Trends-in-Medicine

April 2004
By Lynne Peterson

SUMMARY

Questions are increasing about the safety of AstraZeneca's Crestor and Exanta, and cardiologists are increasingly concerned about both. ♦ Pfizer's Lipitor beat out Bristol-Myers Squibb's Pravachol in a head-to-head cholesterol lowering trial, and evidence is mounting that lower is better when it comes to cholesterol. ♦ Sanofi-Synthelabo appears to have a winner with Acomplia both as a diet drug and a smoking cessation aid. ♦ SCD-HeFT confirmed the benefits of ICD therapy, and it is likely CMS will expand coverage, but the trial results raised enough questions that CMS may not grant reimbursement for a broad MADIT-2 indication. ♦ A raft of new data helped Johnson & Johnson steal some of the drug-eluting stent fanfare from Boston Scientific, which got its Taxus stent approved just before ACC. In addition, questions were raised about safety in the TAXUS-V trial and Taxus pricing. J&J's Cypher marketing deal with Guidant raised eyebrows, but sources weren't sure how helpful it would be.

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The annual American College of Cardiology (ACC) meeting has gotten so large, that it is only possible to report on selected topics. This report will review some of the data presented or discussed on cholesterol, anticoagulation, a promising new diet drug, hypertensions, pulmonary arterial hypertension, ICDs, drug-eluting stents, carotid stenting, and bypass grafting.

D R U G S

Aventis's Lovenox (enoxaparin): SYNERGY Results Disappointing

The SYNERGY trial found that Lovenox was non-inferior to heparin but caused more bleeding. The non-inferiority study looked at higher risk acute coronary syndrome patients. An investigator defended the results and cast them in a more positive light, saying, "Enoxaparin is at least as good as UFH (unfractionated heparin)…and there is tantalizing data from this and other trials that switching back and forth (from one to the other) not only may not be good for efficacy but also may be associated with a prohibitive rate of bleeding…The practical implications are that you can safely and effectively use Lovenox through the whole

hospital, instead of unfractionated heparin, or instead of switching to UFH in the cath lab…75% of patients got one or the other (Lovenox or UFH) before randomization, and there was a much stronger treatment effect with Lovenox in the pure treatment (no prior treatment) group…We did not show superiority in the primary analysis (ITT), and bleeding is a concern, but there was no increase in transfusions…There is more (blood) oozing, but it was the view of the steering committee that this was not important, and the DSMB didn't stop the trial because it didn't think this was clinically significant."

SYNERGY Results

Measurement	Lovenox 1 mg/kg SC Q12h n=4,993	UFH 60 U/kg → 12U/kg/hr n=4,985	p-value
Primary endpoint: 30-day death/MI (by ITT)	14.0%	14.5%	p=0.396
Death	3.2%	3.1%	p=0.705
MI	11.7%	12.7%	p=0.135
Death/MI in patient with no prior treatment	8.1%	9.5%	N/A
TIMI major bleeding	9.1%	7.6%	p=0.007
TIMI major bleeding in patients with no prior treatment	9.7%	6.9%	N/A
GUSTO severe bleeding	2.9%	2.4%	p=0.106
GUSTO severe bleeding in patients with no prior treatment	3.1%	1.8%	N/A
Transfusions	17.0%	16.0%	p=0.155

AstraZeneca's Crestor (rosuvastatin)

Word is getting around among cardiologists about Public Citizen's petition to the FDA to have AstraZeneca's Crestor (rosuvastatin) removed from the market. Doctors were questioned about what it means to their use of Crestor, and all but one agreed that they will not prescribe Crestor for new patients until this issue is clarified either by the company or the FDA. Following are some physician comments on Crestor safety.

- *Indiana*: "This is very concerning. It is one thing to prescribe a drug that later develops a problem and quite another to knowingly give something to patients about which questions have been raised…Obviously, I won't start new patients on Crestor now. It's not safe to subject patients to this."

- *New York*: "I'm very concerned. I've only used Crestor sparingly, but now I will avoid it."

- *New England*: "I think the petition is ridiculous, but I haven't used Crestor yet, and I don't need it now."

- *Massachusetts*: "The Public Citizen petition is compelling…There is little reason to use Crestor now…The FDA needs to review the cases and have an advisory panel…I'm very concerned, but withdrawal of Crestor could chill patient use of statins…And the more statins on the market the better because of patient variability in efficacy and side effects – and because that helps bring the price down."

- *North Carolina*: "I take this very seriously…With such stupendous results with atorvastatin, why would you want to use a drug that doesn't have long-term data. I won't start Crestor now unless patients insist or they can't take all the other statins. Why use something unproven?"

- *Pennsylvania:* Dr. Gary Ledley of Albert Einstein Medical Center in Philadelphia PA said, "Every drug has some side effects. What you really need to know is what the incidence is, and whether it is higher than any other drug. So, it is important to know what the denominator is…My reaction to the data is that it's an eye opener, and it raises my interest level. I definitely want to know more about it, but my gut feeling is that the number of patients who have a side effect is very low and is probably similar to the other statins. Right now, if someone is on Crestor and doing well, I won't change anything. To be honest, I haven't put that many people on Crestor because the other statins are very good and very well-known and well-studied. And with the Baycol fiasco, I didn't see that there was a great need to use a brand new drug."

- *Connecticut*: "It is alarming and certainly bears watching…It has happened where other drugs came to market and then flared out when side effects were found after marketing started...This is anecdotal, but I wouldn't be dismissive…Crestor has some desirable benefits, but at this point many people are being cautious about it…I'd like to see further clarification from the FDA…Safety has to be our foremost consideration, particularly when there are six other statins on the market."

At an AstraZeneca-sponsored dinner on hyperlipidemia, a speaker commented, "All of the statins have proteinuria. Clearly, you have to monitor patients, but this is something that has been seen with other statins…Most of the concern is at 80 mg, but there is a slightly increased risk at 40 mg." Another speaker, questioned about the petition, asked, "Where is the additional data on the cases? Patients are sick, and sometimes they end up dying. Crestor has been well-studied. Simvastatin has toxicity at 160 mg, and why do you think 80 mg is the highest dose of Lipitor? Because of toxicity at higher doses. More than 1 million patients have taken Crestor."

After the dinner, AstraZeneca officials were observed discussing what to do about the Public Citizen petition. One option they were considering was sending out a Dear Doctor letter, but they had not yet decided if or when to do that. An official commented, "Thousands of doctors called their sales reps (the day after the petition was filed)."

AstraZeneca's Exanta (ximelagatran)

Questions about the safety of Crestor are starting to bleed over to Exanta. Several sources predicted that if Crestor were withdrawn from the market or the FDA issued a safety

warning about it, that could make it more difficult to get Exanta approved, given 6% of patients had elevated ALT (>3xULN) in SPORTIF-V.

A dinner on anticoagulation in AF (sponsored by Astra-Zeneca) attracted a standing-room only crowd, and almost everyone stayed to the end. Speakers urged an expanded use of anticoagulation for AF patients, and they presented data indicating that neither aspirin nor resumption of sinus rhythm is sufficient. They also went into detail on the efficacy of warfarin, but stressed how difficult it is to use, causing under-use. No new data was presented on Exanta; speakers just reviewed the SPORTIF-III and SPORTIF-V trials.

There was only a brief mention of the liver elevations with Exanta, and the speaker concluded: "There is no reason to panic and stop the drug unless the ALTs are very much elevated." A doctor in the audience asked if Exanta could be given with statins since statins can raise ALT levels, and the panel agreed that it could. Asked about liver elevations with Exanta, an expert said, "I think Exanta is safe if you are monitoring the ALT and bilirubin levels carefully. I would leave patients on it if their ALT went up because they usually come down by themselves."

However, at an official ACC session, a pooled analysis of SPORTIF-III and SPORTIF-V was presented, and the liver safety was slightly more concerning in this review. Older patients and women had even higher rates of liver enzyme elevations.

