Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Pfizer/Pharmacia's Inspra (eplerenone) convincing for heart failure, but the cost and need for hyperkalemia monitoring may make it a substitute for spironolactone but not expand the market very much unless Pfizer makes a real commitment to marketing it. Use of Scios/J&J's Natrecor was expected to continue to increase, but a study raised new concerns about safety that may chill use. Cath labs are increasing their use of The Medicine Company's Angiomax and several are planning to switch to it 100%. Schering-Plough's Zetia was shown to lower CRP and is gaining popularity. There is real excitement about AstraZeneca's warfarin replacement, Exanta, but not much about Crestor, Biovail's CCB Cardizem LA or Mylan's beta blocker nebivolol.

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In addition to the many presentations at the American College of Cardiology (ACC) annual meeting, 32 cardiologists were interviewed at the meeting about the outlook for various drugs. Their comments precede the data for each drug as it is presented: AstraZeneca's Crestor (rosuvastatin) and Exanta (ximelagatran), Biovail's Cardizem LA (diltiazem), The Medicine Company's Angiomax (bivalirudin), Merck's Aggrastat (tirofiban), Mylan's nebivolol, Pfizer/Pharmacia's Inspra (eplerenone), Schering-Plough/Merck's Zetia (ezitimibe), and Scios' Natrecor (nesiritide).

ASTRAZENECA'S CRESTOR (rosuvastatin)

Cardiologists expressed little enthusiasm for this drug. The idea of a "super statin" no longer has the appeal that it once had. An Illinois doctor asked, "Why do we need a more potent statin when it could only potentially lead to trouble? Crestor will be a hard sell because of the concern with rhabdomyolysis. Zetia has a better chance." A Missouri doctor said, "I'm not excited about Crestor; there's not a whole lot of benefit." A Massachusetts doctor added, "It will be a tough sell, but it's a big market. The company must focus on HDL." Another New England doctor said, "Crestor's value has been blunted."

Sources thought Crestor's ability to raise HDL would probably be its strongest marketing point. They generally agreed that Crestor will be a tough sell, but they also described AstraZeneca as a savvy marketer. Several sources pointed out that doctors and patients have become reluctant to up-titrate statins, and suggested they may be willing to try a similar or lower dose of Crestor before increasing the dose of another statin or adding Zetia. A source said, "Crestor simplifies the treatment options."

The results of the randomized, open label STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin) trial were presented, comparing rosuvastatin to atorvastatin (Pfizer's Lipitor), pravastatin (Bristol-Myers Squibb's Pravachol) and simvastatin (Merck's Zocor). In STELLAR, 2,431 patients with hypercholesterolemia (LDL-C =160 mg/dL and <250 mg/dL; triglycerides <400 mg/dL) were randomized to one of 15 treatment arms for six weeks.

STELLAR Results

Measurement	Crestor 10-40 mg	Lipitor 10-80 mg	Simvastatin 10-80 mg	Pravastatin 10-40 mg
LDL reduction	46% - 55%	37% - 51%	28% - 46%	20% - 30%
HDL increase	7.6% - 9.6%	5.7% - 2.0%	5.3% - 6.8%	3.2% - 5.5%

Statin	10 mg	20 mg	40 mg	80 mg
HDL increase				
Rosuvastatin	7.6%	9.4%	9.6%	8.5%
Atorvastatin	5.7%	4.8%	4.4%	2.0%
Simvastatin	5.3%	6.0%	5.2%	6.8%
Pravastatin	3.2%	4.4%	5.0%	---
LDL reduction				
Rosuvastatin	-45.8%	-52%	-55%	-58%
Atorvastatin	-37%	-43%	-48%	-51%
Simvastatin	-28%	-35%	-39%	-46%
Pravastatin	-20%	-24%	-30%	---

A New York doctor asked about Crestor patients with renal failure in STELLAR, and a speaker replied, "There were two cases at 80 mg; one was a woman in her 70s, and the other was a person in the 40s with a complicated medical history on a variety of concomitant medications. It was not rhabdomyolysis, but it is not clear what the etiology was. Both patients improved and recovered…This (renal failure) usually is not seen (in statin trials), but this was a large study.

