Trends-in-Medicine

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by Lynne Peterson

SUMMARY

DRUGS

Atrial fibrillation . . . . . Page 1
Anticoagulation . . . . . Page 3
Heart failure . . . . . Page 6
Hypertension . . . . . Page 8
Metabolic syndrome . . . . . Page 11

DEVICES

Defibrillators . . . . . Page 12
Drug-eluting stents . . . . . Page 13
Label changes and pricing . . . Page 14
Medtronic's Endeavor . . . . . Page 16
PFO closure . . . . . Page 19
Percutaneous valves . . . . . Page 20

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EUROPEAN SOCIETY OF CARDIOLOGY

September 2-7, 2005
Stockholm, Sweden

More than 18,000 cardiologists attended the European Society of Cardiology (ESC) meeting this year, with more than three-quarters of them from Europe. Interestingly, more than half the European doctors attending ESC had their way to the meeting paid by a pharmaceutical or device company.

A record number of abstracts were submitted to ESC this year – more than 9,000 – and 2,985 were chosen to be presented, and the number of basic science abstracts also increased, comprising 26.7% of the total. A key focus of this year's meeting is heart disease in women. In the U.S. men and women are about equally affected by heart disease, but in Europe 55% of women compared to 43% of men die of cardiovascular (CV) disease. In Europe, more women die of CV than all cancers combined, with mortality 4-8 times higher in eastern Europe than in Spain, France, or Italy.

ATRIAL FIBRILLATION (AF)

Sources agreed that there is a big market potential for a pharmacologic cardioversion agent. They estimated that 10%-30% of AF patients need cardioversion annually. Currently, that is done electrically, but pharmas have been trying to find a pharmacologic way to cardiovert patients. A U.K. doctor said, "The efficiency of electrical cardioversion is very high. A drug may be easier to give, but cardioversion is not the issue; it is maintaining sinus rhythm."

ASTRAZENECA'S AZD-7009, for cardioversion – QT issue raising questions

This intravenous AF drug, a mixed potassium and sodium channel blocker, is in Phase III and has the lead over competitors, but it also has a longer infusion time than Cardiome's RSD-1235. An AstraZeneca official said, "Our average cardioversion was 26 minutes, so we think a maximum 30-minute infusion could be used, with the drug stopped at cardioversion."

More importantly, AZD-7009 also has a QTc prolongation problem and perhaps a TdP problem. AstraZeneca plans to discuss this with the FDA and is hoping that CV Therapeutics can get Ranexa (ranolazine) approved in early 2006, and then AstraZeneca plans to coat-tail Ranexa, using the same argument that the QTc prolongation is not clinically significant and was not associated with Torsade de Pointes. "It is the same increase that is seen with ranolazine," an AstraZeneca official said, adding, "If they get approved, it will help us. CV Therapeutics is 'paving the way' for us."

A dose-finding Phase II trial is ongoing, with data probably not available until the American Heart Association meeting in 2006. This trial is testing three dosing regimens: 50 minutes, 30 minutes, and two 15-minute infusions. Once this trial is

completed, the company plans a Phase III trial. A researcher said the idea would be to cardiovert patients with arrhythmia, and then send them home on something like Sanofi-Aventis's investigational agent, dronedarone.

The oral version of AZD-7009 is on hold "because of non-cardiac side effects that were not seen with the IV formulation – fever reaction thought to be tied to the extended release formulation." An AstraZeneca official said, "We need to understand that."

Two posters at ESC discussed IV AZD-7009:

➢ **D1460C00024.** This study showed AZD-7009 is effective at pharmacologic conversion of AF patients, but it raised safety questions. This was a double-blind, placebo-controlled, parallel-group, multicenter, 122-patient study assessing safety and efficacy of multiple ascending doses (0.25-2.5 µmol/L) in AF/AFl patients. Researchers reported that the majority of patients with a successful pharmacologic conversion were in sinus rhythm at 24 hours after the start of the infusion, with overall heart rhythm stable over the 24-hour period.

One patient at the 2.5 µmol/L dose experienced an asymptomatic, non-sustained polymorphic VT of 2 seconds with TdP-like features. This episode started 86 minutes after termination of the infusion. An official said the patient "didn't feel bad, and it wasn't seen in the hospital, but we found it later." QTc prolongation ≥500 ms also was seen with all doses higher than 0.5 µmol/L, with 18 patients having QTc >500 ms at the end of the infusion. Researchers insisted AZD-7009 is not proarrhythmic.

➢ **1460C0016.** This was a 51-patient, randomized, double-blind, placebo-controlled, parallel group, multicenter study of four dosing regimens in patients undergoing AF ablation. In the trial, the QT interval increased in a concentration-dependent manner (p=.02), with a clinically meaningful 11 ms (10%) increase at the highest dose level. However, the QT increase also appeared to plateau as the plasma concentration of AZD-7009 increased. The only serious adverse events were considered unrelated to the drug.

AZD-7009 Study D1460C00024

Measurement	AZD-7009 0.75 µmol/L n=11	AZD-7009 1.5 µmol/L n=11	AZD-7009 2.0 µmol/L n=12	AZD-7009 2.5 µmol/L n=12	Placebo
Patients converted to sinus rhythm at 2 hours					
Total	18%	45%	58%	58%	0
AF patients	18%	45%	64%	70%	0
AFl patients	---	---	0	0	0
Adverse events for all doses tested (0.25-2.5 µmol/L)					
Hypotension	22%				---
Nervous system disorders	5%				---
GI symptoms	3%				---
Discontinuations for adverse events	1 patient	1 patient	1 patient	4 patients	---

CARDIOME'S RSD-1235, for cardioversion – Could come from behind

The IV version of this drug is in Phase III development, and a Phase II trial is being designed for the oral formulation. It is further behind AZD-7009 in development, but it could take the lead if AstraZeneca doesn't solve the QT prolongation problem with AZD-7009.

Compared to AZD-7009, RSD-1235 has a shorter infusion time. The conversion rate was 52% with a median infusion time of 11 minutes. Infusions are continued until patients cardiovert. RSD-1235 also hasn't seen any QTc prolongation so far, no TdP, and no proarrhythmic effects.

SANOFI-AVENTIS'S dronedarone, for AF prevention – Likely to be a niche product

Experts predicted that this oral Class III antiarrhythmic, which would be a first-in-class, is likely to get approved. A U.K. cardiologist said, "It will come to market; dronedarone will get approved." A U.S. doctor agreed, "Dronedarone is very interesting…Dronedarone is moderately effective. It's not amiodarone. But it has minimal side effects. It will do well if it can show a 35% effect without proarrhythmia. Right now, I wouldn't use it in NYHA Class III or IV patients. That is the only patient group harmed, but that is a small part of AF."

At a session on atrial fibrillation therapy, a speaker reviewed the history of dronedarone trials:

- **EURIDIS** in Europe. This 1,237-patient trial compared dronedarone to placebo.
- **ADONIS** in Canada, the U.S., and some other countries. This was an identical trial to EURIDIS.
- **ANDROMEDA**, which was stopped for excess mortality.
- **ERATO**.
- **ATHENA**, an ongoing pivotal outcome trial. The first patient has been enrolled in North America, and enrollment is about to start in Europe.

In EURIDIS and ADONIS, the primary endpoint of time from randomization to first documented AF/AFl recurrence and the secondary endpoint of median ventricular rate during AF/AFl at the first recorded incidence were statistically significant favoring dronedarone. And a pooled analysis of the primary endpoint in the two trials showed a statistically significant benefit in favor of dronedarone. There was no evidence of proarrhythmia. A speaker said, "This drug not only prevents recurrent arrhythmia but has a significant rate smoothing effect… which is hoped to translate into symptomatic relief for patients."

Dronedarone Trials in AF

Measurement	EURIDIS		ADONIS	
	Placebo	Dronedarone 400 mg BID	Placebo	Dronedarone 400 mg BID
Number of patients	201	411	208	417
Hypertension	53.7%	62.0%	46.6%	58.0%
Primary endpoint: Time from randomization to first documented AF/AFl recurrence	41 days	96 days p=.0138	59 days	158 days p=.0017
Secondary endpoint: Median ventricular rate at first AF recurrence (based on TTEMs)	115	100 p<.0001	114	101 p<.001
Pooled safety analysis				
	Placebo		**Dronedarone 400 mg BID**	
Patients with any adverse event	65.8%		69.8% (Nss)	
Patients with any serious adverse event	24.4%		19.8%	
Deaths	0.7%		1.0%	
ANDROMEDA results				
	Placebo n=317		**Dronedarone 400 mg BID n=310**	
NYHA Class III/IV	62.8%		59.3%	
ERATO trial results				
	Placebo		**Dronedarone 400 mg BID**	
Ventricular rate reduction at 6 months	76.2 bpm		90.2 bpm p<.0001	
Ventricular rate during maximum exercise	159.6		129.7	

Factor Xa Inhibitors in Development

Company	Drug	Status
IV formulations		
GlaxoSmithKline	Arixtra (fondaparinux)	Approved, seeking expanded indications
Sanofi-Aventis	Idraparinux	Phase III
Sanofi-Aventis	Otamixaban	Phase IIb
Oral agents		
Bayer	BAY-59-7939	Phase III
Bristol-Myers Squibb	Razaxaban	Phase IIb completed, but development stopped due to increase in major bleeding. A second compound is being tested.
Daiichi	DX-9065a	Phase II
Daiichi	DU-176b	Phase IIb
GlaxoSmithKline	GSK-913893	Phase I/II
Kissei	KFA-1982	Preclinical
Merck	EMD-503982	Preclinical
Portals	MLN-1021	Preclinical
Teijin	N/A	N/A
Yamanouchi	YM-150	Phase IIb

However, the next trial – ANDROMEDA, a mortality trial in heart failure patients, was stopped early by the DSMB with 627 of the planned 1,000 patients enrolled when more deaths were found in the drug group than in placebo (25 vs. 12). The speaker said, "A lot of secondary analysis is going on to explain this…The only certain information at this point is that there was no case of proarrhythmia detected during that trial, and none of the excess mortality is thought to be due to excessive arrhythmic mortality." Another expert said, "The ANDROMEDA trial was poorly designed. Patients were started in the trial too soon, and the drug has a peculiar effect – it can raise serum creatinine but not because of renal dysfunction. I also understand a fair number of patients had their ACE or ARB stopped, and that could be a factor. There also wasn't sufficient monitoring of the patients."

A speaker concluded that dronedarone is superior to placebo in preventing recurrent AF, effective at heart rate control, and has shown good efficacy and safety in all studies, with excellent cardiac tolerability. He said the overall incidence of adverse events is similar to placebo, and there is no evidence of amiodarone-like toxicity (thyroid, pulmonary).

