Trends-in-Medicine

December 2002
By Lynne Peterson

SUMMARY

Cardiologists are excited about Schering-Plough's Zetia (ezitimibe), and many predicted that it would be even more popular with primary care doctors, but cost and managed care coverage may limit use, at least initially. ♦ Mixed data on Alexion's pexelizumab. The trial missed its primary endpoint, but there was an unexplained mortality, warranting further investigation. ♦ Unimpressive results from CV Therapeutics' trial of tecadenoson (CV-510). ♦ Strong positive results from The Medicine Company's REPLACE-2 trial of Angiomax (bivalirudin), but many interventional cardiologists remain leery of it. Most plan to try it, but uptake will be slow, with about 12% of cath lab patients getting Angiomax in 12-months. ♦ Pfizer's Inspra (eplerenone) is generating little excitement among cardiologists. ♦ Long-term post-procedure use of Sanofi's Plavix (clopidogrel) is gaining popularity.

Trends-in-Medicine
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American Heart Association
November 16-20, 2002
Chicago, Illinois

ALEXION/PROCTOR & GAMBLE'S pexelizumab

In a Phase II trial, pexelizumab (2 mg/kg) missed its primary endpoint, but it dramatically reduced mortality, a secondary endpoint, so there may still be some hope for it. The CARDINAL trial (a combination of the COMMA and COMPLY trials), looked at the effect of pexelizumab, a single chain antibody against C5 complement protein, on infarct size in 1,734 AMI patients getting either angioplasty or a thrombolytic.

CARDINAL Trial Results

Measurement	COMPLY (in Lytic patients) n=920	COMMA (in Angioplasty patients) n=814
Primary endpoint: Infarct size	At 72 hours: No statistically significant benefit to pexelizumab	No statistically significant benefit to pexelizumab
Composite endpoint: carcinogenic shock, death, stroke, CHF	No statistically significant benefit to pexelizumab: 18.6% placebo 18.4% pexelizumab bolus 19.7% pexelizumab bolus+infusion	At 90 days: No statistically significant benefit to pexelizumab: 11.1% placebo 10.7% pexelizumab bolus 8.5% pexelizumab bolus+infusion
Death	At 90 days no statistically significant benefit to pexelizumab: 9.4% placebo 11.2% pexelizumab bolus 9.7% pexelizumab bolus+infusion *	At 90 days a statistically significant benefit to pexelizumab bolus+infusion: 5.9% placebo 4.1% pexelizumab bolus 1.8% pexelizumab bolus+infusion * At 6 months a statistically significant benefit to pexelizumab bolus+infusion: 7.4% placebo 4.2% pexelizumab bolus 3.2% pexelizumab bolus+infusion *

* ($p<.05$ v. placebo)

Sources agreed that the mortality data is intriguing and likely warrant additional research, but since the mechanism of action for a death benefit is unknown, it may require additional research as well as a larger trial. A researcher said, "This effect on mortality not only appeared early, but became greater over time. It appears that there is something beneficial going on, we just don't understand the exact

mechanism yet." An expert said, "The findings create a lot of uncertainty about this agent. You have to be very cautious in interpreting the positive results in an endpoint with a very low event rate, such as reduction in death. The number of patients is small, so it could just be a chance finding. What is the mechanism? You need to know the mechanism to explain the finding, and that is usually a reduction in infarct size – which we don't have here. There may be some benefit that we don't understand, but we will need a good trial to determine that. This trial just raises questions."

AstraZeneca's Crestor (rosuvastatin)

There was nothing new about Crestor and little enthusiasm for this statin among sources at AHA. Comments included:

- A cardiologist said, "Crestor is a damaged product that will be a tough sell."
- A Netherlands doctor said, "I've used it in trials. AstraZeneca has an enormous research program, so Crestor will get used, perhaps taking 10% of the market in a year. It will mostly hurt Lipitor because Crestor and Lipitor have similar profiles. There is more data on simvastatin and pravastatin and people usually have a reason for being on those, so Crestor is likely to have less effect on them."
- A Connecticut doctor said, "I prefer pravastatin, but I'll use some Crestor if it gets approved."
- A Missouri doctor said, "It will be tough for AstraZeneca to sell Crestor because people are happy with Lipitor – unless Crestor is very inexpensive and gets on formularies."
- A U.K. doctor said, "Crestor 10 mg might be good, but I don't think doctors will push it."

Aventis' Lovenox (enoxaparin)

The TETAMI trial showed enoxaparin equivalent – but not better – than UFH in STEMI patients not getting PCI. There was no advantage to adding Merck's Aggrastat (tirofiban) to either UFH or enoxaparin in these patients.

Another trial compared the addition of either Lovenox (enoxaparin) or UFH to TNK-tPA in patients with MI in the pre-hospital setting, and Lovenox lost this one. Researchers concluded: "Pre-hospital (ambulance) use of TNK-tPA plus UFH appears as safe and effective as when given in-hospital. TNK-tPA plus Lovenox reduces in-hospital ischemic events but appears associated with an elevated risk of major bleeding and intracranial hemorrhage in patients (especially females) age >75." Aventis is starting the 20,000-patient EXTRACT trial, testing lower and different doses in elderly patients.

Bristol-Myers Squibb's Pravachol (pravastatin)

The PROSPER trial looked at 6,000-patients age 70-82, comparing pravastatin to placebo. A slight increase in cancer in the pravastatin patients took some of the shine off the otherwise positive news. The study found:

- No rhabdomyolysis problem.
- 48 patients need to be treated to prevent one event, and in the highest risk patients, only 25 need to be treated to prevent one heart attack, fatal or non-fatal.
- No benefit in terms of stroke reduction or cognitive function.
- Borderline significance (p=0.051) in TIAs.
- An increase in cancer in the pravastatin patients.

