Trends-in-Medicine

January 2005
by Lynne Peterson and D. Woods

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AMERICAN HEART ASSOCIATION

November 7-10, 2004
New Orleans

Several studies being presented at the American Heart Association (AHA) meeting were described as **most likely to change practice over the next year**, including:

- **PEACE trial.** This large study found no benefit to adding an ACE inhibitor to heart failure patients whose blood pressure is already well-controlled. As a result, AHA guidelines for ACE inhibitor use are likely to change. *(See this page)*
- **Vitamin E.** A study reported that high dose vitamin E not only is not heart-protective but actually is dangerous. *(See page 5)*
- **REACT trial,** which found that patients who don't respond to lysis should be transferred for PCI. *(See page 13)*
- **SCD-HeFT** cost effectiveness data, which an AHA official said "will impact on Medicare coverage decisions." *(See page 15)*
- **ACORN'S CorCap CSD.** Even before the results were released, an AHA official said, "If the CSD proves simple, safe, and efficient, it could have a big impact." *(See page 17)*

Items of interest that were described as **still too far away** to have an impact yet but which are likely to be very important in the future include:

- A-HeFT results on **NITROMED'S BiDil.** *(See page 8)*
- **SANOFI-AVENTIS'S Acomplia (rimonabant)** was described as "interesting" but too far away to have any immediate implications. *(See page 11)*

DRUGS

ACE INHIBITORS

The PEACE trial, funded by the NHLBI, found no evidence that an ACE inhibitor adds any further benefit to patients with heart failure or left ventricular systolic dysfunction who are already well-controlled on other agents. The addition of Abbott Laboratories' trandolapril did not improve any of the outcomes measured – death from cardiovascular causes, MI, or coronary revascularization.

AHA officials indicated the AHA guidelines are likely to be revised as a result of this trial. The AHA currently recommends ACE inhibitors for all patients who have had a heart attack and others with coronary or other vascular disease.

PEACE was a double-blind, placebo-controlled study of 8,290 patients in the U.S., Canada, and Italy. The median follow-up was 4.8 years. Sources indicated the results will be considered a class effect that applies to all ACE inhibitors, especially since trandolapril is a tissue-ACE.

Among the comments on PEACE were:

- *Researcher:* "We found that patients are very well cared for…I guess we are getting to the point where some of our therapies are redundant…If there is something you have to take off (stop), it may be the ACE inhibitor if blood pressure is down."
- *Discussant:* "PEACE reinforces the notion that an ACE inhibitor reduces coronary events. The effects with an ACE was modest in all three studies, and society should decide what benefit warrants taking an additional medication each day."
- *Expert:* "PEACE is very important in terms of impact. It suggests that ACE inhibitors may not always be necessary…PEACE addresses lower risk (than the HOPE and EUROPA trials) and suggests if other treatments will be utilized, that the further addition of an ACE may not be needed. It is good news in terms of pill burden…Lower risk patients on an optimal dose of other medications may not benefit from an ACE…PEACE will stimulate me to look at other medications."
- *AHA official:* "The AHA/ACC guidelines committee will take this into consideration, and it will be incorporated into our recommendations in January 2005…Significant consideration will be given to the risk of the patient. If a patient is really low risk, they may fall into a group where they may not need an ACE."
- "One explanation for the PEACE findings is that more and more patients are getting to guidelines with aspirin, beta blockers, and statins."

PEACE vs. Other ACE Inhibitor Trials

Measurement	HOPE n=9,297	EUROPA n=12,218	PEACE n=8,290
Average age	65	60	64
Prior MI	53%	65%	55%
Average baseline BP	129/79	137/82	133/78
Statin use	29%	58%	70%
Beta blocker use	40%	62%	60%
Death due to CV causes*	63%	59%	47%
Annualized CV mortality rate	1.62	0.97	0.77

*U.S. general population is 35% by Census Bureau data

PEACE Trial Results

Measurement	Trandolapril 4 mg/day n=4,158	Placebo n=4,132	p-value
Primary endpoint: Revascularization	21.9%	22.5%	.43
CV death	3.5%	3.7%	Nss
Non-fatal MI	5.3%	5.3%	Nss
Hospitalization due to CHF	2.5%	3.2%	.048
Stroke	1.7%	2.2%	.09
Death due to any cause	7.2%	8.1%	Nss
Composite of death from CV causes, non-fatal MI, revascularization, or unstable angina	25.5%	2.8%	Nss
Death from CV causes, non-fatal MI, or stroke (outcome in HOPE)	9.5%	10.2%	Nss
Death from CV causes, non-fatal MI, or cardiac arrest (outcome in EUROPA)	8.3%	8.6%	Nss
Onset of new diabetes	9.8%	11.5%	.01

COXIBS

Asked about the cardiac safety of replacement NSAIDs for Merck's Vioxx (rofecoxib), an expert said, "Many of us were disappointed that Vioxx is not appropriate…Hopefully, we will learn more about the mechanisms of atherosclerosis from this. It is a tough issue. We are looking at ibuprofen and recommending that regular use of ibuprofen be avoided." Another expert said, "100% of those agents (NSAIDs) will affect blood pressure…I've had patients referred because they start on an NSAID or Cox-2, and all I do is modify the dose, and the blood pressure comes right down…You will lose the effects of beta blockers and ACE inhibitors from NSAIDs. Also, early morning blood pressure may be affected by those agents…and that probably is contributing to some extent to the risk with those (NSAID) agents."

Coxibs and hypertension. An independent meta-analysis by Australian researchers concluded that coxibs in general and Vioxx in particular increase blood pressure more than placebo and more than non-selective NSAIDs (NS-NSAIDs). The researchers looked at prospective, randomized trials of parallel design with data on blood pressure and/or hypertension that had a minimum of 50 patients, lasted more than four weeks, and were not conducted in healthy volunteers. They found almost 50,000 patients, two-thirds with osteoarthritis and one-third with rheumatoid arthritis:

- Coxibs vs. placebo – 4,362 patients
- Coxibs vs. NS-NSAIDs – 39,614 patients
- Pfizer's Celebrex (celecoxib) vs. Vioxx – 2,833 patients

Comparison of Cox-2 Inhibitors and Non-Selective NSAIDs
(in all cases Coxibs and/or Vioxx were worse than comparator)

Comparators	Increased risk/change with coxib	Significance
Overall change in systolic blood pressure		
Coxibs vs. placebo	3.85 mmHg	---
Coxibs vs. NS-NSAIDs	2.83 mmHg	---
Coxibs vs. Vioxx	2.83 mmHg	Nss
Overall change in diastolic blood pressure		
Coxibs vs. placebo	1.06 mmHg	---
Coxibs vs. NS-NSAIDs	1.34 mmHg	---
Relative risk of developing hypertension		
NS-NSAIDs vs. placebo	1.81	p<.05
Vioxx vs. placebo	2.63	p<.05
Celebrex vs. placebo	1.53	Nss
Merck's Arcoxia (etoricoxib) vs. placebo	1.25	Nss
Coxibs vs. NS-NSAIDs	1.29	N/A
Vioxx vs. NS-NSAIDs	1.78	N/A
Celebrex vs. NS-NSAIDs	0.82	Borderline significant
Arcoxia vs. NS-NSAIDs	1.47	Nss
Vioxx vs. Celebrex		
Risk of developing systolic hypertension	1.54	p<.05
Risk of developing diastolic hypertension	1.55	p<.05

NOVEL THERAPIES FOR HYPERCHOLESTEROLEMIA

Two basic science sessions reviewed the HDL-raising drugs in development. Following is a brief review of these presentations.

1. CETP Inhibitors – ROCHE'S JTT-705 (acquired with the Japan Tobacco acquisition) and PFIZER'S torcetrapib.

According to one expert, "For every 1% increase in HDL, there is a 1%-3% decrease in CHD risk." Speakers made the case for the efficacy of these two agents in raising HDL, concluding that CETP inhibitors:

- Effectively raise HDL, though the clinical benefits in humans still need to be documented.
- Augment the efficacy of statins in reducing LDL and triglycerides.
- Work in combination with statins to normalize LDL, HDL, particle size, etc. A speaker said, "Clearly, what we are seeing is that the addition of torcetrapib to atorvastatin, gives you more LDL lowering than atorvastatin alone plus an HDL increase. From a lipid standpoint, this is very favorable."

Perhaps just as importantly, a speaker discussed negative issues that have been raised about CETP inhibition, including:

- Deleterious effect of inhibiting HDL too much? A speaker warned, "CETP inhibition probably should not exceed 70%, so that there is no dysfunctional HDL produced." A Pfizer official disagreed with this, claiming there is no danger to inhibiting HDL.
- Deleterious effect on CHD? A Honolulu Heart Study found four deleterious effects on CHD, but a more recent analysis reportedly contradicts that initial finding. Some Japanese studies indicated that some mutations affecting CETP might have a deleterious effect on CHD risk, but a study in centenarians disputes this.

Measurement	Roche's JTT-705 600 mg/day	Pfizer's torcetrapib 120 mg BID	Torcetrapib 120 mg QD + Lipitor 20 mg/day
LDL	Down 5.4%	Down 17%	Down 17%
HDL	Up 26.4%	Up 106%	Up 61%
Triglycerides	Down 5.9%	Down 26%	Down 18%
Particle size	N/A	Up 382%	Up 136%

Pfizer has multiple Phase III trials underway now to test the clinical effect of torcetrapib, and the pivotal trial was reported to still be enrolling patients. A speaker said the 60 mg dose is the one going forward, and it has shown 35% inhibition of CETP, with a corresponding increase of ~60% in HDL.

2. Lp-PLA2 inhibitors – GLAXOSMITHKLINE'S GW-480848.

The Atherosclerosis Risk in Communities (ARIC) study presented at AHA reported that high levels of Lp-PLA2 are responsible for inflammatory events in atherosclerosis. Researchers also concluded that Lp-PLA2 is an independent factor – over and above standard risk factors – for identifying individuals with an increased risk of stroke.