ANTICOAGULATION

FACTOR XA INHIBITORS

Factor Xa inhibitors are being tested in three areas:

1. Prevention of VTE.
2. Treatment of VTE.
3. Treatment of ACS.

At a session on Factor Xa inhibitors, a speaker declared, "Oral Factor Xas are coming…We now have a number of agents which are orally active, have rapid onset, have a predictable anticoagulant effect, don't require monitoring, and have a good safety profile." He noted that there have been promising Phase II data and a large number of Phase II trials are currently underway.

ASTRAZENECA'S AZD-6140 – Potential competitor for Plavix

New results from the DISPERSE trial indicate that this oral, reversible ADP receptor antagonist could become a viable competitor to Plavix (Sanofi-Aventis, clopidogrel). DISPERSE was a Phase IIa, randomized, double-blind, double-dummy, parallel

28-Day Results of DISPERSE Trial with AZD-6140

Measurement	AZD-6140 50 mg BID n=41	AZD-6140 200 mg QD n=39	AZD-6140 200 mg BID n=37	AZD-6140 400 mg QD n=46	Plavix 75 mg n=37
Maximal inhibition of platelet aggregation	~10%	~40%	~50%	~60%	~65%
Final platelet aggregation	~5%	~50%	~70%	~90%	~95%
Safety					
Any adverse event	51%	67%	81%	76%	70%
Serious adverse events	0	3%	3%	7%	5%
Major, non-fatal bleeding	0	0	0	1	0
Death	0	0	0	0	0
Minor bleeding	29%	44%	51%	48%	32%
Epistaxis	1%	10%	11%	17%	5%
Contusion	12%	23%	24%	26%	22%
Dyspnea	10%	10%	16%	20%	0
Dizziness	10%	5%	3%	9%	3%
Headache	0	13%	3%	2%	8%

group study done in Denmark, Hungary, and Norway, comparing AZD-6140 and Plavix in 200 atherosclerosis patients. AZD-6140 was reported to have more consistent platelet aggregation (from 28%-35% at high doses), a faster onset of action (on Day 1), and no requirement for metabolic activation. Dyspnea appears to be the side effect to watch.

BAYER'S BAY-59-7939 – Early data are promising

Substantial data are available on the PK and PD of this very specific selective inhibitor of Factor Xa, and data from two dose-finding Phase II trials were presented recently at an international meeting. In humans, it has high bioavailability and is rapidly absorbed, reaching peak levels in 2.5-4 hours, with a half-life of 5.8-9.2 hours in healthy people. It has dual excretion – renal and fecal/biliary. Bayer is currently testing both QD and BID dosing. Researchers reported a flat dose response in both studies with respect to efficacy but a clear dose response with respect to bleeding. At lower doses, the rate of major bleeding was not statistically significantly different from Lovenox (Sanofi-Aventis, enoxaparin).

BAY-59-7939 European Phase II Results

Measurement	2.5 mg	5 mg	10 mg	20 mg	30 mg	Lovenox (enoxaparin)
European hip study, using Lovenox dose of 40 mg QD						
Primary endpoint #1: Major bleeding	0.8%	2.2%	2.3%	4.5%	5.4%	(p=Nss)
Primary endpoint #2: Composite of any DVT, non-fatal bleed, or symptomatic PE	N/A	N/A	N/A	N/A	N/A	N/A
North American knee study, using Lovenox dose of 30 mg BID						
Number of patients	63	57	60	57	59	N/A
Primary endpoint #1: Major bleeding	1.0%	0	1.9%	3.1%	7.5%	1.9%
Primary endpoint #2: Composite of any DVT, non-fatal bleed, or symptomatic PE	15.4%	13.8%	11.9%	18.2%	6.9%	17.0%

Bayer has other ongoing Phase II studies of BAY-59-7939 in VTE prevention after elective hip surgery and VTE treatment and stroke prevention in AF. A Phase III trial is expected to start by the end of 2005, after the results of a Phase IIb study to determine whether BID or QD dosing is better. The results of that Phase II study will not be presented this year.

The company is looking to BAY-59-7939, at least initially, for:

- VTE prevention in major orthopedic surgery.
- VTE treatment and secondary prevention.
- Stroke prevention in AF.

GLAXOSMITHKLINE'S Arixtra (fondaparinux) – Big win

Based on data presented at ESC, Arixtra, a synthetic intravenous Factor Xa inhibitor, could almost entirely replace the leading low molecular weight heparin (LMWH), Sanofi-Aventis's Lovenox (enoxaparin). The OASIS-5 study, one of two trials making up the MICHELANGELO program, found that at nine days after a cardiac event, Arixtra was as effective as enoxaparin in preventing heart attacks, death, and ischemia with ***far*** less major bleeding.

The only three points made in support of continued use of Lovenox were:

1. A Sanofi-Aventis official pointed to the millions of patients who have been treated with Lovenox since it was approved.
2. A U.S. doctor noted that Arixtra has a longer half-life than Lovenox, but, unlike Lovenox, Arixtra can't be reversed.
3. A few doctors suggested that the results in OASIS-5 may have been biased by the Lovenox patients getting a small dose (~100 units) of heparin in the pre-filled syringe. They suggested that the higher bleeding rate with Lovenox may have been due to this heparin. OASIS-5 researchers had no comment on this.

Previous studies have shown that patients who have a major bleed in an acute coronary syndrome (ACS) exhibit a much higher risk of death in the weeks following the event. Anti-thrombotic therapies have substantially decreased the risk of a heart attack but

have also been associated with a significant increase in bleeding risks.

OASIS-5, the largest study to date in acute coronary syndromes, was a randomized, double-blind, placebo-controlled trial of 20,078 patients from 41 countries. The trial found that 2.5 mg Arixtra QD significantly reduced both mortality and bleeding compared to enoxaparin 1 mg/kg BID at Day 9, and the benefit continued out for six months. The trial was designed to, first, show non-inferiority to enoxaparin on efficacy and secondly to show superiority to enoxaparin in safety, and it met both those goals. The same results were seen in every subgroup, including the elderly. The three primary endpoints were:

- **Efficacy:** Death, MI, and refractory ischemia at Day 9.
- **Safety:** Major bleeds.
- **Risk:benefit analysis:** Death, MI, refractory ischemia, and major bleeds.

Secondary endpoints were each component separately, especially death at Day 30 and Day 180.

OASIS-5 Results

Measurement	Lovenox (enoxaparin)	Arixtra (fondaparinux)	p-value
Efficacy at Day 9			
Primary endpoint: Death, MI, refractory ischemia	5.8%	5.9%	<.00001 Relative risk reduction 18%
Death/MI	4.1%	4.1%	<.0001
Secondary endpoint #1: Death	1.9%	1.8%	<.0001
Secondary endpoint #2: MI	2.7%	2.7%	<.0001
Secondary endpoint #3: Refractory ischemia	1.9%	2.05%	<.0001
Safety (bleeding) at Day 9			
Total bleeds	7.0%	3.2%	<.00001 Relative risk reduction 56%
Major bleeds	4.0%	2.1%	<.00001 Relative risk reduction 47%
TIMI major bleeds	1.3%	0.7%	<.00001 Relative risk reduction 46%
Minor bleeds	3.1%	1.1%	<.00001 Relative risk reduction 65%
Results at Day 180			
Death, MI, refractory ischemia	13.1%	12.1%	.055
Death/MI	11.2%	10.3%	.036
Death	6.3%	5.6%	.037
MI	6.3%	6.0%	.33
Strokes	1.6%	1.3%	.029
Death/MI/stroke	12.3%	11.1%	.005

The principal investigator, Dr. Salim Yusuf of Canada, said, "The study findings demonstrate that fondaparinux is likely the anti-thrombotic drug of choice in patients with acute coronary syndromes who are already receiving aspirin and clopidogrel…Major bleeding increases the risk of mortality independently by 400%...Treating 1,000 ACS patients with fondaparinux instead of enoxaparin will prevent 10 deaths or MI, 4 strokes, and 25 major bleeds…The trial clearly demonstrated that fondaparinux is the preferred anticoagulant for the treatment of ACS…Fondaparinux is 70% the cost of enoxaparin, and it is already on the shelves of most hospitals, so we have a drug that gives a net benefit at no greater financial cost." Another investigator said, "Any physician, before writing a prescription for enoxaparin, should think twice or three times now."

A second trial in MICHELANGELO, the 12,000-patient OASIS-6 study, is underway, with the results expected at the American College of Cardiology meeting in 2006.

Other trials in the Arixtra cardiology program include:

- **PENTALYSE**, which found increased patency with Arixtra vs. UFH.
- **PENTUA**, a pilot, dose-finding study which found Arixtra at least as effective as Lovenox in the primary endpoint of death, MI, and re-ischemia.
- **ASPIRE,** a pilot trial done prior to MICHELANGELO to determine the safety of Arixtra in PCI patients. The study found it is safe to administer Arixtra in combination with aspirin and Plavix.

At the American Heart Association meeting in November 2005, Dr. Steve Nissen and Dr. James (Terry) Ferguson are scheduled to debate the use of Lovenox vs. unfractionated heparin (UFH), though that could now be changed to include Lovenox vs. UFH or Arixtra.

DIRECT THROMBIN INHIBITORS

BOEHRINGER INGELHEIM'S dabigatran – Cautious optimism

This oral direct thrombin inhibitor will enter Phase III this year, with a 15,000-patient, unblinded, non-inferiority trial having three-year follow-up. Two BID doses – 150 mg and an unidentified dose <150 mg (probably 100-125 mg) will be tested. An investigator said he is "cautiously optimistic" about dabigatran because "there has been no liver signal, and I know the drug is effective from D-dimer levels which are an index of the activity of the coagulation system." He said AstraZeneca's experience with Exanta (ximelagatran) taught him:

- To assume a liver problem until it is proven not to exist, so the trial will have careful liver enzyme monitoring.
- That the SPORTIF trial was well-designed, and he wants to capitalize on that.

ANTI-THROMBOTICS

SANOFI-AVENTIS'S Lovenox (enoxaparin), which is sold in Europe as Clexane – Lost to GlaxoSmithKline's Arixtra except in the cath lab

If anything could take the sting out of the results of the OASIS-5 trial for Sanofi-Aventis, the STEEPLE trial did. STEEPLE showed that an IV bolus of Lovenox (at either 0.5 mg/kg or 0.75 mg/kg) just prior to PCI – with no monitoring of coagulation – was, in addition to being easier to use, as effective but safer than an ACT-adjusted regimen of UFH (with or without a GP-IIb/IIIa inhibitor) in efficacy. STEEPLE was a prospective, randomized, open-label, parallel group trial in 3,528 patients with stable angina.

In November 2004, the DSMB recommended stopping enrollment in the trial based on a significant difference on all-cause mortality in favor of Lovenox. The investigators strongly disagreed with the DSMB about stopping the trial, but in December 2004 they decided to follow the DSMB guidance. The study showed no statistically significant difference between either the Lovenox arm and UFH in death, non-fatal MI, urgent TVR, or the composite of all of those.

