Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Devices reviewed include:

Among the drugs reviewed are:

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There wasn't as much new data At this meeting as usual, but there was still a lot of interesting information on both drugs and devices.

DEVICES

BNP TESTING

ESC guidelines already recommend use of BNP testing in the diagnosis of patients with dyspnea. However, a marketing battle is emerging over what test to use to measure BNP. Not surprisingly since this was a European meeting, Roche made a strong showing.

The BASEL study (BNP for Acute Shortness of Breath Evaluation), sponsored by Biosite, looked at patients presenting to the ER. It found that rapid BNP testing reduces the time to hospital discharge. The trial, which was sponsored by Biosite, also found that BNP testing reduces total treatment cost, time to adequate therapy, hospital admission rates, and ICU admission rates – without impacting 30-day outcomes.

BASEL Trial Results

Measurement	Clinical Group n=227	BNP Group n=225	p-value	Relative Risk Reduction
Primary Endpoint #1: Time to discharge	13.7 days	10.6 days	P=.009	23%
Primary Endpoint #2: Total treatment cost	$7,264	$5,410	p=.006	26%

The BASEL trial lost some of its marketing impact when the principal investigator said his testing was done entirely in the central lab and commented, "We checked to see if was more time consuming to do the test in the central lab than at the bedside, and we felt it was more efficacious to do it in the central lab."

A BASEL researcher offered several interesting comments about BNP testing:

- About 50% of patients in the BNP group were in the "gray area" of 100-500 pgs, where "BNP adds something, but is by far not as helpful as in other areas."
- He believes the use of BNP testing will expand. Another expert commented, "This is one of many presentation at this meeting, indicating that there should

be considerable expansion of BNP testing in acute patient and outpatients. The results are consistent among many abstracts at this meeting."

CLOSURE DEVICES

Closure devices got little attention at the ESC meeting. The only patch on display in the exhibit hall was from a new player – Medafor, a private company. Medafor has entered both the U.S. and European market with an interesting patch to compete with the other patches: Medtronic's Clo-Sur PAD, Marine Polymer Technologies' Syvek patch, Abbott's Chito-Seal, etc.

Mechanical devices were on display. St. Jude/Kensey Nash's **AngioSeal** appear to be doing well in Europe, and sources inside and outside the company (even competitors) expect them to continue to grow European sales. In contrast, a Datascope official said sales of VasoSeal have plateaued in Europe. Doctors continue to like Perclose, though the cost is too high for many European doctors.

CRT AND CRT-D

A new analysis of Guidant's COMPANION trial was done for the ESC meeting. The presenter said the results from a preliminary analysis are not qualitatively different from the locked data set which will be available shortly. The analysis, comparing 308 optimal medical therapy (OPT) patients with 617 CRT patients and 585 CRT-D patients, found a statistically significant benefit in favor of CRT-D.

However, there was a higher than expected event rate in the control arm (68% instead of the expected 40%). An expert said, "Clearly, this probably contributed to the positive result of the study and the early termination. There was no clear response for CRT alone, and the absence of significant influence of heart failure etiology on the mortality reduction by CRT-D. This is a surprising but very interesting finding. Thus, COMPANION has to be considered as primarily an ICD (plus CRT) study in heart failure with ventricular dystrophy. COMPANION does not provide any clear response on the global clinical impact of CRT alone."

Preliminary COMPANION 12-Month Results

Measurement	OPT n=308	CRT n=617	CRT-D n=585
Primary Endpoint: Death or any hospitalization	67%	35.8%	39.5%
Secondary Endpoint: All cause mortality	19%	23.9%	43.4%

IVUS

IVUS is being used increasingly, especially for anti-sclerotic drugs. An IVUS expert said, "The FDA is recommending that everyone who wants to get an anti-sclerotic drug approved use IVUS, telling them they can do morbidity and mortality in Phase IV."

DRUG ELUTING STENTS

Cost and Cost-Effectiveness

An independent study of the cost-effectiveness of drug eluting stents was conducted by Dr. Patrick Serruys in Rotterdam, Netherlands, with virtually every patient getting drug eluting stents at that lab. Many people are anxiously waiting for those results, but he does not expect to present them before the EuroPCR meeting in May 2004.

Determining drug-eluting stent prices, at least in Europe, is getting more difficult because companies are bundling products together. However, sources agreed that the price of **bare stents** in Europe is coming down – gradually not dramatically. A source at a very large center said, "At our hospital, electrophysiology, surgery and stents are all bundled together, so I can't figure out what we are paying for stents any more. And prices are different at every institution." A French doctor said, "We are paying about 300 euros for a bare stent now." A Spanish doctor said he is paying about 1,000 euros for a bare stent. A Belgian doctor said, "Bare stent pricing is coming down gradually. Officially, there hasn't been any change in price, but we are getting better deals."

Should drug-eluting stents be used in all patients?

An expert argued that the safety of Cypher stents has been proven, and they can be used in every patient. He cited the 1,600-patient RESEARCH Registry at the ThoraxCenter in the Netherlands, which is providing interesting information on drug-eluting stents. Dr. Serruys said, "Unrestricted use of sirolimus-eluting stents in our 'real world' population was safe and resulted in a 30-day adverse event rate similar to conventional stent implantation in the historical control group." Data on 1,171 of these patients found a stent thrombosis rate of 0.4% with Cypher compared to 1.4% for control.

However, another expert reminded doctors about the Dear Doctor letter Johnson & Johnson recently sent out, warning of the rare but potential risk for thrombosis associated with Cypher use. He emphasized, "Cypher is ***not*** indicated for the treatment of restenosis, and it has not been adequately evaluated for use in AMI, SVG, or bifurcation lesions."

This speaker also pointed out that only 71% of the patients in the RESEARCH registry got a drug-eluting stent, primarily due to inventory shortage, commenting, "So, you cannot give it to everyone. And there are differences (in that registry) in

antiplatelet use which may affect events and cost comparisons. It's good news that there were no safety issues with sirolimus-eluting stents in the first 30-day data (of RESEARCH) and out to one year. However, there really was no effect on death (4.1% vs. 3.7%) or death/MI, so sirolimus-eluting stents do not impact death or MI…It is still legitimate to use bare stents, and reserve drug-eluting stents for selective patients."

Stents per patient

On average, European cardiologists estimated that they are using 1.3 stents per patient. When a drug-eluting stent is used, additional stents generally also are drug-eluting stents – unless there is a lack of availability.

Drug-eluting stent failures

A French study of 354 consecutive drug-eluting stent patients, found 18 failures after three to six months (15 de novo, 3 ISR). Ten of these were treated with brachytherapy, and three with balloon – and both options showed good results at six months.

BOSTON SCIENTIFIC

There had been reports that **Taxus** would be reviewed by the FDA Circulatory System Devices Panel on October 11, 2003, but that has been cancelled, and there is now talk of Taxus getting on the agenda for the scheduled December 11-12, 2003, panel.

