Trends-in-Medicine

December 2003
By Lynne Peterson

SUMMARY

Among the positive trials reported at this meeting were: AstraZeneca's Exanta in SPORTIF-V, Pfizer's Lipitor in REVERSAL, and Otsuka Pharmaceutical's Pletal (cilostazol) in CREST. ♦ Negative trials included Alexion's pexelixumab in PRIMO-CABG, Otsuka's tolvaptan in ACTIV, and Johnson & Johnson's ReoPro and Retevase in BRAVE. ♦ Mixed, incomplete or inconclusive data were presented about The Medicine Company's Angiomax in REPLACE-2 and Novartis's Diovan in VALIANT. ♦ Other topics discussed at the meeting and discussed in this report include endothelin-1 antagonists, BNP, ICDs, and subacute thrombosis with drug-eluting stents.

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Orlando, FL

DRUGS

Tidbits

- A source who has seen the data on **Pfizer's Lipitor/Norvasc** combination pill said it looks very good, that **Pfizer** is moving ahead with this actively but is keeping a low profile.
- **Esperion's apoMilano** was generating a significant amount of excitement. Esperion will need another trial, sources agreed, and more patients, but is likely to "result in a paradigm shift to IVUS."
- **Biogen's BG-9928,** an oral adenosine antagonist for heart failure: The poster was never put up.
- The issue of cardiac safety of **Vioxx (Merck, rofecoxib)** came up at a session on Cox-2 inhibitors, but the speaker downplayed the problem, saying it was

likely due to a protective effect of naproxen, dosing of Vioxx, or both. There were no questions from the audience about this, and concern over this issue does not appear to be escalating among cardiologists.

ALEXION/PROCTOR & GAMBLE'S Pexelizumab: PRIMO –CABG Trial

Alexion/Proctor & Gamble's pexelizumab missed the primary endpoint in its Phase III trial (PRIMO-CABG) – just as it did in an earlier Phase II trial – but the drug was shown to significantly reduce early and late post-operative MI as well as early mortality. PRIMO-CABG was a trial of 3,099 patients at 205 centers in North America and Europe, who underwent CABG either with or without valve replacement surgery. Pexelizumab did not show a statistically significant reduction in death and MI through day 30 in CABG-only patients, but it did when valve-replacement patients were included. The most frequent adverse events in both groups were atrial fibrillation, nausea, pleural effusion, post-procedural pain, anemia, hypotension and post-operative wound infections.

PRIMO-CABG Results

Measurement	CABG-only Patients (n=2,746)				All Patients n=3,099			
	Placebo n=1368	Pex n=1378	RRR	p-value	Placebo n=1546	Pex n=1553	RRR	p-value
Primary Endpoint: Death/MI at Day 30	11.8%	9.8%	18%	.069				
Secondary Endpoint: Death/MI at Day 30					14.0%	11.5%	18%	.030
Secondary Endpoint: Death/MI at Day 4	10.0%	7.4%	26%	.014	11.9%	9.1%	24%	.008
Secondary Endpoint: Death at Day 90	4.0%	3.2%	19%	.282	4.8%	3.6%	25%	.096
Death at Day 180	N/A	N/A	---	---	N/A	N/A	---	---
Adverse Events	N/A	N/A	---	---	85.2%	85.5%	---	Nss

In the Phase II CARDINAL trial, pexelizumab (2 mg/kg) also missed its primary endpoint of reduction in infarct size in AMI patients getting either angioplasty or a thrombolytic, but it dramatically reduced mortality, a secondary endpoint. Sources agreed that this Phase II mortality data was intriguing, but the mechanism of action for a death benefit was unknown, creating a lot of uncertainty about this drug. The Phase III researcher said the mechanism of action is still not known, "We don't know the mechanism, but we know complement is highly involved."

What happens to pexelizumab now? An Alexion official said the company will be discussing the results with the FDA to see what the agency will require for approval. In the meantime, the company plans to start another trial in high risk patients. The principal investigator, a cardiac surgeon, said, "I'm not overly concerned. There is overwhelming data that there is improvement in death and MI at Days 4 and 30, and the benefit carried out to Day 180, particularly in high risk patients…The choice of a death/MI endpoint at Day 30 was an arbitrary decision and doesn't necessarily reflect the robustness and benefit of the drug…What's very interesting is that if you look at the subgroup with more than one risk factor, the drug had a highly significant effect – a 28% relative risk reduction in the composite of death and MI, and a similar reduction in the components."

ASTRAZENECA'S Crestor and Exanta

Crestor (rosuvastatin)

AstraZeneca gave Crestor a big push at the meeting, but there wasn't any criticism of the company's marketing tactics, and the booth was overflowing with doctors. Cardiologists questioned about the outlook for Crestor were much more conservative in their approach to the drug than family practice doctors said they would be. Many indicated they are not rushing to use it, but aren't afraid of it either. Several commented, "The other statins work well."

Exanta (ximelagatran)

The results of SPORTIF-V suggest Exanta is likely to be a safe alternative to warfarin, at least in AF patients. SPORTIF-V was a randomized, double-blind, double-dummy trial of 3,922 patients with non-valvular AF.

Patients, who were followed a minimum of 12-month follow-up, were given either 36 mg of Exanta BID or unfractionated heparin plus a IIb/IIIa inhibitor. The trial met the primary endpoint – an event rate within 2 points, plus or minus, of warfarin – and showed Exanta was not inferior to warfarin.

There was no statistically significant difference in major bleeding, but the rate of major and minor bleed combined was lower with Exanta than with warfarin. There was one death in the Exanta arm, a fatal GI hemorrhage in an 80-year-old patient after corticosteroid therapy.