CV Therapeutics' tecadenoson (CVT-510)

The data looked good, but sources did not consider the results reliable. In the 181-patient TEMPEST trial (randomized but not blinded), all five doses of CVT-510 were significantly better than placebo in terminating induced PSVT. At the 2 lowest doses, most patients had to have a second dose for effect. The highest dose had transient AV block, and the middle dose had an excess of parasthesia. The principal investigator said the company has not decided what dose will be proposed for commercialization.

CVT-510 has a half life of 30 minutes. An investigator said the potential market is "several hundred thousand patients" annually.

Questions were raised about the FDA-approvability of CVT-510 based on this study. Among the issues are:

a. CVT-510 was not compared to standard of care (adenosine).

b. The trial was not blinded.

c. The trial design was described as "poor."

d. The principal investigator did not appear knowledgeable.

TEMPEST Results

Measurement	Placebo n=30	A n=32	B n=31	C n=29	D n=29	E n=30
Dose	--	75µg/150 µg	150/300 µg	300/7600 µg	450/900 µg	900/900 µg
Conversion of SVT	7%	50%*	59%*	90%**	83%**	87%**
Parasthesia	3%	0	10%	16%	0	3%
Flush	0	0	10%	3%	0	7%
Tachycardia	0	0	3%	7%	0	3%
Headache	0	3%	3%	7%	0	0

* $p<0.0005$

** $p<0.0001$

GENVEC'S Ad_{GV} VEGF121.10

The unblinded REVASC trial of gene therapy with Ad_{GV} VEGF121.10 (using adenovirus) administered by intramyocardial injection found:

- On the primary endpoint of time to onset of 1 mm ST depression on ECG, there was no benefit at 12 weeks, but there was a marked (and statistically significant) improvement at 26 weeks vs. control.
- Both secondary endpoints (time to onset of angina and total exercise time) were significantly improved at both time periods.
- There were no serious adverse events related to gene therapy itself.

THE MEDICINE COMPANY'S Angiomax (bivalirudin)

The REPLACE Part-2 (also referred to as REPLACE-2) data was one of the highlights of the AHA this year. The data was surprisingly strong, favoring the use of Angiomax over heparin during PTCA, and investigators claimed the trial will change the way cath labs operate, but interventional cardiologists were dubious, and Millennium officials were out strongly defending its Integrilin (eptifibatide) and raising questions about bivalirudin.

The double-blind REPLACE-2 trial compared heparin 65 U/kg as an initial bolus plus a planned IIb/IIIa to bivalirudin 0.75 mg/kg as an initial bolus and then 1.75 mg/kg/hour during PCI plus a provisional IIb/IIIa inhibitor at the operator's discretion. The trial was conducted at 233 hospitals in nine countries an enrolled 6,010 patients, including 4,658 in the U.S. The primary endpoint was the quadruple composite of death, MI, urgent revascularization, and major in-hospital hemorrhage. The secondary endpoints were death, MI or urgent revascularization. This presentation was 30-day data, but six-month and on-year follow-ups are planned. Researchers concluded, "This therapy is better than heparin and non-inferior to heparin+IIb/IIIa.

30-Day REPLACE Part-2 Results

Measurement	Bivalirudin	Heparin
Provisional use of a IIb/IIIa	7.2%	5.2%
ReoPro	3.5%	0
Integrilin	3.7%	0
Requiring a second bolus	2.9%	12%
Primary endpoint: the composite of death, MI, urgent revascularization, and major in-hospital hemorrhage	9.2% (p>.05)	10.0%
Death	0.2%	0.4%
MI	7.0% (nss)	6.2%
Urgent revascularization	1.4%	0.2%
Combination of death, MI, urgent TVR	7.6% (nss)	7.1%
Non-Q-wave MI	5.8%	6.6%
Major in-hospital bleeding	2.4% (p=.001)	4.1%
Minor bleeding	13.4%	25.7%
Transfusions	1.7%	2.5%
ICH	0	0.1%
Retroperitoneal hemorrhage	0.2%	0.5%
Sheath-site hemorrhage	0.8%	2.5%

A subset analysis of the patients who got a IIb/IIIa in both arms of the trial might seem to indicate that combining ReoPro with Angiomax is safer than combining Integrilin to Angiomax. However, experts warned that (1) subset analyses should be viewed with caution and (2) no conclusions can be drawn about how the IIb/IIIas compare in combination with Angiomax.

30-Day REPLACE Part-2 Results

Measurement	Bivalirudin	Heparin
Primary endpoint in patients receiving Integrilin	10.1%	8.8%
Primary endpoint in patients receiving ReoPro	9.8%	9.8%

Interestingly, half the patients in REPLACE-2 got clopidogrel, and a speaker suggested that may explain, at least in part, why bivalirudin did well in this trial, "It may have an antiplatelet function as well as an anticoagulation function."

The Medicines Company officials and researchers were stressing potential cost savings with bivalirudin. A speaker said, "The cost is less than $350, which is $100 less than Aggrastat and Integrilin and $600 less than ReoPro, suggesting this is a cost effective strategy even though it is more expensive than UFH. Sheath removal is important from a nursing and patient standpoint, and that begs the question: If you are pre-treating with this, early sheath removal will allow outpatient stenting in low-risk patients…We can ignore this data and continue with UFH and wait for more data, or we can embrace this as our antithrombotic strategy in lieu of a IIb/IIIa – or take a hybrid approach, using clopidogrel + bivalirudin for low risk patients and reserving a IIb/IIIa for high risk patients, such as those with thrombus in the artery under intervention."

However, some sources close to Millennium suggested Millennium most likely would lower its price to a large cath lab customer before losing that customer to Angiomax over cost. An interventional cardiologist (Dr. Jimmy Cheng) said, "If the cost of the IIb/IIIa and Angiomax were the same, the advantage would go to the IIb/IIIa."