TAXUS

Miscellaneous tidbits relating to the TAXUS program:

- There did not appear to have been any leaks of the **TAXUS-IV** data. None of the key interventional cardiologists have seen the data yet. However, TAXUS principal investigator Dr. Gregg Stone gave an overview of the TAXUS-IV program, hinting that TAXUS-IV may closely mirror SIRIUS. Thus, there are now predictions that the restenosis rate in TAXUS-IV may be about 9%, but these are all speculation.
- ➢ A J&J source suggested that there is some backlash developing against Boston Scientific because of the way the **TAXUS-II data** kept being changed.
- ➢ The **Express²** was fixed and re-launched in Europe a couple of weeks before the Euroepan Cardiology meeting.

Among the issues about Taxus stents that were discussed at the meeting were:

Vascular healing/thickening in and around the Taxus stent. An investigator said, "There is vascular remodeling in the stented vessel with thickening…We conclude that paclitaxel is eluted evenly over the entire length of the stent. There is no correlation between plaque burden and post-procedure and subsequent neointimal hyperplasia."

Sources doubted that CDRH will be overly concerned with this issue, but they suggested it could delay (not bar) approval by CDER. Some independent researchers are doing some pig studies of their own to try to discover more about this phenomenon. A source said J&J already is using this issue to counter-market Taxus.

There is less concern about the Taxus vessel thickening because – as with Cypher malapposition or stent aneurysms – it does not appear to be associated with clinical adverse events. However, a prominent IVUS expert insisted that it is likely to result clinical problems in the future.

Edge effects. There may be less edge effect with Taxus than Cypher, but this is not yet a major issue. A source said, "TAXUS-II showed the distal edge was better with Taxus than Cypher, but it is too soon to see if there is any clinical advantage because of this."

A TAXUS-II IVUS substudy of the edges found the beneficial effect of Taxus extends beyond the stent on the distal edge, resulting in the absence of lumen reduction usually seen with a bare stent. An investigator said, "There was no edge stenosis, and there was a beneficial edge effect that was more prominent distally than proximally."

Incomplete stent apposition. Incomplete stent apposition was rare, and an investigator said the incidence is not causally related to the use of Taxus stents, and the presence of incomplete apposition does not translate into a higher incidence of MACE or stent thrombosis. He commented, "Incomplete apposition was comparable to control."

TAXUS-II Incomplete Apposition

Incomplete Apposition	Control	SR	MR	p-value
Resolved	4.6%	7.1%	2.6%	Nss
Persistent	3.3%	4.4%	0	Nss
Acquired	5.4%	8.0%	9.5%	Nss

Elution rate. There was a buzz about the fact that 90% of the paclitaxel remains on the Taxus stent at one year, and numerous sources expressed "concern" about this. However, no one appears to be avoiding use of Taxus, and no one plans to stop using the stent, because of this. Yet, many experts suggested this could be a regulatory issue, and all sources intend to keep a close eye on this. An expert said, "No one knows yet what the 90% means. We don't know at what moment the blockage of diffusion occurs." A German doctor said, "The 90% is not a concern, but I think sirolimus is a better drug." A Spanish doctor said, "The 90% has not stopped me from using Taxus stents, but I'm watching it."

GUIDANT

Sources said the company is very, very nervous about its drug-eluting stent program, and is developing **everolimus** on its own polymer in parallel with the Biosensor's stent to be safe. One expert commented, "Guidant simply does not want another failure, and it is proceeding very cautiously." However, the FUTURE-II data definitely will be at TCT2003, an investigator said.

FUTURE-I AND FUTURE-II TRIALS

Data was presented indicating that the FUTURE-I data on Biosensor/Guidant's everolimus-eluting stent held up at one year. Six-month data on Future-II will be presented at TCT2003. FUTURE-II is a randomized trial comparing the everolimus-eluting and biodegradable Guidant/Biosensor stent to a bare stent in de novo lesions. The 126-patient trial was conducted at 29 centers, using 2.75-4.0 mm stents in 14 mm and 18 mm lengths. An investigator said there was no dose-finding study in humans before either FUTURE-I or –II was started, "The dose was chosen on the basis of animal studies. Based, on good outcomes in 90-day pig data, this dose was chosen… I don't think we need a dose-finding trial in humans. That's why we have pigs. Humans are a little more forgiving than pigs, so pigs tell us about safety, but I think pig studies should be 90 days if possible."

FUTURE-II Results

Measurement	Everolimus	Bare
Primary Endpoint: MACE at 30 days	0	2.3 (1 q-wave MI)
Secondary Endpoint: Binary restenosis at 6 months	Tba	Tba
Average lesion length	11.07	11.62

DELIVER II: Six Month Data

This was a registry of 1,533 patients in Europe, the Middle East and South Africa, with 1.986 lesions. It was a prospective, non-randomized multicenter evaluation of Guidant's paclitaxel-eluting Achieve stent that is no longer in development. This was not a randomized trial, but investigators still believe the findings are important.

DELIVER-II Six-Month Results

Drug	Result
Primary Endpoint: TLR	10.5%
TLR-CABG	2.5%
TLR-PCI	8.8%
MACE	15.7%
TVF	16.7%
Death	2.3%
Q-wave MI	2.3%
Non-Q-wave MI	2.6%
TVR (CABG/PCI)	1.1%

The key risk factors for six-month TLR were, in order of occurrence: history of angina, post-procedure MLD, small vessels, post-procedure RVD, restenotic lesions, LAD, use of 2.5 mm stent, pre-procedure MLD, pre-procedure RVD, number of diseased vessels, and total stent length. Diabetes was not identified as a risk factor.

Vision

Guidant's Vision stent is doing well in Europe. Doctors all said they like it, and it is vying for No. 1 place with Medtronic's new Driver stent.

JOHNSON & JOHNSON

A J&J official confirmed that J&J and Guidant are in the process of "refining" their agreement over the stent delivery system, but he said that there is no question that Guidant will continue to provide the delivery system to J&J for the length of the agreement or until J&J has its own delivery system, which reportedly is not a priority right now. He also indicated that both sides are happy with the revisions.

REALITY

The first two patients have been enrolled in REALITY trial, a head-to-head comparison of Cypher and Taxus. Several experts believe this trial is a major risk for J&J. They are dubious that it is sufficiently powered to show a statistically significant difference. One expert said, "If restenosis is 8% with Cypher and 14% with Taxus, it can show a benefit to Cypher, but if the restenosis is 10% with Cypher and 12% with Taxus, J&J will be subsidizing an equivalency trial. The only way J&J can win is on late loss."

J&J does not plan to let Boston Scientific take market share just based on lower stent **pricing**. A J&J official said, "We will price Cypher competitively with Taxus – if the Taxus lawsuit allows Boston to sell it, and if TAXUS-IV is comparable. We are going to be competitive." On September 8, 2003, after the ESC meeting, J&J announced that the U.S. price for Cypher was being lowered, with high volume users to pay about $2,400 per stent and low volume labs about $2,700.