Event Difference between Exanta and Warfarin

SPORTIF-III	SPORTIF-V	Pooled Results
-.66	+.45	=.03 (p=.94)

The results were almost identical to the open-label SPORTIF-III, which was presented at the American College of Cardiology in March 2003. A pre-specified pooled analysis of

SPORTIF-III and SPORTIF-V further confirmed the non-inferiority of Exanta to warfarin in this patient group.

One-Year Results of SPORTIF-V

Measurement	Warfarin	Exanta 36 mg	Absolute difference	p-value
Primary Endpoint: All stroke and systemic embolic events on an ITT basis	1.2% 37 events	1.6% 51 events	0.45%/year	p=0.13
Systemic embolic events by on-treatment analysis	N/A	N/A	0.55%/year	p=.089
Combined all cause mortality and systemic embolic events on ITT basis	N/A	N/A	0.10%/year	p=.86
Stroke and major bleeding	47% / year	37% / year	---	p<.0001
ALT >3xULN	0.8%	6.0%	---	p<.001
Bilirubin >2xULN	1 patient	0.4% 9 patients	--	---
INR 2.0-3.0	68%	---	---	---
Mean INR	2.4	---	---	---
INR 1.8-3.2	83%	---	---	---
ICH	0.06%	0.06%	---	Nss
Major bleeding	3.1%	2.4%	---	p=.16

The principal investigator in SPORTIF-V suggested that the results with Exanta may be even better in clinical practice because the warfarin in SPORTIF-V was much better managed than is typically the case in clinical practice. He said, "Warfarin was given with extreme care in this trial, and (patients were in the ideal INR range) 68% of the time…which is far better than happens in clinical practice."

One of the key concerns about Exanta has been liver toxicity. In the open-label SPORTIF-III trial, there was a 6.5% incidence of ALT >3xULN, but researchers pointed out that most of this occurred in the first six to eight months, and, in most cases, the abnormalities went away when the drug was stopped or even sometimes when it was continued. A comparable incidence of liver enzyme elevations occurred in SPORTIF-V, and the pattern appeared to be the same.

Experts expect that liver monitoring will be required with Exanta, but they do not see that as a barrier to use. An investigator said, "I can't speak yet to what the FDA will recommend in terms of liver monitoring if this is approved, or what the experience will be when it is more widely used in a marketing way, but it is prudent to monitor liver enzymes once a month for the first six months, and if elevations occur, then treatment should be interrupted. And I would expect levels to return to normal in most cases…This seems to be a transient phenomena…Blood test monitoring with warfarin is a lifetime commitment…The liver testing (with Exanta) appears to be a short phenomenon that is over in the first several months, perhaps six months. I think it will be important at the beginning of treatment…but think I think it will dissipate." Another expert commented, "I want to move patients to something other than an INR clinic…The downside is the liver enzyme abnormalities…AstraZeneca will have to work out some risk management program with the FDA…I have no idea what they will come up with…I was impressed that the incidence of ALT elevations is very low...Maybe it is different patient types…But there were some ALT elevations."

There have also been questions about elevated bilirubin, and that was seen again in SPORTIF-V, but the level was low. A researcher said, "There were concomitant levels of bilirubin above normal within 30 days…which is less than half of one percent."

AF affects more than 2 million Americans and is associated with at least a five-fold increase in the risk of stroke if no preventive therapy is given. Previous trials have found that warfarin can reduce the risk of stroke by 62%, but it requires frequent dose adjustments followed by blood tests, making it a difficult drug for patients to take and physicians to monitor. Thus, there have been predictions that Exanta will quickly replace heparin.

However, Exanta is not expected to completely replace warfarin. A researcher said, "The future of warfarin is waning, but there is a wide array of additional cardiovascular diseases where these new medications have not been tested, so, unfortunately, we will be living with warfarin for a long time to come." An AHA official added, "We don't like to extend findings beyond the groups that have been studied when we have established therapies that work."

Even if doctors only used Exanta for AF – and that is unlikely, sources said – there is a large pool of untreated AF patients. A speaker estimated that, at the primary care level, 65% of AF patients are not on warfarin, and among those who are:

- 6% are above the INR target range
- 13% have a subtherapeutic INR
- Only 15% are in the INR target range

AstraZeneca reportedly plans to file Exanta with the FDA by the end of the year, and a speaker, critiquing the data, said, "This is a huge advance on what we currently have. All things currently considered, my impression is that this should be approved…and the recommendation that the LFT be monitored closely is a good one."

AstraZeneca sponsored an audience-participation dinner on Exanta before the release of the SPORTIF-V results, and it was very well-attended. The doctors stayed for the whole

Exanta talk and the Q&A, though many left when the discussion turned to statins. The audience answers included:

Question	Answer
Knowledgeable about recent data on Factor Xa or direct thrombin inhibitors	67%
% of patients with AF who are currently taking an anticoagulation	54% said >75% of patients 23% said 51%-75% of patients
Most common reason for patients with AF not taking anticoagulants	38% fear of bleeding 30% non-compliance with INR testing and dietary restrictions
Which guidelines for anticoagulation followed	60% ACC/AHA/ESC guidelines
% of patients within the INR range of 2-3 most of the time	45% in range 51%-75% of the time 32% in range 76%-100% of the time

Competitors include Organon/Sanofi's:

- Idraparinux (SanOrg34006), a selective Factor Xa inhibitor, a pentasaccharide. This is in development for pulmonary embolisms and deep vein thrombosis. It has a very prolonged half-life and is administered once weekly.
- Arixtra (fondaparinux), another selective Factor Xa inhibitor, pentasaccharide. This is already on the U.S. market.