3. Apo-A-1 mimetic peptides

- **ESPERION/PFIZER'S ESP-24218 (Apo-A-1-milano).** A speaker praised the Apo-A-1-milano data previously presented. An expert said the company is making more material, but he was not sure when the company could start trials.

- **PROTEOPHARMA/BOREAN PHARMA'S trimeric Apo-A-1.** This has a long half-life. A speaker said, "Initial studies suggest there is a significant decrease in atherosclerosis in mice. This is a very interesting additional approach."

4. Phoresis – LIPID SCIENCE'S LSI-S955.

This selective delipidation solvent is being tested as a plasma phoresis agent. There is phoresis of plasma, the plasma is mixed with the solvent – which selectively delipidates the HDL – and then the solvent is removed and the delipidated plasma put over a charcoal filter and returned to the patient. A primate study showed a 74% increase in HDL with this therapy.

5. Synthetic peptides.

6. Microsomal triglyceride transport proteins (MTPs). A lot of companies have been working in this area, and at least two compounds are believed to still be alive – Merck/ Schering's implitapide (BAY-13-9952, obtained from Bayer) and a Bristol-Myers Squibb agent which is now in the hands of University of Pittsburgh researchers. However, several companies – including GlaxoSmithKline, Pfizer, Bristol-Myers Squibb, and Johnson & Johnson – reportedly have discontinued research with these agents. A Merck official said, "Bristol-Myers claimed there is a class toxicity issue… but there still may be a role for these agents in specific conditions…We want to take the BAY-13-9952 compound and see if the industry threw out the baby with the bath water and missed a safe dose that adds value…The joint venture is looking to see if we can identify non-responders."

The problems with these agents have included:

- A significant number of patients with diarrhea.
- 25%-30% of Bristol-Myers Squibb patients at the highest doses – 80 mg and 160 mg – had ALT>3xULN, which was unexpected.
- Hepatic scans in patients on the Bristol-Myers and Bayer drugs showed hepatic fat accumulation.

There are three studies of implitapide ongoing. Current development is at 15-40 mg/day. The company is starting with patients with the most severe and resistant forms of (a) high cholesterol, where even high dose statins are ineffective and (b) high triglycerides, where no current therapy is optimal. An official said, "Our main concern is safety. We expect some accumulation in the liver. There is also a concern with interference with vitamin E absorption. We found CT scans are good for monitoring hepatic fat accumulation. We are starting all with a low dose of 20 mg/day and titrating by 5 mg every five weeks to a maximum of 40 mg/day vs. placebo."

7. LXRs. These are nuclear receptors that sense cholesterol. These increase HDL but also triglycerides in serum and in the liver in mice. A speaker said, "HDL goes up over a few days and then flattens. The bad news is serum triglycerides which rise rapidly and then fall abruptly. A few hours after taking an LXR, you find the highest serum triglyceride level, and then, after a few weeks, it comes down, even below baseline a little. But liver triglycerides just keep on increasing, and that is the problem. So measuring serum triglycerides is not sufficient. The take-home message is: Complete assessment of these drugs requires dose response and/or time course and measurement of liver triglyceride content…Is there a solution? I think there is – subtype selective agonists for LXR-β and not LXR-α."

These agents include:

- **TULARIK'S T-1217**
- **GLAXOSMITHKLINE'S GW-3965**
- **MERCK'S Compound A**

PULMONARY ARTERIAL HYPERTENSION

MYOGEN'S ambrisentan – no news.

UNITED THERAPEUTICS'

- **Remodulin (treprostinil)** – subcutaneous, with IV formulation in development. A speaker said, "Remodulin has been shown to improve exercise capacity when given as initial therapy, and it has a significant dose effect, but patients have to be on a higher SQ dose than IV to get a similar effect."
- **Beraprost.** No news. Development was stopped because the efficacy seen at three months was lost at 12 months.

ENCYSE'S Thelin (sitaxsentan). No news

ACTELION'S Tracleer (bosentan) – oral. No news.

GLAXOSMITHKLINE'S FloLan (eprostenol) – IV. A speaker said, "FloLan is relatively difficult to use, but it has been shown to work. The hemodynamic effects are fairly dramatic and quick. A majority of the hemodynamic effects are on cardiac index, which improves significantly and quickly."

PFIZER'S Viagra (sildenafil) – oral. Sildenafil is not approved for PAH, and if it gets approved, it will become a new therapeutic class. So far, only sildenafil – not tadalafil (Lilly's Cialis) or vardenafil (Bayer's Levitra) – has been shown to have an effect in PAH. An expert said, "Until we know more about Cialis's effect on PDE-11 and cardiac contractility, I would be reluctant to pursue that in a heart failure population."

In a randomized, multicenter, placebo-controlled, 12-week clinical trial presented at the CHEST meeting in October 2004, sildenafil (tested at 20 mg TID, 40 mg TID, and 80 mg TID) was shown to improve 6-minute walk (the primary endpoint), but not clinical disease worsening in a study of about 300 symptomatic patients with Class I-IV PAH. While there is no long-term data, researchers and other experts believe sildenafil is effective. Experts said they are prescribing sildenafil – when the patient can afford it. Among the comments on sildenafil were:

- "I have eight or nine patients on it off-label, where I could get enough samples…and I've seen good results, but I would like to see more long-term data."
- "I think the 12-week data look positive. My concern is whether that benefit lasts…Some studies indicate the effect may wane over time. Before I put sildenafil in an algorithm as a first-line therapy – now that we have long-term data with other drugs – I would want to see similar long-term data with sildenafil."
- "In Australia, we don't have prostenoid analogs…but recently I had a few patients with a rare condition, and they had tremendous results with sildenafil."
- "I'm a little concerned about the sildenafil data…If the patients walked too far in the study, they were excluded,

and I believe more patients walked too far…So, it was really the sicker Class II patients in that Viagra study."

Sources said Pfizer is expected to submit sildenafil to the FDA in early 2005 at doses different from the marketed Viagra doses – and with a different name. Pricing also is expected to differ between Viagra and the PAH formulation of sildenafil. Pfizer clearly doesn't want to endanger its Viagra franchise with the marketing of sildenafil for PAH.

A speaker predicted that Thelin and sildenafil will get approved for PAH at about the same time, commenting, "It will be good to have additional choices. Sitaxsentan still will find a place, even in the face of Pfizer marketing…Sildenafil is something to think about in patients not responding to more established therapies…(In the future) sildenafil may become a viable alternative in patients already treated with calcium blockers…(And) PDE-5 inhibitors may be additive to other vasodilators."

OTHER DRUGS

Vitamin E

Daily doses of 400 IUs of vitamin E were shown to do more harm than good in a study presented at AHA. Vitamin E doses increased the risk of death, and researchers warned that at least this dose actually should be avoided.

Previous animal and observational studies have found that vitamin E supplementation could prevent cardiovascular disease and cancer, but other studies suggested that high doses of vitamin E could be harmful. This study was designed to settle the debate – and it did.

Researchers studied various doses of vitamin E supplements (from 15-2,000 IU/day) vs. placebo in 14 studies from 1993 to 2004, with the average intake ~400 IU/day. An investigator said, "Increasing doses of vitamin E were linked to an increase in death."

The study found no increased risk of death with a dose ≤200 IU/day – and perhaps some benefit – but with >200 IU/day, a significant risk was found, and a significant risk of death was reported at ≥400 IU/day. Researchers reported the risk of death was ~10% higher in patients taking ≥400 IU/day.

ABBOTT'S Clivarine (reviparin) – an effective LMWH

The CREATE trial studied 15,570 patients with ST segment elevation or new bundle branch block, presenting within 12 hours of symptom onset were randomized to reviparin vs. placebo given for seven days in addition to usual therapy on the primary outcome of death, reinfarction, or strokes at seven and 30 days. Reviparin is approved in Europe but not the U.S.

The benefits were best in those treated within eight hours of symptom onset, but benefits persisted at 30 days with significant reductions in mortality and reinfarction, with no significant differences in strokes. The principal investigator said, "Adherence to the protocol was excellent…We expected a benefit on death and MI, and we were uncertain what would happen with stroke…At 30 days the benefits were even more amplified; it continued to be 13%…When you look at the components of the composite, there was a heightened significant reduction in mortality, there was a highly significant reduction in MI, and there was no significant excess in strokes. There was an increase in life threatening bleeds, but the threat was small, including fatal death and fatal bleeds as well as stroke…This is a simple and inexpensive therapy, and it can be used in rich and poor countries. Clearly, I believe it's the first study to show that an antithrombotic reduces clots."

CREATE Trial Results of Reviparin in STEMI

Measurement	Reviparin	Placebo	p-value
Patients treated within one hour or before therapy	70%		.006
Patients getting treatment for 7 days	75%		---
Patients receiving heparin	10%		---
Primary endpoint: **outcome (death, MI, stroke)**			
At 7 days	9.6%	10.9%	.006
At 30 days	11.8%	13.6%	.001
Other Results			
Mortality	9.8%	11.3%	.005
Reinfarction	2.0%	2.6%	.014
Increase in life-threatening bleeds (not included in primary outcome)	0.1%	0.2%	.07

ASTRAZENECA'S Crestor (rosuvastatin) – beats PFIZER'S Lipitor (atorvastatin)

The six-week ARIES trial – sponsored by AstraZeneca – compared Crestor and Lipitor in 774 African-American patients, and it found that 10 mg and 20 mg doses of Crestor work better than Lipitor in reducing LDL, total cholesterol, HDL, and ability to achieve the target LDL goal. Crestor was well-tolerated and its safety profile was similar to that of atorvastatin. But this trial did not dispel the safety concerns raised by Public Citizen in its March 2004 petition to the FDA to have Crestor withdrawn from the market.

