Trends-in-Medicine

September 2001
By Lynne Peterson

UPDATE ON
CHOLESTEROL LOWERING MEDICATIONS
from
XXIII EUROPEAN SOCIETY OF CARDIOLOGY
Stockholm, Sweden
August 31-September 5, 2001
and
DRUGS AFFECTING LIPID METABOLISM (DALM)
New York, NY
September 9-10, 2001

SUMMARY

AstraZeneca's *Crestor* (rosuvastatin) was shown to be more effective than Pfizer's *Lipitor* (atorvastatin), but safety questions remain. The recent withdrawal of Bayer's *Baycol* (cerivastatin) – and the lack of a clear understanding of what caused the problem with cerivastatin -- has made doctors and regulatory authorities nervous about new agents, so the outlook is for a possible delay in approval of *Crestor* and a slower-than-expected launch.

Schering Plough's cholesterol absorption inhibitor, ezetimibe, may be the big beneficiary of the *Baycol* withdrawal. The drug was shown to lower cholesterol either as monotherapy or in combination with a statin, with no serious side effects, and it may be more appealing to doctors than a "superstatin."

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For subscription information, contact

Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
561-334-7409 • 800-589-5018
Fax 561-334-0856

www.Trends-In-Medicine.com

Physician Attitude

Cardiologists in Europe as well as the U.S. bemoaned all the bad publicity about the withdrawal of Bayer's *Baycol* (cerivastatin), and they said they are being inundated with patient telephone queries. They emphasized the value of statins in general and defended their use, pointing out that they save far more lives than are lost.

European cardiologists appeared to find the withdrawal of cerivastatin a good excuse not to prescribe the more expensive *Lipitor* (Pfizer, atorvastatin), and every European doctor questioned said it will be hard for AstraZeneca to sell *Crestor* (rosuvastatin) in Europe. A Swedish doctor said, "I've been over-run with patient calls. I use simvastatin (Merck's *Zocor*) mostly, but some *Lipitor*. I wouldn't use any *Crestor* until it has been on the market a long time." Another Swedish doctor said, "Simvastatin and pravastatin (Bristol Myers-Squibb's *Pravachol*) have been proven to save lives. We are concerned about cerivastatin and about other statins that have not been proven in major clinical trials to save lives. All statins lower cholesterol. That is not the issue. Saving lives is the issue. You don't have to worry about traditional statins. You can keep on using them, but when a new drug comes on, you don't want surrogate endpoints, you need hard endpoints."

American doctors were less negative about *Lipitor*, but most said they plan to prescribe more of Bristol-Myers Squibb's *Pravachol* or *Zocor* in the future. No source plans to increase *Lipitor* use, and most sources said they will approach use of *Crestor* very cautiously. A doctor at ESC said, "If *Crestor* is approved, I probably will try it, but only for patients who fail to respond to other statins."

Clinicians also were questioned at both meetings about whether they would use *Crestor* if it were approved today, and they were remarkably uniform in their

responses – NO. They all insisted they would wait for more long-term safety data before using much if any *Crestor.* A few said they might use *Crestor* for patients who couldn't take another statin or who failed more than one other statin, but none of *Crestor* very cautiously. A doctor at ESC said, "If *Crestor* is approved, I probably will try it, but only for patients who fail to respond to other statins."

Atorvastatin

Several sources predicted that *Lipitor* is not out of the woods on this issue yet, and a Pfizer official said the FDA currently is reviewing all the company's *Lipitor* data "with a fine tooth comb." Some Pfizer speakers have been emphasizing that the rhabdomyolysis event rate is lower with *Lipitor* than with other statins, but other experts pointed out that there have been more total cases of rhabdomyolysis with *Lipitor* than with pravastatin or simvastatin. Bristol-Myers Squibb also released a new safety analysis of 25,000 pravastatin patients, and the chief scientific officer of the American Heart Association praised that data, saying it represents about 200,000 patient years.

Cerivastatin

One of the key topics of discussion at the ESC this year was the cause of the cerivastatin problem. Numerous theories were proposed, but none emerged as the predominant theory. As a reminder, most, *but not all*, deaths were in patients taking concomitant gemfibrozil, even though that combination was contraindicated. Even Bayer officials are not certain which theory is correct.

