Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Nine-month safety data from the SIRIUS trial showed Johnson & Johnson's sirolimus-eluting **Cypher** stent is safe, and use is increasing in Europe ♦ **Achieve**, Guidant's paclitaxel-eluting stent, got CE Mark during the meeting, but there was little enthusiasm for it, mostly due to insufficient data. ♦ Biosensor is in human trials of its **everolimus**-eluting stent and may apply for CE mark in early 2003. ♦ AstraZeneca's **Crestor** beat out Pfizer's Lipitor across all dosage ranges, and doctors indicated it may do well – if it performs well clinically. ♦ Pharmacia announced that the EPHESUS trial of its anti-hypertensive, **eplerenone** ended, with data expected at ACC2003. The concern with hyperkalemia appears to be waning. ♦ Cardiologists are not convinced of the utility of **Zetia**, Schering Plough's new cholesterol absorber, and the problem is lack of outcomes data more than need to take two pills (Zetia plus a statin).

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In Europe, the outlook for pharmaceutical companies and medical device manufacturers is for increased sales over the next several years, with significant increases expected in ICDs, pacemakers, LMWH, and antihypertensive drugs, among other things. An ESC official said, "There is a huge under-use of drugs in Europe. Doctors are not following the guidelines and are prescribing far less drugs than is recommended. We hope to improve that with publicity and education."

DRUG ELUTING STENTS

Interventional cardiologists are convinced that drug-eluting stents are good technology, and they plan to embrace them quickly and broadly, but there are several issues that they are continuing to debate, including:

- **Delivery systems.**
- **Stent design.**
- **Drug.** It appears that doctors are convinced that sirolimus is the best drug so far, but there is increasing conviction that paclitaxel (at least with on a polymer) as well as rapamycin analogs may yield good results, if not quite as spectacular as sirolimus. One expert said, "Don't get concerned with whether restenosis is 0% or 3%…The compounds are pretty similar." Another commented, "Personally, I think the data will be equally good with both paclitaxel and sirolimus, but technique does matter…We have good reason to believe both drugs are safe."
- **Operator technique**
- **Balloon overhang.** An expert said, "Stents are always shorter than the balloons, and the balloon overhang is the difference. If you put a drug on a stent, they you are hopeful of covering the injury with the drug, but at the overhand, you don't have any drug, and yet you cause injury, and this is one possible mechanism for what we call persistent or edge injury or proliferation. The explanations for peri-stent injury have to do with deployment technique. We don't like dissections, so we pull back the balloon a little and deploy with higher pressure. Obviously, with higher pressures you might cause higher injury at that site."
- **Lack of good animal models** to test these stents and drugs.
- **Cost.** A doctor said, "We are excited by 0% restenosis, and maybe the premium we are paying for these stents is worth it, but in more complex lesions, maybe the premium is too much. A price of 2,000E is very expensive when we are talking about market penetration and the number of stents used in an individual." Currently, there is wide variability on stent prices in Europe, but German hospitals, for instance, can obtain bare stents for about US$200-$500, and UK hospitals are paying about £350 (~US$525) for bare stents.

- **Aneurysms.** There have been numerous rumors about this. There has been one small aneurysm in the sirolimus trials, and at least three in the TAXUS trials, some of which could be significant. However, there have been no events as a result of any of these aneurysms, and there has been some controversy over the definition of a stent-related aneurysm.
- **Polymer vs. non-polymer.** An expert said, "The polymer itself may make a difference. The carrier on the metal is not inert. It is supposed to be, but it really isn't. It is very dangerous to put something on top of the stent unless you know it really doesn't cause any inflammation. So far, most carriers have a risk of inflammation, and that is proliferation and some sort of narrowing of the lumen."

An expert concluded: "So far, in the trials the different stent designs, carriers and drugs, apparently come out equally good. But we are very early on, and considering the level of excitement, we don't have much data, particularly not for the complex lesions where we want to use these drug-eluting stents. It's possible we don't need drug-eluting stents in single, easy lesions, but that is where you start with a new technology."

For interventional cardiology, the main message out of this meeting, according experts, was:

- "Restenosis <5% is possible, so a new milestone has been reached in interventional cardiology."
- "ESC last year was RAVEL, Berlin this year is a little more sobering and a little more realistic, meaning we are dealing with an excellent concept, but not the magic bullet of zero. I think we are a little more realistic now."
- "There is robustness in the drug-eluting stent story."

Market Outlook

- *Asked how they would choose between a Boston Scientific paclitaxel stent and a Johnson & Johnson Cypher stent (if both were priced the same),* sources all said they would split their use about 40% BSX/60% Cypher -- to try them out. The split would be even except doctors said they don't like the Express stent as well as the BX Velocity stent.
- *Asked how they would choose among a Boston Scientific paclitaxel stent, a Guidant paclitaxel stent and Cypher (if all were available and priced the same),* sources estimated about 40% share for Cypher, 40% for BSX and only 20% for GDT. The problem for GDT is that doctors like the stent but don't like the dipped coating. A Dutch cardiologist, for instance, said he wouldn't use the GDT stent at all (though I suspect he probably would play with it a little).