6-Week ARIES Results

Measurement	Crestor 10 mg	Lipitor 10 mg	Crestor 20 mg	Lipitor 20 mg
LDL % change from baseline	-37% (p<.001)	-32%	-46% (p<.0001)	-39%
% patients reaching LDL goal by risk category				
Low Risk	92%	85%	92%	86%
Medium Risk	80%	66%	79%	66%
High Risk	24%	16%	63%	27%
All	66%	58%	79%	62%

ATHEROGENICS' AGI-1067

In late September 2004, AtheroGenics announced positive interim results from the CART-2 Phase II trial of standard-of-care vs. AGI-1067, an oral pill, which the company hopes will reduce the level of fatty plaque deposits (atherosclerosis) in a patient's arteries, thus lowering the risk of heart attack. The trial was originally designed as a restenosis trial, with change in atherosclerosis plaque volume from baseline at one year as a secondary endpoint, but the company decided to change the trial to an atherosclerosis study, with this as the primary endpoint.

When the decision was made to change the primary endpoint, AtheroGenics commissioned Dr. Steve Nissen of the Cleveland Clinic to review all of the IVUS scans in a blinded manner to identify the patients who were most suitable for quantitative analysis of plaque volume. Dr. Nissen identified 133 patients, who were the patients used for the interim analysis. Dr. Nissen described the interim results as "very promising" and a "proof-of-concept" study.

Interim 1-Year Results of CART-2 Trial

Measurement	AGI-1067	Standard of care	p-value
Primary endpoint: Change in plaque volume	-7.4 mm^3	-4.4 mm^3	Nss
Change in plaque volume in most severely disease subsegment	-3.0 mm^3	-1.3 mm^3	Nss

CV THERAPEUTICS' Ranexa (ranolazine)

In October 2003, the FDA issued an approvable letter for Ranexa, asking for additional clinical data before approving this anti-anginal agent. In August 2004, CV Therapeutics announced two new trials:

➢ **ERICA.** Under a Special Protocol Assessment (SPA), the company is seeking approval of Ranexa in a restricted patient population. In August 2004, the ERICA trial was initiated under this SPA. This is a six-week, multicenter, randomized, double-blind, placebo-controlled, parallel group trial in 500 patients who remain symptomatic despite 10 mg daily of amlodipine, a CCB.

- **Primary endpoint:** A statistically significant reduction in angina frequency (by patient diaries). **Secondary endpoints:** N/A, but there is no treadmill measurement in this trial.
- **Principal investigator:** N/A
- **Enrollment:** An official said the trial has enrolled faster than expected; it was not expected to finish enrollment until the end of 2005, but it is now expected to complete enrollment at the end of 1Q05. Thus the data should be available by summer 2005.
- **Duration:** 6 weeks.
- **Therapy:** 1000 mg ranolazine BID vs. placebo BID, with both arms also getting 10 mg of amlodipine**.**

➢ **MERLIN TIMI-36.** Under a second SPA, CV Therapeutics is seeking approval of Ranexa as first-line therapy for (a) patients suffering from chronic angina, (b) treatment of acute coronary syndromes (ACS), and (c) long-term prevention of ACS. The MERLIN trial was initiated in October 2004 under this SPA. This randomized, double-blind trial will involve >550 centers in 17 countries and 5,500 patients with non-ST elevated ACS. Enrollment has begun and an investigator said, "We are pleased with progress so far." A CV Therapeutics official said, "With the SPA, even if we miss the primary endpoint and don't show an improvement in survival, we can get a broader label if the safety is good (just not a label for ACS patients in that case), so there are two ways for us to win."

- **Primary endpoint:** CV death, MI, or recurrent ischemia.
- **Secondary endpoints:** CV death, MI, severe recurrent ischemic events, and positive Holter (with a 30-day endpoint).
- **Principal investigator:** Dr. David Morrow, Brigham & Women's Hospital.
- **Duration:** Event-driven, with an expected length of 12 months.
- **Follow-up:** Day 14, Day 30, Month 4, and every 4 months thereafter until completion. Average follow-up is expected to be 8-12 months.
- **Therapy:** Ranolazine IV followed by oral vs. placebo matched IV/oral. All patients will be on a background of standard medical therapy, which includes: beta blockers, ACE inhibitor, anti-platelets, PCI/CABG, aspirin, UFH/LMWH, statins, etc.
- **Enrollment:** Starts 48 hours after last resting symptom. Then patients will be treated with IV ranolazine or IV placebo for 12-96 hours, then transitioned to oral therapy.
- **Monitoring:** Holter monitoring of all patients for the first 7 days. An investigator said, "The Holter allows us to evaluate patients during the period of highest recurrent risk." He said it is not to watch for QT elevations but just to monitor for ischemia.
- **Exercise performance:** Planned measurement at 8 months.
- **Other analyses:**
  - Biomarkers to evaluate reduction in the extent of injury during ischemia and the increase in LV performance during ischemia. The objective is to determine whether ranolazine decreases: peak troponin, troponin area under the curve, CKMB and other biomarkers. At selected centers, patients with negative or falling troponin will be followed with more frequent samples and Holter monitoring during PCI.
  - Exercise.
  - Additional Holter measurements in a subgroup to assess the total burden of ischemia reduction and the suppression of arrhythmias.

- Substudy of HbA1c in diabetic patients. The objective is to see if ranolazine improves glycemia and/or delays the new onset of diabetes.

GLAXOSMITHKLINE'S Coreg (carvedilol) – trounced NOVARTIS'S Lopressor (metoprolol tartrate)

The GEMINI trial showed that Coreg is superior to Lopressor in patients with Type 2 diabetes and hypertension. Not only should this head-to-head trial give Coreg a marketing boost, but it should help beta blockers in general.

GEMINI was a six-month, randomized, double-blind, active control trial studying 1,235 patients who were also on standard of care treatment consisting of antidiabetic therapies and ACE inhibitors or ARBs. The primary investigator said, "There was a clear significant difference in the change in HbA1c from the baseline favoring carvedilol: no change in carvedilol and a significant increase in the metoprolol group…Also insulin resistance was significantly improved with carvedilol and worsened with metoprolol."

- **Primary endpoint was met – Diabetes control:** HbA1c was not negatively affected by Coreg (up 0.02%), but it worsened in Lopressor patients (up 0.15%). Insulin resistance was reduced significantly (9.1%) with Coreg, but Lopressor had no statistically significant effect on insulin resistance (-2.0%).
- **Secondary endpoint #1 was met – Blood pressure:** Patients on Coreg reached blood pressure goals at a mean daily dose of 18 mg twice daily, which closely matches the dose commonly prescribed in clinical settings. Patients on Lopressor required a mean daily dose of 128 mg twice a day to receive a similar benefit.
- **Secondary endpoint #2 was met – Microalbuminuria:** The risk of developing microalbuminuria was decreased 40% with Coreg vs. Lopressor. The albumin:creatinine ratio (ACR) was reduced in Coreg-treated patients by 16% compared to Lopressor. There was a 47% risk reduction for the development of microalbuminuria in patients on Coreg versus those on Lopressor.
- **Weight:** Patients on Coreg did not gain weight, while patients on Lopressor had a weight gain of 2.6 pounds. Weight change was not a secondary endpoint, but it was a pre-specified measure.
- **Side effects:** More patients dropped out due to worsening glycemic control with Lopressor (6%) than with Coreg (2.2%).

The results of this head-to-head trial were well received. An expert said, "We've known for decades that beta blockers have particularly useful action…and yet clinicians frequently say that they are somewhat reluctant to use them …A lot of that has been laid to rest with this trial."

However, there were a few criticisms of the trial, including:

- Exercise might have been a better indicator of heart rate than change in blood pressure.
- How to interpret the weight gain. While it might be surmised that the weight gain with Lopressor have accounted for the lack of improvement in insulin resistance, but, at the same time, less weight gain should have occurred with Lopressor since there was less improvement in insulin resistance.
- The alpha-blocking effect of Coreg may account for its benefit.

KOS PHARMACEUTICALS' Niaspan (niacin) – combination with a statin better than a statin alone on atherosclerosis progression

The ARBITER-2 trial was a double-blind, placebo-controlled study of once-daily (1000 mg) extended-release niacin Niaspan added to background statin therapy in 167 patients with known coronary heart disease and low levels of HDL-C (<45 mg/dL). An investigator said, "Patients treated with statins who have known coronary heart diseases and who are at goal for LDL still demonstrate a substantial progression of atherosclerosis, but when we added niacin to the statin therapy, we were able to demonstrate…that there was 68% slower progression. This is the first trial showing combination therapy targeting HDL slows the progression of atherosclerosis. It calls for prescription niacin to improve patient outcomes."

Secondary endpoints included changes in serum lipid concentrations, adverse events, including liver-associated enzyme elevations, and a composite of clinical cardiovascular events including any hospitalization for an acute coronary syndrome, stroke, an arterial revascularization procedure, coronary bypass surgery, or sudden cardiac death. The only adverse effect noted was flushing, which is harmless and

1-Year Results of ARBITER Trial

Measurement	Niaspan + statins n=78	Statin alone n=71	p-value
Primary endpoint: CIMT progression at 12 months	No thickening (68% reduction in CIMT progression)	thickening	.08
CIMT progression in patients without insulin resistance	N/A	N/A	.26
Cardiovascular events	3.8%	9.6%	.20
Mean CIMT increase (mm)	.014	.044	<.001
Within-group comparison of baseline to 12 months			
Total cholesterol	.92	.06	.73
LDL	.42	.37	.61
HDL	<.001	.61	.003
Triglycerides	.07	.03	.009

common among patients taking niacin, but which caused some patients to drop out of the study.