Pooled Analysis of SPORTIF-III and -V

Measurement	Men	Women	Patients <75 years old	Patients ≥75 years old
Overall ALT >3xULN	5.1%	8.4%	5.3%	7.5%

DAIICHI'S DX-9065a

This IV Factor Xa inhibitor missed its primary endpoint in the 402-patient, Phase II XaNADU-ACS trial, but researchers are still hopeful that it will prove beneficial in a larger, Phase III trial. There is no oral version of DX-9065a in development. A researcher explained, "It's not a bioavailability issue; it's because there are a number of oral Factor Xas in development, including one by Daiichi, mainly looking at deep vein thrombosis, pulmonary emboli, AF, and embolic stroke."

MERCK'S Vioxx (rofecoxib)

Questions continue to swirl about the cardiac safety of Vioxx, and the waters got muddier with a study released at ACC. A New England insurance carrier's database of ~3 million patients was evaluated retrospectively to determine incidence of cardiovascular events (AMI, stroke) in normotensive and hypertensive arthritis patients from January 1, 1999, through June 30, 2001. The study was funded by Pfizer. [Remember: Pfizer's Celebrex (celecoxib) was approved by the FDA on December 31, 1998, and Vioxx was approved May 13, 1999.] The study found no increased risk in normotensives, but a significantly higher hazard ratio for stroke or AMI in hypertensives with Vioxx than Celebrex (p=0.004). An investigator said, "We believe this issue is inherent in the molecules themselves and is not related to the mechanism by which they provide suppression of inflammation."

Asked what this means for arthritis patients, the presenter said, "It says that either for patients or, most particularly, for practitioners, they should be cognizant of the fact that during the treatment of high blood pressure, NSAIDs – either OTC or prescription – and some Cox-2 inhibitors can destabilize blood pressure, and the recommendation is to keep that in mind."

Measurement	Non-NSAID therapy n=1,798	NSAID n=1,594	Celebrex n=1,288	Vioxx n=841
Total patients	8,579	15,950	9,608	
Treated hypertension patients	1,798	1,594	1,288	841
Average daily consumption for OA	---	---	25% 100 mg 75% 200 mg	~4% 50 mg 75% 25 mg 21% 12.5 mg
Average daily consumption for RA	---	---	18% 100 mg 82% 200 mg	~7% 50 mg ~80% 25 mg ~13% 12.5 mg
Normotensive Patients				
Hazard ratio for AMI and stroke	1.24	.70	1.17	
Hypertensive Patients				
Hazard ratio for AMI and stroke	1.0	1.11	1.35	2.45
p-value vs. non-NSAID	---	---	p=0.06	p<0.0001
p-value vs. NSAID	---	---	p=0.4	p<0.001

PFIZER'S Lipitor: PROVE-IT Trial Proves Lower Cholesterol is Better

Pharmaceutical companies don't often fund head-to-head trials with a competitor, and the PROVE-IT trial shows why. Bristol-Myers Squibb sponsored this comparison of its Pravachol (pravastatin) with Pfizer's Lipitor (atorvastatin), and Pravachol lost.

PROVE-IT found 80 mg Lipitor is more effective than 40 mg Pravachol (the highest FDA-approved dose at the time the trial started) at lowering LDL cholesterol. The results of this 4,162-patient trial conducted at 349 sites worldwide (more than two-thirds in the U.S.) were presented at ACC, and they appeared in the *New England Journal of Medicine* the same day. At two years, researchers reported 3.9% fewer events – defined as a composite of death from any cause, myocardial infarction, documented unstable angina requiring hospital-

2-Year PROVE-IT Results

Measurement	80 mg Lipitor	40 mg Pravachol
Primary endpoint: Composite of all-cause death, MI, unstable angina, revascularization, and stroke	22.4% 16% RRR*	26.3% (p=.005)
~30 day change in LDL	Down 49%	Down 21%
Mean LDL at end of trial	62	95
Risk reduction at 30 days	1.9 Down 17%	2.2
Death/MI or TVR	12.9% 25% RRR	16.7% (p=.0004)
All cause mortality	2.2 Down 28%	3.2%
CHD death	1.1% Down 30%	1.4%
ALT>3xULN	3.3%	1.1% (p<001)
CK>3xULN	1.5	1.1
MI	8.3% Down 18%	10.0%
Stroke	1.0%	1.0%

* RRR = relative risk reduction

ization, revascularization, and stroke – with Lipitor than Pravachol, a 16% relative reduction in event rates.

Benefits were shown for all subgroups: gender, DM, age, prior statin use, HDL, LDL, etc. An investigator added, "Benefits emerged within 30 days and continued throughout the 2.5 years of follow-up…The benefits were consistent across all cardiovascular endpoints, except stroke, and in most of the clinical subgroups…Our findings indicate that patients recently hospitalized for an acute coronary syndrome benefit from early and continued lowering of LDL to levels substantially below current target levels…For all patients with cardiovascular disease, the results emphasize the essential role of lowering cholesterol in reducing morbidity and mortality from heart disease."

The trial also found that the lower the cholesterol is, the better, at least for patients with cholesterol >125. However, in patients with cholesterol <125, there was no statistically significant benefit to further lowering cholesterol. An investigator commented, "We sought to ask the question: If you go even further down in LDL, is that a benefit? And in the lowest group, the achieved cholesterol was 87 on standard therapy. When that was taken down to 50, there did not appear to be a benefit in that subgroup…but studies reaffirm the importance of statin therapy in reducing all cardiac endpoints vs. placebo…and we see that further lowering of cholesterol can lead to added benefit."

Dr. Robert Eckel, a spokesperson for the American Heart Association, said, "The group with the greater reduction in LDL (bad) cholesterol had the greater benefit. There is no information to let us know whether the LDL would have been lower and the benefit greater in the pravastatin group if the (pravastatin) dose had been higher, but this study represents a segment in a continuing line of research that lowering LDL cholesterol below the currently recommended goal of less than 100 mg/dL will be an important way to further reduce these patients' risk of cardiac death."

Asked about the low two-year mortality in this trial, an investigator responded, "We enrolled patients at the time of hospital discharge…and these patients were very intensively managed, so we feel this offers some insight into optimally managing patients…and the added benefit of further lowering of LDL in high risk patients."

SANOFI-SYNTHELABO'S Acomplia (rimonabant)

It looks as if Sanofi has a winner with rimonabant – both as a diet drug and as a smoking cessation agent. Rimonabant is an endocannabinoid – a CCB_1 blocker – and the first in a new class of drugs. The most significant side effect is nausea, but researchers said this is not the reason for the weight loss. An investigator said, "We served a buffet, and monitored what patients ate, and we knew when they were on rimonabant because they wouldn't touch the chocolate cake."

In the 10-week, double-blind, placebo-controlled Phase III smoking cessation trial, STRATUS-US, 787 smokers at 11 sites not only stopped smoking with rimonabant, but they didn't gain weight, as usually happens when people stop smoking. On average, patients enrolled in this trial were age 42, smoked 23 cigarettes a day, had been smokers for 11-24 years, were classified as moderately to heavily nicotine-dependent (based on the Gagerstrom Scale), and were motivated to quit but had previously failed to do so.

STRATUS-US Results

Measurement	Placebo n=454	Rimonabant 5 mg/day n=262	Rimonabant 20 mg/day n=261
Stopped smoking	20.6%	20.2% (nss)	36.2% (p=.002)
Nausea	9.2%	8.8%	15.7%
Upper respiratory infections	5.7%	11.1%	10%
Dropouts	27.9%	31.2%	28.2%
Discontinuation due to adverse events	4.2%	6.1%	6.9%
Weight Change			
Overall	Up 2.4 pounds	N/A	Down 0.66 pounds (p=.001)
Normal-weight smokers	Up 2.2 pounds	N/A	No change
Overweight smokers	Up 2.0 pounds	N/A	Down 1.1 pounds
Obese smokers	Up 2.9 pounds	N/A	Down 1.3 pounds

The double-blind, placebo-controlled, Phase III RIO-LIPIDS trial enrolled 1,036 patients with a mean BMI of 34 (range 27-40), mean body weight of 212 pounds, low HDL, and high triglycerides. At the highest dose, patients reduced their abdominal obesity almost 20 pounds in one year – and their cardiovascular profile improved.