Asked how interventional cardiologists will choose between Lovenox and The Medicine Company's Angiomax (bivalirudin) in lieu of UFH, the STEEPLE investigator said, "We are moving away from UFH in angioplasty…Now, we can do direct comparisons of two studies…If you do that, you would see that, clearly, enoxaparin is good in terms of safety…In REPLACE (with Angiomax), the major message has been safety…STEEPLE safety looks even better."

STEEPLE Results

Measurement	Lovenox 0.5 mg/kg	Lovenox 0.75 mg/kg	UFH	Relative risk reduction with Lovenox
All cause mortality vs. UFH	p=0.15	p=0.62	---	---
Primary endpoint: Major and minor non-CABG bleeding ≤48 hours	6.0 % (p=.014)	6.6% (p=.052)	8.7%	Down 31%
Major bleeding	1.2% (p=.005)	1.2 (p=.007)	2.8%	Down 57%
Minor bleeding	4.9% (Nss)	5.4% (Nss)	---	Nss
Secondary endpoint: Death, MI, and urgent revascularization at 30 days	7.2% (Nss)	7.9% (Nss)	8.4%	Nss

SANOFI-AVENTIS'S Plavix (clopidogrel) – The data gets better and better

Plavix got a nice boost at ESC. The PCI-CLARITY trial – a subset study of the CLARITY-TIMI-28 trial – was simultaneously released at ESC and published in the ***Journal of the American Medical Association***. It found Plavix pre-treatment significantly reduces the incidence of CV death or ischemia complications both before and after PCI. There was a 46% reduction in the primary endpoint of CV death, MI, or stroke (3.6% with Plavix vs. 6.2% without it). The results favored Plavix regardless of:

- Whether the PCI was urgent or elective.
- The time from randomization to PCI.
- Use of IIb/IIIas.

There was no difference in either major or minor bleeding. A speaker said the study means that 23 patients need to be treated to prevent one CV death, stroke, or MI at 30 days; and for every 100 patients undergoing PCI, Plavix use prevents four major CV events.

PCI-CLARITY Results

Measurement	Relative risk reduction
Primary endpoint #1: Combined CV death, MI, or stroke	Down 46% (3.6% with Plavix and 6.2% without it)
MI or stroke before PCI	Down 38%
CV death, stroke, or MI at 30 days	Down 41% (7.5% with Plavix vs. 12% without it)

Another trial reported at ESC found that medical reperfusion of STEMI patients with heparin, aspirin, and Plavix is feasible before reaching the hospital in medically equipped ambulances without an apparent increase in bleeding.

HEART FAILURE

ABBOTT/ORION'S Simdax (levosimendan) – Cautious optimism

Levosimendan is a first-in-class calcium sensitizer that improves cardiac function and symptoms. It currently is available in an intravenous formulation and is approved in approximately 30 countries. Levosimendan is in Phase III clinical studies in the United States and Europe and has been granted fast-track status by the FDA. Upon completion of clinical trials already in progress, Abbott will seek approval to market levosimendan in countries where it is not yet available.

The final results of the SURVIVE trial, a mortality trial of an IV oral calcium sensitizer, Abbott/Orion's Simdax (levosimendan), were on the final ESC program, but they were not presented at ESC. Dr. Michel Kamajda of France, Chair of the ESC Program Committee, said, "We were informed the database analysis would not be ready for Stockholm. In SURVIVE, there were promises we would have final results ready for Stockholm, and something went wrong logistically."

Expectations are positive but not high for SURVIVE, especially after the release of less-than-impressive data on another inotrope, Myogen's enoximone, at the Heart Failure Society of America (HFSA) meeting last year, and disappointing results from the ESSENTIAL trial, which were presented at ESC. ESSENTIAL, which was comprised of two trials (a North/South American trial and a European trial) tested a lower dose of enoximone (25 mg and 50 mg QD) in 1,854 NYHA Class III/IV patients, followed for an average of 16.4 months. There was no evidence of benefit – no difference in all-cause mortality or six-minute walk – in the pooled analysis. In June 2005, the company issued a statement saying development of enoximone was being halted, but an official at ESC insisted development is only on hold until a subgroup analysis of ESSENTIAL can be completed to see if patients can be identified who benefit more than others (e.g., sicker patients) and the size of that subgroup. If a patient population of sufficient size can be identified, he said the company would do a Phase III trial in those patients.

SURVIVE is an international (Finland, France, Germany, Israel, Latvia, Poland, Russia, and the U.K.), multicenter, randomized, parallel group, double-blind, double-dummy trial in ~1,300 patients with acute heart failure requiring inotropic support. SURVIVE originally planned to enroll 700 patients, but the steering committee recommended changing it to an event-driven study (330 events). A loading dose of 12 µg/kg levosimendan was followed by 0.1 µg/kg levosimendan for 50 minutes and then 0.2 µg/kg levosimendan vs. dobutamine, not placebo. The primary endpoint is all-cause mortality at 180 days. Secondary endpoints include:

- Days alive and out of hospital at 180 days.
- All-cause mortality at 31 days.
- Global assessment at 24 hours.
- Change in patient evaluation of dyspnea at 24 hours.

Data from SURVIVE will now be presented at the American Heart Association meeting in November 2005 along with the results of the REVIVE trial. Both trials will be late breaker presentations. An Abbott official claimed levosimendan is more likely to be successful than other inotropes for two reasons:

1. It is a different mechanism of action.
2. It is very long acting (80 hour half-life, which allows it to work up to 14 days).

Heart failure expert Dr. Milton Packer of the University of Texas Southwestern Medical Center in Dallas spoke at an Abbott-sponsored session, and he was very positive about the outlook for Simdax. He pointed out that:

- There is no real evidence that IV peripheral vasodilators make patients feel better or live longer.
- There is "zero" evidence from randomized clinical trials that positive inotropic agents make people feel better.
- There is a "possibility" that positive inotropic agents positively affect mortality, but that has not been shown yet in randomized clinical trials.
- Heart failure specialists use IV inotropes "because we believe this is a hemodynamic disease, and we want to make the hemodynamics better. But this is a clinical disease. Patients don't say, 'My cardiac output is low,' or, 'My wedge pressure is high.' They say, 'I feel lousy, and I'm afraid I'm going to die.' They want you to make them feel better and save their life."
- The hope is that Simdax will improve symptoms without adversely affecting (and perhaps even improving) survival.

JOHNSON & JOHNSON'S Natrecor (nesiritide) – In big trouble

Sources all predicted Natrecor is dying or dead following the FDA warning earlier this year that the drug may increase a patient's risk of death within 30 days of treatment. Dr. Packer commented, "You will hear that 75% of patients treated with nesiritide had relief and improvement in dyspnea, but 65% of patients got better with placebo…So there is something here, but probably not as dramatic as you might expect."

PROTEIN DESIGN LABS' ularitide – Positive data

Positive results were reported from the Phase II SIRIUS-II study of ularitide in acute decompensated heart failure (ADHF). Ularitide is a synthetic version of urodilatin, a natriuretic peptide produced in the kidney, that would compete with Johnson & Johnson's Natrecor (nesiritide) – if it gets approved. When injected into the blood stream, ularitide causes relaxation of blood vessels, specifically in the arteries that feed the kidneys, lungs, and heart, and stimulates natriuresis (excretion of abnormal amounts of sodium into the urine) and diuresis (increase in urination).

SIRIUS-II was a randomized, double-blind, placebo-controlled, proof-of-concept, European (Germany, Russia, and Serbia) trial of 221 patients, comparing three doses of ularitide (7.5, 15, or 30 ng/kg/min given IV as a 24-hour infusion) to placebo. The principal investigator, Dr. Veselin Mitrovic of Germany, concluded ularitide did not worsen renal function through 72 hours, length of hospital stay (at the two highest doses), and was well tolerated. He indicated the optimal dose (15 ng or 30 ng) may depend on baseline blood pressure.

A company official said the 15 ng/kg/min dose will go forward, but a decision has not yet been made on the 30 ng/kg/min dose. The official said the company plans to file for an IND later this year and to begin enrollment in a Phase II U.S./European trial in late 2005 or 1Q06. The trial will be somewhat different from SIRIUS-II, with less focus on PCWP, more focus on symptomatic relief, physician assessment scores, and use of fewer rescue medications. He said,

SIRIUS-II Results of Ularitide in ADHF

Measurement	7.5 ng/kg/min n=60	15 ng/kg/min n=53	30 ng/kg/min n=55	Placebo n=53
Primary endpoint #1: Dyspnea score at 6 hours	(p<.05)	(p<.05)	(p<.05)	---
Primary endpoint #2: Change in PCWP from baseline at 6 hours	Down 10 to 12 mmHg (p<.05)			Down 4 mmHg
Secondary endpoint #1: Serum creatinine out to 72 hours	Unchanged compared to placebo except at 25 hours with 15 ng dose, where it tended to be decreased			
Secondary endpoint #2: Length of hospital stay	192 hours	122 hours	158 hours	200.5 hours
Secondary endpoint #3: 30-day mortality	3.3% (p=0.08)	3.8% (p=0.16)	1.8% (p=0.029)	13.2%
Safety				
Hypertension	8.3%	11.3%	16.4%	1.9%
Blood pressure decrease	5.4%			0
Cardiac failure	4.8%			2%
Increased sweating	4.2%			0
Dizziness	3.6%			1.9%
Fatigue	2.4%			0
Death	2 patients	2 patients	1 patient	7 patients

"Our study would explore earlier in-hospital use than with Natrecor."

The exact values (results) by dose for the two primary endpoints were not presented at ESC, just the p-values, and company officials declined to provide them.

Other drugs

Among the other drugs identified by a speaker as promising in heart failure were:

- **TEIJIN/IPSEN'S febuxostat (TMX-67)**, an xanthine oxidase (XO) inhibitor. This is in development for gout, but he suggested that in the future it may be shown to have utility in heart failure.
- **AMGEN'S Aranesp (darbepoetin).**
- **ARK THERAPEUTICS' imidapril**, an ACE inhibitor for cachexia, which is in Phase II development. He said 12%-16% of CHF patients have cachexia.
- **VASOGEN'S Celecade**, a device-based therapy in which a small amount of blood is withdrawn from a patient and then processed in a machine that exposes it to heat, oxidation, and UV light. The treatment purportedly stresses the blood cells and causes them to die. The treated blood is then given back to the patient in the form of an intramuscular injection. However, the speaker suggested this may only be appropriate for patients with inflammation, and Vasogen announced earlier this year that it was halting a trial of Celecade.
- Appetite stimulants, such as megastrol acetate.
- Insulin sensitizers.

Among the agents that have not proven to be useful or which are unlikely to succeed in CHF, he identified:

- **CARDIOME'S Oxyprim (oxypurinol)**.
- Growth hormone.
- Immune modulators, including TNF inhibitors.