ASTRAZENECA'S EXANTA (ximelagatran)

Data from SPORTIF-III, the first of two Phase III trials comparing Exanta, an oral direct thrombin inhibitor, to warfarin (Coumadin) was presented. Exanta proved non-inferior and in some analyses, it was even superior to warfarin. However, periodic liver testing is likely to be required for up to a year after Exanta is initiated.

More than two million people have atrial fibrillation (AF), mostly elderly. AF is associated with 75% of strokes (a 35% lifetime risk). Warfarin reduces the risk of stroke in AF patients by 60%-70% but causes bleeding and is difficult to manage. The average AF patient takes five or more concomitant medications, so warfarin is underutilized. Only about half the medically-eligible AF patients actually are taking it because of doctor and patient resistance. The oldest AF patients are at greatest risk of stroke (>50% of strokes occur in people >75 years of age), and these are the patients who find oral warfarin the most difficult to take.

SPORTIF-III was an open label, multinational trial of 3,407 patients that is expected to be used for CE approval. The primary objective of the trial was to establish non-inferiority of Exanta for prevention of strokes (ischemic and hemorrhagic) as well as systemic embolic events based on an intent-to-treat analysis. A researcher said, "We know warfarin is very effective if given well, but most patients can't tolerate it well over a long period of time…We wanted to show Exanta is at least as effective, more convenient and has less need for blood test monitoring. We found Exanta as effective as warfarin in preventing stroke and systemic embolic events, and it caused less bleeding than warfarin."

In a real-world setting Exanta might do even better, researchers suggested. Compliance was over 80% in both arms of the trial, and that was described as much higher warfarin compliance than is typically seen. A researcher said, "It is very difficult to keep warfarin patients in the narrow range of INR 2-3. Even good patients have a minimum of 12 encounters per year with the doctor's office."

Elevated liver enzymes (3xULN) were reported in 6.5% of patients, but researchers said that in most cases the abnormalities went away when the drug was stopped or even sometimes when it was continued. One commented, "The problem only occurs in the first six or eight months the drug is taken…Typically they occurred between two and six months into the treatment phase. In every case where there was an abnormality, there was something else that would account for it. We think it is a problem of early-on treatment. When we stopped the drug at that level, in all cases the levels returned toward normal…The liver elevations with Exanta are twice the problem with statins…but it is not an ongoing problem, just an issue for the first six to eight months."

The SPORTIF-III data needs to be borne out in the pivotal SPORTIF-V trial, a double-blind, randomized trial being conducted in the U.S. and Canada in 3,913 patients. The results of SPORTIF-V are expected at American Heart Association 2003, but they could be presented at the European Society of Cardiology meeting in September 2003. An expert said, "This is exciting data. You have to keep adjusting the dose of warfarin, and it's a constant battle to keep the warfarin at the right level. Contrast that with something you take twice a day. I think there will be a lot more use of anticoagulation in AF patients with this…Exanta will cost more...but you have to weigh that against the cost of the blood tests you otherwise have to do -- and the strokes prevented."

Asked how new point-of-care and self-tests for warfarin would affect Exanta, an Exanta researcher said, "Those will be helpful, but patients will still have to translate those tests to dose regulation, and that means contacting the doctor's office month after month. It's still an ongoing issue."

There doesn't appear to be any debate among doctors that Exanta will be easier to administer than warfarin. The issue will be the liver elevations, which are twice what happens with statins. A New York neurologist said, "The uptake of Exanta

will be slow. We have more than 50 years experience with warfarin. Safety is the issue with Exanta."