Thrombosis

There does not appear to be any concern that the thrombosis with Cypher is due to the Medicine Company's Angiomax (bivalirudin). In fact, there was little concern or talk about this issue at all. A source said, "My conviction is that sirolimus is less thrombogenic than bare stents…Thrombosis with Cypher is ***not*** a concern." Another doctor commented, "SAT with Cypher is not a concern. It is lower than with bare stents." A French cardiologist said, "The rate is not zero, and it could be related to malapposition, which is mechanical, not drug-related."

Long Lesions

There was incremental new data on Cypher at the meeting. This included a study of Cypher stents used in long lesions. Data from the RESEARCH Registry being run at the ThoraxCenter in Rotterdam, Netherlands, may help dispel concern about the safety of using the sirolimus-eluting Cypher stents in very long lesions (>36 mm). The substudy compared short stenting (≤36 mm) with "long" stenting (>36 mm). The Cypher stents used ranged in diameter from 2.5-.3.0 mm, with 8 mm, 18 mm and 33 mm lengths. Researchers concluded: "Cypher in patients with either a long or a short segment were shown to be equally safe at 30 days, and at six months there was no significant difference in MACE."

RESEARCH Substudy

Measurement	"Short" stents (≤ 36 mm) n=458	"Long" stents (>36 mm) n=105	p-value
Duration of clopidogrel	3 months	6 months	---
Differences in baseline characteristics	More LAD lesions	More history of MI, more multivessel disease, more RCA lesions	---
Number of treated segments	1.8	2.8	p<.01
Stents per patient	1.9	3.6	p<.01
Bifurcations	16%	20%	---
Stent diameter ≤2.5 mm	31%	53%	---
IIb/IIIa use	17%	24%	---
At least one 33 mm Cypher	22%	94%	---
30-Day Results			
Primary Endpoint: Any event	3.3%	4.8%	p=.6
Death	1.5%	0.9%	Nss
MI	1.3%	1.9%	Nss
TLR	0.9%	2.8%	Nss
TVR	0.9%	2.8%	Nss
Stent thrombosis	0.2% (1 patient)	0.9% (1 patient)	Nss
6-Month Results			
Primary Endpoint: Any event	9.6%	7.9%	Nss
Death	3.3%	1.6%	Nss
MI	2.8%	1.6%	Nss
TLR	4.2%	5.6%	Nss
TVR	5.9%	5.6%	Nss

Bifurcations

A poster reported on a Netherlands study of 58 patients who got Cypher stents for bifurcations. TLR was 8.6%, and angiographic restenosis was 9.1% in the main artery and 13.6% in the branch, for an overall restenosis rate of 22.7%, which was lower than comparable bare stents. T-stenting was used for 3% of these cases, and crush for 26%. Most of the restenosis cases were in the T-stented lesions, leading the researcher to conclude that the crushing or kissing techniques are better, but "it's most important to cover the ostium, no matter what technique we use."

MEDTRONIC

Medtronic sales reps were very excited about their new cobalt chromium stent, Driver. Doctors also seem to like it, and it is quickly gaining market share in Europe. A Polish doctor said, "Driver and (Guidant's) Vision are between bare stents and drug-eluting stents. They are a mid-range stent with a mid-range price."

DRUGS

STATINS

Data continues to mount that CRP is associated with a pro-inflammatory response and a fibrinolytic response. This is causing doctors to look at new uses for statins. For instance, at a meeting of the ESC Vascular Biology Working Group, a Scottish rheumatologist said he was planning a large trial of statins in rheumatoid arthritis (RA). A cardiologist commented, "Instead of just using statins (to lower CRP), perhaps we should develop drugs with CRP as the target." Another speaker said, "Statins may have a beneficial effect on the progression of RA, which adds to the evidence that statins have anti-inflammatory effects." However, an expert also warned that CRP should not be used routinely yet and recommended waiting for the five-year, 15,000-patient JUPITER trial, which will study the effect of Crestor vs. placebo on cardiac morbidity and mortality in patients with normal LDL but elevated CRP.

Some other interesting points made about statins include:

- Suggestions that everyone over the age of 50 might benefit from a statin.
- Predictions that statins may be beneficial in ESRD, heart failure and rheumatoid arthritis.
- Estimates that only about half the people who could benefit from a statin are on one.
- When a statin is discontinued, the benefit probably takes months or years for the risk to return.

ASTRAZENECA'S Crestor (rosuvastatin)

Most U.S. doctors questioned said they plan to try Crestor, but there was a decided lack of excitement over this drug at the meeting. AstraZeneca was giving it a big push at their booth,

and the company is planning a big U.S. launch. A prominent American cardiologist said, "Crestor is a powerful statin, that – certainly in patients with really significant hyperlipidemia – should play a role. It may be used in patients who are not able to tolerate other statins and who don't have symptoms on Crestor. A lot will center on the cost and how it is priced. There are other products that lower LDL, so Crestor will have to distinguish itself. If the first pill gets patients to goal quickly, that will be an advantage, but we have a lot of good statins out there, and the real challenge (for AstraZeneca) will be to see how it differs. There are opportunities for Crestor if it costs less or if it somehow has fewer symptoms of myositis, but myositis is already low with statins in general." Another American doctor said, "Insurance companies will drive the decision on Crestor usage." A West Virginia cardiologist said, "I'll use Crestor for patients who can't get their LDL down – but that's a small percentage of patients."

At ESC, AstraZeneca's marketing approach for Crestor emphasized Crestor:

- Significantly lowers CRP and does so more than all other statins except atorvastatin, with which it is relatively comparable.
- Is more potent than other statins.
- Has the longest half life of all statins.
- Has a "small advantage" in raising HDL over other statins. Surprisingly, officials did not overplay this point, describing the advantage as "small."
- Is hydrophilic. A speaker said, "A speaker said, "Rosuvastatin is hydrophilic, so it doesn't get across the muscle membrane easily (neither does pravastatin), but cerivastatin (Bayer's Baycol), simvastatin (Merck's Zocor), fluvastatin (Novartis' Lescol), and atorvastatin (Pfizer's Lipitor) all cross the membrane as if it weren't there. So, we are not dealing with new cerivastatin just because it (rosuvastatin) is a very powerful drug…It is hard to induce toxicity in an organ if the drug can't get in the organ…The trend is there to say that hydrophilic drugs (statins) are better."
- Has a good safety profile, comparable if not better than other statins. A speaker said, "As clinicians, we benefit from the cerivastatin events. They mandated that the rosuvastatin safety program has been very extensive and much bigger pre-approval than for other agents. So, rosuvastatin was looked at extensively in a large number of people and in challenging situations, such as renal impairment. The safety profile of rosuvastatin 10-40 mg compares to other marketed statins."
- Has a low interaction with the P-450Y enzyme, so it has a low potential for drug-drug interaction.
- Can be used with fenofibrate but not gemfibrozil. A speaker said, "There is no reason to think rosuvastatin is any less safe with fenofibrates than other statins."
- Is no different from other statins in terms of proteinuria. A speaker said, "All statins cause tubular proteinuria, and rosuvastatin does to the same extent – about 1% of patients across the dose range of statins manifest some proteinuria. It is all tubular. There isn't any albuminuria. And the proteinuria is not associated in any statin with deterioration of renal function as measured by creatinine."

