, Abbott got approval of its IDE for the ZoMaxx stent (which elutes ABT-578 from a TriMaxx stent). This means the company can start enrolling patients in the ZOMAXX-II trial, a randomized, head-to-head, non-inferiority trial vs. Taxus in 1,670 patients. The primary endpoint is non-ischemic TVR at nine months, and the secondary endpoint is in-segment late loss at nine months. Assuming six months for enrollment, a nine-month trial, and three months for data analysis, Abbott could submit ZoMaxx by the end of 2006, with possible approval in late 2007.

The advantage of ZoMaxx is that the stent is thinner. The disadvantages include the delivery system, which an expert described as "terrible." He said, "What Abbott has now is too old."

Abbott presented three posters at the meeting, providing a rare look into the development of ABT-578 and ZoMaxx.

- A porcine study comparing the bare TriMaxx to Taxus, Cypher, and ZoMaxx. All three drug-eluting stent platforms were comparable in neointimal area, neointimal thickness, and % area stenosis.
- An elution-profile study looked at the elution rates with different doses, and the curves followed the same track. There was slightly more separation by dose in vitro than in animals, but the curves were the same.
- A study of the lipophilicity of ABT-578, which was shown to be twice as lipophilic as sirolimus.

Aqueous Solubility of Drugs Used in Drug-Eluting Stents

Drug	Types	Water solubility
Sirolimus	Amorphous or crystalline	22.2 µg/mL
ABT-578	Amorphous	1.9 µg/mL
Paclitaxel	2 crystalline forms	1.2 µg/mL

Biosensors' A9

Sources predicted this biolimus-eluting S-stent with a bioabsorbable polymer will gain a CE Mark.

Boston Scientific's Taxus

Sources generally insisted the stent thrombosis issue has not affected their use of Taxus since ACC, and they said the ISAR-DIABETES trial reported at ACC, which found Cypher superior to Taxus in diabetics, has not caused a shift from Taxus to Cypher. However, many sources also admitted that they are using fewer Taxus stents now than they were a month ago – or that they expect their use of Taxus to decline slightly (about 10%) over the next few months. A Virginia doctor said, "In our experience, we have not faced a situation that raised a safety concern." A Washington DC doctor said, "In the real world, we don't have any evidence yet of a difference between the two (Taxus and Cypher)."

The apparent explanation for this seeming inconsistency: Sources simply did not want to characterize any change in usage as a market share shift, especially not one due to stent thrombosis. Yet, shifts do appear to be taking place, and the market appears to be headed for a fairly even split between Taxus and Cypher. *(See Cypher vs. Taxus on page 4.)*

Washington Hospital Center Stent Thrombosis Experience

Stent	Acute thrombosis	Subacute thrombosis	Late thrombosis
Cypher	0.1%	1.1%	0.3%
Taxus	0.3%	0.8%	0.5%

Shortly after CRT, Boston Scientific got FDA approval for its bare Liberté stent, which is the platform for the company's next-generation drug-eluting stent.

CONOR MEDSYSTEM'S CoStar

Sources insisted that the CoStar stent is credible, and several said they believe it is the technology of the future. A Dutch doctor said, "Conor has the best concept of a drug-eluting stent, but I think a fully bioabsorbable stent will be even better." He suggested that a bioabsorbable version of CoStar may be in the works, with Conor and Biotronik (which has an absorbable magnesium stent in development). A German doctor said, "I haven't used a Conor stent, but the study looks okay." An Italian doctor said, "I know Conor well. It's credible, but the data are not powerful, except at higher doses…And I don't think we need more drugs (on drug-eluting stents)." A U.S. doctor said, "The Conor stent may be particularly promising, and it looks credible, but it is very early." A Virginia doctor said, "I'm always fascinated by new possibilities, but I'm not excited about the Conor stent."

GUIDANT

Sources were optimistic about the **SPIRIT** program, with the ML Vision eluting everolimus. Sources were less optimistic about the **FUTURE** program, with Xience, an everolimus-eluting stent (formerly called Champion) with a bioabsorbable coating. One expert said, "I have my doubts about it. The results are not as good as expected." A European doctor said, "Even if Champion gets to market, it won't get a lot of attention…Champion is ***not*** an outstanding platform for a biodegradable stent."

JOHNSON & JOHNSON'S Cypher

Supply problems continue to limit cath lab use of Cypher stents, and the issue is not limited to small cath labs. Sources at small, mid-sized, and even some large cath labs said availability has improved but remains an issue, except perhaps for J&J's best customers. Sources do not expect availability to disappear as an issue until after the Guidant merger is completed – probably in fall 2005. A Pennsylvania doctor said, "We are a large hospital, but we get our stents on consignment, and we still have supply issues with Cypher." A Georgia doctor said, "We still can't get Cypher. Availability is still a big issue."