In considering the regulatory issues for Exanta, it might be useful to review the liver problems with Warner Lambert's Rezulin (troglitazone). At an FDA panel meeting on Rezulin in 1999 these points were made:

- The liver failure risk substantially declines after six to eight months of Rezulin therapy.
- There were no cases of death or liver transplantation after 11 months of Rezulin use.
- An FDA official put the risk of liver failure with Rezulin at one in 900 patients over a year, but the company claimed the risk was much higher, from 1:38,000 to 1:57,000.
- Liver monitoring was ineffective because patients didn't come in, doctors got sloppy, etc.
- The patients most at risk could not be identified. No clear-cut risk factors emerged, and the acute liver failure appeared to be unpredictable.
- FDA officials believed there was both a continuing long-term risk and a cumulative risk.

Liver Problems in Rezulin Clinical Trials

Trial Sponsor	Number of patients exposed	Jaundice cases	Hepatic deaths
Warner-Lambert	7,656	3	1
NIH	585	1	1
Sankyo	4,147	0	0
GlaxoSmithKline	3,203	0	0

BIOVAIL'S Cardizem LA (diltiazem)

Doctors also had little interest in Cardizem LA, comparing it to Covera HS. One commented, "There is certainly nothing wrong with that, but is it ground-breaking? No."

THE MEDICINE COMPANY'S Angiomax (bivalirudin)

The attitude toward Angiomax has warmed up since the American Heart Association meeting where the REPLACE-2 data was released. At that time, interventional cardiologists were leery of it. Most planned to try it, but the uptake was expected to be slow, with about 12% of cath lab patients getting Angiomax by late 2004. At ACC, two of 10 doctors interviewed about Angiomax said their lab was planning to switch to Angiomax 100%, and another two are considering doing the same thing. A Michigan doctor said, "We will be switching whole hog to Angiomax." An Illinois doctor said, "We are considering a wholesale switch to Angiomax because it is more reliable and has a short half-life, so it can be turned off quickly." An Ohio doctor said, "We are meeting next week to consider a wholesale switch. The data was impressive." Three doctors said their cath lab has not started using Angiomax, but all said they would start in the near future.

On average, these cath labs currently are using Angiomax for only 3% of patients, but sources predicted that in six to 12 months they would be using it for an average of 47% of patients. Thus, during the remainder of 2003, Angiomax use may increase much more dramatically than has been predicted.

MERCK'S AGGRASTAT (tirofiban)

The A-to-Z Trial (Aggrastat-Phase of the Aggrastat to Zocor Trial), sponsored by Merck, compared the safety of unfractionated heparin (UFH) with enoxaparin (a low molecular weight heparin) in 230 acute coronary syndrome patients. All patients in the trial got Aggrastat and aspirin (ASA). The trial proved non-inferiority, and there was even a consistent trend in favor of enoxaparin for all subgroups and for higher risk patients. However, there also was a trend to increased bleeding with enoxaparin.

Results of the A-Phase of the A-Z Trial

Measurement	Enoxaparin 1 mg/kg q12h n=2019	UFH (weight adjusted) n=1952	p-value
Primary endpoint: Composite of death, MI, refractory ischemia	8.4%	9.4%	p=0.27
Patients on treatment: Composite of death, MI, refractory ischemia	8.5%	9.5%	p=.89
Secondary Endpoints			
Death	1.1%	0.9%	N/A
MI	3.6%	4.4%	N/A
Refractory ischemia	4.0%	4.9%	N/A
Urgent revascularization	5.1%	5.2%	Nss
Total	12.6%	14.1%	Nss
Safety			
Bleeding	3.1%	2.2%	p=.093
Minor bleeding	0.9%	0.4%	N/A
Major bleeding	2.2%	1.8%	N/A

MYLAN'S nebivolol

There was little interest in nebivolol, a selective beta blocker Mylan hopes to introduce in the U.S. Nebivolol already is on the market in Europe, but cardiologists predicted it will be hard to differentiate or sell it here. One doctor said, "I'm not

too excited unless it has special effects in AF rate control – that might be useful." An Illinois doctor said, "I don't have any interest in it; it's not an advance." A New England doctor said, "I can't see it being more than a me-too." Another doctor said, "Nebivolol has been around a long time. It will be a tough sell, and sales will depend on how the company positions it."

