Trends-in-Medicine

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SUMMARY

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HIGHLIGHTS

- There is little concern among European cardiologists over the Taxus recall.
- A Taxus advantage over Cypher in diabetics is not clear, and Cypher continues to show better restenosis and MACE rates and better performance in in-stent restenosis. However, most cardiologists consider the two stents fairly comparable, with Taxus slightly more deliverable.
- Medtronic reported slightly worse, revised results of the ENDEAVOR-1 trial, but the company is not dropping the Endeavor program. Most European doctors believe the stent is commercially viable with this data, even if it is priced comparable to Taxus or Cypher.
- Monthly liver testing is likely to be required for more than the initial six months of treatment for AstraZeneca's Exanta until longer-term data is available. Exanta showed no difference from warfarin in any pre-specified subgroup in the pooled meta-analysis of the SPORTIF-III and SPORTIF-V trials.
- Lilly's prasugrel (CS-747) looks as if it will be a strong competitor to Sanofi-Aventis/Bristol-Myers Squibb's Plavix, but several issues need to be watched in the Phase III trial or answered with other data, including deaths, QT prolongation, and bleeding. It appears the company has chosen a middle dose for that trial. The Phase II data looked very good, but it was not enough to convince experts at ESC that this can replace Plavix yet, but it is on the right track.
- Mylan/Menarini's nebivolol is starting to differentiate itself from other beta blockers. The SENIORS trial showed a good effect in elderly patients (>age 75). If nebivolol is marketed well, it may be successful, despite the lack of a landmark trial.
- Sanofi-Aventis's Acomplia (rimonabant) diet and smoking cessation drug continues to be a winner. The only clouds are GI (nausea) and neuropsychiatric issues (depression and anxiety). The numbers of neuropsychiatric problems aren't high, but they have attracted the attention of experts.

DRUG-ELUTING STENTS

BIOTRONIK'S AMS

This bioabsorbable (a researcher said bioabsorbable better describes this stent than biodegradable) magnesium alloy stent is getting increased attention. Many stent sessions at ESC were poorly attended, but the room was full for this presentation. The first five patients were enrolled in PROGRESS-AMS, a 36-patient first-in-man coronary trial, in July 2004. The primary endpoint is MACE at four months.

Comparison of Drug-Eluting Stents

Measurement	Johnson & Johnson's SIRIUS	Boston Scientific's TAXUS-IV	Boston Scientific's TAXUS-VI	Medtronic's ENDEAVOR-1	Guidant's FUTURE-2
Stent	Cypher	Taxus	Taxus	Endeavor	Champion
Drug-eluting stent patients	533	662	446	100	21
Time period	9 months	9 months	9 months	12 months	6 months
Late loss (in-stent)	0.17 mm	0.39 mm	0.39 mm	0.61 mm	0.12 mm
Restenosis in-segment (drug vs. control)	8.9% vs. 36.3%	7.9% vs. 26.6%	12.4% vs. 35.7%	5.4%	0% vs. 19.4%
Restenosis in-stent (drug vs. control)	3.9% vs. 42.3%	5.5% vs. 24.4%	9.1% vs. 32.9%		0
TLR (drug vs. control)	4.1% vs. 16.6%	3.0% vs. 11.3%	6.8% vs. 18.9%	1.0%	4.8%
TVR (drug vs. control)	6.4% vs. 19.2%	4.7% vs. 12.0%	9.1% vs. 19.4%	N/A	---
MACE	7.1%	8.5%	6.9%	2.0%	4.8%

Secondary endpoints include device success, procedural success, etc. An investigator said, "At four weeks those five patients are all doing well, except one patient who needed repeat angiography because of symptoms but showed no signs of restenosis by IVUS."

New points made about the AMS stent at this meeting included:

- **Allergy.** There is only one case report of an allergy to the stent.
- **Imaging.** The stent does not show up on fluoroscopy, and it shows up as black holes on 16-slice CT, but it is clearly visible by IVUS or MRI.
- **Degradation rate.** The type of magnesium alloy selected affects the degradation rate. Biotronik chose an alloy which has a 60-day degradation rate, but there are alloys with degradation rates as short as one or two days.
- **Degradation effects.** An investigator said that when the stent starts to degrade, it will fracture, but he said this is normal and has no clinical effects.
- **Overlapping stents.** So far, no overlapping stents have been used, but that is being considered.

BOSTON SCIENTIFIC'S Taxus

Interesting news on Taxus:

- **Deflation.** There was a report of one case of non-deflation with the newer, "fixed" Taxus, but that could not be confirmed. Dr. Mary Russell, Vice President for Cardiovascular Affairs at Boston Scientific and the TAXUS chief, neither confirm nor deny the report, but she commented, "The real concern I have with the (Taxus) recall is that it is creating an expectation that there will be zero deflates in the future. There are always a few deflates with any system."
- **FDA.** A source said the FDA is telling Boston Scientific it has to change the instructions for use (IFU) to say to allow at least 27 seconds for deflation and to retract the guiding catheter when the stent is deflated. Experts have suggested that Boston Scientific should be providing deflation instructions to physicians, which apparently they have not been doing. One said, "It is amazing there are no instructions on how long to deflate Taxus…There should be instructions on how to deflate, and put some liability back on the doctors and not the stent."
- **Future data.** The three-year TAXUS-I data will be presented at either TCT 2004 or the American Heart Association meeting in November 2004.
- **Recall reaction.** Few European cardiologists expressed any real concern over the Taxus recall. A U.K. doctor said, "I'm continuing to use Taxus. We never had a problem at our hospital." A German doctor said, "Our use is unchanged. Our largest problem is price, so we have no choice." An Italian cardiologist said, "I stopped using Taxus after the recall, but I was a lower user anyway. Boston Scientific has always had problems with its devices. Remember Rotoblator, Nir on Sox, and now this. It seems to have more problems than the other stent companies."

Results were presented from the 1,900 European patients in the web-based Taxus MILESTONE-II Registry, which has a total of ~3,689 "real world" patients worldwide. 12-month data is expected in 2005.

6-Month European Results from MILESTONE-II Registry

Measurement	Taxus
Clinical follow-up rate	96%
MACE (cardiac death, MI, repeat procedures)	7.1%
Repeat procedures	4.2%
Stent thrombosis (acute and late)	0.9%
Results in Diabetics	
% diabetics	~30%
% of diabetics who are insulin-dependent	11.5%
MACE	8.9%
Repeat procedures	5%

Meta-analysis of 12-Month Results of Diabetics in All Taxus Trials

Measurement	Diabetics n=458	Non-Diabetics n=1,831	p-value
RVD	2.69	2.76	.0002
Average lesion length	14.8	13.9	.0211
Average stent length	23.5	22.1	.0081
IIb/IIIa use	43.0%	40.0%	.26
PCI of non-target vessel	19.7%	20.6%	.73
TLR (in-stent restenosis)	22.9%	N/A	N/A
In-segment restenosis	N/A	N/A	---
Late loss for Taxus	.37	.36	---
Late loss in control (bare stent)	.86	1.03	---
% diameter stenosis for Taxus	19.0%	19.4%	---
% diameter stenosis in control	32.6%	41.8%	---

A new meta-analysis of all diabetics in Taxus trials was presented. The subset of diabetic patients in the 446-patient, European TAXUS-VI was presented May 2004 at EuroPCR. A researcher concluded, "Coronary artery disease in diabetic patients is characterized by long lesions in smaller vessels, presenting less frequently with stable angina. Diabetics with bare stents had a worse clinical and angiographic outcome than non-diabetic patients."