Once J&J completes the acquisition of Guidant, the outlook for J&J's drug-eluting stent program is unclear. Sources believe that, at least initially, J&J will continue to produce and sell Cypher while developing new Guidant drug-eluting stents, but they also predicted next-generation Cypher programs will be abandoned in favor of a Vision-based system with Guidant's polymer. But they are not predicting that J&J will abandon sirolimus in favor of everolimus.

In the interim:

- The next-generation J&J Neo (a sirolimus-eluting cobalt chromium stent) appears to be on hold. A J&J source said this stent would not be available in the U.S. until 2007, and it may get scrapped altogether. Another source said the problem is that adding a polymer to cobalt chromium is proving more difficult than expected.
- Cypher Select is approved outside the U.S., except Canada, but J&J still does not have approval to do a trial in the U.S., and officials would not discuss their regulatory strategy, suggesting this may be on hold as well.
- Cypher on Guidant's Vision delivery system continues to get delayed. The best estimate now is the end of 2005 or early 2006. The FDA is requiring a clinical trial before approving this change.

However, sources are optimistic that the merger will be positive. One source said, "At the end of the day, there will be synergy, and J&J will pick what's best – but I have no idea what that will be."

Cypher vs. Taxus

Sources generally believe that the differences between Taxus and Cypher are getting more and more blurred:

- **In diabetics.** Taxus had appeared to have an advantage, but newer data appear to indicate comparable restenosis rates in diabetics.
- **Deliverability.** In trials, Cypher appears just as deliverable as Taxus, but sources continue to insist that in their clinical experience, Taxus is somewhat more deliverable than Cypher.
- **Longer lesions.** Both Cypher and Taxus appear to work in long lesions. In one study, Cypher appeared better, but in another Taxus was better.

Fifteen cardiologists were questioned about their choice of drug-eluting stent and any market share shifts. On average, sources questioned at CRT use Taxus for an average of 62% of their patients, and Cypher for an average of 38%. Overall, they said their use of Taxus has not decreased significantly since ACC, and only five have seen a decrease in Taxus use or plan a decrease in Taxus use. On average, these five sources estimated use would go down 7% over the next few months, but the others said their Taxus use would remain unchanged.

- *Pennsylvania:* "Prior to ACC, we only used 4.0 mm Cyphers, and now we'll order more Cyphers…We use more Taxus than Cypher because it is more deliverable, but we will move to more Cypher – and we may use more bare metal stents. But we will continue to overlap Taxus stents."
- *Indiana:* "There are no significant differences between Taxus and Cypher. I'll continue to choose the cheapest."

- *Europe:* "In Europe, the choice is based on safety predominantly. REALITY didn't show a safety concern, despite J&J analysis. (Taxus) safety could be the biggest issue in the future, but it hasn't been shown yet."
- *Maryland #1:* "We use Taxus, and I don't see that changing. It is a price issue, not a supply issue."
- *Virginia:* "We use Cypher and Taxus equally. There has been a lot of hype around the stent thrombosis issue, and it is pushed directly or indirectly by industry, so I don't adopt the last breaking news I heard."
- *Michigan:* "I'm mildly worried about the Taxus safety issue, but I don't plan to change my use."
- *North Carolina:* "Stent thrombosis is worrisome, but the experts don't seem too worried about it."
- *Maryland #2:* "We use Taxus and Cypher equally. Clinically, there is no difference. There may be a little tilt to Cypher going forward because of the stent thrombosis and late loss, but my sense is that Taxus is more deliverable."
- *Colorado:* "I'll follow the stent thrombosis issue, but it's only been an issue in one trial. I haven't seen any excess stent thrombosis in my own experience. It is inappropriate to draw conclusions at this point, but we will all monitor the issue."
- "There are no major differences between Cypher and Taxus. A final answer on subacute thrombosis needs a 10,000-patient trial, perhaps 5,000-6,000 if it focused on diabetic patients, etc…The take-home message is stent thrombosis is there, but overall, I don't think this is a done-deal issue. It could be chance. REALITY was not powered to say one stent is safer than the other. But on efficacy, I believe Cypher is preferable to Taxus. And the stent thrombosis issue is not resolved…If you can get Taxus cheaper, I can't say not to use it."
- "Tell your friends to be increasingly careful in stent placement as they increase the complexity of patients. Elderly, diabetic, more complex patients require extremely careful technique."
- "Is Cypher more effective than Taxus? No, period…It looks like MACE is higher with Taxus in general. At best, Taxus equals Cypher, but I think the data are starting to separate them."
- "They are both effective, but the difference is if it is your grandmother and she has stent thrombosis a year later when she stops Plavix. There is a hint of a problem with Taxus, not Cypher, so if I have to choose, I'd choose Cypher."

MEDTRONIC'S Endeavor

The results of ENDEAVOR-III, a randomized, 436-patient, non-inferiority trial comparing 327 Endeavors to 109 Cyphers, will be presented at TCT 2005. Medtronic officials continue to predict that this trial will be positive (meet its primary endpoint), but other experts – including some Endeavor researchers – are less optimistic, indicating it is "just too close to call." One source said, "The data are not as robust now as I would like. The TLR is okay, but the late loss is not fine."