PFIZER/PHARMACIA'S Inspra (eplerenone)

Four of 11 doctors commenting on eplerenone believe it is a major advance. A Massachusetts doctor said, "The evidence is that it's important." Another doctor said, "The data is impressive." A New York heart failure specialist said, "It is a pretty significant drug. It's hard to see why people won't be excited about it."

However, the other doctors weren't excited about eplerenone. One commented, "It's not a new drug." Another said, "The data is what I expected. It works. The lack of neurohormonal side effects is great, but I don't like the need to closely monitor the creatinine and hyperkalemia."

Doctors cited two reasons for not using more spironolactone, another aldosterone inhibitor – gynecomasty and hyperkalemia – but it was the hyperkalemia that most concerned them. A New York doctor said, "I use very little spironolactone – first because of hyperkalemia, and then because of gynecomasty." Another said, "The gynecomasty is not an issue." A New Jersey doctor said, "Hyperkalemia is the issue…NYHA Class III and IV patients don't live long enough to get gynecomasty." A fourth said, "I don't use much spironolactone because of the need to monitor for hyperkalemia." A fifth said, "Gynecomasty is not the issue; cost is."

Only four sources predicted that eplerenone would expand the market for aldosterone inhibitors. A Pennsylvania doctor said, "I'm not excited yet about eplerenone, but its use will grow." A New York doctor predicted, "The data will expand the use in heart failure – both early and middle – but not in hypertension." Another doctor said, "I'll use it in lieu of spironolactone for patients who can afford it. It will expand the market in CHF and hypertension."

Rather, most doctors plan to use eplerenone mostly as a replacement for spironolactone. An Illinois doctor said, "I'll use it in lieu of spironolactone. There will be very little market expansion." A New York doctor agreed, "I'll mostly switch existing spironolactone patients. Eplerenone won't expand the market." A Midwest doctor said, "Eplerenone will have a very difficult time, but there will be a lot of sue, and it's something new so it will find a niche." Another doctor said, "I may use eplerenone earlier than NYHA Class II or IV, but it won't change my use of aldosterone inhibitors much – and it may actually increase the use of spironolactone because of the cost issue."

Doctors generally agreed that cost will be a real issue for eplerenone sales. A New York doctor said, "I would use eplerenone in heart failure where spironolactone benefits, but I would start with spironolactone first because it is cheap." Another doctor said, "I would use eplerenone for males, but I'd have less interest in it for women because of the cost." A third said, "The data is solid, but eplerenone is expensive. I won't use it if it's significantly more expensive than spironolactone."

4E Eplerenone Study in Hypertension

Measurement	Eplerenone 200 mg	Enalapril 40 mg	Combination: of eplerenone 200 mg and enalapril 10 mg
Number randomized	64	71	67
Withdrawals	21.9%	19.7%	16.4%
Add on therapy required to maintain BP	30%	59.3%	20.4%
Blood pressure changes	Down 12.1%	Down 14.3%	Down 14.3% p<.05
Change in LV Mass by MRI	Down 14.5%	Down 19.7 grams	Down 27.2 p<.05
% change UACR from baseline	Down 24.9%	Down 37.4%	Down 52.6%
Hypotension	1.6%	2.8%	1.5%
Hypokalemia	0	2.8%	0
Potassium ≥6.0 mmol/L	10.9%	2.8%	4.5%
Cough	3.1%	14.1%	9.0%

At a Pharmacia-sponsored dinner on aldosterone in hypertension speakers made several interesting points, including:

- Post the ALL-HAT trial, the number of patients on a thiazide diuretic is expected to increase substantially, and studies have shown that there is an additive effect of Inspra and a diuretic, but there is not enough data yet to say the combination is synergistic.
- The stopping point in EPHESUS was 1,012 deaths, and there were actually 1,031, of which 1,019 were adjudicated. These include: 352 sudden cardiac deaths, 171 MIs, 229 progression of heart failure, 52 strokes, 66 other CV, 108 non-CV, etc.
- A speaker noted that Inspra is not being recommended as a monotherapy for heart failure because all of the trials to date have been on top of an ACE. He said, "It's clearly a tantalizing idea…but you would have to demonstrate that

by studying them head-to-head, and I don't think that will ever be done because ACE is standard of care, and it would be unethical to do a study without an ACE." However, monotherapy could be an option in hypertension.

- Eplerenone might be useful in lowering CRP, though the value of lowering CRP has not yet been proven.

The EPEHSUS trial comparing 25-50 mg of eplerenone to placebo was powered to show an 18.5% reduction in total mortality, assuming 15% deaths in the control group. The trial did not reach an 18.5% reduction, but the control group only had 13% deaths. The trial was positive for eplerenone and did reach statistical significance.

EPHESUS Safety Results

Adverse events	Eplerenone 25-50 mg n=3319	Placebo n=3113
GI	19.9%	17.7%
Gynecomasty	0.5%	0.6%
Menstrual disorders	0.4%	0.4%
Impotence	0.9%	0.9%
Metabolic disorders	17.2%	19.2%
Hypokalemia	8.4%	13.1%
Hyperkalemia	5.5%	3.9%

EPHESUS Efficacy Results

Measurement	Reduction with eplerenone over placebo	p-value
Primary endpoint #1: Total mortality	15%	p=0.008
Primary endpoint #2: CV mortality/CV hospitalization	13%	p=0.002
Secondary endpoint #1: CV mortality	17%	p=0.005
Secondary endpoint #2: Total mortality/total hospitalization	18%	p=0.02
All cause mortality in patients on an ACE or ARB + beta blocker	27%	N/A
All cause mortality in patients on an ACE or ARB + beta blocker+ASA+statin	26%	N/A
Sudden cardiac death	21%	p=0.03
Sudden death in patients with EF<30	33%	p<.05
Patients hospitalized for HF	15%	p=0.03
Episodes of hospitalization for HF	23%	p=0.02

The subgroup analysis of total mortality was relatively uniform in favor of eplerenone, but there were a few subgroups (not specified) where there was a signal of an interaction with eplerenone, but the researcher (Pitt) dismissed these because none of them were significant for the other co-primary endpoint.

An EPHESUS researcher said the problem for eplerenone is whether Pfizer will make a real commitment to this drug. He said that decision has not yet been made. He also indicated that Pfizer/Pharmacia would be talking to the FDA when the heart failure data is submitted, and will try to get an idea of what kind of label is likely in heart failure. At that point, Pfizer will make the decision whether to launch in hypertension or wait for the heart failure label. He described the hypertension label as "terrible," and said how much effort Pfizer puts into eplerenone will depend on the heart failure label.

In terms of time frame, the researcher said that no action by Pfizer on eplerenone is expected for at least six months or longer. Pharmacia officials would not (and indicated they did not know) when eplerenone would launch. The eplerenone researcher seemed really discouraged about the outlook for this agent with Pfizer, saying that Pfizer wouldn't push it unless it was going to be a billion dollar drug, and he said it doesn't look as if it will be that big. A Pharmacia marketing official said, "Our team is working hard to get ready for the (FDA) filing. We hope to say it is filed soon in the U.S. and the world. In the interim, we are looking at a potential approach to making the drug available to specific patients in need *(NOTE: he indicated this would be an expanded use or compassionate use type program)*…We are looking at approaches for those physicians who identify patients who they believe are candidates, so that there will be an approach prior to approval for them to get the drug, but we don't have any details on this program yet."