Comparison of Different Polymers

Coating	Example	Advantages	Disadvantages
Synthetic biodegradable polymers	Polyurethane, polyester (Guidant and Medtronic)	Thin Uniform coating Tailored drug release	Long-term biocompatibility
Synthetic biostable polymers	Medtronic, Biocompatibles and J&J's Cypher	Thin Uniform coating Tailored drug release Improved biocompatibility	More difficult to impregnate these polymers with drugs
Biologic Biostable polymers	BiodivYsio's phosphorylcholine	Think Uniform coating Biocompatible	Limited total drug dose Fixed release profile
Biologic Biostable Polymers	Jomed stent	Think Uniform coating Biocompatible Allis high dose drug loading	Coating stability
Inert anorganic coatings	NiRoyale (gold)	Think Uniform coating Biocompatible	Limited drug loading capacity Galvanic effects Desquamation
Direct coating	Guidant/Cook Achieve paclitaxel	No polymer concerns	Limited rug amount Lipophylic drugs Single release curve

Following is a discussion of some specific companies with drug-eluting stent programs:

ABBOTT/BIOCOMPATIBLES

- **Dexamethasone-eluting stent**. Abbott officials said they will be launching the Dexamet stent in November 2002. Interestingly, this stent has a thicker polymer (which is both hydrophilic and hydrophobic) on the outside of the stent than on the inside. Data from the STRIDE trial using a 0.5µg/mm^2 dose of dexamethasone showed a 13.3% restenosis rate at six months and 0% MACE. Diabetics were excluded from this trial, but a researcher said they would not be excluded in future trials, including a randomized European study, EMPEROR, scheduled to start in 4Q02. A European researcher said that in animals 80% of the drug is released in the first day, and the remaining amount over seven days, but it elutes slower in humans – 80% over seven days and the rest over 14 days.
- **Mitoxantrone** (Amgen, Novantrone) **plus cisplatin** on a BiodivYsio stent. This was tested in 15 pigs with mixed results, leading the researcher to conclude: "The delivery system is feasible, but further studies are needed to determine efficacy."
- **ABT-578** (a rapamycin analog). This was due to begin human trials by October 2002 in Europe. The company reportedly is still trying to get FDA approval to go straight to a Phase III trial in the US, but there is no word on progress of those talks.

BIOSENSOR

This company has completed the first human trial of its everolimus-eluting stent, and it already has begun a second trial. Thirty-day MACE data from FUTURE-1 will be presented at TCT 2002, and the full FUTURE-1 data will be presented at the American Heart Association meeting in November 2002. The 90-patient FUTURE-2 trial may be presented at ACC2003. Reportedly, Biosensor will apply in 2Q03 for a CE mark based on these two trials plus the preclinical animal data. An investigator indicated the data looks very good, "This is a very good stent, a perfect polymer, and the results are excellent." A source said Biosensor does not need a partner to sell its everolimus-eluting stent outside the U.S. and the expectation is that this will be priced *significantly* lower than Cypher and could be a spoiler for other drug-eluting stent manufacturers, at least in Europe.

BOSTON SCIENTIFIC

The TAXUS II trial was to be opened on Friday, September 6, 2002, and the data to be reviewed by investigators. They will also be meeting to agree on the definition of aneurysm. Sources indicate the TAXUS II efficacy data should be good, though – as in SIRIUS -- there is likely to be a higher restenosis rate in-segment than in-stent, probably due to balloon overhang. Safety remains the issue, but sources are becoming slightly less worried about this.

An analysis of the Quanam paclitaxel trial, which was halted, found a 13% restenosis ate at 6 months but 61.5% restenosis at 12 months, and a TLR of 20% at six moths and 60% at 12 months. Doctors were concerned that this may mean a late effect could show up in other paclitaxel trials, but a Quanam researcher said, "Our first experience with QuaDS-QP2 was good at six months, but the anti-proliferative effect was not maintained at 12 month follow-up. These results should not be extrapolated to current devices." Another researcher suggested it was polymer toxicity after the drug was gone that caused the problem.

GUIDANT

- **Actinomycin D.** The ACTION trial of actinomycin-D showed restenosis as well as safety problems. This 360 patient trial, conducted at 28 sites, was stopped early by the data safety monitoring board, but the patients were continued to be monitored data. A speaker said, "We saw some edge effect, a classic candy wrapper effect, like with radiation." Another expert suggested that the problem may have been (1) too low a dose, (2) inappropriate stent design, or (3) a polymer reaction.

180 Day Results of ACTION Trial

Endpoint	Control	Actinomycin-D 2.5 µg	Actinomycin-D 10 µg
In-stent late loss	.76	1.02	.93
Restenosis	11%	25%	17%
Proximal edge late loss	.28	.51	.53
Restenosis	14%	27%	28%
TLR	9.1%	17.5%	23.1%
MACE	??	18.3%	28.1%

- **Everolimus. No news.**
- **Paclitaxel.** Although GDT got CE mark approval for the Achieve paclitaxel-eluting stent during the meeting, there was little hoopla about it at the meeting. Guidant put a sign up at the booth, but there was almost no afternoon traffic at any of the stent booths that day.