Sources predicted that enrollment in the U.S. in ENDEAVOR-IV may not take as long as the company has said (10-12 months). The first patient was enrolled on April 11, 2005.

Endeavor still does not have a CE Mark, but sources predicted it would gain approval and be launched in Europe in June 2005. Driver (the bare Endeavor) is a very popular stent, considered very deliverable, and sources believe Endeavor will be used in the U.S. as well as Europe if and when it is approved, though probably for only about 10%-15% of the drug-eluting stent market.

- *Europe:* "I like the Driver. I expect to use it when it is available."
- *Germany:* "Medtronic customers will use Endeavor, but Abbott's ZoMaxx may be as popular as Endeavor. Cypher and Taxus will continue to dominate the market."
- *U.S.:* "I would probably try Endeavor, but I'm happy with Cypher."
- *Italy:* "Endeavor is not likely to see broad use based on the existing data. Driver is a real workhorse stent, especially for less skillful doctors, but you don't need to sacrifice the performance of the drug-eluting stent."
- *Israel:* "I would use Endeavor if it were available in Israel. It is easier to deploy than Cypher. Driver is a great stent. The late loss is a trade-off."
- *Colorado:* "I'll probably use Endeavor. The late loss may be high, but the Driver stent can deliver where others can't."

There was no information available at CRT on Medtronic's internal polymer program for future drug-eluting stents.

THE COST OF DRUG-ELUTING STENTS

Dr. David Cohen of Beth Israel Deaconess Medical Center in Boston described how his hospital is handling the cost of drug-eluting stents. He said his newest cost-effectiveness study (soon to be published) found that drug-eluting stents:

- **Save money.** Medicare data for almost 12,000 patients found 16.2% had some revascularization, 12.7% got percutaneous coronary intervention (PCI), and 4.2% got CABG. He said, "If we had a perfect device that eliminated restenosis and didn't cost anything, we would save $2,550 on every patient undergoing stenting…We are not currently saving money because drug-eluting stents are not free, and we don't use only one stent per case."

- **Don't save lives.** He said, "So far, the data on life saving are fairly disappointing. In a meta-analysis of all clinical trials with drug-eluting stents, mortality is right on the unity line. There is no evidence drug-eluting stents save lives."
- **Improve quality of life.** There are data that drug-eluting stents improve quality of life, at least in terms of SF-36 vitality, SAQ anginal frequency, SAQ disease burden, SF-36 bodily pain, and SF-36 physical role.
- **Need reimbursement changes.** He said, "There is a lot of work going on behind the scenes to justify cases with the use of two, three, or four drug-eluting stents, particularly for multivessel disease. Clearly, we are not using a single stent…We need to increase reimbursement on multivessel cases."
- **Are reasonably cost-effective,** even with the cost of Plavix factored in, because they avoid repeat revascularization. Dr. Cohen said, "We save ~$10,000 per patient when revascularization is avoided. In 2003 we concluded that drug-eluting stents are reasonably cost-effective if the bare metal stent TVR rate is >12% and 1.4 stents are used per patient, with a 75% reduction in TVR risk…A lot has changed since then…The cost of drug eluting-stents has come down (more than the cost of bare metal stents), we are using more stents per case, and drug-eluting stents have reduced TVR."

Cost of Stents at Beth Israel Deaconess Medical Center

Stent	2003	2005
Drug-eluting stents	$3,100	$2,300
Bare metal stents	$1,100	$700
Incremental cost of using a drug-eluting stent	$2,000	$1,600
Number of stents per patient	1.4	1.7
Reduction in TVR with drug-eluting stents	N/A	80%-82%

Cost-Effectiveness of Drug-Eluting Stents at Beth Israel Deaconess Medical Center

Vessel diameter	Lesion length				
	10 mm	15 mm	20 mm	25 mm	30 mm
2.5 mm	23%	26%	29%	31%	34%
3.0 mm	15%	17%	20%	22%	24%
3.5 mm	10%	11%	13%	15%	16%

PERCUTANEOUS VALVES

The *Workshop with the FDA* at CRT focused on three areas: drug-eluting stents, percutaneous valves, and distal protection devices. Following is a summary of the percutaneous valve session.

Companies involved in percutaneous valve development may not like it, but the FDA, the FDA's consultants, and cardiac surgery experts all agreed that randomized clinical trials will be a requirement before approval of any percutaneous valve. Even some industry sources believe this is a wise course.