HYPERTENSION

CV THERAPEUTICS' Aceon (perindopril) – Good data but still a hard sell

Perindopril is an ACE inhibitor by Servier (which sells it in Europe as Coversyl). The rights in the U.S. were licensed to Solvay, but Solvay opted not to put much effort into marketing Aceon. Then, in December 2004, CV Therapeutics obtained co-marketing rights in the U.S.

Can CV Therapeutics boost sales of Aceon the way King did for Altace (ramipril) after the HOPE data? That remains to be seen. A company official, who commented that it shouldn't take much to grow U.S. Aceon sales from the current level of $30 million a year, may be right.

CV Therapeutics recently hired 270 sales reps and is just beginning to market Aceon – and its anti-angina drug, Ranexa (ranolazine), is expected to get FDA approval of its SPA in January 2006. U.S. doctors questioned about the outlook for Aceon were not sure how it would do. Most insisted that all ACE inhibitors are equivalent – "an ACE is an ACE is an ACE." Some doctors admitted that the company may be able to use the trial data to build a market for Aceon, but others said the environment has changed since the HOPE trial, and the equivalency of ACE inhibitors is now more ingrained.

CV Therapeutics also has some strong trials to use for marketing. In PROGRESS, the benefits of perindopril were shown in stroke prevention. In 2003, the 12,218-patient EUROPA trial found that ACE inhibitors (specifically perindopril) are beneficial in low risk patients. Then, earlier this year, the 1,500-patient PERSUADE trial extended those benefits to diabetics. PERSUADE researchers estimated that treating 27 patients with 8 mg Aceon daily over four years would prevent one cardiovascular death or MI.

At ESC two other perindopril studies were presented, and both were positive:

➢ **The PREAMI trial** of perindopril in the elderly with MI. From 60%-65% of AMIs occur in patients older than 65, and

80% of deaths due to AMI occur in patients >age 75, and perindopril appears effective and safe in elderly patients. PREAMI was a 1,259-patient trial in five European countries. Patients were given perindopril 4 mg for one month and then 8 mg for 11 months. The trial met its combined primary endpoint, but it only showed a statistically signification reduction in risk in cardiac remodeling, not mortality or hospitalization for heart failure. An investigator said, "Blood pressure decrease was one of the explanations for the beneficial effect, but prevention of cardiac remodeling also could be a main feature of the drug…The absence of a significant effect on the other endpoints is probably explained by the relatively short-term duration of treatment."

PREAMI Results with Perindopril

Measurement	Relative risk reduction vs. placebo	p-value
Primary endpoint #1: Combined death, hospitalization for heart failure and cardiac remodeling	38%	<0.001
Cardiac remodeling	46%	<0.001
Hospitalization for heart failure	27%	0.24
Mortality	0	0.90

Asked if the results of PREAMI can be considered a class effect, an investigator said, "That is a difficult question. We have evidence with perindopril. We might extrapolate (to other ACE inhibitors), but with ACE inhibitors – and particularly lipophilic ACE inhibitors, which I tend to think are very similar…You have to be careful when extrapolating data." However, he definitely believes this trial shows all post-AMI patients should get an ACE inhibitor, "After the good results in HOPE and EUROPA, we found that all patients should get an ACE inhibitor, and PREAMI offers some explanation for why."

➢ **The ASCOT-BPLA trial**, a substudy of the EUROPA trial showed that Pfizer's calcium channel blocker (CCB) Norvasc (amlodopine) plus Servier's ACE inhibitor perindopril (sold in Europe by Servier as Coversyl and in the U.S. by Solvay and, just recently, by CV Therapeutics as Aceon) are more effective in reducing CV events (e.g., heart attacks and strokes). The 19,257-patient ASCOT-BPLA trial, funded primarily by Pfizer, was stopped early (in December 2004) by the DSMB because of a higher event rate in the atenolol + diuretic arm.

The results of this trial were first presented at the American College of Cardiology meeting in March 2005. A more complete data presentation was made at ESC along with simultaneous publication in ***The Lancet***, and the trial became hot news and a much more important study. Norvasc + Aceon significantly reduced major CV events, stroke, CV mortality, and new-onset diabetes, far better than atenolol + diuretic. These findings were true for every one of the many pre-specified subgroups, and adding a statin to the Norvasc + Aceon arm was an even more efficient approach, cutting fatal MI and non-fatal CHD by 48% and reducing fatal/non-fatal stroke by 44%.

Dr. Salim Yusuf of McMaster University in Ontario, Canada, who discussed the study, declared, "This is a wonderful study that will influence clinical practice even though the primary endpoint was not significantly lower." Should the early termination of the trial take away from the good results? Dr. Yusuf doesn't think so. He said, "The way to interpret this trial is not in isolation, but in the totality of the data." Dr. Yusuf also suggested that the benefits of this combination therapy can be extrapolated as a class effect for CCBs and ACE inhibitors, "You have to decide if it is appropriate to extrapolate. I won't guarantee the same results, and you might not get the same results, but I think by using the newer agents we are likely to get a slightly better effect than the older agents, but the older agents still have a place."

Experts all agreed that ASCOT-BPLA will boost ACE inhibitor use, though not necessarily use of Aceon. Some sources suggested that the trial proved more about Norvasc than it did about Aceon or ACE inhibitors, and there are several issues Aceon competitors can bring up about the data, including:

- The trial missed its primary endpoint, though this probably was due to the early termination of the study.
- The Aceon arm achieved lower average systolic blood pressures. ASCOT-BPLA researchers insisted the perindopril advantage was driven by more than blood

Results of the ASCOT-BPLA Trial

Measurement	Relative risk reduction with Norvasc + Aceon	p-value
Fatal and non-fatal stroke	Down 23%	Nss
Primary endpoint: Stroke (fatal and non-fatal) and coronary revascularization	Down 16%	.1257 (Nss)
Major cardiac events	Down 16%	<.001
Strokes	Down 23%	.003
All cause mortality	Down 11%	.0247
CV mortality	Down 24%	---
Unstable angina	Down 32%	.0115
Chronic stable angina	No change	Nss
Peripheral artery disease	Down 35%	.0001
Heart failure	Down 16%	Nss
New onset of renal impairment	Down 15%	.0187
New onset diabetes	Down 30%	<.0001
Adverse events		
	Norvasc + Aceon	**Atenolol + diuretic**
Total adverse events	25%	25%
Serious adverse events	2%	3%
Cough	19% (p<.0001)	8%
Dizziness	12%	16% (p<.0001)

pressure lowering, but competitors are likely to make that connection.

- Compliance may have affected the results. Compliance data were not presented.
- ***The Lancet*** commentary suggested the advantage to the Norvasc + Aceon arm may be due primarily or exclusively to the Norvasc since, on average, a CCB can be expected to lower blood pressure by 2.7 mm more than a beta blocker and this gradient "is sufficient to explain the cardiovascular benefit of (Norvasc) with or without (Aceon)."

MYLAN'S nebivolol

European doctors questioned agreed nebivolol works, but they indicated it generally is being used in only a few patients. Sources described nebivolol as a niche product, insisting it would stay that way until "decent studies with real endpoints" are done. One doctor commented, "It lowers blood pressure, and patients tolerate it well. I use it in patients who can't tolerate other drugs because of leg aches/pains. They can tolerate nebivolol better."

MYOGEN'S darusentan

The positive Phase II results in treatment-resistant hypertension for this ET_1 are considered "provocative" and "very interesting," but sources all agreed that it will be very difficult for the company to get FDA approval for this indication since the drug is teratogenic. A source pointed out that the Phase II results were positive, but only showed efficacy, not a mortality benefit.

NOVARTIS/SPEEDEL'S aliskiren (SPP-100) – Very promising

Aliskiren, an oral renin inhibitor, is the first in this new class of drugs to reach Phase III development for hypertension as a single agent and in combination with the generic ARB losartan. Numerous other renin inhibitors have failed in development, primarily due to: lack of oral availability, low efficacy, short half-life, and the cost of production. Novartis has said it plans to file aliskiren with the FDA in early 2006 and with European regulators in 4Q06. In both cases, Novartis plans to seek approval for both monotherapy and combination treatment with other antihypertensive agents.

There was no new data on aliskiren at ESC, but a Novartis-sponsored seminar on renin inhibition was extremely well attended, and doctors were optimistic about it. A speaker said, "Aliskiren has the unique potential to achieve optimal RAAS suppression, providing benefits beyond blood pressure control, alone or in combination with other therapeutic approaches."

Speakers emphasized that aliskiren appears synergistic with both ARBs and ACE inhibitors. It is oral and long-lasting (half-life of approximately 25-30 hours, which supports QD dosing). In animals, it has shown dose-dependent reduction in blood pressure and renin activity (PRA), target organ protection (reduction in albuminuria, left ventricular hypertrophy, etc.). Interestingly, the circadian rhythm of blood pressure is preserved.

Aliskiren is currently in four Phase III trials, but these are ***not*** pivotal trials. The data from two of these, both unnamed trials, were expected shortly after ESC, probably by press release. The other two trials are:

- **AVOID**, a 396-patient trial in Type 2 diabetics, of aliskiren + losartan.
- **ALLAY**, a 480-patient trial in overweight hypertensives with left ventricular hypertrophy, of aliskiren + losartan.

Asked if it may prove more effective to use aliskiren with an ARB or an ACE inhibitor, an expert said, "In my mind, I think it will be better with an ARB because there are more escape ways with an ACE inhibitor. I think it will be more complementary with an ARB, but there are no data to support that yet."

Asked how much more effective aliskiren is at suppression of renin than a beta blocker, an expert said there is broader activity with aliskiren, "Beta blockers suppress some renin, but only beta-1 secretion."

Shortly after ESC, Novartis and Speedel reported positive data from three Phase III trials demonstrating that aliskiren is effective and safe, both as monotherapy and in combination with the diuretic hydrochlorothiazide (HCTZ). The monotherapy trials were Study A-1201 in 455 patients and Study A-2308 in 672 patients. The data from the three trials showed:

- 24-hour blood pressure lowering, including good reduction in the early morning.
- Clinically significant reductions in blood pressure across all doses (75, 150, 300, and 600 mg QD).
- Consistent blood pressure lowering across all studies.
- Good safety and placebo-like tolerability up to 300 mg.
- In combination with HCTZ, aliskiren was associated with significant additional blood pressure lowering, good response rates, and very good safety and tolerability at all doses tested.

Watch for more data in 2006 on aliskiren, including:

- ➢ Aliskiren in combination with an ACE inhibitor and a CCB.
- ➢ Data on end-organ protection.

Novartis also plans to start three major outcome morbidity and mortality studies in 2Q06, with data expected in late 2011.