A Swiss cardiologist suggested these findings may help Taxus overcome the findings with Cypher in E-SIRIUS, where the in-segment restenosis was 10.8% for diabetics.

GUIDANT'S Spirit

The final results of the 30-patient first-in-man trial of a durable polymer on a Vision stent eluting everolimus, SPIRIT-1, may be presented at TCT 2004 instead of the American Heart Association 2004. The last patient is scheduled to be examined on September 22, 2004, and the principal investigator, Dr. Patrick Serruys, said he may have the data ready for TCT 2004. Use of two Spirit stents was not permitted in this trial, so a bare stent was used when a second stent was required. The question for this program does not appear to be the physical properties of the polymer, but the elution properties may be the issue to watch.

SPIRIT-2 is not due to start until after the presentation of the SPIRIT-1 trial. Dr. Serruys is not the principal investigator for that trial.

JOHNSON & JOHNSON'S Cypher

Two-year results of the European E-SIRIUS trial, sponsored by J&J, found Cypher continues to be superior to a bare metal BX Velocity stent, and there was no evidence of a late catch-up phenomenon. An expert, reviewing this data, concluded, "For Cypher, the two-year E-SIRIUS results fit nicely with RAVEL and SIRIUS, though E-SIRIUS included higher risk patients. He said, "So far, no late catch-up has been observed with either Cypher or Taxus, showing a sustained benefit (to drug eluting stents), but more data is needed."

A German Cypher registry, also sponsored by J&J, found:

- The outcome in "real world" patients is not very different from the results of randomized trials.
- Because of cost constraints, drug-eluting stent usage in Germany has remained relatively low (<10%).

An expert said one take home message appears to be not to use drug-eluting stents in vein graft patients.

6-Month Results German Cypher Registry

Measurement	Cypher (n=3,155)
Death	0.8%
Non-fatal MI	1.3%
Minor bleeding	22.3%
Major bleeding	0.5%
CABG	1.5%
Re-PCI	12.1%
Death and AMI in diabetics	2.9%
Death and AMI in ACS patients	3.4%
Death and AMI in ISR patients	2.5%
Death and AMI in vein graft patients	5.3%
Restenosis by angiography at 6 months (n=1,345)	11%

2-Year Results of E-SIRIUS Trial

	1-Year		2-Year		
Measurement	Cypher n=175	Bare BX Velocity n=177	Cypher n=175	Bare BX Velocity n=177	p-value
MACE	8.6%	26.6%	10.3%	29.9%	<.001
TLR	4.6%	24.9%	5.1%	26.6%	<.001
Deaths in Year 2	---	---	4 deaths (all cardiac)	2 deaths (1 cardiac)	---
Survival-free MACE	91.4%	89.7%	89.7%	70.0%	N/A
Events in Year 2	---	---	10 events in 9 patients	5 events in 3 patients	---
Q-wave MI	---	---	0	1 patient	---
Death	---	---	2.3%	2.8%	Nss
MI	---	---	5.7%	3.4%	Nss
Emergent CABG	---	---	0	0	Nss
TL-PCI	---	---	4.6%	25.4%	<.001
Stent thrombosis	---	---	1.1%	0	Nss
Survival-free MACE	---	---	89.7%	70.0%	N/A

Data from the REALITY, the head-to-head Cypher vs. Taxus trial, probably won't be ready for American Heart Association and is likely to be released by press release before the American College of Cardiology meeting in March 2005.

MEDTRONIC'S Endeavor

Medtronic sponsored a seminar on its ABT-578-eluting Endeavor stent, but it was very poorly attended, with only a scattering of people showing up, most of whom were competitors, Wall Street analysts, or Medtronic employees. Endeavor researchers are defending the stent and minimizing the importance of both the late loss and restenosis rates. Another expert believes the Endeavor polymer is safe and any problem is likely due to release kinetics.

UPDATED Results of Phase I ENDEAVOR-1 Trial

Measurement	30 Days	31 Days - 4 Months	5 - 12 Months	Cumulative 12 Months
MACE	1% *Primary endpoint*	1%	0	2%
Death	0	0	0	0
All MI	1%	0	0	1%
Q-wave MI	0	0	0	0
Non-Q-wave MI	1%	0	0	1%
TLR	0	1%	0	1%
TVR (non-TLR)	0	0	0	0
TVF	---	2%	0	2% *Secondary endpoint*
Late incomplete apposition	---	0	0	0
Restenosis				
In-stent	---	2.1%	3.3%	5.4%
Proximal	---	---	0%	0%
Distal	---	---	0%	0%
In-segment	---	2.1%	3.3%	5.4%
Late Loss				
	At 30 days	**At 4 months**	**At 12 months**	**Cumulative 12 months**
In-stent	---	0.33	.61 up from .58	.61
In-segment	---	.21 *Primary endpoint*	.43 up from .40	.43
Proximal edge	---	.12	No change .30	.30
Distal edge	---	.09	.22 down from .23	.22
%DS	---	21.5%	26.8%	26.8%
Other Findings				
	At 30 days	**At 4 months**	**At 12 months**	**Cumulative 12 months**
% in-stent MLD	2.84	2.51	2.24	2.24
% in-segment MLD	2.52	2.3	2.09	2.09
RVD	3.02	2.96	2.91	2.91

The ENDEAVOR-1 principal investigator presented the final, updated results from that trial. The key 12-month changes were:

- In-stent late loss was revised **up** from 0.58 to **0.61**.
- In-segment late loss was revised **up** from 0.40 to **0.43**.
- Distal edge late loss was revised **down** from 0.23 to **0.22**.
- There was no change in proximal edge late loss.
- In-stent restenosis was revised **up** from 3.3% to **5.4%**.

Perhaps surprisingly, European doctors questioned about the market outlook for Endeavor are not very negative about the stent. Most believe it is still commercially viable and would have a role, especially if priced lower than Taxus (in the $1,300-$1,600 range) but even if it were priced comparably to Cypher and Taxus. The main reasons cited for this positive outlook for Endeavor were: (1) deliverability of the Driver stent (a bare Endeavor), (2) the desire to have more competitors in the market. A French doctor said, "I'm nervous and concerned about the restenosis, but if the restenosis rate comes out around 5.5%, I would still use it because the Driver delivery is much better than Taxus…Late loss is not so important…Endeavor will have broader use if it is priced from 1,000-1,200 euros, but I would use it for complex lesions if the price is comparable to Taxus." An Italian cardiologist said, "Late loss of .25 is okay, but .58 is a bit worrisome. Still, I would use Endeavor, especially if it is cheaper. Driver is very deliverable, but for Endeavor to do well in the market, it will have to fight for market share. But it would be good to have more stents because that will help lower prices." A German cardiologist said, "Endeavor has a role, but I'd never change a winning team if the price were the same as Taxus."