A Boston Scientific official said, "I think it is appropriate to pursue the highest common denominator, especially for a therapy that has to displace an established therapy (surgery). It is hard to take an established procedure from one group and give it to another without solid data…You also have to look at the learning curve. Dr. Cribbier (Edwards aortic valve) has had good results, but others haven't. This is tough stuff to do…When we look at these procedures, we look with allure, not knowing how weak or strong some of the surgical data may be. We have long-standing data, surgical exclamations, but not necessarily long-term data…That makes percutaneous valves potentially attractive, but we don't know without a randomized clinical trial. In markets like this...getting in is less hard than making it a fairly expansive procedure. The real question for industry is not whether we can displace a terrible outcome for the toughest patients but make this a bridge to displacing the core common practice. Can we actually make this a viable mainstream therapy? We can't necessarily comfort ourselves with reasonable data against a worst case scenario. That often is not good enough."

Issues facing percutaneous valves include:

- **Defining the appropriate patient population for therapy.** Can outcomes be improved overall or in subgroups? Currently, the focus with percutaneous valves is on patients who are candidates for surgical valve repair/replacement either because they are too sick or not sick enough, but the major role for percutaneous valves may be in NYHA Class II-III heart failure patients. Dr. Richard Kuntz of Brigham & Women's Hospital said, "There is a notion about percutaneous valves that the non-invasiveness should count for a lot, and the ostensible reversibility of something that doesn't interfere with the natural history of a disease should count for something… but reversibility is not completely established, though it is probably close."
- **Evaluation.** How should a new device that is perhaps less effective best be evaluated against an established 'gold standard' (surgical valve repair/replacement)?
- **Reversibility.** Does a percutaneous valve preclude subsequent standard (surgical) therapy? A speaker noted, "In the Evalve trial, already seven patients have gone to surgery (post-percutaneous valve placement), and at least one has not been surgically repairable. There is another patient who under-went (surgical) replacement (post-percutaneous valve), but that was planned."
- **Current surgical outcomes (early and late).** A speaker said, "We know the (surgical) re-intervention rate, but I don't think we know echographically how good mitral valve repair is five years down the line."

- **What trade-off for less efficacy makes improved safety worthwhile?** A cardiologist noted that percutaneous valves may offer quicker recovery but shorter long-term results." A cardiac surgeon said, "In some patients it is too early to answer that, but does the patient with an 18-month life expectancy need a 20-year valve? Are the new complications better than the old ones…If I left the operating room with moderate mitral regurgitation (MR), it would be unacceptable, but in this setting, decreasing MR from 4+ to 2+ may be good enough." Another speaker said, "What is the trade-off in efficacy you will accept for increasing safety? That is a totally moving target…The definition will not be the same in three years as it is right now."
- **Identifying appropriate patients for a randomized clinical trial.** An FDA official compared this issue to a similar problem in carotid stent trials – getting surgeons and cardiologists to agree on which patients should get surgery and which should get PCI.
- **Learning curve.** A speaker said, "There is a lot of operator variability, especially with mitral valve repair…So, only centers experienced in valve surgery and repair should be involved in the trials. That means 100-150 procedures, and 40-50 in the particular valve used in the trial…Right now the average case in the Evalve trial takes 6-8 hours in experienced hands." Dr. Mitch Kruckoff of Duke University, who moderated the session, said, "It is not just the valve and the lesion but other descriptors that make these patients more difficult to come by, which makes enrollment slow. Having more sites gets into the questing of the operator learning curve. So, there is a conundrum there."

Dr. Bram Zuckerman, head of cardiovascular devices at the FDA, had some interesting comments, including:

- **On aortic valves.** "There is a lack of best data the FDA would like…Balloon valvuloplasty is potentially not the best control in high risk aortic valve population…but where the Agency is coming from is that we have recently asked a cardiac surgeon to review a high volume balloon valvuloplasty hospital, and not surprisingly the results are as you predicted (poor)…Then, it behooves us to develop including criteria for higher risk aortic valve

Percutaneous Valve Programs

Company	Description of valve	Status
Aortic		
Edwards Lifesciences	Balloon-expandable stainless steel stent with equine pericardium tissue valve.	First U.S. patient treated in mid-March 2005.
CoreValve	Self-expanding stented valve with no balloon.	First 2 patients implanted in India in 2004. First patients have been done in Europe. U.S. trial unlikely in the near future.
3F	Valve inserted into the apex of the heart, not through the femoral artery.	Trial underway in Belgium. Phase I U.S. trial expected to start by the end of 2005.
Pulmonary		
Medtronic	Bovine jugular venous valve mounted on a platinum iridium stent (Numed) that can be collapsed on a balloon and inserted.	Currently being tested in the U.K. and France, with U.S. trial expected to start in late 2005.
Mitral		
Cardiac Dimensions	Early-stage percutaneous approach to annuloplasty, with a device inserted into the coronary sinus to reduce the size of the dilated mitral annulus.	Feasibility studies completed.
Edwards Lifesciences/Jomed	Alfieri-type repair.	First-in-man studies of 10-20 patients are expected to begin soon outside the U.S.
Edwards Lifesciences/Viking	A coronary sinus appraoch.	In animal trials and may enter clinical trials in the next 6-12 months.
Evalve	Edge-to-edge repair method uses a tiny metallic clip coated with polyester fabric that can be attached to a telescoping catheter. It imitates the edge-to-edge open surgical technique.	30-patient pilot trial completed. Company waiting for FDA permission to start a pivotal trial.
EV3/Mitralife	An annular ring implant that placed transvenously into the coronary sinus is crimped and detached.	Animal studies ongoing.
Mitralign	Suture-based device that performs percutaneous mitral annuloplasty using magnetic guidance.	Animal studies ongoing.
Myocor Surgical	Robotic surgical approach with a Teflon cord is inserted through the wall of the heart and tightened to close the valve's cap. The device then stays anchored on both sides of the heart.	Phase I surgical study in U.S. ongoing.
3F	Apical approach.	Company working on stent for delivery.
Viacor	Catheter threaded into the coronary sinus to deliver three thin but stiff telescoping alloy rods which push the posterior portion of the mitral valve anteriorly, straighten the coronary sinus, and then are left in place.	Human testing has begun.