Interesting points made about eplerenone: There is no change in body weight. One life is saved for every 50 patients treated. The benefit was similar whether the patients were ischemic or non-ischemic. In the EPHESUS trial 55% were ischemic and 45% non-ischemic.

There was a 1.6% absolute ***increase in hyperkalemia*** with eplerenone, but a 4.7% ***decrease in hypokalemia***. One patient died from hyperkalemia, but it was a placebo patient. Dr. Pitt admitted the hyperkalemia is a concern but he felt that doctors (and perhaps the company) can find ways to better select patients to avoid hyperkalemia. He said, "If you ignore the exclusion criteria, prescribe too high a dose, don't monitor serum potassium or don't adjust the dose, you can get in trouble. If you are going to use a potent drug like this and not monitor it, you will get in trouble. There is no doubt in my mind that you can get in big trouble if you don't watch what you are doing, but I think this is a great drug that saves lives."

Asked what happened to patients who developed hyperkalemia, Dr. Pitt said, "If it was over 5.5, we looked to see if there were any contributing factors. If not, then we down titrated the drug. And if it got to 6.0, we withheld the drug, and sometimes we could give it back again and sometimes we couldn't."

A researcher said EPHESUS could have negative implications for CRT/CRT-D use, suggesting eplerenone should be tried before a device is implanted, "Although ICDs may be helpful in these patients, I doubt they will be cost-effective compared with this reduction in mortality…If you put a defibrillator in, it would be effective but you would have to put a lot of ICDs in to save one life, and that is very expensive…This (eplerenone) will make those costs go through the roof, so maybe our friends in government should think about things more. I think ICDs are useful, but I think we need to find a subset where there is a high enough risk to do it. We heard the COMPANION data, and that is reasonable…that they were effective…but it will be very expensive per QALY. We think there is still room for defibrillators, but you have to learn which of the people are still at risk of sudden death…There were some clues from T-wave alternans...but I think we should pause and learn how to pick these people out before we rush to do them (ICDs) on a large scale…I don't think ICDs will be cost effective unless we do a little more to find the high-risk subsets. We had one clue today, and I think we can find others."

The moderator at the EPHESUS presentation commented that he was "troubled" that there was no benefit to eplerenone in 1,500 patients who were not taking a beta blocker or the 900 patients who were not taking an ARB. The presenter responded, "We need to look at the data in detail, which we haven't done yet, but the relative lack of efficacy in patients not on an ACE, ARB or beta blocker might reflect the selection criteria for those patients and might reflect the reasons they are not on one of those drugs."

Asked about the differences between spironolactone and eplerenone, a researcher said, "There is no evidence spironolactone was effective in patients post-infarct…so we did a placebo-controlled trial, which was correct. Our guess is that aldosterone blockade is similar whether you use spironolactone or eplerenone. The main difference is in the side effect profile. There is no increase in gynecomasty or breast pain with eplerenone. In the RALES trial, we would have expected a 10% increase in gynecomasty and a marked increase in menstrual irregularities with spironolactone…If you are dying of heart failure, maybe these things are not important, but in asymptomatic patients, they are more important…Very few doctors choose to use spironolactone because of the side effects, so this drug has the potential to extend benefits to a wider group of patients, and hopefully, it will have a great impact."

How long should eplerenone be taken? The principal investigator said: "You should monitor ejection fraction, and if it is low, then keep the patient on the drug indefinitely, but if the patient's ejection fraction recovers then use it short term (one year or less)…The one group of hypertensives in which eplerenone may be useful are the 7%-10% of patients who get hypokalemic on a diuretic; eplerenone could be added to the diuretic in those patients."