However, sources generally think Endeavor can do little more than fill a niche. A French cardiologist disagreed, saying, "Endeavor is not commercially viable."

At the seminar, Medtronic experts and speakers offered the same explanations for the relatively high late loss in ENDEAVOR-1 as they did at EuroPCR in May 2004: That the results could have been influenced by the initial RVD or by acute gain. An investigator said, "When you correct for RVD, the results are fairly comparable (to SIRIUS and TAXUS-IV)…There is greater late loss (with Endeavor), but this hasn't proven significant in terms of TLR, and there is relatively low binary restenosis."

Dr. Jeff Popma, Director of Interventional Cardiology at Brigham & Women's Hospital, which is the core lab for ENDEAVOR-3, suggested that % diameter stenosis (%DS) may be a better measure than late loss. For example, he explained, in TAXUS-IV the accuracy of predicting TLR was: .918 for late loss, .940 for MLD, and .944 for diameter stenosis, making that the best predictor. He said, "The suggestion is that in-lesion late loss may have to get to 0.7 or 0.8 before it increases an individual's probability of TLR…We don't know the upper limit of late loss, but from 0.2 to 0.6 there is a relatively flat curve with respect to clinical events…The optimal angiographic endpoint for clinical TLR is % diameter stenosis rather than late loss, but both will work for clinical trials…Angiography and IVUS for % volume obstruction are better indices for the magnitude and distribution of tissue growth within the stent than a single measurement of late lumen loss. We don't know the upper 'landing zone' of late lumen loss, but there may be a beneficial effect even if the late lumen loss is in the range of 0.6 – 0.7 mm." ***There will be a debate at TCT 2004 between Dr. Popma and Dr. Richard Kuntz, also of Brigham & Women's Hospital, on late loss as a predictor of TLR.***

He cited these limitations to use of late loss:

- Edge of stent may be difficult to identify
- Calibration efforts from final to follow-up
- Axial shifting of the MLD from final to follow-up
- Dependent on acute gain with higher loss
- Single patient measurement may correlate with clinical endpoints but not IVUS findings
- One view-two view errors

Medtronic officials offered two interesting comments:

- Medtronic hopes to file Endeavor with the FDA on time – in the summer 2005 by using 30-day data from Endeavor-4 and then supplementing that with more data when it is ready. They are having long and frequent discussions with the FDA and are hopeful this will be allowed.
- Medtronic plans to find a new polymer for its next generation drug-eluting stent.

Other Stent News

Do drug-eluting stents increase the risk of thrombosis?

Pathologist Dr. Renu Virmani and Dr. Eberhard Grube of Germany debated this issue at ESC. Following are some selected comments from their debate:

Dr. Virmani: "Thrombosis is the Achilles' heel of drug-eluting stents…It is clear that thrombosis is going to be a problem…Over time, I think it will be shown that I am right that thrombosis is increased in drug-eluting stents."

Dr. Grube: "We should watch this issue but not be worried…Every acute stent thrombosis is serious…But we had the same issues with bare metal stents…Be careful, but be reminded that there are patients dying of this disease…I would say if we adequately prescribe Plavix – for at least six months and perhaps a year – then I think we are safe."

Dr. Virmani: "The reason Plavix is helpful is that we keep patients on it for six months (with drug-eluting stents) and only one month with bare metal stents…Any patient who dies is unacceptable, especially if a procedure is done by a doctor…Imagine a drug on the market and the FDA learns it had fatal events. Then, that drug would be taken off the market…I don't understand why drug-eluting stents are still on the market."

Moderator: "I am concerned about the SAT rate (with drug-eluting stents)."

Asked if Cypher and Taxus stents can be used in the same patient or overlap each other:

Dr. Grube: "I do not object to Cypher in one vessel and Taxus in another…if the patient is on an antithrombotic regimen."

Other Endeavor Trials Underway and Planned

Trial	Design	Endpoints	Status	Expected Data Presentation
ENDEAVOR-2	Pivotal, 1,191-patient U.S. and European trial	***Primary:*** MACE at 30 days	Enrollment complete	9 month data at ACC 2005 (Blinded 30-day results were presented at EuroPCR 2004)
ENDEAVOR-2-Registry	Open label safety registry	***Primary:*** MACE at 30 days ***Secondary:*** TLR, TVR, QCA & IVUS at 8 months	Enrollment complete	9 month data at ACC 2005; 30-day data on the 300-patient safety registry at ACC 2005
ENDEAVOR-3	Confirmatory trial of Endeavor (n=327) vs. Cypher (n=109)	***Primary:*** In-segment late loss by QCA at 8 months ***Secondary:*** MACE at 30 days, 6-9-12 months; TLR, TVR, and TVF at 9 months	Near completion	30-day blinded results either pooled or as Group A vs. Group B at AHA 2004; Full 9-month data at TCT 2005
ENDEAVOR-4	~900-patient, randomized, single-blind U.S. confirmatory trial of Endeavor vs. Taxus (PIs are Dr. Marty Leon and Dr. Kandzari of Duke)	***Primary:*** TVF at 9 months ***Secondary:*** MACE at 30 days, 6-9-12 months. Other endpoints include: TLR and TVR at 9 months; QCA and IVUS subset at 8 months	First patient to be enrolled in 4Q04, probably October	30-day clinical data possible at TCT or AHA 2005

Dr. Virmani: "I have not seen (autopsies of) both used in the same patients…but know instances where Cypher is being overlapped on Taxus…They have different polymers…They will crack, will get more inflammation…I wouldn't use different stents in the same patients, especially overlapping but even if they are in different vessels…You will get double the reaction because of the two different polymers."

Cypher vs. Taxus

Two investigator-initiated and sponsored studies – a 2003 study in Canada and a 2003/2004 study in Germany – compared Taxus to Cypher and found them fairly equivalent. Taxus was a little worse on MACE and TVR but not statistically worse. The researchers – both of whom use Taxus and Cypher and are not committed to one company or the other – said the REALITY trial (a head-to-head comparison of Taxus and Cypher sponsored by Johnson & Johnson) still may be able to show a statistically significant advantage of Cypher over Taxus because the numbers are larger.

Researchers for an investigator-sponsored study, ISAR-DESIRE, also found that Cypher may be a better choice than Taxus for in-stent restenosis (ISR), but both Taxus and Cypher are better than balloon angioplasty. An investigator suggested the dose of sirolimus or paclitaxel may need to be higher.