METABOLIC SYNDROME

Did Sanofi-Aventis ignite the current controversy over whether or not metabolic syndrome is a real condition? Dr. Robert Eckel, president-elect of the American Heart Association (AHA), said, "I don't know if you can target one pharma as an explanation for why the controversy exists. The fact that there is no FDA indication for treatment (of metabolic syndrome) may concern the pharmas, but it doesn't concern the scientists who work on the (treatment) guidelines."

In August 2005, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a joint statement that advised doctors not to diagnose or treat metabolic syndrome but, instead, to treat all cardiovascular (CV) risk. Officials wrote: "While there is no question that certain cardiovascular risk factors are prone to cluster, we found that the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a cardiovascular disease risk marker."

However, the major cardiac organizations – the American Heart Association (AHA), the American College of Cardiology (ACC), and the European Society of Cardiology (ESC) – may not agree. AHA President Dr. Eckel said, "It is important to state that the controversies around the definition are relatively modest, and I think, in time, can be resolved to where we can agree on what the syndrome is and is not…Because this is a relatively new entity in the medical enterprise, I think more time and research is needed to refine the definition…but the goal of all the groups is to work for a unifying definition."

Dr. Eckel suggested that the ADA and EASD position is based on three things, all of which he said are valid questions to raise:

1. Definitions of metabolic syndrome vary. For instance, he said, waist circumference may not need to be excessive for a patient to have characteristics of metabolic syndrome.
2. The syndrome may not be the same in everyone in terms of what causes it.
3. There may be concerns that drug therapy may be targeted to the syndrome, and in the U.S., at least, there is not an FDA criteria for metabolic syndrome.

Doctors already recognize metabolic syndrome, Dr. Eckel insisted. He said, "The syndrome is a world-known phenomenon. Yes, there are multiple criteria that differ modestly, not tremendously…Physicians around the world are recognizing it…It is bringing more attention to the importance of lifestyle...and ultimately may give rise to therapeutic drug therapy…The syndrome is accepted by the world…Issues were raised that need to be acknowledged, but the syndrome has been at least accepted on a world-wide basis…Physicians have accepted this and are dealing with it in their practices…So, though the science remains somewhat uncertain and controversial, the emphasis on lifestyle still is the mainstay for approaching therapy."

The president of the ESC, Dr. Michal Tendara of Poland, said, it is unlikely the ESC will be silent on this matter. He said, "It is still a matter of controversy...We (ESC) don't have an official statement on this…but this may be worked out at this meeting or afterwards…We want to think it over and perhaps in a few months release a statement…It is likely we will say we do agree, but it does take time, and we will make time to address the issue…It is very likely we will come up with the same conclusions."

There do not appear to be any plans for a joint AHA-ACC-ESC statement on metabolic syndrome at ESC. Dr. Eckel said, "At this point there are no plans to identify a single definition for the syndrome among the organizations…but we are working together as we know more about it, its cause and definition, to resolve this issue for the benefit of physicians around the world…With further time and a better understanding of the syndrome and its causation, we can come up with a better definition."

ASTRAZENECA'S Galida (tesaglitazar) – Positive data in metabolic syndrome

The 12-week results of the SIR trial of this dual PPAR-α/γ were presented at the American Diabetes Association (ADA) meeting in June 2005, but a post hoc analysis of the effect of the drug on metabolic syndrome was presented at ESC. Despite the recent joint ADA/EASD statement advising doctors not to diagnose or treat metabolic syndrome, Dr. Steen Sender of Denmark, suggested Galida is effective in reducing the prevalence of metabolic syndrome. He noted that all improvements were dose-related.

SIR was a randomized, double-blind, placebo-controlled, 12-week Phase II study in 390 non-diabetics with insulin

12-Week Effect of Galida on Metabolic Syndrome in the SIR Trial

Definition of metabolic syndrome	Patients on Galida 0.1 mg n=60	Patients on Galida 0.25 mg n=70	Patients on Galida 0.5 mg n=58	Patients on Galida 1.0 mg n=65	Placebo patients n=137
NCEP	69%	46%	81%	76%	74%
WHO	41%	44%	38%	33%	29%
IG baseline	52%	60%	61%	59%	50%
Change in metabolic syndrome					
NCEP	-13%	-14%	-49%	-45%	-6%
WHO	-8%	-15%	-67%	-89%	+25%
IG baseline	+14%	-13%	-23%	-59%	+22%

resistance. The metabolic syndrome analysis compared 12-week outcomes with Galida using three different definitions: NCEP, WHO, and ADA. All improvements in metabolic syndrome were dose-related. Dr. Sender predicted that Galida may be a life-long therapy "if it turns out to have an effect on hard endpoints." The side effects he said need to be watched are: weight gain, fluid retention, increases in creatinine levels (but not reduced creatinine clearance), and an effect on leukocytes.

SANOFI-AVENTIS'S Acomplia (rimonabant) – More confirmatory data

The two-year results of the RIO-North America trial were presented at the American Heart Association meeting in November 2004, and two-year results of the RIO-Europe trial were presented at the American College of Cardiology meeting in March 2005. At ESC, researchers presented a pooled analysis of the two-year data from those trials, concluding that the results in the first year with Acomplia 20 mg continued through the second year.

Pooled Analysis of 2-Year Results from RIO-North America and RIO-Europe Trials

Measurement	Placebo n=912	Acomplia 5 mg QD n=1,517	Acomplia 20 mg QD n=1,491
Absolute weight loss	-1.2 kg (2.65 pounds)	-2.3 kg (5.1 pounds)	-5.1 kg (11.2 pounds)
≥5% weight loss	18.0%	---	41.6%
≥10% loss	7.6%	---	18.7%
Waist circumference (average decrease)	-2.1 cm (0.8 inches)	-2.9 cm (1.1 inches)	-5.3 cm (2.1 inches)
Metabolic effects			
% of subjects with metabolic syndrome	---	---	42% reduction in prevalence (p=.001)
Change in HDL	+9.5%	+12.1%	+17.7%
Change in HDL in patients with low baseline HDL	+13.4%	+15.6%	+22.2%
HDL increase not attributable to weight loss	---	---	54%
Change in triglycerides (TGL)	+7.7%	+4.1%	-2.8%
Change in TGL in patients with high baseline TGL	-6.3%	-10.6%	-17.0%
TGL loss not attributable to weight loss	---	---	47%
Change in blood pressure	Down 0.2 mmHg	---	Down 0.6 mmHg (Nss)
Safety			
Any adverse event	77.0%	74.4%	76.7%
Any serious adverse event	5.4%	4.7%	4.5%
Discontinuations for adverse events (in Year 2)	4.7%	4.5%	4.7%
Mood alterations	4.1%	4.8%	5.4%
Nausea	5.9%	15.6%	N/A

MISCELLANEOUS

Kos Pharmaceuticals' Niaspan (extended release niacin)

Sources indicated that Niaspan is underutilized, but they do not see any significant increase in usage on the horizon. The problem, as one source put it, is that Kos "has not done the trials, so it is harder for them to gain further (market share)."

DEVICES

DEFIBRILLATORS

CAMERON HEALTH'S S-ICD – Early but worth watching

The concern is whether an S-ICD has sufficient energy for defibrillation. The results of the prospective, randomized, multicenter, international trial comparing an S-ICD and transvenous (TV) ICDs in 51 mostly NYHA Class I/II patients, of whom 47 completed the trial, was initially presented at the Heart Rhythm Society meeting in June 2005, and it was repeated at ESC.

In the trial, the TV ICDs included 34 from Medtronic, 15 from Guidant, and 2 from St. Jude; and 32 were single-chamber, 14 dual chamber, and 5 biventricular. Four patients did not complete DFT testing, so there were data on 53 patients. Lead repositioning was allowed for the TV system but prohibited for the S-ICD. An investigator noted that this S-ICD required approximately three times the energy as the TV defibrillator but that fluoroscopy is not required with an S-ICD, provided basic anatomical rules are followed. The expectation is that future generations of the device will require less energy.

The discussant concluded that this is feasible for acute use, and there is a real need for non-cardiac lead ICD systems, in particular S-ICDs and that there are patients who could benefit from an S-ICD that offers only shock therapy without ATP capability or pacing, including:

- CHF patients without a CRT indication (SCD-HeFT patients).
- Non-obstructive hypertrophic cardiomyopathy patients.
- Patients with ion-channel abnormalities, and particularly the Brugada syndrome.
- Patients with idiopathic VF without a CRT indication.
- Younger patients who will be treated for decades.

However, he also pointed out that there were no data on the critical point of the quality of the sensing and tachycardia, and tolerability is not

Comparison of S-ICD and TV ICD

Measurement	S-ICD n=49	TV ICD n=49	p-value
ICD implanted	Cameron Health	34 Medtronic 15 Guidant 2 St. Jude	---
DFTs	36.6 J	10.2 J	<.001
Procedural complications	0	0	Nss
Repositioning of leads	Not permitted	17% 8 patients	---
Time to insertion	6 minutes	N/A	---
Fluoroscopy	Not permitted	Yes	---
Failure to defibrillate	1 patient	1 patient	Nss
Lead repositioning required	0	9	---
Advantages	Cost No TV lead	Optimal sensing Pacing ATP functions	---
Disadvantages	Pain/discomfort No ATP functions No pacing Less sensing	Lead failure (<2%/yr) Lead infection (1%/yr) Chronic vein occlusion	---

clear. He concluded, "Many technical obstacles will have to be surmounted before S-ICD can be used in clinical practice…but the rationale is right and the concept is of interest."

Shock boxes

Cheap "shock boxes" with shocking capability but few of the bells and whistles seen on other devices haven't really caught on in the U.S., but experts at an ESC session predicted they will catch on, in Europe and the U.S. Among the comments were:

- "First, you should optimize background therapy, and we haven't even done that yet in Europe, and then you can consider an ICD. We need to define who should not have it – and patients with end-stage heart failure is one group that should not get them. They have not been in the trials and invest in an ICD is an upfront cost that has to be paid off over a substantial period of time. If the patient has a chance of surviving more than one year, it starts to become reasonable. But if the patient is very terminal, then an ICD is not the treatment because it is not cost-effective in that situation…ICD therapy is a potential bomb in the whole community because the cost can be enormous, and each society has to make its priorities…To make them (ICDs) cost-effective is a must, but I also think the cost of ICDs will come down once volume increases. We have already seen that in Sweden. Prices have come down substantially."
- "I believe that new technologies, new ICD technology, will probably allow the cost to decrease significantly and to allow wider use. But the indications for primary use of an ICD in the general population of heart failure patients is not very clear for me. These indications are only based on one study – SCD-HeFT – and it had a very particular population with a low mean age (60), when the mean age in the general population is >70 years, and there was a very low rate of females in that trial. I'm not sure SCD-HeFT data can be generalized to the real life heart failure population."
- "The idea of a cheap ICD was born in Europe by Biotronik…Biotronik has created a cheap device which started to be implanted two years ago…These devices are an idea, but if you look at who is a candidate for a cheap device, you recognize there are a lot of issues to be solved (What about patients with narrow QRS, heart failure, or atrial fibrillation? What is the role of CRT in right ventricular failure? Who is the ideal candidate?)."