SCHERING-PLOUGH/MERCK'S Zetia (ezitimibe)

Most doctors questioned are already using Zetia, not only as monotherapy for patients who can't tolerate a statin, but also for patients who haven't reached their cholesterol goal on a statin, who complain of muscle aches or who are reluctant (or resistant) to titration of a statin. A New England doctor said, "I titrate Zocor because the cost of 40 mg is the same as 80 mg, but some patients can't tolerate the higher doses, and that's when Zetia is valuable." A Missouri doctor said, "I use Zetia primarily in combination with a low dose statin…Use will increase. Cost is an issue, but not a limited factor so far." Another doctor said, "There is a big problem with patients who think they have muscle aches – false muscle aches -- and Zetia is good for those patients."

Doctors predicted that Zetia usage will continue to increase. For patients with drug coverage, they did not consider cost much of a barrier to use, and they did not think the two-pill regimen was discouraging patient willingness to take Zetia. Doctors generally said that managed care coverage of Zetia has not been a problem.

Zetia scored points in three analyses presented at ACC. In the first, a 12-week, randomized, double-blind, placebo-controlled study of 578 patients with primary hypercholesterolemia showed Zetia reduced mean CRP more than placebo and more than simvastatin alone at any dose.

Change in CRP by Baseline CRP Value

	Simvastatin Monotherapy 20-40 mg n=34	Zetia + Simvastatin N=66
<1 mg/L	33.3	---
1-3 mg/L	-18.2	-37.8
>3 mg/L	-32.5	-41.0

A second double-blind study showed Zetia+simvastatin lowered LDL cholesterol better than simvastatin alone. This was a study of 100 patients with heterozygous familial hypercholesterolemia, coronary heart disease or two or more cardiovascular risk factors, comparing. Patients were titrated up from 20 mg to 40 mg simvastatin, with the dose of simvastatin doubled again after four or nine weeks if the LDL cholesterol level was still >100 mg/dL. The study showed that adding Zetia to ongoing treatment with simvastatin provided significantly greater reductions in LDL cholesterol than doubling the dose of simvastatin alone.

A third study evaluated whether adding Zetia to low-dose statin therapy would lower LDL cholesterol as much as adding it to high-dose statin monotherapy. This was a meta-analysis of four 12-week, Phase III, double-blind, placebo-controlled studies with a total 540 patients with primary hypercholesterolemia. Patients were randomized to placebo+simvastatin 10 mg or to Zetia 10 mg plus one of these statins: 10 mg Zocor, 10 mg Lipitor, 10 mg Pravachol or 10 mg Mevacor. These were compared to placebo plus one of these statins: 80 mg simvastatin, 80 mg Lipitor, 40 mg Pravachol, or 40 mg Mevacor. Pooled data from eight different treatment arms showed that the addition of Zetia to low statin doses provided similar effects on LDL cholesterol, HDL cholesterol and triglycerides as high-dose statin monotherapy.

A Merck official indicated that the combination pill of simvastatin/ezitimibe (Zocor/Zetia) is expected to be launched in June 2004. This may be a little sooner than many people had expected.

12-Week Study of Zetia

Measurement	Placebo n=62	Zetia 10 mg n=55	Simvastatin (all doses) n=232	Zetia 10 mg + Simvastatin n=229
Baseline				
HsCRP	1.8	2.4	2.5	2.8
Triglycerides	265	271	265	264
LCL-C	177	181	179	176
HDL	53	51	51	50
With Treatment				
HsCRP	N/A	N/A	2.15	1.8 (p<.05)
Mean change in CRP	+11.5	+1.2	-18.2	-34.8 (p<.01)
Triglycerides	1.2	-11.2	-20.4	-30.2
LCL-C	-0.5	-18.3	-37.1	-51.4
HDL	1.0	5.5	7.2	9.7

Scios's Natrecor (nesiritide)

Clinical cardiologists and heart failure specialists questioned at the meeting generally agreed that that use of Natrecor will continue to increase, not dramatically but gradually and steadily. At least that was the opinion until a poster was presented that suggested that Natrecor may increase mortality. The poster attracted quite a crowd and the findings, while only suggestive, not conclusive, may have a chilling effect on future Natrecor usage.