Bayer's withdrawal of *Baycol* (cerivastatin) was the silent attendee at the DALM meeting. While *Baycol's* problems were not directly the topic of lectures, several speakers made reference to the issue, offering some insights into how troubling this is for doctors, patients and the other statin manufacturers. A German doctor said, "Cerivastatin led to lot of confusion among patients, undermining their sense of the security and safety of medications and the necessity for lifelong intake. This is true for all the statins. The active agent has increased in potency and become inherently more dangerous. Incidents with serious consequences are unavoidable despite the trials. Statistics in Germany indicate 1.5 billion prescriptions are written per year, carrying a risk of 75 million cases of side effects. These can be harmless or fatal organ failure. In the view of the multiplicity of undesirable side effects, doctors have been forced to make a

decision – and this is more difficult because the side effects often mimic disease that appears spontaneously. Because of all the warnings pharmaceutical companies issue with data sheets, the rate of side effects should have dropped

precipitously, but this has not been the case. Perhaps physicians are not sufficiently aware of the possible complications or didn't heed the warnings with enough care. In my opinion, the dramatic increase in side effects is due to more and more people taking more and different drugs – more drugs taken simultaneously will lead to more and varied side effects. It is estimated that in Germany, 500,000 adverse events occur annually. Of these, 25% are unpredictable, but the other 75% are dose-dependent and predictable. Most experts believe >50% of these events -- if not 80% -- could be avoided by circumspect attention by doctors. It has been postulated that our doctors are not well-versed in applied pharmacology. At least that's true in Germany. … Even if we succeed in individualized drug therapy for each patient, an element of risk will remain. The responsibility lies not only with doctors but also with patients themselves. Most patients prefer easy therapy -- popping a pill is easier than changing lifestyle."

A U.S. cardiologist said, "Cerivastatin is bothering many patients. Three trials – West of Scotland, CARE and LIPID (a secondary prevention trial) – were carried out on pravastatin. Before these trials began, investigators agreed they would pool the data afterward, and a number of papers appeared, and four are in press now describing these nearly 20,000 patients. What is interesting is that the day that cerivastatin was taken off the market, a doctor put into the mail a manuscript (which hasn't been accepted yet) describing the safety of pravastatin. We have data on 90,800 patients with a median follow-up of five years. That's 110,000 patient-years of pravastatin and placebo. There was not a single case of rhabdomyolysis in either group. CPK elevations >5x ULN were found in 23 patients on pravastatin and 24 on placebo. There were 6% malignancy on pravastatin and 5.9% on placebo. The drug was extremely well tolerated. The only significant difference we observed in this study: more patients went off placebo than off pravastatin. So I'd like to leave with the message: when you are bombarded by patients and physicians -- the track record of the other statins is really terrific. Pravastatin is extremely well documented. The clinical evidence is there, and we should be practicing evidence-based medicine. Many, many more patients -- perhaps hundreds of thousands of patients -- have had their lives extended than the few tragic instances with one statin."

Theories include:

Synthetic. Cerivastatin, like atorvastatin, fluvastatin (Novartis' *Lescol*) and rosuvastatin, is a synthetic statin. In contrast, simvastatin and pravastatin are natural statins. At an ESC-sponsored press conference, a Swedish doctor proposed this theory and said it is the reason he will use only natural statins in the future.

Liver metabolism. The chief medical officer of AstraZeneca suggested that cerivastatin is different and unique in that it has liver specificity and more peripheral action, "Most statins are absorbed, go into the liver and are metabolized. The majority of cerivastatin bypasses the liver and goes to the periphery."

Dual pathway. Cerivastatin, atorvastatin and rosuvastatin are excreted through both the kidney and liver. Pravastatin and simvastatin are secreted only through the liver. A Bayer official suggested that the renal involvement may be part of the issue. Another expert said, "Fibrates are mainly excreted by the kidney, and cerivastatin also is more excreted that way, and mild renal impairment may be a factor in induced myopathy."

Plasma level. Bayer officials suggested that cerivastatin, particularly at the higher dose, is found at higher levels in plasma.

Hydrophilicity. Cerivastatin is the most hydrophobic of the statins, which means it passes through the blood brain barrier the easiest. Pravastatin reportedly is the least hydrophobic (most hydrophilic). Atorvastatin is somewhere in the middle, and rosuvastatin is closer to pravastatin, sources said.