The key paclitaxel trials are:

- **DELIVER-1**. This is the pivotal US trial, with 1,203 patients randomized as of the end of August, and the trial was fully enrolled on February 3, 2002.
- **DLEIVER-2**. This is a European registry of 1,500 pts at 100 centers.
- **RESOLVE ISR**. This trial compares brachytherapy to Achieve for in-stent restenosis.

According to a senior Guidant official:

- Achieve is being priced at $2350 in Europe, a slight premium to Cypher. However, the company expects to make "deals."
- He refused to say whether Guidant will do restenosis guarantees the way JNJ is doing in Germany: "We have no plan but we have done that in the past."
- At TCT2002 there will be 30-day MACE data for a subset of the 1,500 DELIVER-2 patients.
- Full DELIVER-1 data will be at ACC2003. Enrollment finished March 1, 2002, so the nine-month clinical follow-up ends December 1, 2002. (There will be 8-month angiographic follow-up.)
- Guidant's approach to selling Achieve will be to:
  - > Work on reimbursement in the various countries.
  - > Re-emphasize the cost effectiveness of its drug-eluting stent.
- In the best case, Guidant does not expect a court decision that would permit it to market Achieve before October 1, 2002. At the time of this interview, the legal ball was in Boston Scientific's court, and Boston was expected to file its response in the next 7-10 days. Then, Guidant would make a formal reply to the Boston filing within another couple of weeks. After that, it is just waiting for the judge's decision.
- There was no 12 month angiographic follow-up in ASPECT, so we will only see clinical data for that, and he didn't know when. It was not at this meeting.

Fifteen European interventional cardiologists were interviewed on the outlook for Achieve. Assuming that both Cypher and Achieve were available tomorrow and at the same price:

- ◆ 8 would continue to use only the Cypher stent, and six of these said the reason was a lack of data on Achieve or more data on Cypher. One German center has a contract for exclusive Cypher use and is happy with that stent and sees no reason to renegotiate or break that contract.
- ◆ 2 would split their use equally between Cypher and Achieve if and when Achieve is available, and the reason they cited is a preference for dealing with GDT (the company), not a preference for paclitaxel.
- ◆ 1 would use predominantly (about 65%) Achieve to about 35% Cypher.
- ◆ 1 is not doing any drug-eluting stents yet, but probably will use all Achieve next year.
- ◆ 1 would split use equally between Boston Scientific's paclitaxel-eluting Express and the Cypher. Yes, the paclitaxel Express is already available in this country (Czech Republic), which probably makes it the first country to approve this stent.
- ◆ 2 couldn't predict what they would do.

However, most sources said that, if one drug-eluting stent were significantly cheaper than the other, then they would use that stent almost exclusively. Many doctors expect price competition, and, as noted above, Guidant has indicated some willingness to negotiate pricing. So, it is possible Guidant will cut some very aggressive deals to gain market share.

JOHNSON & JOHNSON

The 30-day and nine-month safety data from the full cohort of SIRIUS patients showed the Cypher stent to be very safe. There has been **one small aneurysm reported with Cypher**, but it is considered by experts as a minor case and not of any concern – and far less than the expected or actual incidence with bare stents.

SIRIUS Safety Data

Measurement	Cypher n=533	Bare stent n=525	P-value
30-Day Safety Data			
Total mace	2.6%	2.3%	nss
Deaths	0.2%	0.2%	nss
All MI	2.4%	2.1%	nss
Q-wave MI	0.6%	0%	nss
Non-Q wave MI	1.9%	2.1%	P=.037
TLR	0.4%	0	nss
TVR	0.2%	0.2%	nss
TVF	2.8%	2.5%	nss
9-Month Safety Data			
Deaths	0.8% (non-cardiac)	0.6%	nss
All MI	0.6%	1.7%	nss
Q-wave MI	0.4%	0.4%	nss
Non-Q wave MI	0.2%	1.3%	p=.037
Acute thrombosis (≤30 days)	0	0	nss
Subacute thrombosis (1-30 days)	0.2%	0.2%	nss
Stent thrombosis	.2% (1 pt)	.6% (3 patients)	N/A
Late thrombosis (31-270 days)	0.4%	0.8%	N/A
Total thrombosis	0.4%	0.8%	N/A

Cypher uptake in Europe is increasing, but slowly. Sources estimated Cypher use outside of clinical trials at: 40% in Switzerland, 5%-7% in Germany, and 5% in the UK. Several doctors said their hospitals are just starting Cypher use. Interestingly, there appears to be variability in the range of sizes available in different countries. A Dutch doctor said he

had a full range of sizes and diameters available, but a German doctor said he could only get certain sizes and diameters.

The cost effectiveness of drug-eluting stents is being tested in a real-world, non-industry study in Rotterdam, the Netherlands. This hospital made a $5 million commitment, began implanting 100% drug-eluting stents in mid-April 2002, and will do its own nine-month analysis, looking at the surgical rate, stent use, re-interventions, quality of life, etc. So far, they have implanted 920 drug-eluting stents. The results are likely to be extremely influential on other European hospitals.