1-Year RIO-LIPIDS Results

Measurement	Placebo + Diet n=334	Rimonabant 5 mg/day n=340	Rimonabant 20 mg/day n=344
Primary endpoint: Weight loss	5.3 pounds	N/A	19.0 pounds (p<.001)
Patients losing >5% of body weight	27.6%	41.8% (p=.002)	72.9% (p<.001)
Patients losing >10% of body weight	10.3%	16.3%	44.3% (p<.001)
Change in waist size	N/A	N/A	Down 3.4 inches (p<.001)
HDL	---	Increased	Increased 23% (p<.001)
Triglycerides (TGL)	---	Nss change	Decreased 15% (p<.001)
% of subjects with metabolic syndrome at baseline (by ITT)	51.9%	55.9%	52.9%
% of subjects with metabolic syndrome at one year (by ITT)	41%	40%	25.8%
CRP	Down 11%	N/A	Down 27% (p<.01)
Nausea	3.2%	7.2%	12.7%
Dizziness	6.7%	8.4%	10.4%
Overall dropouts	37.6%	39.9%	36.3%
Discontinuations due to side effects	7%	8.4%	15%

Additional Trials Underway

- STRATUS-EU, a European study with the same design as STRATUS-US. Results are expected in about a year.
- STRATUS-WW, a one-year maintenance study currently underway at 54 sites world-wide. Results of this trial also are expected within the next 12 months.

SCHERING PLOUGH'S Zetia (ezitimibe): EASE Trial

Adding Zetia to a statin is more effective than statin monotherapy in lowering LDL. The six-week, randomized, double-blind, placebo-controlled EASE trial enrolled 3,030 patients on stable doses of statins who had not achieved their LDL goals. There was no new data on Vytorin, the combination of Zetia and Merck's Zocor (simvastatin). However, several cardiologists mentioned that their use of Zetia was likely to go up in light of the safety questions being raised about Crestor. An expert said, "PROVE-IT is the latest in a series of trials that suggest lower is better with LDL. The data in EASE show the next step to lower LDL is to add Zetia to a statin, not just boost the statin dose."

Results of EASE Trial

Measurement	Ongoing statin + 10 mg Zetia n=2,020	Ongoing statin + placebo n=1,010
Patients achieving LDL goal	71.0%	20.6%
LDL Reduction		
Overall	23%	3%
Patients with ≤2 risk factors	25.7%	5.8%
Patients with >2 risk factors	23.8%	4.1%

Both statin monotherapy and Zetia monotherapy reportedly reduce CRP, but there was a rumor that the EASE trial found that combining Zetia with a statin reduces or eliminates Zetia's ability to reduce CRP. An investigator said the CRP data from EASE has not yet been analyzed, but he said he is not expecting to find much effect on CRP with the combination therapy. He suggested that any effect on CRP of the combination could be confounded because "CRP is a product of the liver, and statins work in the liver." He added, "The CRP level (in combination therapy patients) may or may not indicate what is going on in the blood vessels… (Combination therapy) could affect the CRP level in the liver and not have a beneficial effect…The best indicator of what's going on in vessels is LDL reduction and other measures are just markers of a variety of things." This investigator, who chaired the ACC's CRP guideline committee, added, "We didn't make a recommendation on monitoring CRP. We don't know if lowering CRP makes patients do better. The fascination with CRP is beyond the data."

SERVIER/SOLVAY'S Coversyl/Aceon (perindopril): PERSUADE Trial – ACE Inhibitors Benefit Diabetic Patients

Adding an ACE inhibitor to standard therapy can reduce cardiovascular events in diabetic patients with documented coronary disease, according to new data presented at ACC. PERSUADE researchers estimated that treating 27 patients with 8 mg daily of the ACE inhibitor perindopril (Servier's Coversyl, marketed in the U.S. by Solvay as Aceon) over four years would prevent one cardiovascular death or MI.

In 1999, the landmark HOPE trial proved the value of the ACE inhibitors [specifically ramipril (King's Altace)] in high risk coronary patients, and in 2003 the EUROPA trial found that ACE inhibitors (specifically perindopril) also are beneficial in low risk patients. Now, PERSUADE extends those benefits to diabetics.

EUROPA was a randomized, double-blind, placebo-controlled trial of 12,218 patients from 24 European countries who had stable, low-risk coronary disease. The study, which included a broad range of mostly asymptomatic patients with documented CAD, was investigator-led but funded by Servier. EUROPA compared 8 mg QD of perindopril (a so-called "tissue-ACE") to placebo – on top of standard therapy with ACE inhibitors, beta blockers, platelet inhibitors, nitrates, CCBs, etc. – over an average of 3.7 years. Patients were given two 4-mg pills once-daily. PERSUADE looked at the 1,500 diabetic patients in EUROPA.

4-Year Results from PERSUADE and EUROPA Trials

Endpoint	PERSUADE relative risk reduction vs. placebo	EUROPA relative risk reduction vs. placebo
Primary endpoint: Composite of CV death, MI, or cardiac arrest	19%	20%
Fatal and non-fatal MI	23%	24%
Heart failure	46%	39%

Principal investigator Professor Kim Fox of Royal Brompton Hospital in London said, "What we've done in PERSUADE is look at diabetics, and we found a very similar reduction (to EUROPA) not only in the primary endpoint but in all the secondary endpoints as well. The relative risk reduction for diabetic patients was the same as for the total cohort, but the absolute effect in diabetics is much greater. The implication of this is that if the patient is diabetic, be sure to treat that patient aggressively with an ACE inhibitor as well as standard therapy."

The effect of perindopril was unrelated to hypertension at baseline or the degree of reduction in blood pressure. Prof. Fox said, "What is different in this trial is the suggestion of an effect beyond blood pressure lowering in terms of reduction of coronary disease."

Asked if the PERSUADE results can be considered a class finding applying to other ACE inhibitors, Prof. Fox said, "I don't know. It could be, but there is evidence in diabetics only with two drugs – ramipril and perindopril – which are different from other ACE inhibitors in that they are fat-soluble, so they get to the tissues earlier than other ACE inhibitors."

Solvay has not aggressively marketed Aceon in the U.S., despite the EUROPA results. However, Prof. Fox said the situation is different in Europe, "Servier has gotten the message out in Europe, and ACE use and perindopril use there has gone up considerably."

PULMONARY ARTERIAL HYPERTENSION (PAH)

A speaker made several interesting points about PAH:

1. **Get pressure down.** "This disease is inherently reversible…Pulmonary pressure can normalize over time in a diseased lung. That gives us hope that we can find a right way to do this…You have to get the pressure down!"
2. **When benefits wane, change therapy.** "Most of the drugs we use in PAH have time-limited beneficial effects, and we need to recognize that when patients start to decline, it is time to move on to something else."
   - Prostaglandins are effective in >90% of patients
   - PDE-5s are effective in 60% of patients
   - ERBs are effect in about 33% of patients
   - CCBs are effective in <25% of patients
3. **Combination therapy may not be better.** "There is a natural impulse to treat patients with multiple drugs...but all drugs have morbidities, and these drugs are particularly expensive. If you can't prove it and justify it, my suggestion is: Don't do it."
4. **Be very aggressive with therapy.**
5. **Beware of the Humpty-Dumpty Syndrome.**
6. **Monitor liver function.** "I'm concerned about ALT which sometimes does progress to liver failure…I think that is a class effect, and you should check for it."