Competing statins are fighting back. Sales reps at the booths for other statins had a similar counter-marketing message. Every rep was saying about almost same thing – emphasizing three things about Crestor:

1. Lack of outcome data.
2. Lack of clinical data and long-term data.
3. The risk of rhabdomyolysis. One rep simply whispered cerivastatin, others mentioned rhabdomyolysis directly, some hinted at muscle issues.

Doctors also don't seem concerned about the proteinuria that has been associated with Crestor. None planned to do additional monitoring for this.

ASTRAZENECA'S Exanta (ximelagatran)

Doctors were very excited about Exanta, an oral direct antithrombin inhibitor that would be given twice-a-day. Several sources commented that there will be an immediate and mass switchover form warfarin to Exanta – if the drug gets FDA approval. A speaker suggested, "Exanta probably will expand the indication for patients with AF, either currently or in the past."

The one real question about this drug is liver toxicity. Several experts said there is still a concern about this, in part because the mechanism of action is not known. At an analyst meeting on October 2, 2003, AstraZeneca plans to discuss the ALT issue with Exanta**.** An official admitted, "The mechanism of ALT elevation needs to be sorted out." An expert said, "Before we can say that Exanta is safe, I need to see the full data on all patients, to see how it works in other ethnicities, in re-treatment, and how it works. These are really small numbers (in the trials) so far."

This exchange was pertinent to the issue of what mechanism causes Exanta to raise ALT:
Q: "Where does the liver come into play, since Exanta is renally excreted?"
A (Exanta investigator): "That is difficult to answer. I doubt that ximelagatran itself is liver toxic. I think we need advice, and we will get that from a world-wide group of liver experts who are looking into underlying mechanisms. But the ALT elevation is transient, and there are no long-term sequelae. Exanta looks like other drugs with certain hepatic toxicity."

Six-months results from the 1,245-patient, placebo-controlled, double-blind, Phase II ESTEEM trial of Exanta in AMI was presented at ESC. ESTEEM was conducted at 191 sites in 18 countries, and enrolled 1800 patients with a recent MI (within

14 days). Exanta was dosed BID at 24 mg, 36 mg, 48 mg and 60 mg vs. placebo, with all arms of the trial getting aspirin. The primary endpoint of combined death, recurrent MI, and severe recurrent ischemia was significantly reduced by 24% with Exanta (12.7% vs. 16.3%, p=.036). The 24 mg BID dose provided the best efficacy with the fewest side effects (bleeding and elevated liver enzymes), and the Phase III trial will use this dose. A researcher concluded, "The benefit occurs in less than 30 days and is maintained over the remainder of the trial." An AstraZeneca official said, "The level of (beneficial) effect in this study surprised us".

Six-Month ESTEEM Results

Measurement	Exanta 24 mg n=307	Exanta 36 mg n=303	Exanta 48 mg n=311	Exanta 60 mg n=324	Placebo n=307
Cumulative risk of new events	12.1%	13.7%	11.6%	13.3%	16.3%
Risk of major bleeding	0.9%	2.0%	0.7%	3.2%	1.5%
Primary endpoint: combined death, recurrent MI, and severe recurrent ischemia	12.7% (p=.036, a 24% reduction)				16.3%
All-cause mortality, nonfatal MI, nonfatal stroke	7.4% (a 34% reduction)				11.1%
All discontinuations	34%	44%	38%	41%	39%
Discontinuation for elevated ALT	7%				1%
Discontinuation for ALT	3%	11%	6%	8%	1%
ALT 2-3xULN	4%	5%	5%	6%	2%
ALT 3-5xULN	4%	4%	5%	4%	1%
ALT>5xULN	3%	9%	7%	9%	1%
Bilirubin >2xULN	1%	1%	1%	1%	1%

The liver elevations in ESTEEM were not excessive, occurring mostly within 30 days and resolving by 120 days, usually without need to discontinue. One patient in each arm developed a bilirubin elevation 2xULN. There was no increase in bilirubin in the setting of transaminase elevation, except at higher doses, but, again, that was described as transient. An investigator said, "For patients who got jaundice, the drug was stopped and the patients were followed weekly, with the condition usually resolving in 60-90 days."

When liver function tests showed an ALT elevation >2-3xULN, patients underwent additional weekly testing. If levels did not return to normal within four weeks or if at any time levels were >5xULN, study treatment was stopped. Researchers and company officials declined to say what the highest ALT measurements were. Study drug was stopped for these reasons in 1% of placebo patients and in 7% of the combined ximelagatran groups.

An expert who critiqued ESTEEM, described it as "a very intriguing study because it proves the concept of oral anticoagulation therapy in post-infarct patients," but he said some major questions remain:

1. **Lack of a dose response curve.** However, he noted, "Other trials have also shown no dose response effect with anticoagulants. Pentasaccharide (Sanofi's Arixta, fondaparinux) didn't show any. So, it is not new that there is no dose with this kind of drug… INR is important, not dosing."
2. **Liver elevations.** He wondered, "If we trade warfarin for ximelagatran, do we replace INR monitoring with liver monitoring? This may be a point of concern."
3. **Warfarin/clopidogrel.** There is no data on the relationship of Exanta to the warfarin and clopidogrel. He said there is a need for a direct comparison of Exanta with clopidogrel and with Coumadin, and a comparison of Exanta plus clopidogrel vs. clopidogrel alone.
4. **Earlier interveniton.** What if there had been an earlier intervention in these patients? He said, "I think the results in ESTEEM would have been the same".

Asked how frequently patients may need to have liver monitoring with Exanta, an investigator said, "Usually you see patients every six months, so a liver test every three months would not be an issue. Currently, in the study (SPORTIF-V), we are doing liver testing monthly." An AstraZeneca official added, "I hope this will be like statins and get to the point where we no longer measure liver enzymes."

In the SPORTIF-III trial of Exanta in AF, which was presented at the American College of Cardiology earlier this year, ALT>3xULN occurred in 6.5% of patients, compared to 0.8% of warfarin patients. A speaker said, "The highest incidence of ALT>3xULN occurred in month three (slightly less than 3% of patients). Seven patients on Exanta and one on warfarin also developed bilirubin 2xULN) – as of 14 days ago."