J&J apparently has agreed to reimburse at least one German insurance company for any patients who require a re-intervention for in-stent restenosis within the first year after receiving a Cypher stent. A German cardiologist said, "I am in negotiations with a big German insurer, and it may be willing to pay the high price for a new stent but not for re-intervention within the first year. If the stent fails, and the patient goes to the hospital, the company that makes the stent says that if the problem is in-stent restenosis, it will pick up the cost."

12-Month RAVEL Safety Data

Measurement	Cypher N=120	Bare stent N=118
Total MACE	5.8%	28.8%
Acute thrombosis	0	0
SAT	0	0
Late stent thrombosis	0	0
No MACE	94.2%	71.2%
TLR-PCI	0	22.9%
TVR-CABG	.8%	.8%
Event-free survival	94.0%	70.7%
ALL MI	3.4% 4 patients	3.4% 4 patients
Q-wave MI	1.7% (2 patients)	0
Non-Q wave MI	1.7%	3.4%
Deaths	1.7% 2 patients (1 cancer, 1 cerebral hemorrhage)	1.7% 2 patients (at least 1 non-cardiac)
Diabetic patients		
TLR/re-PCI	0	32.0%
Total MACE	10.5%	48.,0%
Event free survival	89.5%	52.0%

Other Cypher results that were discussed:

- 18-month IVUS results from 15 patients with short <15 mm de novo lesions who received a single 18 mm Cypher stent found one TVR, no "catch-up" effect, and a virtual absence of neointimal hyperplasia. There were no aneurysms found in these patients. A researcher said, "The data is quite compelling."
- Doctors are continuing to analyze the previously-reported in-stent restenosis trial where two patients died, but the level of concern appears to have decreased. An Irish cardiologist said, "I think the bottom line here is have we have to remember that the stent was probably effective but the doctors perhaps were not. This is powerful technology, and you have to be careful when using it and do it properly. The technology seems to work, but doctors have to do it properly."
- 30-day data from E-SIRIUS, a European multi-center randomized, double-blind trial in 353 patients with de novo lesions found, also was positive. The full data from this trial will be presented at ACC2003, but there may be more information on this trial at TCT2002 as well. Researchers concluded that

E-SIRIUS 30-day Safety Data

Event	Group A	Group B
Death	0	0
MI	1.7%	2.9%
Q-wave MI	0	0.6%
Non-Q-wave MI	1.7%	2.3%
Thromboses	0	0
Average number of stents used	1.5	1.4

JOMED

The company is continuing to work on a tacrolimus-eluting stent, with data from its EVIDENT trial expected at TCT2002.

MEDTRONIC

No news whatsoever was available at the meeting on Medtronic's' drug-eluting stent program.

ORAL RAPAMUNE (rapamycin, sirolimus)

This therapy is still alive, though not particularly promising. ORBIT, an investigator-sponsored, single center, 60-patient, open label trial studied two doses: 2 mg/day and 5 mg/day, both following a loading dose of 5 mg. The six-month data on the 2 mg dose was presented, and researchers found: in-stent restenosis 5.1%, in-segment restenosis 7.7%, TLR 15.6%, and TVR 15.6%. Compliance was good, with 10% of patients discontinuing treatment, but the complication rate was high (25% MACE, 50% of patients experiencing side effects – mostly minor). The researchers is hopeful that the data on the 5 mg dose will be more positive and justify a larger clinical trial. A speaker said, "There will be more side effects with 5 mg. I don't think we can go higher than 5 mg if don't want to increase the adverse events."

TERUMO

The company showed positive animal data on its simvastatin-eluting stent, but the company still has not begun human trials. This is worth watching because in cell lines statins are more effective than even rapamycin.

PHARMACOLOGICAL THERAPIES

ACTELION'S Tracleer (bosentan)

The 30-patient BREATHE-2 study comparing bosentan+Flolan (GlaxoSmithKline, epoprostenol) to placebo+Flolan in pulmonary arterial hypertension (PAH) found that the bosentan/Flolan combination was well-tolerated and resulted in greater hemodynamic improvement than Flolan alone but the results were not statistically significant. The full data will be presented at a future meeting, but which meeting is not yet clear.

Bosentan also may have a role in IPF as well as in digital ulceration in scleroderma patients. It is being investigation in interstitial lung disease, vasculopathy in connective tissue disease, and hypertension. The **data on scleroderma will be presented at the American College of Rheumatology** meeting in New Orleans in October 2002, and a researcher revealed that the primary endpoint is highly significant in favor of bosentan.

Some of the points made about bosentan use included:

- An expert said, "I think we are still at too high a dose at least in heart failure. It is clear that many of the bosentan problems in CHF do not occur in pulmonary arterial hypertension (PAH).
- The benefit can be seen as soon as six weeks and continues for at least six months of treatment.
- The dose effect is not clear cut. An expert said, "Some patients do well with the starting dose and experience no further improvement with a dose increase, while others say that only when they get the full dose of 125 mg/bid do they sense improvement."