LILLY/TAKEDA'S Actos (pioglitazone) – soundly beats GLAXOSMITHKLINE'S Avandia (rosiglitazone) in improvement in overall lipid profiles

Head-to-head trials can be dangerous for the sponsor, but for Lilly/Takeda this comparison study was a winner. The trial was a randomized, double-blind, multicenter study in 802 patients with Type 2 diabetes and dyslipidemia.

Actos vs. Avandia at 24 Weeks

Measurement: Change from baseline in:	Actos 20 mg QD titrated to 45 mg QD n=363	Avandia 4 mg QD n=356	Best Drug
Primary endpoint: Triglycerides	- 12.0%	+ 14.0%	Actos
HDL	+ 14.9%	+ 7.8%	Actos
Non-HDL-C	+ 3.8%	+ 18.6%	Actos
LDL	+ 15.7%	+ 23.3%	Actos
LDL particle concentration	- 7.8%	+ 12%	Actos
LDL particle size	+ 2.4%	+ 1.7%	Actos
Apolipoprotein B	+ 1.5%	+ 11.5%	Actos

The discussant said, "(This head-to-head trial) looks like an exciting study in terms of measuring the impact for clinical outcome of patients with diabetes…So, I believe it's a significant step forward to have done the study." However, he noted that there was a 20% dropout rate, no information on the dropouts, and few African-Americans in the trial…These two drugs are in a class of drugs used by tens of thousands of people with established heart disease…Despite the fact that both drugs have been on market for five+ years, we didn't know the impact on cardiovascular outcomes or mortality… While this is a valuable study, I'd put forward the possibility that the companies that make these drugs might have invested more money sooner in getting the answer as to which was better…It is remarkable that a class of drugs used so commonly with so much at stake in terms of length of life and outcomes have been studied so little with respect to outcomes…I know outcome trials are underway, but one has been completed for more than a year, and it hasn't yet been published…Many people have said that head-to-head trials are like Coke vs. Pepsi – a matter of taste. I would argue that may not be the case. This could be water vs. Gatorade."

MERCK/SCHERING-PLOUGH'S Vytorin (Zetia+Zocor)

A Merck-sponsored symposium on this was very well attended for a pre-conference day. There was no news, just a review of the science behind the combination. Doctors in the audience who were questioned about their Vytorin use all said they had started prescribing it, and some were using it first-line in patients with very high cholesterol. So far, they said they have been satisfied with the results.

NITROMED'S BiDil (a fixed-dose combination of isosorbide dinitrate 20 mg plus hydralazine 37.5 mg) – a winner

The results of the pivotal, six-month, 1,050-patient, Phase III A-HeFT trial in African-Americans was presented, and the principal investigator called the results "significantly positive." They showed that BiDil, an oral combination of two generic drugs – isosorbide dinitrate (ISDN) and hydralazine (HDL) – significantly increases survival by as much as 43% in African-Americans with advanced heart failure. The study in patients with NYHA Class III-IV, met the trial's composite endpoint, which included death from any cause, a first hospitalization for heart failure, and quality of life measures.

Experts said they believe that, based on this trial data, BiDil should be approved for general use, not just for African-Americans. Comments by researchers and other experts included:

- *Expert:* "The FDA advisory panel probably will approve it because there would be a huge uproar if it weren't approved."
- *Researcher:* "We followed a trail of evidence suggesting that there would be a response (in African-Americans), but it's now important to identify what, beyond self-identification as an African-American, would identify responders to treatment…There will clearly be a broader population; it's a matter of identifying the determinants of the response."
- *Investigator:* "Maybe we should do a trial to prove that the subgroup responds. That doesn't mean it's unique to that group, but when you do a trial, you'd like to really look at the response of the population, and then you can extrapolate beyond that – that's what we expect people will do."
- *AHA official:* "We all agree that race is a crude marker here because there is an enormous genetic variation in both Caucasians and African-Americans, and potentially somewhere in that general variation there's a reason why some drugs work and some don't."
- *Dr. Salim Yusef, the principal investigator in the HOPE trial:* "I'm delighted with the results. I'm pleased, but I would use it beyond African-Americans."
- *Former AHA official:* "The likelihood is that this drug combination will perhaps benefit other groups, but what we can say, assuredly, is that African-Americans will benefit from this therapy."

The reaction of African-American doctors to the results was very positive. One commented, "The results are amazing, and it should be pointed out that they had 100% follow-up. That is

extraordinary." Another said, "I think this trial will lead to many more trials in other patient populations."

Randomization in A-HeFT began in June 2001. In July 2004, at the recommendation of the DSMB, NitroMed halted the trial due to a significantly higher mortality in the placebo group than in the BiDil group (10.2% vs. 6.2%, p=0.02). This therapy in trial was on top of best current therapy (which variably included beta blockers, ARBs, aldosterone inhibitors, digoxin, and diuretics), and patients were titrated up to a target daily dose of 125 mg ISDN and 225 mg HDL. A principal researcher said, "We think these data strongly suggest that the addition of a fixed dose of ISDN and HDL improves survival, decreases hospitalization, and results in improved quality of life for African-American patients with advanced heart failure. Nitric oxide enhancement is a new and potentially highly effective treatment for heart failure, especially in African-Americans."

Asked when BiDil will be submitted for FDA approval, a primary researcher said, "We haven't submitted it yet; we are still working through the data and that's the responsibility of the sponsor."

Scoring System for the Primary Composite Endpoint

Endpoint	Score
Death (at any time during trial)	-3
Survival to end of trial	0
First hospitalization for heart failure	-1
No hospitalization	0
Change in quality of life at 6 months ***(or at last measurement if earlier than 6 months)***	
Improvement by ≥ 10 units	+2
Improvement by 5-9 units	+1
Change by <5 units	0
Worsening by 5-9 units	-1
Worsening by ≥ 10 units	-2
Possible Score	-6 to +2

One worry about BiDil, based on these results, was the high rate of headache and dizziness. The discussant said, "There is a question of whether these adverse events may affect compliance and use of the drug over a longer period of time." An African-American doctor added, "Once people realize the benefits of this drug, they will be willing to accept the side effects."

Secondary endpoints were not presented at AHA; researchers said they are still "culling the data." Those endpoints included individual components of the primary composite score, death from cardiovascular causes, the total number of hospitalizations for any reason, total number of days of hospitalization, overall quality of life throughout the trial, number of unscheduled emergency room and office or clinic visits, change in B-type natriuretic peptide level at six months, a newly recognized need for cardiac transplantation, and a change in the LV ejection fraction, the LV internal diastolic dimension, and the LV wall thickness at six months.

18-Month A-HeFT Results

Endpoint	BiDil n=518	Placebo n=532	p-value
Primary composite score	-0.1	-0.5	0.01
Components of the primary composite score			
Death from any cause	6.2%	10.2%	0.02
First hospitalization for heart failure	16.4%	24.4%	0.001
Change in quality of life score at 6 months (range -6 to 2, with higher better)	-5.6	-2.7	0.02
Change in systolic blood pressure	-1.0 mmHg	+1.2 mmHg	0.002
Change in diastolic blood pressure	-2.4 mmHg	+0.9 mmHg	0.001
Adverse events			
Exacerbations of CHF	8.7%	12.8%	0.04
Severe exacerbation of CHF	3.1%	7.0%	0.005
Headache	47.5%	19.2%	<0.001
Dizziness	29.3%	12.3%	<0.001
Dosing			
Target dose of 225 mg HDL+125 mg ISDN reached	68%	88.9%	p<.001
Mean number of tablets per day	3.8	4.7	p<.001

Dosing in this trial was one potential issue, but sources were satisfied with the results. All patients were started on a half a tablet to one tablet of 75 mg HDL and 20 mg ISDN. The target dose of 225 mg HDL and 125 mg ISDN was reached by 68% of patients, and 20%-25% reached partial dose. A principal investigator said, "I use one of the generic drugs routinely in my practice, and it's very difficult to titrate the generic drug – very hard to recreate the fixed dose combination that has been produced here and used for the first time in this trial."

Experts pointed to the growing evidence that nitric oxide protects against myocardial and vascular remodeling. An investigator said, "Nitric oxide is an important regulatory molecule; it inhibits the growth and remodeling that occurs in heart failure…It reduces impedance to blood flow and relaxes the blood vessel…African-Americans between the ages of 45 and 64 have about 2.5 times the mortality rate from heart failure than do other populations…There is a particularly favorable response to the combination of ISDN and HDL seen in African-American patients."

According to an investigator, the company's message at AHA was that there are three advantages to BiDil:

1. **New treatment.** "This is a new, dramatically effective treatment for heart failure."

2. **New patients.** "A group of patients we previously had poor outcomes with in heart failure now have a novel therapy that works best for them."
3. **New approach.** "Even though we don't know the mechanism of action, this is a new approach."

Several issues may plague this product, including:

1. **Racial politics.** There has been some criticism recently of the idea of targeting African-Americans specifically, but Dr. Clyde Yancy of the University of Texas Southwestern Medical Center (an A-HeFT investigator) said, "I understand why people raise that issue, but we target moderate or worse heart failure in patients at high risk. Race is just an arbitrary placeholder. I don't believe these findings apply only to African-Americans."

African-American cardiologists questioned about BiDil were generally positive about it. One commented, "I've never known a study to show this better."