DRUG-ELUTING STENTS

One of the key lectures at ESC each year is the Grunzig Lecture. This year it was delivered by Dr. Jean Marco of France on "Drug-Eluting Stents – Promises and Precautionary Attitude." Among the points he made were:

- **Primary endpoints.** The power of randomized clinical trials is only valid for the primary endpoint.
- **Cypher vs. Taxus.** No comparisons can be made between the Cypher and Taxus studies. Although the reduction in restenosis appears higher (83% with Cypher vs. 70% with Taxus), he warned against interpreting that to mean Cypher is more effective.
- **Late loss.** Significant differences in late loss may be clinically meaningless.
- **Clinical outcomes.** Clinical outcomes – e.g., TVF, TVR, or mortality – are more important than angiographic parameters. He said, "We have to give priority in day-to-day practice to trials with clinical endpoints with an adequately powered sample that reaches the primary endpoint…The trials examining drug-eluting stents have been underpowered to examine mortality, MI, or other potential complications of drug-eluting stents…The substantial reduction in the rate of MACE observed with drug-eluting stents is entirely driven by the different rate of TVR between drug-eluting stents and bare metal stents, without any effect on death or MI." He noted that TVF was reduced 59% by Cypher in SIRIUS but only 47% by Endeavor in the ENDEAVOR-II trial, but, again, he insisted comparing these numbers is invalid.
- **Stent thrombosis.** Drug-eluting stent trials were not powered to detect rare events such as late acute stent thrombosis (LAST), which may occur in 0.35%-0.72% of patients – and in patients where it does occur, mortality is in the range of 30%-50%. Yet, he estimated that more than 70% of drug-eluting stent patients are over age 70,

and 20% of these patients will require some interventional procedure within a year of PCI that may cause a doctor to stop antiplatelet therapy. He suggested that these concerns are spurring interest in non-polymer drug carriers or reservoirs (an oblique reference to Sorin's Janus stent and Conor Medsystems' CoStar stent)."

Taxus and Cypher label changes – Bad news for Taxus

In August 2005 the FDA changed both the Taxus and Cypher labels. Taxus got two significant and ***negative*** changes – warnings about use of overlapping stents and stopping antiplatelet regimens. Cypher also got new wording about antiplatelet use, but it was not as severe. The Cypher language on overlapping stents also was milder, and Cypher got positive new wording on MRIs.

The changes were not widely known or reported until ESC. A Boston Scientific official said doctors who signed up on their website for electronic notification of changes in the "Directions for Use" got an email update, and Boston Scientific sales reps were given a Q&A explaining the changes to hand to doctors. Cypher users each reportedly got both a mailed and a hand-delivered letter. Both companies make the instructions/directions for use available on their website.

To see the updated labels See page 15 or go to:

- *Taxus Directions for Use (DFU) –*

http://www.bostonscientific.com/templatedata/imports/collateral/Coronary/dfu_taxexp_01_us.pdf?_requestid=37967

- *Cypher Instructions for Use (IFU) –*

http://www.cordislabeling.com/pdf/1892095_6.pdf

Taxus vs. Cypher

Italian researchers presented the six-month results of their RECIPE trial comparing Cypher and Taxus in 2,400 consecutive, unselected patients between April 2002 and May 2004. They reported that both Cypher and Taxus provided a similarly low risk of TLR at 6-month follow-up, that both stents are safe and effective, and that the two stents were associated with similar rates of mid-term adverse events. The researchers also found that dissections left untreated after a drug-eluting stent may have a major adverse clinical impact at both one-month and six-month follow-up.

Comparison of Drug-Eluting Stent Trials

Measurement	SIRIUS n=533	TAXUS-IV n=662	ENDEAVOR-II n=598
TVF	8.6%	7.6%	8.0%
MACE	7.1%	8.5%	7.3%
In-stent late loss	.17	.39	.62
In-segment late loss	.24	.23	.36

Source: Medtronic

Stent pricing – Coming down in Europe

Medtronic launched Endeavor in Europe in August, but use is dependent on reimbursement, and that is a country-by-country process. A Medtronic official said that, so far Germany, the U.K., Spain, and Italy will cover the cost of Endeavor, with France and Belgium expected to start reimbursing in 1Q06.

Medtronic officials insisted that Endeavor pricing is comparable to very slightly higher than Taxus, but doctors reported that Endeavor was undercutting Taxus by up to €200 in some markets, especially Switzerland, Germany, and the U.K. The Endeavor price in Sweden reportedly is €1,100-1,300. In the U.K., a doctor said the price has gone as low as €1,000 vs. €1,300 for Cypher and <€1,300 for Taxus. Other interventional cardiologists agreed that Endeavor is comparable-to-slightly cheaper than Taxus in their country, depending on the hospital.

6-Month Results of RECIPE Trial Comparing Cypher and Taxus

Measurement	Cypher n=1,227	Taxus n=1,059	Difference between Taxus and Cypher
Lesions treated	2,265	1,680	---
Stents used	2,606	1,897	---
Diabetics	26.8%		---
1-month results			
MACE	1.1%		Nss
Death	0.7%		Nss
MI	0.3%		Nss
TVR	0.4%		Nss
6-month results (unadjusted analysis)			
Overall MACE	5.9%		Nss
Death	1.4%		Nss
MI	0.7%		Nss
TVR	4.3%		Nss
TLR	3.1%		Nss
Late stent thrombosis	0.1%	0.5%	.07
Dissections			
Measurement	**Patients with dissection**	**Patients without dissection**	**p-value**
Final dissections	77 dissections (1.6%) in 67 patients (2.8%)		---
MACE in-hospital	11.9%	5.2%	.026
1-month results			
MACE	13.6%	6.1%	.013
CABG	3.0%	0.1%	.002
TVR	4.6%	0.9%	.027
Stent thrombosis	6.2%	0.9%	.004
6-month results			
MACE	18.8%	11.3%	.064
Death	6.3%	2.0%	.040
CABG	3.1%	0.5%	.049

Taxus and Cypher Label Changes *(differences in red)*

Taxus	Cypher
5.2 Antiplatelet regimen	
In clinical trials of the Taxus Express Stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of **six** months post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. See *Section 9, Clinical Studies,* for more specific information. ***Added wording:*** It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. **Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding, should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.**	In the pivotal clinical trial of the Cypher **s**tent, clopidogrel or ticlopidine was administered pre-procedure and for a period of **three** months post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce risk of thrombosis. It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to Percutaneous Coronary Intervention (PCI), if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI treatment choice. Following PCI, should a surgical or dental procedure be recommended, the risks and benefits of the procedure should be weighed against the possible risk associated with early discontinuation of antiplatelet therapy.
5.3 Overlapping stents	
Added wording: **The use of multiple stents (bare metal or drug-eluting) and the resulting increase in stented length in the setting of extensive disease (e.g., long lesions >26 mm) may increase the risk of patient complications.** The use of multiple drug-eluting stents will expose the patient to larger amounts of drug and polymer. **The use of multiple TAXUS Stents (including overlapping and non-overlapping placement) in a single lesion has recently been associated with a higher rate (<5%) of peri-procedural non-Q wave myocardial infarctions (NQWMI; CK levels >2.0 x ULN with positive CK-MB) relative to bare metal controls. To date, in the TAXUS trial experience, the higher incidence of NQWMI has not been found to be associated with an increase in mortality or target vessel revascularization, up to 9 months post-implantation. However, longer-term data are still being collected. When considering placement of multiple TAXUS Stents, the benefit of reduced target vessel revascularization should be weighed against the increased risk of NQWMI. At this time, the risk of NQWMI is higher in patients with more complex, e.g. longer lesions, but the reason for the increase is not fully understood. Updates to the product label will be made as additional information becomes available.** When more than one stent is required, resulting in stent-to-stent contact, stent materials should be of similar composition to avoid the possibility of corrosion due to the presence of dissimilar metals in a conducting medium. Potential interactions of the Taxus Express Stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.	***No language changes. Existing wording is:*** The extent of the patient's exposure to drug and polymer is directly related to the number of stents implanted. Use of more than two Cypher Stents has not received adequate clinical evaluation. Use of more than two Cypher Stents will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical studies. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible. Potential interactions of the Cypher Stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.
5.12 Magnetic Resonance Imaging (MRI)	
(No language whatsoever)	**New language:** **Through non-clinical testing, single and two overlapping CYPHER Stents have been shown to be MRI safe at field strengths of 3 Tesla or less and a maximum whole body averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of MRI. Single and two overlapping CYPHER Stents should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than 3 Tesla.** **In this testing, single Cypher Stents up to 33 mm in length produced a temperature rise of less than 1 degree Celsius (1°C), and two overlapped 33 mm length Cypher Stents produced a temperature rise of less than 2 degrees Celsius (2°C) at a maximum whole body averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of MRI. The effect of heating in the MRI environment for stents with fractured struts is not known. The effect of heating in the MRI environment on the drug or polymer coating is not known.** **MR imaging quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.**

Cost effectiveness of drug-eluting stents – Maybe, but not for all patients

A Swiss study, the BASKET trial, found that drug-eluting stents are cost-effective but more expensive than bare metal stents. The study, conducted from May 2003 to May 2004, was presented at ESC and simultaneously published in ***The Lancet***. It compared Taxus and Cypher stents to Guidant's bare Vision stent. An investigator reported that the there were subgroups where drug-eluting stents were more attractive: (1) high risk elderly patients and (2) patients with 3-vessel disease needing multiple stents and/or long stents in predominantly small vessels.

Asked if drug-eluting stent use will now change at his hospital, he said, "We had two-thirds drug-eluting stents for this time period. Now, I think we can say the single vessel or double vessel, short lesion, large stents fare very well with bare metal stents, from a cost-effectiveness point of view. But there are other considerations. Some patients come and say they want a drug-eluting stent…About two-thirds to three-fourths of patients are still good candidates for drug-eluting stents."

BASKET Trial Results

Measurement	Cypher n=79	Taxus n=78	Vision n=79
Diabetics	16%	19%	21%
Stented segments per patient	1.5	1.5	1.7
Number of stents per segment	1.2	1.3	1.3
Number of stents per patient	1.9	1.9	1.9
Total stent length per patient	36 mm	33 mm	32 mm
≥1 stent ≤2.5 mm	30%	29%	25%
Results at 6 months			
MACE	7.2% (p<.02)		12.1%
TVF	3.0% (Nss)		6.0%
MI	2.3%		2.1%
Total cost	€900 more (p<.001)		---
Cost to avoid one MACE	€18,031		---

Dr. Raymond Gibbons, an American Heart Association spokesman, said the study could help some U.S. doctors and hospitals justify using drug-eluting stents in fewer than the national average of 80% of PCIs. "The question comes at a time when healthcare costs are skyrocketing…These data will shed some light on when that is a good decision and when it is not such a good decision. I can't predict how interventionalists will respond to this info, but…it is never too late to reassess what we are doing to see what is the best use of resources. There are individual physicians who are using less than the market. These data will provide rational support for them." The problems with cutting drug-eluting stent use in the U.S. include patient demand, physician competitiveness, and the medicolegal environment. Dr. Gibbons said some patients ask for drug-eluting stents, and some doctors think they have to use them to compete.