SPORTIF-III Liver Elevations (through late August 2003)

Measurement	Exanta
ALT>3xULN	107
Continued on treatment	59
Normalized	55
Returned to <2xULN	3
>2xULN pre- and post-study	1
Discontinued treatment	48
Normalized	42
Returned to <2xULN	4
Died (1 unrelated)	2

Where will Exanta be used? One speaker commented, "Exanta may be useful in all fields where Coumadin, UFH and LMWH are used – maybe early in ACS with or without reperfusion therapy. It may replace heparin in the cath lab, and it may be used in patients with artificial heart valves." Another speaker said, "The place for Exanta, in my opinion, is in patients at high risk or with moderate risk factors. In clinical practice, this new drug should be given to AF patients at higher risk for stroke who are not suitable for warfarin – where monitoring or compliance are difficult. The limitations of the SPORTIF-III study, in my view, are:

1. It was an open label study.
2. Exanta is not inferior to warfarin, but according to an intent-to-treat analysis, it is not significantly superior.
3. The number needed to treat to prevent one stroke is 143 per year. This is a relatively high number.
4. Exanta might have more liver enzyme elevations than warfarin, though they seem to be transient.
5. Higher costs are the main obstacle. I don't know what it will cost, but that will drive the decisions of the various guidelines committees."

An Exanta investigator said Exanta should not be used in patients with: (1) bleeding, (2) poor renal function (which is ~10% of patients), (3) drug-drug interactions, which probably exist, and (4) ReoPro or Plavix, etc., until that is studied.

Among questions that were asked about Exanta at an AstraZeneca-sponsored session were:

Q: Is the liver toxicity due to concomitant statin use? Is there any interaction with statins?
A: "We did an extensive multivariate analysis for all possible interactions, but to our surprise, it seemed statin patients had less elevations of ALT on Exanta rather than more. Maybe exposure to the two agents has a sensitizing effect on the liver, leaving some kind of message there, so the next time a patient takes a drug that impacts the liver, you have some sort of tolerance…Right now we have more than 30,000 patients in the database, and within a few weeks, we will meet and look into all possible interactions available from that…The U.S. is still testing liver enzymes with statins, and Exanta is in the same ballpark as statins."

Q: Is there a dose relationship between Exanta and ALT elevations?
A: Yes, so we might titrate patients to avoid that. That is a challenging idea, and I look forward to seeing the results of that idea in a year or so."

Q: Will the dose be different by condition?
A: "No one is arguing for higher doses than 24 mg or 36 mg."

Q: What is the role of clopidogrel?
A: "Clopidogrel is effective but only a little more effective than aspirin. Studies are ongoing of the combination of clopidogrel/aspirin, but the results are not in for efficacy or risks. Therefore, at this point, there is no superiority proof to warfarin, except for (Exanta in) ESTEEM."

For the rest of 2003, there will be a steady flow of Exanta news. The data from SPORTIF-III (36 mg Exanta b.i.d.) in AF is coming out "soon" in ***The Lancet,*** and there will be 12-month ESTEEM data as well as the results of the pivotal SPORTIF-V trial (36 mg Exanta in stroke) at the American Heart Association meeting in November 2003. The start date for the Phase III trial in AMI has not been chosen because, according to an AstraZeneca official, "We are focused on the FDA filing (for stroke)."

ASTRAZENECA'S Atacan (candesartan)

The CHARM (Candesartan in Heart Failure – Assessment of Reduction of Mortality and Morbidity) trial of Atacan in heart failure is likely to expand the role for Angiotensin Receptor Blockers (ARBs) in general, and perhaps Atacan in particular. However, experts also insisted the trial will be viewed as a class effect for all ARBs, not just Atacan, and several sources noted that the 5 mmHg drop in blood pressure may have made the difference in favor of Atacan.

CHARM, which was actually a combination of three trials plus a combination analysis, proved that ARBs can be used in these patients when an ACE inhibitor cannot be tolerated or in addition to an ACE inhibitor – but not in patients with a LVEF>40. The trial should settle any questions about the safety of triple therapy of ARB, ACE and beta blocker. The trial may be promoted as extremely positive, but it missed several endpoints, so on balance it is positive but a little weak.

The CHARM trials validate the use of an ARB in patients with chronic heart failure in addition to an ACE inhibitor or when an ACE inhibitor cannot be tolerated. CHARM is actually a group of 3 trials, also analyzed in combination, comparing Atacan QD to placebo. CHARM involved 7,601 patients in 26 countries, with patients titrated to 32 mg of Atacan and followed for a minimum of two years.

The primary endpoint in each of these three trials was the combination of CV death and CHF hospitalizations.

1. **CHARM-Alternative.** This trial enrolled patients who are ACE inhibitor intolerant (mostly due to cough) with a LVEF ≤40. The treatment effects began between three and six months. In addition to meeting the primary endpoint, there was a trend towards reductions in CV death, but the difference was not statistically significant. However, the result became significant after adjusting for covariates (p=0.02). There were significant reductions in the number of patients hospitalized for CHF as well as in the total number of hospitalizations for CHF.

2. **CHARM-Added.** This trial enrolled patients who were on an ACE inhibitor and had a LVEF ≤40. In addition to

meeting the primary endpoint, candesartan treatment was associated with a significant decrease in CV death (p=0.029), in the number of patients hospitalized (p-.014), and in the number of hospitalizations (p=0.002).

3. **CHARM-Preserved.** This trial enrolled patients with an LVEF >40, with ACE inhibitor use allowed but not frequently used. This trial failed to show a statistically significant reduction in the primary endpoint, even adjusting for covariates (p=.051). In addition, the trial did not show a significant reduction in the individual endpoint of CV death, though there was a significant reduction in patient hospitalizations (p=.017) and total hospitalizations (p=.014). A pre-specified analysis found patients were 40% less likely to develop diabetes with candesartan than placebo (4% vs. 7%, p=0.005).

When the three trials are studied in together, the combined analysis did not meet the primary endpoint of all cause death, but it did become statistically significant when it was adjusted for covariates. CV death and CHF hospitalizations, considered individually were statistically significant.

Combined CHARM Results

Endpoint	Relative Risk Reduction vs. placebo	p-value
Number of patients enrolled	7,599	
Combined Primary Endpoint: All cause death	9%	p=.055
All cause death adjusted for covariates	10%	p=.032
CV death	12% (18% vs. 20%)	p=.012
CHF hospitalizations	21% (20% vs. 24%)	P=.0001
Non-CV death	N/A	NSS

CHARM Results

Endpoint	CHARM-Alternative	CHARM-Added	CHARM-Preserved
Number of patients enrolled	2,028	2,548	3,025
Criteria	ACE inhibitor intolerant and LVEF ≤40	On ACE inhibitor and LVEF ≤40	LVEF >40, with or without ACE inhibitor use
Women	32%	21%	40%
Hypertensive	64%	50%	48%
Diuretic use	86%	90%	75%
Length of follow-up	33.7 months	41 months	36.6 months
Relative Risk Reduction			
Primary Endpoint: combined CV death or CHF hospitalization	23% (33% vs. 40%) p=.0004	15% (27.9% vs. 42.3%) p=.011	NSS (22.0% vs. 24.3%)
Concomitant Drug Use			
Commonly prescribed	spironolactone	beta blockers	CCBs
Long-acting nitrates	37%	33%	33%
Amiodarone	12%	11%	8%
Oral anticoagulants	31%	38%	25%
Aspirin	58%	52%	58%
Lipid lowering drugs	42%	42%	42%
Bronchodilator (use at baseline)	9.2%	8.2%	9.2%
Diuretic	86%	90%	N/A
ACE inhibitor	10%	0	N/A