ASTRAZENECA's Crestor (rosuvastatin)

The company received an approvable letter from the FDA for Crestor, but additional clinical trials were required. Reportedly, AstraZeneca will not get approval for the 80 mg dose, and the fate of the 40 mg dose is still in question. An official said the myalgia seen in the Crestor trials "tended to be commoner in older people, but there was no gender difference. The myalgia was not exclusively older women; the patients were older but there was no clear gender split. The incidence of myopathy was only seen at the 80 mg dose and was similar to other statins in terms of the dose relationship and demographics. We had some muscle symptoms and CK rises, but where the myopathy is drug-related, it was all at the 80 mg dose."

Data was presented comparing Crestor to Pfizer's Lipitor (atorvastatin) across all dosage ranges (Crestor 5mg-80mg and Lipitor 10mg-80mg). This six-week, randomized, double-blind trial of 374 patients found Crestor performed better than Lipitor almost across the board. An AstraZeneca official said this data will be given to the FDA to help convince the agency to approve Crestor.

Compared to Lipitor, Crestor:

- Lowered total cholesterol by an additional 4.9%.
- Improved the LDL/HDL ratio by an additional 6.9% .
- Lowered the total cholesterol/HDL ratio by an additional 6.9%.
- Improved the non-HDL/HDL ratio by an additional 8.4%.
- Improved the ApoB/ApoA ratio by an additional 7.8%.

Study 0033: Comparing Crestor and Lipitor

Endpoint	Crestor 5-80 mg n=209	Lipitor 10-80 mg n=165	Crestor Advantage	p-value
LDL: % reduction from baseline	-46.6% to –61.9%	-38.2% to –53.5%	-8.4%	p<.001
HDL *	12.3% at 40 mg 9.6% at 80 mg	4.1% at 40 mg 2.1% at 80 mg	8.2% at 40 mg 7.5% at 80 mg	p<.001

* no statistically significant difference between the two statins at other doses

Crestor v. Lipitor Mean LDL Reduction

Dose	Crestor	Lipitor
5 mg	-41.5	NA
10 mg	-46.6	-38.2
20 mg	-51.7	-43.3
40 mg	-56.8	-48.4
80 mg	-61.9	-53.5

An AstraZeneca official described the approach the company will take to marketing Crestor, saying Crestor would be described as:

- An advance in treating patients
- Lowering LDL more than other statins
- Raising HDL better than other statins
- Getting more patients to guidelines – and at lower doses
- Requiring lower dosing. Lipitor requires almost twice the mg of Crestor for a similar effect. In fact, a 20 mg dose of Crestor lowers LCL almost as much as 40 mg of Lipitor.

A leading cardiologist (Packer) commented: "I think this will do very well. AstraZeneca will have a big marketing push behind it. But how it does out of the box will determine its future. If it doesn't succeed right away, it will fall flat. There

is a lack of outcome data, but the company will have a strong message. And it may follow on the Lipitor experience — doctors tried that, it worked quickly and well. If Crestor does that, and can be titrated up, I think this will do very well. This makes sense and is in line with how doctors practice, so I think it has a chance of doing very well."

AstraZeneca has started GALAXY, a group of studies that will provide more long-term data on Crestor in terms of cardiovascular risk reduction. An official said, "These studies will look at the science of statins and answer significant questions in general on lipids and statins. GALAXY is a way of bringing all the studies together and building confidence in the physician community."

BRISTOL-MYERS SQUIBB's Vanlev (omapatrilat)

An expert said, "The side effect that has haunted Vanlev in hypertension is not even a concern in heart failure -- angioedema. So, the only difference in safety (in CHF) is a little more dizziness and renal insufficiency combined with a 9-10% lower event rate. What is important is that the executive committee of the trial and the sponsor spent an extraordinary amount of time carefully thinking out the trial design, the endpoints, dose, doing very carefully. Having done all of that, we now have a result which is tantalizing but not persuasive. That is the heartbreak of clinical trials. We don't like a trial that is close but not persuasive, that psychologically is the worst outcome in a clinical trial. If we had unlimited resources, we would do the trial again." However, he said he didn't know yet whether Bristol will invest any more money in Vanlev trials.

ELI LILLY'S ReoPro (abciximab)

Lilly was trying to remind doctors that IIb/IIIas in general, and ReoPro in particular, are still valuable in the drug-eluting stent era. The company sponsored a round-table discussion by several prominent cardiologists who agreed that ReoPro is the preferred IIb/IIIa in the cath lab, especially for troponin positive patients, but they said price continues to limit use. A source reported that Lilly has started to deal on pricing, at least in the U.S., selling ReoPro for as little as $500 per patient to some labs.

However, ReoPro use also is being affected by clopidogrel. A Dutch doctor said his hospital is authorized to use ReoPro for 40% of cases but only uses it in 17% of cases, largely because of an increase in clopidogrel and aspirin use.

Sources said there do not appear to be any plans for a ReoPro-eluting stent, and they indicated this would be unlikely to be useful. One expert said, "We did a few patients, and six of 10 came back with restenosis." Another said, "There is no benefit to long-term delivery of a IIb/IIIa; a 24-hour hour infusion bolus is all that's needed. Prolonged delivery with a drug-eluting stent is unlikely to work. We know that for a IIb/IIIa to be efficient and not have negative side effects, you should *not* dwindle down the dose; you need to keep the dose high and then quit."