There are a number of agents currently available or in development to treat PAH. A speaker said, "Nothing to date works better than IV epoprostinol (GlaxoSmithKline's FloLan). Nothing comes close." Another speaker said he isn't very excited about anything, except Pfizer's Viagra (sildenafil). He said that studies of Viagra in PAH were initially investigator-led, but Pfizer has a 150-200-patient trial running that will be reported later this year and which will be the basis for an sNDA, if positive. He believes that data will show Viagra works in PAH, and since Viagra is inexpensive compared to other PAH medications, he predicted it will find widespread off-label use. He commented, "Viagra is the closest to a breakthrough we have. It would be a big deal if industry got behind it…In terms of clinical efficacy, walk time is better with Viagra than even FloLan…There have been reports of increased bleeding time with Viagra, but we haven't seen that. And there is no LFT elevation…Everywhere I go I hear of success with Viagra."

➢ UNITED THERAPEUTICS

- **Remodulin (treprostinil)** – FDA approved for subcutaneous administration. An IV formulation is in development, but sources were not interested in this. One expert said, "Remodulin has a relative lack of potency. The effect is not large…There is no evidence that IV Remodulin is better than FloLan, but IV is more convenient (than subcutaneous), and there are line kinks and blockages with FloLan that occur less often with Remodulin."

- **Beraprost** – development stopped because the efficacy seen at three months was lost at 12 months.

➢ **MYOGEN'S ambrisentan**

➢ **ENCYSE'S Thelin (sitaxsentan)**. A speaker noted that there have been two deaths with this drug, "This certainly is no safer than bosentan. But as a user of both, I think it is better than bosentan, though there are no head-to-head studies and probably won't be any head-to-head studies...But sitaxsentan has a theoretical advantage – it doesn't block the ETB receptor – but theory and practice often differ." He was concerned that the company has "separated the doctors from the data, and the company is analyzing the data."

➢ **ACTELION'S Tracleer (bosentan)**. An expert said, "Mostly, this is used for Class II or III patients who fail a CCB. It is getting to be first-line without the data to support that…A lot of pulmonologists are wedded to bosentan, but cardiologists are less committed to it."

➢ **GLAXOSMITHKLINE'S FloLan** – with or without bosentan.

➢ **PFIZER'S Viagra**. A Canadian doctor said, "I don't use CCBs or bosentan, but I might use sildenafil. I'm biased to that because there are no problems with it, and it is cheaper. At 50 mg TID, it costs about $7,000 a year, compared to $60,000 for bosentan. My understanding is that the Viagra data will be positive." He said Lilly's Cialis (tadalafil) and Bayer's Levitra (vardenafil) have not yet been tested in PAH. Lilly, he said, has not been willing to supply Cialis for this purpose because the drug reportedly didn't work in rats. However, he also is concern that Cialis may be too PDE-5-specific for use in PAH.

D E V I C E S

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDS)

SCD-HeFT: Value Confirmed of ICDs in Heart Failure

The long-awaited results of the SCD-HeFT trial (Sudden Cardiac Death in Heart Failure Trial) show ICDs in combination with conventional therapy reduce mortality by a statistically significant degree in heart failure patients. However, there also were some surprising findings in SCD-HeFT.

SCD-HeFT, which was sponsored by the National Heart, Lung, and Blood Institute (NHLBI), Medtronic, and Wyeth, enrolled 2,521 Class II and Class III heart failure patients with LVEF ≤35 at 148 sites in the U.S., Canada, and New Zealand. It is the largest ICD trial ever conducted. Patients were enrolled from September 1997 to July 2001, with follow-up ending in October 2003. Median follow-up was 45.5 months. Patients in the ICD arm received an older and simple ICD, the Medtronic VVI model 7223 which was programmed to VF therapy only.

SCD-HeFT Results

Measurement	ICD	Amiodarone	Placebo
Three-year mortality	17.1%	24%	22.3%
Five-year mortality by ITT	28.9%	34.1%	36.1%
Total deaths at study end (n=666)	22% (n=182)	28% (n=240)	29% (n=244)

SCD-HeFT Demographics

Measurement	Start of Trial	Last Follow-up
Beta blocker use	69%	78%
Spironolactone use	19%	31%
ACE use	85%	72%
Statin use	38%	47%
Class II	70%	
Class III	30%	
Mean QRS	112	
QRS≤120	59%	
QRS>120	41%	
Ischemic patients	52%	
Non-ischemic patients	48%	

Hazard Ratios in SCD-HeFT Subgroups

Measurement	ICD vs. Placebo	Amiodarone vs. Placebo
Mortality in all patients	.77 HR (p=.007) (23% decreased risk)	1.06 (p=.529) (6% increased risk)
NYHA Class II	.54 (46% decreased risk)	.85 (15% decreased risk)
NYHA Class III	1.16 (16% increased risk)	1.44 (44% increased risk)
Non-ischemic patients	.73 (27% decreased risk)	1.07 (7% increased risk)
Ischemic patients	.79 21% decreased risk)	1.05 (5% increased risk)
QRS<120	.84	1.06
QRS≥120	.67	1.05

Experts were surprised with the findings on two pre-specified endpoints in the trial:

➢ The reduction in deaths was comparable for patients with ischemic heart failure and non-ischemic heart failure.

➢ Class II CHF patients had a statistically significant reduction in mortality with ICD therapy, but Class III patients did not. A researcher at Duke University, which was the data-coordinating center for the trial, speculated, "It seemed that the more severe the case of heart failure, the more likely the patient died from causes other than arrhythmias." Another expert said, "Amiodarone increased mortality in Class III patients, and there is no other data indicating this. In all other trials amiodarone is equal or better than placebo."

The SCD-HeFT principal investigator, Dr. Gust Bardy, refused to answer questions about subgroups in the trial, including pre-specified subgroups. He emphasized that the focus should be on the primary, overall findings of a 23% reduction in sudden death. He said, "All subgroup analysis should be interpreted conservatively, with the emphasis on the primary endpoint."

Sudden cardiac arrest is the No. 1 killer of Americans, killing almost half a million Americans each year. Sixty percent of patients with mild to moderate heart failure die due to sudden cardiac arrest. SCD-HeFT raises two key questions:

1. *Will the trial help encourage eligible patients to get an ICD?* ICDs have been widely under-utilized with only about 20%-25% of eligible patients getting them, even before the new QRS and LVEF guidelines went into effect.
2. *Will it expand the number of patients eligible for an ICD?* A decision from CMS on whether or not to broaden its Medicare reimbursement criteria – which currently limit ICD coverage to patients with LVEF ≤30 and QRS >120 – is expected in about nine months or less.

A former president of NASPE reviewed the SCD-HeFT data and said convincing CMS to broaden coverage is not a slam dunk. He explained, "CMS will want to see the p-value. The number of patients (the percent) will also be important. If 1% are helped, it is not enough. This substantiates all the other trials, and, in my opinion, the major benefit is that we now have something to support ICDs in non-ischemics…If you look at the DEFINITE trial and SCD-HeFT, it is clear that patients with Class II heart failure should have an ICD…CMS should give approval…but CMS won't give its approval willy-nilly. For CMS to broaden coverage, it will want QRS data. I think about 50% of patients in SCD-HeFT had QRS>120, and I think CMS will want to see the results by QRS…These SCD-HeFT results extend the use of ICDs to non-ischemics, and I hope the subgroup analysis will help CMS's ruling."

A past president of ACC said several things that appear to give CMS a lot of wiggle room not to expand coverage significantly post-SCD-HeFT. He said:

1. "SCD-HeFT **missed its primary endpoint**, but it is consistent with other trials, so that is why I am comfortable with it, and it clearly shows the superiority of ICD therapy."

2. "I am not comfortable with slicing and dicing the data (into subgroups). The finding that ICDs are not as effective in Class III as Class II is at total variance with other studies...I don't want to discuss subgroups because they are not consistent with (data from) other trials."

3. "The absolute benefit in mortality reduction was 1.7%."

This expert hopes that CMS will focus on the big picture, but he admitted that if CMS does look beyond the big picture and focuses on the primary endpoint or a subgroup analysis, that could muddy the waters for any broader CMS approval. He hopes that doesn't happen.