surgery…Just as we had difficulty with carotid stent trials – where not everyone agrees on which patients should get surgery – perhaps the professional societies can help in identifying patients where 80% of surgeons might agree with cardiologists that these are higher risk patients…One of the considerations we have to get to before running a pivotal trial is what the exclusion/inclusion criteria are."

- **On mitral valves.** "This is a complex situation, and we need to take it step-wise…The ultimate success criteria for percutaneous heart valve approval is not going to be along a traditional statistical paradigm pathway. We will need to look at the totality of data…not along the traditional way, which underlines the need for good clinical trial conduct and objective data at the end of the day."

At another session at CRT, a speaker reviewed the status of some of the percutaneous valves in development. He said, "I believe valve replacement in the next few years will be very important for aortic stenosis. Surgery really is superior for mitral incompetence…(Medtronic's) Bonhoeffer pulmonary valve is better proven than either percutaneous atrial or mitral valves." However, most experts continue to predict that it will be at least five years before valves are commonly repaired percutaneously, and it may remain a procedure restricted to tertiary centers for much longer than that.

Following is information on some of the specific valve companies discussed at CRT:

- **EDWARDS LIFESCIENCES' aortic Percutaneous Heart Valve (PHV).** This is a proprietary balloon-expandable stent technology integrated with a percutaneously-delivered equine pericardium tissue heart valve. It involves crimping a balloon on a stainless steel stent, and then inserting it into the aortic valve up to the heart. The crimped device is expanded in the aortic valve. The device is held in place by an absorbable suture that, as it dissolves, cinches slowly down. He said, "The balloon generally can expand pretty well – better than I expected…You have to pace the patient correctly to stop the heart…The leak around the stent is being worked on with the technique of valve placement…The proof of principle is there…The first two cases have been done in the U.S., and a trial is starting soon."

- **COREVALVE'S aortic Percutaneous ReValving System.** This self-expanding valve does not require a balloon; the valve works on the stent's spring force. The speaker said, "This should be easier to place, and you don't have to stop the heart (as you do with the Edwards device). Three human cases have been done with a patient on percutaneous bypass, and the company is starting the first registry trial with all patients on percutaneous bypass." Another expert said, "There are issues that mean this will not be in U.S. trials soon."

- **3F THERAPEUTICS' Entrata.** This is a very different approach, taking a valve already approved and used in Europe and inserting it into the apex of the heart, not through the femoral artery. Reportedly, a clinical trial has begun in Belgium. The company plans a full PMA in the U.S. and expects to do a 400-patient trial vs. surgery. A Phase I U.S. trial is expected to start by the end of 2005, with 25-patients at four centers enrolled, and then a pivotal trial will be conducted. An official said the company expects it will take about three years for U.S. approval. New data reportedly will be presented at the Society for Heart Valve Disease in Vancouver, Canada, in June 2005, and at the European Association of Cardio-Thoracic Surgery (EACTS) meeting in October 2005 in Barcelona.

- **EVALVE'S mitral valve Cardiovascular Repair System.** This percutaneous edge-to-edge repair method uses a tiny metallic clip coated with polyester fabric that can be attached to a telescoping catheter. In the 27-patient EVEREST-I trial reported at ACC, researchers found the system can reduce mitral regurgitation to ≤2+, with low MACE complication rates. The FDA recently granted approval for the EVEREST-II trial to begin. But an expert indicated that FDA permission for this pivotal trial may not be assured, commenting, "The FDA now has to decide if the company can proceed to a pivotal trial."

DISTAL PROTECTION DEVICES

Currently, several distal protection devices (DPDs) have received 510K approval from the FDA for use in SVGs, inlcuding Boston Scientific's FilterWire, Medtronic's Percu-Surge GuardWire, and Kensey Nash's TriActiv. Five other DPDs are being tested under IDEs, including Rubicon Medical's Rubicon Filter. The value of DPDs in SVGs has been proven, and they are widely used for that indication. DPDs are also mandatory for carotid stenting, even though there is no randomized clinical trial that has shown they are beneficial for that. In acute MI, the data has not favored DPDs, so their role in that indication remains uncertain.