Cytokine P450 (CYP450) *Pathway*. The active metabolic pathways for cerivastatin, simvastatin and lovastatin (Merck's *Mevacor*) but not pravastatin or rosuvastatin. Many other common drugs also utilize this pathway, including verapamil and erythromycin. A speaker said, "Statins are efficacious and safe, and they will be used more, but there are new challenges, mainly because the statins are being used more and more in aging populations in combination with other drugs, and sometimes they are not studied carefully. Over a five or six year period, at least half of statin patients are likely to receive concomitant drugs metabolized by CYP450.

Simvastatin

In contrast to *Crestor,* where the HDL benefit appeared to disappear with time, Merck presented data on simvastatin which indicated its HDL benefit increases over time.

Simvastatin 80 mg

Time period	Total cholesterol	LDL	HDL
6 week	-37%	-46%	+10%
3 months	-38%	-46%	+10%
6 months	-39%	-47%	+10%
1 year	-39%	-47%	+14%
2 years	-39%	-48%	+19%

AstraZeneca's *Crestor* (rosuvastatin)

Without a good explanation for the mechanism by which statins cause rhabdomyolysis, the regulatory outlook for *Crestor* appears gloomy. Several sources predicted that *Crestor* would be delayed but not outright rejected by the FDA.

A *Crestor* investigator said that AstraZeneca has been asked to do additional studies on *Crestor,* including drug-drug interaction studies, but AstraZeneca's chief medical officer denied this. He said the company has not been asked by the FDA to conduct any additional tests (not safety, drug-drug interaction or other trials) since cerivastatin was withdrawn, and he insisted AstraZeneca does not plan to do any additional tests that are not required, "We stand on the 5,000 pages we submitted to the FDA." Asked why *Crestor* shouldn't have the same adverse event problems as cerivastatin, he said, "It is important to monitor and look for things, particularly after cerivastatin, but the

cerivastatin side effect seemed to be extremely isolated to that drug. … It was a very isolated effect. There is, to me, no particular concern about any of the other statins or *Crestor*, but of course we have to watch this closely."

Asked if *Crestor* can really be called a superstatin when the comparison was to 20 mg atorvastatin, the chief medical officer said, "We compared the recommended starting dose the two statins. Now, we will look at other dose comparisons. It seems that rosuvastatin-wise, we are achieving an LDL effect which is about 6%-8% higher than atorvastatin and is and maintained over all dose ranges."

A Swedish researcher presented the 12 week and 52 week (Trial 4522IL/0026) efficacy data on *Crestor* at ESC, but the details on the 52-week safety were not released until the DALM meeting in New York on September 10, 2001. That safety data was a pooled analysis of Phase II and Phase III rosuvastatin trials. In placebo-controlled trials of 936 patients (647 rosuvastatin, 289 placebo), 55% of patients on the drug and 53% of placebo patients had at least one adverse event. In all controlled phase II/III trials (n=3747 patients), the most frequent side effects were flu syndrome, headache, myalgia, pain and pharyngitis.

Crestor Pooled Side Effects

AE category	Rosuvastatin N=2579	All statin comparators* N=1275
All Adverse Events	63.6%	64.9%
Non-fatal serious AEs	3.4%	3.2%
AEs leading to death	0.2%	0.2%
AEs leading to withdrawal	3.9%	4.5%
AEs considered drug-related by investors	20.2%	22.7%

*comparators were atorvastatin, pravastatin, and simvastatin

AstraZeneca officials spent hours answering questions at the DALM meeting. Asked how rosuvastatin is different from cerivastatin, one official said, "*Crestor* has more cell, selectivity, particularly for the liver. It also is the most hydrophilic. There is less drug-drug interaction because it does not utilize the CYP450 pathway. Excretion is mostly by the liver; only 10%-15% of excretion is renal. The feeling we have is that the safety is comparable to other statins."

Comments made by sources about the *Crestor* safety data presented at DALM:

- There were no p-values. An ASTRAZENECA official said that was deliberate and would not be provided.
- The *Crestor* overall numbers, (3,747 patients) might have been fine for a me-too drug, but following a recall, it looks like a very small sample.
- There were no demographic subgroup analyses.
- HDL levels declined over time, so the HDL benefit may not be sustained.
- The safety poster displayed was slightly different from the abstract. In the abstract, it said that all the myopathy occurred in patients started on the 80 mg dose, but on the poster, it said myopathy also occurred in patients who were titrated up (from 20 mg) to 80 mg without regard to goal.