CMS Chief Medical Officer Dr. Sean Tunis said his agency will consider the SCD-HeFT results "with great interest over the coming weeks and months." He said CMS "will place a tremendous amount of weight and emphasis on SCD-HeFT. A trial this large and this well-done I highly suspect will make us a lot more confident in how we conclude related to MADIT-2 patients." Dr. Tunis indicated that:

- CMS will accept the Medtronic filing within a week or two of submission, issue a draft decision within 6 months, and a final decision by 9 months – or sooner.

- He believes the overall results of SCD-HeFT are "quite impressive for the total population for ICD or no-ICD. And there are clearly other patient populations for whom we will be extending reimbursement."

- Serious weight will be given to the NYHA Class II vs. Class III findings because they were a pre-specified endpoint. Thus, NYHA Class could replace or be added to QRS as an eligibility criteria.

- CMS is re-looking at ICDs in general, not just QRS.

- A broad coverage decision is unlikely. It is more likely that CMS will find some risk stratifiers, whether it is QRS or NYHA Class orxe something else.

- CMS may try to introduce incentives for doctors to use inexpensive "shock-boxes."

- CMS is ***considering*** using a meta-analysis of all ICD trials to help them make a decision.

- CMS is concerned about the already low use of ICDs for reimbursable indications and may take a pro-active position to encourage use regardless of the decision on expanding coverage.

DRUG-ELUTING STENTS

TIDBITS

ABBOTT

Abbott's drug-eluting stent program is continuing to chug along. The company's new cobalt chromium, ultra low profile stent was described as "very slick," and sources expect this to replace the BiodivYsio for the drug-eluting stents program.

BOSTON SCIENTIFIC

a. The TAXUS-V problem may actually be real. When questions about the trial first arose in February 2004, there appeared to be some issue, but nothing that was likely to hold-up FDA approval. At that time, the issue appeared to be a subgroup enrollment problem – if, indeed, there was any problem at all. Sources insisted that the DSMB has identified a safety problem in TAXUS-V. The issue has not halted the trial, but it may have slowed enrollment down to a snail's pace. Investigators were demanding to know what is wrong, what is delaying enrollment, and why they have to be so careful about enrollment. No additional information as to the nature of the problem was available, and Boston Scientific has denied there is any problem with TAXUS-V.

b. It is possible Boston Scientific may not take as much market share from Cypher as expected because of misjudgment on pricing for Taxus – at least so far. Asked how Lenox Hill Hospital will split its use between Cypher and Taxus now that both are FDA-approved, Dr. Jeff Moses said that price will be the driver, but he said Boston Scientific's ***initial*** pricing of Taxus is at a slight ***premium*** to Cypher – at least at his hospital. He said, "Boston Scientific doesn't seem to grasp the economics of hospitals yet. Maybe they will, but at first blush, they don't seem to get it yet. They will have to be more competitive to encourage usage. Boston may have miscalculated the market. Watch this space." Dr. Marty Leon said Boston Scientific had priced Taxus ~$500 more than Taxus to his hospital.

GUIDANT

Sources believe:

- Guidant's polymer-based drug-eluting stent will fail. They insisted it just isn't working.
- Guidant's bioabsorbable programs will take longer than the company has indicated.
- The company has lost significant R&D personnel recently from its drug-eluting stent program.

JOHNSON & JOHNSON/GUIDANT DEAL

a. Experts said Cypher with a Guidant Vision delivery system will be a good system, putting Cypher in a better competitive position against Taxus. J&J does ***not*** expect to have the Cypher/Vision on the market in 2004. An FDA official said a delivery system change is considered a minor change and may be able to be done under a PMA supplement, but it may still require a 30-day clinical trial, which J&J sources insisted will take at least six months.

b. The alliance between Guidant and J&J gives J&J more "feet" visiting cath labs. The deal costs J&J very little unless Guidant sells sufficient Cyphers.

MEDTRONIC

There was no new data at ACC from the ENDEAVOR trials of Medtronic's ABT-578-eluting stent. The 12-month ENDEAVOR-1 data is available and will be presented at EuroPCR in May 2004.

There also was a report that Medtronic's pivotal Phase III ENDEAVOR trial is "cutting it close" with the enrollment numbers. Investigators reportedly wanted ~800 drug patients, but the company elected to enroll 400, which is sufficient if all goes well but allows little room for a margin of error in calculating the effect.

GUIDANT'S Everolimus Program

- Six-month data was presented from the FUTURE-II trial, and the results were consistent with the findings of FUTURE-I.
- The non-U.S. FUTURE-III trial will test everolimus on the Champion stent in 800 patients, with 3:1 randomization vs. a bare stent.
- Guidant was expected to file in late March for an IDE for its pivotal FUTURE-IV U.S. trial of everolimus on the Champion stent in 975 patients, with 3:1 randomization vs. a yet-to-be-named drug-eluting stent. The goal reportedly is to start the trial in late June 2004. The delay in getting this trial going, according to one source, has been the animal studies. However, this source said Guidant can change the delivery system without new animal studies, though the company has "hundreds of animal studies" with the new delivery system.

FUTURE-II

Measurement	Everolimus on Challenger stent	Bare stent	p-value
In-stent late loss	0.12	0.85	P<.0001
% DS	2.9%	30.4%	P<.0001
In-segment late loss	0.16	N/A	N/A
Late loss at proximal edge	0.21	0.14	N/A
Late loss on distal edge	0	0.12	Nss
Restenosis	0	19.4%	p=.039
In-segment restenosis	4.8%	30.6%	N/A
MACE at 6 months	4.8%	17.5%	p=0.2
MI	0	2.5%	N/A
SAT	0	0	---
Acute thrombosis	0	0	---
Aneurysms	0	0	---

JOHNSON & JOHNSON'S Cypher

The results from three drug-eluting stents studies were presented. They showed:

- Cypher can be safely direct-stented – the DIRECT trial.
- A benefit with Cypher in small vessels – the SES-SMART trial.
- Cypher stents were cost-effective when first launched but some of that is eroding as more complex patients are enrolled.

There were quite a few jokes and raised eyebrows about the alliance between J&J and Guidant under which both will sell Cypher stents in the U.S. In an update on Cypher stents, an expert called sirolimus the "Fat Albert of cardiology – the tremendous force that crushes everything in its path." He described the alliance as "interesting" and compared it to Ford Motor Co. promoting the sale of Chevys: "For Guidant to say Cypher is a better car and a better way to get there – it is interesting to think about that."

New Data on Cypher

Measurement	E-Cypher n=10,936	U.S. Post-Marketing Surveillance Study n=1,536
Diabetic patients	29.2%	32%
Single vessel stenting	43.8%	48.6%
3-vessel stenting	23.5%	27.6%
AMI	7.3%	---
Average lesions per patient	1.2	---
Restenotic lesions stented	13.6%	7.4%
Multiple Cyphers implanted	25%	---
MACE at 30 days (n=7,025)		
Cardiac death	0.44%	0.3%
Q-wave MI	0.14%	0.5%
Non-q-wave MI	0.33%	0.3%
MACE	1.38%	1.0%
TLR	N/A	0.7%
SAT	N/A	0.4%

The subacute thrombosis rate with Cypher was described as 1.5% in Milan, which is in the acceptable zone of 1%-2%, but it has been lower than 1% at all other major trial sites. In addition, the long-term data from First-in-Man look very good. Dr. Holmes commented, "This stent does not guarantee immortality, but the numbers are exceedingly low out to two years…We are seeing a dramatic and continued improvement in event-free survival."

More Long-Term Data on Cypher

Measurement	4-Year Results in First-in-Man	3-Year Results in RAVEL
In-stent late loss	0.1 mm	N/A
In-lesion late loss	0.2 mm	N/A
TLR	2.8%	5.0% Cypher vs. 14.4% bare (p=0.01)

DIRECT Trial: It's Safe to Use Direct Stenting with Cypher

This trial found direct stenting with Cypher is as successful, and in some cases, better than the traditional approach of predilating the vessel before stenting. Dr. Jeff Moses said about 30%-40% of Cyphers are currently placed with direct stenting but predicted that may go up after this trial. The exclusions generally are heavily calcified lesions, very long blockages, or very torturous vessels.