The poster was a retrospective analysis of two previously published studies (VMAC and PROACTION) with a total of 735 patients, and they found a trend toward increased 30-day mortality with nesiritide, compared to nitroglycerin (7.3% vs. 3.9%). The researchers warned that the trend appears to continue out to six months, and they called for a mortality trial. Another expert said, "The p-value was not significant; it was only a trend. There was a small number of patients drawn from two studies. It is provocative, and it is a 'hint' of a negative mortality effect. There has never been a mortality study of Natrecor."

This study may slow Natrecor usage growth. An expert said, but people who know the biology and physiology won't be affected."

Sources said that Johnson & Johnson and Scios do not appear interested in doing a mortality trial, but researchers have approached NIH to do such a trial. The Heart.org quoted a researcher as saying, "Until such a prospective mortality trial proves the safety of nesiritide, its use should be considered only when a combination of diuretics and nitroglycerin proves inadequate…Mortality trials should be standard for acute heart failure drugs just as they are for chronic heart failure drug. I am not claiming to have proven anything, but I am saying that these data are a signal about a possible increased risk with this drug that needs to be pursued."

After ACC, the Heart.org polled cardiologists, asking, 'Do you think nesiritide should be used in acute heart failure only when a combination of diuretics and nitroglycerin proves inadequate?" ***Yes***, said 66% of poll respondents.

A cardiologist discussed how doctors at his hospital handle what he called "wet and warm" heart failure patients. He said, "All of us use IV diuretics. Beyond that, most commonly: 10% get nitroglycerin, 6% dobutamine, 7% dopamine, 8% Natrecor, and 3% milrinone." He suggested using Natrecor in the following patients:

- Instead of milrinone and dobutamine, when additional therapy is needed in "wet and warm" patients.
- When high dose diuretics will be needed.
- As an alternative to IV nitrates and nitroprusside.
- Perhaps in patients with renal disease for hemodynamic and symptom relief.

The FUSION trial is ongoing, testing the value of Natrecor in an outpatient setting. A knowledgeable source said there is a rumor that the FUSION outpatient study will be "positive but not overwhelming."

Drugs that Failed in Heart Failure

Drug	Reason for Failure	Examples
Endothelin	Not shown effective and in two trials worsened heart failure for the first few months of treatment.	Tracleer (Actelion, bosentan)
Cytokine antagonists	Results of RENEWAL trial of Enbrel and ATTACH trial of Remicade were both disappointing.	Enbrel, Remicade

A speaker said he thinks that initial data on both natriuretics (e.g., Scios' Natrecor) and aquaretics look very encouraging. He said, "If they are successful, they would be used in conjunction with loop diuretics to control volume and normalize electrolyte abnormalities." However, he does not think a meaningful inotropic drug is on the horizon. This speaker was excited about aldosterones in general, more than Inspra (eplerenone) specifically. He said, "The good news is that aldosterones have been shown to have value in both the RALES and EPHESUS trials…So, now in NYHA Class II and III patients I think we will see an algorithm like this -- even without a randomized clinical trial: Diuretic, followed by ACE inhibitor, then beta blocker, then aldosterone.

He also pointed out some other key things doctors should keep in mind in treating heart failure:

- **Optimize conventional therapy, especially the use of diuretics**. He said, "If you don't get volume right, almost everything else you do doesn't work very well."
- **Treat anemia.** He said, "This may be important and there is increasing interest in doing so."
- **Correct supraventricular arrhythmias.** He said, "I don't mean convert. It is better to leave AF alone and control the ventricular response and anticoagulate than to take any other approach."
- **Discontinue drugs that can exacerbate heart failure**. Drugs to avoid in heart failure include: glitazones, CCBs, anti-arrhythmics, NSAIDs (including Cox-2s), centrally acting sympatholytics, TNF-inhibitors, and endothelin antagonists.

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