Cypher vs. Taxus *

Measurement	Taxus	Cypher
German/Italian Study		
Follow-up time	7.9 months	10.2 months
SAT	1.5%	0.9%
TVR	7.4%	~5.4%
Canadian Study		
# of DES used	225	125
% multivessel procedures	10.0%	14.0% (p<.05)
Average stent length	19.7%	17.6%
30-day MACE	8.1%	5%
180-day MACE	12.2%	9%
365-day MACE	14.5%	12%
30-day death	1.1%	0
180-day death	1.7%	0
365-day death	2.9%	1%
30-day TVR	0	0
180-day TVR	3.4%	4%
365-day TVR	4.6%	6%
30-day SAT	.58	0
180-day SAT	.58	0
365-day SAT	.58	0
30-day event-free survival	91.9%	95%
180-day event-free survival	87.8%	91%
365-day event-free survival	85.5%	88%

*** All differences in this chart are Nss unless noted otherwise.**

ISAR-DESIRE Trial Comparing Cypher and Taxus for ISR

Measurement	Cypher n=100	Taxus n=100	PTCA n=100
Primary endpoint: In-segment restenosis at 6 months	14% (p<001 vs. PTCA)	22% (p=.002 vs. PTCA)	45%
In-stent restenosis	8%	19%	33%
Death at 9 months	2%	1	1
Late loss in-segment	0.45 (p=.02 vs. Taxus)	0.66	---
Late loss in-stent	.21 (p=.006 vs. Taxus)	.48	---
TVR	8% (p=.02 vs. Taxus)	9%	---
Angiographic restenosis	14% (p=.19 vs. Taxus)	22%	---
Death at 9 months	2%	1%	2%

Other experts said these results are too preliminary to cause them to opt for Cypher over Taxus for ISR in their practices, and they called for additional tests to confirm these findings. An Irish cardiologist said, "This is a moderately-scaled trial… Personally, I would wait for more information to make decisions." A German cardiologist said, "This is a preliminary observation that needs to be confirmed."

In addition, a comparison of the European registries for Cypher (E-CYPHER) and Taxus (MILESTONE-II) is interesting, again seeming to favor Cypher.

6-Month European Taxus MILESTONE-II Registry vs. 6-Month European E-Cypher Registry

Measurement	Taxus in MILESTONE-II Registry n=~3,683	Cypher in E-CYPHER Registry n=9,473
MACE (cardiac death, MI, need for repeat procedures)	7.1%	2.5%
Repeat procedures	4.2%	1% (TLR)
Stent thrombosis (acute and late)	0.9%	0.3%
Results in Diabetics		
Number of diabetic patients	~504 NIDDM ~66 insulin-dependent	2,716 >814 insulin-dependent
MACE	8.9%	4.2% NIDDM 5.9% insulin-dependent
Repeat procedures	5%	1.4% (TLR) NIDDM 1.5% insulin-dependent
SAT	N/A	0.5% NIDDM 0.4% insulin-dependent

Two more trials will be presented at TCT 2004 in which the MACE rate with Taxus is reported to be worse than Cypher: 14.4% with Taxus in T-SEARCH vs. 6.6% with Cypher in RESEARCH (p<.05).

Systemic Therapy for Restenosis

Dr. Ron Waksman of the Washington Hospital Center reviewed some of the oral agents in development to prevent restenosis. He said, "The take home message is that systemic therapy reduces CVD mortality, but drug-eluting stents do not."

- **GLAXOSMITHKLINE'S Avandia (rosiglitazone).** Oral rosiglitazone (4 mg/day) has been shown to reduce restenosis in diabetic patients by 11% vs. 45.0% with placebo when given for six months.

- **OTSUKA'S Cilostazol.** A 700-patient study found:

Measurement	Cilostazol	Plavix
In-segment late loss	0.75	.91
In-stent late loss	0.56	1.06

- **Oral verapamil.**

VESPA Trial (n=700)

Measurement	Verapamil 240 mg BID	Placebo
Primary endpoint: Restenosis	7.8%	12.5%
TVR at 12 months	17.5%	26.2%

- **Prednisone.**

Measurement	Prednisone	Placebo
MACE at 12 months	7%	33%
Late loss	.39	.85
12-Month results of IMPRESS-2 Trial (n=100)		
MACE	4.7% (p=.03)	34.6%
TVF	7% (p=.03)	27%
Recurrence of angina	4.7% (p=.01)	25%
Restenosis	3.8%	N/A

- **Wyeth's Rapamune (rapamycin).** Dr. Waksman concluded, "Fifteen days is probably enough to give this…This therapy can work. The late loss has been 0.45-0.65 across all trials…And it is cost-effective."

Rapamune in Stented Patients with High CRP

Measurement	Rapamune	Placebo
Restenosis	0	22.2%
In-stent late loss	0.56	1.06

ORBIT-2 Trial Results

Measurement	Rapamycin 2 mg	Placebo
TLR	4.8%	17.4%
Restenosis	4.8%	6.9%

Stenting vs. CABG

Dr. Patrick Serruys presented the five-year results of the ARTS-I study, which found that there is no mortality difference between CABG and stenting for multivessel disease. The was a higher incidence of repeat revascularization with stenting, but that was not associated with increased mortality. These findings contradict the results of a meta-analysis of previous randomized trials, which found a significantly higher mortality rate with PTCA.

The SYNTAX trial, which is due to start in December 2004 or January 2005, will compare CABG to multivessel stenting in 4,500 patients. The primary endpoint is one-year MACE. This is an all-comers trial, with no inclusion or exclusion criteria. Dr. Serruys, who is the principal investigator, said, "The FDA was shocked at the design at first…This trial should give us a profile of who should get surgery, defined by both interventionalists and surgeons."

5-Year Results of ARTS-I Trial

Measurement	Stent (Crown or CrossFlex) n=547	CABG n=543	p-value
Secondary endpoint: MACCE at 5 years	18.2%	14.9%	.14
MACCE-free survival	58.3%	78.2%	<.0001
Freedom from death/CVA/MI	85.1%	81.8%	N/A
Death	8.0%	7.6%	.83
CVA	3.8%	3.5%	.76
Q-wave MI	6.7%	5.6%	.47
Non-Q-wave MI	6.7%	5.6%	.47
Freedom from death, stroke, MI, or any revascularization	17.5%	19.9%	N/A
Any repeat revascularization	30.3%	8.8%	<.001
CABG	10.5%	1.2%	N/A
Repeat PCI	23.2%	8.3%	N/A
Anginal symptoms	21.2%	15.5%	.08
Patients on short-acting nitrates	6.1%	2.4%	.003
Long-acting nitrates	6.1%	2.4%	.003
Beta blockers	53.9%	46.5%	.016
CCBs	29.1%	18.9%	<.001

New EuroPCR Journal

A new cardiologist journal may be launched soon, the Journal of EuroPCR, tentatively named ***Euro Intervention***. Dr. Serruys said, "Negotiations are progressing quite well. The political will is there, and our Board of Directors wants to do it." The launch goal is May 2005.

DRUGS

ASTRAZENECA'S Exanta (ximelagatran)

On September 10, 2004, the FDA's Cardiovascular and Renal Drugs Advisory Committee recommended against approval of Exanta for all the proposed indications, and FDA approval, therefore, is highly unlikely without additional pre-approval tests. *(A **Trends-in-Medicine** report on this committee meeting will be available later in September 2004.)*

The pre-specified subgroup analysis of the pooled meta-analysis of the SPORTIF-III and SPORTIF-V trials reported no difference in any subset – BMI, age, race, or weight. Exanta was non-inferior to warfarin in every subgroup, except that bleeding was less with warfarin ($p<.05$). Yet, Exanta appeared to have more beneficial effect in patients with normal creatinine, whites, men, and patients with normal body size. An investigator said, "In terms of protection for thromboembolism, nothing favored ximelagatran over warfarin."