Boston Scientific's Taxus

The recent publication of the SIRTAX and ISAR-DIABETES results – and an accompanying editorial – in the ***New England Journal of Medicine*** raised questions again about the safety of Taxus. However, European cardiologists continued to insist that they are not worried about the safety of Taxus.

Conor Medsystems' CoStar

Cardiologists continue to be very positive about this stent, but few have experience with it. Sources predicted a CE Mark in 4Q05, probably in October 2005.

Guidant

The consensus was that Guidant will not get a CE Mark for any of its drug-eluting stents until 1Q06 or later. In fact, sources were emphatic about that, suggesting it is laughable to think the company will be able to get a CE Mark sooner.

Medtronic's Endeavor – Off slowly in Europe but likely to take large market share, hurting Taxus most

Doctors reported uptake in Europe is slower than may have been expected. Some cardiologists said they have only gotten Endeavor in their cath lab in the last two or three weeks, and many are still waiting to get it. Cardiologists who have tried Endeavor said they like it. They reported that it works as well as the bare Driver stent, and they described it as the most flexible and deliverable drug-eluting stent. Sources predicted that over the next six months Endeavor would cut Taxus use in half, with much less (but some) impact on Cypher use.

Dr. Ian Meredith of Australia presented the 24-month results from the 100-patient, first-in-man ENDEAVOR-1 trial of the Endeavor stent, which elutes zotarolimus (ABT-578) from a Driver stent coated with phosphorylcholine. The trial was conducted in Australia and New Zealand, and it included 100 patients with symptomatic ischemic heart disease due to single de novo lesions <15 mm in length in native coronary arteries. Endeavor stents with 18 mm length and a diameter of either 3.0 mm or 3.5 mm were used. Patients were started on aspirin before the procedure, and they were given a 300 mg loading dose of clopidogrel, followed by 75 mg daily for 12 weeks.

Dr. Meredith reported that the four-month and 12-month results were sustained at 24 months. MACE-free survival was 97% at 24 months. There was no angiography at 24 months, so there are no late loss data for that time point, but a Medtronic official indicated the company may do angiography on these patients at three years to check for late loss then.

Among the events in these patients were:

- 1 non-Q-wave MI with subacute closure/stent thrombosis at 10 days post-procedure.
- 1 non-cardiac death (metastatic melanoma) at 379 days post-procedure.

- 1 TVR post-procedure at 409 days, got re-PCI.
- 1 TVR that went to CABG at 515 days post-procedure, got CABG.
- 1 stent thrombosis at 10 days, no further events to 720 days.

Dr. William Wijns of Belgium presented the 12-month results of the larger (1,200-patient) ENDEAVOR-II trial, which found that Endeavor continues to be both safe and effective. Dr. Wijns reported no stent thrombosis after 14 days.

Dr. J. J. R. (Hans) Bonnier of the Netherlands presented new data from the ENDEAVOR-II Continued Access trial. Investigators in this trial were allowed to use direct stenting. Dr. Bonnier said, "Since the CE Marking of Endeavor, I have done 32 mm if necessary with direct stenting because I think this is a good stent for direct stenting." Dr. Wijns added, "(In this trial), there was no stent thrombosis. Endeavor is at least as safe – and maybe more safe – than one of the devices (perhaps an oblique reference to Taxus)."

24-Month ENDEAVOR-I Results

Measurement	Endeavor 30 days n=100	Endeavor 4 months	Endeavor 9 months	Endeavor 12 months	Endeavor 24 months n=97
MACE	*Primary endpoint #1* 1%	2%	2%	2%	3% *
TVF	1%	2%	*Secondary endpoint #1* 2%	2%	4% **
TLR	1%	2%	*Secondary endpoint #2* 2%	2%	2%
In-segment late loss	---	*Primary endpoint #2* 0.21	N/A	0.43	N/A
In-stent late loss	---	0.33	N/A	*Secondary endpoint #3* 0.61	N/A
Subacute thrombosis	0	0	0	0	0
Late-acquired malapposition	0	0	0	0	0

* One additional death from 12-24 months from metastatic melanoma.
** Two non-TLR TVRs.

12-Month ENDEAVOR-II Results

Measurement	Endeavor 8-9 months n=598	Endeavor 12 months n=588
TVF (cardiac death, MI, TVR)	*Primary endpoint* 8.0%	9.9%
TLR	4.6%	6.0%
TLR-free survival	86.9%	94.0%
TVR (non-TLR)	1.5%	1.8%
MACE	7.3%	8.8%
Death	1.2%	1.4%
Subacute thrombosis	0	0
Late-acquired malapposition	0	0
In-stent late loss	0.61 mm	N/A
MI	2.7%	2.7%
Q-wave MI	0.3%	0.3%
Non-Q-wave MI	2.4%	24%
Stent thrombosis	0.5% *	0.5% *

* All in first two weeks; no additional stent thrombosis out to 12 months.

ENDEAVOR-II Continued Access Trial

Measurement	0-30 days n=296	0-9 months n=289
MACE	*Primary endpoint* 5.4%	10.4%
Death	0	0.7%
MI	4.7%	5.2%
Q-wave MI	0.3%	0.3%
Non-Q-wave MI	4.4%	4.8%
TLR	0.3%	4.8%
TVR (non-TLR)	1.9%	4.2%
TVF	5.6%	13.1%
8-month angiographic results (n=147)		
Restenosis in-stent	---	14.2%
Restenosis in-segment	---	15.8%
Late loss in-stent	---	0.56
Late loss in-segment	---	0.38
	Direct stenting n=127	**Predilatation n=170**
MACE	10.6%	10.2%
MI	5.7%	4.8%
TLR	3.3%	6.0%
Emergency CABG	0.8%	0

Dr. Sigmund Silber of Germany discussed the Endeavor findings. Even though there are several drug-eluting stents currently on the European market, he welcomed Endeavor as the No. 3 drug-eluting stent, saying, "Endeavor is the third drug-eluting stent to do its homework." He explained that only Endeavor, Johnson & Johnson's Cypher, and Boston Scientific's Taxus have A or B level data – which he defined as a randomized clinical trial that met a clinically significant primary endpoint. The only trials he believes meet this criteria are SIRIUS, TAXUS-IV, TAXUS-V, TAXUS-VI, and ENDEAVOR-II, and he described them as fairly comparable in outcomes. The slightly higher MACE rate in TAXUS-IV was attributed to a different definition of MACE.

Dr. Silber's Comparison of Drug-Eluting Trials

Measurement	TAXUS-IV	SIRIUS	ENDEAVOR-II
Lesion length	10-28 mm	15-30 mm	14-27 mm
Vessel diameter	2.5-3.75 mm	2.5-3.5 mm	2.25-3.5 mm
Primary endpoint reached	Yes/TVR	Yes/TVF	Yes/TVF
TLR at 12 months	4.4%	4.9%	6.0%
TVF	10.0%	9.8%	9.9%
MACE	10.8%	8.3%	8.8%

Dr. Silber insisted that:

- Not all drug-eluting stents are equal.
- There is no class effect of drug-eluting stents.
- A CE Mark is not sufficient to prove the safety and efficacy of a drug-eluting stent.
- The equivalency of Endeavor to Cypher or Taxus will be determined by the ENDEAVOR-III and ENDEAVOR-IV trials.

At ESC, Medtronic was emphasizing two things about Endeavor: the deliverability and shorter-term Plavix use (3 months). A speaker said, "The safety results are the most important issue in this trial (the ENDEAVOR-II Continued Access trial)…because dual antiplatelet therapy had to be followed for only three months post-procedure. This is remarkable compared to other drug-eluting stents. And there was absolutely no stent thrombosis after the first 10 days. Why?...I don't know why there is low stent thrombosis, but it certainly is a combination of the polymer and this mild-to-moderate tissue proliferation (0.61 mm late loss)." Another investigator said, "What is intriguing is stent thrombosis is lower (with Endeavor) than control, though it is not a statistically significant difference. We have to see what this is in larger groups. If that is true…then the role of the polymer becomes important…and that raises questions about who is the bad guy in stent thrombosis…Maybe it is the polymer."

Among the comments by doctors who have tried Endeavor were:

- *Germany #1:* "It is very flexible."
- *Germany #2:* "I will use it, depending on the data in special populations. The ENDEAVOR-III results are important. Cost also is an issue, and so is the company's willingness to give them to us on a consignment basis. We will decide in the next month or so whether or not to switch from Taxus to Endeavor."
- *U.K. #1:* "I just started using it. NICE is assessing it now. If NICE recommends it, then cost will be the issue."
- *U.K. #2:* "We've had Endeavor for three weeks. It is a good stent for tortuous or difficult lesions. It is a better stent, more deliverable and more flexible, but the concern is late loss…In six months, I probably will be using Taxus, Cypher, and Endeavor equally. Even if the Taxus price is cut, that may not help it keep market share."
- *Spain:* "Endeavor has a good drug and a good platform. It is better than Janus on deliverability."
- *Ireland:* "We are experimenting with Endeavor to see how we like it. The first 50-60 have been fine. I lost one in a calcified lesion, but got it out with a gooseneck snare…How many Endeavors I'm using in six months will depend on the cost."
- *Italy:* "The choice between Cypher, Taxus, Endeavor, Janus, and Conor will depend on cost."
- *Netherlands:* "We currently use 25% Cypher, 50% Taxus, and 25% Janus. I'm switching all of my Cypher use to Endeavor. I'm not convinced the sirolimus dose on Cypher is correct."
- *France:* "Endeavor will be used a lot even if the late loss is high because of deliverability."

Other ongoing Endeavor trials include:

- **ENDEAVOR-III.** The results from this pivotal, Phase II trial will be presented at TCT in October 2005. No new Endeavor data are expected at the American Heart Association meeting in November 2005.
- **ENDEAVOR-IV.** Investigators insisted that enrollment is "on track" to finish in 12 months and not enrolling slowly. Sources reported no problems with enrollment. The first 328 patients are getting angiography, and a Medtronic official predicted enrollment will speed up after those patients are enrolled. In addition, Canada recently approved participation in ENDEAVOR-IV, which will add another 10 sites and should speed up enrollment.
- **ENDEAVOR-V.** This 8,000-patient world-wide registry is due to start by early October 2005.