Interventional cardiologists questioned about how REPLACE-2 will change operations in their cath lab offered a number of reasons most are very reluctant to switch to Angiomax, including:

- **Lack of antidote.** A Michigan doctor said, "There is no antidote to Angiomax. You can reverse heparin if you need to."

- **Drug eluting stents.** An Italian researcher (NOTE: Colombo) said he now uses a IIb/IIIa in 70% of his patients, explaining, "Drug-eluting stents are more thrombogenic. I had some cases of periprocedural thrombosis. With smaller vessels, more metal and possibly a costing risk, a IIb/IIIa is now routine in all drug-eluting stent patients, so you can't relay on heparin alone." He estimated that 70% of drug-eluting stent patients get a IIb/IIIa, which compares to a European average of about 15% of patients.
- **Cost.**
- **Bailout rate.** A New York cardiologist said, "I suspect there will be a higher bailout rate with Angiomax."

Twelve interventional cardiologists were asked about the outlook for Angiomax use. They estimated that in a year Angiomax would be used for an average of 28% of their angioplasty patients. This is skewed by two hospitals that plan to switch completely; among the rest, the average outlook is for 12% of patients to get Angiomax. Two doctors said they will not use Angiomax at all, but seven sources said they will try Angiomax to gain experience with it and see if it performs in clinical practice the same as in REPLACE-2. Following are some of the comments doctors made.

- *Virginia*: "I'll use a little, mostly patients at high risk for bleeding, those are the real niche for it...Unless there is a very clear advantage, you are just adding cost. Our hospital wouldn't save money with Angiomax because we don't use IIb/IIIas in our low risk patients, so Angiomax would raise our costs."
- *Florida*: "I'll try it in low risk patients."
- *New Jersey*: "Personally, I'll wait for something worth the money…My problem is that the majority of us no longer use ReoPro because of cost. We use Aggrastat instead because it is cheaper, so we won't have the same economic pressures as heavy ReoPro users. We are *not* walking away from REPLACE-2 saying, 'Wow' because when you look at the individual, not composite, endpoints, they don't all line up. There is no trial of Angiomax vs. Integrilin. Angiomax needs more data to back it up."
- *North Carolina*: "There won't be a wholesale switch, but clearly Angiomax is an advance in low risk patients where I feel comfortable not using a IIb/IIIa. Now, we will look at it in combination with a IIb/IIIa, but the cost of that combination will be an issue when we have to pay for drug-eluting stents."
- *California*: "I want a second study and a cost-analysis before I use it very much. I may try it in patients at high risk for bleeding."
- *Michigan*: "I may try it, but very little. Without an antidote, I won't use it even in low risk patients."
- *Illinois*: "We'll talk about using Angiomax, but I doubt we will use much. Low IIb/IIIa users will have more trouble with the Angiomax data, and I am a low IIb/IIIa user. I mostly have VA patients who come to the lab already on a drug. IIb/IIIa use won't go away, and we won't use Angiomax in the ED. In labs with low bleeding statistics, there will be less interest in Angiomax."

Three doctors said they plan to switch from heparin to Angiomax for most patients. A New York doctor said, "We were in REPLACE and we will switch to Angiomax…We won't replace Integrilin, just the heparin." A doctor at another New York hospital said, "We are switching 90% to Angiomax (except for total occlusions, which are 10% of procedures). We will use it with a IIb/IIIa as a bolus, which is less expensive. We did 200 patients and were impressed with the lower bleeding, and we confirmed that in 500 patients." An Ohio doctor said, "I switched to Angiomax a year and a half ago, and I'll try to switch our other doctors now. Angiomax is a way to save money and pay for drug-eluting stents. ReoPro users can use Angiomax to eliminate ReoPro, and that will save money."

As use of Angiomax goes up, sources expect use of closure devices to go down, but they also do not expect a sudden drop in closure usage. A cardiologist who switched completely form heparin to Angiomax said, "Angiomax could eliminate closure devices."

There was a very good turnout for a Millennium-sponsored dinner – and a stellar panel of speakers -- a few hours after the REPLACE data was released, but more than half the audience left before the talk had even reached its mid-point. Among the points speakers made about Angiomax, REPLACE-2 and cath lab practices that raise questions about the advisability of switching from heparin to Angiomax were:

- **ACT level.** Target ACT is supposed to be 200-250 for a patient to get a IIb/IIIa, but the median with bivalirudin in REPLACE-2 was 320. A speaker said, "This may explain the higher bleeding rate with bivalirudin. We need to see the REPALCE data in more depth."
- **Long-term results.** The Bivalirudin Angioplasty Trial (BAT) data looked good at seven days but the results did not hold up at 90 days, so a speaker insisted we are going to need to see longer term REPLACE data. "I'm also a little suspicious of someone telling me I can treat someone with bivalirudin for two hours and then shut it off, and you can prevent MIs. When MIs were shown in ESPRIT, they occurred out to 18-24 hours, so it would seem you have to treat longer than two hours…and there can be a rebound effect with bivalirudin."
- **Rebound.** "Heparin took quite a blow today in the REPLACE-2 trial…but I think when you look at this data, you have to be careful what population this is addressing…One of the problems with heparin is that

when you turn it off, that's when you see a lot of events. IIb/IIIas have been helpful in preventing that heparin spike by preventing some of that thrombin rebound. There also is some very good data that you actually turn down thrombin production with a IIb/IIIa. Direct thrombin inhibitors block the thrombin that is there, but a IIb/IIIa turns down the thrombin in the first place…Enoxaparin (Lovenox) also turns down production of thrombin…so the SYNERGY trial will be important."

- **Time to PCI.** "The median time it takes a patient to get to the cath lab varies by hospital. In facilities in the lowest quartile, it takes about half a day, which means that at least 70% of patients are waiting 12 hours to go to the cath lab."