In the EUROPA trial, only 10% of patients couldn't tolerate the ACE inhibitor perindopril (Servier's Coversyl, marketed in the U.S. as Aceon), but CHARM researchers said other estimates indicate up to 20% of patients cannot take ACE inhibitors – and may be candidates for an ARB. However, investigators claimed that the CHARM results support the use of an ARB, and candesartan in particular, in ***all*** patients with chronic heart failure, irrespective of EF, age and sex. One investigator said, "The benefits were achieved on top of other effective concomitant therapies, including ACE inhibitors and beta blockers. Candesartan is not to replace an ACE or a beta blocker, but to be used in addition to them." Another investigator said, "What was striking was how similar the groups were in terms of efficacy. There was a reduction in all cause mortality, CV death – anything we measured. The efficacy was pretty similar across all the trials. We can say there is a benefit to candesartan whether the patient is on an ACE or not."

A past president of the American Heart Association took a slightly more conservative approach. He believes the findings help establish a class effect that applies to other ARBs, commenting, "The early evidence suggests this is most likely a class effect…When an ACE inhibitor can't be used, candesartan has a reasonable benefit, and in many patients with systolic dysfunction on an ACE inhibitor, the add of an ARB may be helpful. But in those patients with an EF >40, I think the added value of an ARB needs further study. The strongest message out of CHARM is that there may be some benefit of ARBs in patients where an ACE inhibitor cannot be used."

BRISTOL-MYERS SQUIBB

Pravachol (pravastatin). Reportedly and not surprisingly, the company is very upset about the upcoming REVERSAL trial comparing 40 mg pravastatin to 80 mg atorvastatin. *(see Pfizer).*

Plavix (clopidogrel). Sankyo has a competitor to Plavix (clopidogrel) in Phase II development, but there was no data at the meeting, and no one at the Sankyo booth knew much about it.

Vanlev (omapatrilat). Two experts confirmed a rumor that Bristol-Myers was thinking of reviving Vanlev, but neither had details. One of these is a member of the FDA's CardioRenal Advisory Panel, and he was influential in the FDA's rejection of Vanlev, but he said, "We left the door open for use in hypertensive patients not controlled on three drugs. The FDA gave Bristol-Myers an approvable letter for that indication, but the approval would be very restrictive, with a label as a last resort drug." Another source said reviving Vanlev would be a good idea – but not in heart failure.

CV THERAPEUTICS' Ranexa (ranolazine)

Data was presented at ESC indicating there is no evidence of rebound worsening of angina when ranolazine is withdrawn. Asked about plans for an **FDA panel** for ranolazine, a CV Therapeutics' official said, "We are submitting additional data, and the FDA could consider that a major amendment. If they do, it would extend the PDUFA date by three months, which would put the planned December (CardioRenal) panel within our window…From our discussion with FDA staff, we have no reason to think the PDUFA date will be missed." The December meeting is scheduled, but the agenda has not been announced.

ESPERION

A source predicted data at the American Heart Association meeting in November 2003 on Esperion's apolipoprotein A-I agonist will be surprisingly positive.

GENENTECH: TNKase (tenecteplase)

The GRACIA-2 Trial was a six-month 200-patient study in Spain and Portugal, comparing optimal primary angioplasty (within 180 minutes of symptom onset) to "facilitated intervention" in which patients received immediate thrombolysis with tenecteplase three to 12 hours prior to stent/CABG. Earlier studies indicated that lytics and angioplasty should not be combined, but this study lends support to a combined pharmacological/mechanical strategy, though the results need to be confirmed in a much larger study.

The two groups in GRACIA-2 were well matched as to baseline demographics, clinical characteristics, and culprit artery, but the facilitated intervention group had a higher percentage of completely reopened culprit arteries (70% vs. 40%) due to previous thrombolysis. The trial found that facilitated intervention resulted in:

- More TIMI grade 3 flow and more vessels without a significant stenosis (due to thrombus dissolution at early angioplasty)
- Less use of abciximab (Lilly's ReoPro) during PCI
- More complete ST segment resolution at six hours
- Similar infract size and LV function
- Fewer deaths and fewer major non-cerebral bleeding
- One case of intracranial hemorrhage and one re-infarction

The lead investigator concluded, "Immediate thrombolysis with TNK followed by catheterization and appropriate intervention within three to 12 hours of the onset of symptoms is an approach available worldwide for heart attacks that seems to be as safe and effective as optimal primary stent-angioplasty. If this equivalency finding is confirmed in further studies, the percent of patients with MI who can benefit from early routine intervention could increase dramatically."

Three trials are ongoing which should help determine the role of lytics in combination with angioplasty: FINESSE, ADVANCE-MI, and ASSENT-4. Experts indicated that ASSENT-4 may be the most definitive, but the results will not be available until early 2005.

GRACIA-2 Six-Week Results

Endpoint	Optimal primary PCI n=108	Facilitated intervention n=104
Deaths	6 patients	3 patients
Re-infarction	1%	2%
Any bleeding	6.7%	10.3%
Minor bleeding	3%	2%
Intracranial hemorrhage	0	1%

GLAXOSMITHKLINE'S Coreg (carvedilol)

New data from the COMET trial was presented, comparing 42 mg carvedilol to 85 mg metropolol. The study showed carvedilol was associated with a highly significant advantage in CV mortality (8.3% vs. 10.0%), a substantial reduction in death from stroke, significantly less new-onset diabetes, and a prolongation in survival (1.4 years). There was no difference between carvedilol and metropolol in all cause hospitalization. The study also found it is necessary to treat 59 patient years with carvedilol to save one life. A researcher concluded, "Both drugs produce substantial reduction in heart rate…but however we cut this data, it is dominated by carvedilol's reduction in death…This is the first head-to-head mortality study comparing two beta blockers…This is a big difference (in favor of carvedilol)…I come to the conclusion that carvedilol is the preferred beta blocker in the treatment of heart failure."

MERCK'S Aggrastat (tirofiban)

In the Dutch study, ON-TIME, researchers found that pre-treating AMI patients with Aggrastat before they got to the hospital, and then transporting them directly to the cath lab, was not harmful and could lead to improved TIMI flow. In ON-TIME, 487 patients were randomized to administration of tirofiban either early (one hour before arrival at the cath lab) or in the cath lab. The primary investigator said, "This trial shows you should not wait to start tirofiban until patients arrive at the cath-lab, but can start treatment as early as possible, on top of aspirin and heparin."