DIRECT Trial Results

Measurement	Direct Stenting n=167	Predilation in SIRIUS Trial n=412	p-value
Late lumen loss (in-stent)	0.18 mm	0.17 mm	N/A
Late lumen loss (in-lesion)	0.21 mm	0.21 mm	Nss
Binary Restenosis by QCA at 8 months			
In-stent	3.6%	3.2%	p=.80
Proximal margin	3.1%	5.8%	p=.27
Distal margin	0	2.0%	p=.10
In-lesion	6.0%	9.1%	p=.30
Edge	3.0%	7.4%	p=.049
Smaller vessels (~2.3 mm)	8.3%	18.3%	p=.12
Medium vessels (~2.8 mm)	6.1%	7.4%	p=1.00
Large vessels (~3.2 mm)	3.6%	1.8%	p=.60
Non-diabetics	5.3%	6.0%	Nss
Diabetic Patients			
In-lesion restenosis in non-insulin dependent diabetics	10.3% (n=54)	13.8% (n=80)	Nss
In-lesion restenosis in insulin-dependent diabetics	0	35.0%	p=.03
TLR in all diabetic patients	2.9%	4.8%	N/A
In-stent restenosis in insulin-dependent diabetics	0 (n=16)	10.5% (n=25)	p<.05
In-stent late lumen loss in insulin-dependent diabetics	0.20 mm	0.33 mm	N/A
In-lesion late lumen loss in insulin-dependent diabetics	0.20 mm	0.58 mm	N/A
TLR at 180 days in insulin-dependent diabetics	0	8.0%	N/A

FINANCIAL IMPACT OF CYPHER STENTS IN THE U.S.

A prospective examination of 27,283 procedures at 75 academic centers which are a part of the University Health System Consortium found that the additional cost of using Cypher stents versus a bare stent was less than expected. Some of the added cost of Cypher was off-set by cost savings elsewhere, such as lower medication costs. However, the savings began to diminish after the first three months, and researchers speculated that this was due to use of drug-eluting stents in more complex patients. A researcher said, "We were able to achieve some cost savings, based on what we expected. What that tells me is that, despite cost predictions, technology

Measurement	1Q03	2Q03	3Q03
Cost for all stent procedures	$192 million	$178 million	$210 million
Incremental cost of using a drug-eluting stent	---	AMI: ~$600 Non-AMI: ~$2,600	AMI: ~$1,300 Non-AMI: ~$1,200
Length of stay	AMI: ~4 days Non-AMI: ~2 days	~3.8 days Non-AMI: ~2.1 days	~3.8 days Non-AMI: ~ 2.2 days

will always cost more. We found opportunities for cost savings elsewhere. With time, we will see if it that benefits patients or whether it is neutral."

Other findings from this study included:

- At these centers, 27,283 stent procedures were performed in 2Q03 and 3Q03: 10,550 with drug-eluting stents and 16,733 with bare metal stents.
- By June 2003, 44% of procedures used drug-eluting stents.
- The cost savings with drug-eluting stents partially eroded with time, as drug-eluting stents were used in more patients and more complex patients.
- The incremental cost of using drug-eluting stents for non-AMI patients remained less than the added cost of a drug-eluting stent.
- Adoption rates of drug-eluting stents were gradual and increased in a predictable fashion.
- Adoption was not uniform across the U.S., suggesting that through 3Q03 there was no standard of care or consensus as to which patients should get a drug-eluting stent.

SES-SMART: Cypher Effective in Small Vessels

This was a randomized study in Italy of Johnson & Johnson's Cypher and an uncoated BX-Sonic stent in small coronary arteries. Researchers concluded that in small arteries, Cypher reduced restenosis and MACE.

SES-SMART Results

Measurement	Cypher n=129	Bare BX-Sonic n=128
Binary restenosis (in-segment)	9.8%	53.1%
Late lumen loss	0.16 mm	0.69 mm
Loss index	0.11	0.68
Death	0	1.6%
MI	1.6%	7.8%
TLR	7.0%	21.1%
Cerebrovascular accident	0.8%	0.8%
MACE	9.3%	31.3%

BOSTON SCIENTIFIC'S TAXUS

Dr. Patrick Serruys presented an update on the Taxus program. He commented, "I'd say 45% of my colleagues are using Taxus as a workhorse for simple, short lesions." He predicted Taxus would be a workhorse drug-eluting stent in the U.S. as well. Dr. Serruys offered this update on ongoing and planned Taxus trials:

- **TAXUS-V**: 1,167 patients enrolled as of March 1, 2004, with 262 patients having long lesions (≥26 mm), and 32% getting multiple stents.
- **TAXUS-V-ISR**: 315 of 488 patients enrolled as of March 1, 2004.
- **TAXUS-VI (MR)**: Ongoing European, prospective, randomized trial of 2.5-3.5 mm stents, with revascularization in non-target vessels allowed and multiple and overlapped stents and long lesions included.
- **TAXUS-VI**: 9-month follow-up is complete, with 19.9% of patients getting a 2.5 mm stent, 36% getting multiple stents, and 28% getting overlapped stents. Mean lesion length is 20.5 mm, and 20.5% of patients are diabetic. Data from this trial will be presented at EuroPCR in Paris in May 2004.
- **WISDOM**: 6-month follow-up to be presented later at ACC on this 778-patient international post-marketing registry.
- **MILESTONE**: Enrollment is expected to be complete at the end of March 2004 in this European post-marketing registry. So far, 3,615 of 3,700 patients have been enrolled.
- **ARRIVE**: This international peri-approval study started February 4, 2004, and 440 of 5,000 patients have been enrolled already.

OTHER DRUG-ELUTING STENT ISSUES

CYPHER OR TAXUS?

At ACC, Johnson & Johnson and Boston Scientific squared off in the upcoming battle for share of the drug-eluting stent market, and J&J made it clear it is not rolling over and giving the game to Boston Scientific. Doctors interviewed said they will base their choice between Cypher and Taxus on price. The list price of Taxus is about $200 less than Cypher, but few hospitals pay list price for stents, so the real pricing comparison between Taxus and Cypher is not yet known. A source said, "The clinical results are so close that price will sway people." Another cardiologist said, "We will use a mix to learn about Taxus, recognizing that the bare Taxus is easy to deliver."

There have been claims that Taxus is easier to delivery than Cypher. Dr. David Holmes of the Mayo Clinic said the REALITY trials belies this. He commented, "Some said you can't get Cypher down the hole…but you can from this study. There was successful stent delivery in 98% of Group A and 99% of Group B, so deliverability is not an issue."

Do Stent Design and Polymer Matter?

At a session on drug-eluting stents, two experts took opposite sides on the question of whether stent design matters to restenosis.

- A German researcher contended that restenosis with bare stents is affected by more than vessel size and stent length. He said, "Stent type can cause a three-fold increase in the risk for restenosis." Citing data from historical trials, he argued that strut configuration, material, thickness, and surface all affect restenosis rates, "Stents with struts under 100 µg are better than thicker struts, especially in large vessels…And restenosis decreases as surface roughness increases…The risk of restenosis after placement of a bare stent is significantly influenced by stent design…In an unselected patient population, the rates of restenosis with a bare stent may vary from 15%-50%, based on design."

- A U.S. cardiologist insisted that the only three variables with a significant effect on restenosis rates are the size of the vessel, lesion length, and diabetes. He said, "It is amazing how study after study show these three factors continue to be the main determinants of restenosis…We do not see an association between strut thickness and outcome…Strut design may have an effect on restenosis, but the strut thickness component is a minor determinant…Stent design likely affects restenosis, but the effect has not been easy to evaluate, and it is not as powerful as the 'big three.' We do detect a slight effect from strut thickness, but it is a minor effect at best. In the drug-eluting stent era, any bare metal stent design effects on restenosis may be negligible."