Crestor Data

Measurement	Atorvastatin 10 mg (n-140)	Rosuvastatin 5 mg (n-138)	Rosuvastatin 10 mg (n-134)
12-week data			
LDL-C reduction	-39%	-46%	-50% *
HDL increase	+65%	+65%	+8%
Trigylcerides	-16%	-15%	-19%
52-week data			
LDL-C reduction	-44%	-47%	-53% *
HDL increase	-1%	+2%	+4% **
Trigylcerides	-19%	-20%	-21%
Patients reaching International goals	87%	88%	98%
High risk patients reaching International goals	61%	65%	97%
52-week safety data			
Any adverse event	75%	74.3%	69.7%
Drug-related adverse event	35%	29.4%	26.5%
Serious adverse events	6.4%	2.9%	9.1%
Withdrawal due to adverse events	8.6%	5.9%	6.1%
Adverse event-related deaths	0	0	1.5% (2 patients)
ALT >3xULN	3 patients	0	2 patients
Myopathy	0	0	0

** p=<.001 ** p=<.05*

Crestor Trial 0028 Results

52-week Data	Simvastatin 20 mg (n-120	Pravastatin 20 mg (n=116	Rosuvastatin 5 mg (n-121)	Rosuvastatin 10 mg (n-115)
LDL-C reduction	38%	32%	N/A	48%
Medium risk patients reaching goal	75.8%	61.8%	79.3%	85.7%
High risk patients reaching goal	29.6%	5.9% *	84.2%	71.4%
All patients reaching goal	72.5%	60.0%	88.1%	87.5%
Patients reaching goal without titration	50%	31%	N/A	79%
mean change in LDL-C	-37.9%	-31.6%	-41.6%	-48.0%
HDL increase	6.2%	4.5%	4.5%	~7%
Triglyceride reduction	N/a	N/A	N/A	N/A
Any Adverse event	85.8%	69.5%	86.2%	86.1%
Serious Adverse events	10.0%	~5%	8.9%	7.8%

*indicates a particular figure may not be reliable

Anther point made about *Crestor*: The drug has a rapid effect, and after two weeks of treatment about 90% of the effect was obtained in all arms.

FDA

An FDA official discussed the agency's concerns with statin safety. He said (his emphasis in italics):

- "Our approvals are based on a finding that a drug is safe and effective *when used according to the label*. This implies that the FDA stance on appropriateness for the marketplace may change after marketing when off-label use and risk rear their heads. The failure of labeling is a major focus for the agency, and it may delay or prevent approval. We are dealing now with congestive heart failure risk and PPARs and the interaction of *Posicor* (Hoffman-La Roche, mibefradile) and the statins."
- "Labeling should reflect the expected benefits and risk, but is not a promotional tool. Approval and labeling may imply efficacy (and safety) beyond what has been specifically documented. The FDA has the power of approval to convey a sense of efficacy and safety for a drug. This leads to a statement of principle that surrogates must be validated as markers of treatment reduction." Outside of the

meeting, the official indicated that the FDA will not approve a statin for use only in selected patients populations, as it has done with other drugs in the past, "If it can't be approved for all patients, we won't approve it."

- Is diabetes a new target for statins? He offered three answers to this:
  1. Diabetic dyslipidemia already has been addressed. (Presumably, he means with other agents.)
  2. Clinical outcome data would be needed across different classes.
  3. Though we concede there is tremendous pre-sumptive evidence of the value of statin therapy in these populations, the acceptability of lipid sur-rogates for approval and endorsement depends on the potential for counterbalancing risks (e.g., mixed PPARs). In some instances, these may carry or appear to carry counterbalanced cardiovascular risk. So, to the extent that treatment of dyslipidemia is intended only to reduce cardiovascular risk, it is obvious that more definitive endpoint data is needed."

- "*Baycol* was an easy one for us. It would appear that the risk profiles of the rest of the class are similarly markedly lower than that of cerivastatin."

- Lower goals and larger target populations will be required going forward, particularly with respect submissions for:

a. Higher doses of new and existing drugs to lower LDL.

b. Combination therapy for:
statin+resin
statin+novel LDL lowering agents
statin+niacin
statin+fibrate
statin+mixed PPARs, CETPi, MTPi, ACATi, etc.