Yet, African-American doctors are worried about the marketing approach that may be taken with BiDil. Among the comments on this issue were:

- "It is a multifactorial issue. There will be some polarization, but I'm not bothered by the issue, and I and my patients will use BiDil."
- "It's not whether it works in whites, but whether whites with the same disorder would be candidates. It is not a drug based on color but on genetics/polymorphisms. I would be comfortable taking it or prescribing it…And I would prescribe it to white patients with the same presenting conditions as well as to black patients."
- "There is the potential for this being a political hot potato because of issues related to profiling and the stigma that could be attached. It's more an issue of political correctness, and there are two sides to that. Some heart disease studies indicated some drugs worked better in whites than blacks, and doctors assumed they shouldn't use those drugs in African-Americans, but later the drugs were found to work in African-Americans, perhaps at a higher dose. Then, we had to re-educate doctors, and that was difficult. This is the reverse. The issue is how to market (BiDil). If it is overly zealous marketing that is specifically for African-Americans, that could influence doctors not to use it in non-African-Americans. **If there is a label only for use in African-Americans, then the company should be required to study it in non-African-Americans.** It would be a mistake not to study it in non-African-Americans. It is dangerous to isolate and study a drug in only one race. If the data are very compelling, I would hate to delay the benefit, so I would require the study in non-African-Americans as a post-marketing study. But if the data are only good, delaying approval is a possibility, that probably would be a better choice."
- "Race is the best surrogate to know in whom the drug will work. Race is just a surrogate."
- "We will have some difficulty if the marketing message is that this is for black patients with heart disease because it will polarize patients…Then, nitric oxide would have a label as a black approach…We will have to overcome some negativity if it is marketed for blacks. I hope it gets approved for heart patients generally."

2. **Lack of data in Caucasians.** This could prevent a broad label, several sources warned. An expert said, "If I were on the FDA panel, I would want a trial done in non-African-Americans or you can't say the drug is good for everyone. It would have been better if there were the same number of non-blacks."

3. **Effect on beta blocker use.** An expert said, "I worry that this drug could have a negative effect on beta blocker use. If doctors think they don't need to give beta blockers with this, that would be a bad message."

4. **Combination issues.** It has been tougher for pharmaceutical companies to get combination products approved than single agents, and many doctors don't like fixed dose combinations. However, doctors questioned about this were generally positive, noting that the combination is likely to help improve compliance. "With a combination pill, even if patients cut out one pill to save money, they will still get both medications, just less. That's better than having them not take one part of the combination." Another doctor said, "Combinations improve compliance, and you get both medications in the same pill."

5. **Generic competition.** There also is a question whether doctors will opt for two generics or NitroMed's combination product. Comments on this topic included:

- "I would use brand because there is a lower pill burden."
- "A generic is not supposed to be different from the brand, and if I found a difference, then I wouldn't prescribe generics. Brand is going to be expensive, and for patients who can't afford it or who are in a managed care organization that puts the generic on the formulary, I would use the generic."
- "In clinical practice, my perception is that the generic is fine, but that is not always the case. Sometimes there are subtle differences, so I tend to lean – in life-saving drugs – toward brand. But I might start with generics before BiDil is approved if the A-HeFT data are very good."
- An investigator argued that the brand combination is a known entity, adding, "A generic is not always the same as the brand."

PROCTOR & GAMBLES' STEDICOR (azimilide) – Possible role in ICD patients

The results of the randomized, double-blind, placebo-controlled, 12-month SHIELD trial of 633 ICD patients showed that azimilide significantly reduced the recurrence of VT or VF terminated by shocks or ATP in ICD patients, thereby reducing the burden of symptomatic ventricular tachyarrhythmia. However, there was no statistically significant reduction in all-cause shocks on either dose.

Up to 50% of ICD recipients eventually require concomitant antiarrhythmic drug therapy to prevent symptomatic arrhythmia recurrences, but available drugs have serious side effects and are not FDA-approved. However, even with this study, the outlook for Stedicor is not clear. An expert praised the study, but he added that azimilide's side effects may restrict its use. He said, "It's very clear in the data that azimilide reduces VT episodes. Unfortunately, no information was presented on the rate of the VT episodes. Were they slow or fast? And, although all the devices were programmed in a similar way, we don't have the information on the devices…(And) the definition of a cluster versus multiple events is unclear. Is a cluster three or four episodes in the course of 10 minutes, or do we do a cluster over the course of a day? I think clarification on the definition of clusters as opposed to multiple events would be helpful. Nevertheless, the trial is highly significant and positive, and antiarrhythmic agents may in fact have a place in ICD-treated patients. So, there is a proof of principle that has been achieved. Azimilide is a somewhat less than ideal agent, and its side effect profile may limit routine use in high profile ICD patients, particularly over long periods of time, but it may be helpful in selective ICD patients."

1-Year Results of SHIELD Trial

Measurement	Azimilide 75 mg	Azimilide 125 mg	Placebo
Relative risk reduction in all-cause shocks plus ventricular tachycardia terminated by anti-tachycardia pacing	57% (p=.0006)	47% (p=.0053)	N/A
Reduction in incidence of appropriate ICD therapies (shock or TP terminated VT)	HR .52 (p=.017)	HR .38 (p=.0004)	N/A
Inappropriate shocks or ATP terminated VT	Reduced (Nss)	Reduced (Nss)	---
Torsade de pointes	5 patients – all successfully treated by ICD		1 patient—successfully treated by ICD
Severe neutropenia	1 patient	0	Nss
Reduction in cardiac-related ER visits and hospitalizations	50%	33%	---

SANOFI-AVENTIS'S Acomplia (rimonabant) – Continues to look like a potential blockbuster

The results of RIO-North America, the third and largest Phase III trial of this weight loss and smoking cessation drug, showed a significant impact on weight loss. This multicenter multinational, randomized, double-blind, placebo-controlled trial was conducted at 72 centers in the U.S. and Canada and enrolled 3,040 patients with BMI≥30 kg/m^2 or BMI>27 kg/m^2 with co-morbidities. At the highest dose (20 mg QD), patients lost an average of 19 pounds over two years compared to 5.1 pounds with placebo. The principal investigator concluded, "This seems to be an encouraging drug with regard to weight loss, particularly fat weight loss…The 20 mg dose seems to be the dose with the significant effect. The 5 mg dose is better than placebo but not effective enough to be a dose to be used…Weight loss went on a little longer than is usually the case with weight loss drugs. Most plateau at 24 weeks, and this continued to cause weight loss. The nadir was at about 32 weeks, and then there was a maintenance of that (weight) for the next period of time out to two years."

2-Year Results of RIO-North America Trial

Measurement	Placebo + Diet	Rimonabant 5 mg QD	Rimonabant 20 mg QD
Primary endpoint: **Absolute weight loss**			
Completers (per protocol)	5.1 pounds	N/A	19 pounds
Secondary endpoints			
Completers losing >5% of body weight	33.2%	36.7%	62.5%
Completers losing >10% of body weight	16.4%	20%	32.8%
Average decrease in waist circumference in completers	1.5 inches	1.9 inches	3.1 inches
Increase in HDL in completers	13.8%	15.6%	24.5%
Reduction in triglycerides (TGL) in completers	1.6%	5.9%	9.9%
Dropouts			
Due to overall side effects	7.2%	9.4%	12.8%
Discontinuation during second year of treatment	6.7%	8.3%	6.0%

Other findings included:

- Insulin response on the Oral Glucose Tolerance Test was improved with 20 mg Acomplia.
- There was no difference with either dose from placebo in the Hospital Anxiety and Depression (HAD) score.
- Discontinuations for adverse events were similar for all groups. A Sanofi-Aventis official said some patients discontinued the 20 mg arm due to adverse events, but patients in the placebo and 5 mg arms were due to lack of effect.

- Overall adverse events were similar for all three groups.
- Half the increase in HDL is due to weight loss and half to another effect of the drug, according to the principal investigator. He said, "So, there is a double whammy…We don't know the effect mechanism. It could be peripheral as well as a central effect."

This trial appears to answer one question that had been raised about Acomplia: What is the long-term effect? The principal investigator said, "Clearly, we consider obesity to be a chronic problem. You don't cure it, you just improve it. It is no different than diabetes or high cholesterol, and you would like drugs you can use long-term…I think that is why the FDA is asking for two-year data. And the results are encouraging; there are no red flags that are coming up. I would think the FDA will make some kind of statement about what they think about taking it longer than two years."

At an evening symposium sponsored by Sanofi-Aventis, the results of the RIO-North America trial were released. This was probably the best-attended meeting at AHA, with the room overflowing. There was a huge buzz among attendees about rimonabant. One doctor commented, "It's obvious that …there's a lot of interest in this drug." Another doctor said, "The potential for the drug is huge, and it's going to be a money-maker, especially if it works in keeping weight off. I can't wait to get my hands on it."

The three RIO trials as well as the STRATUS-US smoking cessation trial have all been concordant, which is helping to give doctors confidence in the data. A speaker said, "What we can take home (from the RIO-Lipids and RIO-Europe trials) is that we find metabolic syndrome is down 21% in placebo, and down 43% and 51%, respectively, with rimonabant. Weight loss was more than 10%...What is striking, as we study the data, is the consistency of the data regarding significant reduction in weight, waist circumference, improvements in lipid and glycemic profiles, increased HDL and reduced triglycerides, improved insulin sensitivity, and a significant decrease in the percentage of subjects with metabolic syndrome." The principal investigator for RIO-North America agreed, saying, "There were consistent one-year results in the three studies, with significant reductions in weight and waist at one year, significant improvement in the metabolic profile, and significant decline in metabolic syndrome. Efficacy was achieved at one year and was maintained in Year 2."

A RIO-North America investigator mentioned that patients in the study might have had even more weight loss if they hadn't had a non-drug period at the beginning of the trial. He said, "The FDA likes to have the protocol that way; it likes to start with a non-drug period. If you hadn't had that and started the drug right at the beginning and not had four weeks, I think the baseline loss of 8.7 kg might have been more like 12 kg."

As for adverse effects, the speakers mentioned psychiatric disorders, including depressed mood disorders, anxiety, irritability, and insomnia. An investigator said, "You get about a doubling of the effect from placebo."