MATISSE Pulmonary Embolism Trial

Measurement	Fondaparinux n=1,103	UFH n=1,110
Recurrence	3.8%	5.0%
Major bleeding	2.0%	2.4%
Death	5.2%	4.4%

JOHNSON & JOHNSON'S ReoPro+Retavase: BRAVE TRIAL

The BRAVE (Bavarian Reperfusion Alternatives Evaluation) trial found that pre-treatment prior to PCI with the combination of reteplase (Johnson & Johnson's Retavase) plus abciximab (Johnson & Johnson's ReoPro) is not superior to abciximab alone in patients with acute MI.

The principal investigator said, "Looking at the results, observing that there was no benefit on the basis of the clinical events, and having a trend to more bleeding complications in the combination therapy, we concluded that combination therapy was not superior to abciximab alone in these patients…The combined rate of death was a little bit higher in the combo group compared to abciximab alone, and there was a trend to more bleeding complications in the combo group."

BRAVE was a randomized, open-label study of 253 patients who presented at the admitting hospital within twelve hours of the onset of the symptoms of an ST-elevation AMI and who had no contraindications to thrombolysis and IIb/IIIa inhibition. The trial focused on heart attack patients who must be transported to other medical centers for treatment; 74% of the BRAVE patients were randomized in community hospitals and then sent to interventional centers for stenting. The remainder were randomized in interventional centers.

Patients were randomized by phone to receive either a half-dose of reteplase (2 boluses of 5 U) plus abciximab (bolus followed by a 12-hour infusion) or abciximab alone before transfer to the cath lab. The primary endpoint was final infarct size (percentage of the left ventricle), and the trial was powered to show a 30% reduction in infarct size with the combination therapy. The final size was measured five to 10 days after randomization. A speaker said, "If you look at the primary endpoint, we didn't find any difference in the final size between patients who received the combination therapy and those who received only abciximab."

Measurement	Combination reteplase+abciximab n=125	Abciximab alone n=123
Primary endpoint: Reduction in infarct size	13%	11.5%
Death within 30 days	2 patients	2 patients
Combined 30-day death, MI, stroke	3.2%	1.6%

Asked if the disappointing study results closes the door on additional trials of combination reteplase and abciximab therapy, Dr. Raymond Gibbons, program chairman of the AHA Committee on Scientific Sessions, said, "I don't think it closes the door. I think that this is a sophisticated endpoint…but we've learned that smaller trials, by the play of chance, don't always give us the best results…Sometimes the play of chance can work against us in small trials, and I don't think this will stop the two ongoing efforts to look at larger trials. I think the investigators are going to be very interested in the time-delay question, which has been widely discussed."

THE MEDICINES COMPANY'S Angiomax (bivalirudin)

The company was highlighting the release of the 12-month data from the REPLACE-2 trial, but that seemed premature. Only the secondary endpoint of mortality was presented in the poster. It did show non-inferiority of Angiomax to heparin. However, there was no information on the primary endpoint of the composite of death, MI, urgent revascularization and major in-hospital hemorrhage. There also was no information

on the other secondary endpoints of MI or urgent revascularization, and no data on side effects. Some doctors who visited the poster commented that it was the MI data they had come to see. One source pointed out that a nearby poster was reporting that LMWH was superior to heparin but Angiomax was only reporting non-inferiority.

Death in REPLACE-2

Drug	6 months	12 months
Heparin + IIb/IIIa	1.35%	2.46%
Angiomax	1.0%	1.89% (p>.05)

NOVARTIS'S Diovan (valsartan): VALIANT Trial

VALIANT, a two-year, 14,073-patient, double-blind, multicenter, international study found valsartan, an angiotensin II receptor blocker (ARB), to be as effective as the ACE inhibitor captopril (Bristol-Myers Squibb's Capoten) in reducing the risk of death as well as subsequent heart failure and MI. However, combining valsartan with captopril increased the rate of adverse events without improving survival. The patients in VALIANT were at high risk for cardiovascular events after an MI.

Researchers said the trial found:

➢ **The non-inferiority of valsartan:** The principal investigator said, "We had pre-specified…a statistical test to tell you whether you can robustly say the therapies are 'as good as.' That means that the patient estimate and confidence interval has to be such that it preserves a particular margin. The margin we chose before starting the study was that it had to preserve at least 55% of the benefit of captopril. When we conducted the test, we did meet those strict criteria on every study population described in the protocol. In fact we preserved 99.6% of the benefits of captopril. When physicians administer an ACE inhibitor, there is not just a reduction of death; ACE inhibitors also reduce the risk of developing heart failure as well as recurrent MI, which are both ominous for patients in the long term. When we looked at valsartan, for each of these cardiovascular endpoints alone or in combination, valsartan was as effective as captopril. We know that we have a dosage of regimen that can match the other and be as effective in reducing lives and reducing morbidity...So valsartan should be considered as effective as the ACE inhibitor captopril or ACE inhibitors in proven dose in reducing cases of death, cardiovascular death, heart failure and subsequent MIs."

Measurement	Valsartan n=4,909	Captopril n=4,909	Valsartan + Captopril n=4,885
Primary endpoint: All cause mortality	19.9% (979 patients)	19.5% (958 patients)	19.3% (941 patients)
Most common adverse events	Hypotension, renal dysfunction	Cough, rash, taste disturbances	Hypotension, renal side effects

➢ **No value – and additional safety issues – with combination ACE/ARB therapy.** A speaker said, "Adding valsartan to a proven dose of ACE inhibitors did increase adverse effects, and there was no added value."