Concern over the liver elevations dominated a review of previously presented pooled SPORTIF data. An investigator made several interesting comments about Exanta:

- It is likely that monthly liver testing – more frequently if ALT is elevated and discontinuation if ALT reaches 5xULN – will be required until and unless the five-year Exanta data indicate the liver elevation problem subsides with time. He implied but did not specifically say that monthly testing will be the recommendation of regulators, "Monthly testing has to be done. I can't see using it any other way."
- The five-year data will not be ready to present to the Exanta FDA advisory panel on September 10, 2004, and he wouldn't say when it will be available.
- He estimated that about 6% of patients experience elevated ALT with Exanta, and 2.8% have elevations ≥5xULN.
- Exanta can be neutralized by FEIVA. He said, "It is a possibility, but reversing coagulation means increasing the risk of coagulation, and FEIVA almost never is used in the clinic. It has turned out to be unnecessary."
- In the pooled SPORTIF data, ALT elevation is higher in the elderly. However, he warned, "It is wise to remember we did the subanalysis on different ages, and the efficacy was more favorable in the elderly than in patients younger than 75 years old."

EXPEDITE, a new trial of Exanta for deep vein thrombosis (DVT) is planned in the U.S. and Europe. This will include patients either with primary DVT or symptomatic pulmonary embolism (PE). The trial may provide more information on the use of Exanta in primary PE patients. It also may provide information on whether it would be reasonable to consider giving a little LMWH for the first few days and then switch to Exanta.

LILLY'S Prasugrel (CS-747, LY-640315)

Prasugrel, which has been referred to as "son of Plavix" has the potential to become a major competitor for Sanofi-Aventis/Bristol-Myers Squibb's Plavix (clopidogrel). Doctors are interested in an alternative to Plavix because of increasing reports of inter-patient variability in platelet inhibition in response to Plavix (referred to as "Plavix-resistance" or "Plavix non-response").

The 30-day results were presented at ESC from the JUMBO-TIMI-26 trial. Prasugrel, which Lilly licensed from Sankyo, is a novel thienopyridine $P2Y_{12}$ antagonist. The data looked good.

However, several questions were raised that deserve continued watching:

1. **Bleeding.** At the highest dose of prasugrel, there was an increase in minor bleeding, but it wasn't statistically significant. A speaker said, "Over time, we noted an increase in this type of bleeding in the follow-up period."

30-Day Results of JUMBO-TIMI-26 Trial of Prasugrel

Measurement	Plavix 300 mg LD 75 mg MD n=250	All Prasugrel n=600	Prasugrel 40 mg LD 7.5 mg MD n=200	Prasugrel 60 mg LD 10 mg MD n=200	Prasugrel 60 mg LD 15 mg MD n=250
Safety Results					
Primary endpoint: Significant (non-CABG) bleeding through Day 30	1.2%	1.7% p=.77`	1.5% *	2.0% *	1.6% *
Major bleeding	0.8%	0.5% p=.62	0.5% *	0.5% *	0.4% *
Major, minor, and minimal bleeding	3.6%	4.1% p=.54	3.5% *	3.5% *	5.1% *
Efficacy Results					
Secondary endpoint: MACE at 30 days	9.4%	7.2% p=.31	7.5% *	7.5% *	6.8% *
MI at 30 days	7.9%	5.7% p=.23	7.0% *	6.5% *	4.0% *
Target vessel thrombosis	2.4%	0.6% p=.03	1.0% *	0.5% *	0.4% *
Recurrent ischemia	3.5%	1.7% p=.09	1.5% *	1.5% *	2.0% *
Death	0	0.5 p=.56	0	0	0.5

*** No statistically significant difference from Plavix**

2. **Deaths.** There were three deaths in the highest prasugrel dose, compared to none with Plavix. An investigator said, "One occurred after only the loading dose of prasugrel. The patient was unable to have PCI off-drug, came back 10 days later for bypass, and died of infection. Another was a sudden death while playing sports and was not found to have had a recurrent ischemic event." He did not provide details on the third patient.
3. **QT prolongation.** There was a rumor that there has been some QT prolongation with prasugrel. At a minimum, the FDA requires Phase I clinical QT testing in addition to any preclinical QT tests. A prasugrel speaker was asked about this, and he said only that no QT prolongation was seen in preclinical data, "We did not measure QT in this trial (JUMBO-TIMI-26), but it was done in preclinical studies, and to date we've seen nothing in terms of QT prolongation." However, he did not specifically say that no QT prolongation has been seen in clinical testing.
4. **Optimal dose.** One prasugrel investigator said the dose going forward into Phase II is the middle dose – a 60 mg loading dose followed by a 10 mg maintenance dose, but another prasugrel speaker refused to say which dose would be used.

MYLAN/MENARINI RICERCHE/ JOHNSON & JOHNSON'S nebivolol

Nebivolol is a new, selective beta-1 blocker with vasodilation properties (through modulation of nitric oxide release that reduces peripheral vascular resistance). An official from Menarini, which currently markets nebivolol in Europe as an anti-hypertensive, said that Menarini has the rights to nebivolol everywhere except the U.S. and Japan but that Johnson & Johnson owns the molecule and may want to co-market it in the U.S. with Mylan. The official said sales have been growing strongly in Europe, "We are the only non-generic beta blocker in Europe…We are consistently growing sales, but it is not a boom."

Menarini Ricerche sponsored a session on nebivolol, and it was packed. At previous meetings cardiologists indicated that nebivolol had not differentiated itself from other beta blockers, but that attitude appears to be changing. An Alabama doctor said, "Nebivolol definitely is different. Whether that matters, still needs to be shown, but many cardiologists, myself included, are beginning to believe that class effect is less true for beta blockers and other drugs than we used to think." Another cardiologist said, "I'm starting to think there are real differences among beta blockers, ARBs, and other drugs. Nebivolol is interesting." Several other doctors said that, with the right marketing, nebivolol could catch on.

Researchers presented positive data on nebivolol in elderly heart failure patients. SENIORS is not considered a landmark trial like HOPE or EUROPA, but it was strong enough to get doctors talking about nebivolol, and most sources agreed that nebivolol has an advantage because it now has data in very elderly heart failure patients (>75), which the other beta blockers do not.

In SENIORS, a multicenter, randomized, placebo-controlled, double-blind, European, three-year study of the effects of nebivolol on outcomes and rehospitalization, in 2,135 European patients older than 70 with congestive heart failure (CHF), followed for up to 40 months (mean follow-up ~20 months). Patients in the nebivolol arm were titrated over 4-16 weeks from an initial dose of 1.25 mg/day to a target dose of 10 mg QD.