However, there was no difference in clinical outcome at 30 days between the two groups. Discussing the findings, an expert said, "In my opinion, the strength of this trial is the extraordinary short patient-related time from door to balloon, and the low mortality (2.0%) and re-infarction (1.0%) at 30 days…If this study has a weakness it is that, despite the higher patency rate and lower thrombus burden with early treatment, there was no benefit in the outcome of PCI. The take-home message is that the earlier tirofiban is started, the better the angiographic presentation…My personal point of view is that the most impressive result of this study is not related to the drug but the showing that a pre-treatment delay can be largely reduced with expected clinical benefits."

ON-TIME Results

Endpoint	Early administration of tirofiban n=243	Cath-lab administration of tirofiban n=244	p-value
Primary Endpoint: TIMI-3 flow	19%	15%	p=.22
TIMI-2 flow	24%	19%	N/A
TIMI-2/3 flow	43%	34%	p =.04
Secondary Endpoint: Incidence of Thrombus			
Yes	25%	32%	p =.06
Fresh occlusion	35%	41%	p =.20
Combined	60%	73%	p =.002
Post-PCI outcome: TIMI-3	89%	91%	p =.56

PFIZER

Inspra (eplerenone)

Inspra is not yet approved in Europe, though an investigator said European approval was expected within the next couple of months. However, European doctors expressed little interest in Inspra**.** All sources said they plan to use it only for patients who develop side effects on spironolactone. Data from the EPHESUS trial was reviewed, but there was no new data from this trial. A Netherlands doctor said, "When eplerenone is available here, I'll probably start patients on spironolactone, and if they get side effects, then switch them to eplerenone." A U.S. doctor said, "I'll use eplerenone only if patient has side effects on spironolactone."

At one session where eplerenone was discussed, there was this exchange:
Q: Can you use spironolactone instead of eplerenone?
A#1: "You shouldn't due to evidence-based medicine, but yes."
A#2: "They are the same, though the side effects are better with eplerenone…Sure, both work."

Lipitor (atorvastatin)

Pfizer made it clear it is not going to give market share to Crestor and Zetia without a fight. The company held a briefing for reporters to outline the program it has underway to counter new agents (e.g., Crestor and Zetia) with a series of Lipitor trials. A Senior Pfizer official offered these three key counter-marketing points about Lipitor:

1. extensive R&D
2. extensive acceptance worldwide
3. experience -- over 57 million patient-years

The linchpin of this program is probably the REVERSAL trial, which will be presented at the American Heart Association meeting on Wednesday, November 12, 2003. This trial has the potential to deliver either a serious blow to Pfizer or give it a ***huge*** marketing advantage. REVERSAL is a 600-patient, prospective, randomized, double-blind, head-to-head trial comparing 80 mg Lipitor and 40 mg Pravastatin (Bristol-Myers Squibb's Pravachol). What makes REVERSAL unique is that the primary endpoint is percent change in total atheroma volume (neointimal volume) as measured by IVUS. The data from this trial is being tightly held; even Pfizer only knows the top-line data.

There are 23 pre-specified sub-group analyses of this trial. Among the questions they should be able to answer are:

1. How much is disease progression reduced by lowering cholesterol, how much is due to other factors, and what some of those factors are (CRP, etc.)?
2. Are there important differences in the effects of different statins on the atherosclerotic disease process?
3. Do statins merely slow atherosclerosis progression, or can they actually stop the disease process?

Other Lipitor points include:

- Data from the CARDS diabetic trial will probably be at the American College of Cardiology in 2004.
- A Pfizer officials said he believes it is probably unethical to do placebo-controlled statin trials any more.

- A Lipitor researcher said he is going to challenge guideline writers, suggesting that maybe lower cholesterol is better -- maybe it isn't a threshold factor. He said, "What if the right answer is as low as can be safely attained. TNT and IDEAL will answer that. If they show 80 mg Lipitor beats 10 Lipitor across the board, then guideline writers have to throw out the guidelines."

Lipitor Trial Completion Dates

2003	2004	2005	2006
REVERSAL	4D (renal dysfunction)	TNT	LEADe
CARDS (diabetes)	SPARKS	SPARCL (stroke)	
ATGOAL	SAGE (elderly)	IDEAL	
ASCOT-LLA	BONES		
	BELLES (women)		
	ASPEN (diabetes)		
	ALLIANCE		

SCHERING PLOUGH/MERCK's Zetia (ezitimibe)

Every doctor questioned said he is using Zetia, both as monotherapy for patients who can't tolerate statins, and in combination with whatever statin the doctor prefers. There is no preference for use of Zetia with simvastatin.

A knowledgeable source said Merck and Schering have agreed to do the QUEST trial, starting in early 2004. This is a head-to-head, IVUS-measured trial of simvastatin vs. the combination of simvastatin and Zetia.

SERVIER/SOLVAY'S COVERSYL/ACEON (perindopril)

Four years ago, the landmark HOPE trial proved the value of the ACE inhibitor ramipril (King's Altace) in high risk coronary patients. Now, EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) may further broaden the use of ACE inhibitors. "Perindopril (Servier's Coversyl, marketed by Solvay in the U.S. as Aceon) should be considered for chronic therapy in all – *all* patients, with coronary disease," concluded a study co-chairman. "The EUROPA trial clearly extends to all patients the need for ACE inhibition," another EUROPA investigator added.

EUROPA was a randomized, double blind, placebo-controlled trial of 12,218 patients from 24 European countries, making it the largest study yet in patients with stable, low-risk coronary disease. The study, which included a broad range of mostly asymptomatic patients with documented CAD, was investigator-led but funded by Servier. EUROPA compared perindopril QD to placebo – on top of standard therapy with ACE inhibitors, beta blockers, platelet inhibitors, nitrates, CCBs, etc. – over an average of 3.7 years. Patients were given two 4-mg pills daily during the trial, but Servier reportedly is developing an 8 mg pill.

Investigators said the reasons for their choice of perindopril for the study was its:

- 24-hour efficacy
- Good tolerance even in fragile patients (heart failure, stroke, etc.)
- Good tissue-ACE affinity
- Lipophilicity
- Anti-ischemic properties

Patients were given a four week run-in with 4 mg perindopril, and about 10% of patients dropped out during this period. Of those who were randomized, 80% were still in the trial at 3 years. A pre-defined subset analysis found perindopril better than placebo for all subgroups, though the difference was not statistically significant for all subgroups. These subgroups included gender, age, previous MI, previous stroke/TIA, hypertension, diabetes, lipid lowering drug or not, beta blocker or not, CCB or not.