Bioabsorbable Stents

These were reviewed by a speaker who said studies have found that the type of polymer used is important, with high molecular weight PMMA (as used in the Igaki-Tamai stent) the least reactive. The bottom line, he said, is, "Why choose a permanent prosthesis for a temporary healing problem?" He offered these reasons for polymeric stents:

- A full-metal-jacket approach with metal stents may block later surgical intervention.
- Bioabsorbable stents leave only the healed natural vessel behind, while metal stents create MRI artifacts.
- A polymeric drug-eluting stent has the potential to outperform a metallic drug-eluting stent by:
  - Avoiding the edge effect.
  - Stable linear elements (by expanding on the outer curvature and compressing on the inner curve), which could make it more deliverable.
- Unstable plaques are more numerous than critical stenoses, and bioabsorbable DES could be a solution to that.

Physician Roundtable on Real-World Experience with Drug-Eluting Stents

Eleven interventional cardiologists spent more than an hour discussing candidly among themselves their current and future use of drug-eluting stents. The forum was sponsored by Johnson & Johnson, but participants included hospitals planning to switch to Boston Scientific's Taxus stent. The discussion provides a good insight into what is really going on in U.S. cath labs. Among their key comments:

- Drug-eluting stent usage is continuing to increase, but cath lab volume is dropping.
- The choice between Cypher and Taxus may be dictated by hospital contracts.
- The negative results of long-term brachytherapy is making interventional cardiologists want longer term data on drug-eluting stents.
- With drug-eluting stents, doctors are using longer stents, cutting IIb/IIIa use, and returning to direct stenting.

Current Drug-Eluting Stent Usage *(by these doctors)*

State	Average stents per patient	% of patients getting a drug-eluting stent
Texas	1.6	95%
New York	1.8	95%
Mississippi	---	70%
Florida	---	70%
Illinois	---	60%
AVERAGE	**1.7**	**78%**

Among the questions they addressed were:

Are there subsets of patients you still don't feel comfortable using drug-eluting stents with?

- *Illinois*: "Our cardiologists are more conservative than others, and they want more experience before employing drug-eluting stents in the majority of patients…Our use in larger vessels (≥3.5 mm) is not huge…and vein grafts are an area where we are uncomfortable using Cypher."

- *Ohio*: "In our hospital, we are aggressive and AMI patients invariably get a Cypher…but some older generation cardiologists who've been in practice 40 years don't do that…They have the idea that it is hard to deliver Cypher…Anatomy dictates what they use, and they sometimes prefer the new cobalt chromium Vision (by Guidant) and Driver (by Medtronic) because of deliverability."

Would you combine drug-eluting stents and brachytherapy?

➢ *Florida*: "Our feeling is that the treatment of in-stent restenosis with Cypher is safe and similar to the results in de novo lesions…but if patients already had brachytherapy before, I would treat in-stent restenosis with Cypher."

➢ *New York*: "My feelings are negative on brachy-therapy…By Year 4, the TLR, TVR, and MACE curves are all worse with brachytherapy...And it is pretty dramatic…I believe more and more strongly that there is a progressive late recurrence from vascular brachytherapy…so that the use for in-stent restenosis is flawed….We don't treat in-stent restenosis with brachytherapy for that reason…There is little data on using drug-eluting stents after brachytherapy…but there is no huge safety concern and no late thrombosis…but there is a major efficacy drop off, and that has made us nervous."

How do you treat restenosis in a drug-eluting stent?

➢ *New York*: "90% of the time in-stent restenosis is focal…and that is easy to treat…If the lesion is focal, and there is no mechanical reason for it, another stent is no better than a cutting balloon or other simple focal treatment."

➢ *Ohio*: "We had a brachytherapy candy-wrapper patient who later had a Cypher and got restenosis of the distal edge of the Cypher…We used a cutting balloon, really focal…and three months later, it was wide open."

How has technique changed with drug-eluting stents?

➢ *Utah*: "We changed quite a bit…We use less IVUS now."

➢ *New York*: "51.1% of our Cyphers are either 23 mm or longer, and for us that is a radical change."

➢ *Virginia*: "We want to cover the lesion, and we don't want to come up short and have to put in another stent, so that is our practice, too. It is a cost issue."

➢ *Ohio*: "Lesion length has increased...We were doing more predilation with Cypher initially…but in the last few months we decreased that again."

➢ *Mississippi*: "We are doing more direct stenting…We direct stent 85% of cases and dilate when the stent doesn't go through on first pass – even to the point of putting a buddy wire down to direct the stent before pre-dilating."

➢ *Florida*: "We are trying to do more direct stenting now to avoid injury."

What types of patients are getting drug-eluting stents?

➢ *Utah*: "We are much more likely now to stage a procedure than to do it all at once."

➢ *New York*: "We have observed some people shifting away from treating multivessel disease because of the cost…I think that is a mistake…but there are clinical reasons to stage a patient."

➢ *Mississippi*: "I've been a lot more aggressive in stenting patients with 50%-70% lesions."

➢ *Illinois*: "I'm at a for-profit hospital, and cost concerns initially were a big player…We are now at 60% adoption, and it is perplexing to me that it is that low…The interesting shift is an increase in the use of drug-eluting stents in complex lesion subsets despite that being financially bad for the hospital…That is coming more from non-interventional cardiologists requesting we do this for their patient. It is an interesting little shift…It is as though they have such faith in interventionalists now that they are asking us to do those lesions and asking us to do complex lesions, large lesions, LAD, etc. This was a shift not expected in a for-profit setting."

A *USA Today* article claimed drug-eluting stents have caused a 15% reduction in CABG. Have you seen less CABG in your local environments?

➢ *New England:* "I'm doing more patients who were not considered a candidate for CABG. That is the one subgroup that has shifted from surgery to stents."

➢ *Texas*: "Our cath lab volume is dropping…Referrals for brachytherapy essentially disappeared considerably…Our interventional volume is down 10%-15% in the last seven to nine months."

➢ *New York*: "I've heard that from a lot of doctors…A (Midwest hospital's cath lab volume) is down 10% even though its drug-eluting stent volume is <50%."

Is there likely to be a reduction nationally in the number of interventional cases performed in 2004 compared to 2003?

➢ *Illinois*: "In the registry environment there will be…The stent most commonly used initially will be the one chosen for the most complex lesions and could bias registries."

➢ *New York*: "People on the other side of the street say Taxus is more deliverable (than Cypher) and should be used preferentially in difficult lesion…We have to sort that out…There is no comparative data yet…but the REALITY trial (a head-to-head comparison of Taxus and Cypher) is enrolled, with a cohort of 1,390 patients with 1,950 lesions…We hope to have the final data by the American Heart Association meeting (in November 2004) and there may be a pre-identified interim analysis at TCT (in September 2004)."

How do you choose between Taxus and Cypher?

➢ *Indiana*: "It depends on what the hospital allows…Our lab has a strong Boston Scientific contingency…and that will govern a lot of it…Deliverability plays a part, as do safety issues and cost."

Are there differences in safety between Taxus and Cypher?

- *Indiana*: "I don't see that now."

- *New York*: "I think we have a little uncomfortable sensation in the pit of our stomach on the long term effects of Taxus…So, I think our initial use will be slow. We want three- or four-year data before we slam a bunch in…(Someone) asked me why I would even consider putting Cypher in again after Taxus is available, and I said we put in 5,000 Cyphers. They have an extraordinary safety profile. We are treating the most complex stuff we can find with Cyphers. So, why switch? Yes, there are deliverability issues (with Cypher) in some patients, but that is a relatively small number in our hands. So, it will be interesting…I used to think six- to 12-month data was fine…but now I want to see more long-term follow-up…Early paclitaxel data doesn't show a drop-off between nine and 12 months or 12 to 24 months, but we need more data…Side branch access may be easier with Taxus…but that is not a large number of patients. That is <10% of patients…and there is clearly a difference in the way the angiograms look at six months. Does that contribute to patient outcome? TAXUS-IV suggests no, but there is a little difference in the way things look."