Researchers concluded that VALIANT establishes valsartan as an alternative to an ACE in patients who cannot take an ACE. A speaker said, "For those (patients) with difficulty with ACE inhibitors, it's a perfect opportunity." An AHA official added, "This trial provides the evidence that there is a suitable alternative, an equivalent alternative (to ACE inhibitors), and I think this will affect clinical practice."

OTSUKA PHARMACEUTICAL'S Pletal (cilostazol) and Tolvaptan

PLETAL (CILOSTAZOL): THE CREST TRIAL

CREST researchers reported that cilostazol, taken orally after stenting, significantly decreased the rate of restenosis, a benefit that extended to diabetics and small vessel sub-groups. The specific aim of CREST (Cilostazol for RESTenosis) was to evaluate whether cilostazol, an antiplatelet agent that selectively inhibits PDE3, will prevent restenosis after stent implantation in a native coronary artery, and researchers found that it does.

6-Month Results of CREST Trial

Measurement	Cilostazol	Placebo
Primary endpoint: Minimal lumen diameter at 6 months	1.77	1.61
Binary Restenosis		
Diabetics	15%	34%
Vessels <3 mm in-segment	21.9%	34.4%
Vessels >3 mm in-segment	17.7%	34.8%
Vessels >3 mm in-stent	17.7%	32%

CREST was a multi-center, randomized, double-blind six-month trial of 705 patients at 19 sites, who received cilostazol 100 mg BID plus aspirin and clopidogrel (Bristol-Myers Squibb/Sanofi's Plavix) or placebo. Clinical events occurred equally frequently with regard to MI, death, revascularization and stroke. Safety with respect to bleeding and re-hospitalization were also similar in the two groups.

A speaker said, "Are the data believable? Yes…There was a 12% absolute reduction in stenosis and a 36% relative risk reduction in restenosis. This is likened to the results of similar studies in Asia. There are absolute and relative reductions."

However, there are still a number of unanswered questions about cilostazol, including:

- What is the mechanism of effect?
- Is it one or a combination of effects producing favorable outcomes?
- How should this go forward?
- Should oral agents be considered to prevent restenosis?
- Should a stent eluting cilostazol be considered?

Tolvaptan: ACTIV in CHF Trial

This 319-patient, 60-day Phase II study in the U.S. and Argentina met one primary endpoint but failed the other. On the positive side, it showed that tolvaptan may improve clinical symptoms in patients hospitalized due to worsening heart failure by reducing body weight at 24 hours. The decrease in body weight was sustained at discharge and out to 60 days, and there was a trend towards lower mortality in patients with severe clinical congestion, hyponatremia, or abnormal renal failure.

However, there was no reduction in worsening of heart failure at 60 days, a second primary endpoint compared to placebo. There also was no dose response curve – all three doses performed similarly.

Tolvaptan is a new class of agent, an oral once-daily vasopressin V_2 receptor blocker. An investigator said, "This could be a new way to get rid of the extra fluid, to make the heart more efficient…In 24 hours, we saw a major decrease in body weight in the tolvaptan groups but not with placebo."

In this trial, tolvaptan was compared to placebo in heart failure patients randomized within 72 hours of admission to the hospital. All patients also received standard therapy that included diuretics (97%), ACE inhibitors (80%), digoxin (70%) and beta-blockers (40%). EVEREST, a large Phase III trial in North America, South America and Europe is now underway, testing only the 30 mg dose.

60-Day Results of ACTIV in CHF Trial

Measurement	Placebo n=80	Tolvaptan 30 mg n=78	Tolvaptan 60 mg n=84	Tolvaptan 90 mg n=77
Mean age	62	60	62	62
Male	75%	68%	60%	79%
History of MI	43%	35%	35%	36%
Edema (%)	59%	68%	71%	75%
Results				
***Primary Endpoint #1*: Body weight change at 24 hours**	Up 0.9 kg	Down 2.0 kg (p=0.18)		
Body weight change at 7 weeks	Down 2 kg	Down 4 kg		
***Primary Endpoint #2*: Reduction in worsening heart failure at 60 days**	Nss	Nss		
All cause mortality	8.7%	5.4% (p>.05)		
Mortality in patients with hyponatremia (< 136 mEq/L)	18.7%	13.2%		
Mortality in patients with BUN (>29 mg/dl)	20%	9.1%		
Mortality in patients with severe congestion	17.8%	5.5%		

PFIZER'S Lipitor (atorvastatin)

The results of the highly touted and long-awaited REVERSAL trial were presented at AHA, and the trial found that high dose Lipitor (80 mg) – but not 40 mg Pravachol – halted atheroma progression. REVERSAL was a 654-patient, randomized, double-blind, multicenter trial comparing 80 mg Lipitor to 40 mg pravastatin (Bristol-Myers Squibb's Pravachol) over 18 months, with IVUS at the beginning and the end. No differences were seen in adverse events or liver and muscle enzyme elevations between the two regimens, and no patient experienced myopathy.

The messages from REVERSAL, according to investigators, were:

- Use more higher dose Lipitor. Dr. Stephen Nissen of the Cleveland Clinic said, "You can reduce the progression rate of atherosclerosis to essentially zero, but you have to use the highest dose of a highly effective statin…We strongly believe that consideration of more intensive treatment with 80-mg atorvastatin is now warranted in secondary prevention, particularly for patients at high risk of morbid events."
- Even pravastatin patients who achieved LDL ≤100 showed a highly significant progression in atheroma volume and obstructive volume. Dr. Nissen said, "At any LDL level, progression was less on atorvastatin than on pravastatin."
- Lipitor may have had a greater effect on atheroma because of its better reduction in CRP.

However, doctors at AHA were less impressed with the findings than might have been expected. Several described the trial as mostly a marketing ploy.