Large clinical trials have demonstrated the benefits of beta blocker treatment in CHF patients, but those studies were carried out in populations with an average age ~ 60. A nebivolol investigator commented. "We know beta blockers are the most effective treatment for chronic heart failure, but nearly two-thirds of patients don't get them who should." He cited two main reasons for this:

1. Doctors feel previous beta blocker studies addressed a much younger patient population than they see. "The average patient age in the community is about 76. The average age in clinical trials was 61.
2. The type of heart failure seen in the community is different than previous trials. "Only low ejection fraction (EF) patients were included (usually EF <35%) in trials,

Comparison of Nebivolol to Approved Beta Blockers for Heart Failure

Beta blocker	B_1 blockade	B_2 blockade	α_1 blockade	ISA	Ancillary effects *	$Beta_1$ selectivity	Vasodilation	Reduce outcome	Key trial and mean age in trial
carvedilol (GlaxoSmithKline's Coreg)	+++	+++	+++	-	+++	-	+	+	COPERNICUS – 63 US Carvedilol – 58 COMET – 62
metoprolol CR (AstraZeneca's Toprol or Novartis's Lopressor)	+++	-	-	-	-	+	-	+	MERIT-HF – 64 COMET – 62
bisoprolol	+++	-	-	-	-	++	-	+	CIBIS-I – 60 CIBIS-II – 61
Arca Discovery's bucindolol	+++	+++	-	++	-	-	+	-	BEST – 60
nebivolol (Mylan/Menarini)	N/A	N/A	N/A	N/A	N/A	++	N/A	N/A	SENIORS – 76

* anti-oxidant

but in the community, a significant percentage of heart failure patients have preserved systolic function (EF >35)."

A co-principal investigator (Dr. Andrew Coats of Australia) said, "This drug demonstrated a very strong safety profile…The chance of this drug damaging or causing events is extremely unlikely…All (pre-specified) subgroups benefited, regardless of ejection fraction, age, or gender."

Preliminary 36-Month Results of SENIORS Trial of Nebivolol

Measurement	Nebivolol	Placebo
Maintenance dose achieved	7.7 mg	8.5 mg
Patients on ≥5 mg	76.4%	83.0%
Patients on 10 mg (target dose)	64.5%	75.9%
Primary endpoint: Mean time to all cause mortality or CV hospitalization	Nebivolol 14% less than placebo (p=.039)	
Number of all cause mortality or CV hospitalizations	332 (31.1%)	375 (35.3%)
Secondary endpoint: All cause mortality	Nebivolol 12% less than placebo (p=.214)	
Number of all cause mortality events	169 (15.8%)	192 (18.1%)
CV hospitalization	Not yet adjudicated	
Death or CV Hospitalization by Subgroup		
LVEF ≤35	32.1%	36.3%
LVEF >35	28.9%	33.6%
Female	24.6%	33.3%
Male	35.2%	36.4%
Age ≤75	27.5%	33.5%
Age >75	34.8%	37.1%
Treatment Discontinuations		
Mandatory indication	3.0%	1.6%
Developed contraindication	2.7%	4.4%
Intolerance	0.8%	2.2%

However, another expert questioned the lower benefit in males than females, and the investigator responded, "It does appear that in percentage terms you might get slightly less effect in older populations. We would not say this is not effective above age 75, but there may be some reduction in the relative protection."

The discussant at the SENIORS trial data presentation (Dr. Milton Packer of Columbia University) said the study "reinforced current recommendations that beta blockers should be given to all patients with heart failure who have systolic dysfunction (possibly LVEF <45). It underscores the need for a definitive study of beta blocker use in patients with heart failure and a normal EF (EF>45). It is insufficient to conclude that beta blockers are effective in patients with an EF>50-55; such patients really need to be the focus of their own trial."

This critic compared SENIORS to the MERIT-HF and COPERNICUS trials, both of which found a benefit to beta blocker therapy in elderly patients (variably ≥65 or 69), but less benefit than in younger patients. He also compared SENIORS to the CIBIS-II trial which found a greater benefit to beta blocker use in elderly patients age ≥71 than younger patients. He described the SENIORS' results as comparable to these three trials, but the magnitude of effect is somewhat less and not statistically significant. He cited four possible causes in SENIORS for this:

1. Chance.
2. Inclusion of patients with EF>35. "These are mainly men in SENIORS, which is not typical."
3. A larger number of patients aged >75.
4. Pharmacological characteristics of nebivolol.

Other nebivolol studies planned or underway include: ECHO and a neurohormonal study.

PFIZER'S Lipitor (atorvastatin)

A Pfizer official said the results of the Pfizer-sponsored TNT (Treating to New Targets) trial will not be presented at the American College of Cardiology meeting in March 2005, but it may be ready for the European Society of Cardiology meeting in late August 2005 or the American Heart Association meeting in November 2005. TNT is an international, five-year, 10,003-patient, event-driven trial comparing the ability of 10 mg and 80 mg Lipitor to reach an LDL goal of either 75 or 100. The official indicated that the enrollment in the trial "has been slower recently than expected."

ROCHE

The European Society of Cardiology took the unusual step of calling a special press conference to present the findings of the global INTERHEART study. This 29,000-patient study in 52 countries found that the two most important risk factors for a heart attack are cigarette smoking and an abnormal ratio of Apolipoprotein B/Apolipoprotein A-1. Together, these two factors account for two-thirds of the global risk of heart attack, researchers reported. If this ratio test catches on, Roche may be an beneficiary since it currently has a test available to measure the ApoB/ApoA-1 ratio. An investigator said, "My guess is this (ratio) eventually will replace testing for HDL, LDL, and triglycerides, but an analysis of that hasn't been done yet."

SANOFI-AVENTIS'S Acomplia (rimonabant)

It definitely looks as if Sanofi-Aventis has a winner with this drug. Acomplia, which is being developed as both a diet drug and a smoking cessation therapy, is an endocannabinoid – a

selective cannabinoid type 1 (CB_1) blocker – that acts both centrally and peripherally. It is the first in a new class of drugs.

One-year data from the Phase III RIO-EUROPE weight loss trial was presented at the European Society of Cardiology meeting today that confirms and replicates the one-year results of the first Phase III weight loss trial – RIO-LIPIDS – which was presented at the American College of Cardiology meeting in March 2004.

RIO-EUROPE is a two-year, multicenter, randomized, double-blind, placebo-controlled, parallel group study of 1,507 patients in Belgium, Finland, France, Germany, the Netherlands, Sweden, and the U.S. (~350-400 U.S. patients). The placebo patients were on a non-specific hypocaloric diet (a 600 kcal/day deficit). At one-year, patients lost about 11 pounds more with a 20 mg once-daily dose of Acomplia than with placebo.

Reaction to these findings by other experts also was generally positive. A Norwegian cardiologist said, "This is striking data." The discussant at the formal Hot Line presentation said, "(This trial) confirms the efficacy of rimonabant in achieving weight loss and metabolic benefits. The safety profile appears reassuring, but a larger database is needed before definite conclusions can be drawn…The single most important news from this was that metabolic benefits have now been demonstrated to exceed what is attributable to weight loss…This is not the first drug to achieve weight reduction…so safety, tolerability, and side effects will require a larger database…We will watch the GI side effects and the neuropsychiatric side effects…And outcome studies in cardiovascular patients are needed for widespread adoption in our patients."