Selected Acomplia Side Effects in RIO-North America

Measurement	Placebo	Acomplia 5 mg QD	Acomplia 20 mg QD
Insomnia	0	<0.1%	<0.5%
Irritability	0	0.2%	0.5%
Anxiety	0.3%	0.6%	1.0%

There are four trials of Acomplia in weight loss – RIO-Europe, RIO-Lipids, RIO-North America, and RIO-Diabetes. There are also three smoking cessation trials – STRATUS-US, STRATUS-Europe, and STRATUS-Worldwide. The results of RIO-Diabetes and STRATUS-Worldwide have not yet been reported. Data for all these trials will be completed by the end of 2004, and Sanofi-Aventis plans to file in 2Q05. A speaker predicted that Acomplia will get expedited review by the FDA.

Other uses of Acomplia

Could rimonabant work with alcohol cravings? What about sexual cravings? Speakers generally agreed that the drug might be used to stop alcohol cravings. As to questions about sex, a speaker said he saw no evidence of a diminished sex drive in patients taking rimonabant. He said, "Quality of life was actually improved as weight was lost, and there was no evidence as to a detrimental effect on sexual dysfunction."

What is the overall safety profile? Would you use SSRIs to combat mood disorders? A speaker said, "I wouldn't want to add an SSRI to this drug; I think adding a second drug when we're not quite sure of the tested action in either isn't a good idea."

What about using rimonabant for hypertensive patients? This wasn't separately analyzed, and the company will have to do a trial on hypertensive patients to get a better idea. It doesn't hurt the blood pressure levels."

Could rimonabant be used with a nicotine replacement/ nicotine patch? That study is underway. There is some reason to think the two drugs might complement each other, perhaps even synergism.

A question about possibility of using the drug in patients with Parkinson's disease was not answered.

More data

There will be additional data presentations on Acomplia at:

- American College of Cardiology in March 2005. (Trial data)
- American Diabetes Association in June 2005.

MISCELLANEOUS

Metabolic syndrome

At a Merck-sponsored session on the metabolic syndrome, Dr. Vivian Fonseca offered a tongue-in-cheek idea for encouraging better lifestyles, "What about taxing food and giving a tax break for a health club?" Another expert suggested posing a healthier lifestyle as an economic issue for patients, "Ask patients, 'How would you like to save money?'…Then make the statement: 'If you lose weight, we can reduce the dose and maybe the number of pills you take for your blood pressure.' That's what we need to (say)…If you have all these risk factors, it costs you more." A third expert said, "I'd tell people if you don't want to take a lot of pills, you need to exercise more. Obviously, if they have diabetes, I don't ignore that. For them, metformin is at the top of my list – and the PPARs."

REACT Trial

This U.K.-based trial was a randomized comparison of rescue angioplasty, repeat lysis, or conservative therapy in patients with failed thrombolysis. Researchers examined safety and clinical outcomes to one year in 426 patients at 335 U.K. hospitals. They found that repeat PCI provided the best clinical outcome.

REACT Trial Results

Measurement	Repeat PCI	Repeat Lysis	Conservative Therapy
Primary endpoint: 30-day event-free survival	88.9%	77.4%	75.2%
6 month survival	84.6%	68.7%	70.1%

CREATE-ECLA International Trial

A large trial has shown that glucose-insulin-potassium (GIK) is a promising early therapy for ST segment elevation MI. The CREATE-ECLA trial was a randomized, controlled trial studying more than 20,000 patients with ST segment elevation myocardial infarction (STEMI) presenting within 12 hours from 518 centers in 212 regions, including India, China, South America, Pakistan, North America, Europe, and the Middle East. The principal investigator said, "About 80% of deaths from heart attacks globally occur in low-income countries; therefore, we need therapies that are simple and inexpensive. In this study we looked at two low-cost therapies, GIK given intravenously for 14 hours, and reviparin, or low-weight heparin. Patients were randomized to receive the GIK solution for 24 hours or control therapy, which is usual care. Overall, the results demonstrate that GIK infusion had no impact on mortality from any cause in patients with acute MI – similarly, no impact on cardiac deaths, cardiac arrhythmias, and development of cardiogenic shock. So it is safe and there were no adverse affects. We did find, unexpectedly, a reduction in recurrent ischemia which was highly significant."

DEVICES

Among the devices discussed below are: drug-eluting stents, ICDs, Acorn's CorCap CSD (a new heart failure therapy), and imaging equipment.

DRUG-ELUTING STENTS

There was little news at AHA on drug-eluting stents, but there were a few tidbits.

Stent market. Sources agreed that the drug-eluting stent market is expanding – and the overall market for all stents is expanding, with the patients coming from patients who previously would have gotten either: (1) CABG, or (2) medical management (for small vessel disease, branch vessels, etc.). An expert said, "We did a three-month registry of 45 European hospitals, and found 8,000 patients with either 3-vessel disease or main stem disease. That's amazing. Two-thirds of them got CABG and one-third were stented."

Stents vs. CABG. Two major trials – SYNTAX and FREEDOM – were planned to study how PCI with drug-eluting stents compares to CABG. Reportedly, the FDA turned down FREEDOM, and the agency has posed 75 questions to SYNTAX planners.

Enrollment in all drug-eluting stent trials is becoming a problem, not just because there are so many of them but also because patients are becoming more resistant to going in a trial when there are two approved drug-eluting stents on the market.

ABBOTT

Doctors who are usually very knowledgeable about the various drug-eluting stent trials said there is very little information available about Abbott's coronary program. One expert described it as "mysterious."

However, Abbott has started a femoral (non-coronary) drug-eluting stent trial. Patients were being enrolled in the bare arm as of early November 2004, and enrollment in the drug (ABT-578) arm was due to start that month. Data are expected at PCR2005.

BIOSENSOR'S biolimus-eluting BioMatrix stent – Good efficacy but has to be hand-made

The final 6-month data on the 120-patient STEALTH-1 trial were presented, and it looked good. The problem for Biosensors is that they intend – for the near term – to make their stents by hand. They can produce 4,500 a month maximum now, and by doubling the plant shift they can double that output. The company has an automation device, but that has not been validated yet, and it may not be for at least a year.

It is possible that the U.S. trials will begin with hand-made stents, which the company insists can be made within FDA tolerances. A Biosensor official said, "I don't think the manual process is inherently any more difficult if you are making relatively small quantities and scaling up. In some ways, automation offers new challenges – like software and validation."

Other interesting news about Biosensors and this stent included:

- A cGMP manufacturer has been chosen and is making biolimus in a facility which Biosensors believes is FDA approvable, and that manufacturer is preparing a full drug master file.
- Biosensors is touting the flexibility and deliverability of the S-stent. An official said, "Flexibility equates with low restenosis."
- However, the company is planning two new stents. A new stainless steel stent platform will be announced this year (2004), which "improves on the S-stent," and Biosensors expects to have that approved in the U.S. in 1H2005 – providing the FDA accepts the new platform as a "design equivalent." Following that, a cobalt chromium stent will be introduced.

6-Month Final IVUS Results from STEALTH-1 Trial

Measurement	Biolimus n=80	Bare S-Stent n=40	p-value
6-month follow-up	100%		---
TLR-PTCA	0	1.3%	Nss
30-Day Results			
Secondary endpoint: MACE	2.5%	3.8%	Nss
Death	0	0	Nss
Q-wave MI	0	0	Nss
TLR-CABG	0	0	Nss
TLR-PTCA	0	1.3%	Nss
6-Month Results			
Primary endpoint: Late loss in-stent	.26 mm	.74 mm	<.001
Secondary endpoint: MACE	7.5%	5.0%	.68
Death	0	0	Nss
TLR-PTCA	0	1.3%	Nss
Binary restenosis	3.9%	7.7%	.40
Proximal edge restenosis	0	0	Nss
Distal edge restenosis	0	0	Nss
% neointimal volume	2.6%	23.5%	<.001
Neointimal volume index	.20	1.90	.001
% cross-sectional narrowing	12.7%	41.6%	N/A
Late incomplete apposition	3%	3%	Nss

- There also is a new delivery system, Gazelle, which Biosensors hopes to get approved in Europe and which will be used in the BEACON registry as soon as it is approved.
- The CE Mark submission should be complete in 1Q05.
- The U.S. plan is for a Phase I IND in healthy volunteers to start in 2005, and to be done at the University of Colorado.
- The next step for this program is a 1,000-patient, prospective, multinational, multicenter, observational, web-based BEACON registry in de novo lesions, conducted at up to 25 sites in Asia, South America, and Europe. The primary endpoint is TVR, with MACE and the correlation between co-morbidities and TLR as secondary endpoints.
- Biosensor partners Devax and X-Tent are working with biolimus on different stent platforms. Devax already is conducting a clinical trial of a bifurcation stent coated with biolimus, and X-Tent is expected to begin a trial of its biolimus-eluting long-lesion stent soon.
- Shelf life and stability testing are done.
- Initial (1-year) toxicity studies will be complete by the end of 2004. Longer toxicity studies will be done simultaneously with the trial programs. However, a Biosensors official commented, "Based on discussion with various (regulatory) agencies, there may be some additional testing required. And further preclinical studies are planned.
- The final IVUS data compare favorably to FUTURE I/II (which had % neointimal volume of 2.1% vs. 22.6%). There was no stent thrombosis. Restenosis and late loss were low, and no restenosis occurred at the proximal or distal edges of the stent in either group.

Terumo has licensed biolimus worldwide except for the U.S. Enrollment is expected to start in 1Q05 in Terumo's first clinical trial of a biolimus A-9 eluting S-stent, named Nobori, using a biodegradable PLA polymer. The ~400 patient trial – to be conducted in Europe, Australia, and Asia – will compare Nobori to Taxus, with a primary endpoint of in-stent late loss at nine months. The principal investigator is Dr. Bernard Chevalier in Paris.

BOSTON SCIENTIFIC'S Taxus

Sources were unaware of any new reports of deflation problems, and they all agreed that this issue appears to be behind Boston Scientific.