In each patient, a series of IVUS measurements were taken, using a branch vein as a marker so the same vessel segment was measured both times. The atheroma area was measured and the lumen area measured, then the differences compared. Dr. Nissen commented:

- "In studies like REVERSAL, we are dealing with a couple hundred cubic millimeters of plaque. There is so much atherosclerosis in these patients that it is mind-boggling."

- "Why do we care about plaques that don't narrow the lumen? Because 68% of MIs occur in patients with <50% stenosis (18% in patients with 50%-70% stenosis, and 14% in patients with >70% stenosis)…This is why angioplasty doesn't reduce death or MI…It has been believed that statins can slow but not stop atherosclerosis. We wanted to explore a lower LDL target range -- go where no man has gone before -- down into the low LDL levels and find out what happens at those levels."

REVERSAL Trial Results

Measurement	Lipitor 80 mg	Pravachol 40 mg	p-value
Primary Endpoint: % change in atheroma volume	+0.4% (no change)	+2.7% (progression)	p=.02
Change in total atheroma volume (mm^3)	-0.9 (no change)	+4.4 (progression)	p=.02
Change in % obstructive volume	0.2% (no change)	1.6% (progression)	p=.0002
Final LDL (mg/dL)	79	110	---
% change in LDL	-46.3%	-25.2%	---
Secondary Endpoint: % change in CRP	-36.4%	-5.2%	P<.0001

At a Pfizer-sponsored dinner, Dr. Nissen showed a sample patient from the trial, without specifying which drug the patient was on. On angiogram, this patient's left circumflex looked pretty good, but by IVUS, there was actually quite a lot of plaque. The patient got a drug for 18 months. Fractions of a percent change in plaque were expected over this period. Instead, the plaque burden was dramatically lowered.

Measurement	Atheroma Before	Atheroma After	Change in lumen
Site 1	8.31 mm^2	5.97 mm^2	None
Site 2	6.36 mm^2	3.67 mm^2	None

DRUGS FOR PULMONARY ARTERIAL HYPERTENSION (PAH)

Among the drugs in development (or newly approved) to treat PAH are:

1. Prostacyclins. Several appear to increase exercise capacity and improve symptoms and hemodynamics. The question is whether they prolong survival, and the jury is still out on that. There are also issues with respect to side effects and convenience.

a. **UNITED THERAPEUTICS' Remodulin** (treprostinil), which was approved by the FDA in 2002. this is a continuous subcutaneous infusion.

b. **UNITED THERAPEUTICS' beraprost.** The European ALPHABET trial demonstrated a statistically significant increase in the 6 minute walk test with beraprost. However, a U.S. trial did not find a statistically significant effect on 6 minute walk at 9 or 12 months, though the three and six months results were similar to the European findings.

c. **SCHERING AG'S Ventavis (inhaled iloprost).** In 2002, the DIRECT trial showed a statistically significant treatment effect (p=.004) with administration six to nine times a day. A speaker said, "There have been significant improvements in the delivery system, and we are optimistic that in 2004, the company will do a similar trial in the U.S."

2. Endothelin antagonists. ET-1 regulates both ET-a and ET-b. It was thought that selective ET antagonists would be superior to a dual antagonist, but experts are now questioning that idea. A speaker said, "A dual antagonist may be better than a selective antagonist…Some patients may do better on a selective ET antagonist, and others may do better on bosentan…We've had patients who failed bosentan but did well on sitaxsentan…Even though the class causes liver toxicity, there are still differences between these drugs. You can even put patients who develop liver toxicity on bosentan onto sitaxsentan, and they do okay…If you start a patient on bosentan, and the patient does great, then keep the patient on bosentan. But if the patient doesn't do well, try another endothelin antagonist."

This speaker suggested that it may be a good idea to give ET-1s earlier. They also may be useful in other diseases, particularly scleroderma, but a PAH expert is concerned that rheumatologists already are using bosentan prophylactically and therapeutically without getting a cath on these patients. She said, "The newer agents should extend the market for endothelin antagonists, but patients need a team approach by physicians to their care."

One of the major drawbacks of the ET antagonist class of drugs is a tendency to cause liver abnormalities, and it was thought the newer agents would avoid this problem, but they are proving to have the same problem.

a. **ACTELION'S Tracleer (bosentan),** a twice-daily oral ET-1 antagonist, which was approved by the FDA in 2001. Asked if patients can be weaned off GlaxoSmithKline's Flolan (epoprostenol) when Tracleer is added, a speaker said, "We add bosentan, and then slowly decrease Flolan. If there is acute reactivity, then we add a CCB to the bosentan. We do caths at three, six, and 12 months to be sure we have an optimal regimen."

b. **ENCYSIVE'S sitaxsentan,** an oral, once-daily, selective ET-a antagonist. The results of the first Phase III double-blind, 178-patient, 12-week trial, STRIDE-1, will be published in a major medical journal in early 2004. The most common side effects with sitaxsentan were peripheral edema, headache, dizziness and nasal

congestion. Overall, researchers believe the 100 mg will be the best does for PAH patients, but the 300 mg dose may be required for the most severe patients. The pivotal trial is currently in progress. An expert said, "I'm not sure the QD is a big advantage over a BID drug."