These experts warned that drug-eluting stents may lead to an increase in thrombotic events – mostly because the clinical use will be different from patient selection in clinical trials. One said, "Drug eluting stents, with their drastic reduction in restenosis, will be a license to kill, to do more and more lesions. The number of lesions treated will increase. Probably 30% of surgical patients could be treated with drug eluting stents…The trend will be to do more lesions in the future because we won't be afraid of restenosis, and in doing that we will generate more thrombotic problems, so the value of IIb/IIIas could be increased because we will manipulate more atherosclerotic burden."

PHARMACIA's eplerenone

The EPHESUS trial reached its ending point of 1,012 deaths the day before the meeting started. Pharmacia told investigators at a meeting during the conference, and then released the information to the public. However, an investigator (Pitt) said the data will not be presented at the American Heart Association meeting November 2002, "The data is still coming in from the various centers, and we won't be able to see all of it until just about the time of AHA, and we might not even make that because of the floods in Europe. Pharmacia doesn't want to make the mistake Bristol-Myers Squibb (with Vanlev) and rush the data, so it will be presented at the American College of Cardiology meeting in March 2003 instead."

Eplerenone was submitted to the FDA for use in hypertension in November 2001, so the PDUFA date is coming up. No FDA cardio-renal advisory panels are scheduled for the rest of 2002, so it would appear no panel is needed. Investigators and other doctors interviewed did not appear very worried about the hyperkalemia issue. There is no problem with co-administration of any dose of beta blocker in hypertension, but there is no data yet (until EPHESUS results) on beta blocker use in heart failure.

SANOFI/BRISTOL-MYERS SQUIBB's Plavix (clopidogrel)

Cardiologists agreed that Plavix should be given to post-stent patients, but they continue to debate how long that therapy should be. One expert said, "For in-stent restenosis patients, who are getting more than two drug-eluting stents, I think they should have more than three months Plavix. If a patient had prior brachytherapy, we might continue it for six months." Another expert (Colombo) said, "I think we should use Plavix for a year or longer with patients getting multiple stents."

Questions about the safety of Plavix were raised by two posters, but this did not attract much attention at the meeting. One, done at a prominent German hospital, looked at 700 patients, comparing the standard 75 mg clopidogrel to 500 mg ticlopidine (Sanofi's Ticlid) four-weeks post-stenting (both elective and emergency). The researchers found a significantly lower mortality with Ticlid (8 deaths vs. 26). As a result of this study, some cardiologists at that hospital already have switched back to Ticlid, and the hospital is now reviewing its use of clopidogrel. A researcher said, "Definitely, if you are using clopidogrel, you should give a high loading dose (600 mg). This study shows we need more studies of clopidogrel. We shouldn't necessarily drop it, but this data is so exciting and important that it calls for additional trials. A single study shouldn't change how we use something worldwide."

The other study was a retrospective look at 4,453 patients between 1995 and 2002: 1806 were on 250 mg Ticlid BID and 2,647 were on Plavix 75 mg qdx4. The study found a significantly higher stent thrombosis rate with Plavix. All the stent thrombosis with Ticlid occurred in the first 30 days, and stent thromboses occurred out to 110 days with Plavix. The researchers concluded: "Clopidogrel is less effective in preventing subacute thromboses and is associate with late stent thrombosis...so patients should get a higher dose and/or take it longer."

Endpoint	Ticlid	Plavix	p-value
Total stent thrombosis	.8%	1.9%	p<.05
Subacute thrombosis	.8%	1.3%	nss
Late stent thrombosis	0	0.6	p<.05

SCHERING PLOUGH's Zetia (ezetimibe)

This cholesterol absorber was submitted to the FDA on December 27, 2001 and is awaiting action by the agency. No advisory panel has been scheduled, and the company views that as an indication that no panel is likely since the PDUFA date is fast approaching.

Initially, ezetimibe will be approved alone, but in the future Schering and Merck plan to submit a combination simvastatin (Zocor)/ezetimibe pill. Schering and Merck announced that they are beginning two new, long-term outcomes trials of combination therapy

- A four-year, double-blind, randomized, placebo-controlled trial examining the effect of combination therapy on morbidity and mortality in 1,400 patients with aortic stenosis. The trial will compare placebo vs. 10 mg ezetimibe plus 40 mg simvastatin. The primary endpoint is CV death, aortic valve replacement surgery, non-fatal MI, CABG, PTCA, hospitalization for unstable angina, stroke and peripheral vascular revascularization. The trial will be conducted in Europe and will be led by Prof. Terje Pederson at the University of Oslo, Sweden. Results are expected in 2007, but a researcher admitted it may be hard to find the patients for this trial.