The key advantages to this drug as a weight reduction agent include:

- **Weight reduction.** An investigator said, "Rimonabant decreases food intake – both palatable and non-palatable food…The excellent weight loss in the placebo patients shows lifestyle interventions were well-performed, but there was still an extra 5 kg weight loss with rimonabant 20 mg and a greater increase in HDL."
- **Positive impact on lipid profiles.** The principal investigator (Dr. Luc Van Gaal of Belgium) said, "This is a robust replication of the RIO-LIPIDS data…The improvement in lipids (HDL and triglycerides) was partially independent from weight loss, implying a direct effect of the drug on lipids…Weight loss accounted for only approximately half the improvement in HDL and about half the improvement in triglycerides seen with rimonabant 20 mg, implying a significant direct effect of the drug on lipid metabolism, independent of weight loss (p=.005)."

1-Year RIO-EUROPE Trial Results of Acomplia

Measurement	Placebo + Diet n=305	Rimonabant 5 mg QD n=603	Rimonabant 20 mg QD n=599
BMI	36.3	36.6	36.8
Waist circumference (cm)	109.7	110.0	110.0
Primary endpoint: **Absolute weight loss**			
Completers (per protocol)	3.6 kg 7.9 pounds	4.8 kg 10.6 pounds (p=.042)	8.6 kg 18.9 pounds (p<.001)
By ITT with LOCF	1.8 kg 4 pounds	3.4 kg 7.5 pounds (p=.002)	6.6 kg 14.5 pounds (p<.001)
Secondary endpoinots			
Completers losing >5% of body weight	30.5%	44.2% (p=.002)	67.4% (p<.001)
Completers losing >10% of body weight	12.4%	15.3%	39% (p<.001)
Average decrease in waist circumference in completers	4.5 cm 1.8 inches	5.3 cm 2.1 inches (p=.002)	8.5 cm 3.3 inches (p<.001)
Average decrease in waist circumference by ITT with LOCF	2.4 cm 0.9 inches	3.9 cm 1.5 inches (p=.002)	6.5 cm 2.5 inches (p<.001)

1-Year RIO-EUROPE Trial Results of Acomplia

Measurement	Placebo + Diet n=305	Rimonabant 5 mg QD n=603	Rimonabant 20 mg QD n=599
Other Efficacy Results			
% of subjects with metabolic syndrome at baseline	39.9%	41.2%	42.2%
% of subjects with metabolic syndrome at one year	31.4%	28.6%	19.6% (p<.001)
Reduction in metabolic syndrome	-21%	N/A	-53%
Increase in HDL in completers	17.3%	19.0%	27.0% (p<.001)
Increase in HDL by ITT with LOCF	13.4%	16.2% p=.048	22.3% p<.001
Reduction in triglycerides (TGL) in completers	6.6%	4.9%	10.6% (p<.001)
Improved insulin response on Oral Glucose Tolerance Test	2.3 µlU/ml reduction	N/A	11.0 µlU/ml reduction (p=.019)
Non-HDL cholesterol change	-0.07	-0.13	-0.22
Safety Results			
Nausea	4.3%	5.1%	12.9%
Diarrhea	3.0%	6.0%	7.2%
Dizziness	4.9%	7.0%	8.7%
Psychiatric disorders	5.2%	3.0%	7.0%
Any adverse event	84.3%	82.6%	87.1%
Any serious adverse event	7.5%	7.5%	8.7%
Dropouts			
Overall	41.6%	37.3%	39.4%
Due to overall side effects	9.2%	8.3%	14.5%
Due to GI side effects	0	0.8%	3.5%
Due to nausea	0	0.2%	2.3%

- **No QT elevation.**
- **Efficacy and safety replicated in two trials.**

There are several remaining issues/questions with this drug, but none were thought by sources to be killer issues. They include:

- **Dropouts**. There was a high dropout rate in all three arms of the trial, but investigators explained this is a common problem in obesity trials. The most common side effect with Acomplia is nausea, but researchers insisted this is not the reason for the weight loss.
- **GI side effects,** particularly nausea.
- **Long-term safety.** A Scandinavian doctor said, "The safety profile appears reassuring, but a larger database is needed before definite conclusions can be drawn." A speaker said, "This is not the first drug to achieve weight reduction…so safety, tolerability, and side effects will require a larger database."
- **High placebo effect** on:
  - *Weight loss.* Rimonabant investigators claimed the relatively high weight loss with placebo in the RIO-EUROPE and RIO-LIPIDS trials was due to doctors recommending diet and exercise, but the diet wasn't monitored and diets were used in placebo and drug arms of other trials with less success.
  - *Increase in HDL.* In other trials, including Merck KgA's Niaspan (niacin) and Roche's Xenical (orlistat), the placebo effect on HDL is in the range of 5%-10%, but in RIO-EUROPE it was 17%.
- **Neuropsychiatric/mood side effects** (depression, anxiety, etc.) A Sanofi official said, "Patients do feel better (with rimonabant). Rimonabant doesn't affect emotion, just the addiction pathway." Investigators argued that the results of the Hospital Anxiety Depression (HAD) score, a well-known and validated self-questionnaire, prove there is no negative effect on mood. An investigator (Prof. Alain Golay of Switzerland) said, "I asked for (the use of the HAD score) in all the studies because it is really crucial to have this data. A person is depressed if the score is higher than 11, but the average in our study is 5."

HAD Scores with Rimonabant

Measurement	Rimonabant	Placebo
Depression	3.0 baseline 3.1 at 12 months	3.0 baseline 3.2 at 12 months
Anxiety	5.3 baseline 5.6 at 12 months	5.1 baseline 5.2 at 12 months

Asked about the 14% of dropouts that were due to depression, Prof. Golay said, "One can only guess, but when you stop smoking on a diet, you start to be anxious for one or two weeks…You can't stop smoking or eating without side effects. People smoke or eat because they are depressed or anxious. Food and cigarettes are an addiction…In the next trial, I will tell all investigators that if a patient is irritated or anxious, then you need to wait a week before discontinuing rimonabant."

Among the additional data experts suggested are needed on Acomplia include:

- **Qualitative changes** in:
  - Hs-CRP
  - Adipolicytokines
  - Lipid particle size
- **Long-term effect.** Whether weight loss is maintained during more prolonged therapy (e.g., the two-year data).
- **Rebound.** Whether weight loss and metabolic benefits are maintained after discontinuation of therapy, whether there is a rebound effect, or whether prolonged therapy is required.
- **Diabetics.** What the effect is in diabetics.
- **Libido.** Whether there is any effect on libido. However, a Sanofi official insisted there is no negative or positive effect on libido.

Acomplia may be able to be combined with Xenical, but without additional studies Prof. Golay would not recommend combining Acomplia with Abbot/Knoll Pharmaceutical's Meridia (sibutramine) since both Acomplia and Meridia are centrally active (in the brain). He said, "There may be ways to give diet drugs periodically for (weight) maintenance…If you go to a big dinner, take Xenical to control yourself. Or if you suddenly have a more stressful life or a death in the family, then take sibutramine to control your diet during that period."

Asked which patients will benefit from Acomplia, Prof. Golay said, "Patients uncontrolled in front of food – binge eaters who are compulsive in front of food."

Two-year data is expected to be presented at the American College of Cardiology meeting in March 2005, and Sanofi-Aventis is expected to file Acomplia with the FDA in 2Q05 with approval and launch expected in 2006. The company does not expect expedited review.