- **LMWH.** "It might be better to inhibit thrombin upstream with LMWH rather than waiting for thrombin to be created and then block it with bivalirudin…The real competition for bivalirudin is LMWH."

- **IIb/IIIa platelet inhibition.** "Integrilin+clopidogrel is superior to bivalirudin (at the REPLACE dose) + clopidogrel and to heparin+clopidogrel in achieving >80% platelet inhibition during the first eight hours…Reduction in procedural-related ischemic events is associated with >80% inhibition of platelet aggregation during the critical time of PCI. Bivalirudin does not inhibit platelet aggregation more than heparin, and admin of clopidogrel 300 mg up to 30 minutes prior to PCI in conjunction with heparin or bivalirudin does not inhibit platelet aggregation optimally."

- **CRP.** The suggestion was that Integrilin – but not Angiomax --may help lower CRP. "New data on CD40 ligand indicates…IIb/IIIas may modulate its release….(and) Integrilin reduces inflammation in a way that ReoPro does not…It would seem that the CD40 ligand would stimulate a rise in CRP, but we have to hold off on firm conclusions until it is reproduced in a larger trial."

- **Combining bivalirudin with a IIb/IIIa.** "I would like to have seen a REPLACE arm with a combination of a IIb/IIIa and bivalirudin, which might have been a real winner." Another speaker said, "Maybe the right combination is a direct thrombin inhibitor and a IIb/IIIa."

PFIZER/PHARMACIA'S Inspra (eplerenone)

Pharmacia officials insisted eplerenone will not be launched in hypertension (despite FDA approval) until some time in 2003 – perhaps not until the heart failure data from the EPHESUS trial is available. However, Pharmacia officials also insisted there would not be a pre-release of the EPHESUS data before the American College of Cardiology in March 2003, but in late December 2002 Pfizer/Pharmacia announced that EPHESUS met all its endpoints. There was little new information on eplerenone at the AHA as everyone waited for the results of EPHESUS.

Thus, the biggest question about the EPHESUS trial is answered – the drug is effective. And these results were achieved despite:

1. A high number of patients (>75%) on both a beta blocker and an ACE inhibitor. This was a heavily pre-treated population, and beta blocker use in this trial was higher than the national average.
2. A relatively low use of digoxin.

Pfizer/Pharmacia still needs to present the safety data from EPHESUS, and doctors will be looking at it to be sure there isn't a hyperkalemia problem. However, concern over that issue has lessened.

The first EPHESUS patient was randomized December 27, 1999, and the last on December 31, 2001. The 6,642-patient trial was stopped at the end of August 2002, with 1031 deaths. The primary endpoints are (1) all cause mortality and (2) cardiovascular mortality plus cardiovascular hospitalizations. Secondary endpoints are: CV mortality, CV hospitalizations, all cause mortality plus all cause hospitalizations. Other endpoints include: new onset of AF, NYHA class, and quality of life.

The principal investigator in EPHESUS, Dr. Bertram Pitt, provided a glimpse of the patients in the trial:

- Mean age 64.6
- 71% male
- 90% white
- Mean EF 35%
- 32% diabetics
- 72% Q-wave MI
- Mean heart rate 74.8
- SBP mean 119.1
- Mean days from MI to randomization 7.3
- 7.8% prior hospitalization for heart failure
- History of:
  heart failure 14.7%, hypertension 60.4%, MI 27%

Concurrent medication use in EPHESUS was:

- 86% ACE inhibitors
- 74% beta blockers
- 87% aspirin
- 59% diuretic
- 15% digoxin
- 46% lipid lowering agent
- 44% statin
- 14% CCB
- 15% potassium supplement

EPHESUS Baseline Comparison

	RALES trial n=1663	EPHESUS n=6642
Mean age	65	67
Male	73%	71%
Beta blocker	11%	74%
ACE inhibitor	95%	83%
Digoxin	75%	14%

Eplerenone Adverse Events in the VG Hypertrophy Study

Adverse Event	Eplerenone	Spironolactone
Impotence	0	2.5%
Gynecomasty	0.8%	13.6%
Menstrual irregularities	0	9.3%
Female breast pain	0	16.1%
Hyperkalemia	0.5%	5.9%
Withdrawal due to adverse events	4.1%	8.4%

Other small but interesting facts that are emerging about eplerenone include:

- The potency of eplerenone is about half to two-thirds of that of spironolactone, so 100 mg eplerenone equals 50-70 mg spironolactone and 50 mg of eplerenone equals 25 mg of spironolactone.
- Spironolactone has a longer half life than eplerenone.
- A Japanese study found no hyperkalemia with a combination of spironolactone (75 mg) and carvedilol, and indicated there is an additive effect of the combination, but the patients were also on an ACE. An eplerenone researcher said this suggests eplerenone plus an ACE will be additive.
- A Japanese study found no hyperkalemia problem with eplerenone.
- Gynecomasty with spironolactone is partially reversible but not always. The mood disorders and impotence associated with gynecomasty are reversible, as is breast pain.
- Pharmacia officials said they believe eplerenone will do very well in Japan and France, where "spironolactone is huge and there is already strong interest in eplerenone."

Physician Perspective on Eplerenone

In hypertension, clinical cardiologists and heart failure experts at the meeting indicated they have little to no interest in eplerenone. All of those questioned said that any use in hypertension depends on how the drug performs in heart failure, despite FDA approval for hypertension. The reasons for lack of excitement in hypertension include:

- Cost
- Need for potassium monitoring
- Low current use of spironolactone. Where spironolactone is used, doctors said they will not replace it with eplerenone because of cost.