- The two-year ENHANCE trial, a 725-patiet, randomized, placebo-controlled study looking at the effect of combination therapy on atherosclerotic thickening of the carotid artery wall in patients with high cholesterol levels. This trial will be conducted mostly in Europe but also in Canada, South Africa and at one U.S. site. It will compare 80 mg simvastatin therapy alone to the combination of ezetimibe plus 80 mg simvastatin. State-of-the-art (digitized) ultrasound imaging will be used to evaluate the results, with the interpretation done at a blinded core lab. **Results are expected in 2005.**

Several concerns overhang this drug:

(1) **Side effects.** *Is there a liver elevation (ALT) issue?* The company is admitting that liver enzyme elevation does occur slightly more frequently with ezetimibe plus a statin (any statin) than with a statin alone, but sources don't think this is enough to be a problem and do not believe it indicates any significant systemic effect. In almost all of the ezetimibe trials, there were more cases of ALT≥3xULN with the combination therapy than with a statin alone, though the numbers were small. One expert claimed that all nine of the patients with ALT≥3xULN had entered the trial with an ALT=2, which put them at the upper limit of acceptable according to the trial protocol. However, there were more than nine cases, and a Schering official admitted that there are more cases of ALT≥3xULN with Zetia+statin than statin alone. However, he insisted that (a) Zetia is like a few other drugs which raise liver enzymes without affecting the liver -- except to make it work harder, and (b) There are no clinical effects from the raised ALT in these patients.

(2) **Questionable physician interest in a two-pill regimen.** *How interested will doctors be in it, particularly when using it means giving a patient two pills instead of one?* Doctors questioned about how they expect to use ezetimibe are still unconvinced of its utility. Surprisingly, several said **the concern is not the two-pill regimen. Rather, these doctors said it is lack of outcomes data on Zetia**, pointing out that there is substantial outcomes data on statins. Thus, most expected to continue to prescribe their preferred statin and the currently preferred dose (e.g., 40 mg simvastatin, 20 mg atorvastatin, etc.). If a patient did not reach goal on that drug and dose, they said they most likely would increase the statin dose, only adding Zetia at or near the top of the statin dose titration range. One expert (Milton Packer) commented, "I can't see doctors using this. Adding a second pill, or dropping the statin dosage is difficult. I can't see this drug doing well. And think the combination drug will have a problem at FDA."

(3) **Changing physician practices.** Schering and Merck speakers suggested that doctors should start patients on the lowest dose of whichever statin they prefer and then add ezetimibe rather than titrating up the statin dose. This will require a change in the way many doctors currently prescribe statins since it is common to start patients on a dose higher than the minimum, though lower than the maximum.

(4) **FDA approval.** Zetia faces the additional hurdle that the FDA generally doesn't like combination medications. An expert (Packer) said, "There are rumors Schering is having problems at the FDA with this. There is no outcomes data. I'm not sure what the problem is, but it may be that."

Miscellaneous

Biventricular pacing. Medtronic has launched its next-generation biventricular pacemaker for CHF, the Marquis. Doctors described it as a "step forward," not a dramatic improvement.

> A German doctor estimated that Guidant has 70% of the German market and Medtronic 30%. He said, "There has been an incredible increase in biventricular pacing, most with an ICD. Insurance companies basically are willing to pay." He said there will be data at NASPE in May 2003 from the PATH-CHF-2 trial, showing that the most improvement comes in patients with QRS>150 but that 40%-50% of patients with a QRS of 120-150 benefit as well. He also predicted that researchers may find that a left ventricular lead along may work for CRT.

> An Italian cardiologist also reported that biventricular pacing use is increasing, and he estimated that about 10% of heart failure patients are now getting a CRT device, with about half of those patients getting an ICD as well.

> A Belgian cardiologist said less than 5% of heart failure patients in his country are getting a biventricular pacer, "When we can select patients better, use will increase, but until then it won't grow much." He said his use is split 70% Medtronic (with ICD) and 30% St. Jude (without ICD).

BNP monitoring. Currently, the only BNP test available is Biosite's hand-held device, Triage, which many hospitals are using not as a point-of-care device but in the central lab. A Canadian doctor prefers this test to the competing tests, and he likes the idea of a bedside test. He is moving to the U.S. and planned to use Triage at his new hospital, but he was unaware of the CLIA requirements in the U.S. and said that could affect his decision.

Three competitors to Triage are on the near horizon:

> **Hoffman-La Roche**, which is expected to launch its Alexis analyzer-based test this fall. This test measures pro-BNP instead of BNP. A U.K. doctor who has studied the different tests said, "It is ludicrous to use this test in the emergency room. I prefer BNP to pro-BNP, and the Roche test is not reliable, but it is more reliable than the Biosite machine." Another U.K. doctor said, "Pro-BNP is just as good as BNP, and doing the test in the lab is cheaper than in the ER." An Austrian doctor said, "Triage is very convenient, but it is very expensive, and you can only do a few per day on one device. The Roche test is not as reliable, but it is sufficient." Reportedly, Roche will give away machines to get into labs, with the expectation of making money on the tests instead of the machine sales.

> **BAYER/SHINOGI**, which is expected to launch its analyzer-based test in the U.S. in 1H03. Bayer licensed Shinogi's BNP test for its automated Advia Centaur and ACS-180 Immunoassay Systems.

> **ABBOTT**, which reportedly will clinical trials in November 2002 with a hoped-for launch in June 2003.

Distal protection. Interest in distal protection devices is low in Europe, but it is growing. An Italian doctor said, "We don't use distal protection because of the cost." A German doctor said, "We aren't using any distal protection yet, but we are considering it for active intervention in SVGs." A Swiss doctor said, "We use distal protection in 65% of our cases."