At the *Workshop with the FDA*, the FDA's Dr. Zuckerman said, "The challenge is to consider whether our science is on the right track for this 510K device, or are there some mid-course corrections the Agency and the investigator community need to take?" An FDA medical officer said, "We understand it has become difficult to conduct randomized trials. We hear that frustration, but:

- We really have no clear idea of the true placebo rate.
- There are no effective surrogate endpoints for SVG trials.
- There are no effective patient-level predictive models.
- We have a concern with outcome drift – that successive non-inferiority studies could set us up for a major problem down the line.
- There is a heterogeneity of device technologies."

Among the interesting comments on DPDs were:

- A speaker said, "For SVG, distal protection is becoming the standard of care...and for carotids I think they also are becoming standard of care."
- A Boston Scientific official warned, "You have to look at the overall clinical (trial) burden relative to the opportunity…We may ultimately see innovation die out in areas like this because (development) may not be justifiable…If the clinical challenge is too high, improved mechanical functionality will not be done."

At another session at CRT, speakers discussed uses for distal protection devices and differences between balloon occlusion and filter systems.

On indications, experts said:

- **AMI** remains a question. Two studies, including the EMERALD trial, found no benefit to distal protection in AMI. A speaker said, "Use must await further trial results. Based on individual characteristics, distal protection is definitely useful and indicated on a case-by-case basis." Another expert said, "For me, EMERALD didn't prove there is no value to distal protection in AMI…I still use distal protection (for AMI). I look at it like a safety belt. It is not how many times you need it. You may not need it in your entire career, but if you use it, and it saves a life, it is worth it. Right now, it is just for the concept of a safety belt, but I think it is still justified to use it."
- **SVG** is proven, and distal protection should be used in every SVG, regardless of how good or bad the lesion looks.
- **Carotid artery** use is not proven but is mandatory. A speaker said, "There is not a single randomized study that shows protection is superior to non-protection."
- **Native coronary artery** use is unproven. A speaker said, "In natives, distal protection is probably overdoing it."

Two principles of distal protection were identified:

1. To benefit from distal protection, distal embolization is required.
2. The most frequent complication of distal protection devices is distal embolization, which is related to:
   - Device placement.
   - Incomplete distal protection due to: limited capture capability, incomplete capturing, or incomplete apposition.

The challenges for the future are:

- Reducing device profile.
- Making devices steerable.
- Better wall apposition – making sure they don't back out and are really opposed to the vessel wall.

Distal Protection Devices

Balloon Occlusion	Filters
Complete control	Continuous perfusions in most patients
Low profile	Simple to use
Good amount of retrieved material	Limit on retrieved material
Efficacy proven in SVGs	Efficacy not proven in SVGs
Devices	
Medtronic's PercuSurge GuardWire	Boston Scientific's EPI FilterWire
Possis Medical's GuardDog	Johnson & Johnson's AngioGuard
Kensey Nash's TriActiv	Microvents' (ev3) Spider
	Guidant's Accunet and Net II
	Medtronic's Interceptor

PercuSurge for SVG *(compared to FilterWire)*	
Advantages	**Disadvantages**
Low profile	Transient occlusion
Captures small particles	Long "parking" segment
	Side branches unprotected
	Requires 2 operators

- Determining optimal pore size.
- Increasing filter capacity.

In mid-April, the Rubicon Filter got a CE Mark, and a U.S. trial is expected to start "soon." The device has a very low profile, small pore size (100 μm). A speaker describe it as a "***very*** elegant and nice device." It is different from other devices because the filter is left in place and a telescoping sleeve is used during retrieval. In a first-in-man trial of Rubicon, there was 93% device success. The device did not cross the target lesion in three patients – but a speaker said no other device could have passed those lesions either. A speaker said, "One of the disadvantages of other distal protection devices is a longer distal part, and this is an advantage to Rubicon."

GLOBAL HARMONIZATION

This was another key topic at the *Workshop with the FDA*. Industry is concerned that the growing world-wide regulatory burden will hamper R&D and slow down innovation. Medtronic's Dr. Susan Alpert (a former FDA official) warned, "We need to pay more attention to making it faster to develop the technology from bench to bedside and not slow down the learning process in the clinic…I think otherwise there will be a revolt on the part of industry." Dr. Hans Bonnier of the Netherlands said European regulators are not likely to slow down their approval process, which currently is much quicker than the U.S., "You can't ask a doctor to slow down when he knows he has that technology and wants to treat his patients…The process to get that done in the rest of the world

should be faster, not the doctors should slow down." Dr. Ron Waksman of Washington Hospital Center said, "I don't think anyone needs to slow down…Europe will continue to have its own regulatory pathway…but I'm hearing from Europe that in certain ways the CE Mark is stepping back." The FDA's Dr. Schultz said, "In a number of areas, we have been able to harmonize a lot of efforts. In clinical data requirements, it has been slower and more difficult, partly because there hasn't been a harmonized consensus when clinical data are or aren't required…(A speaker) talked about not harmonizing to the highest standard, but we need to be sure we don't harmonize to the lowest level either…We need a level where we are all comfortable…Harmonizing the clinical requirements is going to be somewhat difficult because, I think, quite frankly, that we are a ways apart."