There wasn't much enthusiasm for eplerenone even among heart failure specialists. Not one doctor was excited about it, and all insisted they will use eplerenone only if EPHESUS is positive. They also said:

- They will continue to use spironolactone because it is cheap.
- Gynecomasty is not common.
- They will switch patients to eplerenone if they start to have side effects with spironolactone.

Among the comments doctors made about eplerenone were:

- Ohio heart failure specialist: "The drug will do pretty well – if EPHESUS is positive. I would consider using it in patients with both hypertension and heart failure, and in patients meeting the EPHESUS criteria."
- Illinois transplant surgeon: "I have one heart failure patient I will put on eplerenone when my pharmacy gets it. I would use it for males on spironolactone who (already) have gynecomasty, but it won't replace spironolactone because spironolactone is cheap. The problem in hypertension is that the label restricts the use in diabetics, which may be the best patients for it, and the requirement for potassium monitoring."
- An ED physician: "Eplerenone won't do well. It has a QT problem that will kill it."
- Washington clinical cardiologist: "I won't use eplerenone until the data is overwhelming. When and if I do, it might be in lieu of spironolactone, but cost will be a big issue."
- Maryland cardiologist: "Eplerenone is not even on the radar yet."
- New York clinical cardiologist: "Eplerenone will take a while to catch on. Spironolactone doesn't have that big a problem – and it isn't used that much. I won't use it in hypertension, but maybe in CHF."
- Another New York clinical cardiologist: "Eplerenone use depends on the EPHESUS results. I won't use it in hypertension; I don't use spironolactone now."
- An eplerenone researcher: "Even if eplerenone is approved for heart failure, I would still use spironolactone. It is cheap, gynecomasty is not a big problem, and we have a lot of experience with spironolactone."

HOFFMAN-LA ROCHE'S pro-BNP Test

The FDA approved Roche's pro-BNP test on November 15, 2002, the day before AHA started, and Roche officials were very excited about that, saying the test would be launched by November 22nd. Although a Roche-sponsored session the first day of the meeting was poorly attended, the doctors and lab directors who were there gave the test a thumbs up. A U.S.

speaker said, "pro-BNP and LVEF offer complementary prognostic information to improve risk stratification. N-BNP is a more powerful individual indicator than LVEF and independently predicts ischemic events in patients with impaired LV function and death and HF when LVEF is preserved."

A New Zealand cardiologist used BNP tests in a 70-patient trial to compare the beta blocker carvedilol to placebo in heart failure patients. He found that there was a benefit to giving carvedilol to patients with high BNP – but not patients with low or medium BNP. He said, "If you are struggling with adding a drug, this might help you make up your mind…Treatment of heart failure guided by N-BNP has value. We've changed to using the Roche assay.

This researcher is testing BNP-guided therapy a larger group of patients in the BATTLE-SCARRED trial, looking at LV function, age, co-morbidity, drugs, etc., in patients admitted to the hospital in decompensated heart failure or NYHA Class III-IV outpatients. As of September 2002, 153 patients were enrolled in BATTLE-SCARRED.

BATTLE-SCARRED
Preliminary 6-Month Results (first 75 patients)

Arm	Heart Failure Admissions	Deaths
N-BNP	5	0
Clinical	8	2

A German researcher also praised the value of pro-BNP tests. He said, "pro-BNP is as predictive as Troponin T with patients having a low Troponin T plus a low BNP having the best outcomes (in terms of death and MI)…In patients with unstable angina and no Troponin elevation, it has prognostic implications. Clinical stabilization is associated with a rapid and significant decrease in BNP levels."

Other interesting comments speakers made at this session included:

- "There is a role for both central lab and point-of-care testing. If you are using it in the ER for rapid decision making, point-of-care offers advantages, but if you have a well-standardized test with a rapid turnaround, like most blood tests, then there is some advantage to a lab-based test. And a lab-based test is better for a screening program."
- "There is high negative predictive value to pro-BNP, especially in the ER."
- "BNP testing is widely used in our ER, which is the biggest user, but it is also being used in the heart failure clinics and intensive care unit."
- "There is huge potential for application in the community for primary care practitioners. A rigorous study in New Zealand in 305 patients with 90 doctors participating found that BNP results improved the accuracy of diagnosis, mainly to rule out people who had been labeled as heart failure patients inappropriately…So, it is good for reassuring people that they didn't need to put patients on anti-heart failure therapy. There is huge potential for use by family doctors."
- Some hospitals will want to use both Roche's central lab test and Biosite's point-of-care test. "There are advantages and disadvantages to each. In our place (Cleveland Clinic), where the labs are heavily computerized, it is nice to have a lab-based definition because it goes in the patient's permanent medical record. On the other hand, a point-of-care test is extremely helpful in the clinic when you don't want a patient to walk to the lab and have delays."

SANOFI'S Plavix (clopidogrel)

The randomized, double-blind CREDO study of 2,116 U.S. and Canadian patients compared a 300 mg Plavix loading dose to placebo when administered 3-24 hours before PCI. Patients then got 75 mg Plavix daily for 28 days. After 28 days, patients in the loading dose group got Plavix daily out to 12 months and control got placebo. A researcher said, "This was the first randomized trial of long-term clopidogrel use in these patients. We found extending it on top of aspirin for one year instead of one-month was associated with a 27% relative risk reduction. We feel the clinical implications are potentially enormous…If the results of CREDO were applied to the 1.5 million PCIs annually world-wide, over 50,000 patients -- who otherwise would suffer a heart attack, stroke or death – would NOT."