At AHA there were rumors that ADVANCED STENT TECHNOLOGIES (AST), which is developing a bifurcation stent (Petal), would be acquired by someone, and in mid-

December Boston Scientific announced that it was purchasing AST. The BOSS trial of Petal is ongoing.

CONOR

Information will be available shortly on 200 patients in the EUROSTAR trial. Enrollment is proceeding as expected. A speaker described the cobalt chromium version as "very good with a low profile," adding, "I'm pretty sure we will do remarkable things with this stent."

GUIDANT

- **Durable polymer/everolimus.** The next SPIRIT trial is not expected to start until 2Q05, even though the company is saying 1Q05. Late loss will be the endpoint, but there is disagreement among these sources as to whether it is in-stent or in-segment late loss. One expert predicted SPIRIT will enroll in three months once it gets going. Another expert described this drug-eluting stent as "acceptable but not exceptional," suggesting the dose may still be low, but he believes the program is now likely to succeed.
- **Biodegradable/everolimus.** According to one source, Guidant put the stainless steel Champion stent "on a back burner" but is keeping it for insurance.

JOHNSON & JOHNSON'S Cypher

As of AHA, 242 cases of hypersensitivity with Cypher stents and 88 with Taxus stents had been identified through the FDA's MAUDE reporting system. The RADAR (Research on Adverse Device and Reports) investigators reviewed cases through August 2004 and concluded:

- Hypersensitivity does occur, resolves, but can reoccur on rechallenge.
- Onset of symptoms from time of drug-eluting stent implantations was: 20% within 1 day, ~55% in 2-7 days, and ~25% in 8-14 days.
- The duration was: ~12% lasted 1-7 days, 35% for 8-30 days, and ~53% for >30 days.
- 15 cases believed to be related to the drug-eluting stent after review: 13 Cypher, 2 Taxus.
- Long-term antiplatelet therapy may be indicated to avoid late subacute thrombosis in patients with suspected hypersensitivity reactions. A speaker said, "We've been trying to work with the manufacturers to develop a skin test to help identify whether the hypersensitivity is related to the polymer – and it should be easy to develop if we could get some cooperation." Another expert said, "If you stop Plavix (Sanofi-Aventis, clopidogrel) and the rash continues, then you have to suspect the rash is from implantation, and you have to put patients on long-term antiplatelet therapy."

Hypersensitivity Reactions with DES

Symptom	Incidence
Rash	79%
Itching	28%
Hives	22%
Dyspnea	15%
Fever	12%
Atypical chest pain	9%
Anaphylaxis	5%
Symptom Seriousness	
Serious	98%
Required emergency interventions	34%
Hospitalized	18%
Permanent disability	5%
Death	2%

MEDTRONIC'S Endeavor

- The ENDEAVOR-2 trial is completed and will be reported at the American College of Cardiology 2005 – or sooner – but there has been no buzz about the results. One expert commented, "I would guess the results are not very good. It's probably better than a bare stent but not much better."
- ENDEAVOR-4. Sources believe that enrollment in the U.S. will be difficult, given the results of ENDEAVOR-1.

TRANSLUMINA'S Yukon

This may be a stent to watch. It has a rough, irregular, porous surface (called PEARL) that allows drug delivery. A speaker said, "I was quite impressed that you can modulate the drug level. I think we will hear more about this stent with other drugs (beside the insulin with which it was reported)."

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDS)

ICD and CRT Cost-Effectiveness – ICD therapy is cost effective

A 46-month study of 2,521 patients enrolled in the SCD-HeFT trial showed that single-lead, shock-only, ICD therapy is cost-effective when used in stable NYHA Class II and III heart failure patients with EF ≤35. And it is less expensive than amiodarone, which, in turn, is more expensive than placebo. An investigator said, "ICD therapy is both more effective and more expensive, but it represents an economically attractive way to increase societal health benefits…When we do all the calculations…we get a cost-effective value of about $33,000 dollars for each life year added…Anything less than $50,000 is considered to be good value for the money, and anything over $100,000 is considered to be economically unattractive

…So, the defibrillator was more effective and does provide cost-effectiveness."

Measurement	Amiodarone	Placebo	ICD
Hospital cost	$31,466	$30,691	$46,804
Total 5-year cost	$49,444	$43,077	$61,967
Lifetime cost	---	$90,749	$159,147
Life expectancy	---	8.41 years	10.87 years
Cost-effectiveness ratio per life-year added	---	---	$33,000

This cost-effectiveness study used an ICD price of $17,500 (including lead), without outpatient implantation. Amiodarone was priced using 90% of AWP, or $3.53/day. The analysis looked at costs out to five years, compared by intent-to-treat. The study assumed the ICD generator would last five years and would be replaced with a single-chamber ICD.

The presenter said, "We could be spending about $2.3 billion in the first year on implantation costs. This is equivalent to increasing heart failure hospitalization costs by 18% – not a trivial amount…Total health spending is $1.2 trillion, and that would be a 0.2% increase. In addition, we're already spending at least that on ICDs. It is estimated we'll be up to 500,000 (implants) among Medicare beneficiaries at some point…The answer is we probably can afford it, but should we afford it?"

The discussant responded, "This is life-saving therapy and in this study we have preservation of life within the trial period and calculation beyond the trial periods…We have a $33,000 per life-year gain, and that's less than the threshold for what our society is willing to pay, which is $50,000...This is somewhat comparable to cost-effectiveness for drug-eluting stents. It's higher than the cost-effectiveness ratios for pharmacological therapies that have been investigated recently, but those therapies, while considerably less expensive, are also not going to save lives directly in the same way as noted in SCD-HeFT."

Hospitalized patients per year	Cost	Hospitalized CRT candidates	Outpatient CRT candidates	First year cost for CRT patients
1,000,000	$12.5 billion	15,000 (5%)	5,000	$2.3 billion

Cost-effectiveness by Subgroup

Measurement	NYHA Class II	NYHA Class III	Ischemic patients	Non-ischemic patients	EF ≤ 30	EF >30
Increase in life expectancy in life years	9.1	---	6.9	10.1	---	---
Cost per life year	$15,570	---	---	---	---	---
Cost effectiveness ratio per life year	$34,714	$44,804	$33,600	$32,170	$33,509	$29,725

ICD Cost-effectiveness by Other Scenarios

Measurement	Cost-effectiveness ratio per life year
Most conservative assumption about survival benefit (with no benefit after 5 years)	$77,000
Mix of ICDs – 30% single, 40% dual, 30% CRT-ICD	$36,618
Post-5 year cost increased by 50% possibly related to extra infections, lead problems, etc.	$46,640
Battery replacement extra costs	$35,586
ICD mix, increased post-5 year cost and battery replacement costs	$53,459

An investigator said, "There was a perhaps unexpected and statistically significant difference between ICD therapy and the NYHA classes, so that NYHA Class II had almost a 60% reduction in mortality with ICD therapy, but Class III had almost no benefit from ICD therapy, so we looked at the cost-effectiveness in two ways – first, assuming this interaction was correct, and, second, assuming the overall 23% reduction in mortality from the overall trial was the better estimate in both Class II and III patients." The discussant said, "There was one interaction and that's by class, and I agree that I wouldn't take it too seriously."

The speaker said there was little empirical data to guide sensitivity analysis as to the most likely cost and outcome scenario after five years, and he added that additional subgroup and sensitivity analyses remain to be done.

Asked about Medicare reimbursement for ICD therapy, an investigator said, "Medicare is evolving its response as we speak, and they have a draft coverage decision issued a month ago which essentially proposes to accept the enrollment criteria of SCD-HeFT as criteria for defibrillators with one difference – they chose a 30% cutoff for EF instead of 35%. I guess they felt they had to exclude somebody. Part of the coverage decision is that patients have to be enrolled in a registry; the shape and details of that are still a work in progress…So, in general, CMS has accepted this as state-of-the-art for medical therapy and are prepared to cover it."

The researcher said CMS has not seen this study yet, adding, "We've done some calculations that have shown cost-effectiveness as good in the 30%-35% EF cases as in the lower (EF) patients, partially because even though the absolute benefit may be lower in those patients, they live a substantially longer amount of time." An AHA official said, "The only guidance that CMS has is a paragraph in decades-old legislation that says that Medicare should cover 'appropriate care.' That was

written before ICDs were invented and before we had the expensive technologies we have today, and I think there's a clear need for more public discussion of issues that these raise for our society. We cover things like dialysis that have a $50,000 per life year cost, and if you keep adding technologies at that level, you'll just contribute to the rising national problem of healthcare costs. I think we need more discussion with, and guidance to, CMS; they're functioning in a very difficult situation."

A physician presenting a report on which CRT devices patients should receive said, "Should patients get CRT pacemakers or CRT-ICD devices?…Patients with ICD and CRT indications could get CRT-Ds. Patients with CRT indication and ischemic cardiomyopathy should get CRT-Ds, and for those with CRT indication and non-ischemic cardiomyopathy, there is more and more evidence for CRT-D. In all cases, we have to select the device according to the patient's status as well as cost of the device...In 2004, CRT candidates are selected according to the guidelines. However, improvements in patient selection are needed, and I see more and more evidence to implant CRT-Ds."

Doctors agreed that CMS reimbursement will boost sales of ICDs/CRT-Ds. An investigator said, "There are a lot of eligible patients. But there will have to be an education effort to get primary care providers to refer them (to cardiologists) …Realistically, I think the number of patients might be a third of two million (660,000 patients)." An electrophysiologist and former AHA official said, "More and more devices will be implanted in patients with advanced heart disease. Manufacturers will have to educate physicians." Asked if there is a backlog of patients, he said, "That's a mixed question. I don't think there is a backlog of patients waiting for therapeutic reasons; however, there may well be a backlog waiting for prophylactic reasons."