From the FDA perspective, *Baycol* had:

- Unique potency – 100 times lovastatin per mg
- Large exposures (1000s) at lower doses premarket without a signal. "There was no rhabdomyolysis, though there were CK elevations at 0.8 mg, with older females apparently more prone to problems. In retrospect, ALT>10x ULN might have been a warning, and that led to a label warning against older women."
- A marked increase in reporting for fatal rhabodmyolysis relative to other statins that voluntary contraindications with *Baycol/Lopid* didn't completely solve.
- "The FDA post-marketing people looked at the reporting rate for fatal rhabdomyolysis for atorvastatin and cerivastatin – two drugs that came to market one year apart, with nearly complete marketing overlap. There was five times the number of rhabdomyolysis cases for cerivastatin than atorvastatin, and in that marketing interval there were 15 times the prescriptions of atorvastatin. Our epidemiologist established a crude reporting odds ratio – the odds of having a report in our data base based on prescription numbers, and there was a 30-40 fold higher ratio for cerivastatin. So, this was an open and shut case."
- Data in women and the elderly. The question is whether AstraZeneca has this. The average age in the pivotal trial was ~48, and AstraZeneca officials said they had no demographic subgroup analyses and would not be presenting any to the FDA. Asked for a description of the *Crestor* patients who had an ALT>3x-5x-10x ULN, officials said they didn't have that. When reminded that the FDA probably will require it, one said, "We will give it to them, but we don't have to give it to you or make it public, and we don't intend to do that." The obvious conclusion is that there is some problem in the data.
- Large exposures skewed towards the highest proposed doses. "We we will push sponsors to higher doses."
- Follow-up >1 year in at least 200 patients
- Data in statin-naïve cohorts.

Killer items for a new drug application would include:

"Any myopathy signal may make the *dose* un-approvable or necessitate further exposures to elucidate the nature of the risk."

"Any one case of rhabdomyolysis would make a new statin unapprovable."

Combination therapy comments:
Resins: "Dispense with them. That combination is dose sparing for statins and doesn't raise new safety issues."

Novel agents: "It is conceivable that a combination may be dose-sparing for both, and that would be something good. But there is a big IF. Clearly, we would need to consider the safety profile of a new agent, have significant combination clinical studies (for endorsement by the FDA by way of approval), and interaction studies to look at the pharmacokinetic data as a potential signal for a risk of rhabdomyolysis."

- **Statin+niacin**: "Not a new topic. They are not dose-sparing for either drug. These drugs target diff fractions. The rhabodomyolysis warning remains, pending more definitive information. It is our position that this should remain in the labeling pending more information, and that sets the bar very, very high. If the risk of rhabdomyolysis, for example, from any given statin in the generally-treated population for discussion is 1:10,000 and if a factor (e.g., niacin) increased the risk to 1:1,000, then an exposure of 3,000 patients will have 95% power to see one case, and seeing one case does not make an increased risk. One can generate no conclusions from that. So, very, very, very large exposures are needed to dispel or prove this fear. Right now, this relies on observational data and likely will for along time to come."
- **Statin+fibrates**: "Dose-sparing for neither. There is an augmented risk of rhabdomyolysis. The risk may be worse with gemfibrozil than with fenofibrate (Abbott's *TriCor*). Interaction studies are needed to weigh a decision on combination use. But the rhabdomyolysis warnings stay.

New indications for monotherapy:
- HDL as a stand-alone therapy. Same as triglycerides. "An HDL increase may be salutary, and we've allowed labeling to convey expected benefits with a disclaimer that there is no independent effect on CHD risk." Monotherapy would require patient population studies of:
  - → Isolated low HDL
  - → Low HDL/high TG
  - → Elevated LDL
  - → Biochemical effects -- Total HDL, apolipoproteins, HDL functionality, reverse cholesterol transport
  - → Atherosclerosis progression
- Triglycerides as a stand-alone indication: "Previously, the FDA has allowed the inclusion conclusion of a statement that a given drug will lower trigyclerides as a statement of expected (additional) effects. That will continue. Whether there is a place for this indication as a stand alone statement of expectation of risk for CHD remains to be proven."