Stride-1 Results

Measurement	Placebo	100 mg Sitaxsentan	300 mg Sitaxsentan
Primary Endpoint: Improvement in breathing capacity	N/A	0	7%
Secondary endpoint: Improvement in 6 minute walk	N/A	9%	9%
Discontinuation due to adverse events	5 patients	0	7 patients
Reversible liver abnormalities	3%	0	9.5%

Encysive has been granted a Special Protocol Assessment by the FDA for sitaxsentan, and it is conducting a pivotal trial, STRIDE-2, under this SPA. STRIDE-2 is a double-blind, 18-week trial testing 50 mg and 100 mg sitaxsentan QD vs. placebo. The primary endpoint is six-minute walk, and secondary endpoints include change in functional class, clinical events, and shortness of breath (on the Borg dyspnea scale).

c. **Myogen's ambrisentan,** a selective ET-a antagonist. An expert said, "I don't know if ambrisentan and sitaxsentan are as different from each other as they both are from bosentan…Ambrisentan only has one pilot study, with no placebo control. It is just starting a randomized clinical trial…It was thought that it would have no liver toxicity, but there is…We had one patient on it who had to come off. So, I don't know if there is less liver toxicity than sitaxsentan."

3. Phosphodiesterase inhibitors. Randomized clinical trials of Pfizer's Viagra (sildenafil) are underway to determine whether this drug is effective in PAH. A speaker said, "In addition to efficacy for erectile dysfunction, sildenafil appears to have a significant impact in the pulmonary vascular bed, so it may be a good agent to consider (for PAH)."

DEVICES

AHA is more a drug than a device (e.g., stent) meeting, but there was some new information on ICDs, stents and BNP testing.

Tidbits

- There was a rumor (for a fairly good source) that Guidant and Johnson & Johnson are discussing an arrangement under which Guidant would distribute Cypher stents after Taxus approval.
- **BIOSENSORS** could get CE Mark for its biolimus-eluting stent by March 2004 or soon thereafter, so keep an eye on that.
- **AVENTEC** is expected to launch its mycophenolic acid (MPA) drug-eluting stent in Japan through Goodman in December 2003.
- A poster reported that T-Wave alternans **do** predict patients at low risk of ventricular tachycardia. The researcher said, "The implication is that a negative T-wave can identify MADIT-II people who could do without an ICD, but this needs to be shown in a clinical trial."

ICDs: The DEFINITE Trial

There are two main causes of CHF:

1. Narrowing of the arteries of the heart and coronary system. This is the most common cause and was studied in MADIT-II.
2. Primary disease of the heart muscle – non-ischemic heart failure. About a third of CHF is believed due to this, and this was the focus of the DEFINITE trial.

DEFINITE looked at 458 CHF patients (mean age 58) with the second type of CHF – patients with non-ischemic dilated cardiomyopathy, LVEF<36 and spontaneous premature ventricular complexes or non-sustained VT. This randomized, multi-center study, sponsored by St. Jude, had a mean follow-up of 26 months and was designed to end when 56 deaths were reached, with an expected 50% reduction in mortality relative to standard therapy. ICD patients received St. Jude's Atlas, Photon or Micro VR devices.

The trial missed its primary endpoint, causing an investigator to say, "We will need more studies, but the fact that it (the ICD arm) did reduce arrhythmic mortality suggests this patient population may benefit…The relative risk reduction is the same as in MADIT-2…We will require additional follow-up analysis before we will be absolutely certain what role the ICD will play…(but) the data suggests the ICD may benefit this population in preventing cardiac arrest."

Two-Year DEFINITE Trial Results

Measurement	Medical therapy only n=229	Medical therapy +single chamber ICD n=229	p-value
Primary endpoint: All cause mortality	13.8% 33 patients	8.1% 23 patients	p=.06
Secondary endpoint: Sudden cardiac death (arrhythmic mortality)	11 patients	3 patients	p=0.01

Asked what these findings mean for the average electrophysiologist trying to choose between a dual or a single chamber device, an investigator said, "There is some data to suggest if you pace, you can worsen heart failure...We specifically excluded pacemakers, so we avoided any deleterious effects…Based on our results in this patient population, the benefit is in single pacing – pacing only the right side -- not biventricular pacing…I think for this particular indication in patients like this, a single chamber device seems to suffice."

DRUG-ELUTING STENTS

In-stent restenosis

Asked how to treat restenosis in a drug-eluting stent, a speaker said, "Our approach is another drug-eluting stent. We've done this in four or five patients, and they did pretty well…Most restenosis is focal, and that means it is not intrinsic responsiveness to the drug, but position, contact, gap, or semi-gap. So, placing another (DES) stent makes sense." Another speaker added, "What is essential in drug-eluting stent restenosis is an extensive investigation with IVUS…We clearly need to understand if the struts are there, if there is a strut gap...if something was missed. Many times there is a mechanical explanation."

Bifurcations

Dr. Antonio Colombo described his experience in Italy with both Cypher and Taxus in bifurcations using the crushing technique. He advised doctors to:

- Stent from normal to normal (which will lower or eliminate peri-stent restenosis).
- If utilizing a long stent and a lot of metal, be aware of thrombosis. "Don't blame drug-eluting stents."
- Do not under-deploy.
- Do not leave residual dissections.
- When in doubt, post-dilate, but always stay in the stent margins.
- Be liberal with IIb/IIIa use.

Measurement	Cypher n=204	Taxus n=58
30-day Results		
Death	0	1.7%
MI	0	1.7%
30 Day to 6-month Results		
Total MACE	0	1.7%
Death	1.8%	0
MI	0.9%	0

DIRECT STENTING

There is no clear advantage to direct stenting over pre-dilation other than cost and time. A speaker said, "When in doubt, pre-dilate; and in complex lesions, always pre-dilate."

BOSTON SCIENTIFIC'S Taxus

A source said Boston Scientific would start a Phase IV trial of Taxus after the FDA Advisory panel but before approval and that sites already were being recruited. This was described as indicating that:

- Approval is nearly certain.
- Approval may not come until April or May 2004.

The Taxus-VI results will be at EuroPCR in May 2004, and a researcher said the data "will be very good."