SORIN'S Janus CarboStent – Doctors sampling but want more data

Uptake of this tacrolimus-eluting, non-polymer stent appears to be very slow. Only a few European cath labs have tried

Janus yet, but the ones that have seem to like it. All sources agree it will be a niche player only, with no more than 10% market share in the best case – until and unless there are good randomized clinical trials. Even two of the speakers at the Sorin-sponsored session on Janus weren't using it yet. One said he will "give it a try," but sources are taking a very cautious approach to Janus.

Dr. Marie-Claude Morice of France presented the clinical results of the JUPITER-II trial. The angiographic data (the primary endpoint in the trial) will be presented at TCT 2005. Asked why coating the Janus stent with tacrolimus appears to work while a stent dipped in paclitaxel failed in another trial, Dr. Morice said, "The technique of releasing the drug is very different, very predictable. Half is released during the first month, and at three months there is nothing…The mechanism of release is closer to the Conor stent (which has reservoirs of paclitaxel), which is a similar design."

Among the comments on the Janus stent were:

- *France:* "I haven't tried it yet; I want to see the final data first."
- *Germany:* "I tried the Janus stent and liked it, so our use will increase."
- *Italy:* "About 10% of our patients get a Janus stent – those for whom a dual antiplatelet regimen is contra-indicated. Janus is priced between Taxus and Cypher, but Italy has 21 regions and the DRG (reimbursement) differs by region."
- *Spain:* "We are doing a Janus trial (at our hospital) to see how it compares to Cypher and Taxus. The advantage to Janus would be cost, if it is cheaper…If I were the patient, with a normal lesion, I would use Cypher or Taxus, and if it were a complex lesion, I would use a Cypher, not a Janus."

JUPITER-II Results

Measurement	Bare Tecnic n=166	Janus n=166	p-value
Direct stenting success	99.3%	100%	---
Number of stents per patient	1.18	1.23	---
Number of stents per lesion	1.04	1.09	---
Maximum pressure	13.9 atm	13.7 atm	---
1-Month results			
TLR	0	0	Nss
MI	0	0.6%	---
6-Month results			
MACE	10.6%	7.6%	.3572
Stent-related MACE	10.6%	6.4%	.1747
Death	0	0.6%	---
MI	0	0.6%	---
Q-wave MI	0	0.6%	---
Non-Q-wave MI	0	0	Nss
TVR	10.6%	6.4%	.1747
TLR stent-related	10.6%	5.7%	.1125
Re-PTCA+stent	8.1%	2.5%	.0433
Acute thrombosis	0.6%	0	---
Late thrombosis	0	0	---

PATENT FORAMEN OVALE (PFO) CLOSURE

There were no new data at ESC on PFO closure, but doctors were interested in the topic. Dr. Horst Sievert of Germany, who has done more than 1,000 PFO closures using different devices, made a number of points about PFO closure, including:

- **Unproven stroke benefit.** Dr. Sievert said it is too soon to say whether strokes can be prevented with PFO closure, even though the PLAATO trial of **APPRIVA MEDICAL'S** device showed a 43% stroke risk reduction in AF patients who had their PFO closed (3.6% vs. an expected 6.3%). However, in his experience, only 1.5% of patients have had a TIA or stroke after he closed their PFO, compared to a historic rate of stroke in patients getting anticoagulants is 2%-14%. Another expert said, "There could be a niche for the PLAATO technique. In (some) hands it is good, but it cannot be done by a beginner. It takes experience with a transseptal approach, so it should be done by someone with real training in transseptal – and with an echo and a team."
- **How many PFOs should be closed.** Dr. Bernhard Meier of Switzerland argued that all PFOs should be closed, but other experts thought only symptomatic patients should have their PFO closed.
- **CIERRA'S RF system**. This U.S. company started early human trials in Europe in April 2005, and Dr. Sievert predicted it "may become the gold standard in most patients as it leaves no foreign material in the heart." However, he didn't think it would totally replace mechanical devices: "Not completely, but in the majority of patients. The current success rate (with RF) is only 70%, but we are still learning. We have to improve the catheter and the delivery system. For sure, it will not be the technique to close very small ASDs, but it will replace about 50% of all PFO closures."

At a PFO session sponsored by AGA Medical, a speaker pointed out, "All the PFO trials have been in patients <age 50, but VTEs start at age 50 and increase geometrically, so we should be more concerned with older patients with a PFO than younger patients." Another speaker said, "You don't need an index event (to close a PFO). Any PFO should be closed – before the first event…The only good PFO is a closed PFO."

A U.S. cardiologist who chaired a session on PFO closure at the 2005 American College of Cardiology meeting said, "The question is who (does the procedure). It is simple to put in, but you need to know pathophysiology. PFO closure should be a niche field that people are specially trained to do. I think

PFO closure is appropriate for patients with:

1. Recurrent neurological events and under age 55 when you can't find another source for the embolism.
2. Younger patients who refuse anticoagulation, after a first event. Coumadin (warfarin) is still the gold standard."

Researchers are also exploring the value of PFO closure to treat migraine headaches, specifically those preceded by an aura. From 25-30 million Americans are estimated to suffer from migraines, and about 10% of these have aura. This has been a very controversial indication, but two companies now have IDEs to research this, and other companies have plans for PFO/migraine trials.

ST. JUDE'S Premiere

This device, which St. Jude got with the acquisition of Velocimed, has a CE Mark. St. Jude recently received the first FDA approval for a trial of PFO closure in migraine. The ESCAPE trial has already started enrolling patients. It is a prospective, randomized, two-arm, double-blind, multicenter trial. A St. Jude official said a randomized clinical trial of PFO for stroke would be too hard to do in the U.S. He pointed out that NMT Medical's CLOSURE-1 trial has only enrolled about 300 patients in 14-15 months.

St. Jude also plans to start a European migraine trial around the end of 2005, and the company currently is interviewing neurologists for that trial.

NMT MEDICAL'S StarFlex

NMT is currently conducting a PFO/migraine study in the U.K., MIST-I. Results of this trial are expected in 1Q06. At EuroPCR researchers reported that about half of the 370 migraine patients examined had a PFO – a much higher rate than would be expected in the general population.

After ESC – in mid-September 2005 – NMT also received FDA permission to begin a one-year, randomized, multicenter (~20 sites), controlled U.S. trial of PFO closure for migraine, MIST-II. The trial will enroll ~600 migraine patients with a PFO, beginning in early 2006. The two principal investigators are Dr. Stewart Tepper in Stamford CT and Dr. Mark Reisman in Seattle WA.

PERCUTANEOUS AORTIC VALVE REPLACEMENT

EDWARDS LIFESCIENCES' Cribier-Edwards Percutaneous Valve

Prof. Alain Cribier of France – a consultant to Edwards and the inventor of the valve – remains positive about the outlook for this and other percutaneous valves. He predicted that percutaneous valves will be in widespread use in two years.

A patient died after getting a Cribier-Edwards valve – a bioprosthesis made of three leaflets of equine pericardium sutured to a balloon expandable stainless steel stent – that was delivered transseptally by a very experienced interventional cardiologist during a live case at TCT last year. And other experts have predicted that percutaneous valves are 5-10 years away from prime time, but Dr. Cribier insisted that three factors will help speed the adoption of this procedure:

1. **More and better training of interventional cardiologists.** Dr. Cribier said, "People will learn from us and be trained. There is no question, they have to be trained…We have decided to be very strict in the training program. People have to be trained in vitro on simulators and have to attend 2, 3, or 4 cases in an experienced center (ours or in Canada), and they are not supposed to perform a procedure without a proctor to provide guidance. This is not something you can improvise. It is something very, very special."
2. **More valve sizes.** A single valve size was all that initially was available, and it was too small (23 mm) for some patients.
3. **Use of the retrograde approach.** The procedure is complex via the antegrade/transseptal route, but the retrograde approach has frequently been associated with failures in crossing the native valve. A new retrograde system, using a 26 mm valve, has been developed. So far, only Dr. John Webb in Vancouver, Canada, is approved to use this new approach and valve, but he reportedly has done a number of cases successfully – and quicker (in about one hour), with a lower rate and severity of paravalvular leak. Dr. Cribier said, "The retrograde approach is much easier. I am confident retrograde will offer much higher opportunity."

At ESC, Dr. Cribier presented the final data from the I-REVIVE trial. The preliminary data from this 20-patient pilot and trial was presented in January 2005 at the Society of Thoracic Surgeons meeting. Another 20 patients were enrolled in the RECAST trial, and Dr. Cribier said there have been no valve failures in either trial – when the valve is successfully placed, which occurred in 80% of cases.

I-REVIVE Trial

Preliminary results		Final results	
Death before implantation	1	Pre-procedural deaths	2
VF during pre-BAV	1	Transient collapse	8
Death after implantation	1	Acute PHV migration	1
Technical failures	3	Vascular complications	5
Patients alive	7 at 3 months 4 at 6 months	Patients alive	2 at 2 years 1 at 1.5 years
Procedural events	1 stroke 1 tamponade	Post-procedure events	1 stroke 1 tamponade
MI	0	MI	0
Valve dysfunction	0	Valve dysfunction	0

Two new multicenter studies have started enrollment in patients considered high risk by a surgeon:

- **REVIVE**, a 90-patient trial in Europe. Two centers in Germany have already begun, and soon France, Sweden, Denmark, the U.K., and Italy are expected to participate.
- **REVIVAL**, a 100-patient, six-month trial in the U.S. comparing percutaneous valves and balloon aortic valvuloplasty. So far, two centers are participating (in Detroit and New York). This trial is on hold at the present time because the company is seeking FDA approval to change from the transseptal approach to a retrograde approach.

CoreValve's Percutaneous ReValving System

There were no new data on this self-expanding stented aortic heart valve at ESC, but Dr. Cribier predicted that this, along with the Edwards valve, would be successful. He said, "CoreValve is already in humans…The concept is different since they are using a self-expanding valve, not a balloon to dilate…The stent goes into the ascending aorta, and that is a very different concept…The results so far are not that bad. I think this device will progress and be competition. The advantage is that it can provide a therapeutic solution for patients with aortic insufficiency. It could be a good valve, too, in aortic regurgitation patients if some technical issues are resolved." Another cardiologist was less optimistic about the outlook for CoreValve's product, "I'm not convinced CoreValve will succeed, but the Edwards valve will."

After ESC, CoreValve announced that it had begun the third phase of a feasibility study of its ReValving System. Dr. Eberhard Grube of Germany implanted the second generation device in two high risk patients, and both reportedly fully recovered and were able to resume normal activities. The new design uses a porcine pericardium heart valve delivered via a 21F catheter, instead of a surgical-type generic bovine valve delivered with a 25F catheter. The time required for the procedure also was reported to be much shorter – 15 minutes instead of 40 minutes.

CoreValve is planning to start an international clinical trial by the end of 2005, and it will use the data from that trial to seek a CE Mark in 2007.

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