Several distal protection devices are available or in development, including: Medtronic's PercuSurge Guidewire, Johnson & Johnson's AngioGuard, Boston Scientific's FilterWire EX, Guidant's AccunNet, Kensey Nash's TriActive, and many others. PercuSurge appears to be the most popular, and there is little interest in the new TriActive device.

Sonotherapy. The 403-patient, randomized, prospective, double-blind Euro-SPAH trial of PharmaSonics' sonotherapy for in-stent restenosis showed no statistically significant benefit over control in terms of restenosis or late loss, but there was a lower rate of revascularization with sonotherapy, and it did prove safe. The investigator called the results puzzling. He said he is not willing to dismiss this technology yet and will continue to investigate it.

Euro-SPAH Results

Endpoint	Sonotherapy n=202	Sham n=201	P value
Death	2 patients	3 patients	N/A
Late Loss	.86	.94	p=.09
Restenosis rate	23%	28%	p=.31
Late Loss index	.54	.58	p=.68
In-segment late loss	.42	.47	p=.28
MACE at 210 days	18.8	25.9	p<.05
Revascularization	14.4%	23%	p<.05
TLR	10.9	16.4	N/A

VEGF-eluting stents. Data showed these reduce stent thrombosis but not restenosis. A researcher commented, "We couldn't find any evidence of beneficial effect on restenosis…Unless we can find a better dose, it is unlikely to have a restenosis benefit, but it may become an antithrombotic eluting stent."

SURMODIX. There was no new information on its second partner for a drug-eluting stent polymer.

The results of several other trials are of interest, including:

GRACIA: Stenting is better than lytics. This randomized trial conducted in Spain and Portugal, compared stenting within 24h of thrombolysis to thrombolysis alone in AMI patients with ST elevation. Five hundred patients immediately treated with r-tPA were then randomized to either (1) PCI plus a stent (if appropriate) or (2) classical conservative drug-based treatment. The primary endpoint was death or CV events at 30 days and 1 year. The 30-day results were presented, and no difference in mortality was found, though there were fewer non-fatal events and shorter hospitalizations with the PCI approach.

PRAGUE-2: PTCA is better than lytics even if patients have to be transported long distances. This trial looked at 850 AMI patients in the Czech Republic who received either thrombolytic therapy at community hospitals or who were transported to specialized centers for primary PTCA. As in the Danish DANAMI study, researchers found that transporting patients for PTCA reduces mortality

PRAGUE-2 Results

30-day Mortality	Transport and PTCA	Lytics given at community hospital
Overall	6.8%	10%
In patients presenting >3 hours after onset of pain (35-40% of all patients)	6%	15.3%
Combined for death, reinfarction,	15.2%	8.4%

MAGIC: magnesium does not reduce mortality post AMI. This randomized NHLBI-sponsored trial, conducted in the Netherlands, looked at placebo vs. magnesium in 6,213 patients (both patients who received no PCI and elderly patients getting PCI). On the primary endpoint of all cause mortality at 30 days, researchers found that there was no benefit to magnesium, with 85% survival with or without magnesium. This is the opposite of the finding of trials in the 1980s, and a researcher said this was probably due to: (1) the relatively small size of the prior trials, and (2) the positive effects of newer therapies (e.g., aspirin, clopidogrel). The researcher concluded that, despite the inexpensive price of magnesium (about $5 for a typical dose), "There is no indication for routine administration of magnesium to patients with ST elevation MI at any level of risk, but there also is no apparent harm, so it may be that we will continue to administer it for repletion of electrolyte deficits (e.g., in torsade des pointes)."

GIPS: There is no benefit to infusing PTCA patients with a glucose-insulin-potassium mix. This 940-patient, three-year study compared a glucose-insulin-potassium to control. Although it missed the primary endpoint, there may be some benefit in subgroups of patients, particularly Killip Class ≥2.

GIPS Trial Results

Endpoint	GIP n=476	Control n=464	p-value
All patients			
Death	4.8%	5.8%	nss
Re-MI	0.85	1.5%	nss
Re-PCI	3.4%	4.3%	nss
Killip Class I patients			
Death	1.25	4.2%	P=.01
Re-Mi	0.7%	1.4%	nss
Re-PCI	2.8%	4.2%	N/A
MACE	4.2%	8.4%	p=.01

RITA-3: PCI is better than conservative medical therapy -- at least for refractory angina. This five-year, randomized trial compared invasive and conservative strategies in 1,810 patients with unstable angina or non-ST elevation MI. A researcher reported that the advantage of PCI was apparently quickly and continued and increased over time: PCI resulted in fewer deaths, MIs and refractory angina events, with the principal impact on refractory angina. There was a consistent impact on recurrent and refractory angina, but the largest impact was on refractory angina.

RITA-3 Results

Endpoint	PCI	Conservative therapy
Primary endpoint	9.6% *	14.5%
Death at 4 months	2.9%	2.5%
Death/MI/refractory angina	9.6%	14.5%
Co-PEP at one year	7.6%	8.3%

* statistically significant difference

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