Dr. Alpert offered this view of the current regulatory situation:

- Required post-marketing evaluations are almost unique to the U.S.
- Industry-initiated post-marketing evaluations are commonly for reimbursement.
- Reimbursement trials are driven by the claim that the product will get in a given country/jurisdiction, but this actually varies. Claims are very delineated in the U.S.; in Europe, the claim structure tends to be broader and more flexible.
- Other post-marketing trials are market-driven for/by the customer (the clinical community).

In Dr. Alpert's opinion, there are several shortcomings or dilemmas today, including:

- Too many trials of the same product.
- Cost.
- Approval timing.
- Medicine is practiced differently in each geography, and the claims that are accepted vary.
- Quality investigators for so many trials are lacking.
- Many clinicians want to be part of the data generation, but they are not all qualified to be investigators.

Dr. Alpert's View of Future Needs to Encourage Development

Near term needs	Mid-longer term needs
Education and training for investigators on goals and conduct of post-marketing trials	Consider combined safety, efficacy, and economic benefit trials globally, with pre- and post-marketing requirements in one trial
Acceptance of cost effectiveness data when it is needed, across jurisdictions	Initiate a large and simple trial for expanded populations and claims
Acceptance of clinical data more broadly, so timing of approval is common	Clarify what types of data would be useful to the desire for common technology and be able to build these data into the early trials
Not adding more regulatory requirements for post-marketing trials in more jurisdictions	Address economics during the pre-market phase

Japanese cardiologists and regulators also spoke at the FDA Workshop. Dr. Kazuhiro Sase of the National Cardiovascular Center in Japan thanked the FDA for issuing a notification in November 2003 about possible subacute thrombosis problems with Johnson & Johnson's Cypher stent. Cypher subsequently was approved in Japan, but it still only has conditional approval in Japan, and J&J is required to report all stent thrombosis to the Ministry of Health. Dr. Sase said that from May 2004 through February 2005, 63,484 Cyphers have been implanted in Japan, and 73 cases of thrombosis have been reported: 67 acute/subacute (<30 days), and 6 delayed (≥30 days), for a stent thrombosis rate of 0.17%-0.23%. Dr. Shingaru Saito of Japan added, "Harmonization (HBD) is complicated, but I think we can do it."

Koji Ikeda, from Japan's Pharmaceuticals and Medical Devices Agency (PMDA), commented, "Trust is important, but I think there isn't much trust of Japan (regulators)." However, he said his country is instituting two new steps:

1. **GPSP**, which applies to new medical devices. Following pre-market approval, there is a three- to seven-year mandatory post-marketing surveillance period, then a re-examination of the application, and, finally, approval. A product is not fully approved in Japan until all of this is completed.
2. **GVP**, which applies after the post-marketing period.

Dr. Saito explained that next-generation drug-eluting stents in Japan:

- Must be safe and effective in a short time-period in comparison with currently available drug-eluting stents.
- Must be effective long-term compared to Cypher.
- Must be safe long-term.

The best approach is for the Japanese trial of a new drug-eluting stent to be started coincidentally with the large-scale U.S. trial, Dr. Saito said:

- **Medtronic's Endeavor.** He said, "This was planned with Endeavor (the ENDEAVOR-III trial), but that trial already has finished enrollment, and the numbers have shown Endeavor has more beneficial effects on patients than the bare metal Driver stent...Thus, it is not ethically permitted to conduct a randomized clinical trial of Endeavor vs. a bare metal stent. As a result the Japanese trial (of Endeavor) is using the ENDEAVOR-II criteria."

- **Guidant's Xience.** The hope is that the Japanese SPIRIT-III trial can be started simultaneously with the U.S. trial, using the same protocol in both countries.

EXCIMER LASERS FOR DEBULKING THROMBUS

Excimer lasers may be finding a role as a debulking tool. Dr. On Topaz of the Heart Center at Virginia Commonwealth University reported on the results of the non-randomized CARMEL study of Spectranetics' excimer laser in 151 patients with continuous chest pain and ischemia within 24 hours of onset. He said, "The acoustic shock waves of the laser basically destroy the fibrin network that holds the thrombus. The higher the laser energy, the more you suppress platelet aggregatability…Frequently, when you lase in the cath lab, we see not only dissolving of thrombus at the point of contact, but we also see thrombus dissolved distally." A Colorado doctor said, "This is interesting, but I'll wait for more data."

There will be new, subgroup data from CARMEL at the Coronary & Peripheral Vascular Interventions Symposium, June 13–17, 2005, in Hilton Head SC.