An FDA official was asked about the "background" incidence of myalgia with lovastatin. The questioner said, "We found 30% of patients had myalgia with or without CK elevation. There was tremendous noise in the system. How do we deal with that?" The FDA official responded, "With all due respect, it is not our issue to deal with. …It is important to establish for the field a sort of criteria short of rhabdomyolysis -- CK elevations that are signals. In the past we talked of ALT >5xULN or 10xULN, and the signal probably was there for *Baycol*. We need some refinement in this area to reassure people we know what we're doing with these drugs."

Asked what constitutes a myopathy "signal," the FDA official said, "For *Baycol* 0.8 mg, where in retrospect at a dose of the drug comparable to the middle range doses of approved drugs, we saw a signal that was 50% of the cases in the *Baycol* program were in older women – that that should have told us it was a pattern, not sporadic CK elevations. And it was seen at a dose that was not impressive compared to what was on the market. And we have not seen similar signals for these other drugs."

Asked what definition of rhabdomyolysis the FDA is using, the official initially said, "The post marketing definition includes renal failure." However, he later corrected this to say renal failure is not required.

Miscellaneous

Brigham & Women's Hospital has a patent on a C-reactive protein (CRP) test that can be used to help identify people who might be the best candidates for statins, which could make it easier to use statins as preventive therapy. No company has yet licensed this technology, and it needs a large study to validate it, but manufacturers reportedly are in discussions with Brigham & Women's about it.

INTERESTING TIDBITS ON OTHER TOPICS

Cholesterol Absorption Inhibitors

Schering Plough's ezetimibe (SCH58235) was described by several speakers as "having promise." It was described as "a potent inhibitor of intestinal cholesterol absorption that, unlike pancreatic lipase inhibitors like orlistat (Hoffman-La Roche's *Xenical*) does not affect the intestinal absorption of fatty acids or fat soluble vitamins." It reportedly has a very, very low drug-drug interaction potential, has a half-life of more than 24 hours, and a rapid onset of action (<90 minutes). It does not matter at what time of day it is given, and it can be taken with our without food.

In a Phase II monotherapy trial, ezetimibe (at doses from 1 mg to 40 mg) was compared to 40 mg lovastatin. At 10 mg, the dose that is being developed, there was an 18.5% reduction in LDL-C, and an increase of 4.9% in HDL. In the 12-week, pivotal, Phase III trial of 827 patients, the primary endpoint was efficacy in lowering LDL-C from baseline. It met that endpoint and had a small but statistically significant increase in HDL as well. The safety profile was similar to placebo.

Two posters at DALM on **Pfizer's avisimibe** raised questions about the efficacy of this agent.

Measurement	Atorvastatin	Avisimibe	Combination
18 week data			
LDL	-18.5%	+5.9%	-22.3%
Total cholesterol	-17.5%	+4.1%	-22.4%*
HDL	-6.3%	-5.2%	-11.3%
Period 1 (6 week data)			
LDL	-13.9%	+5.3%	-23.55
Total cholesterol	-14.0%	+3.3%	-22.8%*
HDL	-2.2%	-8.0%	-11.6%
Total cholesterol: 8 weeks			
500 mg	---	-4.8%	---
250 mg	---	-1.8%	---
Placebo	---	-0.7%	---

Pharmacia's Eplerinone

This is a novel selective aldosterone receptor antagonist (SAR) with low affinity for androgen and progesterone receptors. In rat studies in normalized blood pressure equally with verapamil and spironolactone. Initially, it is intended as a replacement for spironolactone, to be administered concomitantly with an ACEI or an ARB. A researcher said, "Monotherapy with an ACEI or an ARB is often inadequate in achieving blood pressure control, and neither adequately suppresses aldosterone long-term. Aldosterone has independent deleterious effects, including increased blood pressure."

New data from a pivotal, 350-patient, Phase III trial (in Europe, S. America and the U.S.) was presented at the meeting on eplerenone's effect on blood pressure in patients with mild to moderate hypertension (Diastolic pressure ≥95, systolic pressure <180). Diabetics were excluded form this trial. Eplerenone was found to significantly reduce systolic blood pressure in patients currently treated with an ACEI, and significantly reduce both systolic and diastolic blood pressure in patients on an ARB. Researchers concluded, "Eplerenone is effective and safe when concurrently administered with either an ACEI or an ARB in patients with mild-moderate HTN whose BP is not controlled by monotherapy. It seems that eplerenone is better added to an ACE than to an ARB, but mechanistically, it is hard to explain why that should be."