Researchers reported no benefit to pre-treating patients with a 300 mg loading dose of Plavix if that loading dose was administered less than 6 hours before PCI. An investigator said, "Our hypothesis is that partial platelet inhibition is not enough, that we need full inhibition, so we need the full effect which takes more than six hours. Some centers are looking a

CREDO Results

Measurement	Clop 300 mg loading+75 mg/day clopidogrel for 12 months	Placebo loading dose +75 mg clopidogrel for 28 days
PEP-1: 28-day composite of death, MI, urgent revascularization	5.5% [18.5% relative risk reduction when administered 3-24 hours prior to PCI (p=.23)] [38.6% relative risk reduction when given >6 hours before PCI (p=.05)	6.9%
PEP-2: 1 year composite of death, MI stroke	8.5% [a 27% relative risk reduction) (p=.023)]	11.5%
Major bleeding at 1 year	8.8% (p=.07)	6.7%

using a 600 mg loading dose…I used to give a 300 mg dose at 8 a.m. and do the cath at noon. Now, I give 600 mg to outpatients, and inpatients get their Plavix the night before." Indeed, several sources said that is what they already are doing – using 600 mg when the Plavix loading dose can't be given more than six hours before PCI.

There also appears to be an added benefit to combining Plavix and a statin. Some doctors also believe that cardiac patients on aspirin should also be on Plavix.

However, a concern was raised about a potential issue with stopping Plavix. One source said, "The question is what we do with PTCA patients on Plavix who need to go to the dentist. What happens if we stop the Plavix?"

SCHERING PLOUGH'S Zetia (ezitimibe)

There was some real excitement at the meeting about this cholesterol absorbing agent, and there was standing room only at a Schering/Merck-sponsored symposium on Zetia. One commented, "People are excited to have a new mechanism of action."

Seventeen doctors were questioned about how they plan to use Zetia (Ezetrol in Europe). They estimated that in a year an average of 12% of their patients on cholesterol-lowering medications will be taking Zetia.

Many doctors commented that patients are somewhat nervous about side effects with statins, and some patients are resistant to increasing their statin dose, but most doctors insisted that patients aren't refusing statins. A New Mexico doctor said, "Some patients worry about liver problems. There is a lot of stuff on the Internet that statins will rot the liver, but patients listen to me."

The biggest factors likely to limit Zetia use are managed care coverage and cost, which Schering sales reps said is slightly less than $2 a day. The need to take two pills a day is not viewed as a real barrier to use. Prescribing Zetia for a patient already on a statin could add a second co-pay, and sources said patients are likely to resist that. Furthermore, increasing a patient's statin dose sometimes can be done at no additional expense to the patient or the payor because some higher dose statins are the same price as lower doses of the same statin. Most sources doubted that managed care would cover Zetia except (1) as monotherapy for patients who cannot tolerate statins (generally because of muscle weakness) and/or (2) combination therapy for patients who had not reached their cholesterol goal despite maximum statin therapy. They estimated that about 15% of their patients fall in these two groups, and those are the patients likely to get Zetia, at least initially. Yet, there is some early movement on the payor front: A Schering sales rep said Indiana Public Aid (Medicaid) already is covering Zetia without prior authorization.

Thus, for now, few doctors plan to use Zetia in lieu of titrating a statin. The exception was a Netherlands doctor who used Zetia in clinical trials who said, "With the limited data we have so far, it seems better to use a medium dose statin plus this than only a high dose statin, but cost is *not* an issue in the Netherlands."

Doctors repeatedly pointed out that statins have benefits over and above their cholesterol-lowering effects, and they do not intend to give up statins. However, lowering the statin dose and adding Zetia may preserve those "extra" benefits. In particular, cardiologists believe Zetia will appeal to primary care physicians. Following are some of the comments U.S. doctors made about how they will use Zetia.

- *Connecticut:* "I might use Zetia in combination with a statin, but not as monotherapy. I prefer Zetia to titrating a statin, but cost is an issue."
- *Maine*: "I'll use Zetia for patients on bile acid sequestrants, transplant patients, and patients not controlled at the highest doses of statins or who complain of muscle aches, whether real or not…I would also use Zetia with statins if the carriers would pay, but I doubt managed care will pay unless Zetia is a last resort."
- *Massachusetts*: "I will use very little initially because I don't know if the clinical benefit will be the same as with a statin. Statins do more than lower cholesterol."
- *Missouri*: "A lot of people have subclinical weakness that gets better off statins, and they will be candidates for Zetia."
- *Nebraska*: Schering needs to show a survival benefit with Zetia because statins improve survival, but 38% of patients don't reach goal with maximum statin therapy, and 5% can't take statins, so there will be a role for Zetia."
- *New Mexico*: "I'll play with Zetia and see what works, but I'll probably try maximum statin therapy first…Two co-pays are an issue with a lot of people."
- *New York:* "After six months, doctors will start adding Zetia before titrating the statin because Zetia offers more benefit than raising the statin dose does. I'll let a few people try it before I jump in, but I think Zetia may be a big advance."
- *Pennsylvania*: "I'll probably try Zetia before titrating a statin, but cost is an issue. A $10 co-pay is manageable, but the problem will be Medicare patients with no drug coverage. Samples and patient assistance programs will be important."
- *Virginia*: "I will *always* titrate the statin to maximum dose first…I'm not worried about patients refusing to take statins…Taking a second pill is not as big an issue as pharmas working on combination pills would have you believe."

- *Washington*: "Statins do much more than cholesterol-lowering, and that is what is exciting. I never add a second medication unless forced to do so, but toxicity issues with Crestor will help Zetia…Primary care doctors will use Zetia because they are afraid of statins."

Zetia is most likely to impact use of Lipitor rather than other statins, sources said. A Missouri doctor explained, "There is an FDA advisory on drug interactions with simvastatin (Merck's Zocor), so a lot of my patients -- and other internists -- don't want their patients on simvastatin." An Illinois doctor said, "I'd drop the Lipitor dose from 80 mg to 20 mg and then add Zetia, repeat liver testing in three months, and then increase the Lipitor dose if needed."

Other combinations with Zetia also are being suggested, not just statins.