Sources do not expect any problems with FDA approval of additional guidewire and catheter sizes, which would expand situations in which this device could be used.

CARMEL Study Results

Measurement	Q-wave MI patients	Non-Q-wave MI patients	p-value
Primary endpoint: Procedural success	89%	93%	Nss
Secondary endpoint: Laser success	95%	94%	Nss
Final MLD	2.7 mm	2.6 mm	Nss
Final RVD	21%	18%	Nss
Deaths	6 patients	1 patient	Nss
Emergency CABG	0	0	Nss
Laser-induced distal embolization	0	1%	Nss
No reflow	4%	1%	N/A

MISCELLANEOUS

➢ **AMERICAN BIOSCIENCES' Abraxane (ABI-007).** This agent is being explored as a possible IV agent to prevent restenosis. The company had a poster at the meeting that described a 23-patient dose-finding SNAPIST-I study. Researchers concluded:

- 10 mg/m^2 is too low a dose for effect.
- 30 mg/m^2 and 70 mg/m^2 both showed some suppression of neointimal proliferation, based on TLR, restenosis, and late loss.

The SNAPIST-II trial is now underway. This is a study of two 35 mg/m^2 doses, with one given at the time of stenting and the other at two months post-procedure, vs. one 35 mg/m^2 dose at the time of stenting. So far, about 20 patients of the planned 80 have been enrolled. There may be data on this trial at ACC 2006.

➢ **FOXHOLLOW TECHNOLOGIES' SilverHawk.** This plaque excision system is FDA-approved for use in de novo and restenotic lesion in peripheral arteries. It uses a tiny rotating blade, inserted through the femoral or radial artery, that shaves away plaque from inside the artery, collects the debris, and removes it from the patient. A vascular surgeon said, "I'm not a huge fan of SilverHawk. It is useful in unique situations, but it is not a workhorse."

➢ **IMPELLA CARDIOSYSTEM'S Recover LP**, a percutaneous left ventricular assist device, got a positive review at CRT by Dr. Patrick Whitlow of the Cleveland Clinic. Recover is a small ventricular unloading catheter, which is placed percutaneously through the femoral artery. It is external, not implantable, and can provide immediate support and restore hemodynamic stability for up to five days with the small version and about seven days with the larger version as a bridge to give doctors time to develop a definitive treatment strategy. Compared to a left ventricular assist device (LVAD), it is inexpensive. Recover is put in with a 13F sheath and a 9F catheter, and the artery is sealed with a closure device (Abbott's Perclose).

Recover received a CE Mark in 2004, and the company launched it in Europe in September 2004. An IDE was submitted in January 2005, and a 50-patient U.S. trial was expected to start in April 2005. The principal investigator will be Dr. William O'Neill of William Beaumont Hospital. This feasibility trial is expected to run just 30 days, and then a pivotal trial will begin. Patients will be randomized to either Recover or intra-aortic balloon pump (IABP). The primary endpoint is comparability to IABP therapy on MACE plus efficacy endpoints for patients undergoing high risk PCI. The safety endpoints are MACE, cardiac death, MI, TVR, and other adverse events.

Dr. Whitlow called Recover a "novel tech to address an unmet clinical need." He noted that 30% of the cases where it is used are AMI patients and 28% cardiogenic shock patients. He said, "We've done 41 patients (at the Cleveland Clinic)…It is very good to support arterial pressure and perfusion. Obviously, because it is a pump, there is no significant increase in free hemoglobin…further studies are necessary to identify the clinical situations that benefit the most beyond cardiogenic shock patients."

➢ **THE MEDICINE COMPANY'S Angiomax (bivalirudin).** Sources indicated that Angiomax is really catching on in cath labs. Many sources are using it for a majority of their procedures already, and other labs plan to start using it or increase their use. A Maryland doctor said, "Our Angiomax use is going up. I'm excited about being able to add it to a IIb/IIIa inhibitor."

➢ **SURMODICS.** This company, which provides the Bravo polymer to Johnson & Johnson for Cypher stent, had a poster at the meeting on a new coating it has developed with heparin, PhotoLink Heparin. The new polymer reportedly is not subject to the agreement with J&J that prevents Surmodics from working with any limus on a drug-eluting stent. An official said, "We hope to generate interest (in this) at this meeting…Next generation drug-eluting stents should have a heparin coating. Our new coating provides an immobilized but active heparin…It can be applied over any drug-eluting stent. The heparin doesn't elute, so it gets around our agreement with J&J." The appeal of the heparin coating is that heparin may reduce SATs.

➢ **Patent foramen ovale (PFO) closure devices.** Dr. Daniel Schultz, Director of CDRH at the FDA, commented, "We still have major concerns with regard to use of PFO closure devices. This is a challenge for us from a regulatory standpoint and for you from a scientific standpoint…We want to get them to market in a way that people know what they should and shouldn't be used for."

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