MEDTRONIC'S ICD with edema feature – Interesting but not a game changer

Doctors questioned about this product expressed interest in it. One physician said, "Devices that can give information that is predictive of deterioration are useful. When you combine that with a lung water examination, you can tell if the patient is getting into trouble. If a device can do that, it can decrease the hospitalization rate, and that would be very helpful." Asked which manufacturers would be hurt by the Medtronic device, a source said, "My prediction is that Medtronic may benefit in the short-term, but the other companies will introduce something similar in very short order."

CONGESTIVE HEART FAILURE (CHF)

ACORN'S CorCap CSD (Cardiac Support Device)

CorCap is a proprietary mesh wrap that is implanted around the heart to provide support and relieve the wall stress of increased heart size associated with LV hypertrophy. Data were presented at AHA that indicated the device improves quality of life and slows worsening of heart failure. Acorn plans to submit CorCap CSD to the FDA in 1Q05. An Acorn official said, "How we believe the device works is by putting gentle pressure on the heart and relieving the stress on the failing heart, allowing it to rest and, in effect, heal. Unloading …is how we think the device works in early animal models… This is breakthrough technology. We have great drugs for heart failure, and great electrophysiologic therapies for heart failure. This device is synergistic with and additive to existing therapies. It is a completely new niche and fits an overall need for moderately-advanced disease, for big hearts, and for patients not doing well on current medical therapy…The device is not for everyone. We did not put it in people with far, far advanced disease that we didn't think would withstand the device; 80% of patients were NYHA Class III. We see this therapy as synergistic with biventricular pacing." An AHA official added, "If the CSD proves simple, safe, and efficient, it could have a big impact."

The trial was a prospective, multicenter study of 300 patients with NYHA Class III-IV heart failure and dilated cardio-myopathy. There were four arms: 193 patients were randomized to mitral valve repair/replacement (MVR) alone or MVR+CorCap, and 107 were randomized to either continued optimal medical therapy with or without CorCap. Median follow-up was 22 months. Among the findings were:

- 70% overall improvement for patients with CorCap.
- 50% decrease in cardiac procedures for worsening heart failure.
- Change basketball-shaped heart to football-shaped heart.
- Improvement in quality of life.
- Out to four years, there has been no evidence of pericardial constriction with the device.

Questions about this device include:

- **The benefit was in LV remodeling and not LVEF.** A company official explained, "Those of us in the heart failure community regard LV remodeling as a better bellwether than LVEF. LVEF doesn't correlate with patient symptomatology…The lay person views EF as most important, but I think most heart failure doctors would look at heart size as the most important predictor of where the patient is going to go."
- **No impact on survival.** There was no difference in survival at three, 12, or 24 months.
- **Lack of impact on hospitalizations.** There was no statistically significant difference in either total hospitalizations or the median number of hospitalizations. A company official said, "What we anticipate is that differences in hospitalizations will emerge over time."

- **Demographics of patients.** A reviewer commented, "Only 10% of patients had ischemic etiology, so this study may have negatively biased the outcome."

The discussant at the formal presentation on CorCap CSD commented, "This device clearly is safe, and an ideal adjunctive procedure when you are already in the chest. The $64,000 question is whether this translates to clinical benefit. The composite primary endpoint was met…but the device did not change the number of hospitalizations. Thus, the device is safe and successfully prevents dilation, but clinical improvement is modest. Though the study doesn't show robust clinical benefit, the subgroup analysis is more positive. If the procedure is to be stand-alone, it would be better if less invasive procedures were developed…Assuming the study results are durable with further follow-up…this appears to have a role in patients who fail maximum medical therapy and cardiac resynchronization therapy, but I would caution that an LVAD or transplant may be more appropriate for NYHA Class IV patients."

CorCap CSD Trial Results

Measurement	MVR+CSD n=148	MVR alone n=152	p-value
Patients who got mitral valve repair/replacement	91	102	---
Primary endpoint: Improvement in patient functional assessment of better-worse-same based on composite of death, major cardiac procedure for HE, and change in NYHA class	38%	27%	.02
Patients who were unchanged on composite endpoint	25%	27%	---
Patients who worsened on composite endpoint	37%	45%	---
Patients who improved on composite of death, major cardiac procedure for HE, and change in NYHA class improved	45%	52%	---
Unchanged	18%	8%	---
Major cardiac procedures	19%	33%	p=.01
Reduction in LV end diastolic volume	N/A	N/A	p=.009
Reduction in end systolic volume	N/A	N/A	p=.017
Change (improvement) in LV sphericity index	~0.35	~0.11	p=.026
Total repeat hospitalizations	305	307	p=.44
Median number of hospitalizations	5.5%	6.3%	Nss
Change in quality of life on SF-36 (with lower number better)	~10	~15	p=.015
Improvement in NYHA Class	52%	43%	p=.12
Any adverse event	81.1%	77.6%	Nss
Arrhythmias	38.2%	32.4%	---
Bleeding	92%	61%	---
Hemodynamic compromise	48%	56.1%	---
Infection	23.0%	31.1%	---
Pulmonary compromise	14.5%	19.6%	---
Renal compromise	5.3%	10.1%	---

IMAGING

CT Angiography and Multislice CT

This technology definitely is starting to get a toehold in cardiology. Cardiologists reported that use and purchases of multislice CT-scanners is increasing, and they foresee them as a useful tool that may replace angiography in certain patient populations. However, reimbursement continues to be a nagging problem.

This technology was included in several different symposiums. At an interventional cardiology session, a speaker predicted that in 2013, 3.1 million angiographies will be done with CT, and only 1.4 million diagnostic caths will be done. He said he already has a 64-slice CT in his cath lab and is just "waiting for CMS reimbursement" to increase use. Speakers at other sessions were equally optimistic about the outlook for this and CT angiography.

Doctors whose hospital or practice do not already have multislice CT-scanners for cardiology said they are planning to purchase one in the next few years. A third of physicians interviewed (5 out of 14) said they have a CT-scanner and use it for cardiac angiography, nearly half (6) said they don't have one but plan to purchase one in the next few years. Reimbursement is an important issue, but most doctors think reimbursement will be approved.

- *Missouri:* "I've seen CT used mostly in university settings; I'm in private practice, and I'm looking at it."
- *North Carolina #1:* "We're thinking about installing one now."
- *Alabama:* "We're purchasing a 64-slice scanner and will start using it next year."
- *Louisiana:* "We're looking at a CT scanner; we're buying an MRI scanner but we are not buying a cardiac package. To do that we'd have to swap off the nuclear imaging."
- *North Carolina #2:* "This technology is pretty brand new and not all hospitals have it. We don't have one, but I think in five or six years many hospitals will have it."
- *North Carolina #3:* "CT is becoming rapidly embraced by the profession. We don't have one but are going to in the next year or so."

Doctors think CT will be a useful tool and may replace angiography in certain low-risk patients. Most said that 64-slice technology is a great improvement over 16 and 32-slice CT. Among their comments were:

- *North Carolina:* "CT will play a much larger role in ruling out coronary disease in the patient without a lot of risk factors."

- *Missouri:* "It can be useful in certain populations of patients and may replace angiography. It's most useful in low-risk and medium-risk populations."
- *Ohio:* "It's not a toy, but it's a definite advance; this is absolutely the future. There are fewer adverse outcomes with CTMR than with conventional angiography, for example, no operator error with echo. There are a lot of reasons to have 64-slice, and both 32 and 64-slice CT are being refined."
- *Maryland:* "CT is a very promising and very important technique."
- *Louisiana:* "It's nice to have a test that can make a diagnosis of coronary artery disease without having to do a catheterization. It's nice not to have to subject patients to the risks of catheterization, including heart attack."

One physician expressed some skepticism about current CT technology, however. The physician/physicist said, "There is a lot of interest and a lot of people investing a lot of money in it, and things have gotten a lot better with 64-slice. However, there is very little data to say it adds anything to current management techniques or is more cost-effective than conventional angiography. However, CT is a non-invasive technology…I see two major issues. One is visualization of the lumen size in calcification; you can't see through calcium, and that's a problem. The second thing is that nobody has shown good visibility of distal coronary territories. It's important to know if someone has distal disease. So there are a lot of issues to work out. You also have to look at the data already out – how many people were excluded, how many never made it to the cath lab, and there are I think some critical holes in the data. Another question is radiation." However, a CT research scientist said, "We have a study (not published) of 30 patients with highly calcified vessels. Only 9% of them could not be analyzed because of the calcification. The study was done with our Toshiba machine, and we think the key is the slice thickness of 0.5 mm, which no other machine has. So we think calcium is going to be a minor issue."

Most physicians said that reimbursement is a problem, but they were confident that reimbursement for coronary angiography will eventually be approved. Among their comments were:

- *Midwest:* "There is no CPT code for it; most payers are waiting for a statement from the AHA. At this point people are using different codes, so it's not specifically directed for coronary angiography, but that will change."
- *New York:* "Reimbursement is the $10 million question."
- *New England:* "Reimbursement is always an issue and we'll be watching carefully."
- *Alabama:* "We'll look at hopefully using CT for peripherals as well as coronaries. We'll continue to work out protocols and we intend to use it for low-risk patients. Finding the right person to evaluate will be the key."
- *Louisiana:* "There are a lot of questions about who's going to get reimbursed – radiologists or cardiologists. Between CT and MRI, CT scanners cost a lot more than other imaging technologies. A used nuclear scanner costs between $125,000 and $150,000, and CT is millions of dollars. So reimbursement is a big issue."
- *Ohio:* "We have to show CMS that we actually get better results and spend less money overall with CT; hopefully that will justify reimbursement."
- *Maryland:* "We heard today that the AHA is coming up with a letter that will address some of the issues regarding reimbursement. The scientific community has to convey that this is useful for MI and come up with some consumer guidelines for CT. If it does that, that will help change the mind of the government."

♦