- **Gallstones**. A speaker suggested one positive side effect to Zetia may be a reduction in gallstones, "Schering and Merck have not looked at cholesterol output in bile, but in experimental animal models, when you give Zetia, biliary output of cholesterol drops dramatically, so I would guess in humans – though it hasn't been studied yet – that it will significantly reduce gallstone formation."
- **Plant sterols**. Combining Zetia with plant sterols (e.g., Johnson & Johnson's Benecol) was described by one speaker as an interesting – and possibly additive -- approach for statin-averse patients.

WYETH'S P-Selectin Antagonist

Three trials have now concluded that there is no benefit in terms of rPSGL-Ig (recombinant soluble P-selectin glycoprotein ligand–immunoglobulin fusion protein) at either 75 mg or 150 mg. The PSALM trial was halted by the company after disappointing results (which have not yet been presented) in the HALT trial. PSALM researchers analyzed the results on the 88 patients that had been enrolled and concluded that, based on either perfusion or flow reserve data, there was no evidence of smaller infarct size at 5-10 days or at 30 days. One said, "There is no evidence for improved tissue reperfusion and/or infract size reduction with P-selectin inhibition. With the HALT-MI and LIMIT trials, these data further question the importance of the role of neutrophils in the reperfusion/injury process."

PSALM Trial Results

30 day Results	Placebo n=28	rPSGL-Ig 75mg n=30	rPSGL-Ig 75mg n=30
Infarct size (by PET)	5.5	4.7	6.4
Death	4%	0	0
Stroke	0	7%	0
Heart Failure	0	10%	7%
Reinfarction	4%	13%	0%

GENERAL TOPICS

Cardiac Resynchronization Therapy (CRT)

Biventricular pacing continues to gain popularity among electrophysiologists. A speaker said, "There is a growing database supporting use of CRT in heart failure, and there is a consistency of findings in the trials. Who should get CRT in 2002? Patients with NYHA Class III-IV despite optimal standard medical therapy, LVEF=35, and QRS of 120-130…I think it is hard not to agree with the effectiveness of CRT, and if you buy that…then it seems logical that high voltage therapy is the way to go." He estimated that:

- 250,000-300,000 U.S. patients meet the standard ICD criteria, excluding MADIT-2.
- Another 300,000 meet the ICD criteria with MADIT-2
- 750,000 meet the CRT criteria, and of these:
  - 600,000 meet the low-voltage criteria for CRT only
  - 150,000 meet the high-voltage criteria for a CRT+ICD

However, two speakers warned doctors against implanting the devices before aggressive medical management has been tried. One said, "Although quality of life appears to be reliably and importantly improved with these devices, it is not enough to just put one in – and that is a disturbing trend we are seeing at our hospital. Patients are not getting maximum drug therapy. It seems easier to put in a device." Another speaker cautioned, "If you put in a CRT in a Medicare patient without trying maximum medical therapy first, you could open yourself to a Medicare fraud charge."

CMS put off making a decision on how it will reimburse for ICDs. Sources predicted that use will increase, even if CMS decides to reimburse only for a subset of MADIT-II patients. An industry official (Guidant) said, "Even with MADIT-II, the numbers will be only about 16% of patients, or one-tenth what CMS and Wall Street analysts are worried about." An electrophysiologist said, "CMS subgroup approval actually could increase the number of implants by causing penetration to rise faster…But as more doctors make referrals, the numbers will increase and penetration will increase beyond 16%…And there will be huge criticism of CMS if it approves only a subgroup. The VA, Aetna, and Cigna already pay (according to MADIT-II criteria)."

Pericardial LV leads may be the way of the future, another expert suggested. He added, "We have no experience with them in people yet, but the concept needs exploration."

C-Reactive Protein (CRP)

CRP was a hot topic at the meeting. Speakers repeatedly emphasized that CRP is a more significant prognostic predictor than other markers, even cholesterol. An expert commented, "You can't pick

up a patient's LDL based on CRP level; they are independent markers." Another expert said, "Don't throw out LDL-C, but add CRP (testing)…CRP provides greater ability to gauge the risk of a well person. The best predictor is CRP and total cholesterol to HDL (TC:HDL)…CRP is a method to target statin therapy in primary prevention… Asked how doctors should use CRP today, he said, "If a patient were in the gray zone…I might measure CRP and use it as a tie breaker for pharmacotherapy…I am not sure CRP is a therapeutic target. It would be a mistake to walk away saying I'll measure CRP until it goes down. It is risk marker, not a therapeutic goal."

CRP Level	TC:HDL	Number of patients needed to treat to prevent a cardiovascular event*
High	High	62
Low	High	35
Low	Low	983
High	Low	43

*Based on a study of 27,000 patients comparing LDL-C and CRP

Drug-Eluting Stents: GUIDANT, BOSTON SCIENTIFIC, JOHNSON & JOHNSON, and more

AHA is not known as a stent meeting, but there were a couple of interesting things that came out about stents at AHA:

- A speaker described the ideal drug-eluting stent of the future as: self-expanding, degradable, MRI-friendly, high deliverability, and biologically friendly.
- Two leading researchers – Dr. Patrick Serruys and Dr. Ron Waksman – debated whether a drug-eluting stent should be used in all patients.

Pro: Dr. Serruys argued that medical liability will play a major role in driving usage. He said, "Before the end of 2003, you will use drug-eluting stents in all patients or face trial for malpractice."

Con: Dr. Waksman warned there is no 0% restenosis – and the audience applauded. He also pointed out that stopping Plavix is associated with a increased thrombosis rate, "What if a (drug-eluting stent) patient has a dentist appointment and stops Plavix? God forbid, patients on Plavix stop it and something happens….With 900,000 stents placed annually, and only 12% requiring re-intervention, why toxify 750,000 arteries that will never restenose?" He predicted that the FDA won't approve all the Cypher sizes. He also pointed out that only one out of 10 patients will benefit from Cypher.