Among the first 235 patients in the WISDOM trial, a web-based data collection of real-time, real-world Taxus patients, the SAT rate was 0.4%, MI 0.4%, cardiac death 0.9% and re-intervention 3.0%.

The Siegburg, Germany, experience with the Taxus Registry includes 282 patients with 370 lesions. Preliminary results from the six-month angiographic follow-up reported 30 day MACE of 2.8% and six-month TLR of 8.8%.

A prominent cardiologist predicted that Taxus stents will be overlapped in the U.S. off-label. He said that is what is being done in Europe now and he expects the same situation in the U.S., regardless of FDA labeling.

TAXUS-IV: One-Year Clinical Results

The data looked good for Boston Scientific's Taxus stent. The one-year clinical results showed no safety concerns, no increased risk of stent thrombosis, a reduction in both CABG and more invasive surgical procedures. The principal investigator, Dr. Gregg Stone of Lenox Hill Hospital in New York, said, "At 12 months, it was shown to be effective in a wide range of complex patients and lesions, and the incremental benefits of having the Taxus stent continue to increase with extended follow-up…The results were uniform throughout the study population."

TAXUS-IV: Clinical Events From 9 to 12 Months

Measurement	Control n=652	TAXUS n=662	p-value
Cardiac death	0.2%	0%	.50
MI	1.1% (7 patients)	0%	0.007
TLR	4.0%	1.4%	0.003
TVR	5.8%	2.4%	0.002
MACE	6.3%	2.4%	0.0006
TVF	6.1%	2.4%	0.0009

TAXUS-IV: 12-month TLR Subset Analysis

Measurement	Control n=652	TAXUS n=662	p-value
All	14.7%	4.2%	<0.0001
Non-diabetics	13.1%	3.4%	<0.0001
Diabetics on oral meds	21.1%	7.7%	0.0063
Diabetics on insulin *	16.7%	5.9%	0.12
LAD	16.0%	5.3%	0.0001
Non-LAD	13.6%	3.5%	<0.0001
RVD ≤2.5 mm	20.1%	5.3%	<0.0001
RVD >2.5-3.0 mm	12.9%	4.3%	0.0006
RVD >3.0 mm	10.8%	3.0%	0.0026
Lesion length <10 mm	12.8%	3.7%	0.0005
Lesion length 10-20 mm	13.8%	4.3%	0.0014
Lesion length >20 mm	21.6%	5.5%	0.0014

*** only subgroup not to show a statistically significant benefit in favor of Taxus**

TAXUS-IV: 12-month Adverse Cardiac Events

Measurement	Control n=652	TAXUS n=662	p-value
Cardiac Death	1.2%	1.4%	1.00
MI	4.6%	3.5%	0.33
TLR	14.7%	4.2%	<0.0001
TVR	16.7%	6.8%	<0.0001
MACE	19.8%	10.6%	<0.0001
TVF	19.2%	9.7%	<0.0001

Asked about the late loss in TAXUS-IV, Dr. Steve Ellis, of the Cleveland Clinic, who did the IVUS analysis of the trial, commented, "Late loss is perhaps more sensitive...but stents can accommodate a certain amount of late loss without clinical ramifications."

Asked whether Taxus has an advantage over Cypher in terms of restenosis, Dr. Stone said, "The 8.9% angiographic restenosis for Cypher correlates to 7.9% for Taxus. Those are roughly comparable. When you look at the two populations, they weren't that different in characteristics that affect restenosis -- 8.9% and 7.9% are very similar. When you try to tease out differences with the relatively small number of diabetics in both trials, Taxus seems to do better than sirolimus, particularly in insulin-dependent diabetic…There also may have been a benefit in small vessels with Taxus (over Cypher), but the numbers were small, and, for the most part, we are trying not to compare the two…Some doctors will be more impressed with the Taxus data, and some will feel a mandate to use it in diabetics…Others will feel Taxus is more flexible and deliverable."

Asked how to explain the different performance in diabetics between Cypher and Taxus, Dr. Stone said, "I don't know, and the numbers are so small that it may just be statistical chance, but my guess is that it is probably not chance…There are different ways paclitaxel and sirolimus work…Sirolimus works on mTOR and requires the presence of an insulin receptor…Paclitaxel works by non-insulin-dependent mechanisms and by a variety of mechanisms, not just one."

Taxus investigators were asked about the FDA's warning about subacute thrombosis (SAT) with Cypher stents, and they insisted they have not seen an increased risk in SATs in Cypher patients at their centers, and they did not try to make a competitive advantage out of this issue. Dr. Stone said, "No study with Cypher has shown an increased risk of SATs. All the controlled studies have shown similar SAT rates with Cypher and the bare control stent. The world registries with Cypher have not supported an increased SAT with Cypher v. the bare stent…We are tracking this carefully at Lenox Hill with more than 2,000 patients and more than 3,500 Cypher stents, and we had 10 SATs or 0.5%, which is exactly the same as bare metal stents…The sense is that the stent thrombosis rate is not increased, but the FDA is appropriately monitoring this."

Investigators said there has been no signal of an increased rate of SATs with Taxus stents either. Dr. Stone said, "The international (Taxus) registries have not shown a concern about stent thrombosis, but Boston Scientific will be very carefully watching this and prospectively doing a large registry to find out what the stent thrombosis rate is…So far, international registries have not shown a concern (with Taxus), but obviously this is something Boston Scientific will carefully watch and prospectively do a trial to determine." Dr. Ellis added, "A quarter million patients have received Cypher, and if you expect a thrombosis rate of 1%…then you could expect about 500 deaths, but, as far as I know, the second FDA letter reported 60 deaths. The question is: What percentage of deaths are being reported to the FDA? You'd think that most would have been reported after the first letter. We lack a US registry to tell us what the true rate is. We've been tracking our own results at the Cleveland Clinic, and we don't see a difference with Cypher stents."