Two other Acomplia weight loss trials recently finished:

- RIO-Diabetes, a one-year study.
- RIO-North America, a study with more than 2,500 patients, that is expected to be presented at the American Heart Association meeting in November 2004.

OTHER DRUGS

Pulmonary Arterial Hypertension (PAH) and Primary Pulmonary Hypertension (PPH)

Oral therapies for PAH include:

Calcium channel blockers (CCBs)

CCBs are not approved to treat PAH, and acute nitric oxide (NO) testing with CCBs is not recommended due to a high incidence of severe deleterious effects (brachycardia, hypotension, shock, etc.), especially in non-responders. However, some uncontrolled data suggest that testing patients with idiopathic PAH may be justified, that IPAH patients (<10% of all PAH patients) who demonstrate a favorable acute response can benefit from long-term CCBs. In other forms of PAH, long-term response to CCBs is extremely rare. An expert said, "It is very important to find this subset of patients because CCBs are an easy, cheap, and efficient treatment…Patients who respond to NO should be treated with CCB monotherapy; in general, they don't need additional treatment…In our experience, we never observed vasoreactivity in patients on another drug, only on CCBs…Personally, I think (the responders represent) a different disease."

Prostanoids

GlaxoSmithKline's Flolan (epoprostenol) is currently the reference therapy for PAH, but it has numerous drawbacks, including the need for a pump, implanted catheter, risk of sepsis, and acute withdrawal problems. Most patients initiated on epoprostenol infusion do not demonstrate an early vasodilation response; clinical benefits are achieved only after several months of continuous infusion. A speaker said, "Survival is about doubled with epoprostenol. It is no cure, but it helps a lot."

Several other prostacylins are in development, including:

- **Oral prostanoid analogues.** Some uncontrolled studies in Japan were described as "rather impressive."
- **UNITED THERAPEUTICS' beraprost.** The three-month European ALPHABET trial was positive, and this looked promising, but a 12-month U.S. trial found the effect didn't last and GI side effects limited further dose escalation. A speaker said, "So, no attempt was made at FDA approval, and the EMEA (European regulators) denied approval."

A study of oral beraprost in twins was published in ***Chest*** earlier this year, and it found oral beraprost patients had progressive worsening compared to subsequent improvement on Flolan at nine months, but after the trial the beraprost patients were switched to Flolan with apparently no irreversible detrimental effect. The speaker added, "Beraprost is tricky to handle…It has to be absorbed after a meal because of variable GI absorption…and many patients can't increase doses because they don't tolerate it due to pain in the abdomen. All those reasons explain the failure of the drug …Since beraprost was withdrawn from development, and there were many patients on it, we had to transition them to other therapies, and that was mostly bosentan (Actelion's Tracleer, a twice-daily oral endothelin-1 antagonist). In most cases, the preliminary data found patients felt the same or a little better (on Tracleer) and felt relief not having abdominal symptoms any more."

Endothelin receptor antagonists

- **ACTELION'S Tracleer (bosentan),** a twice-daily oral ET-1 antagonist, which was approved by the FDA in 2001. Many of the doctors in the audience at a session on PAH indicated

Integrins Approved or in Development

Company	Drug	Type	Use	Status
"Old" Integrin-Targeted Drugs				
---	Allicin	Garlic	N/A	Natural
---	Echistatin, triflavin, kistrin	Snake venoms	N/A	Natural but hard to collect
Johnson & Johnson, Millennium, Merck	ReoPro, Integrilin, Aggrastat	IIb/IIIa inhibitors	Platelet inhibitor	FDA approved
"New" Integrin-Targeted Drugs in Development				
Ube Ind., Japan	UR-3216	Oral IIb/IIIa inhibitor	Platelet inhibitor	N/A
GlaxoSmithKline	SB-273005	Vitronectin receptor inhibitor	Arthritis, osteoporosis, angiogenesis	Preclinical
Pfizer	S-247 and SC-6448		Cancer, angiogenesis, metastatic cancer	Preclinical
Merck KgA	Cilengitide (EMD-121974)	αvβ3 integrin receptor inhibitor	Refractory squamous cell carcinoma, angiogenesis, and restenosis	Phase I and II successful, may begin Phase III
Bristol-Myers Squibb (Dupont)	XT-199	Vitronectin receptor inhibitor (active against integrin AvB3)	Restenosis	N/A
Bristol-Myers Squibb	AvB3 and A5B1	---	Angiogenesis and restenosis	Preclinical
Merck KgA	SPAV3	---	Osteoporosis	Preclinical
BASF/Abbott	Compound 11a and Compound 16b	---	Restenosis, cancer, osteoporosis, rheumatoid arthritis, diabetic retinopathy	Preclinical
MedImmune	Vitaxin (LM-609)	Monoclonal antibody	Angiogenesis and cancer	Possibly Phase III

they are currently prescribing Tracleer. A speaker said the main problem with this is liver elevation, but data indicate it improves survival. A new retrospective, 27-patient study presented at ESC found that Tracleer also works in patients with congenital heart defects, improving functional class, exercise capacity, and perhaps hemodynamics – with improvement observed as early as three months and maintained long-term. A speaker said, "When we treat patients with bosentan, the liver enzymes increase, but we use diuretics and (another drug) with it to prevent peripheral edema."

- **MYOGEN'S ambrisentan,** a selective ET-a antagonist.

- **ENCYSIVE'S Thelan (sitaxsentan),** an oral, once-daily, selective ET-a antagonist. The most common side effects with sitaxsentan have been peripheral edema, headache, dizziness, and nasal congestion, but a speaker at ESC said ALT increased 9.5% at the 300 mg dose (0% with the 100 mg dose, which appears the most promising dose at this point).

An abstract on extension data (mean 26 weeks, maximum 58 weeks) from the pivotal Phase IIb/III STRIDE-1 trial in PAH. The company indicated the more favorable safety/efficacy profile of 100 mg supported the selection of that dose as the maximum clinical dose in ongoing trials.

Results of STRIDE-1 Extension Trials

Measurement	100 mg Thelan n=79	300 mg Thelan n=91
Improvement of ≥1 NYHA Class	53%	44%
Improvement of ≥1 NYHA Class within 12 weeks of initiation of therapy	64%	70%
ALT >3xULN during first 12 weeks of therapy	0	10%
ALT >3xULN during entire treatment course	5%	21%
Deterioration in NYHA Class	5%	8%

Asked if there is an advantage to starting patients on IV Flolan and then switching them to an oral agent, an expert said, "In my center, some patients have been treated with prostaglandins for 20 years…We start orals first line, and in the case of a failure, then we do IV (Tracleer)…I'm not sure that this is a good idea. Maybe an aggressive combination in all PAH patients is the most effective therapeutic approach."

Phosphodiesterase-5 inhibitors

Off-label use of **PFIZER'S Viagra** (sildenafil) is growing, and that may lead to an sNDA for a PAH indication. A multi-national, 12-week (with further follow-up out to two years), 280-patient, randomized, double-blind, double-dummy, placebo-controlled trial is ongoing and data is expected to be released "soon." The trial has four arms: placebo, 20 mg TID, 40 mg TID, and 80 mg TID. An expert said, "We had 20 of these patients. Though we don't know what the patients are getting, in many cases we saw quite significant improvement." ♦