There will be additional new eplerenone data at the American College of Clinical Pharmacology (www.accp.com) meeting (October 21-24, 2001, in Tampa FL) on hormone values and subsequent BP response. Side effects were minimal and there was less incidence of gynecomasty with eplerenone than with spironolactone.

Cox-2 Inhibitors

Cardiologists all are aware of questions that have been raised about the cardiac toxicity of the Cox-2 inhibitors in general and Merck's *Vioxx* (rofecoxib) in particular. While they pointed out the incidence is small, they believe it is real, and they believe it is a class effect.

Most cardiologists questioned said they do not want to use Cox-2s any more unless absolutely necessary, and they are discouraging their rheumatology colleagues as much as they can. One commented, "My rheumatologists really have to convince me now to use a Cox-2." Another said, "If *Vioxx* is pro-thrombotic, it is a class effect even though *Vioxx* is more specific than *Celebrex* (Pharmacia, celecoxib). *Vioxx* has a longer half life (about 11 hours compared to about 6 hours with *Celebrex*). Where *Vioxx* may be different, is that it may have more of a problem with blood pressure than *Celebrex*." Another cardiologist indirectly mentioned the blood pressure issue with *Vioxx*: "If you give a Cox-2 alone to patients in the age group prone to coronary heart disease, it is less effective. … It appears the Cox-2s also are able to adversely affect renal function, which is an important issue for patients in heart failure. So, there are some concerns about safety, and some of them increase blood pressure -- not dramatically, but measurably so. You can use them if you watch the patient carefully in terms of blood pressure and renal function."

European doctors indicated there will be little use of Cox-2s there for the foreseeable future. More importantly, leading American cardiologists also predicted that Cox-2 use will go down, perhaps significantly. A New England doctor said, "Cox-2 use will go down because of physician concern but even more because third party payors will become even more adamant about limiting their use or requiring failure on a traditional NSAID first."

Endothelin-1 Antagonists

At a session on ET-1 antagonists at ESC, sponsored by Actelion, speakers reviewed some of the non-selective ET-1s under investigation. There are about 40 of these compounds in development, but the leaders probably are:

GlaxoSmithKline's enrasentan. "In ENCORE, enrasentan was not effective in the treatment of heart failure, and it was associated with adverse clinical effects. Maybe the dose was too high."

Takeda's TAK-044

Genentech/Actelion's tezosentan, an IV agent. In the pivotal RITZ1 study – tezosentan did not meet the primary endpoint, and a speaker suggested that may be due to different patient populations in the two groups. He also speculated that a lower dose may provide a better benefit:risk ratio, "Maybe the drug just doesn't work, but I don't think that will be the answer. There also was no hemodynamic verification by catheter of the illness." Several other trials are ongoing.

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10701 S. Ocean Drive #693
Jensen Beach FL 34957

Actelion's *Tracleer* (bosentan), an oral agent. The results of the pilot REACH-1 study are available, but they have not yet been published. The drug decreased hospital stays in severe CHF by 37% and days in the hospital by 53%. An expert said, "Clinically, the drug is very effective, and the adverse events profile looked quite good. Liver function was a problem, though; 16.5% of patients had ALT≥3xULN, compared to 5.2% for placebo, and this turned out to be dose dependent." Another speaker said, "In the REACH-1 trial, bosentan showed a steady improvement in clinical status out to six months. Those results have not been replicated with other ET-1s in other trials." Another speaker said, "There is a benefit to adding (Actelion's) bosentan to an ACEI, and the combination may be synergistic."

ACE Inhibitors

Several studies have suggested a negative interaction between ACEIs and aspirin, and data at ESC appeared to confirm this. In one study of 174 congestive heart failure (CHF) patients, readmission to the hospital occurred in 8% of ACE-only patients and 12% of ACE+ASA patients. Researchers concluded: "Patients with long-lasting CHF receiving ACE+ASA therapy are more likely to develop fluid retention and renal function deterioration." However, the moderator of the session did not agree with the presenter's conclusion, commenting, "Your conclusion is not well-grounded, but it needs to be followed up. There also is a question of dosing."

In addition, a poster at ESC suggested ACE use at the time of stenting increases the risk of in-stent restenosis by about 10%.