BIOSENSOR

Data from Biosensor's FUTURE-1 trial was expected to be presented at the meeting, but it wasn't. An investigator said AHA rejected the abstract, wanting longer MACE data, but he insisted there is no problem in the trial. He said, "It looks very, very good. There are no problems." However, there will be FUTURE-2 and probably FUTURE-1 data at the American College of Cardiology meeting in March 2003. Interestingly, a source said Biosensors' total cost so far for its everolimus-eluting stent project is only $5 million.

Biosensor Trials

	Future-1	Future-2
No. of patients	27 DES 12 bare	90 total
Location	Single center, Germany	Multi-center, Europe
Stent diameter	2.75-4.0 mm	N/A
Stent length	18 mm	N/A

Biosensor reportedly has spent only about $5 million so far on development of its everolimus and everolimus plus programs. There is some concern about the protein-binding properties of everolimus, which is more lipophlic than sirolimus (rapamycin), and everolimus+ is even more lipophilic.

BOSTON SCIENTIFIC

Boston Scientific's TAXUS program is continuing to move ahead, and the data is holding up – so far.

TAXUS III Trial Results (with Nir stent)

Measurement	30 days	6 months (angiographic)	12 months (clinical)
MACE	3.6%	28.6%	28.6%
Death	0	0	0
Q-wave MI	0	0	0
Non-Q MI	3.6%	3.6%	3.6%
TLR	0	21.4%	21.4%
CABG	0	3.6%	3.6%

IGAKI-TAMAI

The company is just starting animal trials with its tranilast-eluting stent.

JOHNSON & JOHNSON

The company received two 483 manufacturing deficiency letters for the Cypher stent in September 2002, but an official insisted that these were answered with the complete response letter submitted to the FDA on October 21, 2002 and would not delay approval. However, J&J officials and other sources are talking more in terms of an April 2003 U.S. launch target, which is later than the January 2003 that had been suggested. A J&J official commented, "The FDA's CDER has been tougher and more involved in the process than we expected…There has been a lot of back and forth on the major deficiencies, but these are not serious issues."

J&J officials said they expect the FDA to approve more sizes than the advisory panel recommended.

Polymers

Following is some of the interesting information on polymers discussed at the meeting:

- A study found that the polymer (a methacrylate) in the Johnson & Johnson Cypher stent is biologically active in a dose dependent manner, not inactive as some experts had previously thought. Guidant is using a polyacrylate, but sources said that is likely to have the same biologic activity.
- Ceramic coatings may create an intimal hyperplasia response in the vessel wall after the drug is gone.
- Biosensor's drug is integrated into the polymer, so it is an asymmetric coating, and most of the drug and polymer are both gone after 90 days.
- The ideal polymer was described as: being bio-compatible, having controlled drug release over a given time period, having high carrying capacity, and with good adhesion.

Hormone Replacement Therapy

Once again the message was a warning against the use of HRT. AHA officials and researchers emphasized women should stop -- and not start -- HRT for cardiovascular prevention. A post-hoc analysis of high-risk women in Lilly's MORE trial of Evista (raloxifene) found a reduction in cardiovascular risk and strokes with raloxifene, but researcher said this is not enough to recommend preventive treatment with raloxifene.

Stents Beat Surgery

In the SAPPHIRE study, carotid stenting – using J&J's Precise stent and J&J's Angioguard distal protection system -- was shown to be superior to endarterectomy. This was the first trial to show superiority of intervention over surgery. It also showed value to distal protection.

Lytics + IIb/IIIas: GENENTECH, JOHNSON & JOHNSON

Adding a IIb/IIIa inhibitor to thrombolytic therapy has been shown in several trials not to have an added benefit, and the FASTER and GUSTO-V trials were no different.

- **Genentech's TNK-tPA**. The FASTER trial examined half dose TNK-tPA+varying doses of the IIb/IIIa inhibitor tirofiban (Merck's Aggrastat). Researchers concluded that the safety profile of the combination was acceptable, but there was no benefit in mortality prevention.
- **Johnson & Johnson's Retevase (rPA, reteplase).** The 16,000-patient GUSTO-V found that half dose rPA + abciximab (Johnson & Johnson's ReoPro) was neither inferior nor superior to rPA alone for reducing mortality (8.3% in both groups) at three years, though there was less recurrent ischemia. However, there were three subgroups that appeared to benefit from the combination: diabetics, patients age = 75, anterior MIs and patients treated >6 hours after onset.

NEWS STILL TO COME

2003

March: American College of Cardiology.

- Details on the results from the EPHESUS study of **Pfizer**/Pharmacia's Inspra (eplerenone) in ~6,200 patients with heart failure due to systolic dysfunction complicating AMI will be presented at ACC. The company so far said only that the trial met all its endpoints.
- There will be **Biosensor's** FUTURE-2 and probably FUTURE-1 data at the American College of Cardiology meeting in March 2003.
- Results from **Pfizer's** ASCOT trial of Lipitor.

2004

Pfizer's Lipitor (atorvastatin). TNT, a five-year, 10,000-patient trial comparing different doses (10 mg to 80 mg) of Lipitor to see whether there are different outcome benefits.

2004/2005

Pfizer's Lipitor (atorvastatin) and **Merck's Zocor (simvastatin).** IDEAL, a five-year trial in 8,888 CHD patients comparing Zocor 20/40 mg to Lipitor 80 mg. The primary endpoints are cardiovascular death and non-fatal MI, and the secondary endpoints are revascularization, stroke, and hospitalization.

2005

Merck's Zocor (simvastatin). SEARCH, a five-year, 12,000-patient trial comparing 20 mg simvastatin to 80 mg simvastatin.