- *Florida*: "We have such long experience, volume, and safety data with Cypher…And we don't have that much of a problem with Cypher deliverability…The only issue for us is availability of sizes that could cause us to switch…Otherwise, we are comfortable using Cypher…We have four-year First-in-Man data with Cypher…and I share the concerns about the lack of long-term Taxus data."

It there really something magical about paclitaxel (Taxus) in diabetics?

- *New York*: "I believe SIRIUS was an outlier…It is the only (Cypher) study to show persistent restenosis (in diabetics), mainly at the proximal end…I think that was due to operator techniques, and I think we evolved beyond that…I don't believe there is a difference (between Taxus and Cypher in diabetics), but we need to see the REALITY results…which has 32% diabetics – to directly compare them…Boston Scientific is making a lot of noise about that (Taxus advantage), but the subsets are too small to reach that conclusions in my personal opinion."

How is Plavix (Sanofi, clopidogrel) being used with drug-eluting stents?

- *New England*: "We use more than we did a year ago…but cost is an issue."

- *New York*: I'm only reassured on safety if patients and doctors comply with the specified platelet regimen…If you go to one month of Plavix, I'd say drug-eluting stents are not as safe as bare stents…There is a requirement for longer dual antiplatelet therapy with drug-eluting stents…We don't know yet if you can get away with less…If a patient can't afford Plavix, I wouldn't give a bare stent, but I would give a Cypher instead of a Taxus."

How do you feel about overlapping Taxus stents?

- *New York*: "We don't have enough data…What we've learned about paclitaxel as a drug is that if you give too much too fast, it does cause problems…We see that again and again and again (in animals)…Is that reached by two stents? Probably not…If you crush with 3 layers, is that a problem? Dr. Antonio Colombo did 70 cases and didn't see a disproportionate rate of SAT…But we are still learning about paclitaxel, and we should have appropriate concern but not important yellow or red flags yet, at least in clinical practice."

What effect has the cost of drug-eluting stents had on your local cath lab?

- *Illinois*: "It depends on your contracts…I don't think interventional cardiology (at our hospital) is making as much money as it used to."

- *Indiana*: "When Cypher was released, we became aggressive analyzing how many patients could be labeled inpatients…We came up with criteria for converting a patient to inpatient, and that made us more profitable at the end of the first year than if we had made everyone an outpatient…You can do this based on bifurcation, prolonged chest pain, etc…We became aggressive with that, and it worked for us for a year…All those things will be under scrutiny by regulatory agencies. We will be audited, I'm convinced, because our percent of inpatients is higher than last year…But we have been aggressive in documenting every case, so we think we will win."

- *New York*: "We used to have some protection on inpatient…but third party payers say it is an ambulatory procedure."

What has happened to IIb/IIIa use?

- *New York*: "We are enamored of bivalirudin (The Medicine Company's Angiomax)…Angiomax use was 70% and IIb/IIIa dropped to 13.4%…We did a registry of all comers and looked at results for the first 30 days…Doctors were obligated to use Angiomax, but IIb/IIIa use was optional, and there was only 5.6% use of IIb/IIIa use in that…So, we have gone way done on IIb/IIIa use."

- *Illinois:* "We have not changed our practice to use more Angiomax…but IIb/IIIa use is down…And now we have shifted to aggressive pre-treatment with Plavix."

- *Virginia*: "I get concerned with that kind of use without data…It takes a big population to see the problem…One thing I'm concerned about with drug-eluting stents is that people would eliminate the IIb/IIIa and forget that the rest of the vasculature is at risk...A drug-eluting stent prevents restenosis, but it doesn't reduce complications for in-hospital to out-of-

hospital...Drug-eluting stents don't give us license to change IIb/IIIa use."

➢ *Indiana:* "We've seen a similar shift…One approach we are tracking and is less expensive than Angiomax is a bolus of heparin and a bolus of Integrilin (Millennium, eptifibatide) at the time of procedure in patients with no Plavix pre-procedure…The cost of a small Integrilin bolus is quite low as opposed to ReoPro (Lilly, abciximab), where you break the vial and pay for the whole thing…This approach seems to be very effective, and we've had no high incidence of non-reflow or surprise thrombus…The people going on to provisional dripping are only 1%-3%."

Carotid Stenting

ARCHeR Trial: Carotid Stenting is as Safe and Effective as Carotid Endarterectomy (CEA)

ARCHeR was a one-year non-inferiority trial comparing carotid stenting using Guidant's Acculink stent delivery system and Guidant's Accunet embolic protection device to a weighted historical control of high surgical risk patients. Researchers reported that the trial proved the non-inferiority of carotid stenting. An investigator said, "In surgical high risk patients, Acculink compares favorably to CEA historical control."

ARCHeR Trial Results

Measurement	ARCHeR-1 n=158 high surgical risk	ARCHeR-2 n=278 high anatomical risk	ARCHeR-3 n=145
30-day endpoint event rates			
Death	2.5%	2.2%	1.4%
MI	2.5%	2.9%	0.7%
Stroke	4.4%	5.8%	6.2%
Death/stroke	6.3%	6.8%	7.6%
Death/stroke/MI	7.6%	8.6%	8.3%
Major + fatal strokes	1.9%	1.4%	1.4%
Events in days 31-65			
Fatal strokes	0	0	---
Non-fatal major strokes	0	1 patient	---
Minor strokes	1 patient	3 patients	---
Results of stenting vs. CEA			
Primary endpoint: 30-day composite of death, stroke, and MI	---	8.6%	8.3%
Primary endpoint: One-year composite endpoint	8.3%	10.2%	---
Event free survival	Stenting: 91.7% CEA: 85.5%	Stenting: 89.8% CEA: 85.5%	---
TLR	6 months: 0.7% 1-year: 2.2%	6 months: 0.4% 1-year: 2.8%	N/A

- The pre-specified non-inferiority endpoints were met.
- The major/fatal stroke rate was low and similar to previous landmark CEA trials.
- Minor strokes had no significant clinical effects.
- The results were durable as demonstrated by a lower TLR at one year.
- Significantly more vessel angulation and calcification in ARCHeR-2 and –3 vs. ARCHeR-1.

ARCHeR-1 and ARCHeR-2 were non-inferiority tests of 1-year composite endpoints vs. a weighted historical control of high risk surgical patients. ARCHeR-3 was a non-inferiority test of the 30-day composite endpoint for ARCHeR-3 vs. ARCHeR-2. The weighted historical control was 14.5% for both ARCHeR-1 and -2.

Coronary Artery Bypass Graft (CABG)

PRAGUE-4 Trial: Off-Pump as Safe as On-Pump CABG

Preliminary data from this trial suggest that beating heart bypass surgery is as safe and effective as on-pump procedures. By intent-to-treat analysis, both treatments had similar results. A researcher said, "Beating heart is applicable in 84% of consecutive surgical patients, reduces the cost, and is as clinically effective and safe as classical on-pump surgery…However, patients in whom off-pump technique was used tended to have better outcomes…One-year angiographic patency was surprisingly low in both groups, with a non-statistically significant trend to higher patency in on-pump patients. The decrease in patency between one week and one year is likely influenced by the generally poor quality of coronary arteries in patients referred to bypass surgery." ♦

Preliminary Findings of Prague-4 Trial

Measurement	On-Pump n=192	Off-Pump n=208	p-value
Primary Endpoint: Death, hemodialysis within 30 days and stroke by ITT	3.8%	2.9%	Nss
Primary Endpoint: Composite among technique users	4.9%	1.6%	p=.12
Mortality	2.9%	1.1%	Nss
Patency of grafts at 1-year			
LIMA	91%	91%	Nss
Saphenous veins	59%	49%	N/A
29 patients with angiographic results	Early: 100% 1-year: 91%	Early: 93% 1-year: 83%	N/A