Asked if users have seen any hypersensitivity reactions with Taxus stents, Dr. Stone said, "No, we haven't…But it is very hard to sort out hypersensitivity reactions when patients are on a lot of other drugs. But we've not seen that to be any sort of problem."

Boston Scientific is planning a pre-approval registry of Taxus, Dr. Stone confirmed. He said the FDA suggested – not mandated – that the company do this, "Boston Scientific is choosing 40 to 50 mid-volume sites -- not high-powered academic centers to start collecting data even before approval of this device."

JOHNSON & JOHNSON'S Cypher

Measurement	Cypher	Taxus
# of patients	731	301
# of lesions	1,430	521
# of stents	1,583	568
Peri-procedural thrombosis	5 patients	0
SAT	0.1%	1%
Late thrombosis	0.2%*	0.3%

*** one patient stopped clopidogrel early**

Subacute Thrombosis (SAT). The Italian experience with Cypher didn't show any SAT problem with Cypher.

The FDA warning letter about SATs and Johnson & Johnson's Cypher stent appeared to be having ***no*** impact on attitudes toward Cypher in either the U.S. or Europe. It also has not been not causing doctors to slow down their use of Cyphers or be more cautious about using Cyphers. Doctors are watching the SAT issue, but they are *not* concerned about it with Cypher. Among their comments were:

- *Major East Coast center:* "We've seen 0.4% SAT with 7,000 patients, but it hasn't caused us to use fewer Cyphers, and we expect Taxus to have the same issue."
- *New England:* "We haven't cut our use of Cypher. We are doing 'watchful waiting,' but we don't know the rate…Taxus will have no advantage because of this issue."
- *Louisiana:* "Our level of concern is not very high, and we haven't changed our Cypher use as a result…We already use IVUS for all drug-eluting stents, which has lowered our MACE rate…The problem may be worse with Taxus."
- *North Carolina:* "There is increased awareness, but it hasn't changed our use of Cyphers. The rate is <1%, and that's better than bare stents. I expect Taxus to have a comparable issue."
- *North Dakota:* "Concern is low. It is not an issue. The data still show the rate is low, and the FDA doesn't give the denominator. Our use of Cypher is stable, and we expect SATs with TAXUS to be comparable."
- *Italy:* "SATs are not an issue. No European doctors are switching form Cypher to Taxus because of this."
- *Germany:* "Right now we have to address technique, pay attention to medication, be more careful…Looking at the number of SAT overall, it is still very low, but it is a new technology, so we have to watch it."
- The exception was this doctor: "First, they said it was the doctor's fault. Then maybe it was the anticoagulation. Then Angiomax (The Medicines Company, bivalirudin). Then patient non-compliance (with anticoagulation therapy). Maybe it is the drug's fault." A speaker responded, "No one is at fault. This is a complex issue…(but) it could be associated with the device."

In-stent Restenosis

Implantation of a Cypher following "failed" vascular brachytherapy (VBT) was reported by one researcher as having a 16.7% TLR, which compares to a 23.5% historical rate with repeat VBT. He said, "Although there is no randomized data, it is fair to say the preliminary observational data indicate the use of drug-eluting stents is a safe and effective treatment for in-stent restenosis and constitutes a reasonable alternative to brachytherapy. Technical mistakes such as persistence of a gap between two stents or incomplete coverage have to be avoided in order to obtain optimal results…The treatment of brachytherapy failures with drug-eluting stents is feasible but probably necessitates a ***permanent*** treatment with a dual antiplatelet regimen...It is not inferior to brachytherapy but is superior to conventional treatment."

RESEARCH Registry: 9-Month outcome

Measurement	VBT n=43	Cypher n=44
Diabetics	26%	25%
Death	7 patients	0
MI	2.3%	2.3%
TVR	11.6%	16.3%
Any event	20.9%	18.6%
MACE-free survival	81.5%	79.1%

Other Cypher issues

- The hypersensitivity reported with Cypher occurs within 30 days, indicating it is more a drug than a polymer issue, sources said.
- The German Cypher Registry of 2,666 patients to date is showing a 7.3% MACE rate and restenosis of 11% at six-month follow-up.
- The Cypher Milan Registry of 738 lesions reported a TLR of 7.2%, TVR of 3.8%, bypass TVR of 1.2% (for a total of 12.2%).

MEDTRONIC'S Endeavor

There was no new data on Endeavor, Medtronic's drug-eluting stent program with ABT-578, but the pivotal trial reportedly is enrolling very quickly.

BNP TESTING

At a session on BNP and LVADs, a speaker was asked which assay he prefers to measure BNP. He said, "They are similar…The only difference is that Biosite may be more effective in acute use, but sensitivity may be better with the Roche assay, and further studies are needed."

A poster from the Cleveland Clinic reported on a retrospective study comparing the **Biosite Triage** and **Roche Elecsys** assays for BNP and pro-BNP, respectively. The conclusions were that:

- The two assays are similarly affected by age and renal insufficiency.
- There was a good correlation between them overall.
- The only statistically significant difference between them was in chemotherapy patients and peri-operative patients, but the poster did not specify which was better.

At a Roche-sponsored dinner, the lectures focused on the value of pro-BNP. There was little discussion of the actual assays (Biosite vs. Roche Elecsys). The speakers neither trashed Biosite's Triage nor touted Roche's test. The real focus was to encourage doctors to do more BNP tests, by convincing them of the value of BNP testing, period.

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