4-Year Results from EUROPA trial

Endpoint	Relative Risk Reduction vs. placebo
Primary endpoint: Composite of CV death, MI or cardiac arrest	20% (8.0% vs. 9.9%)
CV death	13.9%
Fatal and non-fatal MI	24%
Cardiac arrest	45.6%
Heart failure	39%
Total death	11% *
Unstable angina	7.1%
Stroke	4.3%
Revascularization	4.2%
CV and non-fatal MI	19%

* not statistically significant

Investigators hope to convince regulators and guidelines committees to recommend ACE inhibitors for all coronary disease patients. A EUROPA investigator said, "We are going to the various regulatory authorities and to people who write guidelines in the various countries. When you do that, you need to do it on the basis of firm knowledge, and we have that. I think the governments will respond…I don't agree with a polypill, but I think all people with coronary disease will be on a statin, aspirin and perindopril."

An American Heart Association past president called EUROPA a very important study, saying, "I'm impressed with it…It is elegant, comprehensive, and provides information that

will be critical for the develop of secondary strategies and guidelines for patients with CAD. We've known for 10 years that ACE inhibitors benefit patients after an MI when they have impaired LVEF (or CHF). The question has been whether or not they will benefit all patients. In the development of the current secondary prevention guidelines, we carefully chose the phrase 'consider the use of ACE inhibitors'…because we felt we needed more evidence…EUROPA is the evidence we need to make the strong statement that an ACE inhibitor should be used rather than 'considered' in all patients. I think the findings for perindopril are so strong that one would have to question why this would not be part of primary treatment…I can't speak for the guideline group, but I am very impressed with these data, and I am very much involved in secondary prevention guidelines, and this is the type of data we need."

Most experts predicted EUROPA would expand the use of all ACE inhibitors, not just perindopril. In the U.S., this looks as if it is likely to be the case since sources doubt that Solvay will be as aggressive at marketing Aceon as King has been with Altace. Thus, Solvay may not prove to be a spoiler for King – or for other ACE inhibitors. An expert said, "The (cardiac) community considers all ACE inhibitors the same. There is no head-to-head data showing an advantage to any ACE inhibitor." Another said, "It would appear that we are dealing with a class effect…I find the evidence very compelling that all patients will benefit, and I think it is a class effect."

A few sources suggested that ramipril and perindopril would benefit most from the EUROPA findings since both are tissue-ACEs. Other sources were dubious about a tissue ACE advantage, but several predicted that EUROPA would give Solvay, which markets the drug in the U.S., a marketing advantage over other statins, including Altace. An investigator commented, "You have to go with the evidence. The regulatory authorities won't allow any ACE. We don't know all ACEs will work in the same situation… I'm not saying other ACE inhibitors don't work, but I do know this one does."

A question was raised about the conduct of the trial: The primary endpoint was modified two years ago. It does not appear that Solvay/Servier discussed this change with the FDA at the time, which could make a labeling change in the U.S. more difficult. A EUROPA investigator explained the modification: "The first secondary endpoint (total mortality) was originally the primary endpoint, and that is also significantly better with perindopril (p=.009). We changed it for two reasons: (1) We did not sufficiently realize the significant mortality from other causes (cancer, etc.), so there was a chance for diluting the effect. (2) The definition of unstable angina was refined by ESC and ACC…so we removed unstable angina from the primary endpoint…That shouldn't pose a regulatory issue because it was done before any results were known." An expert who had been unaware of the change said he was actually reassured by it, "I'm relieved that unstable angina was not included in the primary endpoint…They tightened up the study."

SERVIER'S ivabradine, an I(f) current inhibitor

I(f) inhibitors are a new class of anti-angina drug. INITIATIVE, a study of 939 patients with stable angina and a documented history of coronary artery disease, compared ivabradine to atenolol. Ivabradine patients were started on either 5 mg QD or 7.5 mg BID and titrated after a month to 7.5 mg QD or 10 mg BID. Atenolol patients were started on 50 mg QD and titrated after a month to 100 mg QD.

The trial found ivabradine equal in efficacy to atenolol in terms of improving exercise capacity and increasing time to exercise-induced ischemia, but with ivabradine had fewer side effects – e.g., less sexual dysfunction, fatigue, brochospasm, etc. Five patients in the ivabradine arms discontinued treatment because of "mild visual symptoms."

Servier reportedly will submit ivabradine first for European approval. An expert said, "It looks like this has the potential to be a helpful addition to our therapies that can improve the lifestyle of patients with coronary heart disease. Initial studies suggest it helps reduce symptoms, but the important question will be, as we gain more experience, whether it has a benefit on mortality and cardiac events. There are certainly patients who don't tolerate beta blockers, and this could be used in that group. It would be good to know how it performs in patients other than those with *stable* angina. For instance, beta blockers are thought to be effective after an MI because of their ability to reduce sudden ventricular arrhythmias and sudden death…There seems to be a continued need for medications to deal with patients where revascularization is not feasible…and this appears to be a promising new medication."

HOPE-TOO:
Vitamin E Not Beneficial and Perhaps Harmful

Vitamin E not only does not help prevent heart failure, it actually increases the risk of heart failure. That was the finding of a new analysis of data from the HOPE-TOO trial, presented at the European Society of Cardiology meeting in Vienna, Austria. HOPE-TOO was a 2.6 year extension of the 4.5 year HOPE trial which compared the ACE inhibitor ramipril (King's Altace) to placebo in high risk patients with vascular disease.

HOPE-TOO found the benefits of ramipril were maintained during the extension period, and there was an apparent incremental benefit in terms of the prevention of MI and diabetes. During the extension period, researchers found a 34% risk reduction in the development of diabetes and a 19% risk reduction in heart attacks.

HOPE-TOO Results

Measurement	10 mg ramipril	400 IU Vitamin E	p-value
Cancer			
Prostate	2.6%	2.6%	Nss
GI	2.7%	2.8%	Nss
Lung	1.4%	2.0%	P=.02 but needed p<.01 to be significant
Breast	0.5%	0.5%	Nss
Melanoma	0.3%	0.4%	Nss
Cardiac Events			
Primary endpoint: MI/Stroke/CV death	21.4%	20.6%	Nss
MI	5.2%	5.1%	Nss
Stroke	5.7%	5.1%	Nss
CV death	10.1%	9.9%	Nss
All cause death	16.8%	16.7%	Nss
All hat failure	13.5%	12.1% (17% increase in relative risk)	p=.04
Heart failure hospitalization	5.8%	4.2%	p=.002

However, natural source vitamin E had no effect on cancer, on major cardiovascular events or on all cause death. An investigator in HOPE-TOO, said, "This trial raises concern about the increased risk for heart failure in these patients."

Experts were quick to accept the findings and recommendations against use of vitamin E in these patients. One commented, "The results are not surprising because they show a continued benefit of ACE inhibitors, but no benefit of vitamin E. Vitamin is not only not effective, but it is harmful because it increases the incidence of heart failure…Why is vitamin E ineffective? I think the ACE-inhibitor is simply a better anti-oxidant…The conclusion is that patients with vascular disease, whether at high or low risk, should not be treated with vitamin E." Another said, "The message to doctors is to take patients off vitamin E, and the message to patients is that vitamin E is an unnecessary benefit and a potentially dangerous." ♦